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Optimization and Its Applications on Pharmaceutical Conventional and Extended Release Solid Dosage Forms

Hann Rong Chueh
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OPTIMIZATION AND ITS APPLICATIONS ON
PHARMACEUTICAL CONVENTIONAL AND EXTENDED RELEASE
SOLID DOSAGE FORMS

BY
HANN RONG CHUEH

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

1991

DOCTOR OF PHILOSOPHY DISSERTATION
OF
HANN RONG CHUEH

APPROVED:

Dissertation Committee

Major Professor _____

DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

1991

ABSTRACT

In the pharmaceutical industry, the product and process development problems usually involve a number of independent variables and are normally characterized by multiple objectives. Computer optimization techniques consisting of statistically valid experimental design can be employed to provide an economical way to obtain efficiently these multiple response parameters.

Acetaminophen is a poorly compressible analgesic and antipyretic drug with high dose level resulting in a corresponding very large tablet and poor compactability, the amount of added compressible excipient required to produce acceptable compaction behavior therefore is increased. Also, most commercially available high dose (500 mg) acetaminophen tablets are manufactured from slugging or a patented roller-compactor process. In this present study, the utility of 50 micron microcrystalline cellulose (Emcocel) as a wet granulation excipient in the high dose acetaminophen tablet formulation was investigated. A four factor factorial, central, composite Box-Wilson experimental design was applied to optimize a tablet formulation containing high dose (500 mg) acetaminophen (ACMP), Emcocel™, a 50 micron microcrystalline cellulose (MCC), and povidone. The percentage of Emcocel™, percentage of povidone, amount of granulating water and wet granulation time were used as independent variables for optimizing some tablets response parameters. Response parameters for final ACMP tablets were percentage of ACMP dissolved at fifteen minutes, disintegration time,

required compression force for producing 8 Kg hardness tablets and friability. The data were analyzed by means of quadratic response surface models. Response surfaces were generated for tablet percentage of dissolution, disintegration time, required compression force and friability as a function of independent variables. The models were validated for accurate prediction of response characteristics and used to identify the optimum formulation. The results suggest that an optimum 500 mg ACMP tablets having a volume similar to commercial products made by precompact ACMP can be produced by wet granulation process utilizing 50 micron Emcocel™. The tablets made also showed acceptable dissolution behavior, hardness, disintegration time and low friability when compared to commercially available 500 mg ACMP tablets.

Additionally, a two factor factorial central, composite Box-Wilson experimental design was employed to develop and optimize a novel extended release floating and bioadhesive tablet formulation containing 240 mg sotalol hydrochloride and polymeric components. The ratio of sodium carboxymethylcellulose (NaCMC) to hydroxypropylmethylcellulose (HPMC) and the ratio of ethylcellulose to crosspovidone were used as formulation variables for optimizing some tablets response parameters, such as bioadhesive capability, dissolution characteristics, tablet density and required compression force for producing 6 Kg hardness tablets. The data were also analyzed by means of quadratic response surface model. Response surfaces were generated as a function of formulation variables. An optimum direct compression bioadhesive and floating tablet

formulation of sotalol HCl tablet was achieved by considering dissolution release characteristic as primary objective and using required compression force, bioadhesive capability as constraints within the experimental region. The surface model was validated by preparing and evaluating the predicted optimum formulation.

To understand the release mechanism of drug from extended release polymeric matrix tablet, the swelling and dissolution behavior of different molecular weight PEO (polyethylene oxide) polymers in distilled water at 37 °C was investigated. Due to the swelling of PEO matrix discs, considerable volume expansion was observed. Molecular weight is an important determinant of PEO dissolution rate, which was inversely proportional to the molecular weight of PEO. The results supported the hypothesis that dissolution of high molecular weight PEO is controlled by the inward diffusion of water and outward diffusion of polymer through the boundary layer. The influence of the molecular size and solubility of four tracer compounds (phenylpropanolamine HCl, theophylline, sotalol HCl and bovine serum albumin) and the effect of the tracer/PEO ratio on the dissolution rate in SIF (simulated intestinal fluid) were determined.

In the process of bioadhesion assessment, an apparatus to be equipped with Instron tensile tester was developed to evaluate quantitatively the bioadhesive properties of various bioadhesive tablets. The equipment was designed to measure the forces required to separate two parallel surfaces (tablet and membrane) in both horizontal and vertical planes. In this work, in addition to the

detachment force and adhesion work, the shear force necessary for separating bioadhesive tablet and synthetic membrane or biological tissue (rabbit stomach mucosa) were also determined since the majority of gastrointestinal mucosa surface area possesses some elements of tangential shear motion. The effects of different quantities and types of bioadhesive polymer on the tablet bioadhesive capability were also determined. The results showed good agreement with some previous findings that the relative adhesion of the tablet formulations was dependent on the bioadhesive polymer content. It was also found that tablet made with sodium carboxymethylcellulose (NaCMC) possessed the best bioadhesive power when compared to tablets made with polycarbophil and carbopol 974P.

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The advice and assistance provided by the faculty members and fellow graduate students of the Department of Pharmaceutics are gratefully acknowledged. To Alain and Mary Kay with whom I have enjoyed the greatest of friendship.

Last but not least, I would like to thank my wife for her love, support and understanding. I want to dedicate this work to my wife, my parents and family members for being a constant source of encouragement and inspiration to achieve my goals in life, especially to my mother who passed away in 1985 but will be in my heart forever.

PREFACE

This dissertation is prepared in accordance with the format of the "Manuscript Thesis Plan" option described in section 11-3 of the Graduate Manual at the University of Rhode Island. The these is divided into four sections.

Section I consists of a general introduction of the problems and objectives of my research. Section II, which is the main body of this dissertation comprises four manuscripts which have been written in the contemporary format required for publication in international scientific journals. Section III contains a manuscript on the topic of bioadhesion assessment which was utilized in our study. Section IV consists of three appendices which contain additional information and some experimental details not normally included in published manuscripts but which are useful background for understanding the manuscripts in section II. The bibliography at the end of the dissertation cites all the sources and literatures used in writing this dissertation.

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LIST OF PUBLICATIONS AND PRESENTATIONS

Manuscript I was presented in part as the 1990 American Association of Pharmaceutical Scientists (AAPS) national meeting in Las Vegas and will be submitted for publication in the International Journal of Pharmaceutics.

Manuscript II will be submitted for publication in the journal Drug Development & Industrial Pharmacy.

Manuscript III will be submitted for publication in the Journal of Controlled Release.

Manuscript V will be presented in part as the 1991 American Association of Pharmaceutical Scientists (AAPS) national meeting in Washington and will be submitted for publication in the journal Drug Development & Industrial Pharmacy.

SECTION I

INTRODUCTION

For many years, pharmaceutical formulation scientists have used knowledge derived from individual experience to develop pharmaceutical dosage forms. The development of formulation and process are mostly based on intuitive and subjective judgement rather than a rational operation, therefore the whole process may or may not be optimal. Often formulation scientists are challenged with the problems of producing a final product which meets not only the requirements placed on it from a bioavailability standpoint, but also the practical mass production criteria of process and product reproducibility with limited time and funds. Trial and error approaches are inefficient and costly, and extrapolations made from them can be inaccurate. Stringent federal regulations, such as those promulgated by the Food and Drug Administration (FDA), require production process to be well-characterized and validated. In addition, during the development of a drug product for New Drug Application (NDA) submission, it is necessary to characterize the performance of the product during the process and to demonstrate that the final dosage form will behave in a predictable manner.

Optimization techniques consisting of statistically valid experimental design were originated in the mathematics and chemical engineering fields (1) to provide an economical way to obtain efficiently the most information while expending the least amount of experimental effort. Although optimization techniques have been utilized on some pharmaceutical formulation development

processes (2-5), the major emphasis in these studies was the optimization of conventional dosage forms. However, there appears to be little published data which demonstrates the application of optimization processes to difficult formulation tasks such as the high dose acetaminophen - microcrystalline cellulose (MCC) (6-9) wet granulation process. When dealing with the manufacturing high dose tablets by means of a low shear mixing and wet granulating technique, there are many formulation and process variables may affect the physical properties of the final tablet, especially, acetaminophen is a brittle, poorly compressible analgesic and antipyretic agent with high dose level, resulting in a corresponding very large tablet and poor compressibility, the amount of added excipient (MCC) required to produce acceptable compaction behavior is increased. The ratio of ACMP to MCC and some other process variables are required to be optimized to produce an acceptable tablet volume and physical properties. Meanwhile, most commercial tablets containing 500 mg acetaminophen are produced from slugging or pre-compacted granulation by variation on a patented roller-compactor process (10) and these newly formulated products would have to undergo bioavailability, stability and possibly even safety studies.

Also, in the pharmaceutical industry there is an increasing interest in the development and utilization of extended-release drug delivery systems. Oral sustained release dosage forms have received a great deal of attention, since they are the most convenient to administer. Nevertheless, the published literature also is devoid of

quantitative data illustrating the utility of optimization techniques to extended-release solid dosage forms (to control extended release characteristic (dissolution behavior) as a function of time and pH of the dissolution medium) (11, 12), I hypothesized that an efficient optimization technique utilizing Response Surface Methodology can be used not only to develop a conventional high dose acetaminophen-MCC wet granulated tablet formulation which would possess suitable physical properties but also to develop an improved extended-release sotalol solid dosage formulation which would retain the active in the upper part of gastrointestinal tract for a satisfactory time so as to exhibit acceptable in vitro dissolution rate and satisfactory in vivo bioavailability. Sotalol is a drug which appears to have absorption from the gastrointestinal tract limited to the upper part of the small intestine, thus it is desirable that an extended release drug delivery system should possess the ability to remain for long periods in the stomach. In recent years, there have emerged two comprehensive approaches for enhancing the drug residence time in the stomach, floatation and bioadhesion drug delivery systems. However, the ability of a floating drug delivery systems to remain in the stomach is distinctly limited as the stomach empties almost completely at quite short intervals. Similarly the efficiency of a bioadhesive drug delivery system will be adversely affected when the stomach is full and semi-liquid contents are churning around under the influence of peristaltic movement. Thus a system which has both floatation and adhesive properties would give a uniquely valuable ability to remain in the stomach. The review of published literature indicates that there is no drug delivery system which

possesses a combination of floatation and adhesion characteristics to prolong residence time in the stomach. It was my intention to develop a novel drug delivery system which is both bioadhesive and capable of floatation to remain in the stomach for a longer period of time and to have an extended release of sotalol from the the delivery system.

The application of an optimization technique consisting of statistically valid experimental design to pharmaceutical formulation development would provide an efficient and economical method to acquire the necessary information to understand the relationship between controllable (independent) variables and performance or quality (dependent) variables (13). The optimization process provides not only efficient use of resources, but also a method to obtain a mathematical model which can be used to characterize and optimize a formulation or process. Furthermore, by accurately defining the whole system, optimization techniques are a useful aid to process validation.

The wet granulation process has been used as an alternative for high dose and poorly compressible active ingredients. It offers several advantages over other methods, for instance, it improves flowability, resistance to segregation and compression characteristics by increasing the particle size and cohesion (14). Acetaminophen is a drug which requires a high dose, thus resulting in a large tablet. Since the drug also has poor compactability, the amount of added excipient (MCC) required to produce acceptable compaction behavior

must be very completely controlled. However, during the wet granulation process, there are many process and formulation variables which will affect the physical properties of the granules and of the final tablets (15). As the number of independent variables increase, the number of experiments required to evaluate the effect of different levels of each variable will be increased substantially. With optimization studies, one is able to obtain the most information with the least amount of experimental effort.

Some physical-chemical properties and limited pharmacokinetic data pertaining to conventional sotalol dosage form have been reported in literature (16-19). The effect of formulation and process variables on the physical properties of sotalol tablets such as release characteristic of sotalol, hardness, friability and compaction characteristic have to be determined. With the application of this optimization technique, it is believed that it is possible to develop a cost effective conventional acetaminophen tablet formulation and also to develop an improved extended release formulation of sotalol with enhanced release characteristic, physical and chemical stability.

The specific objectives of this research were:

1. To investigate the utility of 50 micron microcrystalline cellulose (Emcocel™) as an excipient in the high dose(500 mg) acetaminophen tablets made by conventional wet granulation process.
2. To address the characterization and optimization of 500 mg acetaminophen wet granulation tablets by using statistical response

surface experimental design, an instrumented low shear planetary Hobart mixer and an instrumented rotary tablet press.

3. To develop an extended release, floating and bioadhesive tablet by using computer optimization techniques employing response surface methodology.

4. To study the release mechanisms of different drugs from swellable and erodible hydrophilic polymers by characterizing the swelling and erosion processes of polymers.

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SECTION II

**OPTIMIZATION OF A HIGH DOSE (500 MG) ACETAMINOPHEN-
MICROCRYSTALLINE CELLULOSE TABLET**

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ABSTRACT

A four factor factorial, central, composite Box-Wilson experimental design was applied to optimize a tablet formulation containing high dose (500 mg) acetaminophen (ACMP), Emcocel™, a 50 micron microcrystalline cellulose (MCC), and povidone. The percentage of Emcocel™, percentage of povidone, amount of granulating water and wet granulation time were used as independent variables for optimizing some tablets response parameters. Response parameters for final ACMP tablets were percentage of ACMP dissolved at fifteen minutes, disintegration time, required compression force for producing 8 Kg hardness tablets and friability. The data were analyzed by means of quadratic response surface models. Response surfaces were generated for tablet percentage of dissolution, disintegration time, required compression force and friability as a function of independent variables. The models were validated for accurate prediction of response characteristics and used to indentify the optimum formulation. The

results suggest that an optimum 500 mg ACMP tablets having a volume similar to commercial products made by precompact ACMP can be produced by wet granulation process utilizing 50 micron Emcocel. The tablets made also showed acceptable dissolution behavior, hardness, disintegration time and low friability when compared to commercially available 500 mg ACMP tablets.

INTRODUCTION

Optimization of product properties originated within the chemical engineering field (1). A practical and comprehensive approach for pharmaceutical use in situations involving more than two variables was reported (2) that requires minimal familiarity with computer programming or optimization mathematics. Through the process of optimization, the researcher may discover solutions to formulation challenges which would otherwise be dismissed as unrealistic. The technique has been extended to obtain some desirable pharmaceuticals and pharmacokinetic parameters by variation of formulation and process parameters (3-7).

Standard formulation methods often involve running a grid search about a formulation or process starting point. The initial point is either an educated guess or deduced from prior art. Such grid searches are expensive in terms of time, labor and materials, and also may result in a missed solution to the problem. One reason for the existence of serendipitous solutions is illustrated by the analogy

of the effects of higher order harmonics produced by constructive from the interaction of two or more fundamental frequencies. Similarly, either the concentrations of two or more ingredients, or the levels of two or more processing parameters may interact to produce an unanticipated result. This is sometimes referred to as synergism or potentiation, in which the effect of supposedly independent factors is many fold the sum of effects of the factors taken separately. Thus, some factors may be discovered to be interdependent. Utilizing the tool of optimization, workers have developed and marketed a tablet formulation containing 800 mg of ibuprofen, a poorly compactable material ~~melting~~ at about 75°C, in a tablet with a minimum of excipient (8). This made possible the manufacture of a tablet of palatable dimensions and acceptable hardness, friability and dissolution performance.

A second advantage obtained when using optimization is the substantial time and cost savings due to the inherent efficiency of a rational experimental design (9). No theoretical model is required to be followed in advance of experimentation, curve fitting yields an empirical function. Subsequently, that function can be used to extrapolate results from those obtained at nodes in the experimental matrix to predict outcomes at points between the nodes, This allows one to draw tentative conclusions for hypothetical experiments, so that it may not be necessary to perform the actual experiment unless the prediction is favorable. One computer package called X-Stat (John Wiley and Sons) includes experimental design, data entry spreadsheets, curve fitting by various functions and contour plotting

of results. Using contour plots, the effects of multiple factors may be viewed simultaneously and conclusions drawn.

In this present study, acetaminophen was selected as a model drug because it requires a high dose (500 mg), resulting in a correspondingly large tablet. Since this drug also has poor compactability, the amount of added excipient, microcrystalline cellulose, required to produce acceptable compaction behavior is increased (10-13), the ratio of ACMP to Emcocel™ and some process variables are required to be optimized to produce an acceptable tablet volume and physical properties. Also, most commercial tablets containing 500 mg acetaminophen are produced from pre-compacted granulation by variation on a patented roller-compactor process. This work shows the attributes of tablets made by an alternative densification process, wet granulation. 50 micron MCC, as opposed to 90 micron MCC, is similar in particle size to the ACMP powder, which is expected to improve mixing in the manufacturing process and wettability in the disintegration process.

EXPERIMENTAL

Wet Granulation

1. Dry Blending - The total weight of both acetaminophen (Ruger Chemical Co., Lot# R36192B15) and Microcrystalline cellulose (Emcocel™, Edward Mendell Co., Lot # 3210X) was held constant at 300 grams for all experiments. Acetaminophen(ACMP) was weighed out and placed into the bowl, Emcocel™ was weighed out and added

on top of the ACMP. The teflon-coated planetary mixer blade was of the cardioid (anchor) type, the blade was run at 64 rpm for ten minutes to achieve dry blending. At ten minute mark, binder (povidone solution) addition was initiated. The pre-dissolved povidone aqueous binder solution was added by peristaltic pump to the powder blend with continuous mixing at 64 rpm. During the course of each experiment, the binder addition rate was constant, as determined by timing the fill rate of a graduated cylinder. Because of the experimental design, the total volume of granulation fluid for each batch was required to be delivered over a different length of time. Consequently, the corresponding flow rate for different batches ranged from 6 to 20 grams/minute. The mixing was continued for one minute longer after the binder liquid addition was completed in order to assure a homogeneous distribution of the last portion of binder solution.

2. Wet Screening- The granulated mass was gently hand-screened through a #6 mesh sieve.

3. Drying- A calibrated crossflow oven was used for drying at 45 °C. The crossflow air was controlled at 1.3 L/sec. Custom-made rectangular drying trays, sized 14 cm by 24 cm, were lined with heavy aluminum foil, the exposed surface area of 200 cm² at a constant bed depth of 3 cm. Drying was halted when a full-thickness sample produced an L.O.D. (Loss On Drying) of 1.0 +/- 0.2 %. The L.O.D. test utilized 10 grams of sample triturated to pass a 20 mesh screen, with the lamp set at five watts for ten minutes.

4. Dry Screening- Dried granules were gently hand-screened through a 12 mesh screen, selected to suit the 0.47 inch flat face punch diameter, for tablet manufacture.

Tabletting

1. Lubrication- Granulations were lubricated with 0.5 % of magnesium stearate. The lubricant was hand-screened through a 40 mesh sieve, then added on top of the granulation in the mixing container. Mixing was continued for five minutes in a Turbular blender.

2. Compaction- Tablets were compressed on an instrumented Stoke B-2 rotary press at 30 rpm. Tablet weight was adjusted to obtain 500 mg of active ingredient. Tablet press pressure was adjusted to obtain 8 kg hardness tablets, the required compression force was measured by the piezoelectric force transducer located in the eyebolt. The analog data from the piezoelectric force transducer were converted to the digital form by the analog to the digital converter. The digital output was then collected and analyzed on personal computer.

Tablet Evaluation

1. In vitro Dissolution- The USP Method II (paddle method) was used and six tablets were tested for each batch. The dissolution medium was 900 ml of pH 5.8 phosphate buffer solution equilibrated at 37 °C and stirred at 50 rpm. The dissolution medium volume was kept constant by adding the same volume of fresh dissolution

medium kept at the temperature of 37 °C. Additionally, to ensure total release of drug , the agitation speed was increased to 150 rpm for additional 30 minute. The dissolution samples were diluted and the concentration were determined on a Diode Array Spectrophotometer(Hewlett Packard) at the wavelength of 243 nm as specified in the USP. The mean percentage dissolved was calculated at the fifteen minute sampling point.

2. Disintegration Time- Disintegration time was measured in a USP disintegration time tester with disc (Vanderkamp; Van-Kel industries) in 0.1 N HCl at 37 °C. Six tablets were evaluated for disintegration time.

3. Friability and Hardness- Twenty tablets were evaluated for friability by a Roche friabilator at 25 rpm for four minutes (100 drops). Ten tablets were measured for hardness from Erweka hardness tester.

Experimental Design

The four independent variables and their ranges selected for wet granulation process were summarized in Table I, X1 represents the percentage of EmcocelTM, X2 is percentage (w/w) of binder, X3 represents amount of granulating water and X4 represents the total granulation time. All other processing and formulation variables remained constant throughout the study. Table II listed a total of 31 experiments required in a four factor factorial, central, composite Box-Wilson experimental design (14). This design is based on

factorial design with additional points added to estimate curvature of the response surface. As shown in Table II, the first sixteen experiments represent a half-factorial design for four factors at two levels, these two levels are represented by +1 and -1, analogous to the high and low values in any two level factorial design. For the remaining formulations, three additional levels were selected. The zero level represents a center point midway between the +1 and -1 and the levels noted as +2 and -2 represent axial point at extreme values. The design also includes seven replicate of center points, this allows a lack-of-fit test for the mathematical model, because standard designs with fewer trials would have resulted in confounding among model terms and increased the risk of inaccurate conclusion.

The translation of the statistical design into physical units for the four independent variables is shown in Table III. Table IV summarizes the response parameters measured on the resulting tablets. These parameters are Y1, mean percentage of drug dissolved at fifteen minute sampling point; Y2, disintegration time; Y3, friability and Y4, required compression force for producing 8 kg hardness tablets.

Analysis of Data

All the statistical and regression analysis procedures on the response parameters were performed using the X-STAT software package. Statistical Analysis was carried out which includes the

calculation of mean values for each of the four response parameters in each of 31 experiments.

The sets of data obtained from the statistical analysis were then subjected to computerized regression analysis to determine the fit to a second-order model. These regression models include an intercept and main effect terms of each independent variable, two-way interaction terms and second order effect terms as shown in Table V. A stepwise regression procedure was used to assess all main effects, some two-way interactions and quadratic terms for usefulness in the model to obtain a more adequate regression model for each response parameter (15-16).

RESULTS AND DISCUSSION

Table VI summarizes the response tablet properties obtained from the 31 formulations in experimental design. The percentage of ACMP dissolved at fifteen minutes ranged from 17.3 to 100%, tablet disintegration time ranged from 0.4 to 55 minutes, the required compression force ranged from 9.3 to 28 KN when friability of tablets ranged from 0.2 to 12.4%. For each response property, some variations were observed among formulations.

Table VII to X show the particular model for each of response parameter, these Tables also include computer regression coefficient for each term in the regression model. As can be seen, most of these standard error values are less than 50% of the absolute values of

their regression coefficients. These results indicate the adequacy of the models, also, the high values of confidence level indicate that these variable terms have standard significant effects on the response parameter. Although, there are few terms which do not contribute significantly at 90% confidence level to the model, however, these terms, as a group, do affect the shape of the contour plot. As shown in Table XI, after selecting a modified quadratic model for each response parameter, the F ratio for lack of fit was decreased when compared to F ratio of general quadratic model and smaller than the critical F ratio for significant lack of fit. It indicates that the lack of fit for each model is statistically insignificant at a 90 to 95% confidence limit which means these postulated models are adequate for fitting data. Meanwhile, the high multiple correlation coefficient values of each response parameter denote the adequacy of these models. It implies that the regression equation explains large portion of variation of response parameter about its mean. In Table XI, the high F ratios of regression indicate that many model terms are important for explaining variability, it also reveals 99% confidence regression equation is non-zero.

For each response parameter, the multiple correlation coefficient was greater than 0.91 indicating that there are at least more than 91% of the total variations observed in the response parameter could be explained as being caused by the independent variables in the way described by the equation as shown in Table VII to X. Also, the predicted minimum and maximum values for each response

parameter show good agreement with the experimental results obtained from 31 batches shown in Table VI.

Contour plots for each of response parameters were generated using selected quadratic response surface model. Figure 1 show the effect of Emcocel™ and povidone on tablet dissolution (% of drug released at fifteen minutes sampling point). As can be seen, the percentage of dissolution decreased with the increasing percentage of povidone as percentage of Emcocel™ decreased when the amount of granulating water and granulation time were held at constant values. This is due to the increased disintegration time. As shown in Figure 2, it demonstrates that the tablet disintegration time increased with increasing percentage of povidone as percentage of Emcocel™ decreased. Tablet formulation containing 25 % of Emcocel™, 1 % of povidone and granulated with 94 gram water in eight minutes gives the shortest disintegration time.

In Figure 3, the required compression force decreased with increasing amount of granulating water as percentage of povidone increased. Figures 4 and 5 indicate that a formulation containing 25% of Emcocel, 4.4% of povidone and granulated with 112 gm water in 10 minutes would require the lowest compression force to produce 8 kg hardness tablet. Without sufficient granulation time, formulation containing high percentage of povidone would increase the required compression force in tablet manufacturing process, this is attributed to those hard and dense granules generated from improper distribution of high concentration of binder solution in the

mixing process. These too hard and dense granules do not consolidate very well under low compression force.

Figure 6 demonstrates the effect of Emcocel™ and granulating water on the tablet friability. It indicates when there is more Emcocel in the formulation, the more granulating water are required to agglomerate and produce less friable tablets. Figures 7 to 13 also show the relationship between the response parameter and the independent variables. These Figures illustrate contour line of equal response and the direction in which the gradient has steeper values.

The optimum values obtained from the contour plots for the independent variables in order to obtain the best values for each of the four response variables are given in Table XII. The optimum level of Emcocel™ for maximum percentage of dissolution and minimum required compression force is 25% when the optimum level of Emcocel for the shortest disintegration time and the lowest friability is 21%. The optimum level of povidone for % dissolution and disintegration time is 1%, however, the optimum values for friability and required compression force are 5.8 and 4.4 %, respectively. A range of 94 gm to 120 gm granulating water is required for obtaining the best results of each of response parameters. The optimum range of granulation time is 8 to 10 minutes.

Since in vitro dissolution data may provide an indication of in vivo bioavailability, therefore, the percentage of drug dissolved at 20

minutes was identified as the response parameter of primary concern. It was maximized so as to obtain the fastest dissolution rate. As shown in Table XIII, the constraints used for obtaining the fastest dissolution were that disintegration time should be greater than 0.3 minute, the friability should be less than 0.8% and the required compression force should be less than 14 KN. Additional constraints were the experimental range limits placed on values of all independent variables. The optimum formulation satisfied all constraints simultaneously and provided an optimal value for the primary function, rapid dissolution.

The formulation according to the optimal solution was prepared as shown in Table XIII and tablets were manufactured on the rotary press, tablets properties were also determined. The comparison of predicted and experimental values for optimum formulation showed very good agreement and are shown in Table XIV. A model is valid despite its inexactness in representing the system, it can give a reasonable prediction of a system performance.

The optimized 500 mg ACMP tablets were compared with some commercially available 500 mg ACMP tablets in terms of dissolution, disintegration time, hardness, friability, weight and volume. As shown in Table XV, the optimized tablets made without any disintegrant exhibit satisfactory and comparable dissolution characteristics. The disintegration time of optimized tablets is even shorter than two of commercial tablets. Tylenol tablets possess the lowest friability. Although the optimized tablets have the highest

tablet weight, however, due to the higher density of the granules, the tablet volume is very similar to the commercial tablets.

CONCLUSIONS

By using computer optimization process, with some constraints on other tablets properties, 300 gm formulation batch containing 25% of Emcocel™, 1 % of povidone in 120 gm granulating water, granulated in 9 minutes was found to be able to produce 500 mg ACMP tablets which possess the best dissolution characteristic, about 95% of drug dissolved at 15 minute sampling time. These tablets also exhibit fast disintegration time, 30 seconds, even without any disintegrant in the tablet, 8 kg hardness, 0.3% friability, 9 KN required compression force for producing tablets and very comparable tablet volume with commercially available 500 mg ACMP tablets. The wet granulation process utilizing Emcocel™ as an excipient to densification seems to be a feasible alternative to the dry compaction approach for producing 500 mg acetaminophen tablet. The expensive drying process of wet granulation process may be offset by saving in starting material costs and in omission of the slugging or roller compaction steps used in dry processing.

In this high dose ACMP tablet formulation development, computer-assisted regression analysis and mathematic model can be utilized to produce accurate representation of the relationship between the independent variables and tablets response properties

and optimize a suitable tablet formulation. The optimization technique can help us to further define and control the whole system.

The predicted values of response tablet properties of the optimum ACMP tablet formulation show good agreement with the experimental results. These ACMP tablets could be produced at rather low compression force to show very comparable dissolution characteristic, disintegration time, hardness, friability and volume with some commercially available tablets.

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TABLE I--- SUMMARY OF IN-PROCESS VARIABLES USED IN THE OPTIMIZATION STUDY

<u>IN-PROCESS VARIABLES</u>	<u>RANGE</u>
X1: Intragranular Emcocel %	5% - 25%
X2: Povidone %	1% - 9%
X3: Granulating Water, gm	40gm - 120 gm
X4: Granulation Time, minutes	2.5 -12.5 min.

TABLE II-- BOX-WILSON EXPERIMENTAL DESIGN FOR FOUR FACTORS

BATCH#	X1	X2	X3	X4
1	-1	-1	-1	-1
2	1	-1	-1	-1
3	-1	1	-1	-1
4	1	1	-1	-1
5	-1	-1	1	-1
6	1	-1	1	-1
7	-1	1	1	-1
8	1	1	1	-1
9	-1	-1	-1	1
10	1	-1	-1	1
11	-1	1	-1	1
12	1	1	-1	1
13	-1	-1	1	1
14	1	-1	1	1
15	-1	1	1	1
16	1	1	1	1
17	-2	0	0	0
18	2	0	0	0
19	0	-2	0	0
20	0	2	0	0
21	0	0	-2	0
22	0	0	2	0
23	0	0	0	-2
24	0	0	0	2
25	0	0	0	0
26	0	0	0	0
27	0	0	0	0
28	0	0	0	0
29	0	0	0	0
30	0	0	0	0
31	0	0	0	0

Table III --- TRANSLATION OF EXPERIMENTAL CONDITIONS

	- 2	- 1	0	1	2
FACTORS:					
X1 = Emcocel™ % eu*: 5 %	5	10	15	20	25
X2 = Binder (PVP) % eu: 2 %	1	3	5	7	9
X3 = Water mass (gm) eu: 20 gm	40	60	80	100	120
X4 = Granulation time (min.) eu: 2.5 min.	2.5	5	7.5	10	12.5

* eu: experimental unit

TABLE IV -- SUMMARY OF RESPONSE PARAMETERS USED IN THE
OPTIMIZATION STUDY

RESPONSE PARAMETERS

Y1: Dissolution, % (% Released at 15 minutes)

Y2: Disintegration Time, minutes

Y3: Friability, %

Y4: Required Compression Force, KN

TABLE V:

General Quadratic Response Surface Model:

$$\begin{aligned} Y = & b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + \\ & b_5X_1X_2 + b_6X_1X_3 + b_7X_1X_4 + b_8X_2X_3 + \\ & b_9X_2X_4 + b_{10}X_3X_4 + b_{11}X_1^2 + b_{12}X_2^2 + \\ & b_{13}X_3^2 + b_{14}X_4^2 \end{aligned}$$

TABLE VI -- SUMMARY OF TABLETS PROPERTIES

Batch#	Dissolution (%)	Disintegration Time (min.)	Compression Force (KN)	Friability (%)
1	39.6	1.5	26	6.4
2	79.2	0.4	28	12.4
3	27.2	48	25	0.8
4	17.3	36	22	2.2
5	45	8	15	0.4
6	100	0.8	9.3	0.7
7	23.8	40	12	0.4
8	24.7	30	14.5	0.4
9	57.6	3	28	5.4
10	62	0.8	26	10.2
11	27.4	55	15.4	0.6
12	21.2	43	20	0.5
13	62.2	4	13	0.9
14	95	1	10.2	0.7
15	29.5	25	11.3	0.4
16	23.7	16	11.4	0.4
17	27.1	21	11.2	0.6
18	93.6	5	9.7	0.7
19	76.6	0.5	17.5	2.1
20	25.2	42	10.2	0.2
21	NA	NA	NA	NA
22	44.4	8	11.3	0.8
23	35.2	12	13.3	0.9
24	28.8	12	11.6	0.7
25	28.2	12	12.0	0.6
26	35.2	12.5	11.7	0.5
27	36.1	12.5	12.3	0.6
28	36.8	12	11.9	0.7
29	35.6	12	11.7	0.6
30	37.3	13	12.5	0.6
31	36.1	12.5	11.8	0.7
Range	17.3 - 100 %	0.4 - 55 min.	9.3 - 28 KN	0.2 - 12.4 %

TABLE VII- Regression Coefficients for DISSOLUTION

=====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
38.40	1.000	12.34	3.111	99.7%
-0.4680	EMCOCEL	0.7847	0.5964	43.4%
-2.036	POVIDONE	1.885	1.080	69.0%
0.09386	WATER	0.1254	0.7485	51.8%
0.07483	RUNTIME	0.3808	0.1965	23.4%
-0.2387	(EMCOCEL*POVIDONE)	0.0583	4.094	99.9%
0.008591	(EMCOCEL*WATER)	0.0058	1.473	84.2%
-0.02157	(POVIDONE*WATER)	0.0146	1.480	84.4%
0.06634	(EMCOCEL*EMCOCEL)	0.0175	3.782	99.9%
0.2670	(POVIDONE*POVIDONE)	0.1096	2.435	98.3%

Confidence figures are based on 20 degrees of freedom

TABLE VIII - Regression Coefficients for DISINTEGRATION
 =====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
0.3235	1.000	8.516	0.0380	17.2%
-0.1389	EMCOCEL	0.1946	0.7137	49.9%
5.024	POVIDONE	1.051	4.780	99.9%
-0.1210	WATER	0.1561	0.7754	53.2%
1.075	RUNTIME	0.5631	1.909	93.7%
-0.04602	(EMCOCEL*POVIDONE)	0.0326	1.412	82.3%
-0.03092	(POVIDONE*WATER)	0.0081	3.796	99.9%
-0.01520	(WATER*RUNTIME)	0.0065	2.333	97.8%
0.1854	(POVIDONE*POVIDONE)	0.0609	3.045	99.6%
0.001706	(WATER*WATER)	0.0008	2.121	96.2%

Confidence figures are based on 20 degrees of freedom

TABLE IX - **Regression Coefficients for COMPRESSION**
 =====

Coefficient	Term	Standard Error	T-Value	Confidence Coef (> 0)
145.3	1.000	13.00	11.17	99.9%
-0.5408	EMCOCEL	0.2889	1.872	93.1%
-7.603	POVIDONE	1.919	3.963	99.9%
-2.216	WATER	0.2376	9.327	99.9%
-1.493	RUNTIME	1.148	1.301	78.3%
0.09250	(EMCOCEL*POVIDONE)	0.0549	1.684	89.6%
0.04594	(POVIDONE*WATER)	0.0137	3.346	99.8%
-0.1525	(POVIDONE*RUNTIME)	0.1098	1.388	81.4%
0.2842	(POVIDONE*POVIDONE)	0.1033	2.752	99.2%
0.01040	(WATER*WATER)	0.0014	7.674	99.9%
0.1259	(RUNTIME*RUNTIME)	0.0661	1.905	93.6%

Confidence figures are based on 19 degrees of freedom

TABLE X - Regression Coefficients for FRIABILITY
 =====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
24.45	1.000	3.105	7.874	99.9%
0.4749	EMCOCEL	0.1078	4.406	99.9%
-2.075	POVIDONE	0.3483	5.957	99.9%
-0.3698	WATER	0.0542	6.823	99.9%
-0.4483	RUNTIME	0.1866	2.403	98.0%
-0.02516	(EMCOCEL*POVIDONE)	0.0108	2.330	97.7%
-0.003234	(EMCOCEL*WATER)	0.0011	2.996	99.5%
0.01754	(POVIDONE*WATER)	0.0027	6.498	99.9%
0.004281	(WATER*RUNTIME)	0.0022	1.983	94.6%
0.04124	(POVIDONE*POVIDONE)	0.0202	2.045	95.4%
0.001294	(WATER*WATER)	0.0003	4.856	99.9%

Confidence figures are based on 19 degrees of freedom

TABLE XI -- REGRESSION SUMMARY AND PREDICTED RESPONSE
PARAMETERS RANGES

Response Parameter	F-ratio Regression	Lack of Fit	R ²	Predicted Min.	Values Max.
Dissolution	18.61 ^a	2.80 < F _{0.05,14,6}	0.92	18.4	95.6
Disintegration	28.33 ^a	3.23 < F _{0.05,14,6}	0.93	0.3	50.4
Friability	15.82 ^a	4.47 < F _{0.025,13,6}	0.92	0.1	10
Compression Force	21.68 ^a	2.66 < F _{0.05,13,6}	0.92	7.9	28.3

a: significant at 1 %

TABLE XII -- OPTIMUM VALUES OF INDEPENDENT VARIABLES TO OBTAIN BEST POSSIBLE RESPONSE PARAMETERS

Factors	<u>Response Parameters</u>			
	Dissolution(%)	Disintegration Time (min.)	Friability (%)	Compression Force (KN)
Emcocel %	25 %	21.1 %	21 %	25 %
Povidone %	1 %	1.27 %	5.77 %	4.4 %
Granulating water (gm)	120 gm	94 gm	101 gm	112 gm
Granulation Time (min.)	9.3 min.	8 min.	10 min.	10 min.
Dissolution	<u>95.6 %</u>	73.3 %	42 %	62.8 %
Disintegration	0.3 min.	<u>0.1 min.</u>	9.5 min.	3.8 min.
Friability	0.26 %	1.8 %	<u>0.1 %</u>	0.1 %
Compression Force	8.54 KN	10.5 KN	8.31KN	<u>7.93 KN</u>

TABLE XIII--- CHOICE OF OPTIMUM FORMULATION

Independent Variable	Value
X1: Intragranular Emcocel %	25 %
X2: Povidone %	1 %
X3: Amount of granulating water	120 gm
X4: Granulation time	9 minutes
Constraints: 1. Disintegration Time > 0.3 minutes	
2. Friability < 0.8 %	
3. Compression Force < 14 KN	

TABLE XIV-- COMPARISON OF PREDICTED AND EXPERIMENTAL VALUES OF RESPONSE VARIABLE FOR OPTIMUM FORMULATION

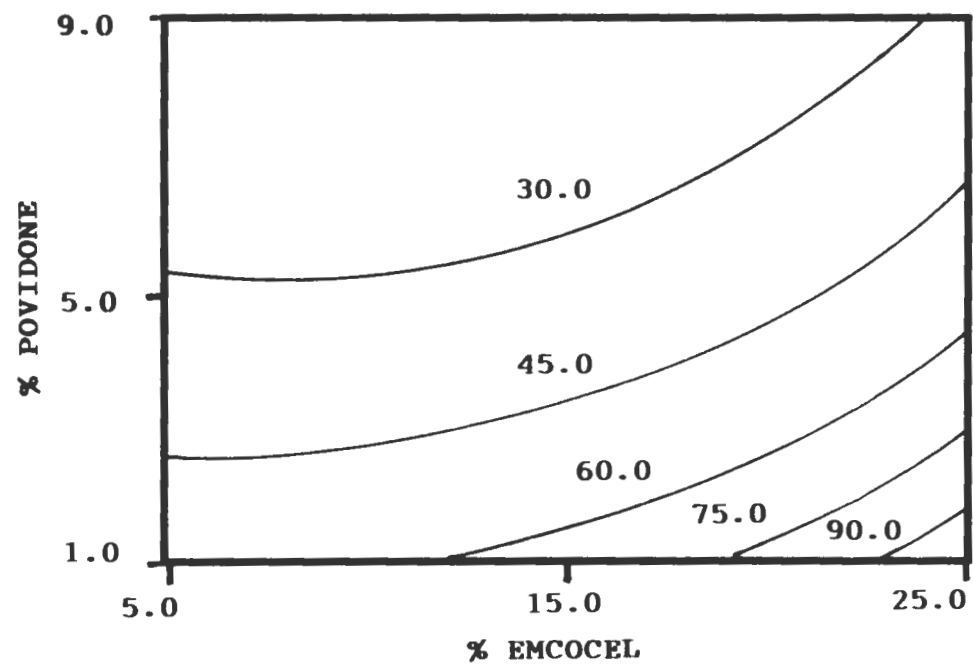
	Dissolution (%)	Disintegration Time (min.)	Friability (%)	Compression Force (KN)
Constraint	> 0.3 min.	< 0.8 %	< 14 KN	
Predicted	95.6 %	0.3 min.	0.26 %	8.54 KN
Experimental	94.3 % (2.1%)	0.5 min. (0.2 min.)	0.31 %	9.14 KN (1.2 KN)

Values in parenthesis are standard deviations.

TABLE XV-- THE PROPERTIES OF VARIOUS ACETAMINOPHEN
(500mg) TABLETS

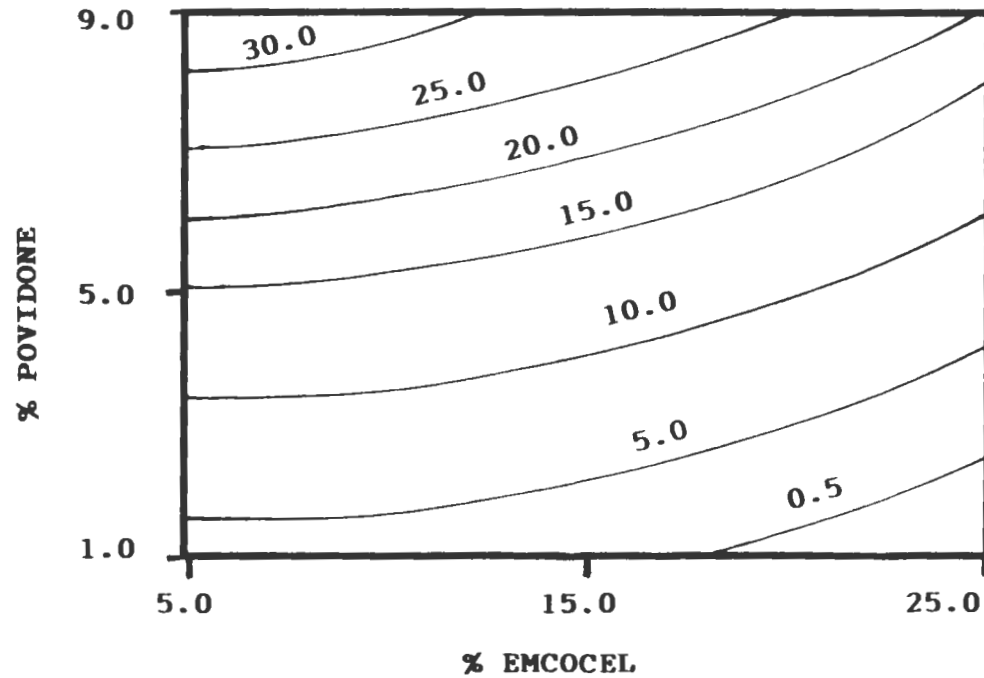
	ACMP-Emcocel™	Tylenol(XS)	Panadol	Datril
Dissolution (% at 15 min.)	95.6(2.1)	99.8(1.8)	98.7(2.3)	98.5(2.5)
Disintegration (minute)	0.5 (0.2)	0.5 (0.1)	2.5 (0.2)	3.5 (0.3)
Hardness (Kg)	8.5 (0.6)	9 (0.5)	10.3 (0.6)	9.5 (0.5)
Friability (%)	0.31	0.15	0.25	0.34
Weight (mg)	660	632	640	625
Volume (cm ³)	0.56	0.56	0.55	0.52

FIGURE 1- EFFECT OF % EMCOCEL AND % POVIDONE ON
TABLET DISSOLUTION (% Released at 20 min.)



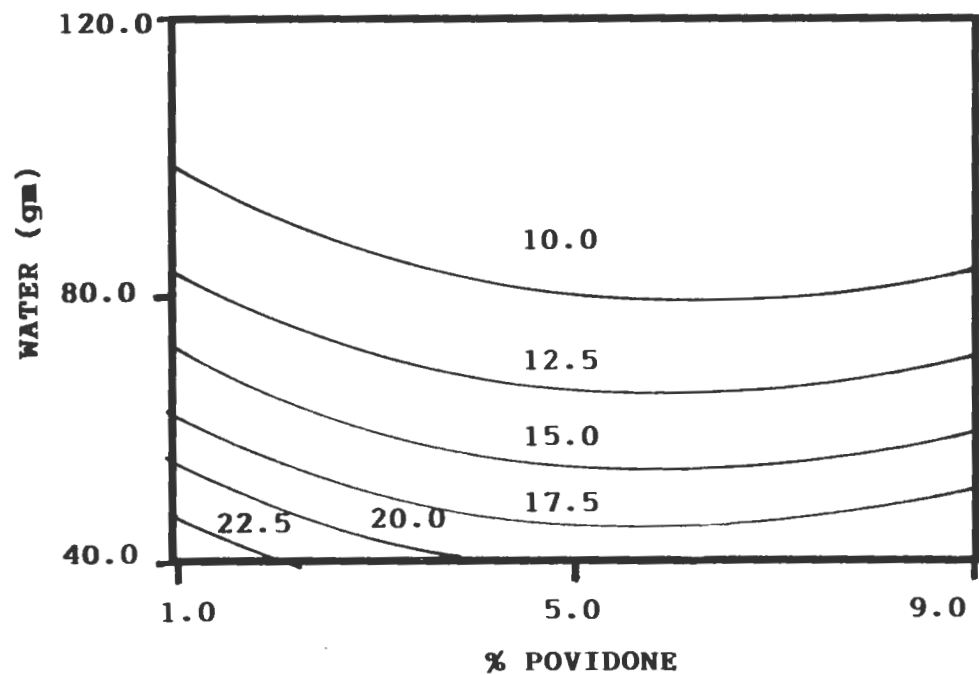
Variables Constants:
Water= 120.0 gm
Gran. Time= 9.5 min.

FIGURE 2 - EFFECT OF % EMCOCEL AND % POVIDONE ON
TABLET DISINTEGRATION TIME (min)



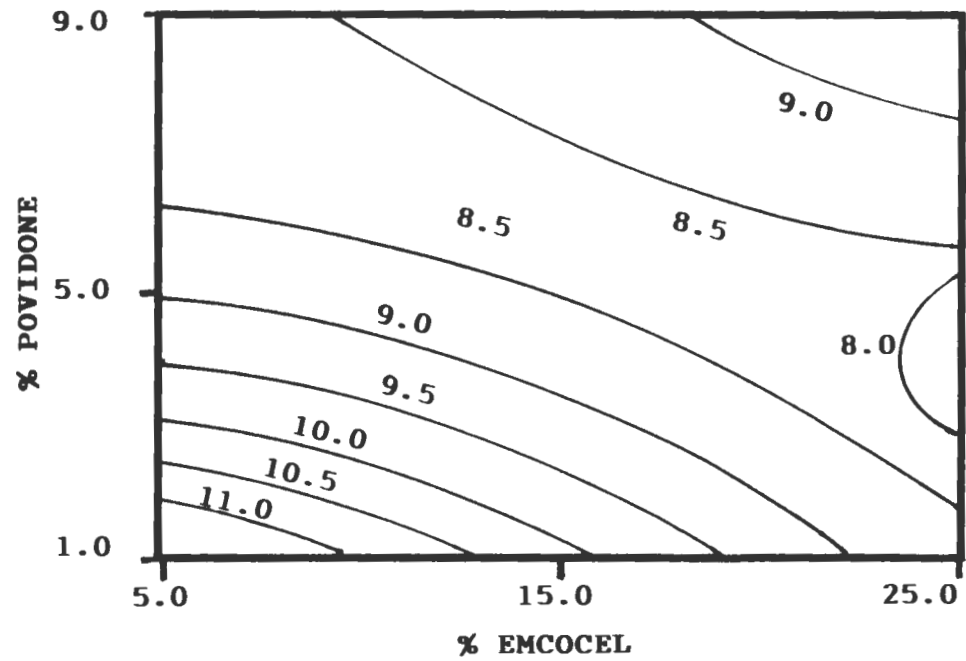
Variables Constant:
Water: 94.14 gm
Granulation Time: 8.1 min.

**FIGURE 3 -EFFECT OF % POVIDONE AND WATER ON
COMPRESSION FORCE (KN)**



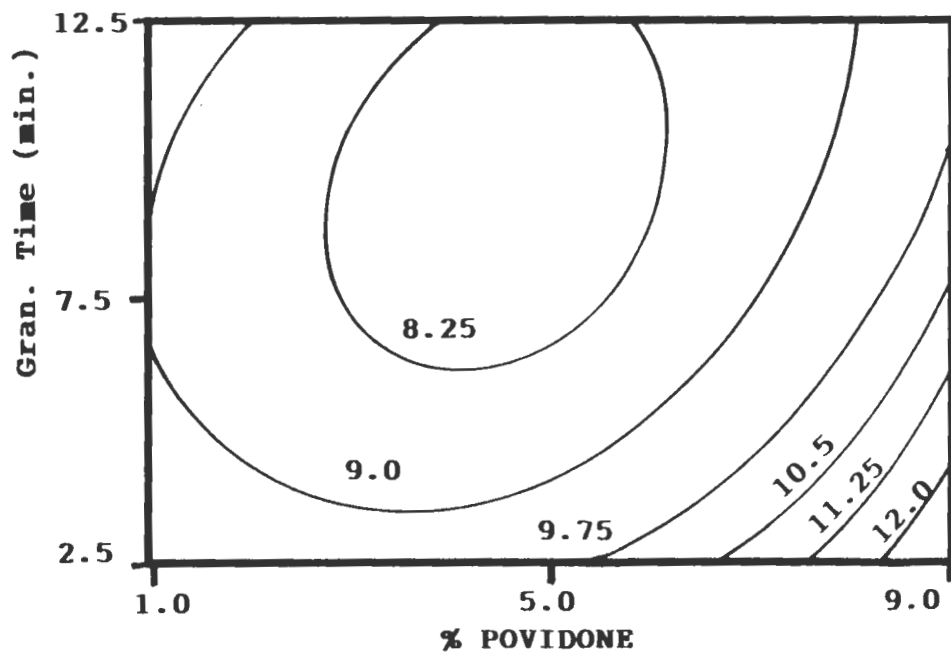
Variables Constants:
% Emcocel = 25.0
Gran. Time = 10 min.

FIGURE 4 - EFFECT OF % EMCOCEL AND % POVIDONE ON COMPRESSION FORCE (KN)



Variables Constants:
Water = 112 gm
Gran. Time = 10 min.

FIGURE 5 - EFFECT OF % POVIDONE AND GRAN. TIME ON COMPRESSION FORCE (KN)

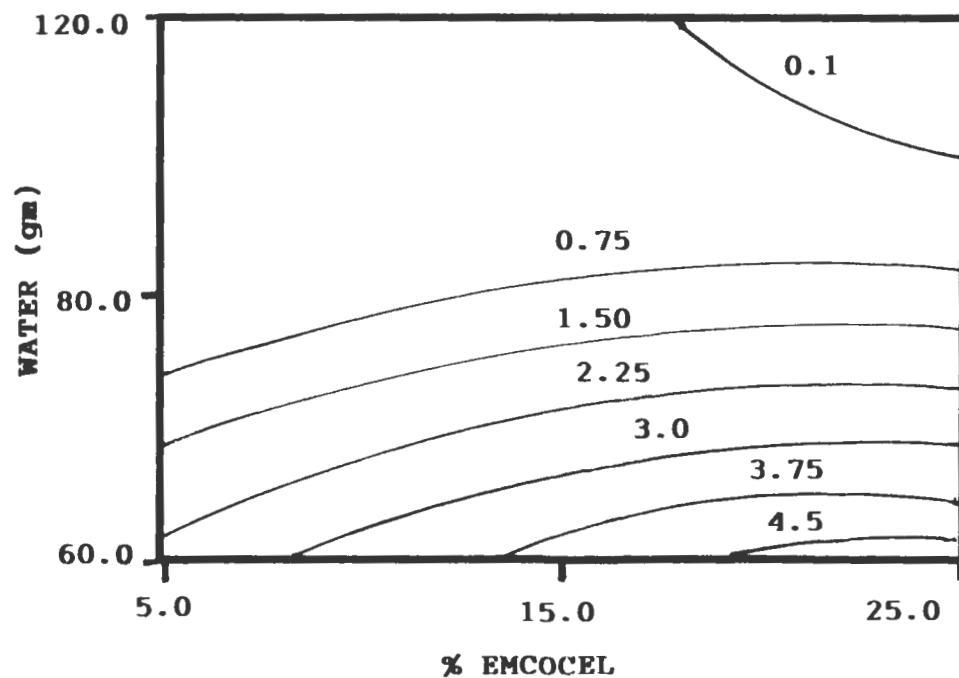


Variables Constants:

% EMCOCEL = 25.0

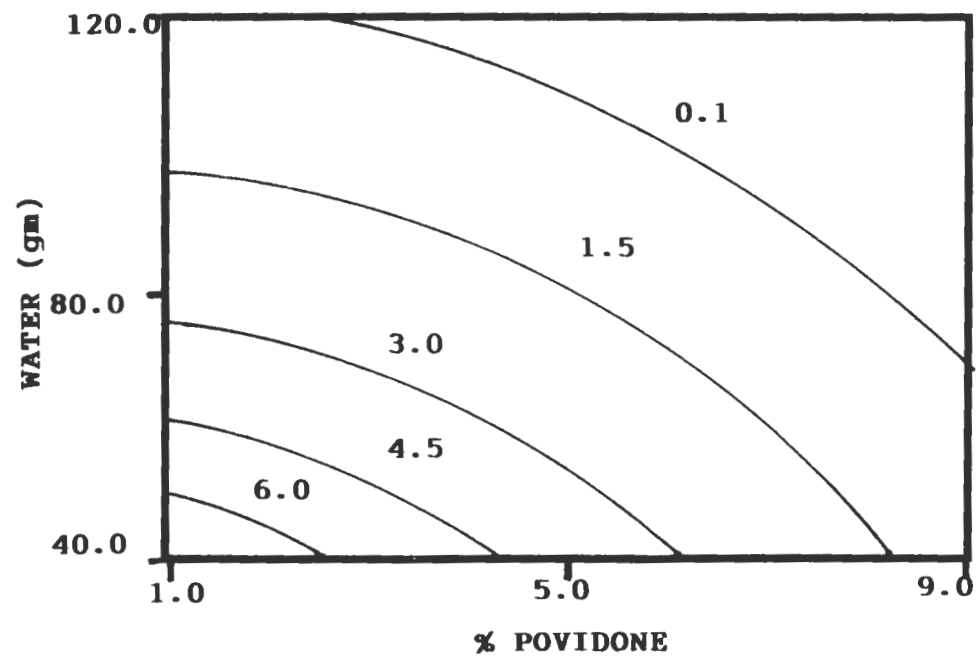
WATER = 112 gm

FIGURE 6 - EFFECT OF EMCOCEL AND WATER ON
TABLET FRIABILITY



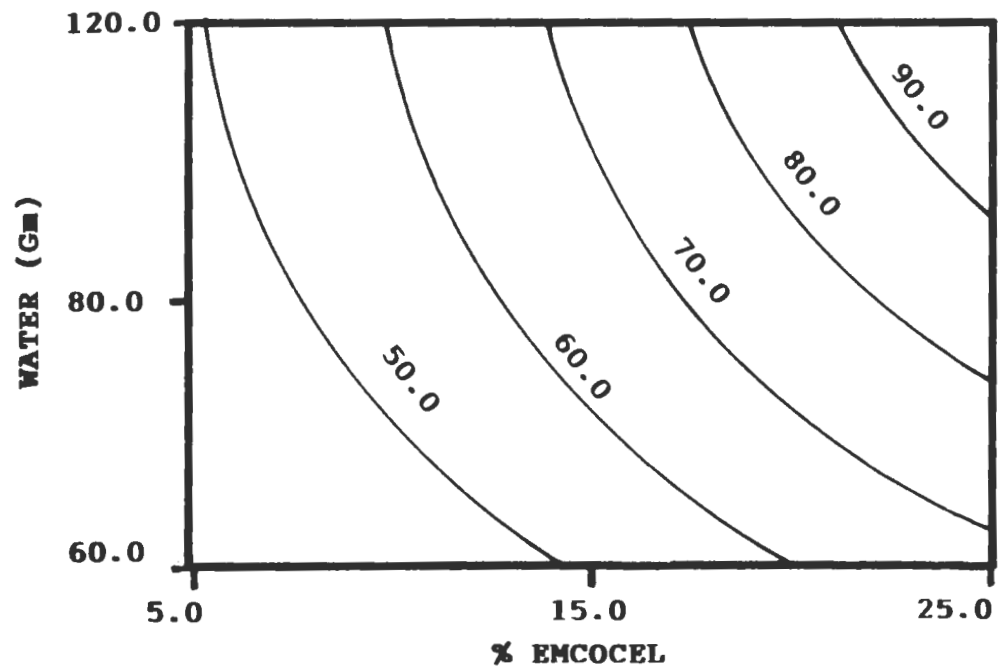
Variables Constants:
% Povidone = 5.8
Gran. Time = 10.0

FIGURE 7 - EFFECT OF % POVIDONE AND WATER ON
TABLET FRIABILITY (%)



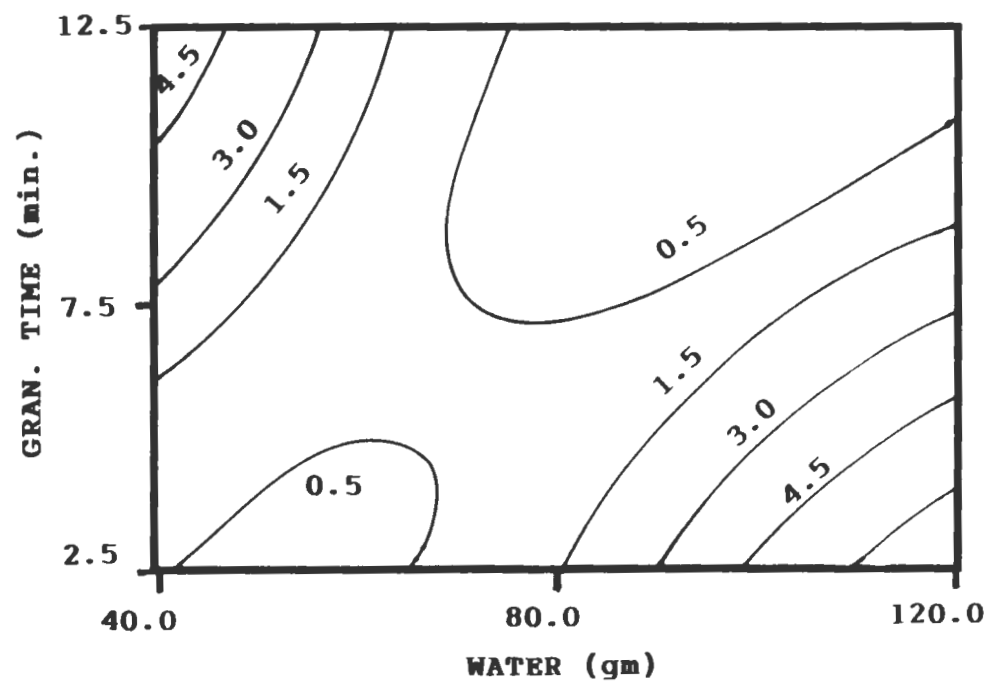
Variables Constants:
% Emcocel = 21.0
Gran. Time = 10 min.

**FIGURE 8 - EFFECT OF % EMCOCEL AND WATER ON
TABLET DISSOLUTION**



Variables Constants:
% Povidone: 1.0
Gran.Time: 9.5 min.

**FIGURE 9 - EFFECT OF WATER AND GRAN. TIME ON
DISINTEGRATION TIME (min.)**

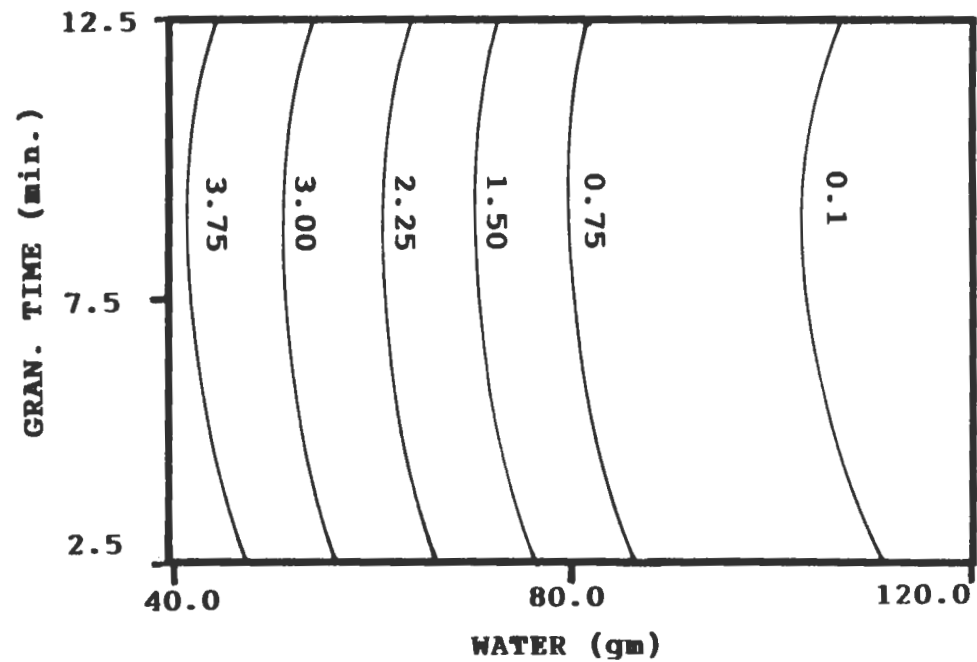


Variables Constants:

% Emcocel: 21.1

% Povidone: 1.27

**FIGURE 10 - EFFECT OF WATER AND GRAN. TIME ON
TABLET FRIABILITY (%)**

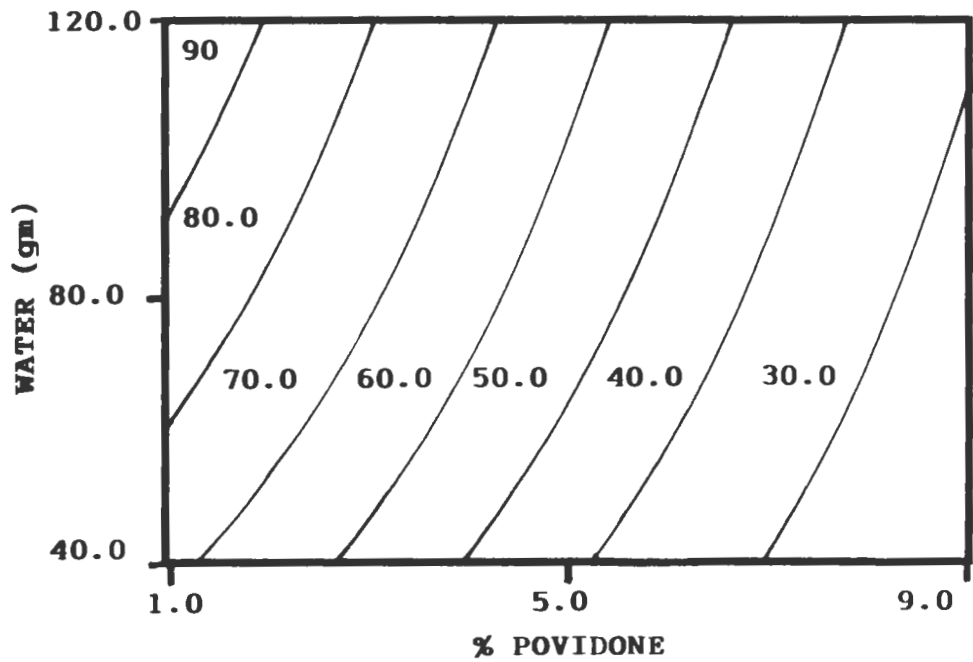


Variables Constants:

% Emcocel = 21.0

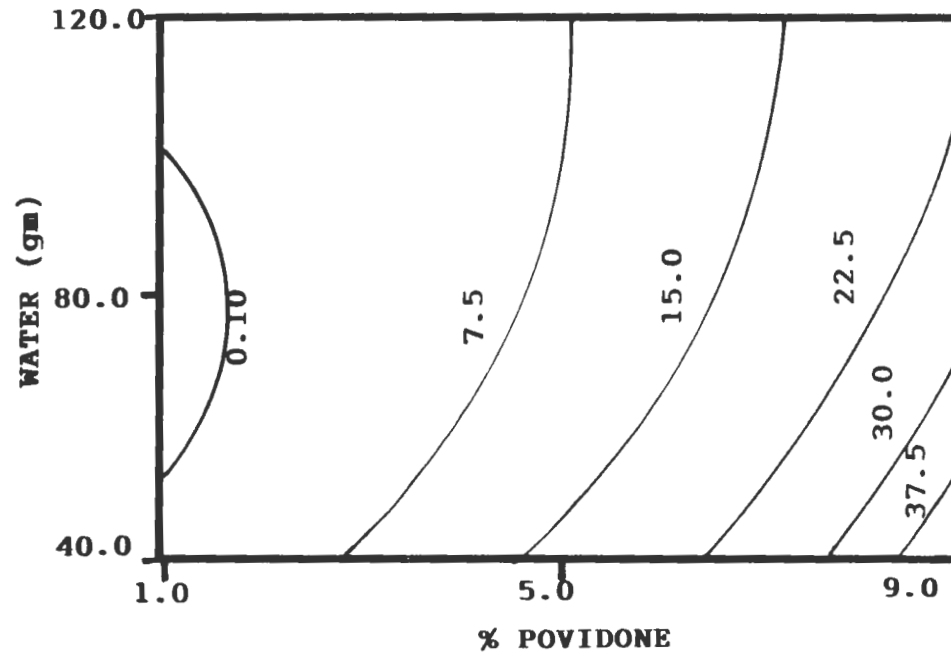
% Povidone = 5.8

FIGURE 11 - EFFECT OF % POVIDONE AND WATER ON TABLETS DISSOLUTION



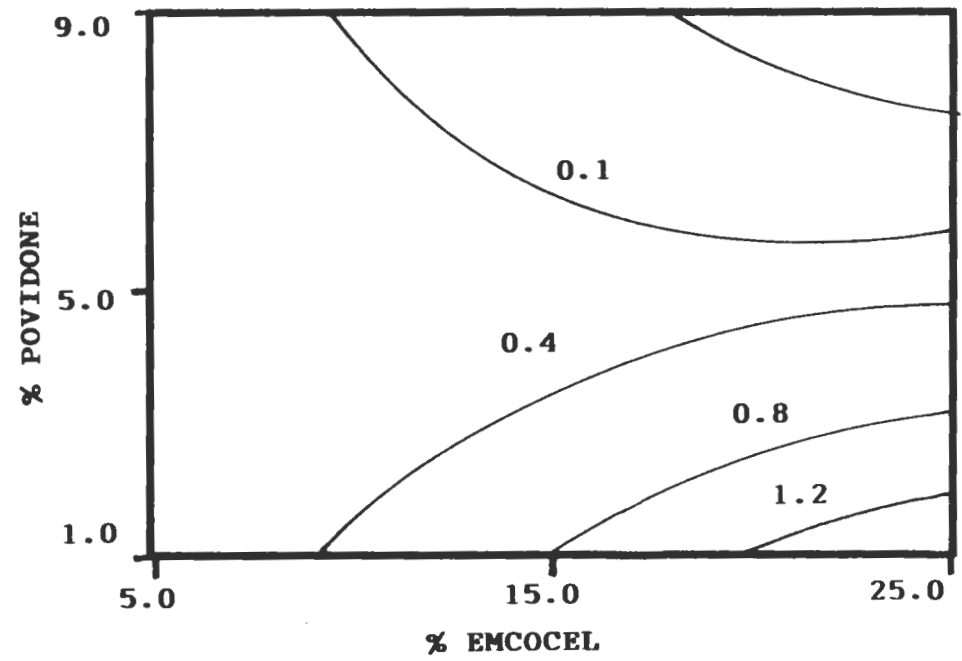
Variables Constants:
% Emcocel = 25.0
Gran. Time = 9.5 min.

FIGURE 12 - EFFECT OF % POVIDONE AND WATER ON
TABLET DISINTEGRATION TIME



Variables Constants:
% Emcocel = 21.0
Gran. Time = 8.1 min.

FIGURE 13 - EFFECT OF % EMCOCEL AND % POVIDONE ON TABLET FRIABILITY (%)



Variables Constants:
water = 100.6
Gran. Time = 10.0 min.

A Review of Floating Drug-Delivery Systems

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1. Introduction

Oral floating dosage forms are designed to prolong the residence time of the dosage form within the stomach. The dosage form should possess sufficient buoyancy to float on the stomach content and release the active ingredient at a controlled rate for an extended period of time.

The first explicit illustration of floating dosage form was probably introduced by Tossounian *et al.* (1). The proposed Hydrodynamically Balanced System (HBS™) is an oral dosage form (capsule or tablet) mainly formulated with a drug or drugs in combination with a gel-forming hydrocolloid or mixture of hydrocolloids. When these dosage forms are in contact with gastric fluid, it is meant to have a bulk density (specific gravity) lower than that of gastric fluids and therefore remain buoyant on stomach contents for an extended period of time. The inventors claimed that floating dosage forms could be used not only to prolong gastrointestinal residence time, but also, if required, to obtain a sustained local action of the latter inside of the stomach (1-4).

During the last two decades, several floating drug delivery systems and formulations have been developed aiming to achieve the same intended intragastric buoyance function (5-14).

The purpose of this article is to review the origin and fundamentals of floating drug delivery systems as they relate to

sustained release, to summarize the major techniques of preparations, to demonstrate examples of few interesting applications as well as evaluation methods of these systems.

2. Development of Floating Dosage Forms

2.1. Reasons for preparing floating dosage forms

For at least the last forty years, sustained release drug delivery systems have attracted considerable attention and recognition. In these sustained release systems, the oral route of administration has received the most attention. This is due to that it is more convenient and flexible to design the dosage form for the oral route. The main objective in designing a sustained-release system is to deliver drug at a rate necessary to achieve and maintain a consistent and uniform drug blood level. In other words, when the dosage form passes through the gastrointestinal tract it is necessary for the dosage form to provide a constant amount of drug for absorption into the blood stream to replace the amount of drug eliminated.

However, in the case of sustained-release dosage forms, the bioavailability of a drug can be affected by the transit of an oral dosage form within different regions of the gastrointestinal (GI) tract. Some drugs are well absorbed during passage through the GI tract, while others are only absorbed from the small intestine. These phenomena can be observed in several drugs and particularly for vitamins and minerals. This can be due to drug's physicochemical properties or favorable sites of absorption, for example, some drugs

will undergo different degrees of change in solubility by passage from the acidic conditions of the stomach to the neutral to alkaline conditions of the intestines (15).

Some vitamins and drugs are primarily absorbed from the upper part of the small intestine. A conventional controlled release dosage form which may deliver the active ingredient beyond this absorption site will not be able to establish an uniform plasma level. Also some compounds such as antacid or nitroso-compound blocking agents are intended to act in the stomach, these drugs would lose their most beneficial effects if they are passed into the intestine. Also, when a drug is administered orally, although there is a certain difference depending upon an individual properties and physiological condition of the person to be treated, usually it takes one to two hours for dosage form to pass away from the stomach to large intestine through duodenum and small intestine. Under these conditions, the conventional controlled release dosage form of certain types of active drug, such as a gastric acid-secretion inhibitor, a gastric acid neutralizer and an anti-pepsin inhibitor as well as other therapeutic preparations to be absorbed through the wall of the stomach would not be appropriate because these drugs are meant to remain and provide their therapeutic effect in the stomach. In addition, there is a drawback that the residual portion of the active ingredient that did not release into gastric fluid from the dosage form may subsequently release into the intestine and produce unexpected or disadvantageous effects.

In view of all these reasons and conditions, it is readily apparent that very frequently, conventional controlled release dosage forms are not suitable for a large number of drugs, vitamins and minerals because these dosage forms are not retained in the stomach and/or may release the drug beyond the optimum site of absorption result in inadequate bioavailability. However, a sustained released formulation which can float in the stomach where it acts as a reservoir and slowly release the drug over an extended period of time will prolong gastric residence time and maximize drug absorption in solution when it reaches its absorption site would be eminently suited to those drugs mentioned previously. Increased or more predictable bioavailability would result from this formulation (16).

The controlled release Hydrodynamically Balanced System (HBS) designed by Sheth, Tossounian et al. (1) was pioneer of these oral floating drug delivery systems. It is a formulation of a drug containing gel forming hydrocolloids which remain buoyant on stomach content for extended period of time and increase the bioavailability. Chlordiazepoxide, diazepam, ferrous salts and several vitamins were applied in HBS to reach the desired therapeutic response. Sheth and Tossounian claimed that the retentive characteristics of HBS floating dosage form are most significant for drugs (1) which are insoluble in intestinal fluid, (2) which act locally and (3) that exhibit site-specific absorption, however, the HBS dosage form also can be used for most drugs where sustained release of the active ingredient from the dosage form is desired by the oral route.

2.2 Types and principles of floating dosage forms

Tossounian et al. (16) have demonstrated that the bioefficient products utilizing the HBS exhibit improved efficiency and bioavailability of some compounds especially for those which are absorbed from the upper portion of the small intestine. The HBS sustained release formulations comprise a homogeneous mixture of one or more drugs with one or a combination of hydrophillic hydrocolloids which, in contact with gastric fluid, will form an outside gel barrier thus causing it to enlarge somewhat and acquire a bulk density (specific gravity) of less than one and therefore remain buoyant in the gastric fluid with a resultant prolonged residence time in the stomach. The drugs will be gradually and uniformly released from the dosage form as the gastric fluid permeates the matrix and as the hydrated outer layer slowly dissolves, ultimately, after all of the drugs are subatantially released, the gelatinous dosage form will disperse.

In the HBS formulations, the floating capability and release characteristics of the dosage form are achieved by the use of specific excipients which play an important role in the design of the product. It was indicated that the formulation of dosage form must comply with three major criteria for HBS products. (a) It is required to possess sufficient physical structure to form a cohesive gel layer. (b) The system must achieve and maintain an overall specific gravity lower than that of gastric fluid (reported as 1.004 to 1.01) result in free floating in the gastric fluid of stomach over an extended period of time to release all of the drug contents. (c) The dosage form should

dissolve slowly enough to serve as a "reservoir" for the drug delivery system.

With respect to the gel-forming barrier, it is also postulated that when the HBS dosage form is in contact with gastric fluid, the hydrocolloid starts to hydrate by forming a gel layer. This surface gel layer then controls the rate of diffusion of gastric fluid in and drug out of the dosage form. When the outer surface layer of the dosage form goes into solution, the gel barrier structure is maintained by the hydration of the immediate adjacent hydrocolloid layer. Meanwhile, the drug dissolves in and diffuses out with the diffusing gastric fluid, creating a so called "receding boundary" within the gel structure. Tu et al. (17) also utilized the principal of HBS to prepare Vit B₆ floating tablet, the HBS tablets were prepared by wet granulating a mixture of HPMC, cetyl alcohol, stearyl alcohol and then compressing into tablets.

Michael et al. (5) utilized a physiologically erodible hollow container which has an internal space for housing a drug delivery system, this device is comprised of a reservoir for housing the active drug ingredient and it is formed of an essentially imperforate and drug release rate-controlling biodegradable material permeable to the drug by diffusion. The reservoir is formed of a polymeric microporous material having a drug distributed thoroughly and whose micropores are a mean for containing a drug release rate controlling medium permeable to the passage of drug. This reservoir is fixed to a deformable hollow closed member which can

inflate on release of the device from its storage container and transport container in physiological environment and then deflate to allow the device to pass from physiological environment. The invention is designed to provide a floating drug delivery system for releasing drug at a controlled rate for a prolonged period of time in the stomach.

Another floating dosage form developed by Watanabe et al. (6) impregnating the active ingredient into a body of empty globular shell or a granular lump in small size of a material having high buoyancy. They also prepared floating systems by suitably adhering a crust of coating containing a desired drug on external and/or internal surfaces of a conventional soft or hard capsules having a bulk density less than that of gastric fluid in the stomach. In another embodiment of their invention, they also plugged a flat tablet containing an active drug ingredient into a half piece of a composite capsule and sealed with a binding agent such as ethylcellulose dissolved in 1,1,1-trichloroethane. This half piece of capsule was coated with a crust of hydroxypropylmethylcellulose phthalate.

Urquhart and Theeuwes also introduced a floating drug delivery system comprising a reservoir containing a plurality of tiny pills (8). In this delivery system, the tiny pills have a core of active drug ingredient which are coated with a wall formed of a drug-release rate controlling fatty acid and wax, these tiny coated pills were then

dispersed throughout a hydrophilic matrix which swells considerably in contact with gastric fluid for retaining the device in the stomach.

A flexible, sheet-like, floating sustained release medicament device having a bulk density of less than one was designed by Mitra et al. (9), the device is of a multi-layer composite construction comprising at least one dry, self-supporting carrier film which is formed of one or more water insoluble polymer matrices and drug. The sheet or film may have an additional barrier on one or both sides. Air spaces are introduced during the manufacturing process causing the material to become buoyant. The purpose of the barrier film is to control the rate of release of drug that is present in the carrier film, another purpose is also to provide buoyancy in the stomach. Synthetic polymers are used in the manufacture of the sheets and various pharmaceutically acceptable excipients are incorporated to obtain desired dissolution and release of the drug. This matrix device does not swell in contact with water but maintain certain flexibility. The dose is administered by cutting of an desired length of the film and folding into a regular capsule, when the capsule dissolves in the stomach, the device is left to float on the gastric fluid for extended period of time.

A recent floating sustained release system was prepared by Bolton et al. (11), the tablets comprise a hydrocolloid gelling agent such as agar, a pharmaceutically acceptable inert oil, such as light mineral oil, the drug, theophylline and water. The final tablets possess a density less than one and therefore will remain buoyant on

gastric fluid in stomach. Typically, the density of tablet is ranged from 0.6 to 0.95. In the preparation of this floating tablet, a solution of the hydrocolloid gelling agent in warm water and a solution of active drug ingredient, theophylline, in the selected oil were separately prepared and these two solutions were mixed and cooled but not to the point where gelation of the gelling agent takes places, the emulsions then were poured into tablet molds and left until the gel forms and drying. Although the resulting tablet is not compressed, the inventors claimed that the final tablets hardness values are comparable to that of most commercially available tablets. These tablets have sufficient mechanical stability to stand up to the normal stress of production, packaging and dispensing. The hardness is characterized by a network of multitudinous air holes and passages. In this invention, the preferred gelling agent is agar, although the inventors claimed other gelling agents may be used. These include, for example, agarose, carageenin, konjac gum, alginic acid and its salts, cellulose derivatives, carbopol and starch. The concentration of gelling agent in the formulation is about 0.5 to 2.0 % by weight. It is very surprising to find that such small amount of gelling agent are capable of forming such rugged tablets without any compression. Beside light mineral oil which has a density of from 0.828 to 0.880, other hydrocarbon oils or vegetable oils can also be employed in the tablet formulation. The inventors concluded that 8 to 30 % of inert oil is necessary in the initial mixture before gelling.

Ushimaru et al. also manufactured a floating sustained release delivery system consisting a substance which forms gel in water, a

fat/oil which is solid at room temperature and drug (10). These substances were simply mixed and filled into a capsule, the capsule is heated at the temperature higher than the melting point of the fat/oil and then cooled to room temperature, the resulting product was then recovered and have a specific gravity of less than 1.0 to be able to float on the gastric fluid in the stomach and to undergo sustained release of active drug ingredient.

Another invention relates to a granule remaining in the stomach for a prolonged period of time was invented by Ichikawa and his coworkers to provide better buoyancy when compared to some floating tablets and capsules (12). The granules comprise a core containing a active ingredient, foaming layer coated on the core and an expansive film coated on the foaming layer. The foaming layer was composed of a bicarbonate or a combination of an inner layer of a bicarbonate and an outer layer of an organic acid. The expansive film was made of a polymer which allow the gastric fluid to penetrate into the inside of the granule and then expand like a ballon because of the gas evolved within the granule to thereby retain the gas within the granule for required period of time.

3. Preparation of Floating Dosage Forms

3.1 Factors affecting floating capability of the dosage forms

In order to remain buoyant in the stomach for extended period of time, it is imperative for HBS dosage forms to maintain an overall bulk density lower than that of gastric fluid after they are in contact

with gastric fluid. Ordinarily, the HBS tablets can be manufactured on conventional tableting equipments, however, in accordance with the HBS tablets floating principals, HBS tablets can remain buoyant in stomach even their initial bulk density is greater than 1 because the buoyancy could be obtained from a combination of an increase in the bulk volume of the tablet due to the hydration and swelling of the hydrocolloid particles on the tablets surface when in contact with gastric fluid and the internal voids in the tablet center remaining dry due to the barrier formed by the hydrocolloid particles (23). Therefore, it is essential that the tablet are not compressed so tightly that rapid hydration is retarded which result in not obtaining a bulk density of less than one after in contact with gastric fluids.

This critical maximum hardness will vary both with the initial density of the formulation and the size of the tablet. Some investigations concluded that the effectiveness of the intragastric buoyancy of floating systems is dependent on particular physiological condition (such as gastric emptying, pH and specific gravity of gastric fluid etc.) and dosage forms characteristics (such as bulk density of the excipients, hardness of the tablet, size, swelling and hydration degree of the final products) (16, 18-26).

3.2 Technologies of preparing floating dosage form

The HBS floating dosage forms were initially prepared in a capsule form, they were prepared by homogeneous mixing one or more drugs with one or more hydrophilic hydrocolloids (27, 28), if necessary, fatty material and some inert pharmaceutical excipients at

the optimized percentages. The formulations then were passed through a Fitzpatrick comminuting machine using different sizes of plate or screen at certain speed, the talc or magnesium stearate were then added to the formulation as a lubricant and blended for an additional time. The blending and milling processes were repeated so that the formulation mixture can pass through a certain size mesh screen and then the mixture was filled into a optimal size soft or gelatine capsules. In the preparation of formulation blends, granulation process sometime was required to prepare granules to increase floating capability and flowability of the formulation.

The HBS products were also manufactured in tablet form. Sheth et al. employed wet granulation process to prepare granules and then compressed those granulations into tablet by using certain sizes and types of punches and dies on single or rotary press (2, 3). However, in the preparation of floating tablets, the hardness of tablet is an important parameter to be controlled with respect to the tablet buoyancy. In some cases, it was necessary to prepare two different granulations separately for the formulation due to the physicochemical properties and incompatibilities of the ingredients in the formulation.

Watanabe et al. utilized spray-pan coating process to apply a coat of a high molecular polymer such as a cellulose acetate phthalate and an acrylic and methacrylic acids copolymers on the body of capsule containing active ingredient and other excipients (6). In another embodiment of Watanabe et al. invention, one half of a two piece

capsules is plugged with a flat tablet containing an active drug ingredient and sealed with a binding agent such as, ethylcellulose dissolve in 1,1,1 trichloroethane.

In Michael et al.'s floating drug delivery device, the drug containing reservoir which was housed inside the capsules can be produced by standard manufacturing procedure, for instance, a drug in solid, liquid solution, emulsion form is first mixed with a polymeric foaming material which can be monomer, a copolymer or a prepolymer in a solid, semi-solid, liquid form (5). The drug is distributed thoroughly by ball milling, calendaring or stirring and then the mixture is shaped into a predetermined shape by molding, casting, pressing, extruding or drawing and depending on the polymeric material used, cured to yield a drug containing reservoir. finally, this reservoir is coated, laminated into a deformable hollow member. The deformable member is suitably made of natural or synthetic bioerodible materials and it is made of film about 0.4 mils to 20 mils thick and the walls of member can be made of a single material, a combination of materials in laminated form or elastomeric materials bonded on thin foils.

Mitra et al. designed a flexible, sheet-like, sustained release, floating multilayers medicament device by overlaying a barrier film on at least one surface of the carrier film and sealing carrier film along its periphery in such a way to entrap a plurality of small pockets of air between carrier and barrier films (9). The barrier and carrier films can be prepared by any of the common techniques

applied for the preparation of polymeric films. For example, one method consists of dissolution of the desired polymer in a suitable solvent at ambient temperatures, followed by the addition of other ingredients such as plasticizer, drug and other additives, to form a homogeneous dispersion or high viscosity solution followed by coating to a desired thickness. The solvent can be removed by heat or evaporation and therefore leaves a self-supporting film. An apparatus is provided for sealing films and entrapping the air between carrier and barrier films.

A floating granules comprise a core of drug, a coated foaming layer and another coated expansive film were manufactured by Ichikawa et al. using a conventional fluidized bed coating procedure followed by drying was used to coat polymer film on the granule cores (9).

In the preparation of Urquhart and Theeuwes floating tablets, the powder drug is mixed with sucrose and passed through a 15 to 30 mesh screen to obtain drug containing cores. Then, a wall-forming composition comprising 85 % glycerol monostearate and 15 % beeswax in warm carbon tetrachloride is sprayed over cores in a revolving coating pan to form a surrounding wall on the cores and produce tiny pills. 50 tiny pills are blended with 200 mg of ground reservoir forming carboxy-vinyl polymer and compressed into tablet on tablet press (8).

3.3 Substances used in the preparation of floating dosage forms

In the HBS products, the gel-forming hydrocolloids are the major component which essentially can be hydrodynamically balanced to acquire a bulk density of less than that of gastric fluid when in contact with gastric fluid to assure buoyancy, therefore, they play a very important role in the floating dosage formulations.

Hydrocolloids suitable for use in the HBS dosage forms include one or more natural, partially or totally synthetic anionic or nonionic hydrophilic gums, proteinaceous substances such as, acacia, tragacanth gums, locust bean gum, guar gum, karaja gum, agar, pectin, carrageen, soluble and insoluble alginates, cellulose derivatives such as, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, carboxypolymethylene, gelatin, casein, zein, bentonite, Veegum. Among these substances, hydroxypropylmethylcellulose is a preferred hydrocolloid which was mostly used in Sheth et al. inventions (29). Generally, the amount of hydrocolloid present in the HBS formulations was between about 20% and 75% by weight.

In HBS dosage form, in order to decrease the hydrophilic property of the formulation and also to increase the buoyancy pharmaceutically inert, edible, fatty materials having bulk density of less than one are often added into formulation, these materials include a purified grade of beeswax, fatty acids, long chain fatty

alcohols such as, cetyl alcohol, stearyl alcohol, myristyl alcohol, glycerides such as glyceryl esters of fatty acids or hydrogenated aliphatic acid such as glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and oil such as mineral oil.

Ushimaru et al. also utilized substances which form hydrated gel when poured into water to prepare floating capsules (10). These substances include cellulose derivatives, dextrans, polysaccharides, polypeptides, protein, acrylic acid derivatives, vinyl derivatives. more particularly, cellulose derivatives include carboxymethylcellulose, carboxyethylcellulose, carboxypropylcellulose, carboxymethylcellulose alkali salts, carboxypropylcellulose alkalisalts, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose. Starch derivatives include alpha-starch, alpha-amyl starch, gelatinized starch, carboxymethyl starch, phosphate starch, acid-treated starch, oxidized starch, dialdehyde starch, soluble starch, thin boiling starch, dextrin. Dextrans include dextran, dextransulfuric acid, carboxymethyldextran. Polysaccharides include alginic acid, pectic acid, arabic acid, alkali salts of arabic acid, chitosan. Gums include arabic gum, tragacanth, carrageenan. Polypeptides include polyglutamic acid, polyaspartic acid, polylysine, polyarginine. Proteins include gelatin, collagen, casein, albumen, globulin, gluten. Acrylic acid derivatives include polyacrylic acid, polymethacrylic acid, alkali salts of polymethacrylic acid, polyacrylic acid-methacrylic acid copolymer. Vinyl derivatives include polyvinylpyrrolidone, polyvinyl alcohol. They also used

fat/oil material which is solid at room temperature in their formulations. These fat/oil are higher fatty acids, high fatty acid ester derivatives, higher alcohols, higher alcohol ester derivatives, and the like.

In another floating drug delivery system, Michaels et al. have used a single material, a combination of materials in laminated form, elastomeric materials bonded on thin foils to prepare the deformable member walls to be fixed to reservoir for housing the active ingredient (5). These materials include silicone, poly(urethanes), poly(acrylonitriles), poly(ethylene), poly(propylene), poly(acrylonitriles), poly(ethylene), poly(propylene), poly(vinylidene chloride), poly(vinylidene fluoride), acrylic elastomers, ethylene propylene terpolymers. laminates such as poly(ethylene)-poly(vinylidene chloride), nylon-poly(vinylidene chloride), etc. The reservoir containing active ingredient are made of some nature and synthetic polymers which are release rate controlling materials such as poly(methylmethacrylate), poly(butylmethacrylate), plasticized poly(vinyl chloride), plasticized nylon, etc. and some silicon rubbers such as poly(dimethylsiloxanes), ethylene propylene rubber.

Ichikawa et al. developed granules of drug which can float on the gastric fluid rapidly after the administration and maintain the buoyant condition for a prolonged period of time (12). They employed a combination of a bicarbonate and an organic acid to coat a foam layer on granular core. Usually sodium bicarbonate is used as the bicarbonate while examples of the organic acid are tartaric,

succinic acid and citric acid. It is recommended that the amount of the foam layer is 5 to 20% by weight, preferably 10 to 15% by weight of the core. They also coated an expansive film on the foam layer to retain the gas within the granule for a required period of time. Polymers such as polyvinyl acetate, acrylic resins, shellac, hydroxypropylmethyl-cellulose phthalate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose are used as expansive film. The amount of the expansive film used in the preparation is 5 to 20% by weight, preferably 7 to 15% by weight of the core.

In Bolton et al.'s floating sustained release tablet, hydrocolloid gelling agents such as agar, agarose, carageenin, Konjac gum, alginic acid and its salts, cellulose derivatives, carbopol and starch. The concentration of gelling agent in the final product is about 0.5 to 2% by weight (11). They also incorporated 8 to 30% therapeutically acceptable inert oil include mineral oil, specifically light mineral oil which ordinarily has a density of from 0.828 to 0.880, hydrocarbon or vegetable oils and waxes.

Tu et al. also used hydropropylmethylcellulose, cetyl alcohol and stearyl alcohol to prepare vitamine B₆ floating tablet (17).

In the floating sustained release capsules prepared by Babu et al., hydroxypropylmethylcellulose, methylcellulose, tragacanth, glyceryl monostearate and ethylcellulose have been utilized to acquire buoyant (14).

4. Evaluation of Floating Dosage Form

4.1 In vitro evaluation of floating capability

Generally, in floating drug delivery system, determination of bulk density and measurement of floating duration have been the main parameters used to define the adequacy of the dosage forms buoyancy (30). However, some investigations concluded the single bulk density determination made before immersion does not enable one to foresee the floating force evolution of a solid dosage form, while the dry material of which is made progressively reacts or interfaces within the fluid to release its drug contents, therefore, the density should not completely be considered as a mean of influencing the gastric residence time of a solid dosage form. To ensure the dosage forms floating capabilities versus time, a novel in vitro resultant-weight measuring system was recently conceived by Timmerman et al. for determining the real floating capabilities exhibited by floating dosage forms as a function of time (31-34). The resultant-weight apparatus enable to monitor the total force F which acts vertically on an immersed dosage form. The force F will determine the resultant-weight of the dosage form in immersed conditions and can be used to quantify the dosage forms buoyant capability.

The resultant-weight measurement apparatus is consisted of a linear force transmitter device (FTD) which can maintain the test dosage form in a chosen fluid medium and transmits the reacting force F of either upward or downward direction to a connected

electromagnetic measuring module of a weighing balance (31, 35). It is required to maintain the test dosage form totally submerged into the fluid during the determination process, therefore, the lower extremity of the FTD is interchangeable for differently designed devices such as, mesh-like or needle-like holders, that will be chosen for the test dosage form with respect to its morphology and characteristics to maintain submerged. The sustained collection as a function of time of the continuously measured resultant-weight values can be obtained by recording equipment connected to the measuring system.

The magnitude and direction of force F and the resultant-weight correspond to the vectorial sum of the buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the object;

$$\begin{aligned}
 F &= F_{buoy} - F_{grav} \\
 &= d_f g v - d_s g v \\
 &= (d_f - d_s) g v \\
 &= (d_f - m/v) g v
 \end{aligned}$$

Where F represents the total vertical force (resultant-weight of the test dosage form); d_f the fluid density; d_s the dosage form's density; g the acceleration of gravity. m the dosage form's mass; and v the dosage form's volume. The total force F acting on the immersed test sample determines the magnitude and direction of the apparent weight of this test sample in the test fluids herein called the resultant-weight values signifies that force F is exerted vertically

upwards and that the test sample is capable of floating , whereas a negative resultant-weight indicates that force F applies vertically downwards and the test sample sinks. Continuous curves of resultant-weight measurement as a function of time for the different types of floating dosage form can be plotted to characterize and quantify the floating capability. By using the novel in vitro resultant-weight measuring system, Timmermans et al. presented different example of floating force kinetics obtained from various polymeric matrix floating dosage forms, among these dosage forms several are market products and others have been tested in vivo studies on human volunteers, the standard test medium was 1200 ml air-free HCl at pH 1.2 with 0.05% Tween 80 and was thermostatically controlled at 37⁰ C, meanwhile, some simulated meal media were also used to measure floating force kinetics of various floating capsules. They defined the floating time of a dosage form as the duration separating time t=0 (immersion into test fluid) from the time point corresponding to the intersection between the positive resultant curve and the zero baseline. They also quantified the floating capabilities of a dosage form by measuring the area under the floating curve, buoyancy AUC. The floating curve obtained was also capable of showing that the floating capabilities of the dosage forms may undergo various modifications upon contact with the fluid. It also translates the evolution of the hydrodynamical equilibrium and can be used to outline the effects upon buoyancy of some of the phenomena happening to the test dosage forms. The results obtained from resultant-weight measurement indicat that the bulk density of a dosage form is not

the most appropriate parameter for ensuring its buoyancy capabilities.

Timmermans et al. concluded that in vitro resultant-weight determinations performed as a function of time have enabled investigation to reveal important and critical variations within the floating force kinetics of dosage forms which had been evaluated to be well- floating on the basis of their density characteristic or observation of remaining buoyant in a beaker for a certain period of time (35). To prevent drawback of unforeseeable floating capability variations during in vivo studies, they also strongly suggested optimization of dosage form formulation to be realised with respect to the significance level, the stability and durability of the floating forces produced.

Tossounian et al. and Bolton et al. determined the bulk density of their final floating products to ensure the buoyancy (16, 11). Tossounian et al. also measured the floating duration of the dosage form by observing the products remaining buoyant in a beaker of simulated gastric fluid for a certain period of time. Photographs of HBS dosage forms remaining buoyant in the beaker were taken at different time sequences to ascertain the residence time and the floating characteristics.

Ichikawa et al. evaluated the buoyancy of their floating granules by determining the buoyancy ratio (12). Granules were immersed in a acetate buffer solution (pH= 4.0) and shaking at a constant rate of

80 times per minute for a specified period of time, the buoyancy ratio therefore was calculated and expressed in the ratio of buoyant granules to the total granules sunked in the buffer solution.

In Usimaru et al.'s slow release floating capsules, a microload transformer was utilized to electrically measure the force required for shaking dosage form into water, an attachment was connected to which capsules are attached for measurement (10). They also measured strength or resistance of capsules against shaking and floatation at various stages, capsule was put into a 200 ml separatory funnel which was filled with 100 ml of water and shaken for 6 hours with a KH shaker and then the shape of capsule was photographed every one hour and floating duration was also recorded.

4.2 In vivo evaluation of floating capability

In order to verify the possible effects of the density of a floating dosage form on gastric retention, there are also several in vivo determinations were conducted on human volunteers by using either noninvasive imaging techniques or drug tracer measurements.

Timmermans et al., Davis et al. and Kaus et al. determined the gastric residence time of various floating dosage forms by the triple radionuclide (^{99m}Tc , ^{111}In and ^{201}Tl) gamma scintigraphic monitoring technique (22,36,37). In their study, three different sizes of floating/non-floating pairs were integrated into the scheme of in vivo measurement. Anatomical position of the floating dosage forms in the gastrointestinal tract was determined as a function of time

after precise superimposition of the outlined region of interest on each taken sequential image using external markers as reference. Gastric residence time (GRT) was defined as the time of the image preceding the first evidence of gastric emptying of the dosage form.

Sheth et al., Erni et al. and Watanabe et al. employed X-ray positional analysis to confirm the floating and the gastric retention characteristics of their floating drug delivery systems (6, 15, 38). In the study of HBS capsules, it contain two small barium sulfate for X ray analysis. Erni et al. and Sheth et al. also utilized external scintigraphy to further study the in vivo behavior of the HBS dosage forms, by using this technique, the in vivo behavior of a dosage form can be monitored noninvasively minute by minute, the floating dosage form was prepared to contain a gamma-emitting radionuclide, swallowed by human volunteers and monitored by external scintigraphy (16, 38). During the process, between the human volunteer and the camera, a collimating plate is placed and only those gamma emissions perpendicular to the collimator can penetrate to the gamma camera and give position analysis. The computer will accumulate the counts impacting on each separate crystal and give a quantitative analysis of the radioactivity in any zone covered by the total crystal array to show the gastric retention as a function of time for the HBS dosage forms. The position and movement of the floating dosage form can be visually monitored on television screen.

Erni et al. studied the floating capability of riboflavin HBS capsule, riboflavin is known to be well absorbed from the duodenum.

Urinary riboflavin excretion was used as an indirect measurement of absorption for HBS capsule and conventional standard capsules. They found the rate of absorption with the HBS riboflavin capsules was much slower than the one with the standard form and the total amount of absorption with the HBS form was by 30% greater than the one with the standard form indicating a prolongation of the period of absorption.

Ichikawa et al. utilized roentgenography to monitor the floating duration of granules in the stomach of beagles while Babu et al. used the same technique in a human volunteer to determine the location and residence time of their HBS capsules in the stomach (12).

5. Conclusion

Oral floating drug delivery systems have been shown to increase the gastric residence time, efficiency and bioavailability of various drugs. The significant features and applications provided by a great number of patents and some successful development of new approaches denote the increasing values and advantages of floating delivery systems in the near future.

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**DISSOLUTION, SWELLING AND RELEASE BEHAVIOR OF
POLYETHYLENE OXIDES: RELEASE MECHANISMS OF FOUR
DRUGS-PHENYLPROPANOLAMINE HCl, THEOPHYLLINE,
SOTALOL HCl AND BOVINE SERUM ALBUMIN**

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ABSTRACT

The swelling and dissolution behavior of different molecular weight PEO (polyethylene oxide) polymers in distilled water at 37 °C was investigated. Due to the swelling of PEO matrix discs, considerable volume expansion was observed. Molecular weight is an important determinant of PEO dissolution rate, which was inversely proportional to the molecular weight of PEO. The results supported the hypothesis that dissolution of high molecular weight PEO is controlled by the inward diffusion of water and outward diffusion of polymer through the boundary layer. The influence of the molecular size and solubility of four tracer compounds (phenylpropanolamine HCl, theophylline, sotalol HCl and bovine serum albumin) and the effect of the tracer/PEO ratio on the dissolution rate in SIF (simulated intestinal fluid) were determined.

INTRODUCTION

General

In the formulation of a controlled release dosage form, an often-used technique is to uniformly disperse a therapeutic substance throughout an excipient matrix. Drug molecules may be delivered to the environment by various mechanisms including release from insoluble matrices, diffusion through insoluble permeable membranes or diffusion through swellable hydrophilic polymers., which may be erodable or non-erodable or cross-linked.

In recent years porous hydrophilic polymers have been extensively used in controlled and sustained release systems for the delivery of various bioactive agents (eg. drugs, insecticides and herbicides) (1). When a polymer is placed in contact with a compatible solvent it generally does not convert directly from the solid phase to the solution phase. Often the polymer passes through an intermediate swollen gel phase which is evident on the surface of the polymer as a soft, tacky mucoid layer (2). In the case of crosslinked polymers, there is no release or dissolution of whole polymer molecules from the surface, but only mobilization of any free segments between cross-links. As a result, a lesser degree of swelling occurs and the resulting gel only swells to some equilibrium state at which the swelling force and retractive or elastic force are in balance. However, if the polymer molecules are not restrained by cross-links, and there is no limiting equilibrium state, but rather an intermediate condition defined by an "entanglement concentration" that progresses eventually to release of polymer molecules from the

surface. When the concentration of polymer is below the entanglement concentration, the polymer molecules do not interact strongly, and the polymer-solvent system behaves as a solution. However, when the polymer concentration is above the entanglement concentration, the macromolecules are intertwined sufficiently to provide some degree of physical integrity and the system behaves as a viscoelastic gel. The entanglement concentration is a decreasing function of molecular weight. Therefore, a polymer of sufficiently high molecular weight will undergo a significant degree of swelling before dissolving. The swelling process will exert considerable stress on the polymer and crazing may occur at the swelling region. This phenomenon can be utilized to release the active agent at a controlled rate.

A number of workers including Lee (3-5), Hopfenberg et al. (6), Colombo et al. (7), Korsmeyer and Peppas (8-10) and Hogan (11) have demonstrated the potential utility of swelling-controlled systems for zero order or near-zero order release. Meanwhile, some previous contributions including those made by Good (12), Korsmeyer et al. (13), Lee (14,15), Peppas et al. (16), and Graham et al. (17,18) provided a preliminary understanding of the mechanism of solute release from swelling-controlled systems. Peppas and his coworkers (19) recently presented mathematical models to predict the mass of drug released and the polymer gel layer thickness as a function of time. The recent developments and applications of swelling controlled release system have been reviewed by Ranga Rao et al. (20).

Erosion and Swelling of PEO

Polyethylene oxide, PEO, is prepared by the polymerization of ethylene oxide, is a water-soluble, glassy, highly crystalline linear polymer. The implications for drug delivery of PEO polymers are as follows :

A PEO matrix system comprising low molecular weight polymer should behave as an erodible system, whereas a matrix system composed of sufficiently high molecular weight polymer should behave as a swellable system. Swellable and erodible matrix system exhibit disparate drug release characteristics. Some of the features of drug release from swellable and erodible systems are summarized in Table I.

It should be noted that while the erosion and swelling release mechanisms place different constraints on drug delivery, a system containing elements of both erosion and swelling could possibly minimize the disadvantages of a system limited to pure erosion behavior or pure swelling behavior. Three model situations will be examined: pure swelling with no erosion (cross-linked polymer), pure erosion with no swelling (hydrolysis of insoluble polymer to produce soluble fragments) , and a hybrid case with initial swelling followed by an added erosion component beginning after a lag time (after swollen polymer concentration has been diluted below the entanglement threshold) . In each case, the assumption is that the rate of dissolution of drug from any solid drug particle is rapid with respect to other processes, so that drug dissolution rate within the matrix is not rate limiting. For instance, in one type of system, the

polymer matrix is initially glassy and crystalline, so that drug is immobilized and cannot diffuse out of the system. Upon entering a compatible medium, the polymer would swell and become rubbery as it was plasticized by inward diffusion of the medium. Once the polymer molecules became mobilized, drug could diffuse through the outer swollen polymer layers. Eventually, the outer gel layer would reach a certain critical thickness at which point the polymer concentration at the outer edge would fall below the entanglement threshold (the polymer then behaves as a solution). The swelling rate and erosion rate would reach dynamic equilibrium. With a constant gel layer thickness and corresponding constant diffusional resistance, diffusion of drug through the gel would become release rate limiting. Such a swelling controlled system would presumably be less dependent on agitation intensity than a different polymer system, such as one in which pure surface erosion controlled drug release. This agitation-independent characteristic would be desirable since agitation intensity is difficult to assess *in vivo*.

In an erosion-controlled system, drug molecules would remain immobilized within a glassy matrix until the moment at which the surrounding matrix eroded and was dispersed into the medium. A hybrid system would be one with both swelling and erosion characteristics. In such a case, the polymer matrix would swell to produce a gel layer, but after reaching a critical thickness, the dilute outer edge of the gel layer would begin to erode and disperse into the medium. As a result, the gel layer would reach a maximum or critical thickness, after which point the gel layer would have a constant

thickness. The result would be a constant rate of drug release controlled by diffusion through the gel layer. Clarification of the drug release mechanisms operating in a given dosage form is useful for design and application purposes.

In general, the behavior of a swellable/erodible delivery system is dependent on the relative rates of three processes: (a) the rate of water penetration into the polymer matrix (b) the dissolution rate of polymer matrix itself, and (c) the rate of drug transport through the polymer matrix. A complicating factor is seen for a matrix containing a high concentration of a low molecular weight solute. In this case, the extent of matrix swelling is initially high due to the high osmotic pressure exerted by yet-unreleased solute. Eventually as the solute is depleted, the osmotic pressure falls, so that the matrix contracts due to dominance of the elastic recovery tendency of the entangled polymer. This also causes a net outward flux of medium as the matrix contracts, and dissolved solute or drug is carried outward at an enhanced rate greater than that due to diffusion alone. Any one or a combination of these processes may control the rate of drug delivery from a system. In the present investigation, the processes of swelling and erosion were studied for different molecular weight types of a model polymer, poly(ethylene oxide) (PEO).

EXPERIMENTAL

Materials

The six grades of PEO used in this study are shown in Table II. The water soluble tracers used in these studies are listed in Table III.

Preparation of Polymer Matrix Tablets

The polymers were sieved to exclude particles larger than 177 μm . samples were prepared in the form of discs by direct compression of 370 mg of pure PEO using flat-faced, 5/8 inch (1.59 cm) punches and die. A Carver press was employed at a compression force of 5000 lbs with a dwell time of 10 seconds. The resulting compaction pressure was 16,246 psi on the upper tablet surface. The manufacture of tablets resulted in correspondingly thicknesses of 0.062 inch. The size and shape (thin discs) of the tablets were selected to simplify interpretation of the swelling and dissolution data, rather than to represent a tablet design suitable for human use.

Swelling and Erosion Experiments with PEO Matrix Tablets

For each PEO type, three 370 mg tablets were prepared. For dissolution studies, a sample tablet was suspended beneath the surface of the dissolution medium in a USP dissolution flask by means of a 21 gauge syringe needle piercing through the center and normal to the planar surface of the sample tablet. The needle-mounted tablets were fastened to disposable syringes, which provided convenient handles for manipulating the samples. The tablet sample was positioned so that the tablet was 1 cm from the paddle shaft and 1 cm above the paddle blade. The flasks were filled with 900 ml of dissolution medium. Each flask was fitted with a USP paddle spaced at 2 cm above the flask bottoms and rotating at 110 rpm. The temperature was maintained at $37^{\circ}\text{C} \pm 0.5$ by a heater-circulator. The tared tablet holder with attached tablet sample was removed, excess liquid was allowed to drain, and then the assembly was

weighed at specified intervals until the tablet became distorted. (no longer disc shaped). Samples (2.5 ml) of the dissolution medium were withdrawn at specified time intervals for analysis of the mass of PEO dissolved from a sample tablet by determination of the PEO concentration using Differential Refractometry. Standard curves were prepared for each type of PEO in which the refractive index ratios (solution/distilled water) were plotted versus the polymer concentration. The standard curves were linear over the sample concentration range so that dilution was not required. The rapid rate of dissolution of the PEO 3.5K precluded obtaining weight measurements.

Diffusion/Dissolution Studies of Drug-Containing PEO Matrix Tablets

Tablets were prepared by direct compression of 500 mg of well-mixed powder blend composed of drug and the selected type of PEO. Mixing of each 10 gram blend was carried out for five minutes in a small bottle which was filled to 10 percent of capacity mounted in a twin arm blender. Tablets were compacted using 7/16 inch bevel-edged punches in a Carver press at a compression force 5000 lbs for 10 seconds. The tablets hardness was greater than 20 Kgf, and tablet thickness was about 4mm.

For tablets containing a mixture of drug and PEO particles, dissolution studies were performed by using the USP paddle method at 50 rpm in simulated intestinal fluid USP (SIF) at pH 7.5, at 37°C. The concentration for theophylline, sotalol HCl and PPA.HCl were

determined by monitoring the absorbance at 272 nm, 228nm and 214 nm, respectively, in a spectrophotometer. Standard curves of prepared theophylline and PPA.HCl solutions showed that plots of the absorbance at 272 nm, 228 nm and at 214 nm versus theophylline, sotalol HCl and PPA.HCl concentration, respectively, were linear. For dissolution studies utilizing BSA, dissolution medium samples were diluted with blank dissolution medium as required to produce tracer concentrations within the standard curve range. The concentration of BSA was measured by the Bradford protein assay method (21).

RESULTS & DISCUSSION

Swelling Behavior of PEO Matrix Tablets

The swelling behavior of polyethylene oxide samples of different molecular weights is demonstrated in Figure 1 and 2. The swelling behavior is presented in terms of the water uptake. The tablet water uptake was calculated by subtracting the dissolved polymer weight from the initial dry polymer weight to obtain the remaining polymer weight (dry basis). Next, the remaining dry polymer weight was subtracted from the gross weight of the wet tablet sample. The PEO 3.5K tablets ~~dissolved~~ smoothly and rapidly, with no visible gel layer being formed, hence its swelling profile is not shown. The weight curves of PEO 100K and 200K show three distinct phases. Initially, the samples imbibed water rapidly. Next, an intermediate gel state was observed, and finally dissolution (erosion) of tablet matrix occurred.

In the cases of PEO 1M, PEO 4M and PEO 5M, the tablet underwent considerable swelling before dissolution. The swelling of these high molecular weight PEO tablets appears to be diffusion rate controlled. As shown in Figures 3, 4 and 5, the plots of tablet weight vs. the square root of time yield the characteristic straight line associated with a rate-limiting gel layer of increasing thickness. Similar results were reported by Parsonage et al (22) for different polymers.

The dynamic swelling process of a representative PEO sample is illustrated in the series of photographs shown in Figure 6 to Figure 9, in which the PEO tablet has been swollen in water. The initially glassy polymer tablet is gradually converted into a rubbery, plasticized state by diffusional influx of water, which acts as a plasticizer for these polymers. The photographs show that a region of high stress (the bright region as seen in the photograph due to the photoplastic effect) develops when the outer portions of the polymer begin to swell. This stressed area moves inward as swelling develops until stress relaxation occurs. This stress rearrangement is associated with plasticization of the center of the tablet.

Effect of Molecular Weight on the Release of PEO

The dissolution profiles of different molecular weight PEO are shown in Figure 10 and 11. As can be seen, the PEO samples of different nominal weights have different dissolution properties, the dissolution rate decreasing as the molecular weight is increased. The dissolution of PEO is clearly controlled by the molecular weight. The precise nature of this relationship is a function of the type and time

dependence of the rate-controlling step. If dissolution is controlled by diffusion of a polymer molecule across a fluid boundary layer, then the rate should be proportional to the diffusion coefficient in solution which according to the Sutherland- Einstein equation, depends on the reciprocal of the diameter of the molecule. In turn, the diameter of a polymer molecule in solution is proportional to molecular weight.

$$D = RT / 6 \pi n r N$$

where: D is diffusivity, n is solution viscosity, r is molecular radius and N is Avagadro's number. Thus, this release mechanism(diffusion across a boundary layer) yields a dissolution rate that is proportional to molecular weight.

If instead, dissolution is controlled by the time it takes a polymer chain to disentangle itself from a concentrated gel, then the rate should be proportional to a higher power of molecular weight. Ueberreiter (23) proposed an empirical relationship between molecular weight and dissolution rate:

$$G = K \times Mw^{-A}$$

where G is the dissolution rate, Mw is the molecular weight, K and A are constants.

This is similar to the Mark- Houwink equation,

$$[\eta] = K M^a$$

where: $[\eta]$ is the intrinsic viscosity of a polymer dispersion, M is the polymer molecular weight, K and a are characteristic for a particular polymer-solvent system. At the outer margin of gelled polymer, the polymer concentration falls below the entanglement concentration and causes the polymer to behave as a fluid. Higher molecular weight would produce a higher intrinsic viscosity. A fluid dispersion with higher intrinsic viscosity would be expected to show slower dissolution.

Taking the log of both sides of the Ueberreiter equation yields the equation of a straight line:

$$\log(G) = \log K - A \log(Mw)$$

The log (dissolution rate) vs. Log (Mw) of PEO is presented in Figure 12. The slope is -0.65 ($S = 0.05$). This value seems more supportive of the boundary layer mechanism than the disentanglement mechanism.

On the dissolution study of PEO 3.5K, the tablets dissolve directly, with no observable intermediate gel state, one would expect that a drug-containing matrix of this material would release the drug at a rate equal to the polymer dissolution rate. As shown in Figure 10, the dissolution of the PEO 100K is constant until most of tablet (75% or so) is dissolved. The dissolution rate does not vary with tablet

thickness. This is due to a nearly constant tablet surface area during the dissolution study. For the thickest (0.62 inch) of these tablets, the initial sidewall surface area ($A_s = 2 \pi r h$) is only 20 % of the initial combined obverse and reverse tablet areas ($A_{or} = 2 \pi r^2$). The weight curves of PEO 100K (Fig. 1) show that tablet picks up water relatively rapidly at first, but then the rates of dissolution and water penetration come into balance. This kind of dissolution behavior is desirable for controlled release. The PEO 100K dissolution appears to proceed by a pseudo-steady-state process in which an outer gel layer is continuously formed as water penetrates the tablet and is simultaneously eroding at the outer boundary. Since both water penetration and dissolution are proceeding at the same rate, it does not matter which process controls release of the drug. A drug which can diffuse through the gel layer has a barrier of constant thickness to traverse and remaining drug is released from the outer boundary when the polymer dissolves.

The dissolution results of PEO 4M and PEO 5M (Figure 11) indicated that they are more useful for controlled release on a longer time scale than the lower molecular weight polymer. However, since the matrix swells considerably before dissolving, different drugs should be released at different rates, depending on whether they diffuse easily through the gel or only released by dissolution of the tablet polymer matrix. The drug solubility and molecular size of a drug limit release: Very low drug solubility may produce matrix dissolution rate control, or controlled by a rate limiting step of dissolution of drug molecules from the surface of individual drug

particles inside the polymer matrix. On the other hand, high drug solubility may result in drug diffusion rate limited rate control.

Influence of the Molecular size and Water-Solubility of the Tracer on PEO Matrix Dissolution

The effect of the water solubility and molecular size of tracers on the magnitude of the release rates and type of diffusional release was determined using four solutes, PPA.HCl, anhydrous theophylline, sotalol HCl and BSA release from PEO matrix systems.

The solute release data of the early portion of the release curve ($M_t/M_\infty < 0.6$) from PEO matrix system were analyzed by using Eqn. 1, where M_t/M_∞ represents the fraction of drug released at time t , K is the kinetic constant characteristic of the drug/polymer system, t is the release time and n is an exponent characterizing the mechanism of release of the drugs. The corresponding release rate per unit area of exposure can be obtained from Equation 2, where A is the surface area of the sample, C_d is the drug loading concentration.

$$M_t/M_\infty = K t^n \quad (\text{Eqn. 1})$$

$$dM_t/Adt = n C_d K t^{n-1} \quad (\text{Eqn. 2})$$

Table IV summarizes the range of values of the diffusional exponent n , and the corresponding release mechanism.

The values of K, n and correlation coefficient (r^2) obtained from various formulation of PEO 100K and PEO 5M are given in Table V.

As shown in Table V, in the case of PEO 100K the n values of PPA.HCl, sotalol HCl and BSA are in the range of 0.45-0.89 indicating that drug was released by non-Fickian behavior and the n value of theophylline are relatively high indicating Super Case II transport. In PEO 5M systems, the n value of PPA.HCl, theophylline, sotalol HCl and BSA are all in the range of 0.45-0.89 indicating that the drug was released by Anomalous transport. The n values also indicated that the release of these three solutes were at least partially controlled by viscoelastic relaxation of the matrix during solvent penetration.

Release profiles of three solutes from the matrices containing PEO 100K or PEO 5M (50% solute/50% PEO) are shown in Figure 13 and Figure 14, respectively. As shown in Figure 10, drug-containing PEO 100K tablets exhibited a linear release profile for approximately two hours. Although the three solutes were released at different rates, these rates did not vary widely. The diffusion coefficient as predicted from the tracer molecular weights are quite disparate, leading to the conclusion that the observed similarity in tracer release rates is probably due to matrix erosion-controlled drug release. This would mean that the gel layer thickness is very small so that most of the mass of drug particles is released into the external medium before drug is dissolved. This is probably due to

the dissolution rate was essentially controlled by the erosion of PEO 100K matrix.

Figure 14 shows that the release of PPA.HCl (smaller molecular size, high diffusivity) from PEO 5M had the faster release rate while theophylline (smaller molecular size, lower solubility) exhibited an intermediate release rate, the release rate of theophylline from PEO 5M was nearly constant (zero order) in the first 20 hours. The release of BSA (larger molecular size) from PEO 5M appeared to be more controlled by its low diffusivity in the gel layer formed as the tablet swelled.

As shown in Table V, the kinetic constant for release, K , which incorporated the overall solute diffusion coefficient and geometric characteristic of the system correlated inversely with the solute molecular weight. K also increased with increasing total solubility of the matrix system. The K values of all three solutes in a PEO 100K matrix are greater than those in a PEO 5M matrix.

Effect of The Tracer/PEO Ratio on The Dissolution Rate

The effect of relative amount of tracer in the PEO formulation on the dissolution rate is shown in Figure 15 and Figure 16. In the case of PEO 100K (Figure 15), tablets prepared with 4 wt% BSA and 96 wt% PEO 100K exhibited faster release than the 50 wt% BSA/50 wt% PEO 100K, this is due to the dissolution of PEO 100K is faster than the dissolution of BSA. The dissolution rate of the system is essentially controlled by erosion of PEO 100K matrix. However, as shown in

Figure 16, tablets composed of 50 wt% BSA and 50 wt% PEO 5M had faster release rate than the 4 wt% BSA/96 wt% PEO 5M. This is attributed to the fact that PEO 5M matrix swells more extensively and the release of BSA is mostly controlled by its low diffusivity in the gel layer. As the relative amount of PEO 5M in the system was increased, the resistance of the gel layer to diffusion of drug was also increased.

CONCLUSIONS

These findings conclude that molecular weight is an important determinant of PEO dissolution rate, which was inversely proportional to the molecular weight of PEO and the release of drug from PEO matrix system follow some anomalous behavior where both diffusion and mechanical relaxation affect the whole process. In the case of theophylline, the release rates are nearly zero order. If a mixture of different molecular weight PEO is chosen carefully, it is quite possible to balance the reduction in resistance to diffusion of the drug, leading to drug/PEO systems which exhibit constant release rate.

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TABLE I. Drug release characteristics of swellable and erodible systems

Swelling Controlled Systems	Erosion Controlled systems
<ul style="list-style-type: none"> * release can be zero order * drug must diffuse through gel (drug solubility and high molecular weight may limit release) * matrix swelling is largely independent of agitation intensity of medium 	<ul style="list-style-type: none"> * release can be zero order * largely independent of drug(it can deliver insoluble and high molecular weight drugs) * matrix erosion is highly dependent on agitation intensity of medium

TABLE II. Various grades of PEO used in diffusion and dissolution studies.

Designation	Nominal Molecular Weight	Source
3.5 K	3,350	Sigma
100 K	100,000	Union Carbide
200 K	200,000	Union Carbide
1 M	1,000,000	Union Carbide
4 M	4,000,000	Union Carbide
5 M	5,000,000	Polysciences

TABLE III. Different tracers used in the dissolution studies.

Tracer	Water solubility	Molecular Weight	Source
Theophylline	8.3 mg/1 ml	180.17	Sigma
PPA. HCl	909 mg/1 ml	187.67	Sigma
Sotalol HCl	200 mg/1 ml	308.8	Bristol-Myer Squibb
BSA	---	69,000	Sigma

PPA. HCl = Phenylpropanolamine Hydrochloride USP

BSA = Bovine Serum Albumin (Cohn Fraction V)

TABLE IV. Diffusional exponent and mechanism of diffusional release from cylindrical swellable controlled release matrix system

Diffusional exponent (n)	Drug release mechanism
< 0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) transport
0.89	Case II transport
n > 0.89	Super Case II transport

when the value of $n = 0.89$ means that the drug release is independent of time, the release is characterized as zero-order release.

TABLE V. Values of Kinetic Constant (K), Release Exponent (n) and Correlation Coefficient (r^2) Following Linear Regression of Dissolution data Analyzed by Equation 1.

System	Kinetic Constant K (h^{-n})	Release Exponent (n)	Correlation coefficient (r^2)
PPA.HCl/PEO 100K	0.46	0.68	0.992
Theophylline/PEO 100K	0.42	1.10	0.999
Sotalol HCl/PEO 100K	0.45	0.76	0.996
BSA/PEO 100K	0.37	0.78	0.998
PPA.HCl/PEO 5M	0.24	0.51	0.992
Theophylline/PEO 5M	0.05	0.83	0.999
Sotalol HCl	0.05	0.75	0.997
BSA/PEO 5M	0.04	0.66	0.996

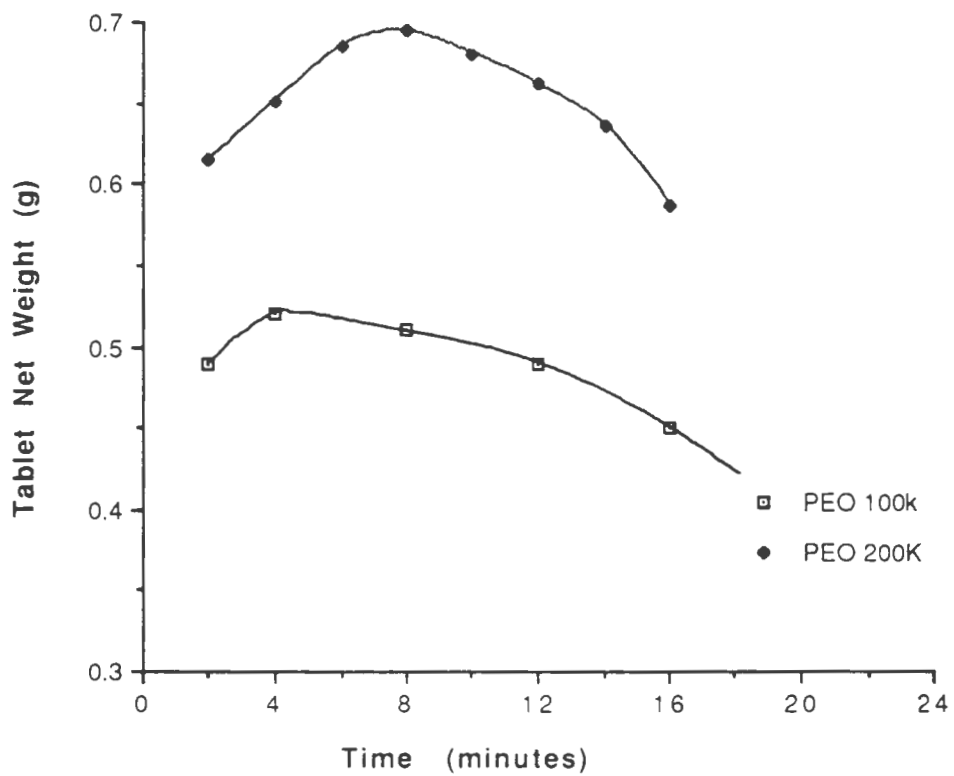


Figure 1. Weight gain (Due to Swelling) curves of PEO 100K and 200K tablets.

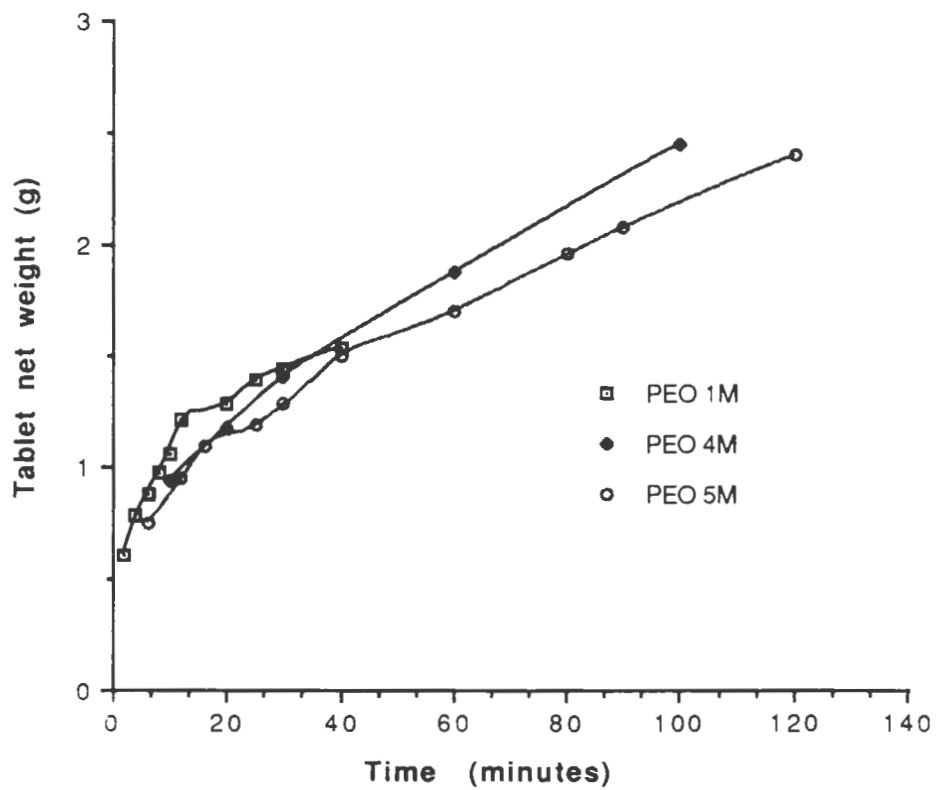


Figure 2- Weight gain (due to swelling) curves of PEO 1M, 4M and 5M tablets.

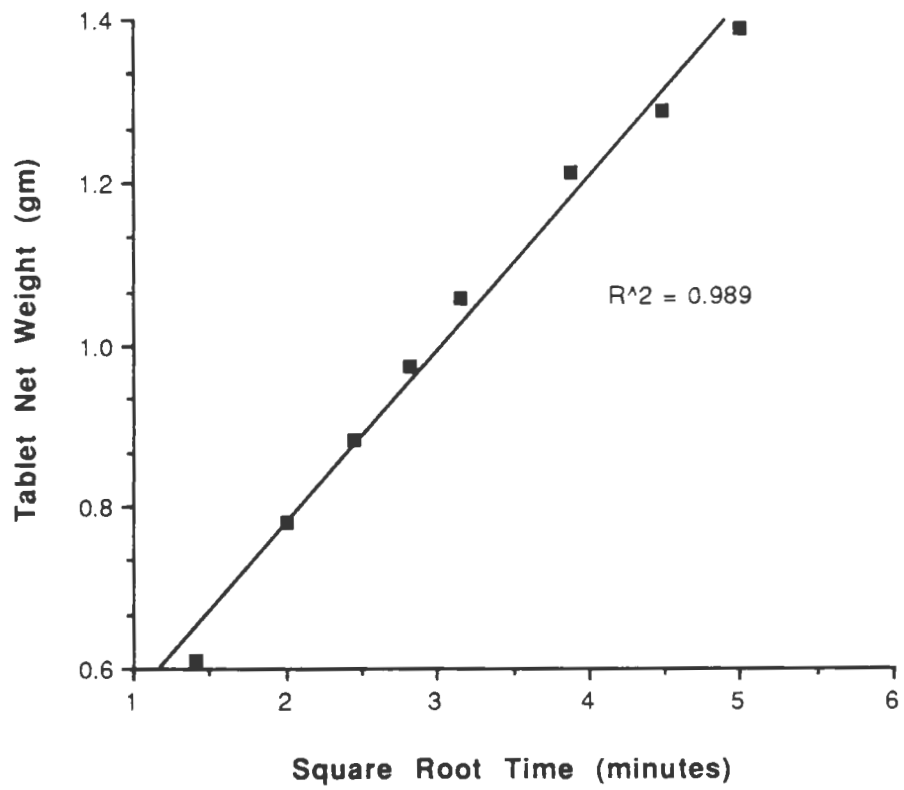


Figure 3- Tablet weight vs. Square root time of PEO 1M

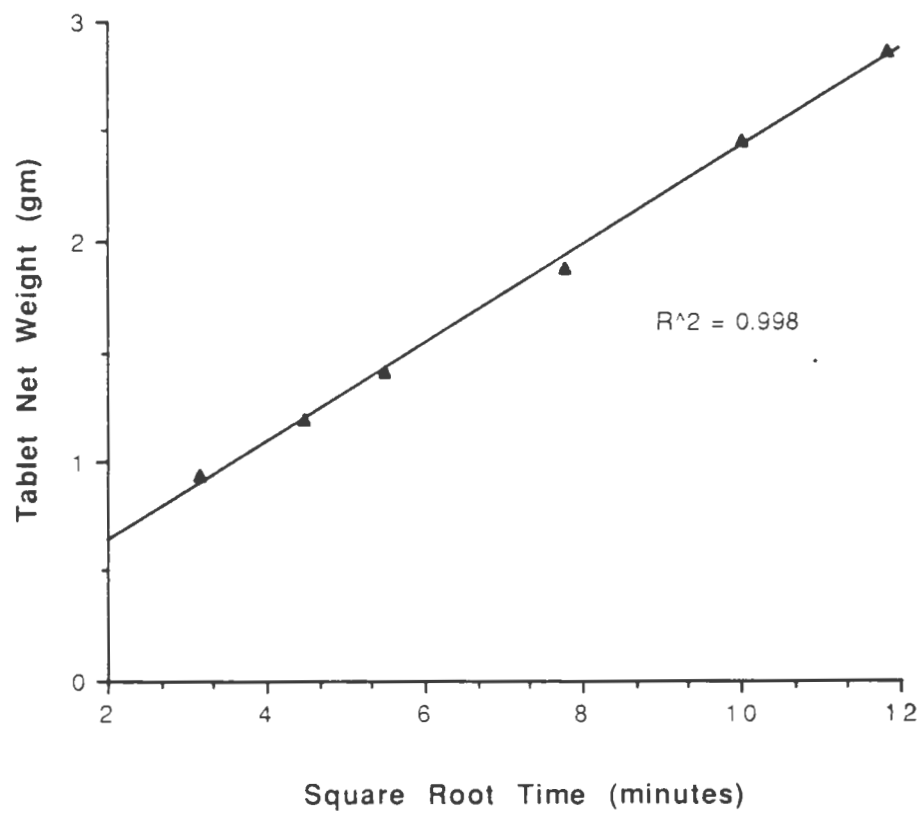


Figure 4- Tablet weight vs. square root time of PEO 4M

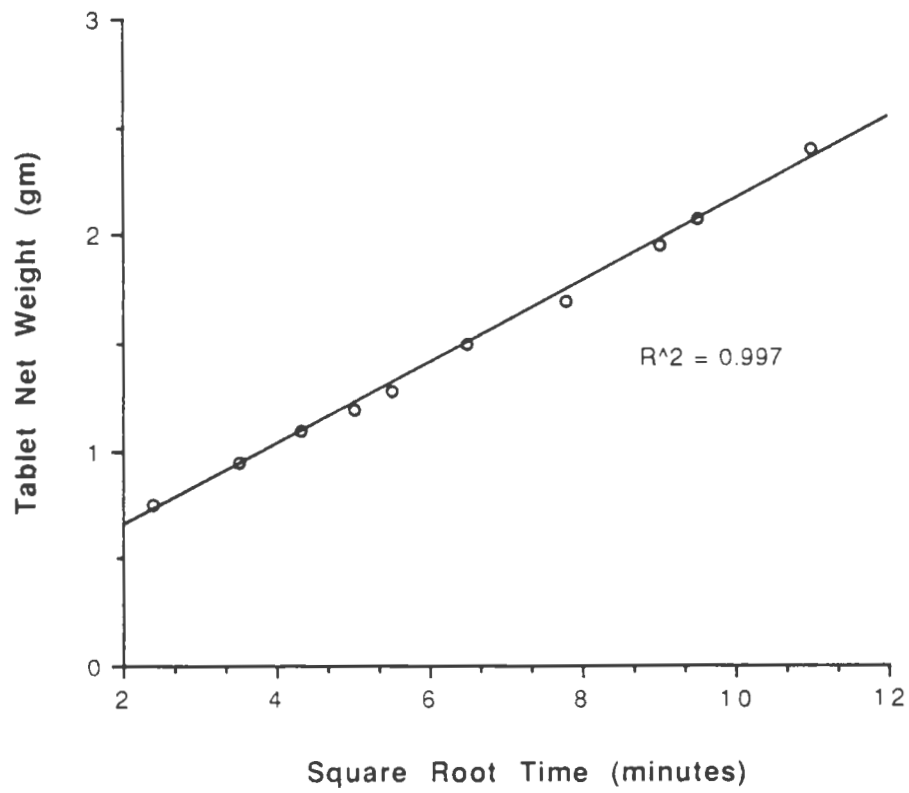


Figure 5- Tablet weight vs. square root time of PEO 5M

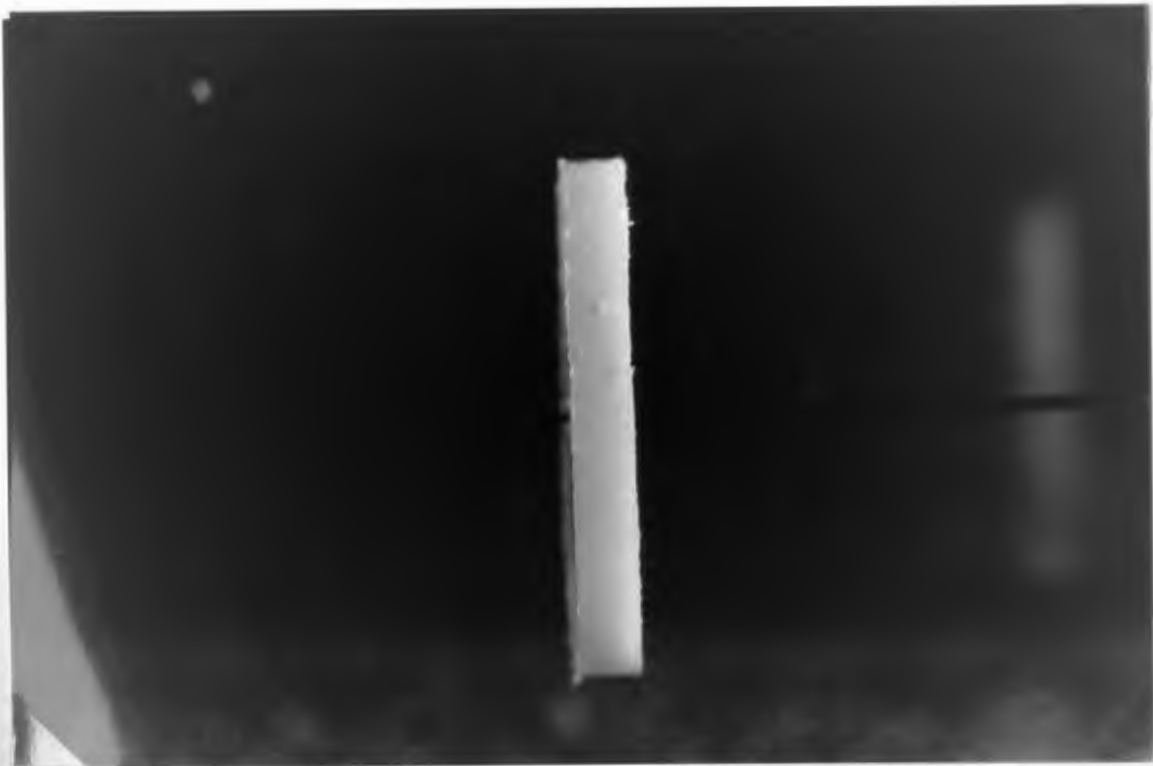


Figure 6 - Dynamic swelling process of a representative PEO 5M tablet in water (time = 0 hour)

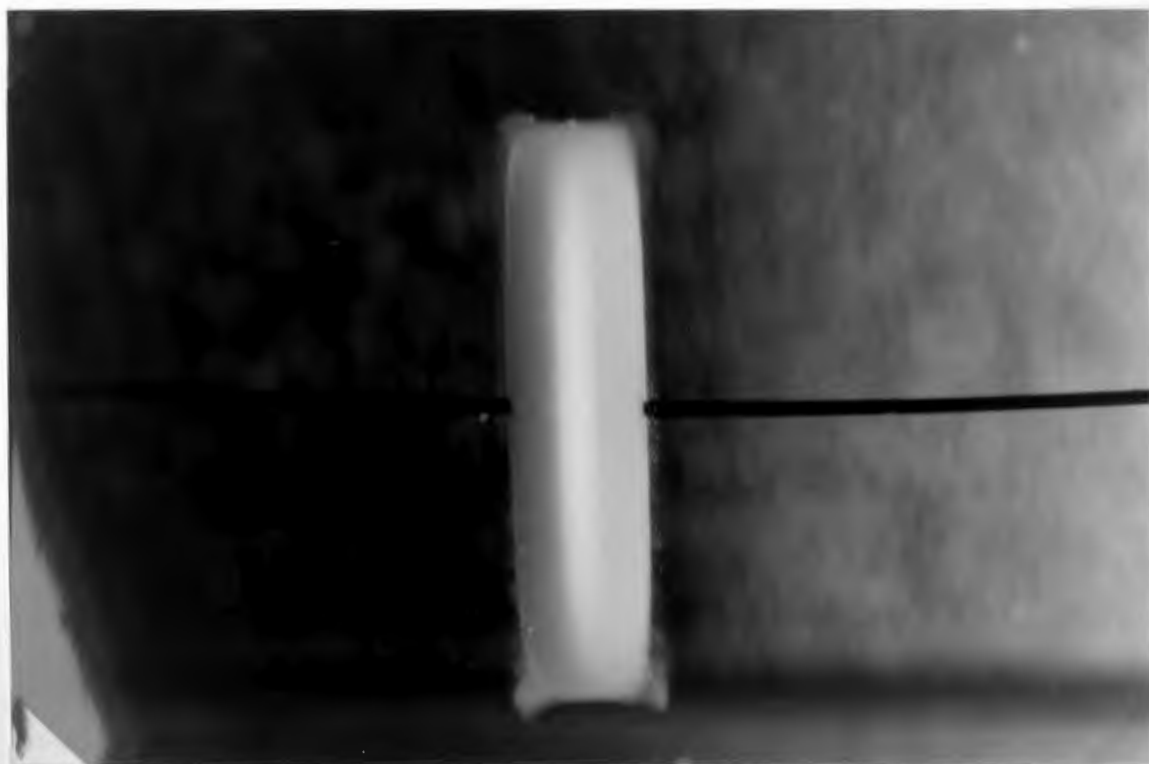


Figure 7 - Dynamic swelling process of a representative PEO 5M tablet in water (after 2 hours)

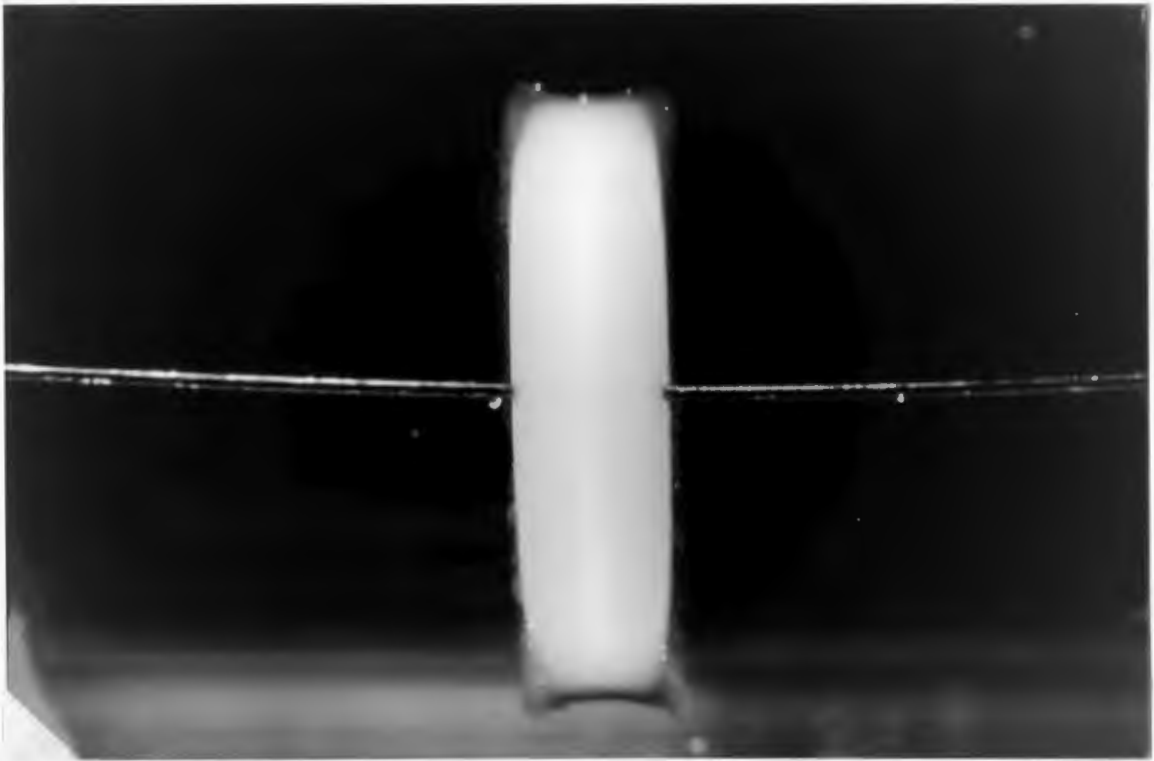


Figure 8 - Dynamic swelling process of a representative PEO 5M tablet in water (after 6 hours)

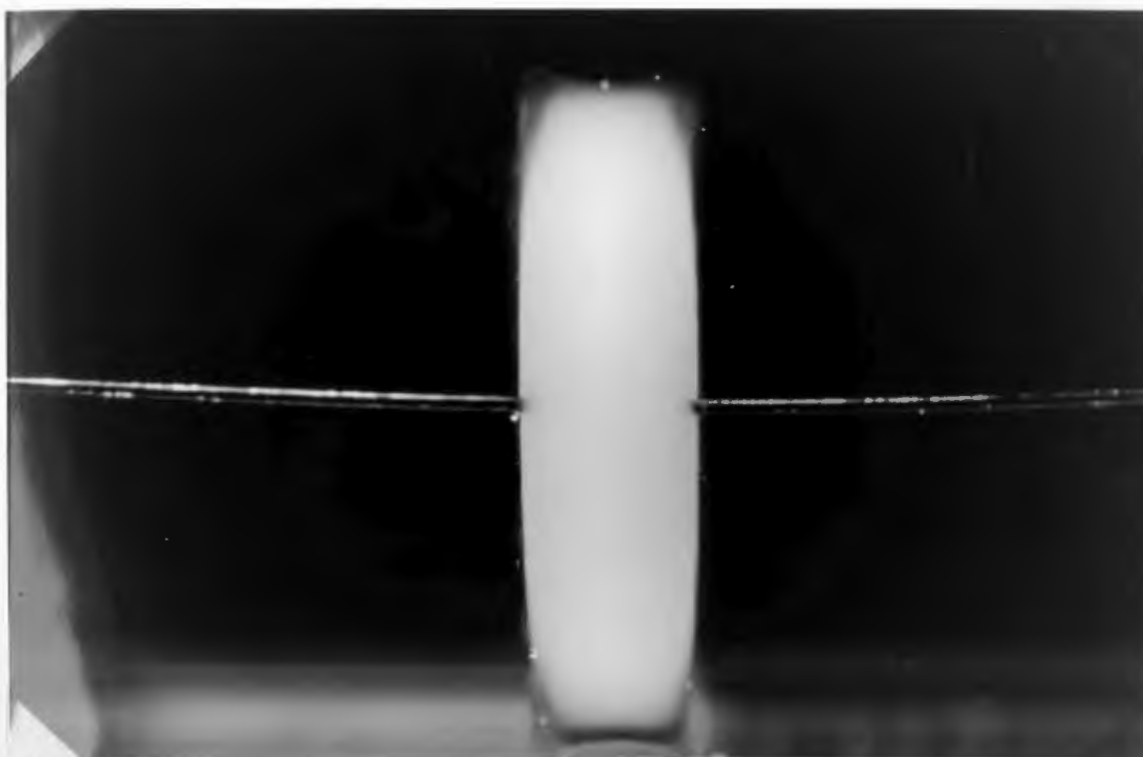


Figure 9 - Dynamic swelling process of a representative PEO 5M tablet in water (after 8 hours)

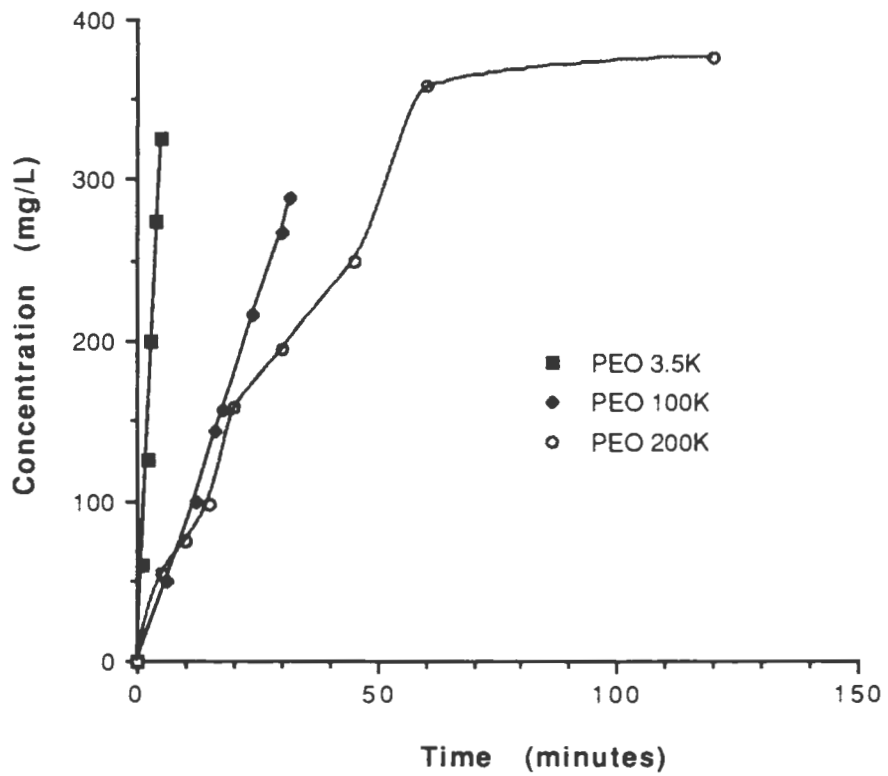


Figure 10- Dissolution of PEO 3.5,100K and 200K tablets (tablet weight: 370mg)

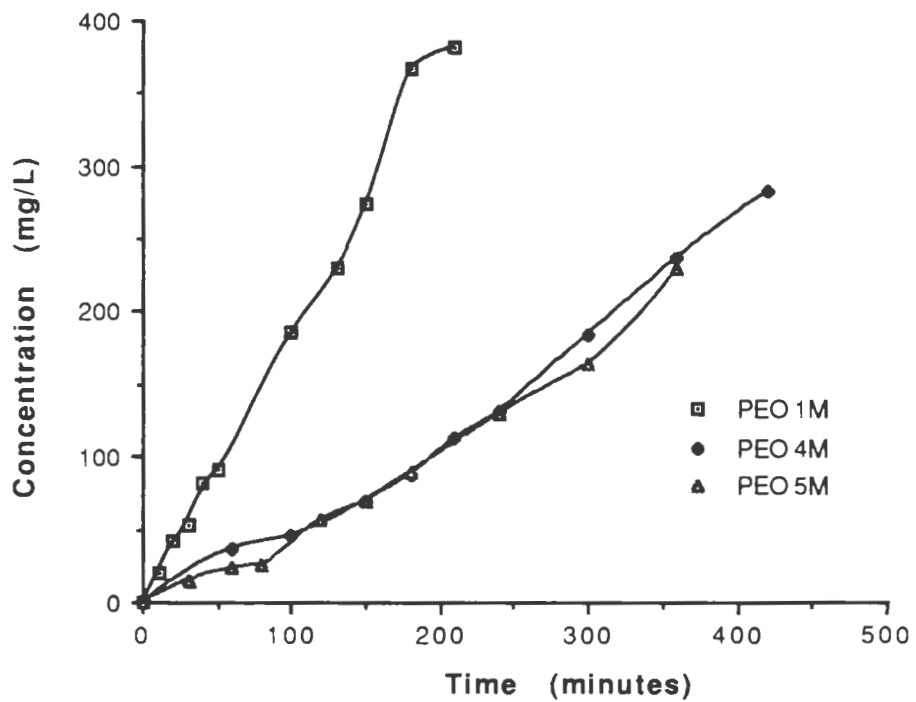


Figure 11- Dissolution of PEO1M, 4M and 5M tablets (tablet weight: 370mg)

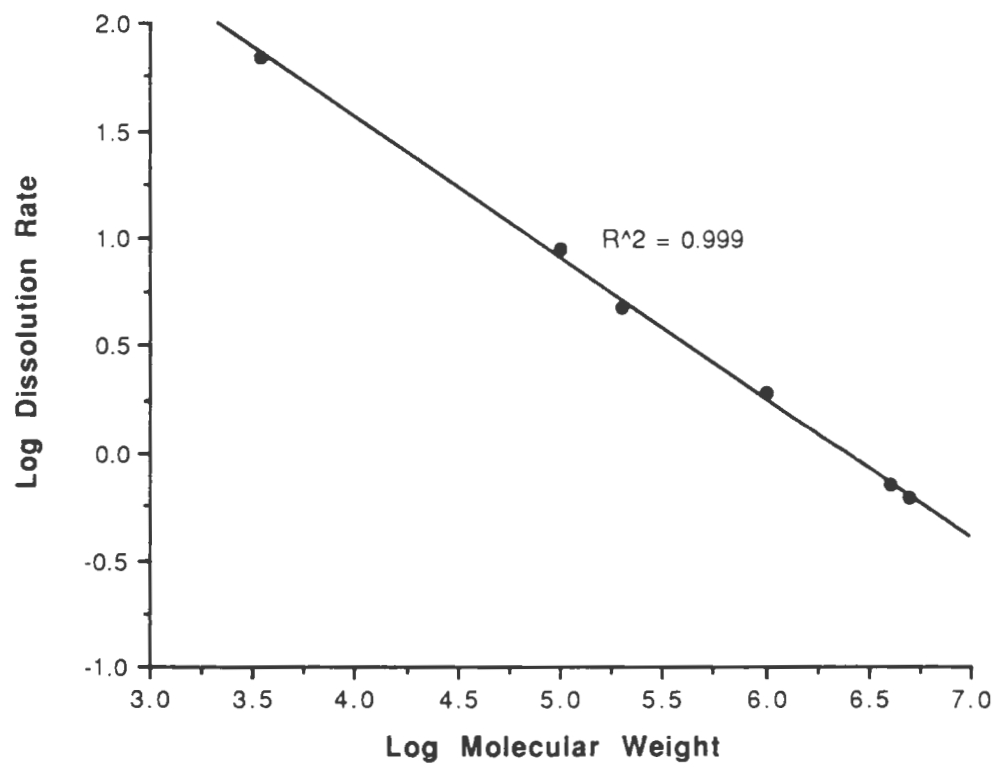


Figure 12- Dissolution rate of PEO as a function of molecular weight.

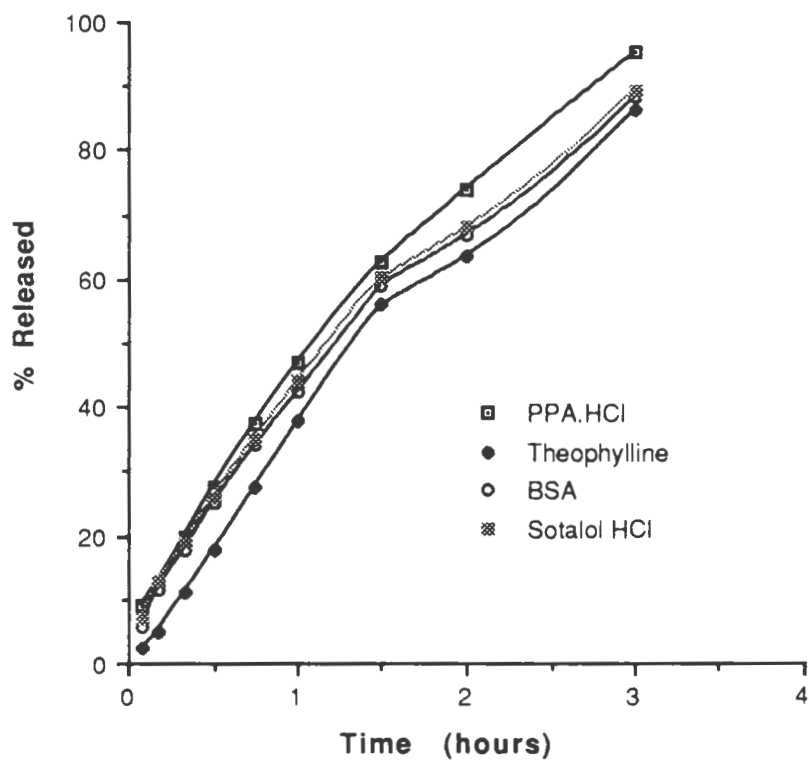


Figure 13- Dissolution profiles of 500 mg tablets containing 50% drug/50% PEO 100K in SIF at 37 C

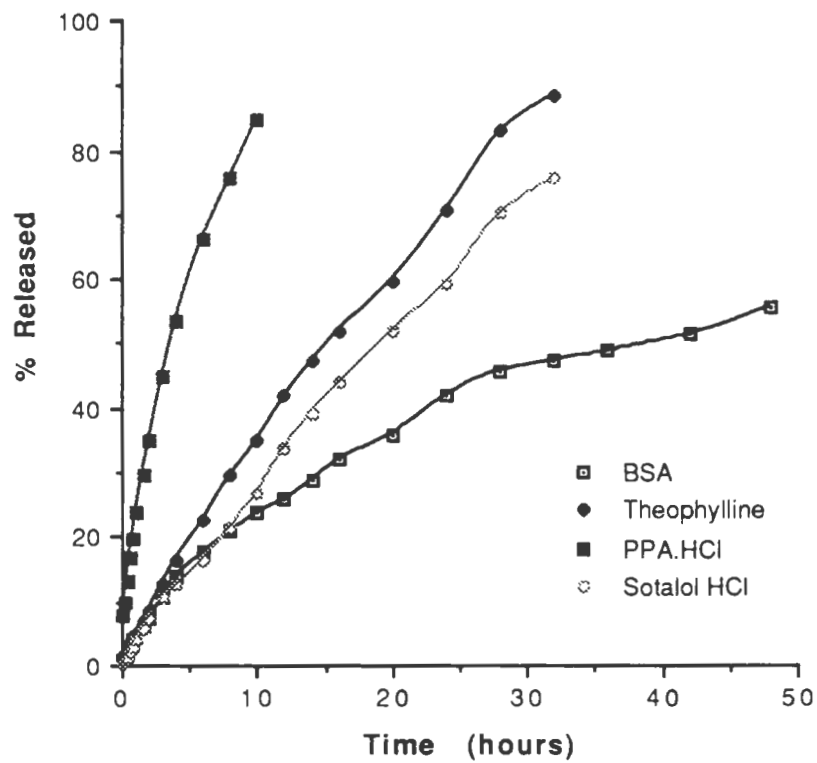


Figure 14- Dissolution profiles of 500 mg tablets containing 50% drug/50% PEO 5M in SIF at 37 C

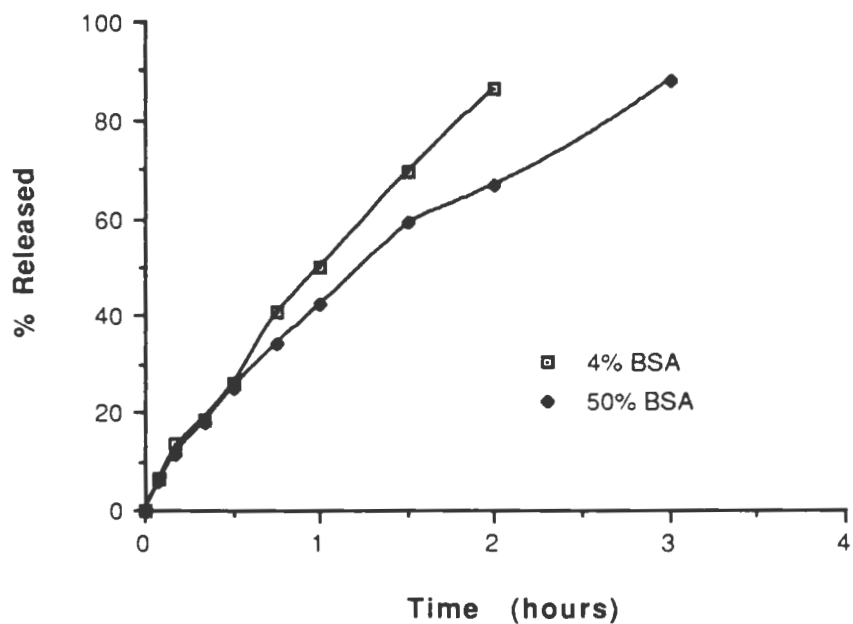


Figure 15- Dissolution profiles of 500mg tablets containing 4% BSA/96% PEO 100K and 50% BSA/50% PEO 100K in SIF at 37 C

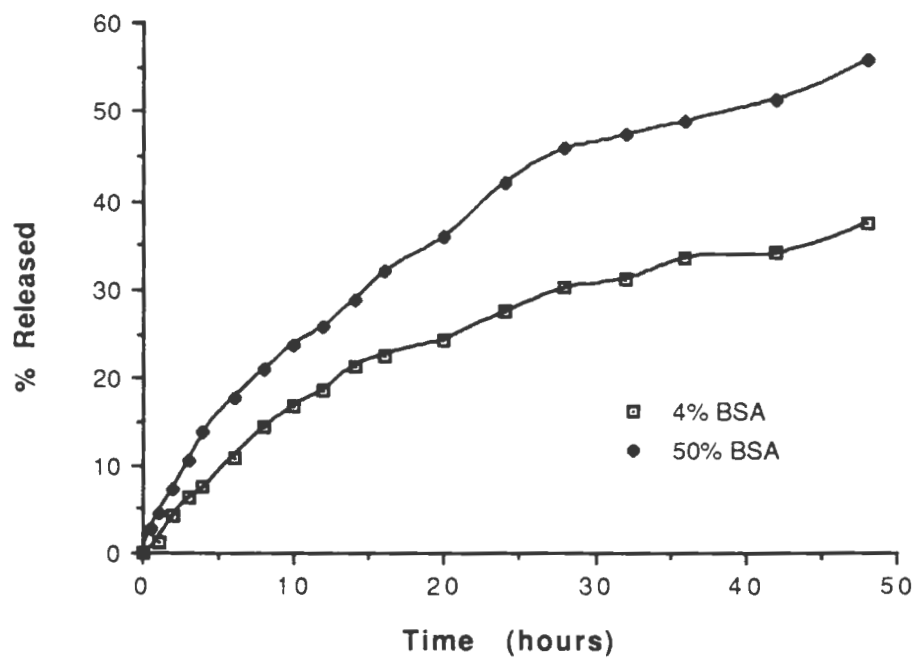


Figure 16- Dissolution profiles of 500mg tablets containing 4% BSA /96% PEO 5M and 50% BSA/PEO 5M in SIF at 37 C

**OPTIMIZATION OF SOTALOL FLOATING AND BIOADHESIVE
EXTENDED RELEASE TABLET FORMULATIONS**

ABSTRACT

A novel extended release sotalol HCl tablet formulation which possesses an unique combination of floatation and bioadhesion for prolonged residence in the stomach was developed. Tablets were produced by direct compression process. A two-factor factorial, central, composite Box-Wilson experimental design was employed to develop and optimize the tablet formulation containing 240 mg sotalol HCl and some other polymeric components. The ratio of two major bioadhesive agents, sodium carboxymethylcellulose (NaCMC) to hydroxypropylmethylcellulose (HPMC), and the ratio of two direct compressible diluents, ethylcellulose (EC) to croscopolvidone, were used as formulation variables (independent variables) for optimizing some tablets response parameters, such as dissolution characteristic, bioadhesive capability, tablet density and required compression force for producing 6 Kg hardness tablets. The data were also analyzed by means of quadratic response surface model. Response surfaces were generated as a function of formulation variables. An

optimum direct compression, bioadhesive and floating tablet formulation of sotalol HCl was achieved by considering the dissolution characteristic as primary objective and using required compression force, bioadhesive capability as constraints within the experimental region. The surface model was validated for accurate prediction of response characteristics.

INTRODUCTION

For the last forty years or so, oral sustained-release drug delivery have attracted considerable attention and recognition (1). However, in the cases of certain classes of active ingredients which are not suited to normal absorption during passage through the gastrointestinal tract (GIT), the conventional oral sustained-release dosage forms can be disadvantageous due to their physicochemical properties or favorable absorption site (2). Some drugs will undergo different degrees of change in solubility by passage from the acidic condition of the stomach to the neutral or alkaline condition of the intestine. In view of all these reasons and conditions, it is readily apparent that very frequently the bioavailability of these drugs in conventional sustained release dosage form can be affected by the transit of the dosage form within different regions of the GIT.

In recent years, many attempts have been made to provide therapeutic dosage form which will provide longer transit time and more efficient absorption for specific drugs which have a window

effect of absorption or stability problem. The floating dosage form was designed to possess sufficient buoyancy to float on the top of stomach content and prolong the stomach residence time of the dosage form (3-8). Meanwhile, significant interest also has been shown in the development of oral bioadhesive systems to adhere the oral dosage form to mucosa wall of stomach or intestine to increase the residence of the drug in the GI tract (9-12).

The floating and bioadhesive drug delivery systems are meant to provide the following advantages (1) increased and more effective absorption for drugs which have specific absorption sites (2) increased contact time for local activity in the stomach where such is required and (3) the ability to limit the number of dosages.

The floating dosage form is meant to remain buoyant on the gastric fluid when the stomach is full after a meal, however, as the stomach empties and the tablet is at the end of the stomach the buoyancy of the dosage form might be impeded (13). It will become increasingly possible that the dosage form will pass through the pylorus into the small intestine. Thus, the buoyant ability of a floating drug delivery system in the stomach could be limited to only three or four hours. In bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the stomach is full and semi-liquid contents are churning around under the influence of peristaltic movement. Also, most of currently available oral floating and bioadhesive systems are made

by wet granulation tableting process and some other tedious and costly procedures.

In light of the above reasons and conditions, the objective of this work was to develop a novel sustained-release tablet made by direct compression process. The tablet possesses an unique combination to prolong the stomach residence time of sotalol HCl, a beta-blocker, which has high aqueous solubility and its absorption from GI tract is limited to the upper part of the small intestine.

In this present study, a computer optimization process utilizing a statistical Box-Wilson design experimental design (14,15) was employed to develop bioadhesive and floating tablet formulations and determine the effects of formulation variables on the response properties of tablets. Finally, an optimum tablet formulation was selected using the technique of response surface methodology.

EXPERIMENTAL

Experimental Design

The two formulation variables and their ranges selected for optimization study were summarized in Table I, X1 represents the ratio of NaCMC(mg) to HPMC(mg) and the second variable, X2 represents the ratio of EC(mg) to polyplasdone XL(mg). All other formulation and processing variables were remained constant throughout the study.

A total of 13 experiments required in a two factor factorial, central, composite Box-Wilson experimental design was listed in Table II. This experimental design is based on factorial design with additional points added to estimate curvature of the response surface. As shown in Table II, the first sixteen experiments represent a half-factorial design for two factors at two levels represented by +1 and -1, analogous to the high and low values in any two level factorial design. For the remaining experiments, three additional levels, +1.414, 0, -1.414 were selected. The zero level represents a center point midway between the +1 and -1, the levels noted as +1.414 and -1.414 represent extreme values for each factor and the experimental levels were calculated by adding or subtracting one-half experimental unit to or from the experimental levels corresponding to +1 or -1 in the experimental design. The design also includes five replicate of center point allowing a lack-of-fit test for the mathematical model. Standard designs with fewer trials would have resulted in confounding among model terms and increased the risk of inaccurate conclusion.

Table III shows the translation of the experimental levels in the statistical design into experimental values. The response parameters measured on the resulting tablets were summarized in Table IV. The objective was to search the levels of the two independent variables that would produce tablets with the desired response parameters. These parameters are Y1, dissolution characteristic (diffusional exponent, n); Y2, the detachment force required to separate tablet from membrane; Y3, the required shear force; Y4, the required

compression force for producing 6 kg hardness tablets; Y5, tablet density.

Preparation of Bioadhesive and Floating Tablets

Materials--- Sotalol hydrochloride (Bristol Myers-Squibb lot NOCO7) was used as active ingredient in the formulation. The following materials were also used: sodium carboxymethylcellulose (NaCMC 7HF, Aqualon Co., Lot 67798), hydroxypropylmethylcellulose (HPMC, Methocel K15M Premium CR Grade, Dow Co., Lot MM89011881K), ethylcellulose, (EC, Ethocel Premium V-10, Dow Co., Lot 6161187), crosspovidone NF (Polyplasdone XL, GAF Chem. Co., Lot S01029), calcium carbonate (Amend Chem Co., Lot S37399805) and magnesium stearate (Fisher Scientific Co., Lot 742748). Tablets were prepared with the following formulations based on the experimental design described above.

Sotalol HCl	240 mg
NaCMC	11 to 209 mg
HPMC	11 to 209 mg
EC	17.6 to 102.4 mg
Polyplasdone XL	17.6 to 102.4 mg
Calcium carbonate	80 mg
Magnesium stearate	2 mg

In the tablet formulation, NaCMC and HPMC were used as bioadhesive agents. When the tablet is in contact with gastric fluid, a combination of NaCMC and HPMC will also possess sufficient structure to form a gel layer and achieve an overall specific gravity

lower than that of gastric fluid therefore remain buoyant in the gastric fluid. Meanwhile, calcium carbonate was used in the formulation to generate carbon dioxide, these carbon dioxide bubbles will become entrapped by the hydrated outer gel layer to enhance the buoyance of the tablet. EC and polyplasdone XL were used as direct compressible tablet matrices in the tablet formulation.

Mixing--- All powders except Mg stearate were sieved through sieve of mesh size 20. The components of the formulation were mixed for 15 minutes in a WAB type T2C turbula mixer.

Lubrication--- Mg stearate (40 mesh sieved) was added into powder blend as a lubricant and mixed for an additional of 3 minutes before compaction process.

Compaction--- Tablets were prepared by direct compression on an instrumented Stoke B-2 rotary press at 30 rpm using 3/8" flat face punches and dies adjusted to obtain 6 kg hardness tablets. The required compression force was measured by the piezoelectric force transducer located in the eyebolt. The analog data from the piezoelectric force transducer were converted to the digital form by the analog to the digital converter. The digital output was then collected and analyzed on a personal computer. The tablet formulations were compressed in a random order.

Tablet Evaluation

In Vitro Dissolution--- Dissolution studies were conducted using the USP basket method. Six tablets were tested for each batch. The dissolution medium was 900 ml of 0.1 N HCl solution (pH 1.2)

equilibrated at 37 °C and stirred at 70 rpm. The samples (3 ml) were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 20 and 24 hours, respectively. The dissolution medium volume was kept constant by adding the same volume of fresh dissolution medium kept at the temperature of 37 °C. The dissolution samples were diluted and the concentration were determined on a Diode Array Spectrophotometer at the wavelength of 228 nm corresponding to the maximum absorbance of sotalol HCl.

Floating Capability--- The lag time required for the tablet to start floating on the top of basket in the dissolution study was measured. The duration of floatation under the rotating condition of the dissolution study was also determined for all formulations.

Measurement of Bioadhesiveness

Figure 1 shows the diagram of the custom-designed apparatus to be equipped with Instron Tensile Tester (Instron, model 1122) for bioadhesion measurement. The system consists of a small polyacrylic cylinder fastened to the side wall of a polyacrylic cubic vessel to hold the membrane by means of an O-ring. A rectangular aluminum pieces with a hole in the middle was used as a support to hold the tablet fixed over the surface of the biological tissue. The vessel was put on the lower plate of the Instron Tensile Tester, while the aluminum support was connected to the vertical rod and fixed to the upper clamp of the tensile tester.

In a typical sliding adhesion test, after placing the tablet in the hole of the aluminum pieces, the stomach mucosa and tablet were brought together just to touch each other. The tablet and mucosa

surfaces were held parallel. The vessel was filled with constant volume of distilled water (1000 ml) at 22 °C. After 30 minutes (pre-swelling time), the force was measured and recorded as a function of time until the tablet had crossed the mucosa surface. Additionally, as can be seen from Figure 1, another polyacrylic cylinder is fixed to the bottom of the vessel to hold a mucosa horizontally by means of an O-ring for the determination of direct detachment force.

In the detachment force measurement, the tablet was stuck on to rectangular aluminum support with a cyanoacrylate glue, the tablet support was fixed to the upper clamp of the tensile tester and lowered to maintain in a similar fashion that tablet and rabbit stomach mucosa surfaces were rigorously parallel. The cubic vessel was filled with constant volume (1000 ml) of pH 2 buffered solution at 22 °C. After 30 minutes, the crosspiece was raised at constant speed (20 mm/min.) The detachment force was measured and recorded as a function of displacement, up to the total separation of the tablet surface and tissue. The adhesion work was determined by calculating the area under the curve necessary for detachment.

The biological tissue used in bioadhesion study was rabbit stomach mucosa, it was maintained in normal saline solution or used immediately after the sacrifice of the animals. The stomach mucosa samples were immersed in normal saline solution and kept in the refrigerator at 5 °C before use.

Analysis of Data

All the statistical and regression analysis procedures on the response parameters were performed using the X-STAT software package. Statistical Analysis was carried out which includes the calculation of mean values for each of the four response parameters in each of 13 experiments.

The sets of data obtaining from the statistical analysis were then subjected to computerized regression analysis to determine the fit to a second-order model. These regression models include an intercept and main effect terms of each independent variable, two-way interaction terms and second order effect terms as shown in Table V.

RESULTS AND DISCUSSION

The dissolution profiles for the tablets are shown in Figure 2 to Figure 5. The sotalol HCl release data of the early portion of the release curve ($M_t/M_\infty < 0.6$) from floating and bioadhesive tablet were analyzed by using Equation 1, where M_t/M_∞ represents the fraction of drug released at time t , K is the kinetic constant characteristic of the drug/polymer system, t is the release time and n is an exponent characterizing the mechanism of release of the drugs (16).

$$M_t/M_\infty = K t^n \quad (\text{Eqn. 1})$$

Table VI summarizes the range of values of the diffusional exponent n , and the corresponding release mechanism.

The response properties of tablets obtained from all 13 formulations in the experimental design were summarized in Table VII. The n values of sotalol dissolution are in the range of 0.36 to 0.60. The lag time of tablet floatation ranged from 5 seconds to 12 minutes. All tablet formulations exhibited floatation capability and maintained buoyant for more than 24 hours in dissolution medium under rotating condition. The required detachment force of tablets in bioadhesion study ranged from 1.0 to 2.11 Newton(N), the shear force ranged from 0.64 to 1.67 N. The required compression force are in the range of 8.42 to 21.68 kilonewton(KN). For each response parameter, variations were observed among formulations.

Each response parameter was fit to the second-order polynomial model and the regression coefficient for each term in the regression model were shown in Table VIII to XII. As can be seen, most of these standard error values are less than 50% of the absolute values of their regression coefficients indicating the adequacy of the model. Also, the high values of confidence level indicate these variable terms have standard significant effects on the response parameter. Although, there are few terms which do not contribute significantly at 90% confidence level to the model, however, these terms, as a group, do affect the shape of the contour plot.

As shown in Table XIII, the high R^2 values of each response parameter equation indicate the good fit and adequacy of these

models. It also implies that the regression equation explains large portion of variation of response parameter about its mean. For each response parameter, the multiple correlation coefficient was greater than 0.91 indicating there are at least more than 91% of the total variations observed in the response parameter could be explained as being caused by the independent variables in the way described by the equation as shown in Table VIII to XII. An F test for the regression equation was performed and the calculated F value was significant at the 99% level for all response parameters revealing that these model terms are important for explaining variability. Also, the predicted minimum and maximum values for each response parameter show good agreement with the experimental results obtained from 13 batches shown in Table VII.

The general quadratic surface model was applied to generate contour plots for each of response parameters. Figure 6 shows the effect of two formulation variables, NaCMC/HPMC and EC/polyplasdone XL, on tablet dissolution characteristic (diffusional exponent value, n). It indicates that tablets made with 105 mg NaCMC, 115 mg HPMC, 90 mg EC and 30 mg polyplasdone XL obtained the highest n value from dissolution profile which indicates sotalol HCl was released by non-Fickian behavior, a near zero-order release, and the release was partially controlled by viscoelastic relaxation of the matrix system during solvent penetration. This increase in the values of n may be attributed to the stronger hydrogen bonding between the carboxyl group on NaCMC and hydroxyl group on the nonionic gum, HPMC, leading to stronger

cross-linking between the two gums. The formulation composed of higher amount of NaCMC or HPMC exhibited lower value of n which represents the drug was released by Fickian diffusion, a first-order release, the diffusional pathlength for the drug increases with time.

As shown in Figure 7, it illustrates that the detachment force required for separating tablet from stomach mucosa surface increased with increasing amount of NaCMC as the amount of EC in the formulation increased. This is due to the stronger bioadhesive capability provided by NaCMC. Tablets made with 180 mg NaCMC, 40 mg HPMC, 90 mg EC and 30 mg polypladone XL will possess the best bioadhesive power. Figure 8 demonstrates the effect of two formulation variables on the required shear force. Again, as the amount of EC and NaCMC in the formulation increased, the required shear force for sliding tablet away from stomach mucosa was also increased.

In Figure 9, the required compression force increased with increasing amount of NaCMC in the formulation as amount of EC increased. This is attributed to the poorer compactability of NaCMC and EC when compared to HPMC and polypladone XL. Formulation containing 40 mg NaCMC, 180 mg HPMC, 30 mg EC and 90 mg polypladone XL only requires 7.5 KN compression force to produce 6 Kg hardness tablets. The effect of four polymeric components on the tablet density was demonstrated in Figure 10, where it shows that tablet density increased with the increasing amount of NaCMC as EC increased. This is because of the higher bulk density of NaCMC and EC

when compared to HPMC and polyplasdone XL. Tablets made with 50 mg NaCMC, 170 mg HPMC, 40 mg EC and 80 mg polyplasdone XL possessed a density lower than 1.0 resulted in no lag time in floatation process. These contour plots illustrate contour line of equal response and the direction in which the gradient has steeper values.

Table XIV listed the optimum values of formulation variables for obtaining the best values of each of the response parameters. This Table was generated from the contour plots without placing any constraint on the response parameters. The optimum X1 and X2 levels for obtaining the highest diffusional exponent value, n , are 109 mg NaCMC/111 mg HPMC and 90 mg EC/ 30 mg polyplasdone XL while the optimum X1 and X2 levels for the minimum required compression force and tablet density are 40 mg NaCMC/180 mg HPMC and 30 mg EC/90 mg polyplasdone XL. In the case of detachment force, tablet formulation composed of 180 mg NaCMC, 40 mg HPMC, 90 mg EC and 30 mg polyplasdone XL would require the highest force, 1.79 N for direct detachment.

The dissolution release characteristic represented by the diffusional exponent value, n , was indentified as the primary response parameter because a zero-order release was desired for this extended sotalol tablet formulation. In addition, the in vitro dissolution usually provides an indication of in vivo bioavailability. The diffusional exponent n value was maximized so as to obtain a near zero-order release characteristic. As shown in Table XV, two

constraints were applied in obtaining the highest n value, the required compression force was constrained under 14 KN and the shear force was required to be more than 1.1 N. Additional constraints were the experimental range limits placed on values of two independent variables. The optimum formulation satisfied all constraints simultaneously and provided an optimum value for the primary concern, the highest n value.

The tablets were prepared on an instrumented B-2 rotary press according to the optimum formulation as shown in Table XIV, tablets properties were also determined. The comparison of predicted and experimental values for optimum formulation showed very good agreement and are shown in Table XVI. This reasonable prediction of the system's performance indicates the proposed model is valid.

CONCLUSIONS

A computer optimization process utilizing Response Surface Methodology (RSM) has been applied not only to develop and optimize a high dose acetaminophen-microcrystalline cellulose wet granulated tablet formulation exhibiting comparable physical tablets properties (15) but also to develop and optimize a novel extended release sotalol HCl tablet formulation which possesses an unique combination of floatation and adhesion for prolonged residence in the stomach. The Box-Wilson experimental design was demonstrated to be an effective and efficient tool for the design, evaluation, and

optimization of a complex mixture for extended release with performance-related compositional constraints. Properties of the optimal formulation are very close approximation to the predicted profiles selected by surface response models. The optimized 240 mg sotalol HCl extended-release tablets showed a satisfactory dissolution profile, strong bioadhesive capability in terms of detachment force and shear force and excellent floatation characteristics (lag time of floatation < 8 minutes, duration time of floatation > 24 hours), and these tablets can be manufactured by an efficient and economical direct compression process.

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TABLE I -- SUMMARY OF FORMULATION VARIABLES USED IN THE OPTIMIZATION PROCESS

FORMULATION VARIABLES	RANGE
X1: The ratio of NaCMC (mg) to HPMC (mg)	11/209 to 209/11
X2: The ratio of EC (mg) to Polyplasdone XL (mg)	17.6/102.4 to 102.4/17.6

TABLE II -- BOX-WILSON EXPERIMENTAL DESIGN FOR TWO FACTORS

FACTORS:	X1	X2
BATCH#		
1	-1	-1
2	1	-1
3	-1	1
4	1	1
5	-1.414	0
6	1.414	0
7	0	-1.414
8	0	1.414
9	0	0
10	0	0
11	0	0
12	0	0
13	0	0

TABLE III -- TRANSLATION OF EXPERIMENTAL CONDITIONS

	-1.414	-1	0	1	1.414
Factors:					
X1=NaCMC(mg) / HPMC(mg) eu*: 70 mg	11/209	40/180	110/110	180/40	209/11
X2=EC(mg) / Polyplasdone(mg) eu*: 30 mg	17.6/102.4	30/90	60/60	90/30	102.4/17.6
* eu: experimental unit					

TABLE IV -- RESPONSE PARAMETERS MEASURED IN THE OPTIMIZATION PROCEE

RESPONSE PARAMETERS

Y1: Dissolution (Diffusional Exponent, n)

Y2: Detachment Force (N)

Y3: Shear Force (N)

Y4: Required Compression Force (KN) for producing 6 Kg
hardness tablets.

Y5: Tablet Density (g/cm^3)

TABLE V-- GENERAL QUADRATIC EQUATION:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2$$

TABLE VI. Diffusional exponent and mechanism of diffusional release from cylindrical swellable controlled release matrix system

Diffusional exponent (n)	Drug release mechanism
< 0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) transport
0.89	Case II transport
n > 0.89	Super Case II transport

when the value of $n = 0.89$ means that the drug release is independent of time, the release is characterized as zero-order release.

TABLE VII --- SUMMARY OF RESPONSE PARAMETERS

	Diffusional Exponent, n	Detachment Force(N)	Shear Force(N)	Compression Force(KN)	Density (g/cm ³)	Lag Time (minutes)
BATCH#						
1	0.40	1.0	0.637	10.03	0.979	0.1
2	0.38	1.372	0.882	16.03	1.056	5
3	0.50	1.390	1.078	10.46	1.036	7
4	0.51	1.67	1.225	19.37	1.077	8
5	0.42	1.26	0.833	8.42	0.997	0.5
6	0.36	1.519	1.078	21.68	1.099	7
7	0.54	1.25	1.029	11.88	0.979	0.1
8	0.60	2.107	1.666	15.08	1.077	12
9	0.58	1.127	1.372	13.46	1.056	8
10	0.59	1.201	1.354	13.21	1.055	8
11	0.58	1.131	1.298	12.95	1.056	8.5
12	0.59	1.135	1.342	13.06	1.056	8
13	0.59	1.126	1.364	13.16	1.056	9
Range	0.36-0.60	1.0-2.107	0.637-1.666	8.42-21.68	0.979-1.099	0.1-12

TABLE VIII - Regression Coefficients for DENSITY
 =====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
0.8550	1 (constant)	0.0212	40.37	99.9%
0.000912	NACMC	0.0002	4.522	99.5%
0.003261	ETHYLCELLULOSE	0.0005	6.339	99.8%
-0.000004	NACMC*ETHYLCELLULOSE	0.0000	2.035	92.0%
-0.000001	NACMC^2	0.0000	1.237	73.3%
-0.000016	ETHYLCELLULOSE^2	0.0000	4.218	99.4%

Confidence figures are based on 7 degrees of freedom

TABLE IX - Regression Coefficients for DETACHMENTFORCE

=====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
1.484	1 (constant)	0.3009	4.932	99.6%
-0.001060	NACMC	0.0029	0.3701	31.2%
-0.02065	ETHYLCELLULOSE	0.0073	2.825	97.5%
-0.000011	NACMC*ETHYLCELLULOSE	0.0000	0.3660	31.0%
0.000016	NACMC^2	0.0000	1.652	85.6%
0.000248	ETHYLCELLULOSE^2	0.0001	4.685	99.6%

Confidence figures are based on 7 degrees of freedom

TABLE X - Regression Coefficients for SHEARFORCE

Coefficient	Term	Standard Error	T-Value	Confidence Coef (> 0)
-0.09344	1 (constant)	0.2594	0.3602	30.7%
0.01299	NACMC	0.0025	5.259	99.7%
0.01474	ETHYLCELLULOSE	0.0063	2.339	95.0%
-0.000012	NACMC*ETHYLCELLULOSE	0.0000	0.4522	35.2%
-0.000050	NACMC ²	0.0000	5.946	99.8%
-0.000054	ETHYLCELLULOSE ²	0.0000	1.175	70.9%

Confidence figures are based on 7 degrees of freedom

TABLE XI - Regression Coefficients for COMPRESSIONFORCE

=====

Coefficient	Term	Standard Error	T-Value	Confidence Coef <> 0
9.243	1 (constant)	1.353	6.833	99.8%
0.000360	NACMC	0.0129	0.0279	16.8%
-0.01459	ETHYLCELLULOSE	0.0328	0.4442	34.8%
0.000346	NACMC*ETHYLCELLULOSE	0.0001	2.575	96.4%
0.000177	NACMC^2	0.0000	4.051	99.3%
0.000092	ETHYLCELLULOSE^2	0.0002	0.3869	32.0%

Confidence figures are based on 7 degrees of freedom

TABLE XII - Regression Coefficients for DENSITY

=====

Coefficient	Term	Standard Error	T-Value	Confidence Coef (> 0)
0.8550	1 (constant)	0.0212	40.37	99.9%
0.000912	NACMC	0.0002	4.522	99.5%
0.003261	ETHYLCELLULOSE	0.0005	6.339	99.8%
-0.000004	NACMC*ETHYLCELLULOSE	0.0000	2.035	92.0%
-0.000001	NACMC^2	0.0000	1.237	73.3%
-0.000016	ETHYLCELLULOSE^2	0.0000	4.218	99.4%

Confidence figures are based on 7 degrees of freedom

TABLE XIII --REGRESSION SUMMARY AND PREDICTED RESPONSE
PARAMETERS RANGES

	F-Ratio Regression	R ²	Predicted Values	
			Min.	Max
Diffusional Exponent, n	23.17*	0.95	0.61	0.37
Detachment Force	11.99*	0.90	1.02	1.79
Shear Force	14.35*	0.91	0.726	1.51
Compression Force	98.75*	0.99	9.6	20.1
Density	41.43*	0.97	0.969	1.09

* Implies at least 99 % confidence regression equation is nonzero

TABLE XIV --- OPTIMUM VALUES OF FORMULATION VARIABLES TO OBTAIN BEST POSSIBLE RESPONSE PARAMETERS

	Diffusional Exponent, n	Detachment Force(N)	Shear Force(N)	Compression Force(KN)	Density
X1	105/115	180/40	120/100	40/180	40/180
X2	90/30	90/30	90/30	30/90	30/90
Diffusional Exponent, n	<u>0.61</u>	0.50	0.61	0.44	0.44
Compression	14	20.1	15	<u>2.6</u>	9.6
Detachment Force	1.6	<u>1.79</u>	1.62	1.06	1.06
Shear force	1.5	1.33	<u>1.51</u>	0.726	0.726
Density	1.07	1.09	1.07	0.969	<u>0.969</u>

TABLE XV --CHOICE OF OPTIMUM FORMULATION

Formulation Variable	Value
NaCMC/HPMC	105/115
Ethylcellulose/Polyplasdone XL	90/30

Constraints: 1. Compression Force < 14 KN
 2. Shear Force > 1.1 Newton

**TABLE XVI --COMPARISON OF PREDICTED AND EXPERIMENTAL VALUES OF RESPONSE VARIABLES
FOR OPTIMUM FORMULATION**

	Diffusional Exponent, n	Detachment Force (N)	Shear Force (N)	Compression Force (N)	Density
Constraint			> 1.1 N	<14 KN	
Predicted	0.61	1.6	1.5	14	1.070
Experimental	0.62	1.72 (0.21)	1.4 (0.16)	14.3 (0.5)	1.064 (0.01)

* values in parenthesis represent standard deviation.

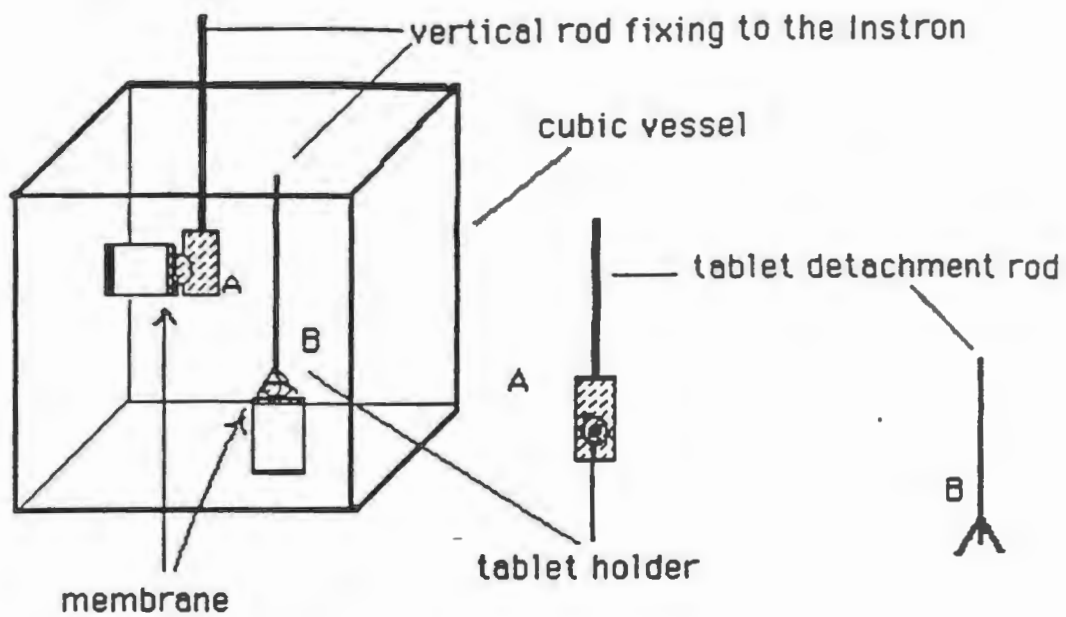


Figure 1. Apparatus for determination of bioadhesiveness of tablets; (A), Sliding Method, (B), Direct Detachment.

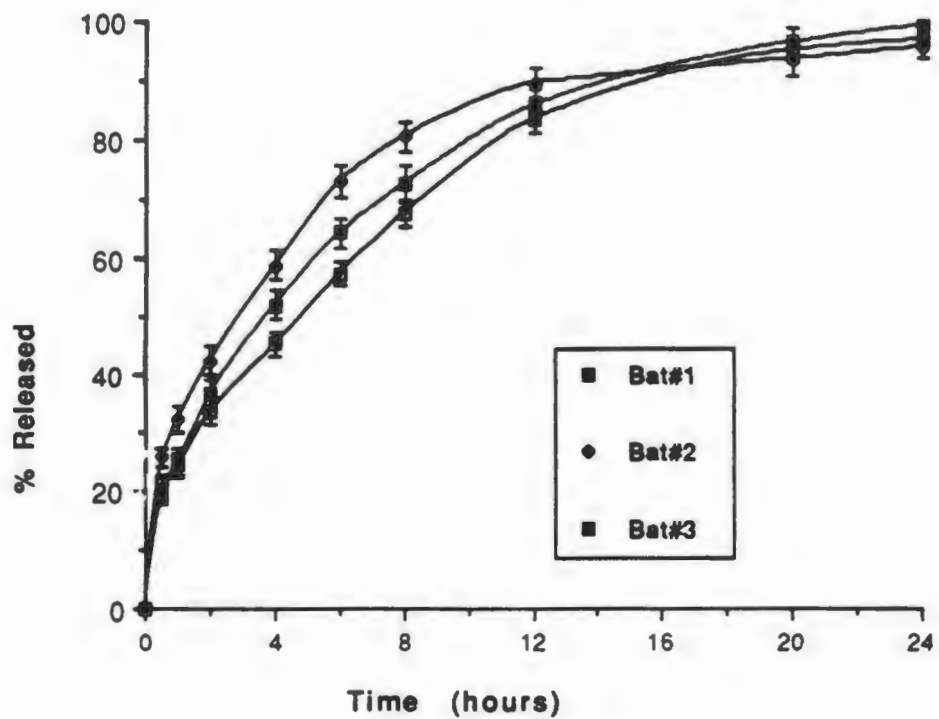


Figure 2- Dissolution profiles of sotalol tablet formulation Bat#1, 2 and 3

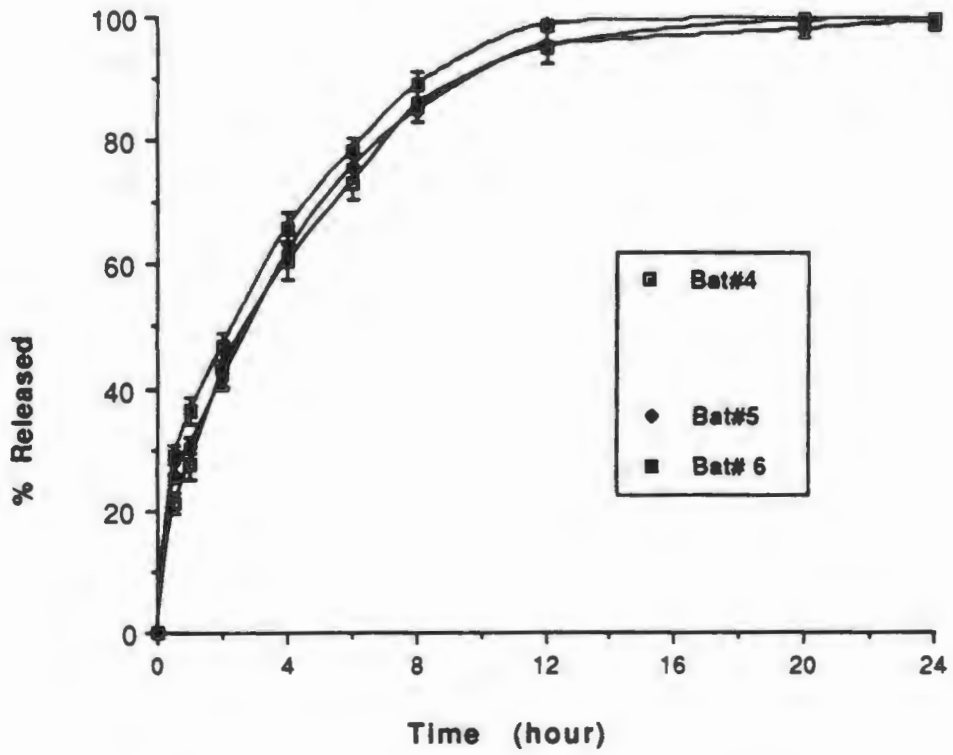


Figure 3- Dissolution profiles of sotalol tablet formulation batch# 4, 5 and 6

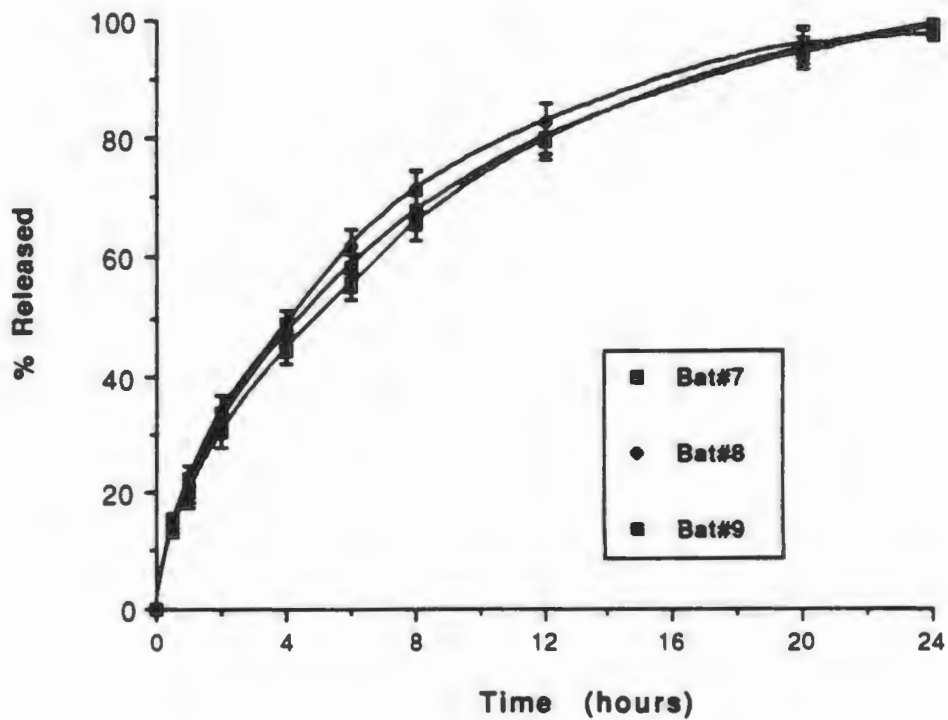


Figure 4- Dissolution profiles of sotalol tablet formulation batch# 7, 8 and 9

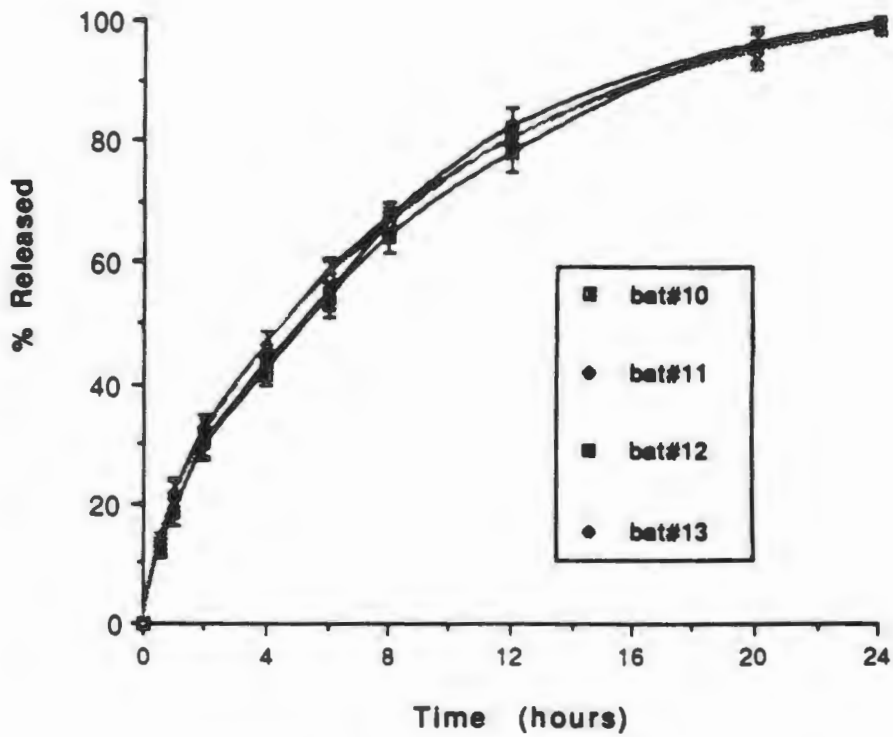


Figure 5- Dissolution profiles of sotalol tablet formulation batch# 10, 11, 12 and 13

FIGURE 6 - EFFECT OF AMOUNT OF NaCMC AND EC ON THE DISSOLUTION (DIFFUSIONAL EXPONENT, n)

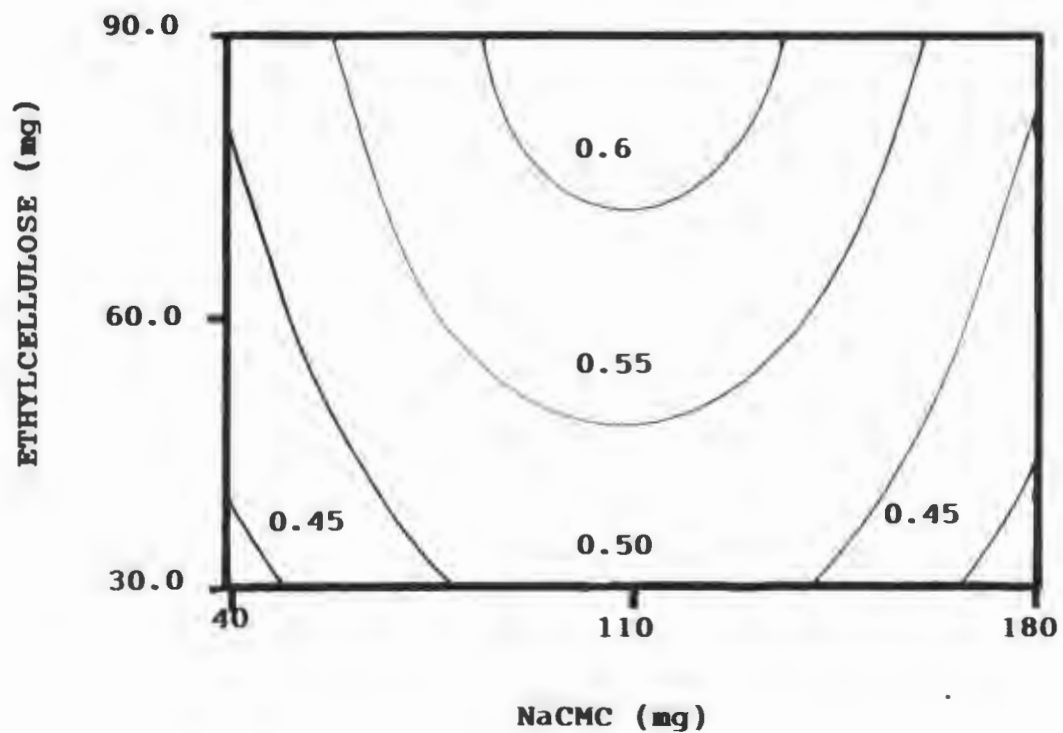


FIG. 7 -- EFFECT OF AMOUNT OF NaCMC AND EC ON THE DETACHMENT FORCE (Newton)

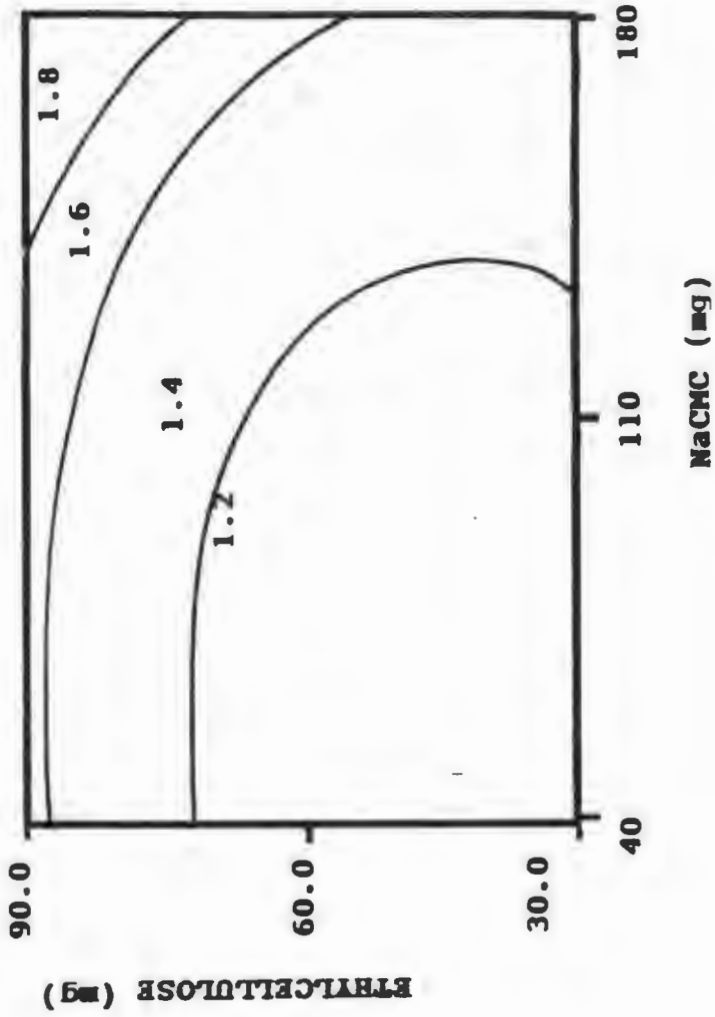


FIG. 8 - EFFECT OF AMOUNT OF NaCMC AND EC ON THE SHEAR FORCE (Newton)

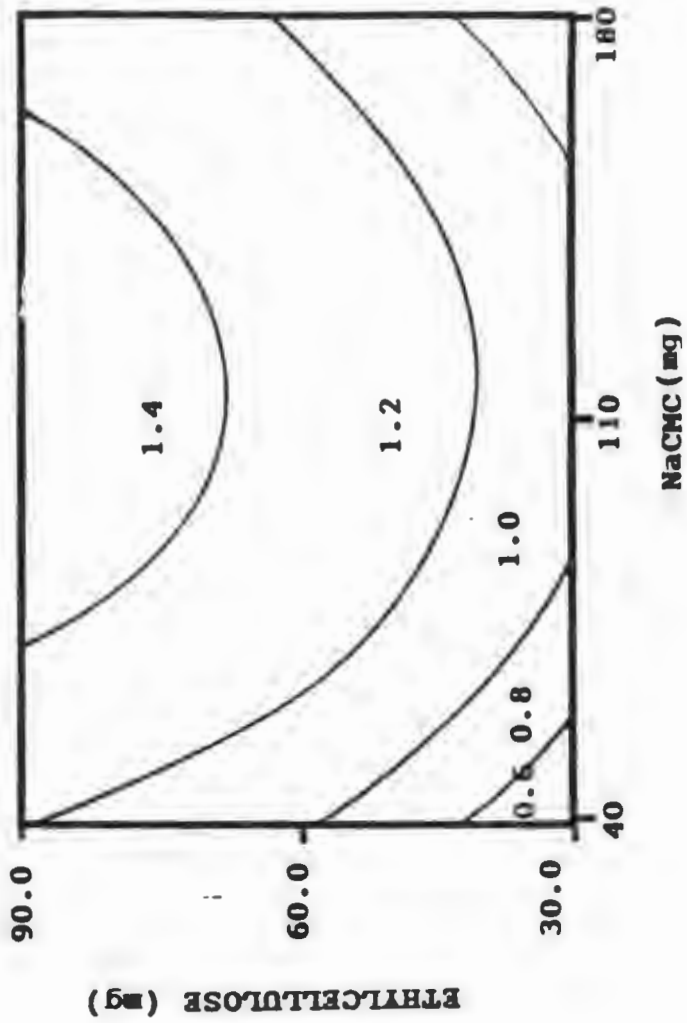


FIG. 9 - EFFECT OF AMOUNT OF NaCMC AND EC ON THE REQUIRED COMPRESSION FORCE (KN)

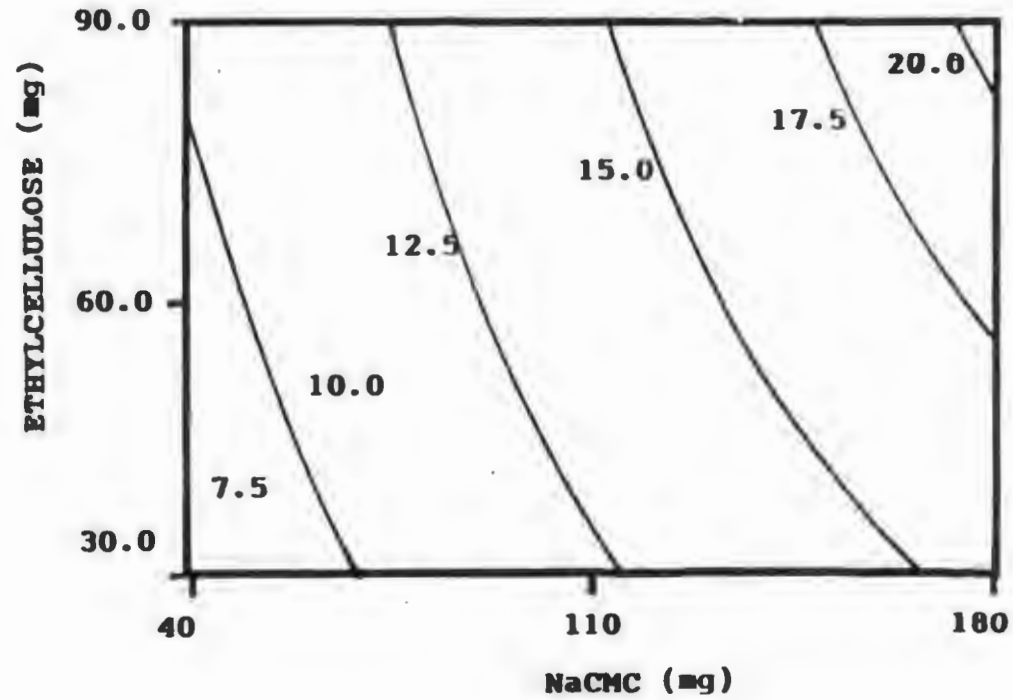
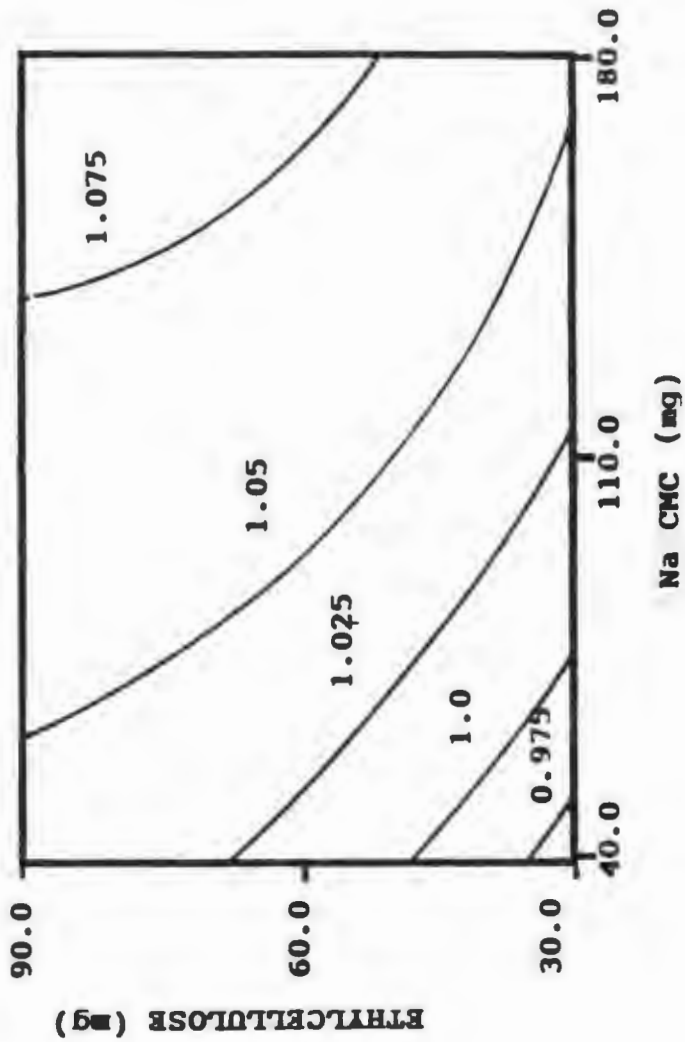


FIG. 10 - EFFECT OF AMOUNT OF NaCMC and EC ON THE TABLET DENSITY



**A NOVEL IN VITRO ASSESSMENT OF BIOADHESION OF
VARIOUS ADHESIVE TABLET FORMULATIONS**

ABSTRACT

An apparatus to be equipped with Instron tensile tester was developed to quantitatively evaluate the bioadhesive properties of various bioadhesive tablets. The equipment was designed to measure the forces required to separate two parallel surfaces (tablet and membrane) in both horizontal and vertical positions. In this work, in addition to the detachment force and adhesion work, the shear force necessary for separating bioadhesive tablet and synthetic membrane or biological tissue (rabbit stomach mucosa) were also determined since the majority of gastrointestinal mucosa surface area possesses some elements of tangential shear motion. The effects of different quantities and types of bioadhesive polymer on the tablet bioadhesive capability were also determined. The results showed good agreement with some previous findings that the relative adhesion of the tablet formulations was dependent on the bioadhesive polymer content. Tablet made with sodium

carboxymethylcellulose (NaCMC) possessed the best bioadhesive power when compared to tablets made with polycarbophil and carbopol 974P.

INTRODUCTION

In the last decade, oral bioadhesive drug delivery systems have attracted considerable attention for localization and sustained release drug delivery, they are designed to prolong the gastrointestinal transit time of the dosage form and improve the bioavailability of drugs (1).

The performance of a bioadhesive dosage form can be evaluated by various parameters, such as adhesion strength, adhesion number, and duration of adhesion. The measurement of mechanical properties of a bioadhesive system is the most direct way to quantify the bioadhesive properties. The tensile, shear and peel stress are more commonly used to quantify the adhesive force of contact joints. In tensile and shear loading, the stress is distributed uniformly over the entire joint. However, in peel loading, the stress is limited to a very fine line at the edge of the joint (2).

Several in vitro techniques have been reported to determine the bioadhesion properties of bioadhesive oral dosage forms (3). The majority of these methods measure the tensile stress between the dosage form and the membranes or biological tissues (4-7).

However, the tensile stress provides only a partial reflection of mucoadhesion, since mucosa surface has some elements of a shear motion (5).

In light of the above reason, an alternative technique was developed in this study to quantify the bioadhesiveness of selected oral dosage forms by measuring both detachment force and frictional force required to separate two parallel surfaces (tablet and membrane).

Among various available bioadhesive polymers, sodium carboxymethylcellulose, polycarbophil and carbopol 974P are more commonly used in the oral bioadhesive dosage forms for both stronger bioadhesive power and lower toxicity reasons (8). In this study, the custom-designed apparatus was also utilized to classify tablets made with these three bioadhesive polymers in terms of detachment force, shear force as well as adhesion work.

EXPERIMENTAL

Preparation of the Bioadhesive Tablets

Tablets free of drug were prepared in duplicate manner by mixing microcrystalline cellulose (Avicel PH 101, FMC Co., Lot 14361) and sodium carboxymethylcellulose (NaCMC 7MF, Aqualon Co., Lot 67108), at four different proportions (12.5, 25, 50 and 75%) in a Turbular Mixer for 15 minutes, then compressing into tablets in a

Carver press. The final tablet has a weight of 500 mg and a hardness of 4.5 kg.

Three batches of tablets made with NaCMC (7HF, Aqualon Co., Lot 67798), Polycarbophil (Noveon AA1, BFGoodrich Co., Lot X055009) and Carbopol 974P (BFGoodrich Co., Lot M710029), respectively, were also prepared by mixing 32.4% bioadhesive polymer, 32.4 % HPMC (Methocel K15M Premium CR Grade, Dow Co., Lot MM89011881K), 17.6 % ethylcellulose (Ethocel Premium V-10, Dow Co., Lot 6161187) and 17.6% crosspovidone NF (polyplasdone XL, GAF Chem. Co., Lot S01029) for 20 minutes, 3% of magnesium stearate (Fisher Scientific Co., Lot 742748) was then added as a lubricant and mixed for additional of 2 minutes before compression. Tablets were compressed in a B-2 rotary press with a weight of 662 mg and a hardness of 6 Kg.

Biological Tissues

The biological tissue used was rabbit stomach mucosa. They were maintained in normal saline solution or used immediately after the sacrifice of the animals. The stomach mucosa samples were immersed in normal saline solution and kept in the refrigerator at 5 °C. These biological tissues were used in the comparison study of different types of bioadhesive polymer.

Measurement of Bioadhesiveness

Figure 1 shows the diagram of the custom-designed apparatus to be equipped with Instron Tensile Tester (Instron, model 1122). The system consists of a small polyacrylic cylinder fastened to the side

wall of a polyacrylic cubic vessel to hold the membrane by means of an O-ring. A rectangular aluminum piece with a hole in the middle was used as a support, to hold the tablet fixed over the surface of the membrane or biological tissues. The vessel was put on the lower plate of the Instron Tensile Tester, while the aluminum support was connected to the vertical rod and fixed to the upper clamp of the tensile tester.

In a typical sliding adhesion test, after placing the tablet in the hole of the aluminum piece, the membrane and tablet were brought together just to touch each other. The tablet and membrane surfaces were held parallel. The vessel was filled with constant volume of distilled water (1000 ml) at 22 C. After 30 minutes (pre-swelling time), the force was measured and recorded as a function of time until the tablet had crossed the membrane surface. Additionally, as can be seen from Figure 1, another polyacrylic cylinder is fixed to the bottom of the vessel to hold a membrane horizontally by means of an O-ring for the determination of direct detachment force.

In the detachment force measurement, the tablet was stuck on to rectangular aluminum support with a cyanoacrylate glue, the tablet support was fixed to the upper clamp of the tensile tester and lowered to maintain in a similar fashion that tablet and mucosa surfaces were rigorously parallel. The cubic vessel was filled with constant volume (1000ml) of pH 2 buffered solution at 22 C. After 30 minutes, the crosspiece was raised at constant speed (20 mm/min.) The detachment force was measured and recorded as a

function of displacement, up to the total separation of the tablet surface and tissue. The adhesion work was determined by calculating the area under the curve necessary for detachment.

RESULTS AND DISCUSSION

Figure 2 demonstrates a typical force versus time graph for one of the formulations studied. In general, the AB portion represents the early stage of the adhesion experiment, the force increased as a function of elongation. Point B represents the maximum adhesion force required to detach the tablet, the BC portion indicates the period where partial detachment of the bioadhesive tablet from the mucosa occurred with slight decrease of the contact area. The portion CD of the curve describes the major change of the contact area due to the separation of the two surfaces. D point indicates the tablet was totally detached from the mucosa surface.

Two parameters can be obtained from Figure 2 to analyze the adhesive characteristics of the tablets. The maximum adhesion force represented by point B, and the work of adhesion, determined by the area under the curve. Lejoyeux *et al.* (9) reported that this last parameter gives more interesting information concerning bioadhesion than the simple maximum detachment force. They also compared the adhesive capability of pure poly(acrylic acid) (PAA) tablets and pure hydroxypropylmethylcellulose (HPMC) tablets to bovine sublingual mucosa in liquid medium containing 100 g/l NaCl.

It showed there is no difference in detachment force measurement, however, in terms of adhesion work, PAA tablets were almost three time greater than HPMC tablets.

The maximum shear force and adhesion work values measured at two different days with NaCMC tablets were summarized in Table I. No significant differences were observed in these two measurements for both parameters indicating the good reproducibility of this adhesion assessment apparatus. Figure 3 shows a linear relationship which was obtained when adhesion forces were plotted against polymer content for NaCMC tablets. As shown in Figure 4, a linear correlation also exists between the adhesion force and adhesion work for NaCMC tablets. These results show good agreement with some previous findings observed by Ishida *et al.*(10). They indicated that within the range of 0 to 30 % PAA, there was a linear relationship between the adhesive properties of white or hydrophilic petrolatum ointment and PAA contents. Hassan *et al.*(11) also showed that N_b values (viscosity component due to bioadhesion) was proportional to the PAA concentration in the bioadhesive system. Leung and Robinson (12) observed that the tensile stress of the PAA-mucin interaction decreased as the percent composition of acrylic acid decreased. Ponchel *et al.* (13) also reported a direct correlation between the work of adhesion and the quantity of the bioadhesive polymer, PAA, in the tablets. Meanwhile, Park (14) showed that the mucoadhesive property of copolymers of acrylic and acrylamide increased sharply until the acrylic acid content reached 70 %.

It is well known that the bioadhesiveness of certain polymers is very much dependent upon their ability to take up water from the medium immersed in, and thus become sticky and adhesive. The designed instrument would definitely satisfy the wetting condition necessary for such evaluations. Table II shows the comparison of work (energy) measured in dry and wet conditions. As is evident from this Table, the works measured in dry condition are almost constant for all tablets made with various polymer contents, while in the wet condition the works which are a total of adhesion and friction are different and proportional to the polymer content.

Table III listed the bioadhesive characteristics of various tablets made with three different bioadhesive polymers. It indicates that tablets made with NaCMC possess the best bioadhesiveness among three different bioadhesive tablets in terms of detachment force, shear force and adhesion work. Tablets made with polycarbophil show similar detachment force and shear force but higher adhesion work when compared to tablets made with carbopol 974P.

CONCLUSIONS

The apparatus and technique designed for the determination of bioadhesion demonstrates good reproducibility, sensitivity and versatility (It can be tested either in dry or wet condition). The instrument enables one not only to determine both adhesional and frictional force but also to measure the adhesion work involved in

the whole separation process which is considered as an important indicator for bioadhesion power.

The results show good agreement with some previous findings that the relative adhesion of bioadhesive solid dosage form was proportional to the bioadhesive polymers concentration. Meanwhile, bioadhesive tablets made with three different polymers all show excellent bioadhesion to stomach mucosa when NaCMC tablets exhibited the best bioadhesiveness.

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TABLE I -- THE SHEAR FORCES AND ADHESION WORKS MEASURED AT TWO DIFFERENT DAYS WITH NaCMC TABLETS

% of NaCMC	<u>DAY 1</u>		<u>DAY 2</u>	
	Shear Force (Kg)	Work (Kg.mm)	Shear Force (Kg)	Work (Kg.mm)
12.5	0.181(0.012)	2.74(0.49)	0.183(0.012)	2.98(0.13)
25	0.255(0.008)	3.35(0.38)	0.250(0.036)	3.62(0.30)
50	0.555(0.057)	4.89(0.24)	0.593(0.037)	4.68(0.53)
75	0.828(0.070)	5.53(0.67)	0.806(0.050)	6.30(0.41)

TABLE II -- COMPARISON OF ADHESION WORK IN DRY AND WET CONDITIONS

% of NaCMC	Work in dry condition (Kg.mm)	Work in water-preswollen condition (Kg.mm)
12.5	1.81(0.52)*	2.74(0.49)
25	1.97(0.38)	3.35(0.38)
50	1.91(0.30)	4.89(0.24)
75	1.98(0.06)	5.53(0.67)

* Values in parenthesis are standard deviations from three measurement.

TABLE III --COMPARISON OF VARIOUS BIOADHESIVE TABLETS MADE WITH
DIFFERENT BIOADHESIVE POLYMERS

	NaCMC 7HF	Carbopol 974P	Noveon-AA1
Detachment Force(N)	1.23 (0.07)*	0.83 (0.06)	0.98 (0.05)
Work(mJ)	0.74 (0.14)	0.31 (0.12)	0.45 (0.14)
Shear Force (N)	1.37 (0.05)	0.34 (0.04)	0.39 (0.05)
Work(mJ)	11.04 (0.23)	3.92 (0.16)	5.33 (0.25)

* Values in parenthesis are standard deviations from three measurements.

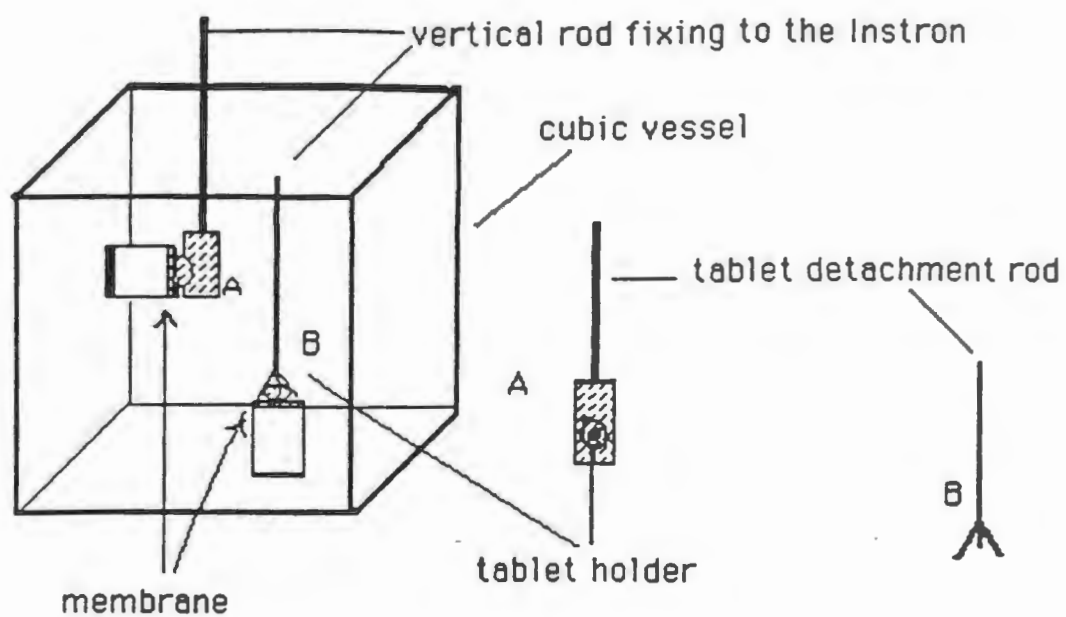


Figure 1. Apparatus for determination of bioadhesiveness of tablets; (A), Sliding Method, (B), Direct Detachment.

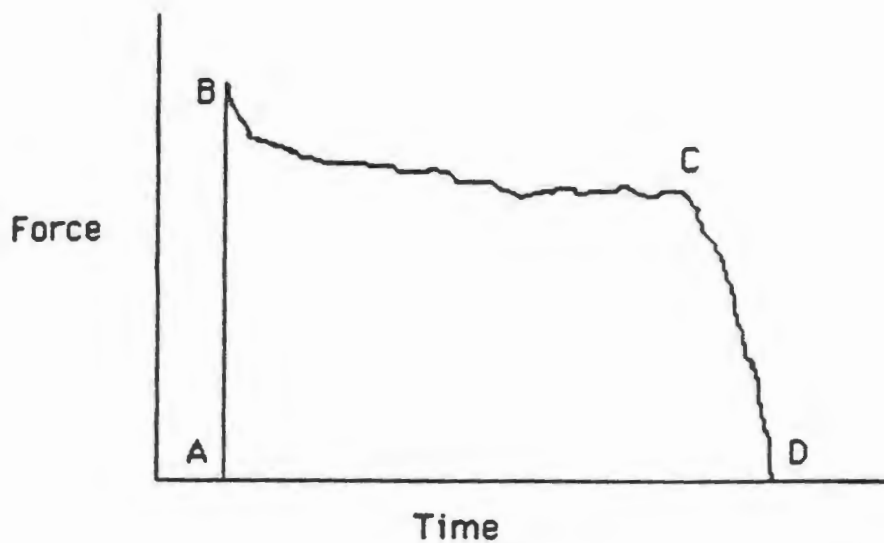


Figure 2. A typical plot of variation of force necessary for sliding a NaCMC tablet over the surface of a membrane as a function of time.

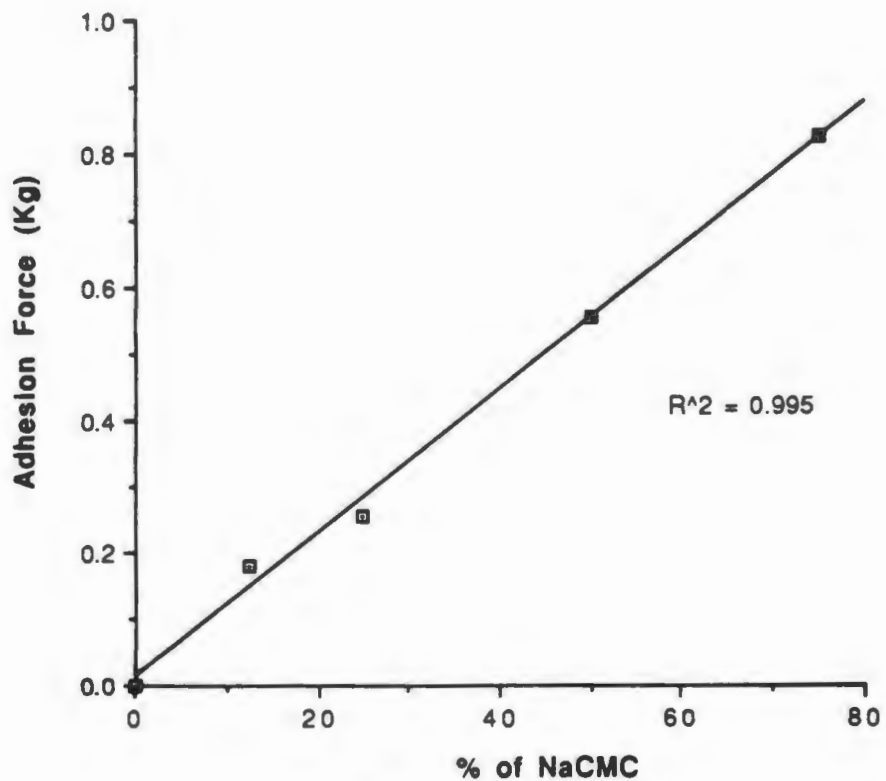


Figure 3 -The adhesion force required for separating NaCMC tablets and membrane as a function of NaCMC concentration (after 30 minutes pre-swollen in water)

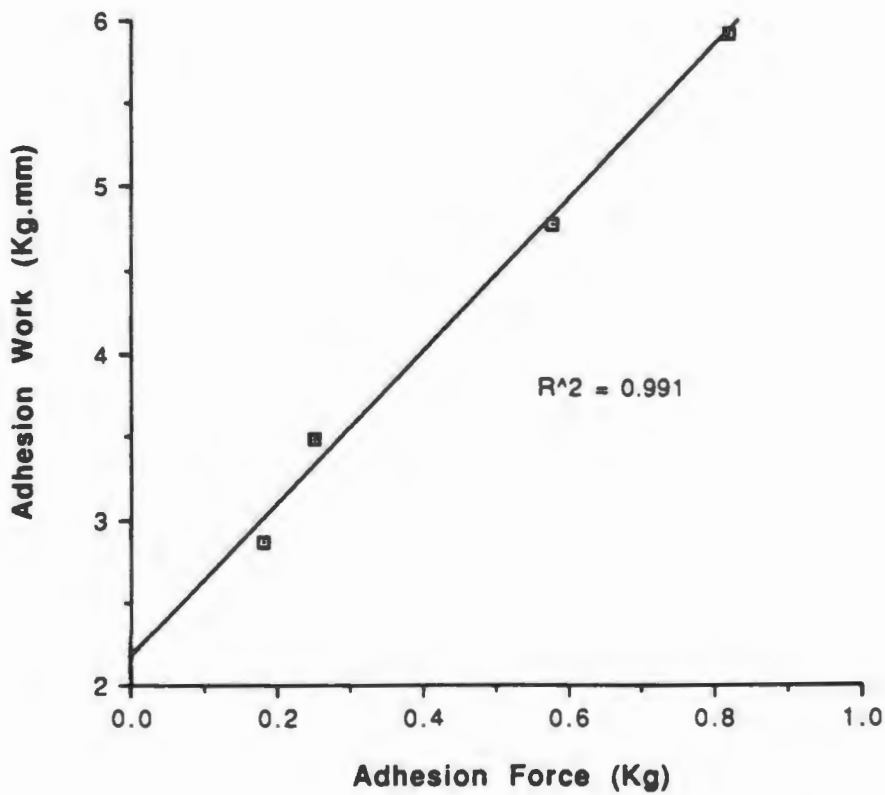


Figure 4 - The linear correlation between the adhesion force and adhesion work

SECTION III

APPENDIX A
General and Analytical Data

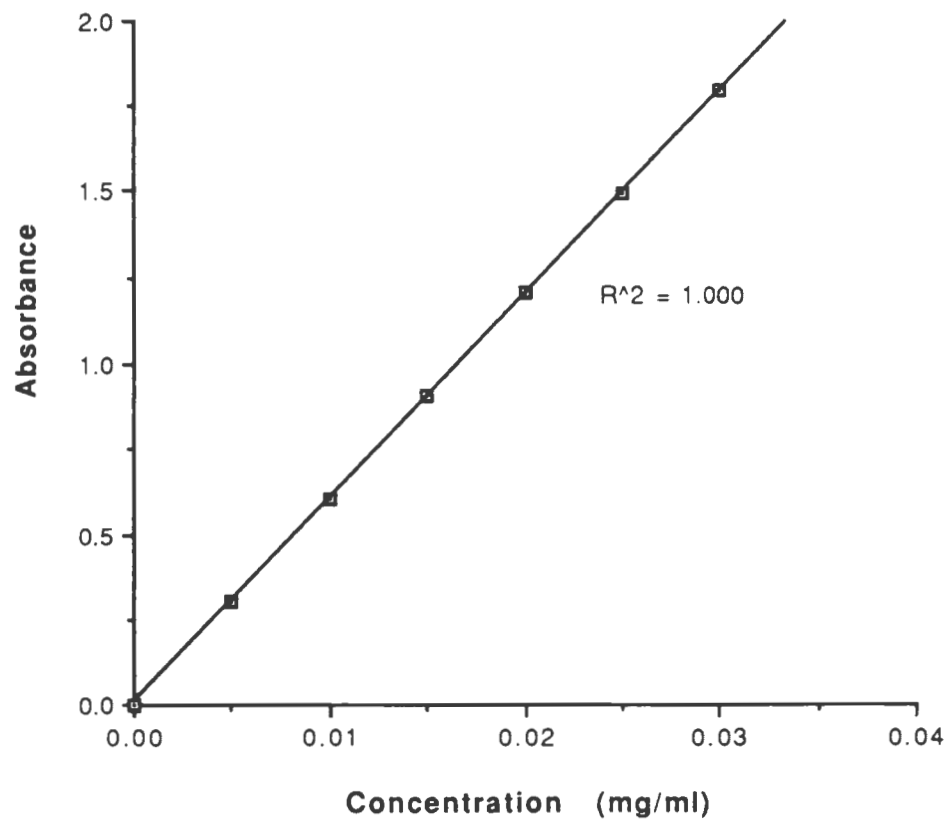


Figure 1 - Acetaminophen UV Calibration Curve

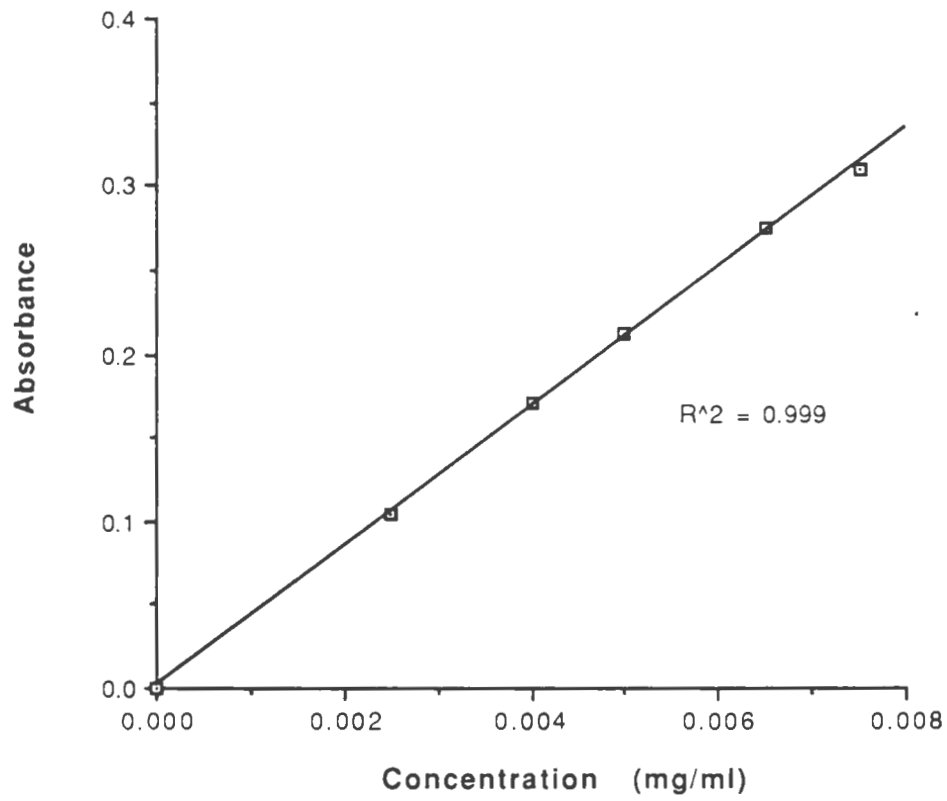


Figure 2 - Phenylpropanolamine HCl UV Calibration Curve

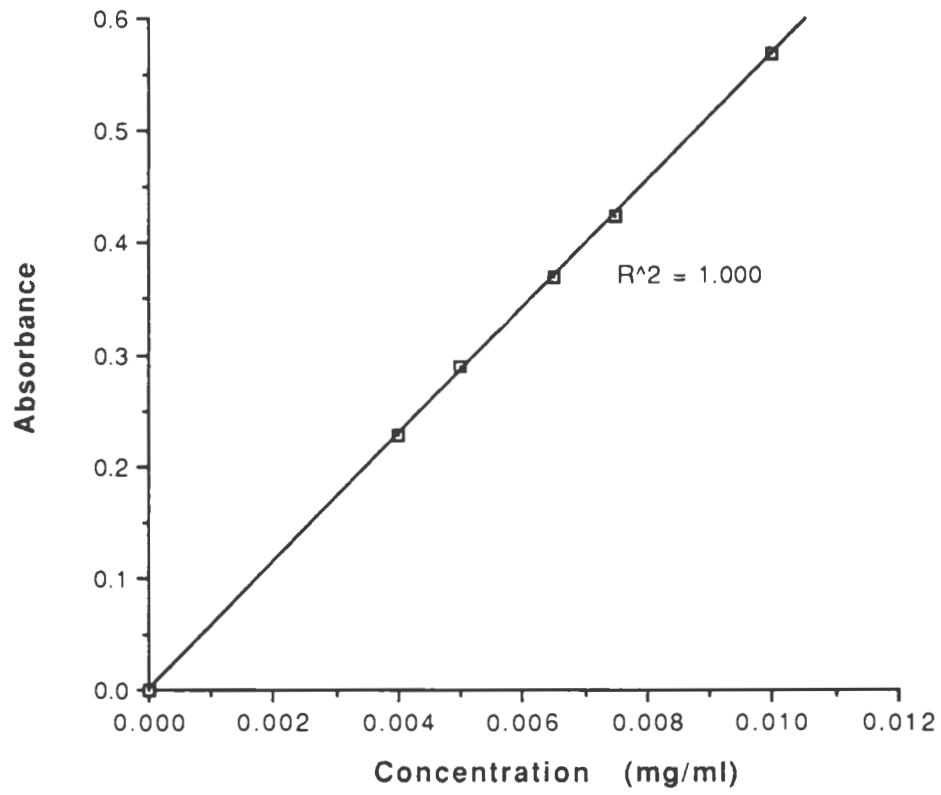


Figure 3 - Theophylline UV Calibration Curve

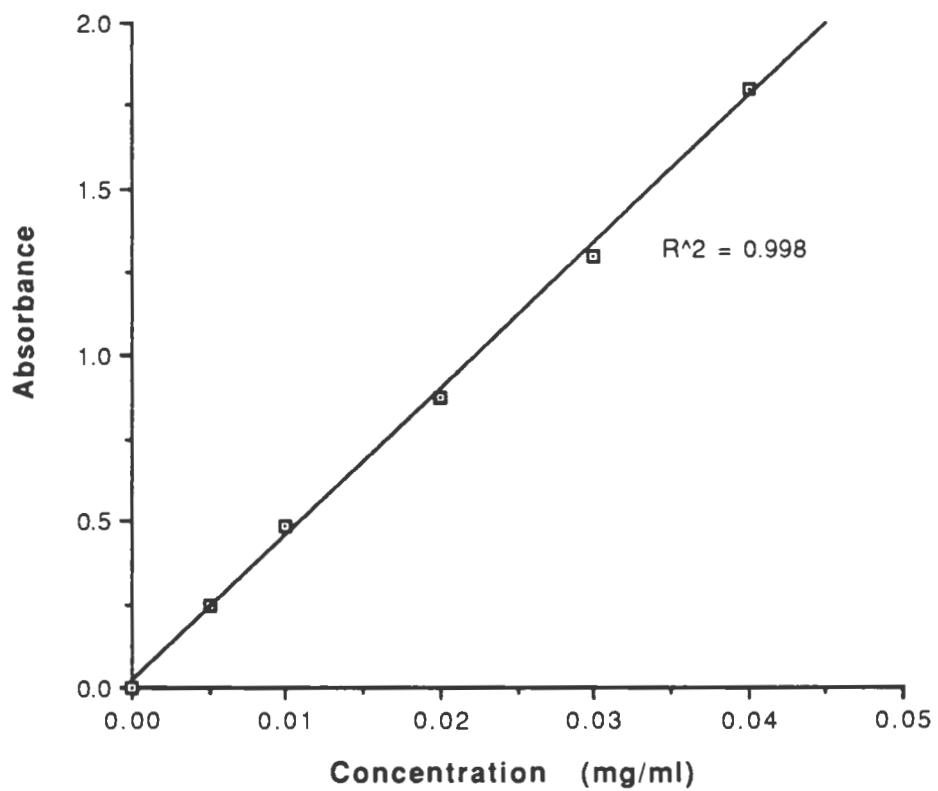


Figure 4 - Sotalol UV Calibration Curve

APPENDIX B

Experimental Complement of Manuscript IV

Table I -- Direct Compression Sotalol HCl Tablet Formulation for Determining The Reproducibility

(Three batches of sotalol tablets were manufactured at three different days with the same formulation)

	Each Tablet (mg)	Percentage
Sotalol HCl	240	34.18
Na CMC 7HF	120	17.09
HPMC K15M CR	120	17.09
Ethylcellulose V-10	120	17.09
Polypladone XL	20	2.85
Ca. Carbonate	80	11.40
Mg. stearate	2.1	0.30
Total Weight: 702.1 mg		

Table II -- Properties of Three Batches of Sotalol Tablets

	<u>Batches#</u>		
	1	2	3
Weight, <u>mg</u>	701.11(1.59)	701.61(1.55)	701.70(1.27)
Powder Flow Rate, <u>g/sec.</u>	16.7(1.2)	15.6(2.1)	16.1(1.7)
Friability, <u>%</u>	0.26	0.29	0.30
Thickness, <u>Inch</u>	0.2385	0.2385	0.2385
Hardness, <u>Kg</u>	6.53(0.14)	6.65(0.22)	6.58(0.24)
Compression Force, <u>KN</u>	15.40(0.33)	16.16(0.44)	15.84(0.23)
Lag Time to Float, <u>Minutes</u>	16.3(1.9)	16.0(1.1)	15.8(1.5)
Content Uniformity, <u>mg</u>	235.8(3.2)	237.4(2.6)	236.6(2.7)

Values in parenthesis are standard deviations.

Table III -- Dissolution Results of Three Batches Tablets

Time (hours)	<u>Percentage of Drug Release</u>		
	Bat.#1	Bat.#2	Bat.#3
0.5	15.94(1.57)	15.63(1.92)	15.16(2.31)
1	21.22(2.69)	23.17(2.50)	21.30(2.63)
2	32.06(2.52)	32.41(2.42)	31.25(2.69)
4	47.98(1.97)	45.98(2.14)	45.07(3.33)
6	59.94(1.55)	57.31(2.22)	55.76(4.04)
8	69.25(3.18)	66.69(2.23)	64.82(3.39)
12	82.24(3.02)	79.42(2.57)	77.37(3.69)
20	93.52(2.60)	94.39(2.39)	91.83(3.47)
24	96.30(1.77)	98.20(2.66)	94.90(2.64)

Values in parenthesis are standard deviations.

Table IV - Sotalol HCl Tablet Formulation for Determining The Effect of Different Grades of NaCMC on The Dissolution

Ingredient	(mg)
Sotalol HCl	240
NaCMC (7MF or 7HF)	120
HPMC K15M	120
EC V10	120
Polyplasdone XL	20
Calcium carbonate	80
Mg. stearate	2.1

Total Weight: 702.1 mg

Table V - Sotalol HCl Tablet Formulation for Determining The Effect of Different Grades of HPMC on The Dissolution

Ingredient	(mg)
Sotalol HCl	240
NaCMC 7HF	120
HPMC (K15M or K15M CR or K100M CR)	120
EC V10	120
Polyplasdone XL	20
Calcium Carbonate	80
Mg. stearate	2.1

Total Weight: 702.1 mg

Table VI - Sotalol HCl Tablet Formulaiton for Physical Stability Test
(Tablets were stored at 40 C, 50 % relative humidity
condition for one, two and three months)

Ingredient	(mg)
Sotalol HCl	240
NaCMC 7HF	120
HPMC K100M CR	120
EC V10	120
Polyplasdone XL	20
Calcium carbonate	80
Mg. stearate	2.1

Total Weight: 702.1 mg

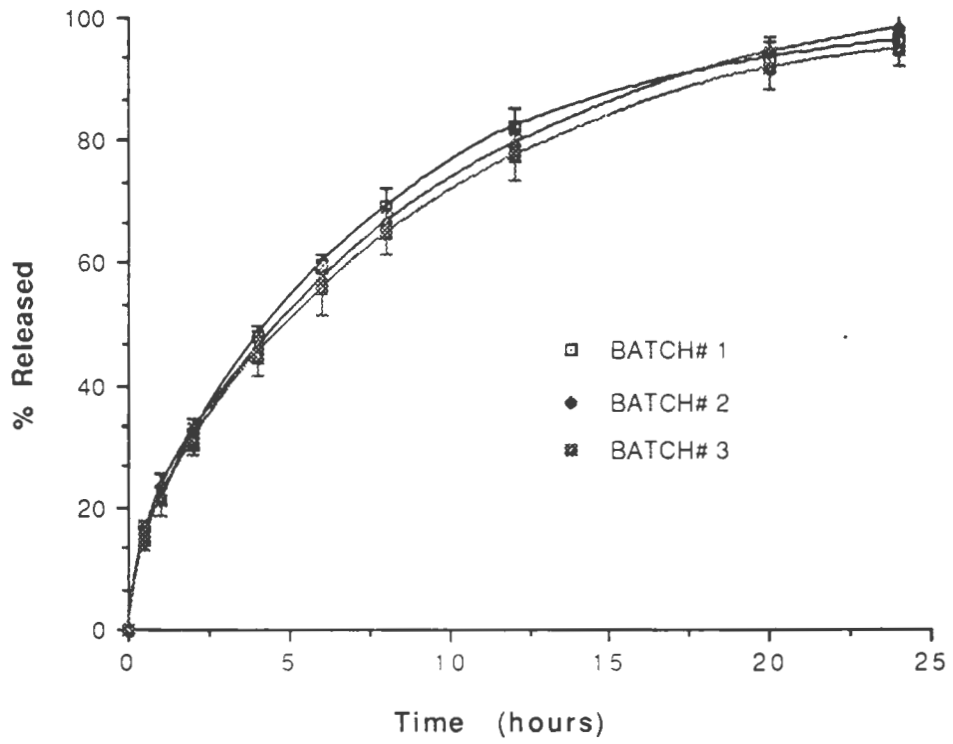


Figure 1 - Dissolution Profiles of Sotalol Tablets (Triplicates of same formulation)

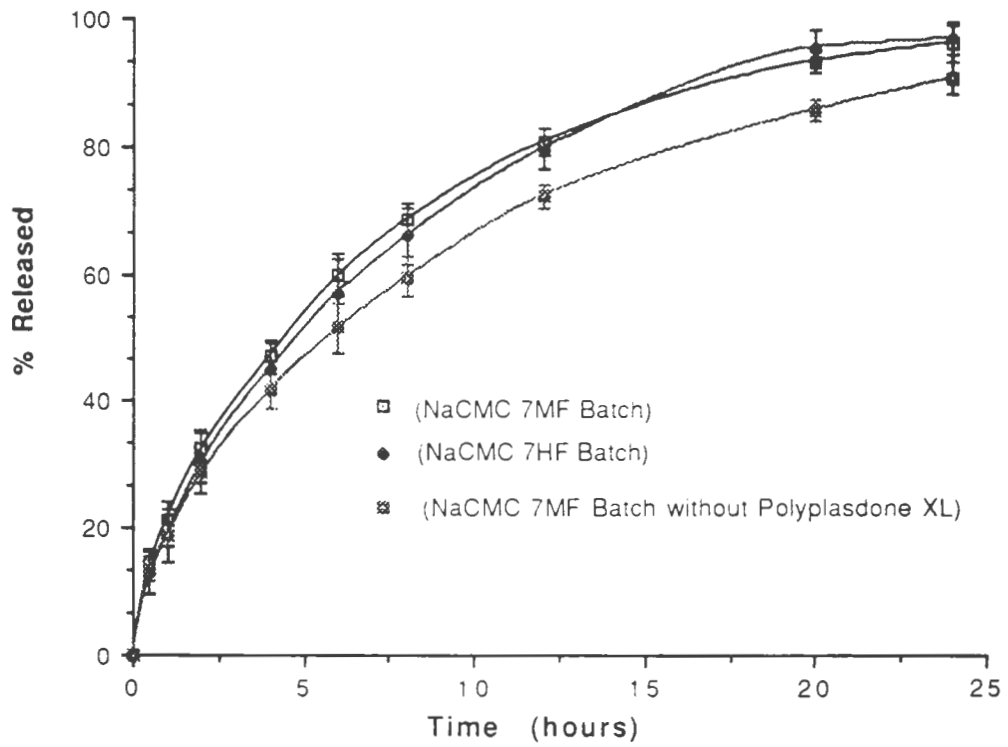


Figure 2 - Dissolution of Sotalol Tablets (The effect of different grades of NaCMC and the effect of Polyplasdone XL on the dissolution)

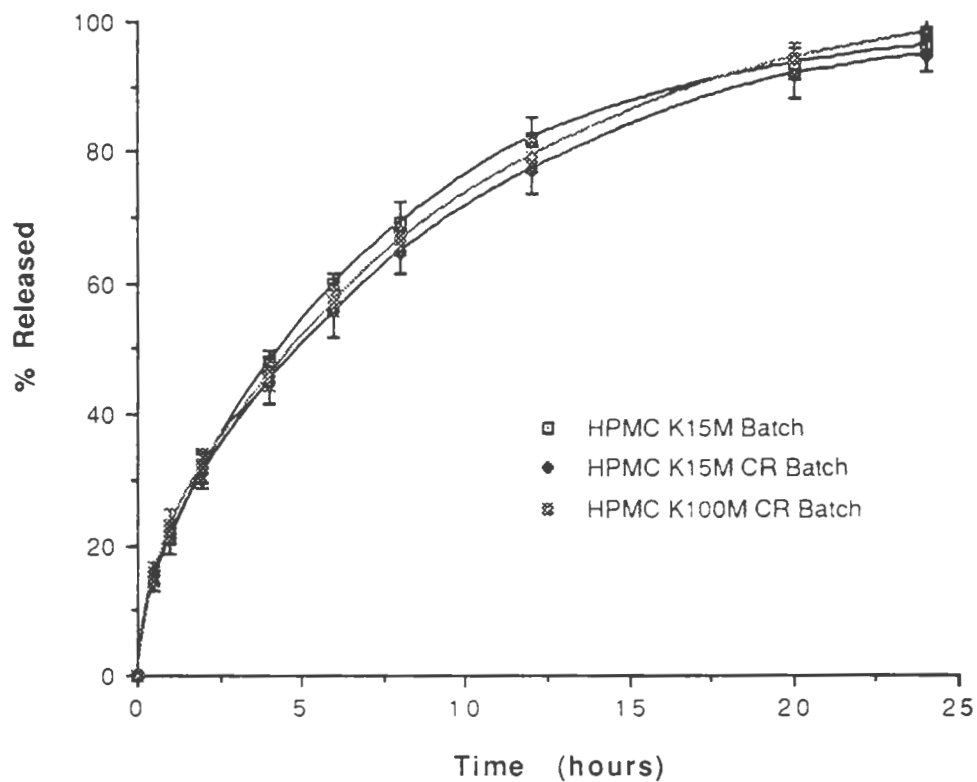


Figure 3 - Dissolution of Sotalol Tablets (The effect of different grades of HPMC on the dissolution)

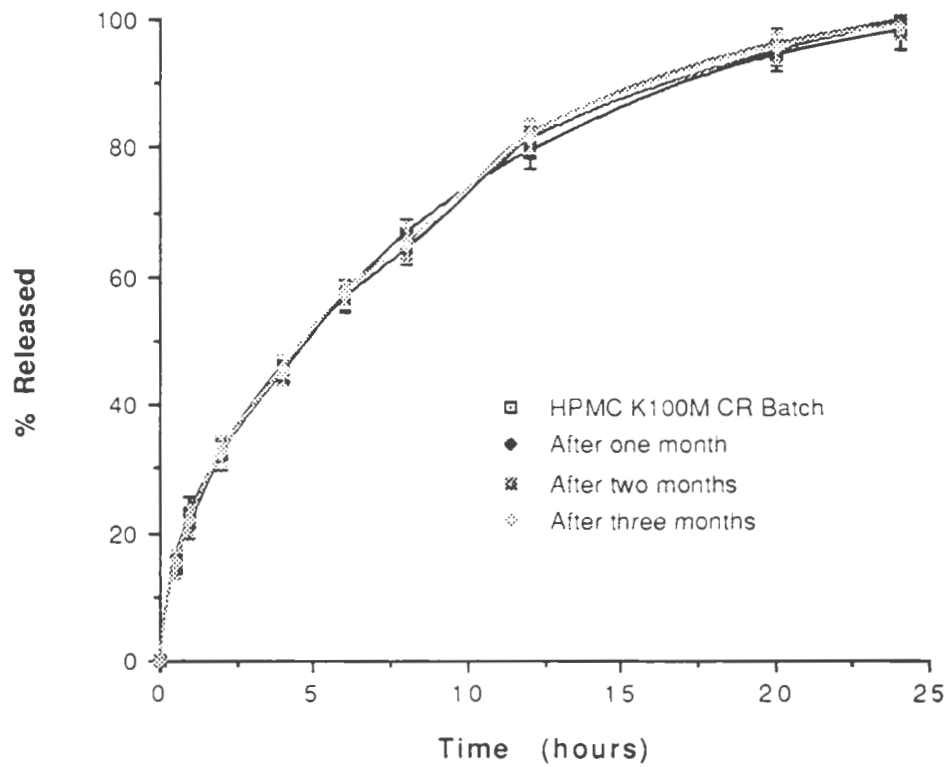


Figure 4 - Dissolution of totalol tablets in stability test (Tablets were stored at 40 C, 50 % R.H. condition for one, two and three months)

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