AAPS PharmSciTech, Vol. 11, No. 2, June 2010 (© 2010)
DOI: 10.1208/s12249-010-9426-8

Research Article

Theme: Advanced Technologies for Oral Controlled Release
Guest Editors: Michael Repka, Joseph Reo, Linda Felton, and Stephen Howard

Preparation and Characterization of Highly Porous Direct Compression Carrier Particles with Improved Drug Loading During an Interactive Mixing Process

Mingna Song,[1,2] Ning Li,[1] Louwrens R. Tiedt,[3] Michael D. Degennaro,[2] and Melgardt M. de Villiers[1,4]

Received 30 December 2009; accepted 5 April 2010; published online 23 April 2010

Abstract. The aim of this study was to prepare highly porous carrier particles by emulsion solvent evaporation and compare the loading capacity of these beads with two traditional carriers, sugar beads, and microcrystalline cellulose granules during an interactive mixing process. The porous carrier particles were prepared by an emulsion solvent evaporation process using cellulose propionate as a binder, anhydrous dibasic calcium phosphate, and ion exchange resins as a fillers, and polyethylene glycol as a pore inducer. Micronized furosemide or griseofulvin powder was mixed with the same volume of each carrier in an interactive mixing process. The tableting properties, drug loading per unit volume of carrier, content uniformity of the mixtures, and dissolution of the drugs from the mixtures were measured. The results showed that highly porous microcapsules with desirable hardness equivalent to that of sugar beads and MCC granules were successfully prepared. On average the loading capacity of the new carrier was 310% that of sugar beads and 320% that of MCC granules during an interactive mixing process with very good content uniformity. The tableting properties of the microcapsules were equivalent to that of microcrystalline cellulose granules, and the dissolution of the drugs from interactive mixtures prepared with the new carrier was equivalent to that of drug suspensions. This showed that the prepared microcapsule carrier could be used to improve the loading capacity during an interactive mixing and to prepare tablets by direct compression.

KEY WORDS: direct compression; emulsion solvent evaporation; interactive mixing; porous carrier.

INTRODUCTION

Powder mixing is a common processing operation in the pharmaceutical industry. Powder mixtures are classified into two major groups, free-flowing mixtures, and mixtures containing interactive constituents (1). In free-flowing mixtures, individual particles move independently while, in interactive mixtures, inter-particulate forces are present because at least one of the constituents, usually the fine drug particles, adheres to a second coarser constituent, the carrier particles (2). Under optimum mixing conditions, these interactive mixtures are nearly perfectly homogenous (3–5).

Optimum mixing conditions for the formation of interactive mixtures include the type of mixer and mixing time, the size distribution of the carrier particles, and the adhesion forces between the components (2,6). Especially, the strength of the inter-particulate forces between the drug and carrier particles determines the successful formation of an interactive mixture (7–9). To achieve this, the adhesion force between the drug and carrier particles must be greater than the autoadhesion forces between the micronized drug particles (10,11). The adhesive force between the drug and carrier particles can be increased by using carrier particles with the optimum size, shape, and surface roughness (12).

In this study, the aim was to prepare pharmaceutically acceptable multi-purpose carrier particles that can be used in an interactive powder mixing process where the drug is adhered to the carrier during a dry powder mixing process. In addition, these particles can also be used to load drugs during the preparation method of the carrier particles (13,14) and for depositing the drug on and/or inside the carrier particles by deposition from a solvent. One process used to prepare larger drug-excipient composites is microencapsulation (15). A number of methods, which include coacervation or phase separation, interfacial reactions, and miscellaneous mechanical methods may be used to prepare microcapsules (15). A commonly used method for the encapsulation of drugs into water-insoluble polymers is the emulsion solvent evaporation (ESE) process (16). This technique has been used successfully in the preparation of drug microcapsules using different biocompatible polymers (13,14,17,18). A schematic illustration of the encapsulation process is shown in Fig. 1.

Many processing and formulation factors can influence the preparation of microcapsules by the ESE process (19). Song *et al.* (13,14) studied the effect of processing and

[1] School of Pharmacy, University of Wisconsin-Madison, 777 Highland Avenue, Madison, Wisconsin 53705-2222, USA.
[2] College of Pharmacy, University of Louisiana at Monroe, Monroe, Louisiana 71209, USA.
[3] Laboratory for Electron Microscopy, Faculty of Natural Sciences, North-West University, Potchefstroom, 2520, South Africa.
[4] To whom correspondence should be addressed. (e-mail: mmdevilliers@pharmacy.wisc.edu)

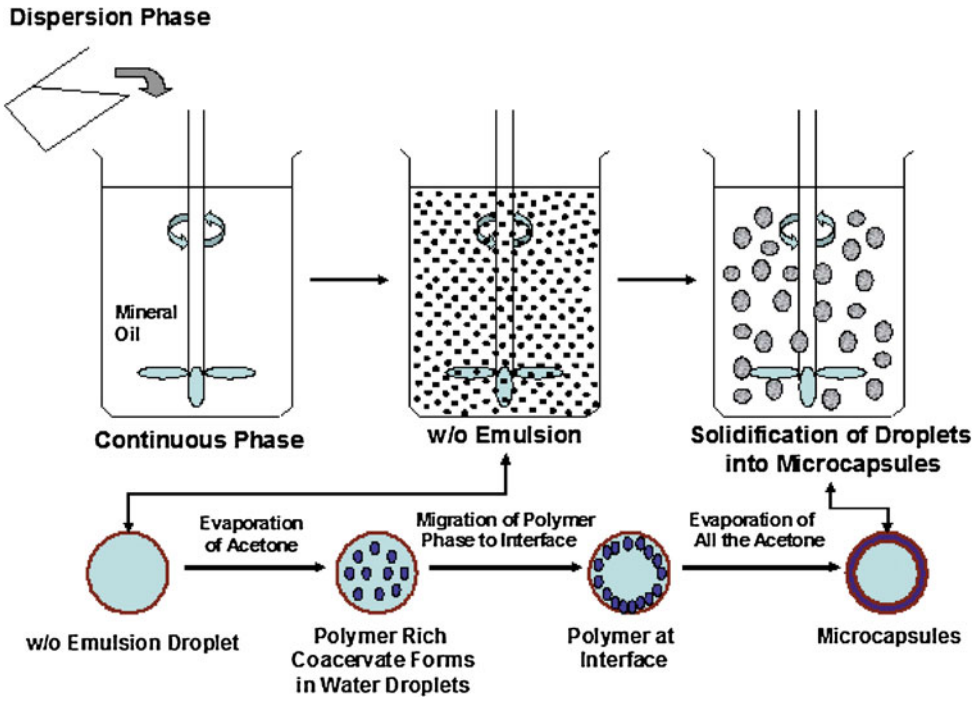

Fig. 1. Schematic illustration of the microencapsulation ESE process

formulation factors on the particulate properties of controlled release water-soluble drug amoxicillin trihydrate microcapsules prepared by an ESE process. Based on the results from the amoxicillin study in this study the ESE process was used to prepare improved porous carrier particles for interactive mixing. The particulate and mixing properties of the prepared porous carrier particles were characterized and compared with that of two carriers that are commonly used to prepare interactive mixtures, sugar spheres, and microcrystalline cellulose granules.

MATERIALS AND METHODS

Materials

To make the ESE microcapsules two ion exchange resins Amberlite IRP 69 (polacrilex resin), a cation exchange resin, and Duolite (cholesterylamine resin, USP), an anion exchange resin (Rohm and Haas, Philadelphia, PA, USA), cellulose propionate (average M_w ca. 130,000, average M_n ca. 70,000, Sigma Aldrich, St. Louis, MO, USA), anhydrous dibasic calcium phosphate (Emcompress, JRS Pharma, Patterson, NY, USA), sorbitan monooleate (Sigma Aldrich, St. Louis, MO, USA), and polyethylene glycol (PEG 400 and 3350, Sigma Aldrich, St. Louis, MO, USA) was used as received. Acetone was used as the solvent and mineral oil as the dispersion phase (Sigma Aldrich, St. Louis, MO, USA). Micronized furosemide (Spectrum Chemicals, St. Louis, MO, USA) and griseofulvin (Sigma Aldrich, St. Louis, MO, USA) were used as model drugs for this study.

Preparation of Porous Carrier Particles

To prepare the optimized porous carriers, cellulose propionate 1.0 g, and PEG 400 and 3350 1:1 *w/w* mixture 0.6 g were dissolved in 25 mL acetone (water was extracted by using a molecular sieve) by heating to about 40°C. Amberlite or Duolite, 1.2 g, and anhydrous dibasic calcium phosphate, 0.3 g, was suspended in the solution by stirring with a magnetic stirrer. This formed the dispersion phase. The dispersion phase was then added into 120 ml light mineral oil containing 1.5% sorbitan monooleate while stirring at 800 rpm with a mechanical stirrer. The whole system was stirred until the acetone evaporated completely from the system. The particles were collected by filtration, washed five times with 20 mL hexane, and dried at ambient temperature. The dry particles were washed three times with hot purified water by shaking with a mechanical shaker for 8 h to remove the PEG 400 and 3350 mixture. The washed particles were then dried in a vacuum oven at 50°C for 48 h before use. This process was repeated multiple times, and the dried beads were combined and stored in a dessicator at room temperature.

Preparation of Microcrystalline Cellulose Granules and Description of Sugar Spheres

Microcrystalline cellulose (MCC, Emcocel 90, JRS Pharma, Patterson, NY, USA) was wet granulated using ethyl cellulose (Hercules, Wilmington, DE, USA) and hydropropyl methylcellulose (Spectrum Chemicals, Gardena, CA, USA) as binders. A 5% ethyl cellulose and 5% hydropropyl methylcellulose in 50:50 ethanol/water solution was prepared as binding solution. MCC powder was fed into the bowl of a planetary mixer (Erweka Corp., Annandale, NJ, USA), and the binding solution was added as the paddle of the mixer agitated the powder. The moist mass was then transferred and pressed through a sieve screen with opening size 850 μm. The granules were collected on trays and dried in an oven at 50°C. Sugar spheres (USP, synonyms: non-pareil, non-pareil 103, non-pareil seeds, Nu-core, Nu-pareil, and sugar seeds) was

obtained from Ingredient Technology Corporation (Pelham Manor, NY, USA). The sugar spheres were approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and no more than 91.5% of sucrose, calculated on the dried base.

Characterization of the Carrier Particles

Morphology

The surface and intersectional appearance of the carrier particles before and after mixing with the micronized drugs were studied using a scanning electron microscope (SEM) (Quanta 200, FEI, Eindhoven, Netherlands or Amray 500, Amray Pty. Ltd., Bedford, MA, USA).

Particle Size of the Carrier Particles

Carrier particles were loaded on to the coarser sieve (700 μm opening) of the assembled stack (a sieve with 600 μm opening size and one with 700 μm opening size), and the nest was subject to mechanical vibration for 20 min. After this time, the particles were considered to be retained on the sieve mesh with an aperture corresponding to the sieve diameter. Only the portion of particles retained on the 600 μm opening sieve were collected for use. This size portion represented 54±6% of the recovered particles.

Measurement of Flowability

A simple method of determining powder flowability directly is to measure the rate at which powder discharges from a hopper flow tester (Erweka Model GDT, Erweka Corp., Annandale, NJ, USA; Gold *et al.* 1966). In this study, the time it took for 50 ml of highly porous cellulose propionate (HPCP) microcapsules, MCC granules and sugar spheres with particle size between 600 and 700 μm to flow through the stainless steel hopper was recorded. The angles of repose of the carriers were also measured by using a fixed cone base method. An excess amount of carrier particles was poured from a fixed-height-vibrating funnel driven by a motor (Erweka, Chemical and Pharmaceutical Industry Co., Inc, NY) at a fixed frequency onto a fixed base with a diameter of 3.0 cm. The height of the cone formed by the drug material was measured, and the angle of repose was calculated using the following equation:

$$Tan\alpha = \frac{\text{height of cone}}{\text{radius of cone}} \quad (1)$$

Carr's Index

Neumann (1967) and Carr (1965) developed a simple test to evaluate flowability of a powder by comparing the poured (fluff) density (ρ_{Bmin}) and tapped density (ρ_{Bmax}) of a powder and the rate at which it packed down. Carr's index is a simple index that can be determined on small quantities of powder and may be interpreted as in follows: 5–15=excellent flow; 12–16=good flow; 18–21=fair to passable; 23–35=poor flow; 33–38=very poor flow; >40=extremely poor flow.

Porosity

The surface area of carrier particles were measured with a FlowSorb III 2300 surface area analyzer (Micromeritics, Norcross, GA, USA) by determining the quantity of a gas that adsorbs as a single layer of molecules, a so-called monomolecular layer, on a sample. For these experiments, a mixture of 30% N_2 and 70% He was used with an outgas temperature of 75°C and outgas time of 180 min.

Hardness

First, an indirect method was used to determine the friability of the carrier particles. An accurate weight of carrier particles, about 50 g, was shaken on a 425 μm opening sieve screen violently for 30 min using a sieve-shaker (Erweka Corp., Annandale, NJ, USA). The carrier particles were recovered completely from the screen and weighed accurately. The difference between the weight of particles before and after shaking as a percentage of the original weight was used as a comparison of particle friability. Second, the hardness of the carrier particles were measured using a TA. XTPlus Texture Analyzer (Stable Micro Systems, Ltd., Godalming, Surrey UK) with a 50 kg load cell and 25-mm diameter AOAC cylinder, acrylic, 35 mm tall. For an initial evaluation of the carrier particles a standard test method, GRN1/P25 "Compressibility of tablet granules using a cylinder probe" was used (20). For this test, the cylinder was set at a height of 3 mm and then moved down at a speed of 0.1 mm/s to a height of 0.2 mm. For each test, five single particles were randomly distributed under the acrylic cylinder and then compressed.

Tableting Properties of the Carrier Particles

To evaluate the tabletting properties of the HPCP microcapsule 1-g mixtures consisting of magnesium stearate (0.5% *w*/*w*), cross-linked form of sodium carboxymethylcellulose (Ac-Di-Sol, FMC Biopolymer, Philadelphia, PA, USA; 5% *w*/*w*), and the carrier particles (qs to 100% *w*/*w*) were prepared in a Turbula mixer (model T2C, WA Bachofen, Basle, Switzerland) at 69 rpm for 10 min as described by Marais *et al.* (21). Flat-faced tablets weighing approximately 120 mg were prepared from each mixture. The mixture powder was placed manually into a stainless steel die with an inner diameter of 8 mm and compressed for 15 s at 77, 154, 231, and 309 Mpa, respectively, on an automated hydraulic press (Carver Inc., Wabash, IN, USA). The crushing strength, diameter, and thickness of six tablets of each formulation at each compression force were determined with a model PTB-311 Pharma Test tablet-test unit (Pharma Test, Basel, Switzerland). The weight and dimensions of each tablet were used to calculate the tablet density.

Preparation and Characterization of Interactive Mixtures

First, an excess amount (800 mg) of drug was mixed with the same volume (1.0 ml) of carrier particles in a 5-ml scintillation glass bottle in the Turbula mixer. The same volume of carrier particles and not weight was used to correct for density differences between the types of carrier particles.

Secondly, 20 ml of the carrier particles were mixed with increasing amounts of the micronized drugs from 0.1–10% *w/v*.

Determination of Drug Loading Capacity of the Carrier Particles During Mixing

The mixtures were rested for at least 24 h to release static electricity before determining loading capacities. When measuring the loading capacity, only the portion of drug particles attached to the surface of carrier particles should be counted as the interactive mixture. Therefore, to eliminate the interference of unattached drug powder on the determination of loading capacity, the 1-ml mixtures were screened gently using the mechanical sieve to remove all the free drug powder. These screened mixtures then represent the interactive part of each mixture. The amounts of drug particles forming interactive mixtures were analyzed by UV spectrophotometry (λ_{max} furosemide=271 nm, y=0.0608x-0.0069, R^2= 0.9997 and griseofulvin 297 nm, y=0.0703x+0.0072, R^2=0.9999) using a Multispec-1510 spectrophotometer (Shimadzu, Kyoto, Japan). Furosemide was dissolved in ethanol and griseofulvin in methanol. Then, the carrier particles were filtered out from the solutions. The solutions containing the drugs were diluted with the same solvents and assayed.

Content Uniformity of the Mixtures

The content uniformity test of uncoated tablets from the USP 30 was used to determine the content uniformity of the interactive mixtures. The drug content of 30 120-mg tablets prepared from each 20-ml mixture was determined and the concentration relative standard deviation (RSD) of the drug substance in the final dosage units calculated. According to the USP, the RSD should not be more than 2%.

DISSOLUTION OF THE DRUGS FROM THE MIXTURES AND TABLETS

Powder dissolution studies of the drugs from the interactive mixtures were performed using the methods described in the USP for furosemide and griseofulvin tablets. For furosemide, the dissolution medium was 900 ml, pH 5.8 phosphate buffer, and the paddles were rotated as 50 rpm. For griseofulvin, the dissolution was 1,000 ml water containing 4% sodium lauryl sulfate, and the paddles were rotated at 75 rpm. Samples were withdrawn from the dissolution medium at 2, 5, 10, 20, 30, 60, 90, and 120 min, and the amount of drug dissolved was determined from the UV absorbances of filtered portions of the solutions taken from the dissolution medium at these timepoints. Dissolution profiles were compared by determining the similarities between the dissolution profiles of different mixtures and that of suspensions (22,23). A model independent approach using a similarity factor ($f2$) first described by Moore and Flanner and then adopted by the FDA was used to compare the dissolution profiles (24). The value of $f2$ is 100 when the test and reference mean profiles are identical and values between 50 and 100 ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

Table I. Materials Used in the Preparation of Porous Carrier Particles and Their Functions

Material	Function
Cellulose propionate (CP)	Wall former
Sodium polystyrene sulfonate (Amberlite IRP69)/cholestyramine resin (Duolite AP143)	Pore inducer/filler
Polyethylene glycol (PEG) 400	Pore inducer
Polyethylene glycol (PEG) 3350	Pore inducer
Dibasic calcium phosphate anhydrous (Emcompress)	Filler/density enhancer
Acetone	Solvent of dispersion phase
Light mineral oil	Continuous phase
Sorbitan monooleate	Emulsifier

Table II. Particulate Properties of the Carrier Particles

	HPCP	HPCP washed	MCC granules	Sugar spheres
Poured density (g/ml)	0.48	0.48	0.34	0.79
Tapped density (g/ml)	0.34	0.34	0.40	0.85
Porosity (m^2/g)	0.48	2.27	0.35	0.19
Flowability (ml/s)	7.9±0.1	8.3±0.1	6.1±0.2	8.3±0.1
Angle of repose (°)	25.9	26.0	29.5	14.4
Carr's index (%)	2.9	3.0	15.0	7.1
Friability (%)	0.8±0.05	0.8±0.04	2.3±0.3	0.4±0.02

RESULTS AND DISCUSSION

In this study, HPCP-based microcapsules were prepared using an ESE process. The materials used for the preparation of porous microcapsules and their functions are summarized in Table I. Microcapsules prepared by the ESE process usually contain a filler and wall former besides the active ingredient. In this study, no active ingredient was included. Cellulose propionate was used as the wall former because it is an effective biocompatible matrix bone structure builder of porous carrier particles (25,26). In addition, anhydrous dibasic calcium phosphate was encapsulated into the HPCP microcapsules to increase the density of the hollow porous particles and to act as filler.

The macro-porosity of the matrix was increased by embedding water-soluble materials, a 1:1 mixture of PEG 400 and PEG 3350, in the matrix that was washed out of the matrix with water. To increase the microporosity of the HPCP capsules, highly porous ion exchange resins, porosities as high as 50%, were incorporated into the matrix. Either Amberlite IRP 69, a cation exchange resin, that is insoluble in water and organic solvents, with a mean volume particle size of 45 μm (d_{90}<150 μm), and a total cation exchange capacity of 10.0 eq/kg or Duolite (cholesteryramine resin, USP) an anion exchange resin that is also insoluble in water and most organic solvents, with a mean volume particle size of 37 μm (d_{90}<150 μm), were used.

In addition to these chemicals, the dispersion phase solvent, emulsifier, and continuous phase were the same as used for the preparation of amoxycillin sustained release

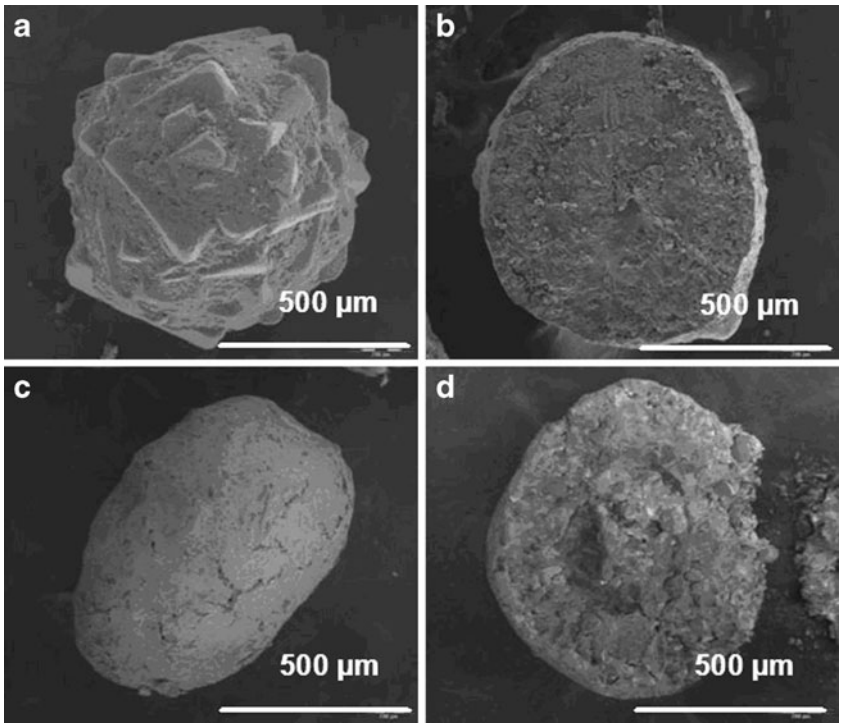

Fig. 2. SEM photomicrographs of sugar beads and MCC granules: **a** intact sugar bead; **b** sugar bead cut in half; **c** intact MCC granule; **d** MCC granule cut in half

microcapsules reported earlier (13,14). Using these ingredients and incorporating the limiting factors into the design process, it was possible to prepare porous carrier particles using the ESE process as shown in Fig. 1. The formulation was optimized by studying the effect of a change in the concentration of each formulation ingredient, namely, cellulose propionate, ion exchange resin, dibasic calcium phosphate anhydrous, and PEG 400 and 3350 1:1 mixture, on the

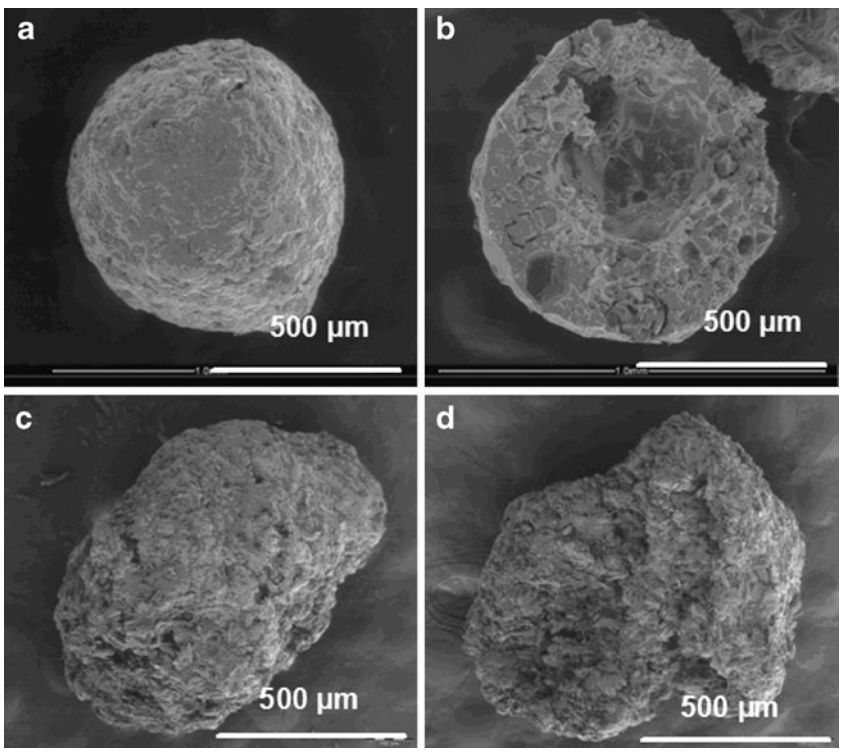

Fig. 3. SEM photomicrographs of microcapsules: **a** intact HPCP microcapsule; **b** HPCP microcapsule cut in half; **c** washed HPCP microcapsule; **d** washed HPCP microcapsule pressed to show the hollow interior

yield, porosity, and friability of the microcapsules. The yield of washed HPCP microcapsules was calculated using the following equation

$$\text{Yield}(\%) = \frac{\text{Weight}_{\text{washed microcapsules}}}{\text{Weight}_{\text{Emcompress}} + \text{Weight}_{\text{cellulose propionate}} + \text{Weight}_{\text{ion-exchange resin}}} \times 100 \quad (2)$$

The mean yield for the optimized formula and process was 95.5±0.8% (n=5).

The largest potential use of the carrier particles is for the production of tablets and capsules and together with mixing properties, the flowability of the HPCP carrier particles is of critical importance in the production of these dosage forms. Comparative flow rates for the materials used in this study are listed in Table II. The results were analyzed using a one-way ANOVA. It was found that the flowability of sugar beads was statistically equivalent to HPCP microcapsules which was significantly better than the MCC granules ($p<0.05$). This could be due to the differences in surface roughness, Figs. 2 and 3, and density between the carriers. SEM showed that the porous particles had rougher surfaces. In terms of the particle morphology, the HPCP microcapsules was more porous than the sugar spheres and MCC granules, especially after the pore-inducing water-soluble PEG was washed out. The values of angle of repose showed that the sugar spheres and HPCP microcapsules had excellent flowability, while the MCC granules had only good flowability. According to the Carr's index, all the three carriers had excellent flowability. The HPCP microcapsules also had a significantly higher surface area per gram material (Table II) compared with the sugar spheres and MCC granules, and the surface area of the HPCP microcapsules also increased almost five times after it was washed.

Another important property of the HPCP carrier particles is the hardness and ability to withstand processing. The difference between the weight of particles before and after shaking on a sieve as a percentage of the original weight was used as a comparison of particle friability (Table II). The results indicated that the HPCP did not lose more weight than the sugar spheres during a rigorous material handling process and that MCC granules were slightly softer than the sugar spheres and HPCP microcapsules. The hardness of the HPCP particles were also measured with a texture analyzer. Force distance curves showed that the sugar beads were brittle because a very sharp peak, representing the force to crack the beads, appeared once the acrylic cylinder descended 2.0–2.5 mm. This was followed by crushing of the broken beads.

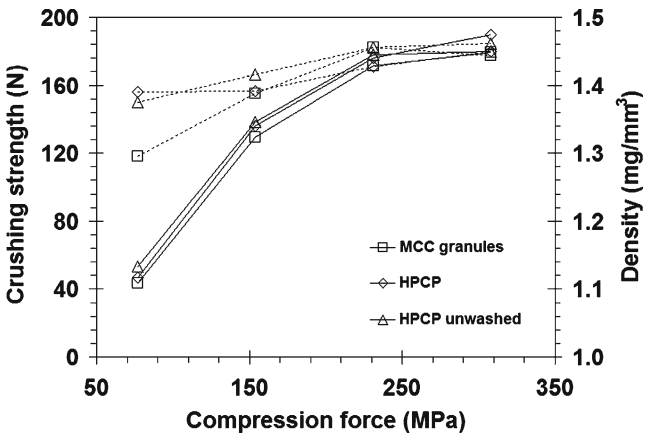

Fig. 4. The effect of compression force on the crushing strength (*solid lines*) and density (*dashed lines*) of the tablets prepared with the MCC granules and HPCP microcapsules

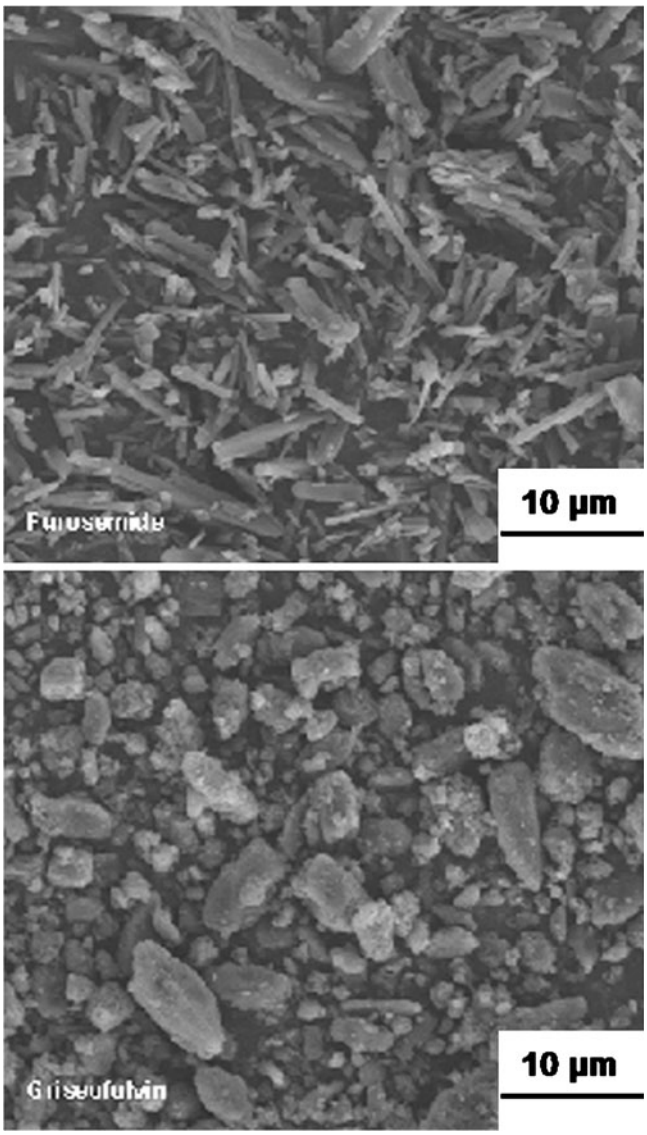

Fig. 5. SEM photomicrographs of the micronized drug powders recovered from the drug suspension: *top* furosemide and *bottom* griseofulvin

Table III. The Particulate Properties of the Model Drugs

	Griseofulvin	Furosemide
Particle size (d, μm)	6.43±0.57	6.07±0.66
Poured density (g/ml)	0.30	0.21
Tapped density (g/ml)	0.46	0.38
Angle of repose (°)	51	50
Carr's index (%)	35	53
Zeta potential (mV)[a]	−26.57±0.81	−26.57±1.20

[a] Measured in DI water

Table IV. Mixing Conditions Used for the Determination of Loading Capacity

	Condition 1		Condition 2		Condition 3	
Number of revolutions	Speed (rpm)	Time (min)	Speed (rpm)	Time (min)	Speed (rpm)	Time (min)
270	27	10	54	5.0	106	2.5

The force required to crack the beads ranged from 7–12 N. Both the MCC granules and the unwashed and washed HPCP microcapsules were elastic materials that required forces of 16–19 N, 3–6 N, and 8–11 N, respectively, to be compressed. These results showed that the HPCP microcapsules behaved more like the MCC granules as opposed to the sugar beads.

Force distance graphs at a faster compression speed also confirmed that the MCC granules and HPCP microcapsules were not brittle materials. The force distance graphs for the sugar beads showed that these carrier particles were brittle with a mean cracking force of 11.27±0.23 N, with an average time to cracking at a compression speed of 0.5 mm/s of 0.64± 0.11 s. A general rule with regard to brittleness is that a brittle product breaks at very little deformation. Because of this, sugar beads are not regarded as a very compressible material when compared with the HPCP particles and the MCC granules. Brittleness is typically also a packaging and shipping concern for tablets, which makes the HPCP carrier particles ideal for preparing tablets.

However, another important property of the HPCP microcapsules is the ability to compress the material into tablets. The relationship between compression force, crushing

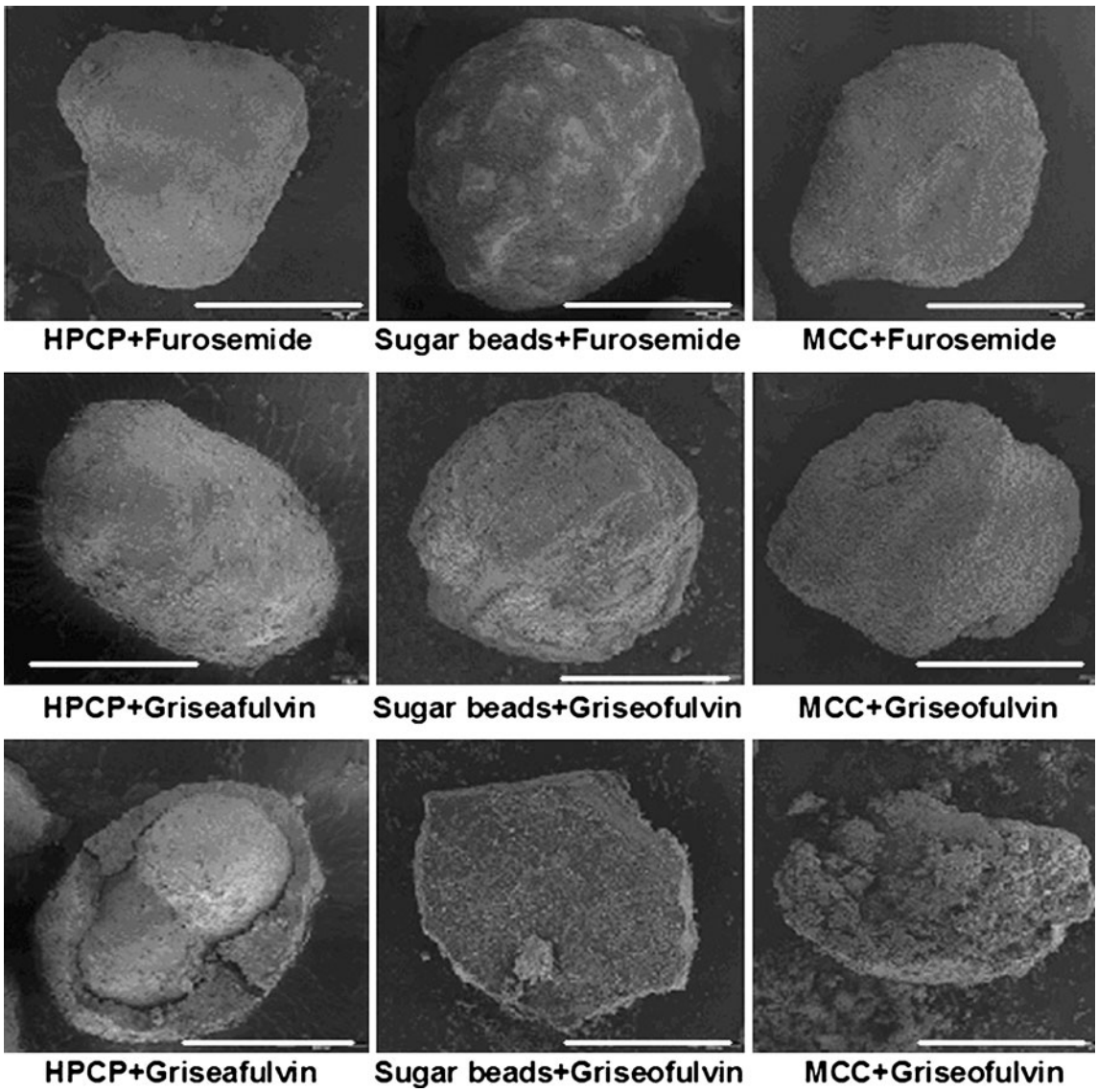

Fig. 6. SEM photomicrographs HPCP particles coated with the model drug materials (mixed for 270 revolutions, 106 rpm for 2.5 min). The *scale bars*=500 μm

strength, and tablet density for flat-faced tablets weighing approximately 120 mg, are shown in Fig. 4. The results showed that, with an increase in compression force, the crushing strength of the tablets increased up to around 180 N at a compression force of 230 MPa, where after the tablet hardness remained constant. The tablet density also increased upon compression. Overall, there was no statistical difference in either the crushing strength or the tablet density between the tablets prepared with the MCC granules or the HPCP microcapsules. This showed that the HPCP microcapsules could be used to replace MCC in tablet formulations.

Due to the high porosity of the HPCP microcapsules surface and the charge, one of the most important properties of these carrier particles might be the increased loading capacity compared with traditional carrier particles, sugar beads, and MCC granules during an interactive mixing process. This study therefore looked at the loading capacity of the HPCP microcapsules during an interactive mixing process with two micronized drugs, furosemide, and griseofulvin, Fig. 5. The two drug materials have distinctly different particle shapes, which correlates with their cohesive properties and therefore mixing properties. The mean particle size and zeta potential, and the poured density, tapped density, angle of repose measured, and Carr's indexes of the drug powders are summarized in Table III. Based on these measurements, both furosemide and griseofulvin were classified as cohesive powders, but the needle-shaped furosemide crystals were the most cohesive (23).

Upon mixing with the carriers, using the mixing conditions listed in Table IV, both drug powders adhered to the carriers in an interactive mixing process (7,12). SEM analysis, Fig. 6, shows that the surface of the carrier particles became smoother due to the coating of drug particles. The SEM images of carrier particles that were cut in half also indicate the thickness of the layer of the drug particles forming interactive mixtures with the carrier particles. From the intersections of the coated carrier particles, one can tell that the layer of griseofulvin or furosemide on the HPCP microcapsules containing either sodium polystyrene sulfonate (HPCP−) or cholesteryramine (HPCP+) was the thickest followed by that on MCC granules, and that on sugar beads was the thinnest. This is directly related to the surface porosity of these carrier particles. The rougher the surface of the carriers, the thicker the layer of drug powder was coated.

Table V. Loading Capacities of Griseofulvin and Furosemide in Weight of Drug (mg) per Volume of Carrier Particles (ml) During the Interactive Mixing Process after 270 Revolutions (n=3)

		Loading capacity (mg/ml)		
Carrier	Drug	27 rpm 10 min	54 rpm 5 min	106 rpm 2.5 min
Sugar beads	Furosemide	47.4±2.1	49.3±3.7	48.4±2.1
	Griseofulvin	86.3±2.8	82.9±2.5	87.7±3.2
MCC	Furosemide	66.9±5.4	67.0±3.6	65.4±1.7
	Griseofulvin	60.0±6.9	67.5±2.9	62.9±5.1
HPCP-	Furosemide	173.4±8.1	175.8±2.4	177.4±4.2
	Griseofulvin	178.1±10.9	176.2±3.3	175.6±2.7
HPCP+	Furosemide	253.4±6.1	223.4±8.2	245.1±7.1
	Griseofulvin	245.1±11.5	243.8±9.2	225.2±12.1

Table VI. Content Uniformity of Tablets Prepared from the Interactive Mixtures

		Content uniformity (RSD, %)			
Drug	Content (%)	HPCP+	HPCP-	Sugar spheres	MCC granules
Furosemide	0.1	0.4	0.5	0.9	1.1
	1	0.6	0.6	1.8	1.7
	5	0.7	0.9	2.1	2.5
	10	1.4	1.3	2.6	3.1
Griseofulvin	0.1	0.6	0.5	1.2	1.5
	1	0.6	0.6	2.1	2.5
	5	0.9	0.8	2.6	3.7
	10	1.2	1.1	4.6	5.3

These results were confirmed by determining the actual amount of drug powders loaded onto the carrier particles. The loading capacity of the carrier particles was calculated by dividing the weight of drug powder forming interactive mixtures, by the volume of carrier particles (Table V). More griseofulvin than furosemide could be loaded onto sugar spheres under all the mixing conditions. Statistically the same

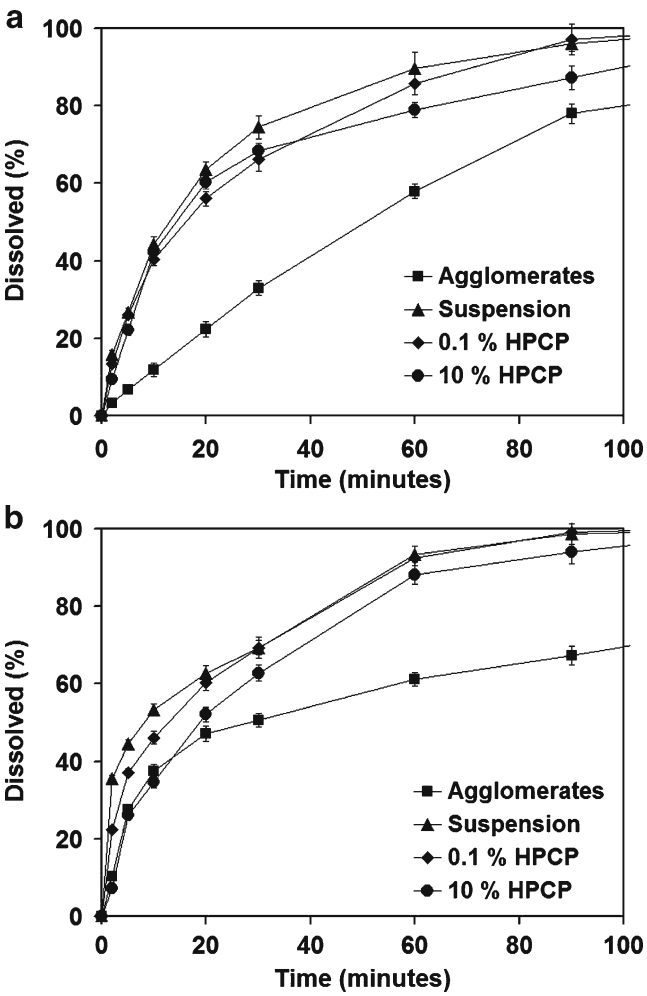

Fig. 7. Dissolution profiles for **a** furosemide and **b** griseofulvin from interactive mixtures prepared with the HPCP carrier compared with suspensions and drug powder agglomerates

amounts of both drugs were loaded onto the MCC granules (Table VI). However, at all the conditions studied, the amounts of the drugs that formed interactive mixtures with the HPCP carrier particles were significantly higher ($p<0.05$) than with sugar spheres (310%) or microcrystalline cellulose granules (320%). Statistical analysis showed that, for the same number of revolutions of the mixer, mixing time and speed did not influence the amount of both drugs coated onto the new carrier particles ($p>0.05$). When the loading capacities of HPCP− (zeta potential −129.66±4.13 mV) were compared with HPCP+ (zeta potential 100.09±2.80 mV) microcapsules, it was clear that the positively charged cholestyramine-containing microcapsules were able to carry even larger loads, 1.4 times, of the negatively charged drugs (zeta potentials listed in Table III).

In practice, interactive mixing is usually employed to prepare low-dose tablets or capsules. For these delivery systems, it is very important that the content uniformity of the tablets or capsules comply with compendial standards. In Table VI, the content uniformity (RSD, percent) of tablets prepared from interactive mixtures containing increasing concentrations of the drugs from 0.1 to 10% *w*/*v* is listed. To comply with USP standards, the RSD must be less than 2%. For both furosemide and griseofulvin up to 10% *w*/*v* of drug per mixture, the content uniformity of the tablets prepared with the HPCP carrier was <2%. In contrast, for tablets containing 5% and above furosemide the RSD was >2% for both the sugar spheres and the MCC granules. For griseofulvin tablets, the RSD was already >2% with a drug load of only 1% *w*/*v*. This illustrated that the HPCP microcapsule carrier particles were better at preparing homogenous interactive mixtures that could be used to prepare low-dose tablets with excellent content uniformity.

If interactive mixtures are used to prepare tablets and capsules, it is important to know the dissolution of the drug from these mixtures (6,22,23). Figure 7 shows the dissolution profiles of furosemide and griseofulvin from 0.1% *w* and 10% *w*/*v* interactive mixtures with the HPCP+ carrier particles compared with that of the aggregated drug powders and suspensions (6). Calculated similarity factors (f_2) showed that the dissolution of the drug agglomerates were significantly different from that of the suspensions, $f_2=27$ and 31 for furosemide and griseofulvin, respectively. However, the dissolution profiles of the 0.1% and 10% *w*/*v* mixtures of the drugs with the HPCP carrier were similar to that of suspensions of the drugs ($f_2>60$).

CONCLUSION

This study demonstrated that HPCP microcapsule carrier particles prepared by an ESE process have the advantage of improved loading capacity during an interactive mixing process compared with sugar beads and MCC granules. Although the loading capacity depended on the charge differences between the drugs and the carrier particles, both the positively and negatively charged carrier particles were able to carry significantly more drugs than the two traditional carriers sugar beads and MCC granules. In addition, these interactive mixtures are compressible and can be used to prepare tablets with better content uniformity and the dissolution of both drugs from these mixtures were similar to that of suspensions of the drugs.

ACKNOWLEDGMENT

We are grateful to the University of Wisconsin (USA) and the North-West University (RSA) for research support.

REFERENCES

1. Harnby N. An engineering view of pharmaceutical powder mixing. Pharm Sci Technol Today. 2000;3:303–9.
2. Fan LT, Chen YM, Lai FS. Recent developments in solids mixing. Pow Technol. 1990;61:255–87.
3. Hersey JA. Ordered mixing: a new concept in powder mixing practice. Powder Technol. 1975;11:41–4.
4. Egermann H. Effects of adhesion on mixing homogeneity, part I: ordered adhesion–random adhesion. Powder Technol. 1980;27:203–6.
5. Staniforth JN. Order out of chaos. J Pharm Pharmacol. 1987;39:329–34.
6. De Villiers MM, Van Der Watt JG. The measurement of mixture homogeneity and dissolution to predict the degree of drug agglomerate breakdown achieved through powder mixing. Pharm Res. 1994;11:1557–661.
7. Kulvanich P, Stewart PJ. The effect of particle size and concentration on the adhesive characteristics of a model drug–carrier interactive system. J Pharm Pharmcol. 1987;39:673–8.
8. Podczeck F. Particle adhesion in powder assemblies. Particle–particle adhesion in pharmaceutical powder handling. London: Imperial College Press; 1997.
9. Berard V, Lesniewska E, Andres C, Pertuy D, Laroche C, Pourcelot Y. Affinity scale between a carrier and a drug in DPI studied by atomic force microscopy. Int J Pharm. 2002;247:127–37.
10. De Villiers MM, Van der Watt JG, Lötter AP. Influence of surfactants and interactive mixing on the cohesive properties of a poorly wettable solid. Powd Technol. 1993;75:159–65.
11. De Villiers MM. Description of the kinetics of the deagglomeration of drug particle agglomerates during powder mixing. Int J Pharm. 1997;151:1–6.
12. De Villiers MM, Van Der Watt JG. Interactive mixing between agglomerated drug particles and coarse carrier particles. Drug Dev Ind Pharm. 1989;15:2055–61.
13. Song M, Li N, Sun S, De Villiers MM. Effect of processing variables on the release and particulate properties of sustained release amoxicillin microcapsules prepared by emulsion solvent evaporation. Die Pharm. 2005;60:278–82.
14. Song M, Li N, Sun S, Tiedt LR, Liebenberg W, De Villiers MM. Effect of viscosity and concentration of wall former, emulsifier and pore-inducer on the properties of amoxicillin microcapsules prepared by emulsion solvent evaporation. Il Farmaco. 2005;60:261–7.
15. Li SP, Kowalski CR, Feld KM, Grim WM. Recent advances in microencapsulation technology and equipment. Drug Dev Ind Pharm. 1998;14:353–76.
16. Kim BK, Hwang SJ, Park JB, Park HJ. Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method. J Microencap. 2002;19:811–22.
17. Herrmann J, Bodmeier R. Biodegradable somatostatin acetate containing microspheres prepared by various aqueous and non-aqueous solvent evaporation methods. Eur J Pharm Biopharm. 1998;45:75–82.
18. Benita S, editor. Microencapsulation: methods and industrial applications. New York: Marcel Dekker; 1996.
19. Obeidat WM, Price JC. Viscosity of polymer solution phase and other factors controlling the dissolution of theophylline microspheres prepared by the emulsion solvent evaporation method. J Microencap. 2003;20:57–65.
20. Simons SJR, Pepin X, Rossetti D. Predicting granule behavior through micro-mechanistic investigations. Powder Technol. 2003;72:463–75.

21. Marais AF, Song M, De Villiers MM. Effect of compression force, humidity and disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant. Trop J Pharm Res. 2003;2:125–35.
22. De Villiers MM, Van Der Watt JG. Dissolution from ordered mixtures: the effect of stirring rate and particle characteristics on the dissolution rate. Drug Dev Ind Pharm. 1989;15:621–7.
23. De Villiers MM. Influence of agglomeration of cohesive particles on the dissolution behavior of furosemide powder. Int J Pharm. 1996;136:175–9.
24. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. Pharm Technol. 1996;20:64–74.
25. Chang RK, Price JC, Whitworth CW. Control of drug release rates through the use of mixtures of polycaprolactone and cellulose propionate polymers. Pharm Technol. 1986;10:24–33.
26. Niazy EM. Bioavailability of meclofenamate from experimental sustained release microcapsules in beagle dogs. Int J Pharm. 1996;134:129–35.