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NOVEL SOLUBILITY ENHANCEMENT METHOD: CRYSTALLO-CO-AGGLOMERATION (CCA) TECHNIQUE

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ABSTRACT

Crystallo-co-agglomeration (CCA) is an innovative technique developed with the intention to provide the drugs with good micromeritic and mechanical characteristics. The process of CCA involves crystallization followed by simultaneous agglomeration of the drug with the aid of a good solvent and/or a bridging liquid and a bad solvent. This process enables designing of spherical agglomerates containing low dose drugs which have poor flowability. This article contains a detailed insight on CCA, general strategies used for obtaining agglomerates, processing vessel, stages of growth, kinetics, solvent system, limitation, significance, applications and evaluation parameters.

KEYWORDS: Crystallo co-agglomeration, bad solvent, good solvent, crystallization, agglomeration.

INTRODUCTION

CCA is a novel technique, which uses the processes of crystallization and agglomeration simultaneously to be done of two or more drugs. Basically, it produces complex agglomerates of drug and excipients, which are directly compressible in nature. The term crystallo-co-agglomeration (CCA) indicates crystallization takes place with another moiety which may be a drug or external inert material. Spherical crystallization technique has limited application to only high actives whereas CCA was can be used for both high and low dose actives.[1,2] Crystallo-co-agglomeration (CCA) is an innovative technique developed with the intention to provide the drugs with good micromeritic and mechanical characteristics. The process of CCA involves crystallization followed by simultaneous agglomeration of the drug with the aid of a good solvent and/or a bridging liquid and a bad solvent. This process enables designing of spherical agglomerates containing low dose drugs which are poorly flowable and compressible.[3] The CCA require less processing time and may reduce the manufacturing as well as processing time during compression. The crystallo-co-agglomeration technique may be utilized to improve the micromeritic properties of powder materials utilized in direct compression. The resultant tablets may show improved crushing, compression, disintegration and dissolution profile when compared with the tablet utilizing other conventional methods.

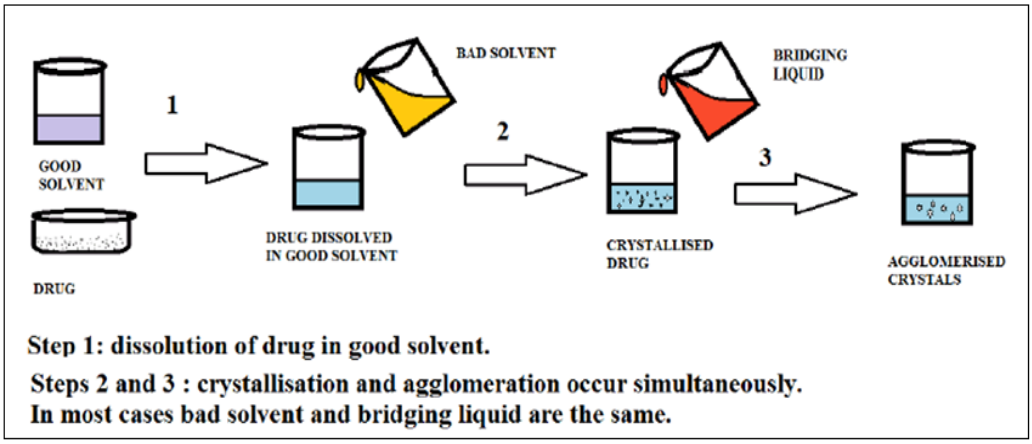

Figure 1: Formation of crystallo co-agglomerates.

PROCESSING VESSEL FOR CRYSTALLO-CO-AGGLOMERATION: MORISHIMA VESSEL[2,4,5]

The processing was done in a vessel designed and developed by Morishima et. al. for spherical crystallisation. It have a motor type propeller, a baffle which are enclosed in a vessel which is lidded and having provision for insertion of various ingredients. The vessel is placed in a thermostatically controlled water bath. Controlled agitation is required for the proper formation of agglomerates. The end point of the process can be determined by the clarity of the supernatant and vaporization of organic solvent from the agglomeration system.

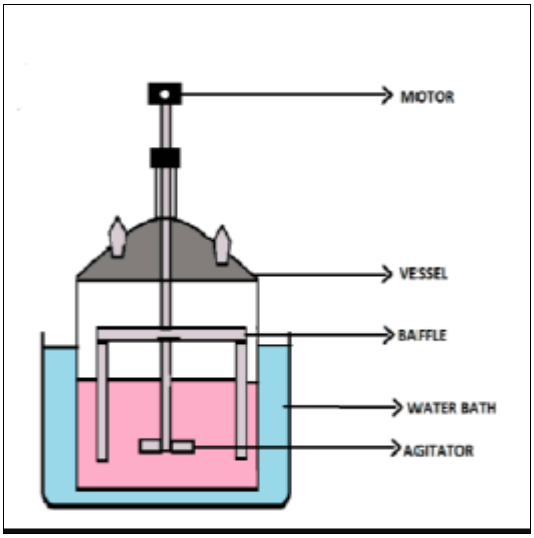

Figure 2: Morishima vessel.

GENERAL STRATEGIES ADOPTED FOR OBTAINING AGGLOMERATES[2,3,5,6]

The methods for obtaining agglomerated crystals can be categorized on the basis of achieving super saturation. The selection of method mainly depends on the nature of the drug and excipients as well as the objective of the study.

In general, drugs and excipients are dissolved separately in their respective solvents. Next, both are mixed in glass vessels with high-speed rotation (approximately 900 – 1000 rpm) to achieve uniformity. The mixture turns cloudy once the agglomerates are formed. Agglomerates are collected by filtering and kept for drying overnight at room temperature. Some of the methods for achieving agglomerates are given below.

A. Spherical agglomeration method[7,8] This method involves use of a quasi-saturated solution of a drug in a miscible solvent, which is poured into a poor solvent of the drug. It is essential that the good and the poor solvents are freely miscible and the binding force between the solvents is stronger than the solvent-solute interaction force with good solvent, for the crystals to precipitate immediately. Next an adequate amount of a third solvent, which is not miscible with the poor solvent but substantially wets the precipitated crystals, is added to the system by continuous stirring. The third solvent or the 'bridging liquid' collects the crystals suspended in the system by forming liquid bridges between the crystals due to the combined force of capillary pressure and interfacial tension at the interface of solid and liquid.

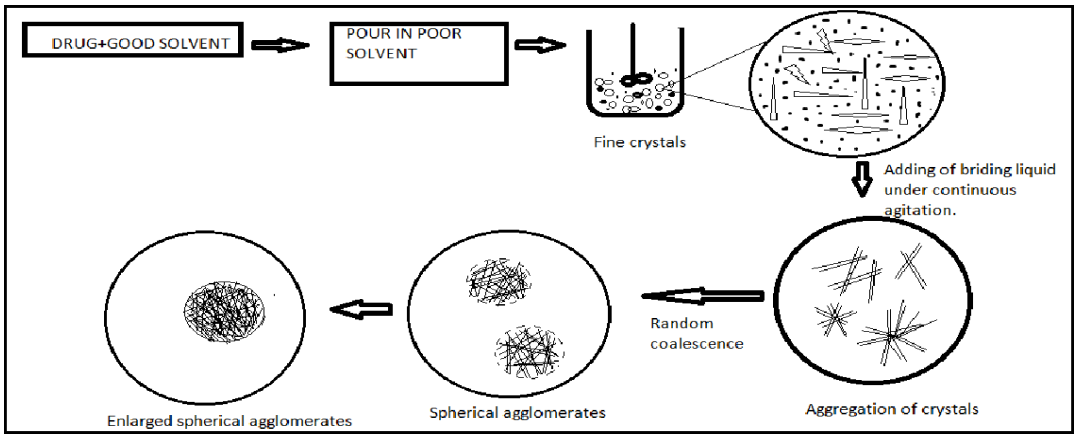

Figure 3: Spherical agglomeration method.

B. Quasi-emulsion solvent diffusion method[8,9] This method is applied when interaction between the drug and the good solvent is stronger than that of the good and poor solvent. First, concentrated drug solution is dispersed in the poor solvent, which produces quasi emulsion droplets due to an increase in interfacial tension between good and poor solvent. Next, the good solvent diffuses gradually out of the emulsion droplets into the outer poor-solvent phase. The counter-diffusion of the poor solvent into the droplet induces crystallization of the drug within the droplet due to its decreased solubility in the poor solvent. This process is also known as the emulsion solvent diffusion process.

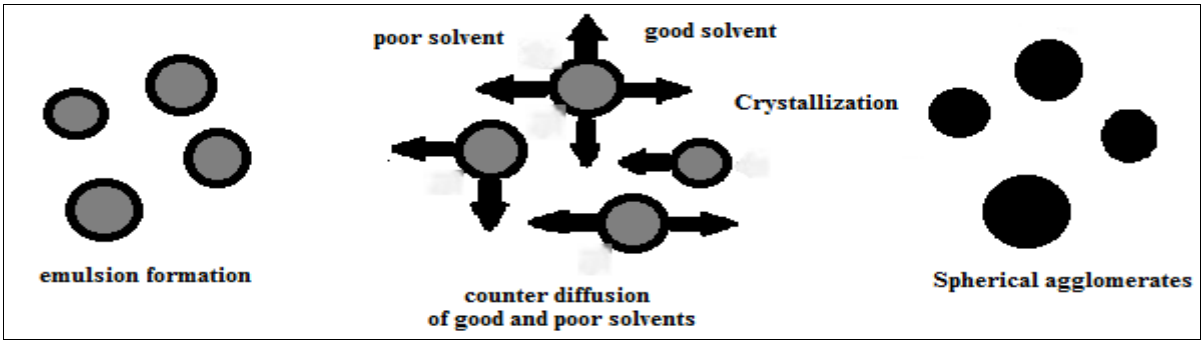

Figure 4: Quasi-emulsion solvent diffusion method.

C. Ammonia diffusion method[7,8] This method can be applied to amphoteric drugs only. It consists of three components: ammonia water acting as good solvent as well as bridging solvent, a bad solvent and a hydrocarbon/halogenated hydrocarbon. The hydrocarbon should be miscible with the system but it should reduce the miscibility of ammonia water with the bad solvent. First, the drug which is dissolved in ammonia water is precipitated and the crystals are collected. Simultaneously as ammonia in the agglomerates diffuses to the organic solvent, its capability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed.

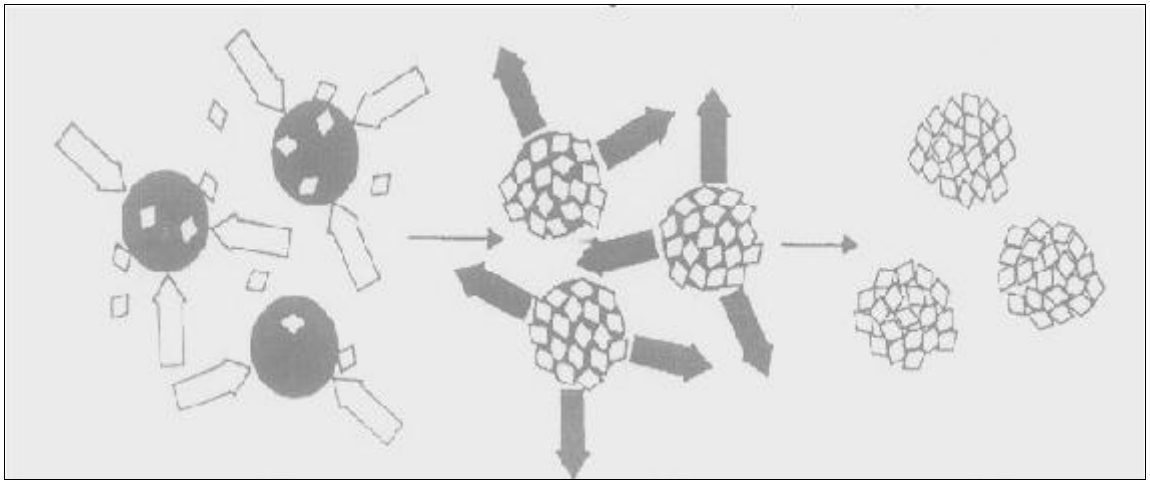

Figure 5- Ammonia diffusion method.

STAGES OF GROWTH OF AGGLOMERATION[10,11]

The growth of agglomerates follow a sequence of zonal divisions.

A. Flocculation zone I- In the flocculation zone, the bridging liquid displaces the solvent from the surface of the particle and and loose flocs are formed by pendular bridges. In the zero growth zone, the loose floccules convert into tightly packed aggregates. The entrapped liquid seeps to the surface of the small floccules.

B. Zero growth zone- In the zero growth zone, the squeezing out of the bridging liquid from the pores of the initial floccules for the formation of the small agglomerates is the rate-limiting step in agglomeration growth process.

C. Fast growth zone- The fast growth zone can be observed at the point where the sufficient amount of bridging liquid has been squeezed out of the surface of the small agglomerates.[39] In the process of coalescence, the large size particles form by the random collision of the well-formed nucleus. For the collision process to be successful, slightly excess surface moisture on the nucleus is required.

D. Constant size zone- The constant size zone involves the arresting of agglomeration growth. Even a slight reduction of size of agglomerates is seen due to attrition, fracture, and shatter.

KINETICS FOR SPHERICAL CRYSTALLIZATION & CRYSTALLO-CO-AGGLOMERATION[12,13]

Initial works reported that spherical crystallization follows first order or second order kinetics, but detailed work on mechanism of agglomeration have shown that agglomeration process follows first order kinetics.[8] This behaviour is explained by the restricted movement of particles in space due to particle interaction, such as layering agglomerates of fine particles on coarse ones.

Spherical crystallization process has been described by a selective coalescence mechanism. The kinetic equation is,

$\text{Log } d = C \log t + C'(\lambda)$

Where, d = diameter of agglomerates (mm)

t = agglomeration time (min)

C' (λ) = function of coalescence time

C = constant

During crystallo-co-agglomeration process, agglomerates were spheronized and compacted. The compaction process of agglomerates was represented by the changes in porosity of agglomerates with agglomeration time. The agglomerates were more easily compacted by increase in agitation speed and amount of bridging liquid, because they increase the sheer force applied to agglomerates as well as enhance the plasticity.[6,7,9]

SOLVENT SYSTEM IN CRYSTALLO-CO-AGGLOMERATION:

The important factor in the process design of crystallo-co-agglomeration is the solvent system. The solvent used contains three components- A good solvent (volatile), bridging liquid and a non-solvent.[12,13,15]

Good solvent- It solubilises the drug while the non-solvent causes the crystallisation or precipitation. It is essential that the bridging liquid and good solvent must be immiscible.

The bridging liquid- It helps in the formation of crystal bridges between crystals and the insoluble particles during the process of agglomeration. In times, they act as good solvent also. As most of the drugs are non-polar and highly soluble in organic solvents, they are preferred as the good solvent as well as the bridging liquid. So automatically, an aqueous solvent is used as the non-solvent. The bridging liquid should carry out preferential wetting of crystals/solids and form liquid bridges during the process of agglomeration, and simultaneously, it should be immiscible with a non-solvent. If bridging liquid is used as a good solvent, it means, it performs dual role of a good solvent and bridging liquid. The good solvent used should be volatile and immiscible with non-solvent to avoid drug loss due to co-solvency. Amount of bridging liquid required can be decided by the trial and error method or the ternary phase diagram. It has been observed that if addition of bridging liquid becomes inadequate, then it leads to generation of smaller size agglomerates with more percentage of fines. And, excess addition of bridging liquid generates bigger size agglomerates and requires more processing time for completion of the agglomeration process.[4.5,7]

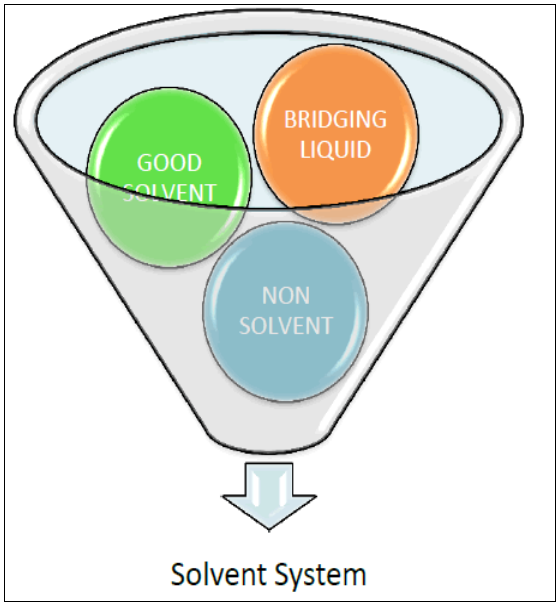

Figure 6: Solvent system used in formulation of CCA.

The process of Crystallo-co-agglomeration can be done in two ways. Solvent change is the most commonly used method for obtaining crystallo-co-agglomerates. The two methods are discussed below.[2,8,10,11]

a) Solvent change method- In solvent change method, Crystallo-co-agglomerates can be obtained by the crystallization as well as the agglomeration. It takes place when one or more drugs are mixed simultaneously from the system containing good solvent and bridging liquid by the addition of a non-solvent.

b) Alternate method- In the alternate method, first, the crystallisation of the drug is done from a system containing good solvent and bridging liquid and then its simultaneous agglomeration is carried out with an insoluble diluent or a drug by the addition of a non-solvent.

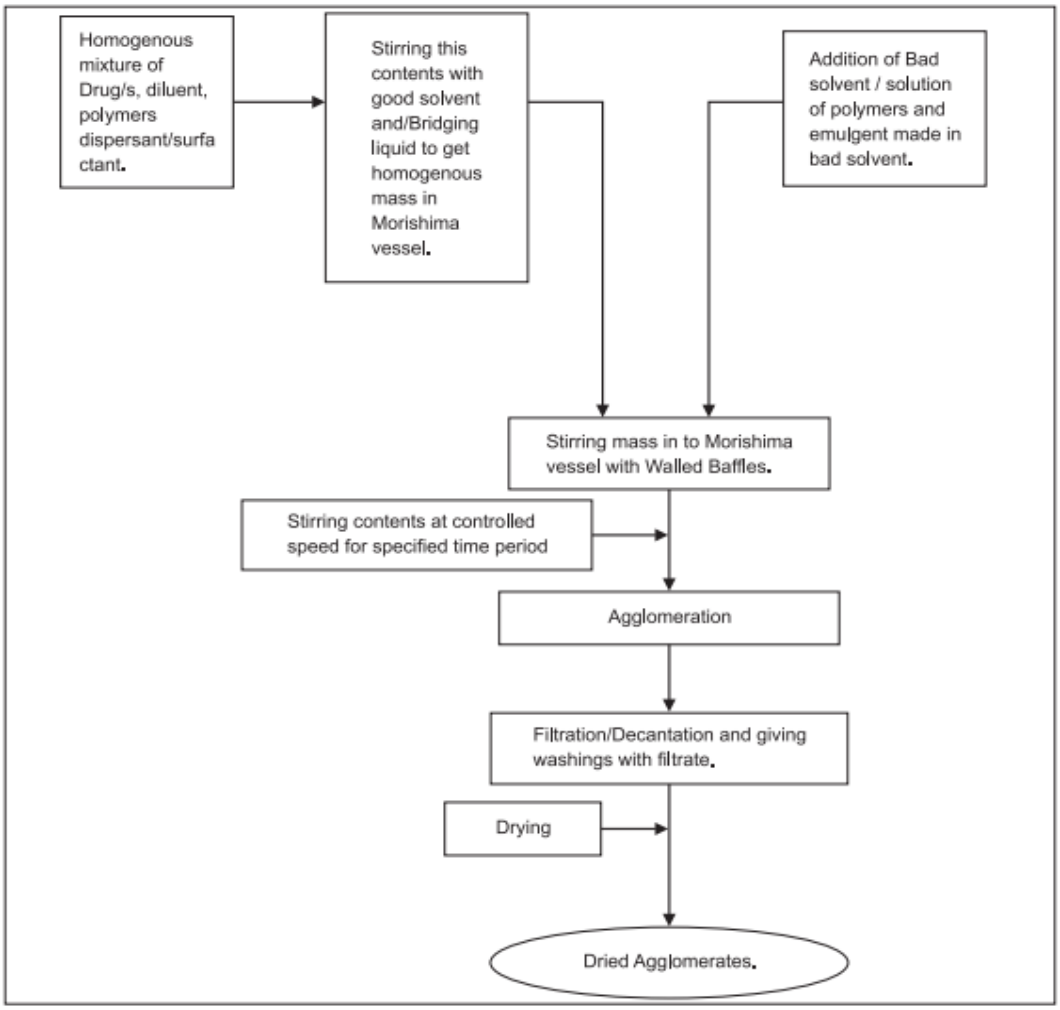

Figure 7: Generalized flow sheet for CCA process.

FACTORS AFFECTING CRYSTALLO-CO-AGGLOMERATION

Physicochemical parameters specifically the drug solubility is shown to have highly significant effects on quality of agglomerates. Crystallization is affected by formulation parameters like source, grade and concentration of excipients used. The type of the polymer usually affects the quality of crystallization. The experimental methodology like type of bridging liquid, concentration of bridging liquid, temperature, agitation speed, and mode of addition of bridging liquid also affect the quality of agglomerates. Process parameters like stirring and cooling rate can affect the final yield.[3,5,14,15]

a) Diluents: These are used for the enlargement of size in low dose drugs. The main characters required for diluents in this process are.

- They should be physico chemically and physically inert and inexpensive.
- They should be insoluble in aqueous phase so that the drug loss through the continuous or external phase can be avoided. One of the most commonly used diluents is talc.

b) Temperature: The Temperature has an effect in the size, shape and strength of the agglomerate. Various studies indicate that the increased temperature will result in increased solubility and as a result there will be more drug loss through supernatant liquid. In most of the cases, temperature is kept as low.

c) Polymers: It was found that the Crystallo-co-agglomerates of pure drugs have poor compressibility and handling qualities. This will prevent the use of direct compressing in tablet making and thus fails the purpose. So various polymers like hydroxy propyl methylcellulose (HPMC), poly ethylene glycol (PEG), ethyl cellulose (EC) and poly vinyl pyruvate (PVP) were used. This improves the micromeritic mechanical and drug release properties of the agglomerates.[14,15]

i. Hydroxy propyl methyl cellulose.

- Provides adequate sphericity and mechanical strength to the agglomerates when used in optimum quantity.
- The excess addition of HPMC will result in deformation and ellipticity of the agglomerates.

ii. Poly ethylene glycol

- It will reduce the interfacial tension between external phase (water and bridging liquid). Thus it reduces the cohesive force and produces small sized agglomerates.
- The agglomerates formed using PEGs are soft and plastic in nature. This will cause plastic deformation and there by provides better compressibility.

iii. Ethyl cellulose

- It provides high yield strength (On crystallisation in non-solvent imparts more strength to the agglomerates).

So in conclusion to have agglomerates of satisfactory sphericity, strength and compacts having adequate strength, the combination of HPMC, PEG and EC in appropriate proportions are used.[5,6.10]

d) Dispersion of internal phase: The internal phase (drug suspension with or without diluents and bridging liquid) should be easily dispersed or emulsified in the external phase. This step can be assisted by distributing agents or dispersants. For this purpose surfactants and hydrophilic polymers like polysorbates, PVP, Polyvinyl alcohol (PVA) can be used in optimum concentrations.[12,13]

e) Drug loading: It was found that the extent of drug loading changes the requirement of solvent system. It has a pronounced effect on the quality of agglomerates. Increased drug loading may result in increased loss of drug through external phase. If the system has an insoluble diluents or excipient there is a chance for the crystallised drug to get deposited on its surface.

f) Loss of drug to supernatant: The loss of drug through supernatant liquid has a significant role in determining the extent of drug entrapment and the overall efficiency of the crystallo-co-agglomeration. It should be ensured that maximum crystallisation and agglomeration occurs during agitation.[8,10]

In order to minimize the loss of drug to the supernatant fluid the following points should be assured.

- ✓ Maintaining low temperature.
- ✓ pH adjustments.
- ✓ Addition of solubility suppressants to the external phase.

g) Yield of the process: The process yield depends on the amount of crystallisation occurred from the good solvent as well as the extent of agglomeration from the bridging liquid. Thus the selection of solvent system holds an important role in the process yield of crystallo-co-agglomeration. The solubilisation of drug is determined by the good solvent and the crystallisation is done by the non solvent. The bridging is an interparticular interaction. Hence for obtaining desirable yield proper selection of solvent system is recommended.[12,13]

Process variables[1,10,12]

a) Agitation: The main function of agitation is emulsification or dispersion. The size, shape, sphericity and strength of the agglomerates were affected by agitation. High speed agitation may result in increased sphericity and decreased strength of the agglomerates. It was also found that with the increase in speed of agitation, it may decrease the time required for the process and it decreases the agglomeration.[1,10]

b) Time required for batch processing: The time of agitation decides the completion of agglomeration. Incomplete agitation leads to incomplete mixing of various ingredients, thus incomplete growth of agglomerates. This also reduces the evaporation of organic solvents from the reaction vessel, while excess agitation result in fine formation. The end point of agglomeration determination is critical in CCA. It can be found out by judging the clarity of the supernatant, residual organic solvent and attainment of proper agglomerate size.[10,12]

LIMITATIONS OF CCA[9,10]

1. Use of organic solvent cannot be avoided.
2. It's difficult to have the similar physico-chemical properties of drug combinations to be crystallo-coagglomerated. Their simultaneous crystallization at the same solvent, pH, or temperature condition is difficult.
3. External/processing phase volume is always more, due to which drug losses may get increased.
4. Due to more external phase volume, resistance for mixing of contents gets increased and as a consequence power requirement also increases.
5. Since, the aqueous phase has been recommended as an external/processing phase, incorporation of disintegrant/ superdisintegrant to the agglomerates is difficult.
6. Technique has multiple formulation and process variables, hence, difficulty in reproducibility.
7. Filtration and drying stages are difficult to be scaled up.
8. It is not suitable for poorly compressible excipients as well as low dose (potent) drugs.

EVALUATION PARAMETERS OF AGGLOMERATES[3,5,8,13,15]

a) Yield: Yield of the agglomerates is the most crucial of all the evaluation parameters. Active ingredients are expensive and if the yield of the drug agglomerates complex is below 80-90%, (depending upon cost) the process may become commercially unviable. So far the yield reported by various researchers in range between 90 to 98 %.

b) Drug content: This represents the percentage of drug in the drug-agglomerates complex. In simple terms it is the percentage purity. Some of the researchers had reported that the drug content between 51 to 58% was optimum. The increase in bulk due to incorporation of excipients in the drug-agglomerate complex is thought to be advantageous for the formulation of potent drugs. However, it could be a problem where the dose is high.

c) Micromeritic properties: This property is the most important in terms of compressibility. During the compression particles are deformed or broken under pressure. Resistance to the pressure is intrinsic property of the crystals. Hence micromeritics of drug-agglomerates is an evaluation parameter.

(1) Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Angle of repose has been used as indirect method of quantifying powder flow ability. Angle of repose for blend of each formulation was determined by fixed funnel method. The fixed funnel method employs a funnel that is secured with its tip at given height, h, which was kept 2 cm, above graph paper that was placed on a flat horizontal surface. With r, being the radius of base of conical pile, angle of repose can be determined using following equation.

$$\tan\theta = \frac{h}{r}$$

Where; θ = Angle of repose
r = Radius of the base
h =Height from tip of funnel to the surface of graph paper.

Table no. 1: Grading of powder flow property according to angle of repose.

Angle of repose	Flow Property
<25	Excellent
25 -30	Good
30 -40	Passable
> 40	Very poor

(2) Bulk density

It is the ratio of mass to bulk volume. It is required to decide the appropriate packing of dosage forms. An accurately weighed 20 gm powder was allowed to flow in a fine stream into a graduated cylinder and final volume was noted. The bulk density was obtained by dividing the weight of the sample in grams by final volume in cm^3 and it was determined by equation given below.

$$Bulk\ density = \frac{mass\ of\ powder}{Bulk\ volume}$$

(3) Tap density

An accurately weighed 20 gm powder was allowed to flow in a fine stream into a graduated cylinder of a mechanical tapping device. The measuring cylinder was tapped for 100 times and final tapped volume was noted. The tapped density was obtained by dividing the weight of the sample in grams by final tapped volume in cm^3 and it was calculated by using equation given below.

$$Tap\ density = \frac{mass\ of\ powder}{Tapped\ volume}$$

(4) Hausner's ratio

Hausner found that the ratio of tapped density/bulk density was related to inter particle friction as such, and could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas more cohesive less free flowing powders have ratio greater than 1.6. A Hausner's ratio of less than 1.25 indicates good flow properties of the powder blends or granules.

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

(5) Bulkiness

Specific bulk volume or reciprocal of bulk density is called as the bulkiness. Bulkiness increases with the decrease in particle size.

$$Bulkiness = \frac{1}{Bulk\ density}$$

d) Surface topography: Surface character of the drug-agglomerate becomes important in terms of binding, finish and glossiness. Increased compression pressure makes smoother tablet surface, which increases the acceptability. A change in surface roughness was thought to be the most likely reason. Hence surface topography is an important evaluation parameter. Scanning electron microscopy can be used.

e) Drug-excipient interaction: From formulation viewpoint, drug-excipient interactions may be categorized in two types.
(1) Planned or intentional interactions and
(2) Accidental interactions.

Drug-excipient interactions may affect the stability of the formulation. They may lead to either enhanced or reduced stability. It is desirable the pharmacological property of drug in the agglomerates remain unaffected. Whether or not the nature of the drug is influenced by CCA process is ascertained by infrared spectroscopy as well as differential scanning colorimetry.

f) Compressibility: Compressibility is a measure of the relative volume change of a fluid or solid as a response to pressure change. The shape and size of crystals in physical mixture decide the compressibility of the tablet. It reflects packing characteristics of particles and also depends on the porosity of material. In the CCA, drug and excipient are made into coherent mass due to the natural affinity for each other and this process ensures higher homogeneity than any form of physical mixture. The agglomerates, when tableted, result in more uniform packing and less weight variation. Hence compressibility is an important evaluation parameter for drug-excipient agglomerates.

Carr's Compressibility index

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It is also known as Carr's index. It can be calculated by following equation.

$$Carr's\ compressibility\ index = \frac{Tap\ density - bulk\ density}{Tap\ density} \times 100$$

Table no. 2: Grading of compressibility of powder according to Carr's index.

Carr's Index	Flow Property
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor

g) In vitro dissolution study: It is the most important parameter. Tablets need to dissolve in the dissolution media to release the active ingredient. The rate and extent of drug release in a dissolution media is often related to bioavailability. Usually drug release is studied by U.V. spectrophotometers at a suitable wavelength and also by HPLC. Dissolution test apparatus is used. U S P suggests dissolution studies for the dissolution studies, which incorporate rotating basket type apparatus, rotating paddle apparatus, reciprocating cylinder apparatus, flow through cell apparatus, and paddle over cell apparatus, cylinder apparatus, and reciprocating plate apparatus. Any of the above gadgets can be utilized for dissolution studies relying on the type of tablet.

h) Differential Scanning Calorimetry: Differential scanning calorimetry includes the measurement of changes that occur when heat flow to the sample while they are subjected tocontrolled temperature programming. DSC studies the thermotropic behaviour of particles. The process like crystallisation can be observed using DSC. When temperature of a sample is increased gradually the viscosity of amorphous solids will decrease. At a particular point the molecules may attain sufficient energy so as to arrange themselves into crystals. This temperature is crystallisation temperature (Tc). This process of conversion of an amorphous solid into a crystalline solid is an exothermic process and is indicated in the thermogram (graph obtained) as a peak. This principle is used in the analysis of crystallo-co-agglomerates. Thermograms of drugs, polymers and agglomerates are performed using a differential scanning calorimetry. The DSC temperature should be calibrated. Accurately weighed samples are sealed in an aluminium crucible. The system should be purged with nitrogen gas.

***i)* Saturation solubility studies:** To evaluate the increase in the solubility of agglomerates, saturation solubility measurements were conducted. An excess amount drug or agglomerates was added to a 50 mL conical flask containing distilled water. The system was agitated on a rotary shaker for 48 h at 100 rpm, maintained at room temperature, and filtered. The filtrate was suitably diluted and analyzed at 201 nm using an ultraviolet UV visible spectrophotometer.

SIGNIFICANCE OF CRYSTALLO-CO-AGGLOMERATION[4,5,7,13]

a) CCA is useful in making agglomerates of one, two, or more drugs, high dose or low dose, with or without excipient.
b) It is possible to directly compress those drugs, which were unless otherwise impossible to do so, with improved micromeritic, mechanical, compressibility, compactability properties possessed through this technique.
c) Drug uniformity of agglomerates is unique.
d) It is possible to make controlled release dosage forms with the proper selection of polymers. Improved dissolution characteristics and bioavailability.
e) It is possible to create placebo drugs by producing agglomerates of plain excipients (talc agglomerates)
f) It is possible to formulate agglomerates in the form of encapsulated dosage form as MUPS.
g) The shear required for compression is less than that of granules.
h) The entire process can be controlled by a single person.
i) The requirement of time and space are less.
j) As the process contains only single step it is possible to carry out it in a closed system. This prevents external contamination. So it is easy to follow cGMP.

PHARMACEUTICAL APPLICATIONS OF CRYSTALLO-CO-AGGLOMERATION TECHNIQUE[12,14,15]

1. Drugs with large dose can be directly compressed with excipients using crystallo co-agglomeration process.
2. Low dose drugs can be agglomerated with excipients to give sustained release formulations with predictable dissolution pattern.
3. The process can be used to improve number of properties: micromeritic properties (flowability, packability, compressibility) mechanical strength of particles, for avoiding contamination due to dust generation, improving solubility and dissolution character of poorly soluble drugs.
4. By adopting the CCA technique, single, two or more, low dose drugs as well as large dose drugs can be agglomerated with or without excipients.
5. The spherical agglomerates obtained can be used as directly compressible tablet intermediates and/or capsules having improved micromeritic properties (flowability, packability), mechanical properties (friability, crushing strength and tensile strength, etc), compressibility, and compactibility.
6. Controlled drug release can be achieved with the help of certain polymers used during the agglomeration process.
7. Drug content uniformity in agglomerates can be easily maintained by agitation.
8. The crystallized drug forms miniscular form, hence, may improve drug dissolution and bioavailability. Agglomerates of plain excipients/diluents can be prepared and used as a placebo therapy.

9. Simultaneously, agglomerates having different drug release profiles can be prepared. The intact agglomerates can be given in the form of encapsulated dosage form as MUPS.
10. The shear required for stirring the liquid system is less as compared to mixing of powders in other granulation technologies. Single person can handle the entire agglomeration process. Hence, manpower requirement is curtailed compared to other methods of granulation.
11. The time and space requirements are less for CCA because of curtailment of various unit operations used in conventional granulation technologies.
12. It is a single step process, carried out in a closed system, preventing contamination, and dust generation, thus guarantying practice of GMP.

CONCLUSION

Using the CCA technique, size enlargement of both low dose and high dose drugs alone or in combination with or without diluent can be carried out in single step. The physical state of drug in agglomerate form can be modified with the help of a suitable solvent system, polymer and diluents. Smart selection of polymers and diluents can extend the release of drug or can improve dissolution of poorly soluble drugs. From available literature, it can be concluded that, CCA technology represents an efficient way of producing directly compressible spherical agglomerates as tablet intermediates or beads to be encapsulated, having improved micromeritic, mechanical, and compressional properties. As a consequence, the wide choice available in manipulation of the process and formulation variables in CCA may open a new area for formulation research.

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