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"Antisolvent Crystallization: A Novel Approach to Enhancement of Drug Bioavailability"

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ABSTRACT:
The enhancement in bioavailability of the drugs is one of the most important concerning aspects of the pharmaceutical industries. Preparation of nanoparticles or microparticles of these drugs is the newest formulation strategies. The size and morphology of a drug are affecting several essential pharmaceutical properties. Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. The particle technology involves several approaches from the conventional size reduction processes to the Novel particle technology that modify the solubility properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage forms. An antisolvent crystallization technique is being used to prepare nanoparticles or microparticles for poorly water soluble drugs at research scale. This method has an ability to change the solid-state properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Therefore, various operating variables and their effect on the particle size of poorly water soluble drugs in an anti-solvent crystallization has been discussed. This review highlights the advantages of anti-solvent crystallization for improving solubility, dissolution and bioavailability of drugs with poor aqueous solubility.

KEYWORDS: Anti-solvent Crystallization, Sonocrystallization, Poorly water soluble drugs, Ultrasound, Operating variables.

I. INTRODUCTION:

Approximately 40% of drugs in the industry are falling in the category of low solubility–high permeability (Class II), and low solubility–low permeability (Class IV). These classes have the limited bioavailability of drugs due to their low solubility and dissolution rate. The bioavailability is defined as the percentage of the quantity of the drug absorbed compared to its initial quantity of dosage, which can be improved by a decrease in their particle size.[1] The dissolution rate of the active pharmaceutical ingredient (API) is proportional to the available surface area for dissolution as described by the Noyes–Whitney equation and, in addition, by an increasing the solubility of nanosized API is also expected to enhance the dissolution rate as described by the Ostwald–Freundlich equation.[2]

The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. It also governs the possibility of parenteral administration of a drug and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an equilibrium measure but also the dissolution rate at which the solid drug or drug from the dosage form passes into solution is critically important when the dissolution time is limited. Poorly water soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, Micellar solubilization, hydrotropy etc.[3]

Crystallization is the process of atoms or molecules arranging into a well-defined, rigid crystal lattice in order to minimize their energetic state. The smallest entity of crystal lattice is called a unit cell, which can accept atoms or molecules to

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grow a macroscopic crystal. During crystallization, atoms and molecules bind together with well-defined angles to form a characteristic crystal shape with smooth surfaces and facets. Crystallization is a commonly used for the isolation of active drug substances from the final stage of a synthesis. It is used for product purification and consolidation as a convenient solid form. As a purification technique, crystallization relies on the stringent structural requirement for crystal formation to exclude impurities. Crystallization from solution can be thought of as a two step process. The first step is the phase separation (or birth) of a new crystal which is followed by the growth of crystals to larger size. These two processes are known as nucleation and crystal growth. The birth of new crystals, which is called nucleation, refers to the beginning of the phase separation process. The solute molecules have formed the smallest sized particles possible under the conditions present. The next stage of the crystallization process is for these nuclei to grow larger by the addition of solute molecules from the supersaturated solution. This part of the crystallization process is known as crystal growth. Crystal growth, along with nucleation, controls the final particle size distribution obtained in the system.[4]

Nanoparticles can be obtained either by top-down approach or bottom-up approach.[5] The top down approach involve the mechanically reduction of previously formed larger particles by the technologies available like; jet milling, pearl mill, spiral media milling technology, and high pressure homogenization. However, these techniques are not efficient due to high energy input and denaturation during the milling process.[6] In contrast, the approach known as bottom up which includes antisolvent precipitation technology is rarely applied. As compared to milling and high pressure homogenization (top-down approach), antisolvent precipitation (bottom up approach) is simple, cost effective, and easy to scale-up.[7]

Anti-solvent crystallization can be used as a substitute for cooling or evaporation crystallization. An anti-solvent crystallization can alter the physical properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Antisolvent crystallization can be used in the production of submicronic particles of pharmaceutical compounds as well as in the manufacture of crystals that require an enhanced drug release rate. Indeed, the polycrystalline drug particles with higher amorphous portions exhibit a faster dissolution rate in solutions. In general, three types of fluids: gas, liquid and supercritical fluids can be employed as anti-solvents. In addition, water can be used as an anti-solvent as it has a low solubility toward most drug compounds and the relatively high miscibility with few of polar solvents. Therefore, additional experimental parameters like; ultrasonic waves can be applied through the crystallization process. The use of ultrasound during the crystallization process is known to affect the rate of nucleation and crystal growth and, also, it can alter the physical properties of the resulting particles. Primarily, it is applied to reduce the particle size of the crystals.[8] Hence, in the present review paper, effect of operating variables on anti-solvent crystallization of poorly water soluble drugs have been surveyed relating to crystal size distribution and their morphology.

II. ANTISOLVENT CRYSTALLIZATION

Antisolvent crystallization has been used to produce granules or powders of drugs and polymers. The technology employs an antisolvent in order to precipitate a dissolved compound in various organic or inorganic solutions. An important feature of the antisolvent crystallization method is that it eliminates the use of thermal energy which can degrade the activity of the temperature sensitive materials such as fine chemicals and pharmaceuticals. In addition, water can be used as an anti-solvent as many drugs are poorly soluble or practically insoluble in it and has high miscibility with polar solvents.[9]

2.1 Antisolvent crystallization process

Anti-solvent crystallization is the separation and purification method which is used as an effective way to prepare micro to nano-size drug particles. This technique produces crystals from solutions and controls the crystalline properties such as particle size and their morphology. The use of the antisolvent in crystallization reduces the solubility of a solute in the solution and to induce rapid crystallization. The physical and chemical properties of the antisolvent can alter the rate of mixing with the solutions and thereby affect the rate of nucleation and crystal growth of the crystallizing compounds. Additionally, parameters of crystallization experiments strongly influence the mechanism of particle formation and govern the form of crystal size and its distribution. Generally, the antisolvent contains hydrophilic stabilizer (i.e. Surfactants) which is absorbed on the crystal surface to inhibit crystal growth. Hydroxypropyl

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methylcellulose (HPMC) is a non-toxic in nature and has good hydrophilic property which is widely used as thickening, emulsifying and stabilizing agent in food and pharmaceutical formulations.[10] However, this technique involves some basic problems, i.e. Difficulty in maintaining the size of the particles produced after precipitation, usually with a rapid growth rate which leads to a broad particle size distribution (PSD). The technique involves dissolution, followed by precipitation and then drying. Thus, the mechanical energy input is minimized but the resulting nanoparticles might be crystalline or amorphous and also depending on the process conditions. Even if the particles are crystalline, the crystal growth rate must be controlled to limit the particle size. Also, Poor micro mixing during anti-solvent process leads to accidental zones of local super saturation and, therefore, aggregation of particles. In contrast, ultrasound proves to be a feasible mixing method to provide uniform conditions throughout the vessel during antisolvent process.[11]

In these processes, different methods of mixing and flow configurations of solutions and anti solvents have been adopted to optimize the properties of the resulting crystals. The operations were performed in either a batch or continuous type, and sometimes the antisolvent acted as a dispersion media to improve the micronization of the precipitated particles. The use of a gas- or supercritical fluid anti-solvent eliminates the concerns regarding residual anti-solvent remaining on the crystal surface and the anti-solvent can be separated easily from the solution. In fact, the residues of solvent used as an anti-solvent could be not only found on the crystal surface, but also entrapped inside the crystals, it is even more difficult to remove them. In addition, gas or supercritical fluid anti-solvent process, however, the crystallization process should be performed in a high pressure apparatus to maintain the anti-solvents under a high pressure or in a supercritical state.

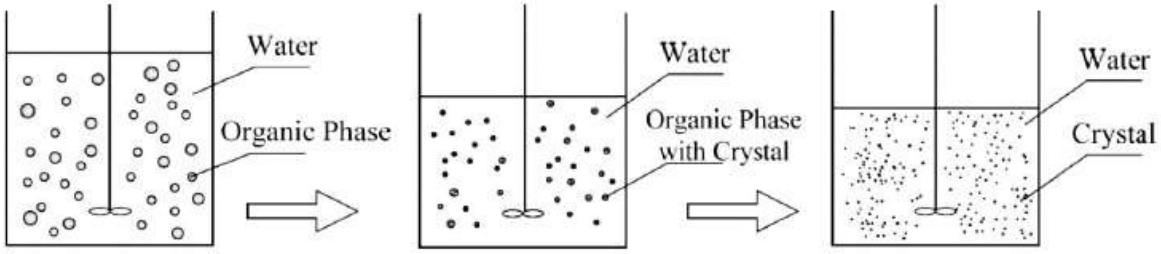

Fig No: 01 Anti-Solvent Crystallization method.

2.2 Ultrasound assisted antisolvent crystallization

Now a day, ultrasound has received much attention to be used as an effective measure to influence the nucleation in crystallization processes. The use of ultrasonic waves in crystallization has been increased at laboratory scale because, (i) rapid and uniform nucleation throughout the syndicated volume leads to smaller and uniform-sized particles, and (ii) reduction of agglomeration of particles and controlling the number of nuclei. The mean particle size and its distribution can be effectively controlled by adjusting ultrasound variables such as the power intensity and ultrasonic time during crystallization. Sonocrystallization can also be used for the high energy materials which are sensitive to friction and impact during size reduction by mechanical means.[12]

When ultrasound waves propagate through a liquid medium, its power will initiate an important phenomenon known as cavitation. The formations of cavitational bubbles are occurring during the negative pressure period of the sound wave. These bubbles will grow up to their resonance size and then they implode, generating a localized hot spot with a high temperature and pressure including the release of powerful shock waves. The power of ultrasound and cavitation phenomena will initiate the nucleation and thereby crystal growth in a crystallization process. The use of ultrasound may also influence the solubility and thereby the super solubility. It can also alter the crystal habit as the ultrasound can increase or decrease the growth rate of certain crystal faces. Localized hot spots may influence the crystal lattice and have some effect on the crystal habit change due to abrasion.[13]

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2.3 Mechanism of ultrasound in crystallization:

They are two types of mechanism involved in nucleation: cavitation and acoustic-streaming

Power ultrasound has been proved to be a promising technique to assist or enhance the crystallization processes due to the following reasons:

- Power ultrasound induces the formation of cavitation bubbles, which is safe because it does not introduce any impurities, and the bubbles act as nuclei themselves
- It affects the primary nuclei, thus creating more crystals.
- It can enhance the rate of mass and heat transfer in the process of crystal growth, thus achieving small, even-distributed and round crystals.

The effects of power ultrasound on nucleation are mainly focused on 3 parts:

- The primary nucleation assisted by power ultrasound,
- The secondary nucleation assisted by power ultrasound,
- The process of crystal growth.[14]

2.4 Ultrasonic cavitation

The most important effect of ultrasound in crystallizing systems is the cavitation, the opening and subsequent implosion of gas or vapour bubbles with a typical diameter of 10-15 µm. The primary effect of ultrasound on a continuum fluid is to impose a vibration pressure on it. At low intensity this pressure wave will induce motion and mixing with in the fluid, this process is known as acoustic streaming. At higher intensities, the local pressure in the expansion phase of the cycle falls below the vapour pressure of the fluid, causing minute bubbles or cavities to grow. A further increase generates negative transient pressures within the fluid, enhancing bubble growth and producing new cavities by the tensioning effect on the fluid.[14]

III. 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.[15]

3.1 Principle of antisolvent Sonocrystallization

- In this process amount of drug is dissolved in suitable solvent (this is saturation solution)
- The saturation solution is added to antisolvent (drug is slightly soluble) drop wise.
- Solvent and antisolvent should be freely miscible.
- Drug should not be miscible with the antisolvent and should preferentially wet the precipitated crystals.[16]

3.2 Mechanism of Antisolvent Sonocrystallization :

The mechanism includes both crystallization and cavitation, measurable variables such as induction time and crystal size distribution are commonly used to examine the effect of Sonocrystallization. Typically observed effects are: a decrease in the metastable zone-width and induction time, reduced crystal size and narrower size distribution, better control of nucleation rate and reproducibility, and polymorph selectivity. It is possible that the intense mixing induced by US increases the opportunity of collisions of solute molecules, and allows them to penetrate the stagnant film adjacent to the crystal and jump into the crystal lattice more easily. The effects induced by US, with the crystals obtained under sonicated conditions being superior in terms of uniformity with respect to size and shape. Crystals obtained with sonication are more regular, and no agglomeration. Various fundamental mechanisms behind this phenomenon, the theories have been grouped based on which crystallization step is affected, which are primary and secondary nucleation, and growth and fragmentation. For primary nucleation, homogeneous and heterogeneous nucleation have been split, listing the effects on the super saturation ratio, on clusters formation, on the critical free energy and on the Mass Diffusion, as part of the Homogenous Nucleation.[16]

3.3 Physicochemical properties of drug crystal prepared by antisolvent Sonocrystallization

1) **Particle size and shape:** crystallization change in crystal habit of pharmaceuticals gives different physicochemical properties.
2) **Stability:** stability does not change crystallinity to amorphous during storage

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process there is no change in stability of drug substances.

3) **Solubility:** In the prepared crystals changes in internal energy of the molecules play an important role to increase solubility.
4) **Dissolution rate and bioavailability:** Prepared crystals Particle size, solubility, particle density and specific surface area increases the dissolution rate and Bioavailability.

IV. EFFECT OF OPERATING VARIABLES

4.1 Effect of Drug Concentration:

The drug concentration and the size of the precipitated particles are inversely proportional to each other. The size of precipitated drug particles decreases with an increase in the drug concentration. This ratio explains how the drug concentration in the solutions from which the drug crystallises affects the nucleation rate. Depending on the drug solution's concentration, the degree of super saturation can change the rate of nucleation. The large number of nuclei produced by the high rate of nucleation results in a rise in the number of crystals, which could reduce the size of each crystal. This phenomenon observed might be due to the formation of the number of nuclei at the solvent/antisolvent interface and the influence on the viscosity of drug concentration. Particle aggregation results from a large number of nuclei decreasing the diffusion from solvent to antisolvent. A rise in the drug solution's viscosity prevents the drug from diffusing between the solution and the antisolvent, leading to non-uniform super saturation and agglomeration. The reverse trend was observed that the higher stirring speed (1000 rpm) that the size of particles decreased as the concentration was increased from 5 to 15 mg/ml. From this observation, it can be interpreted that, as mixing increases, the super saturation effect dominates the agglomeration effect of drug concentration. Therefore, the smaller particles are produced at a higher stirring speed, or even at higher drug concentrations.[17,18]

4.2 Effect of Drug Solution Flow Rate:

The particle size is controlled by the rate at which the solution and antisolvent are mixed. The faster and slower mixing of the two liquid media produces smaller and the larger crystals, respectively. At a low flow rate, the mixing efficiency of solvent/antisolvent becomes lower, which increases the prolonged crystal growth process and results in the formation of larger crystals. In contrast, increasing the flow rate increases the mixing of the amount of solvent/anti-solvent per unit time results in the shortest of time for allowing the crystal growth and forms smaller crystals.[19]

4.3 Effect of Temperature:

According to crystallisation theory, that the rate of nucleation is inversely proportional to temperature. Therefore, it is considered that the temperature is a key regulating factor that can affect the final particle size and its distribution. According to general observation, larger crystals are produced when the crystallisation process takes place at higher temperatures. The particles that precipitated at 30°C had an irregular flake-like morphology and a mean size of about 2 m, whereas the particles that precipitated at 3°C had a rod-like morphology and a mean size of around 240 nm. At low temperature, the solubility of the drug in the solvent-antisolvent mixture decreases, which results in a higher super saturation condition. Therefore, low temperature would decrease the diffusion and growth kinetics at the crystal boundary layer interface. As a result, smaller drug particles are obtained at low temperature.[20]

4.4 Effect of the Solvent to Antisolvent (SAS)Volume Ratio:

An important factor that impacts particle size is the volume ratio of the solvent and the antisolvent. As the ratio increases, the particle size decreases drastically. When the drug solution is added to the antisolvent, rapid reduction in the drug concentration occurs with an increase in the amount of antisolvent, leading to rapid precipitation of the drug into nanoparticles. Furthermore, a greater amount of antisolvent leads to a greater nucleation rate and produces smaller nuclei and simultaneously the growth occurs. In the subsequent growth, the higher antisolvent amount increases the diffusion distance for growing species and consequent diffusion becomes the limiting step for the growth of nuclei.Compared to the crystal growth rate, the nucleation rate is more dependent on super saturation and has a significant impact on the final particle size distribution. The critical size and the logarithm of the super saturation ratio are inversely correlated. Therefore, high super saturation conditions result in small particles due to the formation of large numbers of nuclei.[21]

4.5 Effect of Stirring Speed:

The stirring speed is an important parameter because it affects the mixing phenomena

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between solvent and anti solvent, leading to a reduction in the solubility of solute in a solvent. An overall phenomenon is that increasing the stirring speed decreases the size of the particles due to the intensification of the micro mixing (i.e. Mixing at the molecular level) between the multi-phases. Increasing the micro mixing efficiency increases the mass transfer and the rate of diffusion between the multi phases and generates a high homogenous super saturation, which induces the rapid nucleation to produce smaller drug particles. When the stirring speed is increased, the high intensity speed generates a lot of heat energy, which raises the temperature , leading to increase in the nanoparticle size.[22]

4.6 Effect of Ultrasound:

In order to create smaller, more uniform crystals with a homogeneous shape, the use of ultrasonic waves in the antisolvent crystallisation process has significantly grown in recent years. The influence of an ultrasonic wave on particle size can be studied by changing three basic parameters: ultrasound addition time, ultrasonic power intensity, and the time at which the sonication is applied. Most often, it is shown that particle size decreases as ultrasonic power input rises. This phenomenon is attributed to the increase in erosion effect on the surface of large crystals with an increase in ultrasonic power and hence, crystal can agglomerate. The other parameter, sonication time is also responsible to decrease the particle size to a certain extent. Prolong sonication time provides more persisting cavitation bubbles and increases the probability of collision between the particles. When the collision occurs, it generates the large number of nuclei and causes the subsequent reduction in particle size. Ultrasound can also cause the reduction of the particle size when the sonication is applied to the solution at the initial stage of crystallization where the crystal growth is about to start. The most important effect of the presence of an ultrasonic wave during crystallization is that it reduces both the nucleation induction time and the metastable zone width. Hence, the ultrasound may control the rate of nucleation and crystal growth and thereby affect the resulting size of each particle.[2,23.]

4.7 Effect of Induction Time:

In crystallization process, the time between creation and establishment of a certain super saturation and first detectable appearance of new-born particles, often resulting in solution turbidity, is called the induction time. The induction time is influenced by several external factors. Many experiments were conducted to show the influence of factors like impurity, addition of seeds, agitation speed, nature of solvent, supersaturation level and temperature. Among these factors, supersaturation is very important because it is the driving force in the crystallization. A general rule to minimize fouling is to work at low supersaturation, however, this decreases nucleation rates even more, highlighting the need to enhance nucleation at low supersaturation. Sonocrystallization was extensively studied in batch and was shown to decrease induction times, increase nucleation rates and reduce the particle size. Ultrasound significantly decreased the induction time, as well as the particle size. The mechanism behind sonocrystallization is that the effects are most likely associated with acoustic cavitation. Acoustic cavitation can be divided into stable cavitation, which entails the formation, growth, and oscillation of microbubbles under the influence of ultrasound waves and transient cavitation, in which these microbubbles also violently collapse.[24]

It is found that the application of ultrasound, metastable zone width decreased significantly under sonicated conditions and that the particle size decreased with increasing initial supersaturation. These studies all indicate the suitability of ultrasound to enhance the nucleation rate in a tubular crystallizer. Both gas bubbles and high shear were shown to enhance nucleation rates and both effects can originate from ultrasound and high-shear mixing. Ultrasound can generate cavitation bubbles that violently collapse, generating high shear and high-shear mixers create high shear due to the velocity differential between the rotor and the stator, which can also result in cavitation bubbles. For both ultrasound and high shear mixing the reproducibility of the process increased with decreasing induction time.[25]

V. OTHER ANTI SOLVENT METHODS

5.1 Supercritical whereas precipitation.

Supercritical anti-solvent micronization has been performed using different process arrangements and apparatuses. Different acronyms were also used by the various authors to indicate the micronization process. It has been referred to as GAS (gas antisolvent), PCA (precipitation by compressed antisolvent), ASES (aerosol solvent extraction system), SEDS (solution enhanced dispersion by supercritical fluids) and SAS (supercritical anti solvent) processes. A short

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description off the various techniques is presented below:

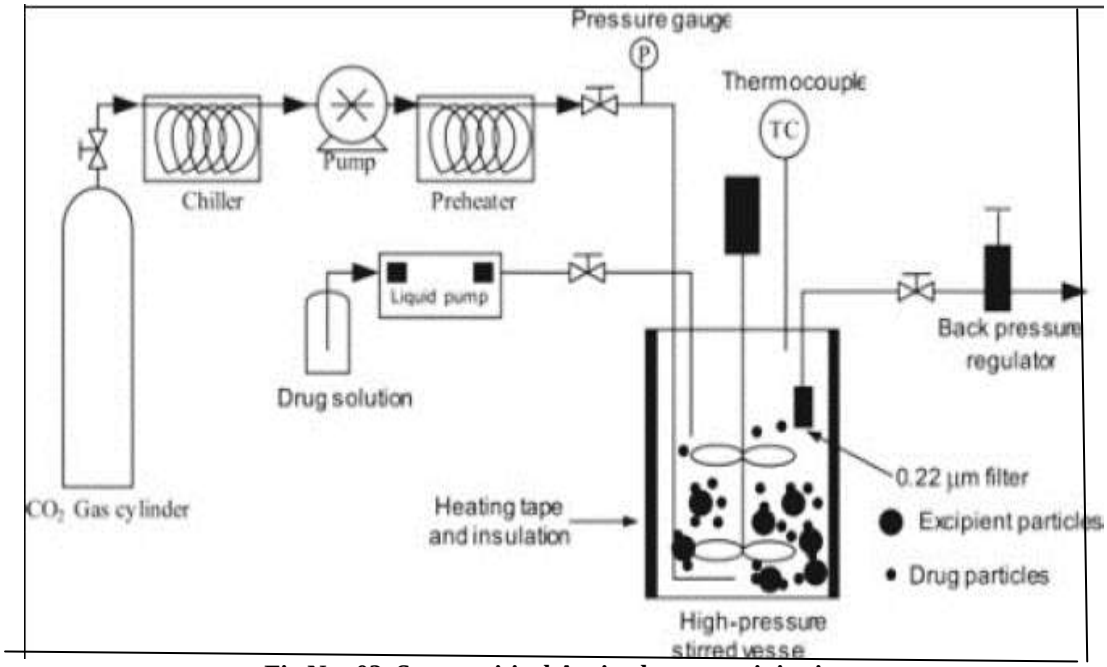

Fig No: 02 Super critical Anti-solvent precipitation.

a) Batch operation

The precipitation vessel is loaded with of the liquid solution and then the supercritical anti-solvent is added until the final pressure is reached. In this mode of operation, the rate of supercritical anti-solvent addition can be an important parameter in controlling the morphology and the size of the solid particles. The anti-solvent can be added from the bottom or from the top of the chamber. This mode of operation can be referred to as the liquid batch operation.

It is also possible to charge the precipitation chamber with the antisolvent and then to perform a discontinuous injection of the liquid solution. This mode of operation can be termed gas batch operation.

b) Continuous operation

The liquid solution and the supercritical anti-solvent are continuously delivered to the precipitation vessel in co-current or counter current mode. In this mode of operation, the flow rate and their ratio can be important for the evaluation of the precipitation process. The pressure at which the operation is performed can also be a revalent process parameter.[26]

5.1 Application

- The possibility of dissolving a large volume of a supercritical fluid by an organic solvent.
- The reciprocal miscibility of the supercritical fluid CO2 and an organic solvent.
- The low affinity of the supercritical fluid for the solute.
- Supercritical antisolvent method is used in various field including explosives, polymers, Pharmaceutical compounds, colouring matter, catalysts and inorganic compounds.[26]

VI. ANTISOLVENT CRYSTALLIZATION OF POORLY WATER SOLUBLE DRUGS

Many researchers have produced microparticles to nanoparticles of different active pharmaceutical ingredients (APIs) using an antisolvent crystallization with water as an antisolvent has been shown in table no:01

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API	Parameters	Particle Size (µm)	Ref
Ibuprofen	Solvent: isopropyl alcohol Stirring speed: 3000 rpm Surfactant concentration: 0.1-1 %w/v	0.2-0.4	1
Nitrendipine	Solvent: mixture of PEG 200 and acetone (1:1 v/v) Drug concentration: 30mg/ml Stabilizer (PVA) concentration: 0.15%(w/v) Temperature: 3°C Stirring speed: 400 rpm Sonication: 400 W, 15 min	0.2-0.218	2
Megestrol acetate	Solvent: Acetone Drug concentration: 30-120 mg/ml Concentration of Kollidon VA 64(surfactant): 0.2 %(w/v)	1.048-3.491	6
Curcumin	Drug concentration: 5-15 mg/ml Flowrate: 2-10 ml/min Solvent: ethanol Stirring speed: 200-1000 rpm SAS volume ratio: 1:10-1:20 Temperature: 5-25°C	Diameter:0.155-0.300, Length:0.920-1.680.	7
Carbamazepine	Temperature: 25-45°C Drug concentration :10-40 mg/ml Flow rate: 1.4-10 ml/min Sonication time: 30-90s	13.9-112.3	10
trans-Resveratrol	Solvent: ethanol Drug concentration: 60 mg/ml Stabilizer concentration: 0.5 wt.% Stirring speed: 1000 rpm Temperature: 5-25°C Stirring time: 5 min	0.232-0.560	11
Artemisinin	Temperature:10-25°C SAS volume ratio:1:10-1:20 Drug concentration:5-15mg/ml Stirring speed:200-1000 rpm Flow rate: 2-10 ml/min Solvent: ethanol	Diameter:1.5 Length: 3.8	18
Quercetin	Solvent: ethanol Drug concentration: 5-15 mg/ml Flow rate: 2-8ml/min Stirring speed: 300-1000 rpm SAS volume ratio: 1:10-1:25	0.17±0.03 -0.255±0.025	19
Beclomethasone	Solvent: methanol	0.2-1.2	21

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Dipropionate	Solution:antisolvent:1:20 Drug concentration:30mg/ml Temperature: 4-40°C Stirring speed: 500-2000 rpm Stirring time: 10s-240s		
Bicalutamide	Temperature: 3-30°C Stirring speed: 1000-15000 rpm	0.326-0.334	20
Celecoxib	Solvent: acetone Drug concentration: 60 mg/ml Temperature: 4°C	0.144-0.174	27
Deflazacort	Solvent: methanol SAS volume ratio:1:1-1:6	3.3-561.0	28
Fenofibrate	Solvent: ethanol Drug concentration: 50 mg/ml Stirring speed:1000 rpm	0.299-0.337	29
Griseofulvin	Solvents: Acetone, Ethanol Temperature: 25℃	1.5	30
Irbesartan	Solvent: methanol Drug concentration: 1 wt% Stirring speed: 2500 rpm Stirring time: 30s Concentration of PVP: 1.5g/1000ml Concentration of SDS: 0.25g/1000ml	0.055	31
Meloxicam	Solvent: DMF Temperature: 8°C Stabilizer concentration: 0.1-0.6%w/v Sonication: 300 W for 20 time length	0.183-0.750	32
Norfloxacin	Solvent: dimethylsulfoxide SAS volume ratio: 1:3-1:10 Drug concentration: 5-20 mg/ml	0.170-0.350	33
Siramesine	Solvent: Ethanol Drug concentration:1%w/v, 50ml SAS volume ratio: 1:4 Excipient concentration: 0.025% w/v, 200ml	5±1-147±28.5	34

VII. ADVANTAGE

- The process of crystallization is quiet easy
- Anti-solvent crystallization is that the process can be carried out at temperatures near the ambient temperature. It is quite convenient for heat-sensitive substances.
- Improved product and process consistency and crystal purity.
- The process demand less energy than a solvent evaporation process.
- The solvent anti-solvent mixture can be separated in order to recover and recycle one or both solvents.

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- Change in solvent composition may favour change in crystalline phases.
- Shorter crystallization cycle times and less frequent work,

VIII. DISADVANTAGE

A potential problem for anti-solvent crystallization methods is the tendency for organic compounds to oil out or agglomerate as fine particles into amorphous undefined structures. One possible cause of oiling out is that drops of the product solution are surrounded by the anti-solvent, in which the solubility is very low, and this low solubility creates localized regions with very high super saturation ratio. Before mixing to the molecular level is achieved, the localized high super saturation forces the product out of solution without allowing sufficient time for ordering of molecules to enable crystal development. The resulting oily particles have tendency to clump together before the occluded solvent migrates throughout the solution. As the mixture is aged, the oiled-out particles may transform into amorphous solids or become crystalline. Solids developed in this manner will likely have poor lattice structure.

IX. CONCLUSION

Various techniques have been employed to decrease the particle size of drugs to the nanoscale. Antisolvent crystallization is one of the most important crystallization process which is being used for the enhancement of the bioavailability of poorly water soluble drugs. Antisolvent crystallization has advantages like controlled particle size distribution, rapid and easy to perform. Various operation parameters like; concentration, temperature, solvent to antisolvent ratio, sonication power etc. have been explained in detail considering their effect on particle size and the morphology. All the parameters have a significant effect on the particle size but ultrasound power has a more influence on the particle size and morphology. Controlling the ultrasound variables one can control the particle size distribution. Therefore, in general, antisolvent crystallization is quite simple, cost effective and easy for scaling-up to produce nanoparticles of poorly water soluble drugs. Additional variable like ultrasound waves can easily be applied as water is used as an antisolvent.

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