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A Study of the Mechanisms of Wet Spherical Agglomeration of Pharmaceutical Powders

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ABSTRACT

Spherical agglomeration of a number of chemical and pharmaceutical powders was effected in a stirred liquid mixture using the novel technique developed by Kawashima and Capes, with modifications. The compounds were first classified into four groups on the basis of their solubilities in the liquid systems employed and, accordingly, agglomerated using appropriately developed methods. Each powdered material was first suspended in a liquid medium (external phase) and agglomeration was achieved by addition of a relatively small amount of "bridging" liquid (internal phase) which was immiscible with the (external) dispersion medium. The resulting spherical agglomerates were examined for size, binding strength, and surface topography. It appeared that a considerable number of the suspended particles initially underwent partial dissolution in the bridging liquid. The dissolved portion then collected the undissolved powder into spherical agglomerates under the influence of continuous stirring. Based on the trials and observations on a number of materials ranging from inorganics to organics, the general guidelines for spherical agglomeration of pharmaceutical powders were established. It is hoped that these guidelines will aid the application of this technique in the pharmaceutical and allied industries.

INTRODUCTION

Many chemical and pharmaceutical products are made by processes that require agglomeration to achieve the desired end product properties or to aid intermediate processing, for example, to ease separation of particulates from a suspending fluid by filtration. 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 products.

Pharmaceutical powders can be agglomerated by a number of techniques, such as dry and wet granulation, fluidized-bed granulation, extrusion and spheronization, spray drying, and spherical agglomeration. Powders are usually granulated or agglomerated spherically since the spherical shape possesses several advantages: (a) spherical agglomerates have free flowability and uniform packability required for pharmaceutical processing; (b) they are suitable for microencapsulation as they can be uniformly coated with a relatively small amount of polymer; (c) they have a more predictable dissolution pattern; and (d) they can be easily compounded with other pharmaceutical powders due to their spherical form.

Traditionally, spherical agglomerates are obtained by either dry or wet granulation (1). They can also be obtained by separating dispersed fine particles from liquid suspension with the aid of flocculants. Two major techniques have been developed, namely, pelleting flocculation and wet spherical agglomeration. The latter technique has gained increasing attention in recent years due to its relative simplicity and ease of operation. With this technique, finely precipitated crystals can be suitably modified for better processing performance during crystallization from solution. Thus drugs with limited solubility can be made available in fine crystalline form and at the same time be assembled into spheroidal aggregates to afford good flow and packing properties. The technique was first developed by Kawashima and Capes using coal (2–4). Coal powder was dispersed in water stirred at a constant speed. Agglomeration was achieved by addition of a small amount of oil as bridging liquid. Kawashima et al. later produced wax matrices of sulfamethazole with prolonged-release property using a similar technique (5). Kawashima and coworkers also studied the parameters affecting agglomeration behavior and showed that agglomeration obeyed first-order kinetics (6,7). The agglomeration technique was further modified, and salicylic acid, aminophylline, and sodium theophylline monohydrate could all be agglomerated using spherical crystallization (8–13). Recently, chlorpromazine agglomerated by this technique has also been tested successfully for use in direct tableting and microencapsulation with a continuous system (14).

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 use of particular bridging liquids and/or reagents 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.

In the present study, a number of compounds have been categorized into four groups according to their solubility patterns in various liquid systems and subjected to spherical agglomeration using suitably developed techniques. The development of these techniques in premised on the hypothesis that particle agglomeration in a liquid medium occurs chiefly as a result of partial dissolution of the particles and recrystallization at the contact points between particles to form solid bridges. The objectives of the present study are twofold: (a) to elucidate the mechanisms of spherical agglomeration; and (b) to establish general guidelines for the spherical agglomeration of pharmaceutical powders. The ultimate goal of this study is to enable broad application of this technique in the pharmaceutical and allied industries.

MATERIALS

Unless otherwise specified, all chemicals and solvents used were of analytical grade. Zinc sulfate, copper sulfate, potassium chloride, ammonium chloride, sodium carbonate, calcium chloride (for use as a bridging agent in aqueous solution), chloroform, and cyclohexane were supplied by BDH Chemicals. Citric acid, resorcinol, phenytoin, polyethylene glycol (PEG) 10,000, and polyvinylpyrrolidone (PVP) 40,000 were supplied by Sigma Chemicals. Polyvinyl alcohol (PVA; 4–6 mPa·s) and dichloromethane were obtained from Riedel–de Haën Chemicals. Carbon disulfide and hexane were supplied by Merck Chemicals and Mallinckrodt Chemicals, respectively. Diphenhydramine hydrochloride, camphor

(synthetic), stearic acid (triple pressed), propyl *p*-hydroxybenzoate, phenobarbital, paracetamol, and methyl salicylate were of pharmacopoeial grade (B.P.) from Wing Hing Chemicals. Kaolin (light) and cephalexin monohydrate were also of pharmacopoeial grade (B.P.) and supplied by BASF Chemicals and Quality Pharmaceuticals, respectively. All water used was double distilled.

The materials for agglomeration were first pulverized and sieved to obtain a particle size of 160 to 850 μm before use.

METHODS

Preparation of Spherical Agglomerates

Prior to spherical agglomeration, the compounds were classified into four different groups according to their solubilities in the relevant bridging liquids (Tables 1–4). Group I includes those compounds which are most soluble in water (>1 in 20). Group II encompasses those which are soluble in organic solvents (>1 in 20) such as chloroform but not in water. All the organic solvents used are immiscible with water. Group III contains those compounds which are most soluble in ethanol, methanol, or acetone (>1 in 20). This group differs from group II in that all the solvents involved are highly miscible with water. Lastly, those compounds which are not sufficiently soluble in water or any other solvents were assigned to group IV. Most of the selected compounds are organics. Where appropriate, inorganics were also employed to ascertain the generality of the approach.

All four groups of compounds were agglomerated at room temperature (20° ± 1°C) and at a stirring speed of 400 rpm, all using the equipment shown in Fig. 1 but slightly different techniques. The agglomeration apparatus consisted of a round-bottomed reaction vessel (1 l) with a three-necked glass lid, a variable speed motor with digital display (Model LR20 from Framo-Geräte-

Table 1

Agglomeration Conditions for Group I Compounds

Compound (12 g)	Bridging Solvent	Amount (ml)	External Phase (400 ml)
Copper sulfate	20% calcium chloride	5	Cyclohexane
Zinc sulfate	20% calcium chloride	2	Cyclohexane
Potassium chloride	20% calcium chloride	3	Cyclohexane
Ammonium chloride	20% calcium chloride	3	Cyclohexane
Sodium carbonate	20% calcium chloride	2	Cyclohexane
Ascorbic acid	20% calcium chloride	3	Cyclohexane
Citric acid	20% calcium chloride	1	Cyclohexane
Diphenhydramine HCl	20% calcium chloride	1	Cyclohexane
Resorcinol	20% calcium chloride	2	Cyclohexane

Table 2

Agglomeration Conditions for Group II Compounds

Compound (12 g)	Bridging Solvent	Amount (ml)	External Phase (400 ml)
Camphor	Chloroform	3	Water
Menthol	Chloroform	1	Water
Aspirin	Chloroform	2	Water
Propyl *p*-hydroxybenzoate	Chloroform	5	Water
Stearic acid	Chloroform	5	Water
Sulfur	Carbon disulfide	3	Water
Vanillin	Methyl salicylate	4	Water
Phenobarbital	Chloroform	5	Water

Table 3

Agglomeration Conditions for Group III Compounds

Compound (12 g)	Bridging Solvent (16 ml/14 ml)	External Phase (400 ml)
Paracetamol	Ethanol + chloroform	Water
Phenytoin	Ethanol + chloroform	Water

technik, Germany), and a propeller agitator with four blades. Each experiment was repeated at least twice to ensure reproducibility, and the mean values of properties determined are presented. The percentage deviations of measurements are normally no more than 20% from the means; in cases where the deviations exceed 20% (e.g., particle size), the range of values instead of the mean is presented.

The group I and group II compounds were agglomerated using essentially the same procedure. The powder was first dispersed in the external phase (dispersion medium) with the aid of stirring (400 rpm), followed by addition of the bridging liquid. Agglomeration was allowed to proceed for 20 min, after which the agglomerates were collected by filtration under vacuum and air dried for at least 3 days before characterization.

The powder to bridging liquid ratio used was about 4:1, which was estimated from Dolan's equation [Eq. (1)] (15,16). This equation has been formulated to calculate the liquid requirements for agglomeration, assuming that the liquid binder replaces the air occupying the space between agglomerated particles.

$$X = \frac{1}{1 + (1 - V_f)d_s/V_f d_l} \quad (1)$$

where X = weight fraction of liquid in the finished agglomerate; V_f = porosity before agglomeration (void fraction); d_s = true particle density; d_l = density of the liquid.

For the group III compounds, a slightly different approach was adopted. The powder was first dispersed in the bridging liquid before adding to the external phase.

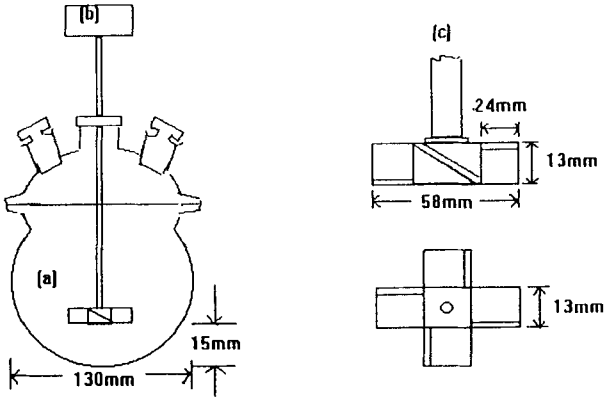


Figure 1. Apparatus for spherical agglomeration: (a) round-bottomed reaction vessel (1 liter); (b) motor; (c) propeller agitator with four blades.

The method employed for agglomerating the group IV compounds is similar to that for groups I and II except that the powder was first blended uniformly with a suitable binder (PVP, PEG, or PVA) by gentle trituration in a mortar prior to dispersion in the external phase.

Tables 1–4 show the amounts of bridging solvents and external phases employed for the different compounds.

Characterization of Micromeritic Properties of Spherical Agglomerates

The morphology and surface topography of both the agglomerated and unmodified samples were examined by scanning electron microscopy (Stereoscan 360; Leica Cambridge) after coating with gold. The size of agglomerates larger than 2 mm was measured for the whole sample using an electronic caliper while size measurement of small agglomerates (< 1 mm) was conducted by

Table 4

Agglomeration Conditions for Group IV Compounds

Compound (8 g)	Bridging Solvent (3 ml)	External Phase (400 ml)	Binder (4 g)
Cephalexin	20% calcium chloride	Dichloromethane	PVP
Cephalexin	20% calcium chloride	Dichloromethane	PEG
Light kaolin	20% calcium chloride	Cyclohexane	PVA
Light kaolin	20% calcium chloride	Cyclohexane	PEG

optical microscopy on a random sample of 30 from each batch. The average particle size for each sample was then calculated. The binding strength of the spherical agglomerates was determined by sieving in a 850-μm sieve on a commercial sieve shaker (Model 3D, Retsch GmbH & Co., Haan, Germany) at a defined frequency (~2500 oscillations/min) for 15 min and the percentage of unfractured agglomerates that was retained in the sieve was reported.

Effect of Bridging Solvent on Spherical Agglomeration

The effect of bridging solvent on the agglomeration behavior of a hydrophilic material, citric acid (group I), and a hydrophobic drug, aspirin (group II), was investigated using the procedure developed for both group I and group II compounds and the following solvent systems:

a. For citric acid: (i) 1 ml 20% calcium chloride; (ii) 1 ml 30% sodium chloride; and (iii) 1 ml water
b. For aspirin: (i) 2 ml chloroform; and (ii) 3 ml dichloromethane

Effect of External Phase on Spherical Agglomeration

Studies on the effect of external phase on the agglomeration of one hydrophilic inorganic and one hydrophilic organic from group I, namely, potassium chloride and ascorbic acid, employed the same agglomeration procedure for both groups I and II compounds and the following solvent systems:

a. For potassium chloride: (i) 400 ml dichloromethane; (ii) 400 ml hexane; and (iii) 400 ml cyclohexane
b. For ascorbic acid: (i) 400 ml cyclohexane; (ii) 400 ml dichloromethane; and (iii) 400 ml chloroform

RESULTS AND DISCUSSION

Development and Assessment of Agglomeration Techniques

Agglomeration of the compounds in groups I–IV was shown to be readily accomplished using the method developed for each respective group. In most cases, hard spherical agglomerates of narrow size range were obtained (Fig. 2). The percentage yield, average diameter, and relative binding strength of agglomerates are recorded in Tables 5–8.

The agglomerates in group I were found to be relatively resistant to fracturing due to attrition except those of ammonium chloride and potassium chloride, as determined by the relative percentage of unfractured agglomerates retained in a 850-μm sieve upon sifting on a mechanical shaker (Table 5). The difference in binding strength of the agglomerates may be explained in terms of the relative ease of formation of liquid bridges between particles and the subsequent dissolution and recrystallization at the solid–liquid interface to form solid bridges. Thus the relatively high friability of ammonium chloride and potassium chloride may be ascribed to the relatively few solid bridges being formed between the particles. The formation of fewer solid bridges may be due to poor wetting between the crystal surface and the bridging liquid, thus giving rise to "brittle" agglomerates. The yield for group I agglomerates ranged from 12% to 84%, the lowest being those of ammonium chloride (16%) and sodium carbonate (12%). With the latter two materials, it was observed that part of the materials dissolved and turned the undissolved powder into a paste form during stirring. The paste tended to attach to the wall of the vessel upon collision and, being denser than cyclohexane, settled at the bottom of the flask and adhered to the fluid-stagnant region, thereby avoiding the propeller impaction. This problem could be circumvented by deactivating the wall of the vessel with dichlorodimethylsilane or by using a denser organic liquid as the external phase.

Group II agglomerates appeared to be less friable. However, the diameters of the agglomerates within the same batch in some cases showed a large variation (Table 6). This was particularly so for the aspirin agglomerates, whose sizes varied between 1.3 and 10.7 mm. This relatively large intrabatch size variation may be due to the uneven distribution of shearing forces produced at the stirring speed of 400 rpm in the 400 ml water. This point was substantiated by the observation that the agglomerate size of aspirin became smaller and narrower in range on increasing the stirring speed to 1000 rpm. The yield of phenobarbital was distinctively low, possibly because of its lower solubility (1 in 40) in chloroform than in other solvents. Menthol also afforded a low yield of 38%, as expected from its relatively high vapor pressure and the resulting material loss through vaporization.

The agglomeration method developed for the group II compounds was found not applicable to the group III materials since the organic solvents in which the latter group of compounds are significantly soluble (e.g., etha-

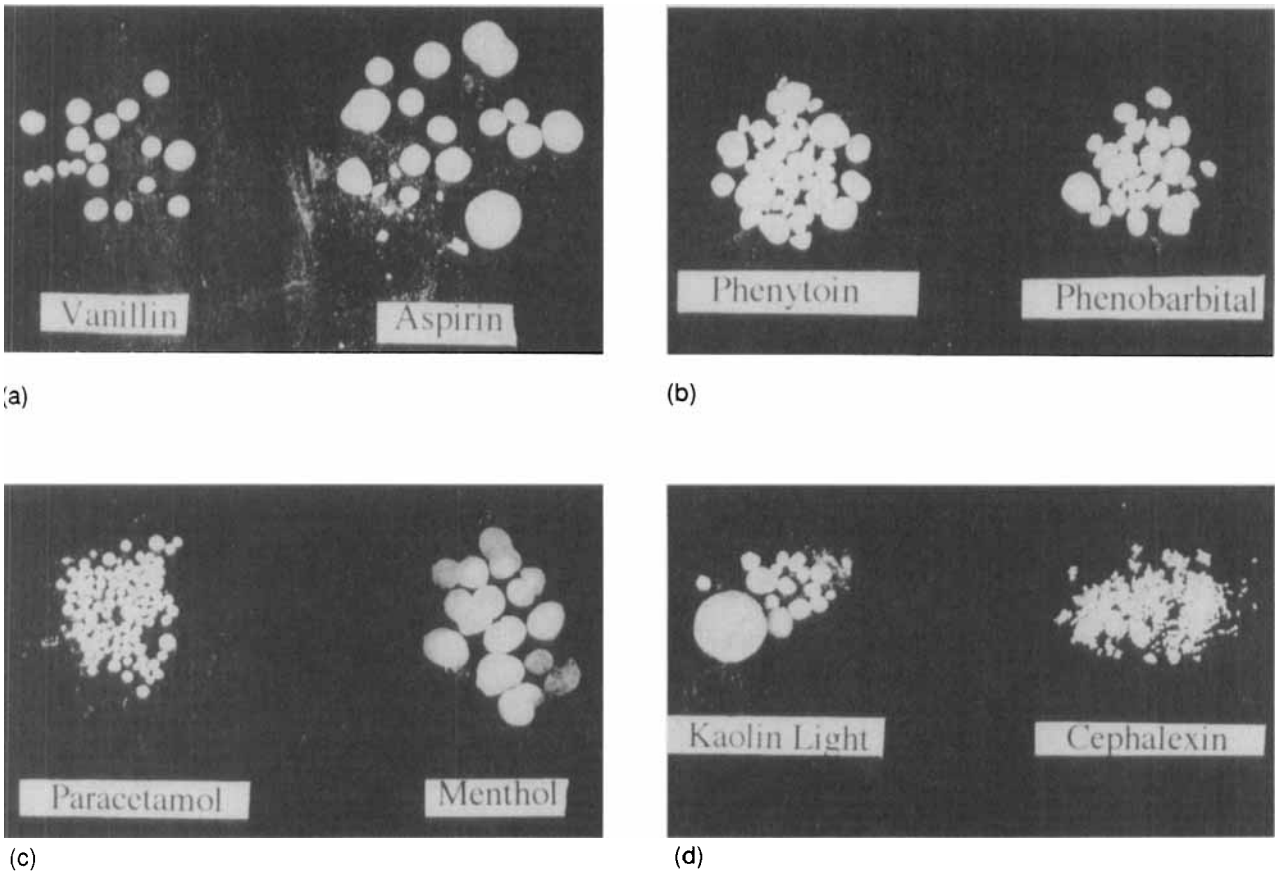


Figure 2. Photographs of representative spherical agglomerate samples. (a) Spherical agglomerates of vanillin (group II) and aspirin (group II). (b) Spherical agglomerates of phenytoin (group III) and phenobarbital (group II). (c) Spherical agglomerates of paracetamol (group III) and menthol (group II). (d) Spherical agglomerates of light kaolin (group IV) and cephalexin monohydrate (Group IV).

Table 5

Percentage Yield, Average Diameter, and Relative Binding Strength of Group I Agglomerates

Compound	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)[a]
Copper sulfate	47	0.5–3	96
Zinc sulfate	84	6.4	83
Potassium chloride	54	8.2	53
Ammonium chloride	16	5.6	11
Sodium carbonate	12	4.9	92
Ascorbic acid	82	2.6	98
Citric acid	46	9.8	97
Diphenhydramine HCl	49	6.1	99
Resorcinol	69	5.9	92

[a]Relative binding strength is defined as the percentage of unfractured agglomerates that is retained in a 850-μm sieve.

Table 6

Percentage Yield, Average Diameter, and Relative Binding Strength of Group II Agglomerates

Compound	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Camphor	82	3.8	96
Menthol	38	6.9	81
Aspirin	53	1.3–10.7	100
Propyl *p*-hydroxybenzoate	75	6.2	100
Stearic acid	92	4.5	96
Sulfur	98	2.5–13.4	65
Vanillin	86	6.4	38
Phenobarbital	8	4.4	74

Table 7

Percentage Yield, Average Diameter, and Relative Binding Strength of Group III Agglomerates

Compound	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Paracetamol with water as external phase	13	2.0	97
Paracetamol with saturated solution as external phase	54	1–2	84
Phenytoin with saturated solution as external phase	95	4.7	100

Table 8

Percentage Yield, Average Diameter, and Relative Binding Strength of Group IV Agglomerates

Compound	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Cephalexin in PVP	69	1–1.5	91
Kaolin in PVA	52	6.5	83
Kaolin in PEG	14	3.4	100

nol and acetone) are all miscible with water. When the same procedure was applied to group III, all the water-miscible organic solvents migrated to the water phase immediately, leaving the drug behind in a suspended form, and agglomeration was not attainable. Thus the emulsion solvent diffusion method involving the use of a mixture of water-miscible and water-immiscible solvents (e.g., ethanol and chloroform) had to be employed here instead. The latter method was shown to readily yield hard compact spherical agglomerates of paracetamol and phenytoin with a size range of about 1–4 mm in diameter (Table 7). However, the yield of paracetamol agglomerates appeared unacceptably low. This is probably attributable to the dissolved paracetamol in the ethanol/chloroform mixture partitioning into the water phase, thereby reducing the concentration of paracetamol in the ethanol/chloroform mixture, and hence, the rate and yield of agglomeration. To avoid the loss of paracetamol due to partitioning into the aqueous phase, a saturated solution of the drug instead of pure water was employed as the external phase. Such a measure increased the agglomeration yield of paracetamol

by about fourfold (i.e., from 13% to 54%). The same technique applied to phenytoin afforded a yield of 95%.

Cephalexin and kaolin were classified into group IV as they both have relatively poor solubilities in either water or organic solvents. They, therefore, could not be agglomerated through a bridging process relying strictly on particulate dissolution and recrystallization. In addition, a suitable binder such as PVP or PEG was required to aid the binding process. Upon stirring, the binder gradually dissolved in the bridging solution (20% w/v calcium chloride in this case) and gathered the particles together into agglomerates. Relatively hard matrice-like cores were then formed. Different binders were shown to exhibit different agglomeration behavior with the compounds. Kaolin agglomerated with PVA was much larger in size and yield than that with PEG (Table 8). This may be due to the different adhesive and cohesive strengths as well as different solubilities of the binders.

Effect of Bridging Liquid on Spherical Agglomeration

The various bridging solvent systems employed for aspirin and citric acid yielded satisfactory agglomerates. There seemed to be no significant differences in performance between the different bridging liquids as long as they could dissolve the compounds to a sufficient extent (e.g., >1 in 20). Agglomerates of citric acid produced by the three bridging liquids were similar in size and binding strength, but the yield with the inorganic salt solutions was higher than that with pure water (Table 9). This may be ascribed to the enhanced wettability and/or solubility of citric acid in the presence of ionic salts (i.e., salting-in effect), leading to the formation of more liquid and solid bridges between the particles and consequently a higher yield. Similarly, the increased yield of aspirin agglomerates obtained using chloroform may be interpreted in terms of the better wettability of aspirin powder with chloroform than with dichloromethane (Table 10). The difference in yield may also be related to the difference in density between the two bridging liquids. Dichloromethane (d = 1.325 at 20°C) is less dense than chloroform (d = 1.484 at 20°C) so that more aspirin powder settled at the bottom of the flask and adhered to the fluid-stagnant region, thus escaping agglomeration. Solubility appeared not to be a major contributing factor in this case since aspirin has very similar solubility in both solvents.

Effect of External Phase on Spherical Agglomeration

The agglomeration of potassium chloride and ascorbic acid using 20% calcium chloride solution as the bridging solvent in several different external phases yielded products which were not very different in size, binding strength, and yield, as shown in Tables 11 and 12.

Table 9

Percentage Yield, Average Diameter, and Relative Binding Strength of Citric Acid Agglomerates

Bridging Solvent	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
20% calcium chloride	90	5.5	91
30% sodium chloride	84	4.5	88
Water	70	5.5	76

Table 10

Percentage Yield, Average Diameter, and Relative Binding Strength of Aspirin Agglomerates

Bridging Solvent	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Chloroform	53	1.3–10.7	100
Dichloromethane	11	4.7	99

Table 11

Percentage Yield, Average Diameter, and Relative Binding Strength of Potassium Chloride Agglomerates

External Phase	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Dichloromethane	24	1–6	61
Hexane	30	4.4	74
Cyclohexane	21	2–4	60

Table 12

Percentage Yield, Average Diameter, and Relative Binding Strength of Ascorbic Acid Agglomerates

External Phase	Yield (%)	Average Diameter (mm)	Relative Binding Strength (%)
Dichloromethane	76	2–4	87
Chloroform	90	1.5–7	99
Cyclohexane	82	2.6	98

The slight variation in diameter of the agglomerates may be due to the different viscosity of the external phase which generates different degrees of turbulence when being stirred. Thus the choice of external phases having similar solubility behavior may affect the agglomeration product characteristics but would not lead to failure of the process.

Characterization of Agglomerate Surface

As revealed by scanning electron microscopy, the agglomerate surfaces of most of the samples were composed of stacks of crystals with roughly the same shape as the unmodified compound rather than a continuous, uniform layer (Figs. 3–10). The outlines of the crystals were distinct but curved around the corners and edges, suggesting that the surface particles did not dissolve entirely but partially dissolved around the corners and edges, and fused with the adjacent ones during interfacial recrystallization. The cores of the agglomerates were dense and almost all fused together, but the surface was porous. As an explanation, part of the particles must have dissolved in the bridging liquid, and these dissolving particles then acted as the nucleus for the initial agglomeration. The remaining undissolved particles were then collected through collision and partially dissolved and recrystallized so as to fuse with the initial agglomerates. As is discussed later, this process can be enhanced up to a certain limit by increasing agitation.

The surfaces of the agglomerates of cephalexin or kaolin prepared with a binder (PVP or PEG) appeared somewhat smoother, with flakes of the binder (PVP or PEG) intermingled with the rectangular chunks of cephalexin or kaolin (Figs. 9 and 10). These surface crystals showed sharper and more defined edges than those on the agglomerates (e.g., aspirin) prepared by other methods (i.e., groups I–III), suggesting that kaolin and cephalexin might not have dissolved at all. PEG or PVP probably dissolved instead, and then bound the undissolved kaolin or cephalexin particles together to form matrice-like agglomerates.

Proposed Mechanisms for Spherical Agglomeration

Based on the findings from the present study and previous literature, the following mechanisms can be postulated.

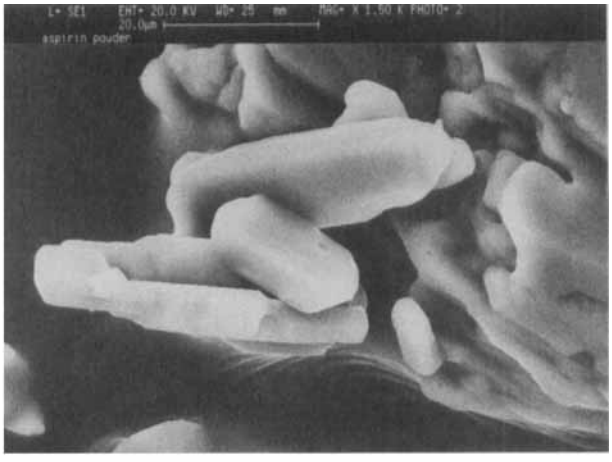
In the spherical agglomeration method for group I and group II compounds, particles are first dispersed in a liquid medium where the compound does not dissolve. The bridging liquid which is immiscible with the external liquid medium is then added. Liquid bridges are formed between particles which hold them together as shown in Fig. 11 (17).

The surfaces of the particles then dissolve within the liquid bridges, where saturation and recrystallization occur, converting the liquid bridges into solid bridges.

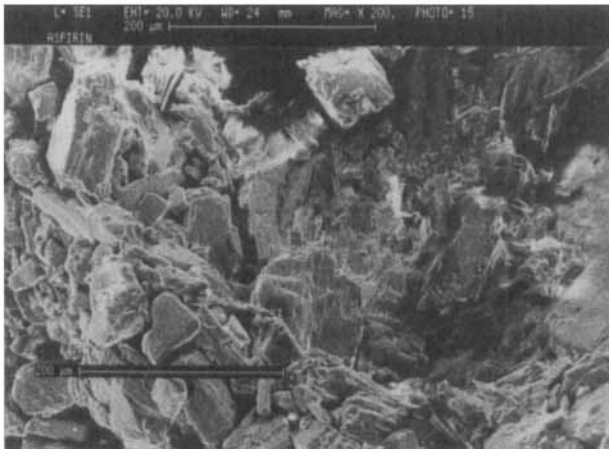
(a)

(b)

Figure 3. Scanning electron photomicrographs: (a) unmodified powder of ascorbic acid (group I); (b) surface of spherical agglomerate of ascorbic acid (group I) prepared with cyclohexane as external phase.



(a)

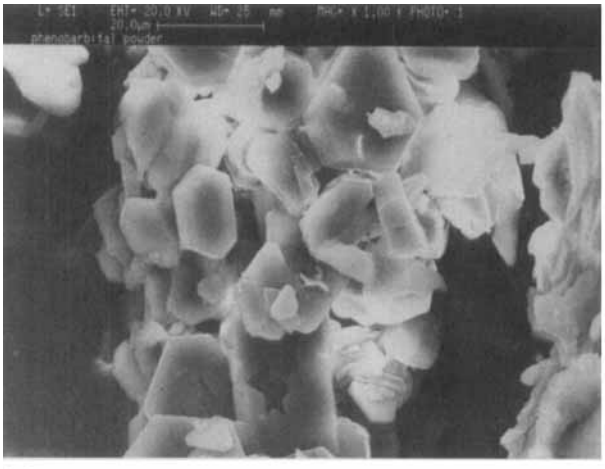


(b)

Figure 4. Scanning electron photomicrographs: (a) unmodified powder of aspirin (group II); (b) surface of spherical agglomerate of aspirin (group II).

The doublets initially formed serve as nuclei, and some of the undissolved particles deposit onto them by rapid random coalescence with the help of the bridging liquid and give rise to primary agglomerates. The formation of solid bridges in the present study has been evidenced by the fusion of crystals seen on the surface and core of the agglomerates (Figs. 3, 4, and 8).

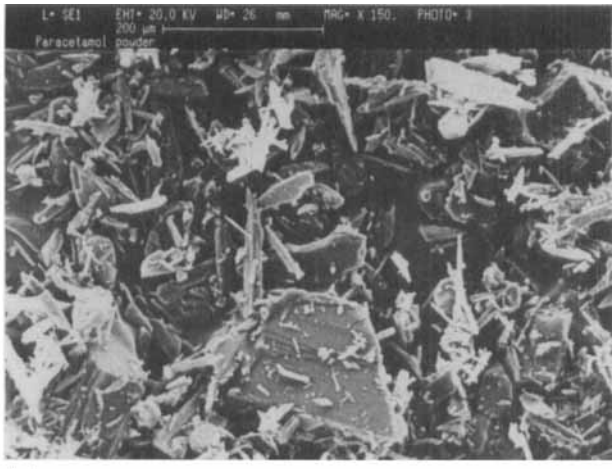
Based on the aforementioned mechanism, the initial growth of spherical agglomerates will depend on dissolution (or solubility, since dissolution is directly related to solubility) and random coalescence. Since only those bridging solvents capable of significantly dissolving the materials were selected in the present study, the rate of particulate dissolution in the various solvents would be rapid, and thus random coalescence would become the rate-determining step. The particular requirement of solubility or rapid dissolution for particulate agglomeration has been further attested by the unsuccessful attempt to agglomerate paracetamol with a bridging liquid (20% w/v calcium chloride solution) in which the drug is relatively insoluble. Thus, for a bridging liquid to be effective, it should be capable, not only of wetting the particle surface so as to form liquid bridges, but also of dissolving the sample particles. A bridging liquid with



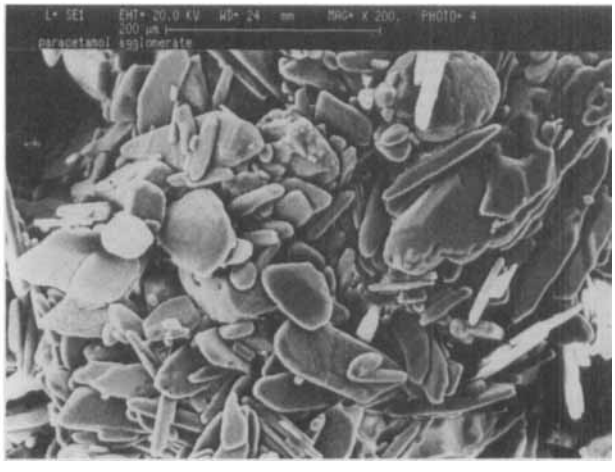
(a)

(b)

Figure 5. Scanning electron photomicrographs: (a) unmodified powder of phenobarbital (group II); (b) surface of spherical agglomerate of phenobarbital (group II).



(a)

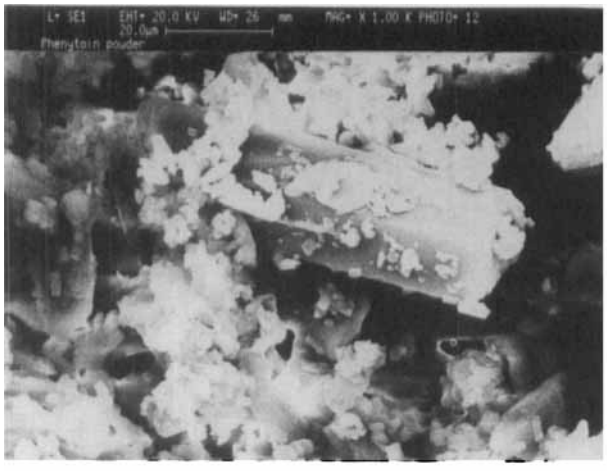


(b)

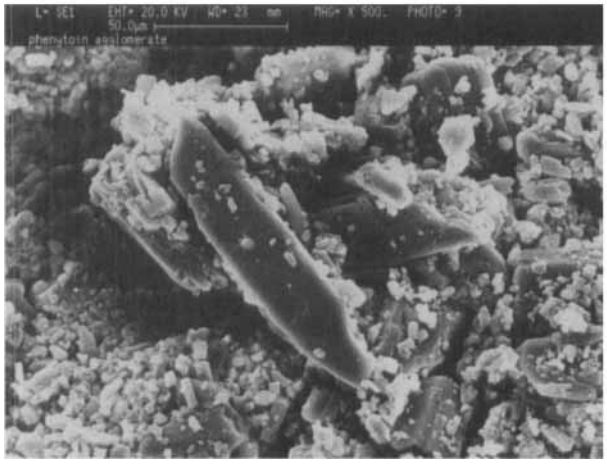
Figure 6. Scanning electron photomicrographs: (a) unmodified powder of paracetamol (group III); (b) surface of spherical agglomerate of paracetamol (group III).

poor wetting property for the powder will likely affect both the rate and extent of agglomeration. The latter arguments have been well illustrated in the present study by the agglomeration of aspirin with chloroform or dichloromethane and citric acid with calcium chloride, sodium chloride, or water, as alluded to earlier. In summary, the bridging liquid may exert a marked influence on the yield and rate of agglomeration as well as on the strength of the resulting agglomerates held together predominantly by solid bridges.

As soon as the primary agglomerates are formed, a secondary mechanism may go along with the above process to yield the secondary agglomerates. As the growth process continues and the size of the agglomerates increases, the intensity of collision is also increased, leading to a steady increase in the agglomerate breakage rate; i.e., particles above a critical size attempting to grow by binary coalescence are often broken into fragments and fines. Also, small agglomerates tend to be completely crushed by larger ones. A preferential growth will then occur whereby large agglomerates will pick up fragments and fines, and continue to grow by layering, albeit at a decreasing rate. The growth continues until some steady-state value is reached at longer

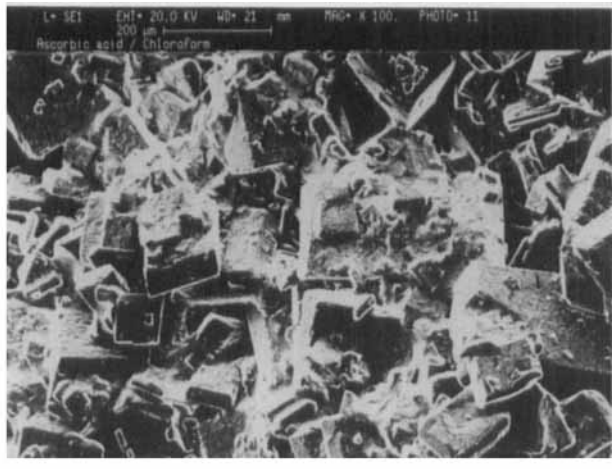


(a)

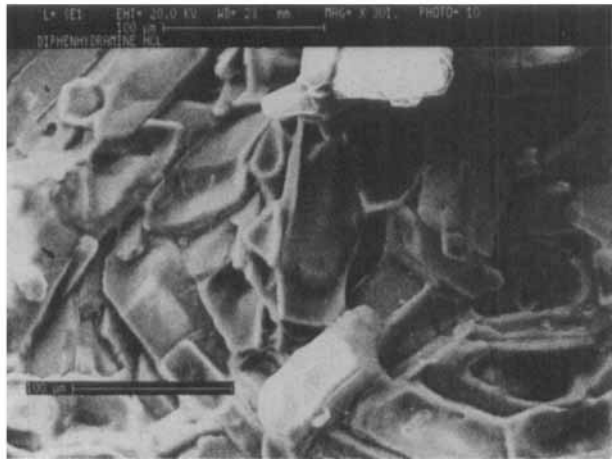


(b)

Figure 7. Scanning electron photomicrographs: (a) unmodified powder of phenytoin (group III); (b) surface of spherical agglomerate of phenytoin (group III).



(a)



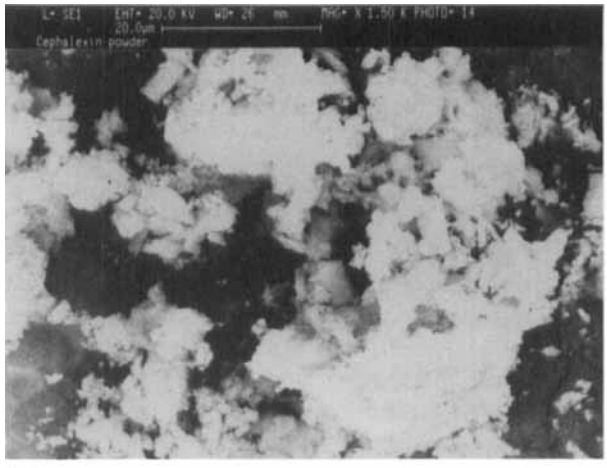
(b)

Figure 8. Scanning electron photomicrographs: (a) surface of spherical agglomerate of ascorbic acid (group I) prepared with chloroform as external phase; (b) surface of spherical agglomerate of diphenhydramine hydrochloride (group I).

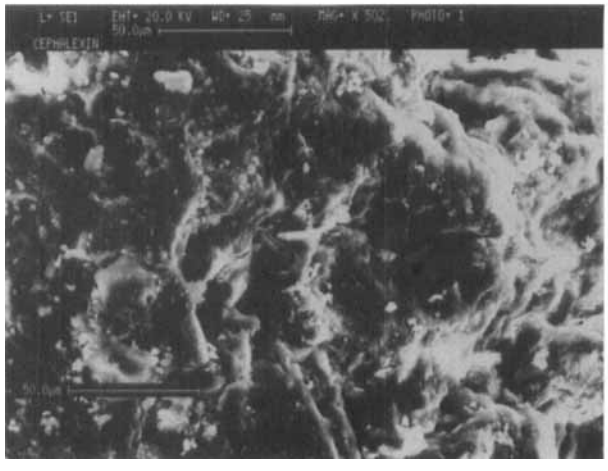
agglomeration times when a balance is reached between cohesive forces in the agglomerates and the destructive forces in the agitated suspension. Thus the particle size would be expected to be increasing initially and approach a constant value at infinite agglomeration time. This phenomenon has been demonstrated in Kawashima and Capes' studies (2).

The technique employed for agglomeration of the group III compounds is technically known as the emulsion solvent diffusion method (11,18,19), which is specially tailored for compounds that are only soluble in water-miscible organic bridging liquids while the method used for group IV is for those compounds which are not adequately soluble in either water or any other organic solvent. The mechanism of transforming primary agglomerates into secondary agglomerates in these two methods is conceivably the same as those for groups I and II, but the mode of formation of primary agglomerates is likely to be different.

With regard to the emulsion solvent diffusion method, the compound is first dissolved partially and dispersed in an ethanol/chloroform mixture. The mixture is then poured into water and dispersed as liquid droplets. Ethanol then diffuses out of the mixture drop-

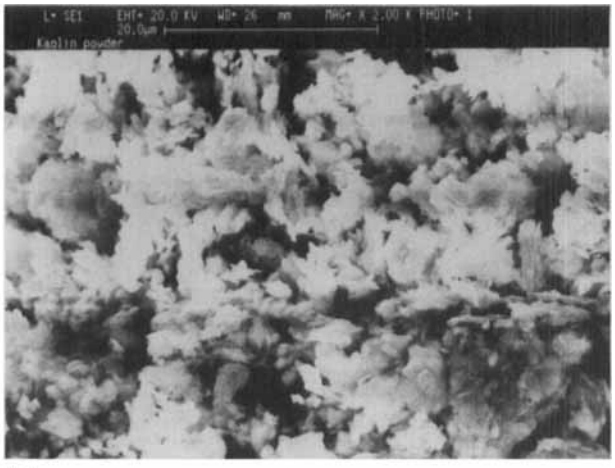


(a)



(b)

Figure 9. Scanning electron photomicrographs: (a) unmodified powder of cephalexin monohydrate (group IV); (b) surface of spherical agglomerate of cephalexin monohydrate (group IV) prepared with PVP as binder.



(a)

(b)

Figure 10. Scanning electron photomicrographs: (a) unmodified powder of light kaolin (group IV); (b) surface of spherical agglomerate of light kaolin (group IV) prepared with PEG as binder.

lets into water, and partitioning of ethanol between water and chloroform occurs. The ethanol content in the droplets decreases and the compound recrystallizes out and acts as primary nuclei for further growth. In this case, spherical crystals are produced which preserve the original shape of the droplets initially formed. This has been observed in the present study for the paracetamol agglomerates, which are highly spherical in shape [Fig. 2(c)].

Group IV compounds (cephalexin and kaolin) have limited solubilities in almost all solvents; hence, binders such as PVP, PEG and PVA are required for agglomeration. These binding agents initially swell in the bridging liquid (20% w/v calcium chloride solution in this case) and dissolve in it. The dissolved binders then collect the undissolved particles together to enable the formation of liquid bridges between the particles. The phase change from liquid to solid within the bridges is brought about by hardening of the binders. This can increase the final strength of the product, and primary agglomerates result. Since the primary agglomerates are in the liquid droplet form, as with the compounds in group III, the resulting secondary agglomerates would be perfectly spherical due to the preservation of the

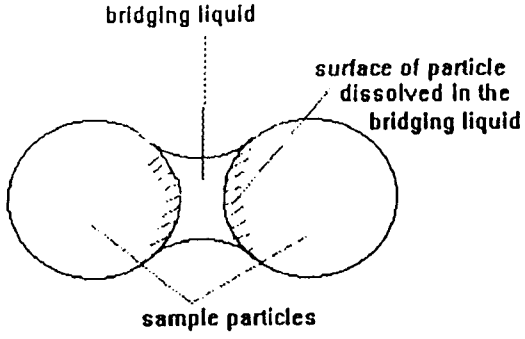


Figure 11. Two sample particles joined together by a liquid bridge.

original shape of the droplets initially formed. This has also been observed for the cephalexin and kaolin agglomerates [Fig. 2(d)].

General Guidelines for Spherical Agglomeration

Based on the above discussions, the following general guidelines for spherical agglomeration of powders are proposed.

For compounds that are water soluble (group I), a water-immiscible organic solvent (e.g., cyclohexane) is used as the external medium and a 20% calcium chloride solution (or other salt solutions of high concentration without common ions) can be used as the bridging liquid.

For compounds that are soluble in one or more organic solvents (group II), water is employed as the external phase and a water-immiscible organic solvent (e.g., chloroform) as the bridging liquid.

For compounds that are only soluble in water-miscible organic solvents (group III), a saturated aqueous solution of the compound can serve as the external phase and an organic solvent mixture (e.g., ethanol and chloroform) as the bridging solvent.

For compounds that are insoluble in water or any organic solvents (group IV), a water-immiscible organic solvent (e.g., cyclohexane) can act as the external phase and a 20% calcium chloride solution as the bridging liquid. In addition, a binding agent such as PVP or PEG is required for agglomeration since the powders are not sufficiently soluble in the bridging liquids to allow binding through recrystallization and fusion.

The weight ratio of powder to bridging liquid used in all cases can be determined from Dolan's equation [Eq. (1)] (15,16). For the group I, II, and IV compounds, the powder is first dispersed in the external phase before addition of the bridging liquid, whereas the material in the group III category is initially dispersed in the bridging liquid before adding to the external phase.

CONCLUSIONS

Pharmaceutical powders with different properties were agglomerated with different solvent systems. Spherical agglomerates of different sizes and binding strength were obtained.

The rate of agglomeration, yield, and the strength of the final product were shown to depend on the choice of bridging liquid. However, the size distribution of the agglomerates appeared to be governed by the viscosity of the external phase.

Employing scanning electron microscopy, solid bridges were observed between the particles on the surface of the agglomerates. Based on this observation and results from the literature, a possible mechanism for spherical agglomeration was postulated. It was suggested that initially particles were joined together by liquid bridges which eventually solidified to form the primary agglomerates. The primary agglomerates further grew in size through random coalescence and were at the same time broken down by collision. A definite size was finally achieved when a balance between the two opposing processes was reached.

The general guidelines for spherical agglomeration of the various groups (types) of powders were established. It is hoped that these guidelines will aid the systematic application of spherical agglomeration in pharmaceutical processing—in modifying the micromeritic properties of the powders and/or for later processing.

ACKNOWLEDGMENT

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