1988

FORMULATION OF AN ORAL CONTROLLED RELEASE DOSAGE FORM FOR NIFEDIPINE

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BY

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

1988

MASTER OF SCIENCE THESIS

OF

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APPROVED:

THESIS COMMITTEE

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UNIVERSITY OF RHODE ISLAND

1988

ABSTRACT

Nifedipine has been shown to be an effective and a well tolerated medication for the treatment of several cardiovascular diseases. Its low water solubility, however, leads to poor drug absorption from oral dosage forms while commercially available soft capsules lead to a short half - life.

In this study a method was developed to prepare controlled release nifedipine tablets which would release the drug quickly and sustain the release for a longer period of time. Solid dispersions of nifedipine with polyvinylpyrrolidone (40T) and polyethylene glycol 8000 were prepared to enhance dissolution and microporous polypropylene containing 75% void space was used to control the release to a desired level.

Various ratios of the two polymers were used. The results indicate that the solid dispersion technique is a good approach to enhance the dissolution of nifedipine. However the polypropylene polymer used as a homogeneously dispersed matrix does not provide a zero - order release rate in low concentrations.

A preliminary study was also carried out to measure the rate of photodegradation of nifedipine solution in a normally lighted lab devoid of sunlight. The results obtained show that the photodegradation of nifedipine follows first order kinetics with a t_{90} of 19 minutes. The pH of the solution in the range of 4.2 - 7.4 did not alter this rate.

The solubility of nifedipine in water was found to be about 5 mg/L at 25 degrees Celcius. There was no significant difference between the water solubility and the solubility in phosphate buffer (pH 7.4) or the solubility in 0.1 N HCl.

"For the things we
have to learn before
we can do them, we
learn by doing them"
- Aristotle

ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to my advisor, Dr. Joan M. Lausier for her interest, support and guidance throughout this project.

I would also like to thank the members of my committee, Dr. Stanley Barnett, Dr. Anthony Paruta, Dr. Christopher Rhodes, and Dr. Chen for their time and effort in evaluating this thesis.

The suggestions and assistance I have received from the faculty members, graduate students and post doctoral fellows of the college of pharmacy is greatly appreciated. In particular I am indebted to Dr. H. Zia and to Dr. Ramesh (Medicinal Chemistry) for their constructive criticism and assistance during several stages of this project.

Finally I would like to extend my thanks to Dr. Mahendra Dedhiya and Miles Pharmaceuticals, Conn., for providing generous samples of nifedipine and to Enka Indusrial Products Inc., Illinois., for providing samples of Accurel.

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I. INTRODUCTION

1. NIFEDIPINE

Nifedipine, a dihydropyridine derivative is one of a group of compounds thought to act by blocking the transmembrane inward movement of calcium. It has been shown to be an effective and relatively well tolerated treatment for stable, variant and unstable angina, mild to severe hypertension, and Raynaud's phenomenon (93).

Clinical trials support the view that nifedipine can be considered a first line choice in all grades of angina, especially when coronary vasospasm is the underlying cause or when hypertension and / or congestive heart failure are added complications. Nifedipine also appears to be particularly useful in clinical situations when a rapid lowering of elevated blood pressure is needed, and there is growing evidence that it is an effective and safe choice for the long term management of patients with mild to moderate hypertension (93).

However, the majority of data have been from medium term studies, and confirmation of its long term usefulness in well designed trials is still required. Additionally, it has convincingly been shown to be a useful adjunct to controlling blood pressure in patients refractory to conventional treatment with beta blockers, diuretics and various vasodilators (12,32). Nifedipine reduces the number, duration and severity of vasospastic attacks in more than 60% of

patients with Raynaud's phenomenon of varying etiology, and in individual cases it apparently facilitates the healing of digital ulcers.

Thus nifedipine is a worthwhile alternative to other drugs available for the treatment of the various forms of angina, acute episodes of hypertension, mild to severe hypertension (18,23,24,35,50,63,67,84,103) and Raynaud's phenomenon (22).

PHARMACOKINETICS :

Few well designed studies have been performed that adequately describes pharmacokinetic properties of nifedipine. The paucity of information detailing the kinetic aspects of nifedipine is due primarily to two factors (93).

Firstly, until recently no parenteral dosage form was commercially available, and laboratory preparation of a solution for intravenous pharmacokinetic studies was difficult due to the photosensitive nature of such solutions. Nifedipine is very light sensitive and breaks down rapidly on exposure to daylight, tungsten bulb light, standard fluorescent light or ultraviolet irradiation to its more stable nitroso or nitropyridine (see fig.1) derivatives (6,21,37,52). Nifedipine is stable, however, when "gold" fluorescent light is used (37).

Secondly, there have been problems in developing a sufficiently sensitive and specific method for analysis of nifedipine plasma concentrations after therapeutic doses. Although the concentrations of nifedipine in body fluids has

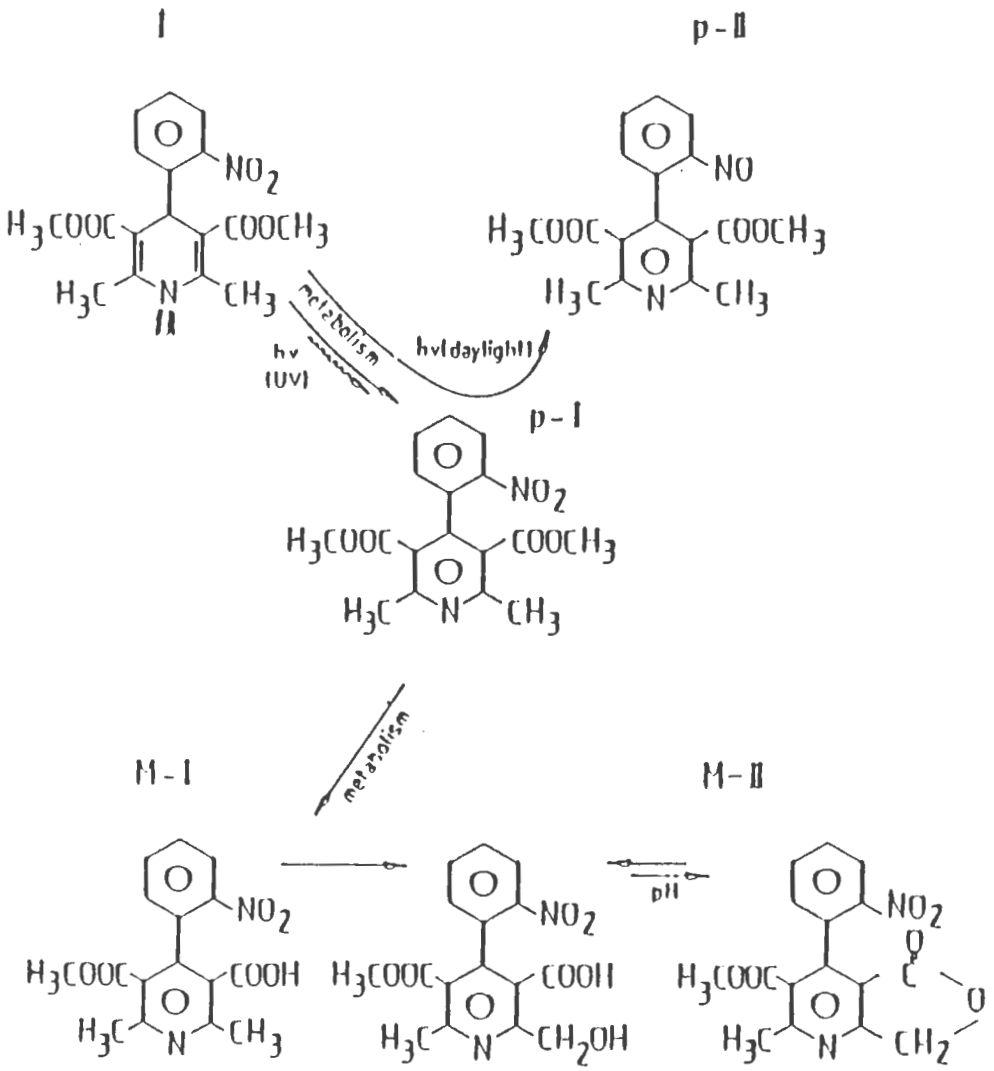


Fig. 1. Photodecomposition and biotransformation scheme. I is nifedipine; p-I and p-II are photodegradation products and M-I and M-II are metabolites (from ref. 52).

been determined by radioisotope (93), high performance liquid chromatograghy (51,52, 64,74), gas chromatography (21,48), fluorimetry (55) and mass spectrometry (40), the various discrepancies reported for nifedipine pharmacokinetic parameters may originate in part from the inefficiency of some of these assay techniques in distinguishing parent from its inactive metabolites and photodegradation products (93).

Clinical studies have shown that the hypotensive effect of nifedipine could be correlated with the plasma drug concenration (4,7,55). The absorption of nifedipine, however, is poor when administered orally in a solid dosage form (96) because of its poor water solubility. Several studies reported that the nifedipine plasma levels increased rapidly after oral administration of commercially available (soft capsule) water soluble formulations (29,78) with peak plasma concentrations occuring after about 30 minutes of administration. With sublingual administration the peak occured after 1 hour (78). The half - life of elimination from the commercial capsule was only about 3.5 hours (29). Consequently, the antihypertensive effects of nifedipine lasts only for a few hours which restricts its use in treating chronic hypertension (101). On the other hand Taburet et al (100) administered a tablet formulation with crystalline form of nifedipine to hypertensive men and found that the resulting t_{max} from the tablets was about 2 hours with an elimination half life of about 10 hours. These values did not differ

between doses of 20, 40, and 60 milligrams.

From these studies it is clear that in order to optimize the delivery of nifedipine a dosage form must be developed which releases the drug quickly (i.e. has a high dissolution rate) while maintaining a longer elimination half life.

2. ENHANCEMENT OF DISSOLUTION RATE

The following section describes briefly the various methods used for enhancing the dissolution rate of drugs in solid dosage forms. The basis of these methods is the Noyes - Whitney equation modified by Underwood and Cadwallader (105):

$$dW/dt = KS(C_{sat} - C_{sol}) \quad (1)$$

where dW/dt is the dissolution rate, K is a dissolution constant, S is the surface area of the solid, C_{sat} is the concentration of the saturated solution and C_{sol} the concentration at any given time.

2.1. USE OF SURFACTANTS

Surfactant adsorption onto hydrophobic drug particles below the critical micelle concentration can aid in wetting of the particles and consequently increase the rate of solution of particulate agglomerates (31,60,79,89). Surfactants may be incorporated into solid dosage forms (26) so that their solubilization action comes into play as disintegration process starts and water penetrates to form a concentrated surfactant solution around the drug particles or

granules. Both facilitation of wetting through lowering of surface tension and solubility increase will aid in dissolution of the drug. Other techniques of incorporating surface - active agents have been reported. Chiou et al (13) have discussed the enhancement of dissoltion of poorly water soluble drugs by crystallization in aqueous surfactant solutions. Ford and Rubinstein (28) have discussed the dissolution characteristics of a glutethimide - nonionic surfactant melt system.

Surfactants cannot be considered to be "inert" pharmaceutical adjuvants which can be used indiscriminately in formulations. Even nonionic surfactants which are generally more acceptable than ionic surfactants because of their lower toxicity are not without intrinsic biological activity of their own (27) which can be ascribed to their affinity for and action on biological membranes.

Apart from their own biological or toxicological effects nonionic surfactants can sometimes act synergistically with a drug substance to promote its absorption or activity, or may decrease activity by entrapping the drug in micelles which diffuse slowly and which cannot cross cell membranes intact.

In any dosage form in which dissoution is the rate limiting step prior to drug absorption, surfactants can, by increasing the dissolution rate, increase the bioavaialability without any effects on the barrier properties of the boundary membranes. However, if the surfactant does modify

the permeabilty of the membranes, then any observed effect on bioavailability is likely to be the result of both a physical and a biological effect. Above the critical micelle concentration, there is the added complication of partitioning of lipophilic drugs into micelles. The measured effect of solubilzer will then be the result of these processes:

(1) increase in wetting and dissolution rate,

(2) increased permeability of biological membranes, and

(3) solubilization.

The efffect of the first two is to inrease and the last to decrease absorption, although at very high solubilizer concentrations solubilization occurs of those components such as cholesterol and protein, essential for the integrety of the membrane, causing a marked increase in drug absorption (26).

2.2. SOLID STATE MANIPULATION

Many compounds exist or are capable of being manipulated to exist in more than one form as solids. Some of these forms are crystalline phases while others are metastable states where the compound is a noncrystalline or molecularly dispersed form. Pharmaceutical scientists have been making use of the differences in the physical chemical properties that exist between these solid states to optimize drug delivery. Some of the ways in which the solubility characteristics are modified by the solid state modification are discussed.

2.2.1. POLYMORPHISM

The ability of many compounds to crystallize in more than one crystal form is known as polymorphism and has been rewiewed by Haleblian (36). The solubility of each form depends on the ability of the molecules to escape from the crystal of the solvent. The stable form possesses the lower free energy at a particular temperature and pressure and therefore has the lower solubility or escaping tendency.

When a metastable form is placed in contact with solvents, it can rapidly undergo reversion to the more stable crystal form. The transformation process in such an environment will depend to a great measure on the degree of supersaturation achieved by the metastable material. There are also instances in which adsorbed water on the surface of the solid will catalyse the transformation process (87).

Using polymorphic modifications a 50 - 100 % increase in dissolution rate can be realistically achieved (16,44,87). However for some drugs a four fold increase has been achieved (1,58). The amporphous form of novobiocin (69) and sulfa drugs (66,92) have been isolated and found to be much more soluble than the respective crystalline form. In case of novobiocin the amporphous form was 10 - fold more soluble than the crystalline drug (69).

2.2.2. SOLVATES

Many drug compounds upon recrystallization retain a stoichiometric amount of the solvent. These crystalline materials, referred to as solvates or pseudomorphs, may be

looked upon as molecular complexes. An important class of solvates are the hydrates which contain water. In an aqueous environment these compounds are the most stable forms and therefore have lower solubilities in aqueous solvents than the anhydrous (crystalline or noncrystalline) forms. When the solvent is not water, the solvent may dissociate in aqueous environment, and, depending upon the solubility product for the solvate in the media, the concentration of the drug in the solution may well reach a level much greater than that attainable from a nonsolvated form of the drug.

Shefter and Higuchi (88) studied the dissolution of the pentanol solvate of succinyl sulfathiazole and found an eightfold increase in solubility over the hydrate. However the nature of the bound solvent in the crystal and the ability of the dissolution media to dissociate the solvent dictates the extent to which there will be a favorable effect.

2.2.3. RACEMATES AND ENANTIOMERS

The racemates and enantiomeric forms of a compound may differ substantially in their solubilities (59,81). If, in addition to possessing higher solubility (and hence dissolution rate), an enantiomer is more active biologically than the racemate then attempts should be made to isolate the enantiomer and this should be used in the formulation.

2.2.4. REDUCTION OF PARTICLE SIZE

The effect of particle size reduction of drugs on their

dissolution rates and biological availability was reviewed comprehensivly by Fincher (25). A reduction in particle size of drugs leads to an increase in the total surface area (S) and the Noyes - Whitney equation predicts that this will result in an increase in dissolution rate. For drugs with poor water solubility a reduction in particle size generally increases the rate of absorption and /or total bioavailability. For example, the therapeutic dose of griseofulvin was reduced to 50% by micronization (5) and a more constant and reliable blood level was produced. The commercial dose of spironolactone was also decreased to a fourth by just a slight reduction of particle size (56). Such enhancement of drug absorption could further be increased several folds if a micronized product was used (8,56).

Partical size reduction is usually achieved by one of the following methods (4) : (a) conventional trituration and grinding; (b) ball milling; (c) fluid energy micronization (d) controlled precipitation by change of solvent or temperature, application of ultrasound waves, and spray drying; (e) administration of liquid solutions from which, upon dilution with gastric fluids, the dissolved drug may precipitate out in very fine particles; and (f) administration of water soluble salts of poorly soluble compounds from which the parent, neutral forms may precipitate in ultrafine form in the GI tract.

Although the reduction of particle size can be easily accomplished by the first four (a-d), the resultant fine

particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent shorter van der Waal's attraction between nonpolar molecules. Another inherent disadvantage of these pure fine powders of poorly soluble drugs is their poor wettability. For these reasons the methods mentioned above are seldom used for dissolution rate enhancement.

2.2.5. SOLID DISPERSIONS

The term "Solid Dispersions" was defined by Chiou and Riegelman (14) and refers to "the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by the melting, solvent or melting - solvent method." Not included in this category are the dispersions of drugs in solid diluents by the traditional mechanical mixing (9).

The selection of the matrix has an ultimate influence on the dissolution characteristics of the dispersed drug. A poorly water soluble drug combined with a water soluble carrier results in a fast release of the drug. On the other hand the release of a water soluble drug can be retarded by the use of a water - insoluble matrix.

Two basic procedures are used to prepare solid dispersions: fusion and cosolvent techniques. Modification of these methods and combinations of them have also been used for the preparation of dispersed systems (14).

The fusion technique involves the heating the components which make up the dispersion (drug plus carrier) to a temperature at which melting occurs and a solution forms. The melted mixture is usually cooled rapidly to entrap the drug particles in the matrix in a very fine state. The cooling rate of the mixture can influence the physical state of the solid obtained and the particle size of the crystals formed (87). The principal disadvantage of this procedure is the possibility of decomposition and / or evaporation of a component at the elevated temperatures required. Low melting polyethylene glycols are used commonly as carriers (9).

The cosolvent approach involves dissolving the ingredients comprising the dispersion in a common solvent. The solvent is then evaporated off with the aid of a vacuum pump. Sometimes heat is used to assist in the evaporation of the solvent. Materials prepared by this procedure are sometimes known as coprecipitates (14). The ingredients of the dispersion should be very soluble in the solvent, or crystallization of one may take place before the other and a uniform dispersion will be derived.

In many instances it is difficult to completely remove the solvent from the dispersion. This in turn may have an effect on the stability of the dispersion, both chemical and physical.

Solid dispersions are generally of the following four types: eutectics, polymeric systems, glass dispersions, and solid surface dispersions.

(a) Eutectics: Eutectics are prepared by rapid solidification of two melted components which show complete miscibility in the liquid state. A number of systems exhibiting eutectic behaviour have been examined. Urea and succinic acid have been found to form simple eutectics with a wide variety of drugs. This approach was first demonstrated by Sekiguchi and Obi (85) in 1961 for formation of a eutectic mixture of sulfathiazole with urea to increase dissolution rate and absorption.

The increase in dissolution rate observed for eutectic mixtures can result from a number of factors. The main causes postulated (87) for the observed dissolution of of these systems are as follows:

(i) The particle size of the drug in the eutectics formed by rapid solidification will be small. This can result in an enhanced dissolution rate as a result of both surface area increase and solubilization.

(ii) The carrier material as it dissolves may have a solubilizing effect on the drug.

(iii) In a eutectic where each crystallite of drug is surrounded by a water soluble crystal, there will be good wettability and dispersibility of the drug in the dissolution media. The enhanced wettability of the drug should retard any agglomeration and aggregation of the particles which can slow the dissolution process.

(iv) The process of eutectic formation may cause the drug to crystallize in a metastable state. As indicated earlier,

these phases in themselves would have a greater solubility and therefore result in faster dissolution rates.

(b) Polymeric Systems: Water soluble polymers have been extensively used to form solid dispersions. Most of the reported investigations have focussed on dispersions made with polyethylene glycols or PVP. Studies with these polymeric substances (14) indicate that the ratio of drug to polymer should be low to maximize the increase in dissolution of the drug. PVP is a noncrystalline polymer able in many instances to disperse a significant amount of a drug in a "high energy form" (61,83,91,95). The amount of drug which can be loaded into PVP as a high energy noncrystalline form is a function of the structure of the drug and the cosolvent used to prepare the coprecipitate (87). In some instances, the drug could be loaded into the polymer such that it would exist almost exclusively in the higher energy state as long as the ratio of drug to PVP was less than one (87).

Inhibition of the growth of the drug crystal structure by PVP in solid dispersions (20) has been linked to improved dissolution behaviour (19,90,92) and the formation of highly supersaturated drug solutions (19,62). The implication is that PVP prevents drug crystallization during preparation by a drug polymer interaction, possibly involving hydrogen bonding, in the liquid state (86,91). Once the solvent is removed, the interaction helps stabilize the amorphous high energy state (47).

The degree of solubilization observed for these systems

is usually high. Reports of 6 to 10 fold increases in solubility is not uncommon. An interesting facet of these dispersions is that the high solubility achieved is maintained in solution for long periods of time (83,90,95).

High molecular weight PEG's which are highly crystalline in nature, are believed to be capable of entrapping low molecular weight compounds in their interstitial spaces (14). When PEG dispersions are prepared with their drug fractions greater than their "solid solubility", ultrafine suspensions of the drug are produced. Although these dispersions exhibit much faster dissolution rates than the pure drug, they are relatively slower dissolving than those dispersions containing the drug in its molecularly dispersed form.

(c) Glass Dispersions: A number of water soluble compounds are known to form glasses when their melts are rapidly solidified. Among these are citric acid and a host of sugars. The glassy or vitreous state is characterized by transparency and brittleness below the glass forming temperature. On heating, it softens progressively and continuously without a sharp melting point. This is primarily due to the fact that the chemical bonds in the glass differ considerably in length and, therefore, in strength and that there is no one temperature at which all the bonds become loosened simultaneously (14). The lower density of glasses resulting from molecular framework in the glasses could provide the environment for the dispersal of drug molecules. Such dis-

persions would be expected to rapidly dissolve in aqueous media. Drugs dispersed in glass matrices of dextrose, galactose, and sucrose have been reported to exhibit very rapid dissolution rates (2). Examples of glass solutions are primidone - citric acid (97), griseofulvin - citric acid and phenobarbital - citric acid (9).

(d) Solid Surface Dispersions: The dissolution characteristics of drugs can be altered by dispersing it on the surface of certain materials. Deposition of the drug by solvents on solid supports and by grinding it with certain materials has produced dramatic results.

Monkhouse and Lach (65) used water - insoluble adsorbents, such as fumed silicon dioxide and silicic acid, as supports for the solvent deposition of a number of drugs. The support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contained the drug in a "molecularly micronized" state on the surface of the carrier.

Yamamoto et al (106) observed that when griseofulvin was ground with microcrystalline cellulose in a vibrational ball mill its dissolution rate and bioavailability were substantially enhanced. The grinding procedure was shown to result in a total loss of griseofulvin crystallinity. Other drugs which have been dispersed similarly on microcrystalline cellulose are aspirin, salicylic acid, chloramphenicol palmitate, diazepam, mefenamic acid and sulfisomezole (70).

Another approach for dispersing drug on solid surfaces

is the roll - mixing method of Nozawa et al (72,73). This method was shown to enhance the dissolution rate of phenytoin (72) and nifedipine (73).

2.3. COMPLEX FORMATION

The alteration of apparent solubility which can be achieved through complexation may be utilized to decrease or to increase solubility. The usefulness of the solid complex obtained will be dependent upon its apparent solubility relative to that of the inherent solubility of the substrate. For instance, Higuchi and Pitman (43) have suggested the use of a relatively insoluble caffeine - gentisic acid complex for reducing the bitterness of caffeine in a chewable tablet. However the more common use of solid complexes is associated with the enhanced solubility of the complex.

An example of a system in which the use of solid complex has been found to substantially enhance dissolution rate is the digoxin - hydroquinone system (42). The dissolution rate of digoxin from the complex (two mols digoxin : three mols hydroquinone) was much more rapid and complete than that of digoxin when powders of equal mesh size and equal digoxin concentrations were compared.

Another example of enhanced dissolution rate through the use of complex is the 1:1 acetaminophen - caffeine complex (15). It was found that the solid complex at 25 degrees Celcius was a hexahydrate form. However, when the complex was dried to yield either the monohydrate or anhyd-

rous complex, the apparent solubilities and the associated dissolution rates of both these species were much greater than with the hexahydrate complex of pure acetaminophen. These results point out the need to carefully characterize the nature of the solid complex for the extent of solvation, as well as the substrate - ligand stoichiometry, before reaching any conclusion about the usefulness of the complex (80).

The use of complexation has several advantages. Among these are the reversibility of the interactions. Dissociation of the complex to the individual reactants occurs rapidly and spontaneously upon dilution. Consequently, the biological effects of complexes can be predicted on the basis of the knowledge of the pharmacologic properties of each of the interactants. The above characteristics of the complexes are in contrast to chemically derived prodrugs which normally require some sort of "triggering" features to aid in release of the parent drug. Another advantage of the use of complexation is the physical stability of these systems in comparison with polymorphs and other crystal modification which are often thermodynamically unstable and therefore may undergo time - dependent changes in solubility behavior.

This approach, however, is not without limitations. Ironically, in some instances, it may be that rapid and total reversibility previously presented as an advantage may prove to be a problem especially in those cases in which

dilution of a system may result in precipitation.

A second problem is the necessary presence of the ligand whose sensory and/or pharmacologic effects may be unacceptable.

Finally, in most reported cases, the apparent solubility increases realized by complexation were an order of magnitude or less (80). Consequently, when solubility increases of 10^2 or 10^3 are required, approaches other than complexation should be used.

2.4. FORMATION OF INCLUSION COMPOUNDS

Inclusion compounds are addition compounds in which one entity fits into and is surrounded by the crystal lattice of the other (17). These are complexes characterized by the lack of adhesive forces between the components of the complex. It is not a chemical interaction which causes an inclusion compound to form, although this may be a factor in the net complexation observed. The steric configurations of the molecules are such that the enclosing, or "host" molecule, can spatially enclose the included or "guest" molecule, leaving unaffected the bonding systems of the component. Thus geometrical rather than chemical characteristics of the molecules are the limiting factors in the interaction (17).

The formation of inclusion complexes of a drug with nontoxic agents is a type of manipulation used to improve the dissolution properties of drugs (30,104). Cyclodextrins, which are products of enzymatic degradation of starch, have

been used extensively as such complexing agents. In these complexes molecules of the drug are enclosed in the hydrophobic cavity of a cyclodextrin molecule or in a channel formed by several molecules of cyclodextrins. Depending on the size of the open space within each molecule the cylodextrins have been classified as alpha, beta and gamma.

Because of their different internal ring sizes the cyclodextrins show different degrees of inclusion formation with different sized molecules. Beta cyclodextrin, which is the most practical to use, unfortunately has low water solubility, and its complexes are also often only slightly soluble. Recently attempts have been made to improve the solubility of beta cyclodextrin by chemical derivatization (68,71,75,77).

However, there have been only a limited number of studies to indicate the lack of toxicity of these new compounds in humans and much more work is needed before these compounds can be used in commercial products.

2.5. DRUG DERIVATIZATION

The use of derivatives to enhance the aqueous solubility of insoluble drugs and has long been recognized as an effective design strategy. The prodrug strategy is based on chemical or biochemical reconversion to the active drug prior to reaching the site of action.

Generally two strategies can be used to increase the aqueous solubility : (a) introduction of an ionic or ionizable group and (b) introduction of a group which decreases

the melting point.

The synthesis of an ionic or ionizable derivative of a drug is perhaps the most common of the prodrug strategies. Some of the progroups used are hemisuccinates, phosphates, dimethylaminoacetates, amino acid esters, choline esters, and betadimethylaminoethyl esters (3).

Examples of increases in solubility by lowering the melting point are seen in allopurinol (46) and ara-A (82). The basis for this strategy is that in order to dissolve, molecules must be removed from the crystal lattice. Any modification which reduces the crystal lattice energy, hence melting point, would tend to increase solubility (in all solvents). The relationship between the aqueous solubility Sw and melting point is expressed by the equation (3):

$$\log Sw = -\log PC - 0.01MP + 0.5 \qquad (2)$$

where PC is the octanol/water partition coefficient and MP the melting point in degrees Celcius.

3. CONTROLLED RELEASE DOSAGE FORMS

A controlled release dosage form is generally defined as one that attempts to (57):

(1) sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a sawtooth kinetic pattern.

(2) localize drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue or

organ.

(3) target drug action by using carriers ar chemical derivatization to deliver drugs to a particular "target" cell type.

In practice, very few of the applied systems embrace all of these actions. In most cases, the release system creates constant concentration of drug within the body over an extended period of time. It is desirable that the duration of drug action become more a design property of a rate controlled dosage form, and less, or not at all, a property of the drug molecule's inherent kinetic property.

3.1. ORAL CONTROLLED RELEASE SYSTEMS

Oral ingestion has long been the most convenient and commonly used route of drug delivery. Indeed, for sustained - release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for other routes.

As in the case for systems for nonoral routes, the design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance. Among these are the type of delivery system, the physicochemical property of the drug, the disease being treated, the patient factors and the length of therapy.

The majority of oral controlled release systems are

either tablets or capsules although a few liquid products are also available. Sustained release tablets and capsules usually consist of two parts : an immediately available dose to establish the blood level quickly and a sustaining part that contains several times the therapeutic dose for protracted drug levels. Several approaches are available to add the immediately available dose to the sustaining part. Simple addition of a nonsustained dose of a drug to a capsule or tablet is the most direct method; placement of the initial dose in the tablet coat with the sustaining portion in the core represents the alternate approach. Potential physical methods that can be used to retard drug release are summarized below (42):

1. Capsules of polymeric material filled with a solid or liquid drug or with a suspension of drug in a fluid, in which drug release is controlled by diffusion through the capsule wall

2. A heterogeneos dispersion of drug particles in a solid matrix which can be either biodegradable or nonbiodegradable and which controls drug release by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion

3. A laminate of agent and polymeric material made by coating a film of biodegradable or nonbiodegradable material with solid drug and then by forming the film into a sealed "sandwich" or "jellyroll", in which drug release is by diffusion, erosion, or both

4. A heterogeneous dispersion or solution of drug in a water - swellable hydrogel matrix, which controls drug release by slow surface-to-center swelling of the matrix by water and subsequent diffusion of the drug from water-swollen part of the matrix

5. Liquid-liquid encapsulation of the drug in a viscous solution of polymer, which controls drug release by slow diffusion through dilution of the media

6. Pumps that either mechanically or chemically (osmotic pressure) provide drug in a controlled manner

7. Drug coated micropellets which have an apparent density lower than that of gastric juice for an extended period, while slowly releasing drug

8. Drug-containing bioadhesive polymer that adheres to the mucin coating of the GI tract and which is retained on the surface epithelium to extend GI transit time of the drug. Drug is released at a constant rate from the bioadhesive polymer for subsequent absorption

9. Chemical bonding of a drug to a polymer backbone by pendent amide or ester linkages, which controls drug release by hydrolysis

10. Formation of macromolecular structures of the drug via ionic or covalent linkages, which controls drug release by hydrolysis, thermodynamic dissociation, or microbial degradation

3.2. POLYMERS IN ORAL CONTROLLED RELEASE SYSETEMS

Other than mechanical pumps, all controlled release devices use polymers in the rate control mechanism. Polymeric devices can be classified into 3 categories: (a) diffusion-controlled devices, (b) solvent-controlled devices, and (c) chemically-controlled devices. Of these, the first two types are used for oral drug delivery while the chemically controlled devices are usually employed for implantable systems or other non-oral systems and will not be discussed here.

3.2.1. DIFFUSION CONTROLLED DEVICES

These may be further classified into monolithic devices and reservoir devices.

In a monolithic device the therapeutic agent is intimately mixed (either dissolved or dispersed) in a rate controlling polymer, and release occurs by diffusion of the agent from the device. For an active agent dissolved in the matrix, release kinetics can be calculated by two equtaions (39). Equation (3), known as the early time approximation, holds true for the first 60% of the release rate, after which it is calculated from eq.(4), which is known as the late time approximation.

$$dM_t/dt = 2M_x(D/pi.l^2t)^{1/2} \quad (3)$$

$$dM_t/dt = (8DM_x/l^2) \exp(-pi^2Dt/l^2) \quad (4)$$

These equations predict active agent release from a slab of thickness l where D is the diffusion coefficient, M_x is the total amount of active agent dissolved in the polymer

and M_t is the amount released at a time t. As equation (3) shows, release rate decreases as $t^{-1/2}$ over the first 60% of the release; over the remainder of the release the rate decays exponentially according to eq. (4).

When the active agent is dispersed in a the polymer, release kinetics have been derived by Higuchi (41):

$$dM_t/dt = (A/2)(2DC_sC_0/t)^{1/2} \quad (5)$$

where A is the area, C_s is the solubility of the active agent in the matrix and C_0 is total concentration in the matrix (dissolved plus dispersed) .

Although active agent release from monolithic systems does not proceed by zero-order kinetics, it is the simplest and most convenient way to achieve prolonged release of an active agent.

In a reservoir device the active agent is contained in a core that is surrounded by a rate controlling membrane. Transport of the material in the core through surrounding nonporous, homogeneous polymer film occurs by dissolution at one interface of the membrane and then diffusion down a gradient in thermodynamic activity (39). It can be described by Fick's first law modified:

$$J = -DKC' / l \quad (6)$$

where J is the flux, D is the diffusion coefficient of the permeant in the membrane, C' is the concentration difference between solutions on either side of the membrane, K is the distribution coefficient analogous to a liquid - liquid partition coefficient and l is the thickness of the membrane.

If the thermodynamic activity of the active agent in the reservoir remains constant, if there is no change in the rate - limiting membrane characteristics, and if infinite sink conditions are maintained at the downstream side of the membrane, rate of active agent release will be constant and can be predicted from a knowledge of membrane permeability and device configuration.

Even though such reservoir type devices should theoretically be capable of delivering active agents at a constant rate, also referred to as zero-order kinetics, in practice several factors contribute to deviations from zero-order kinetics. The two most important factors are boundary layer effects and the burst effect.

Boundary layer problems arise in applications in which the rate of removal of the active agent from the membrane is slow so that the concentration of the drug at the membrane surface increases with time. Then as predicted by eq.(6), the term dC decreases and consequently the flux J also decreases.

Burst effects occur when during storage the active agent contained in the core saturates the membrane surrounding the core; then, when the device is placed in the desorbing medium, the active agent will rapidly desorb from the membrane.

Reservoir devices are capable of very long term zero-order drug delivery. However they may require more complex fabrication procedures than monolithic devices.

3.2.2. SOLVENT-CONTROLLED DEVICES

Solvent-controlled devices release active agents as a consequence of controlled penetration of a solvent into the device. Although non-aqueous solvents can be used, only water is of importance in controlled release applications for human or veterinary applications. The two general mechanisms used for solvent-controlled devices are osmosis and swelling.

a. Osmotically-Controlled Devices: In these devices the active agent is placed in an innermost impermeable flexible reservoir surrounded with an osmotic agent, which in turn is surrounded with and sealed within a rigid cellulose acetate semipermeable membrane (39). When the device is placed in an aqueos environment, water is osmotically imbibed across the semipermeable membrane, and the active agent contained within the flexible reservoir is pumped out of the device. Because the driving force is the osmotic transport of water across the membrane, performance of the device is essentially independent of the environment within which the pump operates.

b. Swelling-Controlled Devices: In these systems an active agent is homogeneosly dispersed in a glassy polymer. Because glassy polymers are essentially impermeable, the active agent is immobilized in the matrix, and no diffusion through the solid polymer phase takes place.

When such a monolithic device is placed in an aqueous environment, water begins to penetrate the matrix and swel-

ling takes place. As a consequence, chain relaxation takes place and the incorporated active agent begins to diffuse from the swollen layer.

II. PURPOSE OF THIS STUDY

As can be seen from the preceding discusion, it would be desirable to formulate an oral solid dosage form, preferably a tablet, offering some degree of control over the release of nifedipine. The final properties will be influenced by the techniques used for enhancing the dissolution rate, by the material and proportion of the rate - controlling matrix, and by the tablet properties (hardness, disintegration, etc).

For the enhancement of dissolution of nifedipine in the present study, the solid dispersion technique has been employed using PEG 8000 and PVP 40T as the polymer for forming coprecipitates. In a preliminary study Sugimoto et al (96) found that nifedipine - PVP coprecipitates gave the fastest release rates. Further, the molecular weight of PVP that gave the best results was 40,000. Compared to the bioavailability from a physical mixture (of nifedipine and PVP) the C_{max} and AUC of the coprecipitates were 5 - fold and 3 - fold higher.

The rationale for using PEG for preparing coprecipitates is the fact that the physicochemical stability of PEG coprecipitates are very high (99). The use of PEG 8000 for the preparation of nifedipine coprecipitates is not reported in the literature. However, Sumnu (98) found no significant differences between PEG 4000, 6000, and 10000 when release of nifedipine coprecipitates with these substances were compared.

For sustaining the release, powdered microporous polypropylene polymer (Accurel) has been used. This new material has small cells and canals formed throughout its structures which are connected by small pores occupying 30 - 90% of the volume (49,94). For this study, powdered polypropylene containing 75% v/v void space has been used. A major advantage of this substance is its property to give good coherence after tabletting (49). Matrix tablet with relatively high drug load show diffusion controlled characteristics and release was approximately zero - order (49).

The objectives of this study were :

1. To prepare an optimized formulation of nifedipine using the coprecipitate approach to improve the dissolution rate.
2. To study the tabletting properties of the variuos formulations.
3. To perform in vitro dissolution tests to evaluate the release rate of nifedipine from the tablet dosage forms. It is desired that about 50% of the dose (i.e. 10 mg) be released within 20 minutes and the remaining 50% be released over an extended period of time (compared to the release of commercial soft gelatin capsules under similar conditions).

III. EXPERIMENTAL

1. MATERIALS

A. Chemicals

Acetic acid, Glacial Reagent A.C.S. (lot # 705283)[1]

Accurel, Polypropylene powder, 75% void space (lot # 40306/1-3/P)[2]

Ac-di-sol TM, Type SD - 711, modified cellulose gum (lot # 7135 - 25)[3]

Acetonitrile HPLC grade (lot # 853747)[1]

Ammonium acetate (lot # 731745)[1]

Cab-O-Sil brand colloidal silica[4]

Ethanol 200 proof, Dehydrated alcohol U.S.P[5].

Hydrochloric acid[6]

Methanol HPLC grade (lot # 864444 & 863081)[1]

Polyethylene glycol 8000 (lot # 106 F - 0020)[7]

Polyvinyl pyrrolidone, PVP - 40T (lot # 74F-0208)[7]

Phosphoric acid HPLC grade (lot # 715056)[1]

Potassium phosphate monobasic (lot # 722964)[1]

Potassium phosphate dibasic (lot # 722337)[1]

Sodium hydroxide, Certified A.C.S. (lot # 720859)[1]

Sodium phosphate dibasic (lot # 772374)[1]

Sodium lauryl sulfate, U.S.P.

B. Drugs

Nifedipine crystalline powder (batch # 167707A)[8]

Nifedipine soft - gelatin capsules (Adalat)[8]

1. Fisher Scientific Company, Fairlawn, New Jersey.

2. Enka Industrial Products Inc., Illinois.
3. FMC Corporation, Philadelphia, Pennsylvania.
4. Cabot Corporation, Boston, Massachusetts.
5. U.S. Industrial Chemical Company, Tuscola, Ill.
6. E.I. du Pont de Nemours & Co., Wilmington, Del.
7. Sigma Chemical Company, St. Louis, Missouri.
8. Bayer AG., Germany; supplied by Miles Pharmaceuticals, West Haven, Connecticut.

2. EQUIPMENT

Electronic Analytical Balance, Sartorus GMBH, Germany.

Electrical Balance, Model H8 Mettler, Will Scientific Inc., Rochester, New York.

Dissolution Tester Six Spindle, Vanderkamp 600, Van-kel Industries Inc., Chatham, New Jersey.

Tablet Disintegration Test Apparatus, Van-kel Industries Inc., New Jersey.

HPLC Solvent Delivery System Model 6000A, Waters Associates, Milford, Massachusetts.

WISP 710B, Waters Associates, Milford, Massachusetts.

mu- Bondapak C18 Column, Waters Associates, Milford, Massachusetts.

LC Spectrophotometer Lambda Max Model 480, Waters Associates, Milford, Massachusetts.

Linear Chart Recorder, Cole Parmer Instrument Co., Chicago, Illinois.

Integrator Model HP 3392A, Hewlett Packard Co., Avon-

dale, Pennsylvania.

Diode Array Spectrophotometer Model 8451A Hewlett Packard Co.

pH - Meter, Model 811, Orion Research Inc., Cambridge, Massachusetts.

Gold Fluorescent Lamp Mopdel F40G0, General Electric.

Tablet Press Single Punch, Stokes.

Friability Tester, Erweka GmbH, Germany.

Water Bath, Precision Company.

Ultraviolet - Visible Spectrophotometer Model Hitachi 200, Perkin Elmer .

Laboratory Mill, Arthur H. Thomas Co., Philadelphia, Pennsylvania.

Rotavapor Rotary Evaporator, Buchi.

Granule Mixer, Turbula, Switzerland.

3. PROCEDURES

Nifedipine is quite light - sensitive and degrades rapidly on exposure to daylight, tungsten - bulb light, or standard fluorescent light. It is however, stable when "gold" fluorescent light is used (37). Therefore all procedures described here were carried out in a laboratory area which was either dark or had only gold fluorescent lighting.

3.1. ASSAY DEVELOPMENT

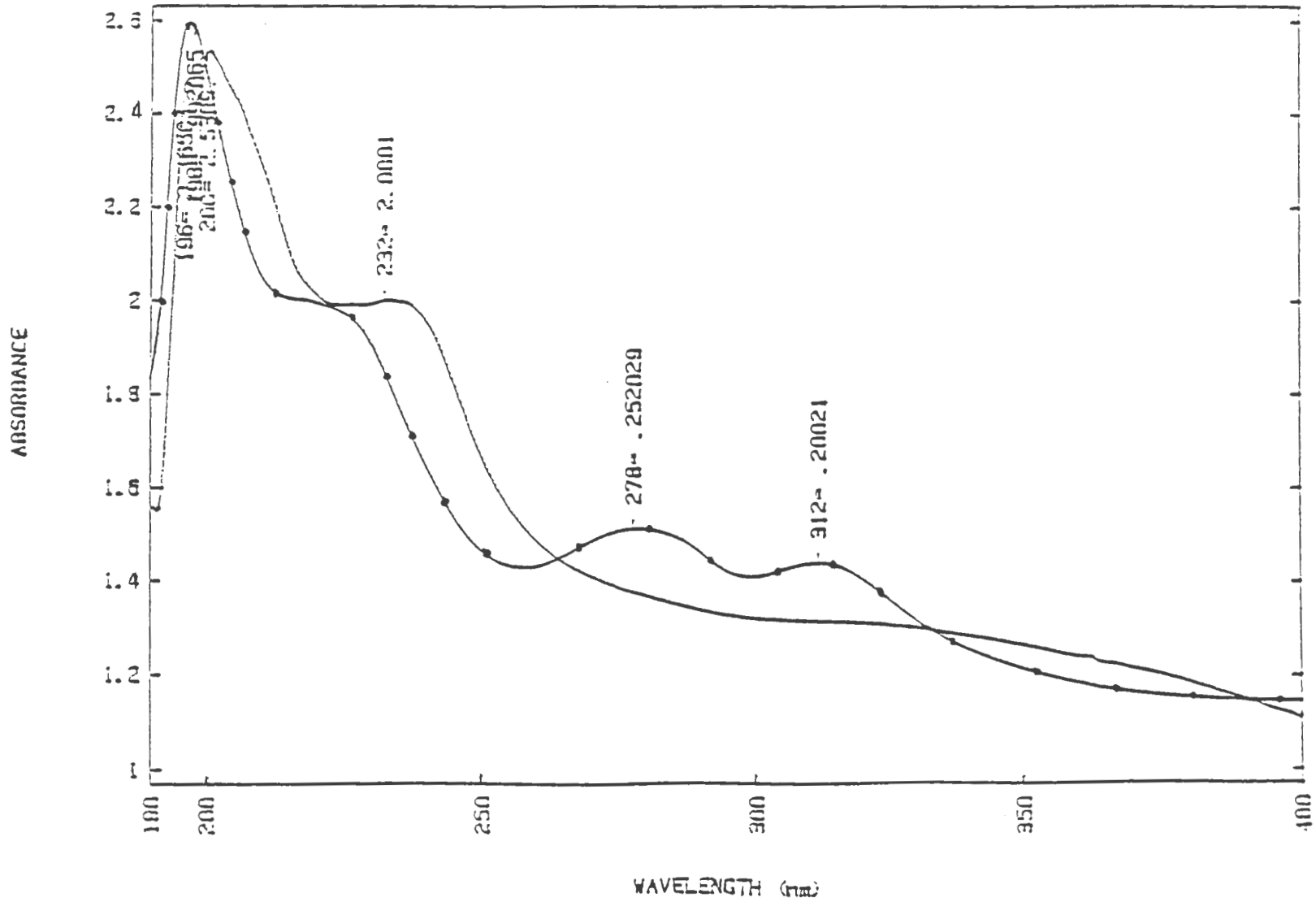
For quantitative analysis of nifedipine an ultraviolet (UV) spectrophotometer was used in conjunction with a rever-

sed phase high performance liquid chromatography system (HPLC). First a 10 mg/L solution of nifedipine in methanol was prepared and allowed to degrade under normal laboratory light for 7 days. After this period a UV spectrum was obtained of the degraded sample (190 - 400 nm). Next a UV spectrum of a fresh solution of nifedipine of the same concentration was superimposed on the first spectrum (fig.2). From the resulting scans it was evident that the difference in the absorbance values of nifedipine and its photodegradation product was greatest at 238 nm with the absorbance of nifedipine being much greater. A standard curve of nifedipine was obtained at this wavelength for concentrations between 0 and 20 mg/L.

Although several authors have used a UV assay at 238 nm for nifedipine (53,54), it is not stability indicating. For this reason an HPLC assay was developed using a 3 - 9 mm (id) x 30 cm mu-Bondapak C18 (reversed phase) column and a variable wavelength detector (Lambda max 480) set at 238 nm. A number of mobile phase systems were tested and the one which provided the best resolution between the peaks of nifedipine and its photodegradation compound was chosen for the assay. This consisted of 49 percent methanol in fresh distilled, deionized water. The chromatographic conditions were as follows:

The flow rate was 1.2 ml/min., the detector sensitivity was 0.05 AUFS and the injection volume (using WISP) was 100 microliters.

Fig. 2. UV absorption spectrum of nifedipine (——) and its photodecomposition product (—•—).



A plot was obtained between peak height / area versus concentration using standard solutions of nifedipine and was used to determine the concentrations of the dissolution samples.

Alternatively, concentrations of dissolution samples were obtained by the spectrophotometric method and stability was checked by the HPLC method.

3.2. PHOTODEGRADATION STUDIES

To study the rate of degradation of nifedipine solution in normal laboratory conditions a preliminary study was conducted in a lighted room at night to exclude the variable intensity of sunlight.

20 mg/L of nifedipine solution was prepared in three different media to test the effect of pH on the rate of photodegradation of nifedipine. The first medium was 49% methanol in water (corresponding to the mobile phase of the HPLC system); the second and the third media were 49% methanol in 0.01 M phosphate buffer with final pH adjusted to 4.2 and 7.8 respectively.

Four ml of each of the three solutions was taken separately in a WISP vial and kept exposed to the light in the room. At 0, 30, 60 and 180 minutes two samples of 25 microliters each were withdrawn from each solution and injected into the HPLC system manually. A set of standard solutions were also injected during the assay to obtain a standard curve at the same conditions. From a peak height analysis of the chromatograms the percent of nifedipine remaining in the

solution was calculated.

3.3. SOLUBILITY STUDIES

The solubility of nifedipine in various media was determined in an attempt to obtain a suitable medium for dissolution studies. The apparatus used was similar to the dissolution apparatus used in the rotating bottle method (38). The media selected were distilled water, hydrochloric acid 0.1 N and 1.0 N, sodium hydroxide 0.1 N, and phosphate buffer 0.01M (pH 7.4). The temperature of the water bath was maintained at 25 $\pm$ 1 degrees Celcius. Glass tubes with screw caps were used for holding the soutions. Each tube was filled with 20 ml of of the medium and about 10 mg of nifedipine thereby ensuring the excess of the drug in the tube. Three tubes were used for each media.

The caps were screwed on the tubes and were wrapped securely with a strip of parafilm to prevent any leakage. The tubes were fixed to the shaft and allowed to rotate in the water bath. At 3.5 and 4.5 hours, the tubes were removed and 3 ml samples were withdrawn from each tube using a pipet fitted with plastic tube containing glass wool to prevent solid particles from entering the pipet. The samples were assayed immediately by UV spectrophotometer at 238 nm. Similarly the solubility of the coprecipitates were determined at 25 degrees.

3.4. PREPARATION OF NIFEDIPINE - POLYMER COPRECIPITATE

Fifty grams of nifedipine powder (crystalline) was taken in a 2L round - bottom flask. To this about 400 ml of ethanol was added with continuous stirring. Two hundred grams of the polymer (PEG 8000 or PVP 40T) was then added with stirring and the solution warmed in a water bath at about 45 degees Celcius. Stirring was continued until a clear solution was obtained.

The solution was allowed to cool to room temperature and the solvent was evaporated under vacuum using a rotary evaporator at 40 degrees Celcius. The semi- dried mass was crushed and collected in a 1L beaker, covered with aluminum foil (with holes punched at the top to allow drying) and kept in a vacuum oven at room temperature for 48 hours. At the end of this period the beaker containing the coprecipitate was removed from the oven and kept in a dessicator for further use.

3.5. TABLETTING

For preparing tablets the nifedipine - polymer coprecipitates were milled separately in a laboratory mill using a #20 screen. The two coprecipitates were then mixed in the desired ratio, according to the formulation (see table I), and 20 grams of the resulting mixture taken in the mixing jar. To this, 700 mg (i.e. 3.5%) of Ac-di-sol (disintegrant) and 200 mg (i.e. 1.0%) of Cab-O-Sil (antiadherent) was added and mixed together in a turbula mixer for fifteen minutes.

TABLE I. Composition of controlled release tablets of nifedipine.

Tablet code	Amount of ingredient per tablet (mg)					
	PEG[a]	PVP[b]	Ac-di-sol	Accurel	SLS[c]	Cabosil
T1	100	0	3.5	0	1.5	1
T2	50	50	3.5	0	1.5	1
T3	25	75	3.5	0	1.5	1
T4	5	95	3.5	0	1.5	1
T5	25	75	3.5	5	1.5	1
T6	25	75	3.5	7.5	1.5	1

[a]Polyethylene glycol 8000 and nifedipine (4:1) coppt.

[b]Polyvinylpyrrolidone (40T) and nifedipine (4:1) coppt.

[c]Sodium lauryl sulfate.

At the end of this time, the jar was taken out and 300 mg (i.e. 1.5%) of sodium lauryl sulfate (soluble lubricant) was added. The whole contents were then mixed for another five minutes.

For tablets T5 and T6 (see table I), Accurel (1.0 gm and 1.5 gm respectively) was added along with Ac-di-sol and Cab-O-Sil to the coprecipitate mixture. The rest of the procedure was the same as described.

Tabletting was done using a single - punch tablet press operated maunually. The humidity of the room was kept below 40 percent with a dehumidifier. The lower punch of the machine was adjusted according to the theoretical weight of the tablet (106 mg for T1 - T4, 111 mg for T5, and 113.5 mg for T6). For each formulation about 120 tablets were obtained. The physical properties of the tablets were studied and the tablets stored in opaque plastic bottles in a dessicator for dissolution studies.

3.6. EVALUATION OF TABLET PROPERTIES

3.6.1 PHYSICAL PROPERTIES:

Weight variation and disintegration time was studied for each type of tablet in accordance with the official method (USP XXI). Hardness was tested on five tablets of each type using Erweka hardness tester. Friability was determined using 10 tablets with Erweka Friability tester at 25 rpm for 4 minutes for each test.

6.2 DISSOLUTION STUDIES:

Dissolution rate was studied for each kind of tablet under two different conditions as described below. In each case the dissolution flasks were filled with 1 L of freshly prepared distilled water and warmed to 37 $\pm$ 1 degrees Celcius. The USP paddle method was used with the stirring speed maintained at 150 rpm. All samples were run three times.

In the first case one whole tablet (containing 20 mg equivalent of nifedipine) was taken in each of three flasks and the procedure was carried out for all six types of tablets T1 through T6. At appropriate intervals, a 3 ml sample was withdrawn by means of a pipette fitted with a small piece of glass wool to filter off any drug particle. The sample volume taken was replaced by an equivalent volume (3ml) of fresh distilled water at the same temperature. The sample was suitably diluted with warm distilled water and assayed using UV spectrophotometer at 238 nm as well as HPLC assay as described before. For comparison of the dissolution profile of the tablets prepared from the coprecipitates a similar procedure was carried out using pure nifedipine powder (20 mg) and also commercially available soft - gelatin capsules of nifedipine (2 capsules per flask - equivalent of 20 mg nifedipine).

In the second case the tablets were cut into small pieces. A small piece (containing approximately 4 mg equivalent of nifedipine) was weighed accurately and taken in 1 L of dissolution media (to approximate sink conditions) and

the above procedure was repeated. From the weight of the tablet fraction the amount of nifedipine was calculated to give the dissolution rate expressed as a percent of the amount dissolved in a given time interval.

IV. RESULTS AND DISCUSSION

This section contains an evaluation of the experimental protocol and assay techniques used in this study and results thus obtained. It also contains a critical discussion of the significance and an interpretation of the results.

For ease of reference the results and discussion are organised into the following sections:

A. Evaluation of the assay methods.

B. Kinetics of Photodegradation of nifedipine.

C. Solubility studies.

D. Evaluation of the physical characteristics of tablets.

E. Disssolution studies.

A. EVALUATION OF THE ASSAY METHODS

1. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Table II summarizes the results obtained from the various mobile phases and flow rates used in developing a stability indicating assay HPLC assay for nifedipine.

The retention times for nifedipine and its photodecomposition product are denoted by Tr2 and Tr1 respectively. The resolution R was calculated using the formula :

$$R = 2\ (Tr2 - Tr1)/\ (W1 + W2) \qquad (7)$$

where W1 and W2 are the base peak width of the degradation product and nifedipine respectively.

From the table it is evident that using 49% methanol in water as mobile phase gives the best resolution. Hence this

Table II. Resolution obtained from the various mobile phase systems.

Mobile Phase	Ratio	Flow (ml/min)	Tr1[a] (min)	Tr2[b] (min)	R[c]
methanol/water	60:40	1.1	5.4	6.0	<0.5
-do-	55:45	1.4	5.6	6.6	0.5
-do-	50:50	1.0	10.1	12.8	0.96
-do-	49:51	1.4	11.1	14.9	1.15
-do-	48:52	1.5	10.4	14.0	1.09
-do-	45:55	1.5	12.0	15.8	0.95
methanol/acetate -buf.(0.05M,pH4.0)	48:52	1.4	7.8	9.8	0.71
-do-	45:55	1.4	10.4	13.8	1.07
methanol/acetate -buf.(0.05M,pH6.0)	50:50	1.4	8.0	10.0	0.92
methanol/phosphate -buf.(0.01M,pH4.7)	62:48	1.0	5.3	6.0	<0.5
acetonit/acetate -buf.(0.05M,pH4.0)	5:7	1.2	7.6	7.6	0
-do-	1:2	1.5	12.4	12.4	0

[a]Tr1 is the retention time of the photodegradation product.

[b]Tr2 is the retention time of nifedipine.

[c]R is the resolution given by the equation :

$$R = 2 (Tr2 - Tr1) / (W1 + W2)$$ (see text).

was selected for the assay of nifedipine. A typical chromatogram is shown in figure 3.

A linear relationship was found to exist between peak height (as well as peak area) and nifedpine concentration. Figures 4 and 5 show that this linearity was held in the concentration range 0 - 10 mg/L. However, the relationship between peak area (or peak height) and concentration varied everytime a fresh mobile phase was used. To overcome this problem a standard curve was generated during each run and the sample concentrations were determined from the corresponding relationship between peak area or height and concentration of the standard solutions.

Another problem with the HPLC assay was that it was very slow. For this reason it was used in conjunction with the UV assay described below.

2. ULTRAVIOLET SPECTROPHOTOMETRIC METHOD

The use of UV spectrophotometer at a wavelength of 238 nm provided a simple, relible and sensitive assay which was also rapid and reproducible. Detection was linear in the range of concentrations tested (0 - 20 mg/L). The absorbance (A) was related to the concentration (C) by the equation (see fig. 6):

$$A = 0.0607C + 0.007 \qquad (8)$$

The coefficient of correlation r = 0.9998

To check for degradation of nifedipine during dissolution or solubility studies, one of the three samples for

Fig. 4. HPLC calibration curve using peak heights.

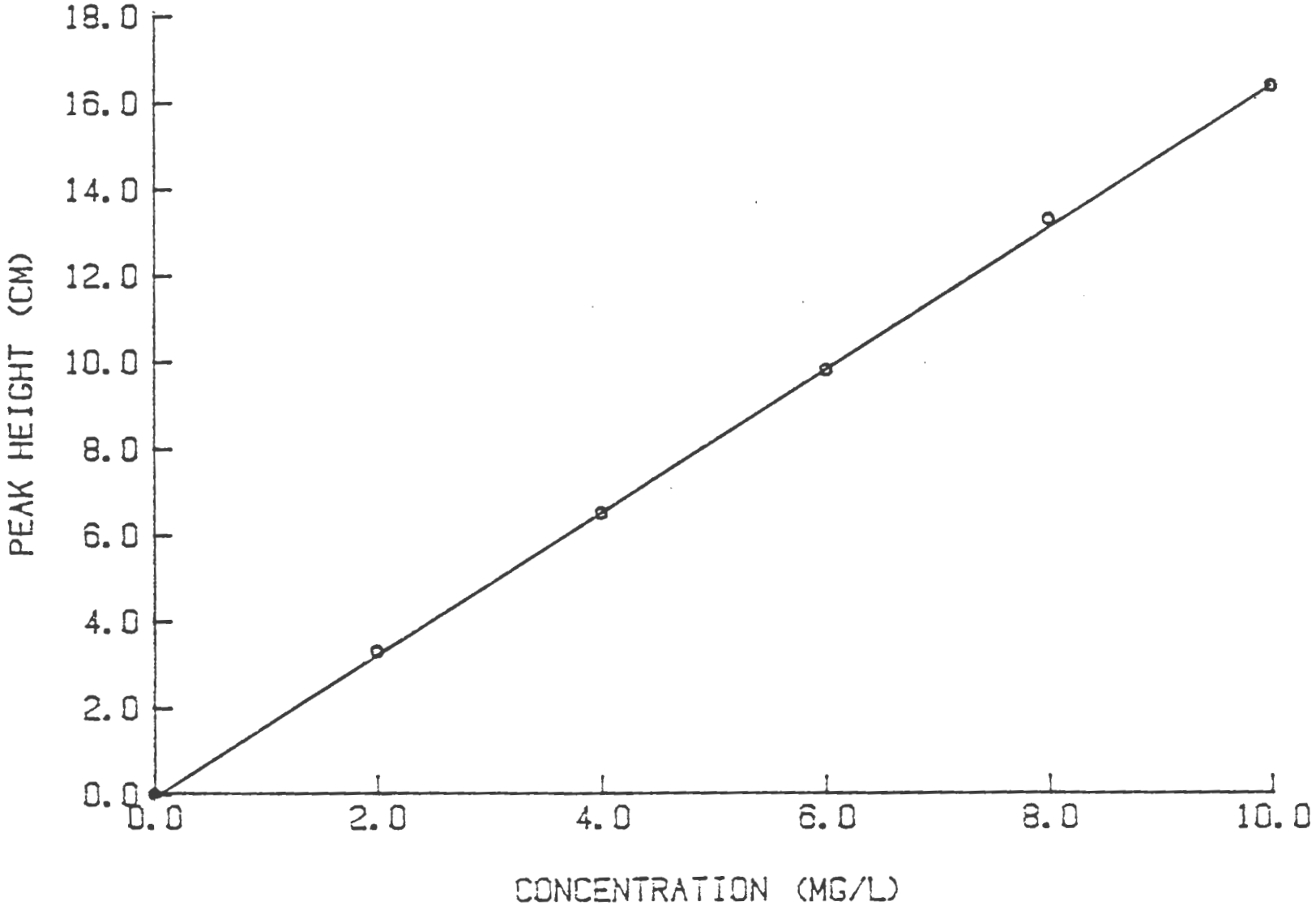


Fig. 5. HPLC calibration curves using peak areas.

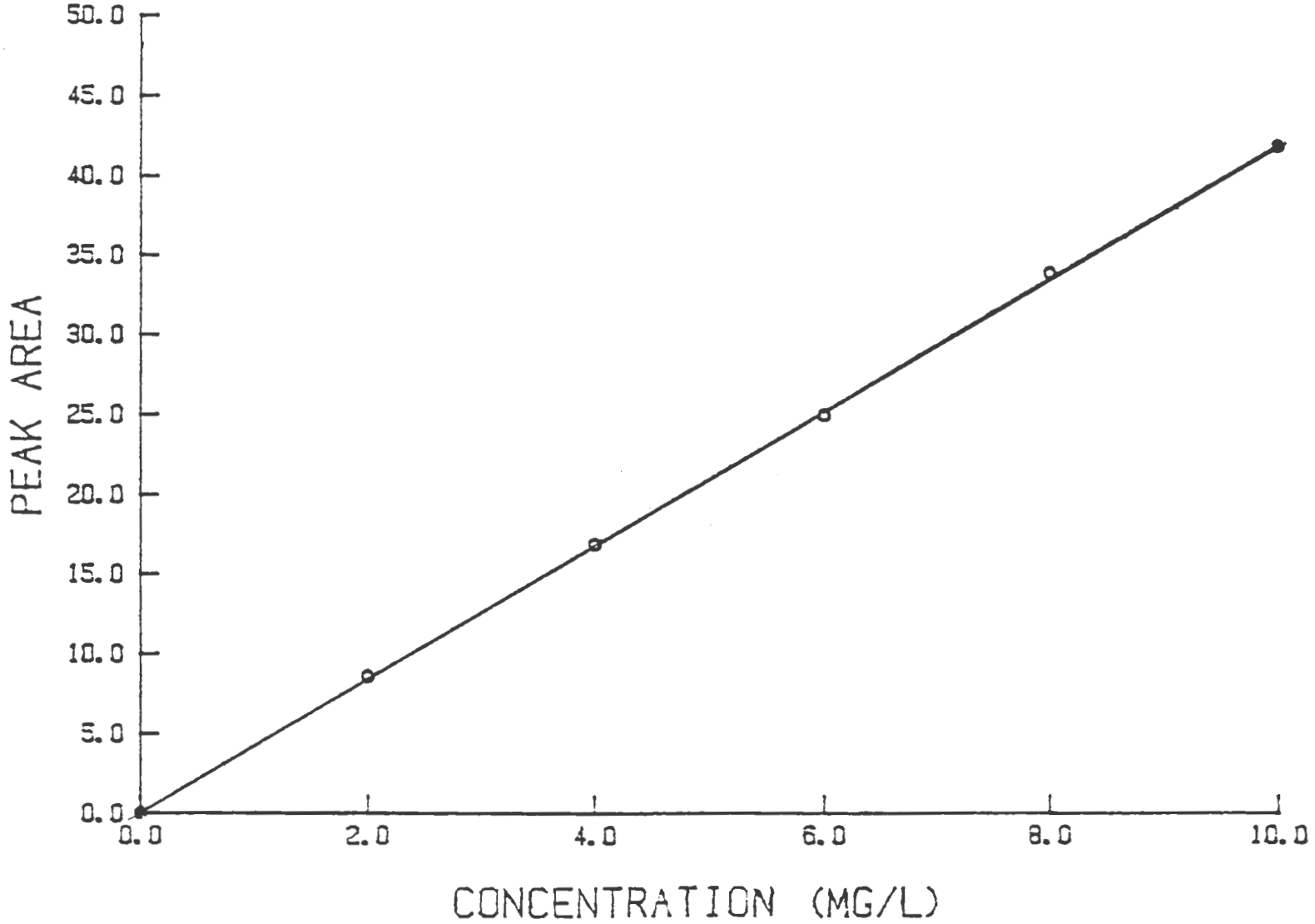
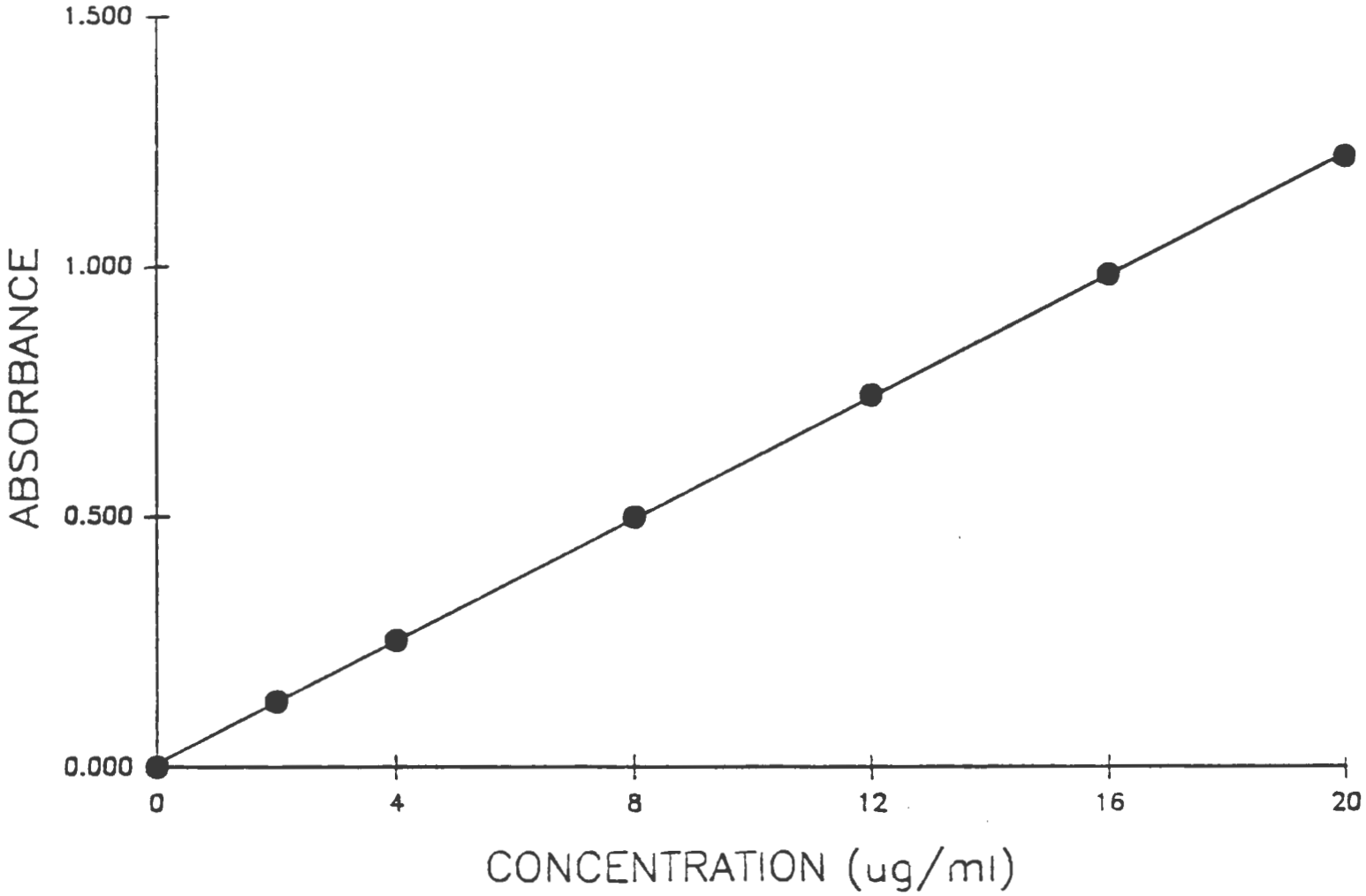


Fig. 6. UV calibration curve for nifedipine (238 nm)



each time point in each batch was also assayed by the HPLC method. The results obtained from the two methods for one study were compared (see under dissolution studies in this section) and it was found that the difference in the concentrations obtained from the two methods is very small.

B. KINETICS OF PHOTODEGRADATION OF NIFEDIPINE

The results of a preliminary study of the kinetics of photodegradation of nifedipine are presented in table III. On plotting the results on a log - linear scale (fig. 7), it is seen that the photodegradation follows first order kinetics. The t_{90} of degradation was found to be about 19 minutes in a normally lighted room during the night.

Thoma and Klimek (102) studied the degradation kinetics of nifedipine in daylight. They reported a t_{90} of about 7 minutes in winter and about 1 minute in the summer. The purpose of our investigations was to see if, by excluding daylight from the room, the degradation of nifedipine could be prevented for a sufficient length of time to perform dissolution or solubility experiments. From the results it is clear that even in the absence of daylight nifedipine solutions are extremely photosensitive to normal laboratory light.

Another objective of this preliminary study was to see if there is a measurable difference in the rate of degradation of nifedipine when the pH of its solution was acidic or alkaline.

Table III. Photodegradation of nifedipine.

Time (min)	% nifedipine remaining in solution[a]		
	A	B	C
0	100	100	100
30	84.0	84.1	83.9
60	74.2	75.1	74.7
120	50.2	--	--

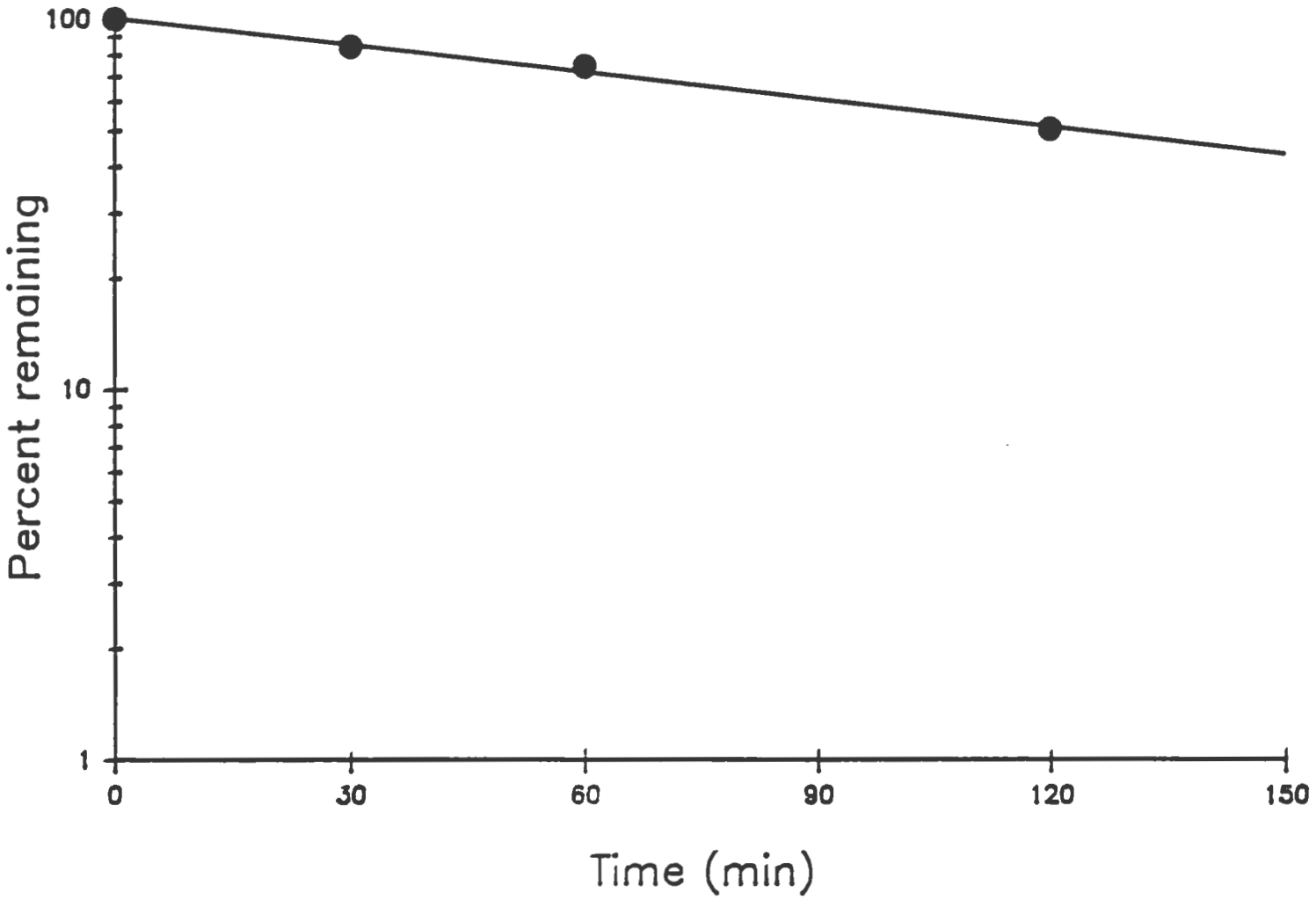
[a]Solution of 20 mg/L prepared in the following solvent:

A. 49% methanol in water.

B. 49% methanol in phosphate buffer (final pH 4.2).

C. 49% methanol in phosphate buffer (final pH 7.8).

Fig. 7. Rate of photodecomposition of nifedipine showing First order decay.



From the results obtained (Table III) it is clear that in the pH range of 4.2 - 7.8 there was no appreciable difference in the rate of degradation.

When solutions of nifedipine were made in methanol and kept in colored glassware in a refrigerator there was no detectable degradation for at least one week.

C. SOLUBILITY STUDIES

The results of the solubility studies are shown in table IV. It is clear that the solubility of nifedipine in water at 25 degrees Celcius is extremely low (about 5 mg/L). Further the solubility is not affected significantly ($P > 0.05$) in the pH range of 1 to 7.4. These results are in accordance with the results obtained by Boje et al (10) who reported a solubility of 5 - 6 micrograms per ml over pH 2.2 - 10.0 at 25 degrees.

With 1N hydrochoric acid or 0.1N sodium hydroxide as the solvent the absorbance values were highly unstable. Hence solubility determinations could not be made with these solvents.

The solubilities of the two coprecipitates were higher than the solubility of nifedipine. Especially the coprecipitate containing polyvinyl pyrrolidone (40T) as the polymer exhibited a four - fold increase in solubility over nifedipine.

Table IV. Solubility of nifedipine and its coprecipitates at 25 degrees Celcius.

Physical Form	Solvent	Absorbance[a] (238 nm)	Solubility[a] (mg/l)
crystalline	water	0.304 ± 0.027	5.01 ± 0.44
-do-	phos.(7.4)[b]	0.259 ± 0.026	4.26 ± 0.43
-do-	0.1N HCl	0.359 ± 0.047	5.91 ± 0.77
-do-	1.0N HCl	--[c]	--[c]
-do-	0.1N NaOH	--[c]	--[c]
peg coppt	water	0.535 ± 0.024	8.82 ± 0.39
pvp coppt	water	1.364 ± 0.036	22.47 ± 1.54

[a]mean ± standard deviation (n = 3).

[b]Phosphate buffer (0.01M) pH 7.4.

[c]Could not be determined because of rapid change in absorbance.

D. EVALUATION OF THE PHYSICAL CHARACTERISTICS OF THE TABLETS

The physical characteristics of tablets can affect the release rate of drug. Also parameters such as weight variation and friability must lie within an acceptable limit for the tablets to be acceptable. Therefore it was necessary to evaluate the physical characteristics of each batch of tablets T1 through T6. Table V shows the results obtained from these studies.

All the batches pass the official weight variation test as described (USP XXI) for this weight category ($\pm$10% variation is acceptable for tablets weighing 130 mg or less).

Similarly, the friability was extremely low for each batch of tablets although hardness was low for batches T3 and T4. In general, the maximum hardness imparted to the tablets decreased with increasing proportion of PVP coprecipitate. With 100 mg PVP per tablet the tablets produced were too soft to withstand any sort of handling and were therefore not taken for study.

On adding Accurel the hardness of T3 tablets increasd as expected. With 5 and 7.5 mg Accurel per tablet (T5 and T6 respectively) added in the formulation of T3 tablets the hardness increasd significantly ($P < 0.01$). However the difference between the hardness in tablets of batches T5 and T6 was not significant.

Addition of Accurel also prolonged the disintegration time of T3 tablets significantly ($P < 0.01$) and here again the difference between T5 and T6 tablets was not significant.

Table V. Physical characteristics of tablets.

	PARAMETER			
	Wt. Var. (mg)	Friability (%)	Disint. Time (min)	Hardness (kg)
T1	100-106	0.1	6.5±0.5	3.6±0.2
T2	107-111	0.1	12.8±1.8	3.6±0.4
T3	104-110	0.0	11.7±0.8	1.8±0.2
T4	106-112	0.0	14.2±1.0	1.6±0.1
T5	106-116	0.0	19.3±0.5	2.4±0.2
T6	112-113	0.0	19.3±1.0	2.6±0.1

[a]Range of weights, n = 10.

[b]For 10 tablets.

[c]Mean ± Standard Deviation, n = 6.

[d]Mean ± Standard Deviation, n = 5.

E. DISSOLUTION STUDIES

Tables VI through IX and figure 8 show the results obtained from the dissolution studies under non - sink conditions. In these studies 20 mg equivalent of nifedipine was taken in 1 liter of water at 37 degrees Celcius. From the results it is clear that the dissolution rate of the pure drug is extremely low. On the other hand the release rate of nifedipine from the commercially available Adalat soft - gelatin capsule is extremely high and plateau concentrations are reached between 10 and 20 minutes.

Among the test tablets the dissolution rate increased in the order T1 < T2 < T3 < T4, i.e., in the order of increasing fraction of PVP coprecipitate. With all of the tablets the dissolution rate was much higher than that of pure nifedipine powder. In the latter case only about 2 mg of the drug dissolved in 2.5 hours. The low dissolution rate was expected due to the poor solubility of nifedipine in the crystalline form which is about 11.5 mg/L of water at 37 degrees (96,98). The enhanced release of nifedipine from the four tablets is probably due to the presence of nifedipine in the amorphous form in the two coprecipitates. Although the exact physical nature of these dispersed systems was not investigated it is believed that reduction of particle size of the drug to the molecular and / or colloidal level is the primary contributing factor for this striking phenomenon (98).

The increase in dissolution rate cannot be ascribed to

Table VI. Dissolution of Adalat capsules[a].

Time (min)	Peak Area[b]	Conc[b] (mg/L)
10	44.5 ± 0.60	17.8 ± 0.24
20	45.9 ± 0.50	18.3 ± 0.20
30	46.8 ± 0.48	18.7 ± 0.19
45	46.9 ± 0.38	18.7 ± 0.15
60	47.8 ± 0.37	19.1 ± 0.15
90	47.32 ± 0.32	18.9 ± 0.13
120	47.35 ± 0.20	18.9 ± 0.08
360	47.60 ± 0.35	19.0 ± 0.14

[a]Two capsules (equivalent to 20 mg of nifedipine) per liter of water. The standard curve was plotted using the equation :

$$Y = 4.17X + 0.65 \qquad (r = 0.9998)$$

The dilution factor for the samples was 5/3.

[b]Mean ± standard deviation, n = 3.

Table VII. Dissolution of nifedipine powder[a].

Time (min)	Peak Height[b] (cm)	Conc[b] (mg/L)
10	2.5	0.26
20	4.2	0.44
30	5.7	0.59
60	9.1	0.95
90	12.8	1.33
120	15.7	1.63
150	20.0	2.08

[a]20 mg of powder / liter of water. Standard curve was drawn (dilution factor of samples was 5/3) using the equation:

$$Y = 9.629X + 0.586 \quad (r = 0.9914).$$

[b]Mean of 2 readings.

Table VIII. Dissolution of tablets[a] T1 and T2 under non - sink conditions[b].

	------- T1 ----------		----------T2----------	
Time (min)	Absorbance[c] (238nm)	Conc[c] (mg/L)	Absorbance[c] (238nm)	Conc[c] (mg/L)
10	0.139±0.005	3.82±0.14	0.223±0.009	6.13±0.25
20	0.185±0.006	5.08±0.16	0.309±0.007	8.48±0.18
30	0.214±0.004	5.88±0.11	0.323±0.005	8.86±0.14
45	0.240±0.003	6.59±0.07	0.340±0.003	9.34±0.07
60	0.259±0.002	7.12±0.06	0.350±0.009	9.60±0.25
90	0.283±0.006	7.76±0.16	0.354±0.005	9.72±0.14
120	0.298±0.004	8.17±0.11	0.366±0.008	10.04±0.22
180	0.320±0.003	8.78±0.07	0.376±0.007	10.32±0.18
480	0.358±0.006	9.83±0.16	0.388±0.003	10.66±0.07
18hr	0.371±0.002	10.18±0.06	0.388±0.003	10.66±0.07

[a]See Table I page 40 for composition of tablets.

[b]One tablet (equivalent to 20 mg nifedipine) per liter of water.

[c]Mean ± Standard Deviation (n = 3) of diluted samples (dilution factor = 5/3).

Table IX. Dissolution of tablets[a] T3 and T4 under non - sink conditions[b].

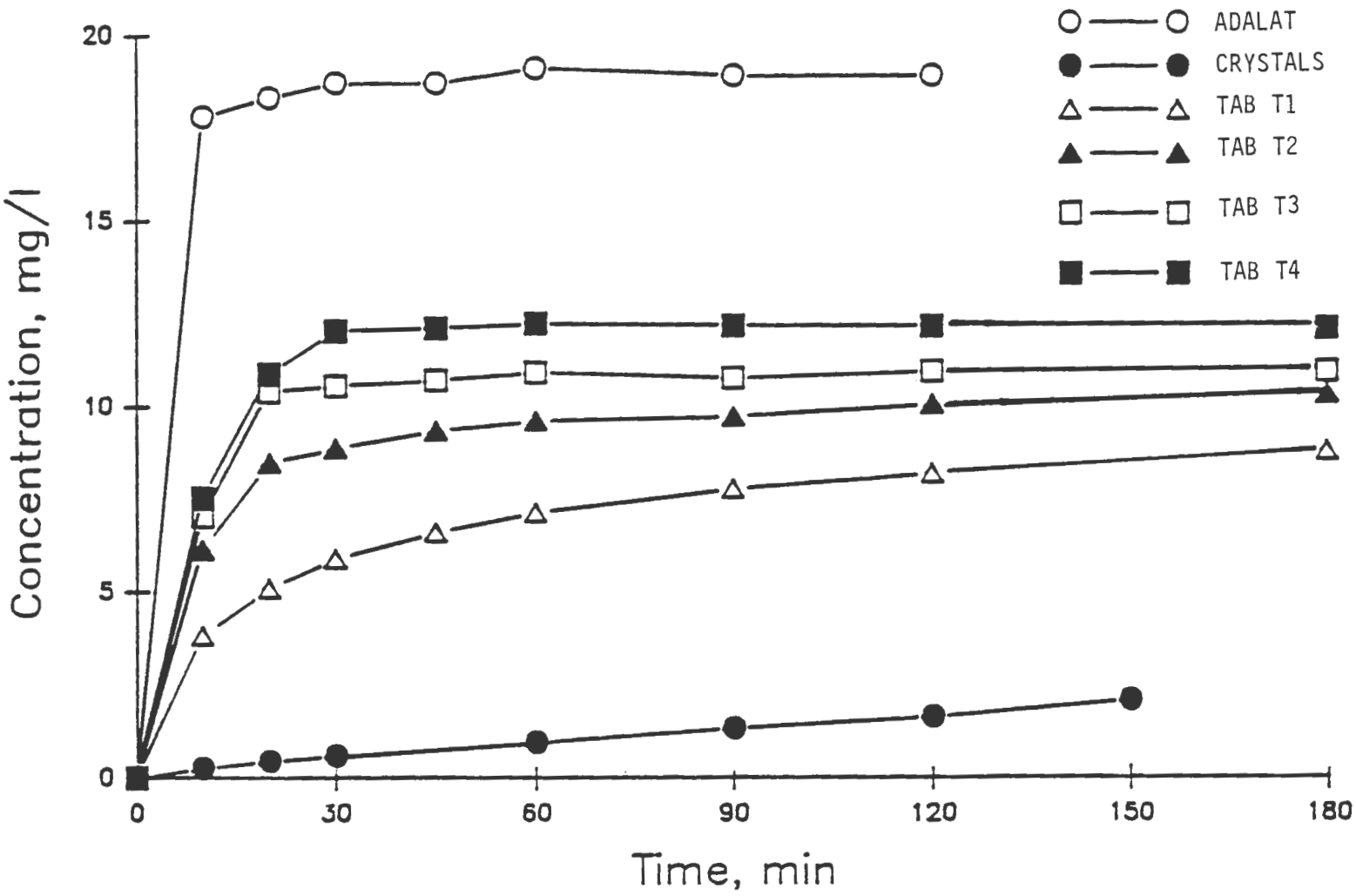
	T3		T4	
Time (min)	Absorbance[c] (238nm)	Conc[c] (mg/L)	Absorbance[c] (238nm)	Conc[c] (mg/L)
10	0.256±0.007	7.03±0.18	0.275±0.007	7.54±0.18
20	0.378±0.002	10.39±0.0	0.396±0.007	10.87±0.18
30	0.384±0.004	10.55±0.11	0.438±0.008	12.03±0.21
45	0.390±0.006	10.70±0.16	0.441±0.008	12.10±0.21
60	0.397±0.006	10.91±0.16	0.445±0.005	12.21±0.14
90	0.392±0.002	10.75±0.06	0.443±0.005	12.17±0.14
120	0.398±0.003	10.93±0.07	0.442±0.001	12.14±0.03
180	0.398±0.002	10.93±0.06	0.440±0.002	12.09±0.06
480	0.414±0.005	11.37±0.14	0.443±0.005	12.17±0.14

[a]For composition of tablets T3 and T4 see table I page 40.

[b]One tablet (equivalent to 20 mg of nifedipine) per liter of water.

[c]Mean ± Standard deviation (n = 3) of diluted samples (dilution factor = 5/3).

Fig. 8. Dissolution profiles of formulations under non - sink conditions.



increase in the solubility of nifedipine since the solubility at 37 degrees was not measured. Although an increase was found in the solubility of nifedipine in the coprecipitate systems at 25 degrees other authors have reported only a slight increase of the drug in aqueous solutions of PVP (96,98) at 37 degrees. Since the saturation concentrations achieved from the tablets (fig. 8) are in the range of the reported solubility of nifedipine (about 11 mg/L) in water at 37 degrees this argument is convincing.

A higher dissolution rate with higher PVP fraction can be explained by the observations of Sumnu (98) who found that in solid disperse systems of nifedipine in PVP (in the ratios 1:3 and 1:9) the drug stayed essentially in the amorphous state with no signs of crystallinity. On the other hand nifedipine - PEG coprecipitates, in the same ratios of drug and polymer, indicated presence of crystallinity.

Other factors that could account for this phenomemon are reduced surface tension on the drug particles (73), formation of soluble complexes with the polymer (33,34), and its dispersion form (11).

Previous studies on the dissolution behaviour of nifedipine coprecipitates have found that in these systems the concentration of nifedipine in the solution increases rapidly in the beginning, forming a supersaturated solution, and then decreases after half an hour due to crystallization of the drug (96,98). We did not observe any decrease in concentrations possibly due to the smaller amount of drug taken

per liter of the dissolution medium. In the reported studies 50 mg equivalent of nifedipine was taken in 500 ml of the medium while we used only 20 mg equivalent of the drug in 1L of water.

Tables X through XIII compare the results of dissolution of the tablets obtained from the UV and HPLC assays. The HPLC assay was performed on one sample per time point in the dissolution profile of each tablet. Therefore the concentrations obtained from the HPLC are compared with the corresponding concentrations obtained with the UV assay for each case. For this reason the concentrations in column 3 in the tables X through XIII are slightly different from the concentrations in column 3 and 5 in tables VIII and IX which are the means of 3 samples.

The difference in the results obtained by the two assay methods is negligible - about 2% for the four taken together. Since the UV assay was less cumbersome, more reproducible and much faster it was used for further dissolution studies.

Tables XIV and XV and figure 9 show the dissolution profiles of all the six tablets in "near sink" conditions. Sink conditions are approximated when the volume of the dissolution medium is five to ten times the saturation volume of the medium (38). Since in our studies a fraction of the tablet equivalent to about 4 mg of nifedipine was taken, and since the solubility of nifedipine has been reported to be about 11 to 12 mg/L at 37 degrees (also seen

Table X. Comparison of UV and HPLC assay results for dissolution of tablet T1.

Time (min)	Absorb (238 nm)	Conc (mg/L)	Peak Area[a]	Conc (mg/L)	Differ (%)
10	0.148H4	3.95	9.08	3.80	3.70
20	0.188	5.16	13.01	5.45	- 5.61
30	0.218	5.98	14.54	6.09	- 1.84
45	0.243	6.67	16.30	6.83	- 2.36
60	0.261	7.17	17.33	7.26	- 1.24
90	0.280	7.69	18.85	7.89	- 2.67
120	0.301	8.26	19.71	8.26	0.00
180	0.320	8.79	20.84	8.73	0.69
480	0.357	9.80	23.32	9.77	0.33
18 hr	0.369	10.13	23.91	10.02	1.09
Mean					- 0.78

[a]The standard curve was drawn using the equation:

$$Y = 3.979\ X + 0.207 \quad (r = 0.9999)$$

Dilution factor of samples = 5/3.

Table XI. Comparison of UV and HPLC assay results for dissolution of tablet T2.

Time (min)	Absorb (238 nm)	Conc (mg/L)	Peak Area[a]	Conc (mg/L)	Differ (%)
10	0.218	5.98	13.53	5.67	5.23
20	0.302	8.29	19.39	8.12	2.03
30	0.318	8.73	20.84	8.73	0.00
45	0.337	9.25	21.91	9.18	0.76
60	0.360	9.88	23.26	9.74	1.39
90	0.356	9.77	23.27	9.75	0.24
120	0.370	10.16	23.71	9.93	2.25
180	0.377	10.35	24.38	10.21	1.33
480	0.390	10.71	24.67	10.33	3.52
18 hr	0.394	10.82	24.76	10.37	4.15
Mean					2.09

[a]Standard curve same as for T1

Table XII. Comparison of UV and HPLC assay results for dissolution of tablet T3.

Time (min)	Absorb (238 nm)	Conc (mg/L)	Peak Area[a]	Conc (mg/L)	Differ (%)
10	0.251	6.89	16.28	6.47	6.09
20	0.380	10.43	24.39	9.70	6.99
30	0.384	10.55	25.98	10.33	2.08
45	0.391	10.73	26.60	10.58	1.40
60	0.390	10.71	25.94	10.32	3.64
90	0.390	10.71	26.36	10.48	2.15
120	0.401	11.01	26.97	10.73	2.54
180	0.400	10.98	27.12	10.79	1.73
480	0.415	11.39	27.85	11.08	2.72
Mean					3.26

[a]Standard curve was drawn using the equation :

$$Y = 4.191 X + 0.044 \quad (r = 0.9999)$$

Dilution factor of samples = 5/3.

Table XIII. Comparison of UV and HPLC assay results for dissolution of tablet T4.

Time (min)	Absorb (238 nm)	Conc (mg/L)	Peak Area[a]	Conc (mg/L)	Differ (%)
10	0.271	7.44	17.24	6.85	7.94
20	0.389	10.68	25.62	10.19	4.59
30	0.430	11.86	28.76	11.44	3.55
45	0.432	11.86	29.30	11.65	1.77
60	0.440	12.09	29.26	11.64	3.72
90	0.438	12.03	29.47	11.72	2.58
120	0.441	12.10	30.06	11.95	1.24
180	0.438	12.03	30.11	11.97	0.50
480	0.442	12.14	29.53	11.74	3.29
Mean					3.24

[a]Standard curve same as for T3.

Table XIV. Dissolution of tablets T1, T2 and T4 in "near sink" conditions.

Time (min)	Percent released		
	T1	T2	T4
10	25.2 ± 4.3	43.7 ± 0.9	65.2 ± 0.4
20	31.5 ± 0.2	55.2 ± 1.7	74.6 ± 1.4
30	36.7 ± 0.8	62.4 ± 2.8	80.1 ± 5.3
45	47.8 ± 1.5	68.2 ± 2.5	83.4 ± 2.7
60	48.9 ± 1.5	74.6 ± 3.6	85.0 ± 3.7
90	55.6 ± 1.3	77.1 ± 0.9	89.6 ± 6.5
120	61.2 ± 1.0	77.5 ± 0.8	92.7 ± 4.4
180	67.6 ± 1.0	83.0 ± 2.5	--
400	--	--	96.4 ± 8.1
540	92.6 ± 1.4	101.0 ± 3.3	--
Tab Wt[a]	4.07	4.01	4.05

[a]Weight (in mg) of fraction of tablet (equivalent of nifedipine) taken in 1 liter of water.

Table RXV. Dissolution of tablets T3, T5, and T6 in "near sink" condition.

Time (min)	Percent released		
	T3	T5	T6
10	65.6 ± 0.9	53.4 ± 1.2	43.8 ± 0.5
20	73.6 ± 3.5	65.0 ± 3.0	52.2 ± 1.5
30	76.5 ± 3.9	66.9 ± 0.8	60.2 ± 1.8
45	82.3 ± 2.7	74.8 ± 0.5	67.4 ± 1.1
60	82.4 ± 1.1	78.5 ± 0.6	72.4 ± 0.8
90	87.6 ± 1.1	85.1 ± 2.5	77.8 ± 2.6
120	87.7 ± 1.8	88.0 ± 1.5	85.5 ± 2.2
180	--	92.7 ± 1.5	87.6 ± 3.1
400	91.7 ± 0.7	--	--
460	--	98.4 ± 1.9	94.7 ± 3.5
Tab Wt[a]	4.03	3.83	3.67

[a]Weight (in mg) of fraction of tablet (equivalent of nifedipine) taken in 1 liter of water.

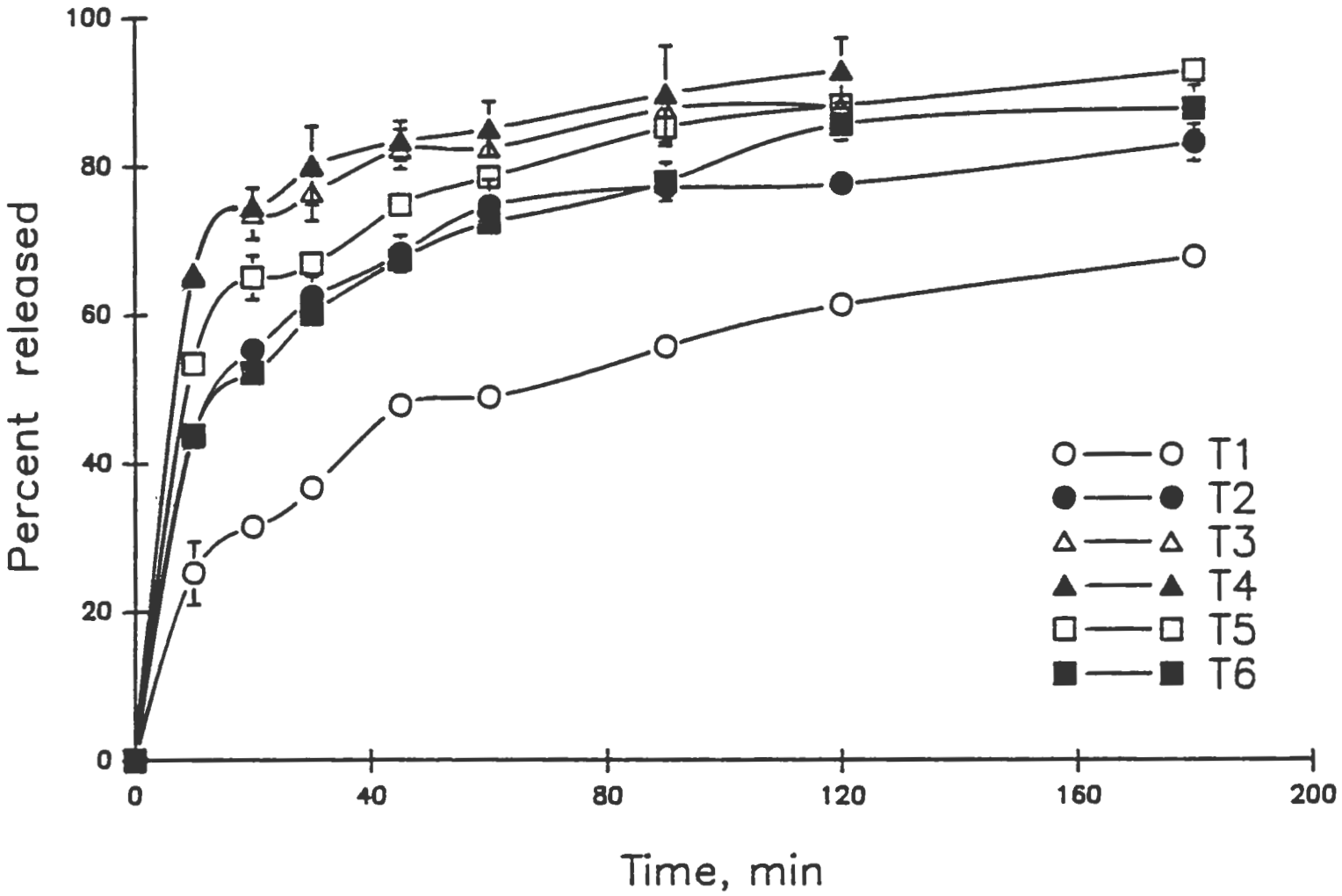
from figure 8), the volume of 1 liter of water taken in our studies was about 3 times the saturation volume. Hence it is appropriate to say that sink conditions were nearly achieved in these studies.

From fig. 9 it can be seen that the dissolution rates of tablets not containing Accurel polymer increase in the order T1 < T2 < T3 = T4. The dissolution rates of tablets T3 (containing 25% PEG coprecipitate and 75% PVP coprecipitate) and T4 (containing 5% PEG coprecipitate and 95% PVP coprecipitate) were not significantly different ($P > 0.05$) for 10, 20 and 30 minutes. For both of these tablets about 75% of the drug was released in the first 20 minutes. It was then decided to formulate a tablet which would release about 50% of the drug in 20 minutes but no more than 90% in 3 hours. For this we chose to modify the formulation of T3 using Accurel polymer. Our hypothesis was that addition of a small amount of this hydrophobic polymer would reduce the dissolution rate and bring it to the desired level.

In the first case (tablet T5) 5 mg of Accurel was added per tablet (total weight per tablet was 111 mg). As expected the dissolution rate decreased but still about 65% of the drug was released in 20 minutes and 93% was released in 3 hours.

In the second case (tablet T6) 7.5 mg of Accurel was added per tablet and for this tablet about 52% of the drug was released in 20 minutes and about 88% in 3 hours. Since the dose of commercially available nifedipine capsules is 10

Fig. 9. Dissolution profiles of formulations under "near - sink" conditions.



to 20 mg tablet T6 would provide a suitable dosage regimen if the in vivo release is similar to the in vitro results obtained from our studies.

The convenience with which the release can be modified from these tablets are encouraging although a zero order release was not seen at the small fraction of the polymer matrix. Further studies are needed with other proportions of PEG or PVP and nifedipine and with formation of bilayer tablets which would produce slower release from one half and quicker release from the other. In this way a higher concentration of Accurel or other rate controlling matrix substance can be used which may give a better control of release approaching zero - order.

Also, *in vivo* studies need to be done in order to better understand the relationship between the *in vitro* release and bioavailability.

V. CONCLUSIONS

1. The UV spectrophotometer at 238 nm was a sensitive, reproducible and reliable assay method for the quantification of nifedipine for the dissolution studies. Stability can be checked by the HPLC method which is also useful for the decomposition studies.

2. The photodegradation of nifedipine in solutions follows first order kinetics with a t_{90} of about 19 minutes in a normally lighted room in the absence of daylight.

3. In the pH range of 4.2 - 7.8 there is no appreciable difference in the rate of photodegradation of nifedipine. However, solutions kept in colored glassware and stored in a refrigerator are quite stable for at least one week.

4. The solubility of nifedipine in water is about 5 mg/L at 25 degrees Celcius. The solubility in phosphate buffer (pH 7.4) and 0.1 N HCl was not significantly different from that in water.

5. The tablets prepared with the various formulations had acceptable weight variation and friability. However tablets prepared with a high PVP fraction had low hardness.

6. Addition of 5% and 7.5% of Accurel increased the hardness and disintegration time.

7. The dissolution rate of tablets increased in the order of increasing fraction of PVP coprecipitate. Hence PVP is a better material than PEG for the enhancement of dissolution rate of nifedipine.

8. Accurel effectively retards the release of nifedipine from the homogeneously dispersed monolithic tablet. However the release rates at low Accurel concentrations do not exhibit zero - order or the square root of time pattern.

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