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## Spherical Crystallization of Drugs

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### 1. Introduction

Oral way is the most important route of drug administration for obtaining systemic pharmacological effects. In this route, the solid dosage form specially tablets, are the first choice of patient because of their some special advantages like easy administration by the patient, unit dosage form with greatest dose precision and least content variability, lower cost and temper proof nature [1]. Due to unfavourable physical and mechanical properties and poor aqueous solubility of some drugs, their formulation process becomes problematic. Crystallization is the main process in the pharmaceutical industry for particle formation and may be defined as the process in which a solid compound precipitates from a saturated solution in the form of crystals [2, 3]. Most active pharmaceutical ingredients are manufactured in a crystalline shape for their chemical stability during transportation, packaging and storage. Many factors including thermodynamic (*e.g.*, solubility, solid-liquid interfacial tension, solvent activity, temperature, *etc.*), kinetic (*e.g.*, supersaturation, molecular mobility, meta-stable zone width) and molecular recognition (hydrogen bonds, non-covalent bonds, molecular networks) influence the rate and mechanisms by which crystals are formed from liquid solutions [3, 4]. The driving force for crystallization is supersaturation. Supersaturation can be generated by increasing the solute concentration (solvent evaporation) or decreasing the solute solubility (*e.g.*, temperature change, anti-solvent addition, pH change, salting-out) [5]. The next step is the formation of macroscopic crystals from stable nuclei, called crystal growth. This step is controlled by internal (crystal structure) and external factors (temperature, impurities, supersaturation, solvent type) and determines the particle morphology [6].

The size and shape are very important parameters that influence the separation process which will in turn have an effect on the yield and quality of the resulting fractions during the crystallization process [7]. Particle orientation was influenced by crystal habit, therefore can modify the flowability, packing, compatibility, syringability, physical stability and dissolution

profile of a drug molecule. For example, it has been showed that symmetrically shaped crystals of ibuprofen have better compaction and flow properties than needle shaped crystals [8, 9]. It seems that optimization of crystal properties is an alternative method for modifying the dissolution properties of drugs and therefore their bioavailability [10, 11].

Poor physical and mechanical properties of drug particles have been traditionally covered by various granulation methods. Enlargement of particle size is an important procedure during manufacturing of tablets [12]. There are different techniques for enlargement of particle size such as wet granulation, dry granulation, extrusion spheronization and spherical crystallization methods [13]. These techniques have important role in modifying primary and secondary properties of pharmaceutical substances. Kawahima and Capes (during the 1970 decade) suggested enlargement of particles size during the crystallization process. According to their report, controlling the crystal's agglomeration leads to spherical agglomerates with accorded properties [14].

In 1986, Kawashima applied the spherical crystallization method for size enlargement of drugs in the pharmaceutical field. Spherical crystallization defined by him as "An agglomeration process that transforms crystalline drugs directly into a compacted spherical form for improving the flowability, solubility and compactability" [14, 15]. Spherical agglomeration (SA) and emulsion solvent diffusion (ESD) are two major techniques for spherical crystallization. In fact the ammonia diffusion systems (ADS) and crystallo-co-agglomeration (CCA) are extended forms of these methods [16]. Spherical agglomeration consists of precipitating fine crystals of the drug substance and then aggregating them using a wetting agent (should be a non-miscible liquid). In the emulsion solvent diffusion technique, the continuous phase is a non-miscible liquid with drug. Indeed in this method, a quasi-emulsion is formed by droplets of solvent containing the drug and then crystallization occurs inside the droplets because of the counter diffusion of the solvents through the droplets [15]. Under controlled conditions, such as solvent composition, temperature regulation, supersaturation generation, or mixing speed, crystallized particles are able to agglomerate into the spherical dense agglomerates simultaneously.

## 2. Spherical crystallization

Good flowability, mechanical strength and compressibility are the main requirements for commercial production of a particulate solid into the tablet dosage form [14]. Nowadays, great advancements are accessible by powder technology, and various studies are made to produce primary and secondary particles of pharmaceutical substances for different applications. The spherical crystallization is a particle size enlargement method that applies crystallization and agglomeration using bridging liquid [17]. Indeed, this method is a particle design technique that crystallization and agglomeration can be performed simultaneously in one step for transforming crystals directly into the compacted spherical forms [18, 19]. By using this method, direct tableting of drug instead of further processing like mixing, granulation, sieving and drying is possible [15, 16, 19]. This technique is capable of subsequent processes such as separation, filtration and drying more efficiently and is able to have an effect on the secondary properties of the crystals such as flowability, compressibility and wettability. Using this technique, the precipitated crystals can be agglomerated during the final synthesis step into

more or less spherical particles with sizes between 300 and 500 mm without any binders. Spherical crystallization has been considered as a very effective method in improving the dissolution profile of some poorly water soluble drugs [13, 14, 19].

Mechanical properties of the spherical agglomerates like packability, flowability, compressibility, mechanical strength and elastic recovery are very important for the handling and bioavailability of the particles [20]. Stronger bonding occurs during compression of agglomerated crystals compared to single crystals and greater tensile strength is obtained from agglomerated crystals compared to single crystals. It was demonstrated that the spherical agglomerates are more compressible and suitable for preparing compressed dosage forms than conventional crystals. The stronger bond forces formed from agglomerated crystals lead to greater plastic deformation and higher tensile strength compared to those created from single crystals [21]. Jbilou et al. reported that the improvement of compression ability of the agglomerated crystals of ibuprofen compared to marketed single crystals (in spite of high crystallinity) is related to the isotropic texture of the agglomerate [22].

2.1. Principle of spherical crystallization

The saturated solution of the drug in a good solvent is poured into a poor solvent. A third solvent known the bridging liquid is added in small amounts to wet the crystal surface and promote the formation of liquid bridges between the drug crystals for forming spherical agglomerates [23]. In this process the poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between drug and the good solvent. Furthermore, the bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals [15]. Advantages and disadvantages of spherical crystallization method are summarized in Table 1.

| Advantages  | Disadvantages   |
|---|---|
| Physicochemical properties of pharmaceutical crystals are mainly improved for pharmaceutical process i.e. milling, mixing and tableting by using this technique [24].       | Selection of suitable solvents is a tedious process [2].                          |
| Use of this technique leads to conversion of crystalline forms of a drug into polymorphic form that may have better bioavailability [23].                                   | Optimization of processing parameters (temperature, agitation) is difficult [16]. |
| This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried out more efficiently [15].                                      |   |
| Preparation of microsponges, microspheres and nanospheres, microballoons, nanoparticles and micro pellets as novel particulate drug delivery system is possible by it [25]. |   |
| It can be used for masking of the bitter taste of drug [15].  |   |

Table 1. Advantages and disadvantages of spherical crystallization

## 2.2. Main steps involved in the growth of agglomeration

Bermer and Zuider Wag classified the growth of agglomeration in four steps: Flocculation zone, zero growth zone, fast growth zone and constant size zone [26].

### 2.2.1. Flocculation zone

The bridging liquid is adsorbed on the surface of crystals and links the particles by forming bridge between them [15, 26].

### 2.2.2. Zero growth zone

In this zone, loose floccules are converted into the tightly packed pellets. The entrapped fluid is squeezed out onto the surface of the small floccules. The driving force for these conversions is governed by the agitation of the slurry, pellet-pellet and pellet-stirrer collision [27].

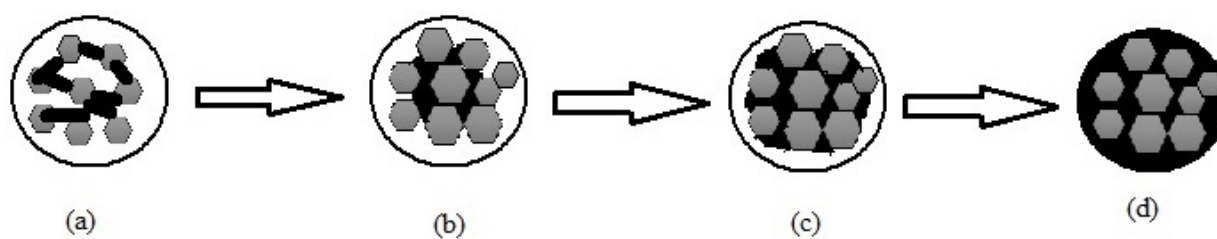
The rate limiting step in agglomeration growth process occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial floccules are transformed into small agglomerates.

### 2.2.3. Fast growth zone

When sufficient bridging liquid has squeezed out of the surface of the small agglomerates, the fast growth zone is observed. Coalescence is the process in which the large size particle is formed following random collision of well-formed nucleus. For successful collision process, slightly excess surface moisture of nucleus is required [27, 28].

### 2.2.4. Constant size zone

This zone involves stopping of agglomeration growth. In this zone, even a slight decrease in size of agglomerates may be observed probably due to attrition, breakage and shatter. Four zones for agglomeration growth are illustrated in Figure 1 [26-28].



**Figure 1.** Four steps for agglomeration growth: a) flocculation zone, b) zero growth zone, c) fast growth zone, d) constant size zone

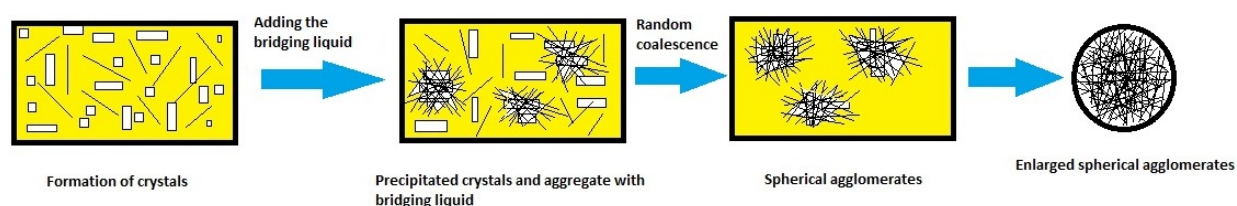
## 3. Spherical agglomeration technique

There are three main stages for spherical agglomeration method. The first stage is the choice of the crystallization method to precipitate crystals from solution. The thermal, physico-

chemical or chemical methods may be used in this stage. The second step is the selection of the wetting agent that should be immiscible with the solvent of the crystallization process. At the end stage, the hardening of the agglomerates is performed. Agglomeration may occur as a consequence of the coalescence of agglomerates with the liberated bridging liquid [29].

Spherical crystallization has been employed for several high dose drugs with poor compressibility and poor water solubility [24].

Spherical agglomeration is a valuable technique in the formulation of microspheres, microsponges, nanospheres, microballoons and nanoparticles as novel drug delivery systems [30]. Spherical agglomeration is also employed in processes such as granulation, balling, pelletization, tableting, compaction, flocking and sintering in order to produce, *e.g.*, nuclear fuel pellets, ceramic powders, carbon blacks, catalysts, commercial fertilizers, pesticides and pharmaceutical products [31]. The main parameters in spherical agglomeration are the choice of the solvent system, amount and type of the bridging liquid, the presence of additives, initial particle size, solubility, the agitation rate and temperature. These parameters influence not only the productivity but also the micrometrics properties such as particle size distribution, morphology and strength of the product [17]. Figure 2 shows the principle of spherical agglomeration.



**Figure 2.** Principle of spherical agglomeration

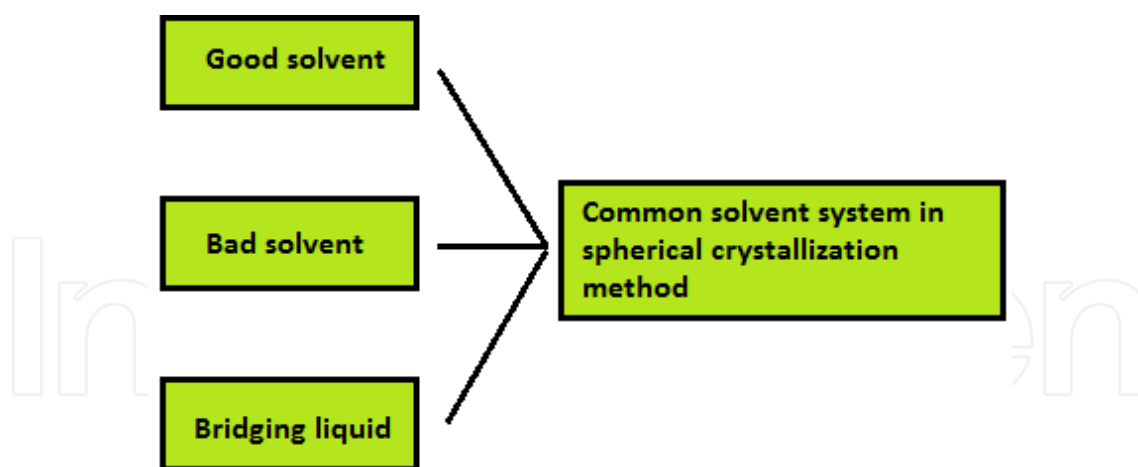
### 3.1. Solvent system

Polarity of the solvent and its interactions with hydrophobic phases of the growing crystals have an influence on shape, surface irregularity and roundness of the crystals agglomerate [32]. Commonly three types of solvents are used in spherical agglomeration [27]: a) A perfect solvent for the drug, b) anti-solvent and c) bridging liquid that should be added for promoting the formation of agglomerates. Bridging liquid not only has wetting property but also acts as an interparticle binder promoting agglomeration. The bridging liquid should not be miscible with the anti-solvent. Meanwhile, anti-solvent and solvent systems should not be miscible and the affinity between them must be stronger than those between drug and solvent [15, 17, 25]. The solvent system and its composition are usually selected by trial and error. Examples of solvent systems in preparing spherical agglomeration of some drugs are given in Table 2. Also the common solvent system in spherical crystallization method is shown in Figure 3.



| Drug                       | Solvent system        |               |                                   | Technique | References |
|----------------------------|-----------------------|---------------|-----------------------------------|-----------|------------|
|                            | Good solvent          | Poor solvent  | Bridging liquid                   |           |            |
| Flubiprofen                | Acetone               | Water         | Hexane                            | SA        | [33]       |
| Salicylic acid             | Ethanol               | Water         | Chloroform                        | SA        | [34]       |
| Aspirin                    | Acid buffer,          | Methanol,     | Chloroform                        | SA        | [35]       |
| Fenbufen                   | THF                   | Water         | Isopropyl acetate                 | SA        | [36]       |
| Nabumetone                 | Ethanol               | Water         | Cyclohexane                       | SA        | [37]       |
| Naproxen                   | Acetone-ethanol       | Water         | Chloroform                        | SA        | [38]       |
| Roxythromycin              | Methanol              | Water         | Choroform                         | SA        | [39]       |
| Mebendazole                | Acetone               | Water         | Hexan,Octanol,<br>Dichloromethane | SA        | [40]       |
| Valsartan                  | Acetone               | Water         | Choroform                         | SA        | [41]       |
| Celocoxib                  | Acetone               | Water         | Chloroform                        | SA        | [42]       |
| Ascorbic acid              | Water                 | Ethyl acetate | Ethyl acetate                     | SA,ESD    | [43]       |
| Aspartic acid              | Methanol              | Water         | -                                 | SA        | [44]       |
| Ibuprofen                  | Ethanol               | Water         | Ethanol                           | SA        | [22]       |
| Ibuprofen-<br>Paracetamol  | Dichloromethane       | Water         | Dichloromethane                   | CCA       | [45]       |
| Benzoic acid               | Ethanol               | Water         | Chloroform                        | SA        | [46]       |
| Aceclofenac                | Acetone               | Water         | Dichloromethane                   | SA        | [47]       |
| Indomethacin               | Dimethyl<br>formamide | Water         | Chloroform                        | SA        | [48]       |
| Indomethacin<br>Mepirizole | Ethyl acetate         | Water         | Ethyl acetate                     | CCA       | [49]       |
| Ibuprofen-Talc             | Dichloromethane       | Water         | Dichloromethane                   | CCA       | [50]       |
| Glibenclamide              | Dichloromethane       | Water         | Chloroform                        | SA        | [51]       |
| Tranilast                  | Acetone               | Water         | Dichloromethane                   | SA        | [52]       |
| Aminophylline              | Ethanol               | Water         | Chloroform                        | SA        | [53]       |
| Bromohexin Hcl             | Dichloromethane       | Water         | Dichloromethane                   | CCA       | [54]       |
| Ketoprofen                 | Isopropyl acetate     | Water         | Choroform                         | SA        | [55]       |
| Propiphenazone             | Ethyl alcohol         | Water         | Isopropyl acetate                 | SA        | [14]       |
| Acetylsalicyclic<br>acid   | Ethanol               | Water         | Carbon tetrachloride              | SA        | [56]       |
| Ketoprofen-talc            | Dichloromethane       | Water         | Dichloromethane                   | CCA       | [57]       |

**Table 2.** Solvent systemsin preparing spherical agglomeration of drugs



**Figure 3.** Common solvent system in spherical crystallization method

### 3.2. Bridging liquid

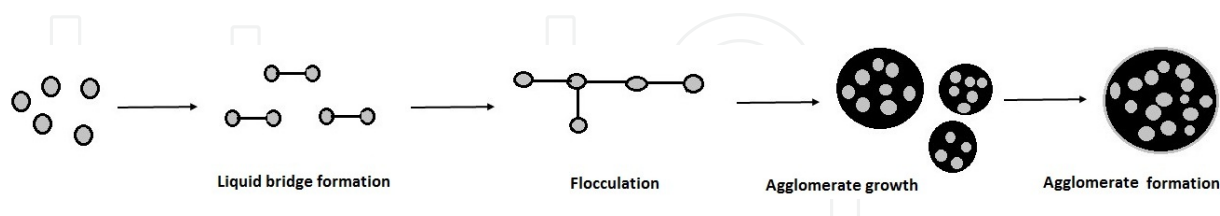
The amount of bridging liquid is a critical factor in the spherical crystallization method. There are some studies about the enlargement of agglomerates by increasing the amount of bridging liquid [58]. Generally, increasing amount of the bridging liquid leads to an increase in agglomerate size [59]. According to a research, addition of a smaller amount of bridging liquid produced larger particles of acebutolol (up to 1,000mm) and vice versa a greater amount of bridging liquid formed smaller particles (around 600mm) [25, 60]. The rate of addition of bridging liquid in the system also influences the spherical nature of the crystals [32, 61]. The strength of the bridges not only depends on the interfacial tension between the bridging liquid and the medium but also depends on the rheology of the bridging liquid [32].

There are very limited reports on the systematic selection of the solvent system and bridging liquid for spherical crystallization. Most articles do not address the reasoning behind their solvent selection. Chow and Leung proposed some rules for selection of solvent system and bridging liquid [26]: For water soluble compounds, an organic solvent that is miscible with water is employed as the poor solvent and salt solutions in high concentration without common ions can be applied as the bridging liquid. In the case of compounds that are soluble in one or more organic solvents, water is used as the poor solvent 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 and an organic solvent could be used as poor and bridging solvents respectively. Finally for materials with insufficient solubility in water or any organic solvent, a water-immiscible organic solvent employ as the poor solvent and salt solutions in high concentration without common ions as the bridging liquid. In the latter case because of insufficient solubility of drug powder in bridging liquids, presence of a binding agent such as PVP 40000 or PEG 10000 is necessary for agglomeration [25].

Chloroform has been employed as a bridging liquid in the preparation of some spherical crystal drugs such as: salicylic acid, Aspirin, Roxithromycin, Trimethoprim, Tranilast anhydrate and



Tranilast monohydrate. Isopropyl acetate has been used in the spherical crystal preparation of Propyphenazone, Acebutolol hydrochloride, Tolbutamide and Fenbufen for this mean. Because the strength of liquid bridges is proportional to the interfacial tension between the bridging liquid and the solid, surfactants are not usually used as bridging liquid [31]. Figure 4 shows the mechanism of liquid bridge formation in spherical agglomeration.



**Figure 4.** The mechanism of liquid bridge formation in spherical agglomeration

### 3.3. The presence of additives

The presence of additives such as polymeric material and surface active agents are able to influence molecular aggregation during the crystallization process [40]. The viscosity of the medium and surface tension are reduced by surfactants that in which affect the nucleation process. The existence of these additives in the spherical agglomeration process may also reduce the processing time and improves the bioavailability and micrometric properties of the drug.

Crystallization is inhibited by some of the polymers such as methylcellulose, hydroxypropyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP). Among these, PVP has been found to be the most effective crystallization inhibitor. These anti-nucleant polymers are incompatible with the host molecules of the growing crystals surface. Then their incorporation into the lattice alters growth characteristics of the host molecules [62].

### 3.4. Particle size

Particle size distributions of the drugs and their excipients can exert major effects on the mixing process and therefore on possible segregation in the mixed materials. The particle size distribution in powder material can also influence the flowability and bioavailability of certain active drugs. When the concentration of the organic phase is close to the saturation of the liquid phase, the particles have soft (gel like) and sticky structure. These sticky structures during the process lead to particles sticking to the impeller and crystallizer wall. Indeed, the gel like structure is achieved when the mass transfer from the organic phase to aqueous phase is too slow. Then the life-time of the emulsion is much higher leading to an enhancement in coalescence frequency of the droplets [61].

### 3.5. Solubility of drug

As mentioned earlier, the solvent system for spherical crystallization includes a poor solvent, a good solvent for the drug and bridging liquid. Venkadari Rammohan Gupta described a method for the selection of solvents that is dictated by the solubility characteristic of the drug

[42]. Physical state of a drug product (whether microagglomerate or irregular macro-agglomerates or a paste of drug substance) may be controlled by selecting of proper solvent proportions. The solvent proportions is determined by performing solubility tests and then constructing triangular phase diagram for defining the region of mutual immiscibility using ternary diagram [63].

### 3.6. Mode and intensity of agitation

Similar to the consolidation in granulation process, in the spherical agglomeration process, the spherical shape particles are formed due to mechanical forces of the agitation over a long period of time. In several reports, effects of the agitation rate were reported, and it is one of the main parameters to determine average diameter of the agglomerated crystals [64]. Mode and intensity of agitation in conjugation with the amount of bridging liquid determines the rate of agglomerate formation and their ultimate size. High speed agitation is required for the dispersion of the bridging liquid throughout the system. Altering of the agitation pattern leads to change in force acting on the agglomerate and therefore has an effect on the shape of the agglomerate.

Some drugs require low agitation rate for crystallization, whereas some need elevated rate. Blandin et al. stated that a higher stirring rate leads to obtaining less porous and more resistant agglomerates [24].

The rate of crystallization in the system determines nature of the agitation speed. If the rate of drug crystallization was high, then the elevated agitation speed is required for agglomeration. The used blade for agitation has important role on the shape of agglomerates. Commonly screw-type agitator with four flat blades is used for maintaining the shape. The sharper blades will cut the agglomerates and irregular agglomerates will be formed [65]. By increasing agitation rate, the shear force of the system increases and the outcome is more consolidated agglomerates. By applying a rate above the optimum stirring rate, and due to an increase in disruptive forces, the agglomeration process becomes less efficient [66, 67].

Maghsoodi et al. showed that increase of the agitation time before adding the bridging liquid leads to bigger and more elongated crystals. According to their report, needle-like particles are more difficult to pack than isotropic particles in this situation. They also changed the stirring time after the addition of bridging liquid. Their results showed that the spherical shape of the agglomerates does not appear immediately but develops gradually [68].

### 3.7. Temperature of the system

Temperature has a major influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is maybe due to its effect on the drug solubility [69]. Kawashima et al. [1984] tested the temperature influence on the spherical agglomeration of salicylic acid in a tertiary system (water-ethanol-chloroform). By increasing the temperature, the solubility of drugs is increased and then a decrease in the recovery of the crystals is observed. At lower temperature, recovery of the crystals increases and the constituent crystal size and the solubility of chloroform in the solvent mixture diminishes [70]. Furthermore,

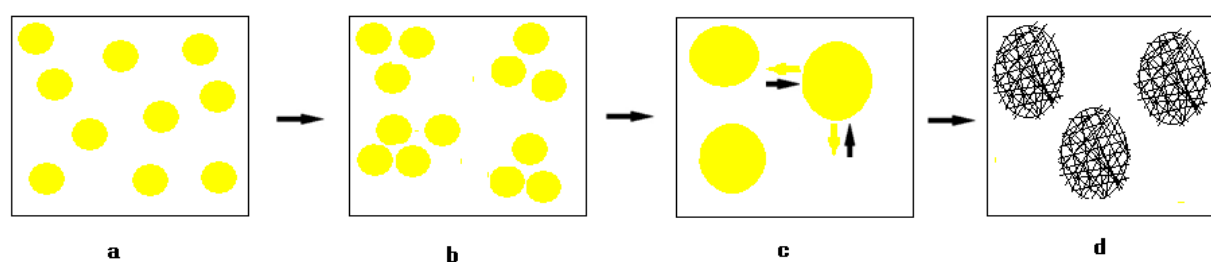
temperature has an effect on the crystallization stages such as nucleation, crystallization and agglomeration of crystals. According to Kawashima and Capes [1984], spherical agglomeration follows first order kinetics with respect to increasing number of agglomerates with time. The bulk density of the agglomerates also decreases by increasing the crystallization temperature [70].

### 3.8. Residence time

The residence time that agglomerates remain suspended in reaction mixture influences the size, shape and strength of agglomerates. During long residence time because of the solubilization of the agglomerates by the bridging liquid, the agglomerates break down into smaller crystals and the size of agglomerated particles decreases [32]. Then the optimization of residence time for the agglomeration of recrystallized crystals is necessary. Below the optimized residence time, incomplete effusion of good solvent and bridging liquid from the formed droplets in the dispersion medium leads to the incomplete agglomeration [32].

## 4. Quasi-emulsion solvent diffusion

In this process, the quasi-emulsion of drug solution in good solvent with a poor solvent (non-solvent) is formed. Due to counter diffusion of good solvent and poor solvent, crystallization of the drug occurs. Stabilization of emulsion by proper polymer is required in this method. In fact, the drug and polymer are co-precipitated in order to form drug crystals according to the polymer properties. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals [8, 27].



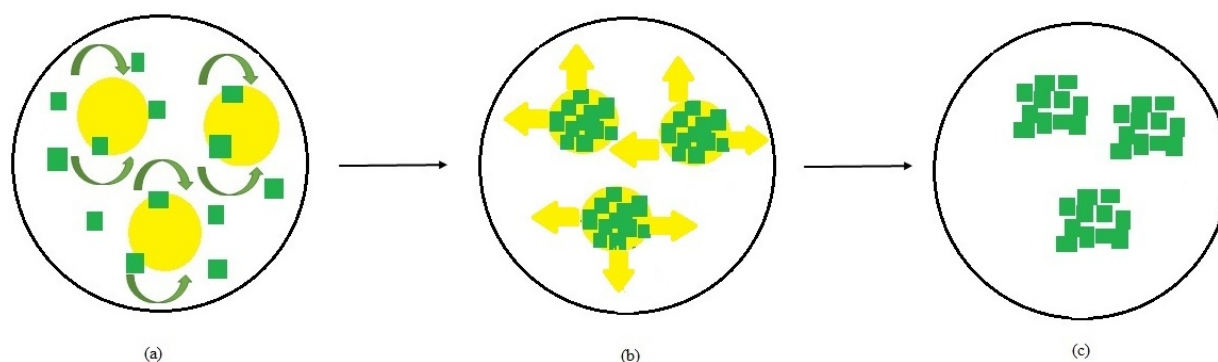
**Figure 5.** The mechanism of emulsion solvent diffusion method: a) emulsion formation, b) coalescence of emulsion droplet, c) diffusion of good solvent to outer phase and poor solvent into of the droplet, d) growth of crystal shell and final agglomerates

Patil and Sahoo prepared the spherical agglomerates of glibenclamide by emulsion solvent diffusion method. They used methanol, chloroform and water as good solvent, bridging liquid and poor solvent respectively. According to their results, particle size, flowability, compactibility and packability of plane and agglomerates with additives except with polyvinyl pyrrolidone were preferably improved for direct tableting compared with raw crystals of glibenclamide. Their results also showed significant improvement in solubility and dissolution

rate of plane and agglomerates with additives except with polyvinyl pyrrolidone, compared with the raw crystals of the drug. The authors believe that improved properties of spherically agglomerated crystals is due to their large and spherical shape and enhanced fragmentation during compaction that is supported by increased tensile strength and less elastic recovery of its compact [28]. The mechanism of emulsion solvent diffusion method is shown in Figure 5.

## 5. Ammonia diffusion method

Ammonia diffusion components consist of ammonia water as a good solvent and also bridging solvent, poor solvent and hydrocarbon or halogenated hydrocarbon (acetone). The hydrocarbon is miscible with the system, and it should reduce the miscibility of the ammonia water with poor solvent. The diffusion process across the droplet consists of moving poor solvent inside and ammonia out of the droplet. Then the drug crystals precipitate in ammonia water slowly and agglomerates are grown [8, 27]. Figure 6 shows this process.



**Figure 6.** Ammonia diffusion method for preparation of spherical crystallization: a) movement of poor solvent into the droplet, b) movement of ammonia out of the droplet, c) the drug crystals precipitate in ammonia water slowly and agglomerates are grown

## 6. Crystallo-Co-Agglomeration (CCA) technique

Due to the hydrophobic nature of most excipients, incorporation of them in the formed agglomerates using organic bridging liquid is complicated [71, 72]. Then spherical agglomeration could not be employed for low-dose or poorly compressible materials. Crystallo-co-agglomeration technique is one of the novel particles designing technique (developed by Kadam et al) that could be able to overcome the mentioned limitation of spherical crystallization [30]. This process includes continuous stirring of drug and excipients in liquid medium. The continuous stirring is necessary for loading of the drug consistently in the agglomerates. In expansion concept, crystallo-co-agglomeration technique involves simultaneous crystallization and agglomeration of drug substance with or without excipients from good solvent and/or bridging liquid by the addition of a poor solvent. The formed crystal of drug has minuscular

form and therefore the drug dissolution and bioavailability are improved by using this method [73, 74]. Sometimes bridging liquid also serves as a good solvent. To overcome drug loss due to co-solvency, the good solvent should be volatile and immiscible with poor solvent [74].

Bridging liquid can affect on the rate of agglomeration and also on the strength of the agglomerates. Smaller amount of the bridging liquid leads to fine particles whereas larger amount produces coarse particles. When the stirring rate is increased, the agglomeration will be reduced (because of increasing disruptive forces). Porosity diminishes by increasing concentration of the solid [66].

Commonly the crystallo-co-agglomeration method can be performed in two ways: solvent change method and alternate method [75]. In solvent change method, crystallo-co-agglomerates can be obtained by the crystallization as well as the agglomeration. One or more drugs simultaneously crystallize and agglomerate from the system containing good solvent and bridging liquid by the addition of a poor solvent. In the alternate method, the crystallization of drug is performed from a system containing good solvent and bridging liquid and then its simultaneous agglomeration is done with an insoluble diluent or a drug by the addition of a poor solvent. Figure 7 shows the steps involved in crystallo-co-agglomeration technique [76].

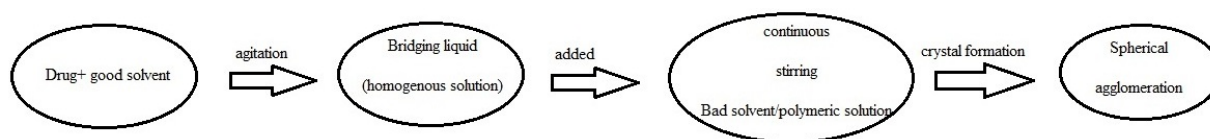


Figure 7. Steps involved in crystallo-co-agglomeration technique

### 6.1. The effect of various factors on crystallo-co-agglomeration process

Crystallo-co-agglomeration technique depends on numerous factors such as the formulation and process variables which have an effect on the processes of crystallization and agglomeration. The selection of diluent, solvent system, internal phase, amount and type of polymers will have an influence on the final agglomerates [75].

Excipients and polymers play a key role in the preparation of crystallo-co-agglomerates, an excellent alternative to wet granulation process to prepare particles for direct compression [77]. The difference in the physicochemical properties of the drug molecules and the excipient is the main factor in the selection of a solvent system for the crystallo-co-agglomeration technique. Various polymers like hydroxy propyl methylcellulose (HPMC), poly ethylene glycol (PEG), ethyl cellulose (EC) and poly vinyl pyrrolidone (PVP) may be used to improve poor compressibility and handling qualities of pure drugs by crystallo-co-agglomeration technique [75]. The micromeritic and drug release properties of the agglomerates are improved as well. About low dose drugs, diluents are applied for the enlargement of size in the crystallo-co-agglomeration technique. Diluents should be inert and inexpensive. They should also be insoluble in aqueous phase so that the drug loss through the continuous or external phase be avoided [74].



In preparation of directly compressible agglomerates, excipients should have affinity toward the bridging liquid. Talc is a hydrophobic excipient and has preferential wetting with bridging liquid therefore is a suitable excipients for incorporation in the crystallo-co-agglomeration process [30, 71, 74].

## 6.2. Advantages of crystallo-co-agglomerates

Agglomerates which are prepared using crystallo-co-agglomeration technique have numerous advantages compared to other spherical agglomeration methods. Excellent flow properties, large surface area and less chances of dose dumping from final crystals are some of these advantages. Large surface area leads to uniform distribution of the drug through gastrointestinal tract and therefore better absorption and bioavailability is achieved and the toxicity is also reduced.

Unlike SA, CCA is utilizable for size enlargement of all, low dose, high dose, single, two, or more drugs in combination with or without diluent [78].

Furthermore, the single step generation of agglomerate, less processing cost, less number of unit operations and simplicity of the process adapted it to an economic method. In fact, simplicity and capability to generate spherical agglomerates in a single step are the reasons for the unique place of crystallo-co-agglomerates technique in the oral drug delivery route. By crystallo-co-agglomerates technique and proper selection of suitable excipients and polymers, modified release of drug substances from drug-loaded agglomerates is achievable [30, 71, 74]. It is also possible to create placebo drugs by producing agglomerates of plain excipients (talc agglomerates) [74].

## 7. Conclusion

Spherical crystallization is the novel particle design technique, in that crystallization and agglomeration may be carried out simultaneously in one step and could be able to transform the fine crystals into a spherical shape directly. In consequence of these modifications, certain micrometric properties may also be modified. Then this technique is an efficient method in the optimization of crystal properties for modifying the required micrometric and dissolution properties of the drugs. In this method, agglomerates with higher bulk density, better flowability and compactibility will be obtained. Then the spherical crystallization can be applied for manufacturing spherical crystals of poorly soluble drugs in order to improve their flowability and compactibility properties. This technique also is helpful in improving wettability, bioavailability and dissolution rate of these types of drugs. An optimized spherical crystallization process, concerning the form of the agglomerates and reproducibility of the product, can be applied as an attractive approach for direct tabletting. The final tablet dosage form prepared using spherical crystallization technique exhibits improvements in strength, hardness, friability, disintegration profile and dissolution rate compared to those prepared using granulation method. As a noticeable point, proper selection of solvent, bridging liquid and diluents has an influence on the release, dissolution, absorption and bioavailability of the



drug substance and reduce toxicity as well. Agglomerates prepared by crystallo-co-agglomeration technique have numerous advantages over the spherical agglomerates. Spherical agglomeration could not be employed for low-dose or poorly compressible materials due to hydrophobic nature of the most excipients. In crystallo-co-agglomeration process, designing of agglomerates containing two drugs or a low-dose or poorly compressible drug in combination with diluents is possible. On the whole, spherical crystallization technique seems to be promising technique in which the drug crystals are changed by applying different solvents for obtaining direct compressible spherical agglomerates. This leads to save money and time in tablet making processes. If it is able to scale up, the direct compression of poorly compressible drugs will be feasible. Other agglomeration techniques are still less economical than direct compression tableting. As an important point, in this process the residues of organic solvent after the formation of agglomerates should be monitored.

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