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Note

Influence of polyvinylpyrrolidone on aggregation propensity of coated spheroids

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Abstract

The influence of polyvinylpyrrolidone (PVP), a commonly used binder and adhesive, on the aggregation of spheroids coated with hydroxypropylmethylcellulose (HPMC) was studied. The aggregation propensities of spheroids coated by HPMC alone and by HPMC with polyethylene glycol (PEG) were compared with those coated by HPMC with PVP and the viscosity of the coating solutions determined. The coating was conducted at a maximum spray rate of 11 g/min to avoid premature termination of the coating process at higher spray rates due to uncontrollable aggregation of spheroids. PVP was able to reduce the extent of aggregation of spheroids. It was more effective in reducing spheroid aggregation than PEG. The reduction in spheroid aggregation propensity was ascribed to viscosity lowering effects of PVP. The viscosity of the coating solutions determined over the temperature range of 28–58 °C was found to increase in the following order: HPMC–PVP < HPMC–PEG < HPMC. © 2002 Elsevier Science B.V. All rights reserved.

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Hydroxypropylmethylcellulose (HPMC) is commonly employed as a coating polymer (Seitz, 1988; Maffione et al., 1993; Heng et al., 1996). A major problem in coating of spheroids is the tendency of spheroids to aggregate during coating due to the viscous nature of the coating solution. Aggregation of spheroids prevents the formation of uniform coating, which is crucial for precise control of drug release. Spheroid aggregation also hinders good flow pattern of spheroids in the coating chamber and may cause premature termination of the coating process. Polyvinylpyrrolidone (PVP) has been used as a binder in granulation and tabletting processes due to its good binding property (Wikberg and Alderborn, 1992; Wan et al., 1996). Previous studies in our laboratory demonstrated that PVP had the ability to lower the viscosity of HPMC coating solution (Chua, 2000) and that the propensity of particle aggregation was predominantly affected by the viscosity of the added liquid (Wong et al., 1999). PVP was, therefore, postulated to be useful in reducing aggregation of spheroids during coating. Hence, this study aimed to investigate the

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level of spheroid aggregation in a coating process using HPMC (Metolose 65 SH, 400 cps, Shin-Etsu Chemical, Japan) alone and in combination with various amounts of PVP (C15, average molecular weight = 9200 Da, ISP, USA). The influence of PVP on the aggregation propensity of spheroids was compared with that of polyethylene glycol (PEG, Lutrol E4000, average molecular weight = 3900 Da, BASF, Germany). The relationship between the aggregation propensity of spheroids and the viscosity of coating solution was examined.

The spheroids used as cores in the coating process were prepared from lactose (200 M, Pharmatose, DMV, The Netherlands) and microcrystalline cellulose (MCC, Avicel PH-101, Asahi Chemical, Japan). A lactose–MCC (ratio 3:1) wet mass (40% of distilled water, expressed as the percentage weight of lactose–MCC powder) was extruded with a 1 mm sieve (E140, Aeromatic-Fielder, UK) and spheronised (S320, Aeromatic-Fielder, UK) at 1000 rpm for 10 min. The formed spheroids were oven-dried at 60 °C for 24 h and the size fraction between 0.7 and 1 mm was used for coating. The coating of spheroids was conducted using 2%w/w HPMC solution throughout the study. The HPMC solution was prepared by dispersing the HPMC in hot distilled water (80 °C) and the dispersion was left to stand in the refrigerator for 24 h before use. HPMC–PVP and HPMC–PEG solutions were prepared by adding the required amount of PVP or PEG into HPMC solutions. The concentrations of PVP and PEG were expressed as the percentage weight of HPMC solution. Two hundred grams of coating

Table 1
Processing parameters employed in coating

Processing parameter	Setting
Fluidising air flow rate (m^3/h)	80–100
Inlet air temperature (°C)	60
Spray nozzle diameter (mm)	0.5
Dead space (mm)	7.0
Atomising air pressure (bar)	1.0
Spray rate (g/min)	6–14
Drying time (min)	1.0
Drying temperature (°C)	60

Table 2
Percentage aggregation of spheroids coated with HPMC at different spray rates

Spray rate (g/min)	Aggregate (%w/w)	Total coating time (min)
6	14.70 ± 1.99	33.33
9	52.68 ± 2.33	22.22
11	57.00 ± 5.04	18.18
12	Premature termination	–
14	Premature termination	–

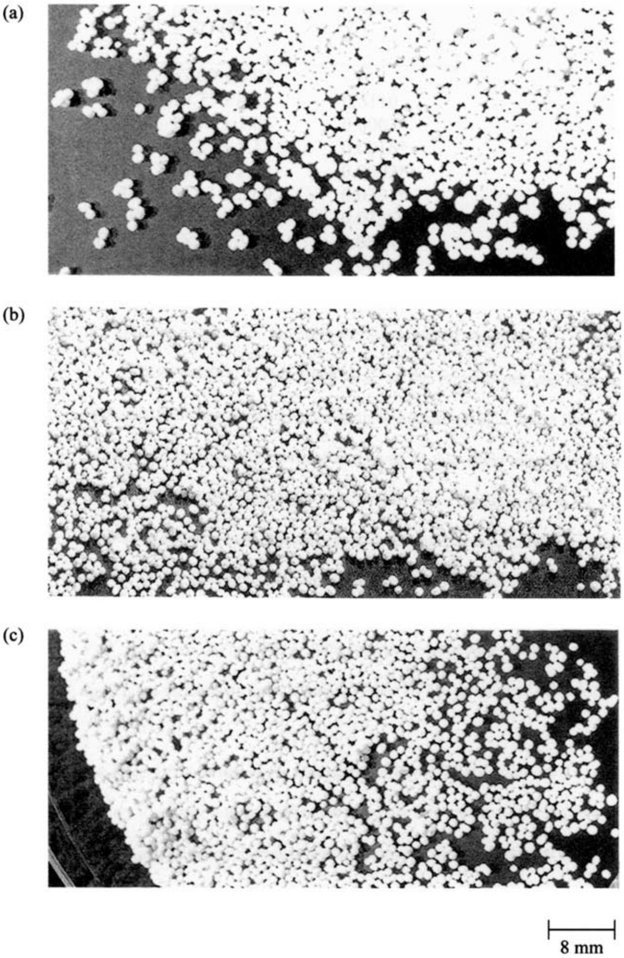

Fig. 1. Photographs of (a) HPMC, (b) HPMC–PVP and (c) HPMC–PEG coated spheroids.

Table 3
Percentage aggregation of spheroids coated by HPMC with various concentrations of PVP and PEG

Composition of coating solution	PVP/PEG concentration (%w/w)	Aggregate (%w/w)	*P* value[a]
HPMC	0	57.00 ± 5.04	–
HPMC + PVP	0.2	59.75 ± 4.29	0.5110
HPMC + PVP	0.4	19.76 ± 1.86	0.0003[b]
HPMC + PVP	0.6	25.27 ± 5.12	0.0016[b]
HPMC + PEG	0.2	46.13 ± 2.69	0.0301[b]
HPMC + PEG	0.4	48.76 ± 3.05	0.0725[b]
HPMC + PEG	0.6	65.90 ± 3.09	0.0594[c]

[a] Student's *t*-test was performed on percentage aggregation of HPMC–PVP and HPMC–PEG coated spheroids against HPMC coated spheroids.

[b] Significantly less aggregation.

[c] Significantly more aggregation.

solution were sprayed onto 200 g of spheroids using a bottom-spray Wurster coater (Strea-1, Aeromatic AG, Switzerland). The processing parameters employed are summarised in Table 1. A spray rate of 11 g/min was used unless otherwise stated. After coating, the spheroids were subjected to only another minute of fluid-bed drying and further drying was carried out in an oven at 40 °C for 24 h. The experiments were carried out in at least triplicates for each coating formula. Aggregated spheroids were taken as the fraction larger than 1 mm. The aggregation propensity of spheroids was the quotient of the weight of spheroids with diameter greater than 1 mm over the total spheroid weight, expressed as a percentage. The viscosity of the coating solution was determined using a suspended level viscometer (size # 3, BP) in a thermostatically controlled water bath. A higher viscosity was indicated by a longer flow time. At least duplicates were carried out and the results averaged. All experiments were subjected to statistical treatment using Student's *t*-test. The level of significance was set at 0.10.

The rate and extent of spheroid aggregation increased significantly with increase in spray rate of the 2%w/w HPMC solution from 6 to 11 g/min (Table 2, $P < 0.10$). At spray rates of 12 and 14 g/min, premature termination of the coating process was necessary as aggregates grew rapidly in size and eventually became too heavy to be fluidised.

At spray rate of 11 g/min, coating of spheroids by HPMC solution gave rise to an average of 57.00%w/w of aggregates. These aggregates consisted of binary or multiple clusters of spheroids (Fig. 1a). The aggregation propensity of spheroids decreased when certain amounts of PVP or PEG were incorporated into the HPMC solutions (Table 3). A sharp decrease in the percentage of aggregates from 57.00 to 19.76%w/w was effected when 0.4%w/w of PVP was employed. The addition of PVP in concentrations ranging from 0.4 to 0.6%w/w gave rise to a markedly lower percentage of spheroids aggregation than that of PEG. At 0.6%w/w of PEG, the percentage of aggregates

Table 4
Flow time of 2%w/w HPMC solution without and with 0.4%w/w of PVP or PEG at various temperatures

Temperature (°C)	Flow time (s)		
	HPMC	HPMC + PVP	HPMC + PEG
28	202.00 ± 2.82	189.00 ± 1.41	194.00 ± 0.71
37	160.00 ± 2.82	136.50 ± 0.71	144.00 ± 0.14
45	124.00 ± 1.41	99.50 ± 0.71	106.00 ± 0.14
53	90.00 ± 1.41	72.00 ± 0.71	74.00 ± 0.14
58	70.00 ± 4.24	55.00 ± 0.28	60.10 ± 0.28
60	58.40 ± 4.60	49.20 ± 0.48	48.40 ± 1.55
62	60.00 ± 0.57	48.40 ± 0.14	48.00 ± 0.08
63	65.00 ± 1.55	100.00 ± 0.71	52.30 ± 0.14
64	73.00 ± 1.41	137.00 ± 1.31	72.12 ± 0.17

obtained was significantly higher than that of HPMC alone ($P < 0.10$). Fig. 1b and c shows the batches of spheroids prepared using HPMC with 0.4%w/w of PVP and PEG, respectively. These coated spheroids were free flowing, discrete and showed marked reduction in the level of aggregation.

The temperature of the inlet air was kept at 60 °C throughout the coating process. However, the temperature of the atomised coating solution would be lower than that of inlet air. Thus, the marked differences in spheroid aggregation propensity might not necessarily be inferred by the viscosity differences between the corresponding batches of HPMC–PVP and HPMC–PEG solutions at 60 °C (Table 4). HPMC–PVP solutions had lower viscosities than the corresponding HPMC–PEG solutions at temperatures lower than 60 °C (28–58 °C). Both were less viscous than HPMC solution at the same range of temperatures (Table 4). The differences in the aggregation propensity of spheroids could be attributed to the effect of viscosity lowering of the coating solution.

PVP was able to reduce the aggregation propensity of spheroids during coating. It was more effective as an anti-spheroid aggregation agent than PEG. The reduction in spheroid aggregation propensity could be ascribed to viscosity lowering effects of PVP.

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