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Spherical crystallization of benzoic acid

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Abstract

This paper deals with the development of a method for spherical crystallization of benzoic acid. Benzoic acid is dissolved in ethanol, water is used as anti-solvent and chloroform is used as bridging liquid. After an introductory screening of different methods, the influence of the amount of the bridging liquid, the solute concentration and the stirring rate is investigated. The product particle characterization includes the particle size distribution, morphology and strength. The mechanical strength of single agglomerates has been determined by compression in a materials testing machine, using a 10 N load cell. It is found that favourable properties are obtained if the bridging liquid is added during the crystallization. Larger and stronger well-shaped agglomerates are formed. The stress–strain curves are J-shaped with no clear fracturing of the particles, and are well correlated by an exponential–polynomial equation.

Keywords: Crystallization; Spherical agglomeration; Benzoic acid; Physico-mechanical properties (size distribution, particle morphology, compression strength)

1. Introduction

Today the tablet is the most popular dosage form, representing 50% of all oral drug delivery systems, and accounting for 70% of all pharmaceutical preparations produced. From the manufacturing point of view, the initial capital outlay is high but tablets can be produced at much higher rate than any other dosage form. The dry dosage form promotes stability, and tablets are readily portable and consumed. The formulation of a tablet is optimized to achieve several goals. The focus today in the business is better drug delivery concepts, but also to make the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find direct compressible formulations and this is especially of interest for large volume products. The required number of unit operations in direct compression is lower which means less equipment and space, lower labour costs, less processing time, and lower energy consumption. Moisture and/or heat in the wet method can influence the drug stability and cause degrading of the drug.

The final purification of the Active Pharmaceutical Ingredient (API) is usually a crystallization step, in which the product properties like the crystal size distribution, crystal shape, degree of agglomeration, and agglomerate properties, depend on how the process is operated. Temperature profile, solvent composition, method and rate of supersaturation generation, hydrodynamics, etc. often have a profound influence on these properties, and can be used to control the process in such a way that more specific solid state properties, suitable for formulation, are obtained. The first step in the formulation is often milling or granulation, in order to provide for better properties for the final tabletting or to increase bioavailability. Often very small particles (less than 10 μm in size) are required in order to increase the dissolution rate, and reach sufficient bioavailability. However, micronisation by milling is extremely inefficient, can cause physical and chemical instability, and produces powders with a wide size distribution and poor flowability. The alternative is to produce quite small crystals directly in the crystallization. However, downstream handling of such small particles tends to be difficult, tedious and expensive. In some cases thin needles are produced having a high surface area to volume ratio, but likewise may be quite difficult to handle. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization, and hence gain favorable downstream

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processing characteristics combined with desirable bioavailability properties. In addition, it has been brought forward that agglomerates may receive properties that make them aimable for direct compression tabletting.

The aim of the present research is to advance the engineering of pharmaceutical agglomerates, for the purpose of tailoring the properties by modulation of processing conditions like solvent composition, hydrodynamics, and supersaturation generation. One interesting method is denoted spherical crystallization (Nocent et al., 2001) that combines several processes into one step, including synthesis, crystallization, separation and agglomeration. Among the advantages of the spherical agglomerates are good physico-chemical properties like compressibility, packability and flowability that improve mixing, filling and tabletting (Kawashima et al., 1995; Lasagabaster et al., 1994). Farnand et al. (1961) suggested that when two immiscible solvents are present and one of the solvents preferentially wets the solid surface, a collision between two wetted particles forms a liquid bridge between the particles, similar to liquid bridge formation in granulation. Kawashima et al. (1982a,b) introduced this technique into pharmaceutical manufacturing and showed that spherical dense agglomerates could be produced suitable for direct tabletting.

There are two main methods for spherical crystallization: spherical agglomeration (SA) and emulsion solvent diffusion (ESD). In both processes is used a solvent that readily dissolves the compound to be crystallized (good solvent), and a solvent that act as an antisolvent generating the required supersaturation (poor solvent). In the ESD method (Sano et al., 1992), the "affinity" between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase.

In the SA method also a third solvent called the bridging liquid is added in a smaller amount to promote the formation of agglomerates (Kawashima, 1994). A near saturated solution of the drug in the good solvent is poured into the poor solvent. Provided that the poor and good solvents are freely miscible and the "affinity" between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. Under agitation, the bridging liquid (the wetting agent) is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid act to adhere the crystals to one another (Kawashima et al., 1984). The SA method has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid (Kawashima et al., 2003). Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles (Bausch and Leuenberger, 1994). Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. In the case of lactose, the agglomerate size distribution was affected by both the size of raw particles and the amount of bridging liquid used. At increasing stirring rate the agglomeration was reduced (Bos and Zuiderweg, 1987), because of increasing disruptive forces. Higher stirring rate produce agglomerates that are less porous and more resistant to mechanical stress, and the porosity decreases when the concentration of solid increases (Blandin et al., 2003). The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates. Amaro-González and Biscans (2002) propose and validate a method for selecting the best wetting agent based on the so-called Washburn's test, and Chow and Leung (1996) have found some general rules to use as a starting point for the design of the process.

Benzoic acid is used as a model compound in the present work. Benzoic acid (C_6H_5COOH) also called benzene carboxylic acid and phenyl carboxylic acid is used as bacteriostatic and bactericidal agent, preservative against yeast and mould. It acts as antiseptic stimulant and also an ingredient in Whitfield's ointment in treatment of ringworm. When crystallized from water or aqueous solutions benzoic acid crystals are shaped like thin plates (Åslund and Rasmuson, 1992) or are strongly elongated in one direction (thin rods or needles) (Holmbäck and Rasmuson, 1999). These crystal shapes have poor flowability, and are unsuitable for direct compression into tablets. However, a needle shape is no hindrance for obtaining spherical agglomerates (Di Martino et al., 1999).

In the present study, the benzoic acid crystals are agglomerated into spherical form during crystallization in a mixture of ethanol, water and chloroform. The aim of the study is to evaluate different procedures and to elucidate the effects of the amount of bridging liquid, the concentration of solids and the agitation rate on the physico-mechanical properties of the product particles like size, shape and mechanical strength.

2. Experimental work

2.1. Materials

Benzoic acid (C_6H_5COOH) 99% purity (Merck) was used as a model drug. Solvents were selected by following the general rules of Chow and Leung (1996). Ethanol (99.7% purity purchased from Solveco Chemicals AB) was found to be suitable as a good solvent and water (filtered and de-ionized) was used as the poor solvent**.** Benzoic acid is low soluble but not sparingly soluble in water. Chloroform (99–99.4% purity; Merck) was used as a bridging liquid because of its excellent wettability of the benzoic acid and immiscibility with water.

2.2. Apparatus

Introductory experiments were performed in test tubes using manual shaking. For spherical agglomeration experiments a

250 ml jacketed crystallizer (6 cm in diameter) was used, equipped with baffles and a three-blade marine propeller (2.5 cm in diameter). The agitator was centrally located 1 cm from the bottom. Solutions were fed by a syringe pump (Yale Apparatus, YA-12), and the temperature was controlled by a heating and refrigerating circulation unit (Julabo, FP50-HP). An oven was used for the purpose of drying the product.

2.3. Introductory experiments

Different experimental procedures were evaluated in introductory work.

2.3.1. Method 1

A certain quantity of benzoic acid is dissolved in ethanol in a test tube at 40 °C, and is allowed to cool down to room temperature (20 °C). Then water is added to produce the needle-like benzoic acid crystals. The mixture is allowed to stand for 1 h, after which agglomeration is initiated by introducing chloroform and the mixture is shaken for some time. The product particles are separated, washed with water and dried. This procedure exactly follows that originally outlined by Kawashima et al. (1984).

2.3.2. Method 2

A saturated ethanol solution is prepared at 40 °C. 20 ml of this solution is poured into an agitated mixture of chloroform and water at 10 °C. The solution is agitated for 1 h, after which the product is separated and dried. Compared to the main method below the solution is poured in at once, the temperature is lower and the agitation starts immediately. No spherical agglomerates were formed by this method.

2.3.3. Method 3

Benzoic acid dissolved in ethanol, and chloroform is added. The solution is poured into the water in the jacketed crystallizer and left to stand for some time. Then the agitation starts and goes on for 1 h. The product is filtered and dried. In this method, the bridging liquid is blended into the feed, and the solution is poured into the water at once and with no agitation. No spherical agglomerates were formed by this method.

2.3.4. Method 4

A certain quantity of benzoic acid is dissolved in ethanol in a test tube at 40 °C. After cooling the solution to room temperature, water is poured into the test tube which caused benzoic acid to crystallize. Immediately chloroform is added by means of a syringe and the mixture is shaken for some time, after which the product is separated and dried. Compared to experiment 1, the solutions are immediately mixed by shaking. No spherical agglomerates were formed by this method.

2.4. Procedure of main experiments

2.4.1. Procedure A

Benzoic acid is dissolved in ethanol at 40 °C and the solution is fed to the syringe pump. This solution (at 20 °C) is pumped at the rate of 2.4 ml/min onto the liquid surface of the poor solvent in the jacketed vessel which is at 20 °C. Then the solution is allowed to mature for 30 min. Agglomeration is initiated by turning on the agitation and quickly introducing the chloroform. The solution is stirred for a certain time at the required speed. At the end of the experiment, the agglomerates are filtered and dried in an oven. This procedure follows that originally outlined by Kawashima et al. (1984), except for that the poor solvent is gradually added to the solution. By following this procedure, smaller agglomerates were formed when baffles were used (1–3 mm) than without baffles.

The operating parameters studied were:

- The amount of bridging liquid: BSR = volume of bridging liquid/volume of solid (0.91, 0.93, 0.95 and 0.97).
- The initial concentration of benzoic acid in the ethanol (C_s) (0.275, 0.325, 0.375 and 0.425 g/ml).
- The stirring speed (N) (500, 600, 700 and 800 rpm).

The volume of solid is determined as the weight of solid originally dissolved divided by the density of benzoic acid (1316 kg/m^3, Kirk-Othmer, 1992). The experiments producing spherical agglomerates are presented in Table 2. Three additional experiments at BSR = 0.95 and C_s = 0.375 and lower or higher agitation rate were unsuccessful. At 200 rpm single crystals were obtained, at 400 rpm irregular agglomerates are formed and at 900 rpm a paste is produced.

2.4.2. Procedure B

A couple of experiments were performed according to the following procedure. Benzoic acid was dissolved in ethanol at 40 °C to a concentration of 0.375 g/ml. The solution was cooled down to room temperature, and a certain amount of chloroform (BSR = 0.93) was added. At the feed rate of 2.4 ml/min this solution was pumped onto the surface of the poor solvent under agitation at 600 rpm in the jacketed vessel. The agglomerates were separated and dried.

Compared to procedure A, in procedure B the bridging liquid is initially mixed into the ethanol solution and the agitation is turn on as the feeding starts.

2.5. Product characterization

The influence of the processing parameters on the particle size, size distribution, shape and compression strength was evaluated. The solid product was sieved with woven wire test sieves of DIN 4188 standard, into 0–280, 280–450, 450–630, 630–800, 800–1000, 1000–1250, 1250–1400, 1400–1600 μm fractions. The sieving was carried out in 10 min intervals until the weight of the different fractions remained constant. The particle size distribution is obtained from measuring the weight of the sieve fractions and are presented as cumulative over size mass distributions. The structure of the agglomerates from each sieve fraction was observed by optical microscopy (Olympus SZX12). Agglomerates were also crushed for microscopic examination. The mechanical strength of single agglomerates was determined by compression in a materials-testing machine

(Zwick Z2.5/TSIS), using a 10 N load cell. Measurements were made on 30 particles randomly selected from the sieve fraction 800–1000 μm of each experiment. Each single agglomerate was placed on a flat and horizontal surface. A force threshold of 10 mN is used to record the moment when the punch gets in contact with the agglomerate to define the starting point of the compression. An extensometer was used to identify the corresponding distance between the upper and lower surfaces of the equipment, a measure used to define the initial diameter (d) of each particle. Crushing tests were conducted at the speed of 0.5 mm/min. The measured force (F)–displacement (l) curve is recalculated into a stress (σ)–strain (ε) curve by Eqs. (1) and (2), using the diameter d initially measured for each particle:

$$\sigma = \frac{F}{(\pi d^2/4)} \tag{1}$$

$$\varepsilon = \frac{l}{d} \tag{2}$$

Initial size (H_1) and the minimum size (Hc) of the agglomerate at maximum compression was determined, as well as the size of the particle after releasing the load (He) to determine the elastic recovery (ER). The first compression was maintained for about 43 s and repeated cycles of compression took 3.5–5 s each time. The elastic recovery ratio for each compression was calculated by Eq. (3).

$$[(\mathrm{He} - \mathrm{Hc})/(H_1 - \mathrm{Hc})] \tag{3}$$

From each sample 30 particles were selected and compressed in the materials testing machine. The data were exported to Excel (Microsoft Office Excel 2003) and then to Origin (Origin 6.1) for processing. The stress–strain curve for a single particle contains roughly 3000 values and for each sample an average curve is determined based on the data over the 30 particles**.** For each strain value an average stress value is calculated from the 30 curves by using the Origin module: "Averaging multiple curves, version 6". When required the program interpolates or extrapolates data while calculating the average Y value. These data of the average curve were fitted to an exponential-non-linear equation:

$$\sigma = P_1^* \exp(P_2 + P_3^* \varepsilon + P_4^* \varepsilon^2) \tag{4}$$

by using Origin's non-linear least squares curve fitter which is very flexible for non-linear fitting. P_1, P_2, P_3, P_4 are parameters to be determined in the fitting procedure.

3. Results and discussion

3.1. Introductory experiments

The introductory experiments were performed to find suitable overall conditions for the preparation of spherical agglomerates of benzoic acid. In Table 1 are presented the outcome of the different methods. As shown, spherical agglomerates were only formed when method 1 was used. However, spherical crystals were not formed in all experiments using method 1. In experiment 9 we believe that the amount of bridging liquid is too low for the formation of spherical agglomerates, and in experiment 2 the amount is too high leading to the formation of a paste. In experiments 3 and 7 the solid concentration is probably too high. In experiments 10 and 11 methods 2 and 3 were used and no formation of agglomerates was found. In experiments 12 and 13, method 4 was used and no spherical agglomerates were formed. The only difference to method 1 is the absence of the maturing time before the addition of the bridging liquid.

3.2. Main experiments

In total 12 "main" experiments were performed in particular evaluating the influence of BSR, initial solute concentration and agitation rate. The resulting product weight mean sizes are given in Table 2. Ten experiments were done according to procedure A and two of the experiments were done according to procedure B. Samples have been examined by powder X-ray diffraction and only the normal crystallographic form (Bruno and Randaccio, 1980) has been found.

Table 1
Introductory experiments

Exp no.	Method used	Conc. of benzoic acid in feed (g/ml)	Amount of good solvent (ml), ethanol	Amount of poor solvent (ml), water	Amount of bridging liquid (ml), chloroform	Standing time (min)	Result
1	1	0.25	2	10	0.3	60	Spheres
2	1	0.3	2	10	0.6	30	Paste
3	1	0.5	2	10	0.1,0.2,0.3,0.4	10	Crystals
4	1	0.25	2	10	0.3	60	Spheres
5	1	0.25	2	10	0.4	20	Spheres
6	1	0.25	2	10	0.4	20	Spheres
7	1	0.5	2	10	0.4	35	Crystals
8	1	0.375	2	10	0.5	45	Spheres
9	1	0.25	2	10	0.1	30	Crystals
10	2	0.33	16	50	3	0	Crystals
11	3	0.32	25	125	3	30	Crystals
12	4	0.25	2	10	0.3	0	Crystals
13	4	0.33	3	15	1	0	Crystals

Table 2
Mean size of the particles at different operating conditions

Experiment	BSR	C_s (g/ml)	N (rpm)	Mean size (μm)
1	0.91	0.375	600	430
2	0.93	0.375	600	930
3	0.95	0.375	600	930
4	0.97	0.375	600	680
5	0.95	0.275	600	480
6	0.95	0.325	600	1050
7	0.95	0.375	600	850
8	0.95	0.425	600	1100
9	0.95	0.375	500	470
10	0.95	0.375	600	900
11	0.95	0.375	700	900
12	0.95	0.375	800	850

3.2.1. Size distribution

The influence of BSR on the product size distribution is shown in Fig. 1, the influence of the initial solute concentration in Fig. 2 and the influence of agitation rate in Fig. 3. As shown, the product particle size distribution is quite wide.

One of the main parameters in spherical agglomeration is volume of bridging liquid. For our benzoic acid system there was however no significant change in the weight mean size with increased volume of bridging liquid. A possible explanation is that the range of amount of bridging liquid is somewhat narrow. Generally, the size of agglomerates increases with increasing amount of bridging liquid (Kawashima et al., 1981).

The agglomerate size increases with increasing initial solute concentration as shown in Fig. 2. With lower initial solute concentration more fines were obtained. This is in agreement with Blandin et al. (2003) who found that the final size of the agglomerates at first increases with increasing initial solute concentration and then reaches a plateau.

Increasing stirring rate increases the size of the agglomerates up to about 600 rpm as shown in Fig. 3. A lower stirring rate reduces the rate of particle collision and a higher stirring rate increases agglomerate disruption.

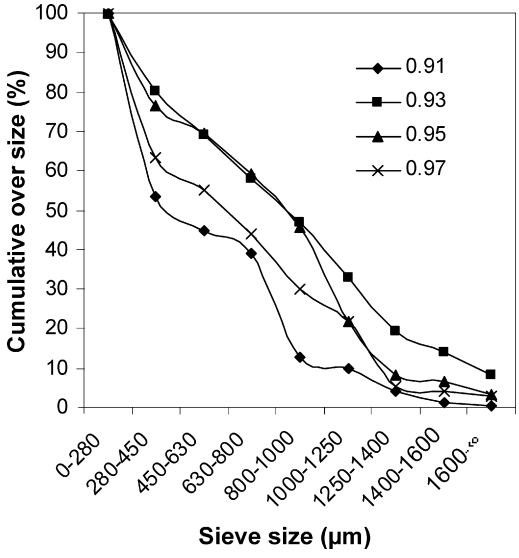

Fig. 1. Change in particle size distribution with BSR (benzoic acid conc. = 0.375 g/ml; stirring speed, 600 rpm).

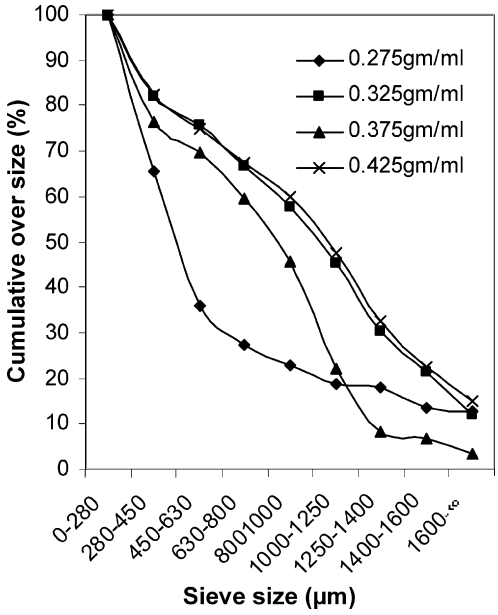

Fig. 2. Change in particle size distribution with dissolved amount of benzoic acid (N = 600 rpm; BSR = 0.95).

The process type B seems to be more favourable for production of spherical agglomerates than the process type A. At comparable conditions, Fig. 4, 85% of the product is well agglomerated by process type B while only 60% approximately by process type A.

3.2.2. Particle morphology

Observations by optical microscopy show that the agglomerates are formed by elementary particles tightly piled up as shown

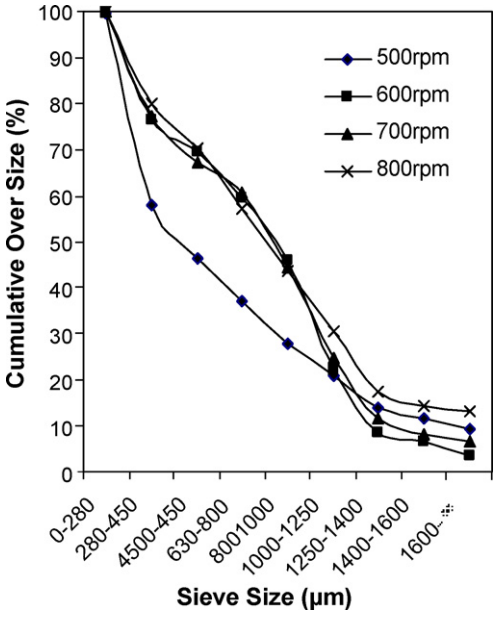

Fig. 3. Change in particle size distribution with stirring rate (benzoic acid conc. = 0.375 g/ml; BSR = 0.95).

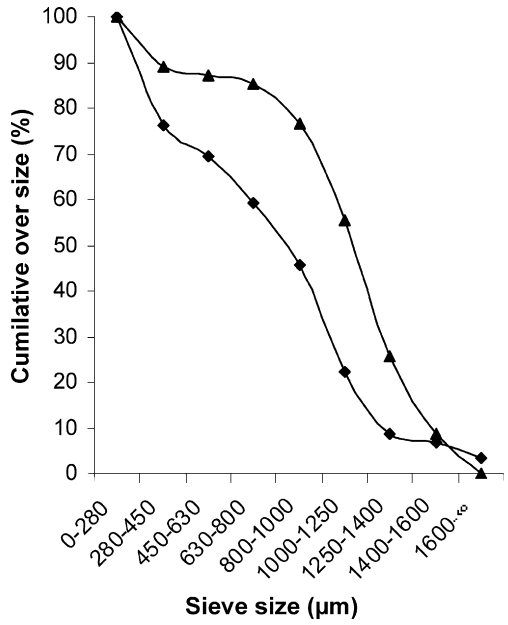

Fig. 4. Product particle size distributions ■ process A, ▲ process B (benzoic acid conc. = 0.375 g/ml; BSR = 0.95; stirring rate = 600 rpm).

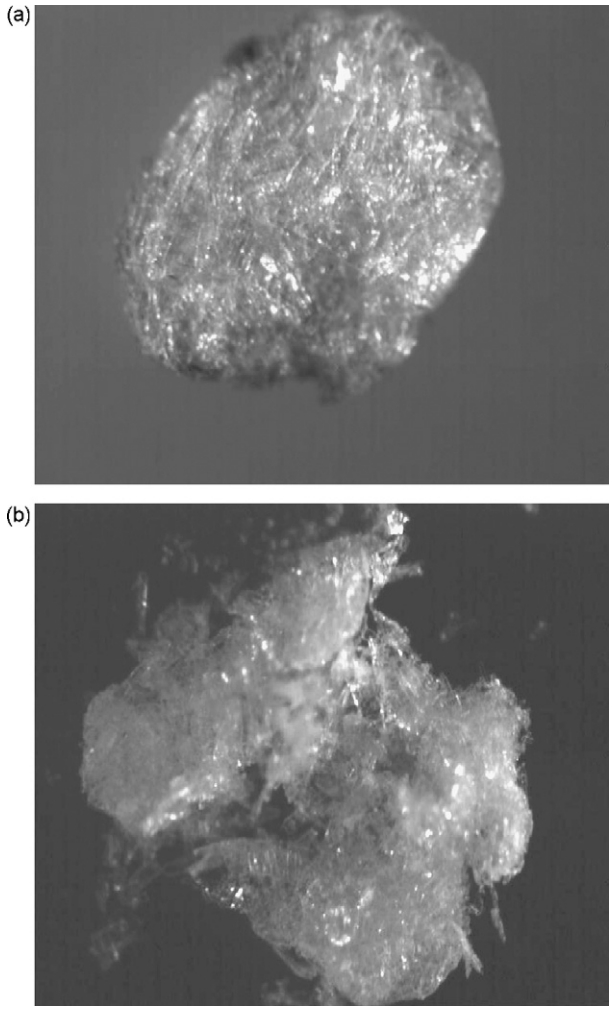

Fig. 5. (a) Particle morphology of spherical agglomerate of size 800–1000 μm (50×). Benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95. (b) Particle morphology of crushed spherical agglomerate of size 800–1000 μm (63×). Benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95.

in Fig. 5a. Observations of some crushed agglomerates (Fig. 5b) show that they are made up of smaller crystals grown together.

As can be seen in Fig. 6, the characteristics of the particles vary with sieve fraction. The two smallest sieve fractions (0–450 μm in size, Fig. 6a and b) are dominated by irregularly shaped agglomerates, consisting of thin and needle like crystals. Particles in sieve fraction 450–630 μm (Fig. 6c) are still irregular in shape, but these agglomerates appear to be denser. Above a particle size of 630 μm the dense agglomerates starts to look spherical. This is illustrated in Fig. 6e showing particles from sieve fraction 800–1000 μm. In reality some of the spherical agglomerates are somewhat tabular and not completely spherical. In comparison, the sphericity of the larger particles from process type B is quite good (Fig. 7e). All examined samples from the main experiments exhibit a similar change from thin and irregularly shaped agglomerates to more dense and spherical agglomerates with increasing particle size. Only particles >630 μm are spherical agglomerates. The smaller particles are either thin, irregularly shaped agglomerates or fragments from larger agglomerates.

3.2.3. Particle mechanical strength

A number of stress–strain curves for different particles from the same experiment and sieve fraction are shown in Fig. 8. The stress–strain curves are 'J' shaped (Mai and Atkins, 1989), and there is a spread among the particles from the same sample. However, this is to be expected partly because the surface area is taken as the cross sectional area of a spherical particle having the same diameter as the initial height of the particle when the compression starts. However, in addition, in our previous work on agglomeration (Ålander et al., 2003), we have experienced a significant distribution in the different properties of the agglomerated particles from an experiment.

Table 3
Elastic recovery: benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95

H_1 = initial size (μm)	Hc = final size (μm)	He = recovered size (μm)	Elastic recovery (%)
543	203.5	214	3
214	184	206	73
206	179	201	81
201	171	192	70
192	168	190	91
190	166.5	188	91
188	166		

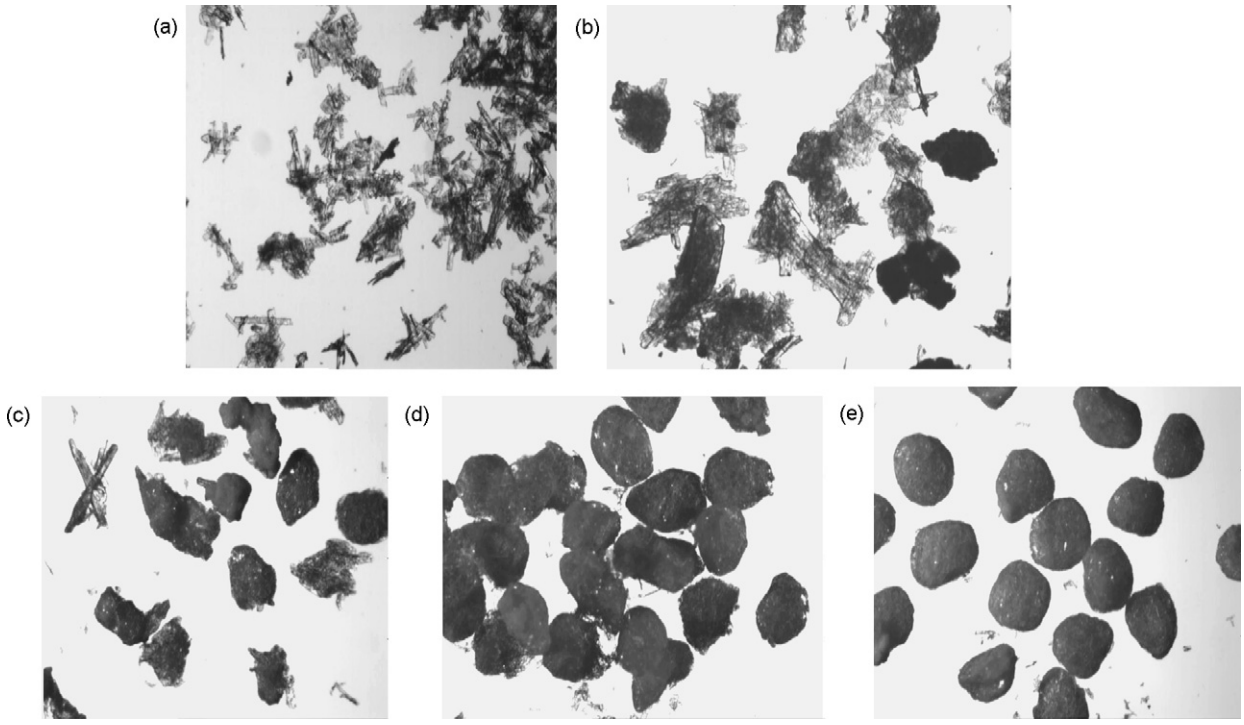

Fig. 6. Particle morphology of different sieve fractions from process A: (a) 0–280 μm (32×), (b) 280–450 μm (32×), (c) 450–630 μm (20×), (d) 630–800 μm (25×) and (e) 800–1000 μm (12.5×). Benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95.

The spherical agglomerates of benzoic acid are easily deformed to a strain of at least 50% without any particle fracture. Single agglomerates have been compressed at 500 mN for several times to check the plasticity. When the compression was made the second time the initial size was not same as the original size, and hence there is a plastic deformation in the first compression. This can be clearly observed in Fig. 9. 100% elastic recovery represents the perfect elastic material. In the first compression the elastic recovery is only 3%. In the following compression steps, there is a very moderate further size reduction and the elastic recovery is high as is shown in Table 3. This illustrates that the agglomerates of benzoic acid mainly compress plastically. Please note that there is essentially no fracturing of the particles into smaller pieces. A plastic deforma-

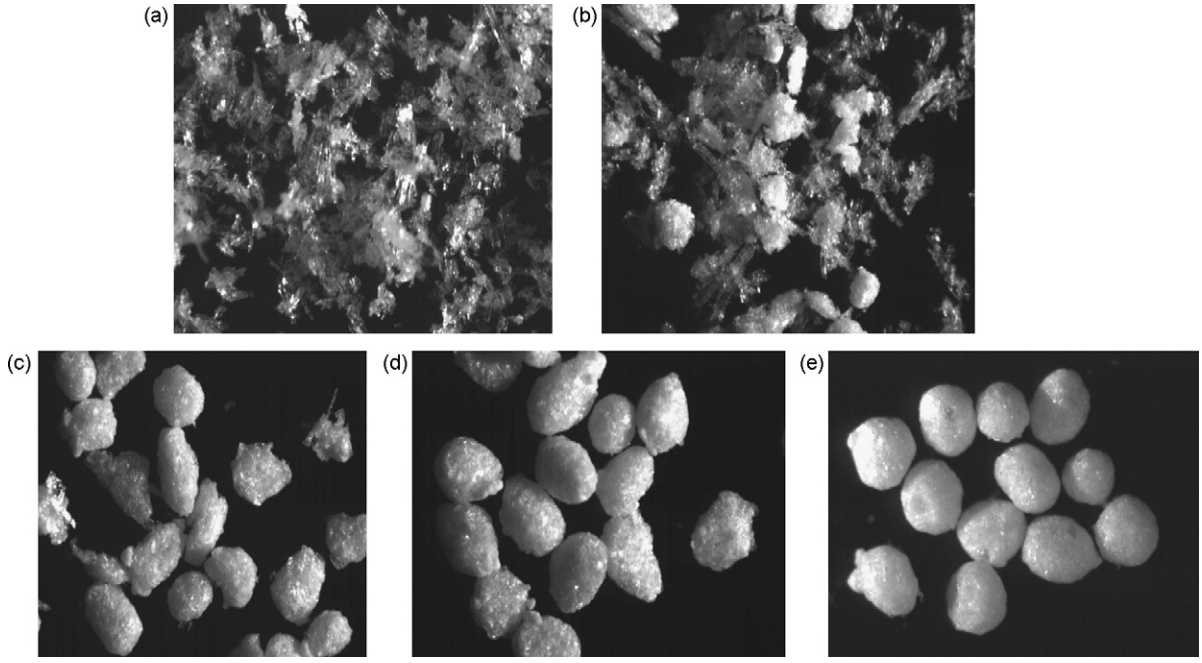

Fig. 7. Particle morphology of different sieve fractions from process B: (a) 0–280 μm (32×), (b) 0280–450 μm (25×), (c) 450–630 μm (25×), (d) 630–800 μm (25×) and (e) 800–1000 μm (20×). Benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95.

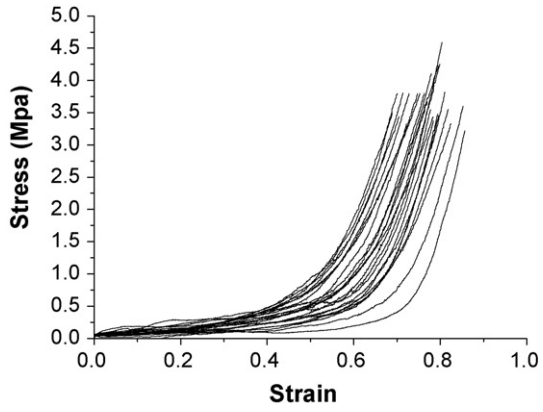

Fig. 8. Compression behaviour of spherical agglomerates from process A: sieve fraction 800–1000 μm. Benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95.

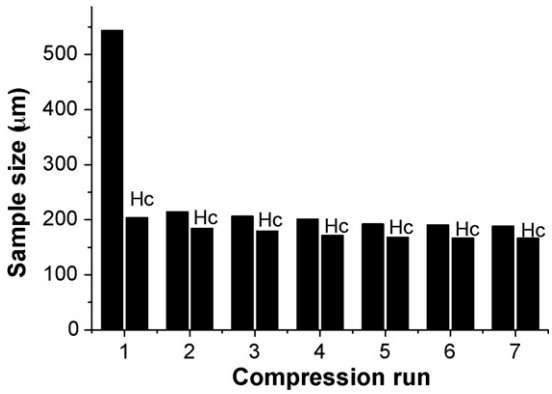

Fig. 9. Repeated compression of single agglomerate: benzoic acid conc. = 0.375 g/ml; N = 600 rpm; BSR = 0.95.

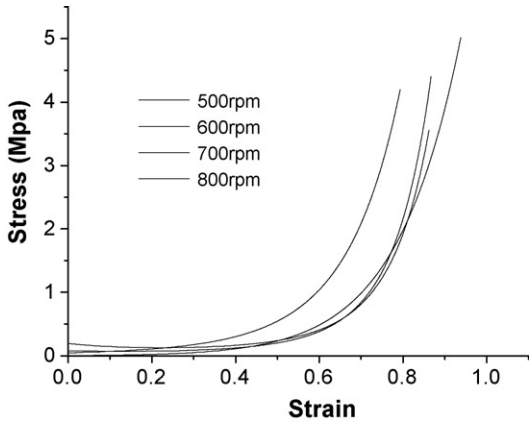

Fig. 10. Average stress–strain curves of product particles from process A experiments at different stirring rates (benzoic acid conc. = 0.375 g/ml; BSR = 0.95).

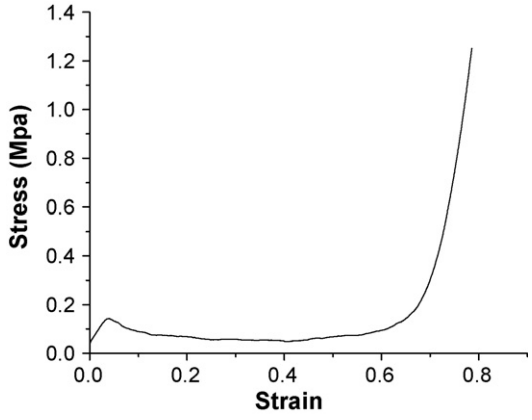

Fig. 11. Average stress–strain curve of product particles from process B (benzoic acid conc. = 0.375 g/ml; BSR = 0.95; stirring rate = 600 rpm).

tion is expected to be more favourable for tabletting than elastic deformation. If the material exhibits extensive plastic deformability the number of weak distance forces would probably be much higher and thereby contribute significantly to the compact strength. Hence, the particles shows promising mechanical strength improvements over the thin and needle-like crystals formed in conventional crystallization of benzoic acid.

The initial part of the stress–strain curve describe a significant compression without much force. Hence, the shear modulus in this region is very low. This first part of the curve represents rearrangements, possibly small crystalline breakages, leading to a reduced agglomerate porosity. The shape of the non-linear part is usually associated with stress induced plastic flow in the specimen. Plastic deformation represents an effective means of creating a large bonding surface area. However, for most of the pharmaceutical materials labeled as plastically deforming, it seems that the plasticity is not as pronounced as needed to form large surface areas for bonding. Materials with a pronounced plastic deformation, such as amorphous tablet binders, may be effective in this respect and are used (Sandell, 1993).

Parameters for average curves at different agitation rates are given in Table 4. χ^2 has very low value and R^2 is close to 1, which shows that Eq. (3) is a very good model to represent the data of stress versus strain for benzoic acid agglomerates. Since this is a non-linear fit and the data for 30 curves exhibit a significant variation, we are not able to estimate the confidence interval of the parameter values.

The average stress–strain curve for each stirring rate is compared in Fig. 10. There is no clear influence of the agitation rate on the average stress–strain curve. In Fig. 11 is shown the average stress–strain curve of the particles from

Table 4
Parameters of non-linear equation for different stirring speeds (benzoic acid conc. = 0.375 g/ml; BSR = 0.95)

Stirring speed (rpm)	P_1	P_2	P_3	P_4	R^2	(χ^2)
500	0.02319	−1.57261	8.19706	−0.84194	0.995	0.00042
600	0.06799	−0.34116	3.53567	2.63484	0.998	0.00186
700	0.08862	−0.08739	−1.93621	7.54353	0.997	0.00043
800	0.13354	0.37768	−3.65623	8.14615	0.994	0.00307

an experiment by process B. Notably, in this case the curve exhibits a small peak early during the compression that is not found among the particles produced by process A. The particles produced by process B exhibit some fracturing behavior.

4. Conclusions

Spherical agglomerates of benzoic acid have been successfully prepared by drowning out crystallization in ethanol–water, using chloroform as the bridging liquid. Spherical agglomerates were produced by the Kawashima method, however the solution had to be slowly added. There is a wide spread in the properties of the particles from each experiment. Spherical agglomerates tend to appear mainly in the larger size fractions, and within each sieve size fraction the properties of the agglomerates vary significantly. The stress–strain deformation curve of single agglomerates is J-shaped, and the deformation is mainly plastic in the range studied.

The results show that the amount of bridging liquid is critical for the formation of agglomerates, but when the amount is in the appropriate range the properties of the agglomerates are not very sensitive to the amount used. The agglomerate size increases with increasing initial solute concentration and increasing agitation rate up to a certain level, but there is no significant influence found on the mechanical properties.

A higher fraction of spherical agglomerates is obtained when the bridging liquid is initially mixed into the feed solution, instead of being added to the agitated solution afterwards.

References

Amaro-González, D., Biscans, B., 2002. Spherical agglomeration during crystallization of an active pharmaceutical ingredient. Powder Technol. 128, 188–194.

Ålander, E.M., Uusi-Pentillä, M.S., Rasmuson, Å.C., 2003. Characterization of paracetamol agglomerates by image analysis and strength measurement. Powder Technol. 130, 298–306.

Åslund, B.Å., Rasmuson, Å.C., 1992. Semibatch reaction crystallization of benzoic acid. AIChE J. 38, 328–342.

Bausch, A., Leuenberger, H., 1994. Wet spherical agglomeration of proteins as a new method to prepare parenteral fast soluble dosage forms. Int. J. Pharm. 101, 63–70.

Blandin, A.F., Mangin, D., Rivoire, A., Klein, J.P., Bossoutrot, J.M., 2003. Agglomeration in suspension of salicylic acid fine particles: influence of some process parameters on kinetics and agglomerate final size. Powder Technol. 130, 316–323.

Bos, A.S., Zuiderweg, F.J., 1987. Size of agglomerates in batch wise suspension agglomeration. Chem. Eng. Res. Des. 65a, 187.

Bruno, G., Randaccio, L., 1980. A refinement of the benzoic acid structure at room temperature. Acta Cryst. B36, 1711–1712.

Chow, A.H.L., Leung, M.W.M., 1996. A study of the mechanisms of wet spherical agglomeration of pharmaceutical powders. Drug Dev. Ind. Pharm. 22, 357–371.

Di Martino, P., Barthelemy, C., Piva, F., Joiris, E., Palmieri, G.F., Martelli, S., 1999. Improved dissolution behavior of fenbufen by spherical crystallization. Drug Dev. Ind. Pharm. 25, 1073–1081.

Farnand, J.R., Smith, H.M., Puddington, I.E., 1961. Spherical agglomeration of solids in liquid suspension. Can. J. Chem. Eng. 39, 94–97.

Holmbäck, X., Rasmuson, Å.C., 1999. Size and morphology of benzoic acid crystals produced by drowning-out crystallization. J. Cryst. Growth 198/99, 780–788.

Kawashima, Y., Furukawa, K., Takenaka, H., 1981. The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. Powder Technol. 30, 211–216.

Kawashima, Y., Aoki, S., Takenaka, H., 1982a. Spherical agglomeration of aminophylline crystals during reaction in liquid by the spherical crystallization technique. Chem. Pharm. Bull. 30, 1837.

Kawashima, Y., Okumura, M., Takenaka, H., 1982b. Spherical crystallization: direct spherical agglomeration of salicylic acid crystals during crystallization. Science 216, 1127.

Kawashima, Y., Okumura, M., Takenaka, H., 1984. The effects of temperature on the spherical crystallization of salicylic acid. Powder Technol. 39, 41–47.

Kawashima, Y., 1994. Part 1 New processes—application of spherical crystallization to particulate design of pharmaceuticals for direct tabletting and coating, and new drug delivery systems. In: Powder Technology and Pharmaceutical Processes. Handbook of Powder Technology, vol. 9, pp. 493–512.

Kawashima, Y., Cui, F., Takeuchi, H., Niwa, T., Hino, T., Kiuchi, K., 1995. Parameters determining the agglomeration behavior and the micrometric properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. Int. Natl. J. Pharm. 119, 139–147.

Kawashima, Y., Imai, M., Takeuchi, H., Yamamoto, H., Kamiya, K., Hino, T., 2003. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder Technol. 130, 283–289.

Kirk-Othmer, 1992. In: Kroschwitz, J.I., Howe-Grant, M. (Eds.), Encyclopedia of Chemical Technology, vol. 4, fourth ed. John Wiley & Sons, New York.

Lasagabaster, A., Martin, C., Goni, M.M., 1994. Preparation of spherically agglomerated crystals of the 3,5-diglucoside of cyaniding (cyanin). J. Chem. Tech. Biotechnol. 60, 397–403.

Nocent, M., Bertocchi, L., Espitalier, F., Baron, M., Couarraze, G., 2001. Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion solvent diffusion (QESD) method. J. Pharm. Sci. 90.

Sandell, E., 1993. Industrial Aspects of Pharmaceutics. Swedish pharmaceutical press, Stockholm, Sweden, p. 91 & 142.

Sano, A., Kuriki, T., Kawashima, Y., Takeuchi, H., Hino, T., Niwa, T., 1992. Particle design of tolbutamide by spherical crystallization technique. V. Improvement of dissolution and bioavailability of direct compressed tablets prepared using tolbutamide agglomerated crystals. Chem. Pharm. Bull. 40, 3030–3035.

Mai, Y.W., Atkins, A.G., 1989. Further comments on J shaped stress-strain curves and the crack resistance of biological materials. J. Phys. D: Appl. Phys. 22, 48–54.