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Melt Sonocrystalization: A Solubility Enhancement Technique for Hydrophobic Drugs

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ABSTRACT

Oral bioavailability of drugs depends on several factors such as aqueous solubility, drug permeability and the solution rate, the most frequent causes of low oral bioavailability are because poor solubility and low permeability. Solubility is one of the important parameters to achieve desired conce. of drug in plasma for achieving required pharmacological response. It has been investigated that new chemical entities currently being discovered most of them have poor water solubility, which limits its therapeutic efficacy. Melt sonocrystalization is newer particle engineering technique involved utilization of ultrasound energy to generate fine particles of drugs that helps to improve aqeous solubility and bioavailability. Melt sonocrystalization offers solvent and carrierless technique for the formation of fine particles which makes this technique more promising for the enhancement of drug solubility in water .

Keywords: Melt sonocrystalization, sonocrystlization,BCS,Ultrasound.

Introduction

Oral drug delivery is most preferred, efficient and simplest way of route for administration of drugs, due to its ease of administration, high patient compliance, and cost-effectiveness, least sterility parameters and flexibility in the design of dosage form.[2] So the most solid dosage forms used are tablets and capsules, amongst these tablets are widely used dosage form. Thus solid oral dosage forms have great advantage and stability over other dosage forms. Near about 40% drug pipeline in pharmaceutical industries are mainly takes part in/categorized in BCS Class II drug that is having high permeability and low solubility. About 40% of identified new drugs faces problem of poor water solubility which produces side effects such as gastric irritation, peptic ulceration etc. But the poor solubility is not only the problem in bioavailability and clinical testing but it also possesses obstacle in pharmacological activity, thus getting disturbance in absorption, distribution and dissolution of drug or dosage form in the body.[1,2] Hence, solubility of drug or relevant dosage form plays important role to give better activity because therapeutic effectiveness of drug depend upon bioavailability, ultimately on pharmacological response and can be directly related to plasma levels. Low water solubility of these drug, give limited bioavailability.[1] The rate limiting step in oral solid drug delivery system is mainly membrane permeability and drug release. The bioavailability of poor water soluble drugs can be increase by enhancing the water solubility of the drugs.[2,3] There are tremendous novel technologies which are utilized for particle engineering and for solubility enhancement of drug and to overcome the same difficulties/challenges in development of new formulation.[4]The older technologies include size reduction with communition, ball mill, micronization and spray drying. Other includes solid dispersion, inclusion complexes, spherical crystallization, use of surfactant, cyclodextrin

complexes, self emulsifying drug delivery systems, hydrotropy,use of solubilizing agent. The novel technologies includes crystal engineering/particle engineering, cryogenic technology, super critical fluid processes, nanocrystal methods. Thus, novel technologies gain a more positive attention to solve the problem associated with delivery of hydrophobic drug or BCS class II drugs. So the novel particle engineering technique or number of solubility enhancement techniques and powder technology are most effective method for enhancing the solubility poorly water soluble drug. Because solubility of drug remains the most challenging aspect in formulation development[5].

1.1 Solubility:

Definitions:

Solubility is the phenomenon in which solute molecules dissolve in solvent to give homogenous system. Generally solubility depends upon solvent used, temperature and pressure[3].Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units [5].[10] Where, Solubilization may be defined as: The spontaneous passage of poorly water soluble solutes molecules into an aqueous solution of the surfactant.[8]

The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. The extent of solubility ranges widely, from infinitely soluble (fully miscible) to poorly soluble, such as ethanol in water to silver chloride in water, respectively. The term insoluble is often applied to poorly or very poorly soluble compounds. Solubility results from the simultaneous and opposing processes of dissolution and phase joining which means that it occurs under dynamic equilibrium, (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give supersaturated solution, which is metastable. Solubility does not also depend on particle size or other kinetic factors; as time proceeds further, even large particles will eventually dissolve . It is possible to predict solubility from Hansen and the Hildebrand solubility parameters which are empirical methods and physical constants such as the enthalpy of fusion. The partition coefficient (Log P) is a measure of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of these two values enables compounds to be ranked in terms of hydrophilicity (or hydrophobicity).[10]

1.1.1 Solubility Expressions [3]:

The solubility of a drug is expressed in a number of ways.
The USP and BP enlisted the solubility of drugs as parts of solvent required for one part solute, regardless of the solvent used, just only in terms of quantification as given in table 1 ; [8,10]

Table 1: USP and BP solubility criteria.

Terms	Parts of solvent required for 1 part of solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble	More than 10,000 parts

Solubility is main factor in case of bioavailability and it also important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. High dose often required by poorly water soluble drugs in order to reach therapeutic plasma concentrations after oral administration. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause limited absorption, low rate of dissolution of drug and insufficient bioavailability[9,10].

Thus the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane, extensive pre-systemic metabolism. Bioavailability of poorly water soluble drugs is a major problem.

The oral bioavailability depends on factors such as aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms2. The most frequent causes of low oral bioavailability is attributed to poor solubility and low permeability.[2,3]

1.2 Biopharmaceutics Classification System (Bcs):[13,28]

Based on solubility and the intestinal drug absorption or permeability , drug can be classified into four classes called as Biopharmaceutics Classification System (BCS) provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability**.** All drugs have been divided into four classes: BCS class I— high soluble and high permeable, BCS class II—low soluble and high permeable, BCS class III—low soluble and high permeable and BCS class IV—low soluble and low permeable.

1.2.1 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.

1.2.2 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 bioavailabiity, 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.

According to the modification of the Noyes-Whitney equation, the factors affecting the drug dissolution rate are defined as the effective surface area, the diffusion coefficient, the diffusion layer thickness, the saturation solubility, the amount of dissolved drug, and the volume of dissolution media. Increases in the saturation solubility and the effective surface area have a positive impact on the dissolution rate of the drugs, and these factors could be increased by efforts of preformulation study and formulation design. Crystal modification, particle size reduction, self-emulsification pH modification and amorphization are considered to be effective for improving the dissolution behavior of BCS class II drugs.

1.2.3 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.

1.2.4 Formulations for BCS class IV drugs

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 intra-subject 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.

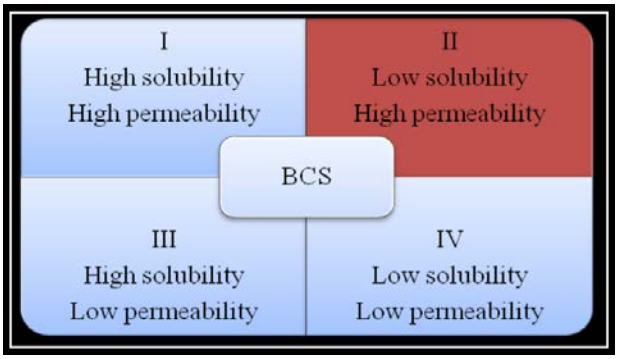


Figure 1: BCS Classification System[28]

1.3 Approaches or Various Methods for Enhancement of Solubility of BCS Class Drugs[6,8]:

I. Physical Modifications

A. Particle size reduction
a. Micronization
b. Nanosuspension
- Homogenization
- Wet milling

B. Other techniques for reduction of the particle size
a. Sonocrystallisation
b. Spray drying
c. Rapid expansion of supercriticle solutions (RESS)
d. Supercritical fluid process
e. Gas antisolvent recrystallisation (GAS)

C. Modification of the crystal habit
a. Polymorphs
b. Pseudopolymorphs
c. Drug dispersion in carriers
- Eutectic mixtures
- Solid dispersions

1. Hot Melt method
2. Solvent Evaporation Method
3. Hot-melt Extrusion
4. Melting –solvent method

d. Solid solutions

D. Complexation
a. Use of Complexing agents

E. Solubilization by surfactants:
a. Microemulsions
b. Self microemulsifying drug delivery systems

II. Chemical Modifications:

A. Salt Formation
B. Co-crystallisation
C. Co-solvent
D. Hydrotropy

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release

profile of these drugs, it is possible to enhance their bioavailability and reduce side effects.

To improve the dissolution and bioavailability of poorly water soluble drugs researchers have employed various techniques such as micronization, salt formation, complexation with polymers, change in physical forms, use of prodrug. Amongst the various approaches, sonocrystallization or melt sonocrystallization is the newly employed particle engineering or crystal engineering technique and has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous.

From the pharmaceutical point of view, today particle engineering or crystal engineering is advanced technique for manufacturing of control particle size of API than traditional techniques such as micronization or size reduction.

It also divides in two parts or types i.e.
1) Top-down method
2) Bottom-up method
1) Top-down method:

It includes the size reduction i.e. destructive method for manufacturing mesoscopic particles such as by using fluid energy mill, micronization, jet milling. It gives the desired particle size powders but disadvantages are[23, 24]

- requires high energy/generate heat
- damage the crystal surfaces
- This leads to highly charged, cohesive particles, so results in the chemical and physical instability of the drug.
- Particle properties may vary from batch to batch.

2) Bottom-up method:

Also known as constructive method or "molecule to particle" technique. In these method one starts from molecules in solution, the molecules are aggregated to form particles, being amorphous / crystalline[23,24].
1) Sonocrystallization
2) Nanosizing

Offer an alternative approach for destructive technique. Hence also recommended by USFDA as quality by design, initiative method and provide superior product quality.

- **Advantages[24]:**
- Alternative approach over traditional or conventional crystallization results from cavitations
- Large amount of energy transferred to reagent molecule in an extremely short time
- Due to cavitations, microbubbles are formed which are short lived micro-reactors.

- **Disadvantages[24]:**
- Cavitations damages the ultrasonic devices and creates problems with ultrasonic probes

1.4 Melt Sonocrystallization Technique :

Melt sonocrystallization (MSC) is novel particle engineering technique, which is combination of melt solidification and ultrasonication, which enhance collisions in molecules of the melt, improve nucleation rather than crystallization. It favours melt solidified bonds and hard surfaces and thus gives porous, amorphous material with high stability. Also called it as a surface modification technique of particles or materials.

Melt sonocrystallization (MSC) is promising technique of sonocrystallization to obtain porous,
amorphous material with high stability and for this purpose probe sonicator or ultrasonic homogenizer instrument[21] is used as shown in Fig no.2(sol enh 12) Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz

1.4.1 Advantages and Disadvantages of MSC[22, 24]:

- **Advantages[29]:**
- Fewer processing steps needed thus time consuming method.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- ✓ Ultrasound to control crystal formation and nucleation.
- ✓ Conversion of crystalline nature to amorphous nature.

✓ Particle rounding potential to improve flowability.
✓ Enhance yield.
✓ De-agglomeration.
✓ Improve crystal purity and physical properties.
✓ Increase reproducibility, robustness, solubility, stability and product quality.
✓ Eliminate seeding
✓ No sonicator contact
✓ No use of organic solvents
✓ No use other excipients such as polymers

➢ **Disadvantages:**

✓ Several drugs can be degraded by the melting process can be a limitation of this method
✓ The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved
✓ There is the possibility that during processing (mechanical stress) or (temperature and humidity stress) the amorphous state or structure of agglomerates may be changed
✓ Poor scale-up for the purposes of manufacturing
✓ Cannot be used at large commercial scale

1.5 Instrument Used:

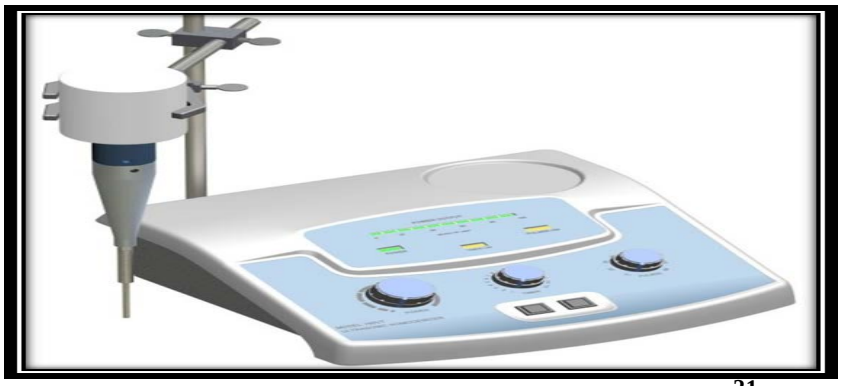


Figure 2: Ultrasonic Homogenizer or Probe sonicator[21]

1.6 Components Of Ultrasonic Homogenizer Or Probe Sonicator[21]:

Table 2: Components of Ultrasonic Homogenizer or Probe sonicator

SR.NO.	COMPONENTS	RANGE
1.	Voltage	115 V/60Hz
2.	Processing Volume	200 µl- 300ml
3.	Tip Diameter	½" (12.7mm)
4.	Power Output	0-150 WATTS
5.	Output Frequency	20 kHz
6.	Timer	0-15 Minute
7.	Amplitude	0 -80%
8.	Pulser	0-90%
9.	Display Type	LED

1.7 Core Details of MSC:

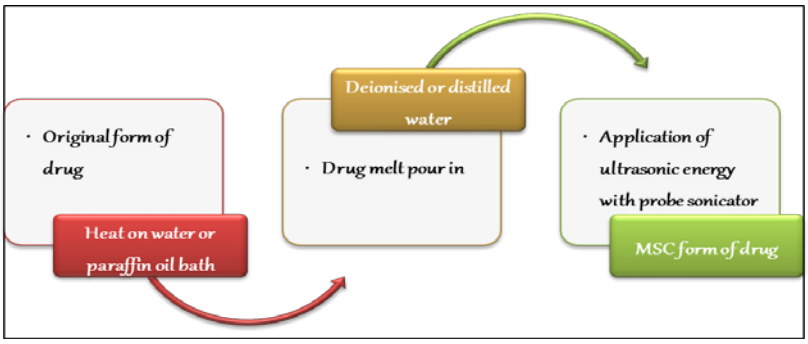


Figure 3: Core Details of MSC

1.8 Ultrasound and Its Implementation[22,24,30]:

1.8.1 Power of Ultrasound[30]:

Ultrasound is a sound–like oscillations of pressure travelling through the air, defined as a mechanical wave propagating through any form of matter(gas, liquid, solid etc) at a frequency higher than 20 kHz. Sonocrystallization or ultrasound-assisted crystallization, relies on the power-ultrasound (20–100 kHz) and extended-sonochemistry (100 kHz–2 MHz) bands of the acoustic-frequency range. By comparison, human hearing responds to frequencies between 20 Hz and 19 kHz.

Sonocrystallisation is the use of ultrasound for influencing the crystallisation of liquids, either melts or solutions. The energy of ultrasound fashions consecutive compression and expansion as shown in figure no.4 process of sonocrystallization[7]. After several cycles a bubble forms and grows then collapses. The collapse of the bubble provides energy to promote the nucleation process. This results in a highly repeatable and predictable crystallization process[27].

Ultrasound may be applied in two ways or at frequencies:

1) High-intensity
2) Low-intensity

At high intensity, ultrasound is applied to alter physic-chemical characteristics of matter irreversibly. And at low intensity of ultrasound, it produces non-destructively study structural properties of materials.

It induces the particle or molecular motion, from which various effects are derived such as heat, stirring, chemical activity, mechanical stress, cleansing, which are responsible for changes in structural and chemical properties of materials[20].

- **Heat:**

As ultrasound progresses through a medium, energy is lost to the medium in the form of heat. At certain interfaces, energy absorption may be high because of shear (friction) across the interface. In addition, the amount of energy converted to heat is directly bonding between proportional to the amplitude of ultrasonic vibration.

- **Stirring:**

Intense ultrasound will produce violent agitation in dispersed material by accelerating the random motion of the particles in the material.

- **Chemical effects:**

Chemical activity, especially oxidation reactions, may be accelerated. This has been attributed to the heat that is generated and also to stress-associated molecular breakdown. Ultrasound has been reported to promote polymerization or de-polymerization depending upon the nature of the molecules being treated.

- **Mechanical effects:**

Stresses developed in an ultrasonic can cause ruptures in materials and severe erosion of surfaces. They may also cause relative motion between which produce selective absorption at the particle surfaces.

- **Cleansing:**

Sometimes a protective coating is removed acoustically from a surface which will allow reactions between two materials that would not be possible otherwise.

In terms of pharmaceutical powder compression high-intensity ultrasound is used and a number of the above mechanisms may be involved to aid the production of a coherent compact[20].

The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation[9].

1.8.2 Process Parameters[25, 26]:

- Solvent and anti solvent choices
- Solubility
- Temperatures of solvents and anti solvents
- Ultrasonic power
- Concentration of feed solution
- Productivity

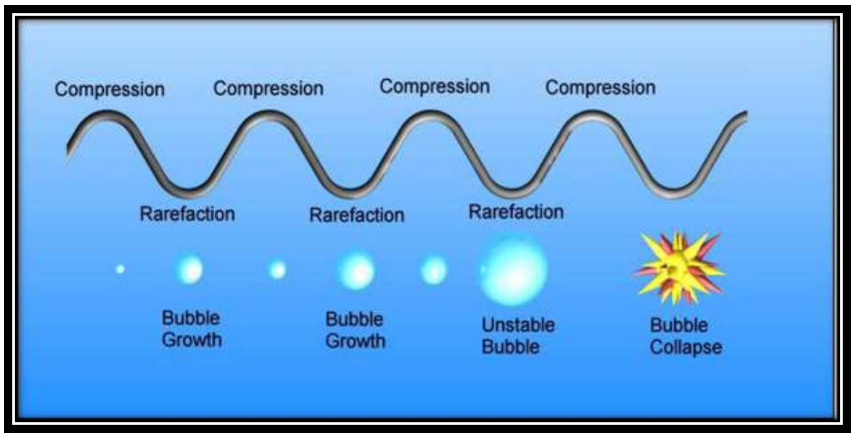


Figure.4: Process of Ultrasound in Sonocrystallization

1.9 Kinetics of The Sonocrystallization[18,25]:

✓ **Sonocrystallization consists of major events:**

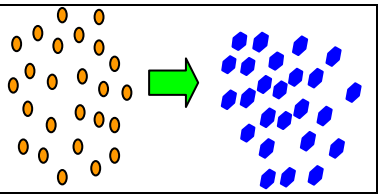
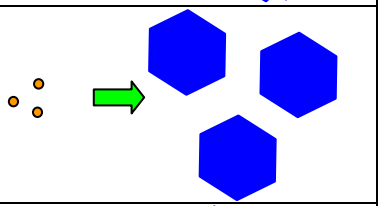
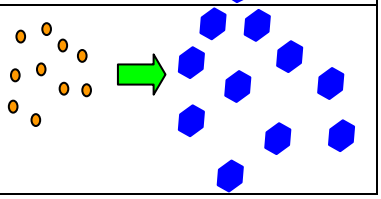
It is consequence of molecular aggregation in a solution, leading to the formation of nuclei and, later, crystal growth. Cavitations, Super saturation, nucleation and crystal growth are the predominant physical phenomena associated with crystallization.

✓ **Cavitations:**

The application of ultrasound to liquid causes the cavitations in the processing liquid. These cavitations create bubbles with successive cycles of compression and rarefaction. Then bubble get collapsed after some time, with extreme region of temperature, pressure and shock waves. Then shock waves may be contributing to super saturation with nucleation somewhat remote from the cavitations events.[25] Cavitation not only improves mixing but also increases the diffusion of molecules towards a precrystal cluster or nucleus.

➢ **General Rules on the Effects of Cavitations**

Table 3: Control of crystal size

1) Continuous insonation produces many nuclei resulting in small crystal	
2) Using insonation to only initiate reaction allows larger crystals to grow	
3) Pulsed insonation gives a combination effect	

- **Supersaturation:**

Supersaturation is the basic driving force for crystallisation and is defined as the concentration of the solute in excess of saturated concentration under given conditions of temperature. It is composed of two zones, the metastable and unstable zones. The two zones are defined so that the metastable region shows crystals growing without nucleating, whereas in the unstable region crystals appear after nucleation.

- **Nucleation:**

Solute molecules gather to form clusters and then critical size is developed to constitute nuclei. Nucleation is the first decisive step in crystal formation, due to random movement of molecules or particles, they collides with each other, which leads to the formation of pre-nucleating clusters. As the population of these clusters increases, they associate to form an embryo. The embryos are not large enough to grow into a crystal in the existing supersaturation. Some embryos – through additional collisions – grow into nuclei (tiny crystallites of the smallest size capable of independent existence), contributing to the formation of macroscopic crystals in the process termed crystal growth. Two controlling processes that can be rate-limiting are:

➢ the diffusion-controlled formation of a liquid-like cluster of solute molecules; and/or
➢ the organization of clusters into an ordered crystalline structure, see Figure 5.

In the nucleation phenomenon, it reveals that nucleation initiation happened in between the volume and surface terms. In terms of volume it favours aggregation as an exothermic process, leads to reduction in Gibbs free energy throughout the system. While, In terms of surface the molecular aggregates get dissolved, or otherwise be nucleating, by utilising energy. Nucleus is the critical radius of molecular aggregates because, pre-nucleating clusters and embryos has a high surface - volume ratio to dissolve.

- **Crystal growth:**

Crystal growth is the gathering or association of the crystallizing components on a crystal. The two main mechanisms operating here are the diffusion of molecules from bulk to the crystal surface and surface integration, i.e. the incorporation of a growth unit into a lattice. A higher level of supersaturation boosts the nucleation process. However, nucleation is more energetically demanding than crystal growth and there are supersaturation regions within metastable zones where crystal growth proceedes while nucleation is suppressed.
In short, In the nucleation stage submicroscopic crystal nuclei are formed which develop into larger crystals during the subsequent growth stage. With homogeneous nucleation the crystals are formed directly from the liquid. Heterogeneous nucleation is nucleation mediated by foreign particles already present in the liquid. Secondary nucleation is nucleation mediated by pre-existing crystals. It is believed that the process of the present invention predominantly affects homogeneous nucleation[18, 19].

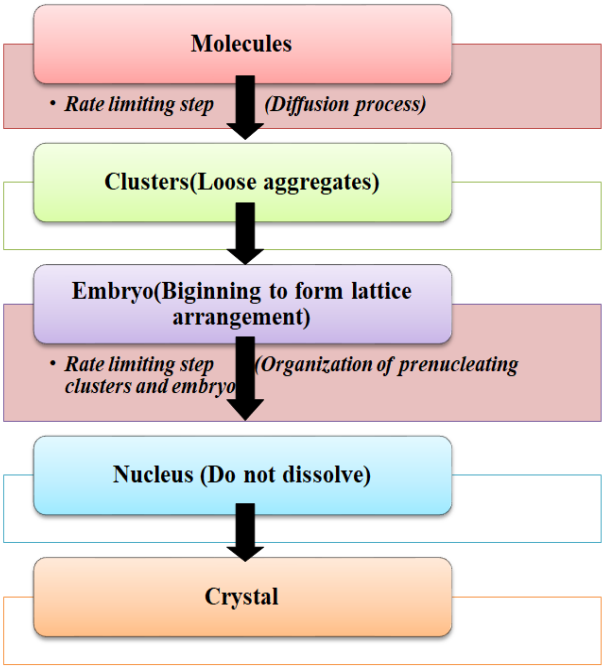


Figure 5: Process of crystal formation with rate limiting steps

1.9.1 What happen when liquid or mixture exposed to ultrasound? [18, 19, 25]

When a liquid is exposed to ultrasound, microscopic gas/vapour bubbles are formed which show a dynamic pulsating behavior. The activity of such ultrasound- induced bubble behavior is denoted as cavitations. At relatively low sound intensities the bubbles do not perish but exhibit stable volume and/or shape oscillations. This type of cavitations is denoted as "stable" or "non-inertial" cavitations. When the ultrasound intensity is increased and exceeds a certain limit, the cavitations threshold, the nature of cavitations changes dramatically which results in the bubbles becoming unstable. Within a fraction of a sound cycle they show rapid growth followed by a violent collapse. The collapsing gas bubbles produce very high pressures and temperatures locally in the bubble as well as a high pressure in the liquid layer surrounding the bubble. Cavitations which shows this violent bubble behavior is denoted as "transient" or "inertial" cavitations.

1.10 Small particles and sonocrystallization:

Sonocrystallization can be applied at any stage of pharmaceutical manufacturing. Most ultrasound work has used either intense probe or ultrasonic bath based equipments. The technique uses transient acoustic cavitations to promote nucleation in the field of metastable solution. If one controls nucleation, it helps to improve in crystal size distribution, morphology, impurities and solid-liquid separation, and it also induce secondary nucleation by mechanically disrupting crystals or loosely bound agglomerates. These molecule to particle engineering technique using ultrasound in which water is used as anti-solvent, favors the advantages of the excellent dispersive.

The drug (having low melting point) melted at low degree than its melting point in a water bath, must be added to the anti-solvent as a water, the ultrasound can be applied using an immersed ultrasonic probe at an optimal rate to generate a dispersion and then eventually, micrometer or sub micrometer sized particles. The form of dispersion depends upon ultrasonic energy. Acoustic cavitations occurs during initial mixing, amorphous particles are produced. Even the continuous ultrasound after mixing leads to formation of crystalline sub micrometer-sized particles through a solution mediated amorphous to crystalline transition.

Sonocrstallization typically helps through a process that disperses the melted liquid into the anti-solvent water, solidifies the melted droplets, and gives the amorphinized particles.

1.10.1 Properties, Advantages of MSC agglomerates:

Agglomeration is a size enlargement process in which primary particles stick together to form agglomerates. Agglomeration is the most widely used pretreatment method for the production of powders with altered solid state properties. Bulk density, angle of repose and compressibility play significant role in flowability of bulk solids. A study was carried out using Hausners ratio and angle of repose as indicator to determine powder flowability. It was revealed that increase in the particle size of a agglomerates results in decrease in cohesiveness.[31]

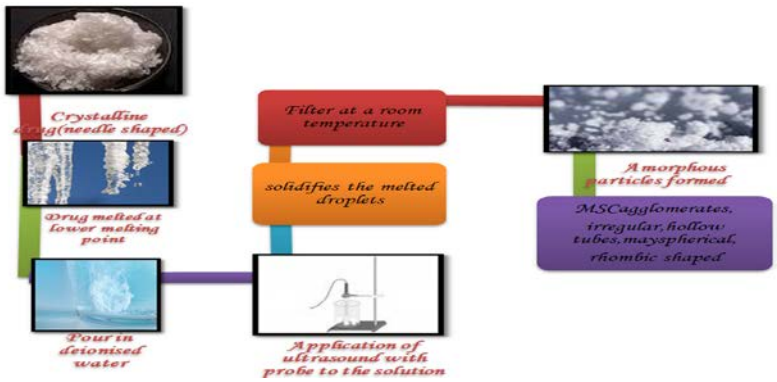


Figure 6: Procedure of formation of MSC agglomerates

➢ **Product properties:**[32]

- Size distribution:

It is generally accepted that, narrow size distribution is best, and thus need post compression properties. And if find wide distribution, it is better to pack and compress improving tablet properties.

- Porosity:

The amount of free air space in agglomerates is significant and provides better dissolution ability.

- Dissolution rate or time:

Dissolution time is important key factor, as the agglomerates formulated may dispersed in the medium.

- Strength and shape:

Strength and shape is very important as it influences bulk properties such as flowability and processing behavior.

- used successfully to manipulate crystal size-distribution, hence to modify solid/liquid separation behaviour
- product purity, product bulk density
- powder flow characteristics
- Smooth surface

➢ **Advantages**:

- Particles with reduced particle size
- Particles with improved flowability.
- Particles with higher porosity
- Drugs in slight amorphous state with different crystal habit
- Water used as solvent instead of organic solvent

1.10.2 Benefits of Ultrasound to sonocrystallization results in[7,22,24]**:**

- Nucleation at the lowest level of super saturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution
- The use of ultrasound provides a non-invasive way of improving crystal properties and process control.
- Non-invasive means no added chemicals or additional mechanical treatment.
- Narrowing of the metastable zone width
- Narrow particle size distribution
- Decrease in the level of cooling necessary to achieve crystallization
- Highly repeatable and predictable crystallization**.**
- Polymorph control
- Removal of secondary unit operations (milling etc)

1.10.4 Limitations:

- Creates very high intensity field
- Cannot transmit into large process volume, hence precludes scale-up
- Increased stress on material, more likely to fail
- Good for laboratory studies but,
- Cannot be used at large commercial scale.

But it not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients[9].

Two of the methods used in industrial level are Ultrasound Mediated Amorphous to Crystalline Transition (UMAX®) and Dispersive Crystallization with Ultrasound (DISCUS®) for the development of inhalational drug delivery. Kamel, 2008, enhanced the dissolution characteristics of Flurbiprofen using melt sonocrystallization technique, Chaudhari and co-workers, 2009, studied the process on Valdecoxib and Paradkar and co-workers,2010, analyzed the various polymeric form of Progesterone[9].

Power ultrasound assisted particle engineering technologies such as Solution Atomization and Crystallization with Ultrasound (SAX™) and now UMAX®, along with Dispersive Crystallization with Ultrasound (DISCUS® - an ultrasound assisted antisolvent method used to promote efficient solute / solvent diffusion into the antisolvent and the formation of microcrystals), can be used for the manufacture of optimal particles designation and formulation. For SAX™, UMAX® and DISCUS® the process conditions must be chosen to maximize crystal nucleation at the expense of growth, via the generation of high supersaturation either in the atomized droplets or liquid dispersion. Acoustic cavitation improves crystallization via improved mixing, increased molecular diffusivity and clustering, and dramatic temperature / pressure changes [26].

1.11 Drug release from Melt sonocrystallized agglomerates:

While a number of potential and realized advantages of melt sonocrystallization have been described, the single most widely cited consideration is the improvement in dissolution rate, with concomitant implications for improving the bioavailability of poorly water-soluble drugs. Such improvements in dissolution rate are often considerable, with increases of up to two to four fold having been observed. It is therefore all the more remarkable that the mechanism underpinning these increases is so poorly understood. Currently accepted range of possible mechanisms of enhanced dissolution includes the following:

- **Particle size reduction and reduced agglomeration:**

Particle size is a critical characteristic that affects dissolution rate and, consequently, therapeutic effect of a poorly-soluble API. Generally, smaller particles have higher intrinsic solubility than larger ones. The existence of a higher interfacial free energy on smaller particles is responsible for formation of a thermodynamically unstable system that causes greater dissolution of them. Particles of the same size but with different surface morphologies may exhibit different dissolution times as well. Particles with a rough surface have larger specific surface areas and, consequently, greater dissolution rates[30].

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of melted drug in solution and its mixture, it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation.

- **Increased solubility or dissolution rate of the drug:**

In addition to the first mechanism of drug release enhancement it is expected that *Cs*, the solubility of the drug, might be increased with melt sonocrystallized systems. Finally, changes in the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category.

Temperature, pressure, the nature of the solvent, crystal characteristics, pH, and the presence of additives are the main factors affecting the balance of intermolecular forces between solvent and solute and, consequently, solubility. In addition to the above mentioned factors, particle size, shape and surface roughness of a drug determine the dissolution rate of the API powder. Improving the dissolution rate is extremely important in the case of poorly water-soluble drugs[30].

The physical state of the drug in melt sonocrystallized systems is often transformed from crystalline to amorphous and the dissolution surface increases because of particle size reduction. The presence of the ultrasound with probe improves the contact between the drug and the dissolution medium and impedes aggregation and agglomeration. The ultimate in particle size reduction are solid solutions in which the drug is molecularly dispersed in the solvent.

1.12 Applications of Ultrasound In Pharmaceutics:[37]

- **In the formation of aerosols :**
- It is reliable for use of ultrasound to prepare aerosols with reduced particle size, which is energy intensive, time consuming. Because sonocrystallization produces smaller sized crystals as compare to conventional crystallization. For example, Sodium chloride, Salbutamol sulphate.
- **To improve flowability and compressibility and For increasing solubility and dissolution rate of poorly soluble drug**:
- Poorly soluble drug possesses a problem regarding aqueous solubility and somewhat crystalline in nature. Thus by inducing treatment with ultrasound for these drugs, it may help to alter or modify physico-mechanical properties of drug, and hence improve the solubility and flow properties of drugs.
- **In transdermal drug delivery**:
- Attractive way of transdermal drug delivery system is that, it offers several advantage over oral and parentral drug delivery system. It avoids first pass metabolism, elimination of pain due to reduction of

particle size with use of ultrasound. It offers absorption of drug through skin. 10 MHz ultrasound for 20 minute resulted in a 4-fold increase and 16 MHz ultrasound resulted in about a 2.5-fold procedure is increase in transdermal salicylic acid transport.

- **Effect of ultrasound in chemotherapy, cell therapy:**
- Ultrasound has been used in diagnostics, biological cell disruption, medical imaging. Traditional preparations used for delivery of drugs include ointments, gels, creams and medicinal plasters containing natural herbs and compounds. The development of the first pharmaceutical transdermal patch for motion sickness. Further the expansion of transdermal drug delivery usage new therapeutic areas includes Parkinson's disease, hyperactivity disorders.

By combining the ultrasound with magnetic resonance imaging, it targets the tissues (e.g., brain, breast, liver tumors) and helps to develop the drug delivery at site of action with effective dose.

- **Effect of ultrasound on the synthesis of drugs:**
- Sonochemistry has been used for many years, for fast reactions and synthesis of products with use of ultrasound. Because it takes less time to complete reaction and higher yield.

- **Role of ultrasound in different processes of extraction:**
- The use of ultrasound in plant extraction demonstrated for the compound of interest to the pharmacology and food industries also. It reduces maceration time, in the extraction of the alkaloid reserpine from Rawolfia Serpentina. With the use of Gas Chromatography has been developed for the determination of nicotine in pharmaceutical formulation.

- **Applications of ultrasound in pharmaceutical tableting:[20]**
  - To Aid the Direct Compression Method
  - To Improve Powder Flow, Tablet Density, and Uniformity
  - To Improve Tablet Mechanical Strength
  - To Avoid Tablet Capping and Lamination

- **Limitations of Ultrasound-Assisted Compression of Pharmaceutical Powders:[20]**
- Possible potential for material decomposition.
  - Additional cost
  - Unclear safety considerations.
  - Lack of understanding of the mechanisms

1.13 Work done on drugs for MSC techniques are summarized below:

Table 4: Work done on drugs for MSC techniques

Sr.No.	Active pharmaceutical ingredients
1.	Ibuprofen
2.	Celecoxib
3.	Flurbiprofen
4.	Valdecoxib
5.	Progesterone
6.	Naproxen
7.	Paracetamol, Indomethacine sand Mefenamic acid
8.	Piroxicam

Conclusion:

Melt sonocryatallization is newer particle engineering technique involved utilization of ultra sound energy on soft or viscous molten mass to create fine particles of drugs that helps to improve aqueous solubility and bioavailability. Melt sonocrystallization offers solvent and carrier less technique for the formation of fine particles which makes this technique more promising for the enhancement drug solubility in water.

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