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STUDIES ON SOME CRYSTALLINE FORMS OF IBUPROFEN

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ABSTRACT

Different crystal forms of ibuprofen were prepared and characterized by IR spectra, melting point, morphological structure, dissolution studies, and stability. Different forms were found to demonstrate variable physicochemical properties and dissolution rates. These ranged in physical appearance from prisms to needles and plates. The dissolution t_{70} ranged from 48 minutes to > 480 minutes. The stability study indicated that most of the crystal forms were stable at room temperature, and also at 60° C over one month.

INTRODUCTION

Optimization of a drug substance through the determination and/or definition of some physical and chemical properties is mandatory in the development of a stable, effective, safe, and reproducible dosage form. Dissolution, crystalinity, pH-solubility profiles, pH-stability profiles, drug-

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excepient interactions, etc. are a few of these parameters. All such properties are the prime determinants of the drugs' physiological availability together with the physical and chemical stability.

The crystalinity of a solid drug substance is of significant importance and has a multifaceted bearing on many aspects related to the performance of a dosage form of a drug. Crystal habit and crystalline modifications are two different aspects of crystalinity. Crystal habit, a description of an outer appearance of the crystal, changes with change in the environment or crystallizing conditions. These could affect its external appearance without alterations in the internal structure. Crystal habits influence many pharmaceutical characteristics of a drug substance. For example, suspension syringebility, tabletting behavior or dissolution of a material.[1]

When an internal structure is considered, it could be crystalline or amorphous. The later are characterized by non-uniform array of atoms in sharp contrast to crystalline solids. The most important examples of advantages of amorphous form of drugs are those of novobiocin.[2] Only an amorphous form could produce therapeutic plasma levels when given orally. Amorphous forms have been successfully used for the manipulation of onset and duration of action of insulin-zinc suspension. The prompt insulin-zinc suspension of USP contains varying proportions of crystalline and amorphous insulin-zinc complex.

Polymorphism is a phenomenon where compounds crystallize as more than one distinct species. Steroids, barbiturates, and antihistaminics are some drugs which exist in polymorphic forms. Phenomenon of polymorphs is studied in context to physical stability of a dosage form, especially suspension, solutions, suppositories, tabletting, etc. [3-5] In many instances, it is reported to alter chemical stability of a compound also. The exploitation of a metastable form of a drug having higher thermodynamic activity to achieve better bioavailability has been successful in some cases. A study of physicochemical factors affecting the absorption of ampicillin showed that t_{50} is 7.5 and 45 minutes, respectively, for anhydrous and trihydrate form, with former attaining higher and earlier peak serum levels.[6]

Solvate are the molecular complexes that have incorporated the crystallizing solvent molecule in their lattice. When the solvent incorporated is water, they are called as hydrates. There are numerous reports of solvate formation of steroids, cephaloridine, phenobarbitones, etc. Solvates can result in higher dissolution rate, increased bioavailability, development of a stable suspension, reduction in particle size, and chemical stability of a compound.[7]

Clathrate are inclusion compounds in which guest is retained in closed cavity provided by the crystalline structure of the host. For example, guest benzene molecule is clathrated in the host, ammonia-nickel cyanide complex. Sodium warfarin clathrate is official in USP XVIII pharmacopoeia. Inclusion compounds of ibuprofen in ß-cyclodextran has been reported by Nambui *et al.* [8]

Thus it is essential, during preformulation work, to conduct a detail study of the drug with reference to existence of different habits, polymorphs, and pseudopolymorphs. The crystalinity of the drug can affect its physicochemical properties. Variable bioavailabilities, as a consequence of differences in thermodynamic activity, and in turns the solubility is the most important consideration. It is also necessary to critically evaluate the drug from the point of view of crystalinity to avoid batch to batch variation of the crystal form that otherwise results in bioinequivalent dosage forms. Furthermore, such a study shall help in selecting a form of a drug which would improve the performance of the drug substance in the dosage form.

The present work envisaged a study on ibuprofen. It is a potent NSAID, practically insoluble in water. Bioinequivalence, as regards to the rate of absorption is observed among marketed tablet and suspension dosage forms. The aim of the present investigations are multifolds: 1. to investigate different forms of ibuprofen, 2. to characterize different forms, and 3. to study dissolution characteristics.

MATERIALS AND METHODS

Materials

Ibuprofen (I.P. grade), Diethylene glycol, Polyethylene glycol (PEG) 4000, PEG 3000, PEG 200, Acetone, Glycerin, Dichloromethane, Methanol,

TABLE 1

FORM	METHOD	SOLVENT AND OTHER DETAILS
I-DEG	B	Solution of Ibuprofen in ethylene glycol at 60 C was poured in an ice-cold water, and kept overnight at 0 C.
I-PEG-3	A	Dispersion of Ibuprofen in 20% PEG-3000 solution at 80 C was cooled to room temperature.
I-AC	B	To a stirring solution of Ibuprofen in acetone at 37 C, water was added dropwise.
I-GLY	B	To a stirring emulsion of Ibuprofen melt in glycerin at 80 C, water was added.
I-DP	B	Solution of Ibuprofen in dichloromethane was added to stirring solution of 20% PEG 3000 and solvent was evaporated with stirring at room temperature.
I-A	B	To a solution of Ibuprofen in methanol, cold water was added and kept overnight at 0 C.
I-BEN	B	Solution of Ibuprofen in benzene was added in water and left overnight at 0 C.
I-ET	A	Warm solution of Ibuprofen in ether was kept at 0 C.
I-PEG-2	B	To a solution of Ibuprofen in PEG 200 (60 C), water was added.
I-PG	B	To a solution of Ibuprofen in propylene glycol, water was added.
I-AL	B	To a stirring solution of Ibuprofen in ethanol, water was added.
I-B	B	To a solution of Ibuprofen in methanol,water was added till opalescence develops.
I-PEG-4	C	To a stirring solution of PEG-4000 containing concentrated sulfuric acid, solution of Ibuprofen in 2% sodium hydroxide was added slowly.
I-2PrOH	B	Water was added to a solution of Ibuprofen in 2-propanol till opalescence develops.

* Chloroform and Carbon Tetrachloride were found unsuitable for crystallization specially by method B because of high affinity of Ibuprofen to these solvents.

Benzene, Propylene glycol, 2-Propanol, Ether, Sulfuric Acid, Sodium Hydroxide. All chemicals were of Analytical Grade purity

Procedure to Prepare Different Crystalline forms of Ibuprofen

Following three general methods were used to produce different crystalline forms of Ibuprofen. Any variations from the general methods and specific details are reported in Table 1.

Method A: Cooling hot solution of Ibuprofen:

A small amount of drug was dissolved in just enough volume of hot solvent. The drug solution thus formed was filtered at the same temperature and the filtrate was allowed to cool down to room temperature (25° C± 1).

Method B: Solvent exchange method:

Small amount of drug was dissolved in sufficient volume of cold or hot solvent and the drug solution was added drop wise into 500 ml of distilled water at room temperature.

Method C: Precipitation from solution:

Drug in solution was precipitated by addition of a substance which would salt out or precipitate the drug.

Crystals of the ibuprofen were separated by filtration on Buchner funnel, rapidly washed with cold water, and then vacuum dried.

Microscopic Observations

Crystals were observed under the microscope and photomicrographed at suitable magnification.

Melting Point Determination

The crystals were crushed and the melting point was determined with Toshniwal Melting Point Apparatus (Bombay, India).

Infra red Spectroscopy

Infra red (IR) spectra of the material was recorded in KBr pellet on Perkin-Elmer 377 Grating IR Spectrometer.

Dissolution Studies

Dissolution studies were conducted in distilled water at 37° C ± 1 using U.S.P. XVIII dissolution apparatus at 175 RPM for 8 hours. A 100 mg drug sample passing through #40 mesh and retained on # 60 mesh was used. The experiments were done in duplicate.

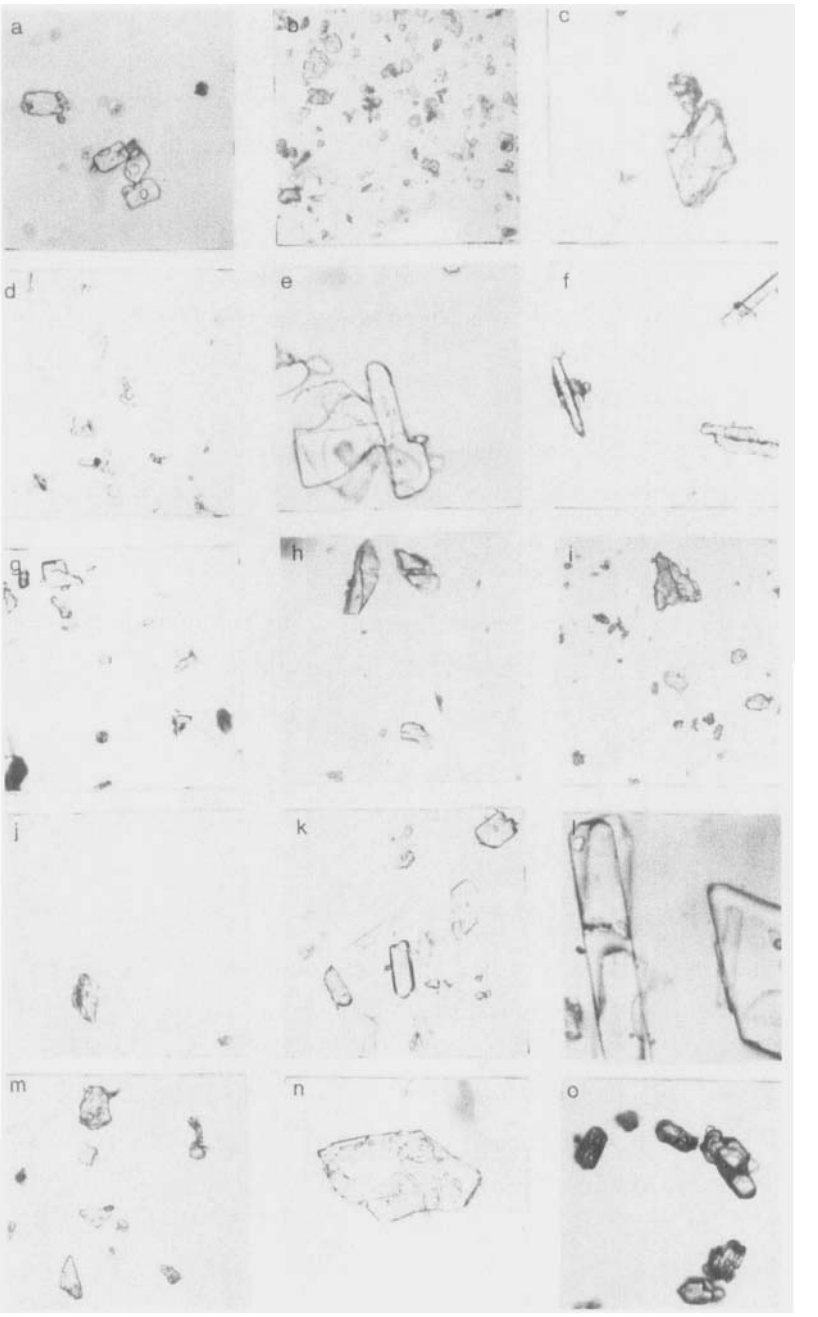

FIGURE 1

Photomicrographs of different ibuprofen forms.

I, (a); I-DEG, (b); I-PEG-3, (c); I-AC, (d); I-GLY, (e); I-DP (f); I-A, (g); I-BEN, (h); I-ET, (i); I-PEG-2, (j); I-PG, (k); I-AL, (l); I-B, (m); I-PEG-4, (n); I-2PrOH, (o).

TABLE 2

FORM	CRYSTAL HABIT	M.P., C	t70 (Minutes)
I	Rectangular Plates	73	390
I-DEG	Plates	64	>480
I-PEG-3	Tabular	68	280
I-AC	Fine Bladed	69	296
I-GLY	Plates	67	207
I-DP	Rods	64	57
I-A	Bladed	73	363
I-BEN	Plates	72	>480
I-ET	Plates	69	48
I-PEG-2	Tabular	64	315
I-PG	Bladed	70	102
I-AL	Bladed	70	Not Done*
I-B	Plates	65	Not Done*
I-PEG-4	Plates	70	Not Done*
I-2PrOH	Prisms	71	200

* Crystals were highly fluffy.

Analysis

Ibuprofen was analyzed on Biocrom UV spectrometer by measuring absorbance at 264 in 0.1 N sodium hydroxide.

Stability studies

About 500 mg of each form of Ibuprofen was placed in an open petridish at room temperature, 40 and 60° C ± 1. The samples were observed for changes in the general appearance after one month of storage period.

RESULTS AND DISCUSSION

Changes in the crystallization conditions of Ibuprofen resulted in the formation of different crystal forms. These were plates, tabular, rods, blades, and prisms (Figure 1). The melting point determination studies indicated that these forms vary in their melting points and range from 64° C to 73°C (Table 2). Melting point of a substance is a measure of the energy required by a molecule to leave the crystal lattice and to overcome intermolecular forces. Alterations in the packing arrangement of molecules in the crystal also alters the hydrogen bonding and other intermolecular interactions. These alterations affect the melting point of a substance. The difference in the melting points observed in this study indicates that ibuprofen could develop in different crystalline forms. IR spectra showed changes in the absorption pattern of some crystal forms, specially in the range of 1600-1800 and at 3000 nm wavelength (Figure 2a and 2b). These alterations could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds, minor distortion of bond angles or even due to presence of a solvent of crystallization.

Different crystal forms of ibuprofen prepared in this study demonstrated significant variation in their dissolution profiles. Cumulative percent release in 480 minutes, dissolution rates, and t_{70} (time required for 70 % drug to go into solution) varied markedly with the crystalline form (Figure 3a and 3b). However, there was no correlation between the cumulative amount of drug dissolved in 480 minutes and dissolution rates. The t_{70} was found to be lowest for I-ET and as high as above 8 hours for I-DEG and I-BEZ (Table 2). This study also indicates that different forms have varying thermodynamic activities which has an important bearing on the overall solubility profiles.

Stability studies indicated that except for I-PEG-3, I-GLY which showed a 10 to 15 % change in their overall crystal appearance, others were stable at room temperature and 40° C. I-PEG-3, I-DP, and I-ET softened at 60° C whereas all other forms were unchanged even after one month.

It appears from the present study that ibuprofen exists in different crystalline forms demonstrating different physicochemical properties.

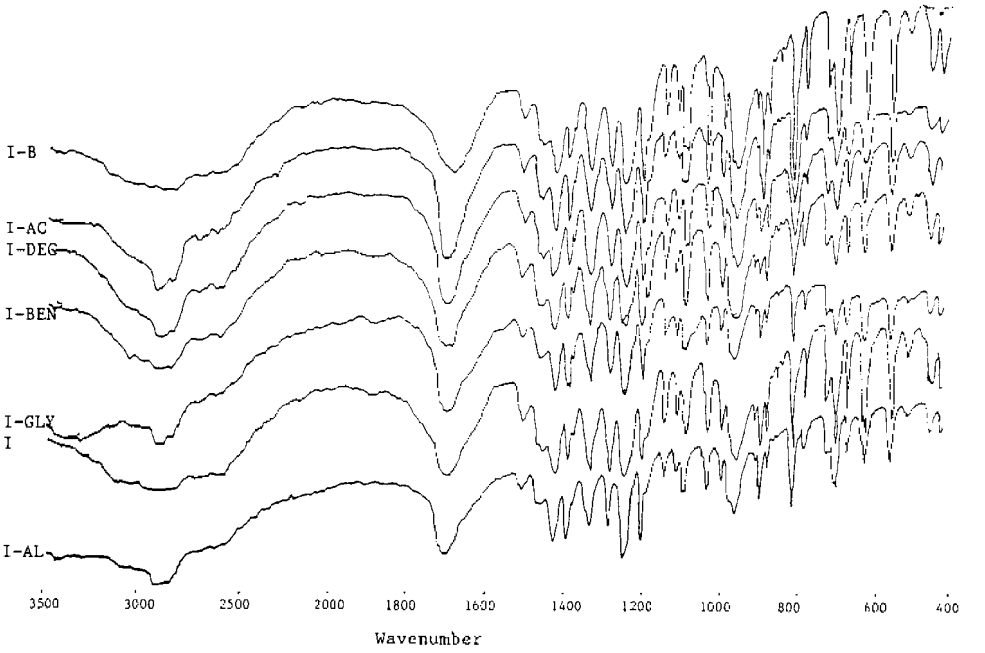

FIGURE 2a
IR spectra of different ibuprofen forms.

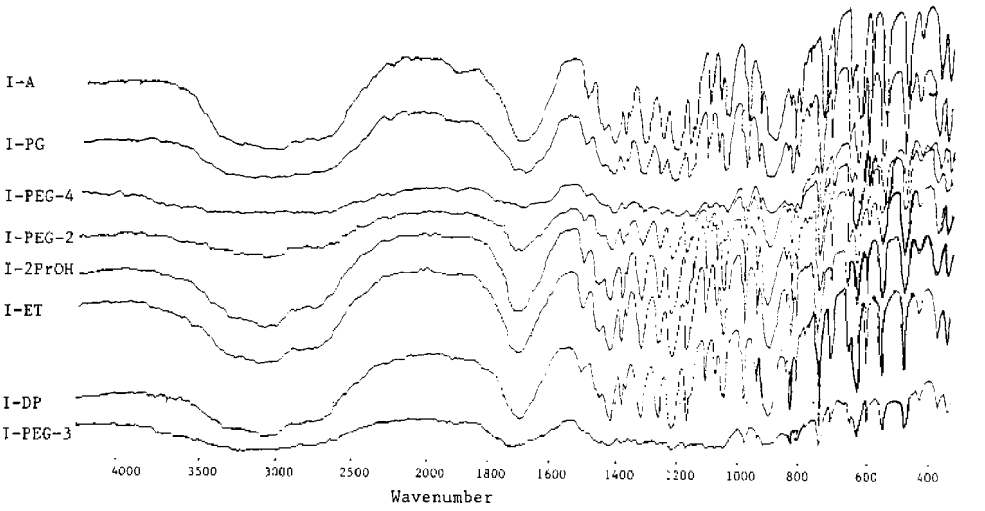

FIGURE 2b
IR spectra of different ibuprofen forms.

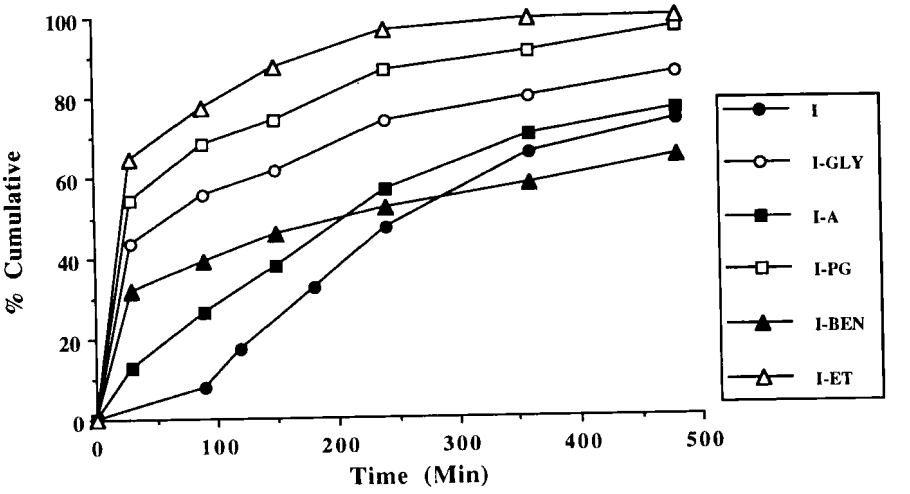

FIGURE 3a

In Vitro dissolution of different ibuprofen forms.

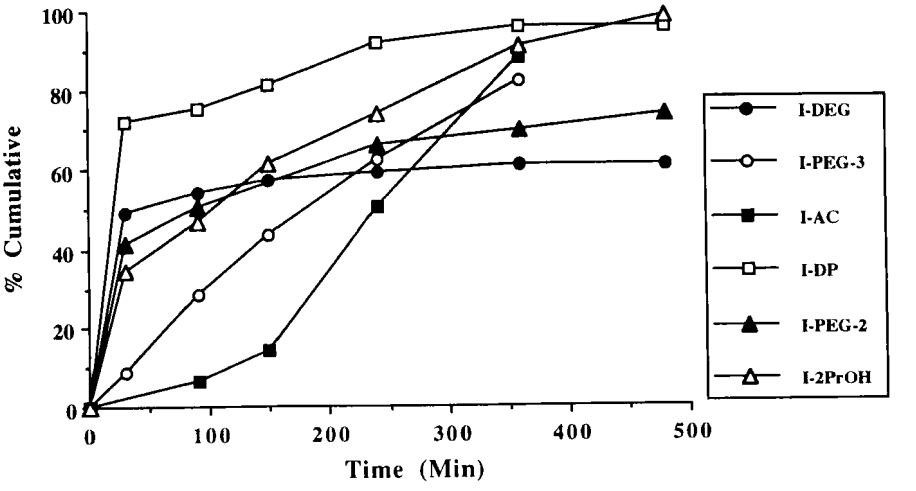

FIGURE 3b

In Vitro dissolution of different ibuprofen forms.

Dissolution studies clearly demonstrated that different forms envisage variable dissolution profiles which could be of significant importance in the formulation of a dosage form of a drug specially when it has a poor aqueous solubility. Such a study would be useful to avoid batch to batch variation in the dosage form. Further study is required to characterize each crystal form observed in this study.

CONCLUSIONS

Ibuprofen was converted into different crystal forms by varying the conditions of crystallization. The different forms were characterized for physical appearance, IR spectra, melting point, and dissolution. The results of the study revealed that ibuprofen forms different crystal forms exhibiting variation in the physicochemical properties. Dissolution profiles varied substantially with the crystal form.

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