ENHANCING SOLUBILITY AND DISSOLUTION OF INDOMETHACIN BY FREEZE DRYING

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ABSTRACT
Indomethacin, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Freeze dried crystals were prepared by freeze drying method. Solvent composition for freeze drying chosen were isopropyl 10 ml of alcohol: water (50:50 %) mixture. Crystallization medium used for freeze drying of indomethacin consisted of isopropyl alcohol: water in the ratio of 50:50, respectively. Spherical agglomerates were characterized by DSC, IR, XRD AND SEM. Micromeritic, mechanical property, solubility study and dissolution behavior studies were carried out. Dissolution profile of the freeze drying was compared with commercial sample and recrystallized sample. Freeze drying exhibiting decreased crystallinity and improved micromeritic properties. The solubility and dissolution of the freeze drying was improved compared with commercial sample. Hence this freeze drying technique can be used for formulation of tablets of indomethacin by direct compression with directly compressible tablet excipients.

Key words: freeze drying, indomethacin, crystallinity, solubility dissolution.

INTRODUCTION
Indomethacin is a member of the non-steroidal anti-inflammatory drugs (NSAIDs). It is used to reduce pain/swelling involved in osteoarthritis, rheumatoid arthritis, bursitis, tendinitis, gout, ankylosing spondylitis, and headaches. The drug is described as poorly soluble and highly permeable (Class II) drug. Because water-insoluble drugs often show low absorption and weak bioavailability, improvement in dissolution rate and/or solubility are important for development of drug preparations. The successful formulation of poorly water-soluble drugs is one of the major problems in pharmaceutical manufacturing. Indomethacin may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract. Additionally, this undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of a prolonged contact time with the mucosa.

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 is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tablet-ting 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 tablet-ting 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. Freeze dried microparticle is one of such techniques to improve the micromeritic properties and dissolution of drug.

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. 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. Various techniques such as melt adsorption, supercritical fluid processes, using different composition of solvents to prepared the microparticle to improve the dissolution rate of poorly water soluble drugs. And amorphous state to improve their dissolution. Manipulation of the solid state by decreasing crystallinity of drug substances through
formation of solid dispersion is one of the methods used for promoting drug dissolution. The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wet ability, drug precipitation as a met stable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug. Freeze drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. The technique also has the advantages of being free from organic solvents compared to freeze drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals. Indomethacin was chosen as a poorly water soluble drug. Indomethacin is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution. The present work was conducted to improve the wet ability, solubility and hence the dissolution of Indomethacin using freeze drying techniques.

**MATERIAL AND METHODS**

**Materials**

Indomethacin was gifted by Micro lab. Bangalore, all water used distilled de-ionized water. All other materials used are analytical grade.

**Preparation of indomethacin freeze dried crystals**

Indomethacin (2 g) was dissolved in 10 ml of (50:50) isopropyl alcohol: water with stirrer until a clear solution was obtained. The resulted solution was then transferred to a ultra low freezer at -55°C and kept in the freezer for 24 hr. The frozen tablets were placed in a lyophilize for 24 h using a Freeze Dryer (IISHIN Lab. Co. Ltd. Korea) with a condenser temperature of -40°C and a pressure of 7×10⁻² mbar followed by a secondary drying at 25°C for 12h. The FDTs were kept in a desiccator room temperature until further experiment. The mean % drug content was found to be 99.54% ± 0.014%.

**Preparation of recrystallized crystal of indomethacin**

Recrystallization of indomethacin was carried out using same solvent composition as was used for freeze drying indomethacin was dissolved in 10 ml of isopropyl alcohol: water with occasional stirring for 30 min. The crystals of indomethacin collected by filtration and were dried at 45°C.

**Determination of drug content**

Freeze dried crystal were triturated with 10 ml of pH 7.2 phosphate buffer. Allowed to stand for 10 min with occasional swirling and pH 7.2 phosphate buffer was added to produce 100 ml. After suitable dilution, 10 ml of solution taken and filtered through a membrane filter (0.45μm) and the amount of dissolved drug was measured at 320 nm using UV spectrophotometric method. Drug content was determined from standard plot. Sample was done in triplicate.

**Differential scanning calorimeter (DSC)**

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

**X-ray Diffraction analysis**

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X’ Pert MPD diffract meter, with Cu as anode material and graphite monochromatic, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (20).

**Scanning electron microscopy (SEM)**

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

**Mechanical Property**

Mechanical Properties like tensile strength of microsphere, recrystallized sample and pure sample of indomethacin were determined by compressing 500 mg of samples using hydraulic press at different ton/cm² for 1 min. The compacts stored in desiccators 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 (ton/cm²) was calculated using following equation.

\[
\sigma = \frac{2F}{\pi D t}
\]

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.
Solubility studies
Indomethacine (100mg), its crystals and physical mixture Equivalent to 100 mg Indomethacin were placed in glass stopper flasks with pH 7.2 phosphate buffer were shaken in a water bath at 37°C for 48 hr. The solutions were filtered through a membrane filter (0.45µg) and the dissolved drug was measured spectrophotometrically at 320 nm. Each sample was done in triplicate.

Dissolution studies
The dissolution profile of pure indomethacin compared with the Physical Mixture and freeze dried crystal, were determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). All tests were conducted in 900 ml of pH 7.2 phosphate buffer maintained at 37 ± 0.2°C with a paddle rotation speed at 100 rpm. After specified time intervals, samples of dissolution medium were withdrawn and replaced by equal amount of fresh medium to maintain sink conditions and then filtered and the amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 320 nm, Each sample was done in triplicate.

RESULTS
The DSC thermograms (fig. 1) show a sharp endothermic peak for all the indomethacin crystals. This one step melt might be due to only one crystal form (Triclinic) of the indomethacin formed during the crystallization process, thus indicating that indomethacin did not undergo any crystal modification.

All the crystals have exhibited general characteristic peaks at 3400-2500 cm⁻¹ (Aromatic C-H stretch carboxylic acid O-H stretch), 1715 -1695 cm⁻¹ (C=O stretch), 1600 cm⁻¹ (Aromatic C=C stretch), 1450 cm⁻¹ (O-CH 3 deformation), 1230 cm⁻¹ (C-O stretch plus O-H deformation), 925 cm⁻¹ (carboxylic acid O-H out of plane deformation), 900-600 cm⁻¹ (C-H out of plane deformation for substituted aromatic) (fig. 2).

All the samples showed similar peak positions (20) in X-ray diffraction, formation of different polymorphs of indomethacin was ruled out. However relative intensities of XRD peaks were modified (fig. 3). The characteristic peak of the indomethacin appeared in the 2θ range of 0–40° indicating that the unprocessed indomethacin was a crystalline material. This could be attributed to the markedly different crystal habits of the samples.

Freeze dried crystals exhibited superior compressibility characteristics compared to conventional drug crystals (fig. 5).

The solubility of freeze dried crystals shows high solubility than recrystallized sample and pure samples.

The dissolution profiles of indomethacin (fig. 6) exhibited improved dissolution behaviour for freeze dried crystal than commercial sample.

DISCUSSION
Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of microspheres were compared with commercial sample and recrystallized sample. In DSC study, the temperature range of the endothermic peak of all the indomethacin crystals lies in the range of 155.5 to 164°. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endothermic for freeze dried crystal indomethacin was 155.5° with decreased enthalpy of (94.83 J/g) indicating decreased crystallinity.

In FT-IR study, 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.

The XRD study shows that 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 may be due to differences in crystal sizes of different indomethacin samples.

SEM study shows that crystals of commercial sample are of the smallest size (5-10 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (10-15 µm) which had rod like shapes. The freeze dried crystals were formed by coalescence of the microcrystalline precipitates, so the resultant freeze dried crystals very small size (1-2 µm).

Tensile strength study shows that increasing the tensile strength of freeze dried crystals 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 freeze dried crystals under plastic deformation compared to that of single crystal.

The solubility of Indomethacin freeze dried crystals was found to be (0.06246) which was higher than recrystallized sample (0.0089) and pure sample (0.0075). According to above result freeze drying technique has good ability to increasing the solubility of poorly water soluble drug then other technique. Dissolution of freeze dried crystal shows increased percentage of release in 60 min. the reason for this faster dissolution could be linked to the better wet ability &
reduction in particle size with increasing surface area of the freeze dried crystals. The amount of drug dissolved in 60 min greatly varied for spherical agglomerates.

CONCLUSION
Freeze dried crystals of Indomethacin were prepared by freeze drying technique to improve the solubility and dissolution rate. Freeze dried crystals exhibited decreased crystallinity and improved Micromeritic & Mechanical properties. DSC and XRD studies showed that there is no change in the crystal structure of Indomethacin during the freeze drying process i.e., polymorphism has not occurred. The solubility and dissolution of the Freeze dried crystals was improved compared with Recrystallized sample and pure sample. Hence this Freeze drying technique can be used for formulation of tablets of Indomethacin by direct compression with directly compressible tablet excipients.

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REFERENCES

Figure 1 DSC of pure drug, Recrystalized drug, Freeze dried crystals
Figure 2 FT-IR of pure drug, Recrystallized crystal, Freeze dried crystals

Figure 3 XRD pure drug, Recrystallized drug, Freeze dried crystals

Figure 4 SEM of pure drug, Recrystallized crystal, Freeze dried crystals
Figure 5 Tenstile strength of pure indomethacin, Freeze dried crystals

Figure 6 Dissolution profiles of pure indomethacin, Recrystalized crystal, Freeze dried crystals

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