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On the mechanism of agglomeration in suspension

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ABSTRACT

***Purpose*:** Agglomeration in suspension is a size enlargement method that facilitates operation of solid processing and preserves the solubilization properties of fine particles. A small quantity of binder liquid is added into a suspension of microparticles, directly in the stirred vessel where the precipitation or crystallization took place. This study deals with the evaluation of the effect of agitation time before and after addition of binder liquid on agglomerates properties in order to give some insights into the mechanism of the formation of the agglomerates. ***Methods*:** Carbamazepine is used as a model drug and isopropyl acetate is used as binder liquid. The agglomerates characterization includes the particle size, morphology and density. ***Results*:** The results showed that, by increasing the agitation time before addition of binder liquid, smaller agglomerates with less density and irregular forms composed of larger crystals were obtained. However, with increasing agitation time after addition of binder liquid the agglomerates size and density increases and morphology improves. Indeed, by continuing agitation along the course of agglomeration the properties of the particles change gradually but substantially. ***Conclusion*:** With optimized agitation time before and after addition of binder liquid, spherical and dense agglomerates can be obtained.

Introduction

Agglomeration in liquid systems with a wide range of objectives including separation of colloidal particles from a liquid, spherical granulation, removal and recovery of fine solids from liquid wastes, and selective separation of some components in a mixture of particles has gained increasing attention in recent years due to its relative simplicity and ease of operation. [1]
The further finding of spherical agglomeration of crystals during crystallization processes, named spherical crystallization by Kawashima et al. [2], has offered a promising approach to particulate design for engineering pharmaceuticals and chemicals. [3] The possibility of agglomerating the microcrystals directly inside the reactor presents many advantages for the processing of these particles.
Agglomeration is capable of modifying the micromeritic properties of pharmaceutical powders, such as flowability, packability, and solubility. It can also reduce the dust-releasing properties of an intermediate or the final product, and avoid segregation caused by vibration during handling and processing. All of these advantages ensure reliable and efficient powder handling and processing (e.g., mixing, granulation) as well as improvement in the bioavailability of the product. [4]
While a significant number of studies have been conducted on spherical agglomeration, the mechanisms of this technique have not been fully elucidated. As a result, there exist very few general guidelines for the application of this technique. The reasons for the preparation of agglomerates in liquid phase in particular conditions in the literature concerned were often not stated. Therefore it would appear that further application of the technique to other compounds could only be based on experience and /or trial and error.
Therefore, this technique is still not extensively used in industry due to the problems in understanding and controlling the process parameters that allow production of agglomerates with the reproducible desired properties. In particular the aim of the present work is to bring further insight into how the agglomerates are formed and evolve during the process, and into the mechanisms behind the agglomeration in suspension. For this purpose the effect of the agitation time before and after addition of binder liquid on the agglomerates properties was investigated. Carbamazepine was used as model compound in the present work. Carbamazepine normally crystallizes as needles or flake that can be difficult to handle in downstream processing and are unsuitable for direct compression into tablets. Carbamazepine was crystallized from ethanol by drowning out with water and agglomerated using Isopropyl acetate as binder liquid according to our previous study. [5]

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Materials and Methods

Materials

In this work carbamazepine was supplied by Arasto Pharmaceutical Chemical Inc, Iran and solvents (ethanol and isopropyl acetate) were purchased from Merck, Germany.

Agglomeration experiments

The crystallization process used in this study was similar to method which was introduced in previous study as the spherical crystallization technique. [5] A solution of 0.5 g of carbamazepine in 10 ml of ethanol was poured into 84 ml of water at 25^{o}C under stirring with a propeller-type agitator with four blades at 400 rpm in a cylindrical vessel. After different agitation time including 5,10 and 15 min for A_1, A_2 and A_3 samples respectively, 6 ml of isopropyl acetate as a binder liquid was introduced into the crystallization medium in a dropwise manner and agitation continued for 40 min. The agglomerates obtained were filtered, washed with water, and dried in an oven at 80 ^{o}C for 12 h.

In series B, the purpose is to be able to track how the properties of the agglomerates gradually change during the corresponding series A experiment. Because of that in series B the conditions correspond to A_1 experiment but agitation continued for different times (5,10, 20 and 40 min for B_1, B_2, B_3 and B_4 samples respectively) after addition of binder liquid.

The analysis of the product includes particle morphology, size and density.

Characterization of the agglomerates

Pictures of at least 60 particles of each powder were taken using a CCD camera (Canon digital, Japan) connected to a light microscope (Leitz, Portugal). Digital images were acquired at 5× magnification. For each particle the heywood diameter and the aspect ratio (AR) were determined by using the scion image software. According to the software specification the aspect ratio as a shape factor was calculated using the following equation

$$AR = dmax/dmin$$

where dmax and dmin were the longest and shortest Feret diameters measured, respectively.

To determine the primary particle size, the agglomerates were disintegrated in an aqueous solution of tween 80 (0.05%) using Ultrasonicator (Model starsonic 18-35, liarre casal flumanese, Italy) for 30s at 100 W before determining the particle size. Then the particle size of the primary crystals, which composed the agglomerates, was measured using a laser diffraction and scattering particle sizer (SALD_2101, shimadzu, Japan).

Apparent particle density

Apparent particle density was determined by the projective image count method as follows. Particles were placed on a glass plate. Heywood diameter and particle number were measured by using the scion image software. Subsequently, the apparent particle density was calculated according to following equation

$$\text{Apparent particle density} = \frac{W}{V} = \frac{W}{\sum(\pi d^3 n/6)}$$

where W = weight of particles, V = volume of particles, d = Heywood diameter, and n = number of particles. [6]

Statistical evaluation of data

Quantitative data were reported as mean ± standard deviation (SD). Statistical analysis was performed using the analysis of variance (ANOVA). Comparison between the two means was determined using the Tukey's test with statistical significance evaluated at $P< 0.05$.

Results

In this study, a three-solvent system was utilized to produce the agglomerates of carbamazepine. The drug was first dissolved in ethanol and the resultant solution was poured into water then isopropyl acetate was added as binder liquid. Before binding liquid injection, the suspension produced by precipitation is totally opaque. Immediately after injection and dispersion of binder liquid, the suspension becomes clearer and particles gather into flocs of all shapes and all sizes which can be measured less than 1 min after injection.

The agglomerates disintegrated easily into primary crystals under ultrasonic agitation of the aqueous suspension of agglomerates. A size analysis was carried out on the constituent crystals of the agglomerates. It can be seen in Table 1 that with increasing agitation time before addition of binder liquid (series A) the obtained agglomerates composed of bigger and more elongated crystals. According to Figure 1 and Table 1 for the bigger primary crystals the obtained agglomerates are smaller, less spherical with rough surface and less density. The morphology of the particles from series B experiments is shown in the Figure 2. This Figure shows that there appears to be a gradual improvement of the shape of the particles as stirring time continues. The particles obtained after 5 min are dominated by irregularly shaped agglomerates, which adhere together as a big clusters and when agitation is continued for up to 20 min the agglomerates were found separately and their surface seems to be much smoother and the overall shape is clearly more regular.

After 40 min agitation the agglomerates starts to look spherical. However, in reality some of the agglomerates are somewhat tabular and not completely spherical. Figure 3 shows the spherical agglomerates prepared after 40min agitation were closely compacted with fine

primary crystals, while after 5 min agitation, the agglomerates composed with loosely compacted fine primary crystals were observed. Table 1 also confirmed this fact and shows that in series B with continuing agitation the particle density significantly increases ($p<0.05$).

Table 1. micromeritic properties of the samples

samples	Aspect ratio	Crystal size (μ) (Length)	Median ±σ (μ)	Particle density (g/cm^3)	Yield (%)
A_1	1.23±0.20	6.0±0.8	1237.4+148.5	0.59±0.09	84.0±0.9
A_2	2.01±0.19	8±0.9	1147.5+188.7	0.40±0.08	84.4±0.8
A_3	2.3 8±0.21	15±0.9	1096.5+222.7	0.34±0.08	76.3±0.8
B_1	1.70±0.23	15±0.8	1456±346	0.66±0.07	86.1±0.9
B_2	1.83±0.20	15±0.9	1118±230	0.65±0.06	86.4±0.7
B_3	2.17±0.19	15±0.7	1136±193	0.75±0.09	84.3±0.8
B_4	1.2 3±0.20	15±0.8	1237.4+148.5	0.97±0.06	84.0±0.9

Figure 1. Particle morphology of series A (× 10).

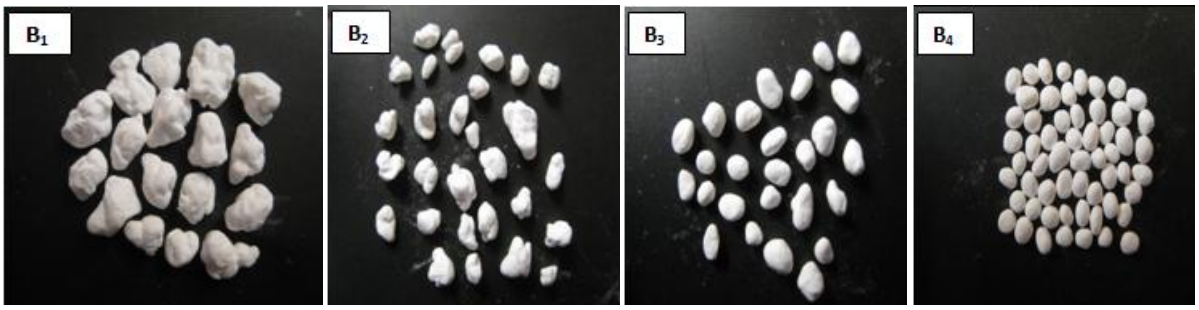

Figure 2. Particle morphology of series B(× 10).

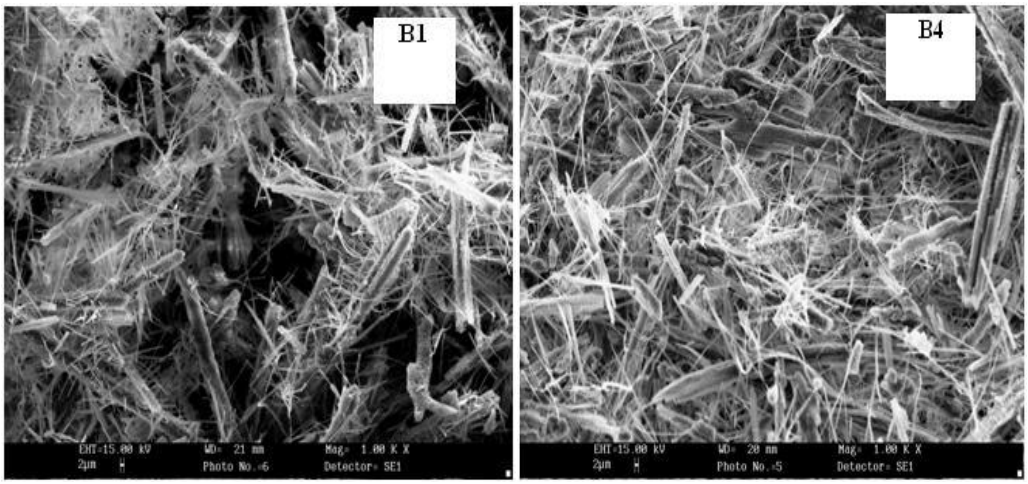

Figure 3. Surface of the particles from series B_1 and B_4.

Discussion

Results of series A showed that agglomeration of large crystals is more difficult especially if they are more elongated, while, smaller crystals give rise to more spherical and larger agglomerates with smoother surface and denser structure. Indeed, the agglomeration process was less efficient for bigger primary crystals and some fines were not incorporated in to the agglomerates (A_3) which consequently results in decreasing agglomeration yield. This fact might be interpreted by considering the other investigation [7] which showed fine crystals required less amount of binder liquid for agglomeration, since the adhesive force of fine crystals with binder liquid was stronger than those coarse crystals as a consequence of higher surface area. Therefore, higher amount of available binder liquid on the outer surface of the agglomerates of fine crystals making the surface more deformable and might promote further agglomeration. Increasing agglomerates size with an increase in the amount of available binder liquid for agglomeration has been shown in the numerous studies. [8-10] On the other hand, smoother surface of the agglomerates composed of finer crystals is expectable since smaller particles will cause smaller surface asperities. Denser structure of the agglomerates obtained at lower agitation time in series A might be attributed to this fact that, the fine and isotropic particles was compacted during agglomeration more closely than that of coarse and needle-like particles. [11] These results can also be interpreted by considering the mechanism of agglomeration.

The process of agglomeration in suspension can be described as a two-step process. [12] The first step is the nucleation period, where the particles come into contact with the liquid binder droplets and form agglomerate nuclei. Several mechanisms of the nucleation period are proposed, which depend on the diameter ratio of the crystals to the binder droplet. [13,14]

When the crystals are bigger than the binder droplet, the nucleation takes place by a distribution mechanism, i.e. the liquid droplets are coating the solid particles. This leads to the formation of agglomerates with an irregular shape and a looser structure. When the crystals are smaller than the binder droplet, nucleation occurs by an immersion mechanism. The particles impact against the surface of the droplet and enter the droplet until the droplet internal volume is saturated with solid particles. This leads to the formation of agglomerates with a narrower particle size distribution and a more spherical shape with a denser structure.

The results of series A can also be described according to above explanation about the nucleation mechanism of agglomeration, because finer crystals offer a greater potential for nucleation by immersion than larger ones, and that immersion leads to the formation of agglomerates with a narrower particle size distribution, a more spherical shape and with a denser structure than distribution.

In other part of this study, in order to bring insight into the mechanism of the agglomeration, agglomerate size, shape and density evaluation was carried out after binder liquid injection and continuing stirring for different time (5,10, 20 and 40 min) which allowed to follow the change in the agglomerate properties during the agglomeration process (series B). Firstly it is notable that, by measuring primary crystal size of agglomerates produced in series B, it was found that the particle size of the primary crystals during agglomeration remained unchanged ($p>0.05$), which was in agreement with some other investigations. [3, 15-17] Results revealed a marked change from irregularly shaped agglomerates to more regular with smoother surface agglomerates throughout agitation in series B. According to Table 1, aspect ratio of these samples decreases ($p<0.05$) with agitation time which confirmed the rounding effect of further agitation. Also, by continuing agitation in series B, particle density markedly increases ($p<0.05$). Results of series B can be interpreted by considering the second step of the agglomeration process. [12] The second step of agglomeration is the growth and consolidation period

by a mechanism of collision and coalescence of the agglomerates in the stirred reactor. According to Figure 2 in initial stage of the agglomeration the particles were adhered together, which indicate the coalescence of the particles. In this stage the coalescence is easier because the agglomerates can be deformed and compacted and the elementary particles can move to be piled up in a more compact way.

By continuing agitation the agglomerates become more and more compact (increasing particle density) and regular (decreasing AR), thanks to the numerous shocks between agglomerates (which are also responsible for the agglomerates enlargement when they induce an efficient coalescence) or between the agglomerates and different parts of the vessel.

This growth period ends when the agglomerates become too compact to be deformed and arranged during the collision.

Conclusion

Results showed that the influence of agitation is of great importance for the creation of the regular shape of the particles by agglomeration in suspension method. With increasing agitation time before addition of binder liquid obtained agglomerates composed of bigger and more elongated crystals. Needle-like particles are more difficult to pack than isotropic particles. Moreover, the particle surface area available is decreased when the particle size is increased for an equivalent solid concentration. These two phenomena have an effect on the deformability of the agglomerates and reduce the agglomeration efficiency when bigger crystals are used. Therefore, in order to control the size of the agglomerates produced, it seems important to control the size of the crystals to be agglomerated. In second part of this study by varying the stirring time after addition of binder liquid, it was shown that the spherical shape of the agglomerates does not appear immediately but develops gradually. The spherical shape is due to the mechanical forces of the agitation exerted on the particles over a long period of time, similar to the consolidation in granulation process.

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Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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