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Dry Coating of Soft Gelatin Capsules with HPMCAS

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Dry coating is an innovative powder-layering technique that enables the formation of coatings on solid dosage forms with no need for using water or organic solvents. This technique envisages the distribution of polymer powder blends onto substrate cores and the concurrent or alternate nebulization of liquid plasticizers. In th*is* work, a dry coating process based on hydroxypropyl methylcellulose acetate succinate (HPMCAS) was set up in a rotary fluid bed equipment to prepare enteric-coated soft gelatin capsules. Promising results were obtained in terms of process feasibility and product characteristics, thus suggesting the possibility of advantageous applications for the investigated technique when dealing with gelatin capsule substrates.

Keywords dry coating; gastric resistance; HPMCAS; soft gelatin capsule; rotary fluid bed

INTRODUCTION

Coating techniques for solid dosage forms are generally based on the use of polymeric materials in aqueous or organic vehicles. However, when aqueous solutions or dispersions are employed, time- and energy-consuming drying phases are required and compatibility as well as stability problems might arise. On the contrary, the use of organic solvents may result in toxicological, environmental, and safety-related drawbacks, with possible repercussions on the manufacturing costs (Cunningham & Fegely, 2001; Nagai, Obara, Kokubo, & Hoshi, 1997). Consequently, remarkable advantages could reasonably be expected from the avoidance of both aqueous and organic solvents in pharmaceutical coating processes. For this purpose, powder-layering techniques, which involve the deposition of coating particles directly onto solid substrates, may represent a valid alternative to spray-coating procedures even when a binding solution is needed to promote particle adhesion (Bodmeier & McGinity, 2005; Cerea, Zheng, Young, & McGinity, 2004; Gupta, Beckert, & Price, 2001; Hogan, Page, Reeves, & Staniforth, 1996; Jarvis et al., 2005; Nastruzzi et al., 2000; Zheng, Cerea, Sauer, & McGinity, 2004). Recently, a powder-layering technique involving liquid plasticizers to enable the application of the coating powder was proposed and generally referred to in the literature as dry coating (Kablitz, Harder, & Urbanetz, 2006; Obara, Maruyama, Nishiyama, & Kokubo, 1999; Pearnchob & Bodmeier, 2003). When aqueous solvents are completely avoided, powder-layering becomes the technique of choice for active ingredients susceptible to water degradation. In this respect, dry coating was also proposed as a promising technique when dealing with nutraceuticals, functional foods, enzymes, and seeds (Ivanova, Teunou, & Poncelet, 2005).

As far as dry coating is concerned, different polymeric materials and several types of equipment were investigated, some of which required purposely adapted powder-feeding devices. In particular, the dry coating of tablets and pellets using the enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS) was already proven to be a viable alternative to the aqueous-based coating procedure with remarkable advantages in terms of process time (Kablitz et al., 2006; Obara et al., 1999).

Spray-coating with aqueous film-forming systems can be especially critical when dealing with capsules considering the particular characteristics of the gelatin substrate, which requires an attentive adjustment of the operating parameters in order to enable efficient drying phases on the one hand and preserve the core integrity on the other (Felton & McGinity, 2003; Felton et al., 1995; Pissinati & Oliveira, 2003). Based on these premises, the aim of the work was to evaluate the feasibility and possible outcome of the application of the enteric polymer HPMCAS onto soft gelatin capsules by the recently proposed dry coating technique.

MATERIALS

HPMCAS (Aqoat® grade MF, Shin–Etsu, Seppic Italia, Milan, I; particle size: 10% <1 μm; 50% <5 μm; 90% <10 μm); triethyl citrate (TEC, Fluka Chemie, Buchs, CH); acetylated monoglyceride (AcGlyc, Cetodan® type 90-40, Seppic Italia, Milan, I); talc (Ph.Eur. grade; Carlo Erba Reagenti, Milan, I); copovidone (Kollidon VA64, BASF Italia, Cesano Maderno, Milan, I).

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Round- and oval-shaped soft gelatin capsules (size and shape 2 round C and 5 oval, respectively) were kindly provided by Pharmagel, Lodi, I. Round capsules were filled with acetaminophen (C.F.M., Milan, I) 38.0%, polyethylene glycol (PEG) 400 (Dow Chemical, Midland, MI, USA) 59.5%, and PEG 4000 (Dow Chemical) 2.5%, and oval capsules with acetaminophen 33.0%, PEG 400 64.5%, and PEG 3350 (Dow Chemical) 2.5%. Round capsule cores filled with mineral oil were used as placebo for preliminary trials. The shell composition was 43.2% gelatin (175 bloom, type B—USP 29; Figli di Guido Lapi, Castelfranco di Sotto, Pisa, I), 32.0% distilled water, 24.2% polyols solution (Anidrisorb® 85/70, Roquette, Cassano Spinola, Alessandria, I), 0.6% red iron oxide for round-shaped capsules, and 45.0% gelatin, 29.3% distilled water, 25.0% Anidrisorb® 85/70, 0.4% red iron oxide, and 0.3% black iron oxide for oval-shaped capsules.

METHODS

Capsule cores were checked for weight (222 ± 15, 500 ± 11, and 225 ± 13 mg for round, oval, and placebo cores, respectively) and disintegration time (<5 min).

Prior to dry coating, a sealing film (≅0.5 mg/cm^2) was applied to soft gelatin capsules by a conventional spray-coating method using a 10% (wt/wt) solution of copovidone in ethanol: isopropanol 1: 1 mixture (Buhler, 2003).

The dry coating process was performed on 1,100 g batches in a tangential-spray rotary fluid bed (GPCG 1.1 Glatt® GmbH, Binzen, D) equipped with a single-screw powder feeder and a concentric three-way port nozzle. HPMCAS and talc blends were used as coating powders, whereas TEC or mixtures of TEC and AcGlyc were sprayed as a liquid plasticizer. The film formation was attained after a curing period inside the coating chamber. The process yield (%) was determined by dividing the measured total weight of the coated units by their theoretical weight calculated on the basis of the core, powder, and liquid amounts employed during the coating process.

The weight gain (w.g.) obtained after coating was determined by subtracting the mean weight of the cores from that of the coated units (n = 20) expressed in percentage.

The coating thickness was measured on cross-sectioned unit photomicrographs acquired by an environmental scanning electron microscope (n = 3; ESEM, XL30 ESEM LaB6, FEI Company, Eindhoven, NL).

Release tests were carried out by a USP 29 paddle apparatus (Dissolution System 2100B, Distek, North Brunswick, NJ, USA) at the stirring rate of 100 rpm according to Method B. The employed media were 1,000 mL of HCl 0.1 N at 37 ± 0.5°C for the first 2 h (acid stage) and 1,000 mL of USP phosphate buffer (pH 6.8 ± 0.05) at 37 ± 0.5°C for 1 additional hour (buffer stage). The model drug was assayed by spectrophotometer at 238 nm (Lambda 25, PerkinElmer, Monza, I).

Coated round- and oval-shaped soft gelatin capsules with different weight gain, packaged either in closed glass containers or individually in PVC/PVDC/Al blisters, were stored under 25°C/75% RH conditions and checked after 3 months.

RESULTS AND DISCUSSION

Following Obara's earliest experiences carried out with different types of cores in a laboratory-scale equipment provided with a purposely adapted device for powder feeding (Obara et al., 1999), the dry coating technique was further investigated particularly for the application of enteric HPMCAS layers onto pellet cores (Kablitz et al., 2006). In this work, the possibility of employing such a technique to attain HPMCAS-coated soft gelatin capsules in a tangential-spray rotary fluid bed equipped with a standard powder feeder was explored. Indeed, a coating procedure that would not require any solvent could be highly advantageous in the case of capsule cores because of the possible alterations undergone by gelatin upon extensive contact with water. For the study purpose, formulation and process parameters were set up with placebo capsule cores provided with a thin sealing film. The previously proposed coating formulation consisted of a HPMCAS/talc powder blend in a 10:3 ratio and a plasticizer mixture based on TEC as the plasticizing agent and an oily wetting agent (AcGlyc) in a 3:2 ratio (Obara et al., 1999). Such a formula was subjected to progressive adjustments until a suitable composition was reached (Formulation A, Table 1). In particular, because of the marked tackiness shown by the substrate in the early stages of the coating process, it was necessary to increase the amount of talc in the powder blend from 16.7 to 30.0%. Thus, it proved possible to reduce the total amount of liquid mixture. Meanwhile, the TEC/AcGlyc ratio was slightly increased in an attempt to maintain a similar polymer/TEC ratio in the final coating formulation.

Owing to core dimensions, which might have hindered a correct fluidization pattern, the possible shrinkage of gelatin shells and the need for preserving their moisture content, the selection of appropriate processing parameters appeared critical, especially with respect to temperature (Felton & McGinity, 2003). Throughout the coating process, the substrate temperature was maintained below 40°C. This was achieved by setting the inlet air temperature at a moderately higher value (45°C).

TABLE 1
Coating Formulations

	Formulation Proposed in Obara et al. 1999 (%)	Formulation A (%)	Formulation B (%)
HPMCAS	55.5	50.0	50.0
Talc	16.7	30.0	30.0
Powder Mixture	**72.2**	**80.0**	**80.0**
TEC	16.7	12.5	20.0
AcGlyc	11.1	7.5	—
Plasticizer Mixture	**27.8**	**20.0**	**20.0**
Total	**100.0**	**100.0**	**100.0**

The air flux at room temperature (≅ 20°C) that was introduced into the coating chamber through the concentric three-way port nozzle helped to maintain the temperature below the fixed limit by locally cooling the product.

Among all the parameters that were shown to have an impact on process yield, the inlet air rate appeared the most important one. Rates >70 m^3/h resulted in the conveyance of large amounts of powder to the upper portion of the process chamber thus hindering the polymer adhesion onto the cores, which were mainly rotating on the bottom of the chamber. On the contrary, rates <30 m^3/h failed to draw the coating powder mixture from the feeder port and led to the infiltration of particles into the gap between the disk and the process chamber. An air flow rate of 50 m^3/h was therefore adopted.

Plate rotational speed was set at 500 rpm, which seemed to be the minimum value that could impart an adequate motion pattern to the core units.

An initial priming phase of 2 min, during which only the plasticizer mixture was nebulized, was proven to enhance particle adhesion onto the core surface, thereby limiting the loss of powder at the beginning of the process. Subsequently, it was possible to concurrently add both the powder and plasticizer mixtures. Rate values (5 and 1.25 g/min for the powder and plasticizer mixtures, respectively) were selected after a series of preliminary trials because they were shown to provide reasonable yields and acceptable processing times.

A curing phase, which is generally required to attain homogeneous coats in dry coating processes, was carried out for 60 min in the same equipment at a temperature of 38°C. This value was not exceeded due to the aforementioned susceptibility of gelatin cores to irreversible heat-induced damage, but the air flow rate was increased to 90 m^3/h in order to promote heat exchange. Although in some studies the addition of a small quantity of water was demonstrated to improve the outcome of curing (Obara et al., 1999; Pearnchob & Bodmeier, 2003), this alternative was discarded in order to avoid the need for drying under more severe thermal conditions (Kablitz et al., 2006).

When operating conditions that could enable a feasible dry coating process were set up with placebo capsules (Table 2), model drug (acetaminophen)-containing cores of differing sizes and shapes (2 round and 5 oval) were coated in order to assess the suitability of the overall coating procedure for preparing gastric resistant capsules. No adjustment was required for the process parameters except for a higher disk rotation speed, which was necessary only in the case of heavier oval-shaped capsule cores. Samples with two different coating levels (approximately 7 and 14% w.g.) were withdrawn throughout the coating processes. After the curing step, HPMCAS-coated capsules showed smooth surface and uniform coating level (Formulation A-coated capsules, Table 3). A photomicrograph of one cross-sectioned oval capsule is shown in Figure 1 as an example. Release tests in HCl 0.1 N solution and 6.8 phosphate buffer were subsequently performed in order to evaluate the gastric resistance properties of the samples. Systems with approximately 22 mg/cm^2 coating level were demonstrated to provide the expected 2-h gastric resistance. In Figure 2 the release profiles relevant to Formulation A-coated round

TABLE 2
Coating Process Parameters

Process Parameter	Dry Coating	Curing
Inlet air temperature (°C)	45	40
Product temperature (°C)	36–38	38
Outlet air temperature (°C)	34–36	38
Inlet air flow rate (m^3/h)	50	90
Product pressure (Pa)	600–700	650
Nozzle port size (mm)	0.8	
Spray rate (g/min)	1.25	
Nebulizing pressure (bar)	1.2	
Powder feeding rate (g/min)	5	
Rotor speed (rpm)	500 *round* 600 *oval*	500 *round* 600 *oval*

TABLE 3
Characteristics of Coated Capsules

Capsule Core (Size and Shape)	Coating Formulation	Sample	Weight Gain (%)	Coating/Area (mg/cm^2)	Coating Thickness (μm ± *SD*)
2 round C	A	rA1	7.0	11.4	103 ± 7
		rA2	14.0	22.5	197 ± 8
	B	rB1	8.5	13.8	119 ± 6
		rB2	13.4	21.8	193 ± 5
5 oval	A	oA1	6.5	9.6	85 ± 9
		oA2	15.0	22.1	195 ± 7
	B	oB1	7.0	10.3	94 ± 7
		oB2	15.6	23.1	203 ± 6

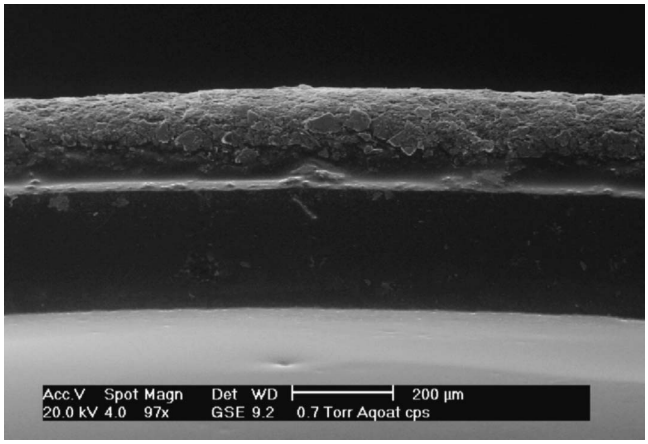

FIGURE 1. ESEM photomicrograph of one cross-sectioned coated soft gelatin capsule (sample oA2).

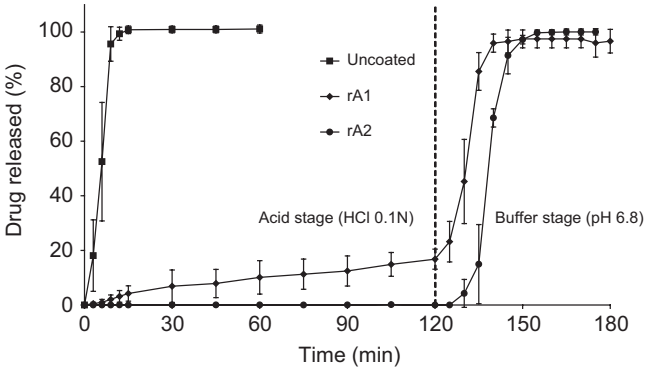

FIGURE 2. Average release profiles of acetaminophen from uncoated and Formulation A-coated soft gelatin capsules with different coating levels (rA1 and rA2). Vertical bars indicate standard deviation (n = 6).

capsules are reported by way of example. As compared with literature data, the 22 mg/cm^2 coating level value appeared higher, probably because of a less effective curing phase, which was necessarily carried out under relatively limited temperature and time conditions to preserve integrity of the gelatin substrate.

Because the role of AcGlyc in the plasticizing mixture seemed controversial (Kablitz et al., 2006), the use of a different coating formulation (Formulation B, Table 1) was evaluated, in which the oily wetting agent was completely replaced with TEC. The physical-technological characteristics of the coated capsules obtained are reported in Table 3. The effectiveness of formulation B-based enteric coatings was comparable with that of formulation A-based ones. Figure 3 shows the release profiles relevant to formulation B-coated round capsules. The only difference observed between the two formulations concerned the process yield, which turned out slightly lower when TEC was used instead of the TEC/AcGlyc mixture (87 vs. 93%).

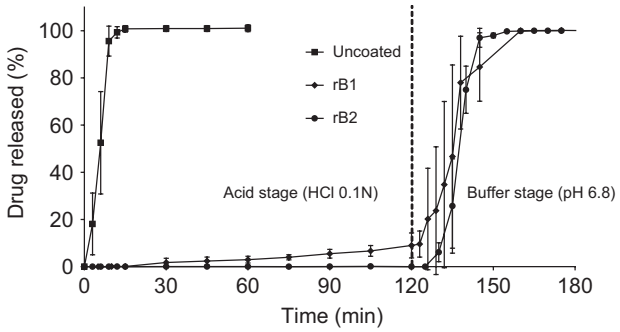

FIGURE 3. Average release profiles of acetaminophen from uncoated and Formulation B-coated soft gelatin capsules with different coating levels (rB1 and rB2). Vertical bars indicate standard deviation (n = 6).

A preliminary stability investigation was carried out on oval and round capsules coated up to 15% w.g. that were stored in closed glass containers or packaged individually in PVC/PVDC/Al blisters. All units were shown to maintain their physical-technological and gastric resistance properties. Release profiles comparable with the above reported ones were obtained. However, units kept in glass containers exhibited a slight tendency to stick to each other.

The HPMCAS dry coating process set up for soft gelatin capsules was proven to be a promising alternative to conventional film-coating. However, the process yield and the coat effectiveness in protecting the core from acidic media still appeared susceptible to improvement. In this respect, further in-depth investigations need to be performed on the powder and plasticizer formulations, the coating process parameters and the curing step conditions.

REFERENCES

Bodmeier, R., & McGinity, J. W. (2005). Dry-coating of solid substrates with polymeric powders. *Drug Deliv. Tech., 5*, 70–73.

Buhler, V. (2003). *Kollidon polyvinylpyrrolidone for the pharmaceutical industry* (7th ed.). Ludwigshafen, Germany: BASF Aktiengesellschaft.

Cerea, M., Zheng, W., Young, C. R., & McGinity, J. W. (2004). A novel powder coating process for attaining taste masking and moisture protective films applied to tablets. *Int. J. Pharm., 279*, 127–139.

Cunningham, C. R., & Fegely, K. A. (2001). One-step aqueous enteric coating systems: scale-up evaluation. *Pharm. Tech. Eur., 13*, 48–54.

Felton, L. A., Haase, M. M., Shah, N. H., Zhang, G., Infeld, M. H., Malick, A. W., & McGinity, J. W. (1995). Physical and enteric properties of soft gelatin capsules coated with Eudragit® L30 D-55. *Int. J. Pharm., 113*, 17–24.

Felton, L. A., & McGinity, J. W. (2003). Enteric film coating of soft gelatin capsules. *Drug Deliv. Tech., 3*, 48–51.

Gupta, V. K., Beckert, T. E., & Price, J. C. (2001). A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development. *Int. J. Pharm., 213*, 83–91.

Hogan, J. E., Page, T., Reeves, L., & Staniforth, J. N. (1996). Powder coating composition for electrostatic coating of pharmaceutical substrates. GB Patent WO 96/35413.

Ivanova, E., Teunou, E., & Poncelet, D. (2005). Encapsulation of water sensitive products: Effectiveness and assessment of fluid bed dry coating. *J. Food Eng., 71*, 223–230.

Jarvis, A., Billington, D., Willsher, P., Tullet, S., King, R., Holroyd, M. J., & Gledhill, D. (2005). Method and apparatus for the application of powder material to substrates. GB Patent CA 254798.

Kablitz, C. D., Harder, K., & Urbanetz, N. A. (2006). Dry coating in a rotary fluid bed. *Eur. J. Pharm. Sci.*, *27*, 212–219.

Nagai, T., Obara, S., Kokubo, H., & Hoshi, N. (1997). Application of HPMC and HPMCAS to aqueous film coatings of pharmaceutical dosage forms. In J. W. McGinity (Ed.), *Aqueous polymeric coatings for pharmaceutical dosage forms* (pp. 177–225). New York: Marcel Dekker, Inc.

Nastruzzi, C., Cortesi, R., Esposito, E., Genovesi, A., Spadoni, A., Vecchio, C., & Menegatti, E. (2000). Influence of formulation and process parameters on pellet production by powder layering technique. *AAPS PharmSciTech*, *1*, E9.

Obara, S., Maruyama, N., Nishiyama, Y., & Kokubo, H. (1999). Dry coating: an innovative enteric coating method using a cellulose derivative. *Eur. J. Pharm. Biopharm.*, *47*, 51–59.

Pearnchob, N., & Bodmeier, R. (2003). Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique. *Int. J. Pharm.*, *268*, 1–11.

Pissinati, R., & Oliveira, W.P. (2003). Enteric coating of soft gelatin capsules by spouted bed: effect of operating conditions on coating efficiency and on product quality. *Eur. J. Pharm. Biopharm.*, *55*, 313–321.

Zheng, W., Cerea, M., Sauer, D., & McGinity, J. W. (2004). Properties of theophylline tablets powder-coated with methacrylate ester copolymers. *J. Drug Deliv. Sci. Tec.*, *14*, 319–325.