AN ABSTRACT OF THE THESIS OF

Soisurin Sartnurak for the degree of Doctor of Philosophy in Pharmacy presented on May 6, 1985

Title: Evaluation of Solid Dispersed Particles for Formulation of Oral Ibuprofen Tablets

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John M. Christensen, Ph.D.

Dissolution profiles of two commercial products (Motrin® and Rufen®) were analyzed and compared at 8 pH levels, ranging from pH 2.0 to pH 8.0. It was demonstrated, as expected, that the rate and extent of ibuprofen dissolution dissolution was pH dependent. In vitro dissolution characteristics of the ibuprofen solid dispersion formulations prepared by freeze-drying method with various proportions of excipients (theobroma oil, lecithin and PEG 20,000) were investigated at 3 pH levels - pH 2.0, 5.4, and 7.2. As the amount of theobroma oil increased from zero to 31%, the dissolution rate and the percent ibuprofen dissolved was decreased. Freeze-dried systems with a combination of lecithin and PEG 20,000 showed a slower dissolution rate and less amount of drug dissolved than the formulation with only PEG 20,000. The optimal ratio of drug to PEG 20,000 was 1:1. Solid dispersions of ibuprofen prepared by the freeze-drying method provided the highest dissolution rate and percentage of drug dissolved when compared with the direct

melting method, the solvent method or the physical-mixing method. Dissolution characteristics of the ibuprofen freeze-dried formulation (ratio of drug to PEG 20,000 1:1) were unaffected after storage in 98% relative humidity, but commercial formulation dissolution was drastically reduced.

Relative bioavailability of ibuprofen solid dispersed tablets were studied in rabbits after a single oral administration of 50 mg ibuprofen preparations. The freeze-dried solid dispersion formulation with ratio of drug to PEG 1:1 exhibited the greatest relative extent of absorption (129.50 $\pm$ 27.99% over control). Preparations with PEG 20,000 enhanced the extent of absorption when compared to the formulation of ibuprofen drug powder. There appeared no advantage in formulating ibuprofen in PEG by freeze-drying over the direct melting method. A slower rate of absorption of ibuprofen was obtained when the amount of theobroma oil was increased in the formulation.

EVALUATION OF SOLID DISPERSED PARTICLES FOR FORMULATION OF ORAL IBUPROFEN TABLETS

by

Soisurin Sartnurak

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Redacted for privacy

Dean of Graduate School

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EVALUATION OF SOLID DISPERSED PARTICLES FOR FORMULATION OF ORAL IBUPROFEN TABLETS

CHAPTER ONE

IN VITRO DISSOLUTION CHARACTERISTICS OF IBUPROFEN AND ITS SOLID DISPERSED PARTICLES

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ABSTRACT

Dissolution profiles of two commercially available products (Motrin® and Rufen®) demonstrated that the rate and extent of ibuprofen dissolution was pH dependent, as expected. In vitro dissolution characteristics of freeze-dried formulations with various proportions of excipients (theobroma oil, lecithin and PEG 20,000) were investigated at 2 pH levels - pH 2.0, 5,4 and 7.2. The dissolution rate and percentage ibuprofen dissolved decreased as the amount of theobroma oil increased from zero to 31%. Freeze-dried products with the presence of both lecithin and PEG 20,000 showed a slower dissolution and less amount of drug dissolved than the formulation with only PEG 20,000 present. The effect of increasing the weight fraction of PEG 20,000 on the dissolution rate of ibuprofen was also investigated. Data showed that the optimal ratio of drug to PEG 20,000 was 1:1. Results from in vitro dissolution of solid dispersions of ibuprofen prepared by other methods such as a direct melting method, a solvent method and a physical mixing method, indicated that the

freeze-dried product provided the highest rate and extent of dissolution for the time studied. However, these differences were within 10% of the direct melting method. Ibuprofen freeze-dried formulation (ratio of drug to PEG 20,000 1:1) was subjected to a humidity aging study along with commercial formulations of ibuprofen (Motrin, Rufen and Advil). Dissolution characteristics of the PEG 20,000 freeze-dried formulation were unaffected after storage in 98% relative humidity, while the commercial products showed a decrease in the rate and extent of dissolution.

INTRODUCTION

Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent, used for the treatment of osteoarthritis, rhumatoid arthritis and mild to moderate pain. It was first introduced in England in 1964 and in the United States in 1974. Ibuprofen has been classified as being prone to bioavailability problems by the Food and Drug Administration (FDA) (Approved Prescription Drug Products with Therapeutic Equivalence Evaluations, 1981). It is a poorly soluble, weakly acidic compound whose rate and extent of dissolution can be expected to be pH dependent. Ibuprofen, with its low solubility in water has demonstrated dissolution rate-limited absorption (Steady et al., 1983). With these characteristics, ibuprofen is a difficult drug to formulate into a good solid oral dosage form. Sugar coated ibuprofen tablets are the currently manufactured products. The technique of sugar coating is time consuming and expensive. Polyethylene glycol (PEG) has been reported to enhance drug dissolution of drug products (Chiou and Smith, 1971; Geneidi and Hamacher, 1980). Tablet formulation of ibuprofen with PEG may be an easier and less expensive method of preparing quality solid oral dosage forms of ibuprofen. The technique, "freeze-drying" is proposed for preparing solid dispersion systems of drug and excipients which will provide an increase in the dissolution rate and consequently drug absorption.

The objective of this study was to investigate in vitro dissolution characteristics of solid dispersions of ibuprofen in PEG prepared by freeze-drying and to compare the results with those prepared by a direct melting method, a solvent method and a physical mixing method at three different pH levels - pH 2.0, 5.4 and 7.2. Dissolution profiles of two commercial products (Motrin and Rufen) were also analyzed and compared at 8 pH levels ranging from pH 2.0 to pH 8.0. The excipients of choice for preparing freeze-dried solid dispersions of ibuprofen were selected to make the tablets containing 100 mg of drug. These tablets were used in a humidity aging study along with other commercial products (Motrin®, Rufen® and Advil®).

Since drug absorption and its bioavailability are highly dependent on having the drug in the dissolved state, this freeze-drying technique is believed to be a potential tool to formulate not only a fast-release dosage form of poorly water soluble drug.

BACKGROUND MATERIAL ON DISPERSED SYSTEMS

When a drug is administered orally, it first must be dissolved in the gastro-intestinal fluids before drug transport can take place across a membrane into the systemic circulation. The drug is then distributed to various parts of the body where it may be stored, be metabolized, exert a pharmacological action or be excreted. Transfer of drug from the site of administration to the bloodstream is called absorption. For drugs whose gastrointestinal absorption is rate limited by dissolution, reduction of the particle size generally increases the dissolution rate and thereby the rate of absorption and often the total bioavailability (Levy, 1963; Fincher, 1968). This commonly occurs for drug with poor water solubility. For example, the therapeutic dose of griseofulvin was reduced 50% by micronization (Duncan et al., 1962) and it also produced more constant and reliable blood concentrations. The commercial dose of spironolactone was also decreased to half by just a slight reduction of particle size (Levy, 1962). Such enhancement of drug absorption could further be increased several folds if a micronized product was used (Levy, 1962; Bauer et al., 1962).

Particle size reduction is usually achieved by: (a) conventional trituration and grinding; (b) ball milling; (c) fluid energy micronization; (d) controlled precipitation by change of solvent or temperature, application of

ultrasonic waves (Scheikh et al., 1966; Hem et al., 1967; Skauen, 1967), and spray drying (Kornblum and Hirschorn, 1970); (e) administration of liquid solutions from which, upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles (Levy, 1963); and (f) administration of water-soluble salts of poorly soluble compounds, from which the parent drug may precipitate in ultrafine particles in gastro-intestinal fluid. Although reduction of particle size can be easily and directly accomplished by the first four methods (a-d); the resulting fine particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of fine particles due to their increased surface energy and the subsequent stronger van der Wall's attraction between nonpolar molecules. This was demonstrated by Lin et al., (1968), who showed that in vitro dissolution rates of micronized griseofulvin and gluthethimide were slower than those for their coarser particles. However, micronized griseofulvin was reported by Chiou and Riegelman (1969) to increase in vitro dissolution rate. Another inherent disadvantage of pure fine powders of poorly soluble drugs is their poor wettability in water. Wetting of powders is the first step for drug to dissolve and sometimes disperse in fluids (Lachman et al., 1970). Furthermore, drugs with plastic properties are difficult to subdivide by method a-c.

They have more tendency to stick together, even if fine powders can be produced by controlled precipitation.

Theoretically, the solvent method (c) seems to be an ideal approach in achieving particle-size reduction. However, it is not frequently employed in the commercial market due to difficulties in selection of a nontoxic solvent, limitation to drugs with a low dose, and high cost of production. Water-soluble salts of many poorly soluble acidic or basic drugs have been widely used clinically in solid dosage forms. However, it may be hard to obtain water-soluble salt forms. In addition, it has been shown that sodium or potassium salts may react with atmospheric carbon dioxide and water to precipitate poorly soluble parent compounds. This occurs especially on the outer layer of a dosage form and thereby retards rates of dissolution and absorption. This precipitation effect is believed to be responsible for slower in vitro dissolution rates and lower novobiocin plasma levels in dogs following oral administration of its soluble sodium salt, rather than the less soluble amorphous form of the parent compound (Mullins and Macek, 1960). The reported failure to obtain a clinical response from three commercial capsule dosage forms containing sodium diphenylhydantoin may have the same cause (Feinberg, 1969). In addition, the alkalinity of some salts may cause epigastric distress following administration (Goodman and Gilman, 1983).

In 1961, a unique approach to reduce particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi and Obi (1961). They proposed formation of a eutectic mixture of poorly soluble drug (such as sulfathiazole) with a phyisologically inert, easily soluble carrier (such as urea). The eutectic mixture was prepared by melting a physical mixture of drug and carrier, followed by a rapid solidification. Upon exposure to aqueous fluid, the active drug was expected to be released into the fluids as fine, dispersed particles because of the fine dispersion of drug in the solid eutectic mixture and rapid dissolution of the soluble matrix. Levy (1963) and Kanig (1964) subsequently noted the possibility of using a solid solution in which a drug is dispersed molecularly in a soluble carrier.

in 1965, Tachibana and Nakamura (1965) reported a novel method for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers such as polyvinylpyrrolidone. They dissolved the drug and polymer carrier in a common solvent and then evaporated the solvent completely. A colloidal dispersion was obtained when the coprecipitate was exposed to water. Mayersohn and Gibaldi (1966) also demonstrated that the dissolution rate of griseofulvin could be markedly enhanced when dispersed in polyvinylpyrrolidone by the same solvent method. The apparent solubility and rate of solution from compressed

tablets containing polyvinylpyrrolidone were found to be greatly increased if sulfathiazole was previously coprecipitated with PVP (Simonelli et al., 1969). The increase noted was found to be a function of the chain length of the PVP used as a coprecipitate and the sulfathiazole to PVP weight ratio of the concentration powder mixture used to compress the tablet.

The dissolution rates of chloramphenicol-urea solid dispersion system were investigated by Goldberg, et al., (1966). Solubility studies indicated that urea increased significantly the solubility of chloramphenicol. The authors suggested that particle size reduction in this mixture played an important role in enhancing dissolution. More recently, a number of poorly water-soluble drugs were studied as a solid dispersion in physiologically innert water-soluble carriers as a potential means to increase their dissolution rates and oral absorption. Enhancement occurred digitoxin (Chiou and Riegelman, 1971), hydrocortisone (Chior and Riegelman, 1971), prednisone (Chiou and Riegelman, 1971), reserpine (Stupak and Bates, 1972), digoxin (Ampolsuk et al., 1974), chloramphenicol (Maulding, 1982), coumarin (Geneidi et al., 1978), tolbutamide (Kauer et al., 1980), indomethacin (Ford and Rubinstein, 1980), glyburide (Geneidi et al., 1980), and phenytoin (Stavchansky and Gowan, 1984). Several carriers have been employed to prepare solid dispersions. The most

successful include polyethylene glycols, urea, dextrose, citric acid, succinic acid, and polyvinylpyrrolidone.

It is believed that this field of pharmaceutical technology will play an important role in increasing dissolution absorption and therapeutic efficacy of drugs. In addition to absorption enhancement, the dispersion technique may have numerous pharmaceutical applications which remain to be further explored. It is possible that such a technique can be used to obtain a homogenous distribution of a small amount of drug at solid state, to stabilize unstable drugs, to dispense liquid compounds, to formulate a fast-release dose, and to formulate sustained-release or prolonged-release regimens of soluble drugs by using poorly soluble or insoluble carriers.

The term "solid dispersions" as used in this study refers to the dispersion of one or more active ingredients in an innert carrier or matrix at solid state prepared by a melting (fusion), solvent or melting-solvent method. Freeze-drying (lyophilization) is proposed in this study as a new method of preparing solid dispersions. The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi (1966). The term "co-precipitates" has also been frequently used to refer to those preparations obtained by the solvent methods such as co-precipitates of sulfathiazole-polyvinylpyrrolidone (Simonelli et al., 1969) and reserpine-polyvinylpyrrolidone

(Stupak and Bates, 1972). Since the dissolution rate of a component from a surface is affected by the second component in a multiple component mixture (Higuchi, 1967), the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, using a water-soluble carrier results in fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of drug from the matrix.

The melting or fusion method was first proposed by Sekiguchi and Obi (1961) to prepare fast-released solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized and sieved. Such a technique was subsequently employed with some modification by Goldberg, et al., (1966a, 1966b, 1966c), and Chiou and Riegelman (1969). To facilitate faster solidification, the homogenous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The solidified masses of drug-polyethylene glycol polymer systems were often found to require storage of one or more days in a desiccator at ambient temperatures for hardening and ease of powdering (Chiou and Riegelman, 1969). Some systems, such as

griseofulvin and citric acid, were found to harden more rapidly if kept at 37°C or higher temperatures (Chiou and Riegelman, 1969; Guillory et al., 1969).

The main advantages of this direct melting method are its simplicity and economy. In addition, supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature (Moore, 1983a). Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification. Similarly, a much finer dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used (Moore, 1983a). The disadvantage is that many substances, either drugs or carriers, may decompose, or carriers may decompose or evaporate during the fusion process at high temperature. For example, succinic acid, used as a carrier for griseofulvin (Goldberg et al., 1966), is quite volatile and may also partially decompose by dehydration near its melting point (The Merck Index, 1976). Melting under vacuum or a chamber of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system (Moore, 1983b). By proper control, the melting point (the temperature at which the mixture completely melts) of a binary system may be much lower than

the melting points of its two components. Under such a condition, this simple melting method can still be used to prepare solid dispersions of steroids (Chiou and Reigelman, 1971; Maulding, 1978), digitoxin (Chiou and Reigelman, 1971), chloramphenicaol (Maulding, 1978), nitrofurantoin, ethotoin, coumarin (Geneidi et al., 1978), griseofulvin tolbutamide (Kaur et al., 1980), and dicumarol (Ravis and Chen, 1981).

The solvent method has been used for a long time in preparation of solid solutions, mixed crystals, organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. This method was used to prepare solid dispersions of several drugs, such as β-carotene-polyvinylpyrrolidone (Tachibana and Nakamura, 1965), steroid-lactose (Johansen and Moller, 1978) reserpine-polyvinylpyrrolidone (Stupak and Bates, 1972), sulfathiazole-polyvinylpyrrolidone (Simonelli et al., 1969), griseofulvin-polyethylene glycol and tolbutamide-polyethylene glycol (Kaur et al., 1980).

The main advantage of the solvent method is that thermal decomposition of drugs or carrier can be prevented because of the low temperature required for evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effects of the supposedly negligible amount

of the solvent on the chemical stability of the drug, selection of a common volatile solvent, and difficulty of reproducing crystal forms. The melting-solvent method was used to demonstrate that 5-10% (w/w) of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property (Chiou and Smith, 1971). Hence, it is possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, obtained below 70°C, without removing the liquid solvent. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. The polymorphic form of the drug precipitated in solid dispersion may be affected by the liquid solvent used. From a practical standpoint this method is only limited to drugs with a low therapeutic dose, eg., below 50 mg. The feasibility of this method was demonstrated on spironolactone-polyethylene glycol 6000 and griseofulvin-polyethylene glycol 6000 system (Chiou and Riegelman, 1971).

Formation of solid dispersions by freeze-drying a drug and carrier mixture is proposed in this study as a new way to prepare solid dispersions. Using this method, decomposition or evaporation of drugs or carriers can be prevented. The main disadvantage of this method is the high cost of preparation. Freeze drying (lyophilization) is a

process of drying which involves freezing of a medium and removal of volatile solvent by sublimation or desorption from a solid surface. This process has been employed to dry some pharmaceutical products containing antibiotics, hormones, enzymes and some parenteral drugs. This method has been used to prepare solid dispersions of tolbutamide and phenylbutazone (Suvanakoot, 1984). Solid dispersions of either drug in polyethylene glycol 20,000 prepared by the freeze-drying method showed greater dissolution rates at both pH 5.4 and 7.4 compared to those prepared by using direct melting, solvent method or physical mixing method. Dissolution rates of both drugs were greater as the ratio of drug to polyethylene glycol 20,000 was reduced (Suvanakoot, 1984).

EXPERIMENTAL

Materials

Ibuprofen, U.S.P.[1] and commercial 400 mg[2] and 200 mg[3] ibuprofen tablets were used in the study. All other chemicals - potassium phosphate monobasic[4], sodium phosphate dibasic[5], polyethylene glycol 20,000[6] theobroma oil[7], lecithin[8], Avicel PH102[9], granulated mannitol[10], cornstarch[11], Ac-di-sol[12], magnesium stearate[13], stearic acid[14], Cab-o-sil[15], sodium laurylsulfate[16] -- were analytical grade and used without further purification. All water was deionized and decarbonated before use.

Preparation of Ibuprofen Solid Dispersions

Direct Melting Method. Ibuprofen and polyethylene glycol 20,000 (ratio of 1:1) were accurately weighed. They were physically mixed and then heated directly with constant stirring to between 60° and 65°C on a hot plate until completely melted. To facilitate solidification the melted mixture was then poured in the form of a thin layer onto a glass slab which was cooled by blowing cold air on the opposite side of the slab. The solidified mass of the mixture was then stored for one day in a desiccator at room temperature for hardening. The final solid mass was crushed, and pulverized using a mortar and pestle. The powder was then sieved to obtain particle size range from 20 to 80 mesh.

Solvent Method. Ibuprofen and polyethylene glycol 20,000 (ratio 1:1) was physically mixed and then dissolved in 100 ml of ethyl alcohol. The solution was evaporated directly on a hot plate with constant stirring until Until formation of ethyl alcohol vapor bubbles were no longer observed. The transparent viscous liquid obtained was allowed to solidify by cooling in a cold air stream. The solidified mass was then placed in a vacuum chamber to remove the last traces of ethyl alcohol. The dried product was crushed, pulverized and sieved to obtain a particle size range from 20 to 80 mesh.

Physical Mixing Method. Appropriate amounts of ibuprofen and polyethylene glycol 20,000 (ratio of 1:1) were accurately weighed and mixed. The mixture was ground together using a mortar and pestle. The resulting powder was then passed through a sieve to obtain particle size range from 20 to 80 mesh.

Freeze-drying Method. The main formulation for freeze-dried product was:

A.	Ibuprofen	10 g
	Theobroma oil	10 g
B.	Lecithin	2 g
	Water	30 g
C.	Polyethylene glycol 20,000 (PEG 20,000)	10 g
	Water	

Preparation was as follows: Theobroma oil was melted

over a water bath at 40°C, ibuprofen was then added and stirred well. PEG 20,000 was dissolved in the water and this mixture was heated on a water bath to about 65°C. Lecithin was also dissolved in the water at 65°C, and this solution was added to PEG 20,000 solution. This mixture was stirred well until the temperature reached 40°C. This well-stirred aqueous phase was slowly added to the oil phase with continued stirring on the water bath at 40°C for about 10 minutes. The dispersion product was then removed from the bath and homogenized using a hand homogenizer[17] four times. The final product was poured in the form of a thin layer into a vacuum flask. This flask was then transferred into a tank consisting of a mixture of acetone[18] and dry ice in order to pre-freeze the dispersion. The flask was removed and put in a vacuum freeze-dryer[19] to lyophilize for 24 hours. The solidified product was crushed, ground and sieved to obtain the particle size range of 20 to 80 mesh. The excipients were varied from (a) theobroma oil 0 to 10 g, (b) lecithin 0 to 4 g with no theobroma oil present in the formulations, (c) using 33.3%, 50%, 60% and 66.7% of polyethylene glycol 20,000 alone as an excipient. The complete formulations of ibuprofen solid dispersion systems are presented in appendix 1-9.

In Vitro Dissolution Studies

Dissolution profiles of ibuprofen from different solid dispersions were obtained. The United States Pharmacopeia

XX (U.S.P. XX) rotating basket dissolution test[20] was used to perform the dissolution studies. A preparation was placed into a wire-mesh dissolution basket[21] at 37°C (0.5°C) contained in the required 1000 ml resin flask. Samples were collected at 0, 10, 20, 30, 45 minute, 1 hour, 2, 3, 4, and 6 hours. Dissolution samples (3.0 ml) were collected and the same volume was replaced using temperature equilibrated dissolution medium. Samples were filtered and diluted prior to assay for ibuprofen concentrations using an ultraviolet spectrophotometer[23] at 221 nm. Dissolution profiles of solid dispersions prepared by melting method, solvent method, physical mixing method and freeze-drying method were obtained at pH 2.0, 5.4 and 7.2. Dissolution characteristics of commercial ibuprofen tablets (Motrin® and Rufen®) were evaluated in ten different pH buffer solutions - pH 3.0, 4.0, 5.2, 5.4, 5.6, 6.0, 6.4, 6.8, 7.2 and 8.0.

Analytical Method. Samples from dissolution studies were filtered and suitably diluted with dissolution medium. They were then assayed spectrophotometrically for ibuprofen concentrations at 221 nm. At these wavelengths, polyethylene glycol 20,000, and lecithin exhibited some UV absorbance. This was corrected using the appropriate blank solutions to obtain the right absorbance for the samples.

Standard Curves. Standard ibuprofen solutions were prepared by diluting various amounts of an ibuprofen stock solution with an appropriate dissolution medium. The UV

absorbance for each sample was measured at 221 nm. At least six data points were used to construct the standard curves. The percentage of drug dissolved from each preparation at predetermined times during the dissolution tests were calculated from the linear relationship of UV absorbance versus standard ibuprofen concentrations. Typical correlation coefficient values were 0.999 with average inversely estimated concentrations being 100.52% of theory with a 2.36% coefficient of variation.

Humidity-Aging. A formulation of solid dispersion of ibuprofen that gave the best dissolution profiles in vitro was used to make 100 mg tablets (complete formulation of tablets is presented in appendix 10) by using a single-punch tableting machine.[24] These tablets as well as commercial ibuprofen tablets (Motrin®, Rufen® and Advil®) were subjected to humidity aging at 75% and 98% relative humidity at ambient temperature for 14 days. Standard all-glass aquariums[y] (50 cm long, 26 cm wide, 30 cm high) with glass covers were used as humidity tanks. A saturated solution of sodium chloride (provided 75% relative humidity) and that of potassium sulfate (provided 98% relative humidity) were prepared in deionized, distilled water and placed in the bottom of the tank to a depth of 2 to 3 cm (approximately 2.6 liters). A galvanized rack was placed in the tank so as to hold aluminum foil lined petri dishes 7 cm above the surface of the solution. Air circulation was maintained

within the tank by means of a small electrical fan. Humidity within the chamber could be calculated accurately in terms of the specific salt solution used and the temperature maintained (International Critical Tables, 1926). It was also monitored using a wet and dry bulb (Mason type) hygrometer.[25] No attempt was made to regulate the temperature within the tank as temperature variability within the laboratory during the study was small, and temperature dependence of relative humidity using sodium chloride solution and potassium sulfate solution is low (International Critical Tables, 1926). The tank was made airtight by the use of foam strips impregnated with petrolatum as a seal between the glass cover and the aquarium.

Tablets were subjected to the aging process by placing them in aluminum foil lined petri dishes without covers, taking care that no tablets touched another. Humidity and temperature were monitored daily. At day 3, 7 and 14, tablets were taken to study their dissolution characteristics in buffer solution pH 7.2 and the results were compared.

RESULTS AND DISCUSSION

Typical standard curves for ibuprofen data at pH 2.0, 3.0, 4.0, 4.8, 5.2, 5.4, 5.6, 6.0, 6.4, 6.8, 7.2 and 8.0 as determined by using linear regression are shown in Figures I.1 to I.12 and Tables I.1 to I.12, respectively. The correlation coefficient for each linear fit was in the range of .9992 to .9999 with the coefficient of variation ranging from 0.80 to 3.5.

Dissolution characteristics of two commercial 400 mg ibuprofen products (Motrin® and Rufen®) were evaluated in nine different pH solutions ranging from pH 2.0 to pH 8.0. The data are displayed in Figures I.13-I.14 and Tables I.13-I.20. Disintegration of these tablets occurred between 5 and 10 minutes after placing them in the rotating basket dissolution apparatus at each pH. The rate and extent of ibuprofen dissolution is pH dependent as clearly shown in Figures 15-16 in which the percent of labeled amount of ibuprofen dissolved in 1 hour and 6 hours were plotted against pH levels for both Motrin and Rufen products. Dissolution profiles for both commercially available products clearly indicate that at pH 8.0 and pH 7.2, complete dissolution of drug occurs within 30 minutes. At pH 6.8, 6.4 and 6.0, greater than 50% of dissolution of drug occurs within 30 minutes. At pH 8, 7.2 and 6.8, about 90% of drug dissolved within 1 hour, and within 3 hours at pH

Table I.1 Typical Standard Curve Data for Ibuprofen Concentration at pH 2.0 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	1.00	0.090	1.009	100.94
2	2.00	0.131	1.987	99.36
3	3.00	0.173	2.989	99.63
4	5.00	0.257	4.992	99.84
5	7.00	0.344	7.067	100.95
6	10.00	0.464	9.929	99.29
7	12.00	0.552	12.027	100.93
Mean				100.0
S.D.				0.7
%C.V.[d]				0.7

[a] R^2 = .9999

[b] Inversely estimated concentration = -1.137 + 23.848 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

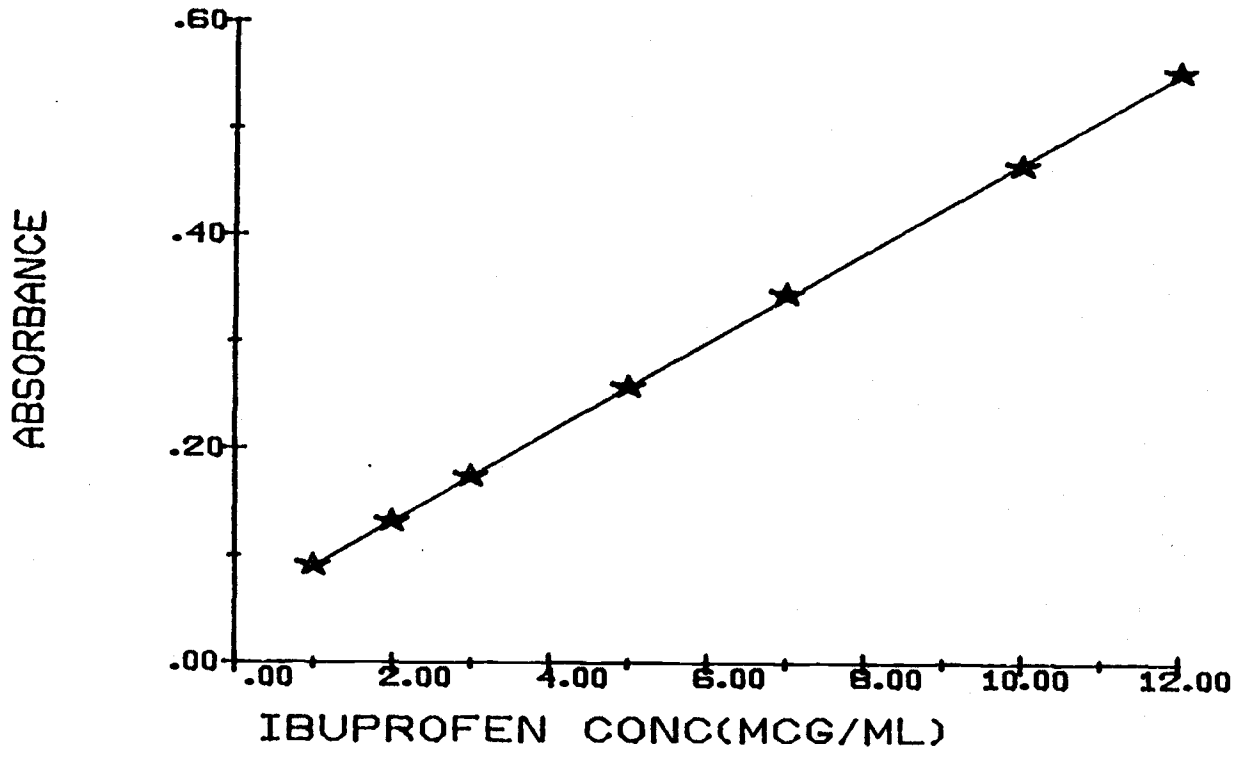

Figure I.1 Typical standard curve for ibuprofen concentration vs. absorbance at pH 2.0 estimated using linear regression

Table I.2 Typical Standard Curve Data for Ibuprofen Concentration at pH 3.0 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	2.50	0.100	2.573	102.92
2	5.00	0.194	4.876	97.52
3	7.00	0.287	7.155	102.21
4	10.00	0.397	9.850	98.50
5	12.00	0.487	12.055	100.46
6	15.00	0.606	14.970	99.80
7	17.00	0.687	16.955	99.74
8	20.00	0.814	20.067	100.33
Mean				100.2
S.D.				1.8
%C.V.[d]				1.8

[a] R^2 = .9997

[b] Inversely estimated concentration = .123 + 24.501 X (Absorbance)

[c] % Theory

[d] % Coefficient of variation = (S.D./Mean) X 100

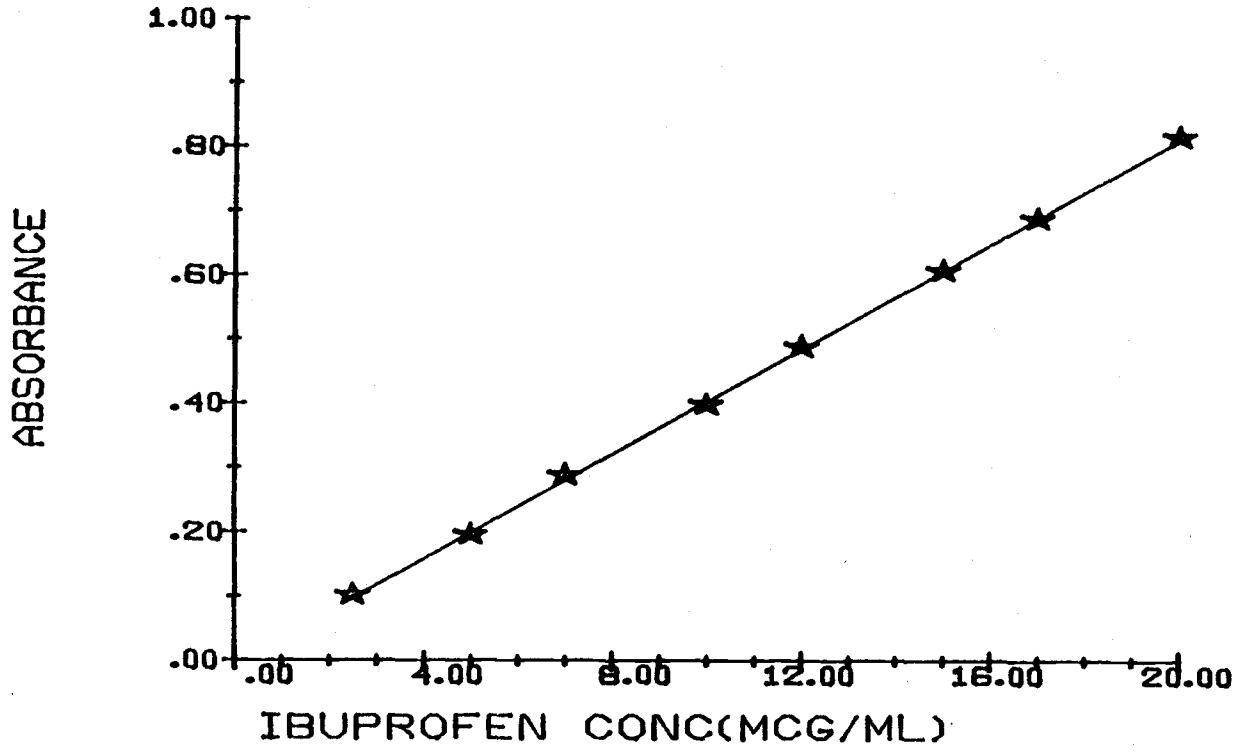

Figure I.2 Typical standard curve for ibuprofen concentration vs. absorbance at pH 3.0 estimated using linear regression

Table I.3 Typical Standard Curve Data for Ibuprofen Concentration at pH 4.0 Estimated Using Linear Regression[a]

Std. No.	Conc. (μg/ml)	Absorbance	Inv. Est. Conc.[b] (μg/ml)	% Theory[c]
1	2.50	0.099	2.560	102.40
2	5.00	0.199	4.984	97.68
3	7.00	0.284	7.045	100.64
4	10.00	0.401	9.881	98.81
5	12.00	0.490	12.038	100.32
6	15.00	0.607	14.874	99.16
7	17.00	0.697	17.056	100.33
8	20.00	0.821	20.062	100.31
Mean				100.2
S.D.				1.1
%C.V.[d]				1.1

[a] R^2 = .9998

[b] Inversely estimated concentration = .160 + 24.241 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

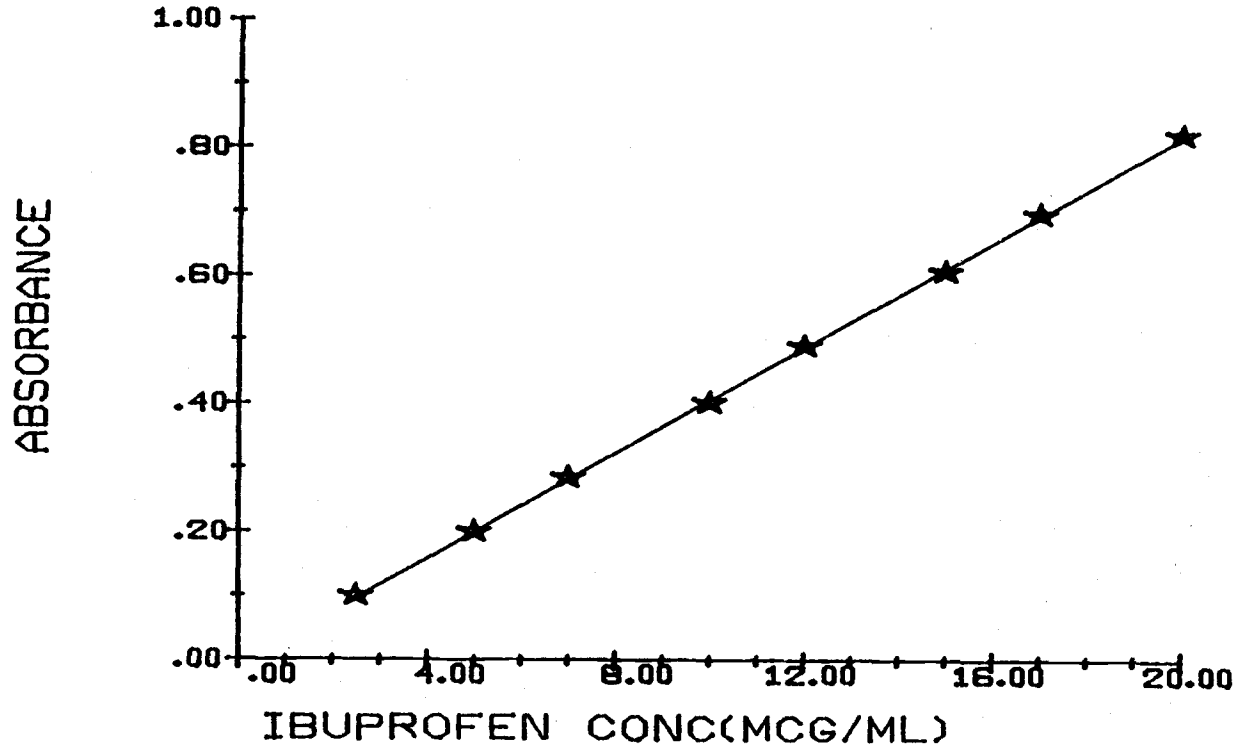

Figure I.3 Typical standard curve for ibuprofen concentration vs. absorbance at pH 4.0 estimated using linear regression

Table I.4 Typical Standard Curve Data for Ibuprofen Concentration at pH 4.8 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	2.50	0.070	2.548	101.95
2	5.00	0.167	4.918	98.35
3	7.00	0.251	6.969	99.56
4	10.00	0.372	9.924	99.24
5	12.00	0.468	12.268	102.24
6	15.00	0.578	14.955	99.70
7	17.00	0.658	16.908	99.46
8	20.00	0.785	20.010	100.05
Mean				100.1
S.D.				1.3
%C.V.[d]				1.3

[a] R^2 = .9996

[b] Inversely estimated concentration = .839 + 24.421 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

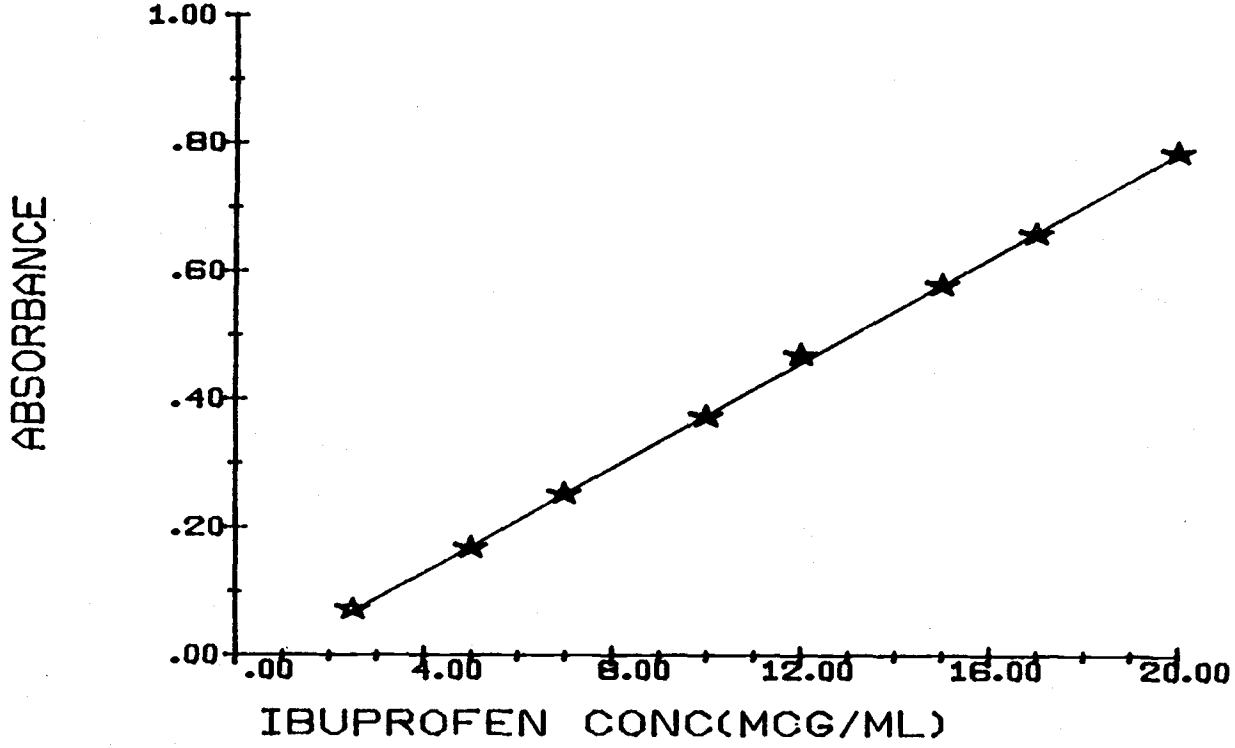

Figure I.4 Typical standard curve for ibuprofen concentration vs. absorbance at pH 4.8 estimated using linear regression

Table I.5 Typical Standard Curve Data for Ibuprofen Concentration at pH 5.2 Estimated Using Linear Regression[a]

Std. No.	Conc. (μg/ml)	Absorbance	Inv. Est. Conc.[b] (μg/ml)	% Theory[c]
1	2.50	0.109	2.501	100.05
2	5.00	0.224	5.131	102.62
3	7.00	0.295	6.755	96.50
4	10.00	0.438	10.025	100.25
5	12.00	0.529	12.106	100.88
6	15.00	0.655	14.987	99.91
7	17.00	0.747	17.091	100.54
8	20.00	0.870	19.904	99.52
Mean				100.0
S.D.				1.7
%C.V.[d]				1.7

[a] R^2 = .9996

[b] Inversely estimated concentration = .009 + 22.868 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

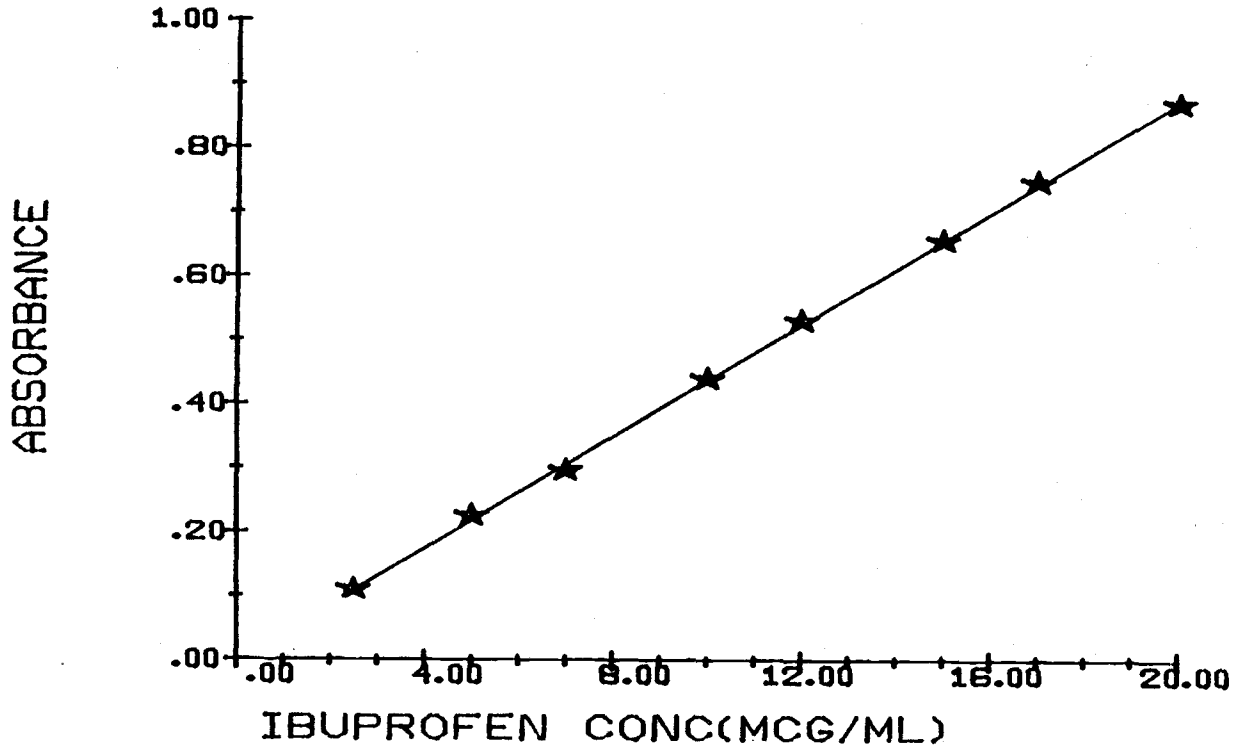

Figure I.5 Typical standard curve for ibuprofen concentration vs. absorbance at pH 5.2 estimated using linear regression

Table I.6 Typical Standard Curve Data for Ibuprofen Concentration at pH 5.4 Estimated Using Linear Regression[a]

Std. No.	Conc. (g/ml)	Absorbance	Inv. Est. Conc.[b] (g/ml)	% Theory[c]
1	1.00	0.075	0.967	96.73
2	2.00	0.117	1.982	99.12
3	3.00	0.158	2.973	99.11
4	5.00	0.242	5.003	100.06
5	7.00	0.328	7.082	101.17
6	10.00	0.448	9.982	99.82
7	12.00	0.536	12.108	100.90
8	15.00	0.654	14.960	99.73
9	17	0.736	16.942	99.66
Mean				99.6
S.D.				1.3
%C.V.[d]				1.3

[a] R^2 = .9999

[b] Inversely estimated concentration = -.854 + 24.167 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

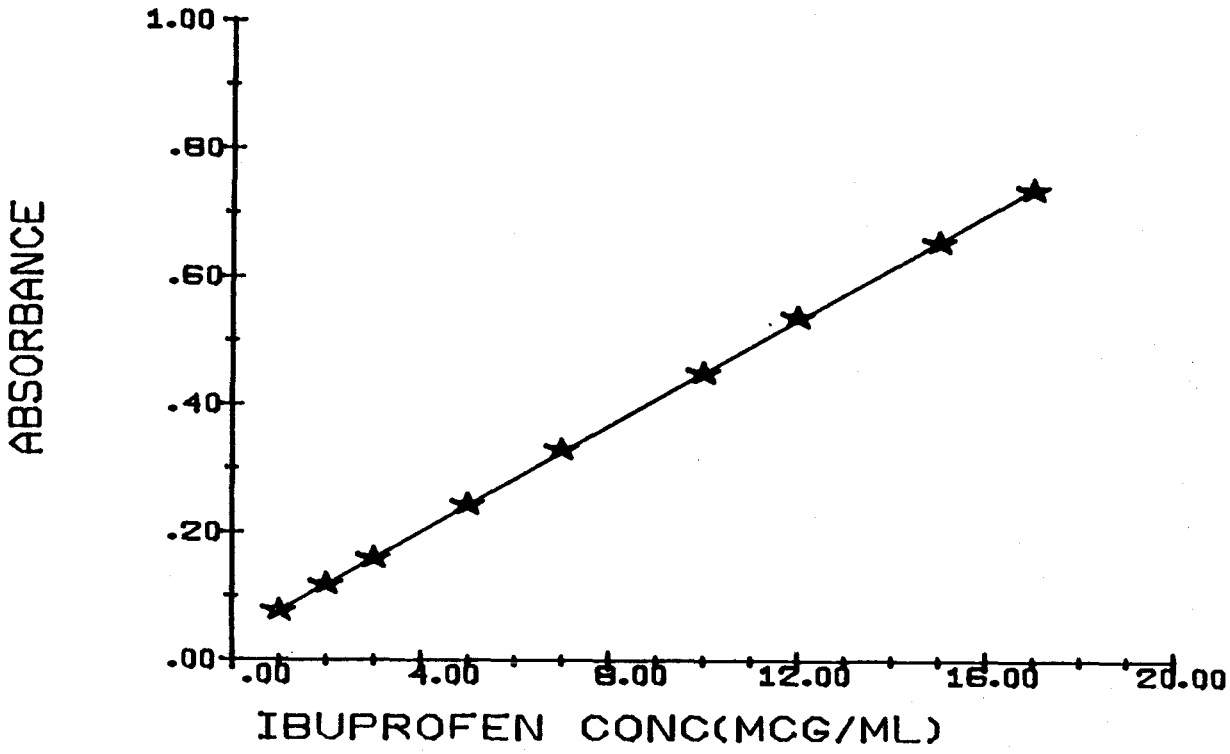

Figure I.6 Typical standard curve for ibuprofen concentration vs. absorbance at pH 5.4 estimated using linear regression

Table I.7 Typical Standard Curve Data for Ibuprofen Concentration at pH 5.6 Estimated Using Linear Regression[a]

Std. No.	Conc. (μg/ml)	Absorbance	Inv. Est. Conc.[b] (μg/ml)	% Theory[c]
1	2.50	0.119	2.452	98.08
2	5.00	0.230	5.002	100.03
3	7.00	0.321	7.097	101.31
4	10.00	0.444	9.917	99.17
5	12.00	0.538	12.076	100.63
6	15.00	0.665	14.993	99.95
7	17.00	0.751	16.968	99.81
8	20.00	0.883	20.000	100.0
Mean				99.9
S.D.				1.0
%C.V.[d]				1.0

[a] R^2 = .9999

[b] Inversely estimated concentration = -.281 + 22.969 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

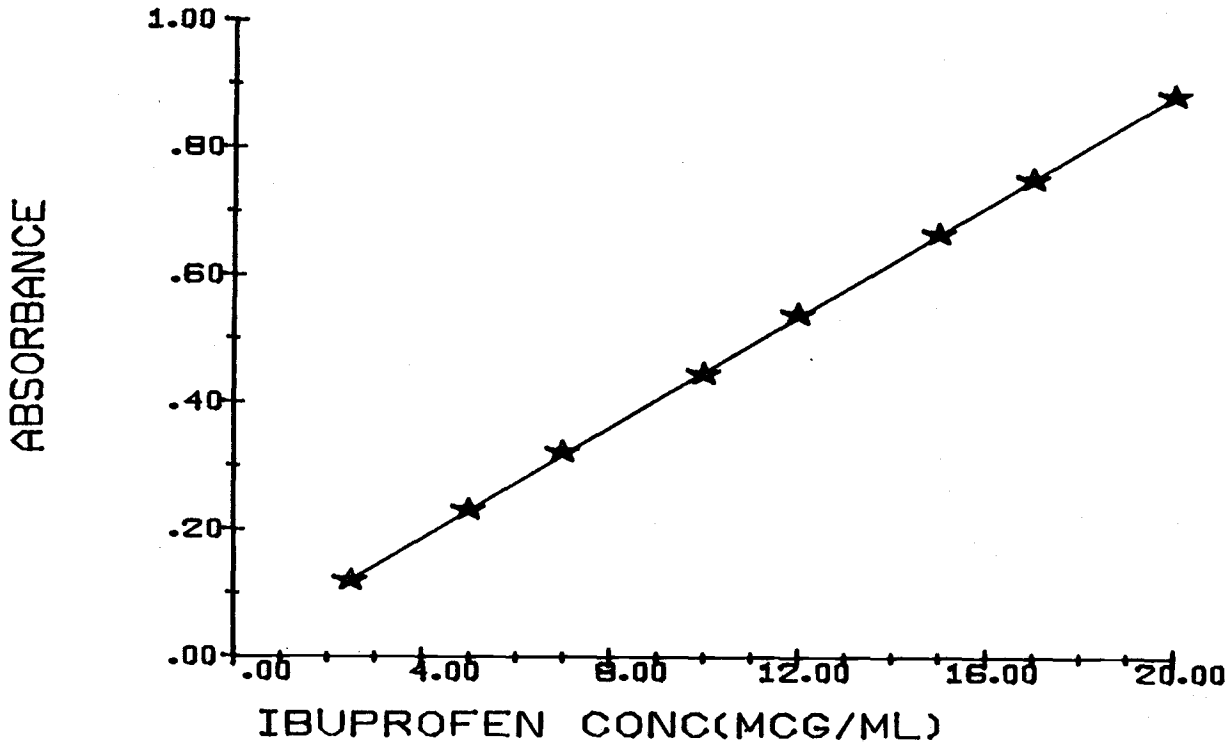

Figure I.7 Typical standard curve for ibuprofen concentration vs. absorbance at pH 5.6 estimated using linear regression

Table I.8 Typical Standard Curve Data for Ibuprofen Concentration at pH 6.0 Estimated Using Linear Regression[a]

Std. No.	Conc. (μg/ml)	Absorbance	Inv. Est. Conc.[b] (μg/ml)	% Theory[c]
1	2.50	0.117	2.645	105.81
2	5.00	0.211	4.964	99.28
3	7.00	0.288	6.863	98.04
4	10.00	0.413	9.946	99.46
5	12.00	0.497	12.018	100.15
6	15.00	0.619	15.028	100.18
7	17.00	0.700	17.025	100.15
8	20.00	0.821	20.010	100.05
Mean				100.4
S.D.				2.3
%C.V.[d]				2.3

[a] R^2 = .9998

[b] Inversely estimated concentration = -.241 + 24.666 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

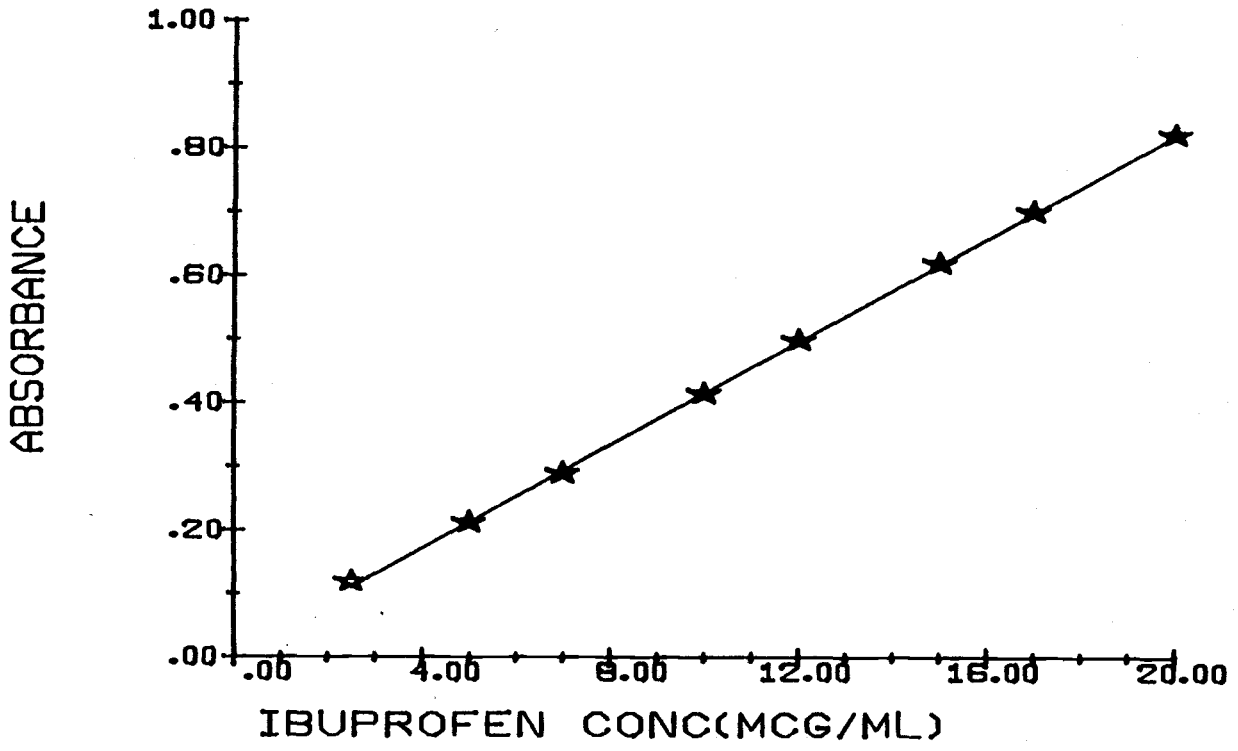

Figure I.8 Typical standard curve for ibuprofen concentration vs. absorbance at pH 6.0 estimated using linear regression

Table I.9 Typical Standard Curve Data for Ibuprofen Concentration at pH 6.4 Estimated Using Linear Regression[a]

Std. No.	Conc. (μg/ml)	Absorbance	Inv. Est. Conc.[b] (μg/ml)	% Theory[c]
1	2.50	0.10	1.868	93.39
2	5.00	0.22	5.021	100.43
3	7.00	0.30	7.124	101.77
4	10.00	0.41	10.015	100.15
5	12.00	0.48	11.854	98.78
6	15.00	0.61	15.270	101.80
7	17.00	0.68	17.110	100.65
8	20.00	0.78	19.738	98.69
Mean				99.5
S.D.				2.7
%C.V.[d]				2.7

[a] R^2 = .9992

[b] Inversely estimated concentration = -.760 + 26.280 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

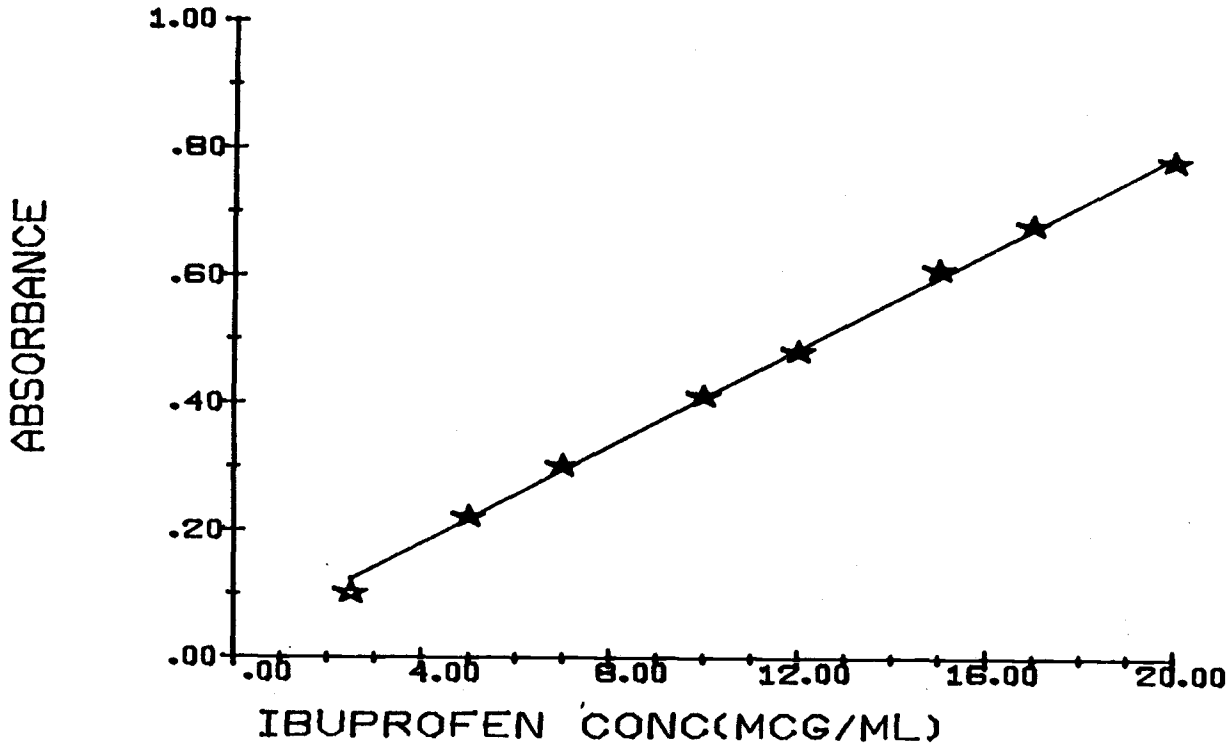

Figure I.9 Typical standard curve for ibuprofen concentration vs. absorbance at pH 6.4 estimated using linear regression

Table I.10 Typical Standard Curve Data for Ibuprofen Concentration at pH 6.8 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	2.50	0.12	2.418	96.73
2	5.00	0.22	4.961	99.21
3	7.00	0.30	6.995	99.92
4	10.00	0.42	10.046	100.46
5	12.00	0.50	12.079	100.66
6	15.00	0.62	15.130	100.87
7	17.00	0.70	17.164	100.97
8	20.00	0.80	19.707	98.53
Mean				99.7
S.D.				1.5
%C.V.[d]				1.5

[a] R^2 = .9994

[b] Inversely estimated concentration = -.633 + 25.424 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

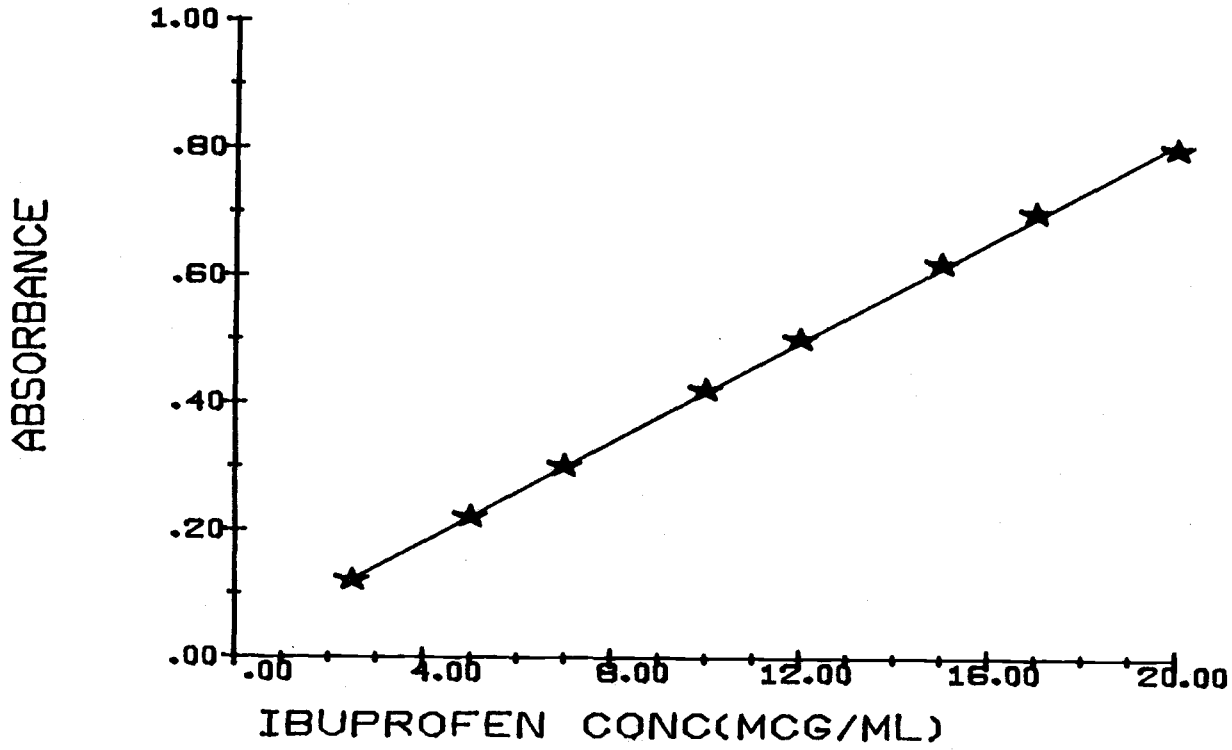

Figure I.10 Typical standard curve for ibuprofen concentration vs. absorbance at pH 6.8 estimated using linear regression

Table I.11 Typical Standard Curve Data for Ibuprofen Concentration at pH 7.2 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	1.00	0.064	0.883	88.34
2	2.00	0.108	1.966	98.32
3	3.00	0.149	2.975	99.18
4	5.00	0.241	5.240	104.80
5	7.00	0.313	7.012	100.17
6	10.00	0.433	9.965	99.65
7	12.00	0.516	12.008	100.07
8	15.00	0.635	14.937	99.58
9	17.00	0.721	17.054	100.32
10	20.00	0.839	19.958	99.79
Mean				99.0
S.D.				4.1
%C.V.[d]				4.2

[a] R^2 = .9998

[b] Inversely estimated concentration = -.692 + 24.613 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

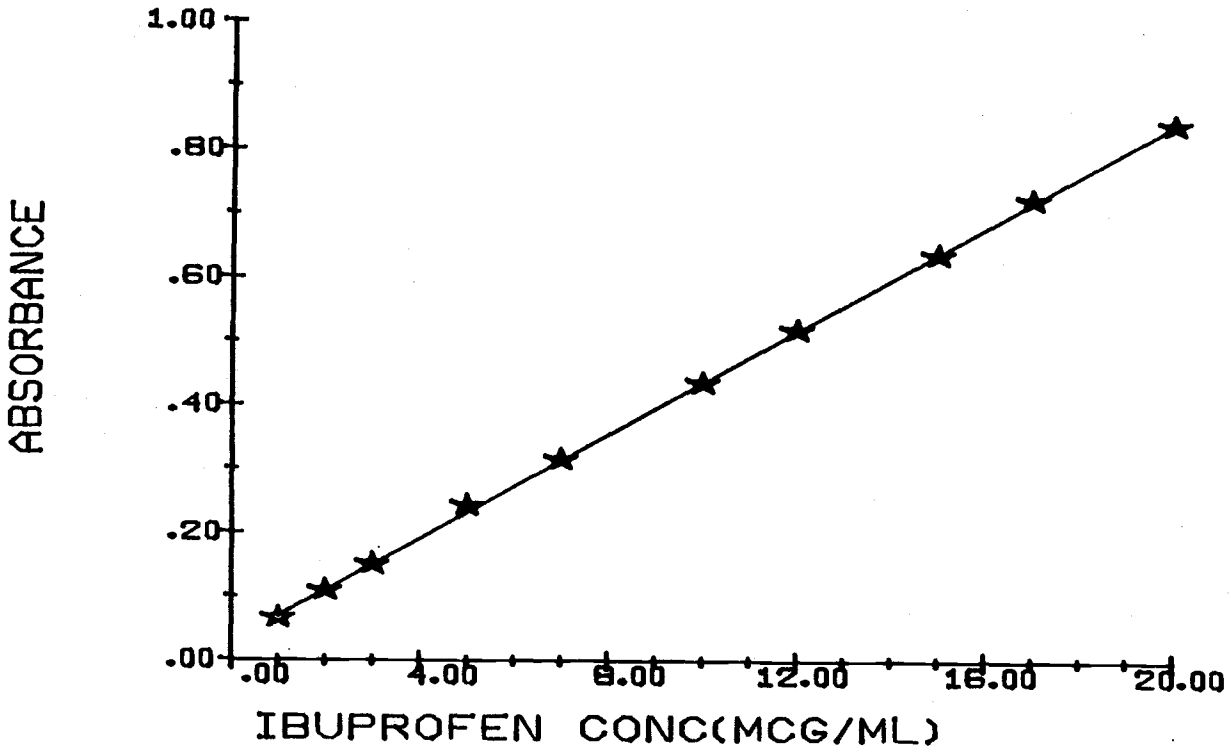

Figure I.11 Typical standard curve for ibuprofen concentration vs. absorbance at pH 7.2 estimated using linear regression

Table I.12 Typical Standard Curve Data for Ibuprofen Concentration at pH 8.0 Estimated Using Linear Regression[a]

Std. No.	Conc. (µg/ml)	Absorbance	Inv. Est. Conc.[b] (µg/ml)	% Theory[c]
1	2.50	0.119	2.487	99.46
2	5.00	0.228	5.018	100.36
3	7.00	0.316	7.062	100.89
4	10.00	0.436	4.849	98.49
5	12.00	0.533	12.102	100.85
6	15.00	0.658	15.005	100.03
7	17.00	0.742	16.956	99.74
8	20.00	0.874	20.022	100.11
Mean				100.0
S.D.				0.8
%C.V.[d]				0.8

[a] $R^2 = .9998$

[b] Inversely estimated concentration = -.277 + 23.225 X (Absorbance)

[c] % Theory = (Inversely estimated concentration/known concentration) X 100

[d] % Coefficient of variation = (S.D./Mean) X 100

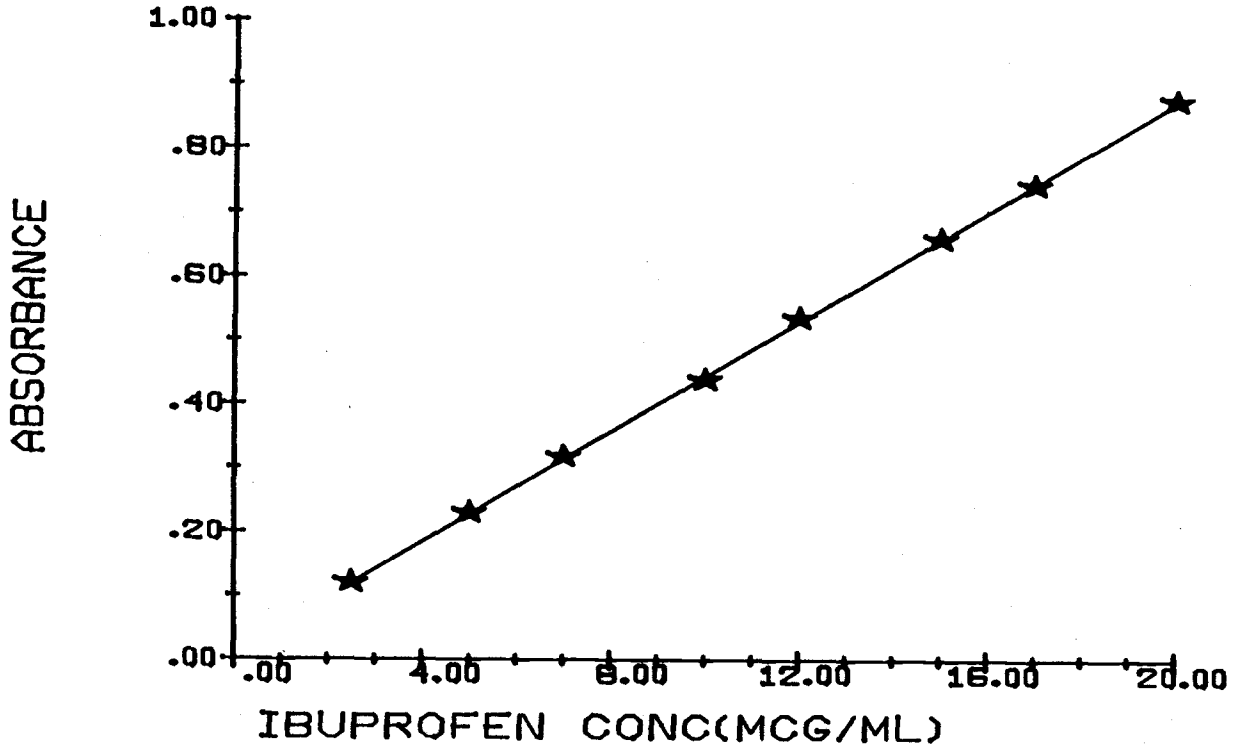

Figure I.12 Typical standard curve for ibuprofen concentration vs. absorbance at pH 8.0 estimated using linear regression

Table I.13 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) at pH 2.0, 3.0 and 4.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 2.0	at pH 3.0	at pH 4.0
10 min	0.94 ± 0.37	1.88 ± 0.69	1.84 ± 0.33
20 min	1.47 ± 0.67	5.14 ± 1.72	6.20 ± 0.82
30 min	2.10 ± 0.78	6.50 ± 0.21	8.08 ± 0.39
45 min	2.65 ± 0.32	6.81 ± 0.64	8.47 + 0.12
1 hr	5.45± 0.78	6.66 ± 0.20	8.49 ± 0.11
1.5 hr	5.33± 0.83	6.58 ± 0.15	8.57 ± 0.23
2 hr	5.33± 0.66	6.59 ± 0.15	8.57 ± 0.13
3 hr	5.28± 0.83	6.62 ± 0.10	8.89 ± 0.25
4 hr	5.29± 0.44	6.60 ± 0.06	8.85 ± 0.22
6 hr	5.65± 0.28	6.69 ± 0.21	8.97 ± 0.16

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.14 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) at pH 5.2, 5.4 and 5.6

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	at pH 5.2	at pH 5.4	at pH 5.6
10 min	1.01 ± 0.35	5.52 ± 1.54	5.82 ± 1.71
20 min	16.94 ± 3.87	20.93 ± 3.44	24.92 ± 1.72
30 min	25.61 ± 2.53	30.14 ± 3.46	33.77 ± 1.33
45 min	29.26 ± 1.34	36.21 ± 0.80	43.20 + 1.46
1 hr	28.96 ± 1.24	40.58 ± 0.90	51.64 ± 3.34
1.5 hr	30.43 ± 0.84	43.98 ± 1.15	51.92 ± 2.33
2 hr	31.35 ± 0.67	46.31 ± 1.48	53.80 ± 1.51
3 hr	32.88 ± 1.36	48.55 ± 2.16	58.03 ± 1.98
4 hr	33.66 ± 2.14	49.51 ± 1.35	62.27 ± 1.70
6 hr	34.78 ± 2.70	50.59 ± 2.48	65.43 ± 1.79

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.15 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) at pH 6.0, 6.4 and 6.8

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 6.0	at pH 6.4	at pH 6.8
10 min	3.37 ± 2.49	15.55 ± 6.74	13.34 ± 5.15
20 min	39.94 ± 6.23	62.90 ± 9.32	65.09 ± 7.63
30 min	51.85 ± 6.57	70.52 ± 7.38	76.30 ± 4.91
45 min	58.65 ± 6.86	75.10 ± 6.22	84.98 + 3.81
1 hr	63.36± 6.15	9.006 ± 4.09	88.70 ± 3.81
1.5 hr	70.31± 8.32	86.99 ± 3.48	89.41 ± 3.39
2 hr	73.72± 6.63	87.71 ± 3.00	94.90 ± 2.92
3 hr	80.28± 5.68	91.10 ± 1.30	94.57 ± 2.39
4 hr	83.92± 5.02	94.25 ± 1.09	95.38 ± 1.41
6 hr	86.40± 2.16	95.71 ± 1.10	96.33 ± 1.90

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.16 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) at pH 7.2 and 8.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 7.2	at pH 8.0
10 min	12.40 ± 6.23	62.38 ± 4.66
20 min	75.52 ± 3.61	94.12 ± 0.97
30 min	84.71 ± 2.39	94.96 ± 2.12
45 min	94.75 ± 1.25	98.23 ± 1.57
1 hr	96.14 ± 1.83	96.34 ± 1.63
1.5 hr	96.4 ± 1.54	95.95 ± 1.57
2 hr	100.61 ± 1.25	96.77 ± 0.52
3 hr	101.61 ± 0.82	97.00 ± 0.56
4 hr	101.10 ± 0.82	97.33 ± 0.31
6 hr	99.7 ± 1.43	98.40 ± 0.88

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

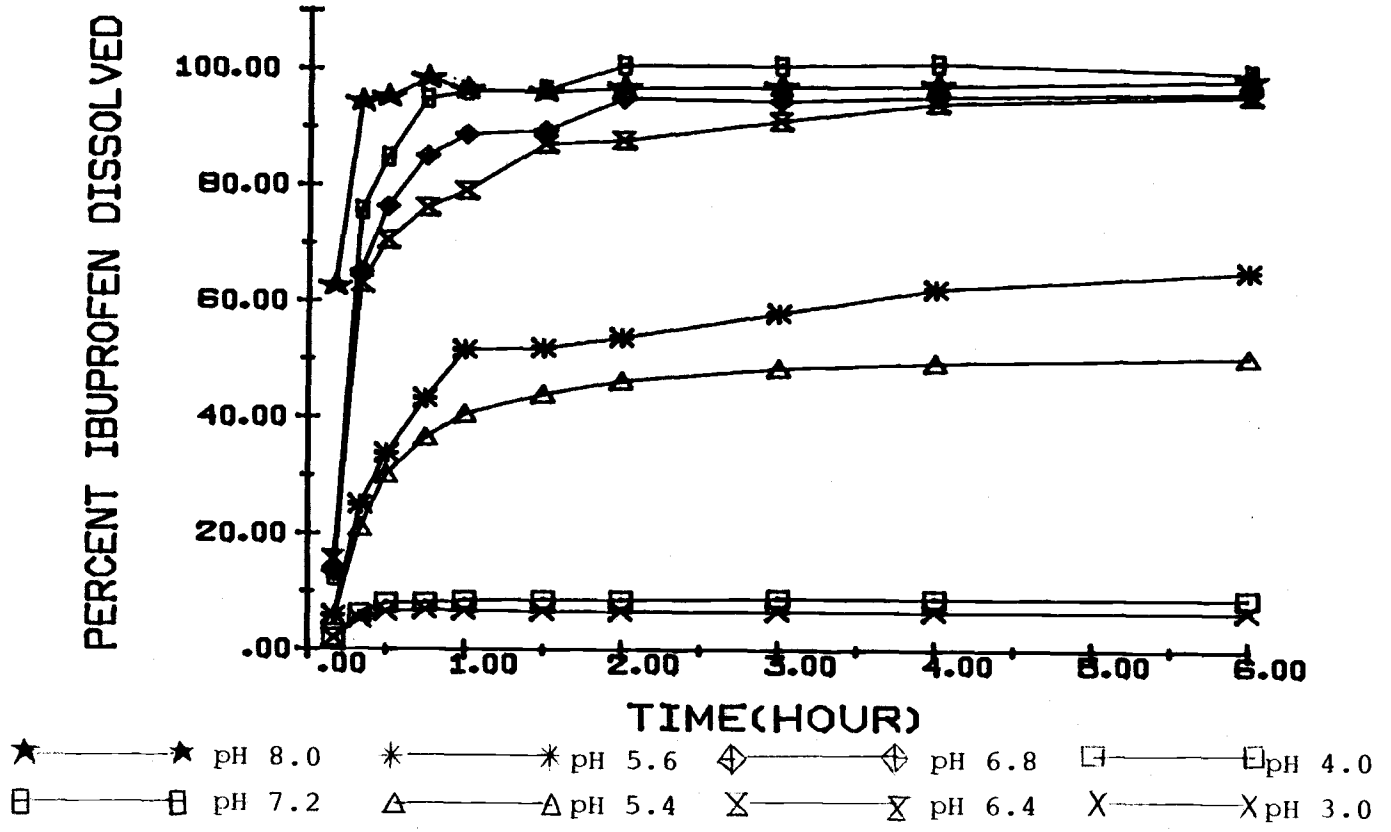

Figure I.13 Dissolution profiles of Motrin Tablets (400-mg ibuprofen) at pH 8.0, 7.2, 6.8, 5.8, 5.4, 4.0 and 3.0

Table I.17 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) at pH 2.0, 3.0 and 4.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	at pH 2.0	at pH 3.0	at pH 4.0
10 min	1.14 ± 0.14	1.54 ± 0.11	3.02 ± 0.61
20 min	1.19 ± 0.11	4.04 ± 0.56	6.30 ± 1.07
30 min	1.48 ± 0.48	5.73 ± 0.54	7.40 ± 3.02
45 min	1.67 ± 0.32	6.54 ± 0.28	7.67 + 0.20
1 hr	2.10± 0.38	6.43 ± 0.26	7.62 ± 0.35
1.5 hr	3.02± 0.84	6.38 ± 0.12	7.82 ± 0.32
2 hr	4.49± 1.36	6.46 ± 0.19	7.68 ± 0.12
3 hr	5.67± 1.28	6.57 ± 0.12	7.68 ± 0.17
4 hr	5.23± 0.99	6.51 ± 0.04	7.95 ± 0.30
6 hr	5.03± 0.44	6.63 ± 0.21	7.92 ± 0.42

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.18 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) at pH 5.2, 5.4 and 5.6

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 5.2	at pH 5.4	at pH 5.6
10 min	5.64 ± 1.25	6.38 ± 1.23	13.25 ± 3.44
20 min	15.67 ± 3.10	17.80 ± 2.35	31.70 ± 3.29
30 min	22.18 ± 3.06	27.34 ± 2.17	40.83 ± 3.06
45 min	26.83 ± 1.57	34.32 ± 2.49	43.98 + 4.38
1 hr	28.48 ± 0.81	38.98 ± 0.86	50.90 ± 2.19
1.5 hr	30.03 ± 1.14	43.13 ± 1.24	55.49 ± 2.12
2 hr	31.63 ± 1.77	45.73 ± 0.70	56.44 ± 1.08
3 hr	31.06 ± 1.61	47.75 ± 1.17	58.74 ± 1.30
4 hr	31.90 ± 1.80	49.30 ± 1.08	62.38 ± 1.23
6 hr	31.92 ± 1.62	48.97 ± 0.38	64.34 ± 2.01

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.19 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) at pH 6.0, 6.4 and 6.8

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 6.0	at pH 6.4	at pH 6.8
10 min	16.03 ± 3.76	45.45 ± 6.27	47.46 ± 6.26
20 min	42.63 ± 4.76	65.86 ± 3.54	78.83 ± 2.54
30 min	54.82 ± 3.32	75.83 ± 4.89	87.80 ± 3.89
45 min	64.74 ± 2.71	81.79 ± 3.30	89.82 + 2.21
1 hr	71.40± 2.13	84020 ± 2.54	91.16 ± 1.53
1.5 hr	78.66± 2.69	89.92 ± 2.10	90.88 ± 0.99
2 hr	82.05± 3.08	91.43 ± 2.82	93.40 ± 1.83
3 hr	85.70± 2.50	92.44 ± 2.27	93.40 ± 1.17
4 hr	87.24± 2.91	92.00 ± 2.27	94.03 ± 1.34
6 hr	89.18± 2.50	93.16 ± 3.25	94.24 ± 0.77

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

Table I.20 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) at pH 7.2 and 8.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b] at pH 7.2	at pH 8.0
10 min	59.68 ± 9.56	74.59 ± 4.09
20 min	93.32 ± 3.34	95.99 ± 0.81
30 min	98.73 ± 1.21	96.01 ± 1.32
45 min	98.94 ± 0.53	97.94 ± 1.03
1 hr	98.97 ± 0.77	97.81 ± 1.24
1.5 hr	99.02 ± 1.57	97.16 ± 0.52
2 hr	98.92 ± 1.51	96.38 ± 1.22
3 hr	99.98 ± 1.23	97.72 ± 1.36
4 hr	99.75 ± 0.73	97.72 ± 1.23
6 hr	100.81 ± 0.75	98.33 ± 1.00

[a] Mean value for six tablets

[b] Standard deviation values for each mean percent of label released value

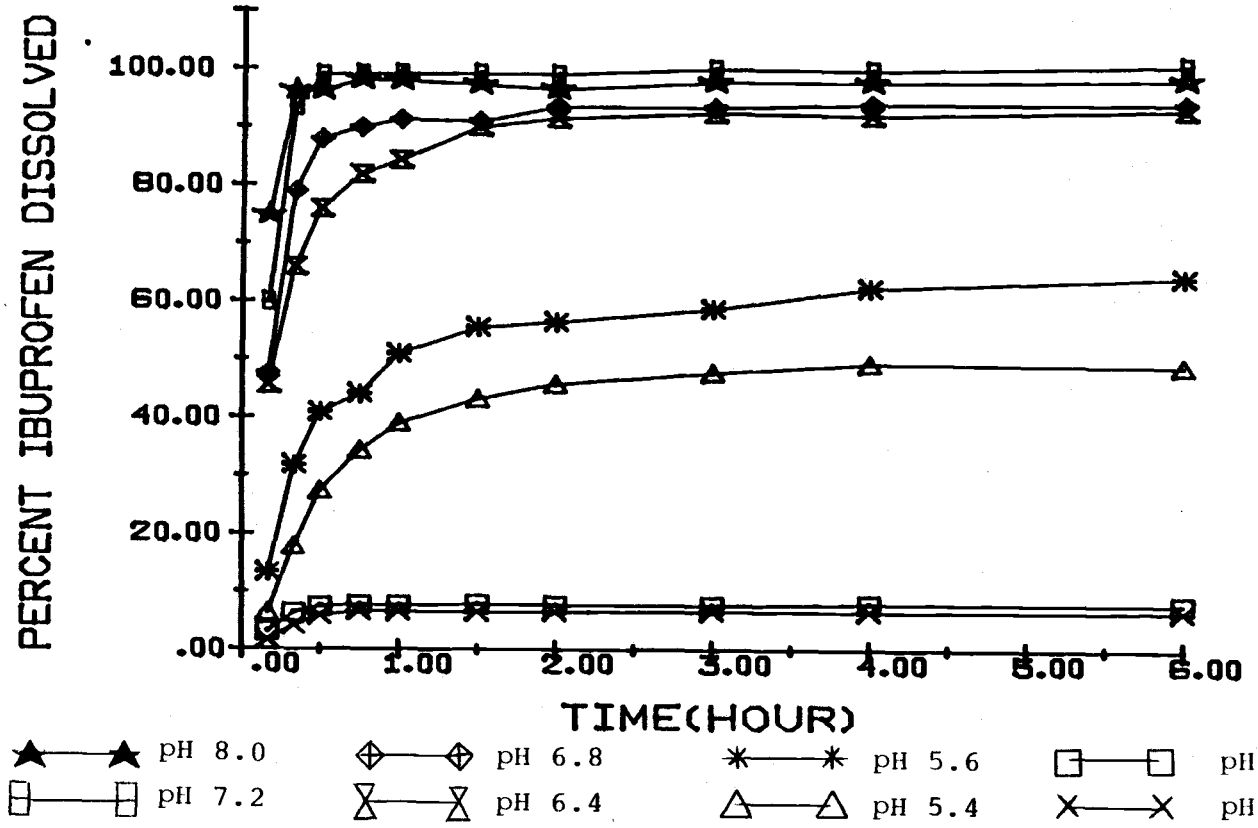

Figure I.14 Dissolution profiles of Rufen Tablets (400-mg ibuprofen) at pH 8.0, 7.2, 6.8, 6.4, 5.8, 5.4, 4.0 and 3.0

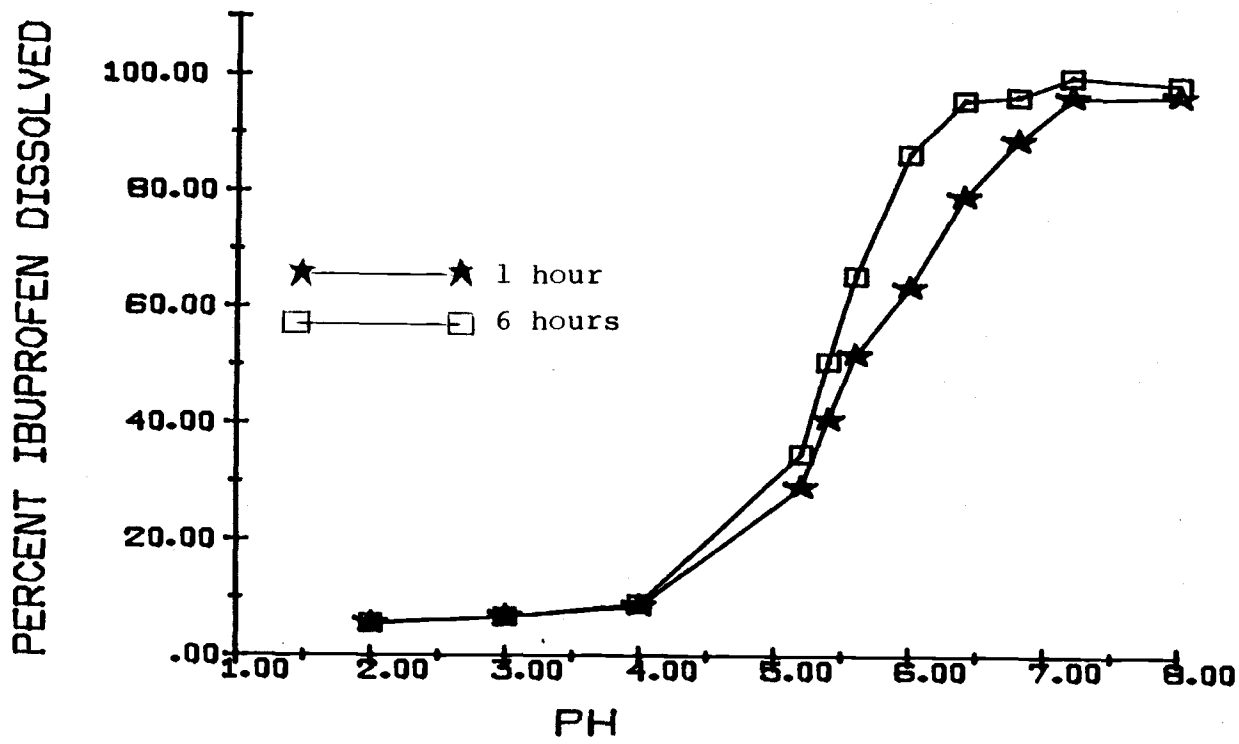

Figure I.15 The percentage of labeled amount of ibuprofen of Motrin Tablets dissolved at 1 hour and 6 hours

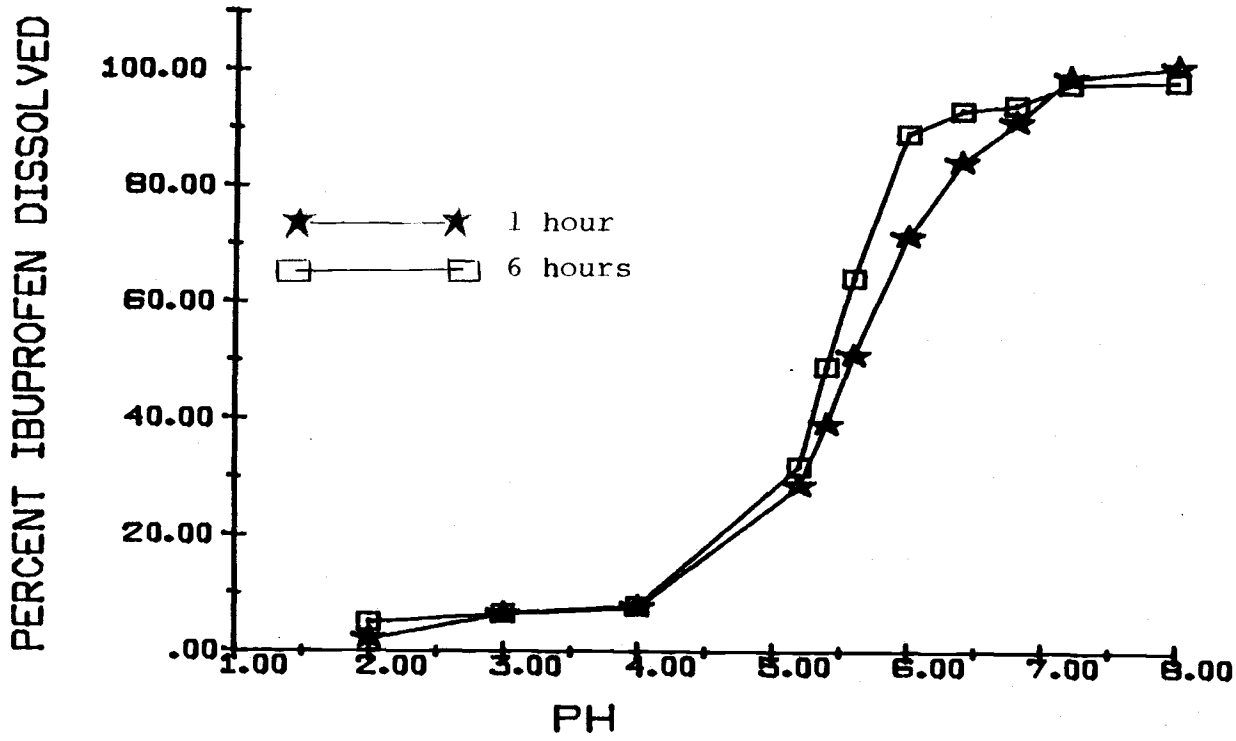

Figure I.16 The percentage of labeled amount of ibuprofen of Rufen Tablets dissolved at 1 hour and 6 hours

6.4. Less than 90% of drug dissolved within 6 hours at pH 6.0 and about 65% and 35% at pH 5.6 and 5.2, respectively. As the pH decreased to pH 4 and 3, less than 10% of drug dissolved within 6 hours. There was no significant difference in the rate and amount of ibuprofen from either product at any appropriate corresponding pH value.

Figures I.17-I.19 and Tables I.21-I.23 show dissolution profiles of ibuprofen powders and the freeze-dried products from a typical formula with varying amount of theobroma oil from 0 to 31% and pH 7.2, 5.4 and 2.0. The dissolution rates of ibuprofen powders at pH 5.4 and 2.0 was slow. This may be a result of aggregation or agglomeration of drug particles due to their hydrophobicity. Dissolution rate and extent of drug dissolved was greater in dissolution medium at pH 7.2 than at pH 5.4 or 2.0 because the pKa value of ibuprofen is 4.8. When solid dispersions of ibuprofen were prepared with varying amounts of theobroma oil using the freeze-drying technique, the average percent of drug dissolved increased with decreasing amounts of theobroma oil at pH 5.4 and 2.0. The rate of drug dissolved in the formula with the highest content of theobroma oil was the slowest at these two pH levels. However, at pH 7.2 complete dissolution of drug occurred within 45 minutes for all the formulas, and the effect theobroma oil has on dissolution is not great.

Table I.21 In Vitro Dissolution of Ibuprofen from 100-mg Ibuprofen Freeze-Dried Products with Varying Amounts of Theobroma Oil at pH 7.2

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	97.85 ± 1.70	23.32 ± 3.05	47.26 ± 4.99	53.22 ± 9.22
10 min	99.75 ± 3.78	37.80 ± 2.49	82.75 ± 3.22	79.26 ± 3.19
20 min	99.18 ± 2.40	59.12 ± 4.63	95.10 ± 3.10	87.15 ± 7.66
30 min	100.25 ± 1.94	79.09 ± 4.78	99.46 ± 1.75	96.61 ± 2.83
45 min	101.04 ± 2.60	90.38 ±10.99	100.73 ± 1.52	97.29 ± 2.59
1 hr	100.38 ± 2.51	95.97 ± 3.16	100.85 ± 1.72	99.69 ± 0.96
1.5 hr	100.97 ± 2.21	97.32 ± 3.95	102.57 ± 0.96	99.29 ± 1.18
2 hr	100.84 ± 2.18	98.00 ± 2.94	99.77 ± 1.91	99.94 ± 1.55
3 hr	99.65 ± 1.68	102.14 ± 1.02	100.79 ± 0.69	99.26 ± 0.42
4 hr	99.18 ± 2.19	102.99 ± 1.40	100.79 ± 1.06	99.11 ± 1.28
6 hr	101.00 ± 2.15	100.44 ± 0.94	100.44 ± 0.83	101.02 ± 1.48

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without theobroma oil

[d] Preparation with theobroma oil 8.33%

[e] Preparaton with theobroma oil 21.43%

[f] Preparation with theobroma oil 31.25%

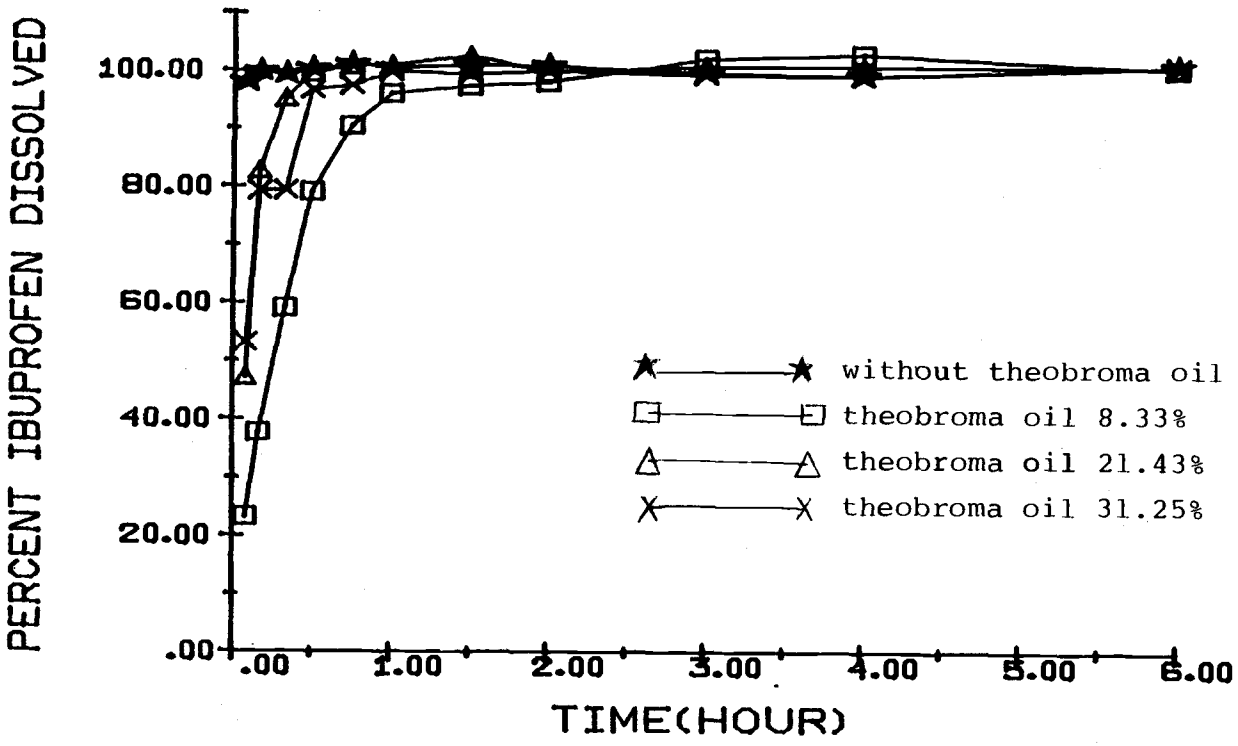

Figure I.17 Dissolution profiles of ibuprofen from 100-mg ibuprofen freeze-dried products with varying amounts of theobroma oil at pH 7.2

Table I.22 In Vitro Dissolution of Ibuprofen from 100-mg Ibuprofen Freeze-Dried Products with Varying Amounts of Theobroma Oil at pH 5.4

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	26.54 ± 2.92	2.94 ± 0.71	9.08 ± 6.79	4.08 ± 0.66
10 min	51.78 ± 9.28	8.41 ± 1.21	9.93 ± 2.93	8.78 ± 1.93
20 min	77.88 ± 5.53	19.83 ± 2.36	17.16 ± 5.10	17.60 ± 2.24
30 min	87.26 ± 2.93	27.16 ± 3.75	26.33 ± 5.63	21.83 ± 5.24
45 min	89.82 ± 2.09	38.58 ± 4.66	37.12 ± 6.37	30.40 ± 5.29
1 hr	90.46 ± 1.86	46.91 ± 5.29	47.94 ± 8.53	35.20 ± 5.46
1.5 hr	91.08 ± 2.27	57.65 ± 5.39	59.30 ± 9.75	46.43 ± 9.77
2 hr	91.06 ± 1.43	65.08 ± 5.70	65.83 ± 8.79	49.21 ± 7.08
3 hr	91.63 ± 1.67	72.64 ± 5.06	73.89 ± 5.30	58.09 ± 8.60
4 hr	91.60 ± 1.69	79.85 ± 3.47	77.32 ± 3.99	64.13 ± 9.30
6 hr	91.32 ± 1.78	84.82 ± 1.94	79.10 ± 4.56	77.12 ± 5.63

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without theobroma oil

[d] Preparation with theobroma oil 8.33%

[e] Preparaton with theobroma oil 21.43%

[f] Preparation with theobroma oil 31.25%

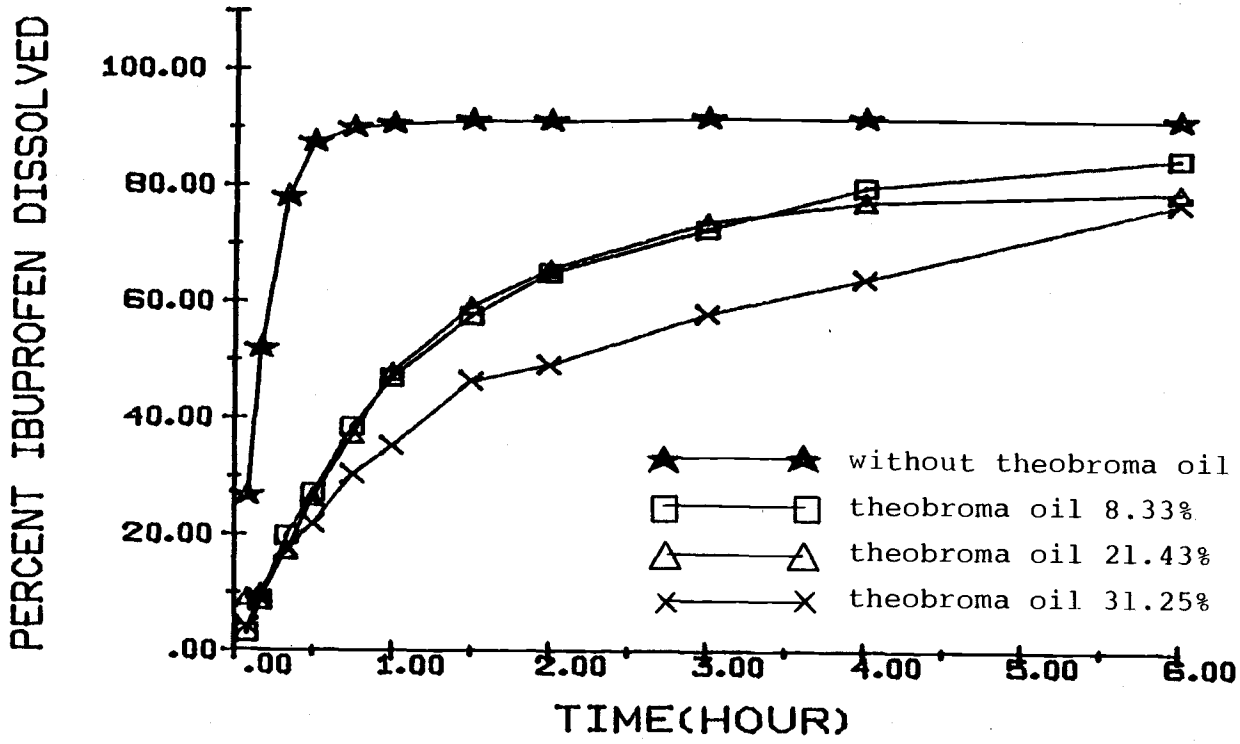

Figure I.18 Dissolution profiles of ibuprofen from 100-mg ibuprofen freeze-dried products with varying amounts of theobroma oil at pH 5.4

Table I.23 In Vitro Dissolution of Ibuprofen from 100-mg Ibuprofen Freeze-Dried Products with Varying Amounts of Theobroma Oil at pH 2.0

Dissolution	Mean Percent of Label Released[a] ± SD[b]			
Time	1[c]	2[d]	3[e]	4[f]
5 min	2.39 ± 0.85	0.87 ± 0.77	3.72 ± 1.15	1.13 ± 0.32
10 min	6.17 ± 1.23	3.16 ± 1.05	4.52 ± 1.79	1.02 ± 0.56
20 min	11.35 ± 2.02	5.76 ± 1.58	7.23 ± 1.52	1.94 ± 0.60
30 min	13.92 ± 3.14	8.65 ± 1.65	8.50 ± 1.03	2.72 ± 0.58
45 min	17.58 ± 3.87	10.94 ± 2.98	9.80 ± 1.20	3.44 ± 1.28
1 hr	20.12 ± 3.78	13.74 ± 3.00	11.14 ± 1.41	4.18 ± 0.87
1.5 hr	21.71 ± 2.97	17.02 ± 3.04	13.12 ± 1.76	5.29 ± 1.06
2 hr	22.92 ± 3.40	19.65 ± 3.13	14.85 ± 2.05	6.78 ± 1.21
3 hr	23.26 ± 2.17	20.61 ± 1.26	17.25 ± 2.12	8.32 ± 1.21
4 hr	24.16 ± 0.41	21.00 ± 0.99	20.03 ± 1.56	10.07 ± 1.32
6 hr	25.22 ± 1.07	21.01 ± 1.23	20.42 ± 1.61	14.16 ± 1.16

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without theobroma oil

[d] Preparation with theobroma oil 8.33%

[e] Preparaton with theobroma oil 21.43%

[f] Preparation with theobroma oil 31.25%

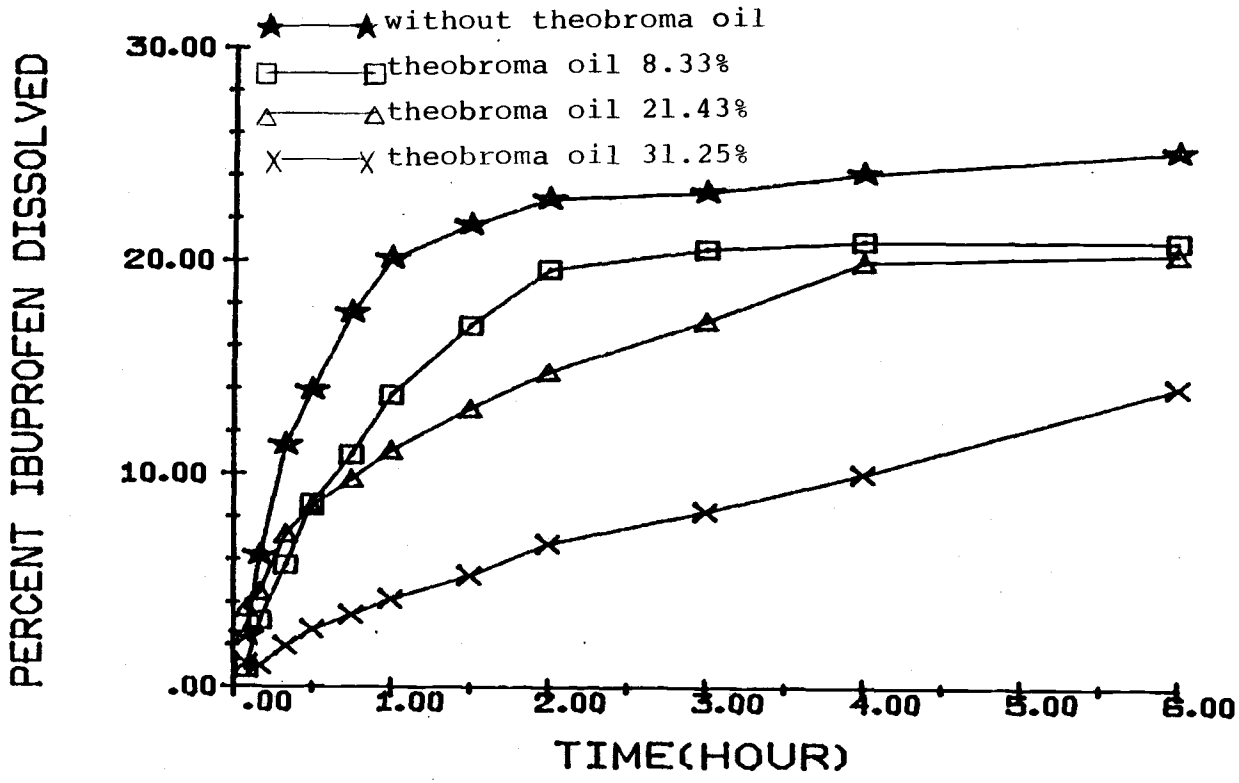

Figure I.19 Dissolution profiles of ibuprofen from 100-mg ibuprofen freeze-dried products with varying amounts of theobroma oil at pH 2.0

The highest dissolution rate of ibuprofen freeze-dried products was seen in the formula without theobroma oil. The most probable explanation for this may be due solely to the increase in hydrophobicity of drug products in the dispersion of theobroma oil. In this study the results obtained for ibuprofen freeze-dried products were the same as reported for tolbutamide and phenylbutazone (Suvanakoot, 1984). However, it was reported for griseofulvin (Grisafe, 1978), sulfisoxazole acetyl and dicumerol (Bloedow and Hayton, 1976) that the dissolution of these drugs increased in the presence of the lipids, such as corn oil, olive oil and triolein.

Dissolution characteristics of ibuprofen freeze-dried products prepared with varying the amount of lecithin are shown in Figures I.20-I.22 and Tables I.24-I.26, respectively. Freeze-dried systems of ibuprofen with the presence of both PEG 20,000 and lecithin as the excipients increased the rate and amount of ibuprofen dissolved at the tested pH levels over ibuprofen powders (Figures I.23-I.25 and Tables I.27-I.29). This effect was significantly evident at pH 5.4 and 2.0. However, the system containing only PEG 20,000 showed the highest dissolution rate and amount of drug dissolved as compared to the system with both PEG 20,000 and lecithin present (Figures I.20-I.22). This may be the result of decreased exposure of drug particles to the dissolution medium. Polyethylene glycol seems to have

Table I.24 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Freeze-Dried Preparations without Theobroma Oil in Various Proportions of Lecithin at pH 7.2

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	52.82 ± 3.07	45.64 ± 14.78	57.96 ± 22.83
10 min	80.23 ± 0.13	68.03 ± 16.87	81.50 ± 12.34
20 min	93.02 ± 0.95	81.58 ± 17.98	89.40 ± 10.11
30 min	99.75 ± 0.88	88.68 ± 6.54	95.49 ± 5.93
45 min	100.61 ± 0.86	95.95 ± 6.54	100.33 ± 4.52
1 hr	100.81 ± 2.22	98.62 ± 2.89	100.88 ± 1.78
1.5 hr	101.31 ± 1.16	100.33 ± 0.68	101.32 ± 1.48
2 hr	100.98 ± 1.55	100.33 ± 0.79	100.17 ± 1.48
3 hr	98.99 ± 1.24	100.14 ± 0.83	101.38 ± 1.22
4 hr	99.18 ± 0.45	100.14 ± 1.67	101.38 ± 1.67
6 hr	99.45 ± 0.41	100.16 ± 1.31	100.02 ± 1.64

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without lecithin

[d] Preparation with lecithin 9.09%

[e] Preparation with lecithin 16.67%

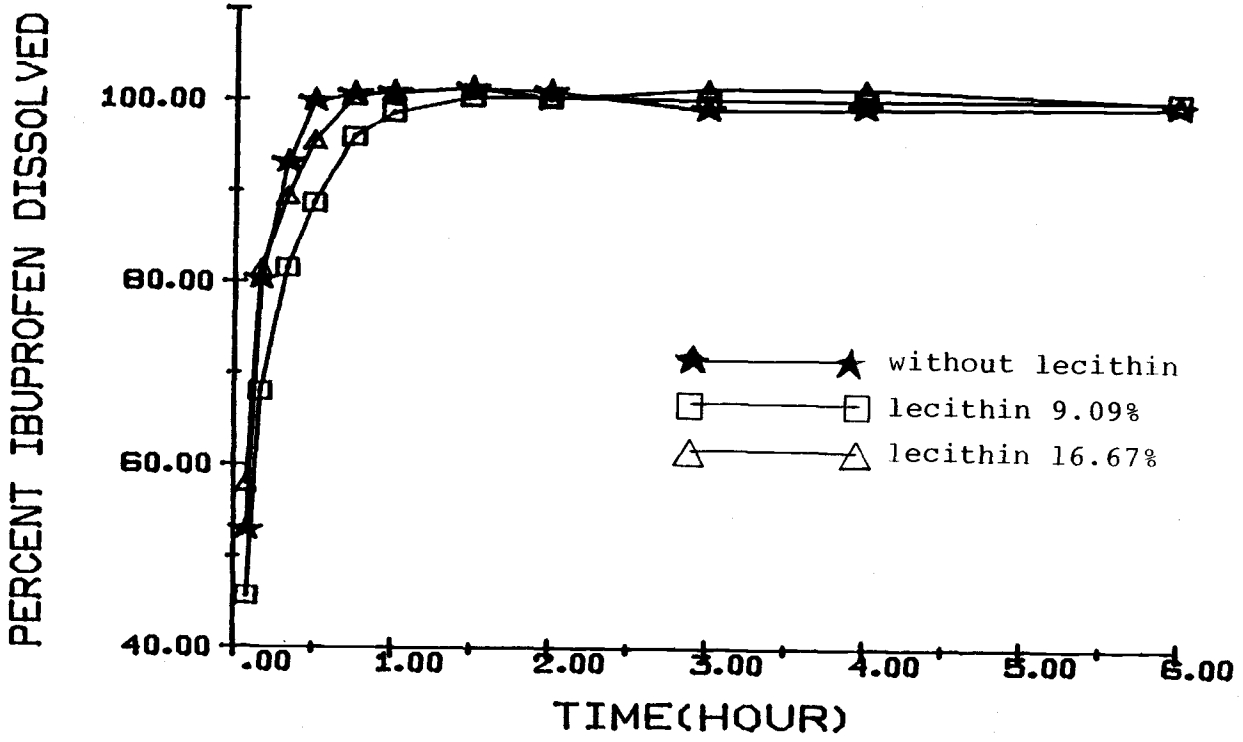

Figure I.20 Dissolution profiles of ibuprofen from 400-mg ibuprofen freeze-dried products with varying proportions of lecithin oil at pH 7.2

Table I.25 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Freeze-Dried Preparations without Theobroma Oil in Various Proportions of Lecithin at pH 5.4

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	38.01 ± 6.02	6.97 ± 3.38	3.77 ± 3.35
10 min	49.00 ± 3.95	18.26 ± 4.07	22.80 ± 5.69
20 min	55.21 ± 3.19	30.12 ± 3.98	38.90 ± 4.76
30 min	57.76 ± 2.41	37.17 ± 3.97	47.50 ± 5.01
45 min	58.39 ± 2.18	45.36 ± 2.88	49.21 ± 4.67
1 hr	59.33 ± 1.82	49.42 ± 3.00	50.37 ± 4.58
1.5 hr	60.27 ± 1.68	50.47 ± 1.91	54.34 ± 1.34
2 hr	61.28 ± 1.21	54.45 ± 0.63	54.29 ± 0.96
3 hr	61.16 ± 1.98	54.38 ± 0.82	54.31 ± 0.86
4 hr	60.19 ± 1.41	53.38 ± 0.38	54.21 ± 1.25
6 hr	61.39 ± 1.94	52.87 ± 0.41	53.68 ± 1.66

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without lecithin

[d] Preparation with lecithin 9.09%

[e] Preparation with lecithin 16.67%

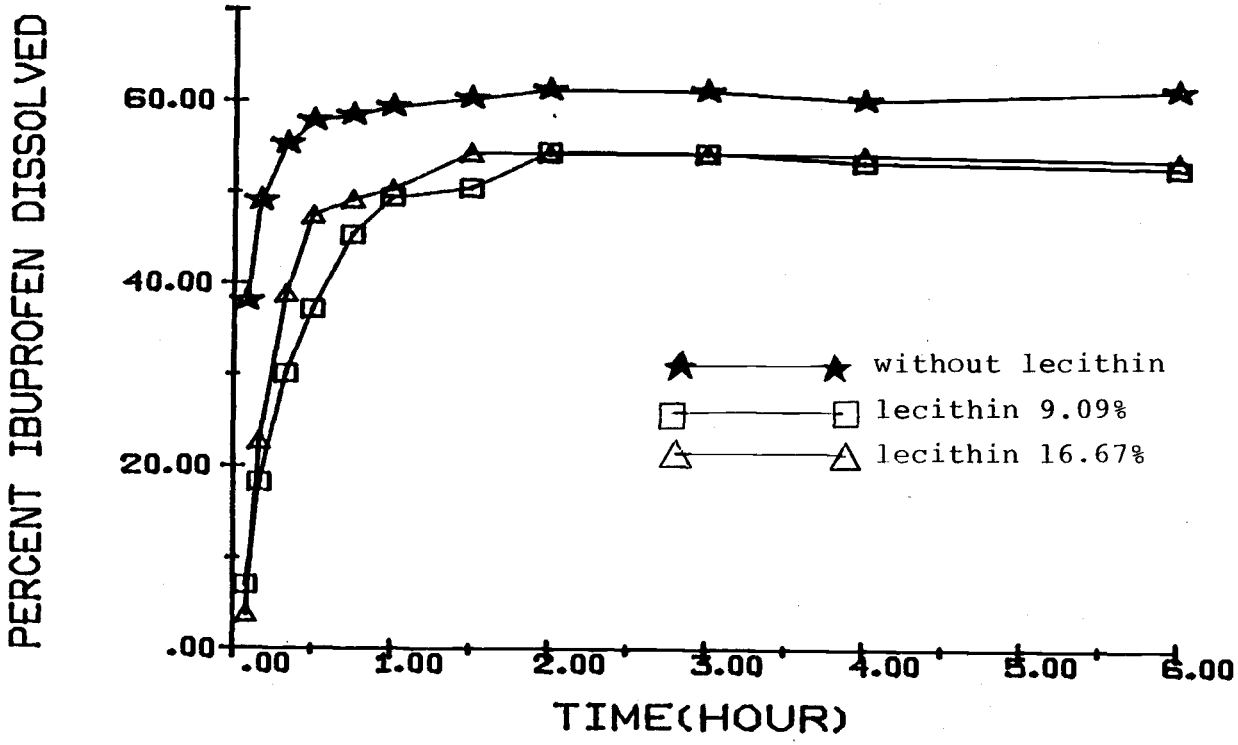

Figure I.21 Dissolution profiles of ibuprofen from 400-mg ibuprofen freeze-dried products without theobroma oil in various proportions of lecithin at pH 5.4

Table I.26 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Freeze-Dried Preparations without Theobroma Oil in Various Proportions of Lecithin at pH 2.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	5.70 ± 2.13	----	----
10 min	9.35 ± 0.42	----	----
20 min	11.96 ± 0.73	----	0.60 ± 1.16
30 min	13.36 ± 0.57	1.30 ± 0.68	1.42 ± 1.36
45 min	12.42 ± 0.54	1.90 ± 1.06	2.70 ± 1.59
1 hr	12.07 ± 0.12	3.36 ± 1.70	3.34 ± 1.71
1.5 hr	12.64 ± 0.62	5.03 ± 1.90	4.39 ± 1.56
2 hr	13.24 ± 0.04	6.08 ± 1.79	5.12 ± 1.63
3 hr	12.71 ± 0.22	6.63 ± 2.05	5.90 ± 1.36
4 hr	12.96 ± 0.25	6.96 ± 1.72	6.51 ± 1.06
6 hr	13.22 ± 0.56	7.16 ± 1.14	7.13 ± 0.92

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation without lecithin

[d] Preparation with lecithin 9.09%

[e] Preparation with lecithin 16.67%

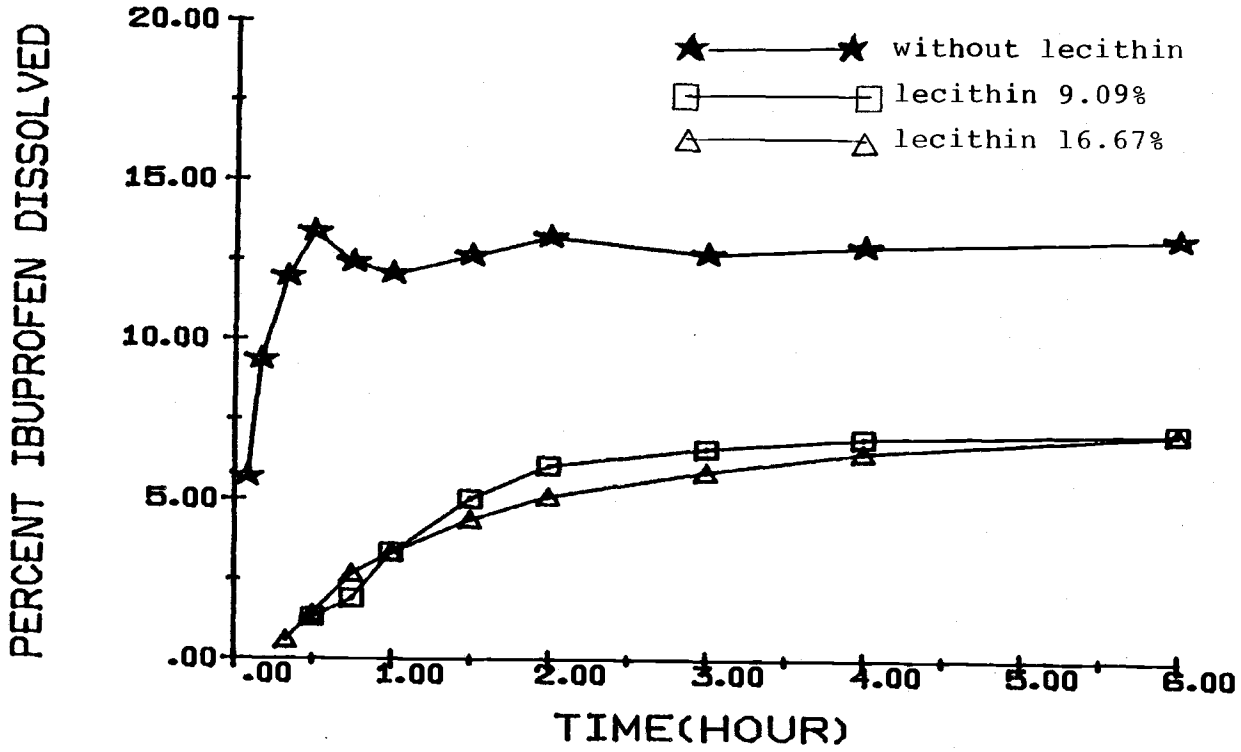

Figure I.22 Dissolution profiles of ibuprofen from 400-mg ibuprofen freeze-dried products without theobroma oil in various proportions of lecithin at pH 2.0

more advantages over lecithin as an excipient in solid dispersion systems. Polyethylene glycol is a crystalline, water-soluble polymer with two parallel helixes in a unit cell (Davidson and Sittig, 1962). A significant amount of drug can be trapped in the helical interstitial space when polyethylene glycol-drug are solidified in a solid dispersed system. Polyethylene glycol is also innert, and a universal solvent for the formation of solid dispersions of most drugs. It is completely soluble in water and a broad spectrum of organic solvents, including ethyl alcohol, acetone and chloroform. Polyethylene glycol can also be expected to produce an ultrafine or colloidal crystallization of pure drug if its concentration is much greater than its solid solubility and the drug polyethylene glycol dispersion is solidified rapidly (Chiou and Riegelman, 1969). Polyethylene glycols with various molecular weights are readily available, such as PEG 4000, 6000 and 20,000. The melt of high molecular weight polyethylene glycol is highly viscous, even at a temperature of 200°C (Davidson and Sittig, 1962), and the viscosity increases rapidly with a decrease in temperature. Therefore, as drug-polyethylene glycol dispersion is allowed to solidify quickly, crystallization of drug is retarded due to reduced solute migration and difficulty in nucleation of the drug in viscous medium (Chiou and Riegelman, 1969; Fox et al., 1963; Buckley, 1963). On the other hand, lecithin,

a physiological surfactant, is insoluble, but swells up in water to form a colloidal suspension. The color of lecithin is nearly white when freshly obtained, but rapidly becomes yellow to brown upon exposure to air (Windholz et al., 1976). This may cause undesirable color or physical/ chemical incompatabilities with other ingredients presented in the formulas. Enhancement in the dissolution rate of drugs in the presence of lecithin is probably due to lowering of interfacial tension between drug and dissolution medium as well as micellar solubilization. However, a number of problems have been observed when surfactants were used in the dosage forms, such as a decrease in absorption of drug and changes in the pattern of gastric emptying (Gibaldi and Feldman, 1970). The presence of both lecithin and PEG 20,000 may decrease exposure of drug particles to the dissolution medium which leads to a decrease in dissolution rate of drug as compared to formula with PEG 20,000 alone. Therefore, PEG 20,000 appears to be the best excipient for ibuprofen in freeze-drying solid dispersions.

The marked increase in dissolution of ibuprofen solid dispersions in PEG 20,000 may be explained by the assumption that both compounds may simultaneously crystallize in very small particle sizes (Chiou and Riegelman, 1971c). The increase of specific area due to this reduction of particle size generally increases rates of dissolution and oral absorption of poorly soluble drugs (Salib et al., 1976).

Ultrafine or colloidal crystallite of a solid dispersion system can also be found in the example of a lead-antimony dispersion (Moore, 1983c). In addition to reduction of the crystallite size, the following factors may contribute to the faster dissolution of the drug dispersed system. An increase in drug solubility may occur if the majority of its solid crystallites are extremely small (Martin, 1976). The absence of aggregation and agglomeration between fine crystallites of pure hydrophobic drug may play an important role in increasing rate of dissolution. An aggregate is defined as a particle or an assembly of particles held together by strong inter- or intra-molecular or atomic cohesive forces (Irani and Callis, 1963). Usually the aggregate is stable to high speed mixing or ultrasonic forces. An agglomerate is defined as a gathering of two or more particles and/or aggregates held together by relatively weak cohesive forces. In many cases, these forces are due to an electrostatic surface energy charge generated during handling or processing operations (Irani and Callis, 1963). Such agglomeration is more severe for very finely divided particles due to a greater specific surface charge. Although agglomerates may be broken, their dispersion in mildly stirred dissolution medium may not be very efficient. As mentioned previously, these problems of aggregation and agglomeration are more detrimental to the use of pure fine particles because their effective specific surface area is

markedly reduced. Serious drawbacks of aggregation, agglomeration and lumping in the dissolution medium between pure drug particles are, however, rarely present in solid dispersion systems because the individually dispersed particles are surrounded in the matrix by carrier particles. Aggregation and agglomeration of solid dispersion powders may not significantly affect dissolution of the drug, which can still disintegrate quickly due to more rapid dissolution of the soluble carrier. Another factor that may also be involved with the faster dissolution rate of drug in solid dispersion system is that a possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time. This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea than that of the pure drug with comparable particle size (Goldberg et al., 1966). A similar rationale was also given to the enhancement of dissolution rates of reserpine and polyvinylpyrrolidone (Bates, 1969). Results from the present study as presented in Figures I.23-I.25 and Tables I.27-I.29 also agree with previous reports. Another factor is that excellent wettability and dispersibility of a drug from solid dispersion systems prepared with a water soluble matrix result in an increased dissolution rate of the drug in aqueous media. This is due

Table I.27 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Drug Powder in Various Conditions at pH 7.2

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	63.76 ± 5.58	9.70 ± 2.03	61.84 ± 2.08
10 min	69.46 ± 4.83	55.35 ± 15.98	72.58 ± 3.92
20 min	79.66 ± 4.41	84.04 ± 6.71	79.44 ± 3.00
30 min	83.06 ± 3.98	92.85 ± 4.51	83.80 ± 3.16
45 min	87.85 ± 2.52	96.83 ± 2.81	85.86 ± 3.12
1 hr	90.69 ± 2.21	99.02 ± 2.37	86.33 ± 5.36
1.5 hr	93.59 ± 1.48	99.50 ± 1.62	88.36 ± 2.93
2 hr	92.31 ± 1.09	100.15 ± 1.34	88.36 ± 2.93
3 hr	93.69 ± 0.72	99.61 ± 1.47	88.11 ± 4.33
4 hr	93.61 ± 0.86	100.33 ± 1.61	89.50 ± 3.93
6 hr	93.78 ± 0.87	101.11 ± 1.30	89.44 ± 3.64

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation of 400 mg Ibuprofen drug powder

[d] Preparation of 400 mg Ibuprofen drug powder with 400 mg of PEG 20,000 dissolved in each 900 ml of dissolution medium

[e] Preparation of physically mixed 400 mg of Ibuprofen drug powder with 400 mg of PEG 20,000

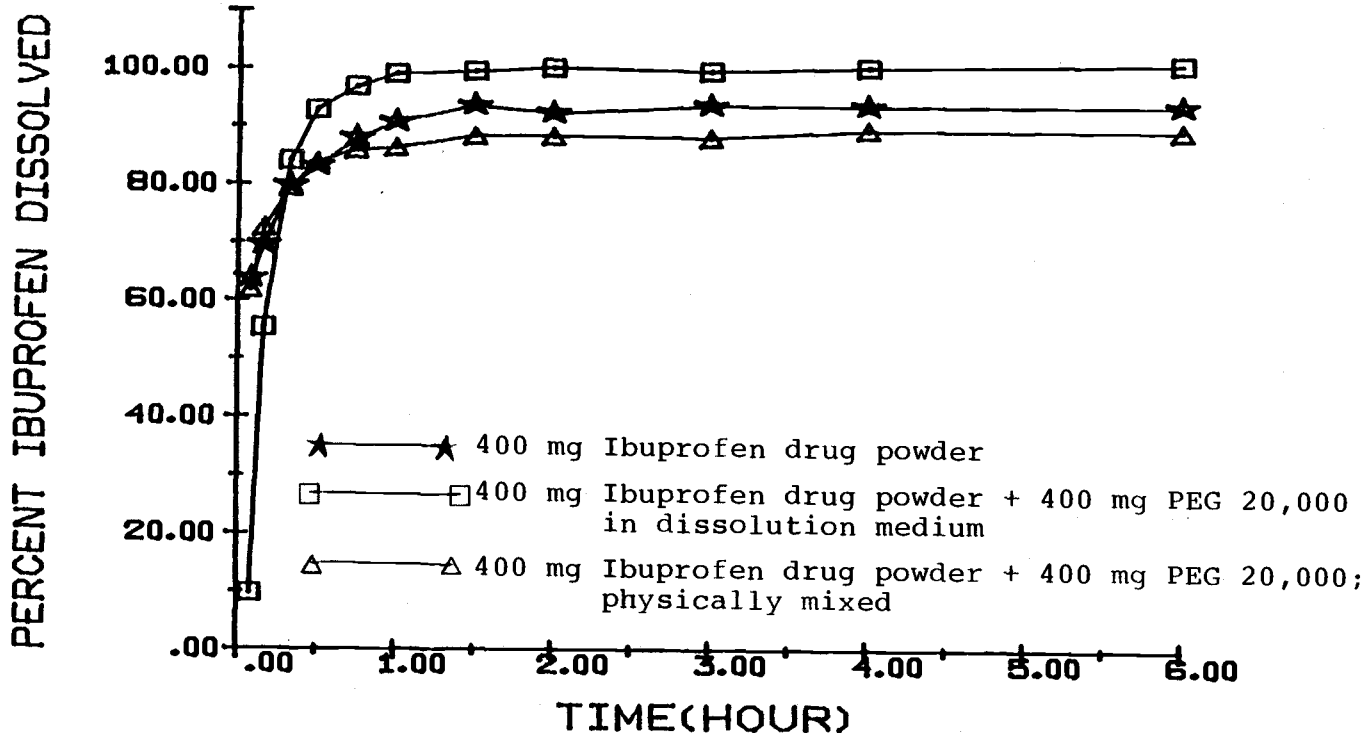

Figure I.23 Dissolution profiles of ibuprofen from 400-mg ibuprofen drug powder in various conditions at pH 7.2

Table I.28 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Drug Powder in Various Conditions at pH 5.4

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	8.66 ± 1.34	2.31 ± 2.31	12.97 ± 2.67
10 min	12.82 ± 2.54	4.77 ± 1.87	29.72 ± 3.78
20 min	19.63 ± 4.22	24.12 ± 3.08	42.00 ± 5.30
30 min	22.85 ± 5.27	33.42 ± 3.28	45.13 ± 4.93
45 min	31.39 ± 4.94	40.12 ± 3.44	48.85 ± 4.38
1 hr	35.26 ± 4.40	44.29 ± 2.75	49.53 ± 4.33
1.5 hr	41.34 ± 3.59	47.08 ± 2.85	49.92 ± 2.86
2 hr	43.05 ± 3.59	48.51 ± 2.38	50.77 ± 1.47
3 hr	46.45 ± 2.70	49.95 ± 1.76	52.24 ± 0.05
4 hr	49.64 ± 1.71	50.54 ± 1.52	53.80 ± 0.69
6 hr	52.04 ± 1.24	50.38 ± 2.09	54.58 ± 0.05

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation of 400 mg Ibuprofen drug powder

[d] Preparation of 400 mg Ibuprofen drug powder with 400 mg of PEG 20,000 dissolved in each 900 ml of dissolution medium

[e] Preparation of physically mixed 400 mg of Ibuprofen drug powder with 400 mg of PEG 20,000

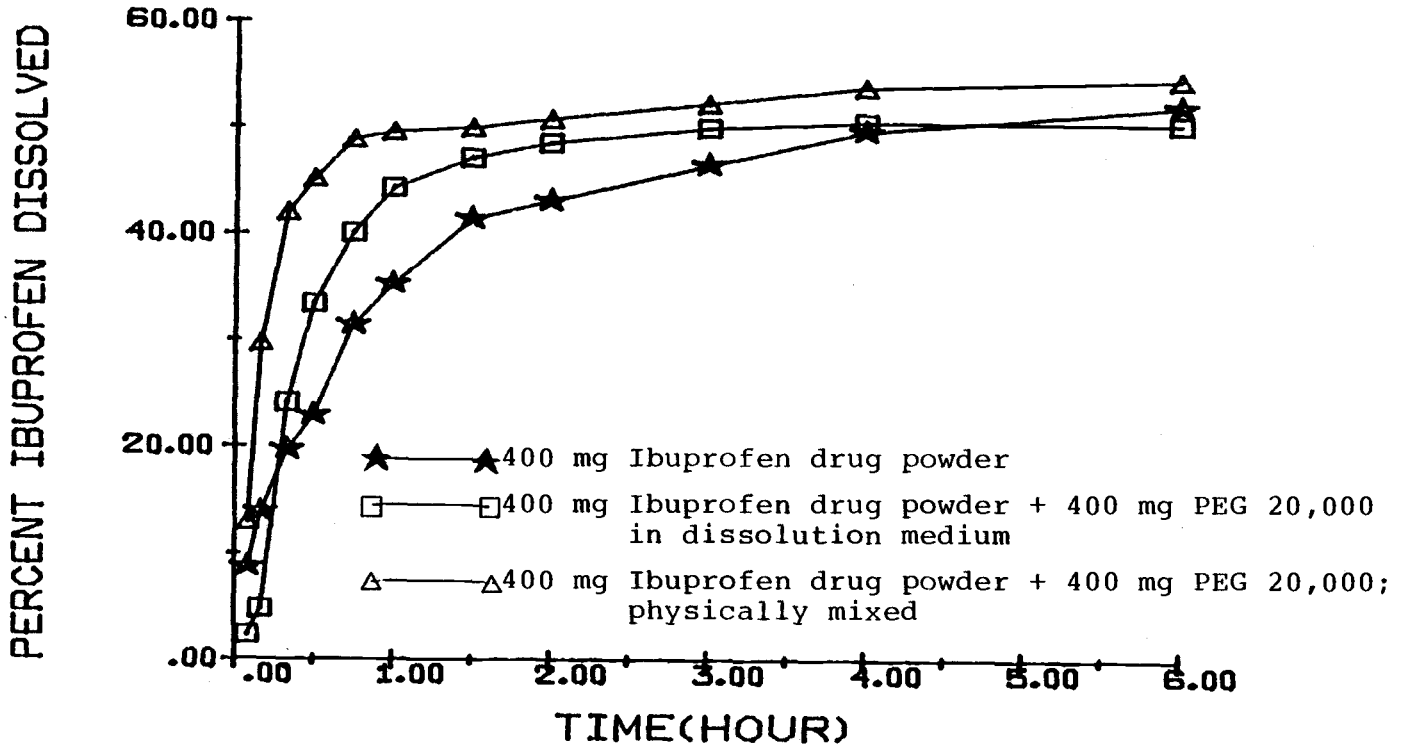

Figure I.24 Dissolution profiles of ibuprofen from 400-mg ibuprofen drug powder in various conditions at pH 5.4

Table I.29 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Drug Powder in Various Conditions at pH 2.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]		
	1[c]	2[d]	3[e]
5 min	----	----	3.16 ± 0.74
10 min	----	----	5.39 ± 0.40
20 min	1.19 ± 0.80	3.59 ± 0.54	7.64 ± 0.40
30 min	1.67 ± 0.33	6.78 ± 0.45	8.09 ± 0.79
45 min	2.20 ± 0.36	8.87 ± 0.44	8.88 ± 0.13
1 hr	3.02 ± 0.38	8.62 ± 0.28	8.67 ± 0.74
1.5 hr	4.26 ± 0.66	8.92 ± 0.55	8.60 ± 0.46
2 hr	5.33 ± 0.84	8.75 ± 0.56	8.48 ± 0.36
3 hr	5.63 ± 0.77	9.28 ± 0.73	9.02 ± 0.35
4 hr	5.46 ± 0.93	9.99 ± 0.26	9.02 ± 0.40
6 hr	5.36 ± 0.78	10.49 ± 0.25	9.71 ± 0.07

[a] Mean value of five determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation of 400 mg Ibuprofen drug powder

[d] Preparation of 400 mg Ibuprofen drug powder with 400 mg of PEG 20,000 dissolved in each 900 ml of dissolution medium

[e] Preparation of physically mixed 400 mg of Ibuprofen drug powder with 400 mg of PEG 20,000

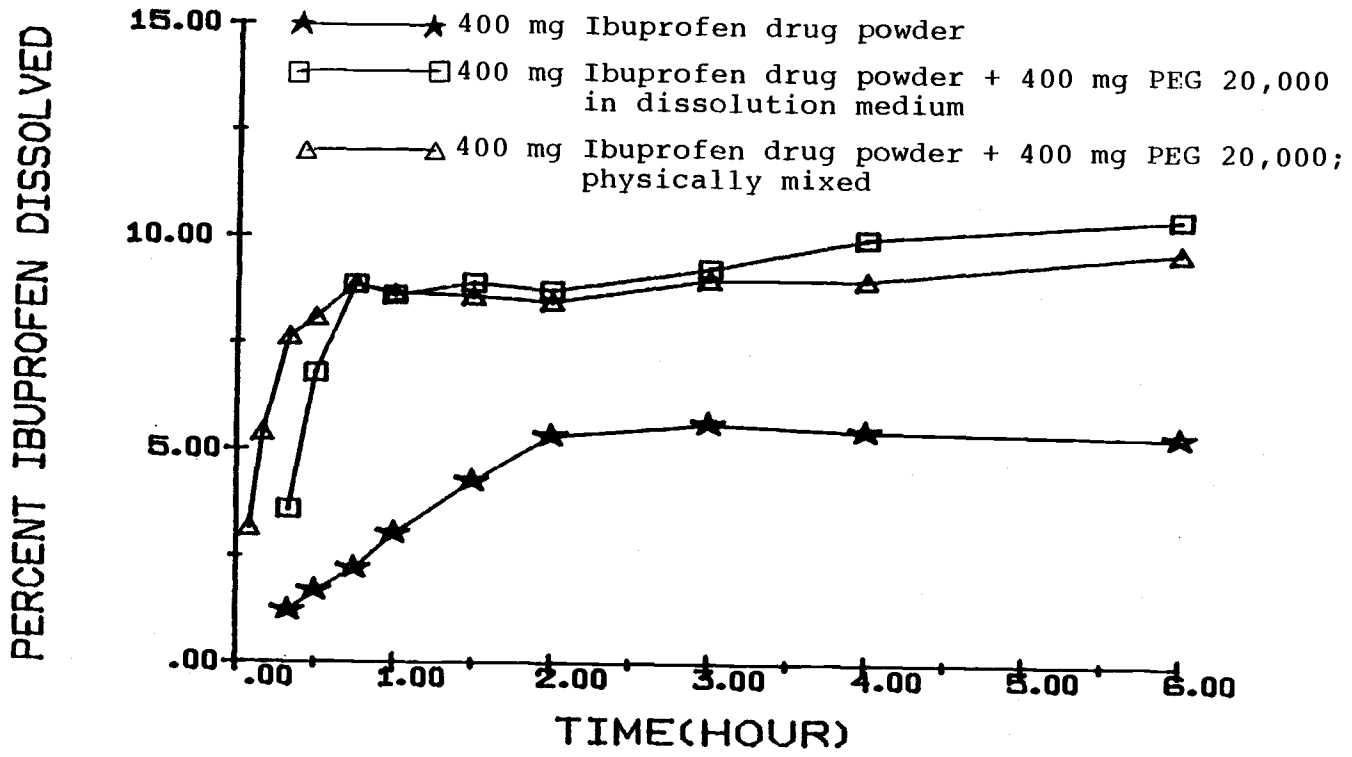

Figure I.25 Dissolution profiles of ibuprofen from 400-mg ibuprofen drug powder in various conditions at pH 2.0

to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier which can readily dissolve and allow water to contact and wet the drug particles. As a consequence, a fine homogenous suspension of a drug can be easily obtained with minimum stirring (Sekiguchi and Obi, 1961). These advantages were observed by Sekiguchi and Obi with various drug-polyethylene glycol solid dispersions. In contrast, the aggregates and agglomerates of poorly soluble pure powders are surrounded by non polar air, which is hard to penetrate or displace by water. An increased rate of dissolution and absorption may also occur if a drug crystallizes in a metastable form after it solidifies from the dispersion system. A metastable crystalline form has a higher solubility which, in turn, leads to a faster dissolution rate, as in the case of phenylbutazone (Matsunaga et al., 1976; Ibrahim et al., 1977). In addition, the drug may also precipitate out in an amorphous form in the crystalline carrier. Since the amorphous form is the highest energy form of a pure drug, it will produce faster dissolution rates than the crystalline form. Amorphous novobiocin has 10-fold higher solubility than its crystalline form (Mullin and Macek, 1060). Crystallinity and dissolution rates of tolbutamide solid dispersions prepared by a melting method was investigated (McGinity et al., 1984). The greater dissolution rate of dispersions prepared by a rapidly cooled process is the

result of a lower degree of crystallinity as compared to those prepared by slowly-cooled process or physical mixing method. Less crystalline or more amorphous forms generally possess greater thermodynamic activities than more crystalline forms of the same substance. Other factors such as high viscosity, complex formation between drug and polyethylene glycol or a combination of these factors may contribute to faster dissolution of drug in dispersed systems.

In this study, ibuprofen solid dispersions were prepared by freeze-drying, direct melting, and a solvent method. An attempt was made to compare dissolution characteristics of ibuprofen prepared by these methods as well as physical mixing of ibuprofen and PEG. Figures I.26-I.28 and Tables I.30-I.32 present the percent dissolved of ibuprofen from solid dispersions obtained by freeze-drying, direct melting, physical mixing and solvent method at pH 7.2, 5.4 and 2.0. Results indicate that dissolution profiles of the freeze-dried product provide the highest dissolution rate and percentage of drug dissolved. However, these differences are within 10% when compared to the direct melting method, and may not provide significant clinical advantages when both products are studied in in-vivo. The most likely explanation for these differences may arise from the methods of preparation of these dispersed systems.

Freeze-drying offers the most rapid cooling process of

Table I.30 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersions in PEG 20,000 at pH 7.2

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	61.84 ± 2.08	66.70 ± 6.16	71.68 ± 10.74	51.88 ± 3.07
10 min	72.58 ± 3.92	86.03 ± 4.07	94.58 ± 4.01	80.23 ± 0.13
20 min	79.44 ± 3.00	98.90 ± 2.66	101.09 ± 0.78	93.02 ± 0.95
30 min	83.80 ± 3.16	101.10 ± 2.21	100.67 ± 0.71	99.75 ± 0.88
45 min	85.86 ± 3.12	100.67 ± 1.30	99.73 ± 0.64	100.61 ± 0.86
1 hr	86.33 ± 5.36	101.46 ± 1.39	100.15 ± 0.36	100.81 ± 2.22
1.5 hr	88.36 ± 2.93	100.35 ± 1.95	99.59 ± 1.75	101.31 ± 1.16
2 hr	88.36 ± 3.69	100.58 ± 2.04	99.11 ± 0.57	100.98 ± 1.55
3 hr	88.11 ± 4.33	99.61 ± 1.89	99.63 ± 1.35	98.99 ± 1.24
4 hr	89.50 ± 3.93	100.00 ± 1.81	99.40 ± 0.29	99.18 ± 0.45
6 hr	89.44 ± 3.64	99.15 ± 1.37	100.01 ± 0.93	99.45 ± 0.41

[a] Mean value of four determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Products prepared by physical mixing method

[d] Products prepared by solvent method

[e] Products prepared by direct melting method

[f] Products prepared by freeze-dried method

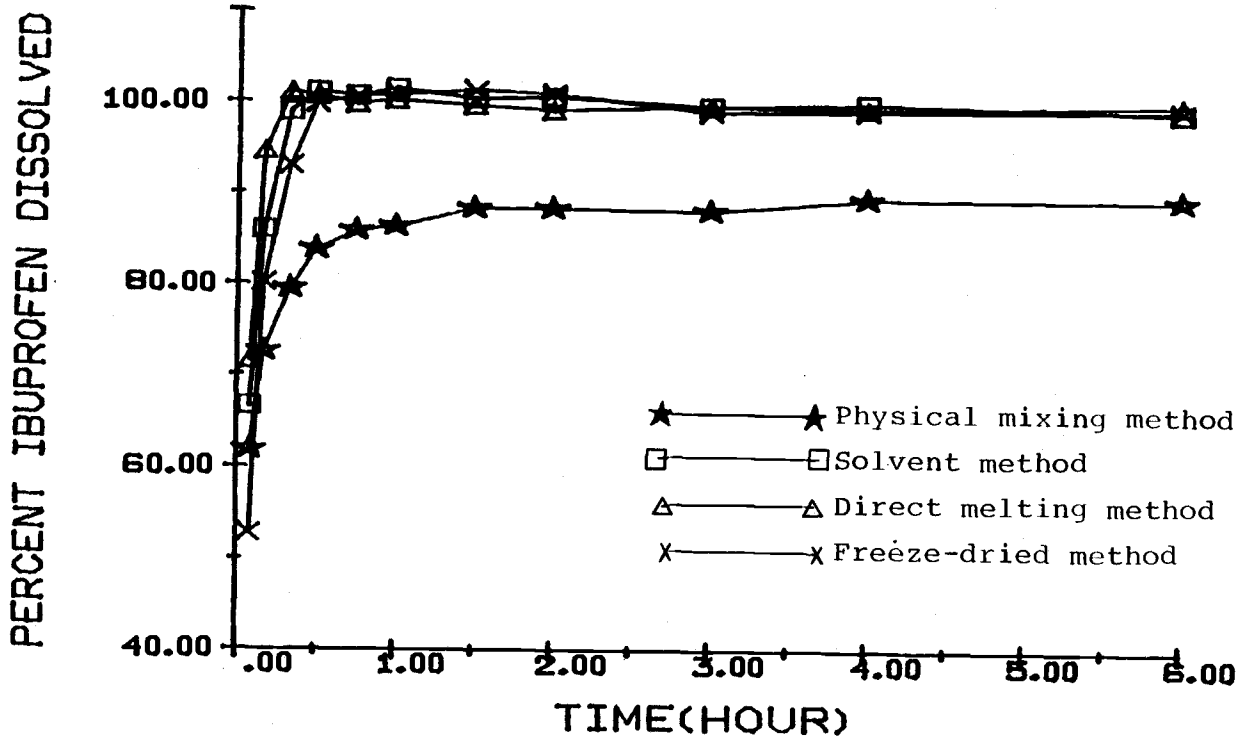

Figure I.26 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersions in PEG 20,000 at pH 7.2

Table I.31 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersions in PEG 20,000 at pH 5.4

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	12.97 ± 2.67	20.91 ± 8.30	18.76 ± 0.89	38.01 ± 6.02
10 min	29.72 ± 3.78	29.70 ± 8.76	27.55 ± 1.01	49.00 ± 3.95
20 min	42.00 ± 5.30	42.01 ± 4.88	36.24 ± 1.36	55.21 ± 3.19
30 min	45.13 ± 4.93	47.29 ± 3.06	41.22 ± 1.62	57.76 ± 2.41
45 min	48.85 ± 4.38	53.02 ± 1.45	47.28 ± 1.87	58.39 ± 2.18
1 hr	49.53 ± 4.33	53.33 ± 1.06	50.06 ± 1.74	59.33 ± 1.82
1.5 hr	49.92 ± 2.86	54.92 ± 0.71	54.19 ± 1.30	60.27 ± 1.68
2 hr	50.77 ± 1.47	55.28 ± 0.74	55.97 ± 1.12	61.28 ± 1.21
3 hr	52.24 ± 0.05	54.56 ± 1.76	58.00 ± 0.29	61.16 ± 1.98
4 hr	53.80 ± 0.69	55.26 ± 1.53	57.47 ± 0.54	60.19 ± 1.41
6 hr	54.58 ± 0.05	55.64 ± 0.75	58.62 ± 0.76	61.39 ± 1.94

[a] Mean value of four determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Products prepared by physical mixing method

[d] Products prepared by solvent method

[e] Products prepared by direct melting method

[f] Products prepared by freeze-dried method

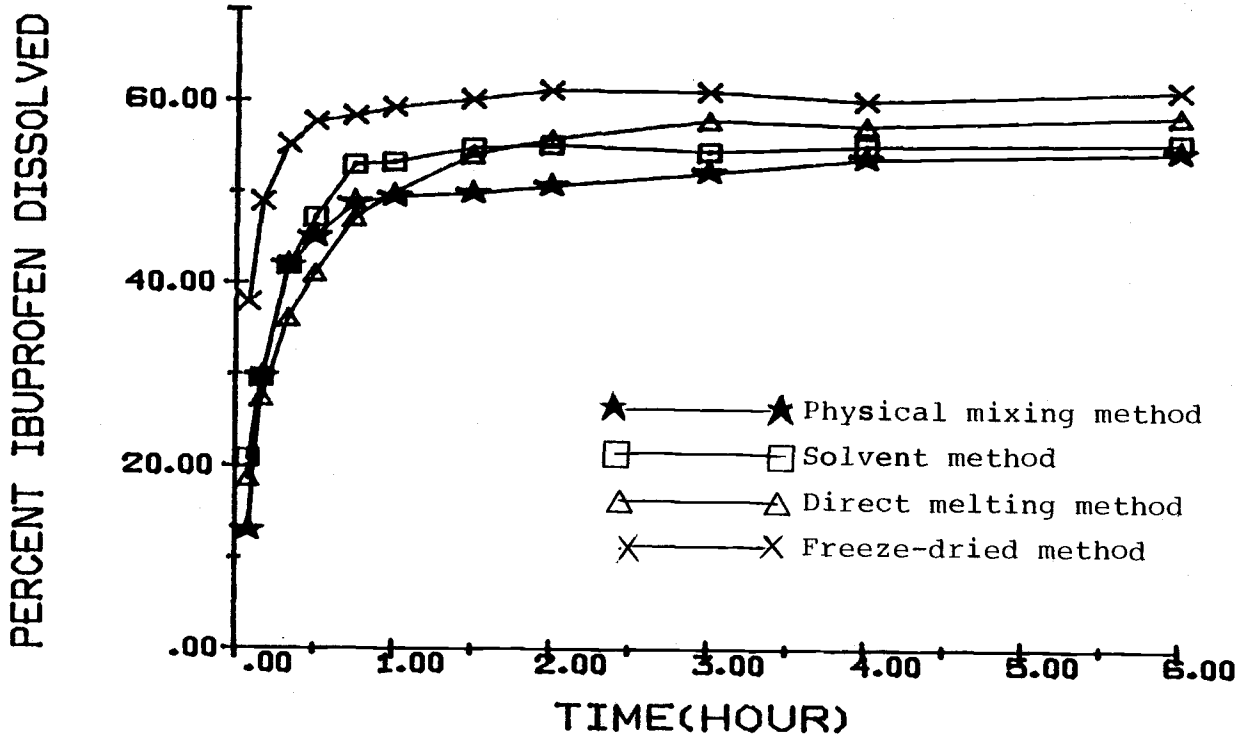

Figure I.27 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersions in PEG 20,000 at pH 5.4

Table I.32 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersions in PEG 20,000 at pH 2.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	3.16 ± 0.74	2.66 ± 0.52	6.93 ± 0.85	5.70 ± 2.13
10 min	5.39 ± 0.40	3.34 ± 1.36	7.51 ± 0.35	9.35 ± 0.42
20 min	7.64 ± 0.40	6.73 ± 0.62	7.98 ± 0.07	11.96 ± 0.73
30 min	8.09 ± 0.79	7.57 ± 1.09	7.96 ± 0.23	13.36 ± 0.57
45 min	8.88 ± 0.13	8.80 ± 0.38	8.43 ± 0.27	12.42 ± 0.54
1 hr	8.67 ± 0.74	9.76 ± 0.53	8.57 ± 0.48	12.07 ± 0.12
1.5 hr	8.60 ± 0.46	9.56 ± 0.27	8.66 ± 0.32	12.64 ± 0.62
2 hr	8.48 ± 0.36	10.18 ± 0.29	8.99 ± 0.42	13.24 ± 0.04
3 hr	9.02 ± 0.35	10.36 ± 0.28	10.01 ± 0.09	12.71 ± 0.22
4 hr	9.02 ± 0.40	10.36 ± 0.29	9.57 ± 0.30	12.96 ± 0.25
6 hr	9.71 ± 0.07	11.11 ± 0.79	10.51 ± 0.22	13.22 ± 0.56

[a] Mean value of four determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Products prepared by physical mixing method

[d] Products prepared by solvent method

[e] Products prepared by direct melting method

[f] Products prepared by freeze-dried method

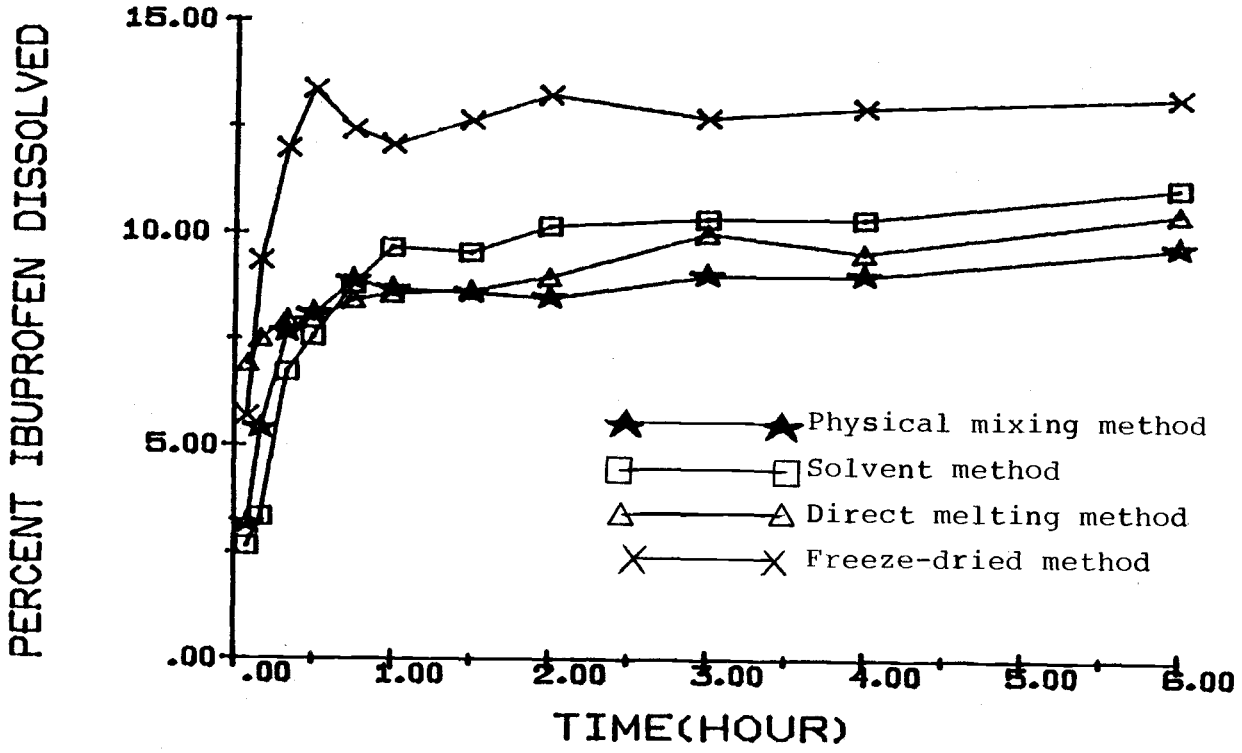

Figure I.28 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersions in PEG 20,000 at pH 2.0

all the methods available for preparing the solid dispersion. The particle size will be in an extremely fine state of subdivision due to the extremely high viscosity of the excipient at the low temperature and the short time interval for completion of solidification during freeze-drying. The formation of metastable or amorphous form of drug can be expected as the result of rapid solidification. Also, crystallization of drug is retarded due to reduced solid migration and the difficulty in nucleation of the drug in the viscous medium if the drug-polyethylene glycol is allowed to solidify rapidly. Thus, quick freezing followed by powdering may be an equally good method without using the "freeze-drying".

When the dispersion systems are prepared by solvent method using ethyl alcohol as a principal solvent, particles of solid drug are deposited from solution in ethyl alcohol, and this process is believed to be largely independent of the nature of the excipient (Kaur er al., 1980). In addition, drug solubility and the low viscosity of the excipient in the solvent during the solidification process can exert influences on particle sizes which drug particles may not be as small as those obtained by freeze-drying technique. For direct melting method, there is no liquid component present in the final product. This results in increased hardness of solidified masses. The effect of such increased hardness may retard dissolution of drug. The

composition of a dispersed system prepared by direct melting may have a significant effect on the particle size of drug. If it is made up of a high weight fraction of drug, an ultrafine crystallization of the drug may not be obtained (Moore, 1983b). As mentioned before, the short interval of solidification is critical in the formation of metastable or amorphous form of drug from the viscous dispersion systems. Therefore, in the direct melting method of preparation, control of temperature and time of solidification are very important to the final physical properties of solid dispersion (McGinity et al., 1984). Also, slow dissolution rates found in physical mixing of drug and PEG 20,000 may be a result of poor wettability of drug particles by the dissolution medium. Dispersion of a drug in an excipient by traditional mechanical mixing is not an effective technique to reduce particle size. However, the presence of PEG in the formula prepared by physical mixing or in the dissolution medium results in increased dissolution rate of drug compared to drug powder alone as presented in Figures I.23-I.25 and Tables I.27-I.29. This may be explained by a possible solubilization effect of polyethylene glycol in lowering the surface tension between drug and dissolution medium.

The effect of PEG 20,000 weight fraction on dissolution rates of drug were also examined by varying amounts of PEG 20,000 in a freeze-dried product. Results are shown in

Table I.33 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersion Freeeze-Dried Products with Various Proportions of PEG 20,000 at pH 7.2

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	81.17 ± 4.18	52.82 ± 3.07	66.56 ± 19.50	66.27 ± 12.07
10 min	97.28 ± 2.39	80.23 ± 0.13	88.41 ± 12.38	93.85 ± 14.55
20 min	100.24 ± 1.17	93.02 ± 0.95	94.25 ± 3.04	100.35 ± 5.93
30 min	100.35 ± 0.95	99.75 ± 0.88	96.84 ± 0.68	103.59 ± 1.98
45 min	100.29 ± 0.54	100.61 ± 0.86	97.59 ± 0.54	104.31 ± 1.60
1 hr	99.99 ± 0.71	100.81 ± 2.22	97.35 ± 0.48	104.10 ± 1.67
1.5 hr	99.91 ± 0.59	101.31 ± 1.16	97.35 ± 0.55	104.07 ± 1.51
2 hr	90.80 ± 0.65	100.98 ± 1.55	96.97 ± 1.50	104.55 ± 1.36
3 hr	99.55 ± 0.86	98.99 ± 1.24	96.81 ± 0.82	103.55 ± 1.30
4 hr	99.66 ± 0.88	99.18 ± 0.05	97.02 ± 0.83	103.93 ± 1.52
6 hr	99.83 ± 0.95	99.45 ± 0.41	97.05 ± 0.53	104.89 ± 1.17

[a] Mean value of four determinations%

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation with PEG 20,000 33.33%

[d] Preparation with PEG 20,000 50.00%

[e] Preparation with PEG 20,000 60.00%

[f] Preparation with PEG 20,000 66.67%

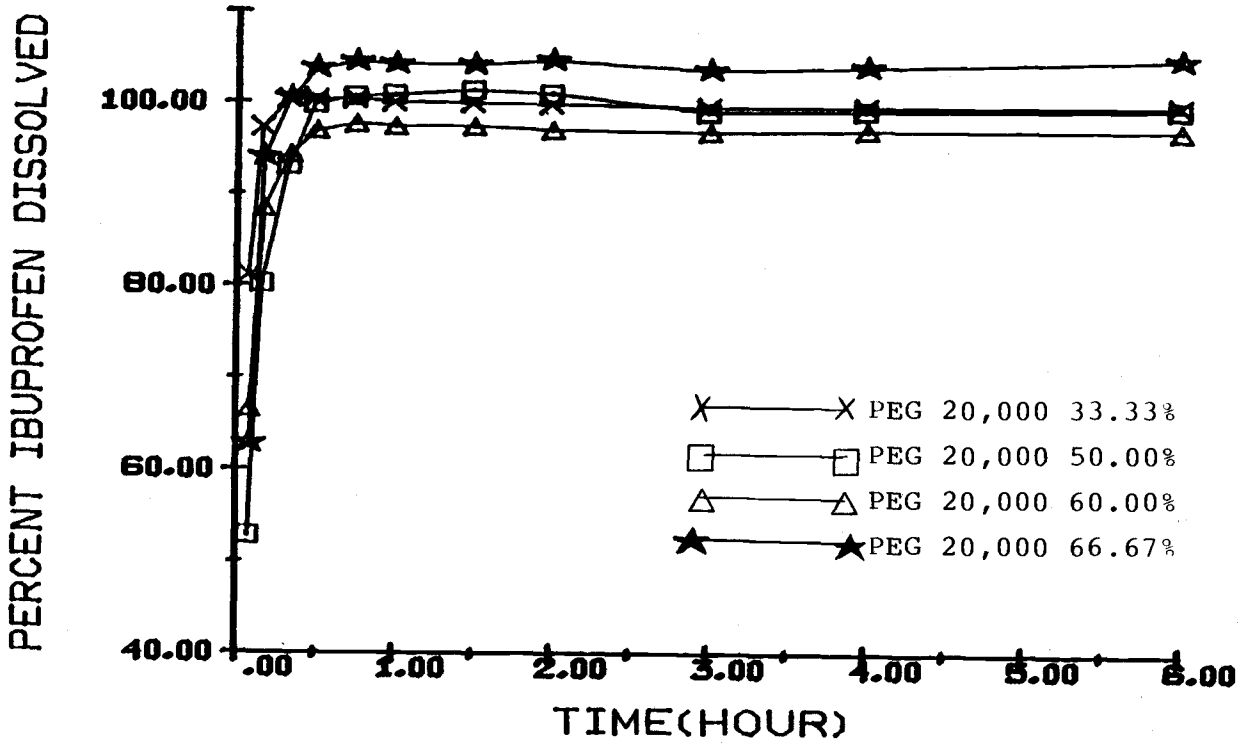

Figure I.29 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersion freeze-dried products with various proportions of PEG 20,000 at pH 7.2

Table I.34 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersion Freeeze-Dried Products with Various Proportions of PEG 20,000 at pH 5.4

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	21.58 ± 1.81	38.01 ± 6.02	37.23 ± 1.32	26.08 ± 3.95
10 min	33.65 ± 3.02	49.00 ± 3.95	45.77 ± 0.91	42.39 ± 2.75
20 min	41.09 ± 2.91	55.21 ± 3.19	50.62 ± 0.59	51.62 ± 0.82
30 min	44.13 ± 2.40	57.76 ± 2.41	52.21 ± 1.35	52.48 ± 1.87
45 min	46.90 ± 2.41	58.39 ± 2.18	52.86 ± 0.90	52.19 ± 2.01
1 hr	48.17 ± 1.77	59.33 ± 1.82	53.38 ± 0.95	52.83 ± 2.25
1.5 hr	50.90 ± 1.95	60.27 ± 1.68	53.83 ± 1.22	54.44 ± 1.32
2 hr	51.90 ± 0.73	61.28 ± 1.21	54.17 ± 0.90	53.58 ± 1.17
3 hr	51.22 ± 0.55	61.16 ± 1.98	56.26 ± 1.28	54.78 ± 0.80
4 hr	51.96 ± 1.17	60.19 ± 1.41	55.98 ± 0.81	53.60 ± 1.65
6 hr	51.92 ± 0.99	61.39 ± 1.94	55.66 ± 0.67	54.78 ± 0.69

[a] Mean value of four determinations

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation with PEG 20,000 33.33%

[d] Preparation with PEG 20,000 50.00%

[e] Preparation with PEG 20,000 60.00%

[f] Preparation with PEG 20,000 66.67%

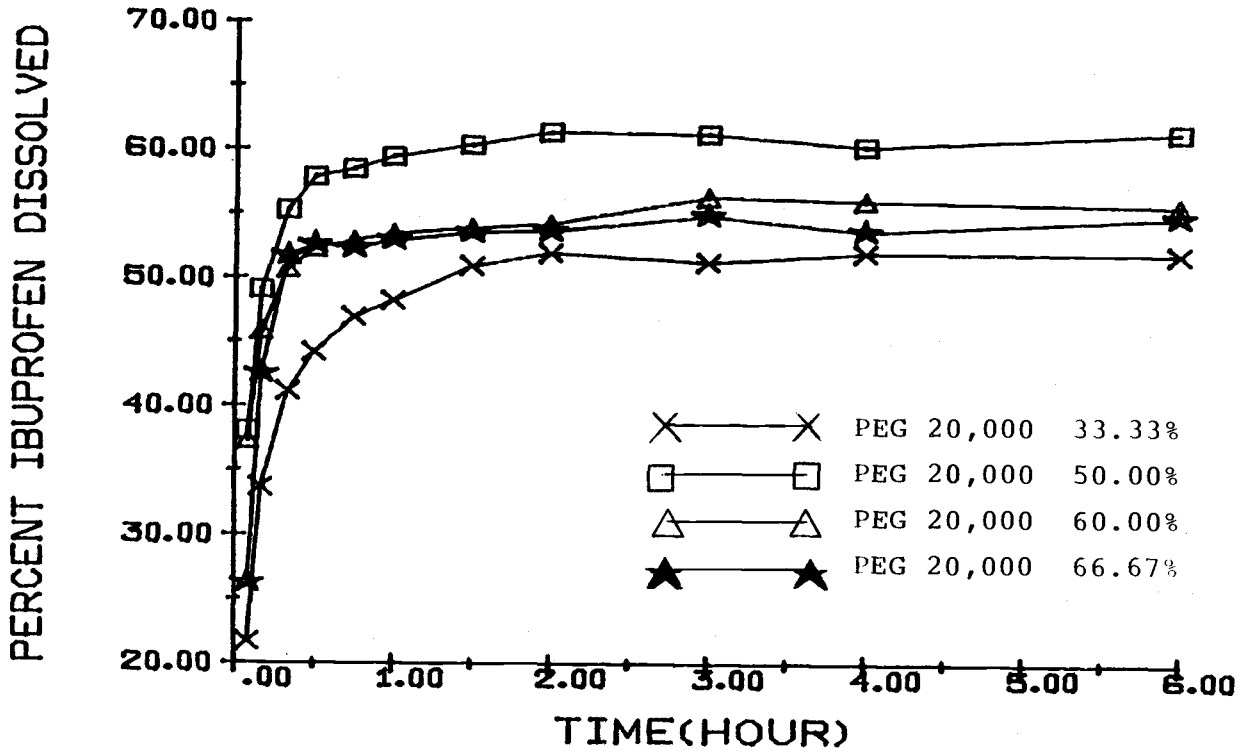

Figure I.30 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersion freeze-dried products with various proportions of PEG 20,000 at pH 5.4

Table I.35 In Vitro Dissolution of Ibuprofen from 400-mg Ibuprofen Solid Dispersion Freeeze-Dried Products with Various Proportions of PEG 20,000 at pH 2.0

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	1[c]	2[d]	3[e]	4[f]
5 min	2.26 ± 0.74	5.70 ± 2.13	4.34 ± 1.44	5.88 ± 1.00
10 min	5.41 ± 0.74	9.35 ± 0.42	6.53 ± 1.53	8.66 ± 0.39
20 min	7.40 ± 0.46	11.96 ± 0.73	7.87 ± 0.79	9.00 ± 0.18
30 min	7.71 ± 0.65	13.36 ± 0.57	8.44 ± 0.22	9.13 ± 0.26
45 min	7.61 ± 0.28	12.42 ± 0.54	8.46 ± 0.25	9.22 ± 0.32
1 hr	7.96 ± 0.21	12.07 ± 0.12	8.65 ± 0.26	8.90 ± 0.09
1.5 hr	7.77 ± 0.13	12.64 ± 0.62	8.62 ± 0.47	9.52 ± 0.31
2 hr	7.83 ± 0.09	13.24 ± 0.04	8.75 ± .26	9.72 ± 0.08
3 hr	8.67 ± 0.11	12.71 ± 0.22	8.78 ± 0.23	9.45 ± 0.09
4 hr	8.35 ± 0.13	12.96 ± 0.25	8.70 ± 0.27	9.35 ± 0.39
6 hr	9.03 ± 0.29	13.22 ± 0.56	8.69 ± 0.29	9.72 ± 0.40

[a] Mean value of four determinations%

[b] Standard deviation values for each mean percent of Ibuprofen released value

[c] Preparation with PEG 20,000 33.33%

[d] Preparation with PEG 20,000 50.00%

[e] Preparation with PEG 20,000 60.00%

[f] Preparation with PEG 20,000 66.67%

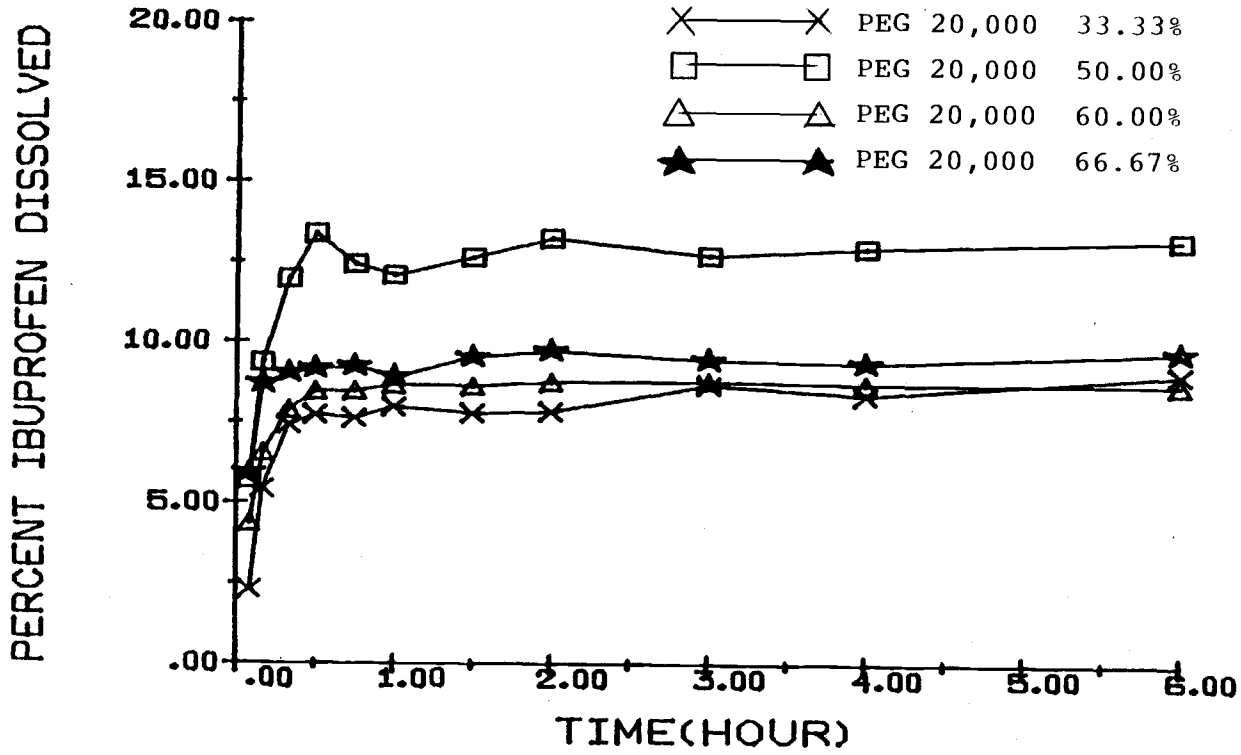

Figure I.31 Dissolution profiles of ibuprofen from 400-mg ibuprofen solid dispersion freeze-dried products with various proportions of PEG 20,000 at pH 2.0

Figures I.29-I.31 and Tables I.33-I.35. The optimal amount of PEG 20,000 was 50%. Less resulted in decreased dissolution rates while more amount results in no significant increase in dissolution of drug. This may be due to the fact that the higher the dilution, the finer the crystalline size of drug its precipitates until this reaches the optimal point where increase in the dilution does not affect the size of the precipitates. This finding agrees with those reported previously (Suvanakoot, 1984; Said et al., 1974; Salib et al., 1976).

Ibuprofen freeze-dried formula (ratio of drug to PEG 20,000 50:50) was chosen to make 100-mg tablets for a humidity aging study because it gave the best dissolution profiles in-vitro. Dissolution rate plots of these tablets as well as those from commercial brands are obtained as a function of storage time and percent relative humidity. The results are shown in Figures I.32-I.35 and Tables I.36-I.39. For commercial brands (Motrin®, Rufen® and Advil®), aging of these tablets in 98% relative humidity result in a significant reduction of the rate and amount of ibuprofen released. After 3 days aging, all commercial brand products failed to meet USP specifications of not less than 50% of drug dissolved in 30 minutes with the average dissolution being only 10.4% for Motrin, 30% for Rufen and 5.8% for Advil. After 7 days or 14 days aging at 98% relative humidity both Motrin and Rufen products dissolved

Table I.36 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) Aged by Exposure to 98% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	12.4 ± 6.23	2.8 ± 0.49	0.7 ± 0.67	1.3 ± 1.04
20 min	75.5 ± 3.61	6.8 ± 3.23	1.0 ± 0.69	2.3 ± 0.01
30 min	84.7 ± 2.39	10.4 ± 5.39	1.9 ± 0.71	2.7 ± 0.44
45 min	94.7 ± 1.25	12.9 ± 4.40	3.2 ± 0.75	2.9 ± 0.47
1 hr	96.1 ± 1.83	14.5 ± 4.87	4.4 ± 1.00	1.3 ± 0.27
2 hr	100.6 ± 1.25	20.3 ± 5.85	6.9 ± 1.71	8.9 ± 1.48
3 hr	100.6 ± 0.82	26.2 ± 7.77	10.1 ± 2.51	13.0 ± 2.71
4 hr	101.1 ± 0.82	32.5 ± 8.01	13.3 ± 3.05	16.1 ± 3.42
6 hr	99.7 ± 1.43	42.5 ± 8.27	----	----
24 hr	101.3 ± 1 57	89.7 ± 2 68	81.2 ±11.35	80.5 ± 7.41

[a] Mean values for six tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

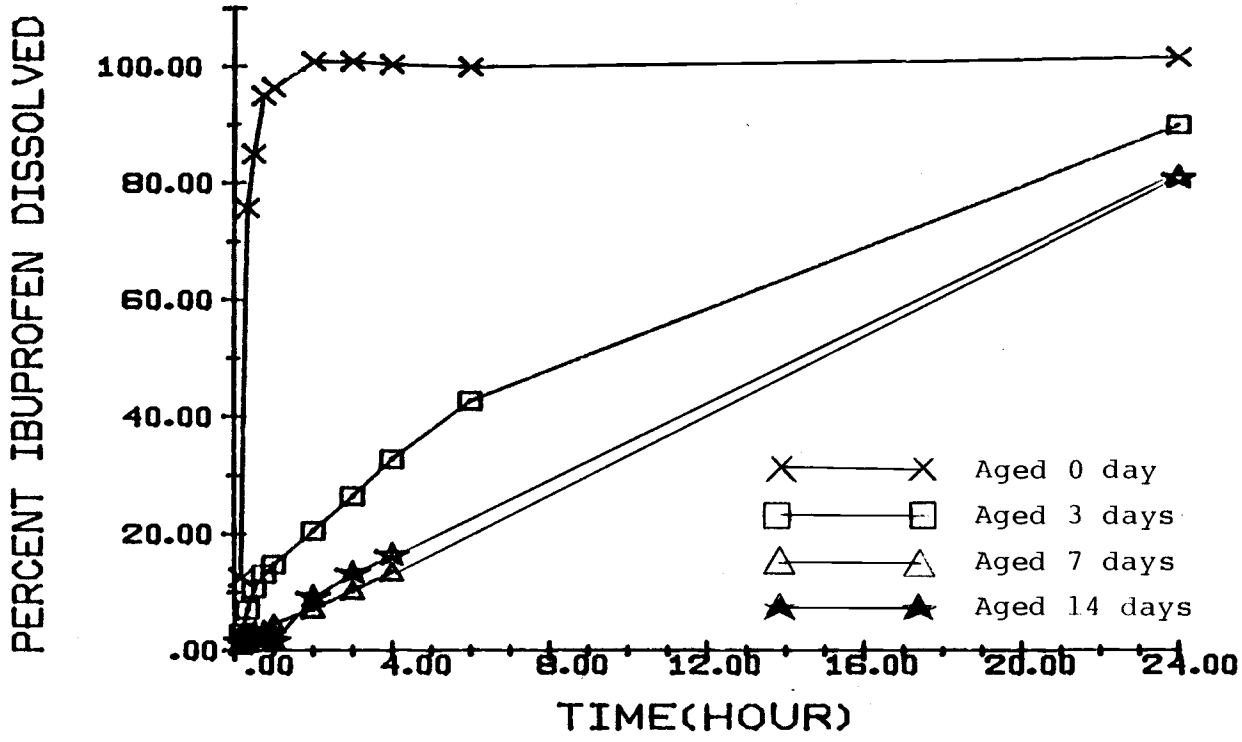

Figure I.32 Dissolution profiles of ibuprofen from Motrin Tablets (400-mg ibuprofen)aged by exposure to 98% relative humidity

Table I.37 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) Aged by Exposure to 98% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	59.68 ± 9.56	7.17 ± 6.69	1.13 ± 0.67	1.9 ± 0.99
20 min	93.32 ± 3.34	21.0 ± 16.57	1.62 ± 0.69	2.6 ± 0.46
30 min	98.73 ± 1.21	30.1 ± 19.00	3.0 ± 0.71	3.6 ± 0.40
45 min	98.94 ± 0.53	39.3 ± 22.74	3.9 ± 0.75	5.1 ± 0.64
1 hr	98.97 ± 0.77	46.1 ± 25.24	5.0 ± 1.00	6.5 ± 0.95
2 hr	98.92 ± 1.51	59.3 ± 27.47	8.2 ± 1.71	9.7 ± 1.66
3 hr	99.98 ± 1.23	67.6 ± 26.38	11.8 ± 2.51	11.9 ± 1.52
4 hr	99.75 ± 0.73	75.8 ± 27.58	14.2 ± 3.05	14.5 ± 1.62
6 hr	100.81 ± 0.75	80.6 ± 25.38	----	----
24 hr	99.65 ± 1.58	100.10 ± 7.37	67.1 ±11.35	71.1 ± 5.90

[a] Mean values for six tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

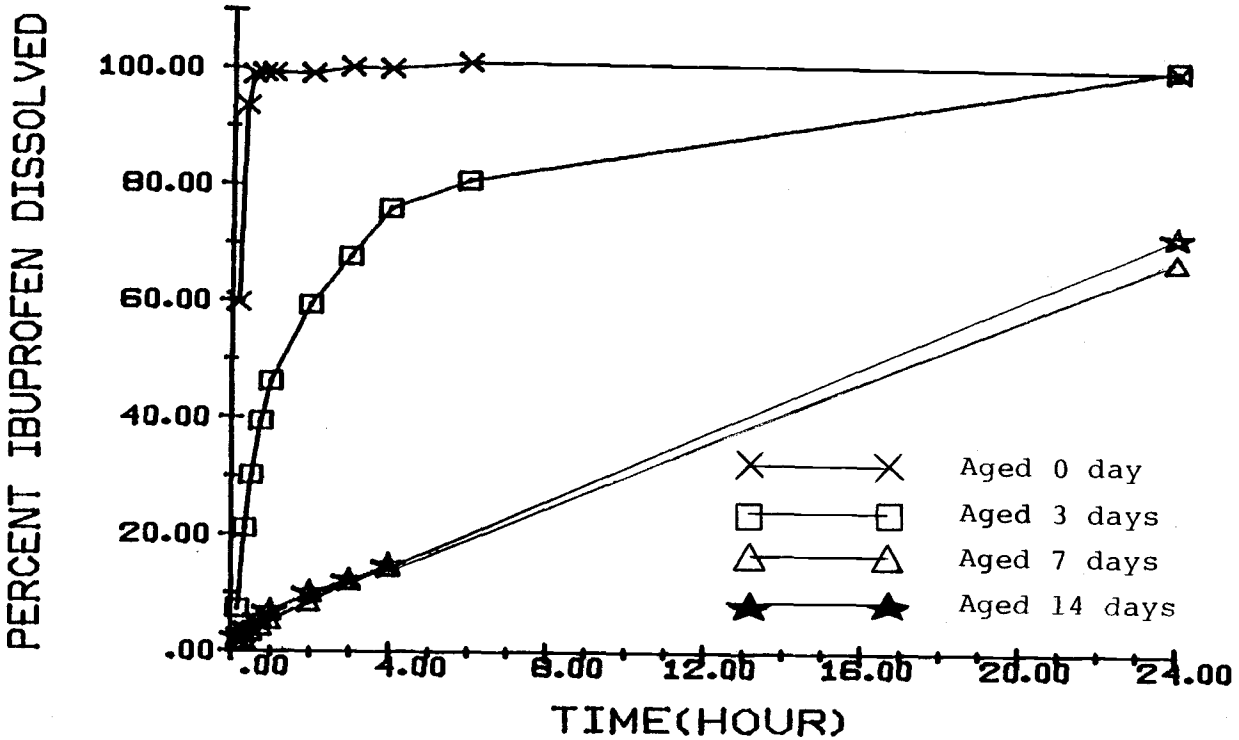

Figure I.33 Dissolution profiles of ibuprofen from Rufen Tablets (400-mg ibuprofen)aged by exposure to 98% relative humidity

Table I.38 In Vitro Dissolution of Advil Tablets (200-mg Ibuprofen) Aged by Exposure to 98% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	9.82 ± 9.14	1.50 ± 0.22	0.74 ± 0.33	1.80 ± 0.30
20 min	85.62 ± 3.00	3.53 ± 0.30	2.86 ± 0.30	3.35 ± 0.42
30 min	98.90 ± 1.60	5.36 ± 0.43	4.93 ± 1.01	5.23 ± 0.30
45 min	100.55 ± 1.21	6.81 ± 0.25	7.19 ± 1.66	7.11 ± 0.59
1 hr	100.62 ± 1.39	17.19 ± 7.24	9.11 ± 2.28	9.82 ± 0.52
1.5 hr	100.65 ± 1.25	26.94 ± 8.90	14.26 ± 2.76	12.58 ± 0.43
2 hr	100.70 ± 1.31	49.81 ±11.15	18.50 ± 4.75	16.59 ± 0.82
3 hr	100.33 ± 1.23	74.18 ± 7.60	28.08 ± 4.45	24.85 ± 1.97
4 hr	100.25 ± 1.32	90.88 ± 6.46	38.33 ± 3.93	33.36 ± 1.86
6 hr	100.26 ± 1.00	102.31 ± 0.94	59.74 ± 1.40	48.34 ± 2.36
24 hr	100.72 ± 1.37	102.89 ± 1.03	100.31 ± 0.17	97.33 ± 0.60

[a] Mean values for three tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

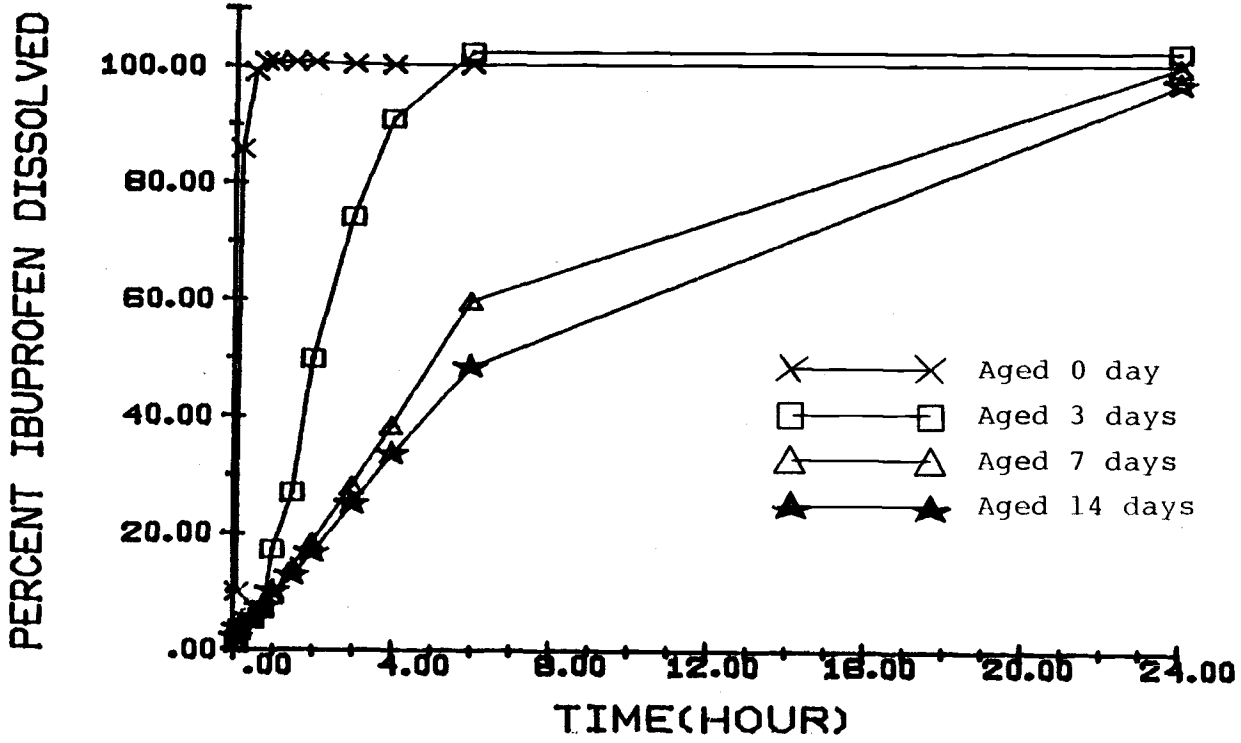

Figure I.34 Dissolution profiles of ibuprofen from Advil Tablets (400-mg ibuprofen)aged by exposure to 98% relative humidity

Table I.39 In Vitro Dissolution of Ibuprofen Freeze-Dried Formulation, 100 mg Tablets Aged by Exposure to 98% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	87.85 ± 6.28	36.94 ± 8.05	44.43 ± 4.60	75.01 ±24.90
20 min	101.86 ± 4.47	73.34 ± 6.12	85.57 ± 2.59	102.55 ± 4.03
30 min	105.27 ± 3.09	97.74 ± 1.09	103.73 ± 2.04	104.00 ± 4.57
45 min	105.16 ± 3.13	106.41 ± 6.00	105.38 ± 1.49	103.77 ± 4.60
1 hr	105.06 ± 3.04	106.69 ± 6.38	105.38 ± 1.16	103.77 ± 4.88
1.5 hr	105.27 ± 3.37	106.65 ± 6.33	105.28 ± 1.33	103.40 ± 4.65
2 hr	105.01 ± 3.00	106.37 ± 6.45	105.18 ± 1.25	103.49 ± 4.62
3 hr	104.96 ± 2.95	106.45 ± 6.53	105.23 ± 1.27	103.30 ± 4.61
4 hr	105.01 ± 3.13	106.69 ± 6.25	105.23 ± 1.27	103.21 ± 4.64
6 hr	105.11 ± 3.22	106.55 ± 6.49	105.28 ± 1.12	103.35 ± 4.53
24 hr	105.06 ± 3.02	106.51 ± 6.45	105.54 ± 1.21	103.86 ± 4.55

[a] Mean values for three tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

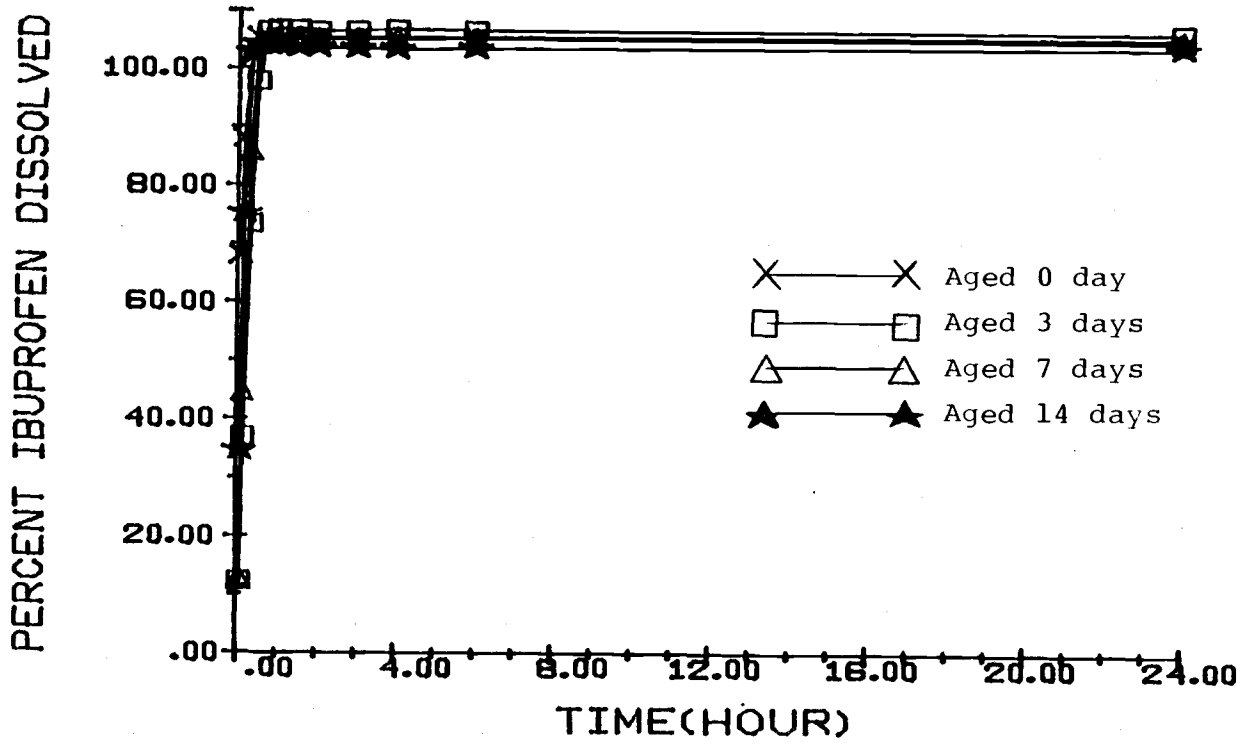

Figure I.35 Dissolution profiles of ibuprofen from freeze-dried formulation, 100-mg tablets aged by exposure to 98% relative humidity

essentially the same, with only about 13% to 16% of the active ingredient dissolving after six hours. For Advil tablets, 48% to 59% of drug dissolved within 6 hours after being stored for 7 to 14 days. This can be explained as less labeled amount of drug for Advil brand as compared to Motrin and Rufen. Figures I.36-I.39 and Tables I.40-I.43 show the effect of 75% relative humidity on dissolution of Motrin®, Rufen® and Advil®. It can be seen that for 75% relative humidity aging, all products were unaffected except one lot of Motrin which showed a depressed dissolution rate after 7 days of storage. However, on the average, it still met U.S.P. dissolution requirements. For tablets obtained from the freeze-dried products, the dissolution rates and amount of drug released were not affected by aging either at 75% or at 98% relative humidity as shown in Figures 35 and 39 and Tables 39 and 43. This is probably the result of the presence of much smaller particle size of drug in freeze-dried products than those in commercial brands.

Table I.40 In Vitro Dissolution of Motrin Tablets (400-mg Ibuprofen) Aged by Exposure to 75% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	12.4 ± 6.23	35.4 ±12.67	13.9 ± 9.73	28.8 ± 13.03
20 min	75.5 ± 3.61	72.2 ±10.31	14.1 ± 6.20	72.0 ± 4.70
30 min	84.7 ± 2.39	82.6 ± 4.51	59.8 ±11.86	83.2 ± 3.49
45 min	94.7 ± 1.25	85.2 ± 4.12	78.2 ± 3.34	87.7 ± 3.53
1 hr	96.1 ± 1.83	87.6 ± 5.76	83.3 ± 7.07	88.4 ± 3.28
2 hr	100.6 ± 1.25	91.7 ± 4.09	85.3 ± 6.95	90.8 ± 2.28
3 hr	100.6 ± 0.82	95.1 ± 2.57	86.6 ± 5.42	91.5 ± 2.08
4 hr	101.1 ± 0.82	97.3 ± 1.45	87.6 ± 5.10	92.5 ± 3.37

[a] Mean values for six tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

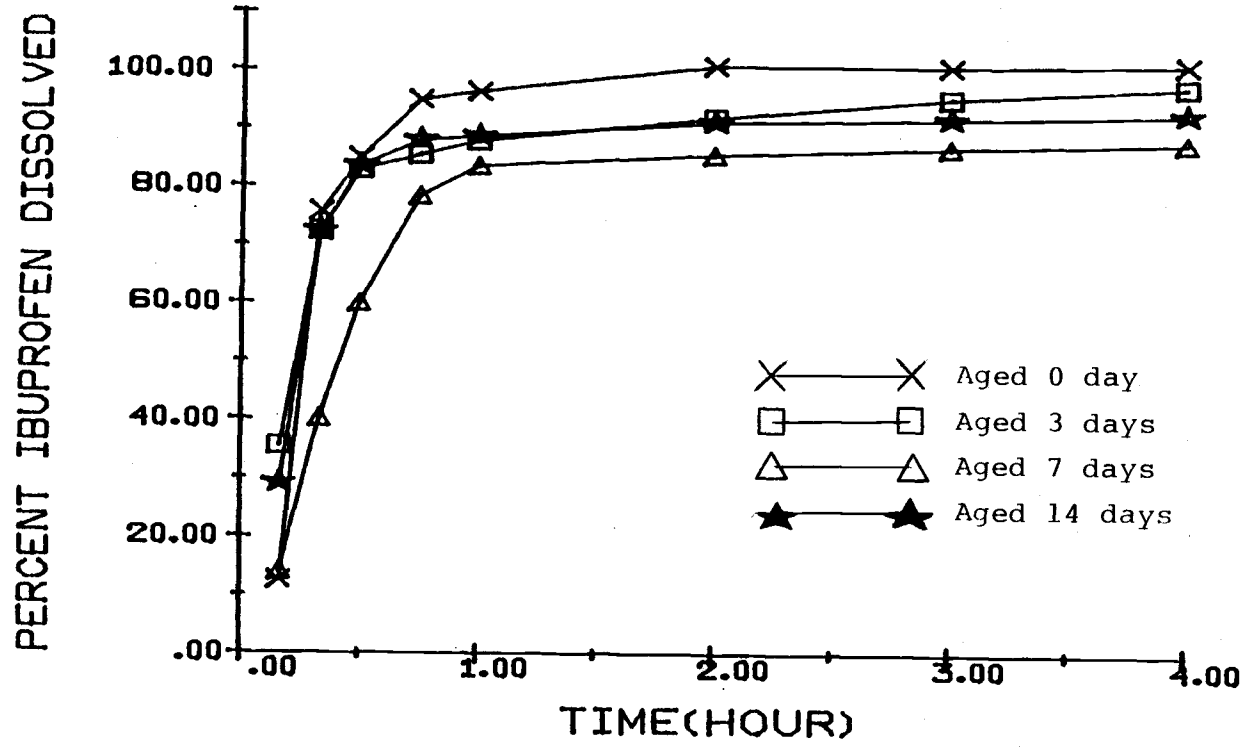

Figure I.36 Dissolution profiles of ibuprofen from Motrin Tablets (400-mg ibuprofen) aged by exposure to 75% relative humidity

Table I.41 In Vitro Dissolution of Rufen Tablets (400-mg Ibuprofen) Aged by Exposure to 75% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	59.68 ± 9.56	59.8 ± 3.61	53.0 ±22.97	59.4 ± 7.43
20 min	93.32 ± 3.34	79.7 ± 1.02	80.3 ± 1.23	75.2 ± 3.07
30 min	98.73 ± 1.21	84.3 ± 1.03	83.3 ± 1.44	85.1 ± 2.83
45 min	98.94 ± 0.53	85.6 ± 1.36	84.6 ± 1.74	86.8 ± 1.94
1 hr	98.97 ± 0.77	86.6 ± 2.39	85.8 ± 1.51	87.9 ± 0.83
2 hr	98.92 ± 1.51	89.9 ± 1.82	86.4 ± 1.79	89.1 ± 1.01
3 hr	99.98 ± 1.23	93.3 ± 1.66	86.8 ± 1.53	90.0 ± 1.24
4 hr	99.75 ± 0.73	96.1 ± 0.98	87.1 ± 1.32	90.8 ± 2.00

[a] Mean values for six tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

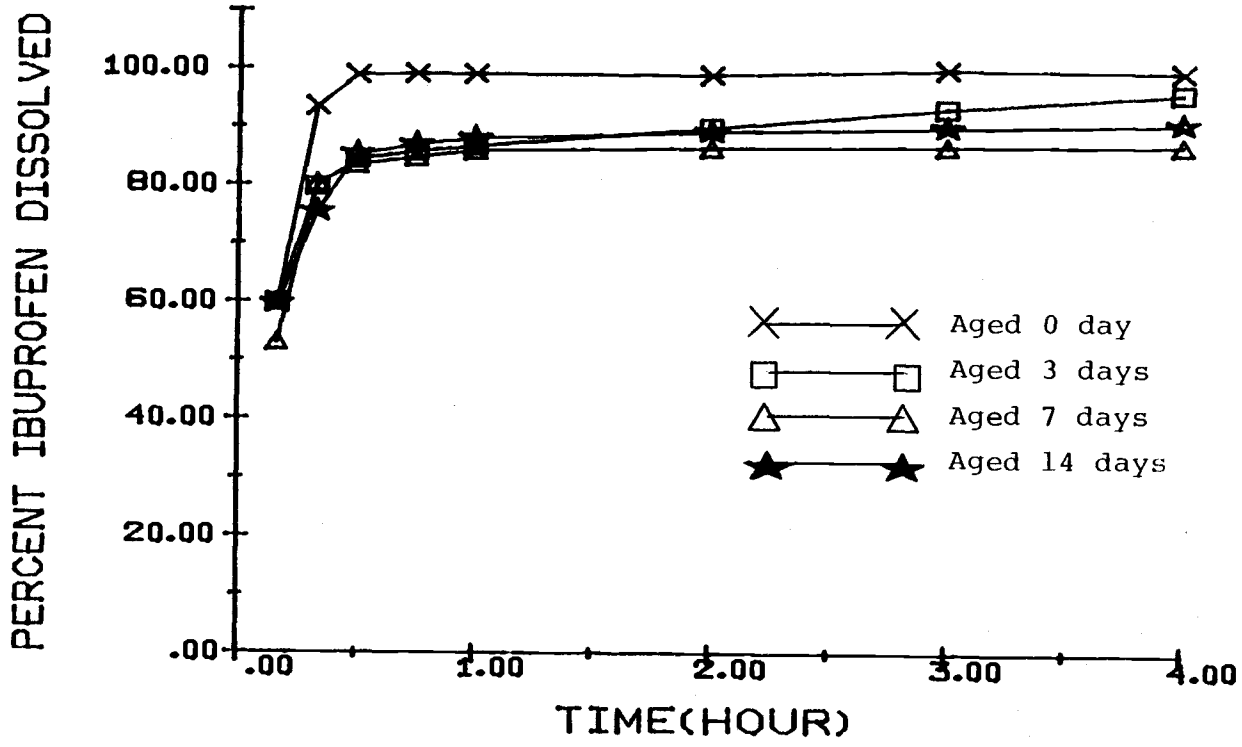

Figure I.37 Dissolution profiles of ibuprofen from Rufen Tablets (400-mg ibuprofen) aged by exposure to 75% relative humidity

Table I.42 In Vitro Dissolution of Advil Tablets (200-mg Ibuprofen) Aged by Exposure to 75% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	9.82 ± 9.14	7.89 ± 0.94	5.08 ± 0.39	5.73 ± 2.26
20 min	85.62 ± 3.00	75.39 ± 6.46	72.75 ± 4.65	72.88 ± 4.46
30 min	98.90 ± 1.60	82.28 ± 1.43	80.02 ± 3.39	79.66 ± 2.75
45 min	100.55 ± 1.21	95.59 ± 1.48	96.55 ± 1.01	89.72 ± 2.98
1 hr	100.62 ± 1.39	98.31 ± 0.96	99.64 ± 2.28	97.59 ± 2.86
1.5 hr	100.65 ± 1.25	99.69 ± 1.00	100.20 ± 2.67	99.48 ± 2.33
2 hr	100.70 ± 1.31	99.78 ± 1.31	99.89 ± 4.50	99.39 ± 2.22
3 hr	100.33 ± 1.23	98.95 ± 1.77	100.02 ± 3.93	99.75 ± 2.39
4 hr	100.25 ± 1.32	98.68 ± 2.02	100.44 ± 2.05	99.44 ± 2.63
6 hr	100.26 ± 1.00	99.72 ± 1.95	100.15 ± 2.78	99.58 ± 1.72
24 hr	100.72 ± 1.37	98.39 ± 1.78	100.17 ± 1.98	99.58 ± 1.68

[a] Mean values for three tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

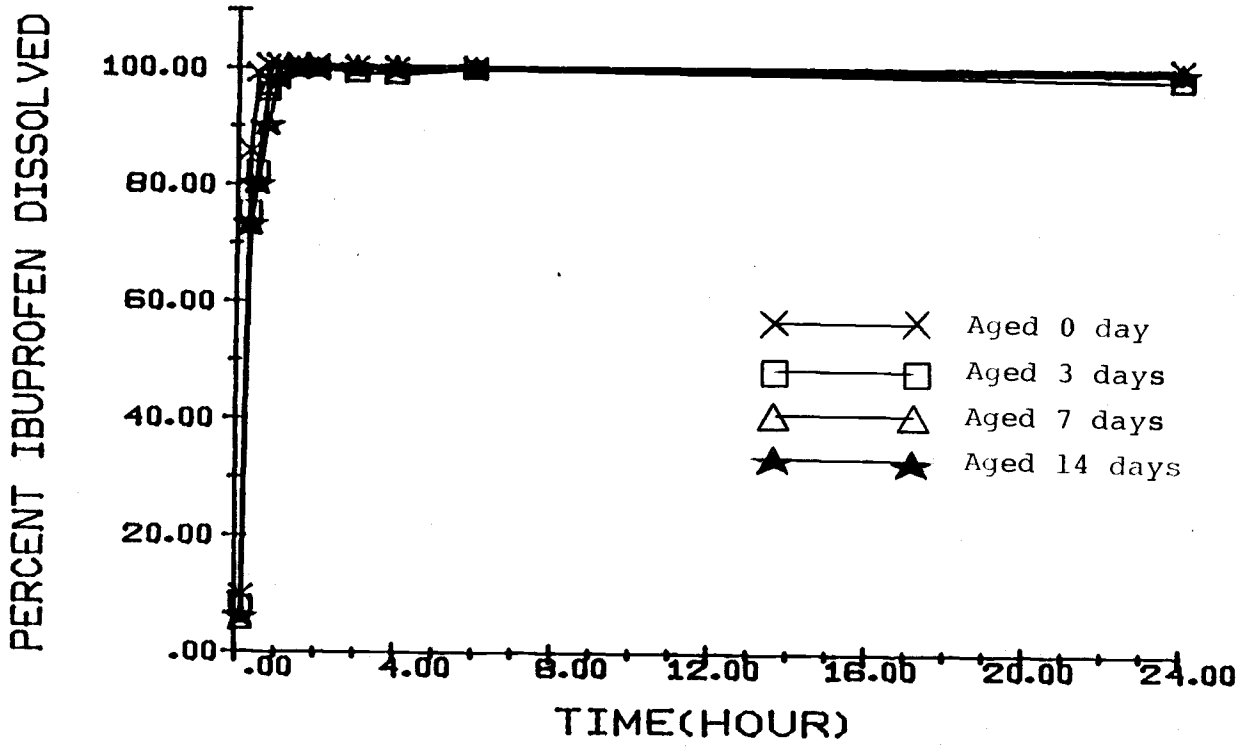

Figure I.38 Dissolution profiles of ibuprofen from Advil Tablets (200-mg ibuprofen) aged by exposure to 75% relative humidity

Table I.43 In Vitro Dissolution of Ibuprofen Freeze-Dried Formulation, 100 mg Tablets Aged by Exposure to 75% Relative Humidity

Dissolution Time	Mean Percent of Label Released[a] ± SD[b]			
	aged o day	aged 3 days	aged 7 days	aged 14 days
10 min	87.85 ± 6.28	80.33 ± 5.58	75.33 ± 4.38	72.66 ±16.22
20 min	101.86 ± 4.47	92.37 ± 3.13	89.67 ± 2.59	87.26 ±18.39
30 min	105.27 ± 3.09	103.46 ± 2.27	103.73 ± 2.04	102.02 ± 3.57
45 min	105.16 ± 3.13	105.41 ± 1.35	106.69 ± 2.38	103.67 ± 2.60
1 hr	105.06 ± 3.04	105.69 ± 2.04	106.28 ± 3.26	103.78 ± 3.88
1.5 hr	105.27 ± 3.37	105.69 ± 2.00	106.37 ± 1.61	104.35 ± 3.56
2 hr	105.01 ± 3.00	105.37 ± 1.95	106.45 ± 1.33	103.98 ± 3.26
3 hr	104.96 ± 2.95	105.62 ± 2.13	106.69 ± 1.52	103.78 ± 3.16
4 hr	105.01 ± 3.13	105.66 ± 1.22	106.55 ± 1.37	104.02 ± 3.46
6 hr	105.11 ± 3.22	105.74 ± 1.03	106.51 ± 1.27	103.88 ± 3.35
24 hr	105.06 ± 3.02	105.76 ± 1.75	106.58 ± 2.31	104.10 ± 3.55

[a] Mean values for three tablets

[b] Standard deviation values for each mean percent of Ibuprofen released value

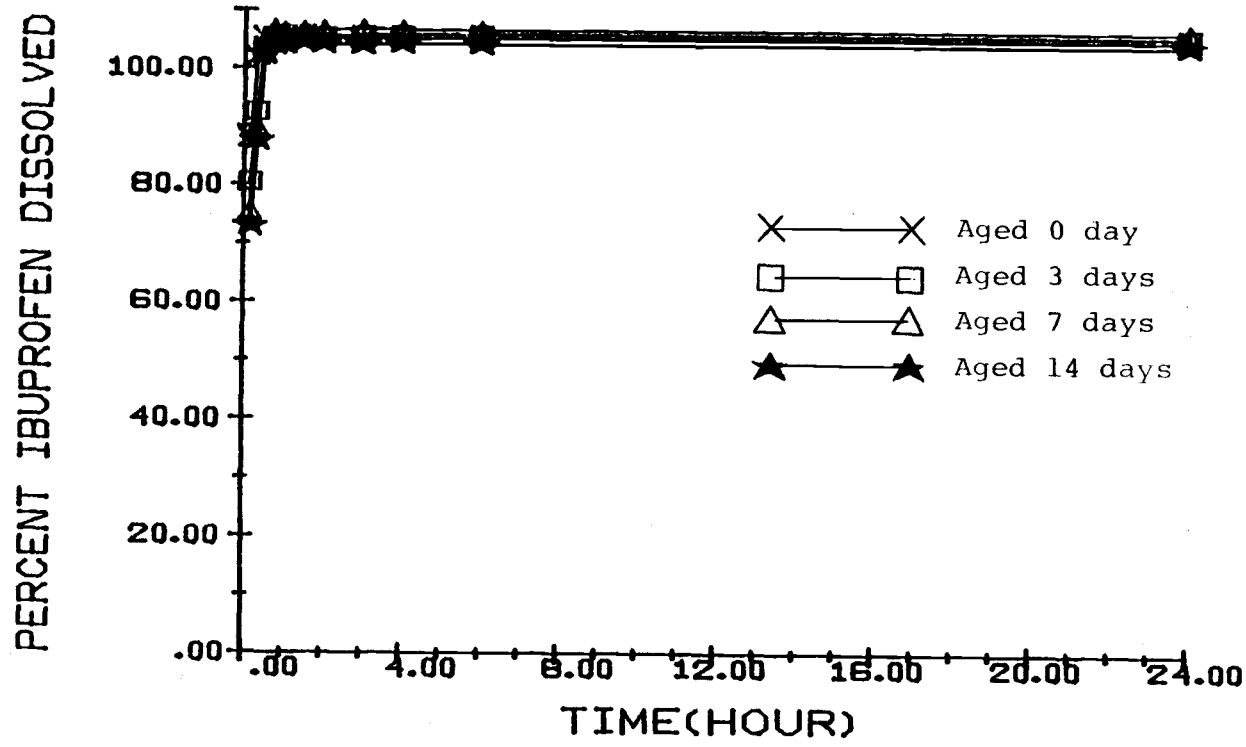

Figure I.39 Dissolution profiles of ibuprofen from Freeze-dried formulation, 100-mg tablets aged by exposure to 75% relative humidity

CONCLUSION

The results of the present study demonstrate clearly that the proposed technique, freeze-drying can be used as an alternative approach to enhance dissolution of ibuprofen. This method appears to be only slightly superior over those reported previously for preparing solid dispersions. Although only one drug is studied, it is believed that freeze-drying approach can be applied to other poorly water soluble drug as well.

Humidity aging study of the ibuprofen freeze-dried formulation (ratio of drug ot PEG 20,000 1:1) indicated that dissolution characteristics of this formulation is unaffected after storage in 98% relative humidity, but dissolution of commercial formulations is drastically reduced. Future work is needed to study the effect PEG has on preventing humidity effects on ibuprofen.

ENDNOTES

1. Ibuprofen U.S.P., E.D.P. No. 142591, lot 1456 L, The Upjohn Compnay, Kalamazoo, MI.

2. Motrin, lot 532PF, The Upjohn Company, Kalamazoo, MI. Rufen, lot 8402, Boots Pharmacueticals, Inc., Shreveport, LA.

3. Advil, lot 4D25, Whitehall Laboratories, Inc., New York, NY.

4. Potassium phosphate monobasic, lot XDX, Mallinckrodt Chemical Work, St. Louis, MO.

5. Sodium phosphate dibasic, lot 846109, J.T. Baker Chemical Co., Phillipsburg, NJ.

6. Polyethylene glycol 20,000, lot 314522, J.T. Baker Chemical Co., Phillipsburg, NJ.

7. Theobroma oil, Hershey Food Corp., Hershey, PA.

8. Lecithin, Corvallis Nutrition Center, Corallis, OR.

9. Avicel pH 102, lot 2840-1715, FMC Corp., Philadelphia, PA.

10. Mannitol, lot 424-6301, J.T. Baker Chemical Co., Phillipsburg, NJ.

11. Cornstarch, lot 501-C2A, Best Foods, CPC International Inc., Englewood Cliffs, NJ.

12. Ac-di-sol, lot T325, FMC Corp., Philadelphia, PA.

13. Magnesium stearate, T-309-U, Mallinckrodt Chemical Work, St. Louis, MO.

14. Stearic acid, Mallinckrodt Chemical Work, St. Louis, MO.

15. Cab-O-sil, FMA Corp., Philadelphia, PA.

16. Sodium lauryl sulfate, lot 63F-0019, Sigma Chemical Co., St. Louis, MO.

17. Hand homogenizer, VWR Scientific Inc., San Francisco, CA.

18. Acetone, lot 307003, J.T. Baker Chemical Co., Phillipsburg, NJ.

19. Vacuum freeze-dryer, model FD-ULT6, Thermovac Industries Corp., Copiague, NY.

20. Dissolution test unit, Hanson Research Corp., Northridge, CA.

21. Model 6460, Hanson Research Corp., Northridge, CA.

22. Rabbit peristaltic pump, Rainin Instrument Co. Inc., Woburn, MA.

23. Beckman Model 34 spectrophotometer, Beckman Instruments Inc., Scientific Instruments Division, Irvine, CA.

24. The Single-Punch Tablet Machine, model TPK-12, Chemical and Pharmaceutical Industry Compnay, Inc., New York, NY.

25. Model 5522, Taylor Instrument, Sybrom Corp., Arden, NC.

REFERENCES

Ampolsuk, C., Mauro, J.V., Nyhuis, N.S. and Jarowski, C.I., Influence of dispersion method on dissolution rate of digoxin-lactose and hydrocortisone-lactose triturations I. J. Pharm. Sci., 63 (1974) 117-118.

Bates, T.R., Dissolution characteristics of reserpine-polyvinylpyrrolidone co-precipitates. J. Pharm. Pharmacol., 21, 710-712 (1969).

Bauer, G., Rieckmann, P. and Schaumann, W., Influence of particle size on the absorption of spironolactone from the gastrointestinal tract. Arzneim. Forsch., 12 487-489 (1962).

Bloedow, D.C. and Hayton, W.L., Effects of lipids on bioavailability of sulfisoxazole acetyl, dicumarol and griseofulvin in rats. J. Pharm. Sci., 65, 328-334 (1976).

Buckley, H.E., Crystal Growth. Wiley, New York, 1963.

Chiou, W.L., Chen, S.J. and Athanikar, N., Enhancement of dissolution rates of poorly water-soluble drugs by crystallization in aqueous surfactant solution I: sulfathiazole, prednisone and chloramphenicol. J. Pharm. Sci., 65, 1212-1214 (1976).

Chiou, W.L. and Riegelman, S., Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J. Pharm. Sci., 58, 1505-1510 (1969).

Chiou, W.L. and Riegelman, S., Absorption characteristics of solid dispersed and micronized griseofulvin in man. J. Pharm. Sci., 60, 1376-1380 (1971a).

Chiou, W.L. and Riegelman, S., Increased dissolution rates of water-soluble cardiac glycosides and steroids via solid dispersions in polyethylene glycol 6000. J. Pharm. Sci., 60, 1569-1571 (1971b).

Chiou, W.L. and Riegelman, S., Pharmaceutical Applications of solid dispersion systems. J. Pharm. Sci., 60 1281-1302 (1970).

Chiou, W.L. and Smith, L.D., Solid dispersion approach to the formulation of organic liquid drugs using

polyethylene glycol 6000 as a carrier. J. Pharm. Sci., 60, 125-127 (1971).

Davidson, R.L. and Sittig, M., Water Soluble Resin. Reinhold, London, England, 1962.

Duncan, W.A., Macdonald, G., Thornton, M.J., Some factors influence the absorption of griseofulvin from the gastrointestinal tract. J. Pharm. Pharmacol., 14, 217-224 (1962).

Feinberg, M., Drug standards in military procurement. J. Amer. Pharm. Assoc., NS9. 113-116 (1969).

Fincher, J.H., Particle size of drugs and its relationship to absorption and activity. J. Pharm. Sci., 57, 1825-1835 (1968).

Ford, J.L. and Rubinstein, M.H., Aging of indomethacin-polyethylene glycol 6000 solid dispersions. Pharm. Acta Helv., 54, 353-358 (1979).

Ford, J.L. and Rubinstein, M.H., Formulation and aging of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersions. Pharm. Acta Helv., 55, 1-7 (1980).

Fox, D., Labes, M.M. and Weissberger, A., Physics and Chemistry of the Organic Solid State. Interscience, New York, 1963, p. 572.

Geineidi, A.S. and Hamacher, H., Physical characterization and dissolution profiles of spironolactone and diazepam coprecipitates. Pharm. Ind., 42, 315-319 (1980a).

Geineidi, A.S. and Hamacher, H., Enhancement of dissolution rates of spironolactone and diazepam via polyols and PEG solid dispersion systems. Pharm. Ind., 42, 401-404 (1980b).

Geneidi, A.S., Ali, F.A. and Salama, R.B., Solid dispersion of nitrofurantoin, ethotoin and coumarin with polyethylene glycol 6000 and their coprecipitates with povidone 25,000. J. Pharm. Sci., 67, 114-116 (1978).

Gibaldi, M. and Feldman, S., Mechanisms of surfactant effects on drug absorption. J. Pharm. Sci., 59, 579-589 (1970).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures.
II. experimental evaluation of a eutectic mixture:

urea-acetaminophen system. J. Pharm. Sci., 55, 482-487 (1966a).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures. III. experimental evaluation of griseofulvin-succinic acid solid solution. J. Pharm. Sci., 55, 487-492 (1966b).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures. IV. chloramphenical-urea system. J. Pharm. Sci., 55, 581-583 (1966c).

Goodman, L.S. and Gilman, A., The Pharmacological Basis of Therapeutics. 3rd edition, MacMillan, New York, 1965, p. 116.

Grisafe, J.A. and Hayton, W.L., Intestinal absorption of grizeofulvin from a triolein digestionmixture in rats. J. Pharm. Sci., 67, 895-899 (1978).

Guillory, J.K., Hwang, S.C. and Lach, J.L., Interactions between pharmaeutical compounds by thermal methods. J. Pharm. Sci., 58, 301-308 (1969).

Haleblian, J. and McCrone, Pharmaceutical applications of polymorphism. J. Pharm. Sci., 58, 911-929 (1969).

Hem, S.L., Skauen, D.M. and Beal, H.M., Mechanism of crystallization of hydrocortisone by ultrasonic irradiation. J. Pharm. Sci., 56, 229-233 (1967).

Higuchi, W.I., diffusional models useful in biopharamceutics: Drug release rate process. J. Pharm. Sci., 56, 315-324 (1967).

Ibrahim, H.G. Pisano, F. and Bruno, A., Polymorphism of phenylbutazone, properties and compressional behavior of crystals. J. Pharm. Sci., 66, 669-673 (1971).

International Critical tables. Vol I, McGraw-Hill Book Company, Inc., New York, 1926, p. 67.

Irani, R.R. and Callis, C.F., Particle Size: Measurement, Interpretation and Application. Wiley, New York, 1963, p. 17,18.

Johansen, H. and Moller, N., Solvent deposition method for enhancement of dissolution rate: importance of drug-to-excipient ratio. J. Pharm. Sci., 67, 134-136 (1978).

Kanig, J.L., Properties of fused mannitol in comressed tablets. J. Pharm. Sci., 53, 188-192 (1964).

Kaur, R., Grant, D.W. and Eaves, T., Comparison of polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide. II. dissolution and solubilities studies. J. Pharm. Sci., 69, 1321-1326 (1980).

Kornblum, S.S. and Hirschorn, J.O., Dissolution of poorly water-soluble drugs. I: some physical aprameters related to method of micronization and tablet manufacture of a quinazolinone compound. J. Pharm. Sci., 59, 606-609 (1970).

Lachman, L., Lieberman, H.A. and Knaig, J.L., The Theory and Practice of Industrial Pharmacy. Lea & Geviger, Philadelphis, 1970, p. 58.

Levy, G., Availability of spironolactone given by mouth. Lancet, 2, 723-724 (1962).

Levy, G., Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. Amer. J. Pharm., 135, 78-92 (1963).

Lin, S.L., Menig, J. and Lachman, L., Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water-insoluble drugs. J. Pharm. Sci., 57, 2143-2148 (1968).

Martin, A., Swarbrick, J. and Cammarata, A., Physical Pharmacy, 3rd Edition, Lea and Febiger, Philadelphia, 1983, p. 134, 272-311.

Matsunaga, J., Nambu, N. and Nagai, T., Polymorphism of phenylbutazone. Chem. Pharm. Bull., 24, 1169-1174 (1976).

Maulding, H.V., Solid-state dispersions employing urethan. J. Pharm. Sci., 67, 391-394 (1978).

Mayersohn, M. and Gibaldi, M., New method of solid-state dispersion for increasing dissolution rates. J. Pharm. Sci., 55, 1323-1324 (1966).

McGinity, J.W., Maincent, P. and Steinfink, H., Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. J. Pharm. Sci., 73, 1441-1444 (1984).

The Merck Index, 10th Edition. Merck & Co, Inc., New Jersey, 1983, p. 1271.

Miralles, M.J., McGinity, J.W. adn Martin, A., Combined water-soluble carriers for copredipitates of tolbutamide. J. Pharm. Sci., 71, 302-304 (1982).

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983a, p. 15.

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983b, p. 16.

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983c, p. 17.

Mullin, J.D. nad Macek, T.J., Some pharamceutical properties of novobiocin. J. Amer. Pharm. Assoc., 49, 245-248 (1960).

Ravis, W.R. and Chen, C., Dissolution, stability, and absorption characteristics of dicumarol in polyethylene glycol 4000 solid dispersions. J. Pharm. Sci., 70, 1353-1357 (1981).

Said, S.A., El-Fatary, H.M. nad Geneidi, A.S., Coprecipitates of tolbutamide with polyvinylpyrrolidone and fusion mixtures with macrogol. Aust. J. Pharm. Sci., NS3, 42-45 (1974).

Salib, N.N., El-Gamal, S.A. and Ismail, A.A., Preparation and disposition characteristics of several fast-release solid dispersions of tolbutamide. Pharm. Ind., 38, 918-921 (1976).

Scheikh, M.A., Price, J.C. and Gerraughty, R.J., Effect of ultrasound on particle size of suspensions of polyethylene spheres. J. Pharm. Sci., 55, 1048-1050 (1966).

Sekiguchi, K. and Obi, N., Studies on absorption of eutectic mixture. I: a comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 9, 866-872 (1961).

Simonelli, A.P., Mehta, S.C. and Higuchi, W.J., Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J. Pharm. Sci., 58, 538-549 (1969).

Skauen, D.M., Some pharmaceutical applications of ultrasonic. J. Pharm. Sci., 56, 1373-1385 (1967).

Stavchansky, S. and Gowan, W.G., Evaluation of the bioavailability of a solid dispersion of phenytoin in

polyethylene glycol 6000 and a commercial phenytoin sodium capsule in dog. J. Pharm. Sci., 73, 733-736 (1984).

Steady, J.A., Freeman, M., John, E.G., Ward, G.T. and Whiting, B., Ibuprofen tablets: dissolution and bioavailability. Int. J. Pharm., 14, 59-72 (1983).

Stupak, E.I. and Bates, T.R., Enhanced absorption and dissolution of reserpine from reserpine-polyvinylpyrrolidone coprecipitates. J. Pharm. Sci., 61, 400-404 (1972).

Suvanakoot, U., Dissolution characteristics of freeze-dried granuales of tolbutamide and phenylbutazone. Ph.D. Thesis, Oregon State University, 1984, p. 2-68.

Tachibana, T. and Nakamura, A., A method for preparing an aqueous colloidal dispersion of organic material by using water-soluble polymers: dispersion of -carotene by polyvinyl pyrrolidone. Kolloid-Z. Polym., 203, 130-133 (1965).

Windholz, M., The Merck Index, 10th Edition. Merck & Co., Inc., New Jersey, 1983, p. 779.

CHAPTER TWO

RELATIVE BIOAVAILABILITY OF IBUPROFEN SOLID DISPERSED TABLETS IN RABBITS

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RELATIVE BIOAVAILABILITY OF IBUPROFEN SOLID DISPERSED TABLETS IN RABBITS

ABSTRACT

Four formulations of ibuprofen solid dispersions were selected and made into 50 mg ibuprofen tablets. Relative bioavailability of these formulations were studied after oral administration of the tablets to rabbits. The freeze-dried solid dispersion formulation with ratio of drug to PEG 20,000 1:1 exhibited the greatest relative extent of absorption (129.50 $\pm$ 27.99% over control). Preparations with PEG 20,000 enhanced the extent of ibuprofen absorption when compared with control (formulation with ibuprofen drug powder). There appears to be no advantages in formulating ibuprofen in PEG by the freeze-drying method over the direct melting method. A slower rate of ibuprofen was obtained when theobroma oil was increased in the formulation.

INTRODUCTION

Ibuprofen [dl-2-(p-isobutylphenyl) propionic acid] is a propionic acid derivative with potent anti-inflammatory properties. It is used extensively in long-term oral treatment of rhumatoid arthritis and osteoarthritis. The pharmacology and metabolism of ibuprofen in man and other species have been reported (Adams et al., 1967; Mills et al., 1973; Davies and Avery, 1971).

In Chapter I, a rationale and a method for preparing solid dispersions of ibuprofen were presented. The rate and extent of absorption of a drug in vivo from the gastrointestinal tract has been shown to correlate well with in vitro dissolution studies (Wagner, 1971; Smolen and Weigand, 1976; Aaron and Rowland, 1977).

The purposes of this study were: 1) to obtain preliminary pharmacokinetic data of ibuprofen following oral administration to rabbits of the solid dispersion formulations which were tableted, and 2) to compare the bioavailability of these solid dispersion formulations with that of a ibuprofen drug powder formulation.

EXPERIMENTAL

Study Design

Five male New Zealand white rabbits ranging from 1.8-2.9 kg in weight were used throughout the study according to the guideline for laboratory animals by Oregon State University. Each rabbit received five treatments. The experiment was a cross-over design (Cochran and Cox, 1976) with each rabbit serving as its own control, and all five treatments given to each rabbit in order to eliminate a substantial amount of intersubject variability. Table 1 contains the layout for this experimental design with five subjects and five treatments, after independent randomization of treatment order.

Four formulations of ibuprofen solid dispersions described in Chapter I as well as the formulation with only ibuprofen drug powder present were selected to make 50 mg tablets which were used in an in-vivo bioavailability study. The ingredients and amounts used for making tablets are listed in Table 1 of this chapter. The preparation with theobroma oil 31.25%, PEG 20,000 31.25%, lecithin 6.25% and drug 31.25%, was chosen because it provided the slowest release of drug in a dissolution test (Chapter I). Formulations with the ratio of PEG 20,000 to drug as 1 to 1, which were prepared by direct melting or freeze-drying were selected for this study as these preparations showed the

Table II.1 Design for Administration of Ibuprofen Tablets to Rabbits

	RABBIT				
Period	1	2	3	4	5
1	A	B	C	D	E
2	B	C	D	E	A
3	D	E	A	B	C
4	E	A	B	C	D
5	C	D	E	A	B

A = Preparation with theobroma oil 31.25%, PEG 20,000 31.25% lecithin 6.25%, ibuprofen 31.25%

B = Preparation with theobroma oil 8.33%, PEG 20,000 41.67% lecithin 8.33%, ibuprofen 41.67%

C = Preparation with PEG 20,000 50%, ibuprofen 50%, freeze-drying technique

D = Preparation with PEG 20,000 50%, ibuprofen 50%, direct melting technique.

E = Preparation with only ibuprofen drug powder

fastest drug release in an in vitro dissolution test. The preparation with theobroma oil 8.33% PEG 20,000 41.67%, lecithin 8.33% and drug 41.67% produced an intermediate release of drug as compared to those described above and was also included in this study. Formulation with only ibuprofen drug powder was used for reference in order to obtain the relative bioavailability of those solid dispersion formulations. All formulations were directly compressed to obtain 50 mg tablets. The experiment was carried out in rabbits.

Animals and Blood Sample Collection

Each rabbit, which received five treatments, had an elapsed time of at least four days between treatments. During a treatment the rabbit was restrained with a cloth body cloak secured tightly by safety pins. The hair on the ear was shaved and the ears were cleaned with warm water and then with alcohol.[1] The rabbit was placed on a heating pad, and lidocaine[2] was injected subcutaneously close to an ear artery for local anesthesia prior to catheterization. A catheter (22 Gauge[3]) was inserted into the mid ear artery for collection of blood samples. The catheter was then closed with infusion plugs.

The ibuprofen 50 mg tablet was given orally to the rabbit. Arterial blood samples were collected through the infusion plug[4] using a needle (21 G by 1½ inches)[5] which had

been connected to 12 inches of heparin[6] washed intramedic polyethylene tubing; P.E. 90.[7] Blood was allowed to flow freely after the needle was pushed into the infusion plug of the arterial catheter. About 300 ul of the first blood collected was discarded and then about 400 ul was collectd in a 500 ul-heparinized microcentrifuge tube.[8] Two hundred ul of 20 units/ml of heparin in D-5-W[9] was injected into the infusion plug prior to and after each blood sample collection. Blood samples were obtained at the following times following oral ibuprofen administration: 5, 10, 20, 30, 45 minutes and 1, 2, 3, 4, 6, 9, 12 hours. The collected blood samples were centrifuged[10] at 2000 rpm at 4°C for 30 minutes. Plasma was then separated and frozen until assayed.

Analytical Method

Two hundred fifty µl of plasma was mixed with 25 µl of internal standard solution (25 µg/ml of butyl paraben[11] in acetonitrile[12]) and 25 µl of methanol[13] in a 10 ml-centrifuge tube. After acidification with 0.25 ml of 1 N hydrochloric acid[14], the solution was extracted with 2 ml of chloroform[15], and then the mixture was shaken for 1 minute on a Rotamixer.[16] After centrifugation at 2000 rpm for 15 minutes, 1.8 ml of the chloroform layer was transferred to another test-tube, and evaporated to dryness at 40 C in a vacuum over.[17] The walls of the test tube were washed with

0.5 ml of chloroform, and the washings were evaporated to dryness. The residue was then dissolved in 100 µl of methanol, and 20-30 µl of the sample was injected into HPLC[18] for assay of ibuprofen concentrations in plasma.

Standard curves of ibuprofen were prepared in the same way as unknown samples by mixing 25 µl of a series of stock stnadard ibuprofen[19] solutions containing 6.875, 5.50, 4.125, 2.75, 1.375, 1.100, .6875, .275 and .1375 µg/ml and 25 µl of internal standard solution with 250 µl of blank plasma. A linear relationship of peak height ratio (drug peak height/internal standard peak height) versus ibuprofen plasma concentration of standard solution was used as calibration curve for determination of drug concentrations in unknown samples.

Bioavailability Study

Individual drug plasma concentration versus time curves for each treatment were plotted. The relative bioavailability of control (Formulation A) and solid dispersion preparations (Formulation B, C, D, and E) for each rabbit was determined through the use of model independent parameters i.e., peak drug concentration (p), mean residence time (MRT), and mean absorption time (MAT). Peak drug concentrations were determined as the actual plasma assayed values. The Tukey method of multiple comparisons (Neter and Wassermen, 1974) of these bioavailability parameters was

used to determine if there were any statistically significant differences among mean values after administration of control and solid dispersion formulations.

Analysis of the extent of bioavailability was performed by using the trapezoidal rule to calculate the area under the plasma concentration-time curve (AUC) after the administration of the control and solid dispersion preparations. AUC from time zero to time of final detectable concentration, was determined by using the linear trapezoidal method. To this value was added the residual area extrapolated to infinity, calculated as the final estimated plasma concentration divided by the terminal slope. The sum of these two areas represents the total AUC from time zero to infinity. Equations for the linear trapezoidal rule with extrapolation to infinity are as follows:

$$AUC_i = \frac{(C_i + C_i + 1)}{2} \times (T_i + 1 - T_i) \qquad \text{eq 1}$$

$$AUC_{Tlast \rightarrow \infty} = C_{last}/\lambda \qquad \text{eq 2}$$

Where C's and T's are drug concentrations and time values respectively. C_{last} and λ are the last estimated drug concentration point and the slope of the terminal phase, respectively.

Relative bioavailability, RF, of ibuprofen solid dispersion formulations (Formulation B, C, D, and E) for

each subject was determined by dividing area under the plasma concentration-time curve from time zero to infinity after oral administration of solid dispersion preparations by that of the control (Formulation A) (Wagner, 1975):

$RF = AUC_{O\rightarrow\infty}$ (Formulation of solid dispersion)/$AUC_{O\rightarrow\infty}$ (Formulation A) X 100%

Application of the statistical concept of moments to pharmacokinetics (Riegelman and Collier, 1980; Yamaoka et al., 1978) and chemical engineering (Himmelblau and Bischoff, 1968) have been reported. The moments are used to analyze the distribution function of drug in the body (Riegelman and Collier, 1980) and are related to the extent and rate of bioavailability (Yamaoka et al., 1978). The extent and rate of bioavailability are estimated in terms of the zeroth (AUC) and the first moment (AUMC). The area under the moment curve (AUMC) is defined as the integral with respect to time between time zero to infinity of the product of time, t, and the plasma concentration, C_p.

$$AUMC_i = \int_o^i Cpt\ dt \qquad \text{eq. 3}$$

$$= \frac{(C_i \times t_i + C_{i+1} \times t_{i+1}) \times (T_{i+1} - T_i)}{2} \qquad \text{eq. 4}$$

AUMC is extrapolated to infinity by

$$\underset{O\rightarrow\infty}{AUMC} = \sum AUCM_i + AUMC_{i\rightarrow\infty} \qquad \text{eq. 5}$$

$$\underset{i\rightarrow\infty}{AUMC} = \frac{(C_{last} \times T_{last})}{\lambda} + \frac{C_{last}}{\lambda^2} \qquad \text{eq. 6}$$

where C_{last} is the predicted value for the last concentration point and λ is the terminal rate constant estimated.

Mean residence time, MRT, which is a model independent parameter, can be defined as the mean time for the intact drug molecules to transit through the body and involves a composite of all kinetic processes, including in vivo release from the dosage form, absorption into the body, and all disposition processes (Culter, 1978). MRT represents the time for 63.2% of the administered dose to be eliminated by all processes, and it gives significant information with respect to kinetic features of the processes which a drug undergoes in the gastrointestinal tract and the body (Riegelman and Collier, 1980). MRT is calculated as the ratio of the zeroth and first moments of the drug concentration versus time curve and approximates the sum of the reciprocals of the absorption and the terminal rate constant.

$$MRT = AUMC_{0\to\infty}(po)/AUC_{0\to\infty}(po) \qquad \text{eq. 7}$$

$$= 1/k_a + 1/\lambda \qquad \text{eq. 8}$$

where k_a is the absorption rate constant and λ is the terminal rate constant.

Mean absorption time (MAT) refers to the mean time involved for in vivo release and absorption processes as

they occur in the input compartment. Statistical moment theory defines mean absorption time as the time it takes for 63.2% of the drug molecules to be absorbed into the body's general circulation. (Riegelman and Collier, 1980). MAT is a useful model independent index of rate of bioavailability because it best reflects the absorption process after the effect of the eliminaton phase on absorption has been removed and can be calculated as follows:

$$MAT = (AUMC_{0\to\infty} / AUC_{0\to\infty}) - 1/\lambda \qquad \text{eq. 9}$$

$$= MRT - 1/\lambda \qquad \text{eq. 10}$$

All bioavailability parameters were subjected to a cross-over design analysis of variance to determine the differences among the subjects and the treatments at the 95% significant level (Cochran and Cox, 1976). In the case where treatment effects were significant ($p < .05$), the Tukey method of multiple comparisons was performed to compare differences between treatment effects (Neter and Wasserman, 1974).

RESULT AND DISCUSSION

Presented in Figure II.1 and Table II.2 is a polynomial relationship of PHR (peak height ratio) for ibuprofen peak height to internal standard (butyl paraben) peak height of typical standard solutions in plasma. This calibration curve (Figure II.1) was used to determine drug concentrations in unknown plasma samples. Regression of PHR on ibuprofen concentration was fit to the following polynomial equation : $PHR = a + b * x + c * x^2$

Where: a is the value of PHR at zero concentration

b is the linear effect coefficient

c is the curvature effect coefficient

Table II.3 to II.7 shows the sampling times and assayed ibuprofen concentrations in individual rabbit's plasma following oral administration to each rabbit of ibuprofen from the five formulations; Formulation A (Formulation with theobroma oil 31.25%, PEG 20,000 31.25%, ibuprofen 31.25% and lecithn 6.25%; using freeze-drying technique), Formulation B (Formulation with theobroma oil 8.33%, PEG 20,000 41.67%, ibuprofen 41.67% and lecithin 8.33%; using freeze-drying technique), Formulation C (Formulation with PEG 20,000 50%, ibuprofen 50%, using freeze-drying technique), Formulation D (Formulation with PEG 20,000 50%, ibuprofen 50%, using direct melting method) and Formulation E (the reference formulation with only ibuprofen presented).

Table II.2 Typical Standard Curve Data for Ibuprofen Concentration Estimation Using Polynomial Regression[a] and Linear Regression[b]

Concentration (μg/ml)	PHR[c]	Inverse[d] Estimate (μg/ml)	%Theory[e]	Inverse[f] Estimate (μg/ml)	%Theory[e]
6.875	6.8414	6.8330	99.39	6.8610	99.80
5.500	5.6147	5.6243	102.26	5.6209	102.20
4.125	3.9711	3.9837	96.58	3.9594	95.99
2.750	2.7607	2.7601	100.37	2.7358	99.48
1.375	1.4942	1.4659	106.61	1.4555	105.85
1.100	1.1416	1.1031	100.28	1.0990	99.91
0.688	0.7288	0.6768	98.37	0.6405	93.10
0.275	0.3263	0.2598	94.48	0.2748	99.93
0.138	0.1910	0.1193	86.45	0.0845	61.23
Mean			98.31		95.28
S.D.			5.61		13.25
C.V.[g]			5.71		13.41

[a]Coefficient of determination $R^2 = 0.9990$

[b]Coefficient of determination $R^2 = 0.9990$

[c]Peak height ratio of ibuprofen versus butyl paraben

[d]Inverse estimated concentration = $-0.0793 + 1.0408(PHR) - 0.0045(PHR)^2$

[e]Inverse estimated concentration = $-0.0550 + 1.0109\ (PHR)$

[f]%Theory = (Inverse estimated conc./known conc.) X 100%

[g]% Coefficient of variation = S.D./Mean) X 100

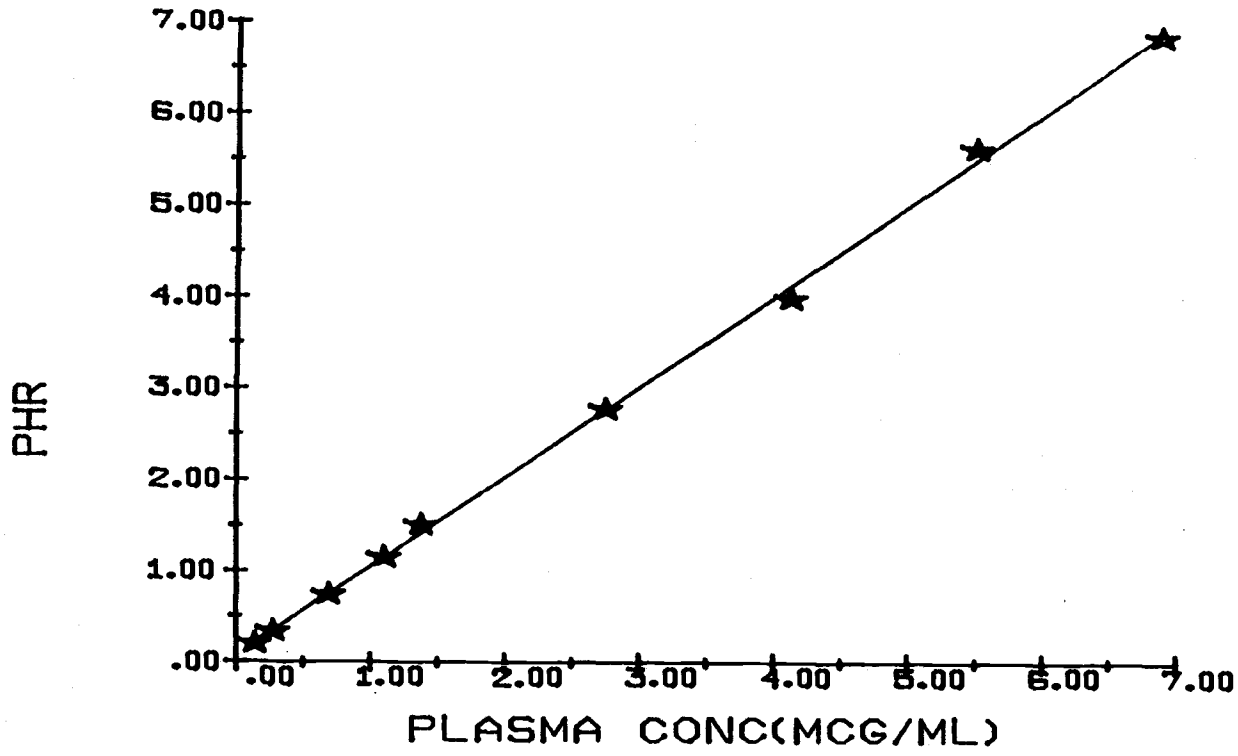

Figure II.1 Typical standard curve for ibuprofen concentration vs. PHR estimated using polynomial regression

Table II.3 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation A in Rabbits 1, 2, 3, 4, and 5

Time (HR)	Rabbit 1 plasma conc. (μg/ml)	Rabbit 2 plasma conc. (μg/ml)	Rabbit 3 plasma conc. (μg/ml)	Rabbit 4 plasma conc. (μg/ml)	Rabbit 5 plasma conc. (μg/ml)
0.0833	2.7510	1.3543	2.6263	1.2754	1.2202
0.1667	2.1019	1.4352	2.4051	1.7164	1.4413
0.3333	1.5574	1.6394	1.5102	1.2278	1.2614
0.5000	1.0625	3.5027	1.1476	1.1678	1.1920
0.7500	0.9439	2.4294	1.1571	1.3278	0.8341
1.0000	0.9352	2.0585	1.1489	1.1549	0.8351
2.0000	0.8996	1.0848	0.9397	0.7674	0.7895
3.0000	0.5594	1.0328	0.6157	0.7398	0.5720
4.0000	0.4125	0.9171	0.5055	0.5844	0.3021
6.0000	0.2292	0.2548	0.3309	0.2158	0.2006
9.0000		0.1513	0.1237		

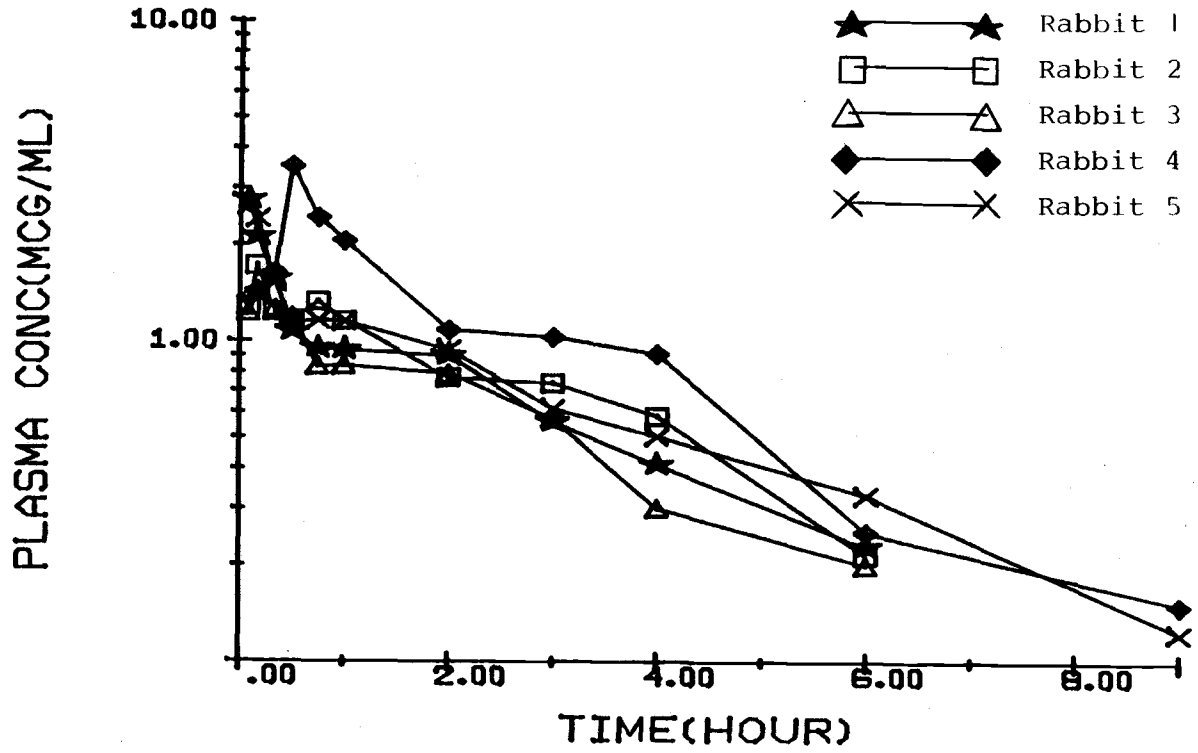

Figure II.2 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation A in 5 rabbits

Table II.4 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation B in Rabbits 1, 2, 3, 4, and 5

Time (HR)	Rabbit 1 plasma conc. (μg/ml)	Rabbit 2 plasma conc. (μg/ml)	Rabbit 3 plasma conc. (μg/ml)	Rabbit 4 plasma conc. (μg/ml)	Rabbit 5 plasma conc. (μg/ml)
0.0833	1.3136	1.2875	1.4352	0.5796	1.0662
0.1667	1.2148	1.6959	1.3543	0.9783	1.2033
0.3333	2.1004	1.3455	1.3048	1.6156	1.6005
0.5000	1.5763	1.5281	2.8604	2.0449	2.0776
0.7500	1.5889	2.2462	3.6027	1.9708	2.7427
1.0000	1.6543	4.3685	2.7083	2.9392	1.7275
2.0000	1.2035	2.5393	1.6086	1.2528	1.0796
3.0000	0.6234	1.7537	1.0051	0.7881	0.6595
4.0000	0.3553	1.1586	0.6102	0.4791	0.5070
6.0000	0.1871	0.5216	0.3034	0.1801	0.2710
9.0000		0.2102	0.1341		

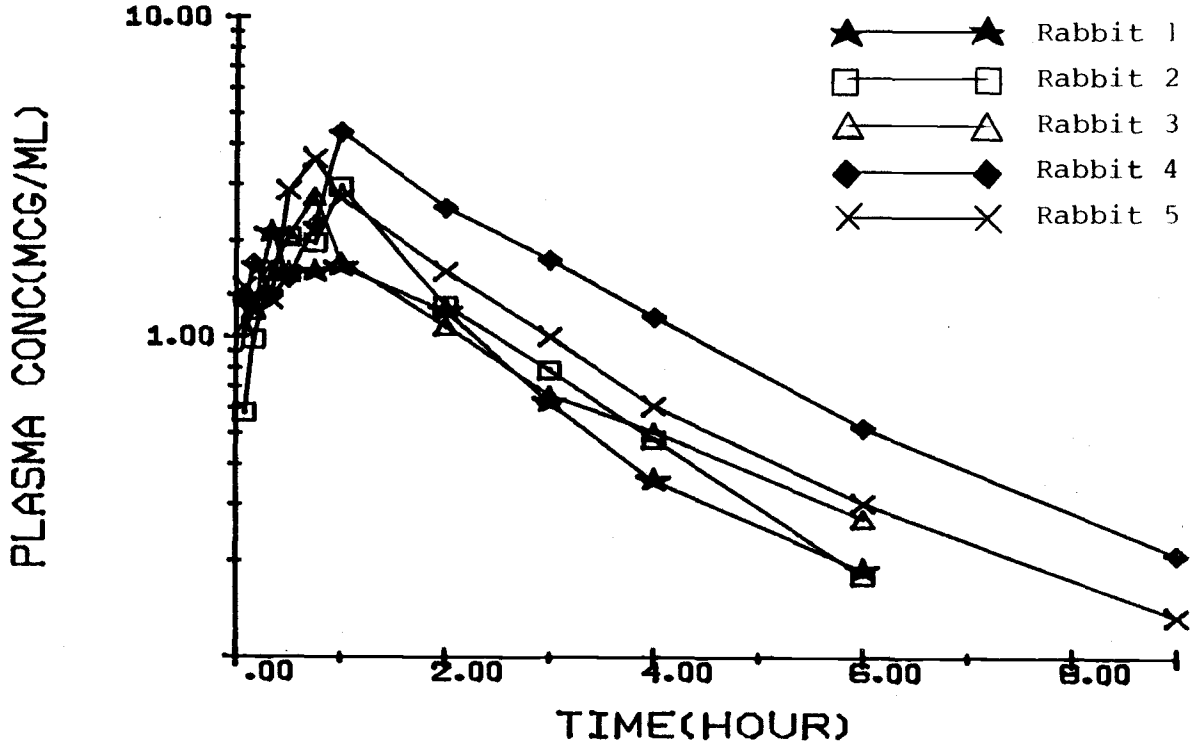

Figure II.3 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation B in 5 rabbits

Table II.5 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation C in Rabbits 1, 2, 3, 4, and 5

Time (HR)	Rabbit 1 plasma conc. (μg/ml)	Rabbit 2 plasma conc. (μg/ml)	Rabbit 3 plasma conc. (μg/ml)	Rabbit 4 plasma conc. (μg/ml)	Rabbit 5 plasma conc. (μg/ml)
0.0833	2.0127	1.6142	2.1721	1.4670	0.9326
0.1667	3.0984	1.8969	1.8002	1.7379	1.7641
0.3333	2.1453	2.3829	1.7482	2.5909	1.7022
0.5000	2.2721	3.3154	1.6079	2.6254	2.0123
0.7500	2.7816	1.7597	2.8867	2.3102	1.6133
1.0000	2.7390	2.3100	3.3755	1.5957	1.5922
2.0000	2.0429	3.0742	2.0396	1.4533	0.8478
3.0000	1.2231	1.9132	1.0221	0.7978	0.6882
4.0000	0.5381	0.3884	0.6922	0.6832	0.3589
6.0000	0.2639	0.1956	0.2301	0.1843	0.1443

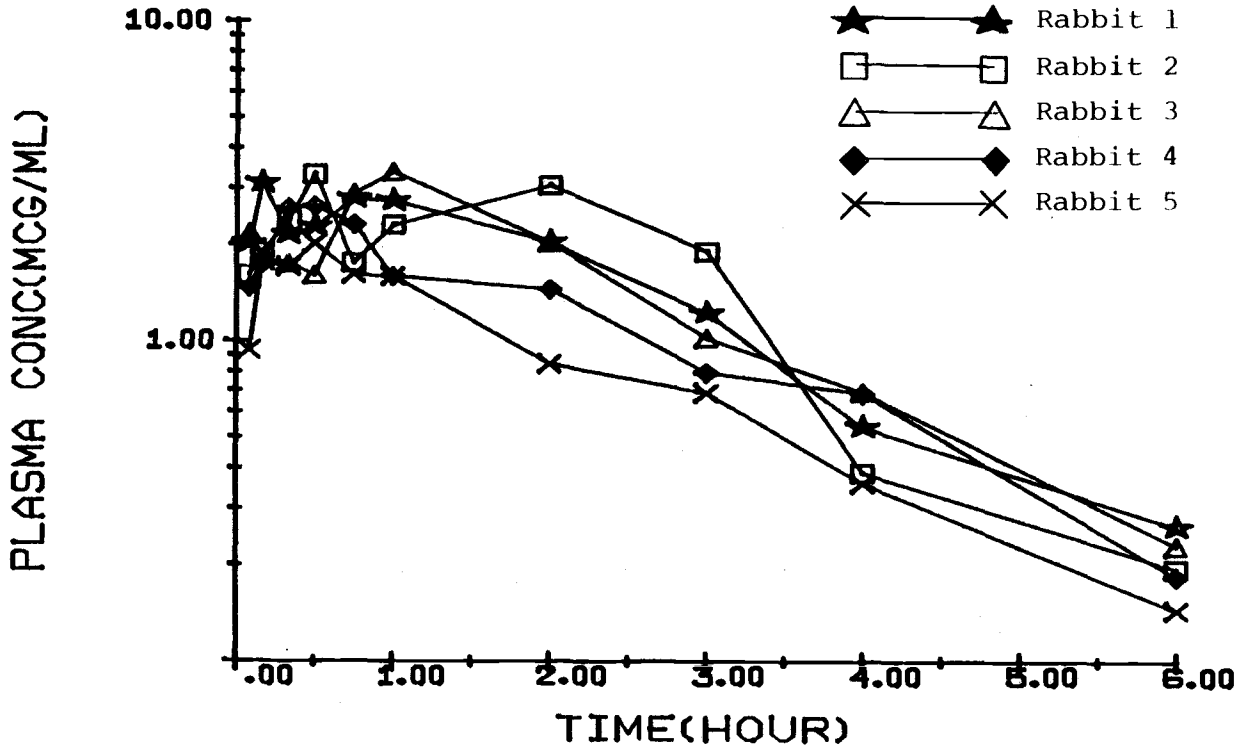

Figure II.4 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation C in 5 rabbits

Table II.6 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation D in Rabbits 1, 2, 3, 4, and 5

Time (HR)	Rabbit 1 plasma conc. (μg/ml)	Rabbit 2 plasma conc. (μg/ml)	Rabbit 3 plasma conc. (μg/ml)	Rabbit 4 plasma conc. (μg/ml)	Rabbit 5 plasma conc. (μg/ml)
0.0833	1.9711	1.7969	2.4292	0.6676	1.0777
0.1667	1.5954	2.4480	2.9750	0.6866	1.5386
0.3333	1.2463	3.9833	3.0919	2.5196	2.2134
0.5000	3.7454	7.4996	3.0904	5.4979	1.9678
0.7500	1.2947	4.6838	2.1836	2.3768	1.4120
1.0000	1.0965	2.1264	1.9457	2.6855	0.9764
2.0000	0.8163	1.7278	1.0374	0.9485	0.8377
3.0000	0.7013	1.1816	0.5209	0.7216	0.7789
4.0000	0.6015	0.8706	0.4625	0.4516	0.4321
6.0000	0.2302	0.2445	0.1590	0.1472	0.1907

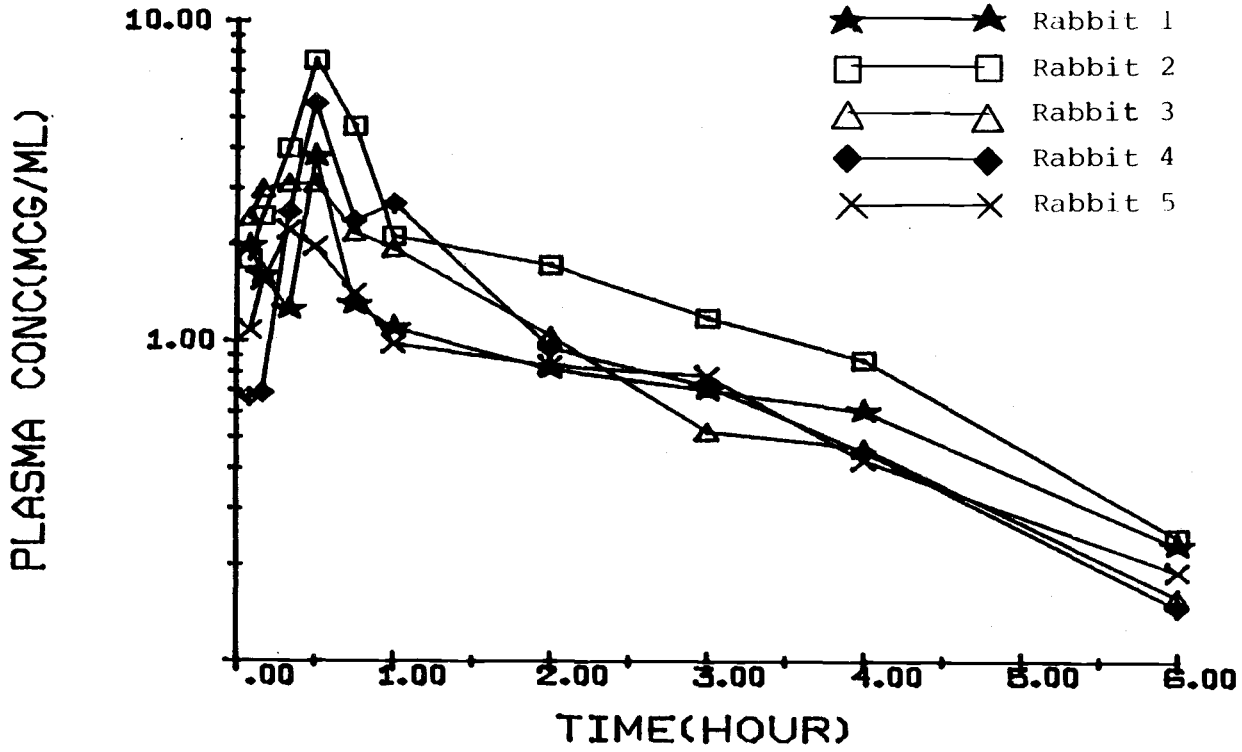

Figure II.5 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation D in 5 rabbits

Table II.7 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation E in Rabbits 1, 2, 3, 4, and 5

Time (HR)	Rabbit 1 plasma conc. (μg/ml)	Rabbit 2 plasma conc. (μg/ml)	Rabbit 3 plasma conc. (μg/ml)	Rabbit 4 plasma conc. (μg/ml)	Rabbit 5 plasma conc. (μg/ml)
0.0833	0.2457	0.1465	0.1733	0.1520	0.2125
0.1667	0.3808	0.2644	0.6440	0.4137	0.5612
0.3333	0.7244	0.3543	0.9439	0.6270	0.7643
0.5000	1.6007	0.6077	2.0711	1.2015	1.8049
0.7500	1.9972	1.2813	3.1611	1.4610	2.3162
1.0000	2.5673	2.4354	1.9745	3.2297	2.4642
2.0000	1.3321	3.6477	1.2461	0.9268	1.1536
3.0000	0.6663	0.9298	0.6710	0.7681	0.4426
4.0000	0.2442	0.6309	0.4067	0.4847	0.2752
6.0000		0.2249	0.1607	0.1964	

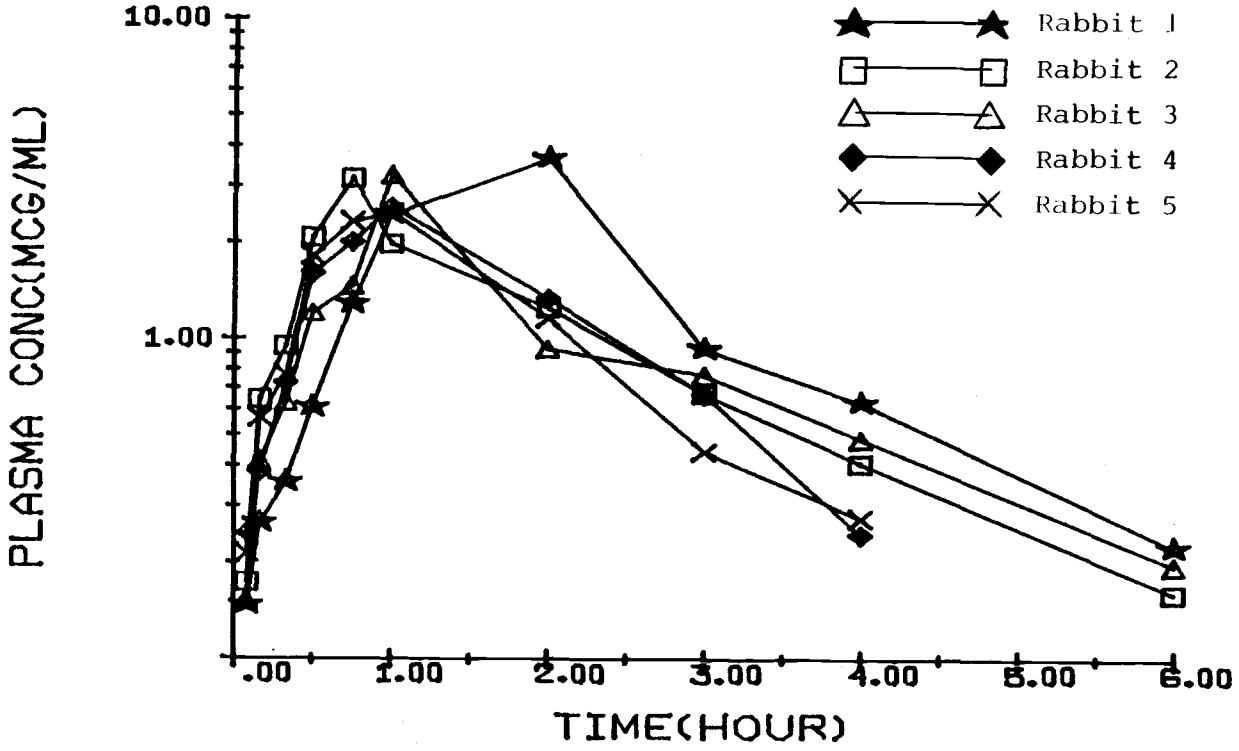

Figure II.6 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation E in 5 rabbits

Mean ibuprofen plasma concentrations in 5 rabbits for each formulation are presented in Table II.8 and Figure II.2. Formulation A seemed to produce the lowest value of mean peak plasma concentration while Formulation D exhibited the highest. Elimination rate constants of each formulation in five rabbits are presented in Table II.9. Analysis of variance of all individual elimination rate constants (Table II.10) indicated there was a significant difference between the mean elimination rate constant of each treatment ($p = 0.003$). In addition, the result from multiple comparison showed that this significant difference was due to a slow elimination rate constant of ibuprofen from Formulation A. When only Formulation B, C, D and E were compared, there was no significant difference between the ibuprofen mean elimination rate constant in these treatments. Considering the relative magnitudes of the ibuprofen mean elimination rate constant for Formulation A with others, a likely explanation is that some continued absorption is occuring at the time intervals in which elimination rate constant was estimated for Formulation A. Thus, rate constants from the reference (Formulation E) were more reliable and used to calculate MAT (mean absorption time) values for Formulation A.

The quality of a drug product as a drug delivery system is determined by the rate and extent of delivery of the active form of drug to the biological environment responsible for the pharmacological effects (Pedersen,

Table II.8 Plasma Ibuprofen Concentration Versus Time Data Following Oral Administration of 50 mg of Ibuprofen in Formulation A, B, C, D, E in five Rabbits

Time (HR)	Formulation A Mean Plasma conc. (μg/ml)	Formulation B Mean Plasma conc. (μg/ml)	Formulation C Mean Plasma conc. (μg/ml)	Formulation D Mean Plasma conc. (μg/ml)	Formulation E Mean Plasma conc. (μg/ml)
0.0833	1.8454 $\pm$ 0.7725	1.1364 $\pm$ 0.3386	1.6397 $\pm$ 0.4881	1.5885 $\pm$ 0.7081	0.1860 $\pm$ 0.0423
0.1667	1.8140 $\pm$ 0.4323	1.2893 $\pm$ 0.2642	2.0595 $\pm$ 0.5839	1.8487 $\pm$ 0.8858	0.4528 $\pm$ 0.1504
0.3333	1.4392 $\pm$ 0.1840	1.5934 $\pm$ 0.3172	2.1139 $\pm$ 0.3886	2.6109 $\pm$ 1.0178	0.6828 $\pm$ 0.2165
0.5000	1.6145 $\pm$ 1.0567	2.0175 $\pm$ 0.5360	2.3668 $\pm$ 0.6474	4.3602 $\pm$ 2.1716	1.4572 $\pm$ 0.5713
0.7500	1.3385 $\pm$ 0.6390	2.4303 $\pm$ 0.7786	2.2703 $\pm$ 0.5778	2.3902 $\pm$ 1.3657	2.0434 $\pm$ 0.7493
1.0000	1.2265 $\pm$ 0.4851	2.6796 $\pm$ 1.1043	2.3225 $\pm$ 0.7655	1.7661 $\pm$ 0.7210	2.5342 $\pm$ 0.4508
2.0000	0.8962 $\pm$ 0.1279	1.5368 $\pm$ 0.5939	1.8916 $\pm$ 0.8254	1.0735 $\pm$ 0.3764	1.6613 $\pm$ 1.1207
3.0000	0.7039 $\pm$ 0.1972	0.9660 $\pm$ 0.4650	1.1289 $\pm$ 0.4846	0.7809 $\pm$ 0.2439	0.6956 $\pm$ 0.1772
4.0000	0.5443 $\pm$ 0.2335	0.6220 $\pm$ 0.3134	0.5322 $\pm$ 0.1574	0.5619 $\pm$ 0.1859	0.4085 $\pm$ 0.1581
6.0000	0.2463 $\pm$ 0.0513	0.2926 $\pm$ 0.1386	0.2036 $\pm$ 0.0455	0.1943 $\pm$ 0.0427	0.1940 $\pm$ 0.0322

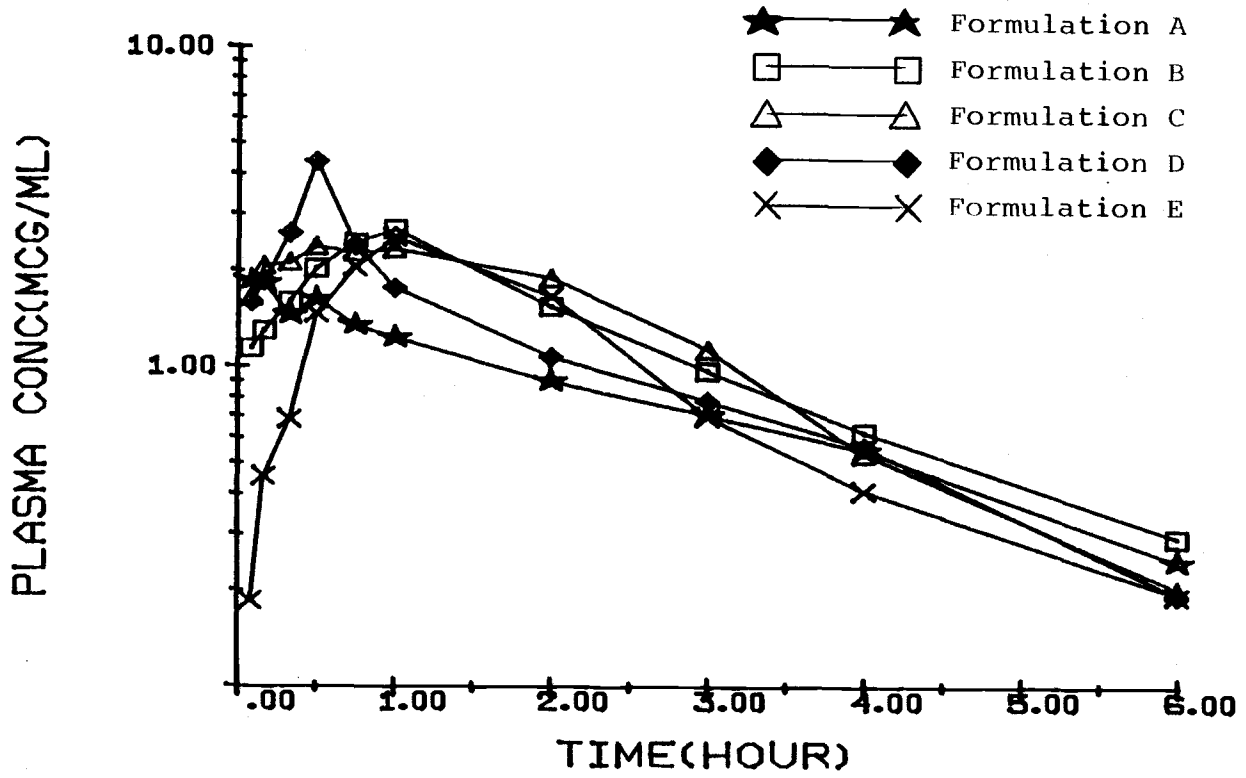

Figure II.7 Plasma ibuprofen concentration vs. time curve following oral administration of 50 mg of ibuprofen in formulation A, B, C, D, E in 5 rabbits

Table II.9 Elimination Rate Constant of Ibuprofen Following Oral Administration of 50 mg Ibuprofen in Formulation A, B, C, D, E, in Rabbit 1, 2, 3, 4, 5

	Rabbit 1 (HR^{-1})	Rabbit 2 (HR^{-1})	Rabbit 3 (HR^{-1})	Rabbit 4 (HR^{-1})	Rabbit 5 (HR^{-1})	MEAN ± S.D.
Formulation A	0.3332	0.3396	0.2852	0.3161	0.3329	0.3214 ± 0.0220
Formulation B	0.4331	0.4565	0.4163	0.4916	0.4397	0.4474 ± 0.0286
Formulation C	0.5204	0.7268	0.5368	0.5012	0.5114	0.5593 ± 0.0945
Formulation D	0.4024	0.5408	0.4941	0.5685	0.4590	0.4930 ± 0.0659
Formulation E	0.7751	0.4792	0.4977	0.4542	0.7535	0.5919 ± 0.1583

Table II.10 Analysis of Variance on Elimination Rate Constant of Ibuprofen Following Oral Administration of 50 mg of Ibuprofen in Formulation A, B, C, D, E in 5 Rabbits

Source of Variation	S.S.	df	M.S.	F
Treatments	0.2300	4.0	0.0575	5.7500**
Block (Rabbits)	0.0085	4.0	0.0021	0.2100 N.S.
Period	0.0262	4.0	0.0066	0.6600 N.S.
Error	0.1197	12.0	0.0100	
Total	0.3844			

1980). When a drug is administered orally in a solid dosage form, both the dissolution and the absorption steps may influence the rate and/or extent of appearance of drug in the blood. Bioavailability is an important parameter in the comparison of commercial drug formulations (Lovering et al., 1975). Bioavailability was defined by Riegelman as the relative rate and extent at which the administered dose reaches the general circulation (Riegelman, 1972). The extent and rate of drug absorption can be affected by the dosage from in which the drug is contained. However, bioavailability is sometimes interpreted as only the relative extent of absorption and is expressed as the percent ratio of the AUC of the test formulation to reference formulation AUC (Wagner, 1976a; DiSanto, 1983). In this study, Formulation E (ibuprofen drug powder only) was used as the reference to study the relative bioavailability of ibuprofen solid dispersion Formulation A, B, C, and D.

Absorption of ibuprofen has been reported to readily occur in rats, rabbits and dogs after single oral administration as a solution (Davies and Avery, 1971). In the rat, some absorption is from the stomach, but the main site of absorption is the intestine. Some of the ibuprofen and its metabolites appeared to re-enter the intestine, probably by excretion in the bile. In rats given a single oral dose of 20 mg/kg, the plasma concentration of ^{14}C-ibuprofen rose to a peak of 78 $\mu g/g$ (wet weight,

original compound plus metabolites) in 20 minutes and declined rapidly to a low level in 6 hours (Davies and Avery, 1971). Most of the plasma content of ^{14}C was presented as unchanged ibuprofen, and the remainder mostly a metabolite, [2,4'-(2-hydroxy-2-methylpropyl) phenylpropionic acid] (Davies and Avery, 1971). In rabbits after 6 hours fast, the time to peak concentration was longer (90 minutes), the clearance from the plasma was slower, and the peak concentration was only 37 μg/g after given a single oral dose of 60 mg/kg as an aqueous solution of the sodium salt. Most of the radioactivity came equally from unchanged ibuprofen and one metabolite, [2,4'-(2-carboxypropyl) phenylpropionic acid]. In dogs, after an overnight fast, the time course of plasma concentrations was similar to that in rabbits, but the amount of absorption was greater. The peak concentraton was 26 μg/g (solely as unchanged ibuprofen) after a single oral dose of 8 mg/kg. In man, mean peak plasma levels of ibuprofen of 37.7, 61.1, and 87.7 μg/ml occurred at 1.3, 1.6 and 1.7 hours after a single oral dose of 400, 800 and 1200 mg after fasting. Estimated bioavailability of one, two and three 400 mg tablets relative to the aqueous solution was reported to be 95%, 90% and 89% respectively (Lockwood et al., 1983).

In this study, moment analysis was used as a method to comprehend drug behavior in the body, that is, absorption, distribution and elimination. For years, pharmacokinetic

characterization of a drug has typically involved curve-fitting drug concentration versus time data to a polyexponential equation using nonlinear least squares regression. Based on the equation obtained, a pharmacokinetic model was selected and kinetic parameters calculated. This method is tedious and time consuming, and the selection of the pharmacokinetic model is usually arbitrary. DiSanto and Wagner (1972) showed that the time-course data for plasma concentrations of methylene blue are fit to both a linear heterogenous one-compartment open model with binding to one type of tissue and the classical linear two-compartment open model. Even if an exponential equation is obtained for time-course data, the pharmacokinetic model cannot be determined directly. Wagner (1976b) then showed that several different compartment models may be expressed by the same number of exponential terms. Where the drug concentration time course following oral dosing is represented by a one-compartment open model, the flip-flop model can occur with short half-life drugs (Wagner, 1976a). Statistical moments offer the advantage of clearly showing the overall properties of drug time course because these moments can be calculated by simple numerical integration of experimental data without a pharmacokinetic model (Yamaoka et al., 1978; Cutler, 1981). Another advantage is that statistical moments can be used to compare pharmacokinetic data from different sources. It is

difficult to compare pharmacokinetic parameters obtained in one model with those of the other. Since statistical moments immediately relfect the overall characteristics of the drug concentration time-course curve (i.e., whether a drug passes through the body quickly or over a long period of time), for the reason cited earlier, statistical moments were utilized to analyze time-course data.

Zeroth statistical moment represents the area under the plasma concentration-time curve (AUC) which is used as a model-independent parameter. The first moment, which is defined as the mean residence time (MRT), gives significant information with respect to kinetic features of the process which a drug undergoes in the gastrointestinal tract and the body (Yamaoka et al., 1978). The absorption of a drug from its oral preparation involves a process too complex to be described by a simple mathematical equation. Therefore, a model-independent approach has been undertaken to evaluate the absorption rate. These methods are based on deconvolution. The mean absorpton time (MAT) is the useful index of the rate of bioavailability.

AUC's were calculated by using trapezoidal rule for all formulations in the five rabbits and are listed in Table II.11. The results from ANOVA (Table II.12) indicated that there was statistically significant difference in AUC values among the formulations. AUC's for Formulation A and E has average values of 5.48 and 5.92 $\mu g \cdot hr \cdot ml^{-1}$, and there is

Table II.11 Extent of Ibuprofen Absorbed Measured as Area Under The Plasma Concentraton-Time Curve from Time Zero to Infinity (AUC) Following Oral Administration of 50 mg Ibuprofen in Preparation A, B, C, D, E in 5 Rabbits

Subject	Formulation A AUC $\mu g \cdot hr \cdot ml^{-1}$	Formulation B AUC $\mu g \cdot hr \cdot ml^{-1}$	Formulation C AUC $\mu g \cdot hr \cdot ml^{-1}$	Formulation D AUC $\mu g \cdot hr \cdot ml^{-1}$	Formulation E AUC $\mu g \cdot hr \cdot ml^{-1}$
Rabbit 1	4.6480	5.2339	8.5064	5.5192	5.0849
Rabbit 2	7.9167	12.2990	9.5326	10.0409	8.2771
Rabbit 3	5.6485	8.3426	8.5274	6.1139	5.6807
Rabbit 4	5.1798	6.4772	6.6913	7.1106	5.8324
Rabbit 5	4.0041	6.0090	4.7416	4.8244	4.7318
MEAN	5.4794	7.6723	7.5999	7.6040	5.9214
S.D.	1.4939	2.8283	1.8982	3.9189	1.3901

Table II.12 Analysis of Variance on AUC Following Oral Administration of 50 mg of Ibuprofen in Preparation A, B, C, D, E in 5 Rabbits

Source of Variation	S.S.	df	M.S.	F
Treatments	19.2476	4.0	4.8119	6.9667**
Block (Rabbits)	64.4839	4.0	16.1210	23.3401**
Period	6.8768	4.0	1.7192	2.4891 N.S.
Error	8.2884	12.0	0.6907	
Total	98.8967			

not statistically significant difference in the mean values between these two formulations. Formulation B, C, and D had AUC values very close to each other, with average values of 7.67, 7.60, and 7.60 $\mu g \cdot hr \cdot ml^{-1}$ respectively. At 95% confidence level, the mean values for AUC for Formulation A and E are significantly different from those for Formulation B, C and D.

Analysis of relative extent of bioavailability for Formulation A, B, C and D by using Formulation E as a reference is shown in Table II.13. This was calculated by dividing the total area under the drug concentration in plasma versus time curve from time zero to infinity after oral administration of the test formulation with that after admininstration of reference formulation. The average fracton of absorption for formulation A is 91.98 $\pm$ 5.78% while the higher values were found for Formulation B, C, and D with the mean value of 127.28 $\pm$ 20.58%, 129.50 $\pm$ 27.99% and 122.93 $\pm$ 29.80% respectively. It should be noted that Formulation C, ibuprofen granules prepared by freeze-drying, showed the greatest extent of absorption which is similar to the dissolution studies performed in the previous chapter. The FDA has imposed a specific bioavailability testing requirement for new formulations of active drug ingredients or therapetuic moieties that have been approved for marketing. The test drug product shall be deemed to meet the bioequivalence requirement for in vivo testing if the following conditions are met. The test product and the

Table II.13 Fraction of Ibuprofen Absorbed Following Oral Administration of 50 mg Ibuprofen in Preparation A, B, C, D as Compared to that of Preparation E.

Subject	Formulation A[a]	Formulation B[b]	Formulation C[c]	Formulation D[d]
Rabbit 1	91.41	102.93	167.29	108.54
Rabbit 2	95.65	148.59	115.17	121.31
Rabbit 3	99.43	146.86	150.11	107.62
Rabbit 4	88.81	111.06	114.73	121.92
Rabbit 5	84.62	126.99	100.21	101.96
Mean	91.98	127.28	129.50	112.27
S.D.	5.78	20.58	27.99	8.90

[a] $(AUC_{0\rightarrow\infty}$ of Formulation A)/$(AUC_{0\rightarrow\infty}$ of Formulation E) X 100%

[b] $(AUC_{0\rightarrow\infty}$ of Formulation B)/$(AUC_{0\rightarrow\infty}$ of Formulation E) X 100%

[c] $(AUC_{0\rightarrow\infty}$ of Formulation C)/$(AUC_{0\rightarrow\infty}$ of Formulation E) X 100%

[d] $(AUC_{0\rightarrow\infty}$ of Formulation D)/$(AUC_{0\rightarrow\infty}$ of Formulation E) X 100%

reference one indicate no more than 20% difference in the comparison of the measured parameter; and in at least 75% of the subjects administered the drug, the test product has a bioavailability of greater than 75% relative to that of the administered material utilizing each subject as his or her own comparison. In this study a new statistical procedure for testing equivalence in 2 groups comparative bioavailability trials were used to analyze the data since this method is more powerful than the confidence interval method and the straightforward ANOVA F-test may not be appropriate for the bioequivalence problem (Hauck and Anderson, 1984). The test statistics for equivalence indicated that Formulation A has the same extent of bioavailability as the reference (Formulation E) with p value < 0.05. However, for formulations B, C, and D it would be very unlikely to accept the hypothesis of equivalence with the reference product (no more than 20% difference), since p values are less than 0.05.

The first order statistical moments (MRT's and MAT's) calculated for each rabbits for Formulation A, B, C, D and E are listed in Table II.14 and Table II.16. The mean residence time (MRT) values were calculated from equations using the trapezoidal rule as expressed in equation 7 which was the ratio of AUMC to AUC. The average mean residence time (MRT) for each formulation is presented in Table II.14. The difference in MRT's among these ibuprofen preparations were statistically significant at the 0.05 level ($p < 0.05$)

Table II.14 Mean Residence Time (MRT) for Formulation A, B, C, D, E in 5 Rabbits

Subject	Formulation A (HR)	Formulation B (HR)	Formulation C (HR)	Formulation D (HR)	Formulation E (HR)
Rabbit 1	3.0764	2.3326	2.2185	2.7476	1.8072
Rabbit 2	2.9714	3.0769	2.2304	2.0493	2.5291
Rabbit 3	3.5564	2.5594	2.2251	2.3523	2.2197
Rabbit 4	3.2894	2.2073	2.3291	1.9945	2.4463
Rabbit 5	3.1035	2.5827	2.2334	2.5351	1.7223
Mean	3.1994	2.5518	2.2473	2.3378	2.1449
S.D.	0.2301	0.3330	0.0461	0.3172	0.3663

Table II.15 Analysis of Variance on MRT Following Oral Administration Ibuprofen Preparations

Source of Variation	S.S.	df	M.S.	F
Treatments	3.5403	4.0	0.8851	8.0864**
Block (Rabbits)	0.1126	4.0	0.0282	0.2571 N.S.
Period	0.1736	4.0	0.0434	0.3956 N.S.
Error	1.3167	12.0	0.1097	
Total	5.1433			

by ANOVA (Table II.15). The MRT values after oral administration of Formulation A in the rabbits exhibited the highest value among other treatment means, and these differences were statistically significant. There was no significant difference observed in MRT values among Formulation B, C, D and E. These results indicated that the mean time of the kinetic processes which ibuprofen from Formulation A underwent in the gastrointestinal tract and the body of the rabbits, was longer than other formulations tested in this study.

The absorption characteristics of pharmaceutical preparations can be compared by using the mean absorption time (MAT) value. MAT expresses the mean overall time since a drug is administered until it enters the systemic circulation. Table II.16 and II.17 list the MAT values (hour) and ANOVA test for all the formulations in the five rabbits. The MAT value was estimated by subtraction of the value of MRT with its corresponding elimination rate constant (equation 10). Statistical analysis of MAT values observed following the administration of the various ibuprofen preparations yielded a significant difference among treatment means ($p < 0.001$). A multiple comparison test showed that Formulation A provided a significant increase in the average MAT value as compared to the other formulations. The average MAT value for Formulation A was 1.42 hours which was about 4 times higher than that for the reference Formulation E. Formulation C and D produced the average MAT values of 0.42 and 0.28 hours, which was

Table II.16 Mean Absorption Time (MAT) for Formulation A, B, C, D, E in 5 Rabbits

Subject	Formulation A (HR)	Formulation B (HR)	Formulation C (HR)	Formulation D (HR)	Formulation E (HR)
Rabbit 1	1.7862	0.1420	0.2969	0.2625	0.5170
Rabbit 2	0.8846	0.2945	0.8275	0.2102	0.4423
Rabbit 3	1.5472	0.1573	0.3622	0.3284	0.2105
Rabbit 4	1.0877	0.1731	0.3339	0.2355	0.2446
Rabbit 5	1.7764	0.3084	0.2780	0.3565	0.3951
Mean	1.4164	0.2151	0.4197	0.2786	0.3619
S.D.	0.4106	0.0798	0.2303	0.0619	0.1307

Table II.17 Analysis of Variance on MAT Following Oral Administration of Ibuprofen in Preparations

Source of Variation	S.S.	df	M.S.	F
Treatments	4.94106	4.0	1.2353	22.8336**
Block (Rabbits)	0.1331	4.0	0.0333	0.6155 N.S.
Period	0.2138	4.0	0.0535	0.9880 N.S.
Error	0.6486	12.0	0.0541	
Total	5.9365			

about 23% and 16% higher than for the reference formulation. However, Formulation B resulted in an average MAT of 0.22 hours, which was 41% less than the MAT of Formulation E. Differences in MAT values among Formulation B, C, D and E were not statistically significant. Thus, indicate that Formulation A exhibited the slowest rate of absorption while Formulation B absorbed faster than the other formulations. Formulation C, D and E were absorbed at similar rates.

Table II.18 presented peak concentrations (C_{max}) observed following administration of different ibuprofen formulations. Statistical analysis (Table II.19) showed significant differences among the treatment means ($p = 0.025$). Ibuprofen Formulation D exhibited the highest mean peak plasma concentration with an average of 4.4096 μg/ml which was 46% more than that for the reference product (Formulation E). This difference was statistically significantly differenct from the other and indicated that ibuprofen may be more rapidly absorbed from Formulation D than from the reference. Formulation D also produced an average C_{max} which was 53% and 39% higher than that for Formulation C and B. There is also a significant difference in peak plasma concentrations of ibuprofen between Formulation D and Formulation A. There was an 83% increase in the mean value of Formulation D compared to Formulation A. There is no significant difference among Formulation A, B, C, and E in mean peak ibuprofen plasma concentrations. However, Formulation A produced an average of C_{max} which was 20% less than the reference preparation (Formulation E).

Table II.18 Maximum Plasma Concentration of Ibuprofen (C_{max}) Following Oral Administration of Ibuprofen A, B, C, D, E in 5 Rabbits

Subject	Formulation A (μg/ml)	Formulation B (μg/ml)	Formulation C (μg/ml)	Formulation D (μg/ml)	Formulation E (μg/ml)
Rabbit 1	2.7510	2.1004	3.0984	3.7454	2.5673
Rabbit 2	3.5027	4.3685	3.3154	7.4996	3.6477
Rabbit 3	2.6263	3.6027	3.3755	3.0919	3.1611
Rabbit 4	1.7164	2.9392	2.6254	5.4979	3.2297
Rabbit 5	1.4113	2.7427	2.0133	2.2134	2.4642
Mean	2.4015	3.1507	2.8856	4.4096	3.0140
S.D.	0.8419	0.8663	0.5698	2.1055	0.4928

Table II.19 Analysis of Variance on C_{max} Following Oral Administration of Ibuprofen Preparations

Source of Variation	S.S.	df	M.S.	F
Treatments	11.1640	4.0	2.7910	4.4893**
Block (Rabbits)	13.9273	4.0	3.4818	25.6005**
Period	4.4529	4.0	1.1132	1.7905 N.S.
Error	7.4601	12.0	0.6217	
Total	37.0043			

CONCLUSION

In the present study, the freeze-dried solid dispersion of ibuprofen (Formulation C) exhibited the greatest relative extent of absorption. Preparations with polyethylene glycol 20,000 enhanced the extent of ibuprofen absorption when compared with the control (Formulation E, formulation with ibuprofen drug powder). There appears to be no advantage in formulating ibuprofen in PEG by the freeze-drying method over the direct melting method. When the amount of theobroma oil is increased in the formulation of solid dispersion, a slower rate of absorption of ibuprofen is obtained as reflected by a significant increase in mean absorption time and mean residence time compared to control. The results of this study are consistent with the dissolution studies performed in the previous chapter.

ENDNOTES

1. Sterile Alcohol Prep. Professional Disparables, Inc., Mt. Vernon, NY., Missisangna, Ontario, Canada.
2. Lidocaine Hydrochloride Injection, U.S.P. 2% (2 mg/ml), Rugby Laboratories, inc., Rockville Center, NY.
3. Quik-Cath, Travenol Laboratories, Inc., Deerfield, IL. INCISIV, Desert Medical Inc., Sandy, UT.
4. Intermittant infusion plug, Argyle, St. Louis, MO.
5. Hypodermic needle sterile, Becton Dickinson and Company, Rutherford, NJ.
6. Panheparin, Heparin sodium injection, U.S.P., Abbot Laboratories, Norht Chicago, IL.
7. Intramedic polyethylene tubing, PE90.
8. Microcentrifuge tube, Centaur Sciences, Inc. Standford, CT.
9. Dextroxe 5% in water, Abott Laboratories, North Chicago, IL.
10. Model TJ-6 Centrifuge, Model TJ-R Refrigeration Unit, Beckman Instruments, Palo Alto, CA.
11. Butyl paraben.
12. Acetonitril, J.T. Baker Chemical Co., Phillipsburg, NJ.
13. Methanol, J.T. Baker Chemical Co., Phillipsburg, NJ.
14. Hydrochloric acid, J.T. Baker Chemical Co., Phillipsburg, NJ.
15. Chloroform, J.T. Baker Chemical Co., Phillipsburg, NJ.
16. Rotamixer, Scientific Products, McGaw Park, IL.
17. Lab-Line/Vacuum oven, Lab-Line Instrument, Inc.,, Melrose Park, IL.
18. Water Associates, Milford, MA.
19. Ibuprofen USP Reference Standard, U.S.P.C., Inc., Rockville, MD.

REFERENCES

Aaron, L. and Rowland, J.M., Use of in vitro dissolution data to predict plasma drug profiles. J. Pharm. Sci., 66, 1359-1362 (1977).

Adams, S.S., McCullough, K.F., and Nicholson, J.S., The pharmacological properties of ibuprofen, an antiinflammatory analgesic and antipyretic agent, Arch. Int. Pharmacodyn., 178, 115-129 (1969).

Cochran, W.G. and Cox, G.M. Experimental Designs, 2nd Edition. John Wiley & Sons, New York, 1976, p. 127-141.

Cutler, D.J., Theory of the mean absorption time, an adjunct to conventional bioavailability studies. J. Pharm. Pharmacol., 30, 476-478 (1978).

Cutler, D.J., Assessment of rate and extent of drug absorption. Pharmacol. Ther., 14, 123-160 (1978).

Davies, E.F. and Avery, G.S., Ibuprofen: A review of its pharmacological properties and therapeutic efficacy in rheumatic disorders. Drugs, 2, 416-446 (1971).

Disanto, A.R., Bioavailability and bioequivalency testing. Remington's Pharmaceutical Sciences, 16th Edition. Mack Publishing Company, Easton, PA., 1980, p. 1369-1377.

Disanto, A.R. and Wagner, J.G., Pharmacokinetic of highly ionized drug. III methylene blue - blood levels in dog and tissue levels in rat following intravenous administration. J. Pharm. Sci., 61, 1090-1044 (1972).

Hauck, W.A. and Anderson, S., A new statistical procedure for testing equivalence in two-group comparative bioavailability trials. Pharmacokin. Biopharm., 12, 83-91 (1984).

Himmelblau, D.M. and K.B. Bischoff, Process analysis and simulation. Deterministic Systems, Wiley, New York.

Lockwood, G.F., Albert, K.S., Gillespie, W.R., Bole, G.G., Harkcom, T.M., Szpunar, G.J. and Wagner, J.G., Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. Clin. Pharmacol. Ther., 34, 97-103 (1983).

Lovering, E.G., McGilveray, I.J., McMillan, I. and Toctowaryk, W., Comparative bioavailabilities from truncated blood level curves. J. Pharm. Sci., 64, 1521-1524 (1975).

Mills, R.F.N., Adams, S.S., Cliffe, E.E., Dickinson, W. and Nicholson, J.S., The Metabolism of ibuprofen. Xenobiotica, 3, 589-598 (1973).

Neter, J. and Wasserman, W., Applied Linear Statistical Model. Richard D. Irwin, Inc., Homewood, Il., 1974.

Pedersen, P.V., Novel deconvolution method for linear pharmacokinetic systems with polyexponential impulse response. J. Pharm. Sci., 69, 312-318 (1980).

Riegelman, S., Physiological and pharmacokinetic complexities in bioavailability testing. Pharmacology, 8, 118-141 (1972).

Riegelman, S. and Collier, P., The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm., 8, 509-534 (1980).

Smolen, V.F. and Weignad, W.A., Optimally predictive in vitro drug dissolution testing for in vivo bioavailability. J. Pharm. Sci., 65, 1718-1724 (1976).

Wagner, J.G., Biopharmaceutics and Relevant Pharmacokinetics, 1st Edition. Drug Intelligence Publications, Hamilton, IL., 1971, p. 121-124, 140-147.

Wagner, J.G., Fundamentals of Clinical Pharmacokinetics. Drug Intelligence Publications, Hamilton, IL., 1975.

Wagner, J.G., An overview of the analysis and interpretation of bioavailability studies in man. Arzneim. Forsch., 26, 105-108 (1976a).

Wagner, J.G., Linear Pharmacokietic models and vanishing exponential terms: Implication in pharmacokinetics. J. Pharmacokin. Biopharm., 4, 395-425 (1976).

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical Moments in pharmacokinetics. J. Pharmacokin. Biopharm., 6, 547-558 (1978).

BIBLIOGRAPHY

Aaron, L. and Rowland, J.M., Use of in vitro dissolution data to predict plasma drug profiles. J. Pharm. Sci., 66, 1359-1362 (1977).

Adams, S.S., McCullough, K.F., and Nicholson, J.S., The pharmacological properties of ibuprofen, an antiinflammatory analgesic and antipyretic agent, Arch. Int. Pharmacodyn., 178, 115-129 (1969).

Ampolsuk, C., Mauro, J.V., Nyhuis, N.S. and Jarowski, C.I., Influence of dispersion method on dissolution rate of digoxin-lactose and hydrocortisone-lactose triturations I. J. Pharm. Sci., 63 (1974) 117-118.

Bates, T.R., Dissolution characteristics of reserpine-polyvinylpyrrolidone co-precipitates. J. Pharm. Pharmacol., 21, 710-712 (1969).

Bauer, G., Rieckmann, P. and Schaumann, W., Influence of particle size on the absorption of spironolactone from the gastrointestinal tract. Arzneim. Forsch., 12 487-489 (1962).

Bloedow, D.C. and Hayton, W.L., Effects of lipids on bioavailability of sulfisoxazole acetyl, dicumarol and griseofulvin in rats. J. Pharm. Sci., 65, 328-334 (1976).

Buckley, H.E., Crystal Growth. Wiley, New York, 1963.

Chiou, W.L., Chen, S.J. and Athanikar, N., Enhancement of dissolution rates of poorly water-soluble drugs by crystallization in aqueous surfactant solution I: sulfathiazole, prednisone and chloramphenicol. J. Pharm. Sci., 65, 1212-1214 (1976).

Chiou, W.L. and Riegelman, S., Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J. Pharm. Sci., 58, 1505-1510 (1969).

Chiou, W.L. and Riegelman, S., Absorption characteristics of solid dispersed and micronized griseofulvin in man. J. Pharm. Sci., 60, 1376-1380 (1971a).

Chiou, W.L. and Riegelman, S., Increased dissolution rates of water-soluble cardiac glycosides and steroids via

solid dispersions in polyethylene glycol 6000. J. Pharm. Sci., 60, 1569-1571 (1971b).

Chiou, W.L. and Riegelman, S., Pharmaceutical Applications of solid dispersion systems. J. Pharm. Sci., 60 1281-1302 (1970).

Chiou, W.L. and Smith, L.D., Solid dispersion approach to the formulation of organic liquid drugs using polyethylene glycol 6000 as a carrier. J. Pharm. Sci., 60, 125-127 (1971).

Cochran, W.G. and Cox, G.M. Experimental Designs, 2nd Edition. John WIley & Sons, New York, 1976, p. 127-141.

Cutler, D.J., Theory of the mean absorption time, an adjunct to conventional bioavailability studies. J. Pharm. Pharmacol., 30, 476-478 (1978).

Cutler, D.J., Assessment of rate and extent of drug absorption. Pharmacol. Ther., 14, 123-160.

Davidson, R.L. and Sittig, M., Water Soluble Resin. Reinhold, London, England, 1962.

Davies, E.F. and Avery, G.S., Ibuprofen: A review of its pharmacological properties and therapeutic efficacy in rheumatic disorders. Drugs, 2, 416-446 (1971).

Disanto, A.R., Bioavailability and bioequivalency testing. Remington's Pharmaceutical Sciences, 16th Edition. Mack Publishing Company, Easton, PA., 1980, p. 1369-1377.

Disanto, A.R. and Wagner, J.G., Pharmacokinetic of highly ionized drug. III methylene blue - blood levels in dog and tissue levels in rat following intravenous administration. J. Pharm. Sci., 61, 1090-1044 (1972).

Duncan, W.A., Macdonald, G., Thornton, M.J., Some factors influence the absorption of griseofulvin from the gastrointestinal tract. J. Pharm. Pharmacol., 14, 217-224 (1962).

Feinberg, M., Drug standards in military procurement. J. Amer. Pharm. Assoc., NS9. 113-116 (1969).

Fincher, J.H., Particle size of drugs and its relationship to absorption and activity. J. Pharm. Sci., 57, 1825-1835 (1968).

Ford, J.L. and Rubinstein, M.H., Aging of indomethacin-polyethylene glycol 6000 solid dispersions. Pharm. Acta Helv., 54, 353-358 (1979).

Ford, J.L. and Rubinstein, M.H., Formulation and aging of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersions. Pharm. Acta Helv., 55, 1-7 (1980).

Fox, D., Labes, M.M. and Weissberger, A., Physics and Chemistry of the Organic Solid State. Interscience, New York, 1963, p. 572.

Geineidi, A.S. and Hamacher, H., Physical characterization and dissolution profiles of spironolactone and diazepam coprecipitates. Pharm. Ind., 42, 315-319 (1980a).

Geineidi, A.S. and Hamacher, H., Enhancement of dissolution rates of spironolactone and diazepam via polyols and PEG solid dispersion systems. Pharm. Ind., 42, 401-404 (1980b).

Geneidi, A.S., Ali, F.A. and Salama, R.B., Solid dispersion of nitrofurantoin, ethotoin and coumarin with polyethylene glycol 6000 and their coprecipitates with povidone 25,000. J. Pharm. Sci., 67, 114-116 (1978).

Gibaldi, M. and Feldman, S., Mechanisms of surfactant effects on drug absorption. J. Pharm. Sci., 59, 579-589 (1970).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures.
II. experimental evaluation of a eutectic mixture: urea-acetaminophen system. J. Pharm. Sci., 55, 482-487 (1966a).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures.
III. experimental evaluation of griseofulvin-succinic acid solid solution. J. Pharm. Sci., 55, 487-492 (1966b).

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption via solid solutions and eutectic mixtures.
IV. chloramphenical-urea system. J. Pharm. Sci., 55, 581-583 (1966c).

Goodman, L.S. and Gilman, A., The Pharmacological Basis of Therapeutics. 3rd edition, MacMillan, New York, 1965, p. 116.

Grisafe, J.A. and Hayton, W.L., Intestinal absorption of grizeofulvin from a triolein digestionmixture in rats. J. Pharm. Sci., 67, 895-899 (1978).

Guillory, J.K., Hwang, S.C. and Lach, J.L., Interactions between pharmaeutical compounds by thermal methods. J. Pharm. Sci., 58, 301-308 (1969).

Haleblian, J. and McCrone, Pharmaceutical applications of polymorphism. J. Pharm. Sci., 58, 911-929 (1969).

Hauck, W.A. and Anderson, S., A new statistical procedure for testing equivalence in two-group comparative bioavailability trials. Pharmacokin. Biopharm., 12, 83-91 (1984).

Hem, S.L., Skauen, D.M. and Beal, H.M., Mechanism of crystallization of hydrocortisone by ultrasonic irradiation. J. Pharm. Sci., 56, 229-233 (1967).

Higuchi, W.I., diffusional models useful in biopharamceutics: Drug release rate process. J. Pharm. Sci., 56, 315-324 (1967).

Himmelblau, D.M. and K.B. Bischoff, Process analysis and simulation. Deterministic Systems, Wiley, New York.

Ibrahim, H.G. Pisano, F. and Bruno, A., Polymorphism of phenylbutazone, properties and compressional behavior of crystals. J. Pharm. Sci., 66, 669-673 (1971).

International Critical tables. Vol I, McGraw-Hill Book Company, Inc., New York, 1926, p. 67.

Irani, R.R. and Callis, C.F., Particle Size: Measurement, Interpretation and Application. Wiley, New York, 1963, p. 17,18.

Johansen, H. and Moller, N., Solvent deposition method for enhancement of dissolution rate: importance of drug-to-excipient ratio. J. Pharm. Sci., 67, 134-136 (1978).

Kanig, J.L., Properties of fused mannitol in comressed tablets. J. Pharm. Sci., 53, 188-192 (1964).

Kaur, R., Grant, D.W. and Eaves, T., Comparison of polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide. II. dissolution and solubilities studies. J. Pharm. Sci., 69, 1321-1326 (1980).

Kornblum, S.S. and Hirschorn, J.O., Dissolution of poorly water-soluble drugs. I: some physical aprameters related to method of micronization and tablet manufacture of a quinazolinone compound. J. Pharm. Sci., 59, 606-609 (1970).

Lachman, L., Lieberman, H.A. and Knaig, J.L., The Theory and Practice of Industrial Pharmacy. Lea & Geviger, Philadelphis, 1970, p. 58.

Levy, G., Availability of spironolactone given by mouth. Lancet, 2, 723-724 (1962).

Levy, G., Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. Amer. J. Pharm., 135, 78-92 (1963).

Lin, S.L., Menig, J. and Lachman, L., Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water-insoluble drugs. J. Pharm. Sci., 57, 2143-2148 (1968).

Lockwood, G.F., Albert, K.S., Gillespie, W.R., Bole, G.G., Harkcom, T.M., Szpunar, G.J. and Wagner, J.G., Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. Clin. Pharmacol. Ther., 34, 97-103 (1983).

Lovering, E.G., McGilveray, I.J., McMillan, I. and Toctowaryk, W., Comparative bioavailabilities from truncated blood level curves. J. Pharm. Sci., 64, 1521-1524 (1975).

Martin, A., Swarbrick, J. and Cammarata, A., Physical Pharmacy, 3rd Edition, Lea and Febiger, Philadelphia, 1983, p. 134, 272-311.

Matsunaga, J., Nambu, N. and Nagai, T., Polymorphism of phenylbutazone. Chem. Pharm. Bull., 24, 1169-1174 (1976).

Maulding, H.V., Solid-state dispersions employing urethan. J. Pharm. Sci., 67, 391-394 (1978).

Mayersohn, M. and Gibaldi, M., New method of solid-state dispersion for increasing dissolution rates. J. Pharm. Sci., 55, 1323-1324 (1966).

McGinity, J.W., Maincent, P. and Steinfink, H., Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. J. Pharm. Sci., 73, 1441-1444 (1984).

The Merck Index, 10th Edition. Merck & Co, Inc., New Jersey, 1983, p. 1271.

Mills, R.F.N., Adams, S.S., Cliffe, E.E., Dickinson, W. and Nicholson, J.S., The Metabolism of ibuprofen. Xenobiotica, 3, 589-598 (1973).

Miralles, M.J., McGinity, J.W. adn Martin, A., Combined water-soluble carriers for copredipitates of tolbutamide. J. Pharm. Sci., 71, 302-304 (1982).

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983a, p. 15.

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983b, p. 16.

Moore, W.J., Physical Chemistry, 5th Edition. Prentice-Hall, Inc., New Jersey, 1983c, p. 17.

Mullin, J.D. nad Macek, T.J., Some pharamceutical properties of novobiocin. J. Amer. Pharm. Assoc., 49, 245-248 (1960).

Neter, J. and Wasserman, W., Applied Linear Statistical Model. Richard D. Irwin, Inc., Homewood, Il., 1974.

Pedersen, P.V., Novel deconvolution method for linear pharmacokinetic systems with polyexponential impulse response. J. Pharm. Sci., 69, 312-318 (1980).

Ravis, W.R. and Chen, C., Dissolution, stability, and absorption characteristics of dicumarol in polyethylene glycol 4000 solid dispersions. J. Pharm. Sci., 70, 1353-1357 (1981).

Riegelman, S., Physiological and pharmacokinetic complexities in bioavailability testing. Pharmacology, 8, 118-141 (1972).

Riegelman, S. and Collier, P., The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm., 8, 509-534 (1980).

Said, S.A., El-Fatary, H.M. nad Geneidi, A.S., Coprecipitates of tolbutamide with polyvinylpyrrolidone and fusion mixtures with macrogol. Aust. J. Pharm. Sci., NS3, 42-45 (1974).

Salib, N.N., El-Gamal, S.A. and Ismail, A.A., Preparation and disposition characteristics of several fast-release solid dispersions of tolbutamide. Pharm. Ind., 38, 918-921 (1976).

Scheikh, M.A., Price, J.C. and Gerraughty, R.J., Effect of ultrasound on particle size of suspensions of polyethylene spheres. J. Pharm. Sci., 55, 1048-1050 (1966).

Sekiguchi, K. and Obi, N., Studies on absorption of eutectic mixture. I: a comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 9, 866-872 (1961).

Simonelli, A.P., Mehta, S.C. and Higuchi, W.J., Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J. Pharm. Sci., 58, 538-549 (1969).

Skauen, D.M., Some pharmaceutical applications of ultrasonic. J. Pharm. Sci., 56, 1373-1385 (1967).

Smolen, V.F. and Weigand, W.A., Optimally predictive in vitro drug dissolution testing for in vivo bioavailability. J. Pharm. Sci., 65, 1718-1724 (1976).

Stavchansky, S. and Gowan, W.G., Evaluation of the bioavailability of a solid dispersion of phenytoin in polyethylene glycol 6000 and a commercial phenytoin sodium capsule in dog. J. Pharm. Sci., 73, 733-736 (1984).

Steady, J.A., Freeman, M., John, E.G., Ward, G.T. and Whiting, B., Ibuprofen tablets: dissolution and bioavailability. Int. J. Pharm., 14, 59-72 (1983).

Stupak, E.I. and Bates, T.R., Enhanced absorption and dissolution of reserpine from reserpine-polyvinylpyrrolidone coprecipitates. J. Pharm. Sci., 61, 400-404 (1972).

Suvanakoot, U., Dissolution characteristics of freeze-dried granuales of tolbutamide and phenylbutazone. Ph.D. Thesis, Oregon State University, 1984, p. 2-68.

Tachibana, T. and Nakamura, A., A method for preparing an aqueous colloidal dispersion of organic material by using water-soluble polymers: dispersion of -carotene by polyvinyl pyrrolidone. Kolloid-Z. Polym., 203, 130-133 (1965).

Wagner, J.G., Biopharmaceutics and Relevant Pharmacokinetics, 1st Edition. Drug Intelligence Publications, Hamilton, IL., 1971, p. 121-124, 140-147.

Wagner, J.G., Fundamentals of Clinical Pharmacokinetics. Drug Intelligence Publications, Hamilton, IL., 1975.

Wagner, J.G., An overview of the analysis and interpretation of bioavailability studies in man. Arzneim. Forsch., 26, 105-108 (1976a).

Wagner, J.G., Linear Pharmacokietic models and vanishing exponential terms: Implication in pharmacokinetics. J. Pharmacokin. Biopharm., 4, 395-425 (1976).

Windholz, M., The Merck Index, 10th Edition. Merck & Co., Inc., New Jersey, 1983, p. 779.

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical Moments in pharmacokinetics. J. Pharmacokin. Biopharm., 6, 547-558 (1978).

APPENDIX

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1.	Theobroma oil	10 g
	Lecithin	2 g
	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g
2.	Theobroma oil	6 g
	Lecithin	2 g
	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g
3.	Theobroma oil	2 g
	Lecithin	2 g
	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g
4.	Lecithin	2 g
	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g
5.	Lecithin	4 g
	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g

6.	Peg 20,000	5 g
	Ibuprofen	10 g
	Distilled Water	60 g
7.	Peg 20,000	10 g
	Ibuprofen	10 g
	Distilled Water	60 g
8.	Peg 20,000	15 g
	Ibuprofen	10 g
	Distilled Water	60 g
9.	Peg 20,000	20 g
	Ibuprofen	10 g
	Distilled Water	60 g
10.	Ibuprofen Freeze-dried powder (PEG: Ibuprofen = 50:50)	210.00 mg
	Avicel pH 102	46.80 mg
	Mannitol	36.85 mg
	Corn starch	35.00 mg
	Ac-di-sol	17.50 mg
	Cabosil	1.75 mg
	Stearic acid	0.88 mg
	Magnesium stearate	0.87 mg
	Sodium lauryl sulfate	0.35 mg

Making 350 - mg tablet weight
Hardness 6 kg
Disintegration time 8 minutes