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Review Article

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A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUE BY MICROCRYSTALS

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ABSTRACT

Poor aqueous solubility and bioavailability of drugs are the important factors affecting the absorption of drugs and consequently their therapeutic effectiveness. Reduction of particle size micro crystallization technique has new opportunities for poorly aqueous soluble drugs. The solubility problem can be solved by changing the crystal habit of a drug. The anti-solvent crystallization has been widely used for micro crystallization of drugs in the presence of polymers for increasing the dissolution rate of poorly aqueous soluble drugs. This review focusses on solubility enhancement of poorly soluble drugs by microcrystals technique.

KEYWORDS: Microcrystals, Crystal Habit, Solubility, Enhancement, Bioavailability.

INTRODUCTION

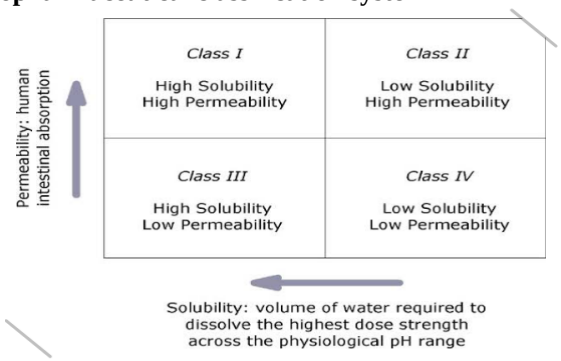
To increase the solubilization and bioavailability of a poorly water-soluble medication, a variety of approaches can be modified. Micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micelle solubilization, hydrotropic, and other procedures are frequently used to solubilize drugs. Poorly soluble medication solubilization is a frequent problem in formulation design and development as well as screening studies of novel chemical entities. Any medication that is to be absorbed must be present as an aqueous solution.

At the absorption, the site is a solution. As solubility and permeability determine how well the medicine will be absorbed in the body, these properties can be changed or improved using enhancement approaches. A given amount of solvent can dissolve a given amount of solute up to its maximum solubility. It can be characterized both qualitatively and quantitatively. It is described mathematically as the quantity of the solute in a saturated solution at a particular temperature. Solubility can be described qualitatively as the spontaneous interaction of two or more compounds to create a homogeneous molecular dispersion. When the solute and solvent are in balance, a solution is said to be saturated. Several concentration expressions, including parts, percentage molarity, molality, volume fraction, and mole fraction, are used to convey how soluble a substance is.[1]

Need of solubility

Poor water solubility and poor membrane permeability of the drug molecule are the two main contributors to inadequate medication absorption from the GI tract. An oral active drug must first dissolve in gastric and/or intestinal fluids before it can pass through the GIT membranes and enter the bloodstream. Hence, increasing solubility and increasing the rate of dissolution of medications that are not well soluble in water are two areas of pharmaceutical research that concentrate on optimizing the oral bioavailability of active substances. A medicinal substance is categorized using the BCS according to its water solubility and intestinal permeability. While drug release from the dosage form and solubility in stomach fluid are the rate-limiting steps for BCS class II & IV medications rather than absorption, increasing the solubility subsequently increases the bioavailability for these drugs.[2]

Biopharmaceutical classification system



Microcrystals for Solubility enhancement – role in poorly soluble

- **Solvent evaporation technique**

This process causes crystallization mostly as a result of the solvent being removed through evaporation and

precipitation in water, where the drug is insoluble. The steps make up the basic process used to create medication microcrystals. Drug solution preparations in various water-immiscible solvents, such as chloroform and ethyl acetate (10%, 20% v/v), with 1gm and 4gm of a drug, respectively. Drop by drop, the previously produced drug solution was added to a beaker of water while being constantly stirred (slow and turbulent). By maintaining the temperature corresponding to their boiling point, the biphasic layer created by the water-immiscible solvent is evaporated. Due to the drug's re-precipitation in water and the evaporation of water-immiscible solvents, micro-precipitation occurs. The precipitated crystals were dried for one hour at 60°C after being filtered using Whatman filter paper.

- **Solvent change method**

The drug was dissolved in a suitable solvent and heated until the solvent boiled. The drug solution was rapidly added to water kept at 20°C while being continuously stirred with a paddle device at 500 (or less than 5) rpm. After 25 minutes of stirring, micro crystals developed and were filtered from the solution. Microcrystals were dried at 45°C for 12 hours. Solvent-induced changes in the crystal lattice might affect a substance's physicochemical qualities.[3]

- **Solvent change precipitation technique**

According to Gassmann and colleagues, the solvent change method of micronization was carried out by instantly combining two liquids with a stabilizing agent. In a nutshell, the drug was dissolved in an organic solvent that is miscible with water, near the saturation concentration. In water, a stabilizing substance was dissolved. Rapidly pouring from a beaker into the drug solution while stirring continuously was the aqueous solution. The micro-suspension was dried in an oven for 24 hours at 37˚C after being filtered through a nylon membrane (0.45 lm).[4,5]

- **Supercritical fluid technique**

Both a back-pressure regulator and a pump for the flowing liquid were used to regulate the inner pressure in the system. The target compound in the sample tube was then dissolved, passed through the filter once the SCF state was achieved by heating under high pressure, and quickly combined with cooled solvent at the same pressure. After precipitating the target chemicals, microcrystals were finally produced in the dispersion state. For stable chemicals, the product's overall yield was close to 100%. DCHD microcrystals were created by precipitating methanol solution from the SCF at 350–420 K and under 8.5 MPa into water. SCF and the cooling solvent flowed at rates of 2 to 5 ml/min and 5 to 20 ml/min, respectively. The sample tube was filled with the target compound, and a filter with a 10 m pore size was placed on the tube to stop the target compound from escaping before heating. By subjecting the DCHD microcrystals to UV light, solid-state polymerization was carried out to create poly-DCHD microcrystals. During sublimation refinement, the microcrystals were also created in the instance of TiOPc in a process that was quite similar to how DCHD microcrystals were created. SEM was used to observe the crystal size and form. By using X-ray powder diffraction, the crystal form was identified among the several polymorphs A thermocouple was used to measure the SCF temperature and the temperature after cooling.[6]

Anti-solvent precipitation method

The fundamental procedure entails rapidly admixing a concentrated aqueous drug solution with a significant excess of a water-miscible solvent. Creating goods with similar morphology can be done continuously or in a batch process with a dynamic mixer. When supersaturation values are at their highest, small crystal nuclei form first, and as they develop in size by absorbing the remaining solute from the solution, the particle formation mechanism of the process is predicted to entail simple nucleation and growth.[7,8]

Static mixing method

30 mixer elements were assembled as part of the precipitation process and put into a stainless steel tube. According to earlier studies, the number of mixer elements is inversely related to the reduction in particle size. They are 90 degrees apart from one another to ensure uniform mixing over the whole pipe cross section. To ensure that the entire cross-section was moistened, a vertical arrangement was used. To ensure that the entire cross-section was wet, a vertical layout was adopted. The tube's design ensures that there will be no mixing before the mixer enters by placing the point where the two liquid flows converge in the middle of the first element. Using two peristaltic pumps, one of which circulates the aqueous phase while the other feeds the organic phase, it is possible to manage the mixing of the two phases at high flow rates. . The OXC concentration in each sample was 50 mg, and the experimental conditions included an organic flow rate of 50 ml/min and an aqueous flow rate of 400 ml/min at 25 and 50°C, respectively. Lastly, lyophilisation without the use of a cryoprotectant was performed on the generated dispersions. In the current investigation, the aqueous phase contained a polymeric solution of MC, whereas the organic phase contained a methanol solution of OXC.[9]

Applications of Static mixture

- Static mixtures are used to combine two or more liquid resins as well as several grades of oil or gasoline.
- Diluted versions of concentrated liquids.
- The treatment of wastewater and water.
- Dispersions of gas and liquid.
- Emulsification of oil and water and the creation of microparticles.
- Homogenizing process streams for sampling. Mixing antioxidants and other additives. Chemical suspensions [10].

A mechanism for increasing solubility

Particle size reduction: Micro crystallization technique provides quick crystallization. Typically, a stabilizing carrier agent is absorbed onto the crystal surface to form a protective coating around the microcrystals, which prevents further crystal formation. This results in the lowering of particle size.[11]

Wettability: The adsorption of a hydrophilic substance can improve the wettability of powder. It is because the surfactant activity increases the effective surface area exposed to the dissolution medium by decreasing the interfacial tension between the hydrophobic drug particle and the aqueous solvent phase. Moreover, this slows the aggregation or agglomeration of the particles, which might delay the disintegration.[12,13]

EVALUATION OF MICROCRYSTALS[14-18]

Particle size determination

The particle size of each prepared batch is examined using an optical microscope. From each batch of 100 particles, the average particle diameter can be calculated using the following 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.

DETERMINATION OF PRODUCTION YIELD

Calculating the initial weight of the microcrystals as follows will produce the yield of the crystals:

Percentage yield = Actual yield of the product x 100

Total weight of excipients and drug

Studies on flow properties

Studies on the flow properties of prepared microcrystals include those on bulk density, tapped density, Hausner's ratio, and Carr's index.

Microscopic study

To research the microscopic features of medicines and products, transmission and scanning electron microscopy are used. Scanning electron microscopes can be used to morphologically analyze the microcrystals (SEM). The microcrystals will be mounted on a brass stud for an electron microscope and covered in gold using an ion sputter. Particle form and surface morphology can be identified by randomly scanning the stud at an accelerating voltage of 25–15 KV to obtain an image of the microspheres.

Differential scanning calorimetry (DSC)

Because it demonstrates changes in the presence, movement, or disappearance of melting endotherm and exo-therm or fluctuation in the related enthalpy of reaction, it enables the quick evaluation of potential incompatibilities. We shall record the gram of both the pure and polymerized medication. Each sample will be individually sealed in a cell made of aluminum. The nitrogen atmosphere will be used for the thermal analysis, which will be conducted between 50 and 100 degrees Celsius.

Studies on X-ray diffraction

Studies on X-ray diffraction are based on how crystals scatter X-rays. Studies using X-ray diffraction are typically used to look into crystallinity, crystallite size, and interior structures. When crystals are in powder form, they display an X-ray diffraction pattern with very distinct peak positions and relative intensities are precisely specified and repeatable. The process of powder X-ray diffraction is quick and reasonably easy. Detection of a form change. The amorphous materials are patternless.

FT-IR Studies

FTIR spectrophotometers can record FTIR absorption spectra in the 400–4000 cm–1 range. Individual FTIR tests are conducted for the drug, polymer, additional excipients, and physical combination of the drug and polymer. Peak matching can be used to identify any presence or removal of peaks by comparing the FT-IR spectra of the physical combination of the drug with all polymers with the FT-IR spectra of the pure drug and polymers.

Determining the drug content

To estimate drug content, several microcrystals that correspond to a dose of the drug are used. By breaking up the microcrystals and extracting them using the appropriate solvent, it is estimated. After that, the extract will be poured into a 100 ml volumetric flask, and the capacity will be filled with the appropriate buffer solution. The absorbance will then be spectroscopically measured against a blank solution after the solution has been filtered, diluted, and measured.

Test for moisture absorption

By combining the dosage unit with a desiccant pellet that reveals its color, the dosage unit's degree and rate of moisture penetration are measured. Set a time limit and expose the packed unit to a known relative humidity. Any color changes signify the presence of moisture. It is possible to determine the amount by measuring the pre-test weight and protest weight pellet.

Solubility studies

A conical flask with a stopper that holds a 25 ml capacity and 10 ml of distilled water is filled with a formulation having identical amounts of the drug. For 24 hours, the sealed flask will be shaken on a rotary shaker. The filtered sample will be examined using a UV spectrophotometer. Studies on solubility were conducted to determine the solubility behaviour displayed by microcrystals in various solvent systems and bodily fluids.

***In vitro* Dissolution studies**

Using a dissolution test apparatus USP type I with a modified basket made of 5 ml stainless steel mesh and rotating at a speed of about 150 rpm, the dissolution profile of microcrystals is examined. To achieve sink conditions, the appropriate dissolution medium is chosen, and the solubility of the active ingredients is taken into account. The sample form dissolution medium is employed with the correct analytical techniques.

CONCLUSION

Increasing the bioavailability of an oral, weakly water soluble drugs is one of the most difficult problems in the pharmaceutical field. Micro crystallisation technology significantly aids in enhancing these drugs ability to dissolve. The many methods discussed in this review can be applied on an industrial scale as well as being effectively employed to create microcrystals in bench and lab settings.

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