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Performance of Multilayered Particles: Influence of a Thin Cushioning Layer

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ABSTRACT Nowadays, oral dosage forms with controlled release kinetics have known an increasing interest. The polymer coating of drug-loaded particles is one of the most common methods used for controlling drug delivery. Such multilayered particles could be either filled into capsules or compressed into tablets for their oral administration. However, many studies have noticed that coating films are damaged during the compression process, leading to significant changes in drug release profiles. The aims of this study were to investigate the effects of a thin cushioning layer [made of HydroxyPropylMethyl Cellulose (HPMC)] applied on coated theophylline particles upon particle characteristics, tablet properties, and then upon their dissolution performance. If no significant effect was shown with particles, this thin HPMC layer played an important role in the tablets. Tablet cohesiveness was decreased due to HPMC cushioning properties and moreover, the theophylline release rate was increased, as HPMC is a water-soluble polymer creating channels in polymer film for dissolution medium. Therefore, a cushioning layer helped to protect polymer coats from fracture during compression but could also affect drug release and so, both effects must be checked in such a drug delivery system.

KEYWORDS Multilayered particles, Cushioning excipient, Dissolution performance, Surelease®, HPMC, Tablets

INTRODUCTION

Oral sustained release drug delivery systems are used to modify the release kinetics of drugs. They can be classified into two groups: single unit dosage forms (e.g., tablets or capsules) and multiple unit dosage forms (e.g., pellets, granules, minitablets, microparticles) (Bodmeier, 1997).

In contrast to monolithic dosage forms, multiple unit dosage forms offer several advantages (Vergote et al., 2002). The subunits spread readily over a large surface area in the gastro-intestinal tract, reducing high local drug concentration and local irritation but improving the bioavailability with less variation in drug release. Multiparticulates systems are also suitable for a

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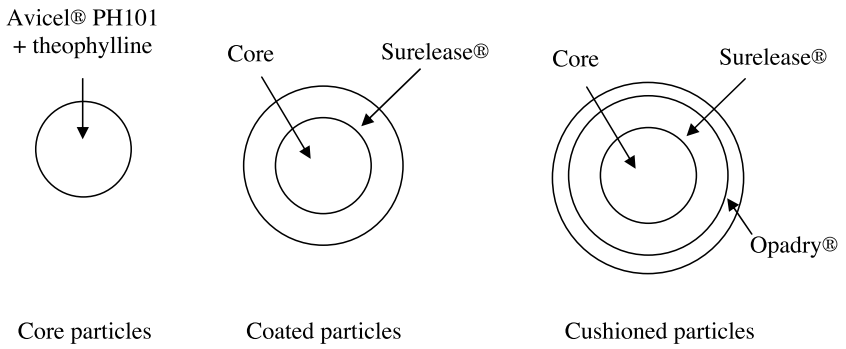

FIGURE 1 **Structure of the Different Particles.**

combination of incompatible drugs or when different release rates of drug are needed from the same dosage form. For oral administration, the multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. As tablets are more tamper resistant, easier to swallow and with a lower production cost, the compression of multiparticulates is becoming an interesting issue. Compaction of multiparticulates into tablets could either result in disintegrating tablets providing a multiparticulate system during gastro-intestinal (GI) transit or in intact tablets due to the fusion of the multiparticulates in a larger compact. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in GI fluids. However, in many cases in pharmaceutical industry, a fusion of the multiparticulates happens providing a non-disintegrating matrix tablet. This matrix formation decreases the drug release, sometimes in a so large extent that the efficacy level cannot be reached. Thus, compaction of coated pellets is an evident challenge. Many studies (Altaf et al., 1998; Miller et al., 1999) have pointed out that coating films generally suffer from damages during compression process, leading to a loss of their sustained release characteristics. To protect polymer films from fracture under pressure, different methods have been evaluated (Vergote et al., 2002):

1. selecting formulation parameters (kind of polymer, plasticizer etc.) to increase the flexibility of the coating layer (Fukui et al., 2001);
2. increasing the amount of coating applied to the pellets to increase thickness of the coating layer (Haslam et al., 1998);
3. mixing the pellets with a powder material acting as a cushioning agent (Yao et al., 1997) or with cushioning beads (Habib et al., 2002; Vergote et al., 2002) before compression to decrease pressure effect and, finally,
4. manufacturing multilayered beads where the outer layers will absorb the pressure and the inner layers would provide sustained drug release (Altaf et al., 1998; Haslam et al., 1998).

The aims of this work were to investigate the ability of a thin cushioning layer (HPMC) applied on coated theophylline particles to reduce the fusion between the multiparticulates during compaction in order to provide a useful drug release pattern. The effects of this thin HPMC layer were checked upon both particle and tablet characteristics and their dissolution performance before and after a compression process.

MATERIALS AND METHODS

Materials

The model drug was anhydrous theophylline, sparingly soluble in water (1 g per 120 mL) and supplied by BASF. Avicel® PH101 was obtained from FMC, polyvinylpyrrolidone (PVP® K-30) from BASF, Surelease® (25% w/w aqueous ethylcellulose dispersion) and Opadry® OY-7240 (HydroxyPropylMethyl cellulose=HPMC 5 cP) from Colorcon.

Preparation and Characterization of Multilayered Particles

Theophylline and Avicel® PH101 (40/60% w/w) were mixed in a trembling blender (Turbula T2C, W. Bachofen, Basel, Switzerland) at 46 rpm for 15 min. Core particles were prepared by wet granulation. This dry blend was dampened with a water solution of

TABLE 1 Process Conditions Used in Particles and Tablets Manufactures

	Formulation	Conditions	Apparatus	Time
Core particles	Avicel® PH101 60% + Theophylline 40%	Mixing	Turbula®	15 min
		Wetting (PVP 7%)	UniGlatt®	30 min
		Drying	UniGlatt®	40–45 min
		Sieving	Tamisor®	10 min
Coated particles	Core particles + Surelease® (EC 10% weight gain)	Inlet air: 40°C Outlet air: 31–34°C Spray rate: 7 g/min Atomizing air pressure: 1.5 bars	UniGlatt® bottom spray	90 min
Cushioned particles	Coated particles + Opadry® (HPMC 1% weight gain)	Inlet air: 40°C Outlet air: 35–40°C Spray rate: 7 g/min Atomizing air pressure: 1.5 bars	UniGlatt® bottom spray	5 min
Tablets	Each batch of particles (core, coated and cushioned)	10 mm flat punches Die height = 10 mm Variable upper punch displacement	Instrumented tableting machine Korsch EK0	15 min per batch

PVP® K-30 (7%) in a fluidized bed apparatus (UniGlatt, Glatt Pharmatech) and dried at 40–50°C down to 5–6% residual water. Dry cores were sieved and the 500–710 μm fraction was kept for the next coating experiments and tablets manufacturing.

These cores were coated by Surelease® using UniGlatt equipped with a bottom spray insert. The coating parameters were: inlet air temperature 40°C, outlet air temperature 31–34°C, atomization air pressure 1.5 bars, flap inlet 30–50%, coating rate 7 g/min. The amount of ethylcellulose applied to the cores was calculated to obtain 10% weight gain.

Coated cores were then overcoated with Opadry® OY-7240 in 10% w/w aqueous solution in the same equipment until 1% weight gain with similar conditions. This last layer formed the thin cushioning layer and these particles were called cushioned particles. Structure of the different particles is presented in Fig. 1.

Particles were characterized by their moisture content (infra-red balance, Mettler PE360), their specific surface area (BET method with nitrogen, Autosorb 1C, Quantachrome), and their bulk and tapped densities (taps until equilibrium=1250 taps, Stampfvolumenometer, STAV 2003). Particle sizes were determined by laser light scattering with a Coulter® LS 130 (Coulter) equipped with a "dry powder module." Particles were suspended in air to form uniform dispersion and size distribution was recorded using Coulter® software. Average particle size (D50) was expressed as volume mean diameter. Particles were either used to produce tablets or evaluated for dissolution performance. All process conditions used in particle and tablet manufacture are given in Table 1.

Tablets Manufacturing

Tablets were produced on an instrumented tableting machine (Korsch EK 0). Different parameters were recorded during compression (Doelker, 1994). Consequent pressure and axial ejection pressure were calculated using a personal software (Gould Windograph 900; Software for uniaxial compression ADOC, University of Burgundy, France). The tableting machine was fitted with 10 mm flat-faced punches (single punch). Compression speed was 10 tablets per minute. Die height was fixed at 10 mm and the upper punch displacement was set to obtain the same powder volume reduction in order to produce tablets with a similar volume. These parameters (diameter and thickness) of tablets were chosen to have a similar condition in term of solid/liquid volume ratio during dissolution experiment. Tablets were produced from each kind of particle without any other excipients. Tablet name depended on particle name, i.e., core tablets, coated tablets, and cushioned tablets. After manufacturing, tablets were characterized by

TABLE 2 Particles Characteristics

Kind of particles	Moisture content (%)	Specific surface area (m^2/g)	Bulk density (g/cm^3)	Tapped density (g/cm^3)
Core particles	6.18±0.38	0.881±0.13	0.453±0.01	0.521±0.05
Coated particles	2.33±0.19	0.985±0.10	0.516±0.01	0.597±0.06
Cushioned particles	2.00±0.25	1.002±0.18	0.495±0.02	0.568±0.04

different parameters measured just after compression (weight, diameter, thickness, friability, and diametrical tensile strenght).

Dissolution Method

In vitro dissolution studies of particles or tablets were performed using the rotating paddle method (Erweka DT6 apparatus) at 37±0.5°C and 60 rpm. The dissolution medium used (1000 mL) was a phosphate buffer solution at pH 7.4. Sampling was done over 6 h at predetermined time intervals. The amounts of theophylline released in each sample were assayed by UV detection at 274 nm (Kontron, Uvikon 930). Then, drug released (in percentage of initial amounts) was plotted versus time. All experiments were done in triplicate (n=3) with both particles and tablets.

RESULTS AND DISCUSSION

Particle Characterizations

Particle properties are important parameters influencing powder flow and compaction processes always involved in the production of solid dosage forms (Brittain, 1995). The different parameters measured, i.e., moisture content, specific surface area, bulk and tapped density, were presented in Table 2, and the particle size distributions were shown in Fig. 2.

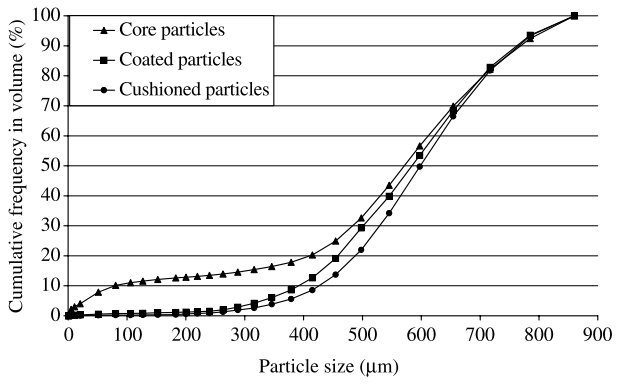

FIGURE 2 Particle Size Distributions by Laser Light Scattering (n=3).

The coating processes decreased the particle moisture content, probably because of the lengthening of the process time. No significant difference was noted in specific surface area for the three kinds of particles. Bulk density was higher for coated and cushioned particles than for core particles. However, the Hausner indices (ratio between tapped density and bulk density) were all close to 1.14 suggesting a good flowability—an expected property after pellets formation (Watano et al., 1997). Average particle size was increased during coating process with a mean diameter of 568.5±9.1 μm for core particles, 581.2±13.1 μm for coated particles, and 598.2±26.8 μm for cushioned particles.

Tablet Properties

Tablets from each kind of particle had similar size with a diameter of 10.06±0.004 mm and a thickness of 3.83±0.005 mm. Their different characteristics, i.e., weight, friability, diametrical tensile strength, recorded consequent pressure, and axial ejection pressure, are exhibited in Table 3. The higher bulk density of coated particles induced a higher loading of the compression die and a subsequent higher weight of these tablets and greater consequent pressures were recorded.

Diametric tensile strength, a parameter evaluating tablet cohesiveness, depended on the kind of particles used. There was no significant difference between core tablets and coated tablets but tensile strength value was lower for cushioned tablets. This parameter was not in relation with the level of recorded pressure, pointing out the major role of the formulation upon tablet performance. The HPMC overlayer induced a weaker cohesiveness of these tablets by its cushioning effect reducing the compression effects on particles (Haslam et al., 1998). Conversely, coating decreased extensively the tablet friability due to a smoother surface of particles. Axial ejection pressures give information about frictions during tablet ejection phase. They were weaker for coated tablets, the

TABLE 3 Tablets Characteristics

Kind of tablets	Weight (mg)	Friability (%)	Diametrical tensile strength (MPa)	Consequent pressure recorded (MPa)	Axial ejection pressure (MPa)
Core tablets	340.2±1.10	0.56±0.11	1.38±0.14	61.74±0.79	5.47±0.51
Coated tablets	379.6±1.43	0.03±0.004	1.42±0.09	105.9±2.16	2.96±0.05
Cushioned tablets	364.3±1.47	0.01±0.005	0.98±0.06	82.55±1.65	1.96±0.04

frictions existing between particles and the die walls being reduced by coating layers.

Dissolution Profiles

Figure 3 shows drug dissolution profiles obtained with the 3 different types of particles, i.e., core particles, coated particles, and cushioned particles. Theophylline release from core particles was fast and was completed within 2 min due to the disintegrant properties of Avicel® PH101 (Lustig-Gustafsson et al., 1999). In comparison, coated particles exhibited an extended release. Particles were coated by Surelease® which is an aqueous dispersion based on ethylcellulose, a well-known polymer, inert and hydrophobic (Rekhi & Jambhekar, 1995). Ethylcellulose is one of the most common water-insoluble polymers for the production of coated sustained-release pellets (Sadeghi et al., 2003) and aqueous colloidal dispersions could be used instead of organic solutions, avoiding toxicological and environmental problems (Pearnchob & Bodmeier, 2003).

Likewise, cushioned particles presented the same release pattern as coated particles. These particles could be described as a porous Avicel® PH101 core including solid drug, surrounded by a thin coating. From such a system, drug release will occur by three

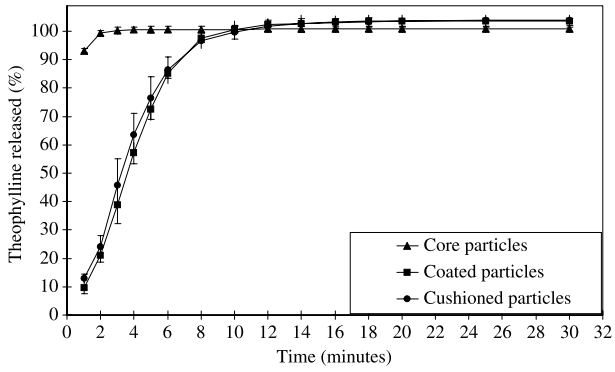

FIGURE 3 Release Profiles of Theophylline with the Different Particles at pH=7.4 (n=3).

different steps (Frenning et al., 2003): 1) inflow of liquid through the coating, 2) dissolution of the drug in the pellet core, and 3) efflux of the dissolved drug through the coating. Surelease® layer controlled the drug dissolution rate and no effect of the HPMC cushioning layer was noticed. Here, the sustained-release effect was not important. However, it could be enhanced by a curing step during manufacturing (Pearnchob & Bodmeier, 2003). This curing step (currently a thermal treatment in an oven) would improve the film formation process around cores: the plasticizer further diffused into and softened the polymer and, therefore, increased the coalescence (fusion) into a denser film. Drug release decreased with increasing curing temperature and curing time.

An Opadry® (HPMC) overcoating is often required to prevent blocking of coated particles after process and to improve other properties such as appearance, ingestibility, and taste of pellets (Sadeghi et al., 2000). So, this thin water-soluble film, which could dissolve quickly from the coated particles, did not interfere on drug dissolution profiles. This effect is already reported by other authors for various drugs with low-viscosity grades of HPMC such as Opadry® OY-7240 (Sadeghi et al., 2000).

Figure 4 gives the release profiles of theophylline from tablets prepared with the three different types of particles. After compression, the dissolution rate extensively dropped whatever the kind of particles. On one hand, compression produced cohesive and densified compacts, and the dissolution medium had difficulty in wetting the tablets, reducing drug release (Doelker, 1994). On the other hand, ethylcellulose is known to produce a non-disintegrating matrix (Chambin et al., 2004) under pressure, maintaining a rate-controlling effect due to fusion of the polymer coat (Altaf et al., 1998). This last point strengthened this sustained effect with tablets prepared from coated particles. Nevertheless, tablets produced with cushioned particles did not present the same release profile: their dissolution rate was increased.

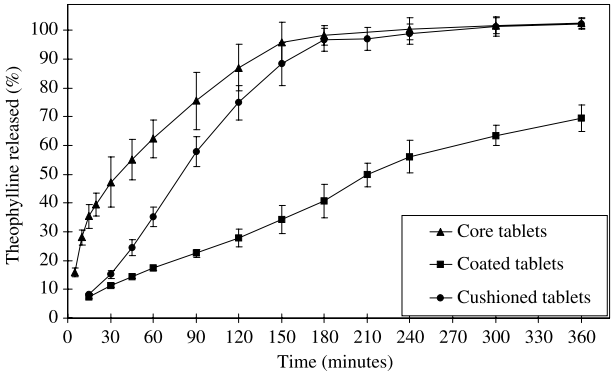

FIGURE 4 **Release Profiles of Theophylline with the Different Tablets at pH=7.4 (n=3).**

In order to better describe the dissolution profiles of these matrices, Higuchi model was applied to data, where $Q(t)=K_H t^{1/2}$ (Costa & Lobo, 2001). A regression analysis was performed on the released amount as a function of square root of time represented in Fig. 5. For comparative findings, the modelization was done between 15% and 90% of drug release, limits of applicability of this model (Sadeghi et al., 2000). The slopes and the correlation coefficients were calculated as well as the lag time (time when the amount of drug released was zero). All the correlation coefficients were close to 1 (>0,99) suggesting that Higuchi model fit the release data well. Therefore, the release mechanism was predominantly controlled by drug diffusion through the matrices. None lag time was obtained for core tablets where drug release started immediately with dissolution medium contact. For coated and cushioned tablets, a lag time was noted with the same value for both tablets. Probably this lag time was caused by Surelease® film, i.e., a hydrophobic film decreasing tablet wettability and the subsequent water diffusion into tablets. However, slope of the Higuchi linearization was higher for cushioned tablets than for coated tablets.

The overcoating of HPMC is advised to protect film coating during compression because it produces a soft and pliable film which could behave as a cushioning excipient (Podczeck & Almeida, 2002). The larger the amount of HPMC overcoating, the less the effect of the previous coating was compromised, with the HPMC layer absorbing and dissipating the compression forces (Haslam et al., 1998). Moreover, the compression process affected less the smaller overcoated beads than the larger ones (Yao et al., 1998). Upon compaction, discrete beads could still be clearly distinguished within tablets by scanning electron micrographs, even if a significant deformation of beads was observed (Altaf et al., 1998).

In this study, the cushioning layer was very thin (1%). It would protect the Surelease® film as it could be assumed by tablets appearance during dissolution test. Tablets made of core and coated particles evolved in the same way: they were laminated in layers, which looked like cardboard. On the opposite, tablets prepared with cushioned particles remained intact throughout the dissolution test. But at the end, they were friable and particles appeared free from each other. However this thin HPMC layer interfered with drug release also, especially with slightly soluble drug. As hydrophilic, it creates channels for the dissolution medium to diffuse through the tablets and to take theophylline out. This finding was in agreement with Sadeghi's work where inclusion of HPMC® E15 in the coating film increased the release rates of two drugs in comparison with pellets coated only with Surelease® (Sadeghi et al., 2001). This effect was related to the leaching of HPMC from Surelease® film, which led to the formation of pores. The pores were thought to act as points for entry of dissolution medium through the film into the core. The position of the HPMC layer seemed to be also an important point. As a matter of fact, a 2% (w/w) coat of HPMC® E5 before Surelease® film decreased the release rate of two drugs (metoclopramide hydrochloride and diclofenac sodium) in comparison to those with Surelease® alone (Sadeghi et al., 2003). This kind of overcoating was called a sealcoat and could be effective in preventing drug migration during the application of the sustained-release

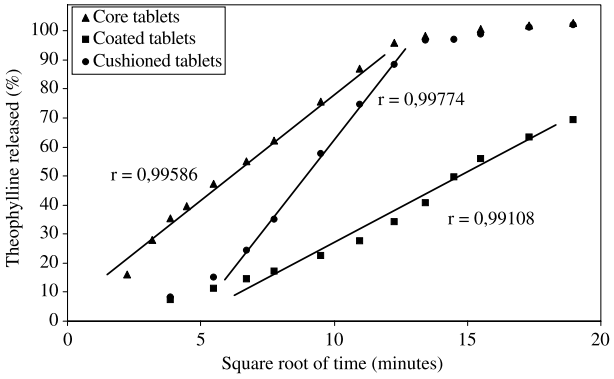

FIGURE 5 **Higuchi Linearization of In Vitro Release Profiles of Theophylline for the Different Tablets.**

coat for drugs soluble in the coating fluid. Here, no effect was pointed out with cushioned particles but the increase of dissolution rate was clear with tablets although the HPMC layer was applied after Surelease® coating.

CONCLUSIONS

In recent years, there has been an increased interest in the development of sustained and controlled release dosage forms, especially in terms of microparticulate systems which could be filled into capsules or compressed into tablets. The structure of the multilayered particles is a major parameter for the behavior of such a system. This study has shown the effects of a thin cushioning layer (HPMC) on multilayered particle characteristics and tablet properties with subsequent influence upon their dissolution behaviour.

The production of multilayered particles was selected in order to avoid segregation during mixing with cushioning excipient (Habib et al., 2002) and, as a consequence, affected weight variation and drug uniformity. With particles, no significant difference was noticed between coated and cushioned particles as well as in particle characterization and in dissolution behavior. However, with tablets, HPMC interfered on compression process, decreasing cohesiveness and rising wettability. These tablet changes had an important effect upon their dissolution performance increasing release rate of a slightly soluble drug such as theophylline. This overcoating with a thin HPMC layer played the role of a protective layer to minimize coating film damage during compression, but it affected drug release behavior also. As a hydrophilic, HPMC creates channels for dissolution medium to diffuse through the tablets. The position of this HPMC layer was also a critical point in order to control drug release. Finally, both the effects on physico-chemical properties and on drug release rate must be investigated when such a formulation was used in a controlled-release drug delivery system.

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