
**Journal of Macromolecular Science, Part A**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

# Novel Supports Based on Polysaccharides for Sustained-Release of Isosorbide Dinitrate

Marcel Popa[a]; Nicu Bajan[a]; Aura Angelica Popa[b]; Liliana Verestiuc[c]
[a] Department of Macromolecules, Faculty of Industrial Chemistry, "Gh.Asachi" Technical University, Iasi, Romania [b] "Petre Andrei" University, Iasi, Romania [c] Department of Biomaterials, Faculty of Medical Bioengineering, "Gr.T.Popa" University of Medicine and Pharmacy, Iasi, Romania

Online publication date: 13 October 2010

**To cite this Article** Popa, Marcel , Bajan, Nicu , Popa, Aura Angelica and Verestiuc, Liliana(2007) 'Novel Supports Based on Polysaccharides for Sustained-Release of Isosorbide Dinitrate', Journal of Macromolecular Science, Part A, 44: 5, 483 — 488
**To link to this Article: DOI:** 10.1080/10601320701234993
**URL:** http://dx.doi.org/10.1080/10601320701234993

*Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry* (2007) **44**, 483–488

ISSN: 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320701234993

# Novel Supports Based on Polysaccharides for Sustained-Release of Isosorbide Dinitrate

MARCEL POPA,[1] NICU BAJAN,[1] AURA ANGELICA POPA,[2] and LILIANA VERESTIUC[3]

[1]*Department of Macromolecules, Faculty of Industrial Chemistry, "Gh.Asachi" Technical University, Iasi, Romania*
[2]*"Petre Andrei" University, Iasi, Romania*
[3]*Department of Biomaterials, Faculty of Medical Bioengineering, "Gr.T.Popa" University of Medicine and Pharmacy, Iasi, Romania*

Received September, 2006, Accepted October, 2006

Novel supports based on carboxymethylcellulose (CMC), crosslinked with epichlorohydrin (EPC), and microparticles based on acetylphthalylcellulose (APC), for sustained-release of isosorbide dinitrate (Isoket, Ik), were obtained. The drug has been included into CMC hydrogels through diffusion from ethanol-water solution. Studies about the ethanol–water ratio influence on including the drug have shown an increased amount of included drug at higher content of water in the alcohol-water mixture. Isoket–ACP microparticles have been obtained by drug and polymer co-precipitation from emulsified aqueous solution.

The kinetics for "in vitro" release of Ik from polymeric materials, in simulated conditions for intestinal tract medium, where the drug is preferentially absorbed, has been analyzed. The experimental data have shown a "zero" order kinetic for drug release, which is characteristic for systems controlled by diffusion.

**Keywords:** hydrogel; particles; polysaccharide; drug release



## 1 Introduction

Currently, heart diseases are the most common disorders and involve careful and continuous treatments. Nitroglycerine and Isoket (isosorbide dinitrate) are especially used in pharmaceutical treatment. Isoket reduces the number, duration and severity of the *angina pectoris* episodes and is efficient in all forms of angina (stable effort angina, mixed angina, unstable angina and vasospastic or variant angina) (1, 2). Isoket is also administered in acute myocardial infarct and ischemic pain control, for blood pressure reduction, pulmonary oedema and congestive cardiac failure treatments (3).

The administering of Isoket is usually achieved either sublingual, as tablet with time dependent dissolution (4), or ointments with transdermal drug release (5–7).

A 30–160 mg/day oral dosage of Isoket has been indicated for ischemic heart disease treatment. Slow releasing formulations are necessary for Isoket because the drug is easily absorbed by oral mucous and the gastrointestinal tract and has a short action length and plasma half-life.

With the intention of preparing sustained drug release systems, drug association with macromolecular compounds, drugs included into hydrogels or encapsulation into microparticles has been tested. Some characteristics are necessary to the polymeric materials used as drug release supports, and are as follows: biocompatibility, biodegradability, nontoxic subproducts and good affinity for active biological compounds. Natural polymers, and polysaccharides are especially very promising materials for these applications (8–10).

The paper presents two novel polymeric systems for Ik release, obtained by drug inclusion into hydrogels based on carboxymethylcellulose or microparticles based on acetylphthalylcellulose. The kinetic *in vitro* drug release studies in intestinal simulated body fluids were performed.

## 2 Experimental

### *2.1 Materials and Method*

The sodium salt of carboxymethylcellulose (degree of substitution, DS = 0.76, Merck Ltd.) was used as received. Acetylphthalylcellulose (APC, 24% phthalyl and 52% acetyl, 50000Da) was purchased from CCH Braila, Romania.

Address correspondence to: Marcel Popa, Department of Macromolecules, Faculty of Industrial Chemistry, "Gh.Asachi" Technical University, 71 A Bd. D. Mangeron, 700050 Iasi, Romania. E-mail: marpopa@omicron.ch.tuiasi.ro

Epichlorohydrin was purchased from Aldrich Chemical Company, Milwaukee WI. Isosorbide dinitrate — Isoket, pharmaceutical grade, was purchased from Sigma Ltd. The drug is a fine, white odorless crystalline solid, weakly soluble in water but soluble in acetone, chloroform, alcohol, and ether. The chemical structure of Isoket is presented in Figure 1.

### 2.2 Synthesis of Crosslinked Carboxymethylcellulose Hydrogel

The sodium salt of carboxymethylcellulose (CMC), 2 g, was dissolved in 10 mL of distilled water followed by 1 mL of 10 N NaOH solution, under strong and continuous stirring and a homogenous gel was obtained. Epichlorohydrin (EPC, 5 g) was added into the formed gel (that moment was considered the reaction start time) and the system was stirred for other 10 min. The resulting mixture was poured into glass molds and kept in an oven, at 60°C, for 6 h. In order to remove the water soluble components (1,2-dihydroxy-3-chlor-propane, glycerine, NaOH), the formed gel was suspended in 500 mL of distilled water, under continuous stirring, for other 6 h. The product was additionally purified from these compounds by extraction in distilled water and washed for 1 h with methanol and extracted with ethanol (Soxhlet, 24 h), in order to remove the entire amount of non-reacted EPC. Finally, the product was dried at 45°C and mortared, obtaining a fine powder.

### 2.3 Swelling of the Hydrogel

For swelling experiments, a series of ethanol-distilled water mixtures were prepared. The swelling properties were determined gravimetrically (11). The mass equilibrium swelling degree (SD, %) was calculated by using relation (1):

$$SD = (m_{eq} - m_o) * 100/m_o, \% \quad (1)$$

where: $m_0$ = initial sample weight (g); $m_{eq}$ = sample weight at swelling equilibrium (g).

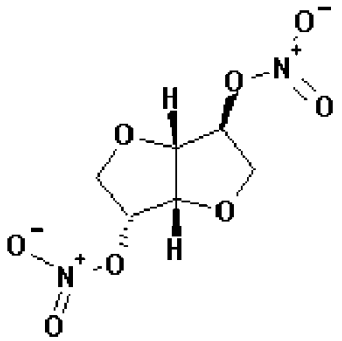


**Fig. 1.** Isoket chemical structure.

### 2.4 Isoket Inclusion into Hydrogel

Isoket inclusion into crosslinked CMC hydrogel was performed by using the diffusional method from alcohol-water solution. A 2 g sample of crosslinked CMC was suspended, under stirring, in 100 mL of 2,5% (w/w) Ik in ethanol-distilled water solution and maintained for 24 h. Different ratios, from 5/1 to 5/4 (vol/vol) ethanol-distilled water mixtures were used for the Ik inclusion study. The loaded hydrogels were separated by centrifugation (5000 rot/min) and dried under vacuum, at 40°C, for 24 h.

The amount of drug loaded into hydrogel was established by UV spectroscopy, at the wavelength characteristic to Ik ($\lambda = 205$ nm). By using a calibration graft, the 46 mg Ik/hydrogel was calculated.

### 2.5 Isoket Calibration Graph

Ik solutions with different concentrations (0.02%, 0.0175%, 0.015%, 0.01%, 0.0125%, 0.005%, 0.002%, 0.0015%, 0.001%) were used in order to obtain the calibration graph. The drug was dissolved in an ethanol-distilled water mixture, with the absorption at $\lambda = 205$ nm measured. The spectrophotometer (UV-VIS Spekord, 71, Carl Zeiss Jena) and a 5 mm pathlength quartz cuvette against ethanol- distilled water blank were used in the study.

### 2.6 Synthesis of APC Microparticles

A 5% (w/w) solution of APC in distilled water was prepared by dissolving the polymer under stirring, for 6 h, at 25°C. To the formed solution, 10% (w/w) Ik was added under continuous stirring.

A 70 mL of APC and Ik prepared solution was added, dropwise, under continuous and strong stirring, in 400 mL of 5% (w/vol) sodium (C8-C14) alkyl sulfonate (emulsifier) in distilled water. After the entire amount of drug–polymer solution was introduced, the system was stirred for other 15 min and the formed suspension was filtered. The suspension was washed three times with distilled water in order to remove most part of the emulsifier and separated by centrifugation at 5000 rot/min.

Finally, the microparticles were dried in the oven at 60°C, for 4 h, and then at 40°C, in the vacuum, for 24 h.

### 2.7 Microparticles Analyses

Microparticles were analyzed by optic microscopy (Microscope IOR-MSC200X, Bucharest, Romania) and dimension was evaluated by images processing.

For Ik loading into the microparticles, a 1 g material was dissolved in 100 mL of acetone, for 24 h. A volume of 10 μL of obtained polymeric solution was diluted with 4 mL of ethyl alcohol and maintained for 1 h at room temperature. The UV absorption of the Ik solution, at $\lambda = 205$ nm, was determined.

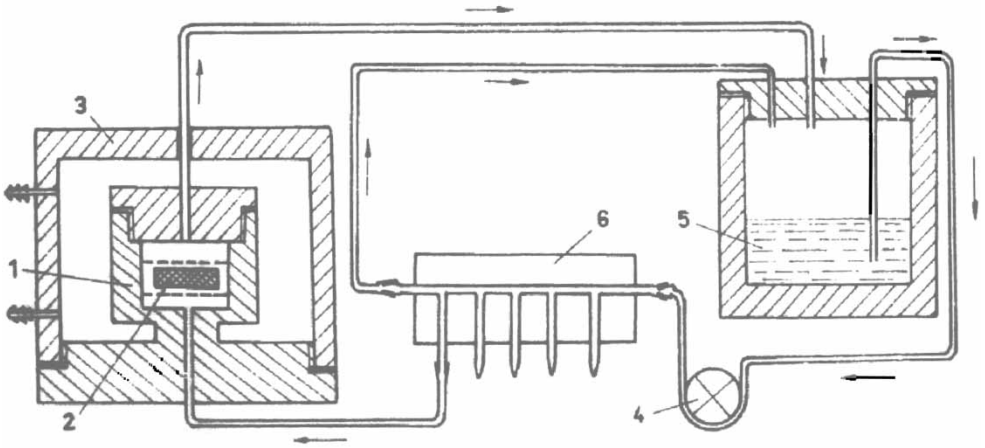



**Fig. 2.** The device for drug release study; 1-cell for sample, 2-tablet, 3-thermostated cell, 4-peristaltic pump, 5-reservoir for eluent (release medium), 6-debit regulator.



By using a calibration graft the amount of Ik loaded into microparticles was established as 76 mg Ik/g polymeric material.

### *2.8 Isoket Release from Hydrogel and Microparticles*

Samples of 0.826 g CMC hydrogel loaded with 46 mg Ik/g and 0.746 g APC microparticles (76 mg Ik/g), respectively, were placed into the stainless steel infrared press and a 8-tone force was applied for 10 min. Three tablets with 1 cm diameter were obtained for each material. The tablets were introduced into a polypropylene basket and placed into the capsule of the drug release device (Figure 2).

Because Ik is preferential retained in the small intestine, an alkaline buffer (pH = 8.2) was used as release medium. The buffer was obtained by mixing the following two solutions: 586.5 ml of solution A (9.27 g boric acid, 75 mL of 0.1 N NaOH and 675 mL of distilled water) and 413.5 mL of solution B (4 ml of 37.5% HCl and 500 mL of distilled water).

The tablet was introduced into the thermostated capsule (1), at 37 ± 0.5°C and 40 mL of eluent solution was circulated through the capsule by a peristaltic pump (4) with a 0.02 mL $sec^{-1}$ debit. The eluent assumes an amount of drug, and the Ik concentration is increasing continuously. At well established times, 2 mL of solution was extracted with a syringe from a lateral aperture of the debit regulator (6) and 2 mL of fresh eluent was reintroduced in order to keep the total volume of eluent constant.

A 1 mL sample of extracted solution was diluted to 25 mL with elution solution and the absorption at $\lambda = 205$ nm was measured. With a calibration graft, the concentration of the Ik released from the materials into a reservoir for eluent (5) was calculated.

The amount of released Isoket was calculated with relation (2):

$$m_i = c_i \times V + \Sigma C_j V_j (mg) \qquad (2)$$

where $c_i$ – the concentration of the sample "i" (mg/mL); V – the eluent volume from device (40 mL); $\Sigma C_j V_j$ – the amount of drug draw out from system by samples assuming, before sample "i" extraction; $V_j$ – 1 mL (the volume of solution for UV analyses).

The rate of release was calculated with relation (3):

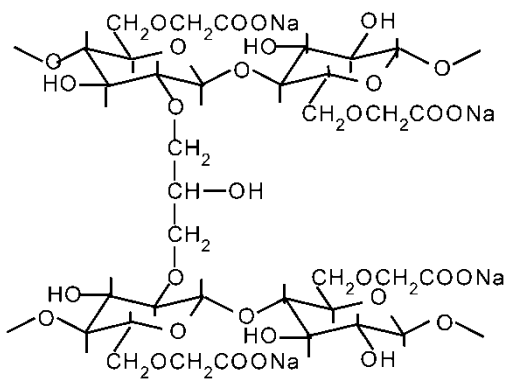
$$V_i = 1/m_p \times \Delta m/\Delta t \,(mg/g \cdot min^{-1}) \qquad (3)$$

where $m_p$ – the weight of drug from tablet; $\Delta m = m_i - m_{i-1}$; $\Delta t = t_i - t_{i-1}$; t – time.

## 3 Results and Discussion

One support for Ik sustained release is a hydrogel, based on the sodium salt of carboxymethylcellulose, obtained by biopolymer crosslinking with epychlorohydrin in an alkaline medium at 60°C, with r = 2.5 g CMC/gEPC and a reaction time of 6 h. The hydrogel structure is presented in Scheme 1.

The hydrogel presents a high capacity for swelling in water (SD = 675%). Also, the hydrogel has a good capacity of swelling in ethanol-water solutions as it is observed from the data presented in Figure 3.




**Sch. 1.** The chemical structure of the crosslinked CMC hydrogel.

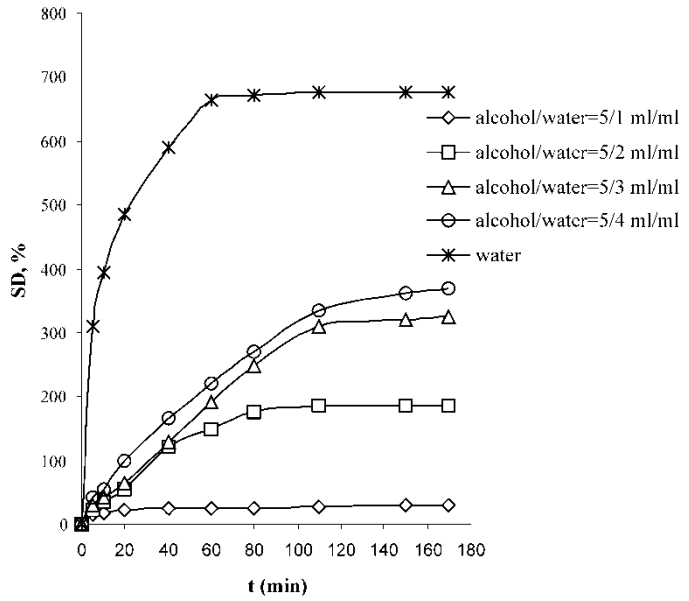



**Fig. 3.** The swelling degree (SD, %) of the crosslinked CMC hydrogel as a function of time, at different ethanol-distilled water (vol/vol) ratios.Conditions for hydrogel syntheses: reaction time − 6 h; temperature − 60°C; r = 2.5 g CMC/g EPC).

**Table 1.** The amount of Izoket included into crosslinked CMC hydrogel as a function of ethanol-distilled water ratio of the drug solution (Izoket concentration, c = 2.5 g Ik/100 mL solution)

| Ethanol/water ratio (mL/mL) | Amount of included Ik (mg Ik/g hydrogel) |
|---|---|
| 5/1 | 9.7 |
| 5/2 | 21.3 |
| 5/3 | 46.0 |
| 5/4 | 54.7 |

It can be observed that the hydrogel is not swollen in alcohol, but it is swollen in the alcohol-water solution, with the degree of swelling being higher in mixtures with increased water content. On the other hand, Ik is soluble in alcohol and alcohol-water mixtures, and drug solubility increases at higher ratios of alcohol. Therefore, for reasonable swelling properties and a good Ik loading a specific ratio alcohol-water is necessary to be used. The Table 1 presents the amount of Ik loaded into hydrogel at different volumetric ratios ethanol-distilled water and a constant concentration of the drug solution.

The amount of drug loaded into hydrogel increases at higher amounts of water in the ethanol-water solution, resulting from the swelling properties of the hydrogel. When the amount of water increases, the swelling capacity of the hydrogel also increases and the drug is able to penetrate into the macromolecular network. A higher degree for Ik loaded is obtained.

The images of optic microscopy, presented in Figure 4, have shown that the microparticles based on APC have a spherical form. By images processing the diameter of the microparticles was established into 2.8–7.1 μ domain.

The kinetic studies of the drug delivery process have established the amount of Ik released at different times, and then the drug release rate has been evaluated.

The quantity of released Ik in 24 h from the hydrogel based on crosslinked carboxymethylcellulose and 46 mg Ik/g hydrogel is presented in Figure 5.

The system has typical behavior for diffusional systems (12, 13). The drug diffusion is more intense in the first 120 min, when 30% from the included Ik is released and after that the process is slower. The maximum amount of released Ik is obtained after 24 h. A maximum value of 38.9 mg Ik was determined for drug release and this means 82% from total Ik loaded into hydrogel. It is interesting to notice that the amount of released drug is similar to the recommended daily dose for oral administration of the Izoket (30–160 mg).

The rate of Ik release from crosslinked CMC as a function of time is presented in Figure 6.

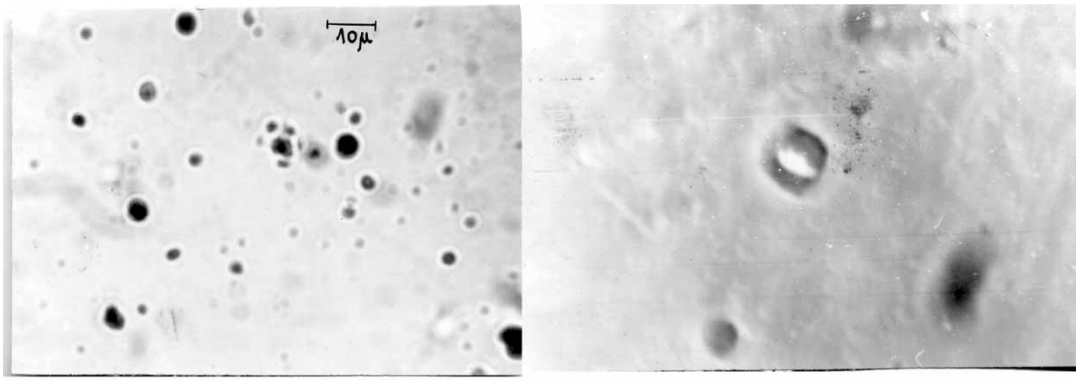



**Fig. 4.** The optical microscopy data for ACP microparticles: a) ×500; b) ×1200.

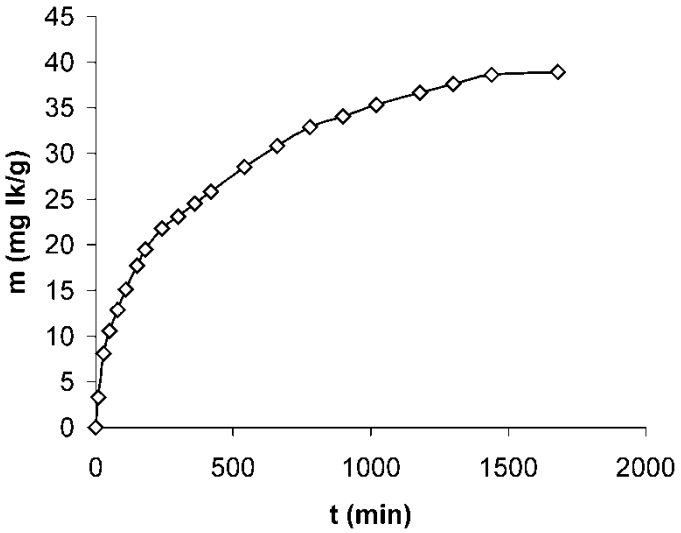



**Fig. 5.** The kinetics of Ik release from crosslinked CMC (elution medium: pH = 8.2 buffer, temperature: 37 ± 0.5°C).

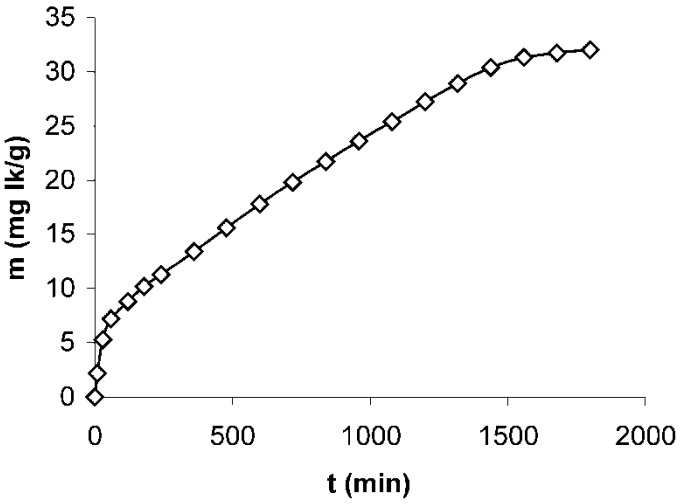



**Fig. 7.** The kinetics of Ik release from APC microspheres (elution medium: pH = 8.2 buffer, temperature: 37 ± 0.5°C).

A very high value can be observed for the rate of Ik release in the fist part of the analyzed period and then a decreasing amount of the evaluated parameter; the value for rate of release becomes practically constant on the domain 6–24 h. From this point of view, the hydrogel is a decent candidate as a support for Ik release in the oral method because medical prescriptions indicate, for a good pharmaceutical effect, a maximum quantity of 10–60 mg Ik delivered in the first 15–45 min and then a slight decrease (14).

On the time domain that is characterized by a zero order kinetic (6–24 h) the value for the rate of drug released is comparable to that indicated for intravenous administration of the Ik, 2–10 mg/h, respectively (3).

The Ik release from the microspheres based on APC presents similar behavior (Figure 7).

The maximum amount of released Ik from microspheres based on APC represents 42% from drug loaded into the polymer, although APC microparticles have included a higher amount of Ik than the crosslinked CMC hydrogel (76 mg Ik/g microspheres and 46 mg Ik/g CMC hidrogel). The phenomenon is determined by higher swelling properties into buffer with pH = 8.2 of the crosslinked CMC hydrogel than APC microparticles. APC is a lower hydrophilic polymer as a result of the aromatic and aliphatic ester groups, which strongly diminishes the affinity of the polymeric material for water or aqueous solutions and a lower diffusion from ACP microparticles is also obtained.

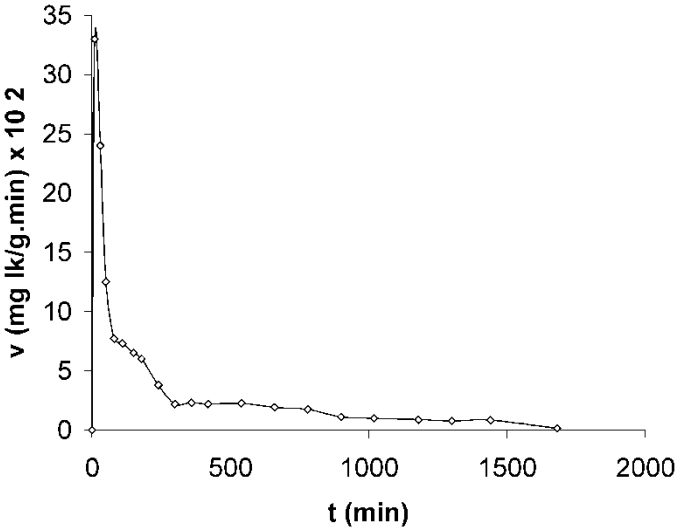



**Fig. 6.** The rate of Ik release as a function of time from crosslinked CMC hydrogel (elution medium: pH = 8.2 buffer, temperature: 37 ± 0.5°C).

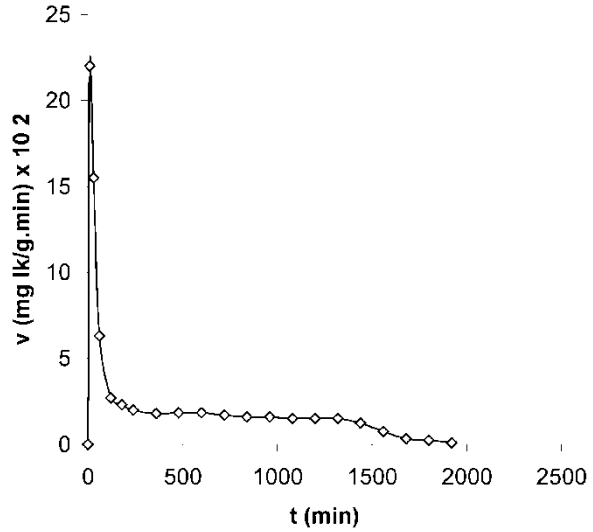



**Fig. 8.** The rate of Ik release as a function of time from APC microspheres (elution medium: pH = 8.2 buffer, temperature: 37 ± 0.5°C).

The rate for Ik release process from APC microparticles is presented in Figure 8.

For APC microspheres, a maximum value for rate of diffusion is observed in the firsts 2 h, but the value is inferior to that obtained for the crosslinked CMC hydrogel. The constant value had been registered faster for the APC microparticles. It can be appreciated that ACP microparticles present good results as support for Ik administration.

The results obtained for both analyzed systems permit one to conclude that diffusion from these materials is governed by a "zero" order kinetic, in principle, on the majority of the studied period of time. These results include analyzed polymeric systems in the category of "sustained-release" supports.

## 4 Conclusions

The carboxymethylcellulose's crosslinking with epychlorohydrin, in alkaline medium, is applied to hydrogels capable of including isosorbide dinitrate (Isoket) from ethanol-water solutions. Stable microparticles based on acetylphthalylcellulose and Izoket have been obtained by drug and polymer coprecipitation with acetone, from aqueous solutions of a suitable emulsifier.

The amount of Ik included into hydrogel based on crosslinked CMC depends on the ratio ethanol-water of the Ik loading solution and it increases with a higher amount of water in the ethanol-water mixture.

The Ik release from hydrogel based on crosslinked CMC and APC microparticles, respectively, is produced in a sustained way for at least 24 h and is controlled by "zero" order kinetics. The amounts of drug released as a function of time and for 24 h are those recommended for Ik administration in heart diseases treatment.

## 5 References


1. Aderka, D., Garfinkel, D., and Bograda, H. (1983) *Acta Haemat.*, **69**, 63–64.
2. McDevitt, D.C. and McConnaelie, S. (1988) Antianginal and B-adrenoacceptor blocking drugs. In *Meyler's Side Effects of Drugs*; Dukes, M.N.G. (ed.); Elsevier: Amsterdam, 359–389.
3. Needleman, P., Corr, P.B., and Johnson, E.M., Jr. (1985) Drugs used for the treatement of angina: Organic nitrates, calcium channel blockers, and B-adrenergic antagonists. In *Goodman and Gilman's the Pharmacological Basis of Therapeutics*; Gilman, A.G., Goodman, L.S., Rall, T.W., and Murad, F. (eds.); Macmillan Publishing Company: New York, 806–826.
4. McQuinn, R.L., Kvam, D.C., Maser, M.J., Miller, A.L., and Oliver, A. (1995) *J. Control. Rel.*, **34**, 243–250.
5. Gosselin, R.E., Smith, R.P., and Hodge, H.C. (1994) *Clinical Toxicology of Commercial Products*, 5th ed. Section III.; Williams and Wilkins Company: Baltimore, MD40.
6. Nagai, T. and Machida, Y. (1993) *Adv. Drug Deliv. Rev.*, **11**, 179–191.
7. Smart, J.D. (1993) *Adv. Drug Del. Rev.*, **11**, 253–270.
8. Sumathi, S. and Ray, A.R. (2002) *J. Pharm. Pharmaceut. Sci.*, **5**(**1**), 12–18.
9. Park, Y.J. and Min, B.M. (2003) *Polym. Sci. Technol.*, **14**(**3**), 287–297.
10. Chellat, F., Tabrizian, M., Dumitriu, S., Chornet, E., Rivard, C.H., and Yahia, H. (2000) *J. Biomed. Mater. Res.*, **53**, 592–599.
11. Alupei, C., Popa, M., Hamcerencu, M., and Abadie, M.J.M. (2002) *Eur. Polym. J.*, **38**(**11**), 2313–2320.
12. Popa, M., Balaita-Rusu, L., Sunel, V., and Bajan, N. (2002) *Euras. Chem. Tech. J.*, **4**(**2**), 119–124.
13. Dumitriu, C.L., Popa, M., Vasiliu, S., and Sunel, V. (2004) *J. Macromol. Sci., Part A.*, **41**(**6**), 727–739.
14. Reynolds, J.E.F. (1989) *The Extra Pharmacopeia*; Martindale (ed.); The Pharmaceutical Press: London, 1503–1505.