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DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 5, pp. 575–583, 2003

RESEARCH PAPER

Film Coated Pellets Containing Verapamil Hydrochloride: Enhanced Dissolution into Neutral Medium

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ABSTRACT

Weakly basic drugs, such as verapamil hydrochloride, that are poorly soluble in neutral/alkaline medium may have poor oral bioavailability due to reduced solubility in the small intestine and colon. Film coated pellets were prepared using two strategies to enhance drug release at high pH values. Firstly, pellets were coated with Eudragit® RS/hydroxypropyl methylcellulose acetate succinate (HMAS) mixtures in proportions of 10:1 and 10:3, respectively. The enteric polymer, HMAS, would dissolve in medium at pH > 6 creating pores through the insoluble Eudragit RS membrane to increase drug release. Secondly, an acidic environment was created within the core by the inclusion of fumaric acid at concentrations of 5 and 10% in order to increase drug solubility. Both strategies enhanced drug release into neutral medium in dissolution studies using the pH change method to simulate GIT transit. Dissolution profiles of samples tested in pH 1.2 for 12 hr were compared with those using the pH change method (pH 1.2 for first 1.5 hr, pH raised to 6.8 for remaining 10.5 hr) using the area under the dissolution curve (AUC), the dissolution half-life ($t_{50\%}$), and the amount of drug released in 3 hr ($A_{3\,hr}$) values. Both strategies enhanced drug release into neutral medium although the strategy using HMAS in the film was more effective. The formulation least affected by pH change was a combination of the two strategies, i.e., pellets containing 5% fumaric acid coated with Eudragit RS 12% w/w and HMAS 1.2% w/w.

Key Words: Film coated pellets; Verapamil hydrochloride; Eudragit® RS; Hydroxypropyl methylcellulose acetate succinate; Controlled release; Dissolution studies.

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DOI: 10.1081/DDC-120018646
0363-9045 (Print); 1520-5762 (Online)

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INTRODUCTION

Many oral controlled release dosage forms are designed to deliver the dose of a drug at a regulated rate so as to achieve zero-order release kinetics. Irrespective of the type of dosage form, drug solubility and hence absorption depends to a large extent upon the constantly changing environmental conditions within the gastrointestinal tract (GIT).[1] Many drugs are weak acids or weak bases, or the salts thereof. It is well known that pH plays a significant role in the dissolution rate of weakly acidic or weakly basic compounds.[2] It follows therefore that an oral sustained release solid dosage form containing a weakly basic drug may potentially lead to bioavailability problems. As the drug enters the small intestine, the pH rises to pH 6.8 or higher. In this environment the solubility of a weakly basic drug decreases greatly and this might translate to a markedly decreased release and absorption in vivo.

Previous work has been directed at achieving pH-independent release of a weakly basic drug from matrix tablets containing substances such as the water-insoluble ethylcellulose, water-soluble hydroxypropyl methylcellulose, and sodium alginate as polymers to regulate drug release.[3–5] It is well known that single-unit dosage forms have definite therapeutic disadvantages when compared with multiple-unit dosage forms comprising such systems as pellets, beads, and granules which are distributed widely over the regions of the GIT. However, most of the previous work has been carried out on matrix tablets, whereas very little work on achieving pH-independent release from film-coated pellets has been reported.[6]

The objective of this work therefore was to investigate whether it was possible to achieve pH-independent release from pellets that have been film-coated with a water-insoluble, but permeable, polymeric material. The film coating material used was Eudragit® RS that is insoluble but permeable to water and drug molecules in solution. Two formulation strategies were used with the aim of achieving pH-independent release. Firstly, an enteric coating material, hydroxypropyl methylcellulose acetate succinate (HMAS) was homogeneously incorporated in the Eudragit RS film. On contact with aqueous medium at pH 6.8 or higher, the HMAS will gradually dissolve and leach away leaving minute pores in the film that would significantly increase the drug permeation rate. Some work has been reported using this concept of making the coating more porous or permeable in this way.[7–11] Secondly, an organic acid with a low water solubility and pKa could be homogeneously incorporated in the spherical core containing the drug prior to coating. On contact with aqueous medium, water molecules would diffuse through the coating material into the core. The organic acid would slowly dissolve creating an acidic microenvironment within the coated core. The solubility of the drug would be increased in the acidic environment leading to enhanced drug diffusion rates. Most of the previous reports using an organic acid to increase the solubility of a weakly basic drug have involved the use of matrix tablets.[3,12] The organic acid selected having the desired characteristics was fumaric acid. The weakly basic drug used as a model substance was verapamil hydrochloride.

MATERIALS AND METHODS

Materials

Knoll AG (Ludwigshafen, Germany) gifted verapamil hydrochloride and Avicel® PH-101 (microcrystalline cellulose NF) was received from FMC (Brussels, Belgium). Eudragit RS was supplied by Röhm GmbH (Darmstadt, Germany) and hydroxypropyl methylcellulose acetate succinate (HMAS) (Shin-Etsu AQOAT®, grade AS-MF) from Shin-Etsu Chemical Co. (Tokyo, Japan). Fumaric acid and sodium phosphate ($Na_3PO_4 \cdot 12H_2O$) were purchased from Sigma (St. Louis, USA).

Preparation of Pellets

Verapamil hydrochloride and Avicel PH-101 were mixed in a planetary mixer for 5 min. In each batch a content of 10% w/w drug was maintained. When fumaric acid was included in the core, the amount of Avicel PH-101 was apportionately decreased. The required amount of distilled water (98 mL per 100 g powdered mixture) was gradually added over a 5-min period to the powdered mixture to form a damp mass. Mixing was continued for a further 10 min. The damp mass was then placed in a PVC bag, sealed, and allowed to stand for 15 min. The damp mixture was then extruded through a 1-mm-diameter die (Model 25 Caleva Extruder) and spheronized at 1500 rpm for 2 min using a Model 120 Caleva Spheronizer (Dorset, England) equipped with a standard spheronizer disc. The approximately 1-mm pellets were then dried in a fluidized bed dryer for 15 min at 60°C.

Table 1. Spray coating conditions applied during the process of film coating of the pellets.

Inlet air temperature	40°C
Outlet air temperature	33°C
Atomizing air pressure	1.2 bars
Coating solution	10% w/v Eudragit RS 100 and HMAS[a] (when included) in isopropanol:acetone 1:1 mixture
Delivery rate of coating solution	8–10 mL min^{-1}
Fluidizing air flow rate	80–100 $Nm^3 hr^{-1}$

[a]HMAS = hydroxypropyl methylcellulose acetate succinate (Shin-Etsu AQOAT, grade AS-MF).

Film Coating of Pellets

Film coating was carried out using an Aeromatic Film Coater STREA-1 (Bubendorf, Switzerland) utilizing the upward spray method. The spray coating conditions are shown in Table 1. After film coating the pellets were dried in the coating chamber for a further 10 min at 33°C.

Dissolution Studies

Weighed samples of pellets equivalent to 50 mg verapamil hydrochloride were filled into size 00 hard gelatin capsules. In vitro dissolution studies were carried out using a SOTAX AT7 smart automated computerized system (paddle method) and WinSOTAX software (Allschwil, Switzerland). The dissolution medium used in each flask was 1 L 0.1 M HCl (pH 1.2) maintained at 37 ± 0.5°C. The agitation speed of the paddles was 100 ± 1 rpm. When the pH change method was utilized, the pH was raised to 6.8 at 1.5 hr by the addition of 20.15 g sodium phosphate to each dissolution flask. At regular intervals, the absorbance of the solution was measured at the λ_{max} for verapamil hydrochloride (278 nm) using a Perkin Elmer UV spectrophotometer. Six replicates were carried out on each batch of capsules produced and the means ± SD were calculated.

Scanning Electron Microscopy

Scanning electron micrographs (SEM) of pellet samples were taken using a Jeol JSM 840 scanning electron microscope at magnification of 500. Samples were coated with gold prior to the microscopic examination using a Polaron E5100 sputter coater.

Calculation of Dissolution Parameters

The areas under the dissolution curves (AUCs) were calculated from the plots of percentage of drug release vs. time using the Simpson's rule for approximate integration. The dissolution half-lives ($t_{50\%}$) and percentage amounts released after 3 hr ($A_{3\,hr}$) were obtained directly from the plots.

RESULTS AND DISCUSSION

As shown in Fig. 1, verapamil-loaded pellets coated with an amount of Eudragit RS 12% w/w released 95% of the drug within a 12-hr time period when 0.1 M HCl (pH 1.2) was used as the dissolution medium for the entire dissolution time period. However, when the pH was raised to pH 6.8 at 1.5 hr after the start of the dissolution test by the addition of 20.15 g of sodium phosphate ($Na_3PO_4 \cdot 12H_2O$), only about 66% of the drug was released after the 12-hr time period. The decreased drug release at pH 6.8 must therefore be due to the reduced solubility of verapamil hydrochloride at this pH. It has been demonstrated in previous work[3] that this drug has a distinct pH-dependent solubility. At pH values below pH 6.35 the solubility was greater than 100 mg mL^{-1}, but at pH 6.8 the solubility was only 2.71 mg mL^{-1} and even lower at pH values above pH 7.0. Due to the potential decrease in bioavailability as a result of the decreased solubility in vivo, it was deemed necessary to formulate the system appropriately such that the solubility and hence absorption of the drug may be enhanced in the presence of neutral to alkaline medium.

Two formulation strategies were applied. In the first, an enteric coating material recently introduced commercially, hydroxypropyl methylcellulose acetate succinate (Shin-Etsu AQOAT, grade AS-MF), was blended with the Eudragit RS to form the film coating. The HMAS was included in two different levels, Eudragit RS:HMAS ratio of 10:1 and 10:3. The coating amount of Eudragit RS was maintained at 12% w/w in all formulations. According to the manufacturer's literature (Shin-Etsu Chemical Co. Ltd., Tokyo, Japan), the grade of HMAS used (grade AS-MF) will dissolve in McIlvaine's buffer solution at pH ≥ 6.0. Therefore, when the pH of the dissolution medium is adjusted to pH 6.8, the HMAS

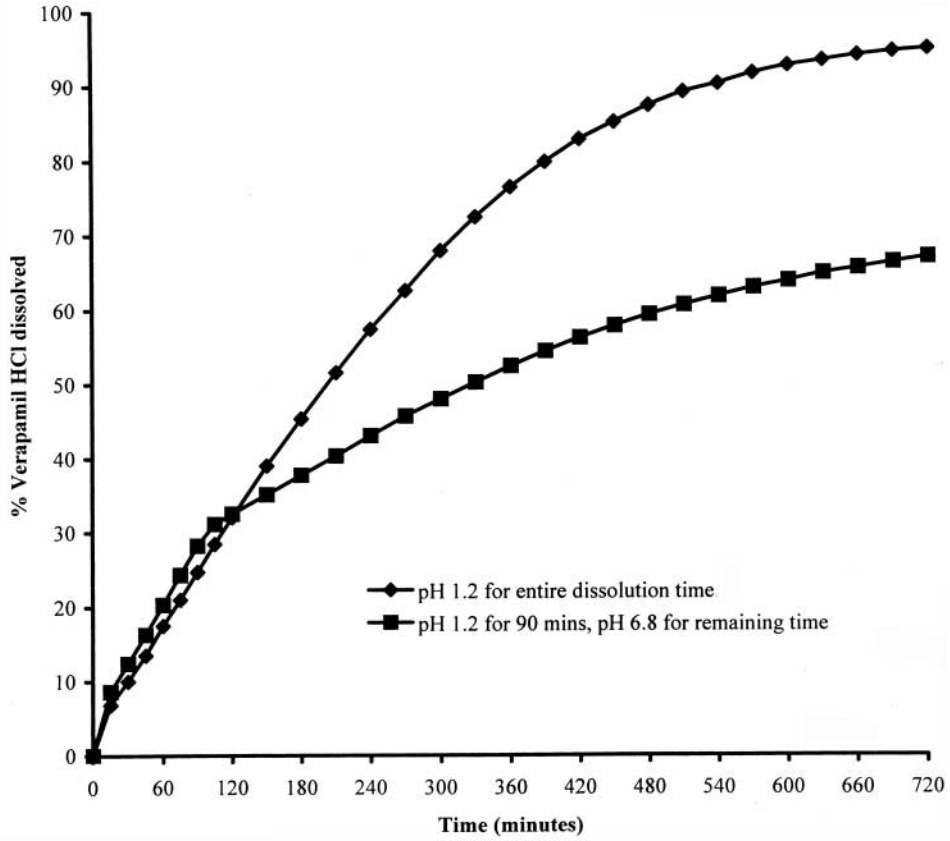


Figure 1. Percentage of verapamil hydrochloride released vs. time (min) from pellets coated with Eudragit RS 12% w/w.

would dissolve creating minute pores in the insoluble Eudragit RS coating material. The dissolved drug molecules in the core would pass through the pores into the dissolution medium at a higher rate than if the pores were absent. Logically the greater the HMAS content, the faster the rate of drug release. This is borne out by examination of Fig. 2 that shows that pellet samples coated with Eudragit RS:HMAS (ratio of 10:3) in pH 6.8 have a mean release profile approximating that produced with similar samples subjected to in vitro dissolution using 0.1 M HCl (pH 1.2). Over the first 1.5 hr, the drug release rates are similar but thereafter a comparison between both levels of HMAS shows that with the higher HMAS level (10:3) there is less deviation from the profile when the pH remains at 1.2 for the entire dissolution period. The pores produced in the film coating are clearly evident in the scanning electron micrograph (Fig. 3b) (Mag 500×). A SEM of the surface of the coated pellet before dissolution testing is shown for comparison (Fig. 3a). These images are produced from pellets coated with Eudragit RS 12% w/w and HMAS 3.6% w/w before and after in vitro dissolution testing in a medium at pH 6.8 for 10.5 hr. These pores are formed as a result of the dissolution of the soluble HMAS within the insoluble Eudragit RS film.

A satisfactory method of analyzing and comparing the full dissolution profiles was to calculate the AUC of the plots of percentage drug released against time using Simpson's rule for approximate integration. For all the samples tested, the AUCs were calculated and these are shown in Table 2. In this table, AUC(1) represents the area under the curve obtained when 0.1 M HCl (pH 1.2) was used as the dissolution medium for the first 1.5 hr and the pH was then changed to 6.8 for the remainder of the dissolution period. AUC(2) represents the area under the curve obtained when 0.1 M HCl was used over the entire 12-hr period. Therefore, AUC(1)/AUC(2) values should be as close as possible to unity if the aim of pH-independent drug release is to be achieved. Table 2 shows that for pellets coated with

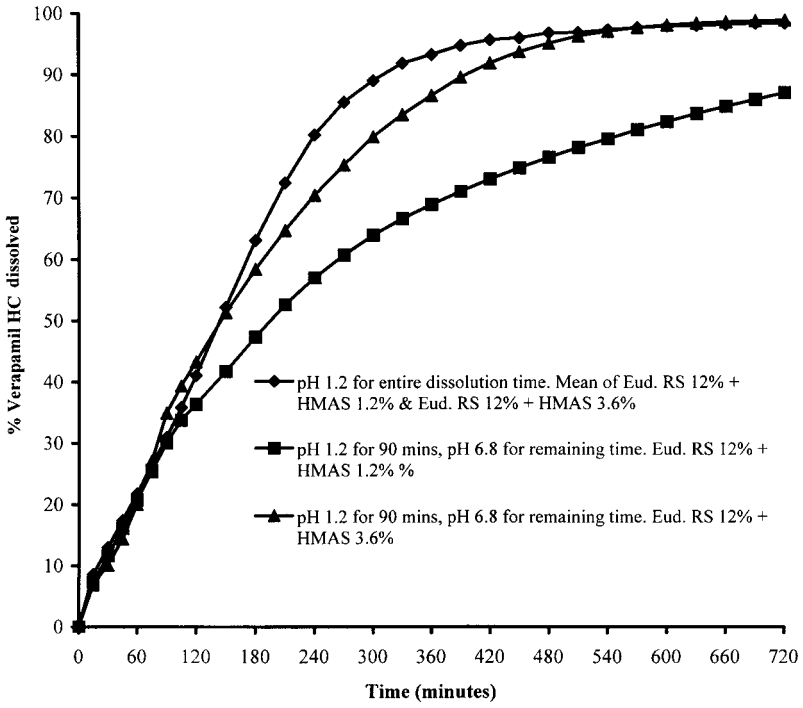
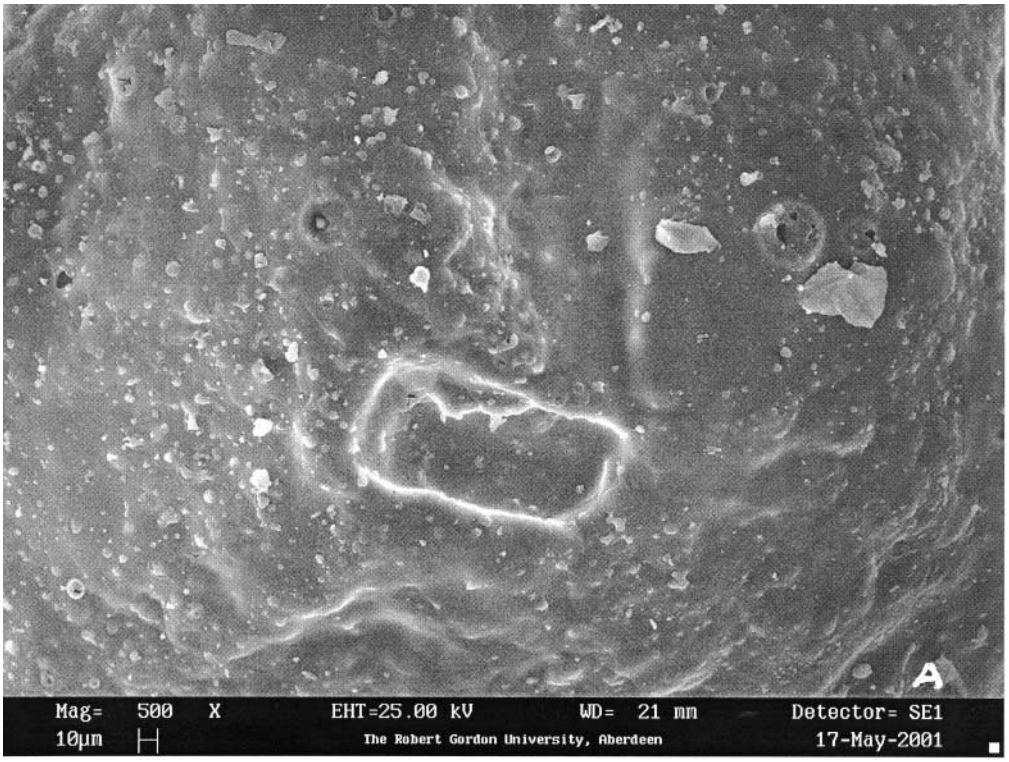


Figure 2. Percentage of verapamil hydrochloride released vs. time (min) from pellets coated with a blend of Eudragit RS 12% w/w and HMAS at levels of 1.2% w/w and 3.6% w/w.

Eudragit RS 12% w/w only, the AUC(1)/AUC(2) value is 0.72. Drug release in this case is solely reliant upon diffusion of the dissolved drug molecules through the polymer coating. In an environment of decreased solubility it is obvious that there would be fewer drug molecules in solution and therefore diffusional drug release would be slower. When a blend of two levels of Eudragit RS and HMAS was used as a coating material (10:1 and 10:3, respectively) and the coating amount of Eudragit RS remained at 12% w/w, the quotient increased slightly to 0.79 in the case of the 10:1 blend. For the 10:3 blend, the quotient was significantly higher at 0.93. This confirms that as the level of HMAS increases so does the rate of drug release. In addition to the diffusion of soluble drug molecules through the film coating, the HMAS dissolves away at pH 6.8 creating pores or channels through the film coat. This allows more water to permeate through the film coating followed by a greater rate of water and drug molecules exiting the pellets in the reverse direction. The increased water entry therefore compensates to some extent for the decreased solubility of the drug at pH 6.8.

In the second approach, fumaric acid, an organic acid with both a low water solubility and pK_a, was selected for incorporation into the drug core prior to coating. The amounts of verapamil hydrochloride and fumaric acid were included on a 1:1 and 1:0.5 basis respectively. Therefore the amount of fumaric acid in the core was 10 and 5% w/w. The amount of Avicel PH-101 was reduced by an amount equal to that of the fumaric acid added. In order to produce satisfactory pellets when fumaric acid was included, the volume of distilled water required was also reduced. For the batch containing 10% w/w fumaric acid, 92 mL per 100 g of powdered mixture was required, whereas in the 5% w/w mixture the volume of distilled water needed was 95 mL per 100 g. Subsequent to manufacture, the pellets were film coated with Eudragit RS 12% w/w. A further batch of pellets containing 5% w/w fumaric acid was film coated with a mixture of Eudragit RS and HMAS (10:1) in which the amount of Eudragit RS was 12% w/w and that of HMAS 1.2% w/w.

A comparison of the dissolution profiles of samples containing 5 and 10% w/w of fumaric acid in the core is shown in Fig. 4. It is evident that water diffuses through the Eudragit film, dissolves the fumaric acid, and creates an acidic solution associated with the verapamil hydrochloride in which



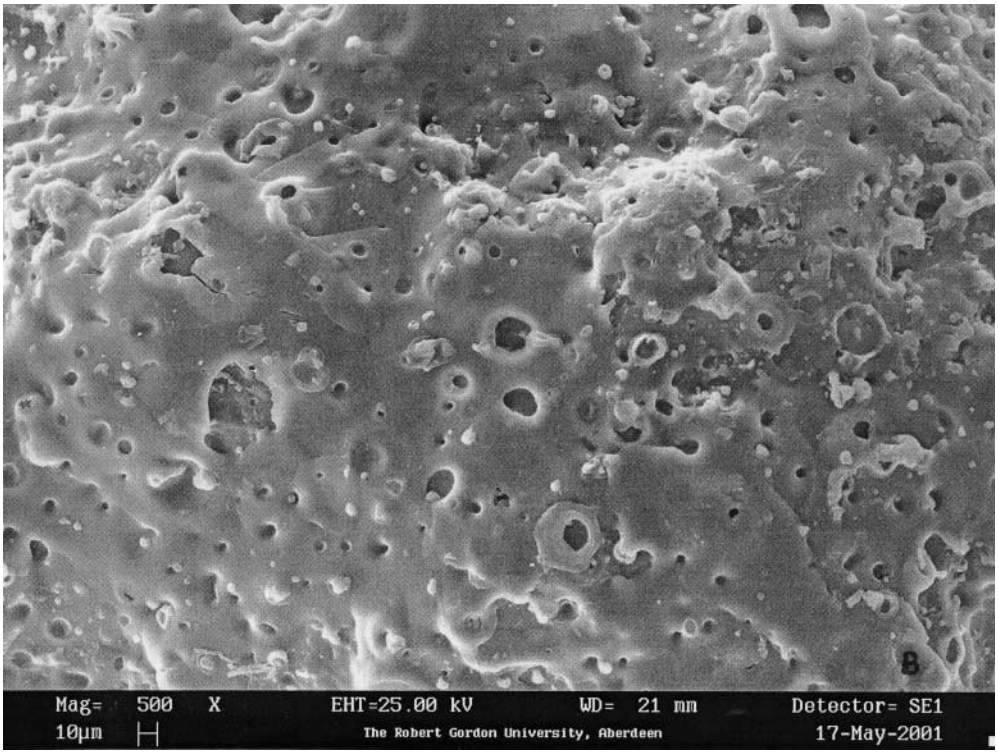


Figure 3. (A)—Scanning electron micrograph showing the surface of a pellet coated with Eudragit RS 12% w/w and HMAS 3.6% w/w prior to the dissolution test (Mag 500×). (B)—Scanning electron micrograph showing the surface of a pellet coated with Eudragit RS 12% w/w and HMAS 3.6% w/w after the dissolution test (Mag 500×).

Table 2. Dissolution parameters calculated from the dissolution profiles of verapamil hydrochloride-containing pellets with and without fumaric acid in the core and film coated with Eudragit RS 12% w/w, or blends of Eudragit RS 12% w/w with HMAS ($n = 6$).

	Composition and amount (% w/w) of coating (no FA in core)			Composition and amount (% w/w) of coating (+ % of FA in core)		
Dissolution parameter	Eud. RS 12%	Eud. RS 12% + HMAS 1.2%	Eud. RS 12% + HMAS 3.6%	Eud. RS 12% + FA 5%	Eud. RS 12% + FA 10%	Eud. RS 12% + HMAS 1.2% + FA 5%
AUC (1) (cm^2)	88.6	112.2	136.9	95.6	114.3	159.9
AUC (2) (cm^2)	123.3	142.4	147.8	129.3	134.6	164.8
AUC (1)/AUC (2)	0.72	0.79	0.93	0.74	0.85	0.97
$t_{50\%}$ (1) (min)	330	195	145	300	235	64
$t_{50\%}$ (2) (min)	205	145	120	210	190	60
$A_{3\,hr}$ (1) (%)	37.7	47.2	58.3	30.6	36.1	85
$A_{3\,hr}$ (2) (%)	45.3	63.0	75.4	40.5	45.0	90.2

Note: (1) Represents a dissolution parameter obtained using a dissolution medium of 0.1 M HCl (pH 1.2) for 90 min and then pH 6.8 for the remaining time.
(2) Represents a dissolution parameter obtained using a dissolution medium of 0.1 M HCl (pH 1.2) for 12 hr.
AUC = area under the curve of the dissolution profile.
HMAS = hydroxypropyl methylcellulose acetate succinate.
FA = fumaric acid.
$t_{50\%}$ = time in minutes for 50% of the drug to be released, or the dissolution half-life.
$A_{3\,hr}$ = percentage amount of drug released in 3 hr.

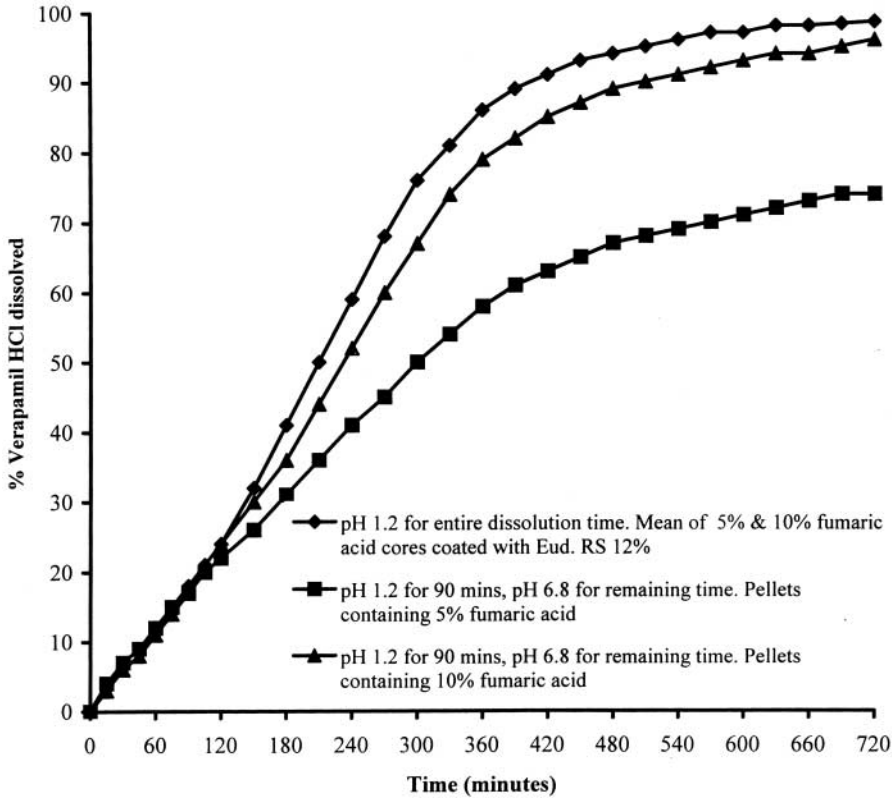


Figure 4. Percentage of verapamil hydrochloride released vs. time (min) from pellet cores containing 5% w/w and 10% w/w fumaric acid and coated with Eudragit RS 12% w/w.

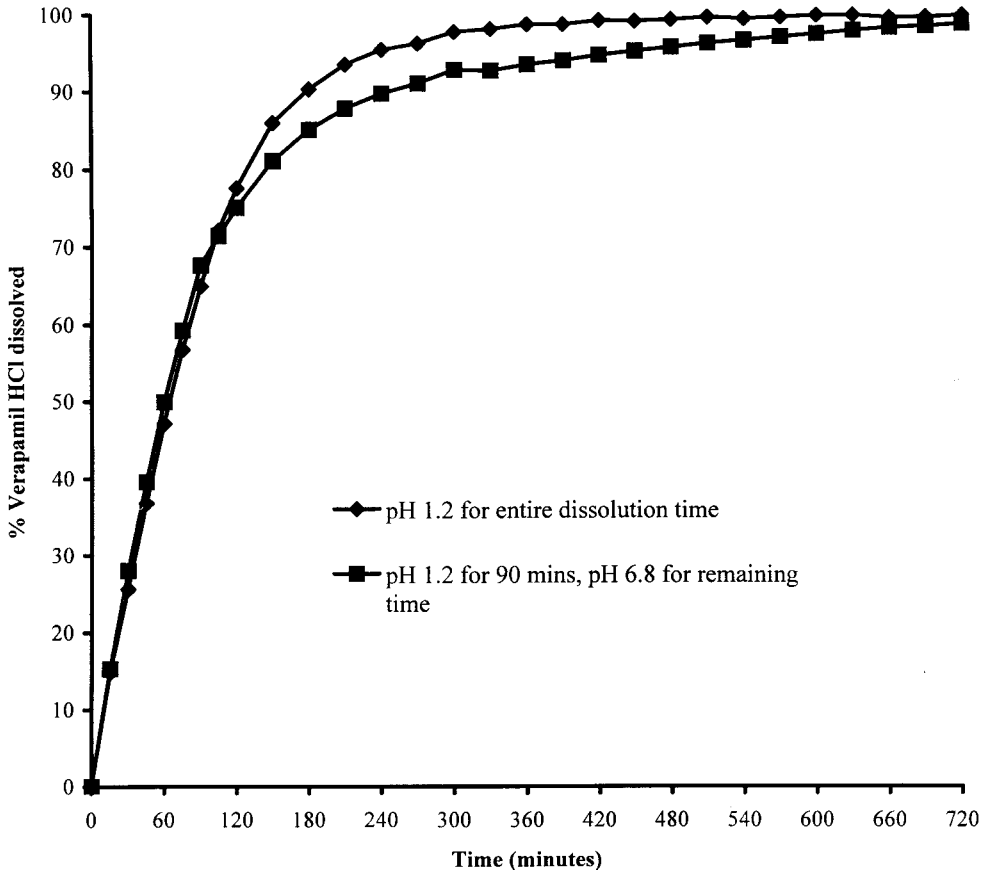


Figure 5. Percentage of verapamil hydrochloride released vs. time (min) from pellets coated with Eudragit RS 12% w/w and HMAS 1.2% w/w containing 5% w/w fumaric acid in the core.

this weakly basic drug will dissolve more readily. It appears also that the fumaric acid concentration influences the drug solubility. As seen in Table 2, the pellet samples containing the higher fumaric acid concentration (10% w/w) have a mean AUC(1)/AUC(2) value closer to unity (0.85). Pellets containing 5% w/w fumaric acid in fact appear to have insufficient acidity to increase the mean AUC(1)/AUC(2) value significantly. A scrutiny of the parameters in Table 2 shows that although fumaric acid does increase the drug release rate to some extent, the incorporation of HMAS has a greater enhancing affect on the in vitro drug release rate. The formulation that produced the AUC(1)/AUC(2) value closest to unity was that which is a combination of the two strategies (see Fig. 5). The cores containing 5% w/w fumaric acid coated with the blend of Eudragit RS and HMAS (10:1) (Eudragit RS 12% w/w and HMAS 1.2% w/w) had an AUC(1)/AUC(2) value of 0.97 (Table 2).

The time for 50% release ($t_{50\%}$) values and the percentage amount of drug released in 3 hr ($A_{3\,hr}$) shown in Table 2 also demonstrate the enhancing effects of both fumaric acid in the core and HMAS in the coating on verapamil hydrochloride release. It is interesting to note further that during the first 1.5 hr of the dissolution time prior to raising the pH to 6.8, the drug release rate from all formulations containing fumaric acid and/or HMAS was enhanced. Release rate enhancement during the first 1.5 hr using fumaric acid could be explained quite simply by the increase in acidity within the drug-loaded core. Hence there is increased drug in solution and faster diffusion through the polymeric film. However, the reason for enhanced release during the first 1.5 hr when a Eudragit RS/HMAS blend was used for coating is not quite so clear but could be due to an interaction between the two polymers. Further investigation into the reason for this phenomenon will be pursued.

CONCLUSIONS

Scrutiny of the AUC(1)/AUC(2), the $t_{50\%}$ and the $A_{3\,hr}$ values of the various formulations confirms that the formulation least affected by a change in pH from pH 1.5 to 6.8 during in vitro dissolution studies were pellet samples containing 5% w/w fumaric acid and film coated with a mixture of Eudragit RS 12% w/w and HMAS 1.2% w/w.

ACKNOWLEDGMENT

This work was originally presented in part at the 4th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, held in Florence, Italy, from 8–11 April 2002.

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