Mechanism of Pellet Coat Rupture and Its Effect on Drug Release

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In the formation of a coated controlled release preparation with functional coat layers, hydroxypropylmethylcellulose was used to form a diffusion layer which swelled immediately upon wetting. Eudragit RS30D was used to form the outer retention layer. The rupture of pellet coat occurred when the Eudragit RS30D was unable to withstand the expansion in volume due to the influx of water and swelling of the hydroxypropylmethylcellulose diffusion layer. The sucrose core was able to contribute an osmotic effect. The hydrostatic pressure built up within the pellet can cause the pellet coat to rupture. Sodium chloride deposited in the diffusion coat was able to delay the bursting of the pellet coat. This was due to the competition for the imbibed water between sodium chloride and hydroxypropylmethylcellulose.

The rupture of the pellet coat did not result in a total failure of the controlled drug delivery mechanism. Similar drug release rates were obtained irrespective whether there was a puncture in the pellet coat or not. Pressure built-up in the region away from the puncture pushed the core material towards the point of puncture and sealed the puncture point. In addition, the swelling of polymer around the point of rupture ensured continuity in the drug diffusion barrier.

Key words pellet coat rupture; drug release; osmotic effect; swelling; multi-layer coating

In the design of controlled release pellets, layered coats are effective diffusion barriers to control the rate of drug release. Swellable polymers are often used as the coats for controlling drug release.[1,2] In some formulations, burst coats were seen at the end of the dissolution testing when an insoluble or poorly soluble outer coat was employed.

The bursting of pellet coat during dissolution may be caused by a defect in the coat, erosion of polymers in coating material or non-elasticity of coating films. In addition, the osmotic pressure gradient can generate substantial hydrostatic pressure in the core causing rupture of the outer insoluble coats used for controlling the drug release.[3] Several factors such as properties of the core material, characteristics of the outer coating polymer, the type of plasticizer and other additives may give rise to variability in the coat properties that could, in turn, affect the drug release profile.[4] Water-soluble materials such as sucrose and urea could enhance drug release by causing the formation of a porous membrane if they are incorporated with the coating polymer.[5] The addition of hydroxypropylmethylcellulose (HPMC) to a water-insoluble membrane was also reported to cause pore formation or mechanical weakness to the membrane resulting a in higher drug release rate.[6]

Plasticizers play an important role in the formation of a film. Generally, the main function of a plasticizer is to make the film softer and more pliable. Several researchers have demonstrated that plasticizers produced significant effects on drug release when they were incorporated with the rate regulatory membranes of coated dosage forms.[7,8] Rowe[9] suggested that the cracks or defects on the polymeric coats enhanced drug release. The addition of a suitable plasticizer prevented the polymeric coat from cracking, thereby improving the drug release retardant properties of the coat.

It is unlikely that any one polymer possesses all the desired coat properties for an ideal controlled release pellet system. A well-designed multilayer coating would be comprised of different polymeric layers that act synergistically to control the release of the drug within. By this method, the total amount of coating polymers needed to achieve a desired efficiency in sustaining drug release is reduced. Multilayer coating was also able to control the drug release rate over a prolonged period and this property depended on the permutation of the component layers of the granule coat.[10]

The aim of this study was to investigate the mechanism of coat rupture of multilayer-coated pellets and its effect on the drug release profile. Non-pareil beads were coated with three different functional layers: deposition layer consisting of the drug, diffusion layer forming the diffusion barrier and retention layer for retaining material and providing an additional diffusion barrier. The thickness of the diffusion layer was expected to affect drug release rate. Since the thickness of the diffusion layer could play an important role in controlling drug release, the effects of an osmotic agent in the multilayer-coated pellets were investigated. The osmotic agent employed was sodium chloride.

Experimental

Materials Chlorpheniramine maleate (BP grade) was used as the model drug. Sodium chloride (AR grade, Merck, Germany) was used as the osmotic agent. Non-pareil beads (Nu-Pareil® PG, 20/25 mesh, Crompton & Knowles, U.S.A.) of sucrose and starch were used as the core substrate on which the coating solution was applied. The non-pareil beads were sized using a stereomicroscope (Olympus, SZH, Japan) with video-camera (SONY, SSC-M370CE, Japan) and image analysis system (Synoptics, Image Analysis System, UK) to have a mean size of 0.76 mm and standard deviation of 0.026 mm. The coating polymers were HPMC (HPMC 4 mPas, Pharmacoat 904 and HPMC 400 mPas, Metolose 90-SH, Shin-Etsu Chemical, Japan) and methacrylate in the form of an aqueous dispersion (Eudragit RS30D, Rohm Pharma, Germany). Polyethylene glycol (PEG 6000, BASF, Germany) was used as a plasticizer. All materials were used as supplied.

Composition of Multilayer Coat and Preparation of Coating Dispersions Three different coating dispersions were used for the multilayer film coats on the non-pareil beads. The innermost deposition layer was a coat containing 2% (w/w) chlorpheniramine maleate (based on the weight of non-pareil beads) and 3% coating level of HPMC 4 mPas. The coating level is the quotient of the weight of dry polymer applied and the weight of the non-pareil beads used, expressed as a percentage. The middle diffusion layer consisted of HPMC 400 mPas at varying coating levels used alone or with sodium chloride. The outermost retention layer comprised 7.5% coating level of Eudragit RS30D. For each of the three coating dispersions, 10%

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Table 1. Process Conditions for the Coating of Pellets

Parameters	Deposition of HPMC 4 mPas and HPMC 400 mPas coats	Deposition of Eudragit RS30D coat
Batch size (g)	200	200
Inlet air temperature (°C)	75	40
Atomizing air pressure (bar)	1.3	1.2
Spraying rate (ml/min)	4.0	7.5
Spray nozzle diameter (mm)	0.8	0.8
Drying air temperature (°C)	75	65
Fluidizing air flow rate (m^3/h)	115	115

(w/w) PEG 6000, based on the dry polymer weight, was incorporated. A batch of non-pareil beads was also pre-coated with a sealing coat of 5% coating level of Eudragit RS30D prior to the application of the deposition layer. This sealing coat was prepared to eliminate the osmotic effect of the sucrose in the pellet cores.

The coating dispersion of HPMC was prepared by dispersing the polymer in hot water and allowing the polymer to hydrate overnight in the refrigerator. The dispersion was made up to volume before coating. Eudragit RS30D was used as supplied. The plasticizer and/or drug were added prior to use.

Coating Process Batches of 200 g non-pareil beads were coated in a bottom-spray fluidized bed using the Wurster air suspension method (Aeromatic, Strea-1, Switzerland). Continuous coating of the beads was carried out using the modified method of Wan *et al*.[11] The process conditions are summarised in Table 1.

The type and concentration of polymer used and the order by which the coating dispersions were applied govern the codes used for identifying the layer coats. Coat layers are separated by a forward slash, starting with the innermost layer to the outermost. The letters G, H, E, S and C denote HPMC 4 mPas, HPMC 400 mPas, Eudragit RS30D, sodium chloride and chlorpheniramine maleate respectively. The accompanying number for the polymer and drug denotes the coating level. For the osmotic agent, the accompanying number denotes percentage weight of the osmotic agent with respective to the dry weight of the HPMC 400 mPas used. For example, E5/C2G3/H10/E7.5 indicates a 5% coating level with Eudragit RS30D followed by deposition layer of 3% coating level HPMC 4 mPas and 2% (w/w) chlorpheniramine maleate, 10% coating level with HPMC 400 mPas and 7.5% coating level with Eudragit RS30D. Pellets after coating had an increase in diameter ranging between 0.75 to 0.95 mm.

Dissolution Studies Dissolution tests were carried out using a paddle apparatus (USP XXIII, Method II; Hanson Research, 72-RL, U.S.A.) at 37± 1 °C with the paddle rotating at 50 rpm. A sample of coated pellets, about 1 g, accurately weighed, was used and the dissolution medium was 1 l deaerated distilled water. At pre-selected time intervals, 5-ml samples were collected over six hours using an automated sampler (Hanson Research, Dissoette 27-6A, U.S.A.). The amount of chlorpheniramine maleate released was determined by UV spectrophotometer (Hewlett Packard, 8451A, U.S.A.) at 262 nm. During dissolution studies, the concurrent release of sodium chloride was also determined. A 2-ml sample was used for sodium chloride assay. The assay was achieved by determining the rate of increase of sodium ions in the dissolution medium with time using atomic absorption spectrometer (Perkin Elmer, 3110, U.S.A.). At least three replicates were carried out and the results averaged.

Bursting Studies The coated pellets were stirred in the dissolution apparatus in accordance with the conditions employed for dissolution. At preselected time intervals, some pellets were removed from the vessel, placed on a petri dish and examined for any fissure on the retention layer using a stereomicroscope (Olympus, SZH, Japan). Thirty pellets were examined at each time interval and the percentage of pellets with evidence of rupture was determined. The pellets were discarded after examination. The determinations were carried out in triplicates and the results averaged.

Swelling Studies The swelling characteristic of the coated pellets was determined by soaking the coated pellets in a small volume of dissolution medium placed in a thermostatically-controlled holder (Fig. 1) at 37±1 °C. At pre-selected time intervals, video prints of the pellets were taken using a stereomicroscope (Olympus, SZH, Japan) connected to a video camera (SONY, SSC-M370CE, Japan) and video printer (SONY, UP-890CE, Japan). The diameters of five pellets were measured from the prints by using a digital vernier caliper (Mitutoyo, CD-6″BS, Japan) and the results averaged. The swelling index, which represents the degree of swelling, is the percentage increase in diameter of pellet.[12]

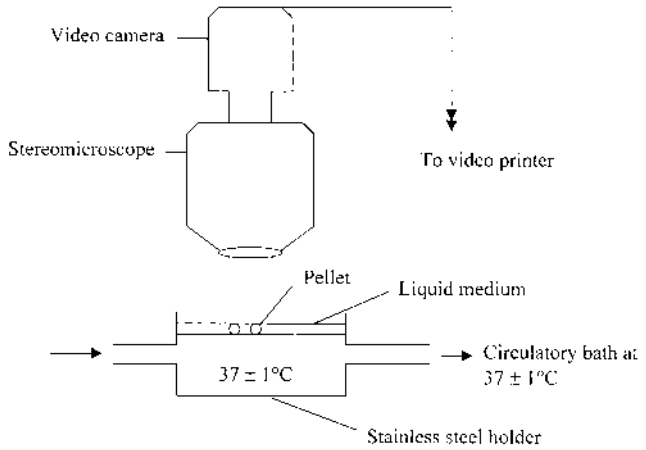

Fig. 1. Diagram of Equipment Used for Swelling Studies

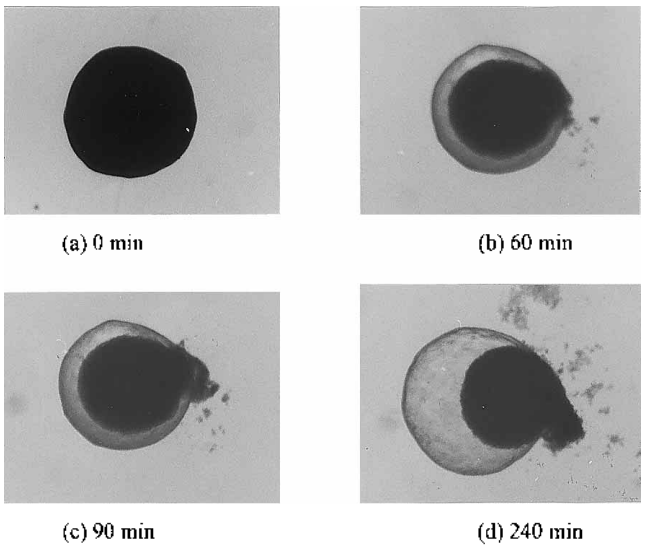

Fig. 2. Photographs Showing the Swelling Process Leading to Rupture of Pellet at Varying Time Intervals

Viscosity Measurement Apparent viscosity at 37±1 °C was determined using a U-tube of size D in accordance with method I stated in the British Pharmacopoeia (1993).

Preparation of Pellets with Pricking Holes A coated pellet was placed in pellet holder with a small depression. A mark about 0.25 mm was made above the tip of a 0.1 mm diameter needle. Using this needle, a small hole was pricked centrally at the apex of the pellet. After pricking, the needle with pellet was raised and examined for any evidence of the needle tip emerging from the opposite end. Only those pellets punctured to the desired depth were selected. The needle was then carefully removed.

Results and Discussion

In a multilayer coat for controlling drug release, the thickness of the diffusion layer is directly related to its extent of swelling. A coat that shows a greater extent of swelling will produce a thicker diffusion layer. This is achieved by the use of an osmotic agent in attracting water through its osmotic effect, thereby producing a thicker diffusion layer. The extent of swelling is determined by measuring the size of the pellets soaked in water over time. The process of swelling leading to rupture of the pellet was closely monitored and is presented in Fig. 2. The coated pellet was opaque prior to the swelling

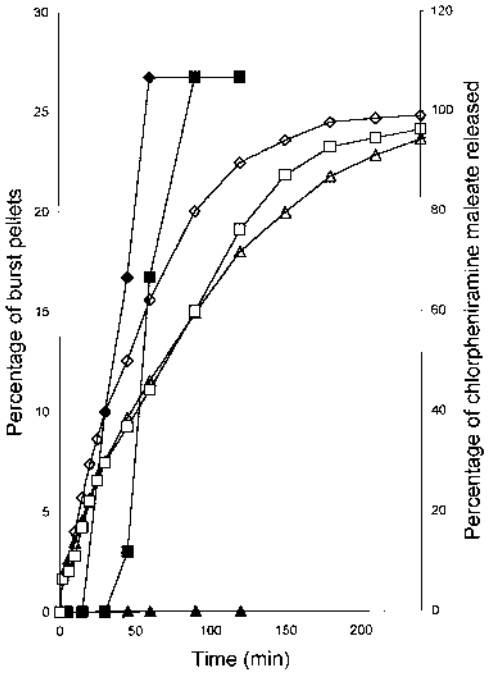

Fig. 3. The Extent of Coat Rupture (Close Symbols) and Chlorpheniramine Maleate Release (Open Symbols) with Time

C2G3/H10/E7.5 (◆, ◇), C2G3/H10S30/E7.5 (■, □), E5/C2G3/H10/E7.5 (▲, △).

test. After soaking for 60 min, a transparent gel layer formed around the pellet (Fig. 2b). The number of pellets with ruptured coats was found to increase significantly when the swelling index, the percentage increase in pellet size after soaking, approached 8%. A translucent gel was found diffusing out from the pellets at the point of rupture. This was eventually followed by leakage of some core material into the surrounding medium (Fig. 2c). After rupture, the core material was found to have shifted from a central location to an eccentric position next to the site of pellet rupture (Fig. 2d).

Control pellets with a sealing coat of Eudragit RS30D (E5/C2G3/H10/E7.5) were prepared. The composition of this sealing coat was similar to that of the retention coat. The purpose of the sealing layer was to minimize the solvation of the sucrose core. The onset of coat rupture began after exposure of C2G3/H10/E7.5 and C2G3/H10S30/E7.5 pellets in the dissolution medium for about 15 and 30 min respectively (Fig. 3). The coats of E5/C2G3/H10/E7.5 pellets showed no evidence of bursting even after soaking for 120 min. This finding demonstrated that the sucrose in the core was able to contribute an osmotic effect that attracted water into the pellet enclosed by a less flexible and poorly water-soluble acrylic coat. The hydrostatic pressure built up within the pellet caused the pellet coat to rupture and the latter was thought to increase the rate of drug release. It has been reported that the internal pressure could be reduced by the presence of pores or by rupture of the outer coat.[13] Other workers investigating an osmotic pump system consisting of an acrylic coat suggested that the bursting strength depended on the level of pore forming agent in the coat.[14]

Rupture of the pellet coat was also partially attributed to the hydration and swelling of HPMC in the diffusion layer (Fig. 4). The coat of pellets with 10% coating levels of HPMC 400 mPas showed no evidence of bursting after soaking for 120 min, whereas coat rupture of pellets coated with 15 and 20% coating levels of HPMC was seen after 30 min. HPMC is known to produce a transparent, tough and flexible film.[15] It was reported to swell immediately upon wetting.[16] The rupture of the pellet coat occurred when the Eudragit RS30D coat was unable to withstand the expansion in volume due to the influx of water and swelling of the HPMC layer within the pellets.

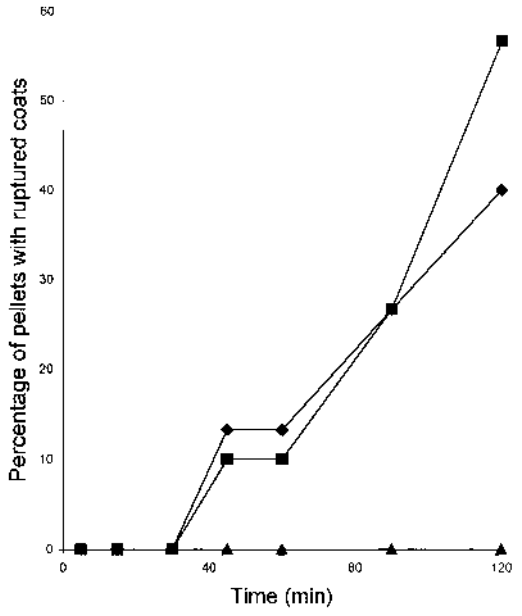

Fig. 4. The Extent of Pellet Coat Rupture with Time

E5/C2G3/H10/E7.5 (▲), E5/C2G3/H15/E7.5 (◆), E5/C2G3/H20/E7.5 (■).

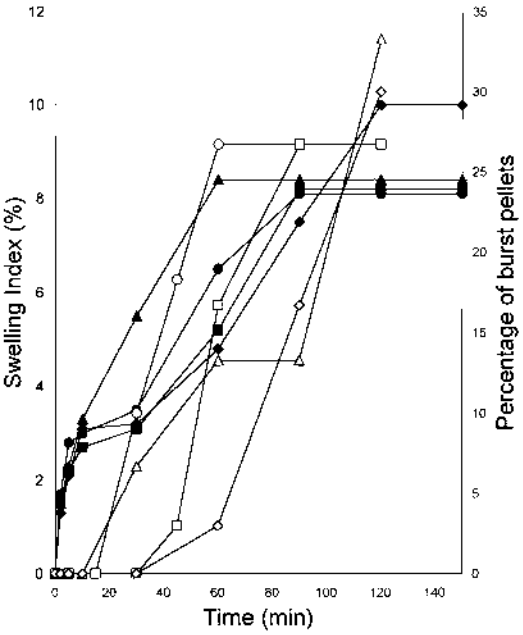

Fig. 5. The Effect of Sodium Chloride on Pellet Swelling (Close Symbols) and Coat Rupture (Open Symbols)

C2G3/H10/E7.5 (●, ○), C2G3/H10S30/E7.5 (■, □), C2G3/H15/E7.5 (▲, △), C2G3/H15S10/E7.5 (◆, ◇).

When sodium chloride was deposited with HPMC 400 mPas in the diffusion coat, it was able to delay the bursting of the pellet coat (Fig. 5). This observation was unexpected

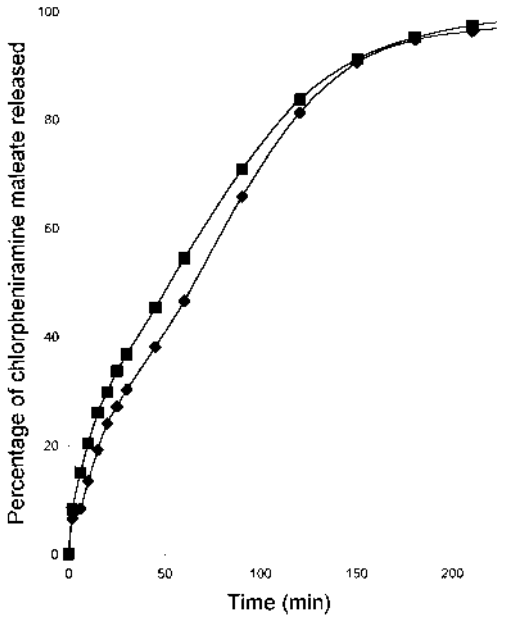

Fig. 6. Drug Release Profiles of Coated Pellets (C2G3/H10S30/E7.5) with (■) and without (◆) Pricked Holes

in view of the osmotic effect exerted by sodium chloride. It showed that sodium chloride affected the pellet in various ways. The competition for the imbibed water between sodium chloride and HPMC 400 mPas reduced the rate of swelling of the diffusion layer. Although Eudragit RS30D is poorly water-soluble, it has been reported to show a certain extent of hydration and swelling in water.[16] In addition to its effect on HPMC, sodium chloride also reduced the hydration of Eudragit RS30D. Similar observations have been made in other studies. Bodmeier *et al.*[17] reported that an increase in the ionic strength of various buffers containing sodium chloride decreased the hydration of Eudragit RS30D polymeric film because of the presence of excess chloride ions. Eudragit RS30D consists of quaternary ammonium groups in the form of chloride salts. Narisawa *et al.*[18] reported that organic acid interacted with Eudragit RS by an ion exchange mode to produce a sigmoidal release system. The introduction of sodium chloride produced a common ion effect which reduced ion exchange and hence hydration of the acrylic polymer.

During dissolution, the thickness of the Eudragit RS30D coat would become thinner with time since the polymer shows some solubility in water. As thinning occurred, the outermost coats gradually became more susceptible to the intra-pellet pressure. In Fig. 5, it can be seen that the rupture of the pellet coat began after 15 and 30 min for C2G3/H10S30/E7.5 and C2G3/H15S10/E7.5 respectively. The percentage of burst pellets was found to increase to about 26% with time.

The influence of coat rupture on the drug release profile of the pellets was studied by manually pricking a hole, using a needle of 0.1 mm diameter, on the coat of each pellet prior to dissolution test. This would create a condition similar to coat rupture during dissolution. Coat ruptures had been attributed to cause rapid drug release.[19] From Fig. 6, the drug release profiles of pellets with and without pricked holes were only marginally different. The time taken for 50% drug to be released was 52.6 and 65.3 min for coated pellets with and without pricked holes respectively. The dissolution curves indicated that similar drug release patterns occurred irrespective of whether there was a puncture in the pellet coat or not. Analysis of the dissolution data obtained in this study showed that drug release followed a zero-order model, with correlation coefficients of 0.9964 and 0.9986 for pellets with and without pricked hole respectively. The difference between the drug release rates obtained from the dissolution curve (20 to 80% drug release) of both pellet types was less than 0.5%.

The rupture of the pellet coat did not result in a total failure of the pellet controlled delivery mechanism. It was observed that upon rupture, core material shifted to an eccentric position (Fig. 2b—d). This was brought about by the development of a higher pressure in the region away from the point of rupture. This pressure build-up pushed the core material towards the point of puncture. This effectively 'sealed' the exit point caused by the puncture. In some cases, the core material was seen to be completely ejected through the puncture opening, leaving an empty water-logged, transparent capsule. As the drug was not in the core, it remained entrapped within the hydrated polymeric gel. Thus, the controlled drug delivery system remained relatively intact. Swelling polymer around the point of rapture ensured that the opening at the site of rapture was sealed and this enabled the maintenance of continuity in the diffusion barrier for retarding drug release.

The primary mode of drug release from the coated pellets was found to be diffusion of drug molecules through the diffusion layer. The release of drug was also partially affected by the osmotic effect. The acrylic retention layer acted as a protective coat to minimise the dissolution and erosion of the diffusion layer.

In addition to the thickness of the diffusion layer, the viscosity of the diffusion layer could also have an effect on drug diffusion. The apparent viscosity of a 2% (w/w) HPMC 400 mPas dispersion, with and without 0.06% sodium chloride were 162 and 210 mPas respectively. This clearly demonstrated that sodium chloride reduced the hydration of HPMC, resulting in a less viscous dispersion and hence a less viscous diffusion layer. In addition, reduced swelling was also evident (Fig. 5), retarding the built up of swelling pressure in the pellet. Thus, pellets containing sodium chloride in the diffusion layer showed a lower coated pellet swelling rate resulting in a delay of pellet coat rupture. Interestingly, the maximum extent of swelling and the maximum percentage of burst pellets remained relatively constant for the corresponding batches of pellets, with and without sodium chloride. This illustrated that the hydrostatic pressure within the pellet was primarily contributed by the sucrose in the core. Since hydrostatic pressure is capable of affecting drug release, it can be deduced that the sucrose in the core plays a role in the drug release process. Further studies were carried out to determine the amount of sodium chloride release together with the drug out of the pellet. It was found that almost all the sodium chloride present in the pellet was released within 90 min. On the other hand, the time taken for all the drug to be released was 240 min (Fig. 7). The relatively rapid loss of sodium chloride further indicated the less significant effect of sodium chloride compared with the sugar core on drug re-

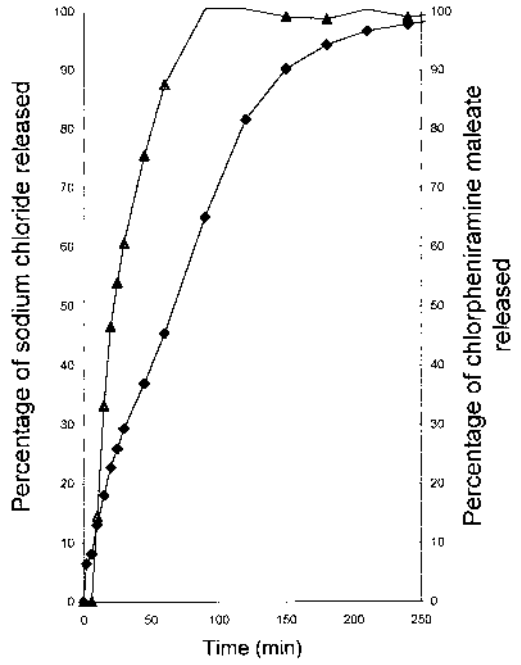

Fig. 7. Release of Chlorpheniramine Maleate (◆) and Sodium Chloride (▲) from Layer Coated Pellets (C2G3/H10S30/E7.5)

lease.

Conclusion

In multilayer-coated pellets, the rupture of pellet coat is an aggregate effect of weakness of the retention layer, swelling of the diffusion layer, and osmotic pressure imparted by osmotic agents. The rupture of pellet coat only marginally affects the drug release. The release rate is dependent on the hydrostatic pressure within the pellet as well as the thickness and viscosity of the diffusion layer. The retention layer plays an important role in preventing the dissolution and erosion of the diffusion layer.

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