A REVIEW: MELTSONOCRYSTALLIZATION TECHNIQUE USED FOR IMPROVEMENT OF SOLUBILITY

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ABSTRACT
Melt sonocrystallization method have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. It is a novel particle engineering technique to enhance dissolution of hydrophobic drugs that is having less water solubility and to study its effect on crystal properties of drug. It forms agglomerates with number of shallow circular pits on the surface leads to increase solubility by improving its shape from crystalline to amorphous that is obtain circular shape. Melt sonocrystallization process was developed for poorly soluble drugs in which these poorly soluble drugs melt was poured in deionized water maintained at 60°C and simultaneously subjected to ultrasonic energy. The agglomerates obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature. Hence this review gives valuable information about on melt-sonocrystallization shows that there is increase in solubility of poorly water soluble drugs.

KEYWORDS: BCS Class, solubility, sonocrystallization, melt sonocrystallization, bioavailability, advantages.
INTRODUCTION
Solubility is nothing but the concentration of the solute in a saturated solution at a certain temperature. The maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. A saturated solution which means the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, molality, percentage, molarity, volume fraction and mole fraction.\(^1\)

Solubility is ability to dissolve or liquefy a substance, hence these processes may occur not only because of dissolution but also because of a chemical reaction. Solubility is not depend on particle size or other kinetic factors; given enough time, even large particles will eventually dissolve.\(^2\) USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in Table 1\(^{3,4}\).

Table 1: Definitions of Solubility

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Part of solvent required per part of solute</th>
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<tbody>
<tr>
<td>Very soluble</td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>From 1000 to 10,000</td>
</tr>
<tr>
<td>Insoluble</td>
<td>10,000 and over</td>
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</table>

The amount of solubility ranges widely, from infinitely soluble such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds.\(^5\)

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule.\(^6\) The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs.\(^7\) BCS Classification System with examples of different drug is discussed in Table.2.
Table 2: Biopharmaceutical Classification System.\[8\]

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>High</td>
<td>B-blockers propranolol, Metoprolol</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>High</td>
<td>NSAID’s Ketoprofen, Antiepileptic Carbazepine</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Low</td>
<td>B-blockers Atenolol, H2 antagonist Ranitidine</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Low</td>
<td>Diuretics Hydrochlorothiazide, Frusemide</td>
</tr>
</tbody>
</table>

To achieve desired concentration of drug in systematic circulation for pharmacological response to be shown. Low aqueous solubility is major problem encountered with formulation development of new chemical entities. Any drug to be adsorbed must be present in the form of an aqueous solution at the site of absorption.

Formulations for BCS class I drugs BCS class I drugs are defined as being highly soluble and highly permeable. For instance, metoprolol, propranolol, and theophylline are categorized into this class. For BCS class I drugs, there would be no rate-limiting step for oral absorption.

Formulations for BCS class II drugs The molecular characteristics of BCS class II drugs are identified as low solubility and high permeability. For e.g. cyclosporine, griseofulvin, and itraconazole are categorized into this class. Generally, the rate limiting step of BCS class II drug is dissolution which further affects on bioavailability, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS class II drugs. Several physicochemical factors control the dissolution rate of the drugs.

Formulations for BCS class III drugs Drugs with high solubility and low permeability are classified as BCS class III. For e.g., atenolol, cimetidine, and metformin are categorized into this class. The bioavailability of BCS class III drugs is rate-limited by the membrane permeability in the gastrointestinal tract. In theory, there are three trans epithelial pathways for the drugs from the intestinal lumen to the bloodstream: transcellular carrier-mediated active or facilitated transport, transcellular passive transport, and paracellular trans-port. A majority of orally administered drugs are absorbed via transcellular passive transport. In this case, the intrinsic lipophilicity of the drug is a determinant of the drug transport across the enterocytes, and drug with relatively high lipophilicity would have high membrane permeability.
Formulations for BCS class IV drugs exhibit challenging molecular properties such as low solubility and low permeability. Since both solubility and permeability are rate-limiting steps for absorption, it would be considered that physiological factors, for example, gastric emptying time and gastrointestinal transit time, highly influence the absorption of BCS class IV drugs. Therefore, the drugs categorized in BCS class IV could exhibit large inter- and intrasubject variability in terms of absorption. This variability in absorption could result in the challenging drug development of BCS class IV drugs as well as their formulation design. There are viable formulation options focusing on improvement of the dissolution behavior that are commonly applied to BCS class II drugs, even though the absorption could be limited by the poor permeability after dissolving in the gastrointestinal tract.\[9\]

**Factors affecting solubility**

1. **Nature of solute and solvent:** The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature.\[10\]

2. **Particle size:** Particle size affect on solubility. As article size decreases, the surface area to volume ratio increases.\[11\]

3. **Molecular size:** The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

4. **Temperature:** If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.\[12\]

5. **Pressure:** For solids and liquid solutes, solubility not affected by change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease.

**Importance of solubility**

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug product.\[13\] Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.\[14\]
However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. Solubility also plays a major role for other dosage forms like parenteral formulations as well.\cite{15}

Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist.\cite{16}

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.\cite{13,16,17}

**Techniques for Solubility Enhancement**

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

- **Physical Modifications**
  
  Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.
- **Chemical Modifications**
  Change of pH, use of buffer, derivatization, complexation, and salt formation.

- **Miscellaneous Methods**
  Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

**METHODS TO ENHANCE THE SOLUBILITY**

Solubility enhancement techniques can be categorized into Physical Modification, Chemical Modification and Other technique.

**Table 2: Various methods to enhance the solubility.**

<table>
<thead>
<tr>
<th><strong>Physical Modification</strong></th>
<th><strong>Chemical Modification</strong></th>
<th><strong>Other Techniques</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Particle size reduction</td>
<td>a. Soluble prodrugs</td>
<td>a. Co-crystalization</td>
</tr>
<tr>
<td>B. Modification of the crystal habit</td>
<td>b. salt formation</td>
<td>b. Cosolvency</td>
</tr>
<tr>
<td>C. Drug dispersion in carriers</td>
<td></td>
<td>c. Hydrotopy</td>
</tr>
<tr>
<td>D. Complexation</td>
<td></td>
<td>d. solubilizing agent</td>
</tr>
<tr>
<td>E. Solubilisation by surfactants</td>
<td></td>
<td>e. Nanotechnology approaches</td>
</tr>
</tbody>
</table>

**Chemical Modification**

- Use of Complexing agents
  - Inorganic Coordination
  - Chelates
  - Metal-olefin
  - Inclusion Molecular complexes

**Other Techniques**

- 1. Microemulsions
- 2. Self-microemulsifying drug delivery systems
- Chemical

**General method**

1. **Hydrotropy**

Hydrotropy describes the increase in the solubility of a less soluble solute by the addition of fair concentrations of alkali metal salts of various organic acids. Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. Essentially the anionic group increases the hydrophilicity and the ring system interacts with the solute to be dissolved. The term Hydrotropy was coined by Carl Neuberg in 1916[18] but
the practical implications were introduced as late as 1976 by Thoma and coworkers. In 1985, Saleh co-workers broadened the virtue of hydrotropic compounds by including the cationic, anionic or neutral molecules having an aromatic ring structure\(^{[19]}\). Hydrotropic polymers were later on added to the list, Park and coworkers,\(^{[20]}\) indentified NPicolylnicotinamide (PNA) was one of the best hydrotropes for paclitaxel; N, Ndiethylnicotinamide (DENA) and N, Ndimethylbenzamide (DMBA) were also used as solubility enhancers.\(^{[20]}\) Maheshwari and coworkers increased solubility of Paracetamol using Urea and of aceclofenac using mixed hydrotropic phenomenon using Urea and Sodium acetate.\(^{[21]}\) Sodium acetate was used as a hydrotropic agent to increase the mass transfer coefficient of salicylic acid by Theneshkumar and co-workers.\(^{[22]}\) Hydrotropy has been used by Tambe and coworkers for developing a chromatographical and spectrophotometrical method of estimation of Cefixime.\(^{[23]}\) Pandey and co-workers used hydrotropic phenomenon of Potassium acetate for analytical estimation of ketoprofen tablet dosage form.\(^{[24]}\) Conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates etc. is lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilisation.\(^{[25,26]}\)

2. Salt formation

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. Approximately 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form.\(^{[27]}\) The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts.\(^{[28]}\) The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behaviour would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion. The criteria used to select counter ion is as follows:

1. There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
2. Counter ion should decrease crystal lattice forces.
3. It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.

3. Co-Solvency
The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents\(^{[29]}\). Cosolvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Examples PEG 300, propylene glycol or ethanol.

4. Particle Size reduction
The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds.\(^{[30]}\)

2. Sonocrystallization
Despite Richards and Loomis reported in 1927 the first study on the effects of US on crystallization, the research in this field was delayed owing to inconsistent results and the lack of proper US devices. Revitalization of the technique occurred in the 1950s and 1960s when many of the benefits of Sonocrystallization discussed in current literature were first observed. A review on this subject by Kapustin emphasized the reduction in grain size in melt crystallizations via US, Turner et al. reported that a short burst of high-intensity US induced crystallization of sugar syrups that were resistant to crystallization, and other authors reported that micronized, uniform crystals of pharmaceuticals were achieved via US-based approaches. Over fifty years have elapsed since early reviews on Sonocrystallization discussed the proposed mechanisms of action attempting to understand the fundamentals and control of Sonocrystallization. In a recent review, the effects of US on crystallization have
been reviewed and the mechanisms of the driving force of US to achieve a desired product critically discussed.

Figure 4: Process of Ultrasound in Sonocrystallization.

Mechanisms involved in Sonocrystallization

A widely used explanation to these phenomena is the so-called hot spot theory, which attributes nucleation to local hot spots, created by the concentration of kinetic energy in the collapsing cavity or due to rapid cooling afterwards. Other popular mechanism is based on the pressure shockwave caused by cavity collapse that creates localized high pressures. There are substances for which the solubility decreases by increasing the pressure, thus increasing local supersaturation and inducing nucleation. A hypothesis related to the shockwave effect states that nucleation starts by segregation of the solute and solvent near the bubble wall.

This is caused by high pressures occurring in the ultimate phase of bubble collapse. Yet, another hypothesis suggests that nucleation occurs during bubble expansion: solvent evaporating into the bubble or cooling of the liquid interface layer increases local supersaturation, which could lead to nucleation around the cavity. It is assumed that nucleation is induced due to the bubble surface acting itself as nucleation center so that the mechanism seems to be of heterogeneous nature. To prove this assumption, gassing has been investigated as nucleation inductor during batch cooling crystallization: the gas bubbles are just expanding, not collapsing. Also of interest is the electrical theory, which proposes the consequences of cavitation as caused by electrical charges on the cavity interface layer.

The most accepted explanation of the small size particle achieved by Sonocrystallization is related to the characteristic effects of US (streaming and cavitation as the most important): the stirring effect causes a reduction in thickness of the diffusion layers in the vicinity of the
crystal surfaces by the high-energy shockwaves impinging on the particle surface. This can create high-velocity interparticle collisions that can alter the particle morphology and size dramatically. It was reported that these interparticle collisions occur with such a great force that even metal particles tend to melt together.

As the exact mechanisms behind US-assisted crystallization are not known yet, the following hypotheses seem to be the most accepted:

1. The effect of US is not directly caused by vibrations of the US waves but by the cavitation bubbles formed by the US field;
2. Both the amount and the size of the cavitation bubbles affect the nucleation rate;
3. Higher US intensities produce more cavitation bubbles and nucleation increases;
4. Larger US frequencies produce smaller cavitation bubbles which have a smaller impact on the nucleation rate; and
5. The segregation and cavitation bubble theories link the nucleation rate to the size of the cavitation bubbles.

In addition, the following US effects have been experimentally supported: (1) improved micro scale mixing occurs from cavitation and associated turbulence, accelerating diffusion rates of reactants and reducing induction times for crystallization as a result.

Reduced induction time increases the rate of nucleation by increasing the growth rates of embryonic crystallites, which prevents their redissolution. (2) By similar phenomena, US also reduces the MZW (i.e. the range of metastability of a supersaturated solution in either temperature or antisolvent concentration), which diminishes the rate of crystal growth and decreases crystal size. (3) The increase in gas–liquid interfaces produced by bubble formation, collapse and fragmentation enhances nucleation rates. (4) Rates of secondary nucleation are also increased by US by breakage of primary crystals due to interparticle collisions or, more importantly, shockwave fragmentation during ultrasonication (i.e. sonofragmentation) increases the number of secondary nucleation sites, which results in increased number of smaller crystals. (5) Turbulent flow from cavitation also diminishes crystal aggregation, which produces smaller solid particulates with narrower size distribution. (6) Antisolvent sonocrystallization, which generates a high level of supersaturation quickly and induces higher nucleation rates, benefited by enhanced mixing between the antisolvent and solution.
Variables affecting sonocrystallization

The sonocrystallization process is influenced by US variables such as frequency, intensity, power, duty cycle, but also by physical variables such as temperature, pressure, time, volume of the cell, size of the probe, and chemical variables such as API concentration, pH. Modelization of the process helps to better understanding the influence of the variables involved in sonocrystallization.[31]

The unfeasibility of general conclusions from the above research because of the use of limited frequency ranges, the lack of calibration of the dissipated power and the use of different intensities, crystallization products and reactor geometries led to recent studies on the effects of the US frequency and intensity on nucleation. Taking into account for the first time, the effect of US frequency on the MZW and crystal size distribution (CSD) was investigated over a broad frequency range of 16–1140 kHz in one single reactor geometry on one single product. In contrast to previous studies, the power inside the reaction medium was kept constant for all frequencies. Furthermore, the effect of the US intensity was investigated in a batch reactor and a US flow cell. The MZW and CSD of both reactor set-ups were compared at different US intensities.

Finally, the optimal US frequency and intensity for enhancement of the nucleation were defined. The effect of US frequencies ranging from 16 to 1140 kHz on the MZW, CSD and crystal shape was tested at a constant intensity of 53 W/l. Figure 2 shows the average reduction in MZW as a function of the applied frequency. A reduction in the MZW, as compared to no US conditions, was observed at all frequencies, but at 850 kHz, it was attributed to degradation products formed by ultrasonochemical degradation of the target drug (paracetamol). Either significant inhibition or promotion of the crystal growth and the appearance of multiple nucleation bursts in the presence of even trace amounts of impurities was already reported in the literature,[32,33] but a degradation level of more than 10% higher at 850 kHz as compared to 580 or 1140 kHz was observed by other authors.[34] Therefore, higher level of degradation could significantly affect the nucleation process and the observed MZW. While Sonocrystallization is under very active investigation for its ability to favourably influence crystallization-related parameters, reports on the effects of US on postcrystallization particles are surprisingly limited.
The most frequently used US-assisted crystallization techniques are discussed below:

**Salting-out Sonocrystallization**
This technique involves fast addition to the solute solution of enough precipitant (salting-out agent) to yield the complete precipitation and immediate or simultaneous application of US, which travels throughout the crystallization vessel to mix, cavitate and blend the precipitant with the solution uniformly. The solubility of the solute in the solvent is sharply reduced, and the solution immediately reaches its maximum supersaturation so that primary nucleation and crystal growth occur rapidly. The exact amount of precipitant is determined by the required yield of the product and its solubility. The maximum supersaturation must be established at the beginning of the Sonocrystallization process to provide enough driving force for continuous nucleation and growth.\[35\]

**Antisolvent Sonocrystallization**
This technique involves selection of an antisolvent that can successfully precipitate the dissolved compounds from their solutions favoured by the application of US during the Crystallization step. The role of the antisolvent is to reduce the solubility of a solute in the solution and induce prompt crystallization, thus making unnecessary the use of thermal energy that can degrade the activity of materials sensitive to temperature, and avoiding expensive energy-intensive equipment required for evaporation-based crystallization. Therefore, the core of antisolvent crystallization is the selection of the antisolvent, while application of US during this step facilitates the process by circumventing the problems associated with antisolvent crystallization using polar antisolvents as water for hydrophobic pharmaceutical compounds.\[36\]

The main advantages of a polar antisolvent as water for crystallization of hydrophobic drugs are the nearly zero solubility of such compounds and complete miscibility with many polar organic solvents, in addition to be an environmentally safe option easily separated from final products. A disadvantage of water as antisolvent successfully circumvented by US application is a delayed mixing rate between the solution and antisolvent owing to a low diffusivity of water in organic solutions.\[37,38\]

**Spray Sonocrystallization**
This recent technique is a sophisticated mode of antisolvent crystallization in which the drug solution is sprayed into the flow of the antisolvent by a channel drilled down in the center of a specially designed flow-through US probe. In this way, the drug solution is atomized upon
its exit from the horn into the flowing stream of antisolvent. The momentum transfer and micromixing created by acoustic cavitation form a fine dispersion of the drug solvent into the flowing antisolvent within 100 ms, which substantially increases the rate of solvent–antisolvent mixing and leads to a rapid formation of nanocrystals at the 100-nm scale.\textsuperscript{[39]}

**Melt Sonocrystallization**

This particle engineering technique involves application of US energy to the soft or viscous molten mass dispersed in an immiscible liquid; thus, solidification/crystallization from emulsified melt is carried out under the influence of US energy. The technique, initially used to produce sintered crystals and porous glassy beads, allows extending the US energy received by the melt in the emulsified state and determines the properties of the resultant particles, which are dependent on US energy input and frequency, and solidification rate of the melt. In turn, this last variable depends on the temperatures of glass transition of the material and that of the medium. Application of US at temperatures above the transition temperature favors crystallization, whereas processing below the transition temperature results in an amorphous state. The mechanical stress due to ultrasonication results in sintered crystals or porous beads. The porous nature and potential for producing crystalline particles as well as amorphous particles offer flexibility to the technology and are looked upon for improving the solubility of poorly soluble pharmaceuticals.\textsuperscript{[40]}

**Melt sonocrystalization**

Melt Sonocrystallization is newer particle engineering technique. In this method by applying ultrasound energy in range of 20 to 100 kHz crystallization process achieve.\textsuperscript{[41]} In pharmacy industry ultra sound energy was introduced traditionally to increase the solubility of sparingly soluble drug. Ultrasound system use to influence the initial nucleation stage of crystallization. The ultra-sonication causes disaggregation or deagglomeration of particle. Cavitation is an important phenomenon of ultrasonication.\textsuperscript{[42]}

In Sonocrystallization the energy of ultrasound cause repeated compression and expansion. After several cycle the bubble forms, grows and collapses. Due to bubble collapses the energy produced .This energy was responsible for breaking of particles. This results in high repeatable and predictable crystallization. Applying Ultrasound to crystallization results in:

a. Nucleation at the lowest level of supersaturation where the crystallization overcomes the tendency of the compound to redissolve in the solution.
b. Narrowing of the metastable zone width.
c. Narrow particle size distribution.
d. Decrease in the level of cooling necessary to achieve crystallization.
e. Highly repeatable and predictable crystallization.
f. Polymorph control.

Particle engineering techniques are developing to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. Number of particle design techniques are reported, such as spherical crystallization, extrusion spherization, melt solidification, spray drying, pastillation, solution atomization and crystallization by sonication (SAXS), where simultaneous crystallization and agglomeration occur. Valdecoxib is non-steroidal anti-inflammatory, analgesic used in treatment of adult rheumatoid arthritis, primary dysmenorrhea. Valdecoxib shows poor dissolution behavior because of its hydrophobic nature. However, for analgesic action rapid release is preferred. To overcome this problem many workers have attempted to improve properties through suitable particle design techniques. Ultrasound (US) was introduced in the traditional process of pharmaceutical technology of few years ago. For instance, several workers reported US assisted compaction and US spray congealing of variety of systems where physical modification of structure of drug or excipients was done to improve drug release and compaction properties of drug.

Cavitation is an important phenomenon of ultra-sonication. The energy produced due to the collapse of bubbles at very high temperature was responsible for breaking of particles. The so generated shock waves can cause the particle collide into one another with great force since these are similar charge particles problem of agglomeration is greatly reduced. There are reports on application of ultrasonic (US) energy during crystallization, i.e. Sonocrystallization.

US energy has been used to achieve nucleation at moderate super saturation during the crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit. Fini et al. studied US assisted compaction of various drugs with excipients such as cyclodextrin and Eudragit. Significant changes in the crystal properties were observe due to US treatment. The effect of application of US energy on the properties of melt sonocrystallized (MSC) valdecoxib was characterize by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), infrared spectroscopy and saturated solubility study.
Method of preparation

1. The drug (2gm) was melted in a vessel on a paraffin oil bath maintained at 190°C. Molten mass was poured in a vessel containing 50ml of deionized water maintained at 60°C using thermostatic water bath and sonicated for 15 minutes using probe ultrasonicator (Ikasonic U 200 s control) at amplitude of 80% and cycle of 0.8 per second. The product obtained after solidification of dispersed droplet was separate by filtration and dried at room temperature. The fraction of MSC agglomerates (−40/+60 #) were used for saturated solubility study.

2. The drug (2 g) was melted in vessel in paraffin oil bath. Molten mass was poured in vessel containing 20 ml deionized water and sonicated for 20 min. using probe sonicator (Chrome Tech ultrasonic) processor at pulse on off 1 s with 5–8 mm probe diameter and 80 %. The product obtained after solidification of disperse droplet was separate by filtration and dried at room temp.

3. The drug (2 g) was melted in a porcelain dish on a paraffin oil bath maintained at 193°C. Molten drug mass was poured in a vessel containing 100 ml of deionized water maintained at 45 to 50°C using cryostatic bath (Haake Phoenix C25P, Germany) and sonicated for 15 minutes at an amplitude of 75 % using probe ultrasonicator (Sonics &aterials Inc. Vibra Cell model VCX 750.). Agglomerates were filtered and the obtained product was dried at room temperature overnight.[49]

Characterization[50]

- Particle size and shape: Spherical crystallization causes a change in the crystal habit of drugs thereby improving their physicochemical properties.
• **Density:** Density of drug substances decreases with an increase in the volume of agglomerates.

• **Stability:** Stability of drug substances changes due to polymorphism taking place.

• **Flowability:** Flowability of agglomerates is improved, exhibiting lower angle of repose due to significant reduction in inter-particle friction compared to that of crystalline drug.

• **Packability:** Angle of friction, shear cohesive stress and shear indexes are lower than that of crystalline drug thereby improving the packability of the agglomerates.

• **Compaction Behavior of Agglomerated Crystals:** Spherical agglomerates possess superior strength characteristics compared to crystalline drug.

• **Wettability:** Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. Wettability increases with decrease in the contact angle. Crystals with poor crystallinity are more wettable than crystals with higher crystallinity.

• **Solubility:** Changes in the internal energy of the molecules play an important role in increasing solubility. Improved solubility of spherical agglomerates may be due to a change in the crystal form, crystal habit and structure. Surface modification can change the surface properties and the reactivity of drug particles.

• **Dissolution Rate and Bioavailability:** Prepared agglomerated crystals with appropriate particle size, solubility, particle density and specific surface area increases the dissolution rate and bioavailability of drug.[56]

• **Flow property**

Flow property of the material depends on the force developed between the particle, particle size, particle size distribution, particle shape, surface texture or roughness and surface area. Following are the methods used to determine of flow property.

(a) **Angle of repose (θ):** It can be obtained from the equation:

\[ \theta = \tan^{-1} \frac{h}{r} \]

Where, h=height of the cone, r=radius of cone.

Values for angle of repose: ≤ 30 indicate free flow and ≥40 indicate poor flow.

(b) **Compressibility or Carr index**

A simple indication of ease with which a material can be induced to flow is given by application of compressibility index. \[ I = (1-V/V_0) * 100 \]

Where \( v \) = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and \( V_0 \) = the
volume before tapping. The value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

(c) Hausner’s ratio

It is calculated from bulk density and tap density.

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Values less than 1.25 indicate good flow (20% Carr Index) and the value greater then 1.25 indicates poor flow (33% Carr Index).

1. **Optical microscopy:** The shape of spherical agglomerates is studied by observing them under optical microscope.

2. **Scanning Electron microscopy:** The surface topography, type of crystals (polymorphism and crystal habit) of the spherical agglomerates is analyzed by using a scanning electron microscopy.

3. **Thin layer chromatography:** TLC studies are carried out and the Rf value is determined. Rf value of drug and spherical crystals are compared. This study is carried out to check if there is any interaction between the drug and the polymer. It also helps in determining the stability of drug in different solvents.

4. **X-ray powder diffraction:** Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound. The form of crystals in agglomerates is determined by using X-ray powder diffraction technique. This is an important technique for establishing batch-to-batch reproducibility of a crystalline form.

5. **Fourier Transform Infrared spectrometer (FTIR):** It is mainly used for identification of drug and its different polymorphic forms. It is also used for distinguishing solvates and anhydrous form of drug.

6. **Differential scanning calorimeter (DSC):** DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. It is also useful to determine thermal degradation, purity and polymorphism and drug-excipient compatibility.

**Advantages**

1. Fewer processing steps needed, thus time consuming method.

2. There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.

3. Ultrasound to control crystal formation and nucleation.
4. Conversion of crystalline nature to amorphous nature.
5. Particle rounding potential to improve flowability.
8. Improve crystal purity and physical properties.
10. Eliminate seeding
11. No sonicator contact
12. No use of organic solvents
13. No use other excipients such as polymers

Disadvantages
1. Several drugs can be degraded by the melting process can be a limitation of this method
2. The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved
3. There is the possibility that during processing (mechanical stress) or (temperature and humidity stress) the amorphous state or structure of agglomerates may be changed
4. Poor scale-up for the purposes of manufacturing
5. Cannot be used at large commercial scale\(^{[51]}\)

Applications
1. Melt Sonocrystallization used for treatment of gastic cancer by Sonocrystallized curcumin.
2. The application of Sonocrystallization can dramatically affect the properties of the crystalline products.
3. The technique, initially used to produce sintered crystals and porous glassy beads.

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