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Evaluation of Rate of Swelling and Erosion of Verapamil (VRP) Sustained-Release Matrix Tablets

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ABSTRACT Tablets manufactured in-house were compared to a marketed sustained-release product of verapamil to investigate the rate of hydration, erosion, and drug-release mechanism by measuring the wet and subsequent dry weights of the products. Swelling and erosion rates depended on the polymer and granulating fluid used, which ultimately pointed to their permeability characteristics. Erosion rate of the marketed product was highest, which suggests that the gel layer that formed around these tablets was weak as opposed to the robust and resistant layers of test products. Anomalous and near zero-order transport mechanisms were dominant in tests and commercial product, respectively.

KEYWORDS Verapamil hydrochloride, Swelling, Erosion, Drug release, Surelease, Eudragit

INTRODUCTION

The release of drugs from sustained release matrix tablets following exposure to aqueous solvents such as in vitro dissolution test media or gastrointestinal tract fluids is largely affected by processes such as the rate and degree of swelling of the polymer matrix, the rate of dissolution of the polymer used in the matrix, and the formation of a protective gelatinous layer through which the drug must diffuse (Huber et al., 1966; Langer & Peppas, 1981; Ford et al., 1991). As the fluid penetrates the matrix, the thickness of the gel layer formed on the glassy core of the swellable polymer increases, thus acting as a barrier to diffusion and subsequently providing a means of controlling drug release from these types of products (Korsmeyer et al., 1983). Gel layer structure and compositional changes occur during matrix swelling due to molecular extension of solvated polymeric chains (Lee & Kim, 1991).

Rigter and Peppas (1987a, 1987b) reported that to achieve a desired release rate, the relative rate of hydration of a polymer plays a critical role, since the polymer selected must hydrate quickly enough to form a gel layer before the contents of the matrix tablet can dissolve. In addition, the higher the viscosity of the gel that is formed, the more resistant the gel is to dissolution and/or erosion. Therefore, the viscosity of the gel layer is also a rate-controlling factor in drug dissolution. If the matrix gel has prolonged durability, water-soluble drugs may diffuse out of the gel before matrix erosion can occur. Thus, both diffusion and erosion will be contributing factors in controlling the release of drug from a hydrophilic matrix tablet.

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However, one process will often play a predominant role over the other based on the specific physicochemical properties of the polymeric material under investigation (Roy & Rohera, 2002).

Interestingly, there is a dearth of information in literature, in which Surelease® E-7-19010 and Eudragit® NE 30D, traditionally known solid dispersions, have been used as aqueous coating systems are used as granulating agents.

Surelease® E-7-19010 is a complete, optimally plasticized ethylcellulose dispersion blended with oleic acid and dibutyl sebacate with a solids content of between 24.0% and 26.0% and a pH of between 9.5 and 11.5 (Surelease® information sheet). Eudragit® NE 30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methacrylate of approximately 30% polymer content (Koleng et al., 2003). Besides ethyl acrylate and methacrylate, the only other compound in the polymer latex dispersion is an endogenous surfactant, nonoxynol 100 (Lin & Augsburger, 2001).

In the case of formulations aimed at controlled delivery, it will help to observe if these fluids have an impact in gel formation or structural changes such as swelling and erosion that occur when matrix polymers are used. For instance, the glue-like fluids bind granules in tableting because their adhesive properties characterize their performance.

Given these premises, the aim of the present work was multifold: to evaluate test formulations manufactured in our laboratory and commercially available Isoptin® SR tablets, with the aim of understanding the release behavior of verapamil from these dosage forms. Isoptin® SR 240 mg tablets are film-coated, scored, light green capsule-shaped tablets with dimensions 6.5 × 18.5 mm for the width and length, respectively. Since the rate of polymer swelling and matrix erosion play a role in defining the kinetics and mechanism of drug release from such matrices, the investigations were designed to study the rate of hydration, rate of erosion, and the kinetics and mechanism of drug release from these systems when using different granulating fluids such as Surelease® E-7-19010 and Eudragit® NE 30D.

MATERIALS AND METHODS

Materials

The following materials were used as received: Verapamil hydrochloride (Aspen-Pharmacare, Port Elizabeth, SA); Carbopol® 974 PNF (Noveon, Inc., Brecksville, Cleveland, OH); Eudragit® RS (Rohm Pharma Polymers, Darmstadt, GmBH); Eudragit® NE 30D (Rohm Pharma Polymers, Darmstadt, GmBH); Emcompress® (Penwest Pharmaceutical Co., Surrey, UK); Emcocel® 90M (Penwest Pharmaceutical Co., Surrey, UK); Ethocel® 10 FP (Dow Chemical Co., Midland, MI, USA); Surelease® E–7–19010 (Colorcon® LTD, Dartford, Kent, UK); and magnesium stearate (Aspen Pharmacare, Port Elizabeth, SA). All other reagents were at least of analytical reagent grade and were used without further purification.

Preparation of Mini-Matrix Tablets

Two different batches of tablets, batches V1 and V2, were produced by wet granulation and subjected to testing. These batches were then compared to the commercially available Isoptin® SR 240 mg product. Surelease® E-7-19010 and Eudragit® NE 30D were used as the granulating fluids for batches V1 and V2, respectively. Batches V1 and V2 were prepared by blending verapamil (VRP), Carbopol® 974P NF, Eudragit® RS, and Emcocel® 90M. The individual powders were weighed separately using a top-loading electronic balance Model PM 4600 (Mettler, Zurich, Switzerland), screened, and granulated with Surelease® E-7-19010 and/or Eudragit® NE 30D, using a Kenwood planetary mixer (Kenwood, UK) set at position 1. Prior to granulation, the Surelease® E-7-19010 dispersion was diluted to 15% solids content whereas the Eudragit® NE 30D dispersion was diluted with an equal volume of purified water, to reduce the viscosity and facilitate spraying of the granulation fluid onto the powder blend. The quantitative and qualitative composition of the formulations of batches V1 and V2 are shown in Tables 1 and 2, respectively. The powder mass was then passed through a No. 20 mesh sieve using

TABLE 1 Wet Granulation Formula for Batch V1

Ingredients	% (w/w)
(1) VRP	33.0
Carbopol® 974P NF	5.0
Eudragit® RS	7.5
Emcocel® 90M	10.0
(2) Surelease® E-7-19010	3.0
(3) Carbopol® 974P NF	5.0
Eudragit® RS	6.0
Emcocel® 90M	10.0
Emcompress®	20.0
(4) Magnesium stearate	0.5

TABLE 2 Wet Granulation Formula for Batch V2

Ingredients	% (w/w)
(1) VRP	33.0
Carbopol® 974P NF	5.0
Ethocel	17.5
(2) Eudragit® NE 30D	3.0
(3) Carbopol® 974P NF	5.0
Ethocel	6.0
Emcocel® 90M	10.0
Emcompress®	20.0
(4) Magnesium stearate	0.5

an oscillating granulator (Erweka, GmbH, Germany) set at 50 rpm. The granules were dried in a convection oven (Gallenkamp and Co., Ltd., London, UK) maintained at 60°C for 12 h, after which, they were rescreened using a No. 20 mesh sieve. The resultant granules were then blended in a cube blender (Erweka, Heusenstamm, FRG) with Carbopol® 974P NF, Eudragit® RS, Emcompress®, and Emcocel® 90M at 100 rpm for 30 min. The blend was lubricated with magnesium stearate and mixed for a further 3 min prior to tableting.

Tablets weighing approximately 240 mg, each containing approximately 80 mg of verapamil, were compressed using a Manesty® F3 single punch tablet press (Manesty Machines Ltd., Liverpool, UK). The tablets were compressed at a compression force of approximately 3.5 tons at a rate of 70 tablets per minute. The resultant flat-faced tablets were 7.0 mm in diameter and 4.5 mm in height. The mean crushing strength of the tablets was approximately 120 N determined using an Erweka TBH 28 Tablet Hardness Tester (Erweka, Heusenstamm, FRG). Environmental conditions were monitored during tableting and the temperature and humidity were 23.0°C/54.0% RH and 23.6°C/47.0% RH during the manufacture of batches V1 and V2, respectively. Three tablets were then placed in a size 00 capsule prior to dissolution testing to produce a dosage form similar in size and shape to that of the Isoptin® SR product. Single tablets were used for swelling and erosion studies without placement in a capsule.

Polymer Swelling and Erosion Studies

The rate of test medium uptake by the polymer was determined by measuring weight gain in the tablets (Efentakis & Vlachou, 2000; Efentakis et al., 2000; Jamzad et al., 2005). Studies were conducted in triplicate on each of the three formulations tested. The tablets were subjected to dissolution testing using USP apparatus 1 (Hanson Research SR 8 PLUS, Chartsworth, CA) filled with 900 mL 0.1 M phosphate buffer (pH 7.4, maintained at 37 ± 0.5°C) and a rotation speed of 100 rpm (Table 3). Tablets were removed at 1, 2, 6 10, 14, and 22 h following exposure and placed on a petri dish. Excess surface water was carefully removed using 125-mm filter paper (41 ashless Whatman® filter paper). The swollen tablets were weighed prior to being dried in a convection oven at 60°C for 12 h. Following drying, the tablets were cooled to ambient temperature and then weighed until a constant weight was achieved. This weight was termed the final dry weight. The increase in weight of the wet mass represented the uptake of the dissolution medium into the matrix tablets and permitted the determination of the swelling index (SI) that was calculated using Eq. (1)

$$\mathrm{SI} = \frac{W_H - Wi}{Wi} \tag{1}$$

where

Wi = mass of tablet before placing in dissolution media,

W_H = mass of tablet after placing in dissolution media (hydrated).

The percentage increase in weight of the tablet, Q, that can be attributed to the uptake or absorption of the dissolution medium was calculated using Eq. (2).

$$Q = \left(\frac{W_H - Wi}{Wi}\right) \times 100 \tag{2}$$

where

Wi = mass of tablet before placing in dissolution media,

W_H = mass of tablet after placing in dissolution media (hydrated).

TABLE 3 Summary of General Dissolution Conditions for USI Apparatus 1

Temperature	37 ± 0.5°C
Test time	22 h
Replicates	n=3
Basket rotation speed	100 rpm
Dissolution medium	0.1 M Phosphate buffer, pH 7.4
Sampling times (h)	0
	1
	2
	6
	10
	14
	22

Matrix erosion studies were performed using a similar method to that described by Efentakis et al. (2000) using USP Apparatus 1 (Hanson Research SR 8 PLUS) for this purpose. The tablets were individually weighed, placed in a basket, and subjected to dissolution testing using the conditions used to water uptake studies in 900 mL of 0.1 M phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C with baskets rotating at 100 rpm. Tablets were removed from the baskets at 1, 2, 6, 10, 14, and 22 h and dried in a hot-air oven at 60°C until a constant weight was achieved.

Efentakis and Vlachou (2000) established that the degree of erosion (E) of a dosage form may be estimated using Eq. (3).

$$E = \left(\frac{Wi - Wf}{Wi} \right) \times 100 \qquad (3)$$

where

W_i = mass of tablet before placing in dissolution media,

W_H = final dry weight after erosion and drying.

In Vitro Dissolution Studies

To determine the effect of continuous pH changes with time, in vitro drug-release studies were performed using USP Apparatus 3 (VanKel Industries, NJ). A Model VK 750D, digitally controlled water circulation/heater (VanKel Industries) was used to maintain the temperature of the dissolution media of the buffers of different pH at 37 ± 0.5°C. The relevant dissolution conditions used for these studies are shown in Table 4. Each formulation was tested in triplicate. Samples were filtered through a 0.45-μm filter prior to analysis. The percent drug released was determined using a validated HPLC method using UV detection at 278 nm. The modular HPLC system consisted of a SpectraSERIES P100 pump (ThermoSeparation Products, San Jose, CA), an automated Waters Intelligent Sample Processor Model 710B (WISP; Waters Associates, Milford, MA). For each dissolution profile, the release data were analyzed by fitting the data to both the Korsmeyer-Peppas and Kopcha models.

TABLE 4 Summary of General Dissolution Conditions for USP Apparatus 3

Temperature	37°C
Test length	22 h
Dips/min	20
Filter size	0.45 μm
Volume drawn	2 mL
Screen size	405 μm top/177 μm bottom

Dissolution media	Row number	pH	Dissolution time
(0.1 M phosphate buffer, 180 m)			
	1	1.6	1 h
	2	3.4	1 h
	3	4.6	4 h
	4	6.8	4 h
	5	7.4	4 h
	6	7.4	8 h

RESULTS AND DISCUSSION

Polymer Swelling and Matrix Erosion Studies

Measurement of the hydration rates of batches V1, V2, and Isoptin® SR were carried out in an attempt to determine whether a correlation between the rate of drug release and associated characteristics and the rate of polymer hydration exists. Visual and tactile observation of the mini-tablets from batches V1, V2, and Isoptin® SR confirmed that swelling was dominant in these formulations and that the polymer developed a viscous gel when exposed to the dissolution media. All tablets were smooth and slippery to touch. The degree of swelling increased dramatically when the pH of the dissolution medium was raised to 7.4. Swelling profiles for tablets of batches V1, V2, and Isoptin® SR are shown in Fig. 1.

Tablets from batch V1 showed the highest rate of swelling when compared to tablets from batch V2 and Isoptin® SR. Swelling results in an increased diffusional path length, within the dosage form, through which the drug must pass, prior to being released. The tablets from batch V2 revealed the slowest swelling rate. This was unexpected, as the excipients used in the formulation studies were similar for batches V1 and V2 except for the polymeric materials used in the granulating fluids. Therefore, the low liquid uptake by tablets from batch V2 is

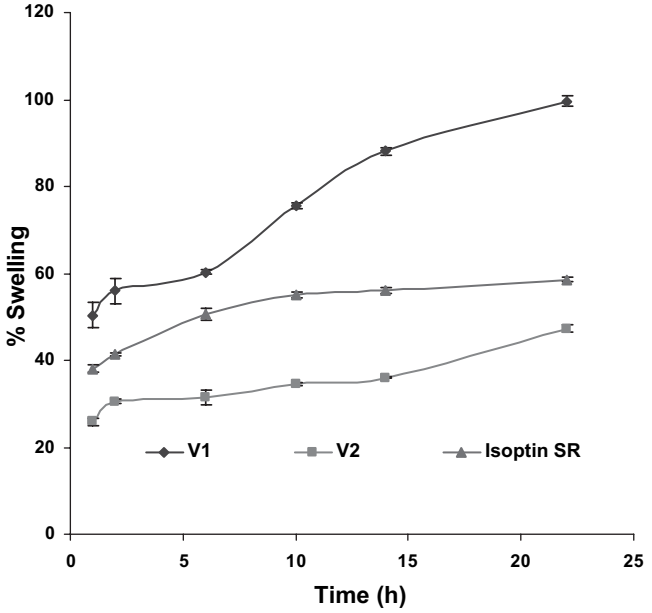

FIGURE 1 Plot of Percent Swelling (Water Uptake) by Tablets From Batches V1, V2, and Isoptin® SR as a Function of Time (Mean ± SD, *n*=6).

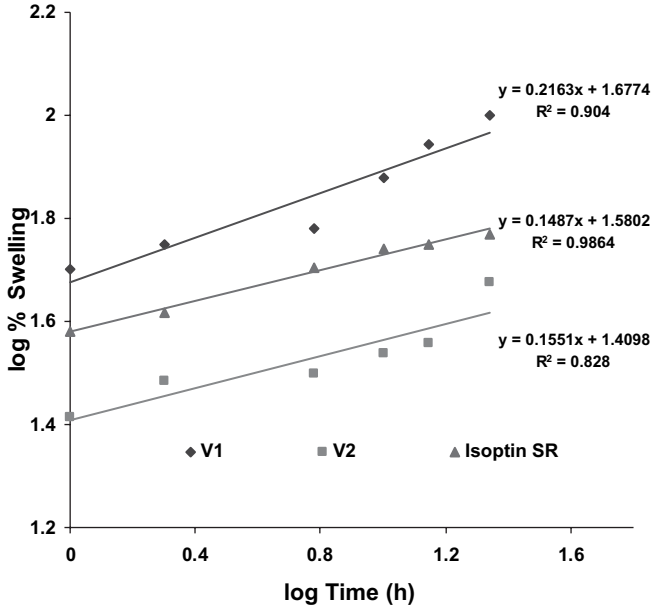

FIGURE 2 Plot of Log Percent Swelling (Water Uptake) by Tablets From Batches V1, V2, and Isoptin® SR as a Function of Time According to the Vergnaud Model.

more than likely a result of the poor uptake of dissolution medium due to the presence of Eudragit® NE 30D, which is known to have poor water permeability characteristics (Azarmi et al., 2002). The aqueous permeability characteristics of a polymer are critical to drug dissolution as the onset of drug release and the subsequent release rates of an API from a dosage form are to a large extent dependent on this feature of the polymer (Bodmeier & Paeratakul, 1990). This was shown by its glue-like nature when granulating, which help explain its plasticity and adhesion characteristic, which made it stronger by reenforcing the network bonds.

The degree of polymer swelling is also an indication of the rates at which preparations are able to absorb dissolution media and for both batches swelling was observed to be proportional to liquid uptake as indicated by the co-efficient of determination values depicted in Fig. 2. These results are in agreement with those observed by De Brabander et al. (2003) for studies in which ibuprofen mini-matrix dosage forms were tested. Isoptin® SR showed swelling behavior that was intermediate to that for batches V1 and V2. In all cases the calculated swelling index (SI) was proportional to the time the dosage form was exposed to the test medium.

The results of water uptake data for tablets from batches V1, V2, and Isoptin® SR were modeled using the method described by Vergnaud (1993) to determine the rate of water uptake. This Vergnaud model was adopted when assessing swelling mechanisms of HPMC-ibuprofen and HPMC-propranolol matrices in pH 7.2 buffer solutions (Wan et al., 1995) and in the evaluation of water uptake for HPMC-acetaminophen and HPMC-pseudoephedrine tablets (Ebube & Jones, 2004). The generalized form of the Vergnaud model is shown in Eq. (4),

$$M = kt^n \tag{4}$$

where

M = the amount of liquid transfered

t = time

k = the swelling constant,

n = the mechanism of water uptake,

Figure 2 depicts the water uptake data plotted according to the Vernaud (1993) model. It is evident from Fig. 2 that tablets from batch V1 hydrate more rapidly than the Isoptin® SR and batch V2 tablets, as soon as the tablets make contact with the dissolution test medium.

Tablets from batch V2 exhibited the slowest rate of hydration or water uptake compared to tablets from batch V1 and the Isoptin® SR tablets. All batches showed a steady rate of hydration for the duration of the experiment in the test liquid.

The characteristic values of the model were calculated by fitting the water uptake data in Eq. (1) to the Vergnaud model and the results obtained are listed in Table 5.

The water uptake data exhibited a good fit to the model with the resultant values of the exponent, n, for tablets from batches V1, V2, and Isoptin® SR being 0.216, 0.155, and 0.149, respectively. Ebube et al. (1997) reported that a value of $n < 0.5$ is indicative of a diffusion-controlled mechanism in which the rate of diffusion is much less compared to the rate of relaxation of the polymer segments in the matrix.

Accordingly, it can be inferred that the kinetics of swelling or water uptake by tablets from batches V1, V2, and Isoptin® SR follow a diffusion-controlled mechanism. In addition, the high values of swelling constants for the formulations of 47.57, 25.69, and 38.09 for batches V1, V2, and Isoptin® SR, respectively, suggest that burst swelling and rapid water uptake is occurring in these dosage forms.

In hydrophilic polymeric matrix systems, the polymeric carrier on the surface of the dosage form, which has formed outer viscous gel layer, will subsequently undergo erosion. The overall dissolution rate and, ultimately, drug availability are controlled by the rate of matrix swelling, drug diffusion through the gel layer, and erosion of the outer gel layer (Roy & Rohera, 2002).

The degree of matrix erosion as a function of time is depicted in Fig. 3 and is reported as % erosion. The percent erosion ranged from approximately 5% during the first hour to about 25% at the end of the run for tablets in batch V1, whereas the values ranged from about 10% after 1 h to about 25% at the end of the dissolution run for batch V2. Isoptin® SR revealed a profound increase in percent erosion of approximately 15% during the first hour to about 70% at the end of the test run.

The use of different polymers in matrix formulations will have a different influence on the rate of tablet erosion and swelling due to variations in the disruption of polymer networks at different times and rates. Since both swelling and erosion are shown to have been occurring at the same time in these matrix systems, though at different rates, resultant drug release patterns will have a tendency to follow a zero-order kinetic release model.

The results depicted in Fig. 3 give evidence that the percent weight loss of the matrices increased progressively over time as erosion progressed. The percent weight loss was linear as a function of erosion time for tablets from batches V1, V2, and Isoptin® SR and the rates of erosion for the tablets from Batches V1, V2, and Isoptin® SR were 1.010, 0.744, and 2.698%/h, respectively. Although the degree of water uptake and swelling of tablets from batch V1 was approximately 1.1 times higher than that of Isoptin® SR (Fig. 2), the rate of erosion of tablets from batch V1 was only approximately 0.3 times that of the Isoptin® SR tablets. This indicates that the gel layer that forms around the tablets from batch V1, which was formed almost immediately after the polymeric matrices came in contact with the dissolution medium, was durable and most likely resistant to erosion. In addition, the degree of water uptake and swelling of Isoptin® SR tablets was found to be approximately 1.5 times higher than that of tablets from batch V2 (Fig. 2) and the rate of erosion of these tablets was identical in the first hour following immersion in the test liquid. However, as the experiment progressed, there was a steady increase of approximately 3 times in the degree of erosion of the Isoptin® SR tablets as opposed to that observed for the tablets from batch V2 (Fig. 3). This further suggests that the gel layer that formed around tablets from batch V2, when the polymeric matrices came into contact with the dissolution medium, was also durable and resistant to erosion compared to the Isoptin® SR tablets.

Figure 4 shows the correlation between matrix swelling and erosion, which indicates that swelling and erosion occur simultaneously but that the rate at which these occur is different for each formulation.

This simultaneous swelling and erosion more than likely result in a balance between an increase in the diffusional path length caused by swelling and a

TABLE 5 **Kinetic Constants Calculated Using the Vergnaud Model**

Formulation	Kinetic constant(k)	Swelling exponent(n)	Coefficient of determination (R^2)
V1	47.57	0.216	0.904
V2	25.69	0.155	0.828
Isoptin® SR	38.09	0.149	0.986

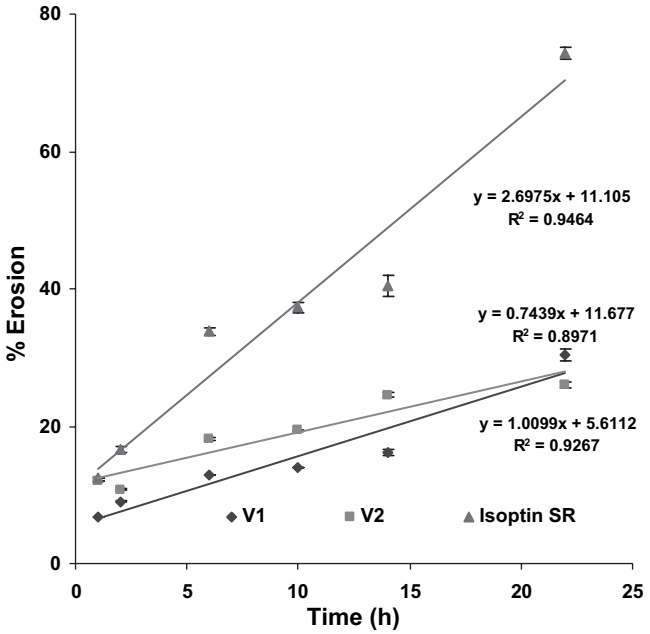

FIGURE 3 Plot of Percent Erosion of Tablets From Batches V1, V2, and Isoptin® SR as a Function of Time (Mean ± SD, n=6).

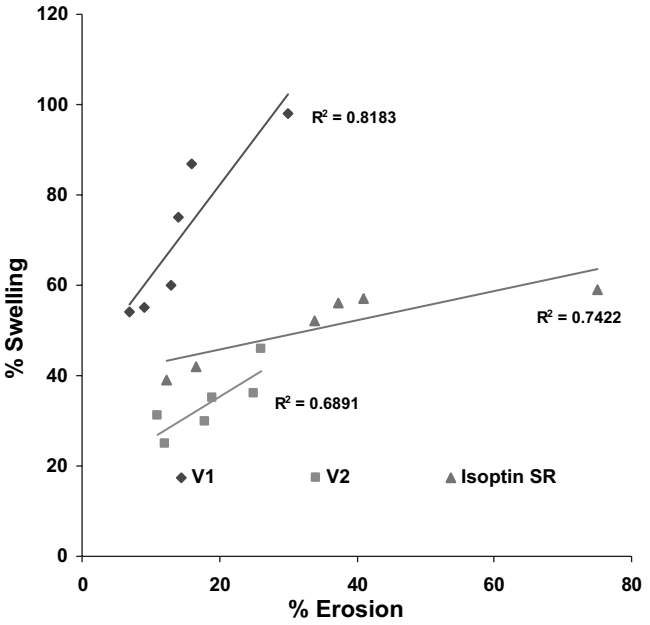

FIGURE 4 Correlation of Matrix Swelling and Erosion for Batches V1, V2, and Isoptin® SR Product.

decrease in the diffusional path length as a consequence of erosion. However, to verify whether in fact such a phenomenon is occurring, release data need to be modeled by fitting data to mathematical models that assess drug release characteristics and mechanisms.

Tablets from batch V1 showed the highest swelling index of approximately 1 and a percent erosion of approximately 40% by the end of a 22-h dissolution run. This demonstrates that there was no balance between the increase in diffusional path length due to swelling with a corresponding decrease in the diffusional path length due to matrix erosion. Tablets from batch V2 showed the least degree of swelling and percent erosion. The reference product showed greater erosion of the tablet than swelling after the 22-h test period when compared to batches V1 and V2; hence, erosion may be considered the dominant factor affecting the release mechanism of VRP from Isoptin® SR tablets.

It is well known that the swelling of carbomer polymers is due to the partial dissociation of the acidic carboxyl group in aqueous solution, producing a coil-like structure (Koleng et al., 2003). Gel formation depends on the electrostatic repulsion between these anionic carboxyl groups. When the magnitude of dissociation of the carboxyl groups is high, there is more repulsion, which in turn results in chain relaxation and a greater degree of swelling of the polymer. This trend was also observed in the study by Meshali et al. (1996), in which the sustained-release of theophylline from matrix tablets containing Carbopol® 974P NF was considered to be largely dependent on the gel layer structure and that the gel layer played a critical role in the sustained-release action.

In Vitro Drug Release

Figure 5 depicts the percent drug released as a function of time for batches V1, V2, and Isoptin® SR. To analyze the mechanism of drug release from these dosage forms, the dissolution data were fitted to Eq. (5), derived by Korsmeyer et al. (1983).

$$\frac{M_t}{M_\infty} = Kt^n \tag{5}$$

where

$\left(\frac{M_t}{M_\infty}\right)$ = the fraction of drug released at time t,

K = a constant incorporating structural and geometrical characteristics of a device,

n = the diffusional exponent of drug release and characterizes the type of release mechanism during the dissolution process.

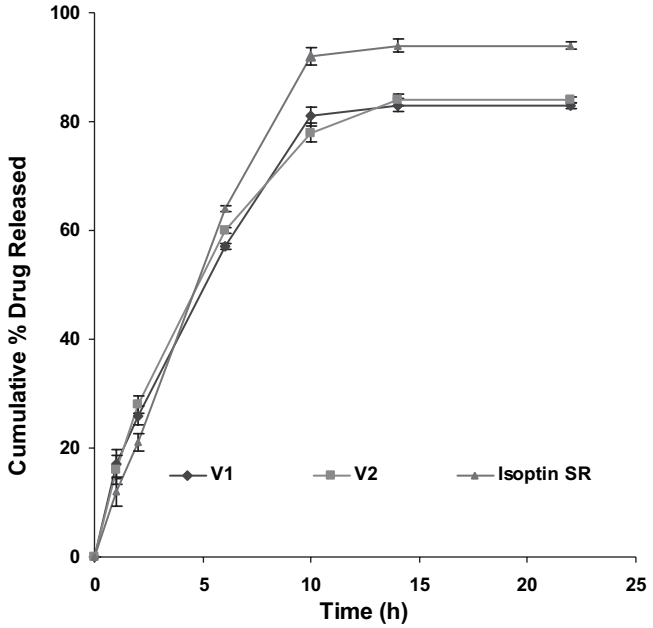

FIGURE 5 Dissolution Rate Profile of Verapamil Hydrochloride Release From Tablets of Batches V1, V2, and Isoptin® SR Tablets (Mean ± SD, n=6), Using USP Apparatus 3.

For non-Fickian release from tablets, n values lie between 0.5 and 1.0, whereas in the case of Fickian diffusion, n=0.5. In tablets where zero-order release or case I transport occurs, n= 1, and for super-case II transport, $n > 1$ (Rigter & Peppas, 1987a, 1987b).

The values of n as estimated by linear regression of a plot of log $\left(\frac{M_t}{M_\infty}\right)$ versus log (t) for the formulations tested are shown in Table 6. The values of n obtained declined to between 0.7 and 1.0 for all formulations for the release of verapamil hydrochloride, indicating non-Fickian release kinetics predominate, which is indicative of drug-release mechanisms involving a combination of both diffusion and chain relaxation mechanisms.

To confirm the mechanism of drug release, dissolution profiles were also characterized by using the relationship proposed by Kopcha et al. (1991). The data were analyzed by using GraphPad Prism, Version 4.00 for Windows, GraphPad software (San Diego, CA), which has been designed to solve nonlinear regression problems. The general mathematical expression, which describes the Kopcha model, is depicted in Eq. (6).

$$M = At^{1\backslash 2} + Bt \qquad (6)$$

where

M =< 60% is the percentage of drug released at time t,

A and B = represent the diffusion and erosion terms, respectively.

If the diffusion: erosion ratio, A/B=1, then drug release is controlled by both diffusion and erosion, equally. If $A/B > 1$, then diffusion prevails, whereas when $A/B < 1$, erosion predominates (Ratsimbazafy et al., 1996).

The in vitro release data were best fitted to the Kopcha model, based on the coefficient if determination; however, fitting the data to the Korsmeyer-Peppas model also produced reasonably good fits, when using this criterion. Values of A/B obtained are greater than 1.0 (Table 6), which indicates that diffusion is the dominant mechanism occurring in these formulations and swelling and erosion do not contribute to a great extent to the release, their involvement is minimal.

The similarity of VRP in vitro dissolution profiles for batches V1 and V2 and Isoptin® SR tablets was determined using the f_1 and f_2 difference and similarity factors (Moore & Flanner, 1996). The fit factors are indices that compare the dissolution profiles of a reference formulation to that of a test formulation (Moore & Flanner, 1996) and the resultant f_1 and f_2 values for these comparisons are depicted in Table 7. The values of f_2 obtained for these comparisons are all greater than 50 and values of f_1 are all less than or equal to 15 for both formulations, indicating that both test batches, V1 and V2, may be considered similar to the reference product, Isoptin® SR in vitro. The percent VRP released with standard deviation (SD) from the

TABLE 6 Parameters Obtained Following Modeling of Dissolution Rate Data to Determine the Mechanism of Drug Release From the Test and Reference Formulations

	Korsmeyer-Peppas		Kopcha			
Formulation	n	R^2	A	B	A/B	R^2
V1	0.7323	0.995	20.26	0.67	30.23	0.941
V2	0.828	0.993	20.60	0.79	20.60	0.922
Isoptin® SR	0.906	0.990	22.64	1.02	22.20	0.901

TABLE 7 f_1 and f_2 Difference and Similarity Factors for the Comparison of Dissolution Profiles From Tablets of Batches V1 and V2 to Isoptin® SR Tablets

	Factor	
Formulation	f_1	f_2
V1	15.2	55.7
V2	12.4	58.1

test and reference dosage forms as a function of time are depicted in Table 8.

As previously mentioned, there seems to be an indication that the incorporation of the hydrogel polymer, carbomer, in formulation V1 had a profound influence on water uptake. The results depicted in Fig. 1 illustrate that as soon as the dosage form comes into contact with the dissolution medium, hydration occurs rapidly; however, drug release was markedly reduced when compared to that from Isoptin® SR tablets, which showed the highest rate and extent of release as depicted in Figs. 5 and 6. The combination of both carbomer and methacrylic acid polymers in formulation V2 resulted in a dosage form that did not favor water uptake as suggested in Fig. 1. The combination of these matrices behave differently to pH changes and it is more than likely that complex macromolecular changes are also occurring during dissolution tsting, which might explain why V2 showed the lowest rate and extent of VRP release as shown in Figs. 5 and 6.

Figure 1 reveals that water uptake increases linearly with time with formulation V1, but with V2 and Isoptin® SR, there the data approach a plateau as indicated by a slight leveling off point. Swelling increases the aqueous solvent content within the formulation and also the polymer size, thus enabling the drug to diffuse through the swollen network into the external environment. It is highly possible that at this point the polymer chains are all fully wetted and the polymer's capacity to hold more water is at its maximum, thus showing the "plateau."

The results of swelling studies do not correlate with the results of dissolution test results. It is possible that due to the complex formulations used in these studies and in vitro performance of the dosage forms that several other factors such as diffusion and erosion, in addition to swelling, control drug release, thereby precluding the establishment of such a relationship.

TABLE 8 **Percent Drug Released From Tablets of Batches V1, V2, and Isoptin® SR Tablets (Mean ± SD, *n*=6)**

	V1		V2		Isoptin® R	
Time (h)	%	SD	%	SD	%	SD
0	0	0	0	0	0	0
1	15.9	0.8	13.1	2.5	9.9	0.1
2	22.4	4.2	18.2	1.6	17.5	0.5
6	56.1	0	56.7	0.5	64.3	1.0
10	78.3	0.6	80.0	1.7	90.7	1.4
14	80	0.9	81.7	1.2	92.4	0.6
22	80	0	81.7	0.5	94	0.3

Interactions between a negatively charged polymer and a positively charged drug molecule are therefore possible and can increase at higher pH values such as 7.4; and drug release rates may therefore be reduced due to expansion of the molecules and the formation of a gel layer. Therefore, the decrease in VRP release at higher pH may be due to the interaction of the dissociated polymer-carboxylic groups with the basic tertiary amine of VRP (Elkheshem, 2001).

A potential interaction between a cationic drug, metoclopramide hydrochloride, and anionic ammonium oleate was also investigated using dialysis equilibrium studies (Sadeghi et al., 2003). In that study, the formation of a precipitate when metoclopramide hydrochloride was added to the ammonium oleate solution resulted in slower drug-release rates compared to those when using an anionic drug such as diclofenac. Therefore, another possible explanation that may account for the slower release of V1 from the tablets is related to a possible interaction between VRP and one component of Surelease® E-7-19010. Surelease® E-7-19010 is a complete, optimally plasticized dispersion consisting of ethylcellulose blended with oleic acid and dibutyl sebacate. In the manufacturing process the plasticized ethylcellulose is directly emulsified in ammonium water. Ammonium oleate is formed in situ by the reaction of oleic acid with gaseous ammonia. This compound is less stable and heat causes it to breakdown, allowing the oleate ion to enter into solution, while the ammonia escapes as a gas. The

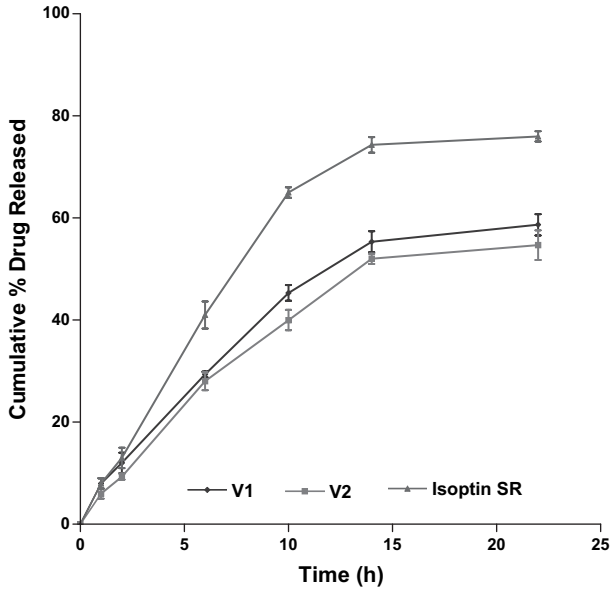

FIGURE 6 **Dissolution Profile of Verapamil Hydrochloride Release From Tablets of Batch V1, V2, and Isoptin® SR Tablets (Mean ± SD, *n* = 6), Using USP Apparatus 1 (pH 7.4).**

anionic oleate then interacts with the cationic VRP, slowing the release.

CONCLUSION

Water uptake studies, including swelling and erosion behavior of the tablets when in contact with the dissolution medium, were undertaken. Swelling and erosion behavior dictate the kinetics and mechanism of drug release from these formulations. Although one process may predominate over the other, as a result of different polymer characteristics, both swelling and erosion often occur simultaneously, as was the case in these studies. It was observed that non-Fickian diffusion was the primary release-controlling mechanism for verapamil from these products. Diffusion of the drug occurs within the polymer and the rate of release is determined by polymer characteristics such as relaxation of the polymer chains on contact with dissolution media. Water uptake studies provided a macroscopic picture of the overall swelling and erosion of tablets that take place, yet provided little detailed information on the nature of the gel layer formed as a consequence of the uptake. Water uptake studies in this study do not show any parallel with drug release, as it is possible that there are so many changes that might be happening in the dosage forms (V1 and V2), such as interaction and gelling, which not only impede release but also impact on structure. The results also showed that the aqueous polymer dispersions used in this study would be useful as granulating fluids in preparation of sustained-release tablets.

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