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PROCESSING FACTORS AFFECTING THE PROPERTIES OF SPHERICAL AGGLOMERATES

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ABSTRACT

Spherical agglomerates, formed through a particle engineering technique known as spherical crystallization, are crucial in pharmaceutical industry. This review explores the key factors and operational parameters affecting the properties of spherical agglomerates, with a focus on their impact in pharmaceutical applications. The judicious choice of solvent addition methods, bridging liquids, and agitation temperatures significantly impacts agglomerate size, morphology, surface texture, and dissolution rates. These properties have a direct bearing on the efficiency of drug delivery systems. Furthermore, mechanical properties, thereby affecting the flow properties and compressibility of agglomerates, which are critical for tablet manufacturing have also been discussed. Nuclei formation, consolidation, coalescence, and layering are integral processes that allow for the customization of agglomerate properties. Control over these factors is imperative for tailoring agglomerates to meet specific product requirements, ensuring efficient drug delivery, consistent product quality, and controlled drug release.

Keywords: spherical agglomerates, processing factors, bridging liquid, nuclei formation, coalescence, consolidation

INTRODUCTION

Agglomerates consist of tiny particles, resulting in a significant volume change when compressed due to fragmentation. This fragmentation increases the number of

contact points between particles, leading to improved inter-particle bonding and, consequently, greater strength. Researchers such as Jbilou *et al*. **[1]** have also proposed that the enhanced compressibility of ibuprofen agglomerates compared to single crystals is due to the agglomerates' isotropic structure.

Spherical agglomeration represents one approach within the sphere of spherical crystallization. This is a particle engineering approach wherein both agglomeration and crystallization take place concurrently, resulting in the production of agglomerated crystals with a compact, spherical structure. This approach offers several benefits, including simplified handling of active pharmaceutical ingredients (APIs) and enhanced tablet-forming properties. Consequently, it reduces the necessity for additional processing steps in the pharmaceutical manufacturing process. There are alternative methods of spherical crystallization, such as solvent diffusion, ammonia diffusion quasi-emulsion.

The physical and mechanical characteristics of spherical agglomerates make them advantageous for drug delivery purposes, as they can be customized to encapsulate small crystals with a high specific surface area. This allows them to achieve enhanced dissolution rates and improved bioavailability. Studies have demonstrated improved dissolution profiles for several drugs like aceclofenac, ketoprofen, tolbutamide and simvastatin **[2][3]**.

METHODS TO PREPARE SPHERICAL AGGLOMERATES

Spherical agglomeration

The spherical agglomeration method involves several steps to prepare spherical agglomerates. Initially, fine particles of the required material are suspended in an anti-solvent, resulting in a slurry. A bridging liquid is then added, which causes the fine particles to aggregate into larger, spherical particles. Lastly, the solvent is removed, leaving behind spherical agglomerates with improved flowability and other desirable properties for various applications, including pharmaceuticals and food processing **[4]**.

The first application of the spherical crystallization (SC) technology, for the production of spherical particles was documented during the early 1960s **[5][6]**. The technique of spherical agglomeration utilizes 'appropriate' solvents and anti-solvents to facilitate the direct crystallization of a solid present in a solution. This process is commonly known as either 'drowning out' or 'solvent change,' involving the addition of a compatible anti-solvent to decrease the solubility of the material that has been previously dissolved in a solvent, thus promoting crystallization. One of the difficulties encountered in the spherical crystallization technique lies in

identifying an appropriate combination of ternary solvent blends, comprising a suitable solvent, an unsuitable solvent, and a connecting liquid, tailored to a specific pharmaceutical compound**.** Drug albendazole and bridging liquid dichloromethane (DCM) as a bridging liquid accompanied by the inclusion of polymeric additives were used to prepare spherical agglomerates. The addition of the polymer during the process enhanced the surface characteristics, resulting in a smoother texture and improved flow properties. The resulting particles could be directly compressed, leading to stronger tablets, and they showed a higher dissolution rate compared to unprocessed albendazole tablets **[7]**.

Ammonia diffusion (AD)

The ammonia diffusion method is a process used to prepare spherical agglomerates. In this method, fine particles of the material are suspended in a solvent. Ammonia gas is then introduced into the solution, leading to the precipitation of the material in the form of spherical agglomerates. The ammonia gas aids in agglomeration by altering the solubility of the material in the solvent. This technique is commonly employed in the pharmaceutical industry to enhance the flow properties and compressibility of drug powders. It involves the use of bridging liquid to form the agglomerates. The selection of the bridging liquid is a critical factor, contingent on its capacity to effectively coat the crystals of the target substance.

This method employs a combination of three partially immiscible solvents, namely ammonia water, dichloromethane and acetone for the crystallization process. Within this system, ammonia water served the dual role of acting as both a bridging liquid and a suitable solvent, while acetone, though miscible with water, behaved as a poor solvent. Consequently, precipitation of the drug occurred due to the change in solvent conditions without forming an ammonium salt. Additionally, water-immiscible solvents like hydrocarbons or halogenated hydrocarbons, such as dichloromethane, facilitated the release of ammonia water in this process **[8][9]**.

Quasi-emulsion solvent diffusion (QESD)

The quasi-emulsion method is a technique utilized to prepare spherical agglomerates. In this process, a solid material is dispersed in a liquid phase called as anti- solvent and surfactant or stabilizer, creating a quasi-emulsion. By controlled agitation or other means, the solid particles agglomerate into spherical shapes within the liquid phase. Subsequently, the liquid is removed, leaving behind spherical agglomerates.

In the emulsion solvent diffusion method, the drug prefers to dissolve in a solvent that mixes well with it, known as the good solvent, rather than in a solvent that does not

mix well with it, known as the poor solvent. Initially, the drug is dissolved in the good solvent. This solution is then mixed into the poor solvent, forming tiny droplets called emulsion droplets, even if the two solvents can mix together on their own. As time passes, the good solvent starts to diffuse out of the emulsion droplets into the surrounding poor solvent, while the poor solvent enters the droplets. This process causes the drug to crystallize inside the droplets. While this method is easier as compared to some other techniques, finding the right excipient to maintain emulsification and improve the diffusion of the poor solute into the dispersed phase can be a challenge **[9][10]**.

OPERATIONAL PARAMETERS

Solvent addition

The success of spherical agglomeration for a specific material hinge on the use of specific solvent combinations. Therefore, it is crucial to carefully choose the solvent system to maximize both the degree of crystallization and agglomeration. Spherical agglomeration heavily relies on the miscibility of solvents. The relative concentrations of these solvents also play a significant role. The solvent/anti-solvent/bridging liquid ternary phase diagram is a useful tool to help choose the appropriate solvent compositions **[3]**.

The method of solvent addition plays a pivotal role in shaping the properties of spherical agglomerates. The choice of solvent addition method can have multifaceted effects on these agglomerates. It influences crucial attributes such as particle size, morphology, surface texture, porosity, density and flow properties. Different methods can yield agglomerates with varying sizes, shapes, and surface textures, which, in turn, impact the flow, compressibility, and dissolution rate of drugs from these agglomerates. Furthermore, the method of solvent addition can influence the stability of the agglomerates, making it a critical consideration in pharmaceutical formulations. Hence, selecting and optimizing the solvent addition method is integral to tailoring spherical agglomerates for pharmaceutical applications, ensuring efficient drug delivery and product quality **[3]**.

Bridging liquid addition

The characteristics of spherical agglomerates are significantly impacted by the choice of bridging liquid. Bridging liquids, such as water, organic solvents, or mixtures thereof, are essential to the process of agglomeration. The selection of a bridging liquid can result in variations in agglomerate size, shape, and surface texture. For instance, when bridging liquid is water, it can lead to spherical agglomerates with smoother surfaces, enhancing flow properties and tablet compressibility.

Conversely, organic solvents like dichloromethane can produce agglomerates with specific porosity, impacting drug dissolution rates. Therefore, choosing the right bridging liquid, like water or dichloromethane, is a critical consideration in pharmaceutical formulations, allowing for tailored agglomerates that ensure efficient drug delivery and product quality. The bridging liquid should possess two key characteristics in the context of agglomeration: first, it should not be miscible with the poor solvent, and second, it must have a preference for moistening the precipitated crystals. This combination of properties is essential because the bridging liquid, through interfacial tension effects and capillary forces, works to bind the crystals together, promoting their adherence to one another **[3] [10]**.

A number of recommendations have been made regarding the choice of solvents and bridging liquids; these are mainly dependent on the miscibility relationships between the bridging liquid, the anti-solvent, and the good solvent, as well as the contact angle between the bridging liquid and the crystals. Alongside the choice of the solvent-bridging liquid system, numerous operational parameters must also be taken into account. These factors collectively influence the rate of precipitation and agglomeration, ultimately shaping the properties of the resulting particles **[3][11]**.

Amaro-Gonzalez and Biscans conducted a study to determine the most suitable liquid for coating lobenzarit disodium particles during crystallization. They tested various solvents to see which one would work best for this purpose. They used a test called Washburn's test to measure how well each solvent spread over the particles. They found that n-hexane was the most suitable because it had formed a thin and even layer on the particles. To confirm their choice, they conducted further experiments involving spherical agglomeration using n-hexane as the coating liquid **[12]**.

Agitation temperature

The agitation temperature during the production of spherical agglomerates in pharmaceutical processes has a notable impact on their properties. This influence spans various aspects of agglomerate characteristics. For instance, higher agitation temperatures tend to encourage faster crystallization and larger agglomerates, which can be exemplified by the formation of larger lactose agglomerates in dry powder inhaler formulations. Conversely, lower temperatures often result in smaller, more densely packed agglomerates with rougher surfaces. **[3][10]**. These variations in temperature can also affect the density, porosity, and mechanical properties of the agglomerates, leading to differences in dissolution rates and tablet compressibility. Therefore, careful control

of agitation temperature is essential to tailor the properties of spherical agglomerates to meet specific pharmaceutical requirements, ensuring consistent drug delivery and product quality. In a study by Kawashima *et al*. **[4][8]**, they investigated how temperature affected the formation of spherical agglomerates using a solvent system involving ethanol, water, and chloroform. Their research showed that temperature had a substantial impact on the agglomerates' size. Initially, as the temperature rose, the agglomerates became smaller. However, the agglomerates' size and size variation both increased as the temperature rose **[11] [14] [15]**.

Residence time

The residence time, which refers to the duration that materials spend within a processing system, can have a profound impact on the properties of spherical agglomerates. Longer residence times often lead to increased agglomerate size as particles have more time to collide, adhere, and grow. For instance, in the pharmaceutical industry, extended residence times in a fluidized bed dryer can result in larger, more well-formed spherical agglomerates, which can be advantageous for uniform drug distribution in tablet formulations. Conversely, shorter residence times may produce smaller agglomerates or less-defined shapes. The choice of residence time can also affect the agglomerates' density, porosity, and flow properties, ultimately influencing factors such as dissolution rates and compressibility in pharmaceutical applications. Thus, optimizing residence time is crucial for tailoring the properties of spherical agglomerates to meet specific product requirements. A study done by Kawashima *et al* **[4]** noted that the size of aminophylline crystals that had agglomerated increased progressively as the residence time was extended and eventually, they reached an equilibrium **[3] [16]**.

Agitation rate

The agitation rate, or the speed at which agglomerate-forming particles are mixed or stirred, has a notable impact on the properties of spherical agglomerates. Higher agitation rates generally result in increased collisions and interactions among particles, leading to more rapid agglomeration. When wet granulating powders to form spherical agglomerates, higher agitation rates can produce larger granules. Conversely, lower agitation rates tend to yield smaller, more densely packed agglomerates. Agitation rate can also influence agglomerate density, porosity, and surface texture, which in turn affect dissolution rates, flow properties, and tablet compressibility. Thus, choosing a suitable agitation rate is a critical factor in shaping the properties of spherical agglomerates to meet specific product requirements across various industries **[17]**.

According to Subero-Couroyer and colleagues **[18]**, the speed of agitation impacts the distribution and dimensions of the bridging liquid droplets, with greater agitation rates resulting in reduced droplet sizes. Additionally, enhanced agitation rates can influence the dispersion of the agglomerates and particles formed initially. Conversely, excessively low agitation rates might lead to clumping, especially when a bridging liquid is not present **[3] [10] [18]**.

PROCESS PARAMETERS

Nuclei formation

Nuclei formation, which represents the initial stage of agglomeration where tiny particles come together to form larger aggregates, is essential in defining the characteristics of spherical agglomerates. The number and size of nuclei formed can impact the final agglomerate characteristics significantly. For instance, a higher number of nuclei may lead to smaller and more numerous agglomerates, while fewer, larger nuclei can result in larger, less numerous agglomerates. In the pharmaceutical industry, controlling nuclei formation is essential for achieving the desired drug release profiles. By adjusting parameters during nuclei formation, such as supersaturation levels or mixing rates, pharmaceutical manufacturers can tailor the properties of spherical agglomerates to ensure precise drug delivery, dissolution rates, and uniformity in tablet formulations, ultimately influencing the efficacy of the pharmaceutical product **[11][18]**.

Agitation causes the agglomerates to consolidate, which in turn reduces their porosity and size. Coalescence causes more growth by pushing the bridging fluids to the surface of the agglomerates. Research on the spherical agglomeration of salicylic acid have also highlighted similarities with granulation rate processes **[19][20]**.

Consolidation

Consolidation, the process of compacting and strengthening agglomerates, has a significant impact on their properties. It primarily affects the mechanical attributes of the agglomerates. For example, under high consolidation forces, agglomerates can become denser and more mechanically robust, which is essential for tablet manufacturing in the pharmaceutical industry. These denser agglomerates tend to exhibit improved compressibility and reduced friability, making them ideal for tablet formulations where mechanical strength and stability are critical. Conversely, insufficient consolidation can lead to weaker, more porous agglomerates with lower mechanical integrity, potentially causing issues during tablet production. Therefore, the degree of consolidation is a critical parameter that manufacturers must carefully control to ensure that spherical agglomerates possess the desired properties for various applications, particularly in

pharmaceutical and chemical industries. Agitation causes consolidation and thus reduction in size and porosity **[17] [18] [21] [22]**.

Coalescence

Coalescence, the merging or fusion of individual agglomerates, can significantly impact their properties. When agglomerates coalesce, they typically form larger, more consolidated structures. This process can lead to increased agglomerate size and reduced surface area, resulting in slower dissolution rates, which can be advantageous in controlling drug release in pharmaceutical formulations. For example, in controlled-release medications, coalescence of drug-loaded agglomerates can be strategically induced to achieve prolonged drug release. However, in some cases, excessive coalescence can lead to oversized agglomerates or agglomerates with irregular shapes, affecting their suitability for specific applications. Therefore, the controlled manipulation of coalescence is essential for tailoring the properties of spherical agglomerates to meet specific product requirements, especially in the pharmaceutical and materials processing industries **[17] [18] [23] [24]**.

Layering

Layering, a process where additional material is deposited onto existing spherical agglomerates, can significantly impact their properties. This method is commonly employed to modify the agglomerate surface or achieve controlled drug release. By adding a layer of a specific material onto the agglomerates, their surface texture and properties can be tailored. For example, in pharmaceutical applications, layering a drug onto inert cores can lead to controlled-release dosage forms, where the drug is released gradually over time. Similarly, layering with excipients or coatings can improve the flow properties, stability, and taste masking. The choice of layering material and its thickness are critical factors in determining the final properties and performance of spherical agglomerates, making it a versatile technique in various industries for achieving desired product characteristics **[8] [11] [17] [25]**.

In the study conducted by S. David and colleagues **[26]**, they noted variations in the agglomeration process as particles transitioned between different fluid flow regimes in response to changes in particle size. To describe the agglomeration occurring during crystallization, they employed a multi-layer agglomeration kernel **[15] [26]**.

Breakage

Breakage, which refers to the fracture or damage of spherical agglomerates, can have significant consequences on their properties. This process can result in smaller agglomerates or the formation of irregularly shaped particles. It can lead to variations in

drug particle size distribution, potentially affecting the uniformity and performance of pharmaceutical formulations such as tablets or capsules. Additionally, agglomerate breakage can impact the flow properties, compressibility, and dissolution rates of the final product. Manufacturers must carefully monitor and control processing conditions to minimize breakage and ensure that spherical agglomerates maintain the desired properties for their intended applications.

According to the findings of Thati **[15]**, it's proposed that at elevated agitation rates, agglomerate breakage could play a role, and these broken fragments might become part of other agglomerates. However, there is absence of agreement on the existence of breakage phenomena in spherical agglomeration processes. This uncertainty arises because the initial wetting phase causes agglomerates to be more deformable, making them more prone to factors that interrupt coalescence because of shear, rather than outright breakage. In simpler terms, while some suggest that agglomerates may break apart at elevated agitation rates and their fragments join other agglomerates, there is debate on whether this actually occurs. Instead, it's believed that the agglomerates deform and merge due to shear forces during the coalescence phase **[4] [15] [27] [28]**.

Table 1: Summary of factors affecting and their effect on properties of spherical agglomerates

Factor	Effect	Reference
Solvent addition method	Particle size, morphology, surface texture, density, porosity, and flow properties, compressibility, dissolution	[3]
Bridging liquid and addition method	Agglomerate size, shape, and surface texture. rate of precipitation and agglomeration, ultimately shaping the properties of the resulting particles	[3][10][11][12]
Agitation temperature	Affect the density, porosity, and mechanical properties of the agglomerates, leading to differences in dissolution rates	[4][8][3][14][15]
Residence time	Dissolution rates and compressibility, density, porosity, and flow properties	[3][4][16]
Agitation rate	Density, porosity, and surface texture, which in turn affect dissolution rates, flow properties, and tablet compressibility.	[3][10][17][18]
Nuclei formation	Higher number of nuclei may lead to smaller and more numerous agglomerates, while fewer, larger nuclei can result in larger, less numerous agglomerates.	[11][18][19][20]
Consolidation	High consolidation forces, agglomerates can become denser and more mechanically robust. insufficient consolidation can lead to weaker, more porous agglomerates with lower mechanical integrity.	[17][18][21][22]
Coalescence	Agglomerate size, surface area and dissolution rates.	[17][18][23][24]
Layering	Flow properties, surface texture	[8][15][17][25][26]
Breakage	Flow properties, compressibility, and dissolution rates of the final product	[4][15][29][30]

CONCLUSION

In this review, multitude of factors and operational parameters that influence the properties of spherical agglomerates were discussed. Spherical agglomerates, formed through spherical crystallization, have proven to be invaluable in pharmaceutical and various other industries, offering a wide

range of benefits, including improved drug delivery and enhanced product quality. The careful selection of solvent addition methods, bridging liquids, agitation temperatures, residence times, and agitation rates plays a pivotal role in tailoring agglomerate size, morphology, surface texture, and dissolution rates. Nuclei formation, consolidation, coalescence, and layering are essential stages in shaping agglomerate properties, each offering unique avenues for control and customization. Understanding these factors and parameters is crucial for pharmaceutical manufacturers and other industries where agglomerates find applications. It ensures that the properties of spherical agglomerates can be fine-tuned to meet specific product requirements, from efficient drug delivery and consistent product quality to controlled drug release and taste masking. In the ever-evolving landscape of materials processing, spherical agglomeration stands as a versatile and powerful technique, allowing for the creation of agglomerates with a wide array of properties. By harnessing the knowledge contained within this review, researchers and industry professionals can continue to explore and innovate in the realm of spherical agglomerates, unlocking new possibilities for drug delivery and product development.

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