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The influence of antitack additives on drug release from film-coated granules

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Summary

In this report, the effect of various antitack additives on the overall drug release properties of methylcellulose (MC) film-coated granules is described, with emphasis on the drug release-enhancing ability of magnesium stearate when it is incorporated as an antitack agent in aqueous MC coating formulations. All the other additives were also found to cause a rise in the release rate of the drug from the coated granules, although it was much less compared with magnesium stearate. The reasons for the effect of the additives on the release properties of the coated product were explored and discussed in terms of the swelling behaviour of the coated granules in water and the possible additive-polymer interactions. The results of the study are important in the film coating of multiparticulate dosage forms with aqueous-based polymeric formulations in which a generally high level of antitack additives is used.

Introduction

The replacement of organic solvents with water in an aqueous-based coating formulation has increased the complexity of the coating process (Pickard and Rees, 1974; Seitz, 1988). The slow rate of evaporation of water coupled with its high latent heat of vaporization entails greater attention on controlling the drying conditions in the aqueous-based coating process. For this reason, aqueous-based polymeric coating formulations are more likely to experience wetting and ultimate tackiness problems than their organic solvent-based counterparts. The addition of antitack additives is often necessary to expedite processing, by alleviating the agglomeration problem caused by tackiness of the polymer film during the coating of particles or tablets. Ideally, antitack agents should be inert with respect to the active ingredient and the release characteristics of the film. In practice, such additives may, however, greatly change the properties of the resultant films and their subsequent applications and uses. A study of the effect of various commonly used antitack agents on the drug release behaviour of the resultant MC film-coated granules was therefore undertaken.

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Materials and Methods

Materials

Lactose granules (Sunward Chemicals, Singapore) of 600–710 μm were used as the inert core material. Methylcellulose (MC, Tokyo Kasei, Japan) of viscosity grades, 13–18 and 350–550 cps, was selected as the coating polymer. The antitack additives studied were magnesium stearate, aluminium stearate, talc (all BP grade), zinc stearate, stearic acid (all Merck, Germany) and silicon dioxide (Aerosil 200, Degussa AG, Germany). As wetting aids, polysorbate 80 (Tween 80, Honeywell-Atlas, U.K.), sodium lauryl sulphate (BDH Chemicals, U.K.) and silicone 190 (Dow Chemicals, U.S.A.) were employed. Diphenhydramine hydrochloride (BP grade) was used as a model drug. All materials were used as supplied.

Preparation of coating formulations

The additives were dispersed separately in 100 ml of distilled water using a mixer/homogenizer (Polytron®, Kinematica GmbH, Switzerland) prior to mixing with the MC solution and then made up to 500 ml with water. This ensured complete dispersion of the additive at low viscosity. For the metal stearates and stearic acid, a 0.1% w/v polysorbate 80 solution was used as the dispersion medium instead. Different surfactants were also employed in the case of magnesium stearate. The coating formulations were prepared from 2% w/v aqueous solution of MC. The content of each additive was 50% w/w based on the polymer. Different concentrations were also investigated for magnesium stearate. The final coating suspension was continuously stirred using a magnetic stirrer throughout the coating process.

Coating procedure

A bottom-spray fluidized bed Aerocoater® (Model Strea-1, Aeromatic AG, Switzerland) was used to deposit diphenhydramine hydrochloride dissolved in MC (13–18 cps) solutions, onto batches of 200 g of lactose granules. The concentrations of drug and MC in the coating solution were 7.5 and 2% w/v, respectively. A total of 500 ml of the coating solution was sprayed for each batch. These initial drug-layered granules were employed as substrate particles for subsequent film coating study. The coating formulations in this case, comprised 2% w/v MC (350–550 cps) instead of MC (13–18 cps) and no drug was added. The process conditions adopted, summarized in Table 1, were similar to those described previously (Wan and Lai, 1991).

TABLE 1

Summary of process conditions

Parameter	Setting
Fluidizing air flow rate (m^3/h)	90–110
Inlet air temperature (°C)	80
Outlet air temperature (°C)	50–54
Spray nozzle diameter (mm)	0.5
Atomizing air pressure (bar)	0.8 (1.0) [a]
Spray rate (ml/min)	5–7
Intermittent spray cycle	1 min spraying/30 s drying
Postcoating drying	80°C, 10 min

[a] A higher liquid atomizing air pressure to produce finer droplets was employed when spraying MC (350–550 cps) formulations.

Release studies

The details of the in vitro dissolution tests were given in a previous report (Wan and Lai, 1991). Accurately weighed samples of film-coated granules (600–850 μm) containing the equivalent of about 100 mg of drug were used. A minimum of three replicates were carried out for each formulation.

Particle size analysis

The size distribution of the coated granules was determined by the mechanical sieving technique described by Wan and Lai (1991). The sieves used were of apertures 1.7, mm, 1.18, mm, 1.0, mm, 850 μm, 710 μm, 600 μm, 500 μm. Sieving was repeated for each formulation.

Optical microscopy

The swelling phenomenon of the film-coated granules in water was observed with the aid of a binocular light microscope (Olympus System Microscope Model SHZ-ILLD, Japan). Photomicrographs of the swelling phenomenon of selected

formulations were taken. The swelling of corresponding free cast films in water were also examined.

Results and Discussion

Efficiency of antitack additives

The various antitack additives selected for this study include magnesium stearate, stearic acid, talc and silicon dioxide. These additives are widely used as abherents in many polymer processing applications such as moulding and extrusion (Kovach, 1970). The simplest measure of the extent of agglomerates generated in the coating process is the large-end particle weight fraction which is essentially zero in the original feed material (drug-layered granules). This is a reasonable assumption because it has been shown that in a film coating process in which surface deposition of the film-former on individual particles is predominant, the particle growth is typically very slow and steady (Smith and Nienow, 1983). From visual inspection, it was found that granule fractions retained on sieves of mesh size 1.0 mm and above were composed of almost entirely aggregated granules. Thus, the 1.0 mm oversize weight fraction could be used as an indicator of the effectiveness of the antitack agent. Table 2 shows the 1.0 mm oversize fraction produced by the different coating formulations. Particle size enlargement would be expected in all cases after coating. However, the coating formulation which incorporated magnesium stearate produced the least amount of oversize rejects, suggesting that magnesium stearate was the most effective antitack additive.

TABLE 2

Extent of granule agglomeration of different coating formulations

Additive	1.0 mm oversize weight fraction (%)
No additive	84.5
Silicon dioxide	77.3
Stearic acid	72.4
Talc	70.0
Magnesium stearate	15.4

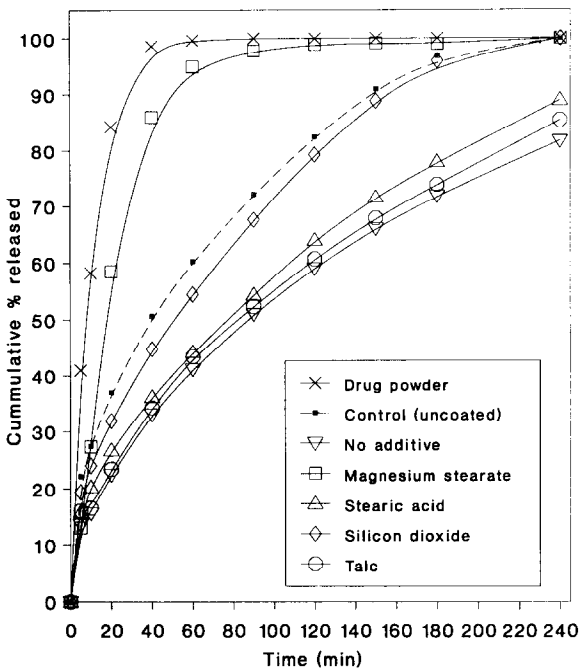

Fig. 1. Drug release profiles of coated granules containing different antitack additives.

Drug release from film-coated granules

The effect of various water-insoluble additives functioning as antitack agents, on the drug release properties of the coated granules was studied. In general, most of these additives when incorporated into the MC film coating were found to cause a rise in the release rate of the drug from the coated granules (Fig. 1). This overall effect of a film additive in increasing the release rate of the coated product is not a new observation. Many workers have reported and accounted for such a finding (Parker et al., 1974; Porter, 1982; Ghebre-Sellassie et al., 1986; Chang and Hsiao, 1989). The effect of insoluble particulate additives on the permeability of polymer films can only be discussed generally assuming a known mechanism of permeation. If cracks and flaws were absent, the presence of low concentrations of insoluble particles in a film tended to serve as a barrier to a diffusing species due to the in-

creased diffusional resistance. Furthermore, finely dispersed particles can act as effective physical crosslinks by adsorbing and immobilizing the polymer segments (Flynn, 1974). However, above the critical pigment volume concentration (CPVC), pigmented films become proportionately more porous and permeable as the amount of insoluble additives incorporated in the formulations is increased. The amount of polymer present is insufficient to bind all the additive particles together so that pores tend to appear in the film resulting in an increased permeability. The overall behaviour of films loaded with insoluble solids can be described by the Chatfield theory (1962). Although no determination on the CPVC of the various additive materials was carried out, the value being dependent inter alia on the packing characteristics of the additive particles and any specific additive/polymer interaction, studies by Rowe (1978) and Gibson et al. (1988) suggested that for hydroxypropyl methylcellulose films used in tablet film coating this value is approx. 25–30%. The content of the antitack additives used in the coating formulation in the present study at 50% w/w with respect to the polymer weight was likely to have exceeded the CPVC of the MC films. It is therefore conceivable that a higher release rate was obtained when these additives were included in the MC films compared with the coating formulation where no additive was added. In practice, filler-polymer interaction in most pharmaceutical film systems is rarely perfect and is dependent on the nature of the components of the systems (Okhamafe and York, 1985). Poor or insufficient particle-polymer interaction would leave voids at the particle-polymer interface which will not only facilitate the diffusion process but also constitute stress locations or concentrations in the polymer film.

What is surprising perhaps, is that the addition of the hydrophobic magnesium stearate into the MC film (Fig. 1) led to a dramatic enhancement of release of the active ingredient from the coated granules; at a rate that was even higher than that from the control batch which was not coated with the second polymer layer. The rapid drug release was unlikely to be caused by any specific interaction between magnesium stearate and the wetting

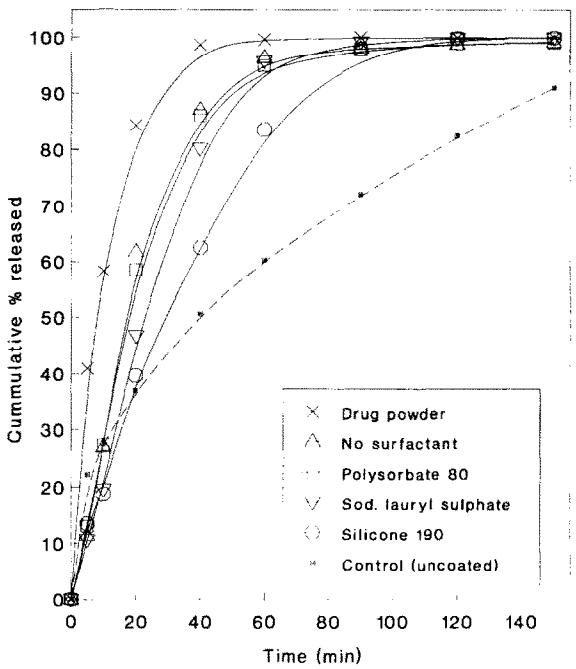

Fig. 2. The effect of different surfactants used as wetting aid for dispersing magnesium stearate in the MC solution on the drug release from the coated granules.

agent used in aiding uniform dispersion of the former in the coating composition. Different wetting agents such as polysorbate 80, sodium lauryl sulphate and silicone 190 used in the formulation all lead to similar rapid release profiles (Fig. 2). Another formulation in which no wetting agent was employed and the magnesium stearate was dispersed, albeit with difficulty, in 100 ml of a 0.1% w/v MC 350–550 cps before mixing into the bulk of the polymer solution, also resulted in similar release characteristics.

Apparently, this release-enhancing effect of magnesium stearate when incorporated into the MC films was highly dominating as evident in the complete negation of the expected dissolution-retarding action of the polymer barrier even when the coating level was increased about 3-fold from 5.7 to 15.4%. This is evident in Fig. 3. In fact, the release at a higher coating level was seemingly slightly faster than from coated granules with a smaller amount of coating. It is pertinent to note, however (Fig. 4), that the release-enhancing effect was not restricted to magnesium stearate

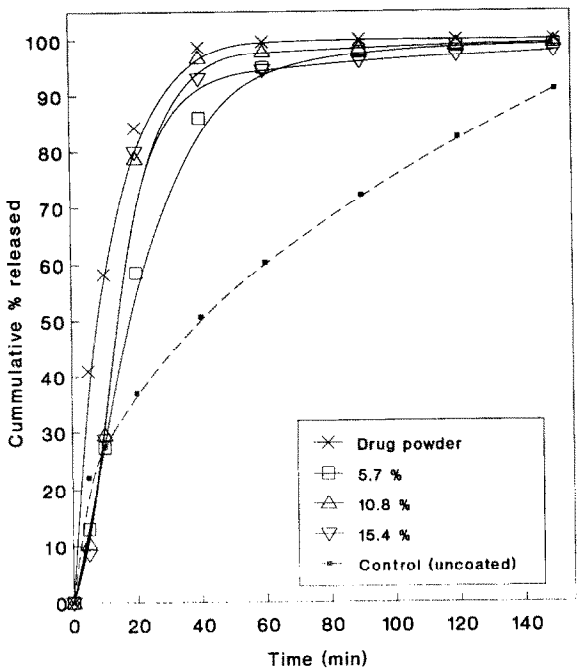

Fig. 3. The effect of coating level (expressed as % of theoretical weight increase of coated granules) on drug release from coated granules with magnesium stearate as antitack additive.

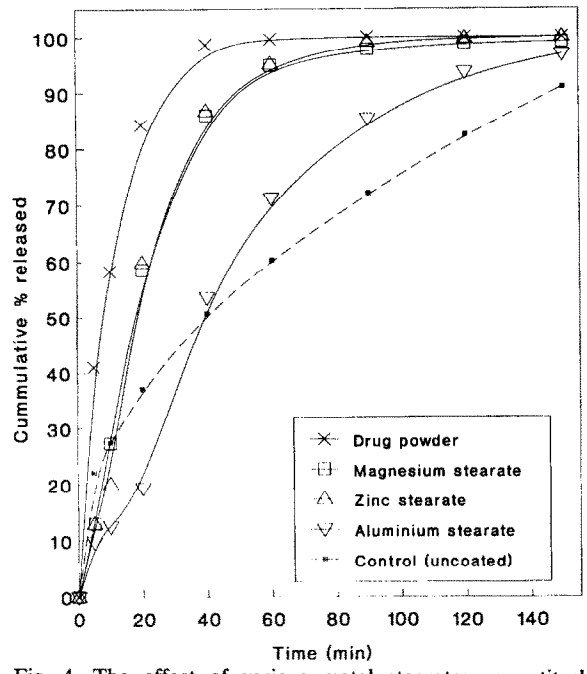

Fig. 4. The effect of various metal stearates as antitack additives on the drug release from the coated granules.

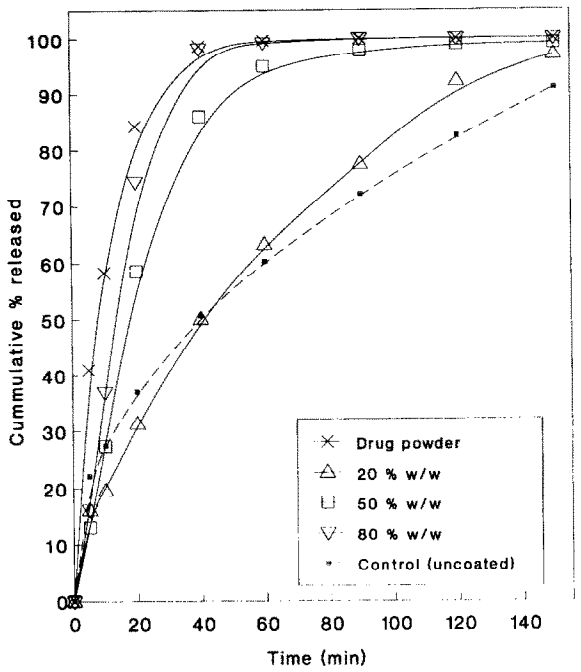

Fig. 5. Variation of drug release with the content of magnesium stearate in the MC film coat.

only, it seemed to occur for the other similarly hydrophobic metal stearate-MC combinations investigated as well.

Swelling of coated granules

Light microscopy showed that MC-stearate film-coated granules, on contact with the aqueous medium, swelled with rapid 'orange peeling' of the film coating (Fig. 6). Similar observations were also noted for aluminium and zinc stearates. The breakage of the film originated at weak points in the coating whereby air entrapped inside the particle core first escaped, i.e., when the pressure of the entrapped air (which is compressed as the liquid medium penetrates into the coated granule) equalled that of the incoming water. This peeling action with its consequential shearing forces would have caused the dislodgement of the underlying drug crystals that were partially embedded in the first drug-MC layer, resulting in an enhancement of drug release. A similar phenomenon was observed when a flat piece of a free cast MC-magnesium stearate film

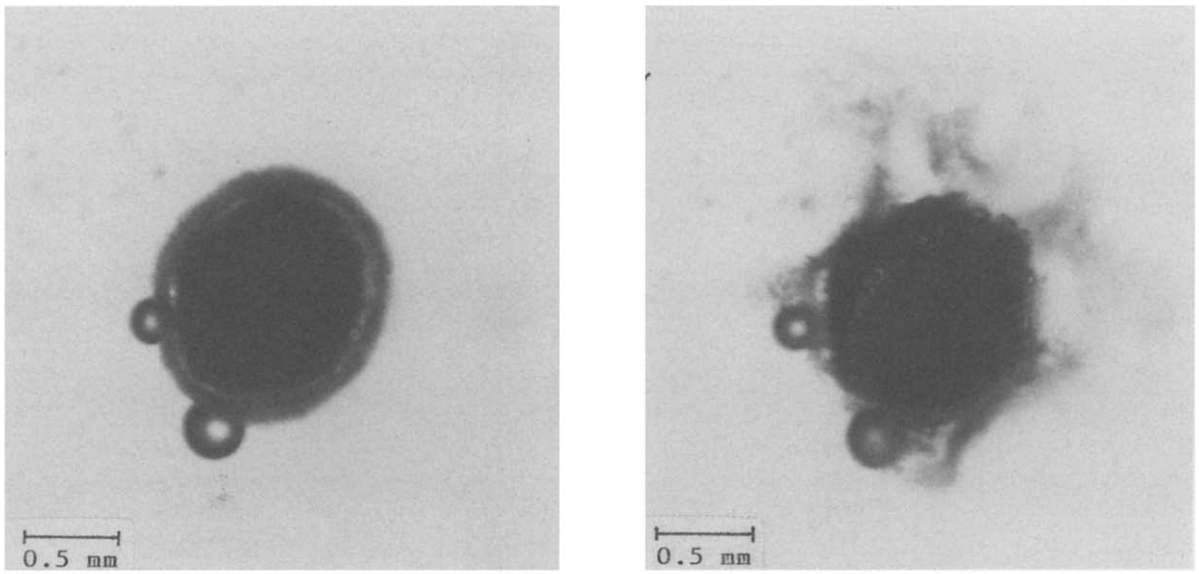

Fig. 6. Photomicrographs showing the 'orange peeling' phenomenon when magnesium stearate-MC film coated granules were placed in water after (left) 30 s, (right) 3 min (25 × magnification).

curled up when it was soaked in water (Fig. 8). This serves to substantiate the peeling action of the swollen magnesium stearate-loaded film coat of the coated granules seen under the light microscope. This peeling phenomenon is not observed at all in the formulations where other insoluble particulate additives, namely talc, stearic acid and silicon dioxide were used (Fig. 7). The

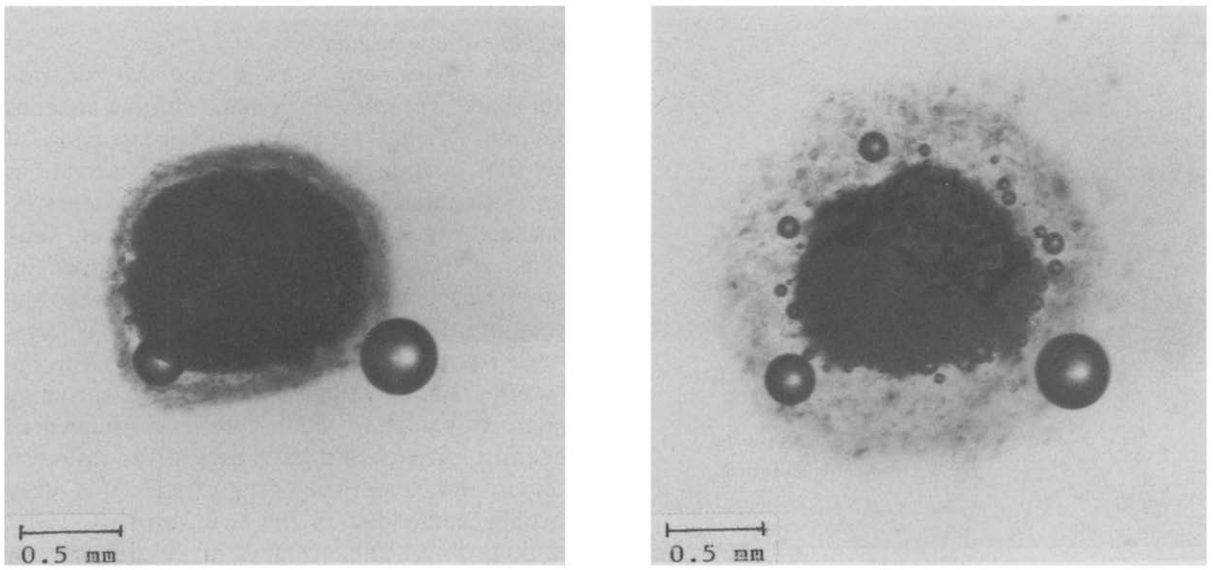

Fig. 7. Photomicrographs showing uniform swelling of the film coat when talc-MC film coated granules were hydrated in water after (left) 1 min, (right) 5 min (25 × magnification).

release of the drug in this case, may have occurred mainly via diffusion through and surface erosion of the coating film.

The amount of magnesium stearate incorporated into the film composition also had an effect on the drug release rate. The higher the magnesium stearate content, the faster the drug release (Fig. 5). It is reasonable to assume that this mechanistic peeling action would be more remarkable as the amount of the loaded magnesium stearate in the MC film was increased. It should be emphasized, however, that the occurrence of this salient mechanistic phenomenon does not preclude the probable involvement of other factors since the hydrophobic additive loaded into the MC film must act to alter the properties of this hydrophilic polymer.

The metal stearates, being highly hydrophobic, having contact angles exceeding 100° (Lerk et al., 1976, 1977), would exhibit strong hydrophobic

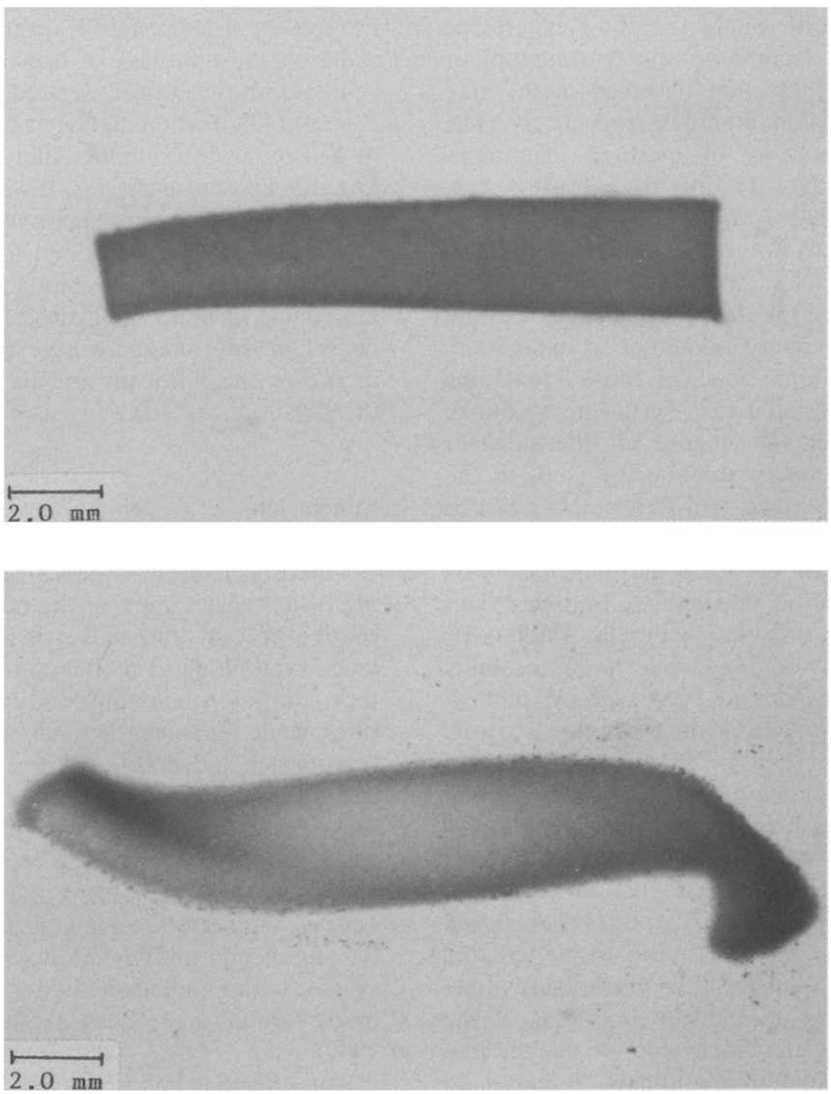

Fig. 8. Photomicrographs showing the swelling with simultaneous 'curling up' of a piece of free cast magnesium stearate-MC film in water (4.3 × magnification): (upper) before immersion in water, (lower) after immersion in water.

interaction. It is plausible that there is a tendency for the hydrophobic particles to exist as agglomerative clusters rather than individually and uniformly dispersed in the hydrophilic polymer film. This in turn, would cause the polymeric molecular chains in the film to adopt a particular orientation. Theoretically, the consequences of this anisotropy-like effect are potentially unfavourable (Nielsen, 1962) which could result in significant variation in the internal stress distribution within the film coat of the granules. On hydration in water, the MC film loaded with magnesium stearate would therefore experience uneven swelling leading to the 'curling up' or 'peeling off' phenomenon observed in the free film and the coated granules respectively. The anisotropy of swelling of oriented macromolecules has been described by Alfrey (1948).

As an additional consideration, it seemed that the water repellent surface of magnesium stearate would not interact effectively with MC. Therefore, it is expected that the interfacial voids would be larger and/or more numerous in magnesium stearate-loaded films than in those containing more hydrophilic additives. According to Funke (1967), the lower the degree of filler-polymer interaction, the more extensive the voids at the filler-polymer interface and hence the faster is the diffusion rate through the polymer film, especially above the CPVC when the polymer matrix is unable to bind all the additive particles. This postulation is consistent with the finding by Okhamafe and York (1984) that the permeability coefficient was higher in hydroxypropyl methylcellulose films loaded with hydrophobic rutile titanium dioxide than in those containing untreated anatase titanium dioxide. Hjärtstam et al. (1990) have also shown that the permeability of composite films of ethylcellulose and hydroxypropyl methylcellulose increased under the influence of an applied tensile stress. It is believed that the application of a tensile stress created alteration in the film structure which could affect the transport and mechanical properties of the films. Likewise, the inclusion of magnesium stearate in the MC films could have counteracted the cohesive forces and caused disruption in the homogeneity of the polymer film structure. All these effects introduce excessive internal stress in the polymer film resulting in an exceptionally high release rate of the coated product.

A sprayed film is inherently less coherent since it is deposited as contiguous layers of polymeric material (Spitael and Kinget, 1977; Li and Peck, 1990; Wouessidjewe et al., 1991). The poor cohesion between contiguous layers, a possible contributing factor to the peeling phenomenon, is further exacerbated by the good lubricating and antitack properties of the metal stearates, in particular magnesium stearate. This is supported by the studies of Rowe (1977) on the effect of lubricants on the adhesion of hydroxypropyl methylcellulose films to tablet surfaces and Johnson and Zografi (1986) who conducted butt adhesion test of hydroxypropyl cellulose films on well defined low energy solid substrates. It was postulated that lubricants such as magnesium and calcium stearate interfered with bond formation and decreased adhesion by presenting a surface consisting mainly of nonpolar hydrocarbon groups. The degree of interference will be dependent on the nature of the lubricant and its concentration in the substrate.

Conclusion

One drawback in aqueous polymer film coating is the tacky nature of the polymer during the coating process; this makes it almost impossible to be used alone as a coating formulation. Antitack additives when employed in sufficient quantities, while reducing the inherent tackiness of the film-former and improving process performance, can also exert significant influence on the drug release behaviour of sprayed films formed from water-soluble polymers. This aspect is particularly important in view of the generally high level of antitack additives recommended for the optimum coating of multiparticulate dosage forms such as granules and pellets with aqueous-based polymeric formulations (Li et al., 1989; Nagai et al., 1989).

An effective antitack agent for a particular coating formulation may be deleterious to the end-use properties of the film that is formed.

This is exemplified by magnesium stearate in the present study. Magnesium stearate was found to be highly effective amongst the additives investigated, as an antitack agent for MC film coating of granules, but the extreme nature of its release-enhancing action is a potential disadvantage in the controlled-release function of the polymer films. It may be possible to formulate a more useful antitack agent that provides the best compromise of properties (acceptably low tack and minimum undesirable effect on the release characteristics) by combining such additives.

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