INTRODUCTION

The oral route is the most desirable for drug administration due to its convenience and good patient compliance. Drug from its dosage form is absorbed from the gastrointestinal tract, only when it is dissolved in gastric and intestinal fluids. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such drugs, as this can lead to an increased and more reproducible oral bioavailability, which subsequently leads to clinically relevant dose reduction and more reliable therapy.

Poor aqueous solubility and bioavailability of drugs in the body after administration are two prime issues which are faced by the pharmaceutical industry at the present time. This problem has been the major problem hampering the release of new chemical entities into the market. Every year more than 50% of the potentially active pharmaceutical ingredients get rejected due to the above stated problems. During the last decade, more than 40% of the new chemical entities launched in the U.S. pharmaceutical market faced the problem of adequate aqueous solubility. Therefore, pharmaceutical companies are focusing on finding a method or technology by which they can enhance the aqueous solubility and bioavailability of the drug. To date, various methods for modification of active pharmaceutical ingredients, those have included physical modification, chemical modification and others controlled solid state methods. Each of the methods given above has their own drawbacks which restrain their use to modify the active pharmaceutical ingredient to improve its aqueous solubility and bioavailability. Some other conventional methods used to improve aqueous solubility and bioavailabilities include: the use of surfactants; pH
Pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area by micronization, solubility and/or wettability of the powder particles by the use of surfactants, the use of polymorphs, and solid dispersion are therefore focused on particle size reduction or generation of amorphous states.

Drugs can exist in different crystal forms. The polymorphs are chemically identical; they exhibit different physicochemical properties like melting point, x-ray diffraction pattern, Differential Scanning Calorimetry and solubility. In addition, crystal habit influences flowability, packing, compaction, syringability, stability and dissolution characteristics of a drug crystals/powder.

Crystallization is commonly employed, as the final step, for purification of a drug. Use of different solvents and processing conditions may alter the polymorphic state and/or crystals habit of the drug, leading to variation in raw material characteristics. There are a variety of reasons for such changes in crystal morphology which largely depends on how the crystallization of the drug is conducted, the nature of solvent(s) employed, the condition of pressure, temperature, cooling rate, agitation, use of surfactants, co-solvents and presence of other solutes and ions. These physicochemical properties further affect the biological properties of drug molecules. Therefore, it becomes necessary to identify the factors which alter the crystal habit of a drug. The use of adjuvants in pharmaceutical formulations has shown to affect the crystalline properties of drug materials and consequently alter the pharmaceutical performance, such as dissolution, equilibrium solubility, compressibility and stability.
The process of crystallization depends on achieving three conditions in succession; a state of super saturation (super cooling in the case of crystallization from a melt), formation of nuclei and growth of crystals or amorphous particles.\textsuperscript{20, 21} Crystal habit is influenced by the degree of super saturation, nature of crystallizing solvents, rate of cooling, presence of co-solutes, surfactants, co-solvents and absorbable foreign ions etc. The crystal habits can influence several pharmaceutical characteristics related to physical shape and nature of the crystals like suspension syringeability and tableting behavior.\textsuperscript{22, 23}

Commonly used crystallization techniques include solvent evaporation; slow cooling of the solution, sublimation and many variations on these themes. Freeze drying, Spray drying and Spherical crystallization are the special techniques employed in recent times to obtain the drug crystals with desired properties.

In the 70s, Kawashima et al.,\textsuperscript{24} suggested the method of performing particle size enlargement at the same time the crystallization, thus controlling crystal crystallization in order to obtain large spherical crystals or grains. Crystallization and spheronization are carried out simultaneously in one step. Due to the characteristic shape, the micromeritic properties such as flowability, packability and compressibility of the resultant crystals are dramatically improved, so that direct tableting or coating is possible without further processing (e.g. mixing, crystallization, sieving, etc.). They are suitable for micro encapsulation as they can uniformly be coated with relatively small amount of polymer; (c) they have a more predictable dissolution pattern; and (d) they can be easily compounded with other pharmaceutical powders due to their spherical form.

In the recent development, the spray-drying technique is a useful method to obtain particles of small size and of close distribution. Moreover, this method has also
been reported to have the advantage of producing a solid dispersion in a one-step process\textsuperscript{25}. Spray drying is used as an alternative to milling to reduce particle size. It has the advantages such as improved particle wetting by adding small amount of surfactants\textsuperscript{26}. Spray drying has been used to convert liquids into powders and to prepare microparticle of drug with polymer. The micronized powders of poorly water soluble drugs produced by a spray drying into novel particle has enhanced the dissolution rate of drug\textsuperscript{27,28}.

Freeze drying or lyophilization, is a dehydration technique, which enables liquid or slurry products, which have previously been frozen to be dried under a vacuum. There are few examples of drugs which exhibited enhanced dissolution by preparing microparticle using freeze-drying process\textsuperscript{29,30}. 
Need for the study:

Powder can be rarely be compressed directly in to the tablets and generally requires pretreatment to ensure tablet formation. The pretreatment involves modification and design of pharmaceutical powder drugs so as to improve the properties, such as flowability and packability of the product.

Mefenamic acid, Ketoprofen and Piroxicam exhibit poor flow, have high tendency of adhesion and show poor dissolution properties. Various methods are applied to increase the flow properties e.g., coating, granulation etc. and others physicochemical properties of drugs. It is more desirable to crystallize these commercial drug directly in to small crystals and spherical crystals that exhibit good properties by using different crystallization techniques.
Drugs candidates were selected based on certain predetermined criteria such as;

- Drug shall exist necessarily in the crystalline form and shall not exhibit polymorphism in the solvent system chosen for the experiments and other experimental conditions as crystallization and crystal habits influence the drug dissolution hence their absorption to a great extent.

- Aqueous solubility of drug is important for bio-absorption and drug action. Dissolution is an important prerequisite for drug absorption in most of the weakly acidic drugs with pKa of 3-5.

- Mefenamic Acid, (pKa 4.2), Ketoprofen (pKa 4.45) and Piroxicam, which has two weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8).

- Drug shall exhibit dissolution dependent bio absorption. Physicochemical properties of drugs under investigation, solvents and process variables are used to bring about generalizations. There are no general guidelines or principles to select the solvent systems and bridging liquid composition to get spherical agglomerates/crystal.