

Crystallo-co-agglomeration: A novel particle engineering technique

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Crystallo-co-agglomeration (CCA) is a novel particle engineering/design technique developed by Kadam *et al*, to overcome the limitations of spherical crystallization (SC). Basically, it's single step process used for size enlargement of single, two or more, small dose or large dose drugs, in combination with or without diluent. The process of CCA involves simultaneous crystallization and agglomeration of drug/s with/without excipients/s from good solvent and/or bridging liquid by addition of a non-solvent. Till date CCA has been applied for spherical agglomeration of talc, bromhexine hydrochloride–talc, ibuprofen–talc, ibuprofen–paracetamol, and naproxen–starch. The spherical agglomerates obtained by CCA can be used as intact beads (encapsulated spansules) or directly compressible tablet intermediates having satisfactory micromeritic (flowability), mechanical (friability, crushing), compressional (compressibility, compactibility), and drug release properties. Modified drug release from agglomerates and compacts thereof can be achieved using suitable polymer composition in the process design. Thus, it can be concluded that, CCA is a simple and cost effective process, which can be tailor-made for particle design of all majority of drugs and combinations thereof.

Key words: *Crystallo-co-agglomeration, spherical agglomerates, spansules, tablet intermediates*

INTRODUCTION

In recent times, particle engineering/design techniques are widely used in pharmaceutical industries to modify primary (particle shape, size, crystal habit, crystal form, density, porosity dust generation etc) as well as secondary (flowability, compressibility, compactibility, consolidation, reduced adhesion of formulation to the processing equipment, reduction in air entrapment during processing, etc) properties of pharmaceuticals. Especially, improvement in the efficiency of the manufacturing process and high degree of particle functionality can be achieved by these techniques.^[1] Though conventional techniques like wet and dry granulation enjoy wide popularity at the industrial scale,^[2] other novel techniques like extrusion–spheronization (ES, direct pelletization, and layering),^[3] fluidized bed granulation,^[4] spray drying,^[5] spray congealing,^[6] solution atomization and crystallization by sonication,^[7] melt solidification,^[8] melt sonocrystallisation,^[9] co-crystallization,^[10] spherical

crystallization (SC),^[11] crystallo-co-agglomeration (CCA), etc^[12,13] have been considered as a value addition to existing ones. Among them, SC developed by Kawashima *et al*, in early 1990s has been considered as promising to modify crystal nature and preparation of directly compressible spherical agglomerates.^[11,14] However, its applicability has been restricted to size enlargement of single large dose drugs/pharmaceuticals only. Hence, to broaden the scope of SC, CCA has been developed by Kadam *et al* and has been explored for spherical agglomeration of some drug/s, with or without diluent.^[12,13]

The reason, why CCA has gained unique place in oral drug delivery system lies in its simplicity and ability to generate spherical agglomerates in a single step. The spherical agglomerates obtained can be used as spansules or directly compressible agglomerates. They offer advantages like excellent flow characters, uniform size distribution, and reproducible packing/filling.^[14,16] Large surface area offered by spheres results in uniform distribution throughout gastro-intestinal tract (GIT) leading to reduction in the localized toxicity. Moreover, this uniform distribution may improve absorption and bioavailability of drug/s.^[17,18] Because of the low surface area-to-volume ratio compared to powder or granules, they can be considered as an excellent coating

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substrate.^[19] Spheres show improvement in the therapeutic qualities of dosage form due to good dosing and handling properties. They are less susceptible to dose dumping,^[20] and failure of a few units may not be as consequential as failure of a single-unit system.^[21] Another very important advantage of spheres lies in that they get least affected by the normal gastric emptying time and hence drug delivery using same is less prone to physiological variables. It has been reported that pellets smaller than about 2.4 mm diameter are free from digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach.^[22] A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation.^[23] Some findings have cited threshold size below 1 mm.^[24] The effect of both density and size of the pellet affects the gastrointestinal transit time. The higher density of the pellets has prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time.^[25,26]

NEED AND IMPORTANCE OF CCA

In last decade, CCA was given birth to extend applications SC. Basically, SC has limited applicability for size enlargement of single large dose drugs having good compressibility,^[27] whereas, CCA is applicable for size enlargement of all, low dose, high dose, single, two, or more drugs in combination with or without diluent.^[12,13]

With the limited objective of size enlargement, initial development of CCA was carried out. But, in a decade, it has been explored as a technique producing spherical agglomerates used in design of multiple unit particulate drug delivery systems (MUPS). By using this technique, blank talc agglomerates as an inert cores/coating substrates and drug loaded talc pellets have been prepared.^[28] The spherical agglomerates prepared by the CCA technique have shown improvement in micrometric, mechanical, and compressional properties.^[29-31] With the use of suitable excipients and polymers, modified drug release has also been achieved from drug-loaded agglomerates or compacts thereof. In nutshell, agglomerates obtained by this technique can be used as directly compressible tablet intermediates and or spansules meeting all advantages offered by spheroids, necessary in design of MUPS.

PROCESS DESIGN STUDIES

In CCA, simultaneous crystallization and agglomeration of particles are carried out in a single step and spherical agglomerates are obtained. The system design for CCA recommends use of good solvent to solubilise drug/s, non-solvent to cause precipitation/crystallisation of drug/s and the bridging liquid which essentially has to be immiscible with non-solvent to form the liquid bridges between crystallized particles and insoluble solids during the process

of agglomeration. Sometimes bridging liquid acts as a good solvent also.^[32] Till date, two methods have been developed for CCA.^[33] Solvent change method involves simultaneous crystallization and agglomeration of two or more drugs from a good solvent and bridging liquid by addition of a non-solvent. The second method involves crystallization of drug from a system containing a good solvent and bridging liquid and its simultaneous agglomeration with insoluble drug/diluent by addition of a non-solvent. Selection of either of these methods requires knowledge of the physicochemical properties of drug and solvent system. Once the method has been selected, then its processing can be done in a vessel described by Morishima *et al.*, for SC.^[11,34] The controlled agitation of contents in Morishima vessel generates spherical agglomerates. The endpoint of the agglomeration process can be judged by the size of agglomerates, clarity of supernatant and vaporization of organic solvent/s from the agglomeration system.^[29] The generalized flow sheet for the CCA process has been given in Figure 1.

Successful design of the CCA process depends on numerous factors affecting the process of crystallization and agglomeration. Rather, it is a very complex process to be analyzed, getting influenced by numerous formulation and process variables. Various factors affecting CCA have been described ahead.

FORMULATION FACTORS/VARIABLES

Diluent selection

The use of diluent has been suggested in CCA for size enlargement of low dose drugs. Diluent selected must be physico-chemically and physiologically inert, and inexpensive. Moreover, it should be insoluble in the aqueous phase to avoid the losses through the continuous/external phase.^[35] Considering desired attributes, talc has been used as a diluent in the development of the CCA process. By using talc, placebo beads have been prepared by Limzerwala.^[35] Subsequently, Gadekar and Jadhav have developed the process for size enlargement of low dose bromhexine hydrochloride (BXH) using talc as a diluent.^[29,35] On the same lines, use of talc has been made by Pawar in the agglomeration of ibuprofen, a high dose drug.^[30] No reports on the gastrointestinal disorders caused by talc upon oral ingestion have been appeared.^[35] Adsorption studies have showed least adsorption of cimetidine^[36] and bromhexine hydrochloride^[28] on talc. Thus, it can be concluded that, claim of talc as an excipient/diluent in bead/pellet making gets strengthened further. Recently, starch and Na-starch glycolate has been used in preparation of rapidly disintegrating agglomerates of naproxen by the CCA process.^[37]

Solvent system (good solvent-bridging liquid-non-solvent)

The solvent system selection for the CCA process depends on solubility and stability of drug/s. Since, majority of drugs are soluble in organic solvents and poorly soluble in water. Use of

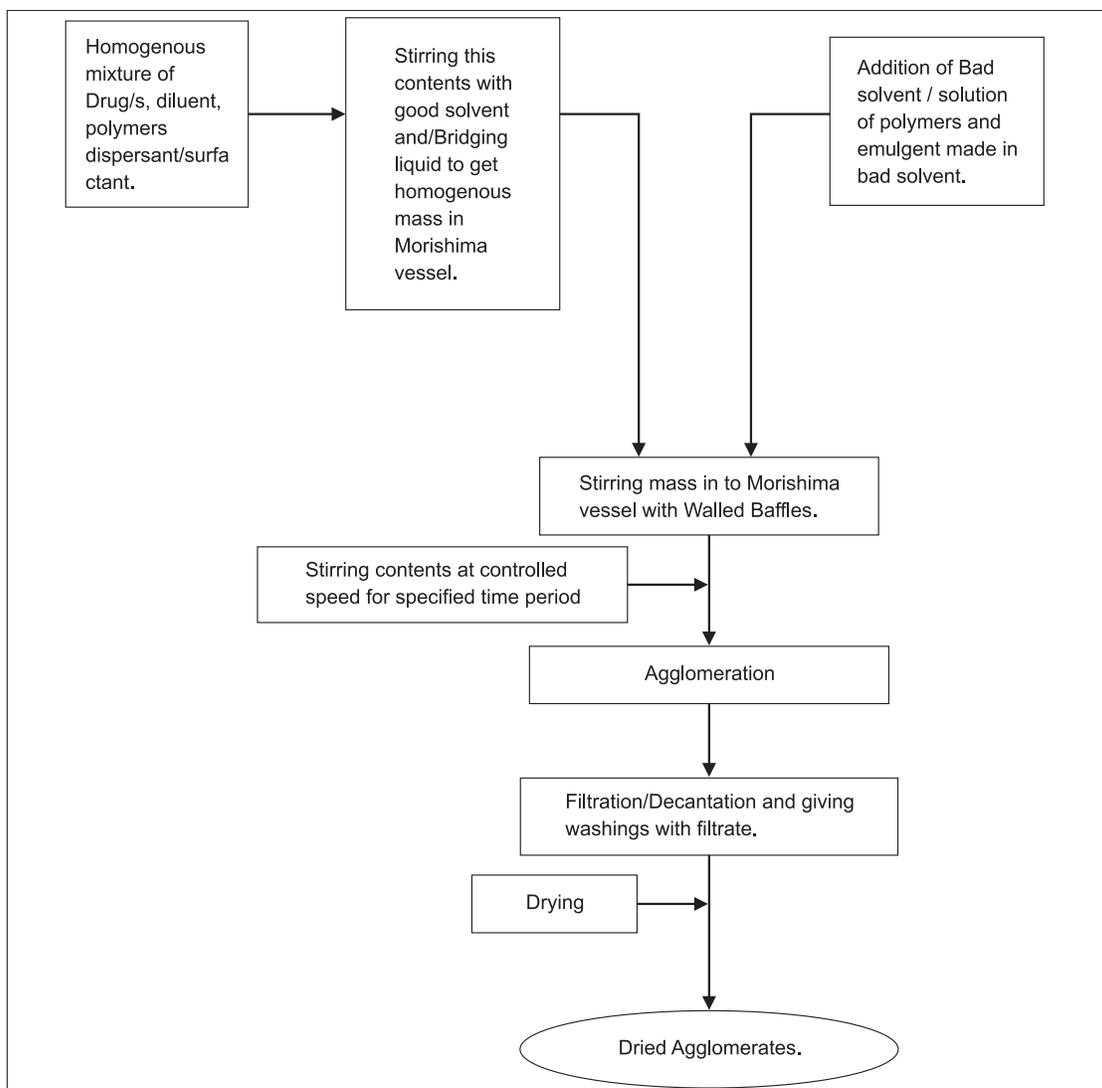


Figure 1: Generalized flow sheet for CCA process

organic solvent (relatively nontoxic) has been recommended as a good solvent and or bridging liquid and water as an external/processing phase (non-solvent). This type of solvent selection has been suggested due to scarce requirement of organic solvent.^[35] 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.^[29,35,38]

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. Toward conclusion of the agglomeration process, complete removal of bridging liquid and good solvent (organic solvents) from agglomerated mass must be ensured to get clearance from ICH limits.^[29,33,35,38]

Dispersion of internal phase

The internal phase composed of drug solution/suspension with or without diluent and bridging liquid should be easily emulsified / dispersed in the external phase. The process can be assisted by selection of various distributing agents/dispersants. Various hydrophilic polymers and surfactants such as polysorbates, polyvinyl pyrrolidone (PVP), and polyvinyl alcohol (PVA) have been reported to facilitate dispersion in optimum concentrations.^[29,32,33,39]

Use of polymers

Studies have revealed that crystallization and agglomeration of pure drug/s (without excipients) show poor compressibility

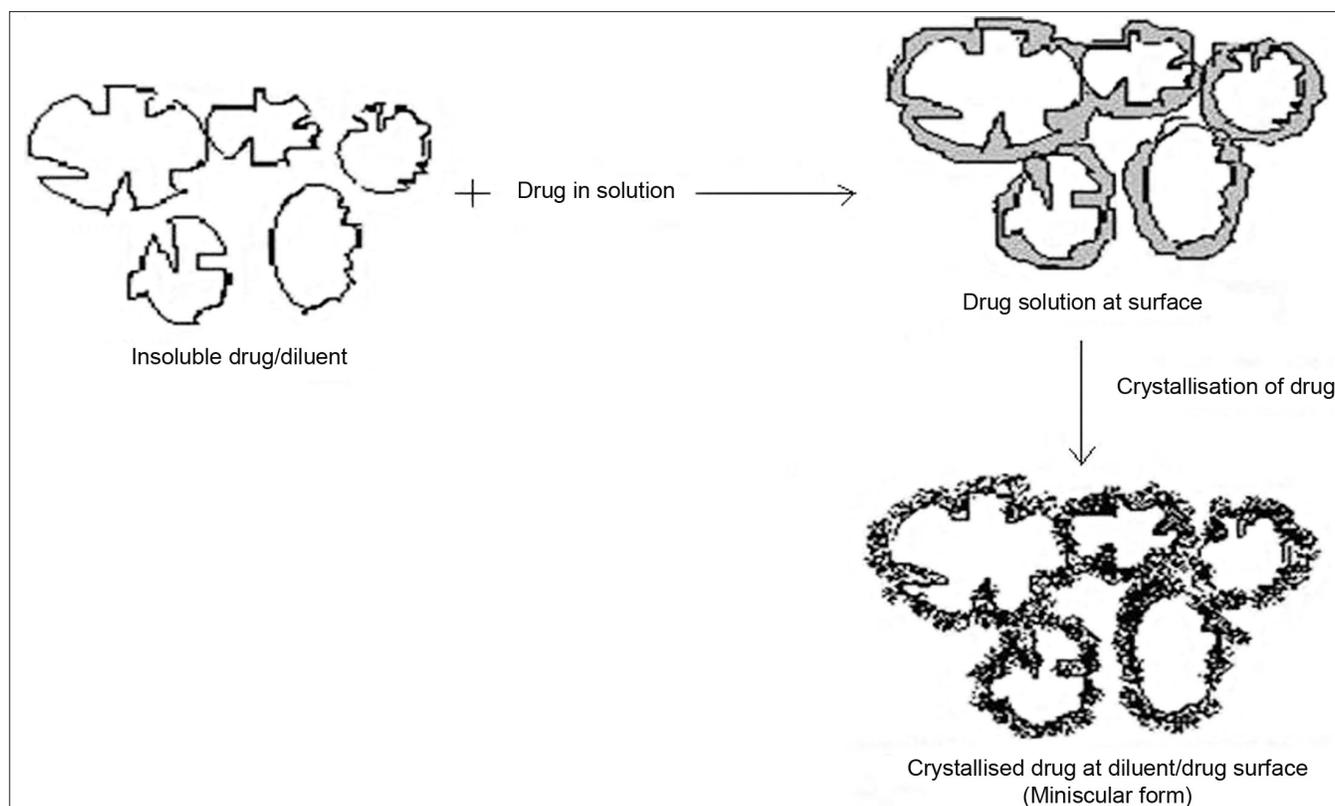


Figure 2: Figure depicting miniscular form of drug

and handling qualities.^[34,36] Addition of various polymers such as hydroxypropyl methyl cellulose (HPMC), polyethylene glycol (PEG), ethyl cellulose (EC), and PVP has been suggested to improve upon these properties.^[17,34,37] The agglomerates prepared using an optimum amount of HPMC has showed adequate sphericity and mechanical strength to the agglomerates, whereas its excess addition imparts ellipticity and deformation to agglomerates.^[29,35] PEG causes reduction in the interfacial tension between water (external phase) and bridging liquid resulting into reduction in the force of cohesion between particles leading to generation of small size spherical agglomerates.^[40,41] PEG, due to its soft and plastic nature, undergoes plastic deformation and gives better compressibility to the agglomerates during the process of compression.^[42,43] Whereas, EC, due to its high yield strength, on crystallization in a non-solvent imparts more strength to the agglomerates.^[42,43] Its solubility in the good solvent and bridging liquid (organic solvent) imparts higher viscosity to the internal phase and results into increased interfacial tension.^[30] The increased viscosity retards the diffusion of bridging liquid, hampers nucleation, crystal formation, and increases the time required for completion of the agglomeration process. Hence, to get agglomerates having satisfactory sphericity and strength, and compacts having adequate tensile strength, a combination of HPMC, PEG, and EC has been recommended during the crystallo-co-agglomeration process.

Drug loading

The extent of drug loading in a agglomerate changes the requirement of bridging liquid, good solvent, and non-solvent in CCA. It has been observed that the drug loading has a pronounced effect on the overall quality of agglomerates. An increase in drug loading has showed increased drug loss through the external phase.^[29,42] If the system has insoluble diluent/excipient, crystallized drug gets deposited on its surface and generates the miniscular form of drug.^[44,45] Figure 2 depicts the miniscular form of drug, wherein crystallized drug has deposited at the surface of insoluble drug/diluent. The effect of drug content on tablettability and drug release characteristics of bromhexine HCl–talc agglomerates prepared by crystallo-co-agglomeration has been studied by Jadhav. It has been reported that despite known poor cohesivity of BXH, its role in improving tensile strength has been established at higher drug load in agglomerates. The effect of tensile strength in achieving extended drug release has also been underlined. Finally, it was concluded that the drug content determining tensile strength of compact is responsible for the achievement of extended drug release from compact.^[28]

Drug loss to supernatant

The drug loss to supernatant determines the drug entrapment and the overall efficiency of the CCA process. During the agitation process, maximum crystallization and agglomeration of drug/s should be ensured. Attempts

have been made to reduce the drug loss by processing the contents at low temperature, pH adjustments, and addition of solubility suppressants to the external phase.^[33]

Process yield

The yield of CCA depends upon the extent of crystallized drug from a good solvent and its agglomeration with diluent/ another drug/s using bridging liquid. Means, it clearly indicates that the solvent system decides the process yield. A good solvent and a non-solvent decides solubilization and crystallization, respectively, whereas, bridging liquid decides the interparticulate interactions. This selection of the solvent system is a major challenge in achieving a desirable yield. Reports state that improvement in the yield of ibuprofen and paracetamol crystallo-co-agglomerates has been carried out at pH 5 using solubility suppressant (dextrose 10% wt/vol) and processing the batch below 5°C.^[33]

PROCESS VARIABLES

Agitation

Agitation of the system is needed to aid the process of emulsification/dispersion of the internal phase in the external phase. It has been reported that, the speed of agitation affects size, sphericity, and strength of agglomerates.^[29,39] A high speed of agitation increases sphericity, but reduces strength of agglomerates. It has been observed that time required for the completion of the agglomeration process gets reduced with higher speed of agitation.^[29,38,39]

Batch processing time

The completion of the agglomeration process depends on the time for which the system was kept agitated. Inadequate agitation/stirring does not ensure uniform mixing of ingredients and may cause incomplete growth of agglomerates. Even, this has resulted into incomplete evaporation of an organic solvent from the vessel. This results into incomplete evaporation of the organic solvent from the vessel. If duration of agitation exceeds the endpoint of the agglomeration process, then it promotes fine formation and initiates the deagglomeration process. Hence, judging the endpoint of the agglomeration process becomes critical in CCA. It can be judged by clarity of supernatant, residual organic solvent, and attainment of proper agglomerate size growth.^[29,32,39]

DRUG DELIVERY APPLICATIONS OF SPHERICAL AGGLOMERATES

Ideally, the spherical agglomerates / beads / pellets used in design of MUPS must be strong enough, non-brittle, and should have low elastic resilience, they must deform under applied load without fracture. It has been stated that core pellets must have some degree of plasticity, so that they can undergo a possible change in shape under tableting.^[46]

In the view of these properties, work was contributed on preparation of talc agglomerates by the CCA technique.^[35,38] But, poor strength of blank talc agglomerates was noted similar to findings Peck (1995)^[47,48] and Hersey (1979).^[49] Difficulties were faced in preparing high strength talc agglomerates having a desired shape and sphericity. In last decade, spherical agglomerates of low dose bromhexine hydrochloride and talc were prepared by the CCA technique^[32] and further studied for micromeritic, mechanical, compressional, and drug release properties.^[29] And, along with size enlargement, satisfactory compressibility and extended drug delivery were noted. Recently, Pawar *et al.* (2004) have applied CCA for agglomeration of ibuprofen–talc and obtained directly compressible spherical agglomerates.^[30] The compacted agglomerates of ibuprofen–talc have shown sustained zero-order release. In this case, drug release retardation was attributed to the hydrophobic nature of talc. They have also studied the effect of polymers and their types on quality attributes of agglomerates.^[43] However, an interesting and common observation noted in the case of agglomerates prepared by CCA, containing high percentage talc (BXH-talc and ibuprofen-talc) was deformation during the process of compaction. This was attributed to interparticle slippage of talc particles rather than the fracture or fragmentation.^[42]

In another study, preparation of direct compressible agglomerates of ibuprofen–paracetamol has been reported by Pawar *et al.*^[31] Preparation of directly compressible naproxen–starch agglomerates for direct compression has also been reported by Maghsoodi *et al.*, using the same CCA technique, wherein naproxen–disintegrant (starch and Na-starch glycolate) agglomerates were successfully prepared for direct tableting.^[37] The micromeritics of the agglomerates, such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tableting without capping. The main factor in the improvement of the flowability and packability was a significant reduction in interparticle friction due to the spherical shape of the tabletted particles. Compactibility of the agglomerates was found to be improved. The dissolution rate of naproxen from the naproxen-disintegrant agglomerates was enhanced significantly with increasing the amount of disintegrant. The tablets prepared from naproxen–disintegrant agglomerates have showed dissolution time below 30 min.

In conclusion, it can be stated that the agglomerates obtained by CCA can act as a matrix beads due to uniform distribution of crystallized drug at the surface of diluent. Drug deposited in miniscular form at the surface of diluent ensures uniformity in drug distribution through out the agglomerate/bead. The agglomerates obtained by this technique resemble to the pellets obtained by ES, which is also called as direct pelletisation. Moreover, the blank talc agglomerates prepared by CCA can be used as a substrate on which drug can be layered and used for drug delivery applications (drug layering). The only difference is that ES

has been industrially explored, whereas CCA is not. In ES, MCC has been used as a pellet excipient, and in CCA, starch and talc have been used as a diluent.

LIMITATIONS OF CCA

Although CCA has overcome major limitations of SC, still some formulation- and process-related difficulties persist.^[29,32,35,39]

1. Use of organic solvent cannot be avoided.
2. Its difficult to have the similar physico-chemical properties of drug combinations to be crystallo-co-agglomerated. 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.
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.

SIGNIFICANCE

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.^[12,13] The spherical agglomerates obtained can be used as directly compressible tablet intermediates and/or spansules having improved micromeritic properties (flowability, packability), mechanical properties (friability, crushing strength and tensile strength, etc), compressibility, and compactibility.^[29] Controlled drug release can be achieved with the help of certain polymers used during the agglomeration process.^[50]

Since, the process of CCA involves continuous stirring of drug/s and excipients in liquid medium, one can assure drug content uniformity in agglomerates. The crystallized drug forms miniscular form, hence, may improve drug dissolution and bioavailability.^[44,45]

Agglomerates of plain excipients/diluents can be prepared and used as a placebo therapy.^[28,32,51] 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.^[50]

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. The time and space requirements are less for CCA because of curtailment of various unit operations used in conventional granulation technologies. It is a single step process, carried out in a closed system, preventing contamination, and dust generation, thus guarantying practice of GMP.^[28]

CONCLUSION

By 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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