Review Article

MICROCRYSTALS FOR SOLUBILITY ENHANCEMENT – EMINENT ROLE IN POORLY SOLUBLE DRUGS

Bhavya*, Viresh KC, AR Shabaraya and Nishmitha

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post Farangipete, Mangalore - 574143, Karnataka, India.

ABSTRACT

Solubility is a major problem in most of the drugs because newly discovered drugs are almost lipophilic in nature. The solubility problem can be solved by changing the crystal habit of drug, which improves the solubility and dissolution. Micronizing the poorly water-soluble drugs with water-soluble carriers as stabilizing agent, which results in the formation of microcrystals have been reduced the incidence of these problems and enhanced dissolution. The focus of this review article on advantages, the method of preparation and characterization of the microcrystals.

Keywords: Solubility, dissolution, water soluble carrier, microcrystals, crystal habits.

INTRODUCTION

Poor aqueous solubility of many new drugs is a major limiting factor for their successful launch in market in spite of their potential pharmacokinetic activity. Poor solubility (less than 10 %) of a drug, leads to poor dissolution in the gastro intestinal tract (GIT).About 40% of drugs in the pipeline of pharmaceutical companies are poorly soluble, which emphasizes the need of a technique to overcome such problems. Thus a greater understanding of solubility and absorption behaviours of drugs with low aqueous solubility is required to successfully formulate them into bio-available drug products.The drugs which are poorly water soluble generally pose bioavailability problems. Therefore bioavailability after oral administration can be improved by enhancement of the solubility rate.[1]

Many approaches such as salt formation, co-solvency, solid dispersion have been commonly used to increase solubility .However all these techniques have potential limitations. In addition to these techniques drug particle size reduction has often been used. Particle size alone can lead to many processing problem. Therefore it is important to micronize a drug along with simultaneous surface modification.[2,3] Particle size is generally important and controllable parameter of API forms, including micro crystals which influence dissolution behavior. Micro crystal (Size ranging between 10-50µm) represents a potential route to achieve pharmaceutical material with improved solubility rate and stability under conditions of high relative humidity.[4]

ADVANTAGES

Micro crystallization technology offers

- Rapid, easy to handle, needs only common equipment and direct process.
- Reduced particle size, improved wettability and improved porosity of drugs can be achieved.
- Improved stability, low sensitivity to environmental condition.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.[5,6]

TECHNIQUES INVOLVED IN THE PREPARATION OF MICROCRYSTALS

1. Solvent evaporation technique.
2. Solvent change method.
3. Solvent change precipitation technique.
4. Supercritical fluid technique.
5. Anti-solvent precipitation method
6. pH change approach.
7. Static mixture technique.
8. Spray drying method

1. Solvent Evaporation technique: In this method, crystallization takes place mainly due to the removal of solvent by evaporation and precipitation in water in which drug is

insoluble. The basic procedure employed for preparing microcrystals of drugs consists of the following steps. Preparations of drug solution in different water immiscible solvents i.e., chloroform, ethyl acetate (10%, 20% v/v) with 1gm and 4gm drug respectively. The above prepared drug solution was added drop-wise to beaker containing water with continuous stirring (slow and turbulent). The biphasic layer formed due to water immiscible solvent is evaporated by maintaining the temperature corresponding to their boiling point. Micro-precipitation takes place due to the evaporation of water immiscible solvents and re-precipitation of drug in water. The precipitated crystals were filtered using Whatmann filter paper and dried at 60°C for 1 hour.[7]

2. Solvent change method: Drug was dissolved in suitable solvent and heated to boiling point of that solvent. The drug solution was poured quickly into water maintained at 20°C under continuous stirring with paddle device, 500 (±5) rpm. After 25 mins of stirring, micro crystals formed and were separated from the solution by filtration. Micro crystals were dried at 45°C for 12 hours**.** Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. The mechanical, micromeritic and dissolution properties of miroparticles were compared with commercial sample and recrystallized sample. [7]

3. Solvent change precipitation technique: The solvent change precipitation [SC] was conducted by instantaneously mixing two liquids in the presence of a stabilizing agent. The organic phase (solvent phase) was a methanolic solution of drug at gm/ml, a stabilizing agent in the aqueous phase (N. Rasenack et al., 2003). The aqueous phase was poured rapidly from a beaker into the methanolic drug solution under stirring using a magnetic stirrer. The process was carried out at room temperature. The effect of experimental variables on the yield of the precipitates was accounted (D. Douroumis et al., 2006). Different solvent ratios like (1:2, 1:4, 1:8 and 1:16 of methanol to water) were tried to select the most appropriate ratio to achieve the smallest particles and the maximum yield of the particles. [8,9]

4. Supercritical fluid technique: Supercritical fluids are characterized by a continuous adjustable solvent power/selectivity obtained by varying pressure and temperature. Therefore, the same supercritical solvent can be used in different sections of the plant to obtain different extraction/separation performances. Since the size and size distribution and sometimes even the morphology of particles produced in different industries are usually not appropriate for the subsequent use of those materials, particle design has been gaining increasing importance in manufacturing advanced ceramic materials, dyes, explosives, catalysts, coating materials, micro sensors, polymers, pharmaceuticals, and many other chemicals. The supercritical fluids, instead, can produce new and improved products with new and advanced processes. Moreover, they have the advantage that they do not pollute the extracts, residues, and, in many cases, the environment.[10]

5. Anti-solvent precipitation method: The basic process involves addition of a concentrated aqueous solution of drug to a large excess of a water miscible solvent (such as Methanol, iso -propanol) with rapid admixing. This may be carried out either as a batch process using a dynamic mixer or as continuous process to produce products of similar morphology. The particle formation mechanism of the process might be expected a prior to involve simple nucleation and growth, where small crystal nuclei are formed first when super saturation values are at their highest, and these nuclei then grow in size by incorporating the remaining solute from the solution. [11,12]

6. pH change approach: The influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals is well documented. The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the importance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration. After pH adjustment, ionisable compounds (may be acids or bases or zwitter ions) are stable and soluble. It can

also be applied to crystalline as well as lipophillic poorly soluble compounds. Bioavailability can be increased, if the precipitation upon dilution is fine or amorphous, due to an increased concentration gradient and enhanced surface area for dissolution.[13]

7. Static mixture technique: The role of static mixers in modern manufacturing and processing continues to be an important one. Although they are relatively inexpensive tools, proper design and selection of static mixers must not be taken for granted to ensure optimal performance, high operational efficiency and long-term useful life.

Applications of Static mixture:

- Blending different grades of oil or gasoline.
- Mixing two or more liquid resins.
- Dilution of concentrated solutions.
- Water and wastewater treatment.
- Gas-liquid dispersions.
- Oil/water and water/oil emulsification.
- Production of Micro sized particles.
- Blending anti-oxidants and other additives.
- Homogenizing process streams for sampling.
- Chemical suspensions.[14]

MECHANISM OF SOLUBILITY ENHANCEMENT

Reduction of particle size: The micro crystallization technology offers rapid crystallization. Generally carrier agent which acts as stabilizing agent which is absorbed on the crystal surface to inhibit the crystal growth by forming the protective layer around the micro crystals .Thus particle size reduction is achieved.[15]

Wettability: Powder wettability can be increased through adsorption of hydrophilic agent. It is due to the surfactant action reduces the interfacial tension between the hydrophobic drug particle and aqueous solvent phase, increasing the effective surface area exposed to the dissolution medium. This also retards agglomeration or aggregation of the particles, which can slow down the dissolution.[16,17]

EVALUATION OF MICROCRYSTALS [18-22]

PARTICLE SIZE DETERMINATION

All the prepared batches are analyzed for particle size by optical microscope. One hundred particles from each batch shall counted and average particle diameter can be determined by using the formula:

$$\text{Average particle diameter} = \Sigma N*d/n$$

Where,
n = total no. of particles in that size range
d = Diameter of the particles of that size range
N = total no. of particles.

DETRMINATION OF PRODUCTION YIELD

The yield of microcrystals can be determined by calculating initial weight of microcrystals as,

$$\text{Percentage yield} = \frac{\text{Actual yield of the product}}{\text{Total weight of excipients and drug}} \times 100$$

FLOW PROPERTY STUDIES

Prepared microcrystals are subjected to various flow property studies like bulk density, tapped density, Hausners ratio and carr's index.

MICROSCOPIC STUDIES

Scanning electron microscopy and Transmission electron microscopy used to study microscopic aspects of drugs and product. The microcrystals can be morphologically studied under scanning electron microscope (SEM). The microcrystals shall place on an electron microscope brass stud and coated with gold in an ion sputter. The picture of microspheres will be taken by random scanning of the stud at an accelerating voltage of 25-15 KV and particle shape and surface morphology can be determined.

DIFFERENTIAL SCANNING COLORIMETRY

Allows the fast evaluation of possible incompatibilities because it shows changes in the appearance, shift or disappearance of melting endotherm and exo-therm or variation in the corresponding enthalpy of reaction, Thermo grams of pure drug and drug with polymer will be recorded. The samples will be separately sealed in an aluminium cells. The thermal analysis will be performed in the nitrogen atm. over a temperature range of 50ºC to 100ºC .

X-RAY DIFFRACTION STUDIES

The X-ray diffraction studies are based on the scattering of X-ray by crystals. X-ray diffraction studies are generally used for investigating the internal structures, size of crystallites and crystallinity. Crystalline materials in powder form exhibit highly characteristic X-ray diffraction pattern in which the positions and relative intensity of peak are well-defined and reproducible. Powder X-ray diffraction is both rapid and relatively simple method for the

detection of change in form. The amorphous materials do not show any pattern.

FT-IR STUDIES

FTIR absorption spectra of pure drug and physical mixture can be recorded in the range of 400 to 4000cm^{-1} by using FTIR spectrophotometer. FTIR studies are carried out individually for drug, polymer, other excipients and physical mixture of drug with polymer .FT-IR spectra of physical mixture of drug with all polymers shall compared with FTIR spectra of pure drug and polymers and and peak matching can be done to detect any appearance or disappearance of peaks.

DRUG CONTENT DETERMINATION

A quantity of microcrystals equivalent to dose of the drug is used for the estimation of drug content. It is estimated by crushing the microcrystals and extracting with the suitable solvent. The extract will be then transferred to a 100 ml volumetric flask and the volume will be made up by using suitable buffer solution. The solution will be then filtered and dilutions are made and the absorbance will be measured against blank solution spectrometrically.

MOISTURE ABSORPTION TEST

The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour revealing desiccant pellet. Expose the packed unit to known relative humidity over a specified time. Any changes in the colour indicate absorption of moisture. By measuring pre-test weight and protest weight pellet, amount can be calculated.

***IN-VITRO* DISSOLUTION STUDIES**

Dissolution profile of microcrystals are studied using dissolution apparatus USP type I having a modified basket consist of 5ml stainless steel mesh with a speed of rotation around 150 rpm. Proper dissolution medium is selected and solubility of active contents are considered to ensure sink conditions. Proper analytical methods are used for the sample form dissolution medium.

SOLUBILITY STUDIES

Formulation containing equivalent amounts of drug is placed in 25 ml stoppered conical flask containing 10 ml of distilled water. The sealed flask will be agitated on rotary shaker for 24 hrs. Sample will be filtered and analyzed on a UV spectrophotometer. Solubility studies done for finding out the solubility behaviour shown by the microcrystals in different types of solvent system and body fluids.

CONCLUSION

One of the most challenging problem in pharmaceutical field is to increase the bioavailability of orally administered poorly water soluble drug. Micro crystallization technology extremely helps in improving the dissolution property of such drugs. Various techniques described in this review are successfully used for preparation of microcrystals in the bench and lab scale and can be used as industrial scale also.

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