PREPARATION AND CHARACTERIZATION OF FREEZE DRIED CRYSTALS OF IBUPROFEN

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ABSTRACT

Ibuprofen, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Crystallization medium used for freeze dried crystals of Ibuprofen consisted of Isopropyl alcohol and water (50:50%) respectively. Freeze dried crystals were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffraactometry and scanning electron microscopy. Micromeritic and mechanical property and dissolution behavior studies were carried out. Process variables such as amount of bridging liquid, stirring time and duration of stirring were optimized. Dissolution profile of the freeze dried crystals was compared with pure sample and recrystallized sample. Freeze dried crystals exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the freeze dried crystals was improved compared with pure sample.

Key words: freeze dried crystals, Ibuprofen, crystallinity, dissolution.

INTRODUCTION

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies that is of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tab-letting method, it is necessary to increase flow-ability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tab-letting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Currently, several solubilization techniques were applied and reported to enhance the solubility of poorly water soluble drugs, as such there are some literature are available on enhancing the solubility and dissolution of Ibuprofen like formation of microparticle by spray drying and spray chilling methods. Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug, Properties of solid dispersions of Ibuprofen in polyvinylpyrrolidone6-7.

Ibuprofen was chosen as a model hydrophobic drug. Ibuprofen (α-methyl-4-(2-methylpropyl) benzene acetic acid) is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market for 30 years. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution. The objective of the present study was to prepare freeze dried crystals of ibuprofen using freeze drying techniques and was evaluated for DSC, FT-IR, XRD, and SEM analysis were performed to determine the physicochemical properties of the freeze dried crystals and compare with recrystallized sample and pure drug and determined the solubility and dissolution characteristics of the Ibuprofen freeze dried crystals and investigate their physical stability in a climate chamber at 40°C and 75% relative humidity (RH) for 90 days.

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from Micro labs, Bangalore, India. All chemicals and buffers used were of analytical grade.

Preparation of freeze dried crystals of Ibuprofen

Ibuprofen (3g) was dissolved in 20 ml of isopropyl alcohol (IPA) heated at 45°C until a clear solution was obtained. The drug solution was poured into 20 ml water maintained at room temperature. Above resulted solution is shifted to 100 ml glass vials and then transferred to a ultra low freezer at -40°C and kept in the freezer for 24 hr. the frozen drug solution were placed in a lyophilizer for 72 hr heating at 45°C until a clear solution was obtained. The drug solution was poured into 20 ml water maintained at room temperature. Above resulted solution is shifted to 100 ml glass vials and then transferred to a ultra low freezer at -40°C and kept in the freezer for 24 hr. the frozen drug solution were placed in a lyophilizer for 72 hr and then transferred to a secondary drying at 25°C for 24 hr. The resulted crystals were kept in a desiccator’s room temperature until further experiment.

Reccrystallization of Ibuprofen

Ibuprofen (3g) was dissolved in 40 ml IPA and water co-solvent systems and heated at 45°C and the above resulted solution 20°C with occasional stirring. The crystals of Ibuprofen were collected by filtration and were dried at 45°C for 12 hours. Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of freeze dried crystals were compared with commercial sample and recrystallized sample.

Characterization of freeze dried crystals

Drug content:

Freeze dried crystals (50mg) were triturated and dissolved in 250ml of phosphate buffer pH7.2. The solution was filtered. After suitable dilution with phosphate buffer pH7.2, solution was analyzed spectrophotometrically (Shimadzu). Drug contents were calculated from calibration curves.

Differential Scanning Calorimetry (DSC)

Thermograms were obtained using a DSC DuPont 9900, with thermal analyzer. Accurately weighed samples were in an aluminum crucible Calorimetric measurements were made with empty cell (High purity alumina discs) as the reference.

Fourier Transform Infrared spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA).

X-ray powder diffraction

Crystal X-ray scattering measurements were performed using Fe Kα radiation (α=1.934Å) and a scan speed of 4° per minute. The data recorded over a range of 2° to 50°. Chart speed was 5mm/2°.
Scanning electron microscopy
The Scanning electron microscopic photographs were obtained to identify and to confirm freeze dried nature, morphological characteristics of the crystals. Scanning electron microscopic studies were carried out using SEM Model Joel- LV-5600, USA, with magnification of 250X.

Mechanical Properties
Tensile strength
Tensile strength of freeze dried crystals was determined by compressing 500 mg of crystals using hydraulic press at different kg/cm² for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (kg/cm²) was calculated using following equation.

$$\sigma = \frac{2F}{\pi \cdot D \cdot t}$$

Where, F, D and t are hardness (kg/cm²), compact diameter (cm) and thickness (cm), respectively.

Solubility studies of crystals
The solubility of Ibufrofen freeze dried crystals in water was determined by taking excess quantity of freeze dried crystals and adding to screw- capped 50 ml glass vials filled with water. The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 221 nm.

Dissolution studies of crystals
The dissolution of ibuprofen pure sample, freeze dried crystals and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.2 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 221 nm.

Determination the physical stability
To determine the physical stability of freeze dried crystals was placed in a climate chamber of 40°C and 75% relative humidity (RH). After 90 days, the % drug release of Ibufrofen in the freeze dried crystals was determined by dissolution study and compare with freshly prepared freeze dried crystals.

RESULT
Drug content
The drug content was found to be in the range of 97-98%.

Differential scanning calorimetry (DSC)
DSC studies were carried out for different crystals of Ibufrofen. The DSC thermograms of ibuprofen crystals are presented in Figure 1. For commercial sample re-crystallized sample and freeze dried crystals respectively. The data obtained from the DSC scans for the crystals are given in the Table 1n terms of onset of melt (T<sub>m</sub>), melting point (T<sub>m</sub>) and completion of melt (T<sub>c</sub>). The melting points of the crystals are in the range of 73-79°C. The melting points of the crystals were estimated by open capillaries and found agree well with the DSC data. In the DSC melt temperature range about 25°C-30°C characteristically a narrow, indicating a high degree of purity with respect to crystallinity.

FT-IR Spectroscopy (FT-IR)
Infrared spectra of ibuprofen, recrystallized ibuprofen and freeze dried crystals showed characteristic principal peaks at wave numbers 1721 (C=O stretching vibrations of –COOH groups), 1268 (aromatic dissubstitution), 1232, (-OH group bending vibrations), 1273, 1185 870 and 779 (Aromatic structure bending vibrations). That showed there is not much significant difference in all spectra’s of ibuprofen.

X-ray analysis (XRD)
The X-ray diffraction patterns were obtained for the crystals of ibuprofen commercial sample, recrystallized sample and freeze dried crystals. The patterns are reported in Figures 3. The observed 20 were processed using multidimension minimization program. The program helps to calculate 20 values and cell parameters a, b, c, α, β and γ which will fit the observed reflections to less than 5% of the mean values.

Scanning electron microscopy (SEM)
The photomicrograph of different crystals forms of ibuprofen under different crystalline conditions are shown in the figure 4. Method of preparation of crystals affected the crystal form and size and shape of the drug. Crystals of commercial sample are of the size (8-15μm) and they have irregular, prismatic and needle like (acicular) crystal shapes. Recrystallization produced crystals with inter mediate size (6-15μm) which had flattened plates and rod like shapes and prepared freeze dried crystals were porous in nature and small in size (Avg. size 254 nm).

Tensile strength
Freeze dried crystals exhibited superior compressibility characteristics compared to conventional drug crystals (Fig. 5).

Solubility study
Freeze dried crystals showed increased solubility than the pure sample in water and increased nearly more than fourfold higher (0.0337 mg/ml) than pure Ibufrofen (0.0117 mg/ml).

Dissolution behavior of crystals
The dissolution profiles of ibuprofen (fig. 6) exhibited improved dissolution behaviour for freeze dried crystals than pure sample.

Determination the physical stability
The results of the stability study of freeze dried crystals stored at 40°C and 75% relative humidity for 90 days. The influence of freeze dried crystals on the physical stability of Ibufrofen was investigated. The % of drug release from freeze dried crystals almost same i.e. (92.82%) after 90 days of storing when compare with the freshly prepared freeze dried crystals i.e. (93.42 %).

DISCUSSION
A solvent system involved an IPA and water for a drug. The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. IPA is miscible in any proportion with water.

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Based upon high solubility of Ibufrofen in IPA, high viscosity and crystal morphology, IPA determined to be suitable freeze drying medium for Ibufrofen because of its high solubility in IPA (1.5 gm/10ml). The controlling of residual IPA was needed though. IPA is a toxic organic solvent based on their concentration and has little detriment to human body. Therefore, the low level of IPA in the freeze dried crystals should not be harmful to both animal and human.

Recrystallization of Ibufrofen was done to find out the changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical and dissolution properties of freeze dried crystals were compared with pure sample and recrystallized sample. Recrystallization of Ibufrofen was carried out using same solvent composition as was used for freeze drying.

In DSC study, during the course of heating, DSC thermograms (Figure 1) of ibuprofen, crystals have not exhibited the presence of polymorphic modifications, i.e., transitional changes due to conversion of one to the other. In other words, all the crystals are highly stable. Thermograms show sharp endothermic transitions corresponding to the melting point (74 to 79°C). The DSC results indicate no significant between the mean values of the melting point onsets and melting points of the ibuprofen samples crystallized indicating that no polymorphic modifications occurred during crystallization process.
The FT-IR spectra of ibuprofen, recrystallized ibuprofen and freeze dried crystals are presented in Figure 2. All the crystals have exhibited general characteristic peaks. Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of a solvent of crystallization.

In XRD study, all the samples exhibited spectra with similar peak positions (2 theta values). Therefore the presence of different polymorphs of ibuprofen in these samples was ruled out. However relative intensities of XRD peaks were modified. This was attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the x ray source would have been altered, producing the variations in the relative intensities of the peak or this may be due to differences in crystal sizes.

SEM figure reveal that the surfaces of some of the freeze dried crystals were dense and almost all fused together, but the surface was rough and porous suggesting that the surface particle did not dissolve entirely but partially dissolved and fused with adjacent ones during interfacial recrystallization. Possible explanation could be, part of the particles must have dissolved in solvents and these dissolving particles then acted as the nucleus for initial agglomeration. The remaining undisclosed particles were then collected through collision and partially dissolved and recrystallized so as to fuse with initial crystals. It could be observed later, the process can be enhanced to certain extent by increasing the agitation.

Freeze dried crystals exhibited superior compressibility characteristics compared to conventional drug crystals. It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the crystals under plastic deformation compared to that of single crystal.

The dissolution profiles of ibuprofen (fig. 6) exhibited improved dissolution behaviour for freeze dried crystals than pure sample. The reason for this faster dissolution could be linked to the better wettability and reduction in particle size of the freeze dried crystals. The amount of drug dissolved in 60 min greatly varied for freeze dried crystals.

Stability result shows that freeze dried crystals of Ibuprofen was stable after 90 days at 40 ºC and 75% relative humidity.

CONCLUSION
Freeze dried crystals of ibuprofen were prepared. Freeze dried crystals exhibited decreased crystallinity and improved micromeric properties. DSC and XRD studies showed that there is no change in the crystal structure of ibuprofen during the crystallization process i.e., polymorphism has not occurred. The dissolution of the freeze dried crystals was improved compared with pure sample. The stability study showed that freeze dried crystals were stable after 90 days. Hence this freeze dried crystals technique can be used for formulation of tablets of ibuprofen by direct compression with directly compressible tablet excipients.

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REFERENCES
Fig. 4 Scanning Electron Microscope photographs of different sample of ibuprofen

Fig. 5 Tensile strength of Pure sample and Recrystallized Sample, freeze dried crystal

Fig. 6: Dissolution profile of ibuprofen crystals.

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