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THE DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A NOVEL MULTI-UNIT ERODING MATRIX SYSTEM FOR POORLY SOLUBLE DRUGS

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THE DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A NOVEL MULTI-UNIT ERODING MATRIX SYSTEM FOR POORLY SOLUBLE DRUGS

BY

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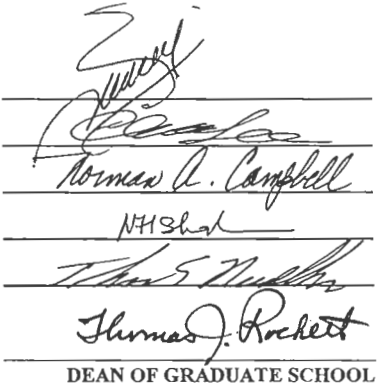

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ABSTRACT

Mechanisms governing the release of drugs from controlled delivery systems are mainly diffusion, osmosis and erosion. For poorly soluble drugs, the existing mechanisms are limited to osmosis and/or matrix erosion. These mechanisms are commonly employed to control drug release from single unit and multi-unit dosage forms. More recently, multi-unit dosage forms have gained considerable popularity for controlled release technology due to their advantages over single unit dosage forms. However, the mechanism of polymer controlled surface erosion from a multi-unit dosage form has never been reported in the literature. This study describes the development, characterization and evaluation of a matrix pellet system which releases an insoluble drug via polymer controlled surface erosion mechanism. Extrusion/Spheronization method was used to formulate matrix pellets. The effect of various formulation and process parameters affecting the drug release were characterized by analytical techniques such as Differential Scanning Calorimetry, X-Ray Diffractometry, and Mercury Intrusion Porosimetry. Different insoluble drugs were used as model drugs to demonstrate universal applicability of this novel system. The effect of drug solubility was also investigated on the mechanism of drug release from this system. Solid dispersions of the model insoluble drug was formulated to increase its solubility. It was observed that when the drug properties were changed towards increasing solubility in water, the release mechanism and rate also changed from pure surface erosion to erosion/diffusion. Drug release of nifedipine pellets in vivo occurred for more than 24 hours following zero order kinetics in fasted dogs. Thus it was proved that the approach of controlling drug release by polymer

controlled surface erosion mechanism from a multi-unit pellet system is possible and such a system may be beneficial than the current marketed dosage forms of insoluble drugs such as nifedipine.

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PREFACE

This work has been prepared in accordance with the manuscript format option for dissertation preparation, as outlined in section 11-3 of The Graduate Manual of the University of Rhode Island. Contained within is a body of work divided in to three sections.

Included within Section I is Introduction, which introduces the reader to the subject of this dissertation, a statement of the hypothesis tested herein, and the specific objectives of my research.

Section II is comprised of five manuscripts, containing the findings of the research which comprises this dissertation. These five manuscripts are presented in the format required by the journal to which they will, or have been, submitted.

Section III contains appendices containing, ancillary data (information essential to, but not usually included in published manuscripts) and other details pertinent to the understanding of the concepts presented in Section II. This dissertation closes with a complete listing of all the works cited in this dissertation, arranged in alphabetic order by the author's last name.

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SECTION I

- Introduction. A general introduction followed by compilation of the specific objectives of this research.

- A statement of the hypothesis tested in this dissertation.

INTRODUCTION

Release of poorly soluble drugs in a controlled fashion is a challenging task for the pharmaceutical scientist. The mechanisms that are utilized to control release of drugs are mainly diffusion, osmosis and erosion. Alza Corporation has developed the GITS (Gastro Intestinal Therapeutic Systems) system for the release of nifedipine, a sparingly soluble drug, over a period of 24 hours. This is an "Oros" tablet that delivers drug under osmotic pressure differences between the GI fluids and the drug formulation encapsulated in the semi-permeable membrane surrounding the tablet. The release of the drug occurs as a fine suspension from the laser drilled hole bored in the tablet [1, 2].

Other approaches used are matrix tablets which release the drug in a controlled fashion. Low to moderate viscosity grade hydrophilic polymers such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose hydroxy ethyl cellulose, chitosans, alginates etc, have been used for this purpose. One of the drawback of these matrices is that they are single units and bioavailability from such matrices is dependent on gastric retention [3, 4].

Single unit dosage forms of poorly soluble drugs that release the drug by osmosis or erosion are commercially available. However in vivo drug release from such dosage forms may not be predictable and complete due to physiological variations in the gastric retention time and gastric emptying rates. Additionally, the frequency of bowel movements is also a factor that seriously influences bioavailability of drugs from such systems.

During the past 20 years there has been a growing interest in multi-unit solid dosage forms such as pellets for controlled drug delivery. Pellets offer significant therapeutic advantages over the traditional single unit dosage forms. Since pellets disperse freely in the GIT, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering the bioavailability of the drug. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter subject variations of plasma concentrations of the drug, which are common for the single unit dosage forms, are minimized. Another advantage of pellets over single unit dosage forms is that the high local concentrations of therapeutic agents, which may inherently be irritant to the mucosal membranes, can be avoided. Pellets, when formulated as modified release dosage forms are less susceptible to dose dumping than the reservoir-type single unit formulations [5].

During the early developmental phase of nifedipine GITS system, 20% of the population in the clinical trials taking nifedipine GITS tablet expelled the tablet intact through the GIT via fecal matter. The pellets on the other hand, due to their small size and large number are dispersed rapidly in the GIT and thus avoid dose dumping or loss of dosage form. Pellets also offer technological advantages over single units such as better flow properties and ease of further processing during tablet compaction or coating for controlled release. Table I shows a partial list of pellet products marketed in the US.

Traditionally coated pellets have been used for controlled release applications. Most of the marketed controlled release pellets available today are coated. More recently, matrix

pellets have gained popularity in controlled release technology. Controlled release via matrix pellets avoids the coating process and thus saves time and money. Pellets, manufactured by the pharmaceutical industry, are sized between 500 and 2000 μm. These can be produced in different ways such as spraying a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer after layer, spraying a melt of fats and waxes from the top into a cold tower (spray congealing) forming pellets as the result of the hardening of molten droplets and spraying a binder solution into the whirling powder using fluidized bed [5]. The most popular method of producing pellets is the Extrusion-Spheronization technique. This process was first reported by Reynolds (1970) and by Conine and Hadley (1970) and involves four steps: preparation of the wet mass (granulation), shaping the wet mass into cylinders (Extrusion), breaking up the extrudate and rounding of the particles into spheres (Spheronization) and finally drying of the pellets.

Traditionally, in the Extrusion-Spheronization technique, microcrystalline cellulose (MCC) has been the excipient of choice to prepare matrix pellets. Due to its excellent plasticity, it is widely used as a carrier or filler in the Extrusion-Spheronization process. However, MCC forms a non-disintegrating matrix and thus incorporation of a swelling or disintegrating agent is necessary for drug release to occur from such a system. Drug release from such matrices has been studied extensively by O'Conner et al. [6] and it was concluded that drug release occurred by Higuchi's square root of time equation and followed first order kinetics. Incorporation of a poorly soluble drug in such a matrix system would minimize drug release since the MCC matrix system is non-disintegrating.

Therefore, such a system would be inappropriate to formulate controlled release pellets of a poorly soluble drug. Additionally, since the drug is poorly soluble, diffusional release will be negligible. Thus, the only choice remains is that of an eroding pellet, which is a matrix pellet system that erodes from the surface as a function of time and releases the drug which is homogeneously dispersed in the pellet matrix. There is no such system reported in the literature.

Hellar et al. [7] prepared discs of poly (ortho esters) and studied in vitro and in vivo drug release of the highly water insoluble levonorgestrel. Poly (ortho esters) are polymers that erode due to pendent group hydrolysis of the ester groups, however; it is not generally recognized as safe for pharmaceutical applications. Hellar et al. concluded from his study that levonorgestrel release from surface-eroding polymer discs has three important consequences which are (1) The rate of drug release is directly proportional to drug loading, (2) The lifetime of the delivery device is directly proportional to device thickness, and (3) The rate of drug release is directly proportional to the total surface area of the disc.

The controlled release systems developed by Hellar et al. using poly (ortho esters) showed zero order release for months. Drug released in vitro was analyzed by measuring the drug present in the device after periodic time intervals of dissolution and the polymer erosion was determined by gravimetry. This study demonstrated that an indirect method such as measuring the drug left in the delivery device after dissolution may be employed

to quantify drug released and also the use of gravimetry to determine polymer erosion profiles.

Based on the information given above, the specific objectives of this research were,

1. To search for a surface eroding "GRAS" (Generally Recognized As Safe) polymeric system suitable for Extrusion-Spheronization technique.
2. To develop pellets of poorly soluble drugs for controlled release which releases the drug following zero order kinetics for 12-24 hours.
3. To characterize and evaluate the release mechanisms by analytical techniques such as differential scanning calorimetery, x-ray diffractometry, mercury intrusion porosimetry, particle size distribution, microscopy and in vitro, in vivo analysis.
4. To test the universal application of the system developed initially by using another poorly soluble drug.
5. If circumstances allow, to test the bioavailability in vivo of one of the model drugs from the pellets tested in vitro.

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Table 1. Partial list of pellet products marketed in the U.S

Product	Company
Sudafed S. A.	Glaxo-Wellcome
Theo-24	Searle Pharmaceuticals, Inc.
Theodur S. R.	Key Pharmaceuticals
Nitrostat S. R.	Parke-Davis
Bontril SR	Carnrick Laboratories, Inc.
Compazine	Smith Kline & French
Hispril	Smith Kline & French
Nicobid T.S.	U.S. Vitamin
Papaverine HCL, T.D.	Lederle Laboratories
Russ-Tuss	Boots Pharmaceuticals
Slow-bid	Rorer
Theobid S. R.	Glaxo-Wellcome
Inderal L.A.	Ayerst Laboratories
Indocrin S.R.	Merck Sharp & Dohme
Xenical	Roche Pharmaceuticals
Novafed L.A.	Merrel-Dow
Fastin	Beecham Laboratories
Catazyme S	Organon Pharmaceuticals

Source: Sellasie, I, G.,"Pharmaceutical Pellitization Technology", Marcell Dekkar, Inc., New York, 12-14, (1989).

HYPOTHESIS TESTED HEREIN

It should be possible to develop a multi-unit controlled release matrix pellet system by Extrusion/Spheronization technique without microcrystalline cellulose (MCC), which can release an insoluble drug by polymer controlled surface erosion mechanism following zero order kinetics for 12-24 hours.

SECTION II

- Manuscript I "Development, Characterization and Evaluation of a Novel Multi-Unit Erosion Matrix for a Poorly Soluble Drug."
  (Submitted for publication in International Journal of Pharmaceutics).

- Manuscript II "Effect of Formulation and Process Variables on Matrix Erosion and Drug Release from a Multi-Unit Erosioin Matrix of a Poorly Soluble Drug."
  (Submitted for publication in Pharmaceutical Research and Developments).

- Manuscript III ""Effect of Formulation and Process Variables on Porosity Parameters and Release Rates from a Multi-Unit Erosion matrix of a Poorly Soluble Drug."
  (Submitted for publication in European Journal of Pharmaceutics and Biopharmaceutics).

- Manuscript IV "Multi-Unit Controlled Release Systems of Nifedipine and Nifedipine:Pluronic® F-68 Solid Dispersions: Characterization of Release Mechanisms."
  (Submitted for publication in the Journal of Controlled Release).

- Manuscript V "Nifedipine Bioavailability in Fasted Dogs from an Eroding Multi-Unit Matrix System."

  (Submitted for publication in International journal of Pharmaceutics).

MANUSCRIPT I

DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A NOVEL MULTI-UNIT EROSION MATRIX FOR A POORLY SOLUBLE DRUG.

Abstract

Mechanisms governing the release of drugs from controlled delivery systems are mainly diffusion, osmosis and erosion. For poorly soluble drugs, the existing mechanisms are limited to osmosis and/or matrix erosion, which are commonly employed via single unit matrix dosage forms. More recently, multi-unit dosage forms have gained considerable popularity for controlled release technology, because their rapid dispersion in the gastrointestinal tract maximizes drug absorption and provides reduced peak plasma fluctuations. Bioavailability from multi-unit dosage forms is affected the least by the presence of food and gastric emptying rate. This study reports the development of a novel multi-unit controlled release system for a model poorly soluble drug (thiazole based leukotriene D_4 antagonist, solubility in physiological pH < 1.3 μg/mL) by a polymer controlled, surface erosion drug release mechanism. The drug, rate controlling and pellet forming agents (Eudragit®L 100 55 and Eudragit® S 100) and a binder (polyvinylpyrrolidone, Kollidon®K90F), were wet granulated, extruded and spheronized to form uniform matrix pellets. *In vitro* matrix erosion and drug release from the pellets were determined using USP Dissolution Apparatus I in pH 6.8 phosphate buffer by gravimetry and UV spectrophotometry, respectively. Results showed that matrix erosion and drug release from the pellets were well correlated. Pellets eroded with a consequent reduction in size without any change in the pellet shape for over 12 hours. Matrix erosion and drug release followed zero order kinetics. Data obtained strongly suggested a polymer controlled, surface erosion drug release mechanism.

KEYWORDS

Extrusion/Spheronization, Eudragit® L 100-55, Eudragit® S 100, polymer controlled surface erosion, controlled release matrix pellets.

1.0 Introduction

Release of poorly soluble drugs from controlled delivery systems is a challenging task for the pharmaceutical scientist. Alza Corporation has developed a gastrointestinal therapeutic system (GITS) for the release of nifedipine, a poorly soluble drug, over a period of 24 hours. The system is an "Oros" tablet which releases the drug under osmotic pressure differences between the GI fluids and drug concentration in the semi-permeable membrane surrounding the tablet. The release of drug occurs as a fine suspension from the laser drilled GITS device (1). Other approaches for the release of poorly soluble drugs from controlled release erosion matrix tablets employing hydrophilic cellulosic polymers are reported (2, 3). These matrices are generally single units and thus may be associated with drawbacks such as irregular bioavailability due to presence of food and dependence on gastric emptying time. Therefore, existing mechanisms for the release of poorly soluble drugs by controlled release are limited to osmosis and/or erosion. Due to their negligible aqueous solubility, diffusion has practically very little or no contribution in the release of such drugs from the controlled delivery system.

More recently, multi-unit dosage forms have gained considerable popularity over conventional single units for controlled release technology. Due to their rapid dispersion in the gastrointestinal tract, they maximize drug absorption, reduce peak plasma fluctuations, minimize potential side effects without lowering drug bioavailability. They also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter-subject variability of plasma profiles, which are common with single-unit regimens,

are minimized. They are also less susceptible to dose dumping than the reservoir or matrix type, single-unit dosage forms (4).

Controlled release of poorly soluble drugs such as nifedipine, ampicillin and isosorbide dinitrate via pellets have been reported (5-9). All these studies primarily employed microcrystalline cellulose as a pellet forming agent. Due to its excellent pellet forming properties, microcrystalline cellulose offers potential advantage in pellet manufacturing by Extrusion/Spheronization technology. Release from such pellets was extensively studied by O'Connor et al (10). It was concluded that drug release follows first order kinetics as described by Higuchi's square root of time equation from such pellets. Since microcrystalline cellulose forms a non-disintegrating matrix when formulated as pellets, incorporation of a poorly soluble drug in such a matrix would only intensify the problems associated with its release. Such a matrix system would often provide no release of the poorly soluble drug at all.

This paper reports the formulation of pellets which release a poorly soluble drug as a result of surface erosion of the matrix pellet. It was postulated that for drug release to occur in zero order fashion, a matrix pellet must erode slowly as function of time from the pellet surface. This will allow the release of homogeneously dispersed drug in the matrix in constant increments as the erosion progresses in the pellets from the surface thus controlling drug release. A schematic representation of such a delivery system is shown in Figure 1.

2.0 Materials And Methods

The poorly soluble drug used as a model was a thiazole based leukotriene D_4 antagonist with a solubility less than 1.3 μg/mL at pH 6.8 (Hoffmann-La Roche Inc., Nutley, NJ). Eudragit® L 100 55 and Eudragit® S 100 (Huls America, Inc., Somerset, NJ) were used as release rate controlling polymers and matrix forming agents. Kollidon® 90 F (BASF Inc., Parsipanny, NJ) was used as a binder. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was employed to prevent inter-pellet sticking during the spheronization stage. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as a plasticizer for the Eudragit® polymers. All other chemicals were used as received.

2.1 Formulation of Pellets:

Eudragit®L 100 55 and Eudragit®S 100 powders were mixed in a turbula mixer (Turbula Mixer, Impandex Inc., Maywood, NJ, USA) for 30 minutes. Triethyl citrate was added to some formulations (Table-1) as a plasticizer and the resultant mixture was triturated in a mortar for 5 minutes. Drug and polyvinyl pyrrolidone (Kollidon®K90F) as a binder were added and mixed for 30 minutes in turbula mixer. This mixture was then granulated with deionized water in a mortar and later extruded (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan) at 40 rpm screw speed. The extrudates were immediately transferred into a rotating plate in the spheronizer (G.B. Caleva Ltd, Model 120, Dorset, England, consisting of a stationary vertical cylinder with a friction plate (diameter 32 cm) of 2 mm cross hatched pattern and a rotation speed of 200-3000 rpm).

Spheronization was carried out for 20 minutes at 500-1000 rpm. During this period, 5% w/w of total batch size Avicel® PH 101 was sprinkled over the rotating extrudates to prevent the pellets from sticking. Pellets obtained were dried on trays at 50°C for 12 hours. Dried pellets were later sieved to obtain different particle size fractions (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, fitted with sieve # 8, 10, 12, 14, 16, 18 and 20). The pellets consisted of drug (10.0% w/w), Eudragit®L 100 55 and Eudragit® S 100 (88.0% w/w) and Kollidon®K90F (2.0% w/w). A flow chart of the manufacturing process is presented in Figure 2. The composition of formulations with different polymer ratios is given in Table 1.

2.2 *Characterization of Pellets:*

2.2.1 *Determination of Glass Transition Temperature (Tg)*

Polymer blends (Eudragit® L 100-55 : Eudragit® S 100 in ratio of 1:3) with or without triethyl citrate as a plasticizer were weighed in a DSC aluminium pan. The DSC (Differential Scanning Calorimeter, Seiko Instruments Inc., Japan, Model SSC5200) was programmed to perform a heat-cool-heat cycle from 0 - 200°C. Heating and cooling rates of 10°C/minute was used.

2.2.2 *Determination of Matrix Erosion*

To study the erosion process of the pellet matrix, three criteria's were monitored, namely; microscopic evaluation of pellets, matrix erosion after dissolution of pellets and volume reduction by erosion of the pellets at different dissolution time intervals.

Pellets were visually inspected, sized and photographed under an optical microscope (Optical Microscope, Nikon HFX,IIA, Japan) before and after matrix erosion and drug release studies. Ten pellets per time interval were evaluated.

Matrix erosion was evaluated by using standard USP dissolution system (Distek, Dissolution System 2100A, USP Apparatus I ,Baskets). Matrix erosion was determined by removing the baskets with pellets at intervals of 2, 4, 6, 8, 10, 12 hours and drying them for 12 hours at 50°C to a constant weight. The difference between the initial and final weight was calculated as percent matrix erosion.

Volume reduction due to erosion of pellets was calculated by using Equation 1.

$$V_s = 1/6\ \pi\ D^3 \qquad \text{Equation 1}$$

Where, V_s is volume (mm^3) of a sphere and D is the diameter (mm) of a sphere.
Cumulative percent erosion volume was calculated by dividing the change in volume at time 't' by original volume at time zero. The result of this was multiplied by 100 to obtain percentages. Rate of erosion volume (%/hr) was calculated by dividing cumulative percent erosion volume with the time interval.

2.3 Dissolution Studies:

Since the drug is poorly soluble, drug release from the pellets was determined by an indirect procedure which involved determination of drug left in the pellets after dissolution by UV analysis. The difference between initial and final amount of drug present in the pellets after dissolution was calculated as percent drug release.

3.0 Results And Discussion

3.1 Pellet Processing by Extrusion/Spheronization:

Extrusion with Eudragit®L 100 55 and Eudragit®S 100 as pellet forming agents was satisfactory and pellets of uniform shape and size were obtained (Figure 3). Spheronization occurs by rotation of the extrudates at high speeds on a friction plate within a vertical cylinder. During this stage each individual pellet rotates on its own axis due to centrifugal force. This action results in liquid migration from the interstices between particles to the surface of the sphere which may be accompanied by migration of ingredients in the formulation. If the drug is soluble in the granulating liquid, then on drying may lead to non homogeneous distribution of ingredients in the pellets (11).

The drug and the polymers used in this study were insoluble which prevented them from solubilizing or retaining moisture within the pellet matrix, resulting in the migration of moisture alone towards the pellet surface. This action created inter-pellet adherence during the spheronization process. Inter-pellet adherence was eliminated by sprinkling 5% w/w of Avicel®PH 101 on the extrudates during the spheronization step.

3.2 Characterization of Pellets:

Release profiles of the pellets (1.2 mm) prepared with and without triethyl citrate as plasticizer is shown in Figure 4. It was observed that 70 to 100 % drug release was obtained within six hours from these pellets. Pellets with 1:1 and 1:3 ratios of Eudragit® L 100 55 : Eudragit® S 100 were formulated. Pellets within each of the two formulation ratios containing plasticizer showed enhanced drug release rates when compared to pellets without plasticizer. This effect was consistent when the polymer ratio of the pellets were increased. The increased drug release from the pellets containing plasticizer may be the result of increased dissolution rate of the polymers after plasticization.

This effect was investigated by determining the effect of plasticizer on the glass transition temperature of the polymer (Figures 5A thru D). Results obtained are tabulated in Table 2. Polymer blends with plasticizer showed a significant reduction in glass transition temperature and enthalpy. Glass transition temperature of both the polymers were reduced by about 60% indicating that the polymer blend became more amorphous after plasticization, therefore its solubility was increased.

3.3 Characterization of Matrix Erosion and Mechanism of Drug Release:

Microscopic studies showed that the pellets during drug release were reduced in size as a function of time while maintaining a constant surface geometry (Figure 6A thru F). To extend the release period to more than six hours, 2.0 mm pellets were formulated. Figure

7 shows the extent of matrix erosion and drug release from the pellets. Matrix erosion and drug release occurred simultaneously (Figure 7). This correlation of matrix erosion with drug release holds true at stirring rates of 25, 50 and 100 rpm as demonstrated by Figure 8. These findings prove that drug release was a direct consequence of matrix erosion and was stirring rate independent.

Figure 9, shows the correlation of drug released with percent volume reduction by erosion. It indicates a direct relationship between drug release and volume reduction by erosion. Volume reduction depends on the diameter of the pellets. As the pellet erodes with time the pellet diameter reduces due to which erosion volume increases to maintain a constant rate of drug release (Table 3). Table 3 shows the changes in pellet volume, cumulative % erosion volume and rate of erosion volume as a function of dissolution time. The rate of erosion volume from Table 3 was observed to be constant up to 10 hours. This indicated that pellets eroded from the surface with consequent size reduction without affecting the erosion volume. Thus drug release following zero order kinetics was obtained.

These discussions explain the zero order release and matrix erosion profiles achieved from pellets and provide strong evidence for a surface erosion mechanism and for negligible diffusional release of the drug.

4.0 Conclusions

Uniform matrix pellets were obtained by using Eudragit®L 100 55 and Eudragit® S 100 as pellet forming agents. Pellets of satisfactory quality without microcrystalline cellulose in the matrix can be formulated.

As hypothesized, multi-unit pellet system formulated for controlled release of a poorly soluble drug by polymer controlled surface erosion mechanism were developed and characterized. These pellets reduced in size as a result of polymer controlled surface erosion of the drug and provided zero order controlled release up to 12 hours.

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Table 1: Formulation of 1.2 mm and 2.0 mm pellets with different polymer ratios.

Eudragit® L 100 55 : Eudragit® S 100 ratio	**Triethyl citrate (% w/w of total Eudragits®)**
1.0 : 1.0	15.0
1.0 : 1.0	-
1.0 : 3.0	15.0
1.0 : 3.0	-

Table 2: Effect of plasticizer (triethyl citrate) on Tg and ΔH of Eudragit® L 100 55 and Eudragit® S 100 polymers.

Polymer blends	T_g (°C)	Δ H (mJ/°C mg)
[a]Eudragit® L 100 55	93.2	0.112
Eudragit® S 100	166.4	0.189
[b]Eudragit® L 100 55	54.5	0.050
Eudragit® S 100	109.4	0.083

(a) Ratio of 1:3 unplasticized polymer blend

(b) Ratio of 1:3 plasticized with 15% w/w of triethyl citrate.

Table 3: Determination of the rate of erosion volume reduction from 2.0 mm pellets (n = 10).

Time (hours)	Pellet Diameter (mm)	Pellet Volume (mm^3)	[1]Volume Change (mm^3)	[2]Cumulative Percent Erosion Volume (mm^3)	[3]Rate of Erosion Volume (%/hr)
0.0	2.08	4.7118	0.8889	0.0000	0.0000
2.0	1.94	3.8229	1.8573	18.8654	9.4327
4.0	1.76	2.8545	3.6645	39.4180	9.8545
6.0	1.26	1.0473	4.1392	77.7728	12.9621
8.0	1.03	0.5721	4.6783	87.8581	10.9822
10.0	0.40	0.0335	4.7077	99.2890	9.9289

1 : Original Volume – Volume at time 't'.

2 : Volume Change divided by 4.7118 (Volume at time zero).

3 : Cumulative Percent Erosion Volume divided by the time interval.

Figure 1

Schematic representation of a novel multi-unit erosion matrix for controlled release of a poorly soluble drug.

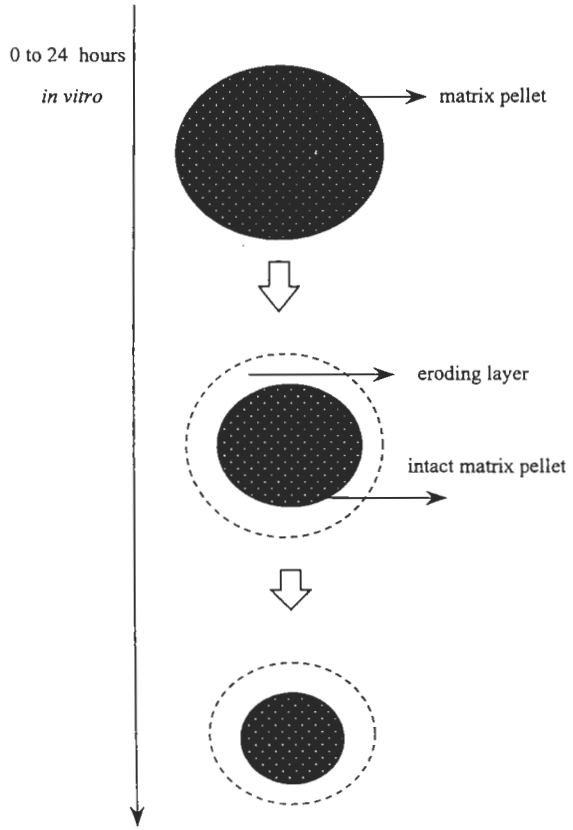


Figure 2

Flow chart of pellet manufacturing procedure.

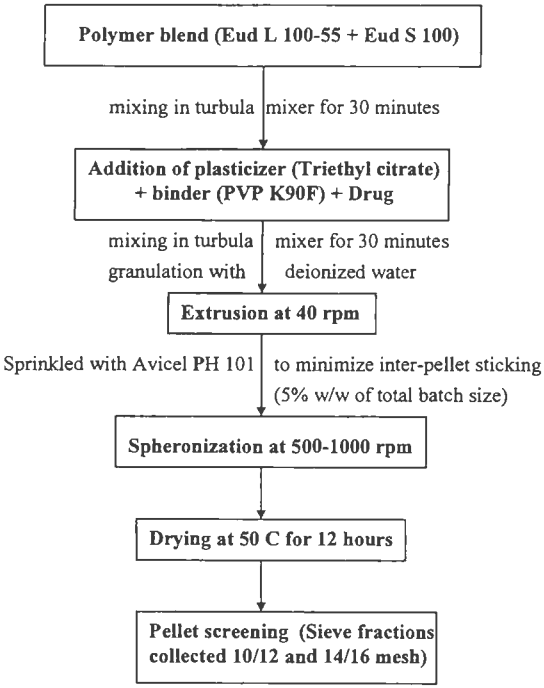


Figure 3

Photomicrographs of pellets (2.0 mm) viewed under an optical microscope, magnification 5X.

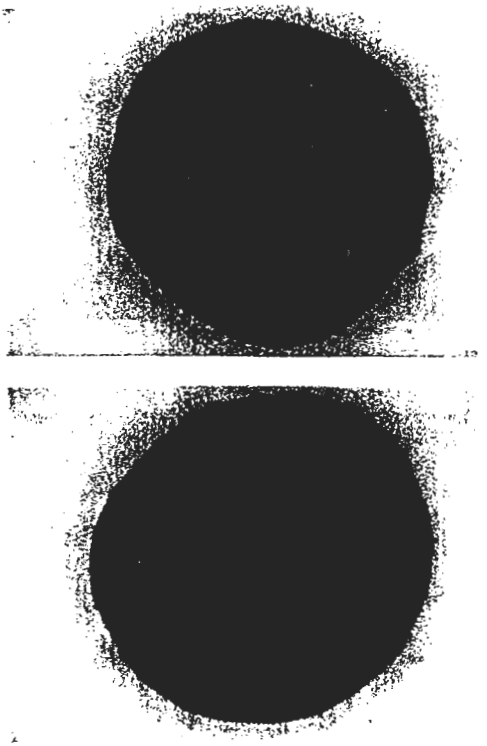


Figure 4

Effect of plasticizer on matrix erosion from pellets (pellet size: 1.2 mm, drug load: 10% w/w, Eud L 100-55: Eud S 100 ratio of 1:1 and 1:3)

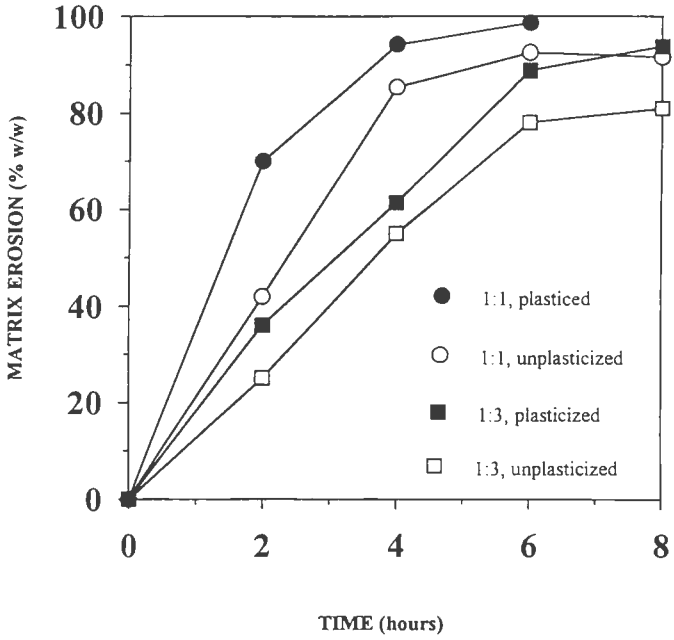


Figure 5A

DSC thermogram showing the glass transition temperatures of Eudragit® L100-55.

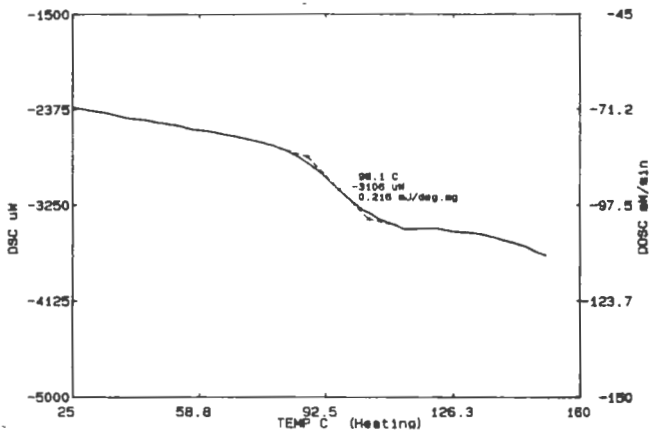


Figure 5B

DSC thermogram showing the glass transition temperatures of Eudragit® S100.

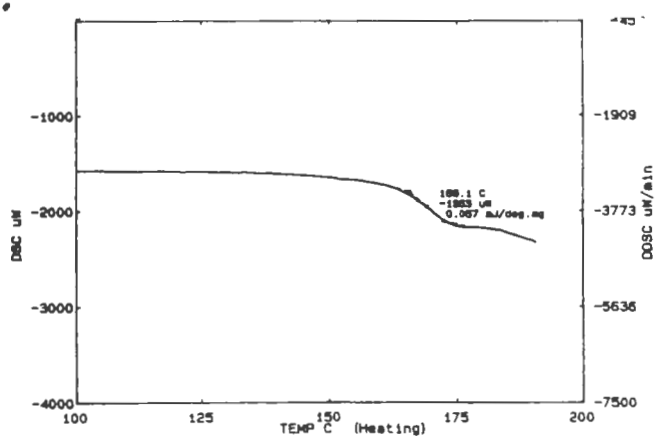


Figure 5C

DSC thermogram showing the glass transition temperatures of Eudragit® L100-55 and Eudragit® S100 mixed in ratio of 1:3.

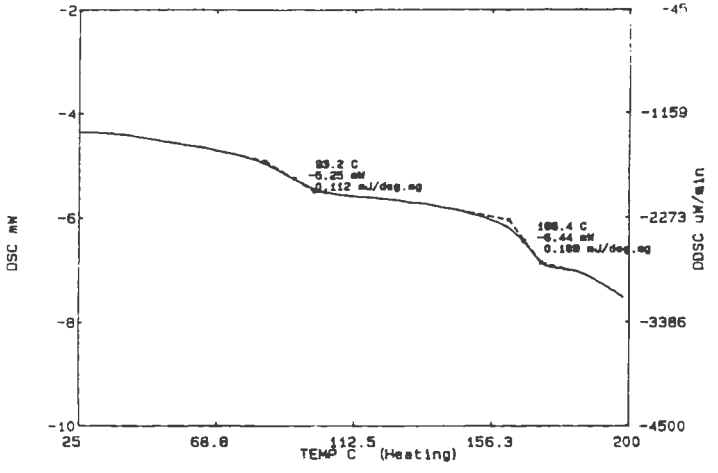


Figure 5D

DSC thermogram showing the glass transition temperatures of Eudragit® L100-55 and Eudragit® S100 mixed in ratio of 1:3 and plasticized with 10% w/w triethyl citrate.

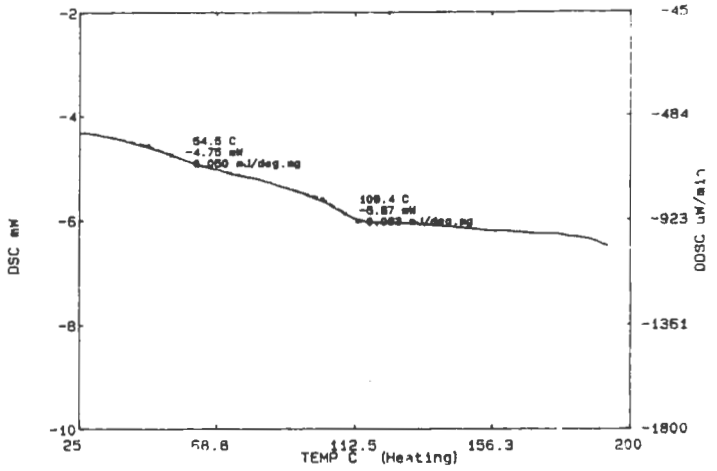


Figure 6

Microscopical evaluation of matrix erosion and size reduction of pellets (magnification: 5X).

A. Time: 0 hrs, Size: 2.0 mm

B. Time: 2 hrs, Size: 1.75 mm

C. Time: 4 hrs, Size: 1.6 mm

D. Time: 6 hrs, Size: 1.4 mm

E. Time: 10 hrs, Size: 0.8 mm

F. Time: 12 hrs, Size: 0.2 mm

Figure 7

Correlation of matrix erosion (% w/w) with drug release (%) from pellets. (pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, n = 5±SE).

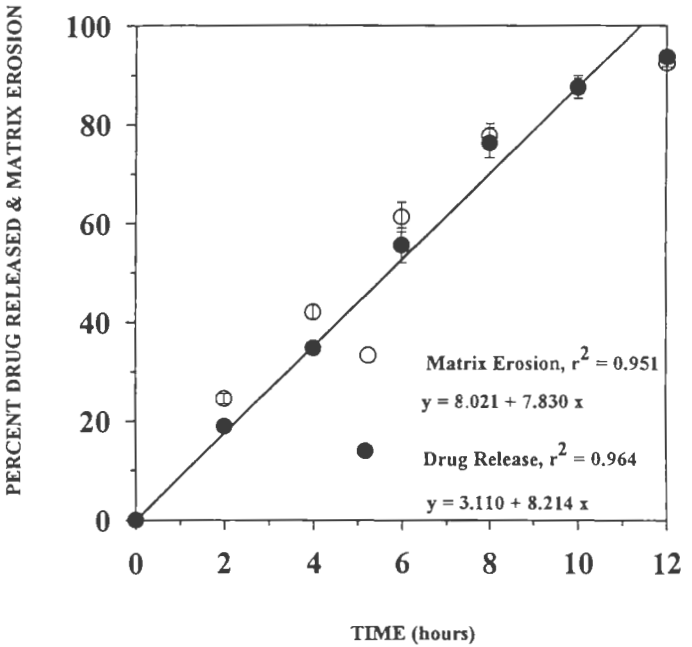


Figure 8

Correlation of matrix erosion (% w/w) with drug release (%) at different stirring speeds. (pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, n = 4±SE).

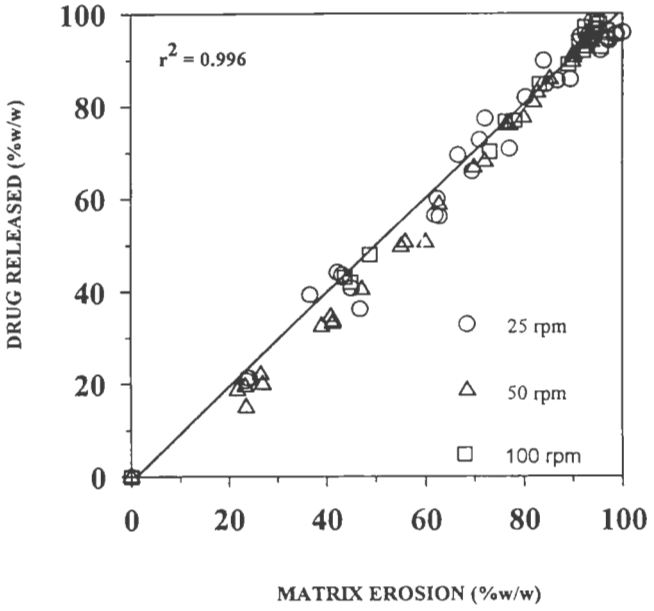
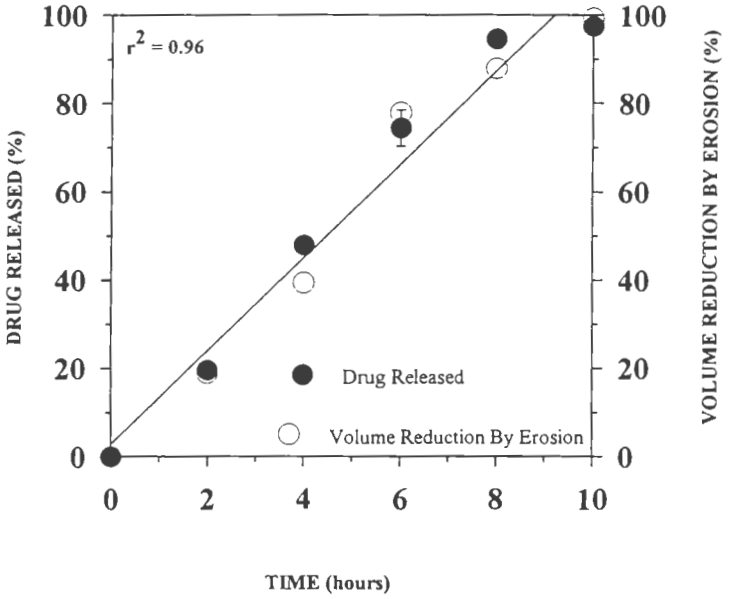


Figure 9

Correlation of drug release (%) with volume reduction by erosion (%) of pellets. (pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, n = 4±SE for drug released and n = 10±SE for volume reduction by erosion).



MANUSCRIPT II

EFFECT OF FORMULATION AND PROCESS VARIABLES ON MATRIX EROSION AND DRUG RELEASE FROM A MULTI-UNIT EROSION MATRIX OF A POORLY SOLUBLE DRUG.

KEYWORDS

Extrusion/Spheronization, Eudragit® L 100-55, Eudragit® S 100, Drug Loading, Granulation Water Requirement, Polymer Ratio, Pellet Size, Spheronization Time.

ABSTRACT

A novel multi-unit controlled delivery system for the release of a poorly soluble drug by a polymer controlled, surface erosion mechanism was reported earlier. The present study was undertaken to determine the effects of formulation variables (ratio of polymers used, drug loading) and processing variables (water required for granulation, pellet size and spheronization time) on matrix erosion and drug release. Powder mixtures containing drug, different ratios of Eudragit®L 100 55 and Eudragit®S 100 were blended with polyvinylpyrrolidone (PVP) and were extruded/spheronized to obtain homogeneous matrix pellets. Drug release was predicted by matrix erosion studies. Matrix erosion was determined using USP Dissolution Apparatus I in pH 6.8 phosphate buffer by gravimetry and UV spectrophotometry, respectively. Matrix erosion and drug release rates were found to be a function of polymer ratio. Drug loading at 5, 10, and 20% w/w levels demonstrated that drug release was predominantly matrix erosion controlled. At 30 and 40% w/w drug levels, matrix erosion and drug release rates decreased. Pellet size had a profound effect on the total duration of matrix erosion and drug release from the pellets. Thus, by optimizing the formulation and process variables, pellets can be prepared which release a poorly soluble drug for 12-24 hours following zero order kinetics.

1.0 Introduction

The design and evaluation of a novel multi-unit erosion matrix that releases a poorly soluble drug by matrix erosion for 12 hours was reported earlier [1]. Several authors have reported factors such as polymer type, drug concentration, drug solubility, pelletization technique used, influencing drug release rate [2-9]. All these factors were evaluated for osmotically or diffusion controlled pellets employing microcrystalline cellulose as the principal pellet forming agent and release rate governing polymer in the pellet.

The pellets used in this study were manufactured by Extrusion/Spheronization technique, therefore any change in the formulation or process parameters may influence matrix erosion and drug release from the pellets [10]. The aim of this study was to investigate the influence of the most critical formulation variables (ratio of polymers used and drug loading) and process variables (water required for granulation, pellet size and spheronization time) on matrix erosion and drug release from the pellets. Previously, the linear relationship between matrix erosion and drug release at various dissolution stirring rates was described [1]. It was concluded that in such systems, matrix erosion and drug

release occurred simultaneously, thus matrix erosion can be monitored to predict drug release from the pellets.

2.0 Materials and methods

The poorly soluble drug used as a model was a thiazole based leukotriene D_4 antagonist with aqueous solubility < 1.3 μg/ml (Hoffmann-La Roche Inc., Nutley, NJ). Eudragit® L 100 55, Eudragit® S 100 (Huls America, Inc., Somerset, NJ) were used as pellet forming and release rate controlling polymers. Kollidon® 90 F (BASF Inc., Parsipanny, NJ) was used as a binder. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was used in the spheronization stage to prevent inter-pellet sticking. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as plasticizer for Eudragits®. All other chemicals were used as received.

2.1 Formulation of Pellets:

Eudragit® L 100 55 and Eudragit® S 100 were dry mixed in a turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. This dry mixture was triturated in a mortar for

5 minutes with triethyl citrate (plasticizer). Drug and polyvinylpyrrolidone (PVP) as a binder were added and mixed in a turbula mixer for 30 minutes. This mixture was then granulated with deionized water in a mortar and later extruded (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan) at 40 rpm screw speed. The extrudates obtained were immediately transferred into a rotating plate in the spheronizer (G.B. Caleva Ltd, Model 120, Dorset, England). The spheronizer consisted of a stationary vertical cylinder with a base friction plate (diameter 32 cm) with a 2 mm cross hatched friction pattern and a rotational speed of 200-3000 rpm. Spheronization was carried out for either 2, 10 or 20 minutes at 500-1000 rpm. During this period, 5% w/w Avicel® PH 101 was sprinkled over the rotating extrudates to prevent them from sticking. The pellets obtained were dried on trays as a monolayer at 50°C for 12 hours. Pellets were later subjected to sieve analysis to collect the desired particle size pellets in a Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, USA, fitted with sieve # 8, 10, 12, 14, 16, 18 ,20 and 25.

2.2 *Composition of pellets prepared to evaluate formulation variables:*

Pellets of 2.0 mm size were formulated to determine the effects of polymer ratio and drug loading. Pellet compositions are tabulated in Table 1.

2.3 *Composition of pellets prepared to evaluate process variables:*

Pellets of 2.0 mm size were formulated to determine the effects of granulation water level, pellet size and spheronization time. Pellet compositions for granulation water study are tabulated in Table 1 Pellets of 0.8, 1.2 and 2.0 mm size were each formulated at spheronization times of 2, 10 and 20 minutes (Table 2) to determine the effect of pellet size and the spheronization time on drug release and matrix erosion. The formulation parameters maintained constant for this study were drug loading (10% w/w), polymer ratio (Eudragit® L 100 55 : Eudragit® S 100 was 1:3), Kollidon® K 90F (polyvinylpyrrolidone) as a binder (2% w/w), Triethyl citrate as plasticizer for Eudragits (15% w/w of total Eudragit content), deionized water for granulation (70% w/w).

2.4 *In vitro release studies:*

Drug release was performed using a standard USP Dissolution Apparatus 1 (Distek, Dissolution System 2100A USP XXII). Pellets (100 mg) were immersed in 500 ml of pH 6.8 phosphate buffer maintained at and 37.0 $\pm$ 0.5°C and stirred at 50 rpm. The baskets were removed at intervals of 2, 4, 6, 8, 10, 12 hours and were dried for 12 hours at 50° C to achieve constant weight. The difference between the initial and final weight of the

pellets was calculated to determine percent matrix erosion. The matrix erosion was determined to predict percent drug release [1].

3.0 Results and discussions

Several studies report the influence of formulation and process variables on drug release from pellets formulated by Extrusion/Spheronization process [2-9]. However, the results of these studies are specific to the formulation and utilize either microcrystalline cellulose (MCC) or MCC with various hydrophilic or hydrophobic in combination. Drug release from such matrices is predominantly characterized by first order kinetics due to the presence of microcrystalline cellulose used as the matrix [11]. Tapia et. al. [2] studied the effect of chitosan on drug release from matrix pellets manufactured by Extrusion/Spheronization and concluded that drug delivery occurred by gel formation of chitosan through diffusion process. Gel formation was found to be a direct function of polymer ratio.

The rate controlling polymers used in this study were Eudragit® L 100 55 and Eudragit® S 100. These polymers dissolve above pH 5.5 and 7.0 respectively. Some of their popular

commercial uses include tablet and pellet coatings to achieve controlled or sustained release.

The effect of increased Eudragit® S 100 content on drug release from 2.0 mm pellets is shown in Figure 1. It was observed that rate of drug release decreased as the ratio of Eudragit® S 100 increased in the formulation without any significant change in the release kinetics.

Figure 2 shows the effect of drug loading on drug release. Matrix erosion data was used to compare the effects of drug loading with that of placebo pellets. The same figure demonstrates that drug release from pellets with 5, 10 and 20% w/w drug loading was similar to that of placebo pellets which strongly indicated that the drug release mechanism was matrix erosion controlled up to 20% w/w drug loading. However, above 20% w/w drug loading, the release rates were found to decrease as the drug load increased up to 40% w/w. The reason for this finding may be hydrophobicity of the drug incorporated into the matrix.

The influence of the amount of granulation liquid on the drug release rate from pellets made by Extrusion/Spheronization has been the topic of many publications (Baert et al.

[4], Jerwanska et al. [5]). Baert et al and his co workers demonstrated that slower release rate was the result of increasing amounts of granulating liquid. They correlated the effects of granulation liquid with the differences in hardness, density and structure of the pellets, whereas Jerwanska et.al and his co-workers, through their study concluded that rate of drug release increased with increasing granulation liquid level due to an increase in porosity obtained after drying. They also correlated these results with differences in hardness of the pellets.

The effect of the granulation water level on the matrix pellets prepared by employing Eudragit® L 100 55 and Eudragit® S 100 as the rate controlling and pellet forming agents is shown in Figure-3. Increased granulation water levels had a direct effect on the drug release rates. These findings are similar to the findings of Jerwanska et al [5]. However, there seemed to be no significant difference in the release rates above 65% w/w granulation water level. This can be explained by the effect of moisture content on the degree of liquid saturation of the extrudates. Jerwanska et al [5], proposed that for a continuous extrusion process, adequate water is required to bridge the particles together until liquid saturation in the granulation is achieved. This is necessary to deform the granulation to form extrudates and consequently shape them in to spheres by spheronization. If the granulation water level is below the liquid saturation point the

spheres obtained will be hard and less porous leading to decreased drug release rates. Above the liquid saturation point the hardness and porosity of the pellets are not significantly affected.

In order to investigate the most critical spheronization times which would have an effect on drug release, pellets were spheronized for 2, 5, 8, 10, 20 and 40 minutes. The hardness of pellets (n = 10) was measured (Chatillon Force Measurement System, Model TCD-200 attached with a 5 lb load cell, Greensboro, NC, USA). The results of pellet hardness test of 10 pellets per spheronization time are tabulated in Table 3. From Table 3, the pellet hardness changes with spheronization time up to about 10 minutes with maximum hardness recorded for pellets spheronized at 8 minutes, where after the hardness decreases up to 20 minutes. No significant difference in the pellet hardness from 20 to 40 minutes was observed. This may be explained by the densification process occurring during the spheronization step. As spheronization time progresses from zero to time 't', the extrudates are cut into uniform particles and shaped into spheres due to the centrifugal and frictional forces present in the spheronizer during operation. These forces act on each and every particle making them more dense and more spherical with time. However, after a critical period no further densification occurs with increase in spheronization time. Data from Table 3 indicates that the pellet densification process

takes about 10 minutes above which very minor changes in densification occur. Thus a spheroinzation time of 2, 10 and 20 minutes was selected to study the effects of time on drug release.

Figure 4 shows the effect of spheronization time on the drug release rate from 0.8, 1.2, and 2.0 mm pellets. Spheronization time appears to effect drug release rates at the 2 and 10 minute processing times for 1.2 and 2.0 mm pellets. This effect became less pronounced when the pellet size increased from 0.8 to 2.0 mm. However, there is no significant difference in the drug release profile of 1.2 and 2.0 mm pellets above 10 minute processing time. It was also observed that the duration of drug release increased as the pellet size increased without any change in release kinetics above 1.2 mm pellet size.

4.0 Conclusions

This study shows the effects of various formulation (ratio of polymers used and drug loading) and process (granulation water level, pellet size and spheronization time) parameters on drug release by surface erosion from multi-unit matrix pellets. Each parameter evaluated, demonstrated a change in drug release from the pellets. Increased

amounts of Eudragit® S 100 retarded the rate of matrix erosion and drug release from the pellets. The drug loading had no influence on drug release mechanism up to the 20% w/w level above which increasing levels of drug up to 40% w/w retarded matrix erosion. Granulation water level at 65% w/w had a significant effect on the rate of matrix erosion and drug release as compared to the formulation with 60% w/w granulation water level. Above 65% w/w, there was no significant effect on the rate of matrix erosion and drug release.

Matrix erosion and drug release rates can be optimized by processing the pellets at different spheronization times. Thus, by optimizing the formulation and process variables pellets that can release a poorly soluble drug by polymer controlled, surface erosion mechanism for 12 hours following zero order kinetics.

ACKNOWLEDGMENTS

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Table 1. Composition of pellets formulated with different polymer ratios, drug loadings and granulation water levels.

Ingredients (% w/w)	Pellet Compositions with Different Polymer Ratios		Pellet Compositions with Different Drug Loadings						Pellet Composition with different Granulation Water		
Drug	10.00	10.00	**0.00**	**5.00**	**10.00**	**20.00**	**30.00**	**40.00**	10.00	10.00	10.00
Kollidon® 90F	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Eudragit®L 100-55	**35.20**	**22.00**	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Eudragit®S 100	**52.18**	**66.00**	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00	66.00
* Plasticizer	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Granulation Water	60.00	60.00	77.90	70.00	70.00	62.00	60.00	65.00	**60.00**	**65.00**	**70.00**

* Triethyl citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).

Table 2. Pellets of different size prepared at different spheronization times.

Pellet Size (mm)	Spheronization Time (minutes)
0.8	2.0 10.0 20.0
1.2	2.0 10.0 20.0
2.0	2.0 10.0 20.0

Table 3. Effect of spheronization time on pellet hardness.

Spheronization Time (minutes)	Pellet Hardness (grams) (Mean ± SD)
2.00	1091 ± 139.39
5.00	1383 ± 177.14
8.00	1511±157.12
10.00	1259 ± 170.25
20.00	1034 ± 177.40
40.00	1110 ± 146.06

Figure 1

Effect of varying polymer ratios on drug released (%) from pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)

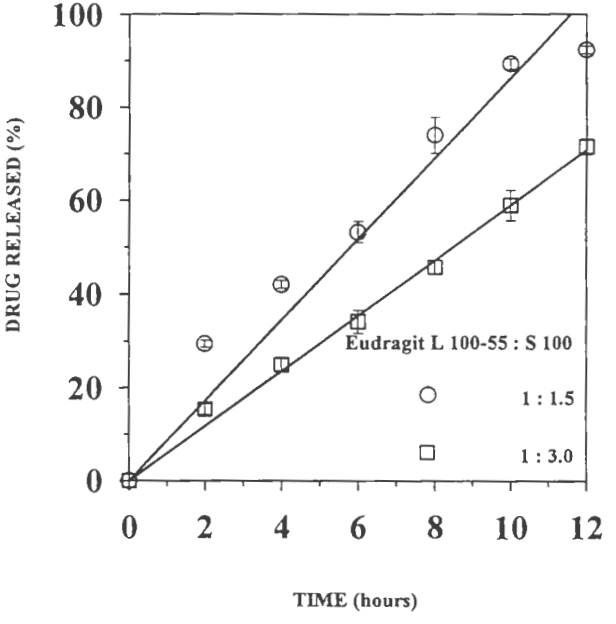


Figure 2

Effect of different drug loading (% w/w) on drug released (%) from pellets.

(pellet size: 2.0 mm, n = 4±SE)

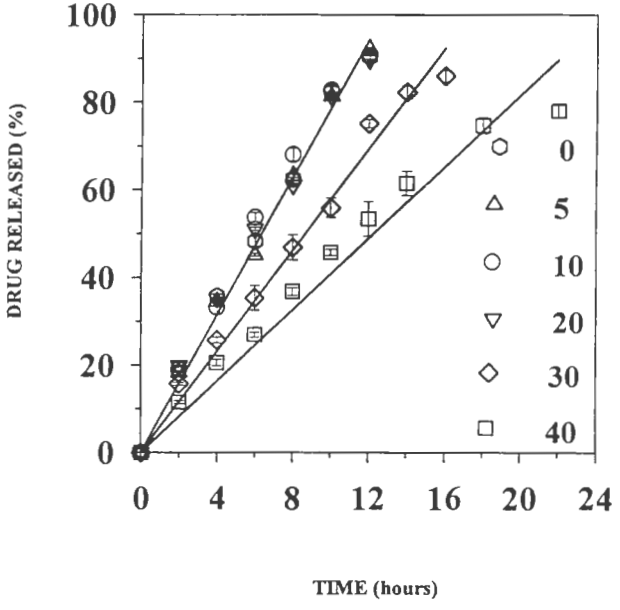


Figure 3

Effect of granulation water level (% w/w) on drug released (%) from pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, n = 4±SE)

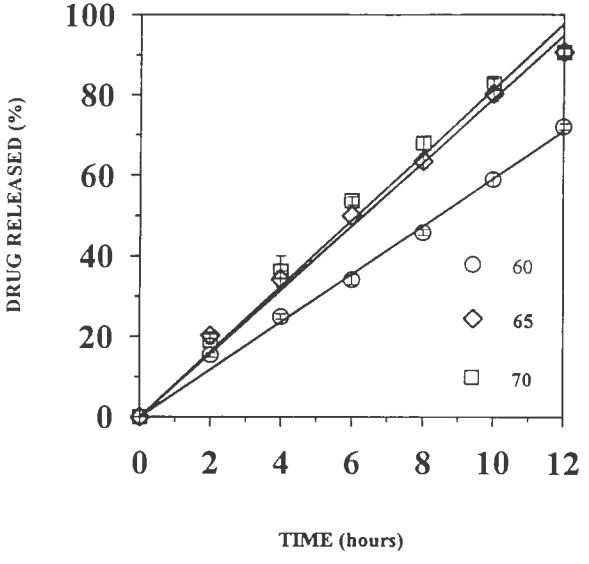
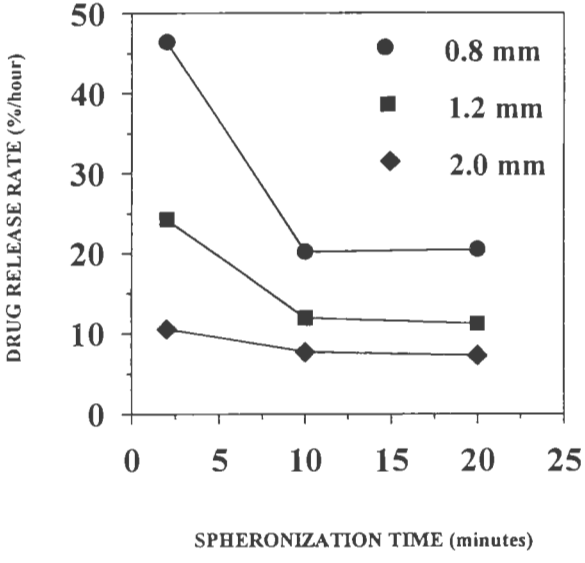


Figure 4

Effect of pellet size and spheronization time on drug release rate from pellets.

(drug load: 10% w/w, n = 4±SE)



MANUSCRIPT III

EFFECT OF FORMULATION AND PROCESS VARIABLES ON POROSITY PARAMETERS AND RELEASE RATES FROM A MULTI UNIT EROSION MATRIX OF A POORLY SOLUBLE DRUG

KEYWORDS

Porosity Parameters, Extrusion/Spheronization, Controlled Release Matrix Pellets, Eudragit® L 100-55, Eudragit® S 100, Polymer Controlled Surface Erosion.

ABSTRACT

Controlled release erosion matrix pellets were prepared by a Extrusion/Spheronization technique. The effect of drug loading, water required for granulation and spheronization time on porosity parameters (intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameter, shape and morphology of pores) and drug release rates were investigated. Porosity parameters were determined by using mercury intrusion porosimetry. In vitro release was performed in phosphate buffer pH 6.8 using USP XXII Apparatus I (baskets, at 50 rpm) by UV spectrophotometery. The drug loading was found to have a profound effect on the porosity parameters. Pellets with low drug loading showed increased pore surface area, with small mean pore diameters and an increased number of total pores. Whereas pellets with high drug loading had decreased pore surface area with bigger mean pore diameters and a decrease in the total number of pores. With high drug loading, drug release rate was found to be decreased. Water required for granulation had a direct effect on the total porosity of the pellets. Dissolution studies showed that release rates were directly related to the water required for granulation. Spheronization time from 2 to 10 minutes had a pronounced effect on porosity parameters and release rates. No changes in porosity parameters and release rates were observed from 10 to 20 minutes of spheronization time. It was shown that each porosity parameter investigated was well correlated with drug release rates and thus it is important to study the effect of porosity parameters in evaluating the In vitro performance of multi-unit erosion matrix for controlled release of a poorly soluble drug.

INTRODUCTION

Porosity is a measure of void spaces in a material and can be generally calculated by using a number of techniques such as density, gas adsorption, water displacement and porosimetry (1). Determination of pore structures of solids can provide important information on disintegration, dissolution, adsorption and diffusion of drugs (2). Pore size measurements provide information on the actual pore structures, including pore diameter and volume, and can be determined by gas adsorption and mercury porosimetry. The gas adsorption method is limited to pore diameters smaller than 2000 Angstroms, whereas mercury porosimetry is capable of measuring larger pores and inter-particle spaces (3). Thus mercury porosimetry is a suitable technique to determine a broad range of pores of a sample.

The method is based on intrusion of mercury into the pores of a solid sample and is quantified by the Washburn Equation (4).

$$P\,r = -2\,\gamma \cos\theta \qquad 1$$

where P = pressure (psi), r = pore radius (μm), γ = surface tension of mercury (dynes/cm) and θ = the contact angle of mercury. This equation holds true only when the surface tension and contact angle of mercury are kept constant and shape of the pores is assumed to be circular.

By mercury penetration under pressure, one can determine the size and quantity of void spaces and pores in porous materials. In addition, mercury expelled from pores as a function of decreasing pressure provides information about the shape and structure of the pores (5). In porosimetry, voids are defined as spaces between particles or the several pieces constituting the specimen, whereas cracks, crevices, holes and fissures within the specimen, whether a single piece or a powder, are termed as pores (6).

Mercury porosimetry has been extensively used in porosity determination of granules (7-11), tablets (12-17) and pharmaceutical powders (18,19). The development, characterization and evaluation of a novel multi-unit erosion matrix for a poorly soluble drug was reported in our previous study (20). In which, matrix pellets of a model poorly soluble drug (thiazole based leukotriene antagonist, aqueous solubility < 1.23 μg/mL) was pelletized with Eudragit® L 100 55 and S 100 used as release rate controlling polymers. The pellets were prepared by Extrusion/Spheronization technique and the effect of formulation (drug load, water required for granulation) and process (spheronization time) variables on drug release were studied (21). In this paper we have used mercury intrusion porosimetry to understand the effect of formulation and process variables on drug release behavior relative to the changes in porosity parameters.

MATERIALS AND METHODS

A thiazole based leukotriene D_4 antagonist (Hoffmann-La Roche Inc., Nutley, NJ) was used as a model poorly soluble drug. Eudragit® L 100 55, Eudragit® S 100 (Huls

America, Inc., Somerset, NJ) were employed as matrix forming and release rate governing polymers. Kollidon® 90 F (BASF, Inc., Parsipanny, NJ) was used as a binder in the formulation. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was used to prevent inter-pellet sticking during the spheronization stage. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as a plasticizer for Eudragit® polymers. All other chemicals were used as received.

Preparation of Matrix Pellets by Extrusion/Spheronization:

Eudragit® L 100 55 and Eudragit® S 100 were dry mixed in a Turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. This dry mixture was triturated in a mortar for 5 minutes with triethyl citrate used as a plasticizer. Drug and polyvinylpyrrolidone used as a binder were added to this mixture and were mixed in the Turbula mixer for 30 minutes. The dry blend was transferred to a mortar and was granulated with deionized water for 10 minutes. The wet granulate was later extruded at 40 rpm screw speed (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan). The instrument used was a single screw extruder capable of extruding at speeds upto 100 rpm. The extrudates were spheronized in a G.B. Caleva Ltd, Model 120, Dorset, England, at 600-800 rpm spheronizer speed. The spheronizer consists of a stationary vertical cylinder which has at the base a friction plate with a 2 mm cross hatched friction pattern and a rotation speed of 200-3000 rpm. Spheronization times used were 2, 10 and 20 minutes. Avicel® PH 101 5% w/w was sprinkled over the rotating extrudates to prevent pellets from sticking. The pellets obtained were dried at 50° C for 12 hours using a tray dryer and were later sieved

through Rotap Sieve Shaker (Model RX-29, W.S. Tyler, Inc., OH, USA), fitted with sieve number 10 and 12 to obtain 2.0 mm size pellets.

Drug Loading:

Composition of pellets formulated to determine the effects of drug loading are given in Table 1.

Water required for granulation:

Composition of pellets formulated to study the effects of granulation water level are given in Table 2.

Spheronization time:

Pellets were processed at 2, 10 and 20 minutes spheronization times. Formulation composition maintained constant for this study were the drug load (10 % w/w), polymer ratio (1: 3) same as in Table 2, Kollidon® 90F as binder (2 % w/w), triethyl citrate as plasticizer (15 % w/w of total Eudragit®L 100 55 and Eudragit®S 100) and water for granulation (70 % w/w of the total batch size).

Drug release studies:

It was shown in our previous study that pellets prepared with the model poorly soluble drug, released the drug as a direct function of matrix erosion (20). In vitro drug release was determined by using USP XXII Apparatus I with baskets at 50 rpm (Distek Inc., NJ, USA) in 500 mL of pH 6.8 phosphate buffer at 37.0 $\pm$ 0.5° C.

Mercury intrusion porosimetry:

Porosity parameters such as intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameters, shape and morphology of the pores were determined by using a Micromeritics PoreSizer 9320 (Micromeritics Inc., Norcross, GA, USA). Incremental intrusion volumes were plotted against pore diameters which represented pore size distributions. The moisture content of pellets were determined with an infra-red moisture analyzer at 105° C (Computrac, Model Max-50, Arizona Instrument Corp., USA) prior to porosimetry studies. The moisture content of all the pellet samples varied between 2.2-3.0 % w/w. The pore diameter was calculated by using Eq 2.

$$D = \frac{-4\gamma \cos\theta}{P} \qquad 2$$

where D = pore diameter (μm)

γ = surface tension of mercury (485 dynes/cm).

θ = contact angle (130 degrees)

P = pressure (psi)

The total pore surface area (S) was calculated by using Eq 3

$$S = \frac{1}{\gamma|\cos\theta|}\int_{0}^{Vtot} PdV \qquad 3$$

where; P = pressure (psi)

V = the intruded volume of mercury (mL/g)

V_{tot} = total intruded volume of mercury (mL/g)

The mean pore diameter (*D'mean*) was calculated by Eq 4.

$$D'mean = 4\frac{Vtot}{S} \qquad 4$$

Pore morphology was characterized from the intrusion-extrusion profiles of mercury in the pellets as described by Orr et. al. (6).

RESULTS AND DISCUSSION

Effect of Drug Loading:

The intrusion volume of mercury is a function of total porosity. In Figure 1 the cumulative intrusion volume was plotted against pore diameters showing the intrusion-extrusion profile of pellets with different drug loading. The intrusion and extrusion curves form a hysteresis indicating that majority of the pores present in the pellets were ink-well type pores that had small openings with broad bases. Although no particular trend was observed in the intrusion profiles with respect to drug loading, the intrusion volume of mercury was significantly lower for 30 and 40% w/w than the 5, 10 and 20% w/w drug loading (Figure 1).

Figure 2 shows the incremental intrusion volume as a function of the pore diameter of the pellets with increasing drug loading. From Figures 1 and 2, the number of pores and mean pore diameters of the pellets can be characterized. The data indicates that as the drug loading increased from 0-10% w/w, the mean pore diameter increased with the total number of pores essentially remaining constant whereas, with 30 and 40% w/w drug loads the mean pore diameters increased and the total number of pores decreased.

Figure 3 shows the effect of drug loading on the total pore surface area and mean pore diameter of pellets; they seem to have an inverse relationship as expected.

Table 3 lists the calculated ranges of pore necks and pore bases as a function of increasing drug loading as characterized from Figures 1 and 2. The data from Table 3 indicates that pore bases were nearly twice the size of pore necks at all levels of drug loading; indicating that all pores have large bases with relatively small necks. This difference

becomes more apparent as drug loading increases above 30% w/w. This interpretation is supported by the relation of drug loading, total pore surface area and the mean pore diameters of the pellets as shown in Figure 3. The results indicate that with increasing drug concentration the pores became wider with larger necks and thus reduced in number. These changes are illustrated schematically in Figure 4.

Figure 5 shows the dissolution profiles of the pellets with different drug loading. Drug release from these pellets occurred via surface erosion. Therefore theoretically, the nature of pores present at the surface of the pellet must influence the erosion rate rather than the total porosity of the pellet matrix during the dissolution process. In pellets with high drug loads, the total polymer content is relatively low. Since the weight fraction of drug per unit weight of the drug-polymer mixture is high, the drug particles associate to form drug agglomerates (22) and this agglomeration tendency of the drug at high drug loads will reduce the number of pores and thus total pore surface area is reduced. Such a system during dissolution will have a low contact surface area with the dissolution media. However, in pellets with low drug loads, the weight fraction of polymer per unit weight of the drug-polymer mixture is high, therefore chances of drug agglomeration are less resulting in more pores with smaller mean pore diameters and increased total pore surface area. Thus, the increase in mean pore diameter and decrease in total pore surface area of pellets with high drug loading were primarily due to agglomeration of the drug particles. As it is discussed above, because of the existence of larger pores, the surface area of contact between the dissolution medium and pellets with high drug load is reduced, which

reduces pellet hydration and consequently the erosion rates. This was confirmed by the dissolution profiles given in Figure 5.

Effect of Water Required for Granulation:

The intrusion-extrusion profiles of mercury for the percent water added to the granulation are shown by plotting cumulative intrusion volume against pore diameter in Figure 6. The total intrusion volume was found to be a direct function of granulation water level. This indicated that total porosity of the pellets increased with the addition of water for granulation from 60-70% w/w. These findings are similar to the results obtained by other researchers (23-26).

Figure 7 is a plot of incremental intrusion volume against pore diameter which shows the pore size distribution of pellets with different granulation water levels. All pores present are between 0.01-0.1 μm in size. Table 4 summarizes the results of granulation water level on the range of pore necks and pore bases. The pore base being the average width of the ink-well type pores inside the pellet matrix. From Figure 7 and Table 4 it is evident that increasing the granulation water level from 60 to 65% w/w increased the total number of pores, but the pore necks and bases were not affected indicating that the water levels used in the study increases the porosity without affecting the morphology of pores. When the granulation water level was increased from 65 to 70% w/w, the pore neck and pore base ranges remain narrow but the number of pores increase, resulting in overall increase in the porosity of the pellets.

Figure 8 shows the effect of total pore surface area and mean pore diameters against granulation water levels. The data indicate that the total pore surface area increases without any significant change in the mean pore diameter as a function of increased granulation water levels. This finding also strongly supports the fact that with the addition of more granulation water, the number of pores increased without any change in the mean pore diameters. These changes are illustrated schematically in Figure 9. Fujiwara and Kato *et al.* reported similar findings with the increase in granulation water level on pore structure and porosity of sucrose and lactose granules prepared by wet granulation (9).

The dissolution profile of pellets formulated at different granulation water levels are given in Figure 10. The dissolution rates increase with the increase in porosity and total pore surface area of the pellets with 60, 65 and 70% w/w water for granulation. This increase in the porosity and total pore surface area of the pellets increased the dissolution contact area of the medium with the pellet surface resulting in faster hydration and consequently caused higher erosion rates.

Spheronization Time:

The sphericity of a pellet is a function of spheronization time. The longer they are spheronized more spherical pellets are produced. The circular motion of the friction plate in the spheronizer, shape the sphagetti like extrudates into smaller and uniform granules.

Eventually, the collision of these granules with the friction plate and the walls of the spheronizer change their shape into small spheres or pellets as a function of time. This transformation may be analogous to tablet compaction. "The term compactability is the ability of the bed of particles to cohere into or form a compact of a defined mechanical strength"(26). In compacting a tablet, the force applied by the upper punch has a direct relation with the compactability of the tablet. It is also generally observed that after a critical force no further increase can change the degree of compaction. Similarly, during spheronization, the pellet is compacted up to a critical strength above which no more compaction is observed. The change in porosity parameters of tablets as a function of compaction force are reported (12-17). However, for pellets no information showing the changes in porosity parameters as a function of spheronization time is reported. Therefore, it was important to elucidate this process with respect to the change in porosity parameters, particularly because the dissolution rates of the pellet were a function of spheronization time.

To understand the changes occurring in porosity with spheronization, the pellets were processed at three different spheronization times, 2, 10 and 20 minutes. Figure 11 shows the total intrusion volume against pore diameters as a function of spheronization time. The data indicate that porosity was not significantly affected by spheronization at 2, 10 and 20 minutes.

Figure 12 shows the plot of incremental intrusion volume against pore diameters which demonstrates that the pores increased with 2 to 10 minute spheronization time. However,

after 10 minutes, no change in the pore size distribution was observed upto 20 minutes. Figure 13 confirms these findings by demonstrating no change in the total pore surface area and mean pore diameter from 10 to 20 minutes.

In summary, following the argument given earlier, processing period from 2 to 10 minutes increased the pores, total pore surface area and decreased pore diameters, beyond this time up to 20 minutes none of the porosity parameters changed. Figure 14 shows the effect of spheronization time on dissolution profiles of pellets which were processed for 2, 10 and 20 minutes. The dissolution rates of pellets processed at 10 and 20 minutes were same. However, pellets processed at 2 minutes spheronization time showed faster dissolution rates. Figure 15 shows a schematic representation of the effect of spheronization time on the porosity of the pellets.

CONCLUSIONS

This study demonstrated that the changes in porosity parameters (intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameter, pore shape and morphology) of pellets made with insoluble drug substance is affecting drug release rates with erosion controlled mechanism when the drug loading, granulation water level and spheronization time are modified.

By increasing the granulation water level, the number of pores are increased without affecting the mean pore diameter. The total porosity of the pellets was increased with

higher granulation water level. This increases the erosion rate of pellets leading to faster dissolution of the drug.

With spheronization time, the porosity parameters are affected depending on the time. Up to 10 minutes of spheronization time, the number of pores increased with total increase in surface area and decrease in pore diameter. No significant increase in porosity parameters was observed when the spheronization time was further increased from 10 to 20 minutes. This difference is reflected by erosion rate and dissolution profiles.

Thus, the study of porosity parameters is important in characterizing and predicting the In vitro performance of multi-unit matrix pellets.

ACKNOWLEDGMENTS

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Table I: Formulations prepared to determine the effects of drug loading.

Drug Load (% w/w)	Kollidon®90F (% w/w)	Eudragit®L 100 55 (% w/w)	Eudragit®S 100 (% w/w)	*Plasticizer (% w/w)
0.00	2.00	24.50	73.50	15.00
5.00	2.00	23.25	69.75	15.00
10.00	2.00	22.00	66.00	15.00
20.00	2.00	19.50	58.50	15.00
30.00	2.00	17.00	51.00	15.00
40.00	2.00	14.50	43.50	15.00

* Triethyl citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).

Table II: Formulations prepared to determine the effect of granulation water levels.

Drug Load (% w/w)	Kollidon®90F (% w/w)	Eudragit®L 100 55 (% w/w)	Eudragit®S 100 (% w/w)	* Plasticizer (% w/w)	Granulation Water Level (% w/w)
10.00	2.00	22.00	66.00	15.00	60.00
10.00	2.00	22.00	66.00	15.00	65.00
10.00	2.00	22.00	66.00	15.00	70.00

* Triethyl citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).

Table III: Effect of drug loading on the size of pore necks and pore bases as characterized from the intrusion-extrusion profiles.

Drug Load (% w/w)	Pore Necks (nm)	Pore Bases (nm)
0.00	15 - 90	50 - 200
5.00	18 - 60	70 - 150
10.00	18 - 60	70 - 150
20.00	18 - 70	40 - 150
30.00	18 - 90	40 -150
40.00	15 -180	50 -300

Table IV: Effect of water required for granulation on pore necks and pore bases as characterized from intrusion-extrusion curves of mercury.

Granulation Water Level (% w/w)	**Pore Necks (nm)**	**Pore Bases (nm)**
60.00	15 - 90	50 - 110
65.00	15 - 90	50 - 110
70.00	20 -60	60 - 100

Figure 1

Cumulative intrusion volume vs pore diameter of pellets with different drug loading (% w/w). (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 4±SE)

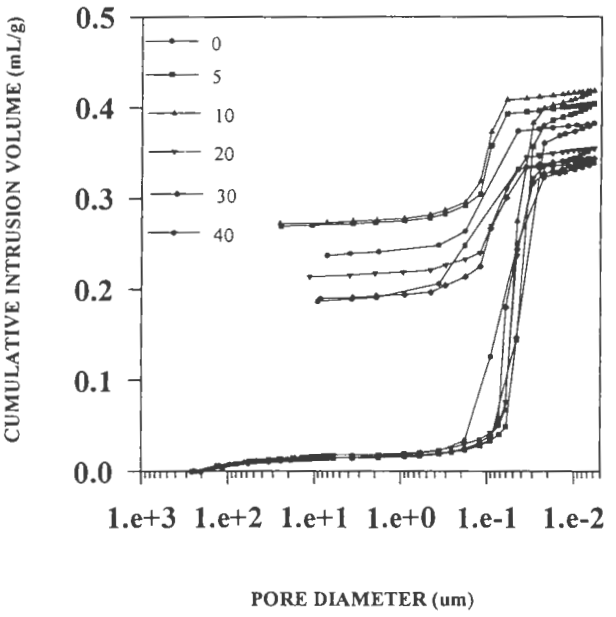


Figure 2

Pore size distribution of pellets with different drug loading (% w/w). (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 3±SE)

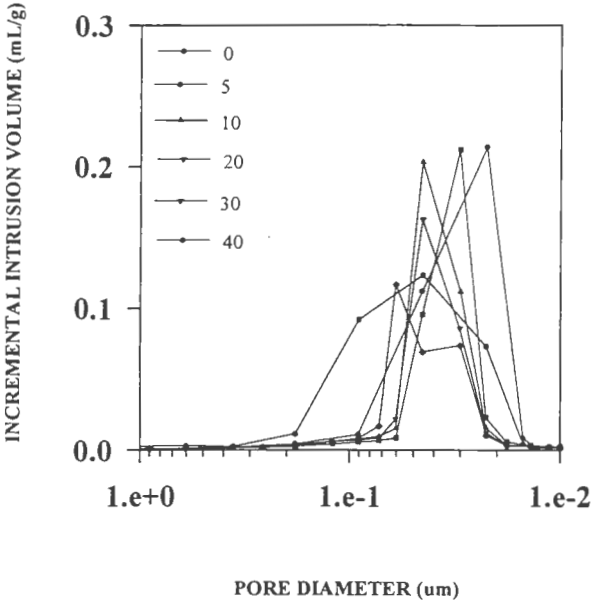


Figure 3

Effect of drug loading (% w/w) on total pore surface area and mean pore diameter of pellets. (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 3±SE)

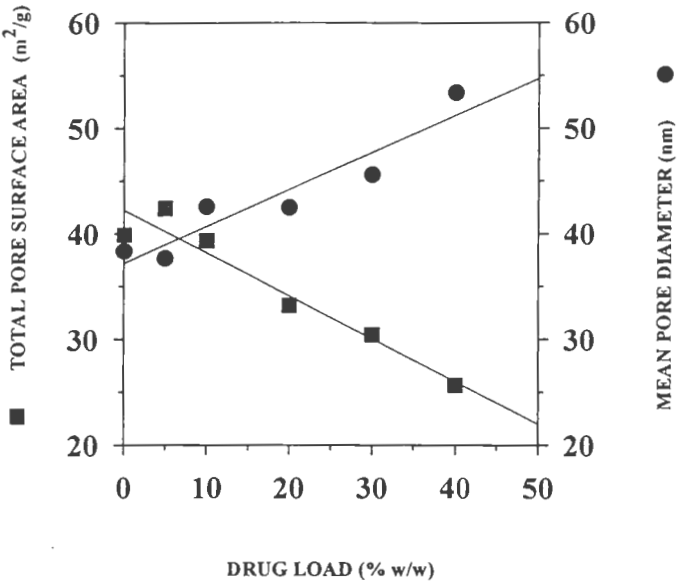


Figure 4

Schematic surface representation of the effect of drug loading on the pore diameters and total number of pores.

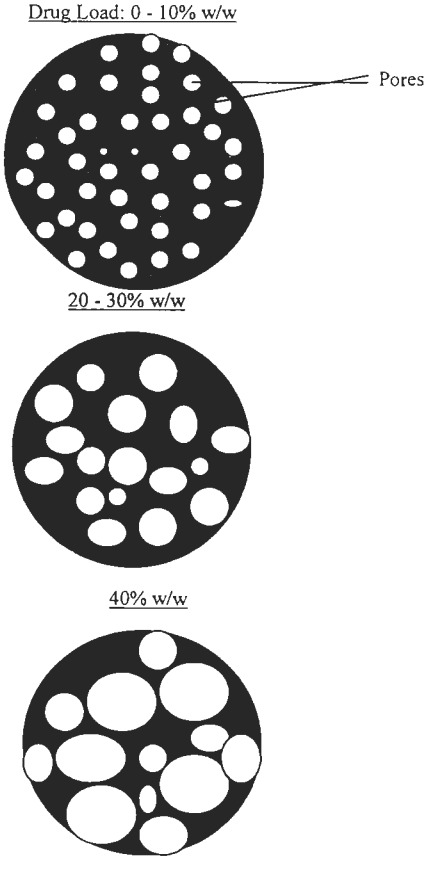


Figure 5

Effect of drug loading (% w/w) on drug released (%) from pellets. (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 4±SE)

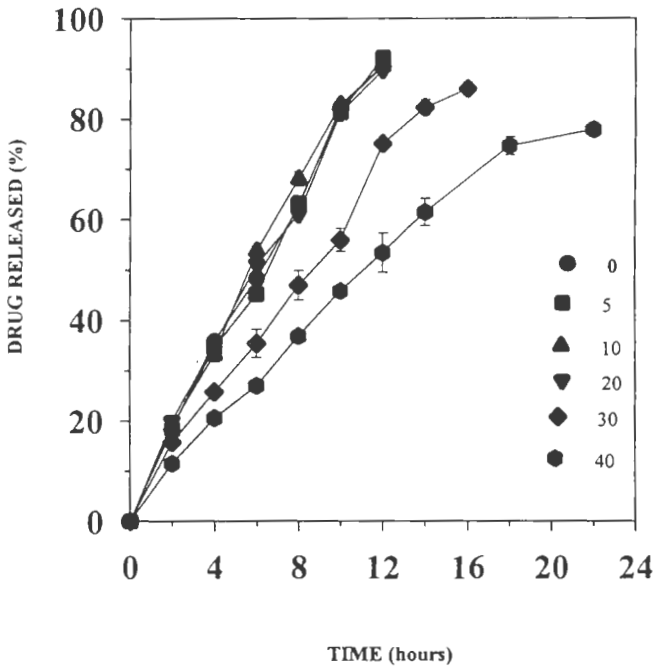


Figure 6

Effect of granulation water level (% w/w) on cumulative intrusion volume of pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)

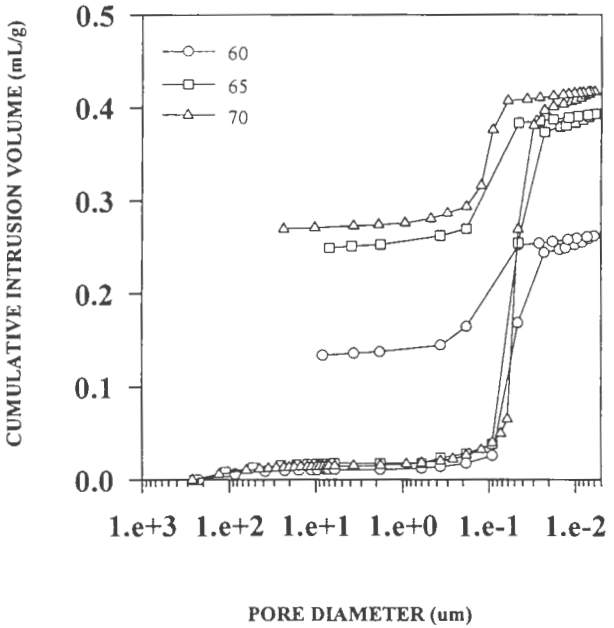


Figure 7

Effect of granulation water level (% w/w) on pore size distribution of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)

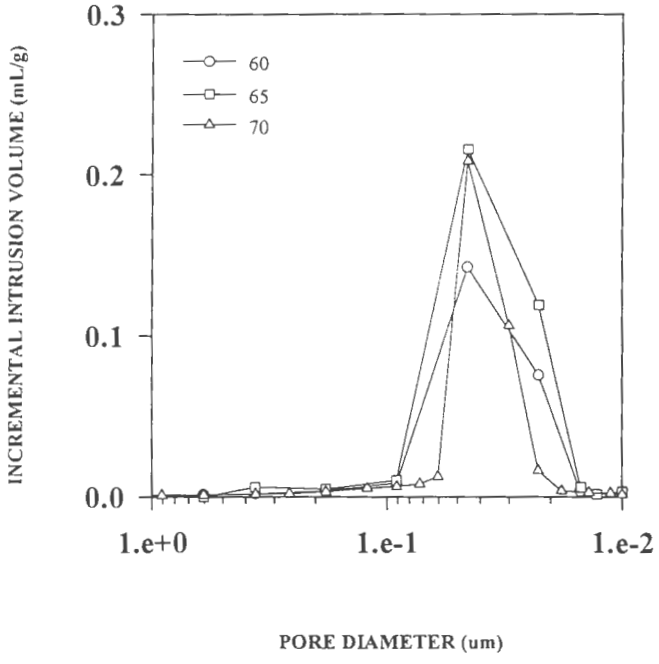


Figure 8

Effect of granulation water level (% w/w) on total pore surface area nad mean pore diameter of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)

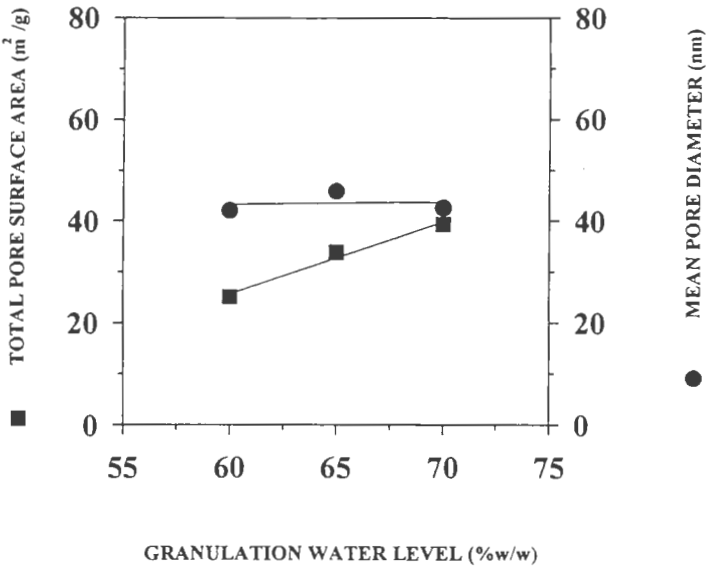


Figure 9

Schematic representation of the effect of increasing water required for granulation on the pore diameters and total number of pores.

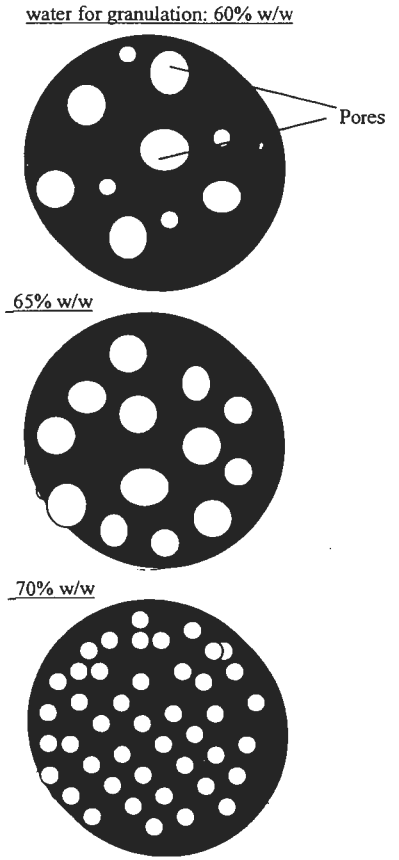


Figure 10

Effect of granulation water level (% w/w) on drug released from pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 4±SE)

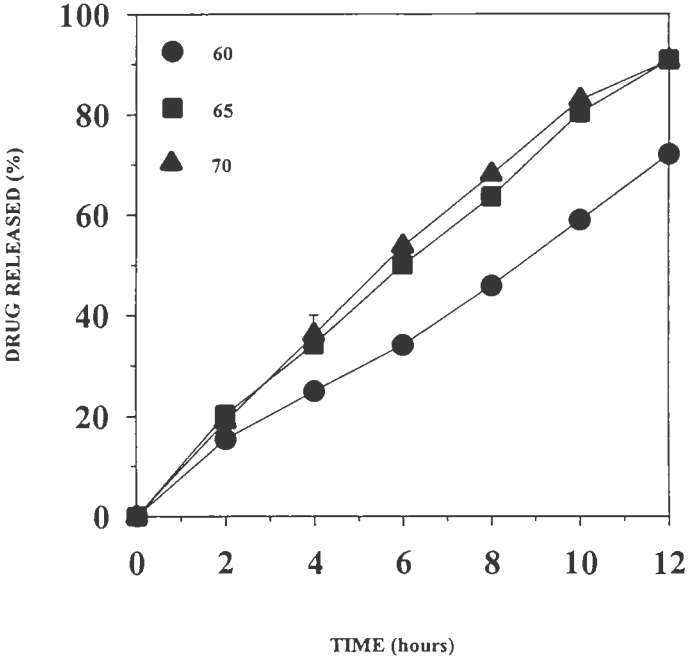


Figure 11

Effect of spheronization time on cumulative intrusion volume of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)

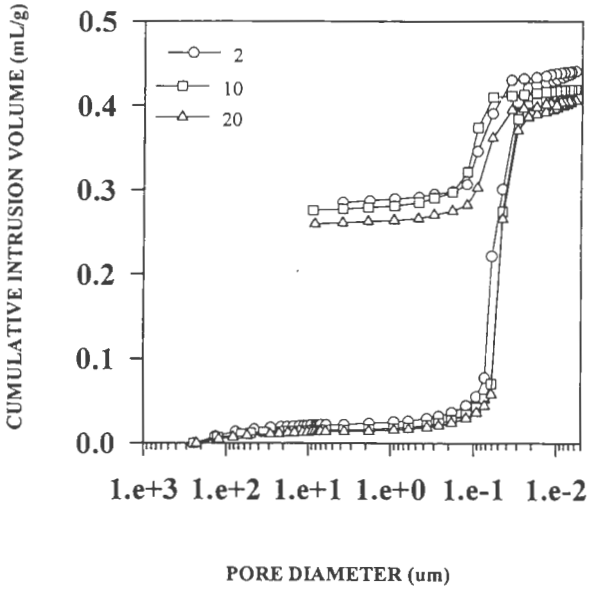


Figure 12

Effect of spheronization time on pore size distribution of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)

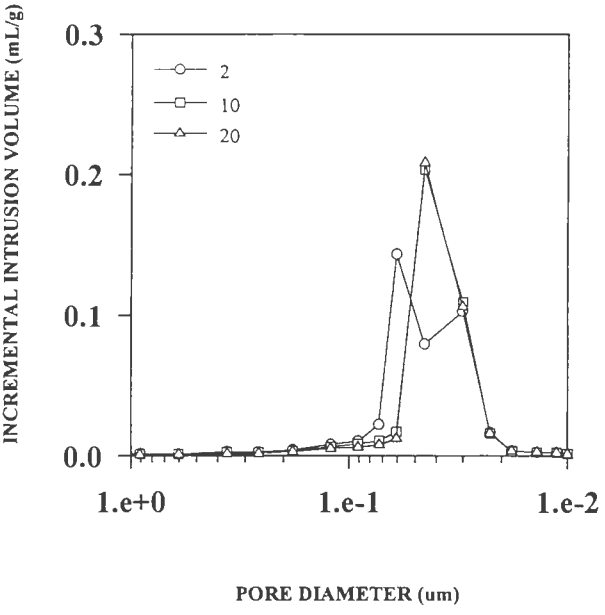


Figure 13

Effect of spheronization time on total pore surface area and mean pore of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)

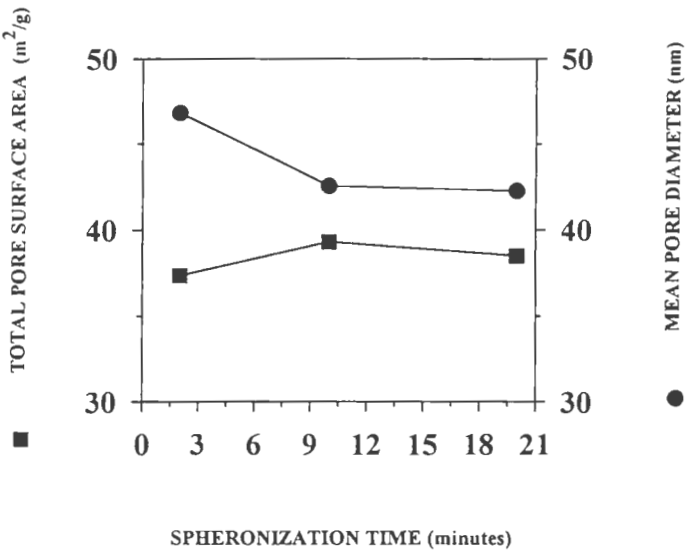
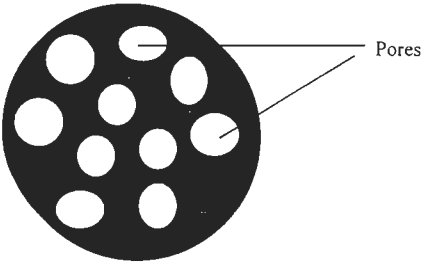


Figure 14

Schematic representation of the effect of spheronization time on the pore diameters and total number of pores.

Spheronization time: 2 minutes



10 minutes

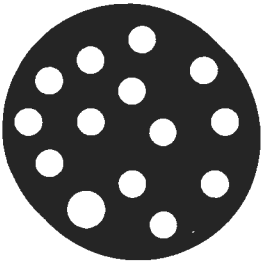
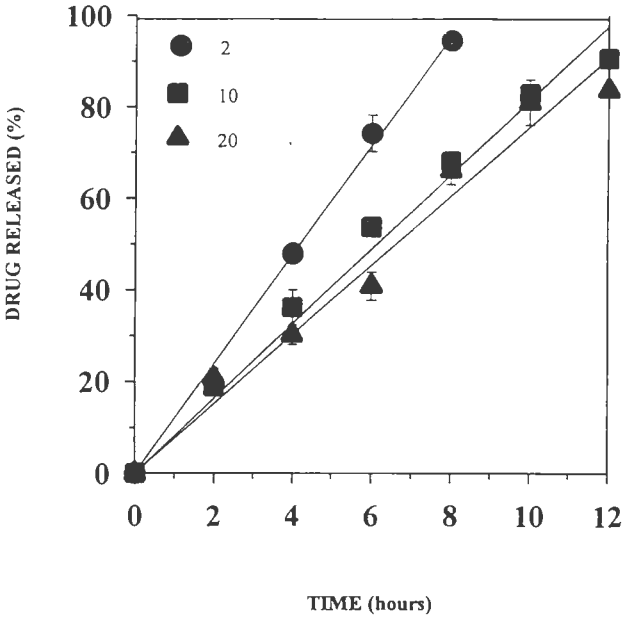


Figure 15

Effect of spheronization time on drug released (%) from pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 4±SE)



MANUSCRIPT IV

MULTI-UNIT CONTROLLED RELEASE SYSTEMS OF NIFEDIPINE AND NIFEDIPINE:PLURONIC® F-68 SOLID DISPERSIONS: CHARACTERIZATION OF RELEASE MECHANISMS

KEYWORDS

Nifedipine, Pluronic® F-68, Solid Dispersions, Extrusion/Spheronization, Controlled Release Matrix Pellets, Erosion, Diffusion, Eudragit® L 100-55, Eudragit® S 100.

Abstract

Nifedipine (N) and nifedipine:Pluronic® F-68 solid dispersion (SD) pellets were characterized for drug release mechanisms from a multi-unit erosion matrix system for controlled release. N was micronized using a jet mill. SD with Pluronic® F-68 was prepared by the fusion method. N and SD were characterized by particle size analysis, solubility, DSC and XRD studies. Samples were subsequently processed into matrix pellets by Extrusion/Spheronization using Eudragit® L 100 55 and Eudragit® S 100 as release rate controlling polymers. Drug release mechanisms from pellets were characterized by microscopy and mercury intrusion porosimetry. DSC and XRD studies indicated no polymorphic changes in N after micronization and also confirmed the formation of SD of N with Pluronic® F-68. Pellets of N showed a 24 hour drug release profile following zero order kinetics. Pellets of SD showed a 12 hour release profile following first order kinetics. Aqueous solubility of N after SD formation was found to be increased by 10 folds. Due to increased solubility of N in SD, the drug release mechanism was found to be changed from pure surface erosion to erosion/diffusion mechanism thereby altering the release rate/kinetics.

1.0 Introduction

Nifedipine is a poorly water-soluble drug and when administered orally in the crystalline form has poor bioavailability. For poorly soluble drugs, dissolution is the rate-limiting step for gastrointestinal absorption of the drug from solid dosage forms. Since dissolution rate is directly proportional to surface area, decreased particle size may increase the dissolution rate. Numerous attempts have been made to modify the dissolution characteristics of drugs to attain more rapid and complete absorption (1-5).

Controlled release Oros® tablets of nifedipine are commercially available. The drug releases in the form of a microfine suspension through a laser drilled hole in the tablet via osmosis following zero order kinetics for 24 hours. Osmotic controlled release multi-unit pellets and granules of nifedipine have also been reported (6).

The mechanism of polymer controlled surface erosion that provides a constant delivery of a poorly soluble drug via multi-unit erosion matrix was reported in our previous study (7). In such a system the drug release was found to be proportional to matrix erosion. Hence, matrix erosion could be used to predict drug release. This system consisted of Eudragit® L 100 55 and Eudragit® S 100 which were used as matrix forming and release rate controlling polymers. These are anionic polymers based on methacrylic acid and methacrylic acid esters. The ratio of carboxyl groups to ester units is about 1:1 in Eudragit® L 100 55 and about 1:2 in Eudragit® S 100. These polymers are soluble above pH 5.5 and 7.0 respectively. The model drug (nifedipine), Eudragits® and

polyvinylpyrrolidone (binder) were wet granulated and later pelletized using an Extrusion/Spheronization technique. The effects of dissolution stirring rate, polymer ratio, granulation water requirement, drug loading, pellet size and spheronization time on the release patterns were reported earlier (8).

Solid dispersions of poorly soluble drugs provide alternatives to increasing drug solubility and bioavailability. Law et al. (9) showed increased oral absorption and bioavailability of nifedipine-polyethylene glycol and nifedipine-phosphatidylcholine-polyethylene glycol solid dispersions in rats. Solid dispersions of nifedipine with different carriers such as urea, lactose, PEG 4000, 6000, 10000 and PVP K-30, K-90 have been studied by Sumnu et al. (10). However none of these solid dispersions were evaluated for their release patterns from the final controlled drug delivery system, and there are no studies determining the influence of solid dispersions on drug release mechanisms via solid dosage forms.

Release mechanisms of a drug from solid dosage forms may be related to the porosity. Porosity is a result of the presence of voids and pores in a sample where voids are the inter particulate spaces and pores are typically the crevices, cracks and fissures located in the particle (11). The porosity can be characterized by mercury porosimetry. The pore structure of a solid can provide valuable information regarding its dissolution and diffusion properties (12). Therefore, porosity and pore size distribution measurements have been extensively used to study tablets (13-18), granules (19-23) and pharmaceutical powders (24,25). Void porosity can be characterized by low pressure mercury

porosimetry (upto 30 psi) and is determined by calculating the pore volume diameter. In contrast, pores are analyzed by high pressure mercury porosimetry (upto 30,000 psi). According to this method, the cumulative volume of mercury intruded is a function of porosity, increased volumes indicate an increased porosity.

The present study was undertaken to develop, characterize and evaluate the multi-unit erosion matrix as described previously (7) with nifedipine and nifedipine:Pluronic® F-68 solid dispersion. A physical characterization of nifedipine solid dispersion by particle size analysis, aqueous solubility, DSC and XRD studies were conducted before they were pelletized. Later, pellets containing nifedipine or nifedipine:Pluronic® F-68 solid dispersions were prepared by a Extrusion/Spheronization technique. The effect of porosity parameters (cumulative intrusion volume, pore size distribution, pore volume diameter, total intrusion volume and total pore surface area) on dissolution time of the pelletized nifedipine and nifedipine:Pluronic® F-68 solid dispersion were determined to better explain the mechanism of drug release from controlled release matrix pellets and to determine the differences that were introduced by the nifedipine:Pluronic® F-68 solid dispersions.

2.0 Materials and methods

Nifedipine (USP/BP) was purchased from Vinchem, Inc, (Chatham, NJ, USA) and was micronized by using a Fluid Energy Aljet Mill (Plumsteadville, PA, USA). Inlet air pressure of 60 psig and grinding air pressure of 80 psig for micronization were used.

Eudragit® L 100 55, Eudragit® S 100 (Huls America, Inc., Somerset, NJ, USA), Kollidon® 90 F (BASF, Inc., Parsipanny, NJ, USA), Avicel® PH 101 (FMC Corporation, Philadelphia, PA, USA), Triethyl Citrate (Morflex, Inc., Greensboro, NC, USA) and Pluronic® F-68 (BASF, Inc., Parsipanny, NJ, USA). All other chemicals were used as received. Since nifedipine is sensitive to light, all experiments were performed under yellow light.

2.1 Particle size determination

Particle size determination was carried out with Master Sizer X, Malvern Instruments Inc., Southborough, MA, USA. An excess amount of drug was suspended in 1.0 % v/v Tween 80 in 100 mL of distilled water and was sonicated for 30 seconds for a thorough dispersion. This suspension was circulated at medium speed for particle size distribution studies.

2.2 Preparation of nifedipine:Pluronic® F-68 solid dispersions

Solid dispersion with different drug:pluronic ratios were prepared by the fusion method (26). The required amount of Pluronic® F-68 was weighed accurately and heated to 100° C until it formed a transparent melt. Nifedipine (mean particle size: 2.31 μm) was added to this melt in small portions with a constant stirring rate of 750 rpm. The temperature of the mixture was kept constant at 100° C. This mixture was stirred for 45 minutes until a clear transparent melt was formed. The melt was then poured on to a glass plate and was

allowed to solidify at room temperature. The solid mass was powdered and uniformly mixed in a mortar and 80/100 mesh (150-180 μm) particles were used for pelletization.

2.3 *Solubility of nifedipine and nifedipine in Pluronic® F-68 solid dispersion*

Solubility of nifedipine alone and nifedipine in the Pluronic® F-68 solid dispersion (1:1) was determined by placing an excess amount of sample in amber glass vials with 10 mL deionized water. The samples were then subsequently allowed to equilibrate at 25° C in an incubator shaker for 24 hours. Samples were filtered and the filtrate was analyzed for nifedipine by an HPLC method. A Waters 600E multi solvent delivery system (Waters Corporation, Milford, MA, USA) connected with a variable wavelength absorbance detector (Model Spectra 100, Spectra-Physics, USA) and a Waters 717 plus auto sampler (Waters Corporation, Milford, MA, USA) was used. The stationary phase consisted of a micro bondapak C_{18} reverse phase column (3.9 x 300 mm, Waters Corporation, Milford, MA, USA). Mobile phase used was acetonitrile : methanol : distilled water (2 : 3 : 5) and the flow rate was 1.0 mL/min with 30 minutes of total run time per injection. Nifedipine was detected at a retention time of 15.8 minutes. The sensitivity of the assay was 1 μg/mL. All studies were performed in triplicate.

2.4 *Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies*

DSC was carried out with a Seiko Instruments Inc., Japan, Model SSC5200 system. Approximately 10 mg of sample was placed in a hermetically sealed aluminium pan and

was scanned at the rate of 10° C/min from 0 to 200° C. Qualitative powder X-ray diffraction was performed by a Scintag X-Ray Diffractometer System, CA, USA by using nickel filtered copper potassium alpha radiation.

2.5 *Preparation of pellets*

Eudragit® L 100 55 and Eudragit® S 100 were mixed in a Turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. Triethyl citrate was added to this mixture as a plasticizer by trituration in a mortar. Nifedipine or nifedipine solid dispersion was then added followed by Kollidon® 90F used as a binder and they were mixed for 30 minutes in a Turbula mixer. The resultant mixture was then granulated with deionized water in a mortar. The granulate obtained was then fed through an extruder (LCI Xtruder, Model DG-L1 by Fuji Paudal Co., Ltd., Japan) which was equipped with a single screw and a screen of 2.0 mm size. Extrusion was conducted at 40 rpm. Extrudates obtained were immediately processed into pellets by spheronization (Spheronizer: Model 120, G.B. Caleva Ltd, Dorset, England attached with a 2.0 mm cross hatched friction plate). The spheronization speed was maintained within 800-1000 rpm and spheronization time was limited to 10 minutes. During this process Avicel® PH 101 (5% w/w of total batch size) was sprinkled on to the pellets to prevent inter pellet sticking. Pellets thus obtained were dried on trays in a hot air convection oven for 12 hours at 50° C. They were then sieved (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, USA) to obtain 2.0 mm sieve fractions. The quantitative composition of the pellets formulated is given in Table I.

2.6 *Determination of In Vitro drug release*

In vitro dissolution was performed using USP XXII Apparatus I in 500 mL of pH 6.8 phosphate buffer with ionic strength of 0.05 M, at 50 rpm and 37.0 ± 0.5° C (Distek Inc., NJ, USA). Pellets obtained after dissolution were characterized for their shape and structure by an optical microscope by Nikon HFX, IA, Japan. Transverse sections of pellets obtained after 2 and 4 hour dissolution times were analyzed for the distribution of drug in the matrix.

2.7 *Determination of porosity parameters*

Pellet dissolution time as a function of cumulative intrusion volume of mercury, pore size distribution, pore volume diameter, total intrusion volume and total pore surface area were determined by mercury intrusion porosimetry. A Micromeritics PoreSizer Model 9320, Micromeritics Inc., Norcross, GA, USA was used for the determinations. Each sample was measured in triplicate.

3.0 Results and discussion

Results of particle size determination are tabulated in Table II. The solubility of nifedipine and nifedipine in the nifedipine:Pluronic® F-68 (1:1) solid dispersion was found to be 9.72±0.13 and 103.06±0.07 µg/mL respectively demonstrating that Pluronic® F-68 increased the solubility of nifedipine by approximately ten fold.

DSC thermograms and XRD pattern of micronized nifedipine indicated no changes in its thermodynamic and crystalline behaviour (Figures 1a and 1b). Data obtained indicates that nifedipine remained the same after micronization. Figures 2a and 2b are the thermograms of nifedipine:Pluronic® F-68 solid dispersions that were prepared in ratios of 1:0.5 w/w drug to polymer (T_m = 167.8° C, ΔH = 50.7 mJ/mg) and 1:1 w/w (T_m = 152.6° C, ΔH = 24.2 mJ/mg) respectively. From these thermograms it was clear that the melting point of nifedipine was reduced in the solid dispersion with consequent reduction in enthalpy Figures 3a and 3b are XRD patterns of nifedipine:Pluronic® F-68 solid dispersions in ratios of 1:0.5 w/w and 1:1 w/w respectively. The characteristic nifedipine peaks were found to be reduced with increased concentration of Pluronic® F-68 in the solid dispersion. These results provide evidence of decreased drug crystallinity due to the formation of a solid dispersion. Similar results were reported for nifedipine solid dispersions with various other substances (9,10) such as polyethylene glycol, urea, lactose, polyvinylpyrrolidone etc.

A linear relationship of drug release via matrix erosion of a poorly soluble drug, similar to nifedipine, was described in our earlier study (7). The validity of this matrix erosion hypothesis was tested with nifedipine and nifedipine:Pluronic® F-68 solid dispersion pellets. The in vitro release profiles of nifedipine pellets before and after micronization and nifedipine:Pluronic® F-68 solid dispersion pellets are shown in Figure 4. Pellets prepared with nifedipine of three different particle sizes provided a zero order 24 hour drug release profile. On the other hand, drug release from the pellets prepared with nifedipine:Pluronic® F-68 solid dispersions was changed from zero to first order and the

release rates had significantly increased compared to the pellets prepared with nifedipine alone. Drug release rates from the solid dispersion pellets was increased as Pluronic® F-68 increased from 0.5 to 1.0 part in the solid dispersions. Dissolution from these pellets followed first order kinetics for about 12 hours for both the strengths. From Figure 4 it can also be concluded that particle size differences of nifedipine did not significantly influence the release pattern and rates from nifedipine pellets.

In order to understand the underlying release mechanism, the pellets collected at different time intervals during dissolution testing were analyzed under the microscope. Figure 5 shows pellets prepared with nifedipine:Pluronic® F-68 (1:1) solid dispersion after 12 hours of dissolution. The size of the pellets was decreased due to surface erosion. Nifedipine pellets also eroded in a similar fashion over a period of 24 hours. Both these pellets maintained their geometrical shape but were reduced in size. Furthermore, pellets of nifedipine and nifedipine:Pluronic® F-68 (1:1) solid dispersion that were removed from the dissolution medium on the 2 and 4 hours of dissolution were dried at 50° C for 12 hours and transverse sections of these pellets were investigated. After 4 hours the pellets became very soft which made it impossible to obtain the transverse. Transverse sections of nifedipine pellets (Figures 6a and 6b) showed that the drug remained uniformly distributed in the matrix at 2 and 4 hours, whereas nifedipine:Pluronic® F-68 (1:1) solid dispersion pellets showed release of the drug from the core by diffusion. The increased aqueous solubility of drug in the solid dispersion explains the enhanced erosion and release rates from nifedipine:Pluronic® F-68 solid dispersion pellets as compared to nifedipine pellets. Increased aqueous solubility had also increased the release of drug

from the pellets of solid dispersion which occurred by erosion and simultaneous diffusion from the matrix. Whereas release of drug from nifedipine pellets was purely by erosion mechanism.

To further confirm the release mechanisms of both the pellets, their porosity parameters were measured and determined by mercury intrusion porosimetry. The porosities were determined after the pellets were exposed to 2. 4, 6 and 8 hours of dissolution media. Figures 7a and b show the cumulative intrusion volume of mercury against pore diameters obtained at different dissolution intervals of nifedipine and nifedipine:Pluronic® F-68 solid dispersion pellets, respectively. Figures 8a and b show changes in the pore size distribution during dissolution. Figure 7a shows that the cumulative intrusion volumes of mercury for nifedipine pellets following dissolution at 2 to 8 hours mainly remain constant with minimal changes, whereas from Figure 7b, pellets of nifedipine:Pluronic® F-68 solid dispersion showed increased pores as the dissolution time increased from 2 to 8 hours. Further from Figure 8a, a trimodular pore size distribution is observed with maximum pores lying within the range of 0.1 to 0.01 μm indicating that the voids and fine pores contribute to the overall porosity of the pellets with the pores occupying a much higher volume than the voids. A reverse pore size distribution was observed (Figure 8b) for pellets of nifedipine:Pluronic® F-68 (1:1) solid dispersion indicating that the overall porosity was due to the voids which were increasing with dissolution time. Figure 9 shows the effect of dissolution time on the pore volume diameter of the pellets. No significant changes were observed in the pore volume diameters of nifedipine pellets indicating no increase in void porosity during the

dissolution period of 8 hours, whereas pore volume diameters of pellets formulated with nifedipine:Pluronic® F-68 (1:1) solid dispersions increased with dissolution time indicating an increase in the void porosity which is the result of increased void diameters. This increase may be due to the enhanced solubility of drug in the solid dispersion which diffused out of the matrix. Figure 10 shows the total intrusion volumes that were obtained at different dissolution times that summarizes the overall effect of dissolution time on pellet porosity. From this Figure the porosity of nifedipine:Pluronic® F-68 solid dispersion pellets increased linearly with dissolution time whereas, the porosity of nifedipine pellets did not change significantly. Total pore surface area is the cumulative surface area of all the pores and voids present in a sample. Figure 11 shows the total pore surface area against dissolution time. The total pore surface area of nifedipine:Pluronic® F-68 solid dispersion pellets increased linearly from 2 to 8 hours of dissolution time. This maybe due to the formation of voids and pores as nifedipine and pluronic was diffusing out of the matrix. However, it is postulated that the total pore surface area is being reduced during dissolution because the size of the pellets becomes smaller. Such a phenomenon can only occur if surface erosion is the only mechanism of release which in fact was observed with nifedipine pellets. Their total surface area decreased linearly with dissolution time (Figure 11). This confirms that surface erosion is the release mechanism of nifedipine pellets. In addition, the results demonstrated in Figure 11 strongly indicate that upon incorporation of a poorly soluble drug like nifedipine in erosion matrix pellet systems, a zero order release for 12-24 hours as described previously (7) is obtained. However, a change in the physical properties and solubility of the drug as it occurs with nifedipine:Pluronic® F-68 solid dispersions alters the release profile and kinetics.

4.0 Conclusions

In conclusion, controlled release of nifedipine (poorly soluble drug) following zero order kinetics for 24 hours from a multi-unit erosion matrix was achieved. It was proved that multi-unit erosion matrix systems as described earlier (7) are universal in their application for controlled release of poorly soluble drugs. Drug release from nifedipine pellets occurred by matrix erosion. Whereas for pellets of nifedipine:Pluronic® F-68 solid dispersion, release occurred by a combination of matrix erosion and diffusion mechanisms for 12 hours following first order kinetics. The solubility of nifedipine was increased by 10 times due to solid dispersion formation in 1:1 nifedipine:Pluronic® F-68 ratio. Porosity parameters studied by mercury intrusion porosimetry proved that drug release was not influenced by the porosity for nifedipine pellets, however the drug release was predominantly porosity controlled for nifedipine:Pluronic® F-68 solid dispersion pellets.

Acknowledgments

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Table 1: Composition of pellets prepared with nifedipine and nifedipine:Pluronic® F-68 solid dispersions.

Formulation Type	Nifedipine (% w/w)	Kollidon® 90F (% w/w)	Eudragit® L 100 55 : S 100 ratio (% w/w)	* Plasticizer (% w/w)
nifedipine pellets D(v, 50) = 7.06 μ	20.00	2.00	1 : 3	11.70
nifedipine pellets D(v, 50) = 2.66 μ	20.00	2.00	1 : 3	11.70
nifedipine pellets D(v, 50) = 2.31 μ	20.00	2.00	1 : 3	11.70
nifedipine:Pluronic® F 68 SD pellets (1:1)	20.00	2.00	1 : 3	11.70
nifedipine:Pluronic® F 68 SD pellets (1:0.5)	20.00	2.00	1 : 3	11.70

* Triethyl citrate (15% w/w of Eudragit® L 100 55 + Eudragit® S 100)

Table 2: Results of Particle Size of Nifedipine and Nifedipine in Pluronic F-68 solid dispersions.

SAMPLE	D(V, 0.5) (μ) *	D(V, 0.9) (μ) **
Nifedipine	7.06	17.29
Nifedipine micronized once	2.87	8.72
Nifedipine micronized twice	2.31	6.96
Nifedipine:Pluronic® F-68 (1:1) SD	3.10	12.93
Nifedipine:Pluronic® F-68 (1:0.5) SD	2.66	8.40

* 50^{th} percentile mean volume particle size.

** 90^{th}percentile volume particle size.

Figure 1 a

Melting point endotherms of nifedipine before and after micronization

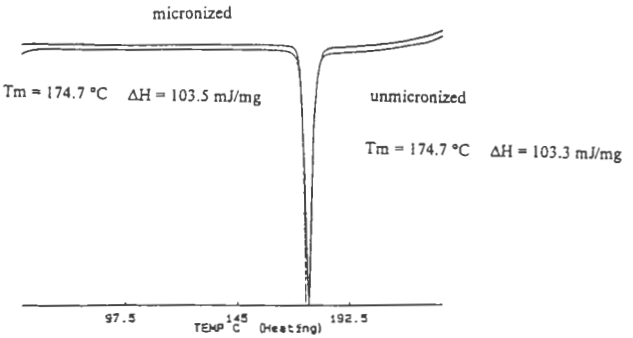
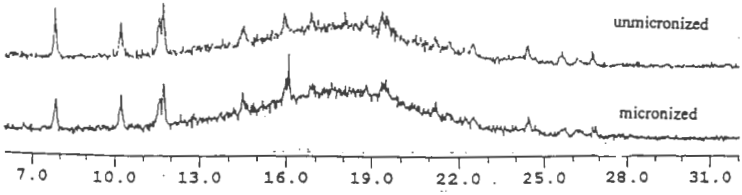


Figure 1 b

X-ray diffraction pattern of nifedipine before and after micronization.



2θ

Figure 2 a

Melting point endotherm of nifedipine:pluronic F-68 solid dispersion (1:0.5)

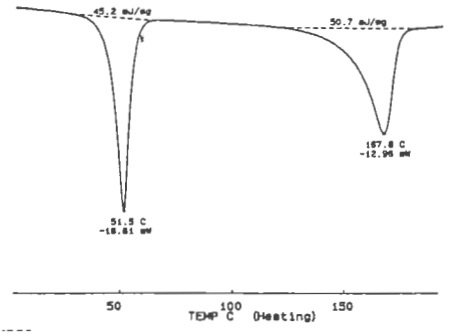


Figure 2 b

Melting point endotherm of nifedipine:pluronic F-68 solid dispersion (1:1)

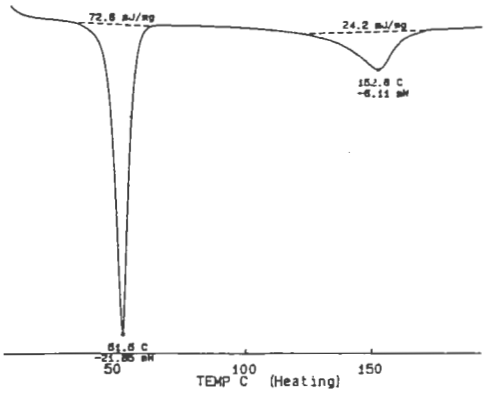


Figure 3 a

X-ray diffraction pattern of nifedipine:pluronic F-68 solid dispersion (1:0.5)

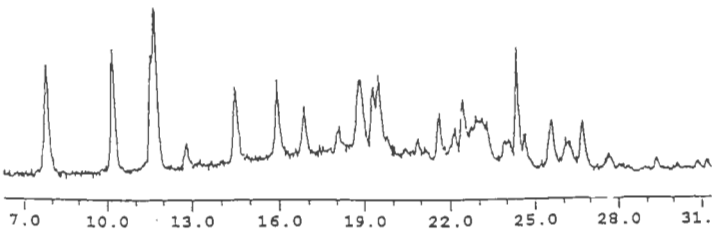


Figure 3 b

X-ray diffraction pattern of nifedipine:pluronic F-68 solid dispersion (1:1)

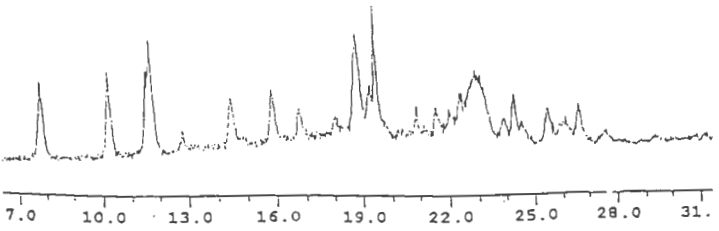


Figure 4

Effect of nifedipine mean particle size and ratio of nifedipine:pluronic F-68 solid dispersion on the release profiles obtained with 2.0 mm pellets.

(spheronization time: 10 minutes, n = 4±SE)

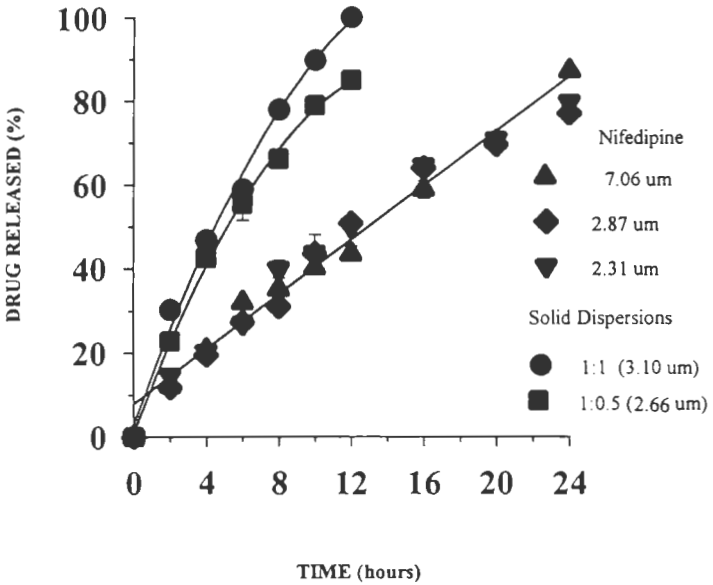


Figure 5

Microscopical evaluation of nifedipine:pluronic F-68 (1:1) solid dispersion pellets after dissolution time intervals.

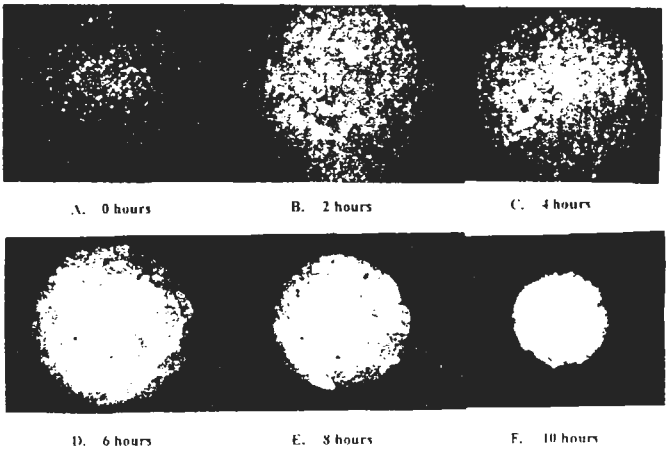
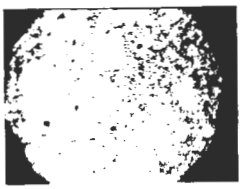
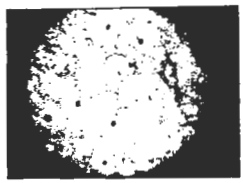


Figure 6 a

Transverse section of nifedipine pellets after 2 and 4 hour dissolution time intervals showing uniform drug distribution in the matrix.



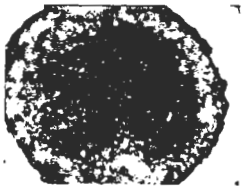
2 hours



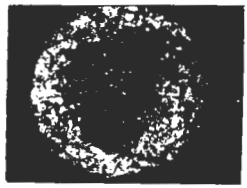
4 hours

Figure 6 b

Transverse section of nifedipine:pluronic F-68 (1:1) solid dispersion pellets after 2 and 4 hour dissolution time intervals showing drug diffusion through the matrix.



2 hours



4 hours

Figure 7

Cumulative intrusion profiles of nifedipine and nifedipine:pluronic F-68 solid dispersion pellets during dissolution.

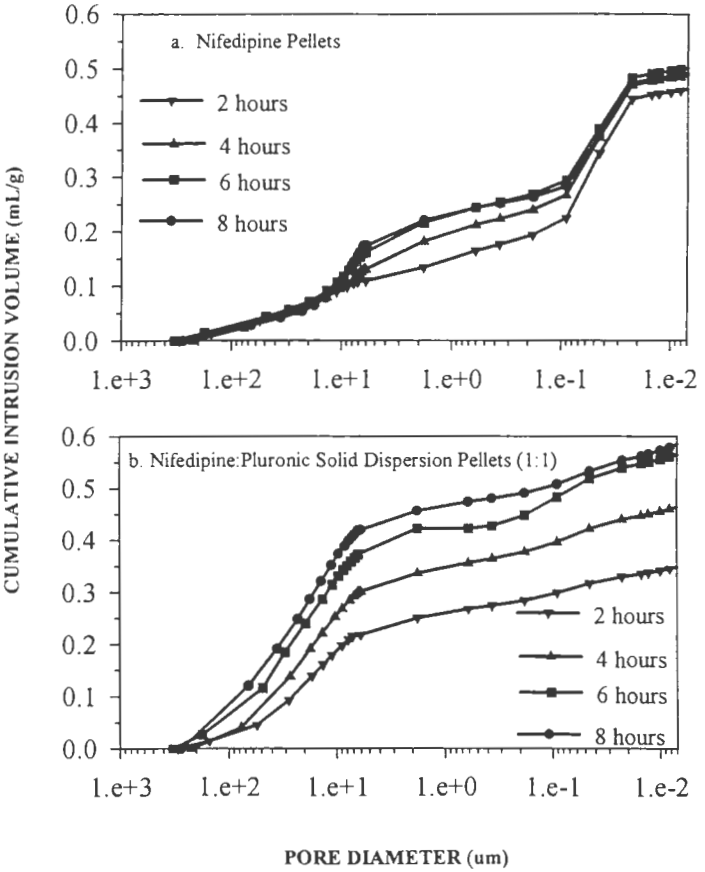


Figure 8

Pore size distribution of nifedipine and nifedipine:pluronic F-68 solid dispersion pellets during dissolution. (spheronization time: 10 minutes, n = 4±SE)

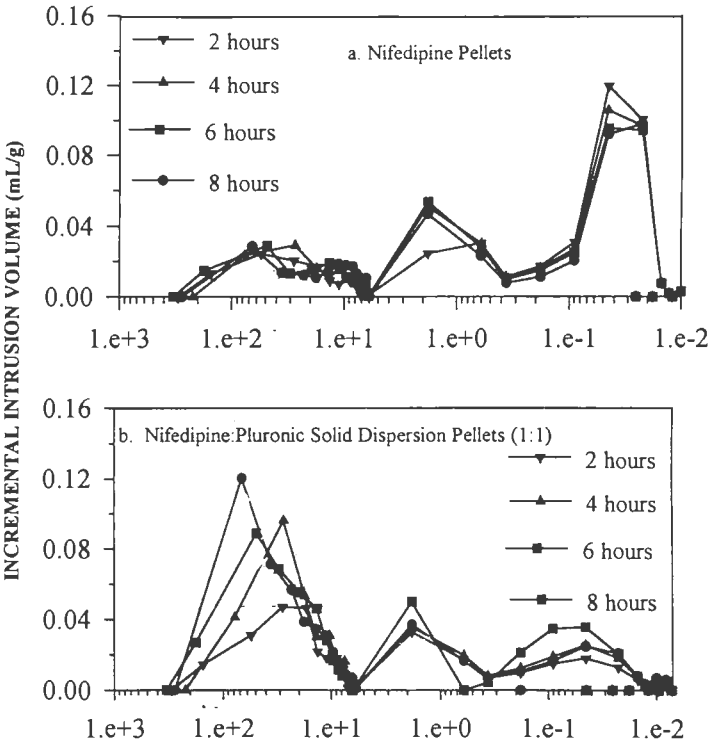


Figure 9

Changes in the pore volume diameter of pellets during dissolution.

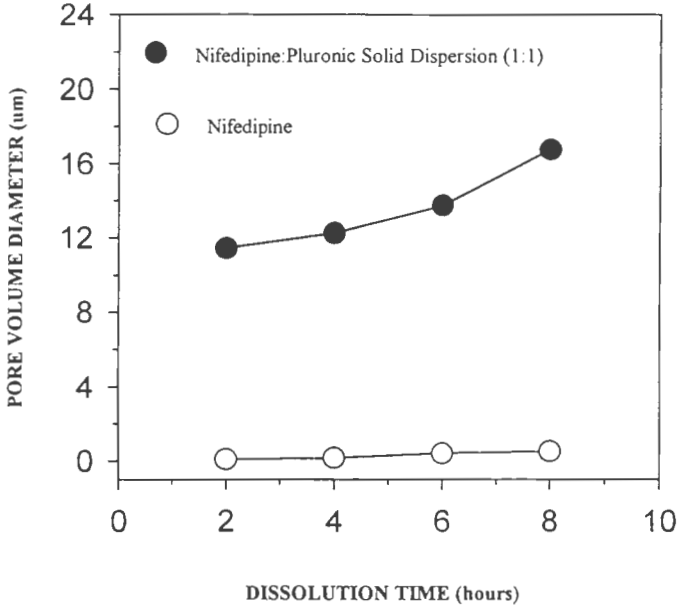


Figure 10

Changes in the total intrusion volume of pellets at various dissolution intervals.

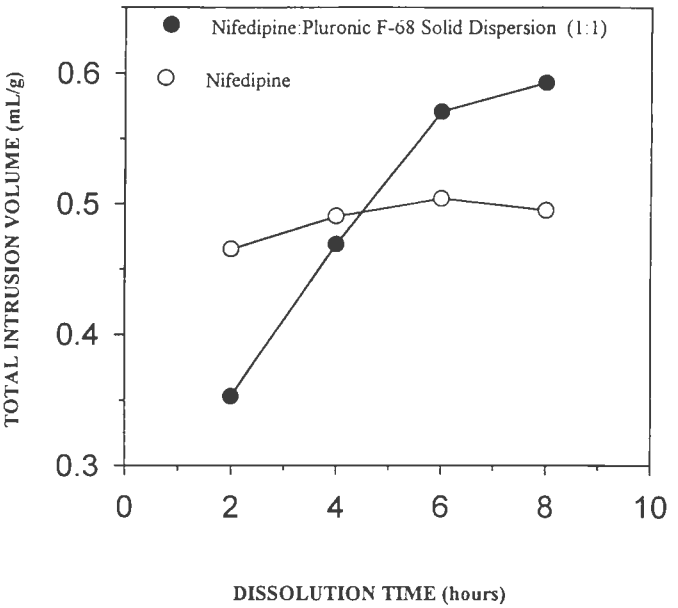
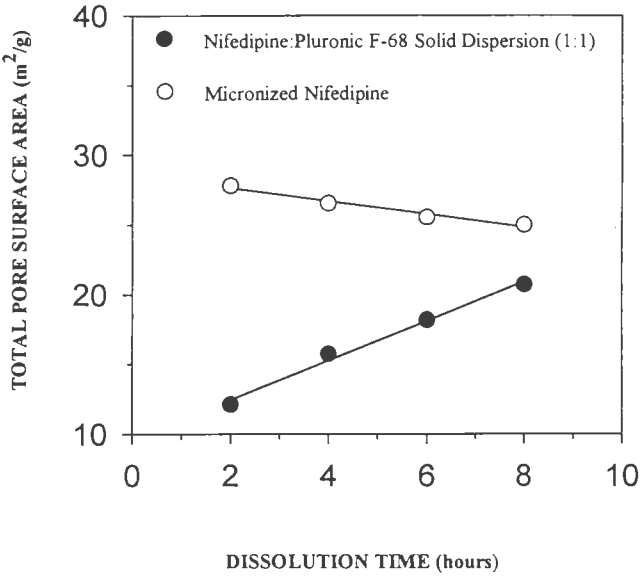


Figure 11

Effect of dissolution time on the changes in total pore surface area of the pellets.



MANUSCRIPT V

NIFEDIPINE BIOAVAILABILITY IN FASTED DOGS FROM AN ERODING MULTI-UNIT MATRIX SYSTEM

KEYWORDS

Nifedipine Erosion Matrix Pellet Capsules, Adalat® Soft Gelatin Capsules, In Vivo, Beagle Dogs, Pharmacokinetic Parameters, Bioavailability, Eudragit® L 100-55, Eudragit® S 100.

ABSTRACT

The development, characterization and in vitro evaluation of a novel multi-unit erosion matrix pellet system of nifedipine was described earlier. The purpose of this study was to evaluate in vivo performance of the erosion matrix pellets prepared with nifedipine and compare their bioavailability with nifedipine immediate release soft gelatin capsules (Adalat® 10mg and 20 mg gelcaps administered together as one dosage form) in fasted dogs. A randomized two way comparative cross-over design was employed for bioavailability studies and four dogs were used. Blood samples were collected over predetermined time intervals up to 12 or 24 hours and analyzed for nifedipine plasma concentrations by an HPLC method for both the dosage forms. Data obtained was fitted to a non-compartmental pharmacokinetic model to determine parameters such as C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$, and $MRT_{0\text{-}24\ h}$. Results indicated that the bioavailability of nifedipine erosion matrix pellets was four times higher than Adalat® gel caps. Nifedipine was detected in plasma within one hour of administration of erosion matrix pellets, thus no significant lag time was observed. Nifedipine multi-unit erosion matrix pellets showed controlled release for more than 24 hours following zero order kinetics.

1.0 Introduction

Nifedipine is a calcium antagonist which is widely used as a coronary dilator in hypertension. Clinical studies have shown that the hypotensive effect of this drug could be correlated with the plasma nifedipine [1]. It is therefore important to prolong the plasma concentrations so as to control and regulate the therapeutic effects of nifedipine over a longer duration. Nifedipine is a poorly soluble drug and its absorption in GIT is rate limited. It has a short biological half life of about 2.3 hours. When administered orally via solid dosage forms, absorption of nifedipine is poor.

Nifedipine is commercially available as soft gelatin capsules and tablets for short term and extended treatments. Controlled release nifedipine is available as an extended release film coated tablet and also as a GITS system. The extended release film coated tablet contains a tablet core coated by a slow releasing layer comprising of the drug and the hydrophilic polymers such as hydroxypropylcellulose and hydroxypropylmethylcellulose. The outer slow releasing layer provides the initial drug release followed by rapid drug release from the tablet core. Drug release from such a tablet typically follows first order kinetics. One of the most desirable outcome in controlled drug delivery is to achieve zero order kinetics in vivo so as to obtain a constant therapeutic effect of the drug for a maximum duration. This is achieved by the nifedipine GITS system for controlled delivery.

The GITS system releases finely powdered nifedipine in a suspension form into the gastrointestinal lumen at a controlled rate over a 24 hour period. The release mechanism involves a "push-pull" process. As water is absorbed across the semi-permeable membrane surrounding the bilayer tablet, nifedipine particles become suspended in solution and are then "pushed" into the intestinal tract as the osmotically active polymers expand. Hydration of the GITS tablet occurs for approximately 2 hours before substantial amounts of nifedipine is detected in plasma. Dose dumping of nifedipine does not occur from the GITS system however approximately 10% of the total GITS tablet content remains unabsorbed after the tablet is emptied [2]. The dosage forms described above are examples to current nifedipine formulations that are available commercially for controlled delivery.

The development, characterization and evaluation of a novel multi-unit erosion matrix pellet system of nifedipine was described elsewhere [3]. It was designed to release a poorly soluble drug by surface erosion as a consequence of the polymer erosion from the matrix pellets. The drug release mechanism from this system is illustrated schematically in Figure 1. In vitro evaluation of this system in pH 6.8 phosphate buffer demonstrated zero order drug release in 24 hours [4].

The purpose of this study was to determine the bioavailability and pharmacokinetic parameters such as C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$, and $MRT_{0\text{-}24\ h}$ of nifedipine from this novel erosion matrix pellet system and compare the bioavailability with Adalat® immediate

release soft gelatin capsules used as a control in a randomized two way cross over design in four fasted dogs.

2.0 Materials and methods

Nifedipine was purchased from Vinchem Inc., Chatham, NJ. Eudragit® L 100 55 and Eudragit® S 100 (polymethacrylic acid esters) were provided as samples by Huls America Inc., Somerset, NJ. Kollidon® 90 F (polyvinylpyrrolidone) was obtained from BASF Inc., Parsipanny, NJ. Avicel® PH 101 (microcrystalline cellulose) was purchased from FMC Corporation, Philadelphia, NJ. Triethyl citrate was provided as a sample by Morflex Inc., Greensboro, NC. Butamben (n-butyl-p-amino benzoate) was provided as a free gift by Abbott Laboratories, North Chicago, IL. Methanol and acetonitrile (HPLC grade), chloroform, acetone, 0-phosphoric acid (80% v/v) were purchased from Fisher Scientific., Springfield, NJ. All the chemicals were used as received.

All work was carried out under yellow light. Turbula mixer (Impandex Inc., Maywood, NJ, USA) was used for mixing dry powders. Extruder utilized was LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan. (Single screw extruder, capable of extruding at speeds upto 100 rpm, with variable screens to obtain extrudates of different size). The Spheronizer used was a G.B. Caleva Ltd, Model 120, Dorset, England. [It consists of a stationary vertical cylinder which has at the base a friction plate (diameter 32 cm) with a 2 mm cross hatched friction pattern and a rotation speed of 200-3000 rpm]. Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH (Fitted with sieve # 8, 10, 12, 14, 16, 18 and

20) was utilized to collect pellets of the desired particle size. In vitro analysis of the pellets was performed in a Hewlett Packard 8452A Diode Array Spectrophotometer (Hewlett Packard Company, Paramus, NJ).

A vortex Mixer with 40 test tube holding capacity Model Typ VX 2V (IKA® Works, Inc., Cincinnati, OH) was used to equilibrate the frozen blood samples at room temperature prior to analysis. Fisher Vortex Genie 2™ with 40 micro-centrifuge tube holding capacity (Scientific Industries, Inc., Bohemia, NY) was utilized for sample processing. A Centrifuge, Model HN-S II (International Equipment Company, Needham Heights, MA) for separation of plasma proteins after drug extraction from the blood samples was used. TurboVap® LV Evaporator with nitrogen gas pressure of 1.0 bar (Zymark Corporation, Hopkinton, MA) was used as a sample concentrator for the assay.

2.1 Formulation of pellets

Eudragit®L 100 55 and Eudragit®S 100 powders were mixed in a turbula mixer for 30 minutes. Triethyl citrate was added as a plasticizer and the resultant mixture was triturated in a mortar for 5 minutes. Drug and polyvinyl pyrrolidone (Kollidon®K90F) used as a binder, were added and mixed for 30 minutes in a turbula mixer. This mixture was then granulated in a mortar with deionized water and later extruded at 40 rpm screw speed. The extrudates were immediately transferred into a rotating plate in the spheronizer. Spheronization was carried out for 10 minutes at 800-1000 rpm. During this period, 5% w/w of total batch size Avicel® PH 101 was sprinkled over the rotating

extrudates to prevent pellets from sticking. Pellets obtained were dried on trays at 50°C for 12 hours. The pellets consisted of nifedipine (20.0% w/w), Eudragit®L 100 55 and Eudragit® S 100 (78.0% w/w total in ratio of 1:3 respectively) and Kollidon®K90F (2.0% w/w). Granulation water level used was 58% w/w of the total batch size. Pellets (150 mg) were filled in a size 2 blue colored capsule before they were administered to the animals.

2.2 *Assay of nifedipine in pellets*

Nifedipine content of the pellets was determined by UV spectrophotometry. The pellets (100 mg) were dissolved in 100 mL of methanol and the resultant solution was diluted to obtain 10 ug/mL nifedipine concentration. This solution was analyzed spectrophotometrically at 237 nm and nifedipine content of 100 mg of pellets was determined

2.3 *In vivo absorption study design and protocol*

2.3.1 *Test animals*

The bioavailability of nifedipine pellets was tested on beagle dogs using a randomized two way comparative cross-over design.

Dogs were supplied by Marshall Farms, North Rose, NY. They were acclimatized for at least two weeks prior to the study and were approximately 9-14 kg in weight and one year

old in age. The study group consisted of two males and two females. Each dog had an ear tattoo for identification and was housed individually in a stainless steel cage. Each cage had an identification card showing the study number, dog number and sex. Room temperature and humidity was maintained at approximately 72° ± 4° F and 50% ± 20% respectively. During the experiments, the animal room was kept on an approximate 12 hour light/dark cycle. Each dog was exercised outside its cage at least three times a week for at least 15 minutes.

2.3.2 Dosage forms administered, frequency and method of dosing

The bioavailability of nifedipine erosion matrix pellets, (30 mg capsules, Lot No. KM 280/2) was tested against an immediate release soft gelatin capsule (Adalat®, 10 mg gelcaps, Lot No 6EAB and 20 mg, Lot No 5 HAX, manufactured by Bayer Corporation, West Haven, CT). All the test articles were stored in a locked area at ambient temperature protected from light.

The dogs were fed with Harlan-Teklad certified 25% lab dog diet (W). Approximately 800 grams diet (approximately 400 grams of dry dog food moistened with approximately 400 mL of water) was provided to the dogs 8 hours after dosing. Reverse osmosis (RO) water was available ad libitum by means of an automatic watering system. This RO water supply for the animal room was monitored for bacterial contamination at least once a month by the Department of Laboratory Animal Resources. In addition, chemical analysis of water was performed at approximately quarterly intervals by the

Environmental Monitoring and Support Laboratory. No contaminants expected to interfere with the study were known to be present in the feed or water.

Each dog received one 30 mg nifedipine erosion matrix pellets capsule or 10 plus 20 mg Adalat® soft gelatin capsules in fasted state. Following a one week washout period, each dog received a different formulation in phase two. The experimental protocol details are given in Table I.

2.3.3 Blood sampling

Blood samples (6 mL) were taken from each dog at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours after dosing for the nifedipine erosion matrix pellets. Blood samples from dogs who received Adalat® soft gelatin capsules were collected at 0, 0.5, 1, 2, 4, 6, 8 and 12 hours after dosing. The samples collected were transferred into test tubes containing lithium heparin, used as an anticoagulant, and to prevent decomposition they were placed in an ice bucket prior to centrifugation. Plasma was separated after cold centrifugation and was frozen in amber glass vials at -20° C under yellow light before analysis.

2.4 Assay of Nifedipine in Plasma

Nifedipine in all samples was assayed using a modified version of the HPLC method described by Miyazaki et al [5].

2.4.1 Processing Blood Samples for HPLC

Methanol (100 µl) containing 2 µg/mL butamben, used as an internal standard and acetonitrile (2 mL) were added to 0.5 mL of plasma in a test tube and were agitated in a vortex mixer for 30 minutes. After centrifugation at 4000 rpm for 20 minutes, 2 mL of the supernatant was transferred into a test tube containing 1 mL of distilled water, to this solution 4.5 mL of acetone-chloroform mixture (1:1 v/v) was added. This mixture was agitated for 1 hour on a vortex mixture to ensure complete extraction of nifedipine into the organic phase and was then centrifuged at 4000 rpm for 20 minutes to separate the organic and aqueous phases. The aqueous phase was discarded and 5 mL of the organic phase was transferred to a fresh test tube, and was reduced to dryness in a sample concentrator under nitrogen at 45° C for 30 minutes. The residue was dissolved in 100 µl of the mobile phase and 20 µl of the solution was injected into the HPLC system.

2.4.2 Chromatographic Conditions

HPLC pump used was a Waters multi-solvent delivery system (Waters Corporation, Milford, MA) with a Waters 717 plus auto-sampler (Waters Corporation, Milford, MA) and a variable wavelength absorbance detector (Model Spectra-Physics, USA). The stationary phase used was a reverse phase Zorbax ODS, 4-6 microns 25 cm x 4.6 mm column (I.D., Dupont Inc., Wilmington, DE). The column was warmed at 55° C using a steel column heater (Model Code 600, Waters Corporation, Milford, MA). The mobile phase consisted of 0.01 M disodium hydrogen phosphate buffer-methanol (45:55). Before mixing, the buffer was brought to pH 6.1 with 50% phosphoric acid. Run time used was 30 minutes and the flow rate was 0.8 mL/min at column pressure of approximately 1200 psi. The wavelength of detection was 237 nm.

2.4.3 Calibration Graph

Standard solutions containing 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 and 10.0 μg/mL nifedipine in methanol that contained 2 μg/mL butamben (internal standard) were prepared under yellow light. The standard solution (100 μl) was added to 0.5 mL of drug free plasma and the samples were processed as described above. The ratios of the peak height of nifedipine to that of butamben were used to construct a calibration graph. Stock solutions of both nifedipine and the internal standard (1 mg/mL in methanol) were stored in complete darkness; these solutions were freshly prepared every 2 weeks. Precision obtained using the described technique was ±5%.

2.5 Pharmacokinetic Analysis

The most suitable model to describe the pharmacokinetics of nifedipine was determined by fitting the data to a hierarchy of models using WinNonlin software. The data most appropriately fitted to a non-compartmental model and pharmacokinetic parameters such as C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$ and $MRT_{0\text{-}24\ h}$ (mean residence time) were calculated by a computer using WinNonlin software by Scientific Consulting Incorporated (Lexington, KY).

3.0 Results and Discussion

The UV assay demonstrated that nifedipine erosion matrix pellets administered to the dogs contained 98 – 102 % of the original nifedipine loading. The Adalat® soft gelatin capsules were not assayed for nifedipine content. Nifedipine plasma concentrations obtained after dosing with Adalat® soft gelatin capsules and nifedipine matrix erosion pellets are tabulated in Tables II and III respectively. Table IV shows the mean pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}24\ h}$, $MRT_{0\text{-}24\ h}$) determined for both dosage forms. Figure 2 shows the nifedipine plasma concentration profile for 24 hours following administration of the pellets and the immediate release capsules. The mean T_{max} for nifedipine erosion matrix pellets from Table IV was 15.50 hours whereas for Adalat® capsules was 0.5 hours. This indicated that time taken to reach maximum plasma nifedipine concentrations was 15.5 hours thus providing controlled release of the drug. The $MRT_{0\text{-}24\ h}$ was 12.5 hours for the pellets and 1.72 for the Adalat® capsules, indicating the presence of pellets in the GIT was prolonged. The mean $AUC_{0\text{-}24\ h}$ of the pellets was four times higher than the conventional immediate release Adalat® soft gel capsules.

Adalat® capsules contain nifedipine in the solubilized form in a polyethylene glycol based co-solvent system. The bioavailability from Adalat® 20 mg soft gelatin capsules was reported earlier by Sallam et.al. [6]. Accordingly, the lower AUC obtained with Adalat® soft gelatin capsules might be due the precipitation of the poorly soluble nifedipine in the gastric fluid. As a result the particle size of nifedipine may also have increased, which can be the cause of reduced nifedipine absorption.

Nifedipine release from the matrix pellets is governed by the polymer controlled surface erosion process. In this mechanism, drug release occurs in a constant fashion in the form of a microfine suspension in the gastrointestinal tract and thus is readily available for a prolonged period. It is also interesting to observe that the nifedipine plasma concentrations were obtained one hour after administration without any significant lag time, Figure 2. The pellet matrix contains Eudragit® L 100 55 and Eudragit® S 100 polymers which dissolve at pH 5.5 and pH 7.0 respectively. Considering that the pellets were very small multi-unit systems (particle size: 2.00 mm), they are expected to have a small gastric residence time after which exposure to pH 5.5 and higher pH's may have caused the pellets to release the drug. The most significant effect that is shown in Figure 2 is that nifedipine release from the multi-unit pellets continued for over 24 hours. Thus, the elimination rate constants could not be calculated for this period

4.0 Conclusions

Controlled delivery of nifedipine via polymer controlled surface erosion of nifedipine provided zero-order drug release both in vitro and in vivo for 24 hours. Bioavailability from the controlled release pellet system was four times more than the conventional immediate release Adalat® soft gelation capsules of nifedipine.

Thus it was demonstrated that the surface erosion mechanism may be used in pellets to obtain a controlled release system that delivers a poorly soluble drug like nifedipine effectively and in a constant fashion.

Acknowledgments

Discussions pertaining to in vivo experimental design and optimization of analytical methods to determine nifedipine in plasma and laboratory support provided by Dr. Surendra Bansal, Head of Bioanalytical section, Department of Drug Metabolism and Pharmacokinetics, Hoffmann-La Roche Inc., Nutley, NJ 07110 were very useful. The primary author wishes to thank Dr. Bansal for this support.

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Table I: In vivo absorption study protocol details

Dosage Form	Condition	Dose (mg/dog/day)	No. of Tablets/Capsules	Males	Females
Phase I					
Nifedipine Erosion Matrix Capsules	Fasted	30	1	1-2	3-4
One week Washout period					
Phase II					
Adalat® Soft Gelatin Capsules	Fasted	30	2	1-2	3-4

Table II: Nifedipine plasma concentrations (12 hours) obtained in dogs (n = 4) after administration of Adalat® soft gelatin capsules (30 mg/dog/day).

Time (hours)	Nifedipine Plasma Levels (μg/mL)				
	Dog I	**Dog II**	**Dog III**	**Dog IV**	**Mean ± SD**
0.0	0.0000	0.0000	0.0000	0.0000	0.0000 ± 0.0000
0.5	0.2216	2.2628	0.6358	1.6288	1.1872 ± 0.9288
1.0	0.2079	0.6548	0.2530	0.7226	0.4595 ± 0.2666
2.0	0.2097	0.2387	0.0940	0.3394	0.2204 ± 0.1009
4.0	0.0897	0.0648	0.0518	0.1293	0.0839 ± 0.3410
6.0	0.0365	0.0321	0.0215	0.0494	0.0348 ± 0.0115
8.0	0.0243	0.0000	0.0307	0.0228	0.0194 ± 0.0134
12.0	0.0387	0.0000	0.0239	0.0000	0.0156 ± 0.0190

Table III : Nifedipine plasma concentrations (24 hours) obtained in dogs (n = 4) after administration of matrix erosion pellets capsule (30 mg/dog/day).

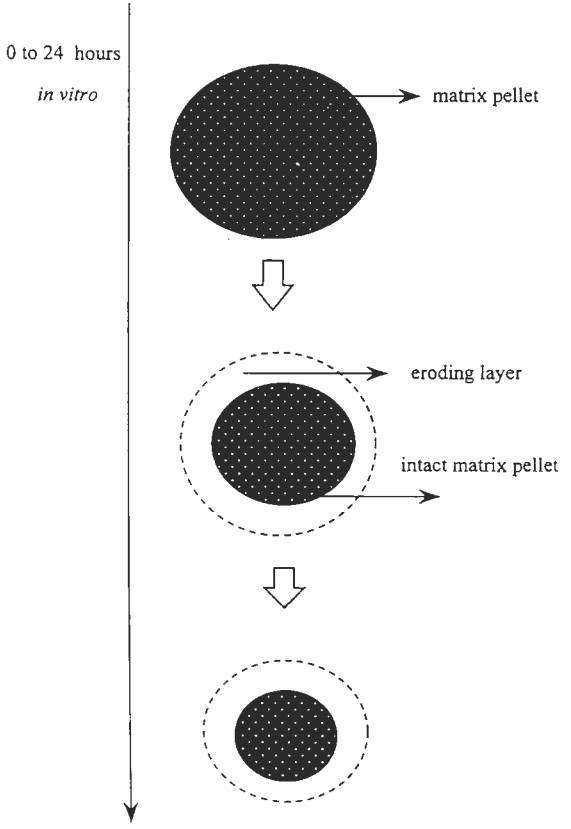
Time (hours)	Nifedipine Plasma Levels (μg/mL)				
	Dog I	Dog II	Dog III	Dog IV	Mean ± SD
0.0	0.0000	0.0000	0.0000	0.0000	0.0000 ± 0.0000
1.0	0.0000	0.1331	0.1536	0.3551	0.1604 ± 0.1465
2.0	0.1333	0.0933	0.0699	0.4714	0.1919 ± 0.1881
4.0	0.0586	0.0952	0.0867	0.3419	0.1456 ± 0.1317
6.0	0.1454	0.1617	0.7161	0.0953	0.2796 ± 0.2923
8.0	0.0727	0.0674	0.7945	0.1438	0.2696 ± 0.3516
12.0	0.1252	0.1035	0.6778	0.0733	0.2449 ± 0.2893
16.0	0.1636	0.1654	0.8409	0.0985	0.3171 ± 0.3505
20.0	0.1869	0.1858	0.8629	0.1449	0.3466 ± 0.3487
24.0	0.1192	0.1275	0.4665	0.0386	0.1879 ± 0.1899

Table IV: Mean pharmacokinetic parameters of nifedipine matrix erosion pellets and Adalat® soft gelatin capsules obtained ny non-compartmental analysison four beagle dogs.

Dosage Form	$C_{max} \pm SE$ (μg/mL)	$T_{max} \pm SE$ (h)	$AUC_{0\text{-}24\ h} \pm SE$ (μg h/mL)	$MRT_{0\text{-}24\ h} \pm SE$ (h)
Nifedipine Matrix Erosion Pellets	0.4268 ± 0.1602	15.5000 ± 4.5000	6.1123 ± 2.8690	12.5561 ± 1.2853
Adalat® Soft Gelatin Capsules	1.1873 ± 0.4644	0.5000 ± 0.0000	1.5049 ± 0.3980	1.7280 ± 0.2959

Figure 1

Schematic representation of a novel multi-unit erosion matrix for controlled release of a poorly soluble drug.



SECTION III

- Appendix 1, 2 ,3a ,3b ,3c and 4.
- Complete listing of references cited.

APPENDICES

1. Solubility studies of nifedipine and nifedipine:pluronic® F-68 solid dispersion (1:1) in water at 25°C.

2. Particle size determination of nifedipine samples before and after micronization and after formation of solid dispersions with pluronic® F-68.

3. Determination of porosity parameters by mercury intrusion porosimetry.

   (a) Pellets formulated with different drug (D_4 Leukotriene antagonist) loads and spheronized at different times.

   (b) Pellets formulated with different granulation water levels.

   (c) Nifedipine and nifedipine:pluronic® F-68 (1:1) solid dispersion pellets after different dissolution time intervals.

4. Determination of nifedipine in plasma after oral administration of nifedipine erosion matrix pellet capsule and Adalat® soft gelatin capsule in fasted dogs.

Appendix 1

Solubility studies of nifedipine and nifedipine:pluronic® F-68 solid dispersion (1:1) in water at 25°C.

HPLC METHOD VALIDATION:

SOLUBILITY DETERMINATION OF NIFEDIPINE AND NIFEDIPINE:PLURONIC® F-68 SOLID DISPERSION (1:1) IN WATER AT 25°C EQUILIBRATED FOR 24 HOURS

1. SOURCE of STANDARD:

Nifedipine, Lot # 9S1172, was purchased from Vinchem Inc., Chatham, NJ, USA.

Pluronic® F-68, Lot # 22415, was obtained as a gift from BASF Inc., Parsipanny, NJ, USA.

2. HPLC METHOD:

System:

Pump:	Waters 600E Multi-Solvent Delivery System
Injector:	Waters 717 Plus Auto Sampler
Column:	Micro Bondapack C_{18} Reverse Phase, 3.9 x 300 mm, Waters Corp.
Detector:	Model Spectra 100, Spectra-Physics,UV/VIS

Parameters:

Flow Rate:	1.0 mL/min
Injection Vol:	20 µL
Temperature:	Ambient
Detector:	λ_{max} 237 nm, 0.01 AUFS

Solutions:

Mobile Phase:

In a suitable flask combine 200 mL of acetonitrile, 300 mL of methanol and 500 mL of distilled water. Mix well and degas under vacuum for 10 minutes. Filter through a 0.5 μ Millipore filter, or equivalent, before use.

3. REPRESENTATIVE CHROMATOGRAMS:

Figures 1 through 3 are the chromatograms of nifedipine samples after injection. Figures 4 and 5 are the chromatograms of nifedipine:pluronic® F-68 solid dispersion (1:1) samples after injection.

4. LINEARITY:

The linearity of nifedipine in the mobile phase was determined by simple linear regression. Figure 6 depicts the standard curve and linear regression of nifedipine in mobile phase.

The following concentrations were used for linearity determinations.

Solution #	Concentration in mobile phase (μg/mL)
1	1.0012
2	5.0024
3	10.0800
4	100.7600

Correlation coefficient for linearity determinations in mobile phase was 1.0000.

5. PRECISION:

Assay precision was determined by plotting the peak areas of triplicate injections of nifedipine samples of known concentration against the standard curves generated in the previous section. The mean % difference between the actual concentration of the samples and that determined by the standard curve were below 4.0 %.

Figure 1

Chromatogram of nifedipine solubility sample 1

```
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Report number.....0
Raw file.....PRDS2:[MEDCAK]AA060.RAW;1
Method file.....NAI$DIR:[NAI.SCRATCH]MIPEANALYSI97993.MET;2
Last method update..25-MAR-1997 18:19:40.13

Device.....Channel 52A,  Model 941 Serial Num:  1133513322
Reprocess number....2

Acq. date.....25-MAR-1997 17:47:10
Sample name.....pure drug-4
Notes.....

Analysis type.....EXTERNAL STANDARD   A/D range.....1.0 volt(s)
Report units.....mg/mL
Sample amount.....1.00000
Volume injected.....20.00000          Conversion factor...1.00000E+00
```

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peak name	R.T. (min)	T.Diff	mg/mL	Peak Area	Ref Std	BL	Group
	0.386			235		BV	
	0.716			283		VV	
	1.185			366		VB	
	1.403			791		BV	
	1.680			1740		VV	
	1.922			4753		VB	
	2.342			690		BB	
	2.920			924		BB	
	3.417			534		BB	
	5.073			219		BV	
	5.332			443		VB	
	5.726			300		BB	
	6.787			1689		BB	
	7.630			300		BB	
	8.150			334		BV	
	8.783			691		VB	
	9.465			154		BB	
	10.416			136		BB	
	11.635			4401		BB	
	12.970			245		BB	
	13.725			376		BB	
Nifedipine	15.156	26.61	1.191E-04	260738	S	BB	
	17.203			189		BV	
	17.601			309		VB	

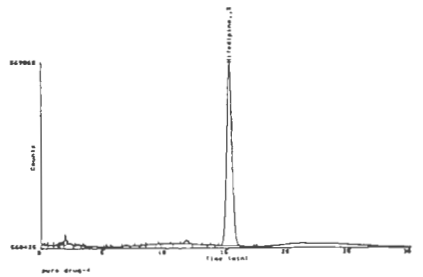

Figure 2

Chromatogram of nifedipine solubility sample 2

```
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Report number.......0
Raw file............PRD$2:[MEHTAK]AA059.RAW;1
Method file.........NAI$DIR:[NAI.SCRATCH]NIFEANALYSI13957.MET;2
Last method update..25-MAR-1997 17:48:59.77

Device..............Channel 52A,  Model 941 Serial Num:  1133513322
Reprocess number....3

Acq. date...........25-MAR-1997 17:16:25
Sample name.........pure drug-3
Notes...............

Analysis type.......EXTERNAL STANDARD   A/D range...........1.0 volt(s)
Report units........mg/mL
Sample amount.......1.00000
Volume injected.....20.00000            Conversion factor...1.00000E+00
```

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peak name	R.T.(min)	T.Diff	mg/mL	Peak Area	Ref Std	BL	Group
	0.939			119		BB	
	1.198			389		BV	
	1.394			1006		VV	
	1.666			1638		VV	
	1.923			5480		VV	
	2.289			2734		VV	
	2.834			939		VV	
	2.998			1056		VV	
	3.444			886		VB	
	4.164			270		BV	
	4.402			513		VB	
	5.711			288		BB	
	6.772			1960		BB	
	8.201			273		BB	
	10.805			263		BB	
	11.655			4897		BB	
	13.023			217		BB	
	13.745			227		BB	
Nifedipine	15.190	24.63	1.215E-04	265927	S	BB	
	16.561			111		BB	
	17.809			1289		BV	
	18.565			322		VB	
	19.634			157		BB	

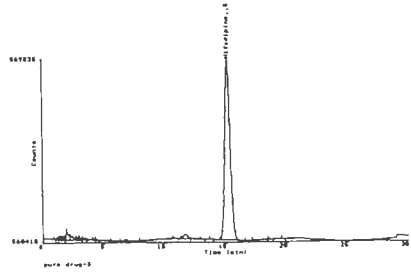

Figure 3

Chromatogram of nifedipine solubility sample 3

```
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Report number.....0
Raw file.....PRDS2:[MEHTAK]AA058.RAW;1
Method file.....NAISDIR:[NAI.SCRATCH]MTPEAANALYSIS4664.MET;2
Last method update..25-MAR-1997 17:39:06.82

Device.....Channel 52A,  Model 941 Serial Num:  1133513322
Reprocess number....2

Acq. date.....25-MAR-1997 16:45:40
Sample name.....pure drug-2
Notes.....

Analysis type.....EXTERNAL STANDARD   A/D range.....1.0 volt(s)
Report units.....mg/mL
Sample amount.....1.00000
Volume injected.....20.00000          Conversion factor...1.00000E+00
```

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peak name	R.T.(min)	T.Diff	mg/mL	Peak Area	Ref Std	BL	Group
	1.210			323		BB	
	1.392			806		BV	
	1.661			1666		VV	
	1.915			4744		VE	
	2.335			1448		EB	
	3.000			818		BB	
	3.461			380		BB	
	4.110			789		BV	
	4.366			512		VB	
	4.766			175		BB	
	5.248			167		BB	
	5.734			190		BB	
	6.798			1723		BB	
	7.305			200		BB	
	7.966			120		BB	
	9.063			377		BB	
	9.571			139		BB	
	10.238			160		BB	
	10.817			338		BB	
	11.684			5851		BB	
	12.567			127		BB	
	13.831			483		BB	
Nifedipine	15.234	21.96	1.185E-04	259309	S	BB	
	16.996			48		BB	
	17.445			310		BV	

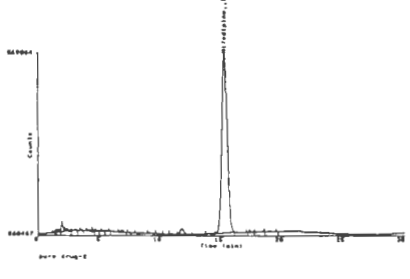


Figure 4

Chromatogram of nifedipine:pluronic® F-68 solubility sample 1.

```
Date.....19-MAR-1997 21:30:41.52
Report number.....0
Raw file.....PROG2:[MERIDAN]AA044.RAW;1
Method file.....NAISDIR:[NAI.SCRATCH]NIFEXANALYSI43566.MET;2
Last method update..19-MAR-1997 21:30:35.85

Device.....Channel 52A,  Model 941 Serial Num:  1133513322
Reprocess number....2

Acq. date.....19-MAR-1997 19:59:57
Sample name.....NPD-F68 dispersion
Notes.....

Analysis type.....EXTERNAL STANDARD   A/D range.....1.0 volt(s)
Report units.....mg/mL
Sample amount.....1.00000
Volume injected.....20.00000          Conversion factor...1.00000E+00
```

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peak name	R.T.(min)	T.Diff	mg/mL	Peak Area	Ref Std	BL	Group
	0.307			149		BB	
	1.221			537		BV	
	1.405			2533		VV	
	1.695			3282		VV	
	2.087			19294		VV	
	2.315			5882		VV	
	2.871			5217		VV	
	3.008			6634		VV	
	3.338			1445		VB	
	3.563			1760		BV	
	3.879			5030		VV	
	4.279			4451		VV	
	4.586			3709		VV	
	4.950			3639		VV	
	5.326			5466		VV	
	5.788			19549		VV	
	6.606			16163		VV	
	7.396			32731		VB	
	8.181			383		BB	
	8.815			181		BB	
	9.645			630		BB	
	10.461			1853		BV	
	10.953			10911		VV	
	11.817			381714		VB	
	12.655			2695		BB	
	13.947			276		BB	
Nifedipine	15.381	13.15	1.245E-03	2724882	S	BB	
	18.703			291		BV	
	19.152			352		VV	
	19.751			307		VB	

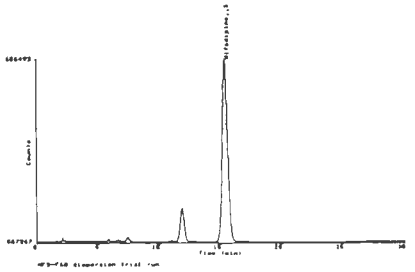


Figure 5

Chromatogram of nifedipine:pluronic® F-68 solubility sample 2.

```
Date.................19-MAR-1997 21:06:55.30
Report number.......0
Raw file.............PRDS2:[MEMCHAK]AA043.RAW;1
Method file.........NAISDIR:[NAI.SCRATCH]NIFEANALYSI95710.MET;2
Last method update..19-MAR-1997 21:05:57.28

Device..............Channel 52A,  Model 941 Serial Num:  11J3513122
Reprocess number....2

Acq. date...........19-MAR-1997 19:29:14
Sample name.........NFD-F68 Disp
Notes...............


Analysis type.......EXTERNAL STANDARD    A/D range...........1.0 volt(s)
Report units........mg/mL
Sample amount.......1.00000
Volume injected.....20.00000             Conversion factor...1.00000E+00
```

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peak name	R.T.(min)	T.Diff	mg/mL	Peak Area	Ref Std	BL	Group
	0.456			112		BB	
	1.221			394		BB	
	1.402			1702		BV	
	1.695			2360		VV	
	2.083			15024		VE	
	2.304			3630		BB	
	2.854			1928		BV	
	3.007			4787		VV	
	3.330			1088		VB	
	3.979			6229		BV	
	4.277			4897		VV	
	4.536			3529		VV	
	4.953			3597		VV	
	5.327			5725		VV	
	5.790			19276		VV	
	6.612			16299		VV	
	7.400			32684		VB	
	8.144			598		BV	
	8.541			330		VB	
	9.624			298		BB	
	10.471			1921		BV	
	10.957			11248		VV	
	11.844			381713		VE	
	12.615			3024		BB	
	14.041			363		BB	
Nifedipine	15.388	12.71	1.246E-03	2727360	S	BB	
	17.933			539		BB	
	18.557			279		BB	
	19.733			315		BB	

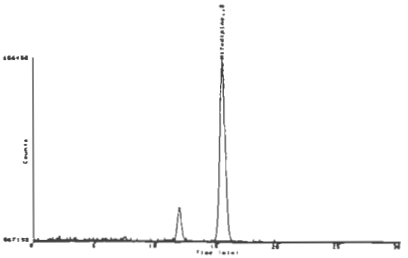
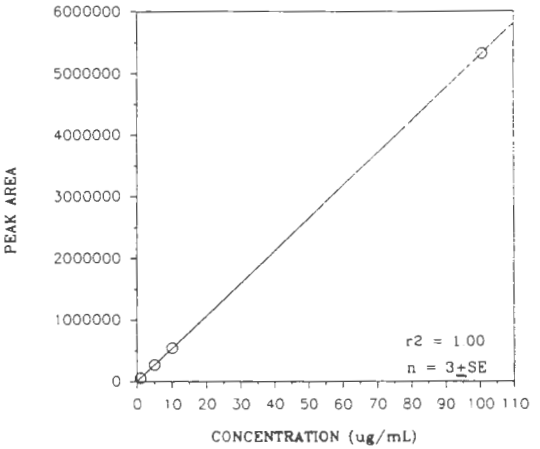


Figure 6

Standard curve of nifedipine in mobile phase

Y = 52774.56 X + 5475.077



Appendix 2

Particle size determination of nifedipine samples before and after micronization and after formation of solid dispersions with pluronic® F-68.

Figure 1

Particle size distribution of unmicronized nifedipine

Presentation: 2$$D
Polydisperse model

Volume Result

Focus = 100 mm

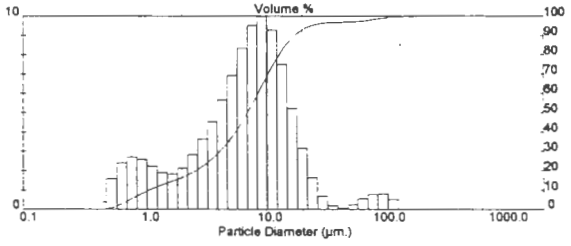
Residual = 0.198 %
d (0.5) = 7.06 µm
D [4,3] = 10.10 µm
Sauter Mean (D[3,2]) = 3.18 µm
Specific Surface Area = 1.8859 sq. m. / gm

Concentration = 0.007 %
d (0.1) = 1.07 µm
Span = 2.30

Obscuration = 13.89 %
d (0.9) = 17.29 µm

Mode = 9.16 µm
Density = 1.00 gm. / c c

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.40	0.48	0.40
0.48	1.58	0.59	1.98
0.59	2.38	0.71	4.37
0.71	2.70	0.86	7.06
0.86	2.58	1.04	9.64
1.04	2.23	1.26	11.87
1.26	1.90	1.52	13.78
1.52	1.82	1.84	15.60
1.84	2.13	2.23	17.72
2.23	2.84	2.70	20.56
2.70	3.64	3.27	24.20
3.27	4.53	3.95	28.72
3.95	5.67	4.79	34.39
4.79	6.92	5.79	41.31
5.79	8.35	7.01	49.66
7.01	9.52	8.48	59.18
8.48	9.99	10.27	69.18
10.27	9.28	12.43	78.46
12.43	7.52	15.05	85.98
15.05	5.22	18.21	91.20
18.21	3.16	22.04	94.36
22.04	1.65	26.68	96.00
26.68	0.70	32.29	96.70
32.29	0.21	39.08	96.92
39.08	0.10	47.30	97.02
47.30	0.27	57.25	97.28
57.25	0.56	69.30	97.84
69.30	0.79	83.87	98.64
83.87	0.83	101.52	99.47
101.52	0.53	122.87	100.00
122.87	0.00	148.72	100.00
148.72	0.00	180.00	100.00



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Serial No. 6376

Figure 2

Particle size distribution of once micronized nifedipine

Presentation: 2$$D
Polydisperse model

Volume Result

Focus = 45 mm

Residual = 0.172 %
d (0.5) = 2.87 µm
D [4, 3] = 4.53 µm
Sauter Mean (D[3,2]) = 1.96 µm
Specific Surface Area = 3.0683 sq. m. / gm

Concentration = 0.004 %
d (0.1) = 0.88 µm
Span = 2.73

Obscuration = 15.23 %
d (0.9) = 8.72 µm

Mode = 3.21 µm
Density = 1.00 gm. / c.c.

Size (Lo) µm	Result in %	Size (Hi) µm	Result Below %
0.05	0.00	0.12	0.00
0.12	0.00	0.15	0.00
0.15	0.00	0.19	0.00
0.19	0.00	0.23	0.00
0.23	0.00	0.28	0.00
0.28	0.25	0.35	0.25
0.35	0.72	0.43	0.97
0.43	1.40	0.53	2.37
0.53	2.31	0.65	4.68
0.65	3.49	0.81	8.17
0.81	4.76	1.00	12.93
1.00	5.82	1.23	18.76
1.23	6.50	1.51	25.25
1.51	7.29	1.86	32.54
1.86	8.16	2.30	40.70
2.30	8.71	2.83	49.41
2.83	9.02	3.49	58.43
3.49	8.86	4.30	67.29
4.30	8.21	5.29	75.50
5.29	7.10	6.52	82.60
6.52	5.64	8.04	88.24
8.04	4.07	9.91	92.31
9.91	2.67	12.21	94.97
12.21	1.59	15.04	96.56
15.04	0.89	18.54	97.45
18.54	0.50	22.84	97.95
22.84	0.35	28.15	98.30
28.15	0.54	34.69	98.84
34.69	0.48	42.75	99.32
42.75	0.37	52.68	99.69
52.68	0.22	64.92	99.91
64.92	0.09	80.00	100.00

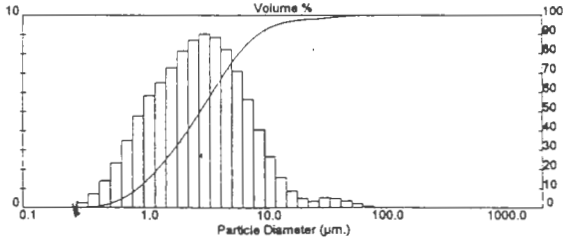

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Figure 3

Particle size distribution of twice micronized nifedipine

Presentation: 2$5D
Polydisperse model

Volume Result

Focus = 45 mm

Residual = 0.141 %
d (0.5) = 2.31 µm
D [4, 3] = 3.80 µm
Sauter Mean (D[3,2]) = 1.74 µm
Specific Surface Area = 3.4530 sq. m. / gm

Concentration = 0.004 %
d (0.1) = 0.83 µm
Span = 2.66

Obscuration = 13.63 %
d (0.9) = 6.96 µm

Mode = 2.41 µm
Density = 1.00 gm / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.05	0.00	0.12	0.00
0.12	0.00	0.15	0.00
0.15	0.00	0.19	0.00
0.19	0.00	0.23	0.00
0.23	0.00	0.28	0.00
0.28	0.08	0.35	0.08
0.35	0.61	0.43	0.69
0.43	1.45	0.53	2.14
0.53	2.68	0.65	4.83
0.65	4.42	0.81	9.24
0.81	6.39	1.00	15.63
1.00	7.88	1.23	23.52
1.23	8.40	1.51	31.91
1.51	8.82	1.86	40.73
1.86	9.12	2.30	49.85
2.30	8.94	2.83	58.79
2.83	8.66	3.49	67.45
3.49	8.08	4.30	75.53
4.30	7.14	5.29	82.67
5.29	5.83	6.52	88.50
6.52	4.26	8.04	92.76
8.04	2.75	9.91	95.51
9.91	1.59	12.21	97.09
12.21	0.81	15.04	97.90
15.04	0.37	18.54	98.27
18.54	0.18	22.84	98.44
22.84	0.17	28.15	98.62
28.15	0.26	34.69	98.87
34.69	0.32	42.75	99.19
42.75	0.32	52.68	99.51
52.68	0.27	64.92	99.79
64.92	0.21	80.00	100.00

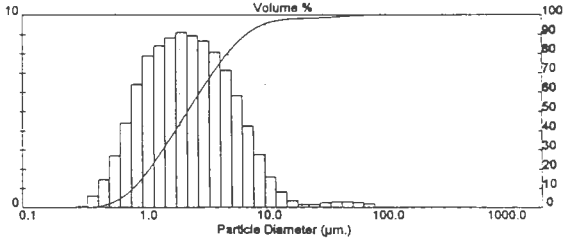

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Figure 4

Particle size distribution of nifedipine:pluronic® F-68 solid dispersion (1:1).

Presentation: 2$$D
Polydisperse model

Volume Result

Focus = 100 mm.

Residual = 0.171 %
d (0.5) = 3.10 µm
D [4, 3] = 7.26 µm
Sauter Mean (D[3,2]) = 2.29 µm
Specific Surface Area = 2.6226 sq. m. / gm

Concentration = 0.008 %
d (0.1) = 1.02 µm
Span = 3.84

Obscuration = 21.29 %
d (0.9) = 12.93 µm

Mode = 3.00 µm
Density = 1.00 gm. / c.c

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %	Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.09	0.48	0.09	8.48	2.35	10.27	88.05
0.48	1.28	0.59	1.37	10.27	1.66	12.43	89.71
0.59	2.29	0.71	3.66	12.43	1.26	15.05	90.97
0.71	3.09	0.86	6.75	15.05	1.06	18.21	92.03
0.86	3.71	1.04	10.45	18.21	0.98	22.04	93.00
1.04	4.21	1.26	14.66	22.04	0.94	26.68	93.94
1.26	4.79	1.52	19.46	26.68	0.91	32.29	94.86
1.52	5.79	1.84	25.25	32.29	0.89	39.08	95.75
1.84	7.57	2.23	32.82	39.08	0.86	47.30	96.60
2.23	9.68	2.70	42.50	47.30	0.83	57.25	97.43
2.70	10.39	3.27	52.89	57.25	0.80	69.30	98.23
3.27	9.77	3.95	62.65	69.30	0.75	83.87	98.98
3.95	8.37	4.79	71.03	83.87	0.66	101.52	99.64
4.79	6.51	5.79	77.54	101.52	0.36	122.87	100.00
5.79	4.79	7.01	82.33	122.87	0.00	148.72	100.00
7.01	3.38	8.48	85.70	148.72	0.00	180.00	100.00

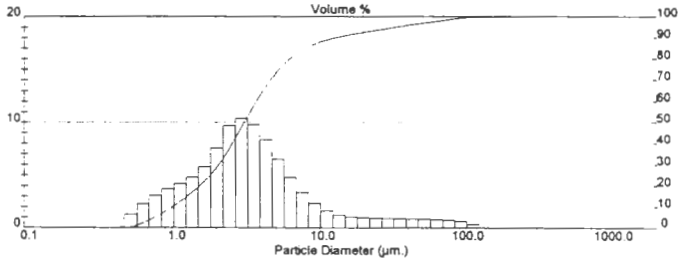

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Figure 5

Particle size distribution of nifedipine:pluronic® F-68 solid dispersion (1:0.5).

Presentation: 2330
Polydisperse model

Volume Result

Focus = 100 mm

Residual = 0.148 %
d (0.5) = 2.66 µm
D [4, 3] = 4.64 µm
Sauter Mean (D[3,2]) = 1.82 µm
Specific Surface Area = 3.2941 sq. m. / gm

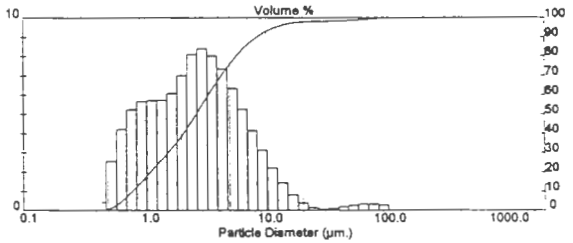
Concentration = 0.004 %
d (0.1) = 0.79 µm
Span = 2.86

Obscuration = 16.29 %
d (0.9) = 8.40 µm

Mode = 2.88 µm
Density = 1.00 gm / c c

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.42	0.48	0.42
0.48	2.56	0.59	2.98
0.59	4.20	0.71	7.18
0.71	5.23	0.86	12.40
0.86	5.66	1.04	18.06
1.04	5.72	1.26	23.78
1.26	5.73	1.52	29.51
1.52	6.09	1.84	35.60
1.84	7.01	2.23	42.61
2.23	8.10	2.70	50.71
2.70	8.38	3.27	59.09
3.27	8.02	3.95	67.11
3.95	7.34	4.79	74.45
4.79	6.33	5.79	80.79
5.79	5.25	7.01	86.04
7.01	4.15	8.48	90.18

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
8.48	3.13	10.27	93.31
10.27	2.21	12.43	95.52
12.43	1.43	15.05	96.96
15.05	0.81	18.21	97.77
18.21	0.39	22.04	98.16
22.04	0.16	26.68	98.32
26.68	0.08	32.29	98.40
32.29	0.11	39.08	98.51
39.08	0.19	47.30	98.71
47.30	0.28	57.25	98.99
57.25	0.34	69.30	99.32
69.30	0.35	83.87	99.67
83.87	0.28	101.52	99.95
101.52	0.05	122.87	100.00
122.87	0.00	148.72	100.00
148.72	0.00	180.00	100.00



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Serial No. 6376

Appendix 3a

Determination of porosity parameters by mercury intrusion porosimetry. Pellets formulated with different drug (D_4 Leukotriene antagonist) loads and spheronized at different times.

Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

```
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SAMPLE DIRECTORY/NUMBER: DATA1   /66
OPERATOR: Ketan Mehta                                  LP  03:43:48 02/25/97
SAMPLE ID: Placebo2mm2minRUN#1                         HP  04:54:34 02/25/97
SUBMITTER: Ketan Mehta                                 REP 04:54:34 02/25/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9270 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4022 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.8710 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7903 psia
      LAST LOW PRESSURE POINT: 25.5791 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.4009 mL/g
                     TOTAL PORE AREA =     36.076 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0469 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0353 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0444 µm
                        BULK DENSITY =      0.8472 g/mL
             APPARENT (SKELETAL) DENSITY =  1.2828 g/mL
                             POROSITY =     33.96 %
                   STEM VOLUME USED =         39 %
```

Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

SAMPLE DIRECTORY/NUMBER: DATA1 /67
OPERATOR: Ketan Mehta LP 06:35:38 02/25/97
SAMPLE ID: Placebo2mm2minRUN#2 HP 07:18:23 02/25/97
SUBMITTER: Ketan Mehta REP 23:07:41 02/25/97

PENETROMETER NUMBER:	13-0868	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.4592 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4025 g
PENETROMETER VOLUME:	3.6991 mL	SAMPLE+PEN+Hg WEIGHT:	112.6135 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 1.0065 psia
LAST LOW PRESSURE POINT: 25.5541 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3944 mL/g
TOTAL PORE AREA =	35.841 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0463 µm
MEDIAN PORE DIAMETER (AREA) =	0.0349 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0440 µm
BULK DENSITY =	0.8633 g/mL
APPARENT (SKELETAL) DENSITY =	1.3089 g/mL
POROSITY =	34.04 %
STEM VOLUME USED =	39 %

Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /6M
OPERATOR: Ketan Mehta                                  LP  06:35:38 02/25/97
SAMPLE ID: Placebo2mm2minRUN#3                         HP  23:49:16 02/25/97
SUBMITTER: Ketan Mehta                                 REP 23:49:17 02/25/97


PENETROMETER NUMBER: 13-0854          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   69.0085 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4005 g
PENETROMETER VOLUME:   3.5541 mL      SAMPLE+PEN+Hg WEIGHT: 111.1867 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  1.0065 psia
      LAST LOW PRESSURE POINT: 25.5541 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3970 mL/g
                TOTAL PORE AREA =    35.552 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0461 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0359 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0447 µm
                    BULK DENSITY =    0.8574 g/mL
     APPARENT (SKELETAL) DENSITY =    1.2998 g/mL
                       POROSITY =     34.04 %
              STEM VOLUME USED =        39 %
```

Drug Load: 0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /69
OPERATOR: Ketan Mehta
SAMPLE ID: Placebo2mm10minRUN#1
SUBMITTER: Ketan Mehta

LP 04:05:15 02/26/97
HP 04:43:20 02/26/97
REP 04:43:21 02/26/97

PENETROMETER NUMBER: 13-0131
PENETROMETER CONSTANT: 10.79 pL/pF
PENETROMETER WEIGHT: 68.0844 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5885 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.4016 g
SAMPLE+PEN+Hg WEIGHT: 111.4668 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7772 psia
LAST LOW PRESSURE POINT: 25.5592 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3825 mL/g
TOTAL PORE AREA =	40.193 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0378 µm
MEDIAN PORE DIAMETER (AREA) =	0.0314 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0381 µm
BULK DENSITY =	0.9733 g/mL
APPARENT (SKELETAL) DENSITY =	1.5505 g/mL
POROSITY =	37.23 %
STEM VOLUME USED =	37 %

Drug Load: 0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

SAMPLE DIRECTORY/NUMBER: DATA1 /70
OPERATOR: Ketan mehta LP 04:05:15 02/26/97
SAMPLE ID: Placebo2mm10minRUN#2 HP 06:19:40 02/26/97
SUBMITTER: Ketan Mehta REP 06:19:41 02/26/97

PENETROMETER NUMBER:	13-0241	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.3061 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4026 g
PENETROMETER VOLUME:	3.5443 mL	SAMPLE+PEN+Hg WEIGHT:	110.2952 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7772 psia
LAST LOW PRESSURE POINT: 25.5592 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3791 mL/g
TOTAL PORE AREA =	39.202 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0390 µm
MEDIAN PORE DIAMETER (AREA) =	0.0317 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0387 µm
BULK DENSITY =	0.8540 g/mL
APPARENT (SKELETAL) DENSITY =	1.2627 g/mL
POROSITY =	32.37 %
STEM VOLUME USED =	37 %

Drug Load: 0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

POREsIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /71
OPERATOR: Ketan Mehta
SAMPLE ID: Placebo2mm10minRUN3
SUBMITTER: Ketan Mehta

LP 00:33:56 03/03/97
HP 01:11:45 03/03/97
REP 01:11:46 03/03/97

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.8073 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4005 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	111.1313 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7640 psia
LAST LOW PRESSURE POINT: 25.6757 psia

HIGH PRESSURE:

RUN TYPE:	AUTOMATIC
RUN METHOD:	EQUILIBRATED
EQUILIBRATION TIME:	10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3843 mL/g
TOTAL PORE AREA =	40.188 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0385 µm
MEDIAN PORE DIAMETER (AREA) =	0.0311 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0382 µm
BULK DENSITY =	0.9608 g/mL
APPARENT (SKELETAL) DENSITY =	1.5231 g/mL
POROSITY =	36.92 %
STEM VOLUME USED =	37 %

Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

SAMPLE DIRECTORY/NUMBER: DATA1 /72
OPERATOR: Ketan Mehta
SAMPLE ID: Placebo2mm20minRUN1
SUBMITTER: Ketan Mehta

LP 00:33:56 03/03/97
HP 03:01:05 03/03/97
REP 03:01:06 03/03/97

PENETROMETER NUMBER:	13-0868	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.9255 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4000 g
PENETROMETER VOLUME:	3.6991 mL	SAMPLE+PEN+Hg WEIGHT:	113.1216 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7640 psia
LAST LOW PRESSURE POINT: 25.6757 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3804 mL/g
TOTAL PORE AREA =	39.534 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0386 µm
MEDIAN PORE DIAMETER (AREA) =	0.0315 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0385 µm
BULK DENSITY =	0.8640 g/mL
APPARENT (SKELETAL) DENSITY =	1.2870 g/mL
POROSITY =	32.87 %
STEM VOLUME USED =	37 %

Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /73
OPERATOR: Ketan Mehta                                LP  05:00:46 03/03/97
SAMPLE ID: Placebo2mm20minRUN2                       HP  05:39:49 03/03/97
SUBMITTER: Ketan Mehta                               REP 05:39:49 03/03/97

PENETROMETER NUMBER: 13-0854          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.8376 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4000 g
PENETROMETER VOLUME:    3.5541 mL     SAMPLE+PEN+Hg WEIGHT: 111.0813 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7587 psia
      LAST LOW PRESSURE POINT: 25.5611 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =   0.3831 mL/g
                     TOTAL PORE AREA =    42.211 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0328 µm
             MEDIAN PORE DIAMETER (AREA) =  0.0354 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0363 µm
                        BULK DENSITY =      0.8654 g/mL
            APPARENT (SKELETAL) DENSITY =   1.2945 g/mL
                          POROSITY =       33.15 %
                    STEM VOLUME USED =       37 %
```

Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /74
OPERATOR: Ketan Mehta                                  LP  05:00:46 03/03/97
SAMPLE ID: Placebo2mm20minRUN#3                        HP  06:58:55 03/03/97
SUBMITTER: Ketan Mehta                                 REP 07:06:47 03/03/97

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.6054 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4012 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.7314 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7587 psia
      LAST LOW PRESSURE POINT: 25.1611 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =   0.3700 mL/g
                     TOTAL PORE AREA =    39.224 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  0.0363 µm
            MEDIAN PORE DIAMETER (AREA) =  0.0331 µm
           AVERAGE PORE DIAMETER (4V/A) =  0.0377 µm
                          BULK DENSITY =   0.8699 g/mL
            APPARENT (SKELETAL) DENSITY =  1.2827 g/mL
                                POROSITY =  32.19 %
                     STEM VOLUME USED =     36 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /13
OPERATOR: ketan                                    LP  05:46:40 11/19/96
SAMPLE ID: 5%2mm2minRUN1                           HP  06:37:45 11/19/96
SUBMITTER: ketan                                   REP 06:37:46 11/19/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.6593 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4027 g
PENETROMETER VOLUME:   3.6417 mL      SAMPLE+PEN+Hg WEIGHT: 111.7730 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5788 psia
      LAST LOW PRESSURE POINT: 26.0516 psia

HIGH PRESSURE:
      RUN TYPE:                AUTOMATIC
      RUN METHOD:              EQUILIBRATED
      EQUILIBRATION TIME:        10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =   0.4236 mL/g
              TOTAL PORE AREA =     39.832 sq-m/g
    MEDIAN PORE DIAMETER (VOLUME) =  0.0491 µm
      MEDIAN PORE DIAMETER (AREA) =  0.0412 µm
    AVERAGE PORE DIAMETER (4V/A) =   0.0425 µm
                BULK DENSITY =       0.8290 g/mL
     APPARENT (SKELETAL) DENSITY =   1.2777 g/mL
                    POROSITY =      35.12 %
              STEM VOLUME USED =      41 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /14
OPERATOR: ketan mehta                                LP  05:46:40 11/19/96
SAMPLE ID: 5%2mm2minRUN2                             HP  07:22:23 11/19/96
SUBMITTER: ketan mehta                               REP 07:22:24 11/19/96

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.0493 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4018 g
PENETROMETER VOLUME:    3.5443 mL     SAMPLE+PEN+Hg WEIGHT: 109.8508 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.3788 psia
      LAST LOW PRESSURE POINT: 26.0516 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.4200 mL/g
                TOTAL PORE AREA =    40.291 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =   0.0491 µm
       MEDIAN PORE DIAMETER (AREA) =   0.0408 µm
     AVERAGE PORE DIAMETER (4V/A) =    0.0417 µm
                BULK DENSITY =    0.8280 g/mL
      APPARENT (SKELETAL) DENSITY =   1.2695 g/mL
                    POROSITY =     34.78 %
           STEM VOLUME USED =        41 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /15
OPERATOR: ketan mehta                                LP  06:39:20 11/24/96
SAMPLE ID: 5%2min2mmRUN3                             HP  07:23:51 11/24/96
SUBMITTER: ketan mehta                               REP 07:23:51 11/24/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.7045 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5315 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4023 g
PENETROMETER VOLUME:    3.5898 mL     SAMPLE+PEN+Hg WEIGHT: 111.8360 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7297 psia
      LAST LOW PRESSURE POINT: 25.9681 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.6209 mL/g
              TOTAL PORE AREA =      40.245 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0490 µm
      MEDIAN PORE DIAMETER (AREA) =   0.0412 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0618 µm
                BULK DENSITY =       0.9312 g/mL
      APPARENT (SKELETAL) DENSITY =  1.5312 g/mL
                  POROSITY =        39.19 %
            STEM VOLUME USED =        41 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /16
OPERATOR: ketan mehta
SAMPLE ID: 5%10min2mmRUN1
SUBMITTER: ketan mehta

LP 06:39:20 11/24/96
HP 08:08:05 11/24/96
REP 08:08:05 11/24/96

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79 µL/pF
PENETROMETER WEIGHT: 68.0809 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5469 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5315 g/mL
SAMPLE WEIGHT: 0.4016 g
SAMPLE+PEN+Hg WEIGHT: 110.0900 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7297 psia
LAST LOW PRESSURE POINT: 25.9681 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3955 mL/g
TOTAL PORE AREA =	41.577 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0420 µm
MEDIAN PORE DIAMETER (AREA) =	0.0356 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0380 µm
BULK DENSITY =	0.8508 g/mL
APPARENT (SKELETAL) DENSITY =	1.2821 g/mL
POROSITY =	33.64 %
STEM VOLUME USED =	39 %

Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /17
OPERATOR: ketan mehta                                  LP  10:47:16 11/24/96
SAMPLE ID: 5%10min2mmRUN2                              HP  11:37:03 11/24/96
SUBMITTER: ketan mehta                                 REP 11:37:04 11/24/96


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE:  130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.4074 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:          13.5315 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:             0.4026 g
PENETROMETER VOLUME:   3.5885 mL      SAMPLE+PEN+Hg WEIGHT: 111.5960 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7073 psia
      LAST LOW PRESSURE POINT: 25.8337 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                    INTRUSION DATA SUMMARY

              TOTAL INTRUSION VOLUME =    0.4041 mL/g
                   TOTAL PORE AREA =     43.531 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  0.0398 µm
            MEDIAN PORE DIAMETER (AREA) =  0.0351 µm
           AVERAGE PORE DIAMETER (4V/A) =  0.0371 µm
                        BULK DENSITY =     0.9439 g/mL
            APPARENT (SKELETAL) DENSITY =  1.5259 g/mL
                          POROSITY =       38.15 %
                   STEM VOLUME USED =        39 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

```
PORESIZER 9320 v2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /18
OPERATOR: ketan mehta                                  LP  10:47:16 11/24/96
SAMPLE ID: 5%10min2ndRUN3                              HP  12:22:24 11/24/96
SUBMITTER: ketan mehta                                 REP 12:22:25 11/24/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    67.8850 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5315 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4010 g
PENETROMETER VOLUME:    3.5469 mL     SAMPLE+PEN+Hg WEIGHT: 109.8288 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7073 psia
      LAST LOW PRESSURE POINT: 25.8337 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:       10 seconds


                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3973 mL/g
               TOTAL PORE AREA =     42.097 sq-m/g
  MEDIAN PORE DIAMETER (VOLUME) =     0.0406 µm
    MEDIAN PORE DIAMETER (AREA) =     0.0353 µm
 AVERAGE PORE DIAMETER (4V/A) =       0.0378 µm
                BULK DENSITY =       0.8410 g/mL
 APPARENT (SKELETAL) DENSITY =       1.2630 g/mL
                    POROSITY =       33.41 %
          STEM VOLUME USED =           39 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /19
OPERATOR: Ketan Mehta LP 03:52:07 11/25/96
SAMPLE ID: 5%20min2mmRUN1 HP 04:39:35 11/25/96
SUBMITTER: Ketan Mehta REP 04:39:36 11/25/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.9063 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4007 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	111.2415 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7293 psia
LAST LOW PRESSURE POINT: 26.1014 psia

HIGH PRESSURE:

RUN TYPE:	AUTOMATIC
RUN METHOD:	EQUILIBRATED
EQUILIBRATION TIME:	10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3860 mL/g
TOTAL PORE AREA =	39.525 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0439 µm
MEDIAN PORE DIAMETER (AREA) =	0.0364 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0391 µm
BULK DENSITY =	0.9616 g/mL
APPARENT (SKELETAL) DENSITY =	1.5290 g/mL
POROSITY =	37.11 %
STEM VOLUME USED =	38 %

Drug Load: 5.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
POREsIZER 9320 v2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /20
OPERATOR: Ketan Mehta                                  LP  03:52:07 11/25/96
SAMPLE ID: 5%20min2mmRUN2                              HP  05:31:23 11/25/96
SUBMITTER: Ketan Mehta                                 REP 05:31:24 11/25/96

PENETROMETER NUMBER: 13.0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.3124 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4011 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.3415 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7293 psia
      LAST LOW PRESSURE POINT: 26.1014 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3852 mL/g
              TOTAL PORE AREA =      39.498 sq-m/g
    MEDIAN PORE DIAMETER (VOLUME) =   0.0438 µm
     MEDIAN PORE DIAMETER (AREA) =    0.0363 µm
   AVERAGE PORE DIAMETER (4V/A) =     0.0390 µm
              BULK DENSITY =          0.8552 g/mL
     APPARENT (SKELETAL) DENSITY =    1.2752 g/mL
                  POROSITY =          32.94 %
          STEM VOLUME USED =             38 %
```

Drug Load: 5.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

```
POREsIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /21
OPERATOR: Ketan Mehta                                  LP  08:18:22 11/25/96
SAMPLE ID: 5%20min2mmRUN3                              HP  11:12:33 11/25/96
SUBMITTER: Ketan Mehta                                 REP 11:12:34 11/25/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.1909 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4008 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.0498 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7443 psia
      LAST LOW PRESSURE POINT: 26.0932 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3862 mL/g
                      TOTAL PORE AREA =    39.090 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0450 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0372 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0395 µm
                          BULK DENSITY =    0.8322 g/mL
            APPARENT (SKELETAL) DENSITY =   1.2265 g/mL
                               POROSITY =     32.14 %
                     STEM VOLUME USED =        38 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /22
OPERATOR: Ketan Mehta
SAMPLE ID: 10%2min2mmRUN1
SUBMITTER: Ketan Mehta

LP 08:18:22 11/25/96
HP 11:59:57 11/25/96
REP 11:59:57 11/25/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.6221 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4011 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	111.6325 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7443 psia
LAST LOW PRESSURE POINT: 26.0932 psia

HIGH PRESSURE:

RUN TYPE:	AUTOMATIC
RUN METHOD:	EQUILIBRATED
EQUILIBRATION TIME:	10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4403 mL/g
TOTAL PORE AREA =	37.712 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0608 µm
MEDIAN PORE DIAMETER (AREA) =	0.0412 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0467 µm
BULK DENSITY =	0.9101 g/mL
APPARENT (SKELETAL) DENSITY =	1.5184 g/mL
POROSITY =	40.07 %
STEM VOLUME USED =	43 %

Drug Load: 10.0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /23
OPERATOR: Ketan Mehta                                  LP  00:27:56 11/26/96
SAMPLE ID: 10%2min2mmRUN2                              HP  01:11:18 11/26/96
SUBMITTER: Ketan Mehta                                 REP 01:11:19 11/26/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    67.8749 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4001 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 110.9875 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.0310 psia
      LAST LOW PRESSURE POINT: 25.8919 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:       10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.4355 mL/g
                TOTAL PORE AREA =    37.098 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0606 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0410 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0470 µm
                BULK DENSITY =       0.9238 g/mL
      APPARENT (SKELETAL) DENSITY =  1.5456 g/mL
                POROSITY =           40.23 %
          STEM VOLUME USED =         42 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

```
POREsIZER 9320 v2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /24
OPERATOR: Ketan Mehta                                  LP  00:27:56 11/26/96
SAMPLE ID: 10%2min2mmRUN3                              HP  01:53:08 11/26/96
SUBMITTER: Ketan Mehta                                 REP 01:53:09 11/26/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9173 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5364 g/mL
MAXIMUM HEAD PRESSURE. 4.6800 psi     SAMPLE WEIGHT:          0.4003 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.6957 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6510 psia
      LAST LOW PRESSURE POINT: 25.8919 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.4355 mL/g
                     TOTAL PORE AREA =     37.260 sq-m/g
            MEDIAN PORE DIAMETER (VOLUME) =  0.0607 µm
              MEDIAN PORE DIAMETER (AREA) =  0.0409 µm
            AVERAGE PORE DIAMETER (4V/A) =   0.0468 µm
                          BULK DENSITY =     0.8211 g/mL
             APPARENT (SKELETAL) DENSITY =   1.2783 g/mL
                               POROSITY =    35.76 %
                     STEM VOLUME USED =        42 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /25
OPERATOR: Ketan Mehta LP 04:56:43 11/26/96
SAMPLE ID: 10%10min2mmRUN1 HP 05:39:15 11/26/96
SUBMITTER: Ketan Mehta REP 05:39:15 11/26/96

PENETROMETER NUMBER: 13-0131 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pF RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 67.9940 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL MERCURY DENSITY: 13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.4012 g
PENETROMETER VOLUME: 3.5885 mL SAMPLE+PEN+Hg WEIGHT: 111.1876 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7328 psia
LAST LOW PRESSURE POINT: 25.9104 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4189 mL/g
TOTAL PORE AREA =	38.994 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0484 µm
MEDIAN PORE DIAMETER (AREA) =	0.0428 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0430 µm
BULK DENSITY =	0.9391 g/mL
APPARENT (SKELETAL) DENSITY =	1.5480 g/mL
POROSITY =	39.33 %
STEM VOLUME USED =	41 %

Drug Load: 10.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /2C
OPERATOR: Ketan Mehta                                LP  04:56:43 11/26/96
SAMPLE ID: 10%10min2mmRUN2                           HP  06:18:09 11/26/96
SUBMITTER: Ketan Mehta                               REP 06:18:10 11/26/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.7230 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4020 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.5390 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7328 psia
      LAST LOW PRESSURE POINT: 25.9104 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.4185 mL/g
                TOTAL PORE AREA =    39.416 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0482 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0429 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0425 µm
                BULK DENSITY =       0.8291 g/mL
     APPARENT (SKELETAL) DENSITY =   1.2697 g/mL
                POROSITY =           34.70 %
           STEM VOLUME USED =          41 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /27
OPERATOR: ketan mehta                                  LP  03:09:15 12/02/96
SAMPLE ID: 10%10min2mmRUN3                             HP  03:53:27 12/02/96
SUBMITTER: ketan mehta                                 REP 03:53:28 12/02/96

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 uL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.0972 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5413 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4026 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 109.9800 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6790 psia
      LAST LOW PRESSURE POINT: 25.9079 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

              TOTAL INTRUSION VOLUME =    0.4170 mL/g
                    TOTAL PORE AREA =    39.553 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  0.0481 um
            MEDIAN PORE DIAMETER (AREA) =  0.0422 um
          AVERAGE PORE DIAMETER (4V/A) =   0.0422 um
                       BULK DENSITY =     0.8369 g/mL
          APPARENT (SKELETAL) DENSITY =   1.2855 g/mL
                         POROSITY =       34.90 %
                  STEM VOLUME USED =        41 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /28
OPERATOR: ketan mehta
SAMPLE ID: 10%20min2mmRUN1
SUBMITTER: ketan mehta

LP 03:09:15 12/02/96
HP 04:41:16 12/02/96
REP 04:41:17 12/02/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.6338 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5413 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4025 g
PENETROMETER VOLUME:	3.6417 mL	SAMPLE+PEN+Hg WEIGHT:	111.8144 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6790 psia
LAST LOW PRESSURE POINT: 25.9979 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4094 mL/g
TOTAL PORE AREA =	38.662 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0481 µm
MEDIAN PORE DIAMETER (AREA) =	0.0426 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0424 µm
BULK DENSITY =	0.8340 g/mL
APPARENT (SKELETAL) DENSITY =	1.2664 g/mL
POROSITY =	34.14 %
STEM VOLUME USED =	40 %

Drug Load: 10.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /29
OPERATOR: ketan mehta                                  LP  06:49:22 12/02/96
SAMPLE ID: 10%20min2mmRUN2                             HP  07:35:44 12/02/96
SUBMITTER: ketan mehta                                 REP 09:19:21 12/02/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    67.6550 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5413 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4010 g
PENETROMETER VOLUME:    3.6417 mL     SAMPLE+PEN+Hg WEIGHT: 110.8876 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7958 psia
      LAST LOW PRESSURE POINT: 25.8911 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:       10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.4059 mL/g
                TOTAL PORE AREA =    38.266 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0483 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0426 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0424 µm
                    BULK DENSITY =    0.8377 g/mL
     APPARENT (SKELETAL) DENSITY =    1.2695 g/mL
                        POROSITY =    34.01 %
              STEM VOLUME USED =        40 %
```

Drug Load: 10.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /30
OPERATOR: ketan mehta
SAMPLE ID: 10%20min2mmRUN3
SUBMITTER: ketan mehta

LP 06:49:22 12/02/96
HP 10:00:45 12/02/96
REP 10:00:46 12/02/96

PENETROMETER NUMBER:	13-0241	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	69.1096 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5413 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4022 g
PENETROMETER VOLUME:	3.5443 mL	SAMPLE+PEN+Hg WEIGHT:	110.8080 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7958 psia
LAST LOW PRESSURE POINT: 25.8911 psia

HIGH PRESSURE:

RUN TYPE:	AUTOMATIC
RUN METHOD:	EQUILIBRATED
EQUILIBRATION TIME:	10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4056 mL/g
TOTAL PORE AREA =	38.603 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0480 µm
MEDIAN PORE DIAMETER (AREA) =	0.0427 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0420 µm
BULK DENSITY =	0.8131 g/mL
APPARENT (SKELETAL) DENSITY =	1.2131 g/mL
POROSITY =	32.98 %
STEM VOLUME USED =	40 %

Drug Load: 20.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /31
OPERATOR: Ketan Mehta                                  LP  05:23:46 12/03/96
SAMPLE ID: 20%2min2mmRUN1                              HP  06:08:29 12/03/96
SUBMITTER: Ketan Mehta                                 REP 06:08:30 12/03/96

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.8036 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4022 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 109.8128 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5768 psia
      LAST LOW PRESSURE POINT: 26.0094 psia

HIGH PRESSURE:
      RUN TYPE:                  AUTOMATIC
      RUN METHOD:                EQUILIBRATED
      EQUILIBRATION TIME:        10 seconds

                    INTRUSION DATA SUMMARY

            TOTAL INTRUSION VOLUME =    0.3814 mL/g
                  TOTAL PORE AREA =    32.887 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =    0.0580 µm
       MEDIAN PORE DIAMETER (AREA) =    0.0414 µm
    AVERAGE PORE DIAMETER (4V/A) =      0.0464 µm
                  BULK DENSITY =       0.8547 g/mL
     APPARENT (SKELETAL) DENSITY =     1.2679 g/mL
                       POROSITY =      32.59 %
              STEM VOLUME USED =         37 %
```

Drug Load: 20.0 % w/w, Spheronization Time: 2.0 minute.

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /32
OPERATOR: Ketan Mehta                                  LP  05:23:46 12/03/96
SAMPLE ID: 20%2min2mmRUN2                              HP  06:49:20 12/03/96
SUBMITTER: Ketan Mehta                                 REP 06:49:21 12/03/96


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.7225 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4018 g
PENETROMETER VOLUME:   3.5885 mL      SAMPLE+PEN+Hg WEIGHT: 112.0378 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5768 psia
      LAST LOW PRESSURE POINT: 26.0094 psia

HIGH PRESSURE:
      RUN TYPE:                  AUTOMATIC
      RUN METHOD:                EQUILIBRATED
      EQUILIBRATION TIME:           10 seconds


                        INTRUSION DATA SUMMARY

                  TOTAL INTRUSION VOLUME =    0.3835 mL/g
                        TOTAL PORE AREA =    33.729 sq-m/g
              MEDIAN PORE DIAMETER (VOLUME) =  0.0545 µm
                MEDIAN PORE DIAMETER (AREA) =  0.0420 µm
               AVERAGE PORE DIAMETER (4V/A) =  0.0455 µm
                           BULK DENSITY =     0.9606 g/mL
                 APPARENT (SKELETAL) DENSITY =  1.5210 g/mL
                                POROSITY =     36.84 %
                          STEM VOLUME USED =     37 %
```

Drug Load: 20.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

SAMPLE DIRECTORY/NUMBER: DATA1 /33
OPERATOR: Ketan Mehta
SAMPLE ID: 20%2min2mmRUN3
SUBMITTER: Ketan Mehta

LP 01:27:16 12/09/96
HP 02:09:50 12/09/96
REP 02:09:51 12/09/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.1041 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4015 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	111.2028 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6823 psia
LAST LOW PRESSURE POINT: 25.7469 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3825 mL/g
TOTAL PORE AREA =	33.843 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0558 µm
MEDIAN PORE DIAMETER (AREA) =	0.0412 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0452 µm
BULK DENSITY =	0.9246 g/mL
APPARENT (SKELETAL) DENSITY =	1.4304 g/mL
POROSITY =	35.36 %
STEM VOLUME USED =	37 %

Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /34
OPERATOR: Ketan Mehta                                LP  07:27:16 12/09/96
SAMPLE ID: 20%10min2mmRUN1                           HP  03:23:38 12/09/96
SUBMITTER: Ketan Mehta                               REP 03:23:39 12/09/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.6317 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4031 g
PENETROMETER VOLUME:    3.5443 mL     SAMPLE+PEN+Hg WEIGHT: 110.7447 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6823 psia
      LAST LOW PRESSURE POINT: 25.7469 psia

HIGH PRESSURE:
      RUN TYPE:                  AUTOMATIC
      RUN METHOD:                EQUILIBRATED
      EQUILIBRATION TIME:        10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3522 mL/g
                     TOTAL PORE AREA =     33.215 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0497 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0419 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0424 µm
                        BULK DENSITY =      0.8707 g/mL
           APPARENT (SKELETAL) DENSITY =    1.2557 g/mL
                              POROSITY =    30.66 %
                    STEM VOLUME USED =      34 %
```

Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /35
OPERATOR: Ketan Mehta LP 05:47:56 12/09/96
SAMPLE ID: 20%10min2mmRUN2 HP 06:32:51 12/09/96
SUBMITTER: Ketan Mehta REP 06:57:21 12/09/96

PENETROMETER NUMBER: 13-0131 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pF RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 68.1160 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL MERCURY DENSITY: 13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.4023 g
PENETROMETER VOLUME: 3.5885 mL SAMPLE+PEN+Hg WEIGHT: 111.6330 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6992 psia
LAST LOW PRESSURE POINT: 25.7719 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3551 mL/g
TOTAL PORE AREA = 33.578 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0496 µm
MEDIAN PORE DIAMETER (AREA) = 0.0419 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0423 µm
BULK DENSITY = 0.9973 g/mL
APPARENT (SKELETAL) DENSITY = 1.5440 g/mL
POROSITY = 35.41 %
STEM VOLUME USED = 35 %

Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /36
OPERATOR: Ketan Mehta
SAMPLE ID: 20210min2mmRUN3
SUBMITTER: Ketan Mehta

LP 05:47:56 12/09/96
HP 07:39:58 12/09/96
REP 07:39:58 12/09/96

PENETROMETER NUMBER:	13-0241	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.7774 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4019 g
PENETROMETER VOLUME:	3.5443 mL	SAMPLE+PEN+Hg WEIGHT:	110.9042 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6992 psia
LAST LOW PRESSURE POINT: 25.7719 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3516 mL/g
TOTAL PORE AREA =	32.877 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0495 µm
MEDIAN PORE DIAMETER (AREA) =	0.0425 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0428 µm
BULK DENSITY =	0.8701 g/mL
APPARENT (SKELETAL) DENSITY =	1.2537 g/mL
POROSITY =	30.59 %
STEM VOLUME USED =	34 %

Drug Load: 20.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /37
OPERATOR: Ketan Mehta LP 03:07:26 12/10/96
SAMPLE ID: 20%20min2mmRUN1 HP 03:57:40 12/10/96
SUBMITTER: Ketan Mehta REP 03:57:41 12/10/96

PENETROMETER NUMBER: 13-0241 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pf RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 67.8050 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL MERCURY DENSITY: 13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.4028 g
PENETROMETER VOLUME: 3.5443 mL SAMPLE+PEN+Hg WEIGHT: 110.0928 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8010 psia
LAST LOW PRESSURE POINT: 25.8091 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3259 mL/g
TOTAL PORE AREA = 30.785 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0495 µm
MEDIAN PORE DIAMETER (AREA) = 0.0411 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0423 µm
BULK DENSITY = 0.8950 g/mL
APPARENT (SKELETAL) DENSITY = 1.2635 g/mL
POROSITY = 29.16 %
STEM VOLUME USED = 32 %

Drug Load: 20.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /38
OPERATOR: Ketan Mehta                                LP  03:07:26 12/10/96
SAMPLE ID: 20%20min2mmRUN2                           HP  05:10:52 12/10/96
SUBMITTER: Ketan Mehta                               REP 05:10:53 12/10/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.7274 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4008 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 112.3340 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.8010 psia
      LAST LOW PRESSURE POINT: 25.8091 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:       10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3339 mL/g
              TOTAL PORE AREA =      31.788 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0495 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0411 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0420 µm
                BULK DENSITY =        1.0104 g/mL
      APPARENT (SKELETAL) DENSITY =   1.5248 g/mL
                    POROSITY =       33.73 %
          STEM VOLUME USED =           32 %
```

Drug Load: 20.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /39
OPERATOR: Ketan Mehta
SAMPLE ID: 20%20min2mmRUN3
SUBMITTER: Ketan Mehta

LP 02:25:45 12/16/96
HP 03:08:58 12/16/96
REP 03:08:58 12/16/96

PENETROMETER NUMBER:	13-0241	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.6530 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4000 g
PENETROMETER VOLUME:	3.5443 mL	SAMPLE+PEN+Hg WEIGHT:	109.9712 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6843 psia
LAST LOW PRESSURE POINT: 25.8844 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3377	mL/g
TOTAL PORE AREA =	31.498	sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0495	µm
MEDIAN PORE DIAMETEK (AREA) =	0.0420	µm
AVERAGE PORE DIAMETER (4V/A) =	0.0429	µm
BULK DENSITY =	0.8937	g/mL
APPARENT (SKELETAL) DENSITY =	1.2800	g/mL
POROSITY =	30.16	%
STEM VOLUME USED =	33	%

Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /40
OPERATOR: Ketan Mehta                                  LP  02:25:45 12/16/96
SAMPLE ID: 30%2min2mmRUN1                              HP  03:49:28 12/16/96
SUBMITTER: Ketan Mehta                                 REP 03:49:28 12/16/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.5499 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4008 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 111.9406 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6843 psia
      LAST LOW PRESSURE POINT: 25.8844 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3628 mL/g
                     TOTAL PORE AREA =     31.031 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0644 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0400 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0468 µm
                        BULK DENSITY =      0.9713 g/mL
            APPARENT (SKELETAL) DENSITY =   1.4998 g/mL
                           POROSITY =      35.24 %
                    STEM VOLUME USED =        35 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /41
OPERATOR: Ketan Mehta                                  LP  07:15:40 12/16/96
SAMPLE ID: 30%2min2mmRUN2                              HP  07:58:34 12/16/96
SUBMITTER: Ketan Mehta                                 REP 07:58:34 12/16/96

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.8934 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4006 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.0767 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6933 psia
      LAST LOW PRESSURE POINT: 25.8376 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3580 mL/g
                      TOTAL PORE AREA =    30.147 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0638 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0406 µm
          AVERAGE PORE DIAMETER (4V/A) =    0.0475 µm
                          BULK DENSITY =    0.8754 g/mL
          APPARENT (SKELETAL) DENSITY =     1.2750 g/mL
                               POROSITY =     31.34 %
                      STEM VOLUME USED =        35 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /42
OPERATOR: Ketan Mehta LP 07:15:40 12/16/96
SAMPLE ID: 30%2min2mmRUN3 HP 08:55:59 12/16/96
SUBMITTER: Ketan Mehta REP 08:56:00 12/16/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.6191 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5364 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4006 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	112.0818 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6933 psia
LAST LOW PRESSURE POINT: 25.8316 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3595 mL/g
TOTAL PORE AREA =	30.107 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0640 µm
MEDIAN PORE DIAMETER (AREA) =	0.0410 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0478 µm
BULK DENSITY =	0.7951 g/mL
APPARENT (SKELETAL) DENSITY =	1.5216 g/mL
POROSITY =	35.36 %
STEM VOLUME USED =	35 %

Drug Load: 30.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

```
PORESIZER 9320 v2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /43
OPERATOR: Ketan Mehta                                LP  00:43:22 12/17/96
SAMPLE ID: 30%10min2mmRUN1                           HP  01:44:25 12/17/96
SUBMITTER: Ketan Mehta                               REP 01:44:26 12/17/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.7465 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:       13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4005 g
PENETROMETER VOLUME:   3.5885 mL      SAMPLE+PEN+Hg WEIGHT: 111.3052 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6858 psia
      LAST LOW PRESSURE POINT: 25.7189 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3440 mL/g
                     TOTAL PORE AREA =     30.610 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0593 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0413 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0449 µm
                        BULK DENSITY =      1.0008 g/mL
           APPARENT (SKELETAL) DENSITY =    1.5261 g/mL
                          POROSITY =        34.42 %
                    STEM VOLUME USED =        33 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

```
POREsIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /44
OPERATOR: Ketan Mehta                                  LP  00:43:22 12/17/96
SAMPLE ID: 30%10min2mmRUN2                             HP  03:32:44 12/17/96
SUBMITTER: Ketan Mehta                                 REP 03:32:45 12/17/96

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.8300 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4000 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 111.0840 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6858 psia
      LAST LOW PRESSURE POINT: 25.7189 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3439 mL/g
                     TOTAL PORE AREA =     29.707 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0623 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0424 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0463 µm
                          BULK DENSITY =    0.8843 g/mL
            APPARENT (SKELETAL) DENSITY =   1.2707 g/mL
                               POROSITY =    30.41 %
                     STEM VOLUME USED =        33 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /45
OPERATOR: Ketan Mehta                                  LP  10:43:17 12/17/96
SAMPLE ID: 30I10min2mmRUN3                             HP  11:26:31 12/17/96
SUBMITTER: Ketan Mehta                                 REP 11:26:32 12/17/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.0809 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4007 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.3431 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6758 psia
      LAST LOW PRESSURE POINT: 25.1961 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

              TOTAL INTRUSION VOLUME =    0.3487 mL/g
                    TOTAL PORE AREA =    30.897 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  0.0608 µm
            MEDIAN PORE DIAMETER (AREA) =  0.0414 µm
          AVERAGE PORE DIAMETER (4V/A) =   0.0451 µm
                          BULK DENSITY =   0.8869 g/mL
           APPARENT (SKELETAL) DENSITY =   1.2840 g/mL
                               POROSITY =   30.92 %
                     STEM VOLUME USED =      34 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /46
OPERATOR: Ketan Mehta                                  LP  10:43:17 12/17/96
SAMPLE ID: 30%20min2mmRUN1                             HP  00:20:48 12/18/96
SUBMITTER: Ketan Mehta                                 REP 00:20:48 12/18/96

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.3189 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:         13.5364 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4014 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 112.0148 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6758 psia
      LAST LOW PRESSURE POINT: 25.5961 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3195 mL/g
                     TOTAL PORE AREA =     28.148 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0584 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0406 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0454 µm
                          BULK DENSITY =    1.0289 g/mL
           APPARENT (SKELETAL) DENSITY =    1.5327 g/mL
                             POROSITY =     32.87 %
                   STEM VOLUME USED =       31 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /53
OPERATOR: KETAN MEHTA                                LP  04:20:19 02/18/97
SAMPLE ID: 30%20min2mmRUN2                           HP  04:58:40 02/18/97
SUBMITTER: KETAN MEHTA                               REP 04:58:40 02/18/97


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.0736 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4036 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 111.6484 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5855 psia
      LAST LOW PRESSURE POINT: 25.4901 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3352 mL/g
                      TOTAL PORE AREA =    28.670 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0473 µm
             MEDIAN PORE DIAMETER (AREA) =  0.0411 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0468 µm
                          BULK DENSITY =    1.0127 g/mL
            APPARENT (SKELETAL) DENSITY =   1.5330 g/mL
                               POROSITY =    33.94 %
                      STEM VOLUME USED =       33 %
```

Drug Load: 30.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /54
OPERATOR: KETAN MEHTA LP 04:20:19 02/18/97
SAMPLE ID: 30%20min2ndRUN3 HP 05:59:31 02/18/97
SUBMITTER: KETAN MEHTA REP 05:59:31 02/18/97

PENETROMETER NUMBER: 13-0241 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pF RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 68.6578 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL MERCURY DENSITY: 13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.4022 g
PENETROMETER VOLUME: 3.5443 mL SAMPLE+PEN+Hg WEIGHT: 110.9184 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5855 psia
LAST LOW PRESSURE POINT: 25.4901 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3263 mL/g
TOTAL PORE AREA =	27.170 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0480 µm
MEDIAN PORE DIAMETER (AREA) =	0.0453 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0480 µm
BULK DENSITY =	0.8911 g/mL
APPARENT (SKELETAL) DENSITY =	1.2564 g/mL
POROSITY =	29.07 %
STEM VOLUME USED =	32 %

Drug Load: 40.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /55
OPERATOR: KETAN MEHTA                                  LP  00:44:16 02/19/97
SAMPLE ID: 40%2min2mmRUN#1                             HP  01:23:03 02/19/97
SUBMITTER: KETAN MEHTA                                 REP 01:23:04 02/19/97


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pf   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    67.9858 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4011 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 111.3648 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5308 psia
      LAST LOW PRESSURE POINT: 25.5334 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3778 mL/g
                      TOTAL PORE AREA =    25.804 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =    0.0949 µm
            MEDIAN PORE DIAMETER (AREA) =    0.0364 µm
           AVERAGE PORE DIAMETER (4V/A) =    0.0586 µm
                          BULK DENSITY =    0.9716 g/mL
           APPARENT (SKELETAL) DENSITY =    1.5350 g/mL
                              POROSITY =     36.71 %
                    STEM VOLUME USED =        37 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /56
OPERATOR: KETAN MEHTA                                LP  00:44:16 02/19/97
SAMPLE ID: 40%2@s\n2mmRUN#2                          HP  03:00:44 02/19/97
SUBMITTER: KETAN MEHTA                               REP 03:00:45 02/19/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.7471 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4009 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.7373 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5308 psia
      LAST LOW PRESSURE POINT: 25.5334 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:         10 seconds


                    INTRUSION DATA SUMMARY

              TOTAL INTRUSION VOLUME =    0.3791 mL/g
                   TOTAL PORE AREA =     26.080 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  0.0952 µm
           MEDIAN PORE DIAMETER (AREA) =   0.0385 µm
          AVERAGE PORE DIAMETER (4V/A) =   0.0581 µm
                        BULK DENSITY =     0.8507 g/mL
          APPARENT (SKELETAL) DENSITY =    1.2557 g/mL
                          POROSITY =      32.25 %
                    STEM VOLUME USED =      37 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

POREsIZER 9320 v2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /57
OPERATOR: Ketan Mehta LP 00:39:33 02/24/97
SAMPLE ID: 40%2mm2minRUN#3 HP 01:16:09 02/24/97
SUBMITTER: Ketan Mehta REP 01:16:10 02/24/97

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.9178 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4028 g
PENETROMETER VOLUME:	3.5885 mL	SAMPLE+PEN+Hg WEIGHT:	112.2790 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8863 psia
LAST LOW PRESSURE POINT: 25.7454 psia

HIGH PRESSURE:

RUN TYPE:	AUTOMATIC
RUN METHOD:	EQUILIBRATED
EQUILIBRATION TIME:	10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3736 mL/g
TOTAL PORE AREA =	25.762 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0933 µm
MEDIAN PORE DIAMETER (AREA) =	0.0361 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0580 µm
BULK DENSITY =	0.9723 g/mL
APPARENT (SKELETAL) DENSITY =	1.5270 g/mL
POROSITY =	36.33 %
STEM VOLUME USED =	37 %

Drug Load: 40.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /58
OPERATOR: Ketan Mehta                                  LP  00:39:33 02/24/97
SAMPLE ID: 40%2mm10minRUN#1                            HP  01:50:09 02/24/97
SUBMITTER: Ketan Mehta                                 REP 02:35:47 02/24/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.7971 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4005 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.0473 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.8863 psia
      LAST LOW PRESSURE POINT: 25.7454 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3392 mL/g
                      TOTAL PORE AREA =    25.045 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =   0.0685 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0452 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0542 µm
                           BULK DENSITY =   0.8861 g/mL
          APPARENT (SKELETAL) DENSITY =    1.2668 g/mL
                              POROSITY =     30.05 %
                     STEM VOLUME USED =        33 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /61
OPERATOR: Ketan Mehta                                  LP  05:18:49 02/24/97
SAMPLE ID: 40%2mm10min RUN#2                           HP  05:55:59 02/24/97
SUBMITTER: Ketan Mehta                                 REP 05:56:00 02/24/97


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    67.8911 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4001 g
PENETROMETER VOLUME:    3.5885 mL     SAMPLE+PEN+Hg WEIGHT: 111.2842 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6190 psia
      LAST LOW PRESSURE POINT: 25.6197 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =   0.3462 mL/g
                     TOTAL PORE AREA =    26.270 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0639 µm
             MEDIAN PORE DIAMETER (AREA) =  0.0453 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0527 µm
                          BULK DENSITY =    0.9718 g/mL
            APPARENT (SKELETAL) DENSITY =   1.4644 g/mL
                               POROSITY =    33.64 %
                     STEM VOLUME USED =       34 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /62
OPERATOR: Ketan Mehta                                  LP  05:18:49 02/24/97
SAMPLE ID: 40%2mm10minRUN#3                            HP  06:31:09 02/24/97
SUBMITTER: Ketan Mehta                                 REP 10:12:20 02/24/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9310 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4000 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 111.1705 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6190 psia
      LAST LOW PRESSURE POINT: 25.6197 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                  TOTAL INTRUSION VOLUME =   0.3414 mL/g
                        TOTAL PORE AREA =   25.649 sq-m/g
             MEDIAN PORE DIAMETER (VOLUME) =  0.0682 µm
               MEDIAN PORE DIAMETER (AREA) =  0.0453 µm
              AVERAGE PORE DIAMETER (4V/A) =  0.0532 µm
                             BULK DENSITY =  0.8835 g/mL
              APPARENT (SKELETAL) DENSITY =  1.2651 g/mL
                                POROSITY =   30.16 %
                       STEM VOLUME USED =     33 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /63
OPERATOR: Ketan Mehta                                LP  00:02:03 02/25/97
SAMPLE ID: 40%2mm20minRUN#1                          HP  00:49:07 02/25/97
SUBMITTER: Ketan Mehta                               REP 00:49:08 02/25/97


PENETROMETER NUMBER: 13-0854          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9900 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4003 g
PENETROMETER VOLUME:   3.5541 mL      SAMPLE+PEN+Hg WEIGHT: 111.2366 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6073 psia
      LAST LOW PRESSURE POINT: 25.7327 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3615 mL/g
                     TOTAL PORE AREA =     28.265 sq-m/g
            MEDIAN PORE DIAMETER (VOLUME) =  0.0577 µm
              MEDIAN PORE DIAMETER (AREA) =  0.0453 µm
             AVERAGE PORE DIAMETER (4V/A) =  0.0512 µm
                          BULK DENSITY =     0.8664 g/mL
              APPARENT (SKELETAL) DENSITY =  1.2614 g/mL
                               POROSITY =    31.32 %
                     STEM VOLUME USED =        35 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

```
POREsIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /64
OPERATOR: Ketan Mehta                                LP  00:02:03 02/25/97
SAMPLE ID: 40%2mm20minRUN#2                          HP  01:28:12 02/25/97
SUBMITTER: Ketan Mehta                               REP 02:33:42 02/25/97

PENETROMETER NUMBER: 13-0868          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.4436 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4005 g
PENETROMETER VOLUME:   3.6991 mL      SAMPLE+PEN+Hg WEIGHT: 112.6359 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6073 psia
      LAST LOW PRESSURE POINT: 25.7327 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3645 mL/g
                TOTAL PORE AREA =     29.098 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0574 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0452 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0501 µm
                BULK DENSITY =        0.8645 g/mL
     APPARENT (SKELETAL) DENSITY =    1.2621 g/mL
                POROSITY =           31.51 %
          STEM VOLUME USED =            35 %
```

Drug Load: 40.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /65
OPERATOR: Ketan Mehta                                  LP  03:43:48 02/25/97
SAMPLE ID: 40%2mm20minRUN#3                            HP  04:18:48 02/25/97
SUBMITTER: Ketan Mehta                                 REP 04:18:49 02/25/97


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.8074 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4002 g
PENETROMETER VOLUME:   3.5885 mL      SAMPLE+PEN+Hg WEIGHT: 111.2090 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7903 psia
      LAST LOW PRESSURE POINT: 25.5791 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                  TOTAL INTRUSION VOLUME =    0.3578 mL/g
                       TOTAL PORE AREA =     28.258 sq-m/g
             MEDIAN PORE DIAMETER (VOLUME) =  0.0580 µm
               MEDIAN PORE DIAMETER (AREA) =  0.0453 µm
              AVERAGE PORE DIAMETER (4V/A) =  0.0507 µm
                            BULK DENSITY =    0.9735 g/mL
              APPARENT (SKELETAL) DENSITY =   1.4939 g/mL
                                POROSITY =     34.83 %
                      STEM VOLUME USED =        35 %
```

Appendix 3b

Determination of porosity parameters by mercury intrusion porosimetry. Pellets formulated with different granulation water levels.

Granulation water level: 60 % w/w, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /73
OPERATOR: Ketan Mehta                                  LP  06:21:30 03/04/97
SAMPLE ID: 10%20min60%waterRUN#1                       HP  09:43:04 03/04/97
SUBMITTER: Ketan Mehta                                 REP 09:43:05 03/04/97


PENETROMEYER NUMBER: 13-0854          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.5228 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4024 g
PENETROMETER VOLUME:    3.5541 mL     SAMPLE+PEN+Hg WEIGHT: 111.3082 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  1.1350 psia
      LAST LOW PRESSURE POINT: 25.6341 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.2643 mL/g
                     TOTAL PORE AREA =     24.830 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0453 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0453 µm
          AVERAGE PORE DIAMETER (4V/A) =    0.0426 µm
                          BULK DENSITY =    0.9527 g/mL
           APPARENT (SKELETAL) DENSITY =    1.2733 g/mL
                               POROSITY =   25.18 %
                     STEM VOLUME USED =       26 %
```

Granulation water level: 60 % w/w, Run # 2

PORESIZER 9320 v2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /79
OPERATOR: Ketan mehta LP 01:09:06 03/05/97
SAMPLE ID: 10%20min60%waterRUN#2 HP 01:45:44 03/05/97
SUBMITTER: Ketan mehta REP 01:45:44 03/05/97

PENETROMETER NUMBER:	13-0854	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.8259 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4007 g
PENETROMETER VOLUME:	3.5541 mL	SAMPLE+PEN+Hg WEIGHT:	110.6407 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7988 psia
LAST LOW PRESSURE POINT: 25.6147 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.2619	mL/g
TOTAL PORE AREA =	24.981	sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0467	µm
MEDIAN PORE DIAMETER (AREA) =	0.0381	µm
AVERAGE PORE DIAMETER (4V/A) =	0.0419	µm
BULK DENSITY =	0.9538	g/mL
APPARENT (SKELETAL) DENSITY =	1.2715	g/mL
POROSITY =	24.98	%
STEM VOLUME USED =	25	%

Granulation water level: 60 % w/w, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /80
OPERATOR: ketan mehta                                  LP  01:09:06 03/05/97
SAMPLE ID: 10X20min60%waterRUN#3                       HP  02:22:13 03/05/97
SUBMITTER: Ketan mehta                                 REP 02:22:14 03/05/97

PENETROMETER NUMBER: 13-0868          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9259 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:          0.4120 mL       MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4003 g
PENETROMETER VOLUME:  13.6991 mL      SAMPLE+PEN+Hg WEIGHT: 113.7579 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7988 psia
      LAST LOW PRESSURE POINT: 25.6147 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.2665 mL/g
                     TOTAL PORE AREA =     25.547 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =    0.0476 µm
            MEDIAN PORE DIAMETER (AREA) =    0.0370 µm
          AVERAGE PORE DIAMETER (4V/A) =    0.0417 µm
                          BULK DENSITY =    0.9622 g/mL
           APPARENT (SKELETAL) DENSITY =    1.2941 g/mL
                             POROSITY =     25.64 %
                   STEM VOLUME USED =        26 %
```

Granulation water level: 65 % w/w, Run # 1

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /75
OPERATOR: Ketan Mehta                                  LP  08:13:56 03/03/97
SAMPLE ID: 10X20min65%waterRUN#1                       HP  04:04:16 03/04/97
SUBMITTER: Ketan Mehta                                 REP 04:05:31 03/04/97

PENETROMETER NUMBER: 13-0868          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   67.9196 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4020 g
PENETROMETER VOLUME:   3.6991 mL      SAMPLE+PEN+Hg WEIGHT: 112.0096 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7065 psia
      LAST LOW PRESSURE POINT: 25.2189 psia

HIGH PRESSURE:
      RUN TYPE:                  AUTOMATIC
      RUN METHOD:                EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

            TOTAL INTRUSION VOLUME =    0.3929 mL/g
                  TOTAL PORE AREA =    34.803 sq-m/g
       MEDIAN PORE DIAMETER (VOLUME) =   0.0453 µm
        MEDIAN PORE DIAMETER (AREA) =    0.0372 µm
       AVERAGE PORE DIAMETER (4V/A) =    0.0452 µm
                    BULK DENSITY =      0.8536 g/mL
        APPARENT (SKELETAL) DENSITY =   1.2843 g/mL
                        POROSITY =       33.54 %
                  STEM VOLUME USED =       38 %
```

Granulation water level: 65 % w/w, Run # 2

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /76
OPERATOR: Ketan Mehta                                  LP  08:13:56 03/03/97
SAMPLE ID: 10%20min65%waterRUN#2                       HP  04:51:31 03/04/97
SUBMITTER: Ketan Mehta                                 REP 04:51:32 03/04/97

PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.7962 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4015 g
PENETROMETER VOLUME:   3.5885 mL      SAMPLE+PEN+Hg WEIGHT: 112.0219 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7765 psia
      LAST LOW PRESSURE POINT: 25.2189 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.3850 mL/g
                     TOTAL PORE AREA =     32.234 sq-m/g
           MEDIAN PORE DIAMETER (VOLUME) =  0.0481 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0389 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.0473 µm
                        BULK DENSITY =      0.9465 g/mL
            APPARENT (SKELETAL) DENSITY =   1.4893 g/mL
                          POROSITY =       36.44 %
                    STEM VOLUME USED =       38 %
```

Granulation water level: 65 % w/w, Run # 3

```
PORESIZER 9320 V2.07                                          PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /77
OPERATOR: Ketan Mehta                                  LP  06:21:30 03/04/97
SAMPLE ID: 10%20min65%waterRUN#3                       HP  07:01:01 03/04/97
SUBMITTER: Ketan Mehta                                 REP 07:01:02 03/04/97

PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 mL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.9284 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.4003 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.8948 g

LOW PRESSURE:
      MERCURY FILLING PRESSURE:  1.0350 psia
      LAST LOW PRESSURE POINT: 25.6341 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds

                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.3863 mL/g
                TOTAL PORE AREA =    34.682 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0453 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0372 µm
     AVERAGE PORE DIAMETER (4V/A) =   0.0446 µm
                BULK DENSITY =        0.8464 g/mL
      APPARENT (SKELETAL) DENSITY =   1.2575 g/mL
                POROSITY =           32.69 %
          STEM VOLUME USED =          38 %
```

Granulation water level: 70 % w/w, Run # 1

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /28
OPERATOR: ketan sehta                                  LP  03:09:15 12/02/96
SAMPLE ID: 70%20min2mmRUN1                             HP  04:41:16 12/02/96
SUBMITTER: ketan sehta                                 REP 04:41:17 12/02/96


PENETROMETER NUMBER: 13-0131          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.6338 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5413 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4325 g
PENETROMETER VOLUME:   3.6417 mL      SAMPLE+PEN+Hg WEIGHT: 111.8144 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6790 psia
      LAST LOW PRESSURE POINT: 25.9979 psia

HIGH PRESSURE:
      RUN TYPE:                  AUTOMATIC
      RUN METHOD:                EQUILIBRATED
      EQUILIBRATION TIME:        10 seconds


                    INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.4094 mL/g
                      TOTAL PORE AREA =    38.662 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =    0.0481 µm
            MEDIAN PORE DIAMETER (AREA) =    0.0426 µm
          AVERAGE PORE DIAMETER (4V/A) =    0.0424 µm
                          BULK DENSITY =    0.8340 g/mL
           APPARENT (SKELETAL) DENSITY =    1.2664 g/mL
                              POROSITY =     34.16 %
                    STEM VOLUME USED =        40 %
```

Granulation water level: 70 % w/w, Run # 2

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /29
OPERATOR: ketan mehta
SAMPLE ID: 10%20min2mmRUN2
SUBMITTER: ketan mehta

LP 06:49:22 12/02/96
HP 07:35:44 12/02/96
REP 09:19:21 12/02/96

PENETROMETER NUMBER:	13-0131	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.6550 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5413 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.4010 g
PENETROMETER VOLUME:	3.6417 mL	SAMPLE+PEN+Hg WEIGHT:	110.8876 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7958 psia
LAST LOW PRESSURE POINT: 25.8911 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4059 mL/g
TOTAL PORE AREA =	38.266 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0483 µm
MEDIAN PORE DIAMETER (AREA) =	0.0426 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0424 µm
BULK DENSITY =	0.8377 g/mL
APPARENT (SKELETAL) DENSITY =	1.2695 g/mL
POROSITY =	34.01 %
STEM VOLUME USED =	40 %

Granulation water level: 70 % w/w, Run # 3

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /30
OPERATOR: ketan mehta                                  LP  06:49:22 12/02/96
SAMPLE ID: 10%20min2mmRUN3                             HP  10:00:45 12/02/96
SUBMITTER: ketan mehta                                 REP 10:00:46 12/02/96


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 pL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   69.1096 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5613 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.4022 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 110.8080 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7958 psia
      LAST LOW PRESSURE POINT: 25.8911 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:         10 seconds


                    INTRUSION DATA SUMMARY

          TOTAL INTRUSION VOLUME =    0.4056 mL/g
                TOTAL PORE AREA =    38.603 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =  0.0480 µm
       MEDIAN PORE DIAMETER (AREA) =  0.0427 µm
      AVERAGE PORE DIAMETER (4V/A) =  0.0420 µm
                      BULK DENSITY =  0.8131 g/mL
     APPARENT (SKELETAL) DENSITY =    1.2131 g/mL
                         POROSITY =    32.98 %
                STEM VOLUME USED =      40 %
```

Appendix 3c

Determination of porosity parameters by mercury intrusion porosimetry. Nifedipine and nifedipine:pluronic® F-68 (1:1) solid dispersion pellets after different dissolution time intervals.

Nifedipine pellets, dissolution time: 0 hours

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /81
OPERATOR: Ketan Mehta                                  LP  07:42:00 04/06/97
SAMPLE ID: 20%nifedipine beads 2mm 0hours              HP  08:17:40 04/06/97
SUBMITTER: Ketan Mehta                                 REP 08:17:41 04/06/97


PENETROMETER NUMBER: 13-0868          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.1624 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:       13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:          0.3010 g
PENETROMETER VOLUME:   3.6991 mL      SAMPLE+PEN+Hg WEIGHT: 114.2917 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7450 psia
      LAST LOW PRESSURE POINT: 25.4604 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.2815 mL/g
                      TOTAL PORE AREA =    27.425 sq-m/g
     MEDIAN PORE DIAMETER (VOLUME) =    0.0480 µm
       MEDIAN PORE DIAMETER (AREA) =    0.0330 µm
     AVERAGE PORE DIAMETER (4V/A) =    0.0411 µm
                        BULK DENSITY =    0.9622 g/mL
      APPARENT (SKELETAL) DENSITY =    1.3198 g/mL
                              POROSITY =     27.09 %
                    STEM VOLUME USED =        21 % ****
```

Nifedipine pellets, dissolution time: 2.0 hours

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /83
OPERATOR: ketan Mehta LP 00:13:47 04/07/97
SAMPLE ID: 20%nifedipine beads2mm2hrs HP 00:48:22 04/07/97
SUBMITTER: Ketan Mehta REP 00:48:23 04/07/97

PENETROMETER NUMBER: 13-0868
PENETROMETER CONSTANT: 10.79 µL/pF
PENETROMETER WEIGHT: 67.9982 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.3016 g
SAMPLE+PEN+Hg WEIGHT: 113.3140 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6052 psia
LAST LOW PRESSURE POINT: 25.5137 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4650 mL/g
TOTAL PORE AREA =	27.813 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.0814 µm
MEDIAN PORE DIAMETER (AREA) =	0.0318 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0669 µm
BULK DENSITY =	0.8086 g/mL
APPARENT (SKELETAL) DENSITY =	1.2960 g/mL
POROSITY =	37.61 %
STEM VOLUME USED =	34 %

Nifedipine pellets, dissolution time: 4.0 hours

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /85
OPERATOR: Ketan mehta LP 05:42:16 04/07/97
SAMPLE ID: 20%nifedipine beads 2mm, 4 hours HP 06:18:05 04/07/97
SUBMITTER: Ketan Mehta REP 06:18:06 04/07/97

PENETROMETER NUMBER:	13-0868	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.1666 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.3017 g
PENETROMETER VOLUME:	3.6991 mL	SAMPLE+PEN+Hg WEIGHT:	113.4587 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8105 psia
LAST LOW PRESSURE POINT: 28.5694 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4904 mL/g
TOTAL PORE AREA =	26.559 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.1530 µm
MEDIAN PORE DIAMETER (AREA) =	0.0305 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0739 µm
BULK DENSITY =	0.8051 g/mL
APPARENT (SKELETAL) DENSITY =	1.3303 g/mL
POROSITY =	39.48 %
STEM VOLUME USED =	36 %

Nifedipine pellets, dissolution time: 6.0 hours

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /87
OPERATOR: Ketan mehta LP 04:37:01 04/08/97
SAMPLE ID: 20%nifedipine beads 2mm, 6 hrs HP 05:12:02 04/08/97
SUBMITTER: Ketan Mehta REP 05:12:02 04/08/97

PENETROMETER NUMBER:	13-0868	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	67.9340 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.2671 g
PENETROMETER VOLUME:	3.6991 mL	SAMPLE+PEN+Hg WEIGHT:	113.6380 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5458 psia
LAST LOW PRESSURE POINT: 28.4731 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.5038 mL/g
TOTAL PORE AREA =	25.529 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.4056 µm
MEDIAN PORE DIAMETER (AREA) =	0.0296 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0789 µm
BULK DENSITY =	0.7816 g/mL
APPARENT (SKELETAL) DENSITY =	1.2893 g/mL
POROSITY =	39.38 %
STEM VOLUME USED =	33 %

Nifedipine pellets, dissolution time: 8.0 hours

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /89
OPERATOR: Ketan Mehta LP 00:04:47 04/09/97
SAMPLE ID: 20%nifedipine beads, 2mm, 8hours HP 00:39:37 04/09/97
SUBMITTER: Ketan Mehta REP 00:39:37 04/09/97

PENETROMETER NUMBER: 13-0868 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pF RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 68.2047 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL MERCURY DENSITY: 13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.2549 g
PENETROMETER VOLUME: 3.6991 mL SAMPLE+PEN+Hg WEIGHT: 114.1119 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6518 psia
LAST LOW PRESSURE POINT: 28.4637 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4950 mL/g
TOTAL PORE AREA =	26.074 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	0.5036 µm
MEDIAN PORE DIAMETER (AREA) =	0.0290 µm
AVERAGE PORE DIAMETER (4V/A) =	0.0759 µm
BULK DENSITY =	0.7823 g/mL
APPARENT (SKELETAL) DENSITY =	1.2768 g/mL
POROSITY =	38.73 %

Nifedipine:Pluronic® F-68 solid dispersion pellets, dissolution time: 0 hours

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /82
OPERATOR: Ketan Mehta                                  LP  07:42:00 04/06/97
SAMPLE ID: 1:1NFD SD 0hours                            HP  08:52:13 04/06/97
SUBMITTER: Ketan Mehta                                 REP 08:52:14 04/06/97


PENETROMETER NUMBER: 13-0854          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    68.3914 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.3004 g
PENETROMETER VOLUME:    3.5541 mL     SAMPLE+PEN+Hg WEIGHT: 112.9926 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.7450 psia
      LAST LOW PRESSURE POINT: 25.4604 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.1636 mL/g
                       TOTAL PORE AREA =    18.159 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =    0.0518 µm
            MEDIAN PORE DIAMETER (AREA) =    0.0164 µm
           AVERAGE PORE DIAMETER (4V/A) =    0.0360 µm
                         BULK DENSITY =     1.0702 g/mL
           APPARENT (SKELETAL) DENSITY =     1.2974 g/mL
                              POROSITY =      17.51 %
                     STEM VOLUME USED =        12 % ****
```

Nifedipine:Pluronic® F-68 solid dispersion pellets, dissolution time: 2.0 hours

PORESIZER 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /84
OPERATOR: Ketan Mehta LP 00:13:47 04/07/97
SAMPLE ID: 1:1Nifedipine SD, 2mm, 2 hrs HP 02:16:35 04/07/97
SUBMITTER: Ketan Mehta REP 02:16:36 04/07/97

PENETROMETER NUMBER:	13-0854	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.3229 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.2612 g
PENETROMETER VOLUME:	3.5541 mL	SAMPLE+PEN+Hg WEIGHT:	112.7089 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6052 psia
LAST LOW PRESSURE POINT: 25.5137 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.3527 mL/g
TOTAL PORE AREA =	12.105 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	11.4396 µm
MEDIAN PORE DIAMETER (AREA) =	0.0109 µm
AVERAGE PORE DIAMETER (4V/A) =	0.1166 µm
BULK DENSITY =	0.8894 g/mL
APPARENT (SKELETAL) DENSITY =	1.2960 g/mL
POROSITY =	31.37 %
STEM VOLUME USED =	22 % ****

Nifedipine:Pluronic® F-68 solid dispersion pellets, dissolution time: 4.0 hours

POREsizer 9320 V2.07 PAGE 1

SAMPLE DIRECTORY/NUMBER: DATA1 /86
OPERATOR: Ketan Mehta LP 05:42:16 04/07/97
SAMPLE ID: 1:1 nifedipine beads, 2mm, 4 hours HP 22:52:28 04/07/97
SUBMITTER: Ketan mehta REP 22:52:29 04/07/97

PENETROMETER NUMBER:	13-0854	ADVANCING CONTACT ANGLE:	130.0 deg
PENETROMETER CONSTANT:	10.79 µL/pF	RECEDING CONTACT ANGLE:	130.0 deg
PENETROMETER WEIGHT:	68.4334 g	MERCURY SURFACE TENSION:	485.0 dyn/cm
STEM VOLUME:	0.4120 mL	MERCURY DENSITY:	13.5335 g/mL
MAXIMUM HEAD PRESSURE:	4.6800 psi	SAMPLE WEIGHT:	0.1880 g
PENETROMETER VOLUME:	3.5541 mL	SAMPLE+PEN+Hg WEIGHT:	113.5487 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8105 psia
LAST LOW PRESSURE POINT: 28.5694 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME =	0.4689	mL/g
TOTAL PORE AREA =	15.734	sq-m/g
MEDIAN PORE DIAMETER (VOLUME) =	12.2373	µm
MEDIAN PORE DIAMETER (AREA) =	0.0112	µm
AVERAGE PORE DIAMETER (4V/A) =	0.1192	µm
BULK DENSITY =	0.8021	g/mL
APPARENT (SKELETAL) DENSITY =	1.2856	g/mL
POROSITY =	37.61	%
STEM VOLUME USED =	21	% ****

Nifedipine:Pluronic® F-68 solid dispersion pellets, dissolution time: 6.0 hours

```
POREsIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1   /88
OPERATOR: ketan mehta                                  LP  04:37:01 04/08/97
SAMPLE ID: 1:1nifedipine SD, 2mm, 6 hrs                HP  06:05:40 04/08/97
SUBMITTER: Ketan mehta                                 REP 06:05:40 04/08/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:    69.0044 g     MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:            0.4120 mL     MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.1489 g
PENETROMETER VOLUME:    3.5443 mL     SAMPLE+PEN+Hg WEIGHT: 114.3570 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.5458 psia
      LAST LOW PRESSURE POINT: 28.4731 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.5703 mL/g
                     TOTAL PORE AREA =     18.161 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  13.7318 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0118 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.1256 µm
                        BULK DENSITY =      0.7293 g/mL
           APPARENT (SKELETAL) DENSITY =    1.2487 g/mL
                           POROSITY =       41.59 %
                    STEM VOLUME USED =         21 % ****
```

Nifedipine:Pluronic® F-68 solid dispersion pellets, dissolution time: 8.0 hours

```
PORESIZER 9320 V2.07                                              PAGE  1

SAMPLE DIRECTORY/NUMBER: DATA1    /90
OPERATOR: Ketan mehta                                  LP  00:04:47 04/09/97
SAMPLE ID: 1:1 nifedipine SD, 2mm, 8 hours             HP  01:13:41 04/09/97
SUBMITTER: Ketan mehta                                 REP 01:13:42 04/09/97


PENETROMETER NUMBER: 13-0241          ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT:  10.79 µL/pF   RECEDING CONTACT ANGLE:  130.0 deg
PENETROMETER WEIGHT:   68.3024 g      MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME:           0.4120 mL      MERCURY DENSITY:        13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi     SAMPLE WEIGHT:           0.0753 g
PENETROMETER VOLUME:   3.5443 mL      SAMPLE+PEN+Hg WEIGHT: 114.8735 g


LOW PRESSURE:
      MERCURY FILLING PRESSURE:  0.6518 psia
      LAST LOW PRESSURE POINT: 28.4637 psia

HIGH PRESSURE:
      RUN TYPE:                 AUTOMATIC
      RUN METHOD:               EQUILIBRATED
      EQUILIBRATION TIME:          10 seconds


                        INTRUSION DATA SUMMARY

                TOTAL INTRUSION VOLUME =    0.5925 mL/g
                       TOTAL PORE AREA =   20.711 sq-m/g
          MEDIAN PORE DIAMETER (VOLUME) =  16.7441 µm
            MEDIAN PORE DIAMETER (AREA) =   0.0097 µm
           AVERAGE PORE DIAMETER (4V/A) =   0.1144 µm
                          BULK DENSITY =   0.6928 g/mL
           APPARENT (SKELETAL) DENSITY =   1.1752 g/mL
                              POROSITY =    41.05 %
                     STEM VOLUME USED =       11 % ****
```

Appendix 4

Determination of nifedipine in plasma after oral administration of nifedipine erosion matrix pellet capsule and Adalat® soft gelatin capsule in fasted dogs.

HPLC METHOD VALIDATION:

DETERMINATION OF NIFEDIPINE IN PLASMA AFTER ORAL ADMINISTRATION OF NIFEDIPINE EROSION MATRIX PELLETS AND ADALAT® SOFT GELATIN CAPSULES IN FASTED DOGS.

1. TEST ARTICLES:

Nifedipine erosion matrix pellets (30 mg capsules, Lot # KM 280/2).

Adalat® soft gelatin capsules (10 mg and 20 mg, Lot # 6 EAB and 5 HAX respectively manufactured by Bayer Corporation, West Haven, CT, USA).

2. HPLC METHOD:

System:

Pump: Waters 600 E Multi Solvent Delivery System (Waters Corporation, Milford, MA, USA).

Injector: Waters 717 Plus Auto Sampler (Waters Corporation, Milford, MA, USA).

Column: Zorbax ODS, 4-6 microns reverse phase, 25 cm X 4.6 mm (I. D., Dupont Inc., Wilmington, DE).

Heator: Column Heator Model Code 600 (Waters Corporation, Milford, MA, USA).

Detector: Variable wavelength detector, Model Spectra Physics 100, UV/VIS (Spectra Physics, USA).

Parameters:

Flow Rate: 0.8 mL/min

Injection Vol: 20 μL

Col Tempt: 55°C

Col Pressure: 1200 Psi

Detector: λ_{max} , 237 nm, 0.001 AUFS

Run Time: 30 minutes

Solutions:

Mobile Phase:

0.01 M disodium hydrogen phosphate buffer : methanol (45:55) was mixed for 30 minutes . Before mixing the buffer was brought to pH 6.1 with 50% v/v phosphoric acid. This solution was then sonicated for 10 minutes and was filtered through a 0.5μ filter.

Extraction Solvent:

Chloroform : acetone were mixed in ratio of 1:1 for 30 minutes and was used as the extraction solvent for nifedipine from the plasma.

3. LINEARITY:

Linearity of nifedipine in methanol and plasma samples spiked with standard methanolic solution of nifedipine was determined by simple linear regression method. Figure 1

depicts the standard curve and linear regression of nifedipine in methanol and plasma. The following concentrations were used for linearity determinations.

Solution #	Concentration in methanol and plasma (μg/mL)
1.	0.05014
2.	0.10028
3.	0.20050
4.	0.40010
5.	0.60480
6.	0.80220
7.	1.00280
8.	10.02800

Correlation coefficient for linearity determinations in methanol was 0.9998 and in plasma was 0.9940. Extraction ratio of drug from plasma to organic phase at all concentrations was not less than 95 %.

4. PRECISION:

Assay precision was determined by plotting the peak height ratios of triplicate injections of nifedipine samples of known concentrations against the standard curves generated in the previous section. The mean % difference between the actual concentration of the samples and that determined by the standard curve were always below 5% during the entire analysis period.

5. REPRESENTATIVE CHROMATOGRAMS:

Figures 2 through 41 are the chromatograms of plasma samples after injection, obtained from four dogs each administered with nifedipine erosion matrix pellet capsule (30 mg/dog/day) at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours. Figures 42 through 73 are the chromatograms of plasma samples after injection , obtained from four dogs each administered with Adalat® soft gelatin capsule (10 + 20 mg/dog/day) at 0, 0.5, 1, 2, 4, 6, 8 and 12 hours.

Figure 1

Calibration graph of nifeipine in methanol and plasma.

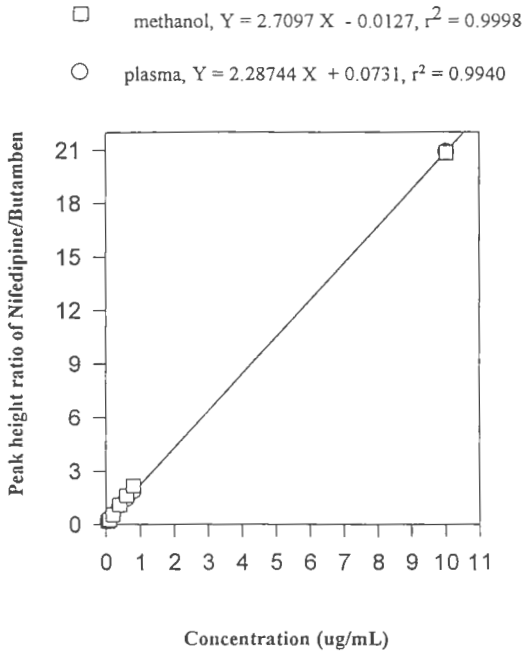

Figure 2

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.

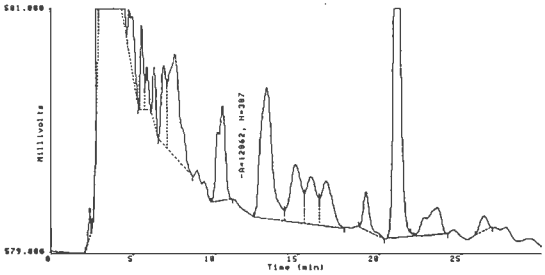

Figure 3

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.

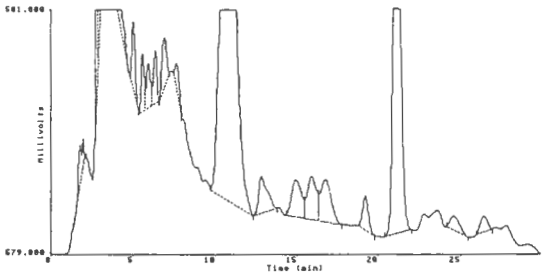

Figure 4

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.

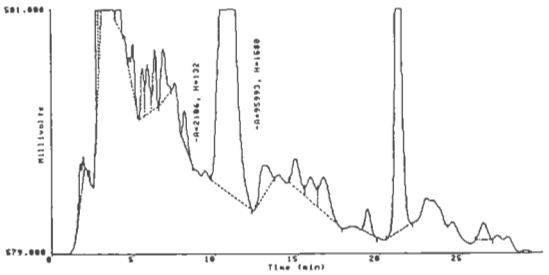

Figure 5

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.

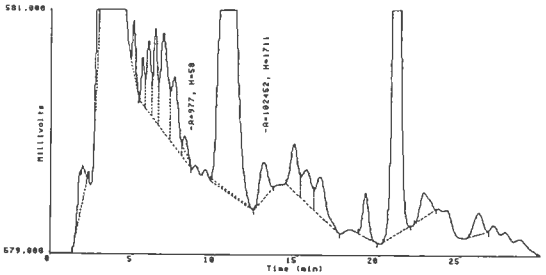

Figure 6

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.

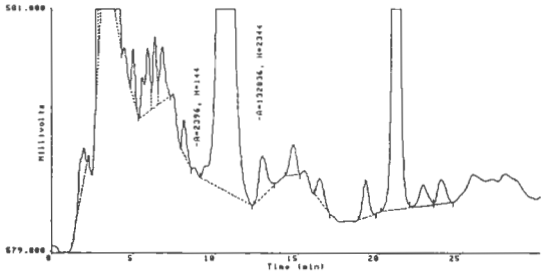

Figure 7

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.

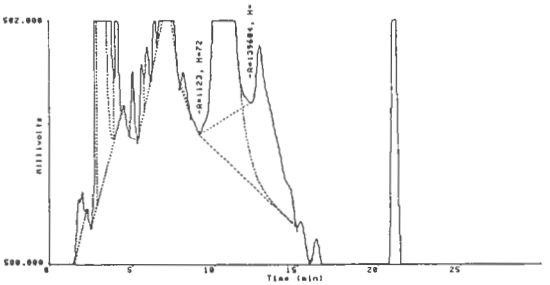

Figure 8

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.

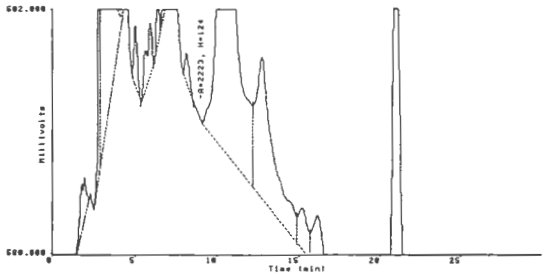

Figure 9

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.

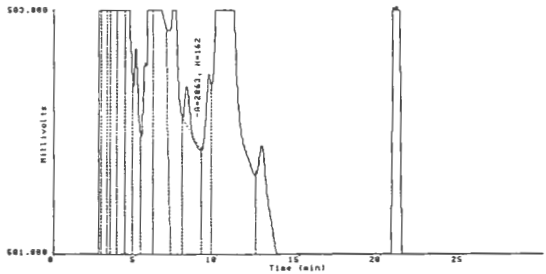

Figure 10

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.

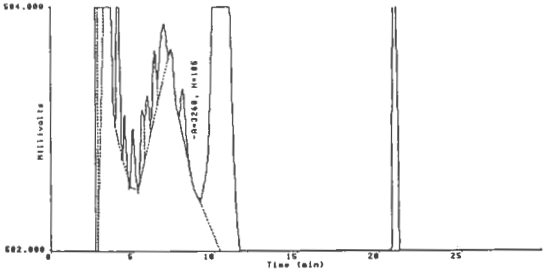

Figure 11

Chromatogram of plasma sample obtained from dog # 1 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.

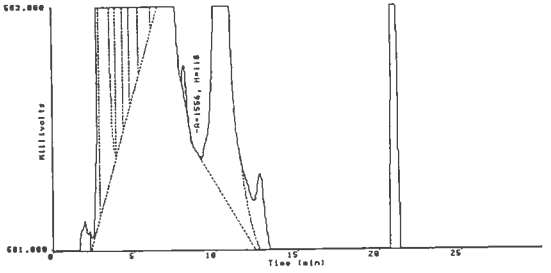

Figure 12

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.

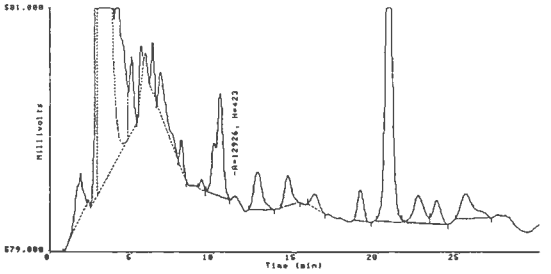

Figure 13

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.

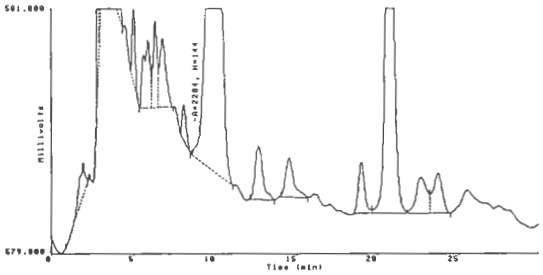

Figure 14

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.

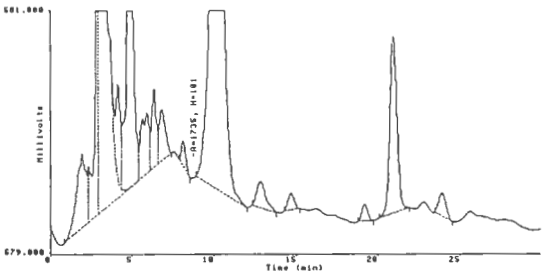

Figure 15

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.

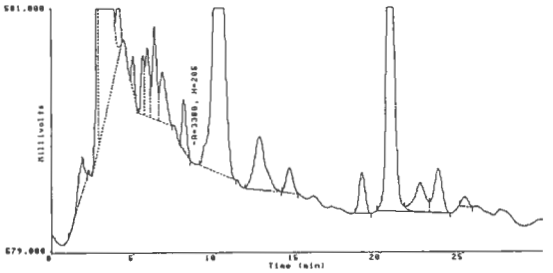

Figure 16

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.

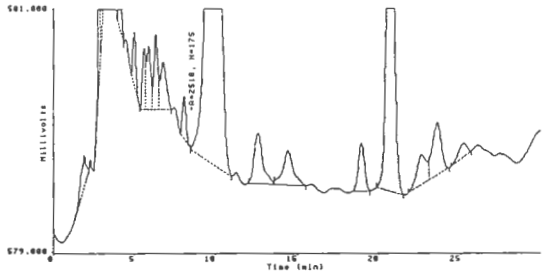

Figure 17

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.

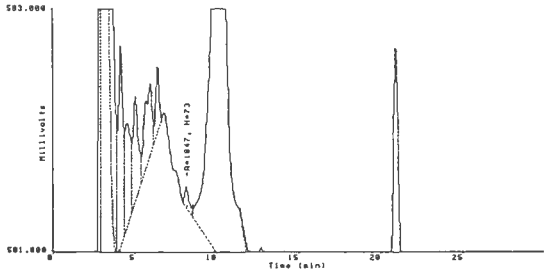

Figure 18

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.

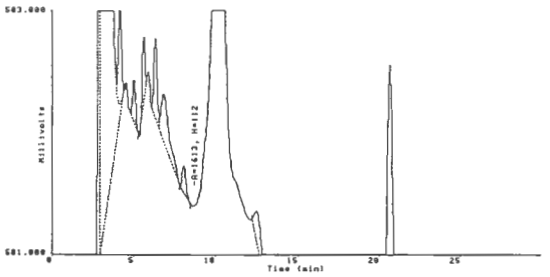

Figure 19

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.

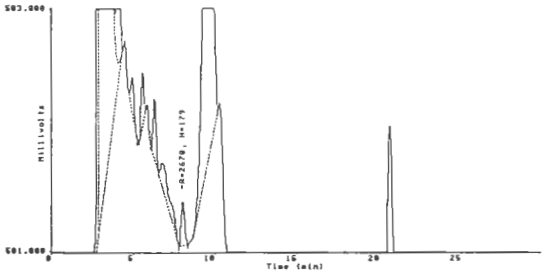

Figure 20

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.

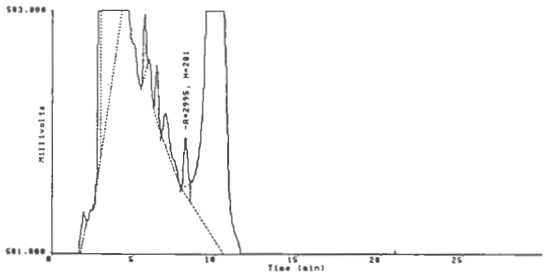

Figure 21

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.

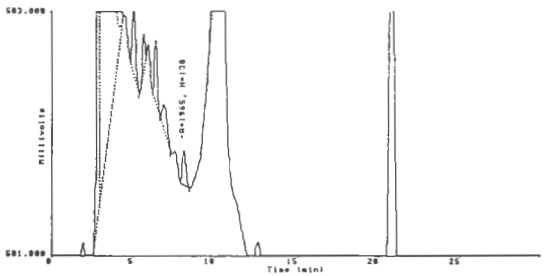

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Figure 22

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.

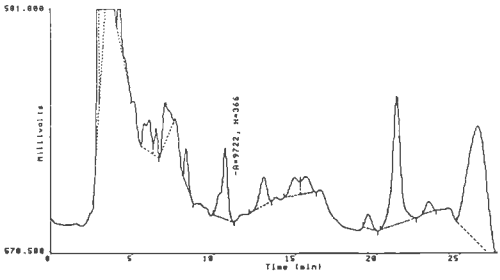


Figure 23

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.

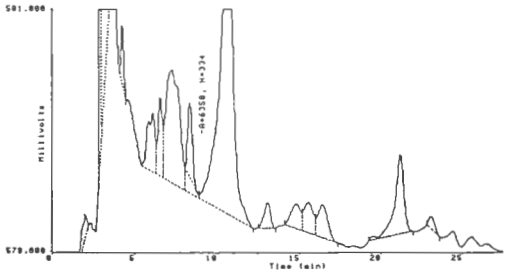


Figure 24

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.

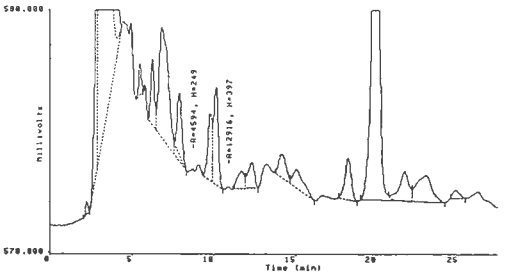


Figure 25

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.

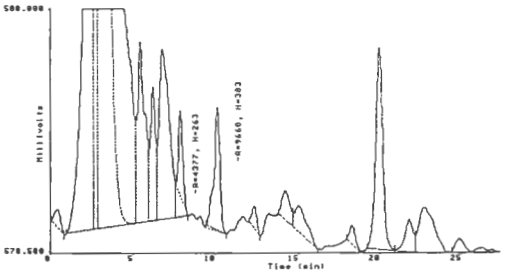


Figure 26

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.

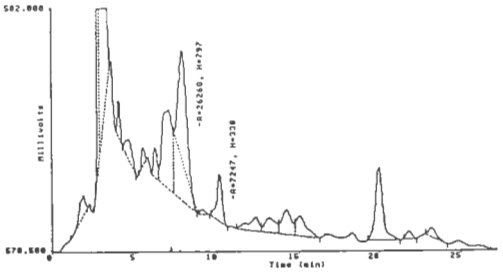


Figure 27

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.

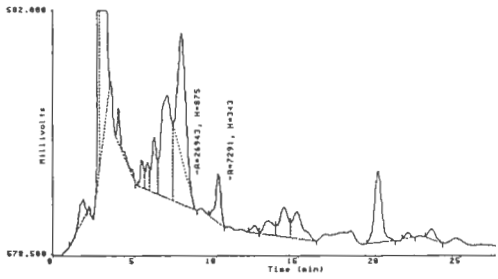


Figure 28

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.

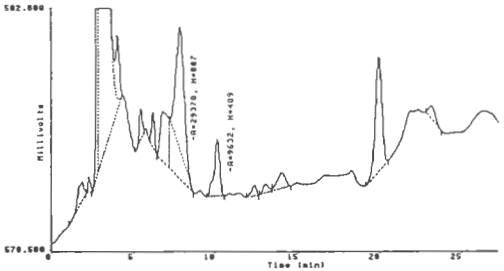


Figure 29

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.

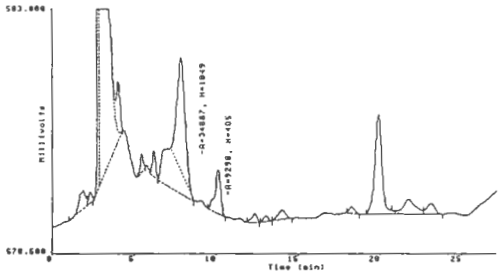


Figure 30

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.

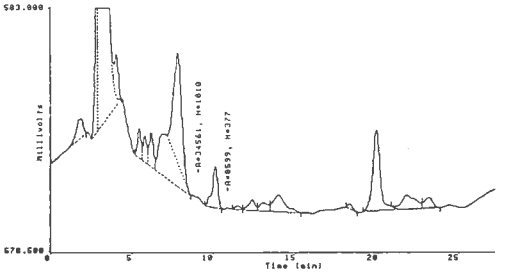


Figure 31

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.

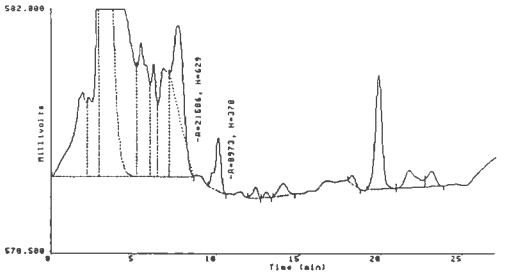


Figure 32

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.

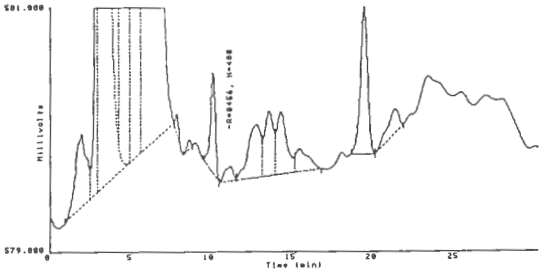


Figure 33

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.

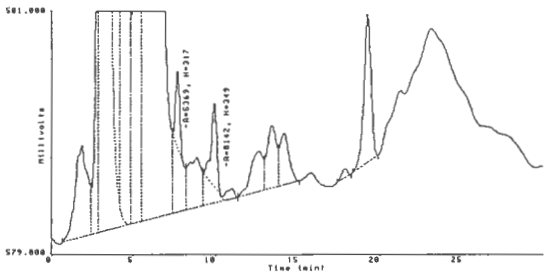


Figure 34

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.

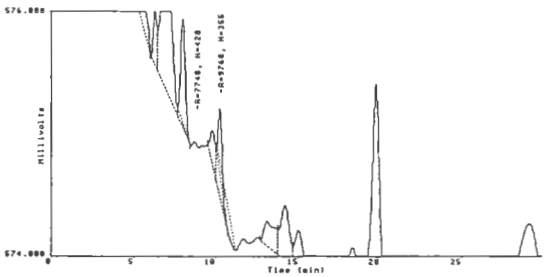


Figure 35

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.

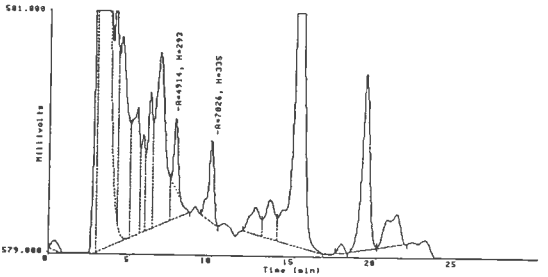


Figure 36

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.

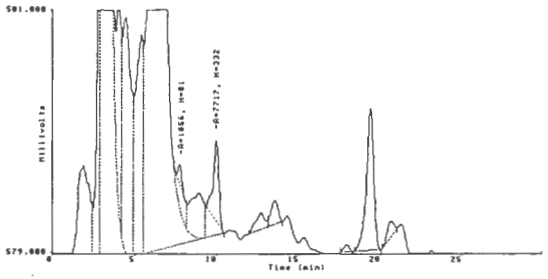


Figure 37

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.

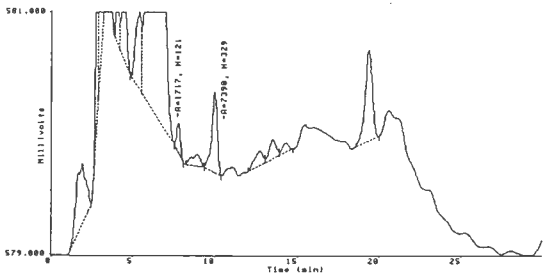


Figure 38

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.

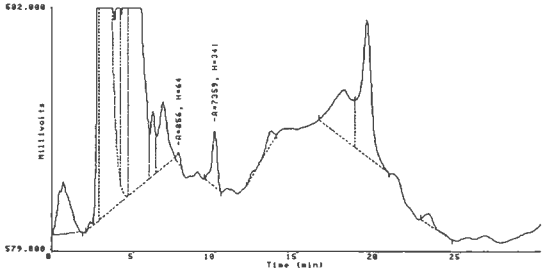


Figure 39

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.

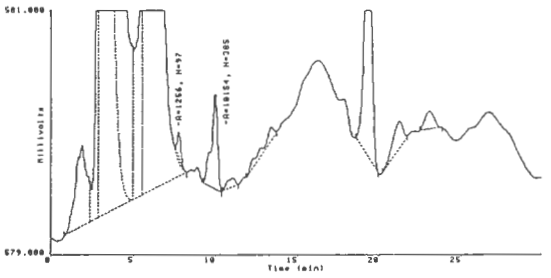


Figure 40

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.

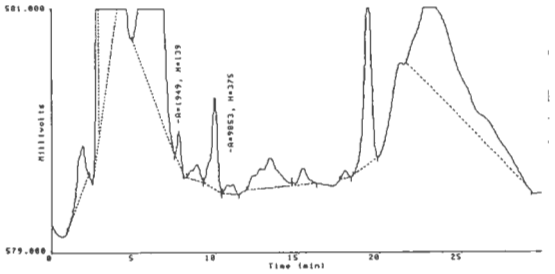


Figure 41

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.

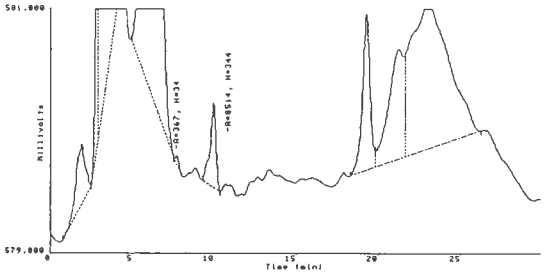


Figure 42

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 0.0 hours.

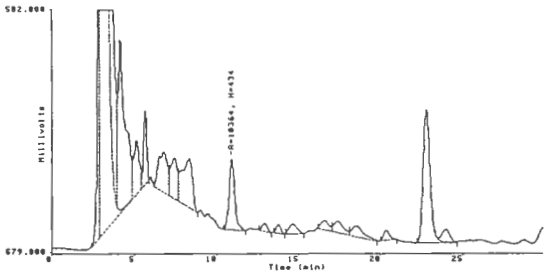


Figure 43

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 0.5 hours.

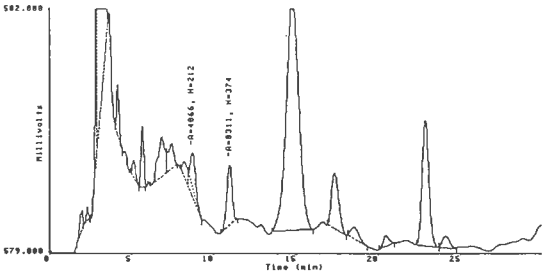


Figure 44

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 1.0 hours.

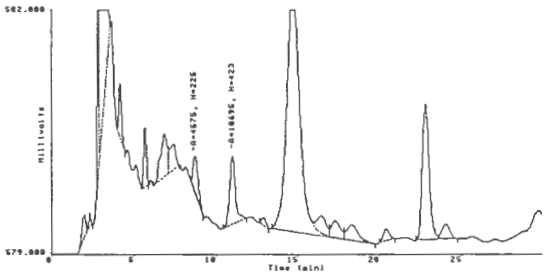


Figure 45

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 2.0 hours.

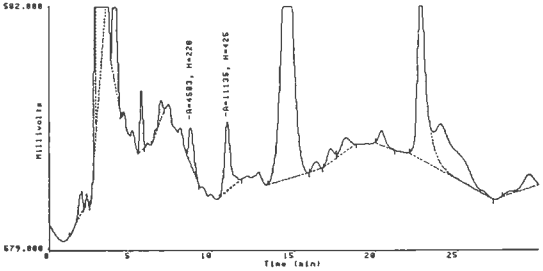


Figure 46

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 4.0 hours.

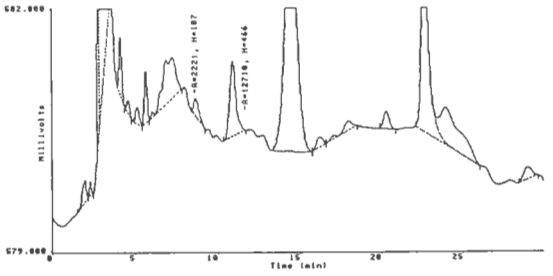


Figure 47

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 6.0 hours.

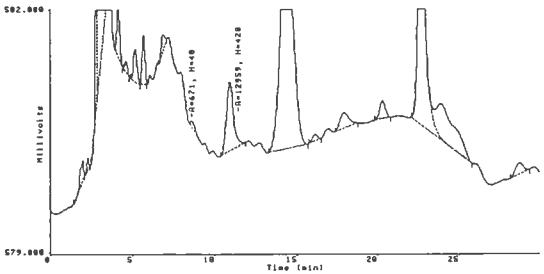


Figure 48

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 8.0 hours.

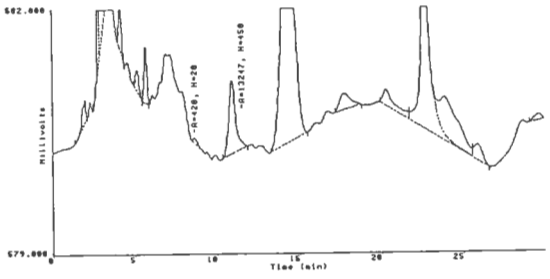


Figure 49

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 12.0 hours.

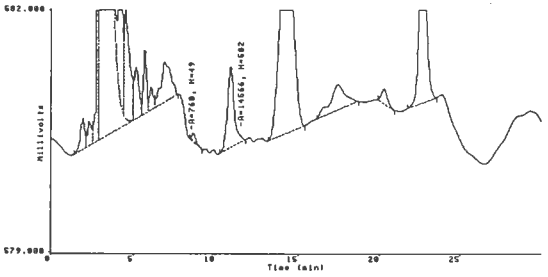


Figure 50

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 0.0 hours.

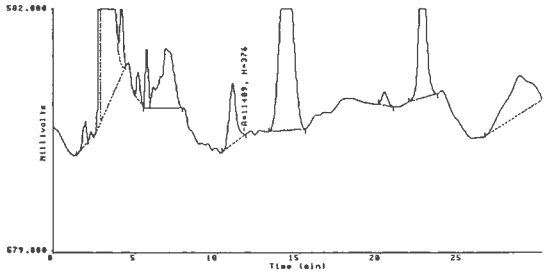


Figure 51

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 0.5 hours.

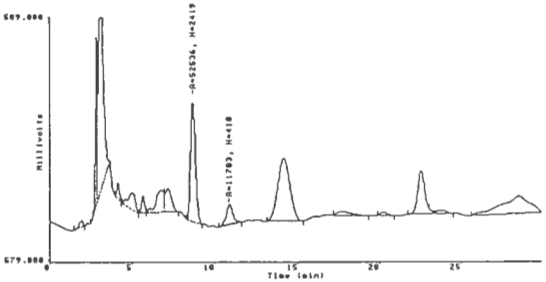


Figure 52

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 1.0 hours.

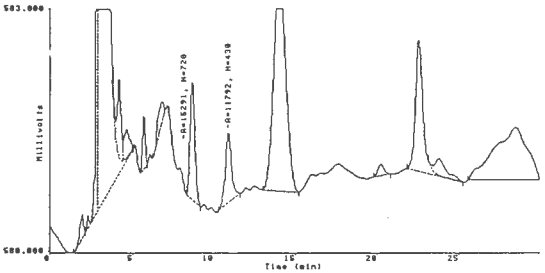


Figure 53

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 2.0 hours.

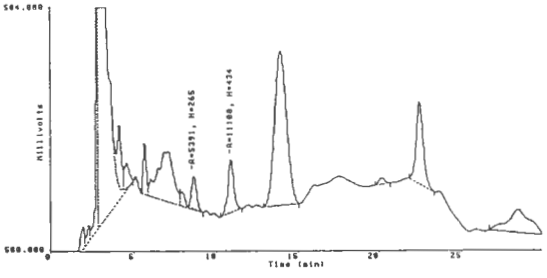


Figure 54

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 4.0 hours.

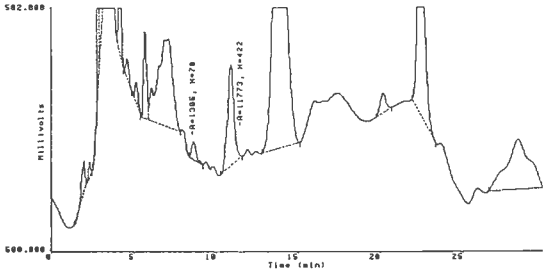


Figure 55

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 6.0 hours.

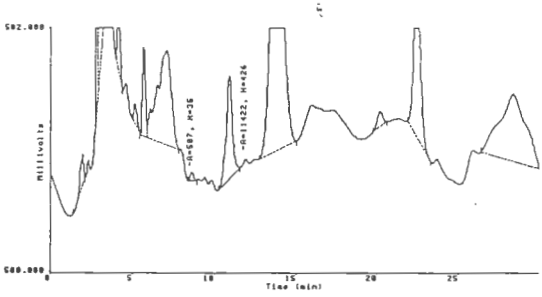


Figure 56

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 8.0 hours.

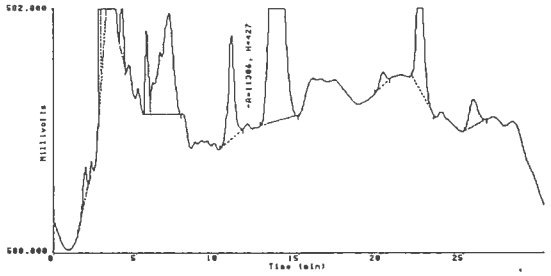


Figure 57

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 12.0 hours.

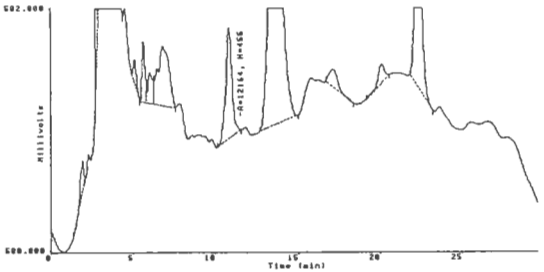


Figure 58

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 0.0 hours.

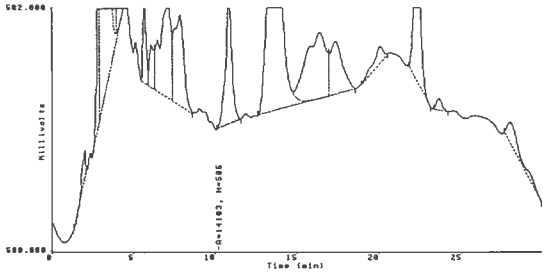


Figure 59

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 0.5 hours.

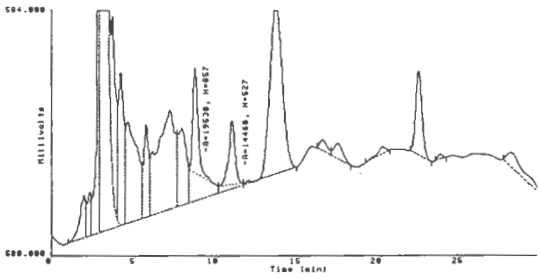


Figure 60

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 1.0 hours.

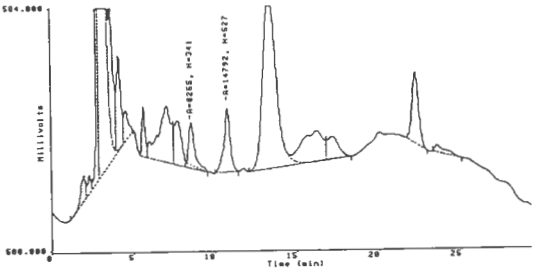


Figure 61

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 2.0 hours.

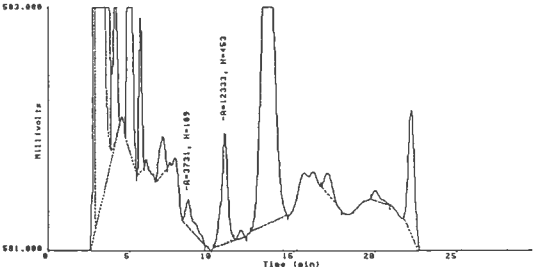


Figure 62

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 4.0 hours.

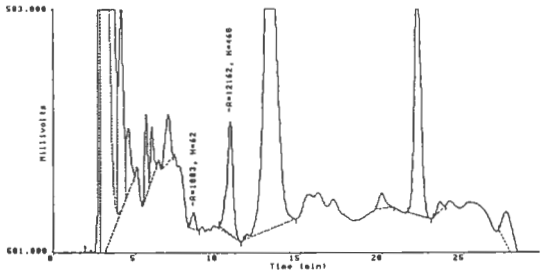


Figure 64

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 8.0 hours.

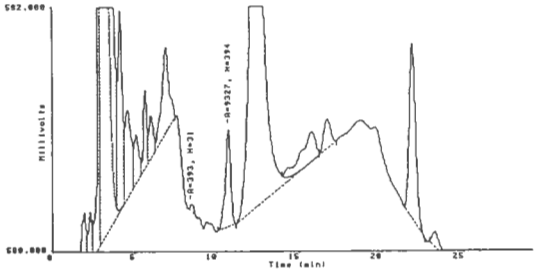


Figure 65

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 12.0 hours.

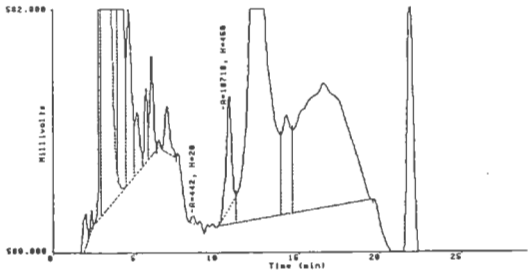


Figure 66

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 0.0 hours.

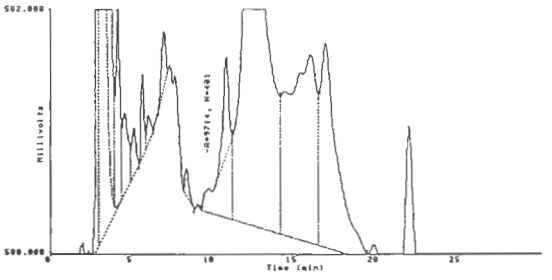


Figure 67

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 0.5 hours.

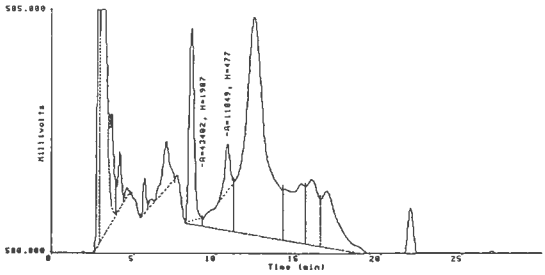


Figure 68

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 1.0 hours.

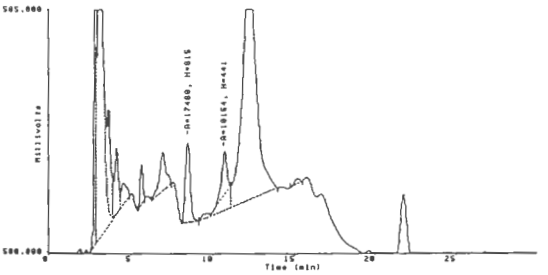


Figure 69

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 2.0 hours.

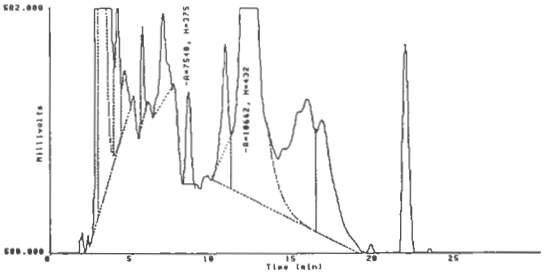


Figure 70

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 4.0 hours.

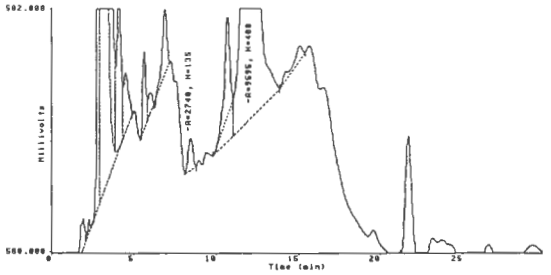


Figure 71

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 6.0 hours.

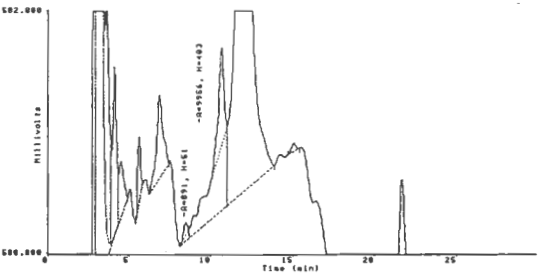


Figure 72

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 8.0 hours.

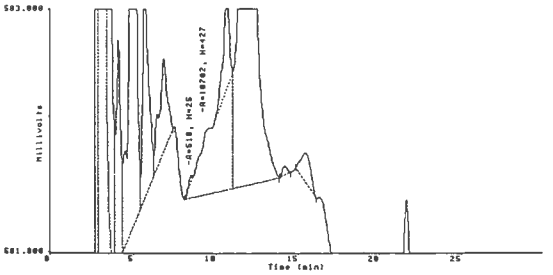
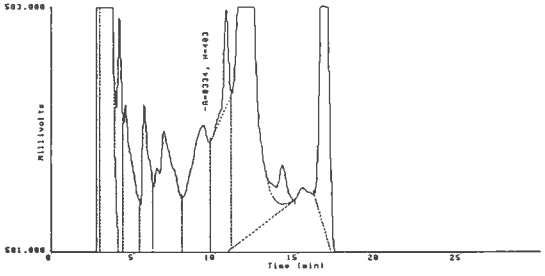


Figure 73

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 12.0 hours.



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