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A SYSTEMATIC REVIEW OF SPHERICAL AGGLOMERATION BY PARTICLE DESIGN OF DRUG FORMULATION

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ABSTRACT

Particle design through various Spherical Agglomeration techniques used for many bulks and fine manufacturing industries with the latest temptation into pharmaceuticals with size modification. By this an addition of an immiscible bridging liquid to the formation of agglomerate crystals beforedeliquoring. The spherical agglomeration method can produce high-performance spherical shape particles in a single crystallization unit, even though it is quitechallenging to control the particle size and shape.Multi-liquid phases play important role in dynamic balance among the intensity of adhesion, dispersion, and capillary action.The search terms spherical agglomeration, spherical crystallization, and drug formulation by spherical agglomeration were used to recognize peer-reviewed publications restricted to the English language in PubMed and Web of Science electronic databases issued from initiation until January 2022. A total of 606 publications were found, of which 24 met the inclusion criteria after all exclusion screening. The review showed that Spherical agglomeration techniques exhibited decreased crystallinity and design particle size and shape. The amount of bridging liquid along with the multi-liquid phase and various mechanical factors affects the characteristics of spherical particles. An *in vitro* and *in vivo* study depicts the effectiveness of spherical agglomeration techniques in many parameters like improved bioavailability and other compression parameters.

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Introduction

Spherical agglomeration has been implemented for various high-dose drugs with poor compressibility and water solubility [1-3]. Spherical agglomeration is a precious technique in the formulation of micro-sponges, microspheres, micro balloons, nanospheres, and nanoparticles as a novel drug delivery system [4-7]. Spherical agglomeration is defined as "a novel approach for particle engineering by which agglomeration and crystallization can be implemented in simultaneously one step to convert crystals directly into compacted spherical form" [8-11]. Spherical agglomeration is a technique for the emergence of aggregates of crystals held together by liquid bridges [12-14]. Besides formulating spherical crystals it also enables co-precipitation of drugs and encapsulating polymers in the form of spherical particles [15-17].

In 1986, Kawashima *et al*. used the spherical crystallization technique for size enlargement of the drug in the field of pharmaceutical technology [12]. Spherical agglomeration can be defined by him as "An agglomeration process that converts crystalline drugs directly into a compacted spherical form for improving the flow ability, solubility, and compact ability" [18-20].

We endeavored to summarize the issued literature on existing Spherical agglomeration and its formulations for pharmaceuticals which describe the limitations of the Spherical agglomeration formulation and emphasize the potential of these methods in pharmacy practice.

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Materials and Methods

This review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Strategy

A structured search of PubMed and Web of Science identified the articles published till January 24, 2022. Search terms Spherical agglomeration, Spherical Crystallization, Drug formulation of agglomeration. Original research articles describing Spherical agglomeration for drug formulation were included. Each abstract was examined to determine eligibility for full-text review. A second reviewer resolved the discrepancies about article inclusion. Article abstracts were screened, and those included were subjected to full-text review.

Study Selection

The study selection was conducted by one of the coauthors individually (VC) with any disagreement being resolved by consensus or a second author (HD) acting as a judge. One review author (VC) conducted the literature survey in the databases separately appraised and extracted the probable titles and abstracts of the articles for inclusion; however, the final selection, inclusion, and exclusion of articles for systematic review were performed after consulting all co-authors. Studies using review articles, book chapters, meta-analyses, conference proceedings, editorials/letters, patents, and case reports were excluded.

Data Extraction

Data from included studies were extracted and summarized separately by one of the authors (VC). **Table 1** summarizes the following information about the studies: (a) Spherical agglomeration preparation methods; (b) Objectives of study; (c) types of substances used in techniques and Results.

Data Analysis

The data is presented as a portrayal. It was not possible to cache data or undertake a meta-analysis due to its heterogeneity.

Results and Discussion

Search Result

A flow diagram shows the search and Selected criteria used for the systematic review in **Figure 1**. A total of 79 citations were identified, and 34 studies met our inclusion touchstone. Abstracted details provided information about the objective(s) of the review; the *"Spherical agglomeration"* and *"drug formulation"* the results. We tabulated the studies in obedience to the substrate used; though, studies can be tabulated using alternative criteria.

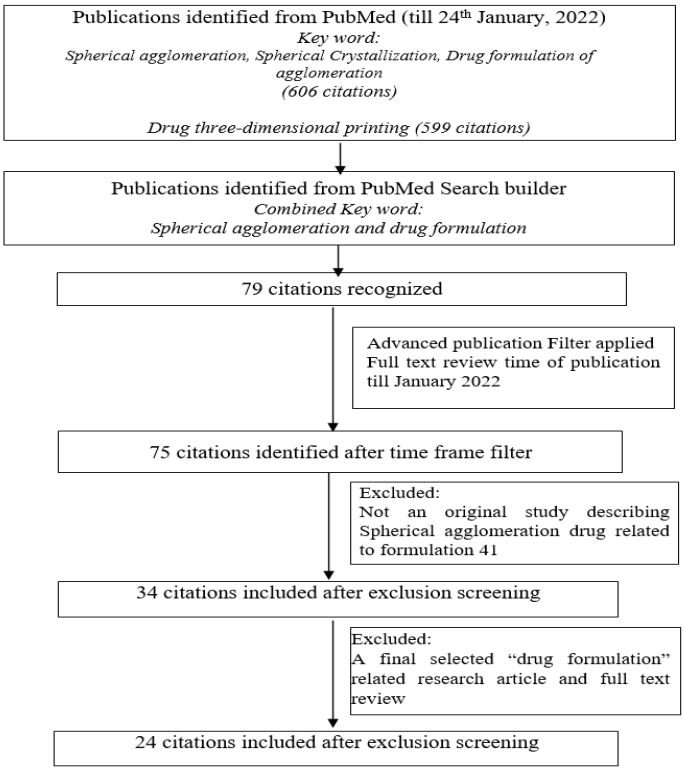

Figure 1. Structured literature search on Spherical Agglomeration technologies

Included Article Characteristics and Quality Evaluation

After exclusion screening total of 24 citations was screened out from the summary of all methods described in **Table 1**.

Table 1. Spherical Agglomeration- Summary of the literature survey met with inclusion criteria

Sr. No.	Technology	Objective(s)	material composition
1	**Crystallo-co Agglomeration Methods**	**A)** The preparation, optimization, and evaluation of a new spherical agglomeration technique for glimepiride as a model of poorly soluble drugs [21]. **B)** To develop directly compressible, high-strength extended-release spherical agglomerates technique, crushing strength, and low friability [22]. **C)** Improving the solubility and dissolution of cilostazol [23]. **D)** Improved flow property and mechanical properties of Racecadotril, a poorly water-soluble antidiarrheal agent [24]. **E)** Improved micromeritic and mechanical properties, solubility, and dissolution of Secnidazole [25].	Starlac/PVP, ethylcellulose 10 cps, HPMC, Polyethylene glycol 6000, polyvinylpyrrolidone K30 talc fine powder Dichloromethane, Tween 80
2	**Quasi emulsion solvent diffusion method**	**A)** Improve flow properties like higher bulk density, and compressibility, also improve the dissolution rate [26]. **B)** The improved powder properties and dissolution performance of the API by SC [27]. **C)** Improved micromeritic properties compared to the plain drug suggested its suitability for direct compression [28]. **D)** The problems Solved related to solubility, dissolution rate, bioavailability, flowability, and compressibility of the drug [29]. **E)** Improved properties for direct compression, the shape of the particle, and enhanced fragmentation during the compaction, also increased tensile strength and reduced elastic recovery of the compacts [30].	Methanol, Ethanol, Dichloromethane, Acetone, Isopropyl Alcohol, DMF, DMSO, HPMC K15M, Ethyl acetate, Dichloromethane, Chloroform, hexane, ethanol
3	**Spherical crystallization method or solvent change method**	**A)** Improved micromeritic and dissolution properties, in equivalence to the pure drug, high-speed compression, and enough stability under accelerated conditions at least for 1 month [31]. **B)** The objectives of this study were to prepare sustained release SAs of mefenamic acid using polymethacrylates by a spherical crystallization method [32]. **C)** Spherical crystallization mechanism to obtain agglomerates with improved physicomechanical properties [33]. **D)** Sustained release matrix pellets weresuccessfully prepared by SC methods [34]. **E)** Directly compressible Naproxen prepared by spherical crystallization which produces microcrystalline forms exhibitingpoor micromeritic properties and poor aqueous solubility shows an increase in the bioavailability [35].	Dichloromethane, acetone, HPC, hydrophilic polymer, Eudragit RS 100, Eudragit RL 100, Eudragit L 100, dichloromethane (DCM), potassium dihydrogen phosphate and sodium hydroxide
4	**Spherical Agglomeration**	**A)** Developed lactose monohydrate solution for spray-drying to improve the aerosolization performance of dry powder inhalers [36]. **B)** Enhance dissolution of poorly soluble drugs; enhancing its rate of release from tablet formulation prepared this technique [37]. **C)** Improved micromeritic properties, thus obviating the need for further processing by granulation and agglomeration [38]. **D)** KSR-592 b-form with lactose was developed to enhance the inhalation properties of DPI formulations via particle designing used in the Jethaler [39]. **E)** Formulate fast-disintegrating pellets by direct palletization in a rotary processor [40]. **F)** Improve the flowability and compression properties of propyphenazone [41]. **G)** Improve their powderprocessing, and micro-encapsulation, by agglomeration, sustained-release gelling microcapsules of CP prolong the pharmacological effect [42]. **H)** The particle design of the powders masked the bitterness without reducing its bioavailability using this one continuous process of agglomeration and microencapsulation [43].	Cross Povidone, Pregelatinized starch, Croscarmellose sodium, Cross povidone XL, Avicel pH 102, Starlac, mannitol, maize starch, Aerosil 200, PVP K30, L-HPC, Carbon tetrachloride, hexane, octanol, toluene, polyethylene glycol, cross-povidone, starch, cross Carmel lose sodium, HPMC, ethylcellulose

Methods of Spherical Crystallization

Crystallo-Co-Agglomeration (CCA) Technique

Crystallo-Co-Agglomeration technique is one of the novel particle designing methods that could be an efficient process to get a better of the mentioned limitation of spherical agglomeration [44]. The spherical agglomeration technique is restricted to only large dose drugs which having poor water solubility because excipients like disintegrating agents and diluents are hydrophilichence the incorporation of these types of excipients in the agglomerates with the help of bridging liquid is difficult [45]. It is the modified spherical agglomeration technique used for Particle designing and size enlargement of all lower and higher doses, poor Soluble and Compressible drugs, and also the combination of the drug with or without diluents [46]. Steps for the preparation of agglomerate through the Crystallo-co-agglomeration technique shows in **Figure 2**. In this technique, agglomerates are produced via a single step; recently it is employed to enhancemicromeritic, compression, and mechanical properties in the design of a multiple-unit particulate drug delivery system. By using this method, the drug is directly crystallized and agglomerated in combination with another drug and excipients with the use of an organic bridging liquid [47].

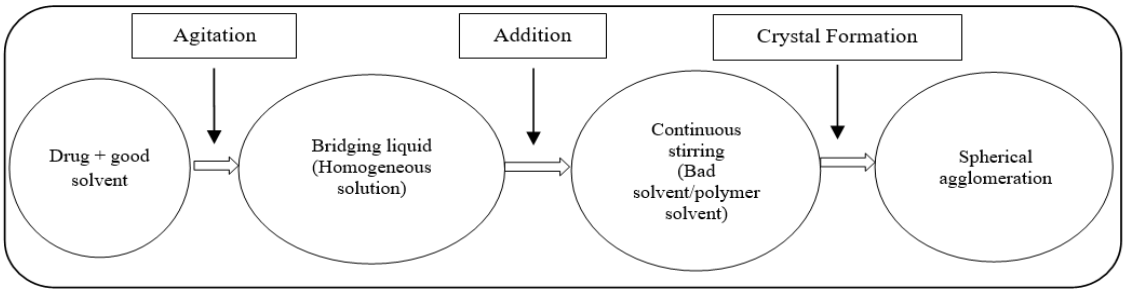

Figure 2. Crystallo-co-agglomeration technique

Advantages of Crystallo-co-Agglomeration [48-50]

- Less unit operation is required.
- Its processing cost is very economic.
- Spherical agglomerates are formed in a single step.
- The whole procedure is handled by a single person, so less manpower is required [51].
- As it is a single-step procedure and carried out in a closed and contamination-free environment proper GMP is followed [52].
- The spherical agglomerates obtained by this procedure are further utilized for direct compression of tablets and in the design of a multiple-unit particulate drug delivery system [53].

Limitation [54-56]

- It is very difficult to reproduce the same result due to the presence of many formulations and process variables.
- The drug combination which has the same physicochemical properties cause problem in simultaneous crystallization of drug combination at the same solvent pH and temperature condition [57].
- It is difficult to scale up the filtration and drying process used in crystallo-co-agglomeration [58].
- The use of organic solvent cannot be avoided [59].
- Due to more volume of external phase drug loss is increased [60].
- More power requirement because of increasing resistance for mixing of content due to more external phase volume [61].
- Adding of disintegrant or super disintegrant is difficult because of aq. the phase has been considered an external phase [62].

Quasi Emulsion Solvent Diffusion Technique

Preparation of Spherical agglomerate by Quasi Emulsion Diffusion technique presented in **Figure 3**. APIs are dissolved in a Good Solvent(GS) and afterward dispersed in a Poor (bad)Solvent(PS), quasi droplets are formed, despite the pure solvent being miscible [63, 64]. GS diffuses gradually out of the emulsion droplets because of the interfacial tension between the GS and PS, into the poor solvent and the poor solvent disperses into the droplet, by this drug crystallized inside of the droplet [65-67]. The crystallization of API happens by counter diffusion of GS and PS. The residual GS available in droplets serves as a bridging liquid to agglomerate which generates liquid bridges in between droplets and helps to form Spherical crystals [68, 69].

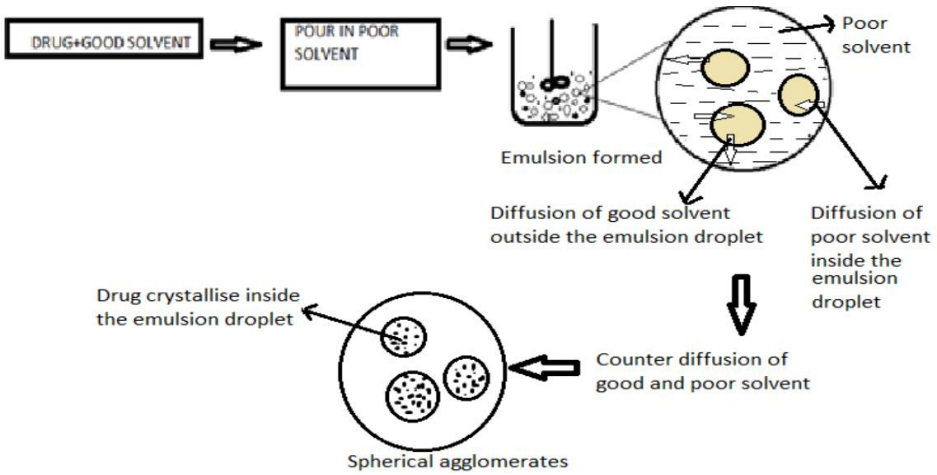

Figure 3. Quasi Emulsion Solvent Diffusion method

Spherical Agglomeration Technique

Spherical agglomeration is a technique in which three types of solvent are incriminated: Good Solvent(GS) in which drug is completely soluble; a Poor Solvent(PS)in which drug is not soluble except GS should be immiscible with PS and the third solvent Bridging Liquid(BL) which incorporated in a small amount after the generation of crystals, to agglomerate them via generating the liquid bridges between the particles. The BL is incorporated with continuous agitation [70, 71]. **Figure 4** shows the preparation method of Spherical agglomerates.

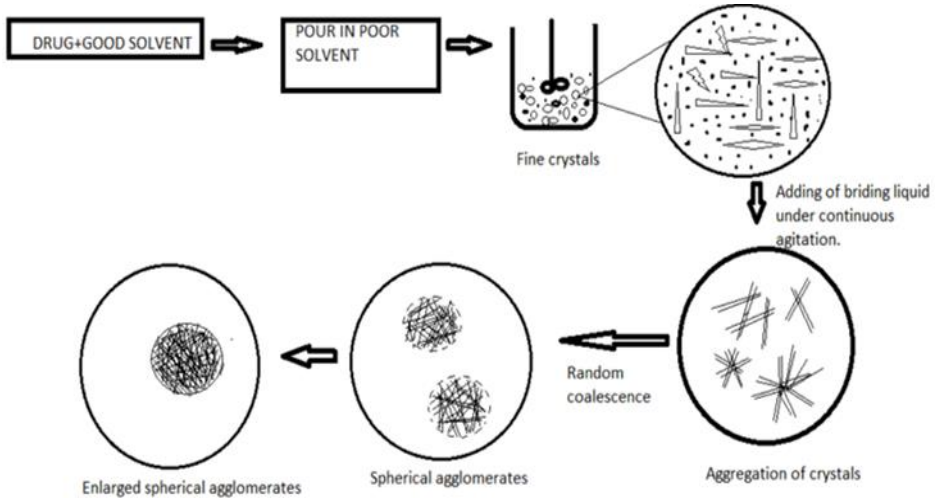

Figure 4. Spherical agglomeration method

Conclusion

The present structured review on the topic explores the different methods of spherical agglomeration employed in pharmaceutical formulation and their potential applications in developing new particulate systems in a drug. From the literature, these techniques have been used to modify pharmaceutical processing, drug product performances, and bioavailability issues. Spherical agglomerates exhibited a decrease in their crystallinity and enhanced micromeritic properties. Quantity of bridging liquid, rate of agitation, and time of agitation influenced the mechanical and micromeritic properties of spherical agglomerates. An *in vitro* and *in vivo* study depicts the effectiveness of the spherical agglomeration technique in many parameters like improved bioavailability and other compression parameters

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