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Research Article

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Formulation Study and Evaluation of Matrix and Three-layer Tablet Sustained Drug Delivery Systems Based on Carbopols with Isosorbite Mononitrate

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Abstract. The purpose of this research was to develop and evaluate different preparations of sustained delivery systems, using Carbopols as carriers, in the form of matrices and three-layer tablets with isosorbite mononitrate. Matrix tablets were prepared by direct compression whereas three-layer tablets were prepared by compressing polymer barrier layers on both sides of the core containing the drug. The findings of the study indicated that all systems demonstrated sustained release. The properties of the polymer used and the structure of each formulation appear to considerably affect drug release and its release rate. The three-layer formulations exhibit lower drug release compared to the matrices. This was due to the fact that the barrier-layers hindered the penetration of liquid into the core and modified drug dissolution and release. The geometrical characteristics/structure of the tablets as well as the weight/thickness of the barriers-layers considerably influence the rate of drug release and the release mechanisms. Kinetic analysis of the data indicated that drug release from matrices was mainly attributed to Fickian diffusion while three-layer tablets exhibited either anomalous diffusion or erosion/relaxation mechanisms. The advantage of Carbopol formulations is that a range of release profiles can easily be obtained through variations in tablet structure and thus Carbopols are appropriate carriers of oral sustained drug delivery systems for soluble drugs such as the isosorbite mononitrate.

KEY WORDS: Carbopol; isosorbide mononitrate; release kinetics; sustained release; three-layer tablets.

INTRODUCTION

Controlled release pharmaceutical systems have been developed and studied to improve the performance of drugs and in particular to increase their pharmacological effect and reduce any side effects (1). The basic characteristic of the systems is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage forms. A number of design options are available to control or modulate drug release from a drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tabletting (2–4). The presence of the barriers-layers modifies the hydration/swelling rate of the core and reduces the surface area available for drug release. By varying the geometry of the device or coupling layers, it is possible to obtain different release profiles. The multi-layer devices may swell, gel and finally erode/dissolve thus modulating the release process (5,6).

The basic ingredients-carriers of sustained release systems are the polymers. A variety of polymers are employed since their nature and characteristics may play a key role and significantly influence the behavior of multi layer formulations. The controlling effect of a polymer material on drug release depends on its physicochemical properties and the embedding procedure during the preparation of the system. To be more specific the effect is due to the polymers' molecular properties, such as the nature of the monomer, type and degree of substitution, molecular weight and viscosity (7,8) and whether the polymer is mixed dry or dissolved.

In this investigation the polymeric materials used as retardant carriers were Carbopols. These synthetic, cross-linked, high molecular weight polymers are commercially available in various grades that differ from each other with respect to their molecular weight and architecture. Contact with water causes the polymers to hydrate, absorb water and swell fast. Their properties make them ideal for direct compression processes (9) and many are currently being used for controlling drug release in various pharmaceutical solid dosage forms (10–12).

Isosorbite mononitrate, an organic nitrate, mainly indicated for the treatment of stable and unstable angina pectoris,

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acute myocardial infarction and heart failure, was used as model drug. Recent studies have shown that sustained release formulations improve tolerance in patients with angina for at least 12 h after dosing (13). A well known oral sustained release isosorbite mononitrate product marketed by Astrazeneca under the trade name IMDURE, in the form of a sustained release film coated tablet.

The aim of this study was firstly the development of controlled release formulations of a rather water soluble drug, isosorbite mononitrate (1 g/20 ml), (14), using three-layer tablet technology and Carbopols as rate-controlling carrier-ingredients. Secondly, to investigate the effect of (a) the structure of the system and (b) polymeric materials on the rate of drug.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: Isosorbite mononitrate [ISN] (Selog AG) and Carbopol 934P[C934], 971P[C971] and 974P [C974], (kindly donated by BF Goodrich, Ohio, USA) were chosen as model polymers. Magnesium stearate was supplied from BDH (Poole, England).

Tablet Preparation

The core tablets (A formulations, Table I) were consisted of 50% *w*/*w* of ISN and 50% *w*/*w* of polymer and 1% *w*/*w* of magnesium stearate. The drug and the polymer were mixed in a cubic mixer Erweka (Germany) for 10 min. Tablets of 150 mg mass were compacted using a 8.75 or 11 mm diameter flat faced punches in a Carver laboratory hydraulic press (Fred S. Carver, Inc., Menomonce Falls, WI) at compression pressure of 500 kg.

Three-layer tablets were prepared by a directly compressing procedure. The die was accurately and progressively filled with weighed amounts of the different mixtures i.e. barrier layer, drug/polymer mixture, barrier layer again (each barrier contained either 100 or 50 or 20 mg of polymer). First, the barrier layer placed in the bottom of the die and compressed at approximately 100 kg, the drug mixture was then added and compressed at 100 kg followed finally by the top layer barrier which was added and compressed at 500 kg. The structure and the dimensional characteristics of B, D, E and F tablets are shown in Table I. Detailed description is given below in the text.

In Vitro Drug Release Studies

The dissolution studies of ISN was carried out using the USP dissolution tester, paddle method (Pharmatest, Germany), in 900 ml with stirring at 100 rpm, at 37±0.5°C. The dissolution media consisted of 0.1 N HCl, pH≈1.2 for 2 h and then phosphate buffer pH≈7.2. At a selected time interval samples of ISN were withdrawn, filtered and analyzed using a Schimatzu HPLC system. Chromatographic separation was performed on a C18 Spherisorb column (4.6 mm×250 mm, 5 μm particle size) at 25°C. The optimized mobile phase composition was water-methanol (80:20, *v*/*v*) at flow rate of 2 ml/min. Detection was performed at 220 nm using a UV detector. An equivalent volume of temperature-equilibrated fluid was replaced in the dissolution bath following removal of every sample. The data represent the mean values of at least three separate experiments. Results are given as mean ± standard deviation.

Dissolution efficiency values (D.E.), first suggested by Khan (15), are a parameter useful for the evaluation of *in vitro* dissolution. DE is defined as follows:

$$D.E. = \frac{\int_{t_1}^{t_2} y \times dt}{y_{100}(t_2 - t_1)} \times 100\%$$

where y is the percentage of dissolved product and D.E. the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100} over the same time period. When a relationship is to be shown between dissolution and another variable, it is considered more realistic to use D.E. which takes into account the dissolution profile as a whole (15). In addition, where a quantitative comparison is required, D.E. is a more suitable parameter and when limits are set on D.E. it

Table I. Characteristics of the Different Formulations and Release Parameters of ISN Tablets

Formulations	Diameter (mm)	Thickness (mm)	Barrier weight/thickness	*t*60 (min)	D.E. (9 h) ± SD	Surface area	*n* ± SD
A974[a]	8.75	2.15	–	210	78±1.50	179	0.59±0.009
A934	8.75	2.15	–	270	73±1.70	>>	0.57±0.009
A971	8.75	2.15	–	305	70±1.15	>>	0.52±0.008
Ba971	11.0	3.50	100 mg/≈0.83 mm	485	36.5±1.00	310	0.77±0.007
Bb971	8.75	5.30	100 mg/≈0.93 mm	520	34.5±0.55	265	0.66±0.006
D974	11.0	2.55	50 mg/≈0.45 mm	125	78±1.55	278	0.85±0.010
D934	11.0	2.55	>>	220	62±1.00	>>	0.87±0.009
D971	11.0	2.55	>>	355	46.5±0.65	>>	0.81±0.007
E971	8.75	4.30	50 mg/≈0.52 mm	390	43±1.00	238	0.80±0.008
F971	2.20	6.00	20 mg	200	65±0.75	–	0.91±0.015
IMDURE	–	–	–	340	52±0.55	–	0.46±0.007

[a] Indicate the polymer material used in each formulation.

can be used for quality control in place of the conventional dissolution level.

Erosion Studies

The tablets were placed in flat bottom dissolution vessels, containing 900 ml of the liquid under the conditions described in the drug release studies section above. To prevent floating, tablets were placed under a bell shape "tent" which was formed from a pre-weighed 4 cm×4 cm metal mesh (no. 10) square. At a selected time interval, an individual tablet was withdrawn using the mesh "tent". The mesh and the tablet were blotted to remove excess liquid and then weighed on a Sartrorius analytical balance (Sartrorius AG, Goettingen, Germany). The wetted tablets were then dried in an oven at 105°C for 24 h, cooled in a desiccator and weighed again. This procedure was repeated until constant weight was achieved (final dry weight). Three different tablets were measured for each time point and fresh tablets were used for each individual time point.

The extent of erosion (E) was determined from

$$E\% = 100(Wi - Wf)/Wi$$

where Wi and Wf are the initial starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively.

Differential Scanning Calorimetry

The possibility of any interaction between the ISN and Carbopol during tabletting was assessed by carrying out thermal analysis on Carbopol, pure drug (ISN) and powdered sample of 50:50 ISN: Carbopol using differential scanning calorimetry (DSC 50 Shimadzu Co, Kyoto, Japan). Samples (10 mg) were accurately weighed into aluminium pans and then hermetically sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 10° C/min conducted over a temperature range of 20–200°C.

Compatibility Studies

Compatibility studies were conducted on ISN tablets (150 mg) with the three polymers in a proportion of 50:50 drug/Carbopol with respect to their appearance, drug content and impurities after storing at 40°C/75% RH, 25°C/60% RH and 5°C for 3 months, utilizing the HPLC method described above. For the determination of contact angles of ISN and Carbopols, a Kruss G40 Contact angle measuring system was used (Kruss GmbH, Hamburg, Germany). Tablets of pure material diameter 11 mm and weight 400 mg were compressed (at 1,000 kPa) and used for these measurements.

Optical Examination

Tablet images were taken with a video camera (JVC TK-C11381, Japan) fitted with a zoom lens (Century Precision Optics AD-5870, USA) and connected to a monitor. The light system consisted of a fluorescent tube fitted under the beaker. The beaker was covered to exclude external light. The tablet was held on a pin and placed in a dissolution beaker with 900 ml of dissolution medium at 37±0.5°C with stirring at 100 rpm, to allow one to observe changes in the device.

Statistical Analysis

Results are expressed as the mean ± standard deviation (SD) and were analyzed using Student's t-test ($P<0.05$).

RESULTS AND DISCUSSION

The three Carbopol polymers used differ in the density of their cross links with the C974 exhibiting the greatest density followed by C934 and then C971. Their swelling is considerably influenced by the pH and at values over 4.5 swell completely. When fully hydrated they do not dissolve, but osmotic pressure from inside breaks up the structure mainly by sloughing off disengaged particles of the gel. The disengaged pieces remain intact and the drug continues to diffuse at a continuous rate (9,11).

Differential Scanning Calorimetry and Compatibility Studies Results

The occurrence of any drug Carbopol interaction in the formulations was predicted by conducting differential scanning calorimetry studies. Thermograms are shown below for Carbopol 971 and pure drug powdered sample in a ratio 50:50, pure drug/Carbopol, see Fig. 1. Based on these thermograms it appears to be no possibility of interaction between the ISN and the Carbopol used in the preparations of the present study.

The results of compatibility studies are shown in Table II. After the 3 months storage in various conditions there appeared no considerable changes, either in physical appearance, or in drug content when compared to the formulations before storage. Moreover it is evident there are no differences in impurity concentration. Therefore, we can conclude that Carbopols are compatible carriers for ISN and suitable excipients for its formulation in controlled release systems. Judging from their contact angle values all the materials used

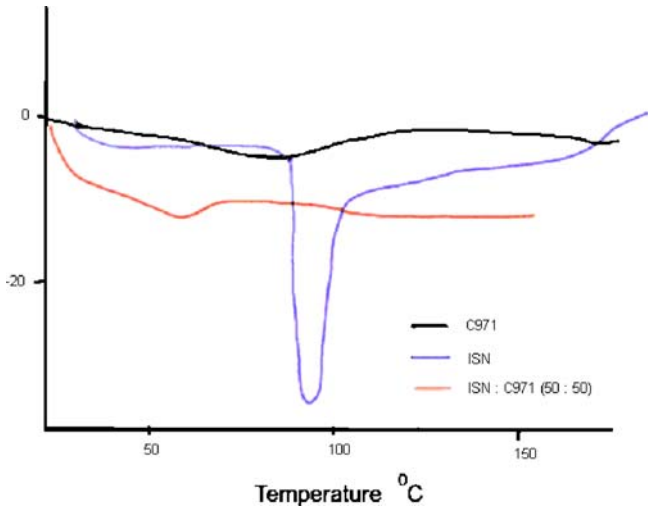

Fig. 1. DSC thermograms of mixture isosorbite/Carbopol 971 (50:50)= ISN/C971 (50:50), isosorbite-5-mononitrate=ISN, C971=Carbopol 971

Table II. Compatibility Studies of ISN–Carbopols

	Months	Conditions	ISN-934	ISN-971	ISN-974
% ISN	0		102.7	101.3	101
ISN impurities	0				
Isosorbite-2-monitrate			<0.5	<0.5	<0.5
Isosorbite dinitrate			<0.5	<0.5	<0.5
Inorganic nitrate			<0.5	<0.5	<0.5
% ISN	3	40°C/75% RH	102.3	101.7	100.8
		25°C/60% RH	103.1	101.5	100.6
		5°C	102.6	101.9	101.3
ISN impurities	3				
Isosorbite-2-monitrate		40°C/75% RH	0.5	0.5	0.5
Isosorbite dinitrate		25°C/60% RH	0.5	0.5	0.5
Inorganic nitrate		5°C	0.5	0.5	0.5

displayed hydrophilic characteristics, particularly ISN with a contact angle 16 it appears to be a very hydrophilic material. In parallel Carbopols showed contact angles in the region of 47–49.

In Vitro Drug Release

Drug release from a matrix tablet may be characterized as a mass transport phenomenon and usually involves three different steps. Liquid penetration into the dosage form is the first step followed by dissolution of the drug and finally its diffusion. Drug release from the multi layer devices appears more complicated, since the movement of drug molecules is also affected by the existing barriers.

Device Structure and Drug Release

In Fig. 2 the release profiles from the matrix-tablet (A formulations, in a ratio 50:50 ISN/polymer), are demonstrated. In this evaluation we also include for comparison the release profile of IMDURE, although it is a different form of sustained release system (i.e., membrane controlled), fabricated with different methology as it is a sustained release film coated tablet.

The ISN/polymer ratio was chosen after preliminary experiments which indicate that this proportion was the most appropriate for the scope of our investigation. From the release profiles it is evident that the release rate of ISN was greater in the C974 tablets followed by the C934 and C971 which exhibited the lowest release. On the other hand IMDURE displayed a lower release.

The above results were confirmed by the *t*60 (time required for 60% drug release) and D.E. (9 h) values, Table II. Formulations A974 exhibited *t*60=130 min and D.E.=78, at the same time the formulations A934, A971 and IMDURE displayed *t*60=145, 165 and 330 min and D.E. values 73, 70 and 52 respectively, Table II. For the Carbopols this behavior may be attributed to the different degree of cross linking density among the polymers used in this study. As mentioned earlier, C971 is the least cross linked polymer and consequently is less porous and has fewer channels, C934 is an intermediate, whereas C974 exhibits the most cross links and has the most pores and channels (9). The channels facilitate liquid penetration and the drug release in a tablet. Therefore, the polymer with more channels, C974, demonstrated the highest release; quite the opposite C971, with fewer channels displayed the lowest release.

From the release profiles of these matrices it is obvious, that an approximately 40% of the drug was released in the first 60 min showing a relatively burst effect, Fig. 2. This could be attributed to the dissolution of the drug mainly located on the surface of the matrix. The dissolution is also facilitated by the fact that in early times (where the pH of the medium was in the region of 1.2) the gel thickness was rather low Fig. 3a, resulting a limited diffusion pathway for the drug molecules to diffuse out. When the matrices transferred in the medium with pH values above 4, Carbopols swelled considerably and an expansion of the matrix is noticed. In addition, a thick gel layer was formed as it is shown in Fig. 3b. The gel thickness increases as the time passes, retarding liquid penetration and drug release. A thick gel layer result in a considerable increase in the diffusion pathway for the drug molecules and consequently the drug release rate was reduced. Figure 3 illustrates the difference of gel layer thickness (in axial and radial dimension) between the first (Fig. 3a) and third (Fig. 3b), hours respectively. All A formulations displayed complete drug release. The release was completed in 5, 7 or 9 h from A974, A934 and A971 formulations respectively. IMDURE exhibited an approximately 75–80% release at the some period of time.

The bar graph shown in Fig. 4 illustrates the release data of ISN presented as the rate of release (percent dissolved per hour) *versus* time (hours). The burst effect is clearly

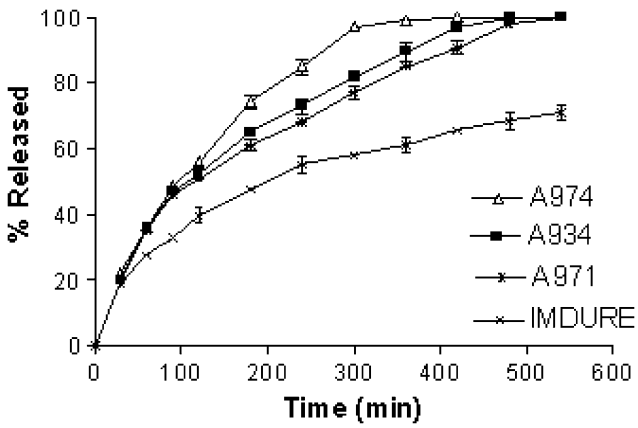

Fig. 2. Dissolution profiles of *A* formulations and *IMDURE* tablets. Each *point* represents the mean value of the three samples and *error bars* show ±SD

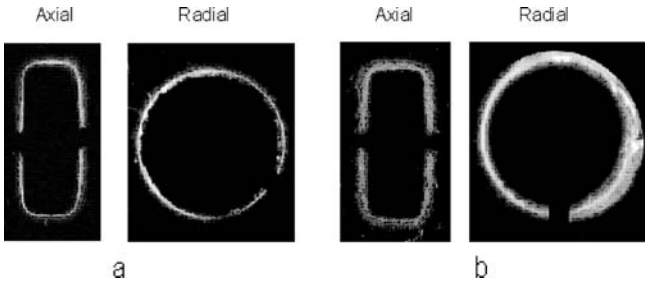

Fig. 3. Typical image of Carbopol tablet undergoing hydration after **a** 1 and **b** 3 h in the radial and axial plane

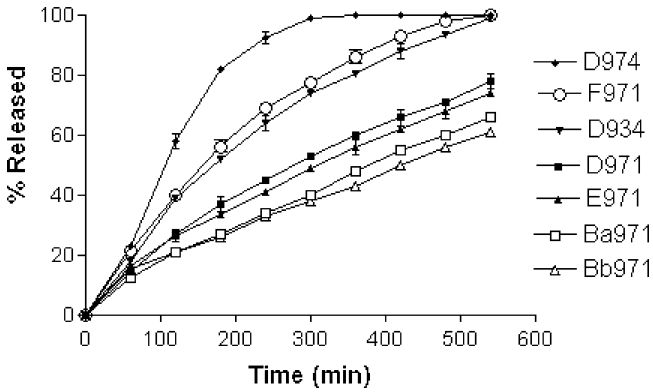

Fig. 5. Dissolution profiles of *B*, *D*, *E* and *F* formulations. Each *point* represents the mean value of the three samples and *error bars* show ±SD

demonstrated in all matrix formulations in the first 2 h. Afterwards A971, demonstrated a rather steady release rate which corresponds to 7–8% per hour. Similarly, IMDURE also demonstrated a rather steady release (after the fourth h) which corresponds to 4% per h.

Based on the above results, indicating that A971 exhibited the maximum retardant effect and a rather steady rate, we decided to carry out our investigation mainly with this material, since it appeared more suitable for our objective. Namely, to prepare three-layer sustained release formulations with desirable drug delivery. In those formulations this material was also used as ingredient in the barrier-layers of the tablets. Except for the formulation A, which is a matrix tablet and the simplest controlled release drug delivery system composed of the drug and the carrier/retarding polymeric material, all the other devices (based on A) had the two surfaces of the core (top and bottom) covered with Carbopol barriers, thus the formulation consisted of a three-layer tablet system.

The preparation of three-layer tablets is based on the idea that the restriction of the tablet area exposed to the dissolution medium may lead to a two fold control in the system performance and modify drug release. This is possible for two reasons: (a) the matrix hydration rate and consequent swelling are reduced and, (b) the surface through which the drug can be delivered is decreased. The drug release mechanism from the three-layer tablets involves the following sequence. In the initial stage, barriers applied to the core are able to obstruct the contact of the core tablet with the dissolution medium by limiting the solvent penetration rate and by reducing the surface available for drug release. Thus, the burst effect can be controlled and the area available for drug release can be maintained at a relatively constant level. Throughout the dissolution, barrier layers may erode and the surface available for drug release increases. Hence, the decrease on the release due to an increase in the diffusion path length is compensated by the simultaneous increase in the available area for drug release. Eventually, the dissolution medium can finally reach the core easily, which can freely swell or erode.

The three-layer formulations Ba971 and Bb971 (based on Carbopol 971) differ in their geometrical characteristics but in both cases top and bottom faces covered with barrier 100 mg weight each. Ba971 has 11.25 mm diameter and 3.50 mm thickness while Bb971 has 8.75 and 5.30 mm dimensions respectively. Due to the difference in diameter, the thickness of the barrier-layers is obviously different, with the formulation Ba971 having thinner barriers, see Table I.

In Fig. 5 the release profiles of formulations Ba971 and Bb971 are demonstrated. It is apparent that the total release of the drug is similar approximately 60–65% in 9 h (D.E. 36.5 and 34.5 respectively), even though Ba971 (with thinner barriers) displayed a slightly greater release. It appears that the different dimensions or the thickness of the barriers, in this case, have no considerable effect on drug release as the *t*60 (485 and 520 min respectively) and D.E. values (36.5 and 34.5) show, Table I. This similarity of release could be explained by the comparable surface area of the cylindrical devices namely 310 and 265 (Table II) for Ba971 and Bb971

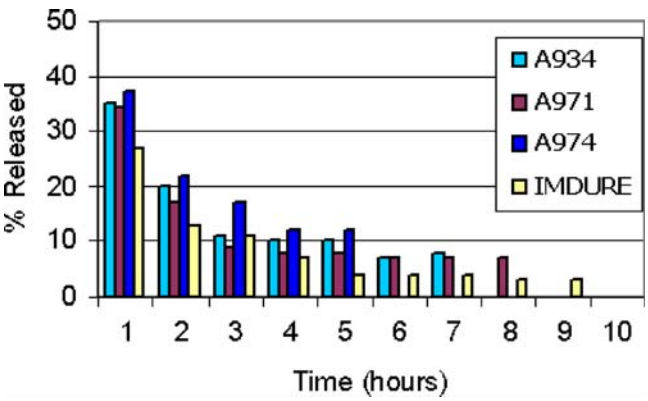

Fig. 4. Rate of drug release (% of drug release/hour) from *A* formulations and *IMDURE* tablets as a function of time

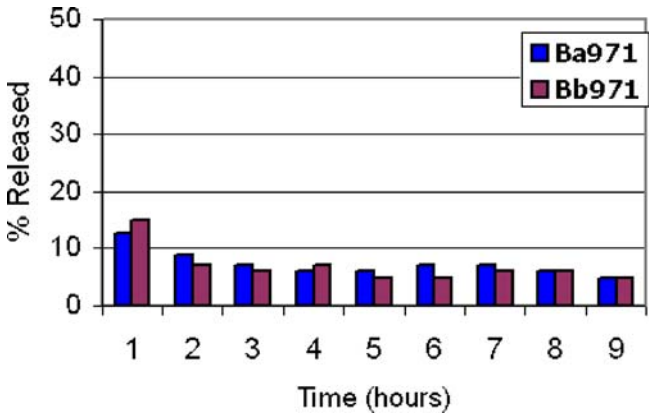

Fig. 6. Rate of drug release (% of drug release/h) from *B* formulations as a function of time

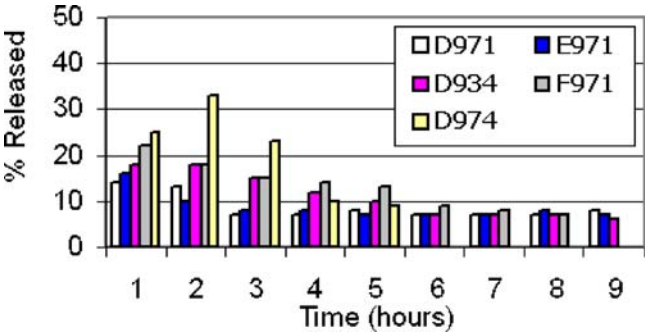

Fig. 7. Rate of drug release (% of drug release/hour) from *D*, *E* and *F* formulations as a function of time

Table III. Loss of Tablet Weight (D971)

Time (min)	% drug release	% loss of weight due to drug dissolution	% loss of total tablet weight	% remaining mass
0	0	0	0	0
60	9	2.1	2.3	97.7
120	24	5.7	5.9	94.1
180	38	9.2	9.5	90.5
240	47	11.1	11.4	88.6
300	53	12.8	13.5	86.5
360	60	14.3	14.7	85.3
420	68	16.2	16.8	83.2
480	72	17.3	18	82

correspondingly, which suggest that both devices exhibited similar available surface exposed to the liquid.

The bar graph shown in Fig. 6 illustrates the release data of the drug presented as the rate of release against time. It is apparent that after the second hour both formulations demonstrated a rather steady release rate, which corresponds to a 5–6% per hour. The burst effect is clearly suppressed compared to matrix formulations, Fig. 4. On the other hand only 60–65% of the drug is released.

In formulations D974, D934, D971 and E971 the barrier-layers weight 50 mg and consist of the core's polymer i.e., C974, C934 and C971 correspondingly. D formulations have 11.00 mm diameter and 2.55 mm thickness, whereas in E971 is 8.75 and 5.30 mm respectively. Consequently, the thickness observed of the barriers is quite different (Table I).

The F971 device consisted of three three-layer mini-tablets, based on C971, weighing 30 mg each. The two faces covered with barrier-layers 20 mg. Therefore, their final weight was 70 mg. Their diameter was 6 mm, the thickness 2.2 mm and were filled into hard gelatin capsules no. 0. This formulation appears more complex and it was prepared and examined in order to detect whether this differentiation results in a considerable variation in drug release, compared to the other three-layer formulations.

The drug release profiles showed the release of ISN is higher from D974 tablets followed by D934 and D971 and it is confirmed by *t*60 (125, 220 and 355 min) and D.E. values (78, 62 and 46.5), Table I, Fig. 5. In formulation E971, with smaller diameter but greater thickness, the drug release was comparable although lower to that of D971, (*t*60=390 min, D.E.=43), Fig. 5. This could be, again, due to the smaller available surface area of E971 exposed to the liquid compared to D971, which exhibited greater surface area (238 and 278 respectively, Table I). Finally, F971 displayed lower release compared to D974 but higher than D934, D971 or E971.

In Fig. 7 the bar graph shown illustrates the release data of ISN presented as the rate of release *versus* time. As it is shown, after the second hour D971 and E971 exhibited a rather steady release rate which corresponds to 7–8% per hour and their total release after 9 h was in the region of 80%. On the other hand, the other three formulations displayed different mode and their release was completed in 9 h.

Barrier Effect

The weight of barrier layer appears to affect noticeably the drug release. Formulations Ba971 and Bb971 with the barriers of 100 mg displayed slower release rates of ISN compared to analogous formulations D971 and E971 with the 50 mg barriers, see *t*60 and D.E. values in Table I and Fig. 5. Thus, it is obvious that the 100 mg layers proved a more effective barrier. This is attributed to the fact that the thicker barrier of 100 mg exhibited increased swelling and stronger gelling compared to 50 mg barrier and as a result it prevents the liquid penetration into polymer mass and consequently decreases the dissolution rate and the diffusion of the drug through the barrier-layer. In addition, it is noted that after 120 min. all formulations with 50 mg barrier, except D974, exhibited a rather linear drug release, Fig. 5.

Optical observations revealed that with the passage of time the barrier-layers swelled simultaneously with the core tablet merged with it and finally engulfed part of the core creating a solid polymer mass (Fig. 8a–c, where a, b and c correspond to 1, 2 and 3 h, respectively).

Total drug release involves both diffusion of drug molecules from the lateral surface of the core tablet, as well as delayed diffusion through the top and bottom barrier-layers as a result of their swelling and "sloughing off" disengaged particles of the formed gel over time.

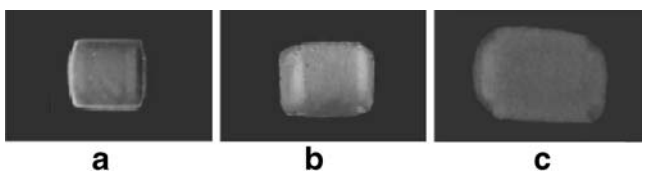

Fig. 8. Morphological changes of three-layer tablet during dissolution

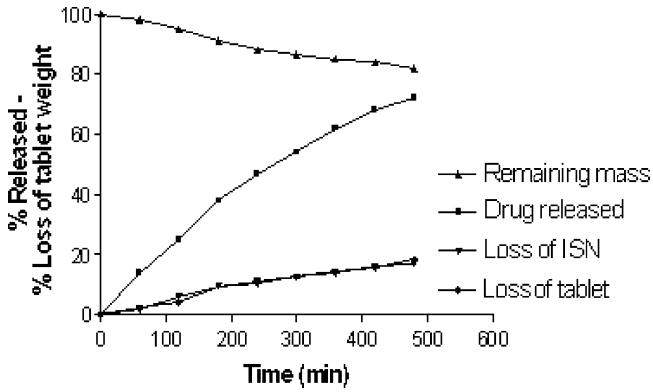

Fig. 9. Dissolution profile and loss of weight from the D971 matrix

A precise description of this procedure is not easy, because the release from the two covered surfaces depends on variable polymer characteristics, such as structure, viscosity and layer's thickness and weight. The interplay of the above factors determines the morphological changes that take place. These in turn affect the area of release surface available and finally the rate of drug release. Clearly, these developments may delay the transport of the drug molecules through the barriers resulting in slower drug release from the three layers formulations compared to the matrices as can be seen in Figs. 2 and 5.

The loss of weight, Table III, Fig. 9, suggests that in Carbopol formulations the loss of tablet weight is due to the drug dissolution and there is practically no polymer erosion/dissolution, since the loss of weight due to the drug dissolution and the total tablet loss of weight are identical. Results display the % loss of tablet weight (D971), but similar results were observed with the other formulations (D974 and D934, not shown) as well. It appears that the drug release is mainly attributed to its diffusion after relaxation and sloughing off disengaged particles from the polymer mass which remain insoluble in the liquid.

Kinetics and Mechanism of Drug Release

From the above, it is clear that the structure and the morphology of the device during dissolution significantly influence drug release. An increase in barrier-layer weight results in a decrease of drug release, additionally polymer characteristics considerably influence this release. In order to clarify, identify and explain the mechanism of drug release, the data were further analyzed, up to 60% drug release, using the familiar empirical equation proposed by Korsmeyer *et al.* (16).

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t is the amount of the drug released at time t, M_∞ is the amount of drug released over a very long time that corresponds in principle to the initial loading, k is the kinetic constant and n is the diffusional exponent which depends on the release mechanism. For a cylindrical matrix, values $n=0.45$ indicate Fickian release. Values $0.45<n<0.89$ indicate anomalous release kinetics (coupled diffusion/relaxation) and $0.89<n<1$ indicate a zero order release also known as purely relaxation-controlled drug release.

The n values obtained, listed in Table I, ranged from 0.46 to 0.91. The n values for the matrices A971, A974 and A934, namely 0.52, 0.59 and 0.57, respectively indicate that the release mechanism was rather Fickian diffusion. IMDURE tablets also displayed an analogous mechanism $n=0.46$. The n values for the three-layer tablets with 100 mg barriers exhibited a coupling of diffusional and macromolecular mechanisms so called anomalous diffusion kinetics (0.66 and 0.76). Formulations with 50 mg barriers and the F971 device consisting of three three-layer mini-tablets displayed higher n values (0.80–0.91) indicating mainly macromolecular relaxation and erosion mechanisms and a near zero-order release. In general, it appears that the barriers not only decrease the drug release from these systems, but also modulate the relative contribution of diffusion and polymer relaxation to drug release and therefore influence drug release mechanisms.

CONCLUSIONS

All Carbopol formulations displayed sustained release, however three-layer tablet formulations demonstrated lower drug release compared to matrix tablets. The structure of the tablets and weight/thickness of the barrier-layers considerably affected drug release and the release mechanisms. The barriers suppressed drug release causing a shift from Fickian (matrix tablet) to anomalous or erosion/relaxation release kinetics (three-layer tablet). The advantage of Carbopol three-layer tablet formulations is that a wide range of release profiles can easily be achieved through variation of tablet structure.

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