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# COATED PELLETIZED DOSAGE FORM: EFFECT OF COMPACTION ON DRUG RELEASE

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## ABSTRACT

The goal of this study was to investigate the effect of compaction of a coated pelletized dosage form on drug release. Three sizes of microcrystalline cellulose and hydrous lactose pellets containing 4% chlorpheniramine maleate (CPM) were manufactured using a rotogranulator (Glatt GPCG-1). Pellets having mesh cuts of: 590-840 μm (20/30 mesh); 420-590 μm (30/40 mesh); and 250-420 μm (40/60 mesh) were then coated with an aqueous ethylcellulose pseudolatex dispersion plasticized with 24% dibutyl sebacate (DBS). Percent weight gains were 25, 30 and 35% for the 20/30, 30/40 and 40/60 mesh pellets, respectively. Coated pellets were blended with 39.3% by weight excipients, then mixtures lubricated and compacted using a Korsch PH106 instrumented rotary press set at 5 kN and 20 rpm (0.30 s contact time). Magnesium stearate was used as the lubricant at a 0.7% level. Excipients used were microcrystalline cellulose, spray dried lactose, pregelatinized starch, dicalcium phosphate, spray dried sorbitol, polyethylene glycol 8000 powder and compressible sugar. Results indicated this coating to be suitable for the controlled release of CPM from small pellets (250-840 μm). However, films did not have the appropriate mechanical properties to withstand compaction stress without rupturing, regardless of the pellets particle size and excipients used. After compaction, depending on pellet size, between 65-100% CPM was released after one hour as opposed to 10-30% for the non-compacted material. The controlled release properties of the pellets were therefore lost during the process.

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## INTRODUCTION

The use of organic solvents for the formulation and process development of pharmaceutical dosage forms is decreasing due to environmental and safety concerns. This poses a problem for monolithic modified release products that utilize a coating technology based on these solvents. This means that controlled release coatings must be developed using an aqueous process for which the technology is still in its developmental stage. Films deposited from aqueous colloidal dispersions must have sufficient mechanical strengths to avoid any rupture in the GI tract that would potentially cause a dose dumping. This concern is also exacerbated by the use of permeability enhancers that are often added during the manufacture of such coatings in order to modulate the film permeability to suit a particular application[1]. Permeability enhancers have deleterious effects on film strengths since they might interfere with bond formation between colloidal particles[2].

One approach to circumvent the problem of film mechanical strength is to develop a coated pelletized system. Mechanical strength of films deposited onto pelletized dosage forms is not problematic since the probability of dose dumping is practically nonexistent. However, the main limitation of a pelletized capsule dosage form is that the maximum achievable dose is generally around 250 mg, due to pellet packing characteristics and size constraint dictated by capsules. Rather than using this approach, pellets could be compacted to form a tablet. Then, higher dose strengths could be administered to patients since large volume tablets generally have greater patient acceptability than capsules. The difficulty involved in such an approach is that films can fracture upon compaction and produce a large difference in the release characteristics from the pellet before and after compaction[3]. In the case of metoprolol pellets coated with an ethylcellulose film deposited from organic solvents, it was found that an

increase in the particle size of pellets (0.44 to 0.85 mm range) gave more rupture during compaction, at a 8-9 kN force. It was later found that microcrystalline cellulose added to phenylpropanolamine-resin and cellulose acetate butyrate complexes, conferred protection against compaction pressures[4]. In another recent study[5], potassium chloride crystals were encapsulated with two solvent-based and four aqueous-based film forming dispersions in order to evaluate the ability of these films to withstand compaction pressures. Results demonstrated that films deposited from organic solvent systems provided more mechanical stability than films that used an aqueous technology. However, a high compaction pressure, i.e. 120 MPa (12 kN/cm$^2$) for a duration of 5 s, was used. The data indicated that it might be difficult to develop a film that will not fracture significantly upon compaction. The ideal situation would be to have coated pellets that would withstand relatively high compaction forces, without excessive film damage.

This study describes the use of a rotogranulator for the manufacture of chlorpheniramine maleate (CPM) pellets. These pellets are coated with an aqueous ethylcellulose pseudolatex dispersion, and then compressed. Ethylcellulose is a water-insoluble polymer widely used for the development and production of controlled release dosage forms. The goals of this study were to investigate the effect(s) of 1) pellets particle size and 2) excipients added before compaction, upon the release profile of CPM coated pellets after compaction. The results provide information about the feasibility of compacting pellets coated with ethylcellulose membranes deposited from a totally aqueous system.

## MATERIALS AND METHODS

### Formulation and Process for Pellets

Chlorpheniramine maleate (CPM)(Sigma, St-Louis, MO) was used as the model compound because of its high aqueous solubility that is

TABLE I

Process Parameters for the Manufacture of Chlorpheniramine Maleate Pellets

| |
|---|
| Batch Size: 1.3 kg |
| Inlet Air Velocity: 10 m/s |
| Inlet Air Temperature: 25°C |
| Height of Rotor Plate: adjusted for 0.5 kPa product pressure difference; rpm: 360 |
| Nozzle: Schlick, 1.0 mm aperture |
| Atomizing Air: 2 bars |
| Spray Rate: 22 g/min. |
| Amount of Granulating Solution (Water): 1200-1450 g[a] |
| Drying Temperature: 60°C[b] |

[a]actual amount is dependent on the desired pellet size. More water produces larger pellets

[b]Pellets were ran for 5 minutes in order to smooth the surfaces before drying. Product discharged when outlet temperature reached 50°C.



independent of pH (pKa = 9.2), i.e. 574 mg/ml in 0.1N HCl and 562 mg/ml in 0.1 M pH 7.4 phosphate buffer[6]. The pellet formulation consisted in 35% microcrystalline cellulose (Avicel PH101, FMC Corp., PA) and 61% hydrous lactose (Pharmatose 200M, Mallinckrodt, Montreal) by weight. CPM was added at a 4% level. Pellets were manufactured using a Glatt GPCG-1 rotogranulator (Glatt Air Techniques, NJ) equipped with a waffled plate. This instrument is capable of producing small pellets. This would be a more difficult task with conventional extrusion/spheronization equipment. Process parameters are shown in Table I.

Several batches of 1.3 kg were consecutively manufactured in order to generate a sufficient amount of material for all the coating and compaction trials. After each run, pellets were sieved (U.S.) and three mesh cuts were collected for the coating trials: 20/30 (590-840 um), 30/40 (420-590 um) and 40/60 (250-420 um) mesh. All similar mesh cuts generated from these

batches were combined together and finally blended in a twin shell blender set at 35 rpm for 3 minutes. Assay and dissolution were done on the final blend for each cut. Pellet surface morphology was evaluated by scanning electron microscopy (Jeol JSM 820). Size distribution was also determined after the manufacture of each batch by sieving.



Pellet Assay and Dissolution

Six samples of one gram were taken from each mesh cut and ground with a mortar and pestle. The powder was transferred into a flask and water added q.s. ad 1000 ml. A magnetic stirring bar was then added and the mixture agitated for 30 minutes at room temperature under subdued light. An aliquot was then collected, filtered on 0.45 μm membrane (Millex-HA, Millipore, MA) and drug measured at 262 nm with a diode array spectrophotometer (Hewlett Packard model HP8451A) for CPM content. The standard solution was prepared at 40 μg/ml concentration. Drug adsorption onto the filtering membrane was assessed and was found to be negligible.

Dissolution was performed at 37 ± 2°C in USP apparatus 2 set at 75 rpm using 900 ml water as the dissolution medium. Five hundred mg of uncoated pellets were introduced in the dissolution vessels and samples collected at different time points for UV measurements at 262 nm. Percent CPM released with time profiles were then calculated. Lactose and microcrystalline cellulose did not interfere with the measurements at 262 nm. Standard curves for dissolution were prepared at 2.5-30 μg/ml CPM concentrations.

Coating Formulation and Process

An ethylcellulose pseudolatex dispersion (Aquacoat™, FMC Corp., PA) was used as the polymeric material. Dibutyl sebacate (DBS)(Sigma, St-Louis, MO) was used as the plasticizer at a 24% level (g/g Aquacoat™

solids). The pseudolatex dispersion was prepared as follows: the appropriate amount of Aquacoat™ was weighed, introduced in a glass beaker and agitated using a magnetic stirrer. DBS was added over a 1-2 minute period and then water was finally added to the plasticized latex to make the dispersion 20% by weight solids. The mixture was agitated for 15-17 hours before use. Pellets (800 g) were coated in a Wurster column (Glatt GPCG-1) with a bottom nozzle configuration. Percent weight gains (g coating/g uncoated pellets) were 25, 30 and 35% for the 20/30, 30/40 and 40/60 mesh pellets, respectively. A 1.5% weight increase HPMC 6 cP (Pharmacoat 606, Shin-Etsu Chemicals, Japan) overcoat was applied to the coated pellets in order to decrease tackiness during the drying/curing period. Coating process parameters are shown in Table II. CPM release profiles were assessed as described above for the uncoated pellets, except that the sample size was 650 mg.



Compaction Studies

Compaction studies were done on an instrumented Korsch PH106 rotary press (Korsch Tableting Inc., NJ) fitted with one set of 19 X 7.9 mm capsule deep concave tools. The press was set at 20 rpm (0.30 s contact time) and 5 kN (range: 4.8-5.2) compaction force. Microcrystalline cellulose (Avicel PH200 and PH101, FMC Corp., PA), spray dried lactose (DCL11, Mallinckrodt, Quebec), spray dried sorbitol (E-Merck, Germany), dicalcium phosphate anhydrous (Di-Cafos A, Germany), compressible sucrose (Di-Pac, Amstar Sugar Corp., NY), polyethylene glycol 8000 powder (Carbowax, Union Carbide, CT) and pregelatinized starch (Starch 1500, Colorcon, PA) were used as excipients for the compaction trials. Each excipient was added to coated pellets at a 39.3% by weight level and the mixture blended in a twin shell blender for 3 minutes at 35 rpm. Magnesium stearate (Mallinckrodt, Quebec) was used as the lubricant at a 0.7% by weight level. It was passed through a 60 mesh (U.S.) sieve, added to the

TABLE II

Process Parameters for Pellet Coating

| |
|---|
| Batch Size: 800 g of pellets |
| Inlet Temperature: 60°C |
| Nozzle: Schlick, 0.8 mm fluid aperture |
| Atomizing Pressure: 1.5 bar |
| Air Velocity: 3.5-4.0 m/s |
| Functional Coat: |
| Spray Rate: 8-9 g/min. |
| Outlet Temperature: 39-41°C |
| Overcoat: |
| Spray Rate: 5 g/min |
| Outlet Temperature: 40-42°C |
| Drying/Curing: 1 h at 60°C |



pellet mixture and blended for 3 minutes. Tablets of 900 mg, containing 540 mg of coated pellets, were manufactured from these blends and evaluated for drug release using the procedure previously described for uncoated pellets. Evidence of film rupture was assessed by scanning electron microscopy.

## RESULTS AND DISCUSSIONS

### Formulation and Process for Pellets

Figure 1 shows scanning electron photomicrographs of 4% CPM uncoated pellets. Surfaces were reasonably smooth and the pellets were also very hard, therefore, suitable for film coating. Pellet integrity was maintained during dissolution, i.e. the pellets did not disintegrate or dissolve upon exposure to water. The granulation end point was determined empirically, based on visual assessment of pellet size. For a given batch, the more water was added, the larger the pellets became. Figure 2 shows

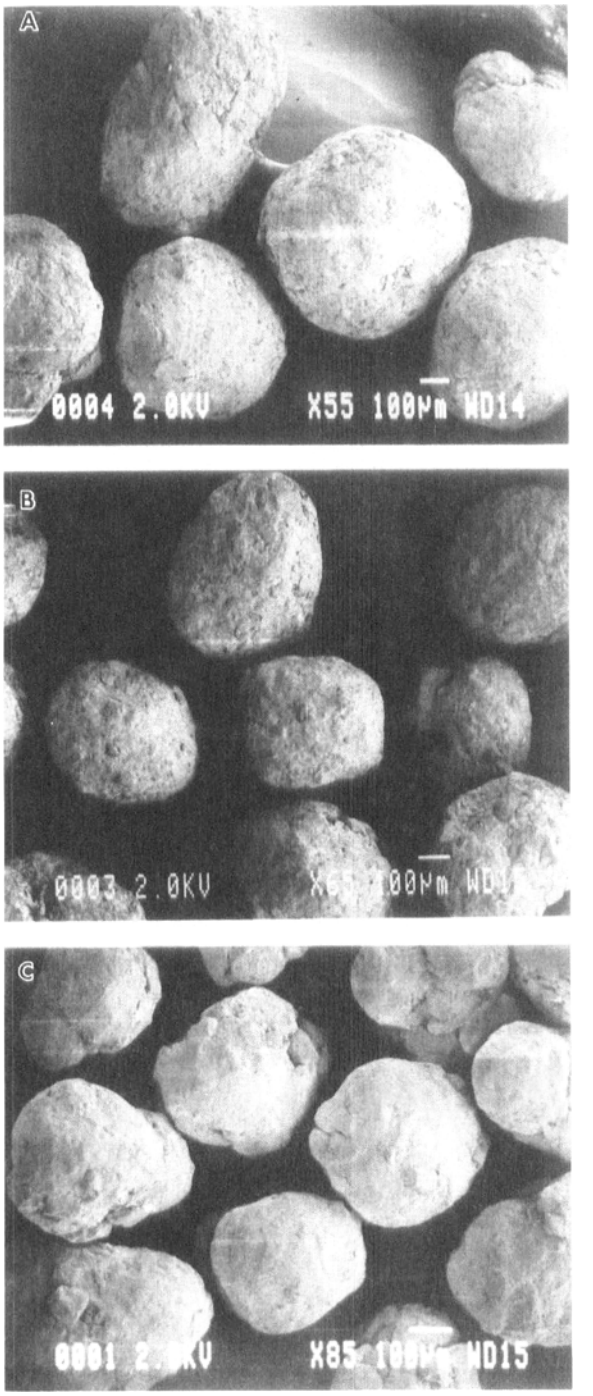


FIGURE 1

Scanning electron photomicrographs of 4% CPM uncoated pellets. A) 20/30 mesh (590-840 µm), X55; B) 30/40 mesh (420-590 µm), X65 and C) 40/60 mesh (250-420 µm), X85.

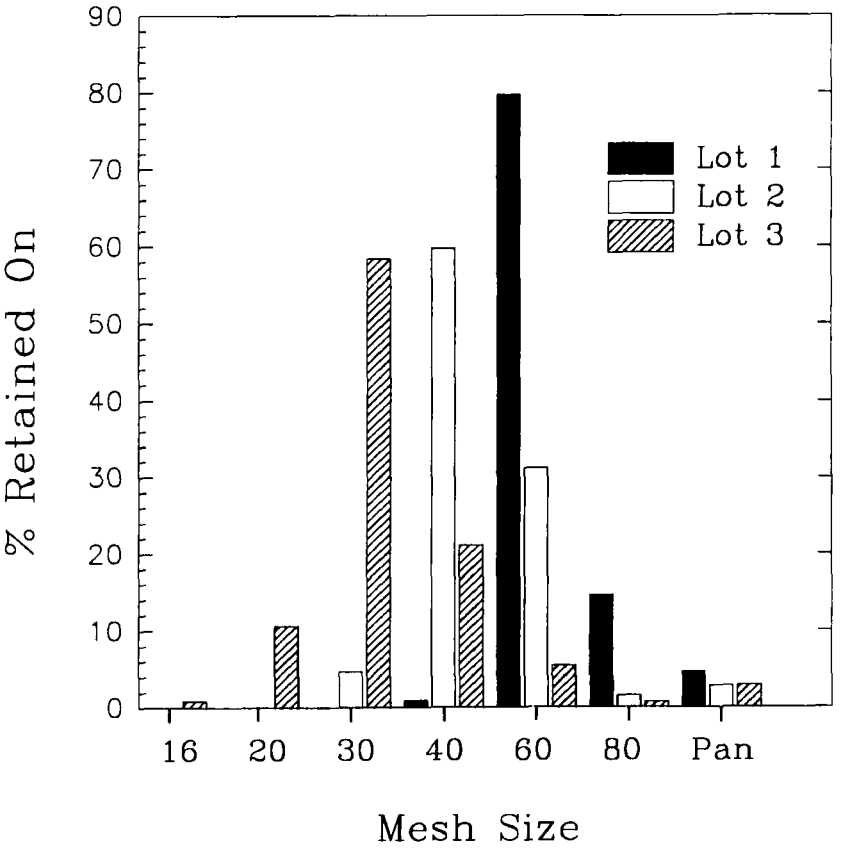


FIGURE 2

Size distribution of three batches of 4% CPM uncoated pellets having different end points. Pellets size was intentionally modified in order to generate the appropriate material for the compaction studies.

typical size distributions for three batches of uncoated pellets, indicating a narrow distribution for a given batch. Pellet size was intentionally modified in order to generate three size fractions that were necessary in order to assess the effect of particle size on CPM release after compaction.

Uncoated Pellet: Assay and Dissolution

Table III shows assay and dissolution data for the uncoated pellets. An interesting finding is that assay values were found higher for the fine

material. The same assay carried out on the material collected in the pan (< 80 mesh) came out at 137% CPM. One possible explanation could be that during drying, the water and CPM dissolved in it migrate to the surface of pellets. By nature of the process, these pellets are continuously subjected to erosion and therefore, excess drug ends up with the fine material. Dissolution data correlated very well with the assay results and indicates that the drug was readily available from the uncoated pellet.



Coated Pellets

Scanning electron micrographs (see fig.3) showed the films to be well deposited onto the pellets with very little defects. Coating efficiency was calculated based on the weight of dried coated pellets and was found to be about 95%. Film thicknesses were estimated by scanning electron microscopy and found to be approximately 20-25 μm for the 20/30 mesh and 30/40 pellets and about 15 μm for the 40/60 mesh pellets. CPM release profiles from coated pellets are shown in figure 4. Higher rates were obtained with the 40/60 mesh pellets due to a higher specific surface area and a reduced film thickness through which the drug must diffuse.

The drug release mechanism for pellets coated with ethylcellulose films, without a pore former, appears to be complex[7]. Osmotic pressure, diffusion through aqueous pores and possibly solution/diffusion through the polymer membrane have been proposed mechanisms. However, it has been suggested that the predominant release mechanism is a function of the coating level applied[8]. At low levels of coating, transport of the drug would occur primarily through cracks or pores in the coating whereas at higher levels, drug diffusion would be through the film itself. Scanning electron microscopy done on pellets exposed for 24 hours to dissolution fluids, did not reveal any cracks or pores larger than 0.5-1 μm. However, the presence of molecular-sized pores could not be assessed by the instrument. An analysis of the microstructure of these films warrants further investigations.

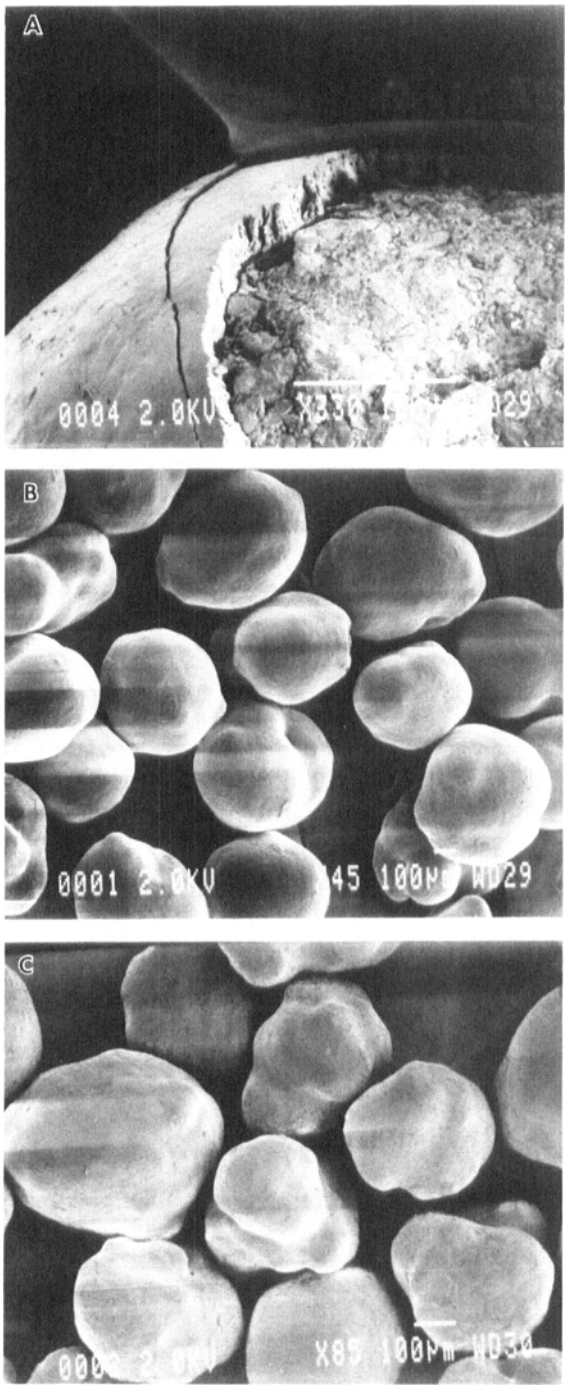


FIGURE 3

Scanning electron photomicrographs of 4% CPM coated pellets. A) 20/30 mesh, showing the functional coat and the overcoat, X33; B) 30/40 mesh, X45 and C) 40/60 mesh, X85.

TABLE III

Assay and Dissolution Results for Uncoated Pellets

| Size (mesh) | Assay[a] | mg of CPM Released[b] |
|---|---|---|
| 20/30 | 36.5 (0.3) | 37.0 (0.6) |
| 30/40 | 36.5 (0.2) | 36.4 (0.6) |
| 40/60 | 38.5 (0.3) | 38.4 (0.6) |
| 60/80 | 50.9 (0.4) | 51.3 (0.4) |

[a]in mg per gram of pellets. Mean (S.D.). Theoretical is 40 mg/g.
[b]after 30 min. Mean (S.D.).

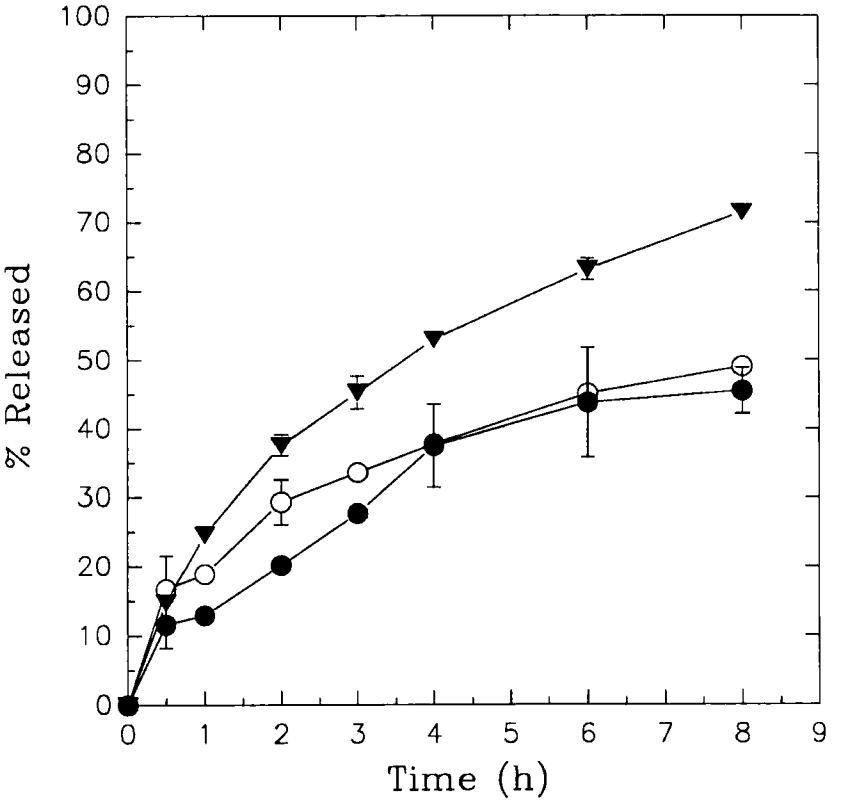


FIGURE 4

CPM release profiles. (●) 20/30 mesh, 72.2% released after 24 h; (○) 30/40 mesh, 87.1% released after 24 h; and (▲) 40/60 mesh, 91% released after 24 h.

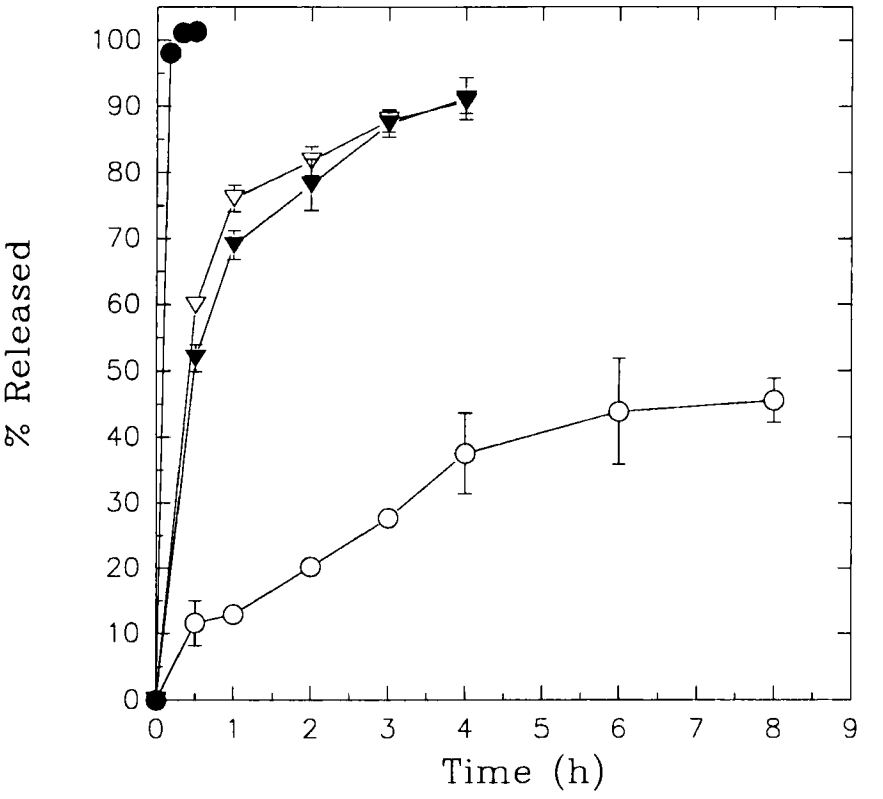


FIGURE 5

CPM release profiles from uncoated (●), coated (O) and compacted 20/30 mesh pellets: (▾) Avicel PH101 and (▿) Avicel PH200.

## Compaction Studies

Preliminary experiments indicated massive film fracture when 10-20 kN forces were used. Therefore, 5 kN was used for all trials because it was the minimal force that could produce a compact when using microcrystalline cellulose as the excipient. Dicalcium phosphate anhydrous and compressible sugar did not form a compact at this force. Microcrystalline cellulose provided compacts that disintegrated and regenerated the coated particles within less than 10 s as opposed to 7-10 m for the other excipients. Figures 5-7 show CPM release profiles from uncoated, coated

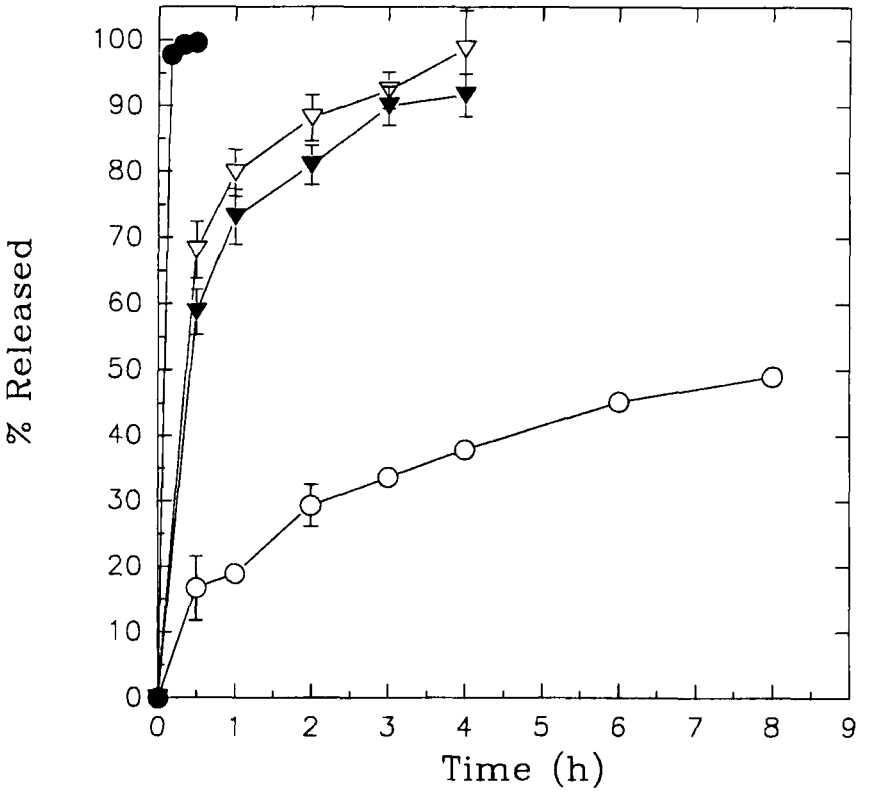


FIGURE 6

CPM release profiles from uncoated (●), coated (○) and compacted 30/40 mesh pellets: (▾) Avicel PH101 and (▿) Avicel PH200.

and compressed pellets. Films did not have the appropriate mechanical properties to withstand compaction stress without rupturing, regardless of the pellets particle size and excipients used. Actually, smaller pellets appeared to be more fragile than larger ones. This is probably due to the film thickness, which was found to be about 15 μm for the 40/60 mesh pellets, as opposed to 20-25 μm for the 20/30 and 30/40 mesh pellets. Nevertheless, the 40/60 (420-250 μm) mesh material was found to be more compatible, in terms of particle size, with direct compression excipients. Figure 8 shows that extensive film fracture was noticed and the damage

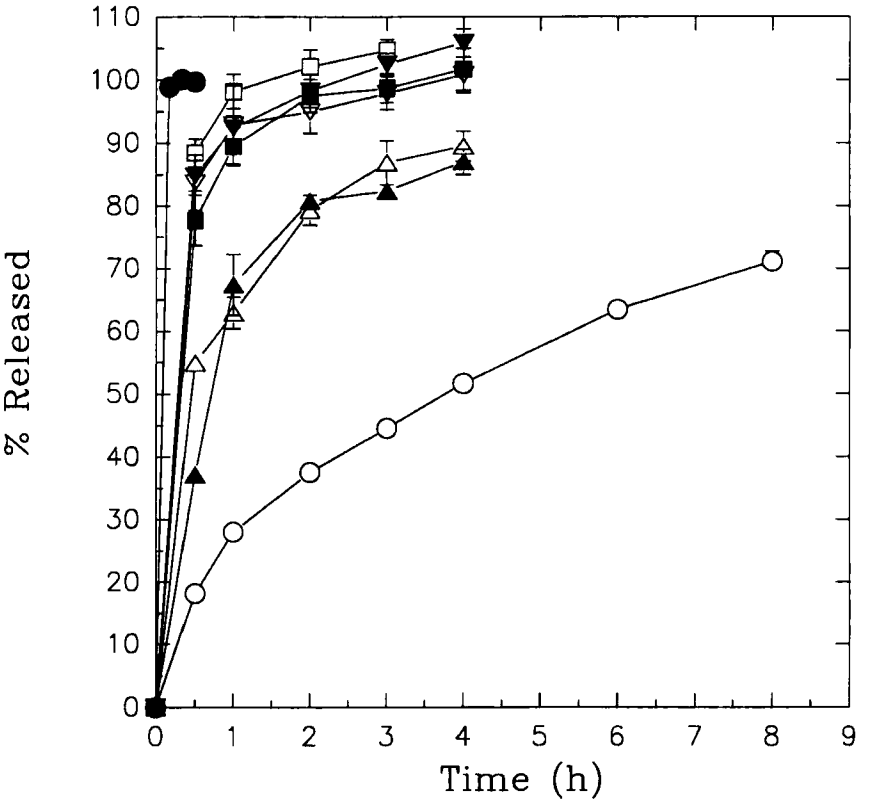


FIGURE 7

CPM release profiles from uncoated (●), coated (○) and compacted 40/60 mesh pellets: (▾) Avicel PH101; (▽) Avicel PH200; (■) lactose spray dried; (□) sorbitol spray dried; (▲) PEG8000 and (△) tablets dried at 75 °C for 24 hours.

was found to be predominant on tablet surfaces. Polyethylene glycol 8000 powder appeared to be superior to all other materials used in this study, but still, a lot of film rupture was seen. The fact that these tablets did not disintegrate but slowly eroded over a 35 minute period, could also explain why polyethylene glycol appeared to protect the coating.

These results are in agreement with a recent study[5] where potassium chloride crystals were coated with Aquacoat™ plasticized with 20% DBS.

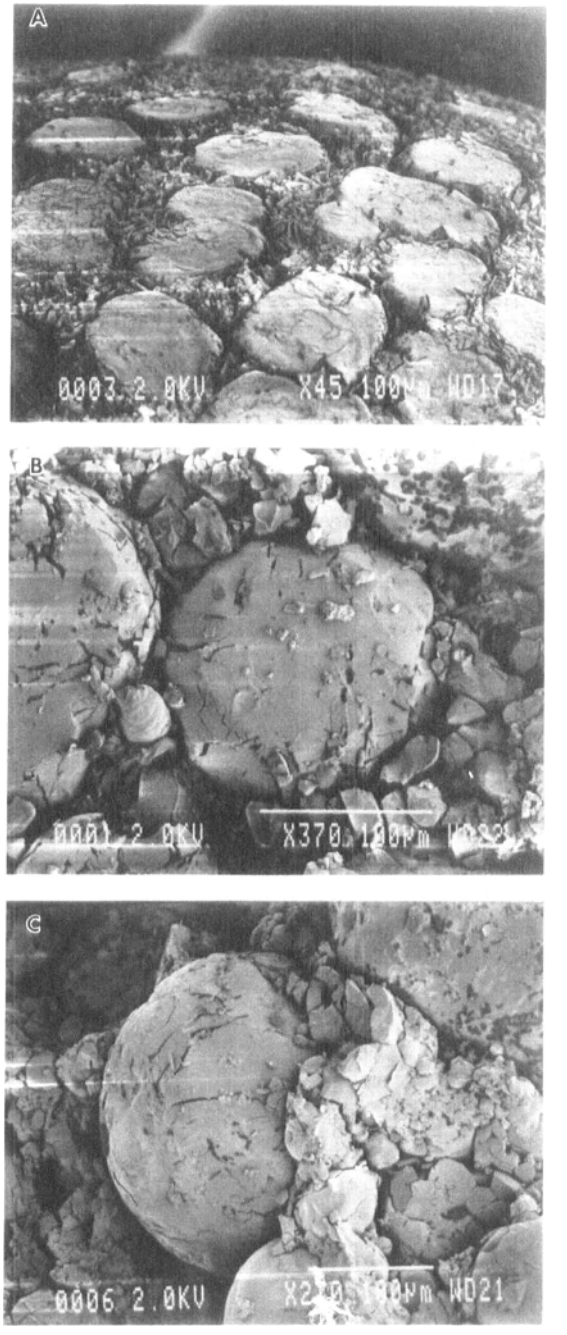


FIGURE 8

Scanning electron photomicrographs of compacted pellets showing film rupture. (A) surface of tablet, 20/30 mesh with Avicel PH101, X45; (B) surface of tablet, 40/60 mesh with PEG8000, X370; (C) tablet cross-section, 40/60 mesh with PEG8000, X270.

These authors noticed that the sustained release properties of encapsulated potassium chloride crystals were lost after compaction. Films deposited from organic solvents were found to be much more mechanically stable to compaction.

Tablets containing 40/60 mesh coated pellets and microcrystalline cellulose (Avicel PH101) were introduced in a convection oven set at 75°C for 24 hours. Then, dissolution studies were carried out on this material (see Fig. 7). These tablets still disintegrated within less than 10 s. After 30 minutes, 55% of CPM was released for the tablets dried at 75°C as opposed to 85% for the non-heated material. This clearly shows that a certain amount of the fissures were sintered by exposing the compacted pellets to a temperature above the film glass transition temperature, which is about 43-44 °C for a film of that composition[9].

Future investigations should look at the effect of plasticizer type and level on viscoelastic properties of coatings as well as other polymers, such as poly(ethylacrylate methylmethacrylate) copolymer films (Eudragit™). Some degree of success has been achieved with this copolymer when used to coat theophylline granules that were later compacted[10].

## CONCLUSIONS

This investigation showed that films manufactured from an ethylcellulose pseudolatex dispersion plasticized with 24% DBS, are suitable for the controlled release of CPM from small pellets (250-840 μm). However, these films do not have the appropriate mechanical properties to withstand compaction forces without rupturing. The controlled release properties of the compacted pellets are therefore lost during the process. More work on the effect of plasticizer type and level on viscoelastic properties of coatings is needed to develop compressed pelletized dosage forms with controlled release properties.

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