Effect of temperature on wet agglomeration of crystals

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ARTICLE INFO	ABSTRACT
	Objective(s): This study dealt with the wet agglomeration process in which a small quantity of binder liquid was added into a suspension of crystals, directly in the stirring vessel where the crystallization took place. The purpose of this investigation was evaluation of the effect of temperature on the agglomeration process in order to gain insight into the mechanism of the formation of the agglomerates. ***Materials and Methods:*** Carbamazepine was used as a model drug and water/ethanol and isopropyl acetate were used as crystallization system and binder liquid, respectively. The agglomeration of crystals was carried out at various temperatures and the agglomerates were characterized in terms of size, morphology, density and mechanical strength. ***Results:*** Evaluation of the agglomerates along the course of agglomeration shows that the properties of the particles change gradually but substantially. Higher temperature of the system during agglomeration process favors the formation of more regular agglomerates with mechanically stronger and denser structure; this can be explained by the promotion effect of temperature on the agglomeration process. ***Conclusion:*** With optimized wet agglomeration temperature, spherical, dense, and strong agglomerates can be obtained.

Introduction

Wet agglomeration of crystals as a size enlargement method was developed in the previous decades for the pharmaceutical industry, where small particles of less than 10 µm in diameter are often produced by crystallization or precipitation, but their processing is very difficult and expensive. The possibility of agglomerating the microcrystals directly inside the reactor presents many advantages for the processing of these particles (1-7).

In spite of numerous researches in wet agglomeration field, the mechanism has not been completely understood and lack of general guidelines for using this technique is realized. In the literature special conditions for agglomeration of drugs were used without comprehensive explanation; therefore, for other compounds rational prediction of wet agglomeration condition is not possible. Thus, 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 the literature, numerous works dealing with wet agglomeration were devoted to measurement of the agglomerates properties; however, the proposed relationships give these properties only after achievement of the equilibrium (see for instance Pacek *et al* (8) for a review). In the present study, the influence of temperature on the product properties during the agglomeration process was investigated. In particular the aim of the present work is to gain further insight into how the agglomerates are formed and evolve during the process, and into the mechanisms behind the spherical shape. For this purpose the effect of temperature on the particle properties through the agglomeration process of carbamazepine as a model compound was investigated. Carbamazepine normally crystallizes as needles or flakes that can be difficult to handle in downstream processing. Carbamazepine was crystallized from ethanol by drowning out with water and agglomerated using isopropyl acetate as the binder liquid according to our previous study (9).

Materials and Methods
Materials

Carbamazepine was purchased from Arasto Pharmaceutical Chemical Inc (Iran) and solvents (ethanol and isopropyl acetate) were from Merck, Germany.

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Methods
Agglomeration experiments

The crystallization process used in this study is a modified method which was introduced in our previous study as the spherical crystallization technique (9). A solution of 0.5 g carbamazepine in 10 ml ethanol (solvent) was poured into 84 ml of water (antisolvent) at room temperature under stirring at 400 rpm. Crystallization equilibrium was determined by confirming that the size of crystals in the system become stable. After crystallization equilibrium was attained, the system was further agitated for 15 min to adjust the temperature of the system to that required (25, 35 and 45°C). Then, 6 ml of isopropyl acetate, used as the binding liquid, was introduced into the crystallization medium and agitation continued for various times e.g. 5, 10, 20, or 40 min.

The solidified agglomerates were recovered by filtration and washed with purified water.

Then the resultant products were placed in a thin layer in an oven at 60°C for 12 hr.

Solubility studies

Solubility measurements were carried out adding excess amounts of carbamazepine to isopropyl acetate at different temperatures (25, 35, 45°C). After stirring the samples in a temperature controlled water bath until equilibrium was reached (72 hr), the concentrations of dissolved drugs were determined by using a UV Spectrometer (UV-160, Shimadzu, Japan) at a wavelength of 285 nm. The temperatures were kept constant ± 0.5°C. Six measurements were taken at each temperature and the average value was used.

The agglomerates characterization
The particle size

Light microscopy pictures of the agglomerates (at least 60 particles) were captured by a digital camera and subsequently analyzed by the Scion image analysis software. The average particle size of a single particle was defined as the average length of the distance measured at two degree intervals joining two outline points passing through the center of gravity of the particle.

The shape of the particles was characterized by the ratio between the height and the width of a box bounding the particle, where the height of the box was parallel to the largest diameter passing through the center. This parameter will be referred to as the aspect ratio (AR) in the rest of the paper (10).

To determine the primary crystal size of the agglomerates, they were disintegrated in an aqueous solution of tween 80 (0.05%) using ultrasonicator (Starsonic 18-35, liarre Casal Flumanese, Italy) for 30s at 100 W. Then, a small amount of obtained primary crystals (about 20 mg) was suspended in mineral oil (Sigma Chemical Co, St Louis, USA) and the suspension was spread onto a microscope slide.

In order to settle this mixture consistently on the slide, a cover slip was used and then crystal size was measured as explained previously.

Apparent particle density

Apparent particle density was determined by the projective image count method as follows. The weighed amount of the agglomerates was placed on a glass plate and number of particles and their Heywood diameters were determined using the Scion image analysis software. Subsequently, the apparent particle density was calculated according to Eq (1).

$$\text{Apparent particle density} = \frac{W}{V} = \frac{W}{\sum(\pi d^3 n/6)} \qquad \text{Eq 1}$$

where W=weight of particles, V=volume of particles, d=Heywood diameter, and n=number of particles (11).

Crushing test

A crushing test in which the agglomerates were crushed between two parallel platens was used. Thirty agglomerates were randomly removed from the final sample and their size (L) was, measured by optical microscopy and image analysis. Then, each agglomerate was crushed, and the load at failure (m_{fail}) was recorded. For approximately spherical agglomerates, it was linked to agglomerate size as follows (12).

$$m_{fail} = \sigma \frac{\pi L^2}{4} \qquad \text{Eq 2}$$

Eq. (2) was confirmed by a log- log plot of load at failure against agglomerate size. The plot yielded the compressive strength (σ).

Solid-state characterization
X-ray diffraction of powder (XRDP)

The X-ray diffraction patterns of CBZ samples were obtained using an X-ray diffractometer (Seimens, Model D5000, Germany) operated at 40 kV, 30mA and a scanning rate of 0.06∘/min over the range 5–40 2θ, using Cu Kα$_1$ radiation of wavelength 1.5405 Å. The cavity of the metal sample holder of X-ray diffractometer was filled with the ground sample powder.

Differential scanning calorimetry (DSC)

Samples of the crystals (about 5 mg) were heated (range 25–250°C) at 10°C/min in crimped hermetically sealed aluminum pans. The melting point could be obtained from the thermograms using the instrumental software (DSC60, Shimadzu, Japan). The calorimeter was calibrated using indium and lead standards.

Statistical evaluation of data

Quantitative data were reported as mean±

Figure 1 shows some photographs taken at different times during the agglomeration process. According to this Figure there appears to be a gradual improvement of the shape of the particles by continuing agitation.

At 25°C, the early formed agglomerates, after a 5 min agitation, associate with each other into irregularly shaped larger entities. After 40 min the shape of these agglomerates becomes clearly more regular and the surface is much smoother. However, it is noticeable that the particles produced at 25°C are dominated by irregularly shaped agglomerates throughout the entire agitation time and even after 40 min agitation most particles are tabular but not spherical.

Agglomerates obtained at 35°C and after 5 min agitation are dominated by irregularly shaped clusters; after 20 min agitation they appear as still irregularly shaped particles. By continuing agitation for 40 min the agglomerates start to look spherical with smoother surface; however, in reality some of the agglomerates are chunky but not completely spherical.

At 45°C, after 20 min agitation the agglomerates appear to have regular shape with almost smooth surface and when agitation is continued for up to 40 min, more regular agglomerates are formed and their surface seems to be much smoother.

Comparison of the agglomerates prepared at different temperatures demonstrates that the obtained particles after 5 min agitation do not appear to be very different and all of them are irregularly shaped particles which mostly adhere together in big clusters. However, when stirring is continued for 10 min a difference in the overall shape of the particles can be observed and this is even more pronounced at 20 min. These results show that although in all temperatures obtained particles exhibit a similar change from irregularly shaped agglomerates with rough surfaces to more regular with smooth surfaced ones throughout agitation, increasing process temperature leads to generally improved particle morphology and achievement of more regular agglomerates faster. This fact is also provable by comparing the AR values of the particles prepared at different temperatures (Table 1). In all temperatures, the AR value of the

Figure 1. Photographs of the agglomerates prepared at different temperatures (×8)

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 poured into water as an antisolvent. After attaining crystallization equilibrium, the temperature of the system was adjusted to that required and then isopropyl acetate as the binding liquid was introduced into the crystallization medium. Precipitation of crystals makes the crystallization medium completely opaque; however, addition of binder liquid rendered the system clearer due to gathering the crystals into flocs. Less than 1 min after injection of binder liquid these flocs in various shapes and sizes can be seen.

Table 1. Shape factor, size, primary crystal size, density and compressive strength of the agglomerates

Samples	Aspect ratio (AR)	Agglomerate size $d_{ln} \pm \sigma$ (µm)	Mean primary crystal size ± SD (µm)	Particle density (g/cm^3)	Compressive strength (kg/cm^2)
45°C-40min	1.10±0.08	951+115	11.7±0.5	1.20±0.09	1.78±0.11
35°C -40min	1.34±0.09	1050+152	11.9±0.5	1.00±0.08	1.11±0.12
25°C -40min	1.52±0.10	1138+255	12.1±0.8	0.97±0.09	0.88±0.13
45°C - 20min	1.33±0.08	942+163	12.1±0.7	1.05±0.08	1.59±0.12
35°C -20min	1.42±0.10	931+149	12.3±0.6	0.92±0.10	0.90±0.11
25°C - 20min	1.71±0.1 0	1118+193	12.1±0.6	0.78±0.09	0.65±0.12
45°C -10min	1.48±0.09	828+125	11.9±0.7	0.83±0.08	1.38±0.11
35°C -10min	1.55±0.09	927+158	11.6±0.5	0.81±0.08	0.89±0.10
25°C -10min	1.85±0.08	1144+230	12.2±0.7	0.65±0.09	0.51±0.11
45°C -5min	1.62±0.10	1110+315	12.1±0.8	0.64±0.08	1.20±0.12
35°C -5min	1.81±0.09	1250+346	12.0±0.6	0. 66±0.1	0.73±0.12
25°C -5min	1.90±0.09	1356+212	11.9±0.8	0.51±0.10	0.35±0.10

Figure 2. X-ray diffraction of agglomerates prepared at different temperatures

Figure 3. Differential scanning calorimetry thermograms of the agglomerates prepared at different temperatures
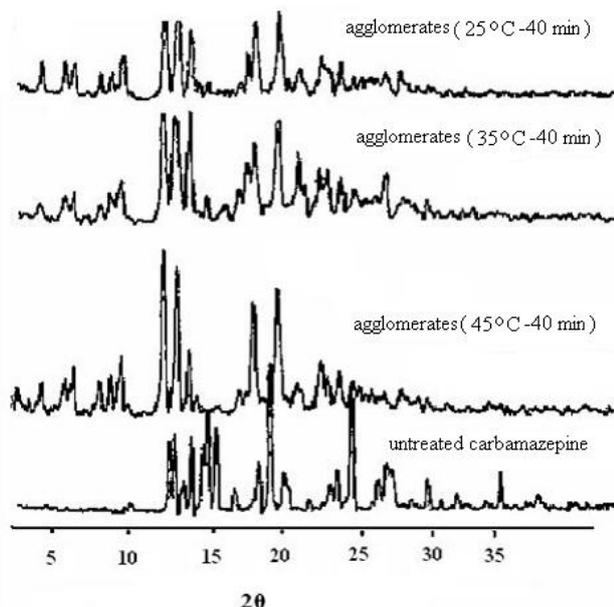
agglomerates decreases by continuing agitation from 5 to 40 min, while, at identical agitation times, higher temperature leads to the agglomerates with lower AR ($P<0.05$).

Generally, when agitation continues a decrease in the mean particle size of the agglomerates appears (Table 1 and Figure 1). This quantity also significantly depends on the agglomeration temperature. At identical stirring times, the mean size of the agglomerates considerably decreases with an increase in the temperature. For instance after 40 min agitation, the average particle diameters are found to be respectively 1138, 1050 and 951 μm for 25, 35 and 45℃.

The obtained agglomerates disintegrate easily into primary crystals under ultrasonic agitation of the aqueous suspension of agglomerates. The mean sizes of primary crystals making up the agglomerates are shown in Table 1. After achievement of crystallization equilibrium, the size of the primary crystals (11.8±0.6μm) remains unchanged throughout agglomeration process irrespective of temperature ($P>0.05$).

As indicated in table 1, density and compressive strength of the particles increase during agitation ($P<0.05$). Moreover, the temperature has a significant effect on these quantities and increasing temperature of the agglomeration process leads to denser particles with higher compressive strength ($P<0.05$).

Solid-state characterization

XRPD is a powerful technique for identification of the various polymorphs of carbamazepine. Each crystalline form of a drug has a distinctive XRPD pattern which can be used for its detection. Unt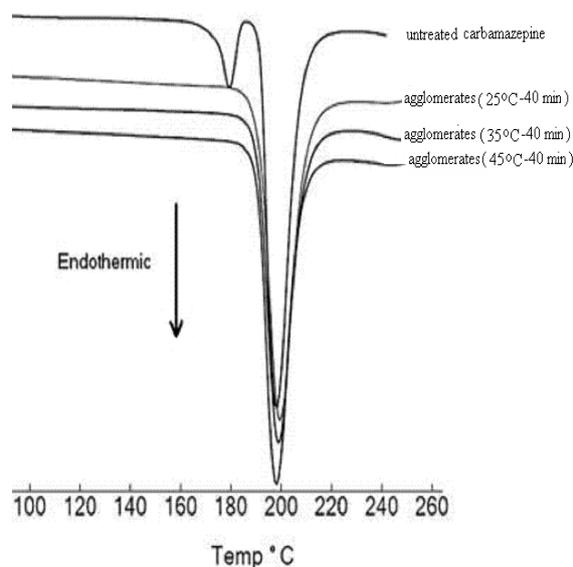reated carbamazepine shows a pattern identical to carbamazepine USP reference standard (Figure 2) and the data obtained in the present study are in good agreement with those published for polymorph III by Lowes *et al* (13). Characteristic high-intensity diffraction peaks are detected at $2°\theta=14.9$, 15.2, 15.8, 27.2, 27.5 and 32.0. Further, the most providing identification is the absence of peaks from 2 to 10 $°2\theta$. X-ray powder diffractograms of the agglomerates obtained at different temperatures are in good agreement with those published for form I by Kala, Krahn and co-workers (14,15) in which typical signals are recorded at $2°\theta=6.1$, 9.4, 12.25, 19.8, 19.9, and 22.8.

Differential scanning calorimetry curves of agglomerates and untreated carbamazepine are illustrated in Figure 3. DSC thermogram of untreated carbamazepine shows two endotherms. The endothermic peak at 179℃ coincides with the melting of form III, followed by exothermic crystallization as polymorph I, which subsequently melts at 197℃. The DSC curves of agglomerates prepared at different temperatures exhibit only one sharp endothermic peak at 197℃. These findings show that the untreated sample and agglomerates are form III and form I, respectively, confirming the XRPD results (16-18).

Discussion

The process of wet agglomeration in suspension of crystals can be described as a two-step process (19). The first step is the nucleation period, where the original crystals form agglomerate nuclei after wetting with the binder liquid droplets. The first step of agglomeration is followed by second step which is the consolidation and growth period by a mechanism of collision and coalescence of the agglomerates in the stirred reactor. In fact, agitation results in a

gradual consolidation of the agglomerates which leads to binder liquid squeeze out from liquid pores to the particle surface and may contribute to growth by coalescence with other agglomerates. Thus, in this step, the coalescence is easier if the agglomerates can be deformed and compacted, i.e., if the elementary particles can move to be piled up in a more compact way.

Considering these steps, it is assumed that the irregular clusters that are observed in initial 10 min of agitation in Figure 1 may be formed due to coalescence of the primary agglomerates. By continuing agitation up to 40 min, the shear forces of the agitated liquid and collisions with equipment surfaces and other particles are squeezing and molding these irregular clusters into almost regular particles as can be clearly seen in this Figure. Therefore, it appears to be obvious that the spherical shape of the agglomerates is not the result of the agglomerates being formed in spherical droplets of the dispersed liquid phase. In fact, the spherical shape is due to the mechanical forces of the agitation exerted on the particles over a longer period of time.

As mentioned in results section, the mean particle size of the agglomerates generally decreases by continuing agitation from 5 to 40 min which may be owing to consolidation of the agglomerates due to collisions. However, it should be mentioned that in some cases, a slight increase in mean particle size of the agglomerates is seen, especially in later stages of the agglomeration course. This may be explained by the fact that some particles break on the high shear region of the trailing vortices of the impeller, or by actual collision with impeller blades, and fragments are incorporated by other particles (20). In addition of repeated breakage and agglomeration, layering phenomenon may also contribute to increase in the agglomerates size. Layering phenomenon leads to enlargement of the agglomerates by attachment of fine material and single crystals to the surface of agglomerates.

According to literature, in order to control the properties of the agglomerates, it is important to control the size of the crystals to be agglomerated (21-23). Because of this fact, in this study the primary crystal sizes of the agglomerates are also evaluated. As mentioned previously, by measuring primary crystal size of agglomerates produced after different agitation time, it is found that the mean size of the primary crystals during agglomeration remains unchanged, which is in agreement with some other investigations (24-27). The results also show that after achievement of the crystallization equilibrium, change in temperature does not cause a significant difference in the size of primary crystals. Therefore, according to these results, it is concluded that the influence of primary crystal size on the agglomerates' properties can be ruled out.

Results indicate that agitation not only leads to improved shape of the agglomerates and decrease in their size but also an increase in density of the particles occurs by continuing agitation. This can be explained by considering the second step of agglomeration wherein the agglomerates become more and more compact thanks to the numerous shocks between agglomerates or between the agglomerates and different parts of the vessel during agitation. It is clear that increase in density ends when the agglomerates become too compact to be deformed and arranged during the collision.

As can be seen in Table 1, in all experiments, there is a clear correlation between particle density and force needed to break the particle. According to literature, the compressive strength of the agglomerates is due to two contributions: first, a mechanical contribution owing to the very tight piling up of the particles inside the agglomerates and second, the contribution of crystalline bridges (28). Therefore, it is expectable that gathering the primary crystals more compactly in denser agglomerates results in higher mechanical contribution and consequently formation of stronger agglomerates.

According to the obtained results, it is obvious that the properties of the particles modify gradually along the agglomeration course. However, it is interesting to note that in all agitation times with increasing temperature the particles on average tend to become denser and stronger, with more regular shape and smaller size. In other words, it seems that increasing temperature has a promotion effect on the agglomeration of crystals. This can be explained by taking into account the probable effects of temperature on both steps of agglomeration process including nucleation, and growth and consolidation as described below. Evidently, at higher temperatures better dispersion of the binder liquid, particularly, by the formation of smaller droplets and accordingly higher surface areas, leads to increase in the wetting rate of crystals and consequently promotional effect on the nucleation step (29). On the other hand, smaller size of binder liquid droplets results in the formation of a higher number of small nuclei and consequently smaller final agglomerates. Also, the crystals and fines will be agglomerated more easily by the small binder droplets, which will enable reduction of the layering phenomenon occurring during the collision–coalescence phase when the binder droplets are too large.

Additionally, it is supposed that an increase in temperature can influence the second step of the agglomeration process, growth and consolidation period, by increasing the rate of particles colliding with each other or the equipment surfaces. This promotional effect of temperature on the compaction of the agglomerates leads to formation of more regular and denser agglomerates, as expected. As mentioned previously, the compressive strength of

the agglomerates is due to two factors: mechanical contribution of piling up of the crystals and contribution of crystalline bridge. In all agitation times, there is a logical relationship between strength and density of the agglomerates and at higher temperatures the agglomerates show higher compressive strengths according to their densities. This correlation is expected due to mechanical contribution of crystals as described previously. Additionally, it is assumable that the temperature affects strength of the agglomerates through crystalline bridge formation as explained below. A diffusion-controlled recrystallization and fusion model of crystals is proposed to describe the formation of crystalline bridges. Indeed, right after the addition of the binding liquid, the agglomeration begins immediately and dispersed binder liquid preferentially wets the surface of the original crystals. Binder liquid adsorption on the surface of the crystals dissolves the crystals in part and makes a solution layer.

The concentration of dissolved crystals in the binding liquid should be higher at rough surfaces with asperities and at finer (smaller) crystalline surfaces, according to Eq. (3) dissolve based on Ostwald (30):

$$\log\left(\frac{S}{So}\right) = \left(\frac{4\sigma mM}{2.303\rho RT}\right)\left(\frac{1}{d} - \frac{1}{do}\right)$$

where S_0 and d_0 are the solubility and diameter of large particles, respectively; S and d are the solubility and diameter of fine particles (or asperities), respectively; σm is the mean interfacial tension; ρ is particle density; R is gas constant; T is the absolute temperature; and M is the molecular weight of the material. The concentration of dissolved crystals in the binding liquid layer becomes uniform following the diffusion of the dissolved crystal molecules from the higher to the lower concentration in the layer. At the same time, the binding liquid diffuses from its adsorbed layer on the surface and at the cross contact point between particles into the dispersing medium. These diffusion processes induce a solubility change in the binding liquid, resulting in the recrystallization (reprecipitation) of the dissolved crystalline material, which preferentially occurs on coarse particle surfaces and smoother surfaces. Thus, a solid bridge is formed by fusion at the cross-contact point of the original crystals. It is assumable that at a higher temperature (e.g. 45°C) recrystallization process of crystals is promoted because of increased diffusion rate and solubility of carbamazepine (9.7 mg/ml) in the binding liquid at higher temperature compared with solubility of the drug (4.1mg/ml) at a lower temperature (25°C). Therefore, it is concluded that generation of stronger agglomerates at higher temperatures may also be related to positive effect of temperature on

formation of crystalline bridges.

Conclusion

Evaluation of the effect of temperature on the agglomeration process showed that higher temperature favors the formation of smaller and more regular agglomerates with denser and stronger structure. This may be related to the promotion effect of temperature on nucleation and consolidation steps of the agglomeration process as is comprehensively discussed in this study. Obtained results prove that temperature is the influential operating parameter of the wet agglomeration of crystals which determines the principle properties of the agglomerates.

Acknowledgment

Conflict of interest

The authors report no conflicts of interest.

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