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The influence of drug type on the release profiles from Surelease-coated pellets

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Abstract

The release of metoclopramide hydrochloride (a water-soluble cationic drug) and diclofenac sodium (a sparingly soluble anionic drug) from pellets coated with ethylcellulose from an aqueous ethylcellulose dispersion (Surelease®) at different coating loads was investigated. The release rates of each drug decreased as the coating load of Surelease® increased. However, despite its lower water solubility, diclofenac sodium was released slightly faster than metoclopramide hydrochloride at equivalent coating loads. Changes in the release rates after curing were more pronounced for metoclopramide hydrochloride and the release rates of diclofenac sodium were lower than those of metoclopramide hydrochloride after curing. Differences between the release behaviour of the two drugs were probably due to an interaction between the cationic metoclopramide and the anionic ammonium oleate present in the Surelease®. The slower release of metoclopramide hydrochloride may be due to an in situ formation of a poorly soluble complex of the drug and the ammonium oleate. This complex, because of its large molecular size, may diffuse more slowly through the film, causing a reduction in the release rate of metoclopramide hydrochloride. This interaction may also account for the differences in release characteristics of the drugs after curing. During curing the surfactant, due to its unstable nature in heat, may be converted to its constituent components. The interaction of drug with the surfactant was reduced as the residue of the ammonium oleate decreased during curing. However, a relatively low volume flow rate of air, and therefore, slower removal of ammonia in the modified side-vented Manesty Accela-cota 10 may also have affected the coating process of the pellets.

Keywords: Sustained release; Pellet; Hydroxypropylmethylcellulose; Aqueous ethylcellulose dispersion; Surelease®

1. Introduction

Film coating is an ideal process for the production of sustained release multi-particulate dosage forms. For application in controlled-release delivery systems, film coats with well-characterised permeability properties are essential. Ethylcellulose is the most widely used water-insoluble polymer in film-coating (Iyer et al., 1993). This polymer is tasteless, odourless and has the ability to form tough, flexible coatings. While ethylcellulose was initially used in organic solvent-based solutions (Kannikoski, 1984), the application of water-based dispersions of ethylcellulose is common place in pharmaceutical industry and is the method of choice for film coating.

Several studies have investigated the parameters that influence the rate of drug release from ethylcellulose-coated pellets. The effects of drug solubility (Ragnarsson et al., 1992), coating equipment (Yang

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et al., 1992), process of coating (Yang and Ghebre-Sellassie, 1990; Bodmeier and Paeratakul, 1991; Parikh et al., 1993) and core characteristics (Porter, 1989) have been demonstrated previously.

Sadeghi et al. (2000, 2001) reported the release of drug from pellets coated with hydroxypropylmethylcelullose (HPMC) E15, the commercial aqueous ethylcelullose dispersion Surelease® or also from Surelease containing HPMC E15. For each type of coating, increasing the coating level resulted in a decrease in the release rate of the drug. Comparison of the release profiles of two drugs from HPMC-coated pellets at different coating loads revealed that diclofenac sodium was released at a slower rate than metoclopramide hydrochloride. This was ascribed to the lower aqueous solubility of diclofenac sodium. On the other hand, the release rates of diclofenac sodium were faster than the rates of metoclopramide hydrochloride from Surelease-coated pellets. The drug's aqueous solubility is of outmost importance to the formulation of coated pellets when the mechanism of release is mainly by transport of the dissolved drug via diffusion through the film or through water-filled pores or channels within the coating (Ghebre-Sellassie et al., 1988; Iyer et al., 1990). Highly water-soluble drugs generally release faster than poorly water-soluble compounds. Aqueous solubility is also a major factor affecting the osmotic pressure inside coated pellets when they are in contact with the dissolution medium. The difference between the osmotic pressure inside the pellets and the dissolution medium plays an important role in the release of drug from coated pellets (Ghebre-Sellassie et al., 1987; Rekhi and Jambhekar, 1995). Sadeghi et al. (2000, 2001) showed that diclofenac sodium was released faster than metoclopramide hydrochloride from pellets coated with Surelease, despite the lower solubility of diclofenac sodium.

The purpose of this current work was to examine the factors that may explain the unexpected slower release of metoclopramide hydrochloride in comparison with diclofenac sodium from pellets coated with the aqueous ethylcellulose dispersion Surelease.

2. Materials

Metoclopramide hydrochloride was obtained from Wilfrid Smith Ltd. (Edgware, Middlesex, UK). Diclofenac sodium was obtained from Industria Chimica Profarmaco (Milan, Italy). Non-pareil sugar spheres (composed of sucrose and starch), 20–25 mesh size (0.710–0.840 mm diameter) were obtained from Forum Chemicals Ltd. (Redhill, Surrey, UK). Hydroxypropylmethylcellulose (Methocel E5, Methocel E15), Surelease E-7-7050 (aqueous ethylcellulose dispersion) and triacetin were supplied by Colorcon Ltd. (Dartford, Kent, UK). Talc, oleic acid and ammonia solution (general purpose reagent with specific gravity 0.88 g ml^{-1} and about 35% NH_3) were obtained from British Drug Houses (Poole, Dorset, UK).

3. Methods

3.1. Preparation of drug-loaded pellets

Metoclopramide hydrochloride was applied on batches of 4500 g of non-pareil seeds using a modified side-vented pan, Accela-cota 10 (Manesty Machines, Liverpool, UK). A small pore mesh was attached to the inner side of the coating pan to prevent loss of pellets from the pan. This affected the air flow dynamics in the pan. A solution of HPMC E15 in water was prepared by dispersing 40 g HPMC powder in 300 ml of pre-heated water (80–90 °C), diluting with an additional 300 ml of cold water and allowing it to stand for 2 h. Metoclopramide hydrochloride (200 g) was separately dissolved in 400 ml of water and was then mixed with the HPMC E15 solution. Talc (60 g), was dispersed in 100 ml of water and then added. The resultant liquid was stirred both before and during the application of the drug layer.

To prepare the diclofenac sodium suspension for drug layering, 200 g of diclofenac sodium (<90 μm) was dispersed in 500 ml of water. The dispersion of drug was passed through a 105 μm sieve with the aid of an additional 100 ml water to remove any large aggregates of drug. A solution containing 40 g HPMC E15 was prepared as above and then was added to the drug suspension. Talc (60 g), was dispersed in 100 ml of water and then added. The suspension was stirred before and during the application of the fixing liquid to the pellets.

The conditions used for metoclopramide hydrochloride or diclofenac sodium layering were: inlet air

temperature: 60–63 °C, atomising air pressure; 275.6 kPa and a spray rate of 15 g min^{-1} (metoclopramide hydrochloride-based formulation) or 18 g min^{-1} (diclofenac sodium-based formulation). The drug layering process produced pellets with a metoclopramide hydrochloride load of 3.95 ± 0.08% w/w or a diclofenac sodium load of 3.93 ± 0.01% w/w.

3.2. Seal-coating of drug-loaded pellets with HPMC E5

Batches (4500 g) of drug-loaded pellets were seal-coated to give a 2% w/w weight gain of HPMC E5. The coating suspension used was HPMC E5 (5.76%, w/w), triacetin (1.44%, w/w), talc (2.13%, w/w) and water (90.67%, w/w). The conditions used were: inlet air temperature: 72–74 °C, exhausts air temperature: 57–59 °C, atomising air pressure; 275.6 kPa and a spray rate of 20 g min^{-1}.

3.3. Coating of drug-loaded, seal-coated pellets with Surelease

Surelease E-7-7050 was diluted to a 15% w/w dispersion, based on the manufacturer's recommendations, by adding distilled water while stirring. For coating, 4500 g quantities of drug-loaded seal-coated pellets were used. The drug-loaded pellets were coated using a modified side-vented Manesty Accela-cota 10 with Surelease to different thicknesses equivalent to theoretical weight gains of 4, 8, 12, 16 or 20% w/w. The conditions used were: inlet air temperature: 60–62 °C, exhaust air temperature: 51–53 °C, atomising air pressure; 275.6 kPa and a spray rate of 16 g min^{-1}.

3.4. Sieve analysis

The particle sizes of the pellets before and after drug layering were evaluated by mechanical sieving using a series of sieves (Endecotts Ltd., London, UK) with aperture size 1, 0.850, 0.710, and 0.600 mm. A sample load of 100 g was shaken using a mechanical shaker (Pascal Engineering, Sussex, UK) for 10 min. The weights of pellets that were retained on each sieve were then determined and used for analysis of the particle size of the pellets. Triplicate samples were run for each batch of pellets.

3.5. Assay of drug content

Quantities (400 mg) of each batch of coated pellets were accurately weighed, ground to a fine powder using a pestle and mortar and made up to 1000 ml of water and allowed to stand for 1 h. Aliquots of the solutions were filtered and assayed spectrophotometrically for metoclopramide hydrochloride and diclofenac sodium at 309 and 275 nm, respectively.

3.6. Curing of the coated pellets

Quantities of pellets containing drug equivalent to 15 mg of either drugs, seal-coated (2%, w/w E5) over-coated with Surelease (12%, w/w) were spread on paper trays and stored at 60 °C for 24 h. Drug release from the cured pellets was studied.

3.7. Dissolution studies

Dissolution from the pellets was measured using a Pharmatest tester (GmbH, Germany) (USP apparatus I) in line with a Hewlett-Packard HP8452A Diode Array spectrophotometer. The release profiles of pellets containing 15 mg of drug was determined in 900 ml of distilled water at a rotating speed of 50 ± 0.5 rpm and 37 ± 0.5 °C. The mean of six determinations were used to calculate the drug release for each formulation and to determine first-order release rate constants (Sadeghi et al., 2001).

3.8. Scanning electron microscopy and energy dispersive X-ray microanalysis

The surfaces of pellets were examined using a scanning electron microscope (SEM) (model Jeol JSM-T200, Japan). The coated pellets were mounted onto stubs using double sided adhesive tape. The samples were vacuum-coated with gold in an argon atmosphere and examined at 25 keV accelerating voltage.

The distribution of metoclopramide hydrochloride across a section of coated pellets was examined using a scanning electron microscope (JSM 840, Tokyo, Japan) coupled with an X-ray spectrometer (model Link 860 II, London, UK). X-ray microanalysis is a non-destructive technique that allows the detection of elements in situ. In this technique, bombarding the sample with an electron beam, results in emission of

X-rays which are specific to each element. The emitted X-rays were detected by the X-ray spectrometer. The coated pellets were sliced using a razor blade, mounted on stubs and coated with gold prior to scanning. Since metoclopramide hydrochloride has chlorine atoms in its structure, the X-ray characteristics of chlorine were used to trace the localised distribution of the drug across the pellets.

3.9. Preparation of metoclopramide base

Metoclopramide hydrochloride (2 g) was added to 100 ml water containing 0.5% w/w ammonia and stirred. The precipitate formed following addition of metoclopramide hydrochloride was collected on filter paper (Whatman No. 1), washed with 20 ml water and dried at 50 °C for 24 h.

3.10. Differential scanning calorimetry (DSC)

DSC was performed using a Perkin-Elmer (Beaconsfield, UK) differential scanning calorimeter (Model DSC7) controlled by a Perkin-Elmer TAC7. The instrument was calibrated with indium (melting point: 156.60 °C) and zinc (melting point: 419.47 °C). Samples (2–3 mg) were sealed in aluminium pans and scanned at 10 °C min^{-1} over the range of 50–220 °C.

3.11. Dialysis studies

To investigate a potential interaction between metoclopramide hydrochloride and the ammonium oleate present in Surelease®, ammonium oleate was prepared by adding 690 mg of 35% w/w ammonia solution to 4 g of oleic acid (based on equimolar interaction between oleic acid and ammonia). The blend was mixed thoroughly and left at room temperature for 24 h to nearly dry. Five hundred milligrams of the prepared ammonium oleate was dissolved in 50 ml water. Samples (1 ml) of the latter solution were added to 5-ml beakers and 15 mg of either metoclopramide hydrochloride or diclofenac sodium, accurately weighed, was added.

A 20-cm length of Visking dialysis tube (size 5, diameter 11 mm, cut-off 12,000–14,000 Da) (Medicell

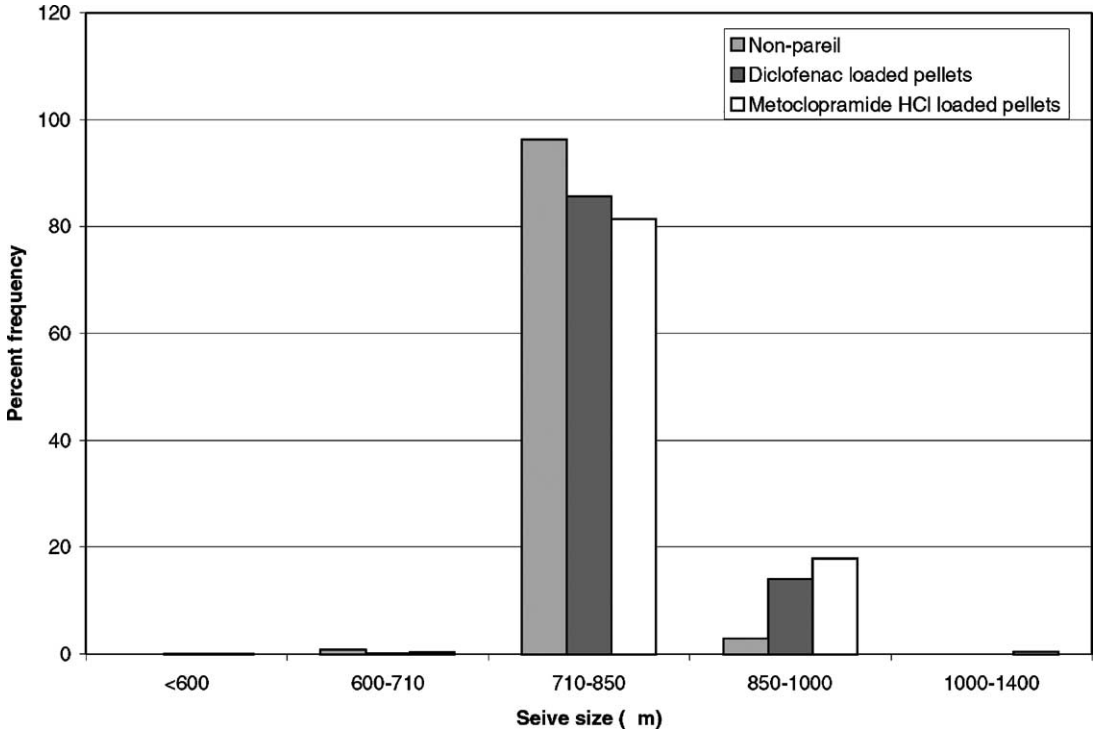

Fig. 1. The size distribution of the pellets before layering and after layering with metoclopramide hydrochloride or diclofenac sodium.

International Ltd., London, UK) was boiled in distilled water for 20 min. A double knot was tied at one end of the tube and then each of the above sample solutions was placed in the tube. The beaker was washed with the aid of an additional 4 ml of water in two steps to ensure complete removal of the contents to the tube and a double knot tied at the top. The length between the two ties was 6 cm. Reference tubes were prepared as above containing 15 mg metoclopramide hydrochloride or 15 mg diclofenac sodium in 1 ml of water. The tubes were immersed into dissolution vessels of the Pharmatest dissolution tester containing 900 ml distilled water at 37 °C and stirred with a paddle at 50 rpm. The amount of drug released from the tubes was determined spectrophotometrically every 30 min for 10 h. The mean of three determinations is reported for each system.

4. Results and discussion

The surface area of coated pellets, which is a function of the mean pellet size, its distribution and the pellet shape (Bertelsen et al., 1994) can considerably influence the release rate of the enclosed drug (Porter, 1989). The results of the sieve analysis for pellets before and after drug layering are shown in Fig. 1. Although the results indicate that the drug-layering process may have increased the average pellet particle size, the Student's *t*-test showed no significant differences ($P < 0.05$) between the sizes of the pellets before and after drug layering for each drug. Student's *t*-test also showed that there was no significant differences between the size of pellets coated with metoclopramide hydrochloride or those coated with diclofenac sodium ($P < 0.05$). Therefore, the differences between release rates of two drugs, observed also by Sadeghi et al. (2000, 2001) may not be attributed to differences in the sizes of the pellets. The size distribution of pellets should be as narrow as possible in order to limit variation in the coating thickness due to variation in the surface area of pellets which must be covered during coating (Mehta, 1989). Fig. 1 also indicates that although the percent of larger particles was highest for metoclopramide hydrochloride-loaded pellets, overall the pellets remained approximately in the same size range as before layering and there were no major differences between the size distributions of the drug-layered pellets. Therefore, mean pellet size and distribution were thought not to contribute to the differences in release behaviour between metoclopramide hydrochloride and diclofenac sodium.

The surface characteristics of the pellets prior to coating, is another parameter that can influence the release characteristics of a drug (Zhang et al., 1991). When equivalent amounts of the coating were applied to the drug-loaded pellets, smoother pellets produced lower release rates than those pellets with rough surfaces (Mehta, 1989; Porter, 1989). This effect was due to the pellets with rougher surfaces having a greater surface area for covering by the coating formulation. When a pre-determined amount of coating is applied to drug-loaded non-pareils, smoother pellets produced

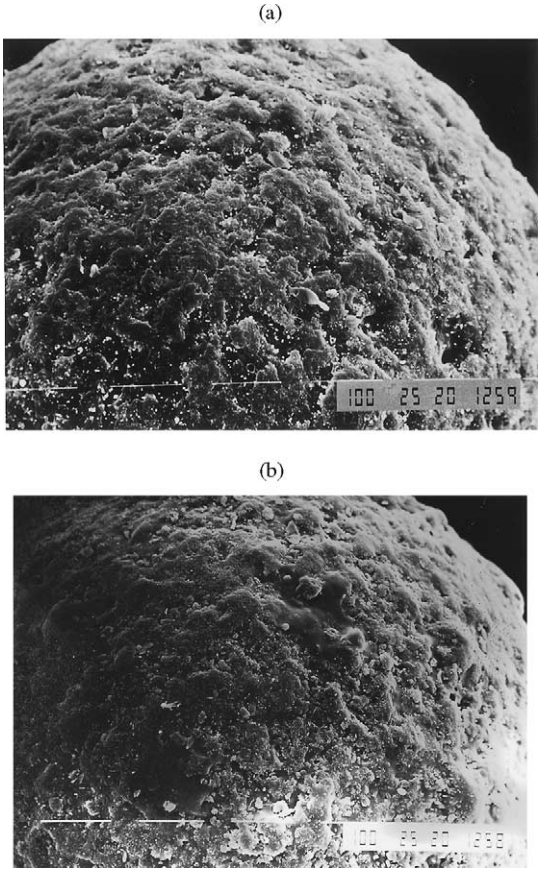

Fig. 2. Scanning electron micrographs of the pellets after drug layering containing: (a) metoclopramide hydrochloride and (b) diclofenac sodium-loaded pellets (150×).

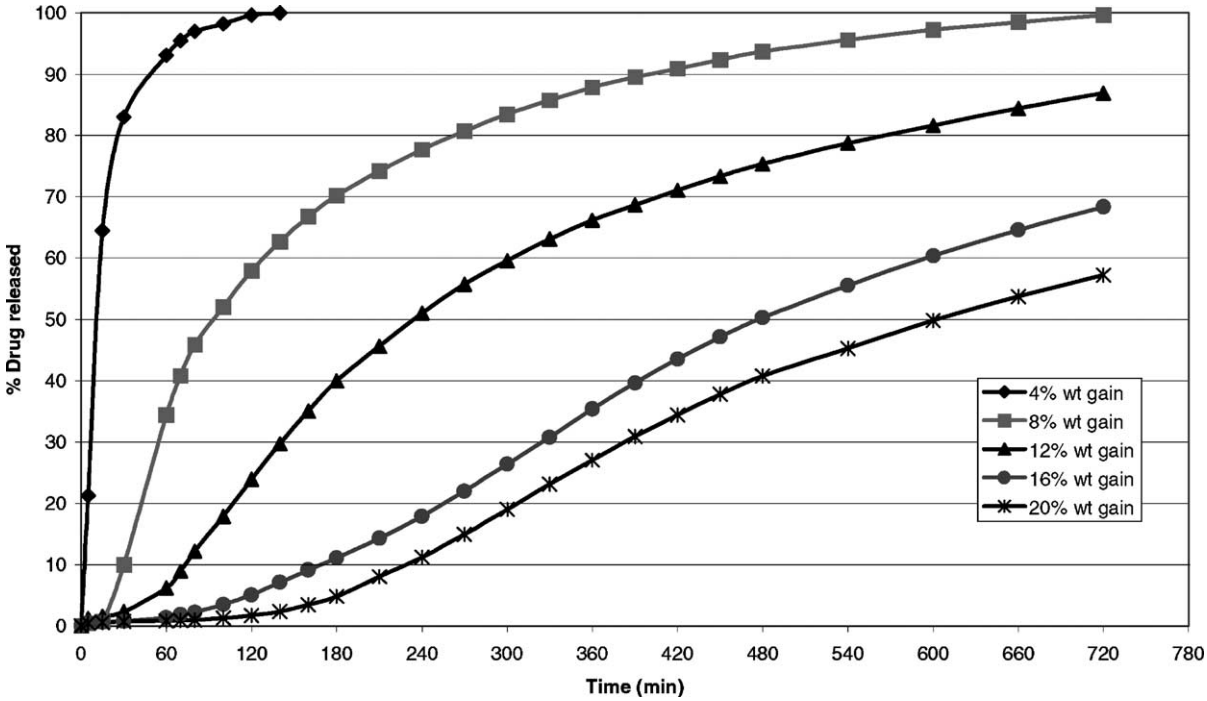

Fig. 3. Effect of Surelease coating load on the release of metoclopramide hydrochloride from pellets which had been seal-coated with 2% w/w HPMC E5.

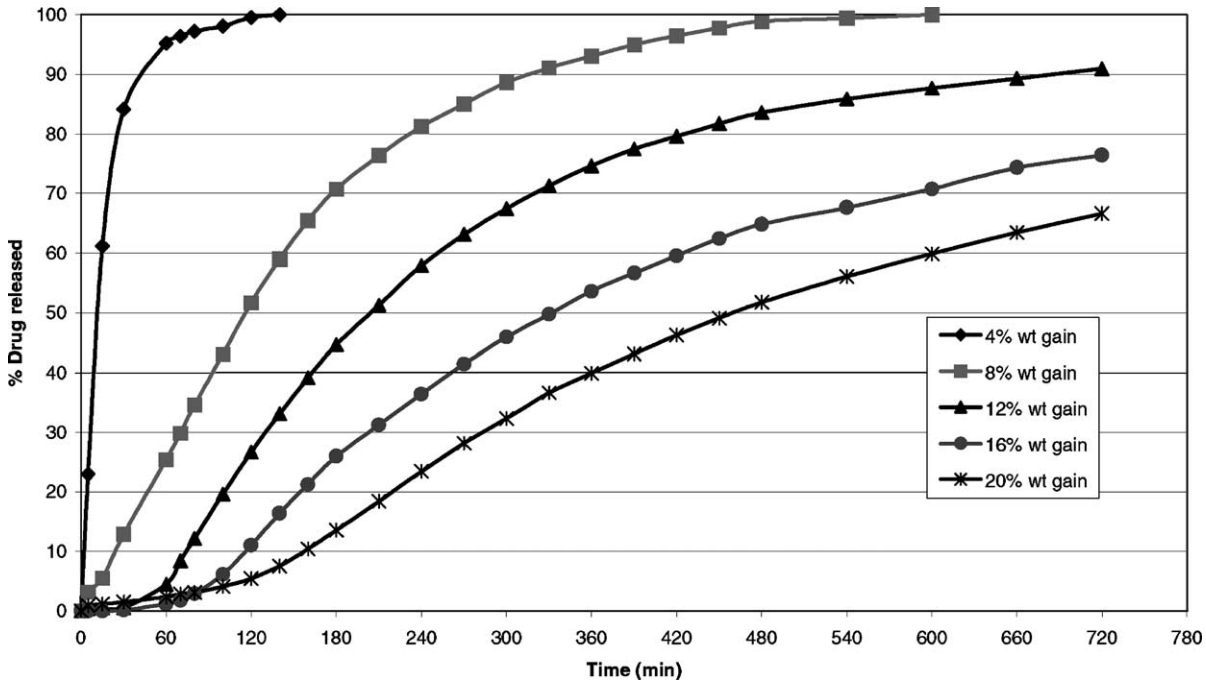

Fig. 4. Effect of Surelease coating load on the release of diclofenac sodium from pellets which had been seal-coated with 2% w/w HPMC E5.

lower release rate than pellets with rough surfaces (Porter, 1989). Scanning electron microscopy (Fig. 2) indicates that there were no major differences between the surface characteristics of pellets coated with metoclopramide hydrochloride or diclofenac sodium. In addition, samples of the same batch of non-pariels were used for both drugs. Therefore, differences in surface roughness were considered not to account for the differences in the release rates of the two drugs.

4.1. Interaction between core ingredients and coating formulation

The existence of any interaction between either of the drugs and the Surelease during film application was assessed by applying a 2% w/w seal-coat of HPMC E5 onto drug-loaded pellets prior to the application of Surelease. The release profiles for seal-coated (sub-coated) pellets over-coated with Surelease are shown in Figs. 3 and 4. The corresponding first-order release rates are shown in Table 1. The addition of a 2% w/w seal-coat of HPMC E5 before Surelease decreased the release rate of both drugs compared to those coated with Surelease without a seal-coat (Sadeghi et al., 2000). This decrease

Table 1
First-order release rates (% min^{-1}) for metoclopramide hydrochloride or diclofenac sodium from seal-coated, Surelease over-coated pellets

Drug	Coating load (%, w/w)				
	4	8	12	16	20
Metoclopramide HCl	0.0796	0.0089	0.0037	0.0021	0.0016
Diclofenac Na	0.0683	0.0069	0.0044	0.0025	0.0018

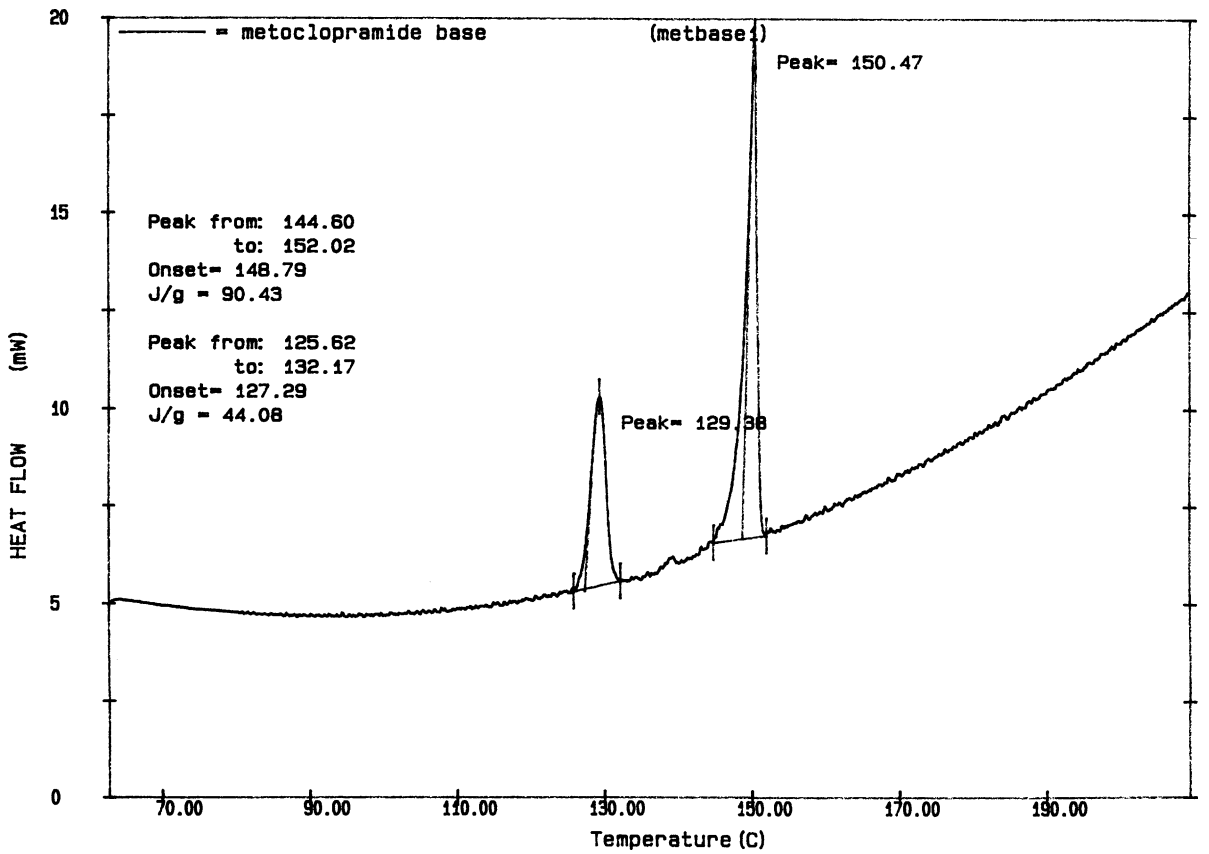

Fig. 5. DSC scan of precipitate formed upon addition of metoclopramide hydrochloride to 0.5% w/w ammonia solution.

in release rate was more pronounced for diclofenac sodium than metoclopramide at low coating levels.

It has been reported that aqueous polymeric dispersions coagulate upon addition of ionic solutions (Lippold et al., 1990; Porter and Ghebre-Sellassie, 1994). The type and concentration of the ions determine the extent of coagulation. Interactions between the active substrate and the aqueous polymeric dispersion during the application of the coat may cause deposition of a non-uniform film in the early stages of the film coating process and therefore, more layers of coating may need to be applied to obtain the desired release profiles (Nesbitt et al., 1994). Sodium salts of active substances are reported to be more reactive than chloride ions in aqueous polymeric dispersions (Porter and Ghebre-Sellassie, 1994).

Diclofenac sodium is the sodium salt of an acidic substance with a p*K*a of 4. Therefore, at a pH 11, which corresponds to the pH of Surelease dispersion (Moore, 1989), 99.99% of the drug is in its ionised form and therefore, may interact with Surelease during the deposition. This problem may be prevented by the application of a seal-coat between the substrate and the Surelease coating. On the other hand, the active substance may be soluble in the coating fluid or coat and migrate to the layers of the coat during the application of the film. The degree of migration of the active substance during the application of the coat may have a significant role in the performance of the coating materials (Ghebre-Sellassie et al., 1987) and may lead to the formation of a porous structure during dissolution. Therefore, a thicker coat may be required for drugs with higher solubility in the coating materials as well as coating conditions need to be carefully considered and controlled.

The use of a seal-coat is also effective in preventing the migration of drugs during the application of the sustaining coat for those drugs which are soluble in the coating fluid. Since diclofenac sodium is freely soluble at pH >6 (Navarro and Ballesteros, 1994) it is more likely to migrate to the applied coat than metoclopramide hydrochloride. Experiments showed

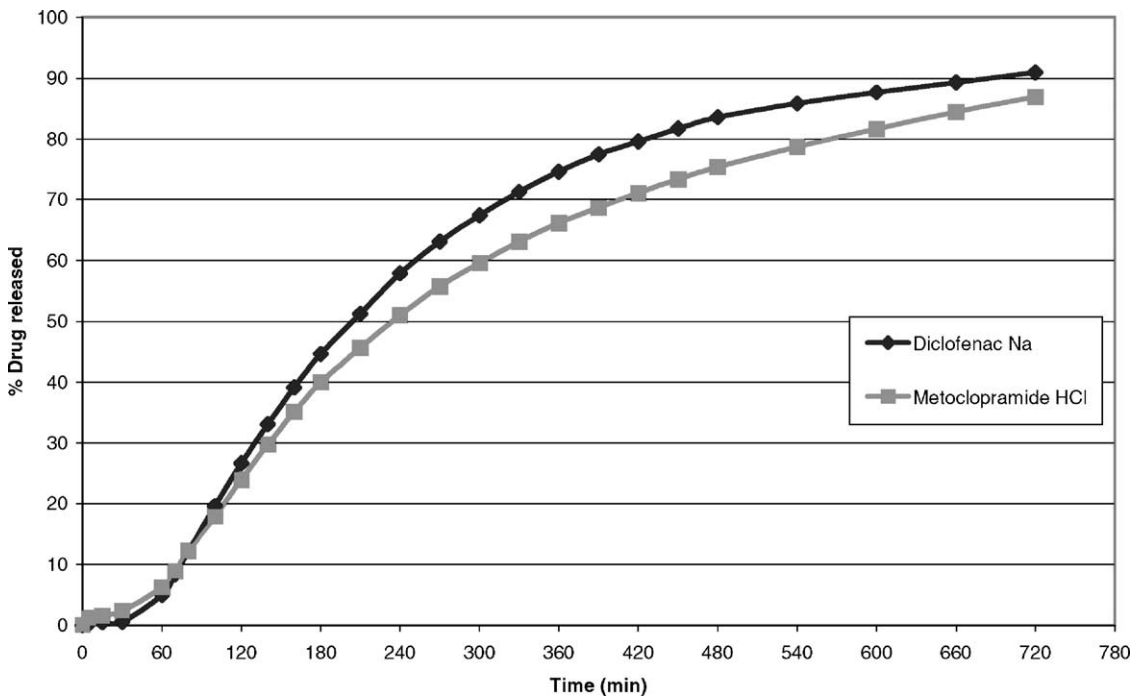

Fig. 6. The release of metoclopramide hydrochloride or diclofenac sodium from pellets coated with 12% Surelease over a seal-coat of 2% w/w HPMC E5.

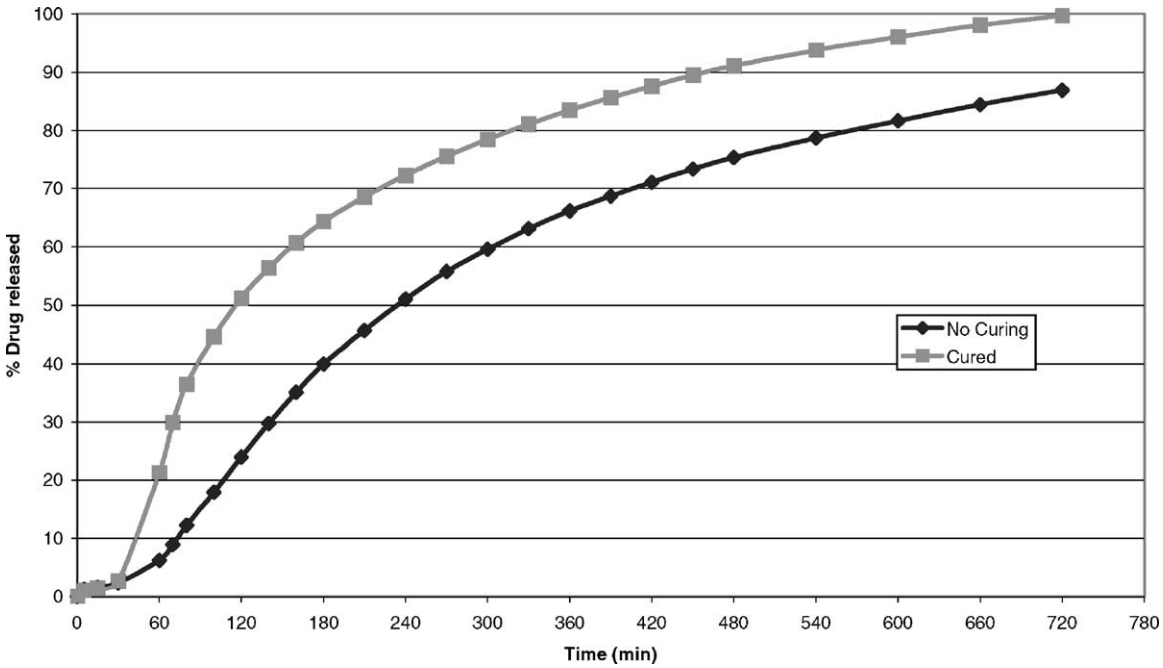

Fig. 7. The effect of 24-h curing at 60 °C on the metoclopramide hydrochloride release from pellets coated with 12% Surelease over a seal-coat of 2% w/w HPMC E5.

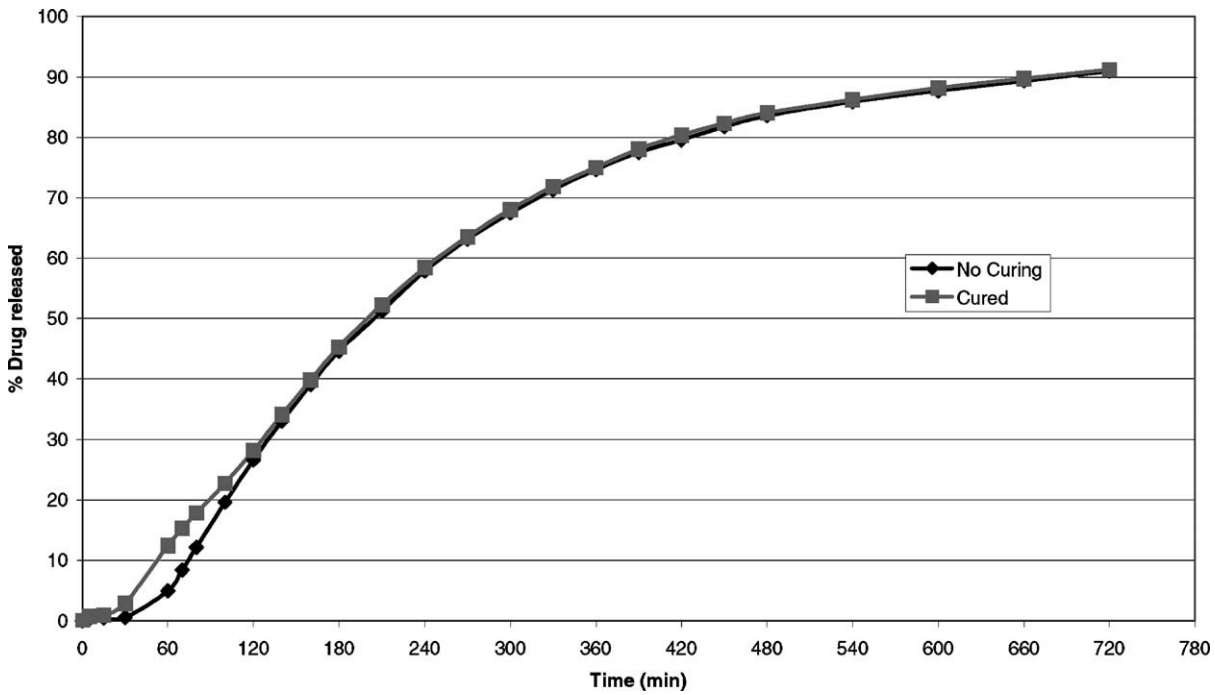

Fig. 8. The effect of 24-h curing at 60 °C on the diclofenac sodium release from pellets coated with 12% Surelease over a seal-coat of 2% w/w HPMC E5.

that a white precipitate was formed when metoclopramide hydrochloride was added to water containing about 0.5% w/w ammonia. Fig. 5 shows the DSC scan of the isolated and dried precipitate. Peaks were observed at 127 and 148 °C, corresponding to those observed for metoclopramide base (Mitchell, 1985). The first peak corresponds to a solid–solid transition while the second peak corresponds to the melting of metoclopramide base (Mitchell, 1985). Therefore, it may be concluded that migration of metoclopramide hydrochloride into the Surelease coat during film application is negligible due to the low solubility of this drug at the high pH of Surelease. Therefore, the decrease in release rate of the drug after the application of the seal-coat may be attributed mostly to the covering of irregularities and smoothing of the surfaces of drug-layered pellets following application of the seal-coat.

The release rates of diclofenac sodium were slower than those of metoclopramide hydrochloride only from pellets coated with 4 and 8% Surelease; at higher coating loads metoclopramide hydrochloride was released more slowly than diclofenac sodium (Table 1). A comparison of the release of metoclopramide hydrochloride and diclofenac sodium from seal-coated pellets coated with 12% Surelease is shown in Fig. 6. Together with data in Table 1, this suggests that interactions between the drugs and the aqueous dispersion, which occurred during the application of the Surelease coat, were not the only factor contributing to the observed differences in their release profiles.

The effect of storage on the release of drugs from seal-coated pellets cured at elevated temperature was investigated for pellets containing metoclopramide hydrochloride or diclofenac sodium coated with 12% Surelease. Since the coalescence of latex particles is often incomplete after the coating process, a curing step which facilitates coalescence of the polymer particles has been recommended with pseudolatex formulations (Bodmeier and Paeratakul, 1991). It has been reported that storage of the latex or pseudolatex-coated pellets at elevated temperature results in a significant decrease in drug release rate with storage time (Goodhart et al., 1984). Their results suggested that a curing step after coating is necessary to prevent changes in the release characteristics of the final products on storage. However, Porter (1989) has shown that this step may not always be necessary. Complete coalescence of a latex or pseudolatex coating is dependent on heat and capillary forces created as a result of water evaporation. These are affected by the process conditions. Optimised process conditions may eliminate the post-coating curing step (Porter, 1989). It must be emphasised that here in the current study there was probably a relatively slow removal of ammonia from the pellets during their manufacture, since a modified Manesty Accela-cota was used to produce coated pellets and the drying rates would be considerably slower than seen in other coating equipment, for example, fluidised bed systems.

The release profiles for coated pellets cured for 24 h at 60 °C are shown in Figs. 7 and 8. The release of diclofenac sodium was almost the same before and after curing, suggesting that complete film coalescence had

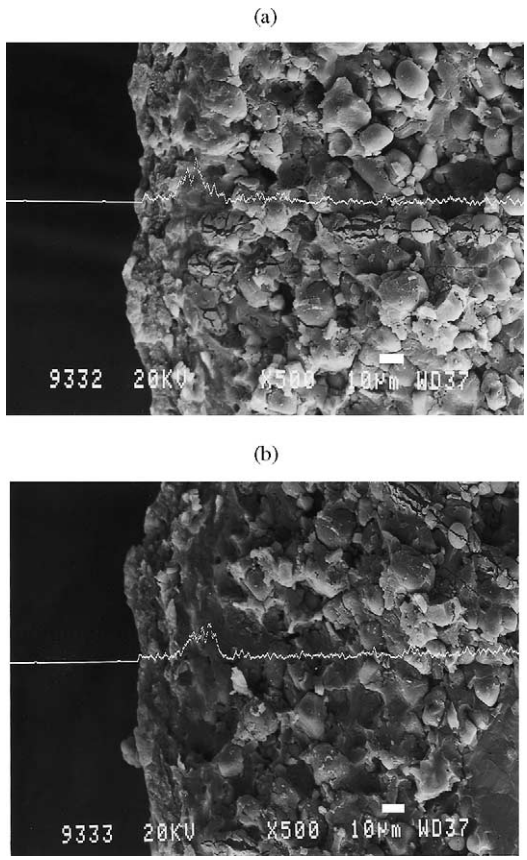

Fig. 9. Metoclopramide hydrochloride distribution across Surelease-coated pellets (a) before and (b) after curing (500×).

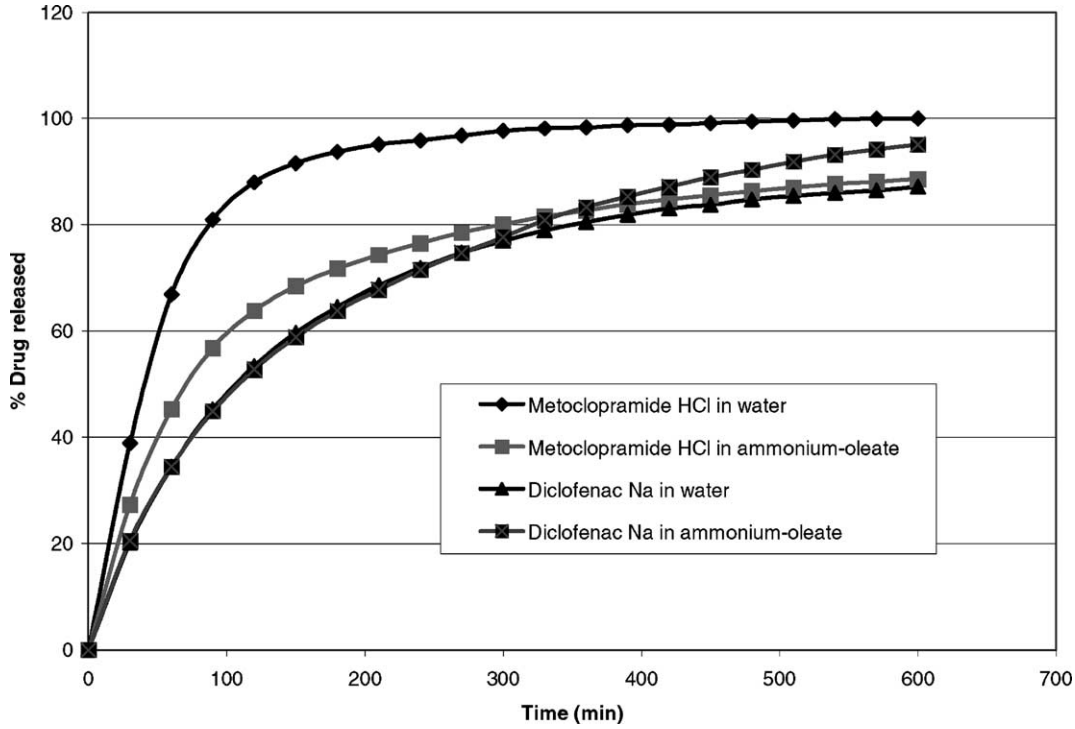

Fig. 10. Release of metoclopramide hydrochloride or diclofenac sodium in the absence and presence of ammonium oleate.

taken place during film application while that of metoclopramide hydrochloride showed a marked increase in the release rate after curing. An increase in the release rates of chlorpheniramine maleate from pellets coated with Aquacoat® has been reported by Porter and Ghebre-Sellassie (1994) and attributed to the migration of the water-soluble drug through the coat during drying.

The migration of metoclopramide hydrochloride during storage at elevated temperature was investigated using X-ray microanalysis. X-ray microanalysis, however, showed no sign of metoclopramide hydrochloride migration after the curing step as depicted in Fig. 9. The white line, which is the scan of chlorine across the sample, shows a maximum just beneath the coat. No chlorine was apparent in the thickness of the coat. Indeed the distinct boundary between the coat and drug layer confirmed that no migration had occurred during storage at elevated temperature. Therefore, the increase in release rate of metoclopramide hydrochloride from Surelease-coated pellets after curing was not related to the migration of the drug into the coat. Similarly diclofenac-loaded pellets showed no changes in drug location before and after curing.

Another possible explanation that may account for the slower release of metoclopramide hydrochloride is related to an interaction between the drug and coating material, i.e. an interaction between the cationic metoclopramide hydrochloride and the anionic ammonium oleate, present in the Surelease. The potential for interaction between either drug and ammonium oleate was investigated by dialysis studies. When metoclopramide hydrochloride was added to the ammonium oleate solution, a precipitate was formed; the solution containing diclofenac sodium remained clear. Fig. 10 shows that the passage of metoclopramide hydrochloride from a solution containing ammonium oleate through the dialysis bag was much slower than that of metoclopramide hydrochloride from water. This retardation was due to the formation of the precipitate. However, the passage of diclofenac sodium from the solution containing ammonium oleate was very little different to that from water.

In general, surfactants are added to aqueous dispersions of polymers in order to decrease the interfacial tension between the organic polymer solution and the aqueous phase during formation of the pseudolatex. The surfactants prevent agglomeration and coalescence of the dispersed polymer particles during storage (Bodmeier and Paeratakul, 1991). Surelease contains oleic acid as stabiliser in ammoniated water. Therefore, the formation of ammonium oleate is predicted which under certain process conditions may remain in the coating after formation of the film.

It has been claimed that ammonia is evaporated during the coating process (Bodmeier and Paeratakul, 1991) leaving oleic acid rather than ammonium oleate. However, under non-optimized process conditions, it is possible that some of anionic surfactant remains in the coat after formation of the film and interacts with the drug. It is also possible that during coating if the drying process is not sufficient, the surface of the substrate over-wets with the dispersion containing ammonium oleate allowing interaction with metoclopramide hydrochloride. Therefore, the slower release of metoclopramide hydrochloride from Surelease-coated pellets may be due to the in situ formation of a poorly soluble complex of the drug and surfactant. This complex, because of its lower solubility than metoclopramide hydrochloride or its larger molecular size, may diffuse more slowly through the film and hence cause a reduction in the release rate of metoclopramide hydrochloride from pellets coated with Surelease.

5. Conclusion

The possible reasons for the observed differences between release rates of metoclopramide hydrochloride and diclofenac sodium were investigated. A slower release for metoclopramide hydrochloride from uncured pellets was attributed to the lower solubility of a precipitate that formed between metoclopramide hydrochloride and the ammonium oleate. This may be dependent on process conditions used to coat the drug layered pellets with Surelease.

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