AAPS PharmSciTech, 2000; 1 (4) article 34
(http://www.pharmscitech.com)

# Development and Evaluation of Oral Multiple-unit and Single-unit Hydrophilic Controlled-release Systems

*Submitted: July 14, 2000; Accepted: November 29, 2000*

Manuel Efentakis,* Antonios Koutlis, and Marilena Vlachou

School of Pharmacy, Department of Pharmaceutical Technology, University of Athens, Panepistimiopolis, Zografou, 157 71 Athens, Greece

**ABSTRACT** This study compared the release behavior of single-unit (tablets, capsules) and multiple-unit (minitablets in capsules) controlled-release systems of furosemide. The swelling and erosion behaviors of these systems, which contained the swellable hydrophilic polymers sodium alginate (high viscosity) and Carbopol 974P, were compared. Swelling and erosion experiments showed a high degree of swelling and limited erosion for the Carbopol preparations, whereas less swelling but greater erosion was observed for the sodium alginate preparations. The sodium alginate preparations were eroded in 6 hours, while Carbopol preparations exhibited limited erosion within this period of time. These results appear to be attributed to the physicochemical characteristics of the polymers used in this study. Polymer characteristics greatly influenced the release of furosemide (model drug) from the formulations prepared and tested. Sodium alginate had a less pronounced sustained release effect compared with Carbopol (ie, in 8 hours all 3 sodium alginate dosage forms displayed complete release of furosemide, while only 30% of the drug was released from Carbopol dosage forms). Finally, all 3 Carbopol dosage forms (single- and multiple-unit) displayed similar release behavior while sodium alginate dosage forms displayed a different and more distinctive behavior. Minitablets and tablets showed a greater sustained release effect compared with capsules. Evaluation of the release data indicates that the release mechanism for sodium alginate formulations may be attributed to erosion/dissolution, while for Carbopol it may be attributed mainly to polymer relaxation and diffusion of the drug from the polymer surface.

**KeyWords:** Single-unit, Multiple-unit, Minitablets, Controlled release, Carbopol, Sodium alginate, Furosemide.

## INTRODUCTION

Controlled-release solid dosage form systems are available either as single-unit (nondivided formulation) or as multiple-unit (divided formulation) forms [1,2]. The single-unit dosage forms usually refer to diffusion-controlled systems where the drug is dissolved or dispersed throughout a solid matrix and the release of the drug is controlled or sustained either by incorporating a suitable filler within the matrix or by coating the matrix with swellable or nonswellable polymer film(s). The former case is known as a monolithic system [3], where the diffusion of a drug through a matrix is the rate-limiting step [4]. The rate of release from such devices usually is not constant and follows a square root of time dependency. In monolithic preparations made of hydrophilic polymers the drug release is governed by the swelling rate of the polymer matrix. Zero-order release kinetics from these preparations can be maintained if the polymer swells at a constant rate, maintaining a constant surface area, and the diffusion of the drug is comparatively rapid. In the second case, commonly known as a reservoir or multilayered matrix system, the diffusion of the drug through the polymer coating or layer of the system is the rate-limiting step [5]. Capsules can also be used as single-unit controlled-release delivery systems provided that suitable excipients are used [6,7].

***Corresponding Author:** Manuel Efentakis, School of Pharmacy, Department of Pharmaceutical Technology, University of Athens, Panepistimiopolis, Zografou, 157 71 Athens, Greece; Telephone: 00-301-7274-025; Fax: 00-301-7274-027; E-mail: efentakis@pharm.uoa.gr

Multiple-unit dosage forms are essential where drug excipients or drug-drug physicochemical interaction is possible in a single-unit formulation; they are also known to have less variance in transit time through the gastrointestinal tract than single-unit dosage forms. These dosage forms usually are based on subunits such as granules, pellets, or minitablets [1]. They are usually delivered in hard gelatin capsules or made into tablets that disintegrate instantly.

The recent interest in multiple-unit dosage forms is a result of the advantages they offer over the single-unit systems [1,2]. For example, multiple-unit forms offer more predictable gastric emptying, gastric emptying less dependent on the state of nutrition, a high degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping. The multiple-unit forms are also more suitable for formulations with acid-sensitive drugs (ie, erythromycin) [8].

On the other hand, multiple-unit preparations exhibit several disadvantages. Their manufacturing is more complicated and more expensive, the filling of gelatin capsules is difficult to accomplish especially in the case where different subunits are involved, and the preparation process of minitablets necessitates extra care and fine adjustments of tabletting machines [1,9].

Although the debate on the particular advantages of the 2 formulations (single- and multiple-unit) has been going on for a long time in the literature [1,8,10], it has not produced any definite conclusion on the performance of those formulations until now and the differences in behavior are controversial. The dosage forms used and evaluated in this study were prepared from hydrophilic swellable materials. Swellable hydrophilic monolithic systems consist usually of a drug dispersed in suitable hydrophilic material and then compressed into tablets. Contact of the system with the medium results in the system swelling and increasing in dimension; the dissolution medium penetrates the hydrophilic swellable polymer mass and drug dissolution starts.

Erosion controlled monolithic systems are similar to swellable systems, but the diffusion rate of the drug within the gel layer is slower in comparison to polymer dissolution. In nonerodible systems, the polymer phase does not degrade but remains unchanged with time, while the polymer in erodible systems decreases with time and the drug is released by diffusion [11].

The aim of this investigation was, first, to develop and evaluate 2 single-unit (tablet and capsule) forms and 1 multiple-unit dosage form (minitablets filled in a hard gelatin capsule) prepared from hydrophilic swellable polymer materials.

Secondly, the release behavior of those was studied in relation to their erosion and swelling to investigate the relationship between their drug-release profiles.

All formulations consisted of 2 different polymers 3/4 sodium alginate (high viscosity) and Carbopol 974P3/4each containing 50 mg of drug and 150 mg of polymer. The multiple-unit formulation consisted of 4 minitablets of 50 mg each.

## MATERIALS AND METHODS

### *Materials*

Sodium alginate high viscosity (Sigma Chemical Co, St Louis, MO), Carbopol 974P (kindly provided by BF Goodrich, Cleveland, OH), magnesium stearate (BDH, Poole, England), and furosemide (a gift of Hoechst AG, Frankfurt, Germany) were of analytical grade and were used as received. Empty hard gelatin capsules of size 0 were obtained from Capsugel (Colmar, France).

### *Methods*

The mixture (the drug, the polymer, and the magnesium stearate) was sieved (315 mm sieve) and thoroughly mixed in a drum hoop mixer (Erweka, Heusenstamm, Germany) for 15 minutes. The formulations prepared contained drug 30% wt/wt, polymer 69% wt/wt, and magnesium stearate 1% wt/wt. The exact weight of powder (200 mg) was manually filled into each capsule of size 0. The filling was performed at maximum bulk density. Tablets weighing 200 mg with a diameter of 10.2 mm and thickness of 1.8 mm were prepared using a single-punch tabletting machine (Korsch, EKO, Erweka, Heusenstamm, Germany). Smaller

minitablets weighing 50 mg each with a diameter of 6 mm and a thickness of 0.7 mm, 4 of which could be filled into hard gelatin capsules of size 0 (multiple-unit preparation), were also produced. The tablets were compressed to a crushing strength of 7-8 kg, while minitablets were compressed to a crushing strength of 5-6 kg, measured in the Erweka hardness tester.

### *Water uptake and erosion determination*

The medium uptake into the preparation and erosion were determined after immersion in the medium. Weighted samples were placed in flat-bottom dissolution vessels (in dissolution baskets rotated at 50 rpm) containing phosphate buffer pH 5.8 at 37 ± 0.2°C. After a selected time interval each dissolution basket was withdrawn, blotted to remove excess water, and weighed on a Mettler analytical balance. The wetted samples were then dried in an oven at 110°C for 24 hours, allowed to cool in a desiccator, and finally weighed until constant weight was achieved (final dry weight). The increase in weight of the wet mass represents the medium uptake. The increase in weight due to absorbed liquid (Q) was estimated according equation 1.

$$Q = 100 ( W_W - W_f ) / W_f \quad (1)$$

Where $W_W$ and $W_f$ are the mass of the hydrated sample before drying and final mass of the same dried and partially eroded sample, respectively.

The percentage erosion (E) of the device was estimated using equation 2.

$$E = 100 (W_I - W_f ) / W_I \quad (2)$$

Where $W_I$ is the initial starting dry weight. Three different samples were measured for each time point, and fresh samples were used for each individual time point. All experiments were done in triplicate.

### *Drug release*

The dissolution studies for the 3 different dosage forms were carried out according to the procedure described in USP XXIII, using a dissolution apparatus (Pharmatest, Hainburg, Germany) basket method, in 900 mL of dissolution medium pH 5.8, maintained at 37 ± 0.2°C and rotated at 50 rpm. Samples were withdrawn at predetermined time intervals and were assayed at 276 nm using a Perkin Elmer Lamba 6 spectrophotometer (Norwalk, CT). Dissolution studies were performed in triplicate for each preparation and the mean cumulative percentage of drug calculated (± standard deviation [SD]) and plotted against the time.

## RESULTS AND DISCUSSION

The characteristics of hydrophilic polymers and their ability to hydrate and form a gel layer are well known and are essential to sustain and control drug release from matrices [12,13]. The hydrated gel layer thickness determines the diffusion path of the drug molecules through the polymer mass into the dissolution medium. None the less, diffusion is not the only mechanism controlling drug release from these systems. The rate and extent of drug release are also dependent on the swelling and erosion of the hydrated polymer mass.

Drug release from 3 different solid dosage forms (capsules, tablets, and minitablets) containing 2 different materials (sodium alginate and Carbopol 974) was studied in this investigation. Alginate is an anionic linear polysaccharide that is soluble at near neutral pH, forms alginic acid at below pH 3 [14], and does not appear to swell at pH 1.2. However, rapid swelling and erosion are observed at pH 6.8 [15]. Carbopol 974 is a synthetic high molecular weight cross-linked polymer of acrylic acid. It hydrates, absorbs water, and swells, but has very low water solubility. It has a pK of 6, so at pH 1.2 it would be virtually un-ionized, and, because of its low solubility, difficult to hydrate. At pH 4.5 it starts to ionize and swell, displaying its greatest degree of swelling at pH 7-7.5 [16,17]. Thus, at pH 5.8 both polymers display increased swelling and the amount of drug released from dosage forms that contain these materials depends on the degree of swelling. The model drug used in this study, furosemide, is a rather poorly water-soluble drug. According to Alderman's study [12], drugs with these solubility characteristics are primarily released through erosion of the polymer gel layer.

## *Swelling*

Swelling results at pH 5.8 for both polymers are shown in **Figures 1** and **2**. The order of swelling observed in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of sodium alginate was achieved after 2 hours and then gradually decreased due to erosion. Carbopol reached maximum swelling after 6 hours and this was maintained until the end of the experiment. The liquid uptake by Carbopol is 3 to 5 times greater than that of sodium alginate.

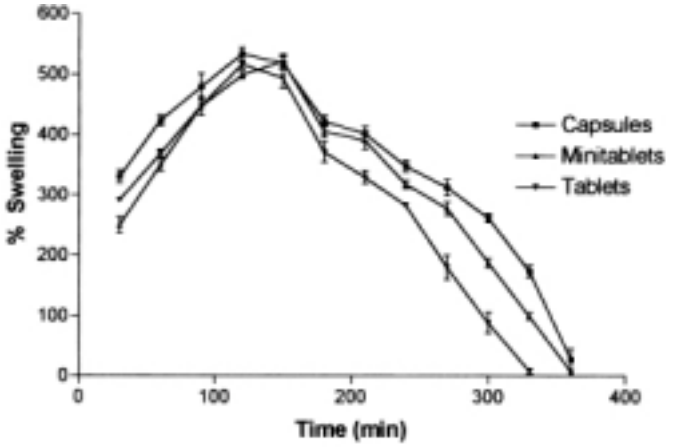


**Figure 1.** Swelling behavior showing the swelling indices (%) against time of sodium alginate dosage forms at pH 5.8. Each point represents the mean value of 3 samples and error bars show ± standard deviation.

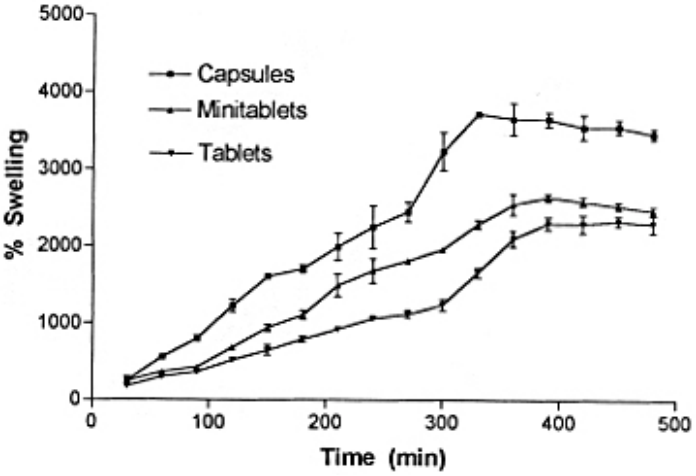


**Figure 2.** Swelling behavior showing the swelling indices (%) against time of Carbopol dosage forms at pH 5.8. Each point represents the mean value of three samples and error bars show ± standard deviation.

The sodium alginate capsules exhibited a slightly greater swelling than the minitablets and tablets (**Figure 1**). On the other hand, the Carbopol preparations exhibited more distinctive swelling behavior (**Figure 2**). The capsules displayed the greatest swelling followed by the minitablets with intermediate swelling, while the smallest swelling was observed in the tablets. The capsules initially exhibited greater swelling because of looser compaction compared with the other formulations, while the more compact minitablets and tablets exhibited less swelling. Carbopol has the ability to absorb and retain a larger amount of liquid and therefore its diffusional path length is much longer than that of sodium alginate.

From a morphological point of view, the capsules appeared swollen almost from the beginning. Visual observation confirmed that both polymers created a highly viscous gel when they came into contact with the medium and within 15-20 minutes after exposure to the dissolution medium the body and the cap of the capsule were dissolved. The remaining mass initially tended to form a gelatinous cylinder that eventually became an amorphous mass. The polymer mass reduced with time in all cases, to a great extent for sodium alginate and to a very limited extent for Carbopol. It was also noticed that as their hydration swelling progressed, the minitablets contained in the capsules rapidly formed a single mass (like a rod cylinder), exhibiting a tendency to adhere to one another, due to the presence of the gelatin capsule.

## *Erosion studies*

The results of erosion studies at pH 5.8 are provided in **Figures 3** and **4**. These results reflect both the amounts of drug dissolved and the erosion of the polymer during the dissolution period. This is because furosemide is soluble at pH 5.8 since it has a pK of approximately 5. Preparations containing Carbopol showed limited erosion of 15%-20% throughout the duration of this study [16]. The sodium alginate formulations started to erode after the third hour (shown in **Figure 1**) and there was a visible break in swelling profiles after this time. They were completely eroded within 6 hours.

The erosion phenomenon appeared more intense in tablets and minitablets compared with that observed in capsules. The presence of the poorly soluble furosemide [12,13] probably resulted in disintegration of the tablet compact. Minitablets consisted of smaller compacts that eventually formed a single mass, a rod cylinder, by adhering to one another. This formation, which is looser than that of the tablets but harder than that of capsules (crushing strength 5-6 kg), probably caused this behavior. In capsules, the loose character of the powder mass facilitates penetration of the medium and allows the transfer of furosemide without extended damage to the polymer mass from disintegration. Visual observations confirmed this behavior. The sodium alginate preparations displayed progressive weight loss with time (**Figure 3**), while Carbopol preparations exhibited great resistance to erosion resulting in a much slower drug release. This phenomenon can be attributed to Carbopol characteristics and especially to strong entanglement due to its cross-linked structure.

### *Drug-release studies*

Dissolution profiles are shown in **Figure 5**. Carbopol preparations exhibited a much greater sustained effect on the release rate compared with sodium alginate preparations (in 8 hours only 30% of the drug was released). All Carbopol formulations exhibited similar release behavior. In alginate formulations the drug was completely released after 6 hours from the capsules, and after 8 hours from the minitablets and tablets, which displayed similar behavior.

It seems that when minitablets adhere to one another they eventually convert to a formation that shares some of the characteristics of both capsules and tablets, although it appears that tablet characteristics predominate. The higher release rates displayed by the alginate capsules, which exhibited the lowest erosion, could be attributed mainly to the loose swollen gelatinous mass. This mass facilitates liquid penetration and provides increased free volume, greater contact area between the poorly soluble furosemide and the dissolution medium, higher drug diffusivity, and therefore faster release [18]. Furthermore, in capsules swelling is more pronounced and the quantity of absorbed medium is higher, favoring drug release.

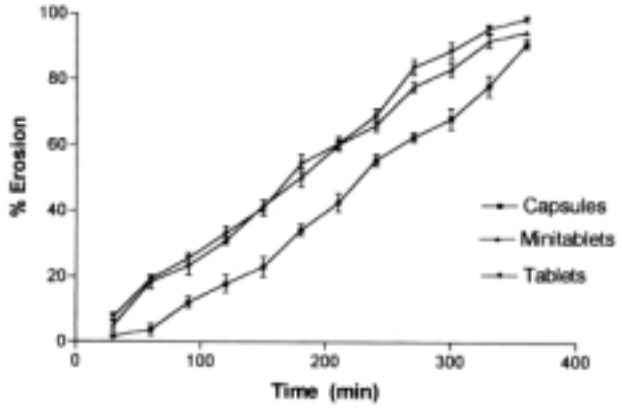


**Figure 3.** The percentage of erosion against time from sodium alginate dosage forms at pH 5.8. Each point represents the mean value of 3 samples and error bars show ± standard deviation.

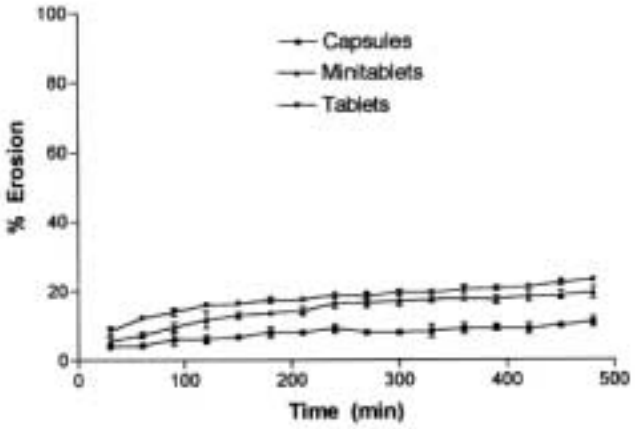


**Figure 4.** The percentage of erosion against time from Carbopol dosage forms at pH 5.8. Each point represents the mean value of 3 samples and error bars show ± standard deviation.

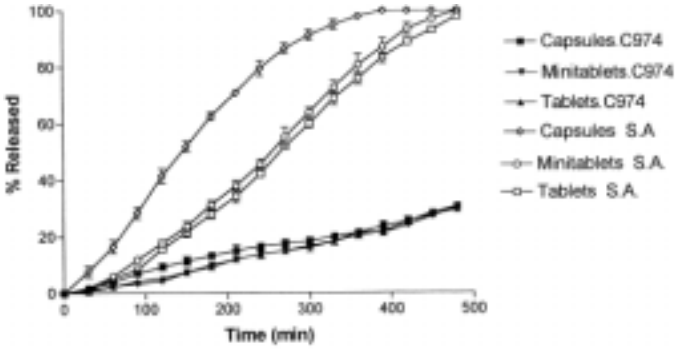


**Figure 5.** Dissolution of furosemide at pH 5.8 from sodium alginate and Carbopol dosage forms. Each point represents the mean value of 3 samples and error bars show ± standard deviation.

The tablets and minitablets exhibited comparable release behavior, which could be attributed mainly to increased erosion of the polymer mass. Moreover, both also displayed less swelling than the capsules. The last may influence the rate of release because limited swelling results in a shorter diffusional path length, which facilitates release. However, this is compensated for, to some extent, by the increased compaction of the polymer mass (due to compression), which makes liquid penetration more difficult, decreases free volume, and prevents, initially, the release procedure. Finally, the tablets showed the slowest release, possibly due to increased compaction (due to compression and a slightly higher crushing strength, 7-8 kg, compared to minitablets, 5-6 kg). Compression, as mentioned above, creates a limited free volume within the polymer mass and this characteristic probably decides the different release behavior of tablets and minitablets.

The Carbopol formulations displayed similar release rates although the capsules exhibited a higher release initially (up to 4 hours) followed very closely by minitablets and tablets. The significant sustained effect is entirely due to polymer characteristics. Carbopol is a cross-linked polymer, which results in a remarkable increase in the molecular volume and reduces the free volume. It is more difficult for a drug molecule to move through a tightly cross-linked network (strong entanglement) [19] than it is to pass through a linear structure like sodium alginate. Furthermore, due to extended swelling and limited erosion, the drug molecule has to follow a longer diffusional path. The capsules exhibited a higher release in the first 4 hours because of a looser gelatinous mass, but subsequently the release rate was similar for all 3 preparations.

**Figure 6** reveals the relationship between the drug release and the erosion process for the sodium alginate formulations. The results demonstrate that erosion plays a significant role and coincides in all cases with the drug release during the dissolution process. All the formulations swelled without significant erosion or polymer dissolution for up to 3 hours (**Figure 1**), after that the erosion of the polymer started and was completed within 6 hours. It appears that the operating release mechanism may include both polymer swelling and erosion/dissolution as was confirmed by visual inspection during the dissolution studies.

The Carbopol erosion experiments demonstrated that for this polymer, drug release is not controlled by erosion (**Figure 4**). The drug release pattern is different and the dominating mechanism is probably polymer relaxation followed by diffusion of the drug, mainly from the surface of the preparation. This is attributed to the strong entanglement of polymer molecules that delay the movement of drug molecules from the interior of the polymer mass toward the surface. This hypothesis is supported by the low release rate observed with all Carbopol formulations.

The higher release from capsules, observed in the first 4 hours, may have been a result of the looser polymer gelatinous mass, however in the following hours the increased swelling and the longer diffusional distance compensated for this effect and

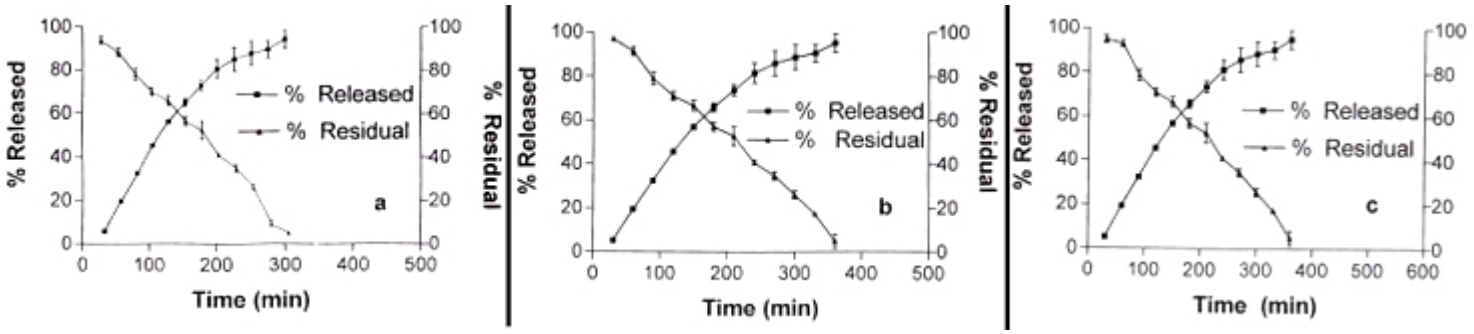


**Figure 6.** Relationship between the fraction of furosemide released and the erosion of sodium alginate formulations: a) capsules, b) minitablets, and c) tablets.

the release rates became equal to the other preparations. Thus it appears that Carbopol single-unit and multiple-unit formulations exhibited similar release behavior, while sodium alginate compressed formulations displayed different release rates from that of the uncompressed system (capsule) since the latter showed a higher release rate. The bar graph shown in **Figure 7** illustrates the release data of Carbopol preparations presented as the rate of drug release (percent dissolved per hour) versus time (hour). The graph clearly shows a fairly constant drug release, which corresponds to about 2% per 30 minutes.

## *Analysis of drug-release data*

Poorly soluble drugs like furosemide are released mainly by erosion [12]. An explanation of the erosion release mechanism is as follows: as the preparation swells it becomes more susceptible to erosion, and leads to an increase in the release of insoluble furosemide. However, the release of furosemide from the Carbopol formulations appears to be associated with its relaxational behavior; the erosion of the polymer is extremely limited (**Figure 4**) given its cross-linked nature.

The sodium alginate formulations, on the other hand, displayed different release kinetics and it seems that drug release and erosion perform simultaneously (**Figure 6**). The presence of poorly soluble furosemide with the soluble sodium alginate results in a release mechanism for the drug that involves a combination of polymer relaxation, which prevails initially in the first hours, and erosion, which dominates in the later stages (when the erosion of the polymer mass becomes more intense).

The kinetics of the release data were analyzed in terms of equation 3 [20]:

$$M_t/M\infty = kt^n \qquad (3)$$

Where $M_t$, $M\infty$, k, and n are the amount of drug released at time t, the total amount of drug, a constant, and the exponent for the release kinetics used to characterize the transport mechanism, respectively.

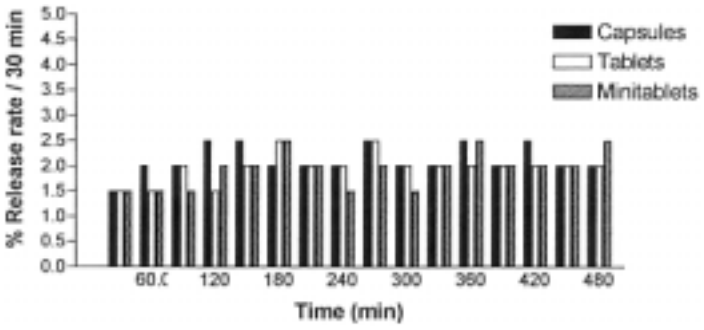


**Figure 7.** Rate of drug release (% of drug released/hour) from Carbopol formulations as a function of time.

According to the known criteria of release kinetics from swellable systems zero-order, anomalous kinetics and Fickian release are represented by $0.89<n<1.0$, $0.45<n<0.89$, and $n = 0.45$, respectively.

This equation generally holds for the early amount of the release profile

(ie, $M_t/M\infty \leq 60\%$). The calculated n values for the release of sodium alginate were $0.96 \pm 0.07$, $0.95 \pm 0.06$, and $0.98 \pm 0.07$, for the capsules, tablets, and minitablets, respectively. These values indicate a rather zero-order release mechanism that may be attributed to swelling and erosion/dissolution of the polymer—a fact confirmed by the swelling and erosion studies (**Figures 1** and **3**). On the other hand the calculated n values for the release of Carbopol were $1.20 \pm 0.08$ for the capsules, $1.10 \pm 0.07$ for the minitablets, and $1.14 \pm 0.05$ for the tablets. These values verify that the release mechanism may be attributed to a purely relaxational behavior as it was confirmed from the relevant swelling and erosion studies (**Figures 2** and **4**).

Further, the data were analyzed and compared using the dissolution efficiency parameter (DE) [21]. The calculated DE480 values of the formulations tested represent the amount of drug released at 480 minutes and are listed in **Table 1**. These values describe in a quantitative manner the extent of drug release shown in **Figure 5** and confirm the significant difference between sodium alginate and Carbopol formulations. They also make a comparison of similarities of the dissolution profiles possible.

**Table 1. Release Characteristics of the Furosemide Formulations**

| | n (±< SD*) | DE† 480 (±< SD / CV) |
|---|---|---|
| C.SA. | 0.96 0.07 | 69.50 5.95/9.46 |
| M.SA. | 0.98 0.07 | 55.0 4.05/7.16 |
| T.SA. | 0.98 0.07 | 51.0 5.03/10.84 |
| C.CAR. | 1.20 0.08 | 17.5 4.40/6.98 |
| M.CAR. | 1.10 0.07 | 15.1 2.67/3.42 |
| T.CAR. | 1.14 0.05 | 15.0 2.14/3.76 |

*SD indicates standard deviation; CV, coefficient of variation; C, capsules; T, tablets; M, minitablets; SA, sodium alginate; CAR, Carbopol. †DE is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

## CONCLUSIONS

From the results of the present study it appears that the release of furosemide was significantly influenced by the characteristics of the polymer used. Because Carbopol is a tightly cross-linked polymer while sodium alginate is a linear polymer, these materials displayed different swelling and erosion behaviors. As a result, the release of furosemide from sodium alginate formulations was completed within 8 hours, while Carbopol formulations showed a significant sustained effect with only 30% of the drug being released within this period of time. Furthermore, the release rates of furosemide from sodium alginate formulations were more distinctive (ie, the compressed systems exhibited lower release rates compared to the uncompressed system, while all 3 Carbopol formulations showed similar release behavior).At gastric pH the release of a poorly soluble drug like furosemide from the sodium alginate preparations is expected to be decreased, as confirmed in earlier studies [15], because its solubility is very low (less than 1 mg/mL [22]) and alginic acid (water swellable but insoluble) is formed [14].

Finally, evaluation of the release data showed that the release mechanism for sodium alginate formulations might be attributed to swelling and erosion/dissolution of the polymer while for Carbopol formulations it may be attributed to polymer relaxation and diffusion of the drug mainly from the surface of the polymer.

## REFERENCES


1. Follonier N, Doelker E. Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms.*STP Pharma Sciences.* 1992;2;141-155.

2. Vial-Bernasconi AC, Doelker E, Buri P. Prolonged release capsules: divided and monolithic forms. *STP Pharma Sciences.* 1988;4;397-409.

3. Fan LT, Singh SK. Introduction. In: Fan LT, Singh SK, eds. Controlled Release-A Quantitative Treatment. Berlin, Germany: Spinger-Verlag; 1989:4-5.

4. Fan LT, Singh SK. Diffusion-controlled release. In: Fan LT, Singh SK, eds. Controlled Release-A Quantitative Treatment. Berlin, Germany: Springer-Verlag; 1989:61-79.

5. Fan LT, Singh SK. Introduction. In: Fan LT, Singh SK, eds. Controlled Release-A Quantitative Treatment. Berlin, Germany: Springer-Verlag;1989:3.

6. Ojantakanen S. Effect of viscosity grade of polymer additive and compression force on release of ibuprofen from hard gelatin capsules. Acta Pharm Fenn. 1992;101:119-126.

7. Efentakis M, Vlachou, M. Evaluation of high molecular weight poly(oxyethylene) (polyox) polymer: studies of flow properties and release rates of furosemide and captopril from controlled release hard gelatin capsules. Pharm Dev Technol. 2000;5:339-346.

8. Digenis GA. The in vivo behavior of multiparticulate versus single unit dosage formulations. In: Ghebre-Sellassie I, ed. Multipaticulate Oral Drug Delivery. New York: Marcel Dekker, Inc.; 1994:333-355.

9. Celik M. Compaction of multiparticulate oral dosage forms. In: Ghebre-Sellassie I, ed. Multipaticulate Oral Drug Delivery. New York: Marcel Dekker, Inc.;1994:181-215.

10. Coupe AJ, Davis SS, Wilding IR. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. *Pharm Res.* 1991;8;360-364.

11. Lowman AM, Peppas NA. Hydrogels. In: Mathiowitz E, ed. Encyclopedia of Controlled Drug Delivery. New York: John Wiley and Sons, Inc.; 1999:407.

12. Alderman D. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int J Pharm Technol Prod Manuf.* 1984:5;1-9.

13. Hogan JE. Hydropropylmethycellulose sustained release technology. *Drug Dev Ind Pharm.* 1989;15;975-999 .

14. McNeely W, Pettitt D. Alginates. In: Whistler R, Bemiller J, eds. Industrial Gums. New York: Academic Press; 1973:68-71.

15. Sugawara S, Imai T, Otagiri M. The controlled release of prednisolone using alginate gel. *Pharm Res.* 1994;11;272-277.

16. Controlled release tablets and capsules. Carbopol Technical Bulletin. 1994;17:1-27.

17. Perez-Marcos B, Ford JL, Armstrong DJ, Elliot PN, Rostron C, Hogan JE. Influence of pH on the release of propranolol hydrochloride from matrices containing hydroxypropyl methylcellulose K4M and Carbopol 974. *J Pharm Sci.*1996;85:330-334.

18. Apicella A, Cappello B, Del Nobile M, La Rontonda MI, Mensitieri G, Nicolais L. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. *Biomaterials.* 1993;14:83-91.

19. Khan Z, Jiabi Z. Formulation and in vitro evaluation of ibuprofen-carbopol 974-NF controlled release matrix tablets. *J Control Release.* 1998;54:185-190.

20. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas, NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25-35.

21. Khan K. The concept of dissolution efficiency. *J Pharm Pharmacol.* 1975;27:48-49.

22. Prasad V, Rapaka R, Knight P, Cabana B. Dissolution medium: a critical parameter to identify bioavailability problems of furosemide tablets. *Int J Pharm.* 1982;11:81-92