Advances in Biological Research 5 (6): 273-281, 2011
ISSN 1992-0067


# A Review on Recent Advancement in Crystallo-co-Agglomeration

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**Abstract:** Particle size enlargement is an important process in manufacturing of tablets to impart some degree of functionality to particles such as improvement in flowability, solubility, dissolution, micromeritic, compression and compactability properties. Crystallo-co-agglomeration is a novel technique for enlargement of particle size developed to overcome the limitations of spherical crystallization and used for size enlargement of all low dose, high dose, poorly compressible drugs and combination of drugs with or without diluent. In this technique drug is simultaneously crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system, using bridging liquid. The manufacturing technique and evaluation parameters for crystallo-co-agglomerates have also been detailed in this review. This technique is simple and carried out in a single step and more advantageous due to less number of unit operations and economic in terms of processing cost. In recent years this technique has been applied to produce spherical agglomerates with improved micromeritic, mechanical and compressional properties. These prepared spherical agglomerates can be used as a tablet intermediates or in design of multiple unit particulate drug delivery systems with improve drug release properties.

**Key words:** Spherical crystallization · Spherical agglomerates · Multiple unit particulate drug delivery systems.

## INTRODUCTION

With increase advancement in powder technology, different attempts are taken to design primary and secondary particles of pharmaceutical substances for several applications [1]. Enlargement of particle size is an important process in manufacturing of tablets and is used to impart some degree of functionality to particles such as improvement in flowability, solubility, dissolution, micromeritic, compression and compactability properties [2, 3]. Different techniques for enlargement of particle size are an important tool in modifying primary and secondary properties of pharmaceutical substances. Nowadays several new techniques combining granulation and crystallization are being developed to improve particle properties [4]. There are various conventional process which are used to enlarge the particle size and involves wider acceptability but recently different non-conventional techniques of particle size enlargement are being developed which include extrusion-spheronization, melt solidification, melt granulation, melt extrusion and spherical crystallization [5-10]. These techniques are advantageous due to less number of unit operations and economic in term of processing cost and depend on the desired properties of the enlarged particle and the physico-chemical properties of the drug and excipients [11].

Spherical crystallization is a non-conventional technique better in comparison to other conventional crystallization technique used for enlargement of particle-size involves simultaneous agglomeration along with crystallization with help of using bridging liquid [12]. Several techniques have been used to attain supersaturation during spherical crystallization used to obtain directly compressible agglomerates of a single water-insoluble drug containing large dose and rarely in combination with a diluent [13, 14]. There are not so much works regarding this technique to obtain agglomerates of more than one drug [15]. This technique is restricted to only water insoluble large dose drugs because several excipients such as disintegrating agent and diluent are hydrophilic in nature hence addition of these excipients in the agglomerates with help of organic bridging liquid is difficult. Due of this limitation, spherical crystallization

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can not be used to obtain agglomerates of low-dose or poorly compressible materials [16, 17].

Recently a novel technique was developed by Kadam *et al.* to overcome the limitations of spherical crystallization, known as crystallo-co-agglomeration [18]. It is a modification of the spherical crystallization technique and used for size enlargement of all, low dose, high dose, poorly compressible drugs and combination of drugs with or without diluents. In this technique drug is directly crystallized and agglomerated in combination with an excipient or with another drug with help of bridging liquid. Excipient or drug may or may not be crystallized in the system [19]. An excipient which is used in this technique should have affinity toward the bridging liquid. Solvent selection for the crystallo-co-agglomeration technique is a major challenge due to difference in the physicochemical properties of the drug molecules and the excipients [20]. In recent studies this technique has been considered as unique place in oral drug delivery system because of its simplicity and ability to generate spherical agglomerates in a single step [11]. Now a days this technique has been used as a novel technique to produce spherical agglomerates with improved micromeritic, mechanical and compressional properties in design of multiple unit particulate drug delivery systems. Agglomeration process is also used to produce controlled drug release with help of different polymers [20].

**Advantages of Crystallo-Co-Agglomeration:** Crystallo-co-agglomeration has various advantages over the spherical crystallization and other particle enlargement techniques which are given as below [11, 20, 21].

- Very simple in comparison to other particle enlargement techniques
- Less number of unit operations
- Economic in terms of processing cost
- Ability to generate spherical agglomerates in a single step
- Less manpower requirement because one person can easily handle the whole agglomeration process due to less shear required for stirring the liquid system as compare to mixing of powders in other granulation methods
- Proper GMP considerations because it is a single step process, carried out in a closed system preventing contamination and dust generation
- Obtained spherical agglomerates are used as a tablet intermediates and in design of multiple unit particulate drug delivery system

**Limitations of Crystallo-co-Agglomeration:** Crystallo-co-agglomeration has been developed to overcome the limitations of spherical crystallization but still it has some difficulties related to formulation and process which are given as below [21]:

- There are many formulation and process variables so it can causes difficulty in reproducibility.
- Similar physico-chemical properties of the drug combinations cause difficulty in simultaneous crystallization of drug combination at same solvent, pH or temperature condition.
- It is difficult to scale up the filtration and drying process used in crystallo-co-agglomeration.
- Use of organic solvent can not be avoided.
- Increase drug loss due to more volume of external phase.
- More power requirement because of increase resistance for mixing of contents due to more external phase volume.
- Adding of disintegrant or superdisintegrant is difficult because aqueous phase has been considered as an external phase.

**Manufacturing Process:** In crystallo-co-agglomeration technique spherical agglomerates are prepared by simultaneous crystallization and agglomeration of particles in a single step. Solvent used for this technique must be volatile and immiscible with non-solvent to avoid drug loss due to co-solvency but it must be of such type so that it can easily solublise the drug [21]. System design also needs use of non-solvent to cause precipitation of drugs and bridging liquid which is used to form the liquid bridges between crystallized particles and insoluble solids and it must be immiscible with non-solvent. Selection of methods depends upon physicochemical properties of drugs and solvent systems. Once the method has been selected, process is carried out in a Morishima vessel using a propeller type stirrer and walled baffle designed by Morishima *et al.* for proper agitation [22]. Homogenous mixture of drugs, diluent, polymers, disintegrant, surfactants are placed in Morishima vessel and wetted by solvent and bridging liquid with proper stirring to form homogenous mass. Walled baffles is then placed in Morishima vessel with aqueous solution of polymer in bad solvent with continuous stirring at constant speed for definite time period until spherical agglomerates is prepared. Endpoint of the process depends upon the size of agglomerates, clarity of supernatant and vaporization of solvent from the system.

After completion of whole process, whole mass is filtered or decanted and washed with filtrate to prevent loss of drug and polymer. Then agglomerates are dried in hot air oven for 24 hours to obtain dried agglomerates [13, 17]. Crystallo-co-agglomeration process depends upon the various factors such as the formulation and process variables which affects the process of crystallization and agglomeration. The formulation variables depends upon the diluent selection, solvent system, internal phase, use of polymers, drug loading and process yield while the process variables is influenced by agitation and batch processing time in this technique [21].

**Factors Affecting the Process of Crystallo-Co-Agglomeration: Solvent System:** Selection of solvent system depends upon the stability and solubility characteristics of the drug. Physical form of final product can be controlled by proper selection of solvent proportions. A mutually immiscible three solvent such as good solvent, bridging liquid and poor solvent are necessary [23]. Mostly of the drugs are soluble in organic solvent due to this organic solvents are selected as good solvent or bridging liquid while water is used as poor solvent. The bridging liquid should wet the crystals to form liquid bridges during the process. Amount of bridging liquid to be used is determined by trial and error method or the ternary phase diagram. Good solvent should be volatile and immiscible with poor solvent to avoid drug loss due to co-solvency [21].

**Diluent Selection:** Diluents are used for size enlargement of drugs having low dose. It must be physiologically and physico-chemically inert and inexpensive. It must be insoluble in water to avoid the losses. It is reported by various investigators that talc is used as a successful diluent in crystallo-co-agglomeration process [21].

**Intensity and Mode of Agitation:** Agitation is necessary to support the process of dispersion of the internal phase into the external phase. High speed agitation is required to disperse the bridging liquid throughout the system. Any change in speed of agitation would affect the shape, size and strength of agglomerate. High speed agitation increases sphericity but reduces strength of agglomerates [24].

**Batch Processing Time:** Completion of the process depends upon the agitation time. Inadequate agitation may cause incomplete growth of agglomerates because of improper mixing of ingredients. It can also causes incomplete evaporation of an organic solvent from the vessel. Endpoint of the agglomeration process can be determined by clarity of the supernatant, attainment of proper size agglomerates and residual organic solvent [21].

**Temperature:** Temperature has also a significant effect on shape, size and strength of agglomerates because temperature directly affects the solubility of the drug [24].

**Advantages of Crystallo-co-Agglomerates:** Agglomerates prepared by this technique have several advantages over the spherical agglomerates prepared by other techniques which are given as below [25-28].

- Excellent flow characters
- Drug content uniformity due to continuous stirring
- Improve absorption and bioavailability of drugs due to miniscular form of drug
- Reproducible packing or filling
- Reduction in localized toxicity
- Uniform size distribution due to large surface area
- Improvement in the therapeutic qualities of dosage form due to good dosing and proper handling
- Due to low surface area to volume ratio they can be considered as an excellent coating substrate
- Less prone to physiological variables such as gastric emptying time
- Less chances of dose dumping

**Evaluation Parameter for Crystallo-Co-Agglomerates: Surface Topography:** Surface topography of agglomerates is evaluated to determine the bulk properties of the agglomerates. The agglomerates are photographed using an optical microscope with camera at original magnification. Photomicrographs of agglomerates are used to observe surface morphology [29].

**Differential Scanning Calorimetry:** Differential scanning calorimetry is used to measure the temperature and heat flow associated with transitions in material as a function of temperature and time. It provides qualitative and quantitative information regarding the heat loss or gain resulting from physical or chemical changes that involve endothermic or exothermic process within a minute amount of sample. It is also used to differentiate between the polymorphic forms of crystal. if mixture of drugs and polymer is agglomerated then change in properties of agglomerates such as purity, thermal degradation, polymorphism, drug-excipients compatibility

and salvation can be measured with help of differential scanning calorimetry [29]. Thermograms of agglomerates are performed using differential scanning calorimeter. The instrument is calibrated at higher temperature using pure indium. Accurately weighed samples are hermetically placed and sealed in an aluminum crucible to prevent moisture loss during heating. Nitrogen gas is used to purge the system at a flow rate of 60 mL/min then samples are scanned from 25°C to 350°C at a heating rate of 15°C/minute [30].

**Powder X-Ray Diffraction:** X-ray powder diffraction is an important technique for determining batch-to-batch reproducibility of a crystalline form. X-ray diffraction pattern is used to differentiate between crystal forms of a drug if it is not sufficiently identified by FTIR and DSC because each diffraction pattern is characteristics of a specific crystalline lattice for a given compound [31]. X-ray diffraction patterns are recorded using X-Ray diffractometer. Sample tubes are filled completely with sample and irradiated with monochromatized Cu Ka radiation and analyzed between 10° and 60° (2θ) at 30 kV voltages and 30 mA current. Finally, after running the sample on slow chart speed, all peaks on the chart corresponding to 2θ values are located and their values are written into the data chart and analyzed accordingly [32].

**Micromeritic Properties:** In order to get uniformity in tablet weight, the agglomerates must flow and pack smoothly into the die cavity of the tabletting punching machine. Therefore, micromeritic properties are evaluated for particle design of agglomerates for direct compression to improve the flow and packing properties of pharmaceutical powders [33]. Agglomerates are evaluated for flowability by the angle of repose using the fixed funnel free standing cone method. Particle size distribution is studied by sieve analysis. In this agglomerates retained on sieves are weighed and the resulting data are used to obtain the mean geometric diameter by plotting the cumulative percentage undersize versus the average particle size on log probability paper [34]. Values for angle of repose = 30 indicate free flowing material while angle of repose = 40 indicate poor flowing material [31].

**Sphericity Determination:** Sphericity of the agglomerates is the most important characteristics and different techniques have been used to determine it. For acceptable quality of agglomerates the shape factor should be between 1 and 1.2 while 0.6 value of shape factor describes good sphericity of agglomerates. The shape factor is determined by estimating the amount by which the projected image of particles deviate from a circle and calculated by means of the projected area of the agglomerates and its circumference [26]. Photomicrographs obtained by optical microscope are used to calculate the area (A) and perimeter (P') of agglomerates. The particle shape of both batches is measured by measuring the shape factor, circularity factor and length-to-width ratio [35].

$$\text{Shape Factor (P)} = P½/P'$$

Where $P'' = 2\pi (A/\pi)^{1/2}$

Circularity Factor (S) = $(P)^2 / (12.56 * A)$

**Crushing Strength:** Crushing strength is evaluated to determine mechanical strength because it directly reflects the mechanical strength of compact or tablet. Agglomerates should possess good mechanical strength because of increased intraparticle force with in the agglomerated crystals [31]. Crushing strength of agglomerates is determined by mercury load cell method. Agglomerates of different batches are randomly sampled and subjected to crushing strength determination and average was taken. The logarithmic relationship was established between crushing strength (CS) and agglomerate size as shown by the following equation [36]:

$$\log CS = m \log D + C$$

Where m is slope, D is agglomerate diameter and C is intercept calculated by regression analysis of the log D vs. log CS.

**Friability:** Friability test is characterized to ensure mechanical strength of agglomerates. The mechanical properties of agglomerates are taken an important part in processing of agglomerates. Agglomerates flake off during handling process resulting in formation of dust. For good mechanical strength, it is desirable to have agglomerates with low friability [26]. Friability study of agglomerates is performed by subjection to attrition in a ball mill to sieve nest of different mesh numbers using sieve shaker. After sieve analysis, fraction retained on each mesh is weighed and mean geometric diameter is obtained by fitting the data in Rosin-Rammler distribution. Percentage friability index (FI) is calculated by using the following equation [12]:

$$FI = [(dg)_f / (dg)_i] \times 100$$

Where $(dg)_f$ and $(dg)_i$ are mean geometric diameters after friability test and initially respectively.

**Contact Angle:** Contact angle is used to measure the wettability of agglomerates. Wettability increases with decrease in contact angle which shows improved dissolution. Agglomerates are compressed in compressed discs at high force by using hydraulic press. Samples which show sticking, picking and having non-uniform surfaces are not used for contact angle determination. A drop of deionized distilled water is placed on the disc using a micropipette. A photograph of the placed drop at magnification of 20 times is used to measure the contact angle [30].

**Pressure-Relative Density Relationship:** Any change in the formulation or process affects the density of agglomerates which may affect other process or factors such as filling and packaging characteristic during tablet compression [26]. Agglomerates are separately compressed by hydraulic press using flat faced punch and dies set at different pressures. Homogenous dispersion of lubricating agent is used for lubrication of dies and punches. Compacts are kept for 24 hrs in vacuum at ambient temperature and then data obtained are subjected to compressional studies by the Heckle equation [37]:

$$Ln (1 - P_f) = KP + A$$

Where $P_f$ is the packing fraction of tablet, P is applied pressure in tons, A is a constant which shows densification at low pressure and K is Heckle constant equal to $1/3\sigma_y$ where $\sigma_y$ is yield strength.

**Pressure-Tensile Strength Relationship:** After determination of pressure-relative density relationship compacts are used for determination of force required to break the compacts. Hardness of compacts is determined by hardness tester and used for tensile strength ($\sigma_t$) determination by the following equation [38]:

$$\sigma_t = 2F / \pi Dt$$

Where F is force required to break the compacts, D and t is diameter and thickness of compacts respectively.
Pressure-tensile strength data are applied to non-linear regression analysis to fit in to the Leuenberger equation to measure compression susceptibility ($\gamma$) and compactibility ($\sigma_{tmax}$) [39]:

$$\sigma_t = \sigma_{t\,max}[1 - e(\gamma P P_f)]$$

Where P is pressure and $P_f$ is pressure-relative density relationship.

***In-vitro* Dissolution:** Dissolution of a drug depends on the physicochemical and physicotechnical properties of drug particles. These agglomerates directly affect the absorption kinetics of a drug and thus affect bioavailability of dosage forms. In case of drugs having low solubility that makes absorption to be dissolution rate-limited, it is established that the modification of the polymorphic state of a compound increases solubility but the influence on other factors such as stability, biological efficacy, metabolism etc. as a result of change in polymorphic state demands a thorough investigation while using this approach [33]. USP dissolution apparatus is used to study the dissolution properties of agglomerates at 100 rpm and at a temperature of 37°C ± 2°C. 900 ml of phosphate buffer of pH 7.2 is used as dissolution medium. Agglomerates are compacted at high pressure by hydraulic press and subjected to dissolution in USP dissolution apparatus in triplicate. Samples are withdrawn at definite time intervals, passed through membrane filter and analyzed by UV-Visible spectrometer. Sink condition is also maintained by replacing the same amount of dissolution medium as amount withdrawn [40].

**Drug Content:** Agglomerates from different batches are weighed, powered and extracted using methanolic hydrochloride solution. After sufficient dilution sample is filtered through whatman filter paper and analyzed by UV-Visible spectrometer. Drug content is calculated by comparison with standard curve [41].

**Recent Studies and Current Trends:** Several pharmaceutical ingredients have been converted into crystallo-co-agglomerates for the improvements of several parameters. Agglomerates of naproxen containing disintegrant were prepared by Maghsoodi *et al.* using crystallo-*co*-agglomeration (CCA) technique. The improved compaction properties of the agglomerated crystals were due to the fragmentation which occurred during compression in direct tableting process without need to additional process of physical blending of agglomerates and disintegrants [42]. Pawar *et al.* prepared directly compressible agglomerates of ibuprofen-paracetamol using crystallo-co-agglomeration technique.

Different properties such as micromeritic, mechanical and compressional properties of agglomerates were affected by nature of the incorporated polymer. Ethylcellulose was used to impart good mechanical strength to the agglomerates as well as compacts and polyethylene glycol showed better compressibility but drug release was affected due to melting and yielding harder compacts [43]. Nokhodchi *et al.* prepared spherical crystals of carbamazepine by spherical crystallization technique to improve particle properties of drug for direct compression of tablets. Agglomerated carbamazepine crystals showed better mechanical and dissolution rate in comparison to untreated crystals [33].

Jadhav *et al.* were prepared agglomerates of talc containing low dose drug bromhexine hydrochloride using crystallo-co-agglomeration technique. Polyethylene glycol was used to impart the desired sphericity and hydroxypropyl methylcellulose was used to impart the mechanical strength to the agglomerates. This technique was used to generate heterogeneous matrix system and provide sustain drug release [44]. Paradkar *et al.* prepared Ibuprofen-talc agglomerates by crystallo-co-agglomeration technique. Prepared agglomerates showed zero-order release rate due to the combined effect of the miniscular form of drug and the hydrophobic nature of talc. Ibuprofen-talc agglomerates showed sustain release and drug release was extended up to 13 hrs [20].

Jadhav *et al.* investigated the effect of agglomerate size and drug content on mechanical, compressional and drug release properties of crystallo-co-agglomerates of bromhexine hydrochloride. Poor strength and large surface area of co-agglomerates were responsible for good compressibility while drug content was responsible for extended drug release from compact [45]. Chavda *et al.* prepared directly compressible spherical agglomerates of ketoprofen with improved flowability and compressibility by crystallo-co-agglomeration technique. Improvement in micromeritic properties and compactibility enabled direct compression without any defect and higher surface strength of agglomerates due to higher amount of talc [46]. Kadam *et al.* investigated the effect of concentration of polyethylene glycol and ethyl cellulose on the properties of agglomerates of ibuprofen-paracetamol obtained by crystallo-co-agglomeration technique and effect was studied by $2^2$ factorial design. Ethyl cellulose with polyethylene glycol showed higher resistance for fragmentation, modulus of elasticity and higher tensile strength [47].

Parrot *et al.* had used a mercury load cell method to study the crushing strength of agglomerates and investigated the effect of surface morphology of agglomerate on granule breakage and extent of deformation had been reported [36]. Peck *et al.* developed talc agglomerates for incorporation in tablets by fluidized bed granulation technique [48].

Table 1: List of various drugs on which crystallo-co-agglomeration technique has been attempted for improving tabletability

| | | Solvent system | | | |
|---|---|---|---|---|---|
| Drug | Crystallization medium | Good solvent | Bad solvent | Bridging liquid | Reference |
| Naproxen | Hydroxypropyl cellulose | Acetone | Water | Acetone | [42] |
| Ibuprofen-paracetamol | Polyethylene Glycol 6000, Polyvinyl Pyrollidone, Ethylcellulose | Dichloromethane | Water | Dichloromethane | [43] |
| Bromhexine hydrochloride | Polyethylene Glycol 6000 and Hydroxypropylmethyl cellulose | Dichloromethane | Water | Dichloromethane | [44] |
| Ibuprofen-paracetamol | Polyethylene glycol 6000, Ethylcellulose, Polyvinyl alcohol | Dichloromethane | Water | Dichloromethane | [47] |
| Ibuprofen | Polyethylene Glycol-6000, Hydroxypropylmethyl cellulose and Polyvinyl alcohol | Dichloromethane | Water | Dichloromethane | [20] |
| Ketoprofen-talc | Polyethylene Glycol 6000, Polyvinyl alcohol and Hydroxypropylmethyl cellulose | Dichloromethane | Water | Dichloromethane | [46] |
| Bromhexine hydrochloride-talc | Hydroxypropylmethyl cellulose and Polyethylene Glycol 6000 | Dichloromethane | Water | Dichloromethane | [45] |
| Indomethacin-Mepirizole | - | Ethyl acetate | Water | Ethyl acetate | [49] |

## CONCLUSION

Crystallo-co-agglomeration technique has been developed to overcome the limitations of spherical crystallization and used for size enlargement of all, low dose, high dose, poorly compressible drugs and combination of drug with or without diluent. It involves combination of crystallization and agglomeration using bridging liquid and crystallization medium. This technique is simple carried out in a single step and more advantageous due to less number of unit operations and economic in terms of processing cost. Proper selection of solvent, bridging liquid and diluent can increase the drug release and improve dissolution, absorption and bioavailability of drug and reduce localized toxicity. From recent studies, it can be concluded that this technique represents an efficient way of producing spherical agglomerates with improved micromeritic, mechanical and compressional properties in design of multiple unit particulate drug delivery systems. There is a wide scope of research in this area and it is continuously attracting the interest of researchers all over the world.

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