An Overview of Optimization of Spherical Crystallisation Process

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ABSTRACT

In this article we describe the optimizing parameters in the process of spherical crystallisation. Particle engineering of active pharmaceutical agents is an innovative area of research in pharmaceutical industry because of several advantages. Spherical crystallization is one of the particle engineering technique in which drug directly gets crystallized and agglomerated into spherical shape. The spherical crystals can be obtained by different methods like solvent change, Quasi-emulsion droplet, ammonia diffusion and neutralisation. The optimization of process of spherical crystallization is important for obtaining the ideal spherical crystal agglomerates. It includes stirring rate, selection of solvent, pH, temperature etc. which affects on the physico-chemical properties of crystals. These optimizing parameters play its specific role in formation of spherical crystals. Stirring rate affects the shape as well as size of the final agglomerates and solvent selection helps in the formation of maximum amount of agglomerates in the system. The factors like pH and temperature should be maintained in case of drugs which show polymorphism. Apart from this, several others physical phenomenon or parameters like interfacial tension and rate of crystallisation are also important for thorough optimization of process.

KEYWORDS: Spherical crystals; Mode of agitation; Bridging liquid; Residence time.

Introduction

The oral dosage form is the most popular dosage form because of its patient convenience and several other advantages (Lachmann et al., 1987). Amongst oral dosage forms compressed tablet is a major dosage form. For the preparation of tablet, granulation is the important step because it improves the micromeritic properties of drug (Gaud et al., 2006). In literature mainly two methods viz is wet and dry granulation have been reported. However this conventional method requires several steps like blending, sieving and drying. This is not only time consuming but also costly (Patil et al., 2009). So the direct compression is the modern and most efficient process used in tablet manufacturing due to its low manufacturing cost and high mechanical integrity of tablets (Sarfaraz et al., 2011).

The technique of spherical crystallisation has been introduced by kawashima in 1986 for size enlargement of drug which can be directly compressed (Biscans et al., 2002). In spherical crystallisation, the drug crystallizes in solvent system and gets agglomerated and this both the steps are carried out simultaneously (Parida et al., 2010). The crystals can be obtained by following methods

- **Solvent change:**
  In this method, the drug is dissolved in good solvent and directly poured in the poor solvent and small amount of bridging liquid is added to form the agglomerates (Khatry et al., 2012). The poor solvent has miscibility with good solvent but low solubility with solvent mixture. Drawback of this method is that it provides low yield because the drug shows significant solubility in the crystallisation solvent.

- **Quasi-Emulsion droplet:**
  The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible (Yadav et al, 2009). The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets.

- **Ammonia diffusion:**
  In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system (Patil P et al, 2011). In this system ammonia water

ABBREVIATIONS: ADS = Ammonia Diffusion System; API = Active Pharmaceutical Ingredient; DCM = Dichloromethane; ESDS = Quasi-Emulsion Solvent Diffusion System; NT = Neutralization Technique; SA = Spherical Agglomeration; SLS = Sodium Lauryl Sulphate

2203
acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. The technique is mainly applicable for amphoteric drugs.

- **Neutralization:**
  The principle of neutralisation reaction is basically applied in this method (Vyas et al., 2007). The drug dissolves in 0.1 N HCl and this solution added in the 0.1 N NaOH with the addition of small amount of polymer.

- **Dispersion method:**
  In this technique, the drug dispersed in poor solvent and small amount of bridging liquid is added to get the agglomerates in dispersion form.

**Apparatus for Spherical Crystallisation**

![Apparatus of spherical crystallisation.](image)

**Steps in mechanism of spherical crystallisation**

Bermer and zuider wag proposed four steps in the growth of agglomeration that is flocculation zone, zero growth zone, fast growth zone and constant size zone (Jain et al, 2004).

- **Flocculation Zone:** In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation; the adsorbed bridging liquid links the particles by forming a lense between them. In these zones, loose open flocs of particles are formed by pendicular bridges.

- **Constant Size Zone:** In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration.

- **Zero Growth Zone:** Loose flocs get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing poor space in the pellet completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet & pellet-stirrer collision.

- **Fast Growth Zone:** The fast growth zone of the agglomerates takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large particles following random collision of well-formed nucleus is known as coalescence.

The technique of spherical crystallisation depends upon the several factors which contribute to the physico-chemical characteristics of the drug. During the crystallization the parameters like stirring rate, temperature, pH, selection of solvent system, addition rate of bridging liquid etc. need to be optimized to get maximum amount of spherical crystals. In this review article, our aim is to focus on how to optimize the processing parameters and how these parameters affect on ideal spherical crystals.

**Factors influencing the process of spherical crystallisation**

1) **Selection of good, poor solvent and bridging liquid**

The selection of solvent is determined by solubility characteristics of drug. A mutually immiscible three solvent system consisting of a poor solvent, good solvent and bridging liquid is needed. When the drug completely dissolves in solvent it is known as good solvent where as when drug is not completely solubilizes in solvent it is known as poor solvent. Physical form of product can be controlled by selection of proper solvent proportions. The proportion of solvent to be used is determined by carrying out solubility study. The dielectric constant of drug in particular solvent also helps in determining the solubility of drug in solvent. The drugs which are polar in nature get easily solubilised in the polar solvent like water, alcohol etc. Where as nonpolar drugs solubilise in nonpolar solvents like DCM, chloroform etc.

Chow et al postulated some general guidelines for the selection of good, bad solvent and bridging liquid in spherical crystallisation (Mahanty et al, 2010).

- For compounds that are water soluble, a water-immiscible organic solvent is used as the external medium and salt solutions of high concentration without common ions can be used as the bridging liquid.

- For compounds that are soluble in one or more organic solvents water is employed as the external phase and a water-immiscible organic solvent as the bridging liquid.

- For compounds that are only soluble in water-miscible organic solvents a saturated aqueous solution of the compound can serve as the bridging solvent.
For compounds that are insoluble in water or any organic solvents a water-immiscible organic solvent can act as the external phase and a 20% calcium chloride solution as the bridging liquid. In addition, binding agent such as PVP or PEG is required for agglomeration since the powders are not allow binding through recrystallisation and fusion.

In solvent change method poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and good solvent, crystals will be precipitated immediately. In the emulsion solvent diffusion the affinity between the drug and good solvent is stronger than that of good solvent and poor solvent (Patil SV et al, 2009).

The shape and surface irregularity as well as surface irregularity and roundness of crystals agglomerate are affected by solvent due to its polarity and interactions with hydrophobic phases of the growing crystals (Hu R et al., 2006).

The composition of agglomeration region can be calculated by ternary phase diagram built from an incomplete SCHEFFE (1958) system. In this diagram the area for agglomerate obtained are shown in figure 2 and 3 (Di martino et al, 2000).

The ratio of solvent system affect on agglomeration process. Increase concentration of bridging liquid will increase the average diameter of agglomerated crystal due to enhanced agglomeration of crystals.

Bridging liquid should not be miscible with poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effect and capillary forces, the bridging liquid causes the crystal to adhere to one another.

Selection of solvent can also alters the polymorphic nature of solid. When solid solubilises in solvent it gets transition motion which will results in molecular mobility and molecular array gets change which will affect on physical properties like melting point, dissolution etc.

**Addition mode of bridging liquid**

The rate of addition of bridging liquid in the system mainly affects on the spherical nature of the crystals. The addition also depends on the stability (mass transfer of drug from droplets) of droplets in the system (Teychene et al, 2010).

The dropwise addition of drug solution responsible for greater contact time of droplet in the system and the residence time after addition of solution will decrease. If the droplets of drug solution unstable in the system it will stick to the paddle so that in such a case the direct addition will work out in some extent. In such phenomenon the drug suddenly comes in the contact with the system so that the surface tension of droplets will reduce and that results in fast mass transfer of drug from the droplet and drug would not stick to the paddle.

**Interfacial tension**

In order to study the influence of the interfacial tension between the crystallizing solvent and water, the crystallization solvents are carefully chosen. The selected solvents have a significant difference in interfacial tension with water and have roughly the same physio-chemical properties (density, viscosity, solubility and miscibility with water) (Teychene et al, 2010).

The reduction in the interfacial free energy of an emulsion system contributes to the emulsion stability. This means that reducing the interfacial energy between the organic solvent and water would reduce droplet coalescence and secondary agglomeration (Teychene et al, 2010).

To increase the yield of the crystallisation process it seems reasonable to increase the volume fraction of the introduced dispersed phase up to miscibility limit of the organic phase in the aqueous phase. When the concentration of the organic phase is close to the saturation of the liquid phase, the particles are soft (gel like structure) and sticky. As a consequence, during the process the particles stick to the impeller and to the crystallizer wall. The gel like structure is obtained when the mass transfer from the organic phase to aqueous phase is too slow. The lifetime of the emulsion is then much higher which leads to an increase of the
coalescence frequency of the droplets (Teychene et al., 2010).

High interfacial tension of good solvent and poor solvent produces large droplets result in coalescence which is incompatible to the process of spherical crystallisation.

Interfacial tension between organic solvents and water can be measured by dynamic Whilhmy plate method. Time-dependent changes in the interfacial tension are detected automatically. The beaker is filled with 70 ml of water saturated with organic solvent. The entire plate is then immersed in the aqueous phase and then 10 ml of organic solvents is carefully deposited on the surface of the aqueous phase. By measuring the applied force according to the immersion depth and dimension of substrate perimeter the contact angle can be calculated as by following equation (Teychene et al, 2010).

\[ \gamma = \frac{F}{L \cos \theta} \]

Where,
- \( \gamma \) = contact angle
- \( L \) = wetted perimeter
- \( F \) = measured force

### Mode and intensity of agitation

In optimization of spherical crystals of drug, the mode and intensity of agitation is an important parameter in concern with the shape and size of the agglomerates. The agitation is necessary to disperse the bridging liquid throughout the system. The agitation speed with circular motion determines the fluid flow in system.

The spherical crystals at high speed will give smaller size of agglomerates where as at lower speed it will give larger size. For obtaining the optimum size of agglomerates the optimization of agitation speed is necessary in spherical crystallisation. The blade used for agitation will be responsible for maintaining the shape of agglomerates. Mainly screw-type agitator with four flat blades is used for maintaining the shape. The sharper blades will cut the agglomerates and formation of irregular agglomerates will form (Kawashima et al., 1983). Some drug required low speed for crystallisation where as some required high speed. The nature of speed mainly depends upon the rate of crystallisation in the system. If the rate of crystallisation of drug is high the agitation for agglomeration required high speed. Because when bridging liquid will collect crystals due to high speed bridging liquid quickly squeeze out and agglomerates will formed with uniform distribution. On the other hand if the crystallisation rate is slow, the crystals required time for come in contact with bridging liquid and formed agglomerates will not uniform in size. It may be due to, when we kept the system at high speed the bridging liquid will squeeze rapidly and agglomeration will not occur. The rate of crystals growth is determined by several steps in the growth process. This can either be the diffusion of materials to the surface or the kinetics of surface process. Both diffusion and surface integration kinetics are process driven by difference in chemical potential. Hence driven force for crystal growth is given as (Bhat et al., 2001).

\[ \mu_s - \mu_s^* = vRT \ln \left( \frac{a_{s^*}}{a_s} \right) \]

Where,
- \( a_{s^*} / a_s \) = Activities of supersaturated and saturated ions
- \( \mu_s, \mu_s^* \) = Respective chemical potential
- \( v \) = Stoichiometric coefficient of the ions

During the crystallisation process specific amount of aliquot is withdrawn from the system at suitable intervals. It is filtered through a membrane filter with a pore size of 0.45 micrometer. The filtrate is evaporated and the residue is diluted with suitable solvent. The drug content remaining in the medium is determined spectrophotometrically (Ueda et al., 1990).

In case of microsphere prepared by spherical crystallisation technique the release rate of drug get affected by stirring rate. Akbuga J. Prepared furosemide microsphere at two different rpm (100 and 1000). The rate of drug release at 100 rpm was found to be higher than the 1000 rpm (Akbuga et al, 1991).

Kawashima et al seen the effect of agitation speed on agglomeration and bulk density. He found that the agglomerates recovery is high at high speed and induction period decreases with increasing agitation (Kawashima et al., 1995).

### Temperature

Temperature mainly affects the thickness of agglomerates. It is inversely proportional to the thickness of agglomerates that is when crystallisation process carried out at high temperature the thickness of agglomerates will decrease (Kawashima et al, 1984).

The average size of agglomerate was smallest at the crystallisation temperature 10°C. At higher temperature, the larger agglomerates were produced initially and the equilibrium attained more rapidly than at lower temperature. At lower temperature, it was characteristic that the growth rate of crystals was slow at the initial stage but become faster at the later stage. At low temperature, the initial numbers of crystals produced were greater than at high temperature i.e. the number of nuclei increased with decreased crystallization temperature (Kawashima et al, 1984).

### pH

The drugs are prone to polymorphism because change in pH so that maintaining of pH during crystallisation is mandatory for avoiding polymorphism. In neutralisation method, the change in pH of good solvent and poor solvent will affect on crystallisation process. In this case, mainly 0.1N HCl and 0.1N NaOH are used for carrying out neutralisation reaction. Some API when comes in contact with light shows polymorphism, the crystallisation of such type of API carried out in umbered coloured vessel.
Residence time

The time for which agglomerates remain suspended in reaction mixture affect their size shape and strength (Parida et al, 2010). Residence time for the agglomeration of recrystallized crystals need to be optimized. Below the optimized residence time the incomplete agglomeration occurs due to incomplete diffusion of good solvent and bridging liquid from the formed droplets in the dispersion medium. At longer residence time the formed agglomerates break down and the size of the agglomerated particles decreases. This might be due to the solubilization of the agglomerates by the bridging liquid that diffuses out from them.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Good solvent</th>
<th>Poor solvent</th>
<th>Bridging liquid</th>
<th>Method</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicyclic acid</td>
<td>Ethanol</td>
<td>Water</td>
<td>Chloroform</td>
<td>SA</td>
<td>(Kawashima et al., 1984)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Ethylene diamine</td>
<td>Aq, NaCl</td>
<td>Water</td>
<td>SA</td>
<td>(Kawashima et al., 1984)</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Ethanol</td>
<td>Water</td>
<td>Chloroform</td>
<td>ESID</td>
<td>(Kawashima et al., 1984)</td>
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<tr>
<td>Tranilast</td>
<td>Acetone</td>
<td>Water</td>
<td>DCM</td>
<td>SA</td>
<td>(Kawashima et al., 1991)</td>
</tr>
<tr>
<td>Tolbutamidate</td>
<td>Ethanol</td>
<td>Water</td>
<td>Isopropyl acetate</td>
<td>ESD,SA</td>
<td>(Kawashima et al., 1992)</td>
</tr>
<tr>
<td>Enoxacine</td>
<td>Ammonia water</td>
<td>Acetone</td>
<td>Ammonia water</td>
<td>AD</td>
<td>(Kawashima et al., 1993)</td>
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<td>Fluoxetine Ethanol</td>
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<td>Water</td>
<td>Isopropyl acetate</td>
<td>ESD</td>
<td>(Morishima et al., 1993)</td>
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<td>Acebutol hydrochloride</td>
<td>Ethanol</td>
<td>Water</td>
<td>Isopropyl acetate</td>
<td>ESD</td>
<td>(Kawashima et al., 1995)</td>
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<td>Propyphenazono</td>
<td>Ethanol</td>
<td>Water</td>
<td>Isopropyl acetate</td>
<td>SA</td>
<td>(Di Martino et al., 2000)</td>
</tr>
<tr>
<td>Norfloxacine</td>
<td>Ammonia water</td>
<td>Acetone</td>
<td>Ammonia water</td>
<td>AD</td>
<td>(2000)</td>
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<td>Flurbiprofen</td>
<td>Acetone</td>
<td>Water</td>
<td>Hexane</td>
<td>SA</td>
<td>(Jain et al, 2002)</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Water</td>
<td>Ethyl acetate</td>
<td>Ethyl acetate</td>
<td>SA,ESD</td>
<td>(Kawashima et al., 2002)</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>Ethanol</td>
<td>Water</td>
<td>Carbon tetrachloride</td>
<td>SA</td>
<td>(Szabo-Revesz et al., 2002)</td>
</tr>
<tr>
<td>Acepromazine trimhydrate</td>
<td>Ammonia water</td>
<td>Acetone</td>
<td>Ammonia water</td>
<td>AD</td>
<td>(Gohle et al, 2003)</td>
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<tr>
<td>Mefenamic acid</td>
<td>Ammonia water</td>
<td>Acetone</td>
<td>Ammonia water</td>
<td>AD</td>
<td>(Agrawal et al, 2004)</td>
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<td>Roxithromycine methanol</td>
<td>methanol</td>
<td>Water</td>
<td>Chloroform</td>
<td>SA</td>
<td>(Jain et al, 2004)</td>
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<td>Water</td>
<td>Cyclohexane</td>
<td>SA</td>
<td>(Viswanathan et al., 2006)</td>
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<td>Carbamazepine</td>
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<td>Water</td>
<td>Chloroform</td>
<td>ESID</td>
<td>(Yadav et al, 2009)</td>
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<tr>
<td>Naproxen</td>
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<td>Water</td>
<td>Chloroform</td>
<td>SA</td>
<td>(Nokhodchi et al, 2007)</td>
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<td>Benozoic acid</td>
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<td>Chloroform</td>
<td>SA</td>
<td>(Rasmussen et al, 2008)</td>
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<td>DCM</td>
<td>SA</td>
<td>(Mutalik et al, 2008)</td>
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<td>Mefenadazol</td>
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<td>Water</td>
<td>DCM, Hexane, Octanol</td>
<td>ESD</td>
<td>(Kumar et al, 2008)</td>
</tr>
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<td>Cefturoxime axetil</td>
<td>Acetone</td>
<td>Water</td>
<td>DCM</td>
<td>ESD</td>
<td>(Yadav et al, 2009)</td>
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<td>Felodipine</td>
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<td>Water</td>
<td>Acetone</td>
<td>ESD</td>
<td>(Tapas et al, 2009)</td>
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<tr>
<td>Griseofulviline</td>
<td>DCM</td>
<td>Water</td>
<td>DCM</td>
<td>ESD</td>
<td>(Yadav et al, 2009)</td>
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<td>Water</td>
<td>Chloroform</td>
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<td>(Bhosale et al, 2009)</td>
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<td>DMF</td>
<td>Water</td>
<td>Chloroform</td>
<td>SA</td>
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<td>(Dwivedi et al, 2010)</td>
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<td>Water</td>
<td>Isopropyl alcohol</td>
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<td>(Teychene et al, 2010)</td>
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<td>Ketoprofen</td>
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<td>Chloroform</td>
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<td>Chloroform</td>
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<td>Mefenamic acid</td>
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<td>Isopropyl acetate</td>
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<td>(Diix et al, 2011)</td>
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<td>(Varshosaz et al, 2011)</td>
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<tr>
<td>Fenofibrate</td>
<td>methanol</td>
<td>Water</td>
<td>DCM</td>
<td>ESD</td>
<td>(Patil et al, 2012)</td>
</tr>
</tbody>
</table>

Concentration of polymers or stabilizers

The number of water insoluble drugs is increasing day by day. Solubility problem of such drugs can be minimised with the technique of spherical crystallisation. Crystal habit of a drug is an important variable in pharmaceutical manufacturing. A number of basic physical properties such as solubility, dissolution rate, melting behaviour and some micrometric properties depend on the modification of a particular drug. Sometimes if in the process of crystallisation the crystal habit (Acicular, Platy, Bipyramidal) modification not occurred, in that case the improvement of solubility will be major problem this problem can be solved by addition of polymers. The change in crystal habit can be determined with the help of surface energy of the crystals (Mitchell et al., 1980). Surface free energy can be calculated by Gibbs equation using melting or solubility method.

Melting method

\[ \Delta G = \Delta H - T \Delta S \]

Where, \( \Delta G \) = free energy
\( \Delta H \) = enthalpy difference
\( T \) = Temperature
\( \Delta S \) = entropy difference

Solubility method

\[ \Delta G = -2.303RT \log \left( \frac{S_o}{S} \right) \]

Where, \( \Delta G \) = free energy
\( R \) = gas constant
\( T \) = temperature
\( S_o, S \) = molar solubilities of agglomerated and pure crystals

When crystals forms the surface free energy remains high, this energy can be minimised by agglomeration of crystals or by addition of polymers which adsorbed on...
The antinucleant polymer molecules are incompatible in both size and shape of host molecules of growing crystals surface. Therefore their incorporation into the lattice alters growth characteristics of the host molecules (Yadav AV et al., 2007). During the crystal precipitation, a hydrophobic surface is formed. Due to the surface energy, the energy of the system increases. Thus, a hydrophobic surface is formed. Due to the surface energy, are stabilized sterically against crystal growth by a layer of protective polymer (Muller et al., 2003). During the crystal precipitation, a hydrophobic surface is formed. Due to the surface energy, are stabilized sterically against crystal growth by a layer of protective polymer (Muller et al., 2003).

In the vessel the agglomerates are actually spherical but they are soft and sticky and their structure is lost during dropwise addition of drug to the poor solvent so the complex of drug polymer crystals complex formed which mainly responsible for improving the solubility of drug. Sometimes if the polymer and drug is not soluble in common solvent then the polymer is dispersed in poor solvent and dropwise addition of drug carried out. The polymer agglomerated on the surface of crystals formed by drug. Crystallisation in the presence of SLS leads to change in habit from needles to plates and rod. Increase in the concentration of SLS in agglomerates will reduce the size (Bansal et al., 2008).

**Conclusion**

Optimization of processing parameters in spherical crystallisation is necessary for producing the unique nature of spherical crystals, which results in the modification of physicochemical properties of API. The difficulties during the optimization of spherical crystals can be overcome by controlling these parameters during the process.

**References**


