Microparticles of Polyvinyl Alcohol for Nasal Delivery. I. Generation by Spray-Drying and Spray-Desolvation

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Spray-drying and spray-desolvation are described for the generation of polyvinyl alcohol microparticles intended for nasal administration. The spray-dried microparticles of polyvinyl alcohol were of an appropriate size distribution but consisted of hollow spheres, which made them unsuitable for nasal delivery, as rapid clearance and a varied deposition pattern would be expected. Microparticles were also produced by spraying polyvinyl alcohol (average molecular weight of 14,000) solution (12.5%, w/v) at 0.332 ml/min onto the surface of acetone (spray-desolvation). These microparticles were solid collapsed spheres with the desired size for nasal deposition (10–200 μm). This method can be applied to encapsulation of drugs that are heat labile such as peptides and proteins.

KEY WORDS: microparticles; microspheres; nasal delivery; spray-drying; spray-desolvation; polyvinyl alcohol.

INTRODUCTION

Water-soluble polymers have been used extensively to prepare pharmaceutical dosage forms (1) that may serve as carriers for peptides for nasal administration (2). The nasal absorption of peptides embedded in polymer matrices has been shown to be enhanced through retardation of nasal mucociliary clearance (3). Other possible enhancement mechanisms include increased concentration gradient or decreased diffusion path for peptide absorption. However, reduction in mucociliary clearance rate has been predicted to be a good approach toward achievement of reproducible bioavailability of nasally administered systemic drugs (4). Microparticles with a diameter of about 50 μm are expected to deposit in the nasal cavity (5,6), while microparticles with a diameter under 10 μm can escape the filtering system of the nose and deposit in the lower airways. Lewis and Kellaway (7) stated that microparticles larger than 200 μm in diameter will not be retained in the nose after nasal administration.

The polymer carrier chosen for this study was polyvinyl alcohol (PVA). This material, used widely in ophthalmic preparations, is a swellable hydrophilic polymer whose physical properties depend on molecular weight, degree of hydrolysis, cross-linking density, and crystallinity (8). Various workers have reported the use of PVA in the coating of dispersed materials through phase separation (9), spray-drying (10), spray-embedding (11), and spray-polycondensation (12,13). A simple spray-drying method is described in this paper.

Reyes (14) described a method of obtaining microcapsules by complex coacervation with an emulsion of PVA containing a drug. The addition of inorganic salts or cooling gelled the emulsion, followed by desolvation, separation, and drying. However, traces of residual solvent may limit the applicability of this method to dosage forms intended for the nasal mucosa. The emulsification process may be omitted, as PVA solution coacervates in the presence of dehydrating liquid such as propan-1-ol (15). This procedure provides the basis for our second method of microparticle generation.

Spray-desolvation involves spraying a polymer solution onto the surface of a dehydrating liquid. The formation of microparticles is due largely to precipitation of PVA from the droplets, as PVA is insoluble in the solvent. Interfacial precipitation occurs first, giving rise to a smooth shell, followed by continual removal of water from the microparticle through the shell until equilibrium is reached. The rate of precipitation depends on the solvent's affinity to the water in the droplets. The gradual precipitation of PVA in the droplets and the reduction in volume of the microparticles lead to their collapse. Patents on related techniques have been assigned to Hecker and Hawks (16) and Pasin (17).

A comparison of the experimental conditions, physical characteristics of PVA microparticles, and percentage of particles with a diameter of 10 to 200 μm generated between spray-drying and spray-desolvation is described.

MATERIALS AND METHODS

Materials. Polyvinyl alcohols (PVA) with average molecular weights of 14,000 (PVA-14) and 40,000 (PVA-40) were purchased from BDH Chemicals Ltd. (Poole, England) and Sigma Chemical Company (St. Louis, MO), respectively. The organic solvents were of analytical grade and used as received.

Spray-Drying. The spray solutions were prepared by dissolving an appropriate amount of PVA in 30 ml of ethanol/water (1:1, v/v) with gentle heating under reflux and agitation. The solutions were cooled and then sprayed using a glass Bernoulli-type nebulizer in a drying chamber (0.5 × 0.6 × 1.5 m) lined with plastic sheets (Fig. 1). A fan was fitted to drive heated air toward the floor of the chamber, forming an ellipsoid pathway. The air saturated with solvent was removed using a vacuum cleaner (via a fine screen) attached to the drier.

The spraying was carried out from the opposite end of the chamber at a height of 15 cm and an angle of 15° from the floor. The airflow was adjusted to allow spraying at 2.5 ml/min, with the temperature within the chamber maintained at 50 ± 1°C by a thermostat. The dried microparticles were collected from the plastic coverings and their moisture content was determined using a Cenco Moisture Balance (John Morris Sci., Australia). The dried microparticles were stored over desiccant to prevent absorption of moisture from the atmosphere.

Various modifications to the conditions of spraying were made through reduction of spray rate, lowering of in-

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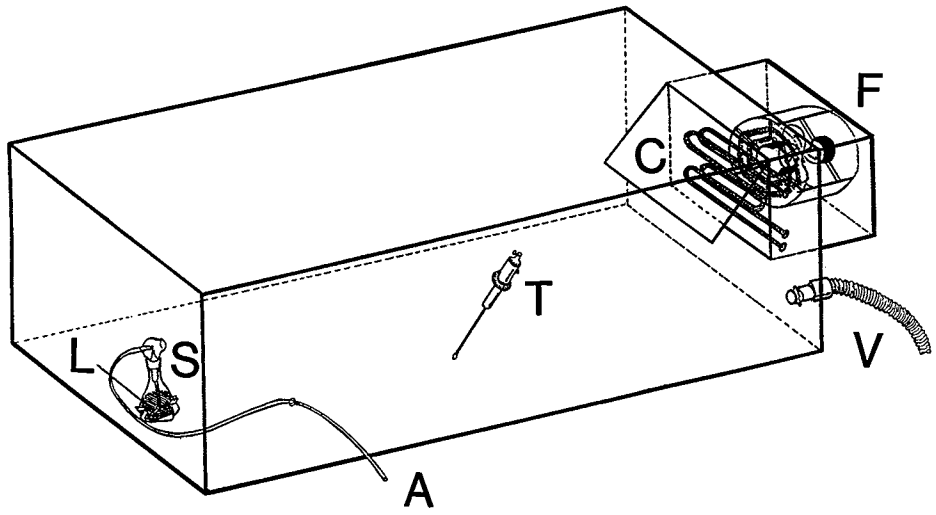

Fig. 1. A schematic representation of the spray-drier. The interior of the drier was lined with plastic sheets. A, supply of air for spraying; C, heating elements; F, fan to blow heated air into the drier and to generate a current within; L, spray liquid; S, glass Bernoulli-type nebulizer, spray rate of 2.5 ml/min; T, thermostat to regulate temperature of the drier at 50°C; V, vacuum cleaner to draw air out of the drier.

terior temperature to 40°C, and addition of one of the following substances: lactose (10 or 20%, w/v), sodium chloride (10%, w/v), glycerol (5, 10, and 20%, v/v), and propylene glycol (10%, v/v) to the spray solutions to study their effects on the resulting microparticles.

Spray-Desolvation. The procedure was carried out by spraying aqueous solutions of PVA-14 using a pneumatic nozzle (Glatt Haltingen Fluid-Bed Drier, Model Uni, Binzem/Baden, Germany), from a height of 8.3 cm onto the surface of acetone (Fig. 2). Various solutions (10 ml) of PVA (10 to 30%, w/v) were sprayed onto acetone (760 ml) in a glass beaker (diameter, 18.5 cm) at room temperature at a flow rate of 0.332 ml/min using a peristaltic pump. The spray was directed toward the center of the beaker for 18 min and the acetone stirred continuously by two magnetic stirrers. The airflow was maintained at 12.5 L/min. When spraying was completed, the microparticles were recovered by vacuum filtration through a Whatman No. 541 filter paper (previously soaked in acetone to prevent adhesion of the particles to the paper), washed twice with 25 ml of acetone, and dried to constant weight under vacuum at room temperature.

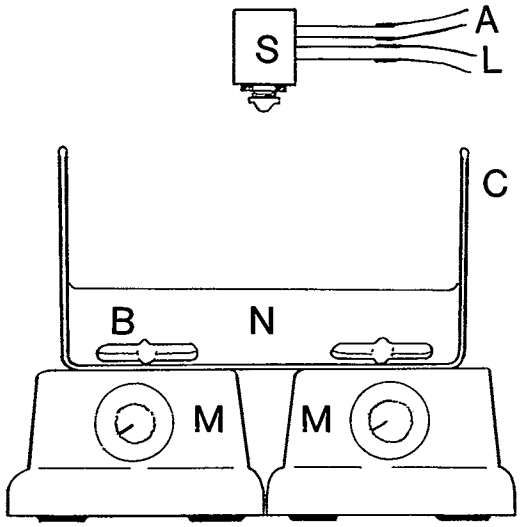

Fig. 2. A schematic representation of the spray-desolvation apparatus. A, airflow maintained at 12.5 L/min; B, stirring bar; C, glass beaker of diameter 18.5 cm; L, supply of spray solution containing polyvinyl alcohol by a peristaltic pump at a rate of 0.332 ml/min; M, magnetic stirrer; N, acetone (760 ml); S, pneumatic spray nozzle from Glatt-Haltingen Fluid-Bed Drier, Model Uni (Binzem/Baden, Germany).

Particle Size Analysis. The particle size of spray-dried microparticles was measured using a computer-assisted image analysis system (Dapple System, Sunnyvale, CA) (18). Small random samples were taken and spread on microscopic slides, which were divided into 1750 squares of equal size. The microparticles in 20 to 30 random squares were sized until the following criteria for geometric mean diameter (X_g) and geometric standard deviation (σ_g) were met in order to achieve adequate precision (19). The n_1 represents the number of squares measured and $n_2 = n_1 + 5$.

$$\text{Criterion 1: } \frac{X_g(n_2) - X_g(n_1)}{X_g(n_1)} \times 100\% \leq 5\%$$

$$\text{Criterion 2: } \frac{\sigma_g(n_2) - \sigma_g(n_1)}{\sigma_g(n_1)} \times 100\% \leq 5\%$$

These criteria were normally met with about 500 to 600 microparticles.

An optical scattering method based on the Fraunhöffer optical diffraction principle (Malvern Particles and Droplets Sizer, Model 2600c, Malvern Instruments, Malvern, England), fitted with a 300-mm Fourier transform lens and with the beam length maintained at 50 mm, was used to measure the spray-desolvated microparticle dispersion in acetone, which was stirred continuously for 5 min to eliminate aggregation.

Scanning Electron Microscopy. The surface morphology was examined by scanning electron microscopy (Jeol JSM 35C, Japan). The samples were mounted onto sample stubs using double-sided adhesive tape and kept in a desiccator for 24 hr before coating with gold under vacuum to a thickness of 200 Å. The electron beam was accelerated at 25 kV and both secondary and back-scattered electron detectors were activated to obtain an image of good illumination and resolution.

RESULTS AND DISCUSSION

Spray-Drying

As the droplets were generated in the heated environment, evaporation of surface solvent occurred, rapidly forming partially dried microparticles. The use of a cosolvent of ethanol and water (1:1, v/v) enhanced drying. With a reduction in weight, the droplets were carried in the air current until complete dryness was achieved before their deposition on the plastic covering. A yield as high as 50% was achievable (Table I). The microparticles contained 5.1 ± 0.4% moisture.

The microparticles formed were spherical in appearance and highly aggregated with a very low density. Their particle size distribution was log-normal. The geometric mean diameters of the microparticles made from the spray solution of concentrations 5 and 8% (w/v) PVA-14 were 17 and 29 μm, respectively. The 8% (w/v) solution of PVA-40 gave only a 2% yield because the shearing force was not strong enough to atomize the polymer solution of high viscosity, and therefore mostly elongated fibers were formed as reported by Nolen and Kool (20).

A combination of PVA-14 and PVA-40 in various proportions with a total concentration of 8% (w/v) yielded microparticles (axial ratios between 1.0 and 1.3) of geometric mean diameters between 46 and 55 μm. Maximal yield was achieved with a 1:1 (w/w) mixture of PVA-14 and PVA-40 in ethanol/water (1:1, v/v). There was very little difference in the size of microparticles for different PVA-14/PVA-40 ratios but a reduction in the yield was observed with higher proportions of PVA-40 to PVA-14 (Table I). This may be explained by the formation of larger droplets which were not dried efficiently. Under the scanning electron microscope, the extensively aggregated microparticles had an apparently smooth and round surface. Quite a large number of ruptured cenospheres and microparticles with buds was found (Fig. 3).

The particles were observed to float after the addition of a drop of water under a light microscope, confirming that nearly all the microparticles generated by spray-drying were hollow spheres. Similar observations were reported by Seager (10) and Nolen and Kool (20).

In the process of drying, the surface solvent is evaporated quickly, leading to formation of a tough shell of solid PVA. The solvent in the droplets must diffuse through this shell. With the diffusion of the solvent occurring at a much slower rate than the transfer of heat to the interior of the droplets, there is a buildup of pressure within the shell, causing expansion of the droplet. The shell becomes thinner, allowing faster diffusion (21). Since the shell is poorly permeable, it may form buds or rupture, producing pores on the original spheres.

A reduction of the temperature by 10°C was attempted, to allow slower drying to generate collapsed spheres. There was no observable difference in either appearance or geometric mean diameters. An increase in concentration of the spray solution was not feasible, as dendritic particles were formed.

Addition of crystalline substances such as lactose and sodium chloride to PVA solutions did not succeed in making the shell more porous through precipitation of these additives. Addition of more lactose and sodium chloride, which

Table I. Micromeritics of the Particles Made by Spray-Drying Using Various Solutions of Polyvinyl Alcohol[a]

Batch no.	PVA-14/ PVA-40	Conc. (%, w/v)	X_g (μm)	σ_g	Axial ratio	% yield
1	5:0	5	17.3	2.1	1.0	10
2	8:0	8	28.6	2.2	1.5	42
3	10:0	10	NP	NP	NP	0
4	0:8	8	55.3	2.1	1.3	2
5	5:3	8	54.5	2.3	1.0	46
6	1:1	8	52.1	2.2	1.1	50
7	3:5	8	53.2	2.1	1.1	44
8	1:3	8	50.3	2.0	1.0	31
9	1:7	8	45.6	2.3	1.2	14
10 (a)	1:1	8	48.4	2.2	1.0	45
11 (b)	1:1	8	47.1	2.1	1.2	47
12 (c)	1:1	8	51.4	2.2	1.1	40
13 (d)	1:1	8	53.2	2.2	1.1	10
14 (e–h)	1:1	8	NP	NP	NP	0

[a] X_g, geometric mean diameter; σ_g, geometric standard deviation; axial ratio, ratio of the longest projected diameter to the shortest diameter; a, a 10°C reduction in temperature within the spray drier; b and c, addition of 10 and 20% (w/v) lactose to the spray solution, respectively; d, addition of 10% (w/v) NaCl to the spray solution; e, f, and g, addition of 5, 10, and 20% (v/v) glycerol to the spray solution, respectively; h, addition of 10% (v/v) propylene glycol; NP, no particle produced.

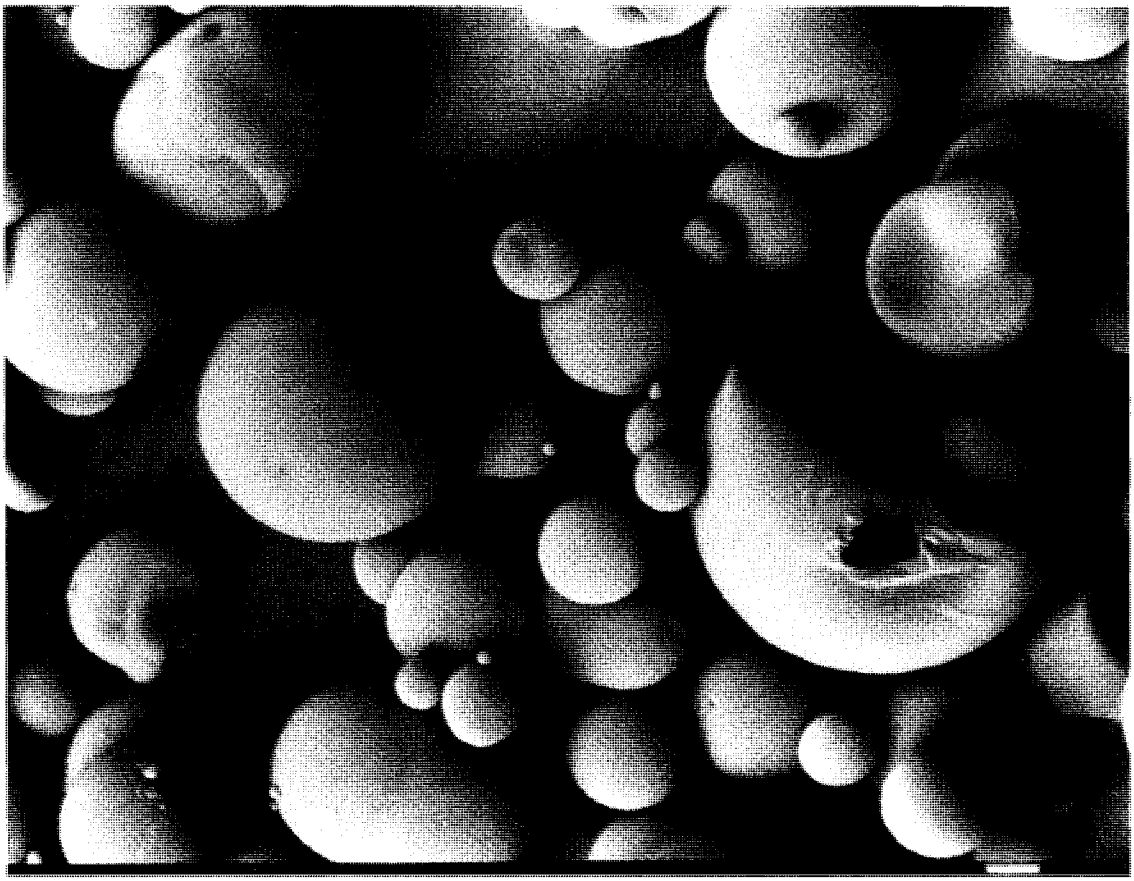

Fig. 3. A scanning electron micrograph of spray-dried microparticles (batch 6, Table I) showing complete spheres and buds or pores on particles. A ruptured particle can also be seen. Bar at bottom right represents 100 μm.

may be effective in reducing shell formation, is undesirable because it may affect nasal functions by disturbing tonicity and causing irritation.

Microparticles formed after the addition of a plasticizer such as glycerol or propylene glycol had fewer hollow microparticles, but these hygroscopic additives impaired drying. These difficulties were not overcome by operating the drier over wider ranges of feed rates and interior temperatures.

A polymer solution that is very dilute could form solid microparticles or thin, collapsed shells (20), but with a reduction in size, significant pulmonary deposition may occur following nasal administration.

Spray-Desolvation

Scanning electron microscopy showed the microparticles to be roughly spherical, with dents on the surface but pore-free (Fig. 4) and free-flowing. The highest yield with this technique was 74.1%. For any one concentration in the range investigated, particle size distributions were not dependent on spray rates (the range tested was 0.083 to 0.414 ml/min).

Particle size analysis showed log-normal distributions for all batches of microparticles. Table II shows a summary of the geometric mean diameter (X_g), geometric standard deviation (σ_g), percentage of microparticles with a size range between 10 and 200 μm, and percentage of microparticles with a diameter less than 10 μm for different batches of microparticles generated. The geometric mean diameter of these particles ranged from 51 to 111 μm for PVA-14 solution with a concentration of 10 to 30% (w/v).

A correlation between the geometric mean diameters and the concentration of the spray solutions ($Y = 2.425X + 26.558$, $r = 0.880$) was established. However, the particle size distributions for the 10 and 1.5% (w/v) solutions of PVA-14 were similar. The geometric standard deviations ranged from 1 to 2, indicating relatively narrow particle size distributions, with the fraction of microparticles between 10 and 200 μm in diameter as high as 95% for spray solutions of lower concentrations (10 and 12.5%, w/v). Removal of microparticles outside this size range may be unnecessary before nasal administration. The percentage decreases to less than 90% for the PVA-14 solution with a concentration above 25.0% (w/v). Microparticles exceeding 200 μm in diameter tend to deposit in the anterior, relatively nonvascular, regions of the nose, which would be likely to result in the loss of bioavailability of the drug embedded in them. On the other hand, a large proportion of microparticles smaller than 10 μm in diameter is expected to escape nasal filtration. The percentage of these microparticles was 1.3% for the PVA-14 solutions of low concentrations (10 and 12.5%, w/v). With higher concentrations of spray solution, this percentage is halved with a concurrent increase in the geometric mean

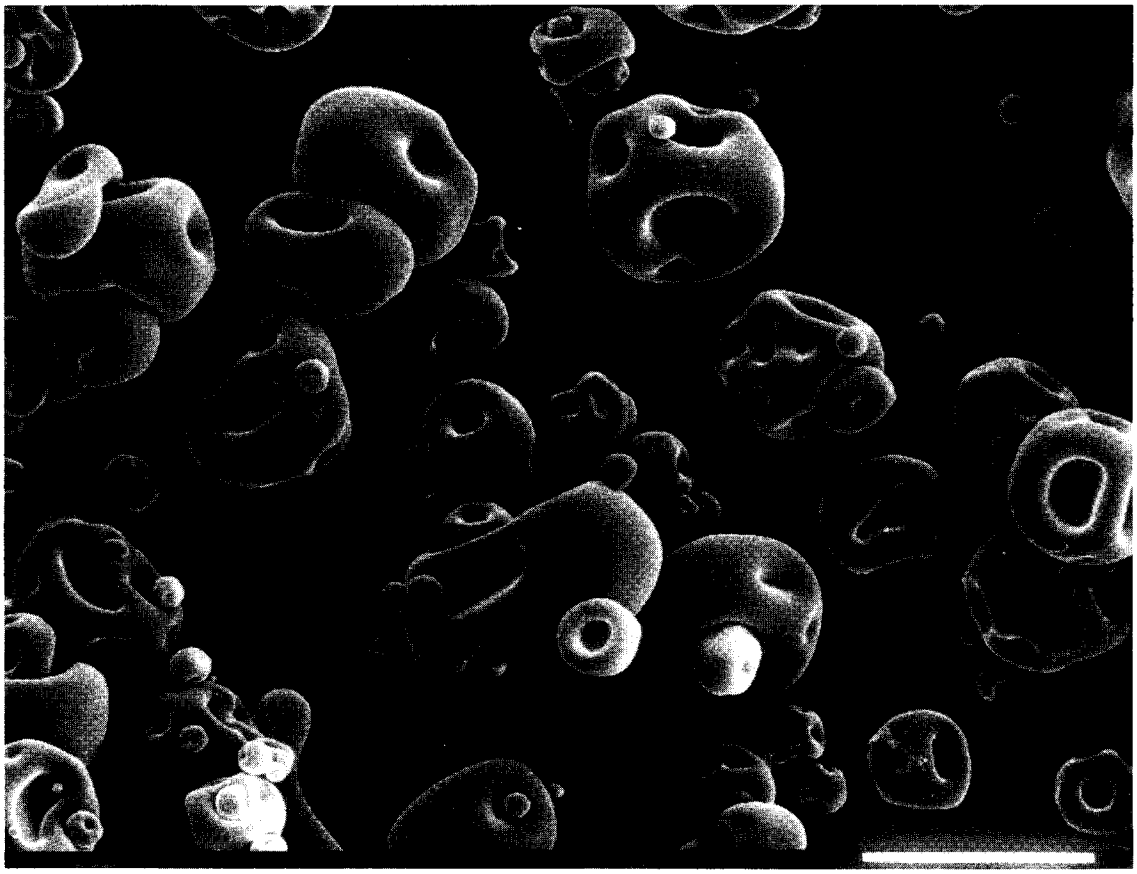

Fig. 4. A scanning electron micrograph of spray-desolvated particles generated from PVA-14 solution (12.5%, w/v) at 0.332 ml/min showing dented surfaces. Bar at bottom right represents 100 μm.

diameter, indicating a general trend toward formation of larger microparticles. The solution of PVA-14 with a concentration of 12.5% (w/v) appears optimal for generation of microparticles for nasal administration.

Particle generation using spray-drying involves fewer steps but above room temperature is necessary for drying. The experimental parameters can be varied to achieve particles with the desired size distribution. However, with non-

Table II. The Micromeritics of Microparticles Generated at a Spray Rate of 0.332 ml/min from a Height of 8.3 cm onto Acetone[a]

Concentration of PVA solution (%, w/v)	n	X_g μm (SD)	σ_g (SD)	% P (SD)	% Q (SD)
10.0	3	53.0	1.8	95.0	1.2
		(2.8)	(0.2)	(2.1)	(0.3)
12.5	3	51.6	1.7	94.9	1.3
		(16.4)	(0.1)	(3.0)	(0.7)
15.0	3	68.0	1.7	94.0	0.9
		(3.6)	(0.1)	(1.1)	(0.3)
17.5	3	75.8	1.6	94.8	0.6
		(10.0)	(0.1)	(0.5)	(0.2)
20.0	3	71.1	1.7	93.6	0.7
		(8.1)	(0.1)	(1.4)	(0.3)
22.5	1	69.9	1.7	93.9	0.3
25.0	1	80.5	2.0	85.6	0.5
27.5	1	111.3	1.7	79.5	0.5
30.0	1	94.4	1.7	88.0	0.6

[a] X_g, geometric mean diameter; σ_g, geometric standard deviation; n, number of batches; SD, standard deviation of the mean of n measurements; P, percentage of microparticles 10 to 200 μm in diameter; Q, percentgae of microparticles under 10 μm in diameter.

crystalline materials such as PVA spray-drying tends to generate hollow, aggregated spheres which are not readily redispersed. Spray-desolvation, on the other hand, uses milder experimental conditions. Hence, it holds promise for drugs that are heat labile. The drug can be suspended or dissolved in the absence or presence of absorption enhancers (22) in cooled PVA-14 solution before spraying, to yield microcapsules or matrix microparticles, respectively (Ting *et al.*, in preparation). The microparticles generated are collapsed spheres which are readily redispersed.

The spray-desolvated microparticles are currently being investigated for their swelling and dissolution characteristics as well as for peptide loading.

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