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Diclofenac sodium releasing pH-sensitive monolithic devices

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Abstract

A non-steroidal anti-inflammatory agent, diclofenac sodium (DFNa), was incorporated into the pH-sensitive monolithic systems prepared by crosslinking/copolymerization of 2-hydroxyethyl methacrylate (HEMA) with acrylate-based acidic and basic comonomers, i.e. acrylic acid (AA) and dimethylaminoethyl methacrylate (DMAEMA). Drug loading was done before polymerization and crosslinking. Hence, DFNa-containing polymeric discs approximately 10 mm in diameter and 3.0 mm in thickness were obtained. In vitro release studies were carried out in simulated gastric fluid for 3 h followed by simulated intestinal fluid at 37 °C. The release rate of DFNa was controlled by changing the composition of polymeric matrix, disc thickness and the drug loading between 5 and 33 mg/disc. Results indicate that in the low pH of the stomach, swelling degree of the AA-containing gels is low and less than 5% of the drug releases during first 3 h. But, in the intestine, the high pH causes the higher swelling degree of the AA-containing discs, allowing all the drug (~97.5%) is released. In the presence of DMAEMA in polymeric structure, opposite behavior was observed. © 2002 Published by Elsevier Science B.V.

Keywords: Diclofenac sodium; Hydrogel; Drug release; pH-sensitive polymers

1. Introduction

Stimuli-responsive polymers which can reversibly swell or shrink in response to external conditions, such as temperature, pH, solvent composition, electrical field and light are of great interest, especially in biomedical and pharmaceutical technology (Shibayama and Tanaka, 1993; Dagani, 1997). Among them, pH-sensitive hydrogels that change properties by depending upon changes in medium pH have been extensively investigated for the development of new drug delivery systems (Brondsted and Kopecek, 1992; Peppas et al., 2000; Basan et al., 2001). These gels can be prepared by the incorporation of one or more weakly acidic or basic monomers such as carboxylic acids (acrylic acid, methacrylic acid) and primary or substituted amines (*N*,*N*-dimethylaminoethyl methacrylate, etc.). Acidic gels are considered as good candidates for oral colon-specific delivery of drugs that are susceptible to enzymatic degradation in the upper gastrointest-

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inal (GI) tract (Peppas et al., 2000; Van den Mooter et al., 1995). While those kinds of systems have slow equilibrium degree of swelling in acidic medium of stomach, their swelling degree increases as it passes down the GI tract due to an increase in pH. Thus, this pH-sensitive drug delivery system protects the drug from the acidity of stomach and it releases all the drug in colon.

In this study, a pH-sensitive matrix system releasing diclofenac sodium (DFNa) was developed. DFNa is a non-steroidal anti-inflammatory, analgesic drug, which is widely used in the treatment of rheumatic disorders (Todd and Sorkin, 1988). Recently, a number of studies describing novel release formulations of DFNa have been performed. In those studies, matrix tablets were prepared from some natural or synthetic polymers including hydroxypropyl methyl cellulose (HPMC) hydrogels, polyvinylchloride, ethyl cellulose, methacrylic acid, cetyl alcohol, crosslinked sodium alginate or poly (ethylene oxide-HPMC), etc. (Vyas et al., 1989; Bain et al., 1991; Romero et al., 1991; Wilder et al., 1991; Liu et al., 1995; Kulkarni et al., 1999; Yang and Fassihi, 1997). Two of these systems are also commercially available by the name of Voltaren SR® consisting of cetyl alcohol matrix and Voltaren Retard® (Sheu et al., 1992; Ho et al., 1997).

In this study, a new formulation different than above-mentioned ones was proposed. pH-sensitive monolithic systems were prepared in disc forms with the acrylate-based acidic (acrylic acid, AA) and basic (dimethylaminoethyl methacrylate, DMAEMA) comonomers of 2-hydroxyethyl methacrylate (HEMA) by crosslinking/copolymerization process in the presence of DFNa.

Release studies were carried out in simulated gastric fluid (pH 1.2) for 3 h followed by simulated intestinal fluid (pH 7.5) at 37 °C. Release of DFNa was investigated by varying polymeric composition, disc thickness and amount of drug loaded. In addition, release characteristics of Voltaren SR® and Voltaren Retard® were compared to those of proposed monolithic systems.

2. Materials and methods

2.1. Chemicals

Acrylic comonomers, HEMA, AA, dimethylamino ethyl methacrylate (DMAEMA) and crosslinking agent, ethyleneglycol dimethacrylate (EGDMA), were obtained from Aldrich Chemical Co. (Milwaukee, WI). Redox initiator, $Na_2S_2O_5$/$K_2S_2O_8$ was supplied by BDH, UK. DFNa was a gift from Faco Drugs Co. (Istanbul, Turkey). Voltaren SR® and Voltaren Retard® purchased from the market are products of Ciba-Geigy Co., Istanbul, Turkey.

2.2. Preparation of polymeric structures

pH-sensitive poly(HEMA)-based hydrogels were prepared by crosslinking/copolymerization of HEMA monomer in the presence of redox initiator, $Na_2S_2O_5$/$K_2S_2O_8$, solvent, deionized water, the crosslinking agent, EGDMA, and ionizable acrylate monomers, i.e. AA or DMAEMA. The hydrogels were prepared in the disc forms (diameter: 10 mm; thickness: 1.6 or 3.0 mm) by polymerizing the monomer solution that contains all constituents described above in Pyrex test tubes at room temperature (25 ± 0.5 °C). Composition of polymeric samples was given in Table 1.

2.3. Swelling studies

The swelling behavior of the polymeric discs was explored by placing the dried samples in 50 ml reservoirs containing simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5). Reservoirs were operated at 50 rpm at 37 °C.

The swollen weight of each sample (W_s) was determined by removing the disc from the solution, blotting, and then weighing it on an electronic balance.

The percent water content was calculated by means of the following equation:

Table 1
Composition of drug-free polymeric samples synthesized by bulk copolymerization

Sample	HEMA (ml)	DMAEMA (ml)	AA (ml)	EGDMA (ml)	Initiator (mg/mg) $Na_2S_2O_5/K_2S_2O_8$	Water (ml)
P1	2.50	–	–	0.1	5/5	1.6
P2	2.50	0.50	–	0.1	15/15	1.6
P3	2.50	–	0.50	0.1	15/15	1.6
P4	2.50	–	0.75	0.1	15/15	1.6

$$\text{Water content } (\%) = \frac{W_s - W_d}{W_d} \times 100, \quad (1)$$

where W_d is the dry weight of discs.

2.4. Preparation of monolithic drug release systems

In order to prepare the drug-loaded polymeric systems, DFNa was dissolved in the HEMA monomer and then the same polymerization procedure described above was performed in the presence of DFNa. Each disc was loaded with the drug between 5 and 33 mg. Thickness of the discs was also varied as 1.6 and 3.0 mm to adjust the release rate of the drug. Definition of drug-loaded devices was given in Table 2.

2.5. SEM study

Surface morphology and cross-section structure of monolithic systems with and without drug were observed by scanning electron microscope (SEM, model JEOL JSM-5410, Japan).

2.6. In vitro release studies

Release studies were carried out in simulated gastric fluid (pH 1.2) for 3 h followed by simulated intestinal fluid (pH 7.5). All release studies were conducted in a shaker agitating at 50 rpm at 37 °C. DFNa was determined spectrophotometrically by measuring the UV absorbance at 277 nm.

Same release studies were performed for the commercially available forms of DFNa which are called as Volteren SR® and Voltaren Retard®. All release studies were repeated three times and the results were reported as average values.

3. Results and discussion

3.1. Preparation and characterization of monolithic systems

The usage of pH-sensitive polymers in controlled drug release devices was investigated. Basic constituent of the selected polymeric matrix was thought to be poly(HEMA) crosslinked with EGDMA. Poly(HEMA) has been used in a number of biomedical and pharmaceutical pre-

Table 2
Monolithic DFNa delivery systems prepared in this study

Device	Polymer composition[a]	Drug loaded (mg/disc)	Disc thickness (mm)
A	P1	33	3.0
B	P2	33	3.0
C	P3	33	3.0
D	P4	33	3.0
E	P3	5	3.0
F	P3	18	3.0
G	P3	18	1.6

[a] Composition is given in Table 1.

parations since it has high biocompatibility and easy sterilizability (Peppas, 1995; Gökçe et al., 1996). While the hydrophilicity of HEMA monomer is causing swellable structure, crosslinking agent, EGDMA, provides three-dimensional network structure. Drug release occurs through the channels and pores of resulting network owing to the countercurrent diffusion mechanism. Release kinetics of drug can be changed by varying the amount of crosslinking agent which affects the swelling behavior of gels. pH-sensitive poly(HEMA) gels can be obtained by the incorporation of pendant acidic or basic groups which change ionization of gel by depending upon changes in medium pH (Kiremitçi-Gümüşderelioğlu, 1999). Their equilibrium degrees of swelling are higher than that of their neutral forms, i.e. poly(HEMA) gels, due to the diffusion of counterions into the gel from the surrounding medium. These pH-sensitive gels are of great importance for the release in gastrointestinal system because pH is variable throughout the GI tract. Thus, pH-sensitive system can control the amount of drug released by depending on the pH changes.

In our previous study, pH-sensitive poly(HEMA) hydrogels were prepared by copolymerization of HEMA monomer with AA and DMAEMA in varying amounts between 5 and 30% (v/v) (Kiremitçi-Gümüşderelioğlu and Pesmen, 1996; Kiremitçi-Gümüşderelioğlu, 1999). By taking into account the results of that study, it was decided that the pH-sensitive system contains one of the weakly acidic or basic comonomer, AA or DMAEMA, as well as HEMA monomer and crosslinker, EGDMA. AA is most often used for the synthesis of mucoadhesive polymeric systems and these systems have potential application as an oral bioadhesive controlled release dosage forms during transit from stomach to colon.

For convenience, a bulk copolymerization method was chosen in order to carry out the polymerization process. In this procedure, a redox initiator ($Na_2S_2O_5/K_2S_2O_8$) which initiates the radical formation at room temperature was used to perform the chain polymerization. In addition, drug loading and molding processes were carried out together with polymerization/crosslinking process and it was completed in 30 min. Another advantage of this method is to get a very clean product which does not contain any impurities, e.g. solvent, surface active agent, etc.

At first, control matrices which do not contain the drug were prepared to examine the effects of comonomers on the swelling abilities of resulting polymeric systems. Their compositions are given in Table 1. As clearly be seen from this table, initiator concentration, amount of solvent and crosslinking content were kept constant by considering our previous data. In vitro swelling studies were conducted in simulated gastric fluid and in simulated intestinal fluid at 37 °C separately and then percent water content was determined gravimetrically. Plots of dynamic water swelling of copolymers in gastric and intestinal fluid are presented in Fig. 1a and b, respectively. Importance of the ionizable monomer type and content on the dynamic swelling characteristics of hydrogel can

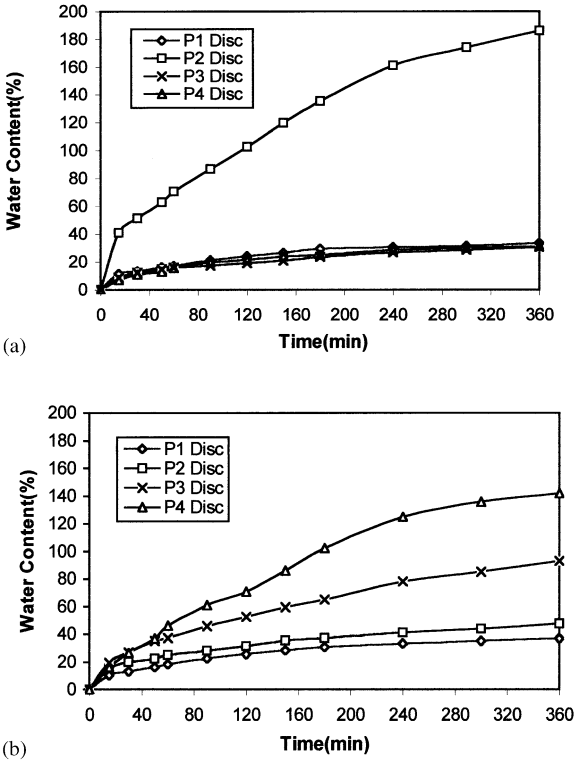

Fig. 1. Swelling kinetics of drug-free polymeric discs (a) in simulated gastric fluid and (b) in simulated intestinal fluid.

be clearly seen from these figures. The neutral hydrogel shows the same swelling characteristics in both media. This means that it does not show pH-sensitivity. In the case of AA-containing discs (P3 and P4), there is no important change of water content in gastric fluid (pH 1.2), similar to the neutral gel, however, in intestinal fluid (pH 7.5) they swell dramatically. In contrast, DMAEMA-containing disc (P2) reaches to high equilibrium water content in gastric fluid, while it is showing the similar swelling behavior with neutral polymer (P1) in intestinal fluid. This situation can be explained as follows. An acidic hydrogel, i.e. AA-containing ones, will ionize at high pH, thus, the degree of swelling at equilibrium will increase at high pH. A cationic/basic hydrogel, i.e. DMAEMA-containing gel, has the opposite pH-dependence of swelling. Therefore, AA-containing poly(HEMA) gel was chosen as a drug delivery matrix to protect the drug in stomach and release it in intestine.

As a model drug, DFNa which is a non-steroidal anti-inflammatory agent useful in the treatment of rheumatic disorders was selected. DFNa exists in its acidic form in an acidic solution such as in gastric fluid and it is practically insoluble in stomach, but soluble in intestinal fluid and water. DFNa is available in a number of administration forms, which can be given orally, rectally or intramuscularly. Recently, oral form of DFNa is given in enteric-coated tablet to prevent its release in stomach. After oral administration, it reaches maximum blood concentration in 1.5–2.5 h. Its bioavailability is around 60% and its half-life varies between 1.2 and 1.8 h (Ho et al., 1997). Voltaren SR®, a commercial product of DFNa manufactured by Ciba-Geigy, is a hydrophobic matrix tablet consisting of a cetyl alcohol matrix. However, there are still some problems related with these systems and researchers have been studying to solve these problems to get better systems. After taking into consideration all these studies, it has been decided that DFNa was a good model drug for the proposed pH-sensitive monolithic system.

Monolithic DFNa release systems were prepared by conducting drug loading before polymerization. Table 2 lists the polymer composition, drug loading capacity and disc thickness of each monolithic system developed here.

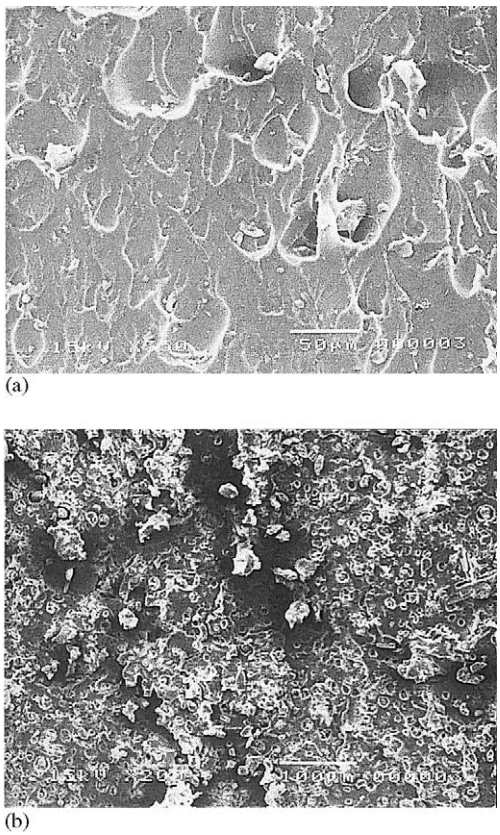

Fig. 2. SEM photographs of cross-sections of polymeric discs (a) without drug (magnification ×350) and (b) with drug (magnification ×200).

In order to observe the DFNa distribution in monolithic system, drug-free and drug-loaded polymeric matrices were observed with a scanning electron microscope. The SEM photographs of the cross-section of matrices are given in Fig. 2a and b. As clearly seen here, the drug was dispersed homogeneously in the polymeric network indicating the monolithic system.

3.2. Release studies

Release studies were performed firstly in simulated intestinal fluid (pH 7.5). While amount of the DFNa released was 97% from poly(HEMA–AA) disc at the end of 10 h, that was between 15 and

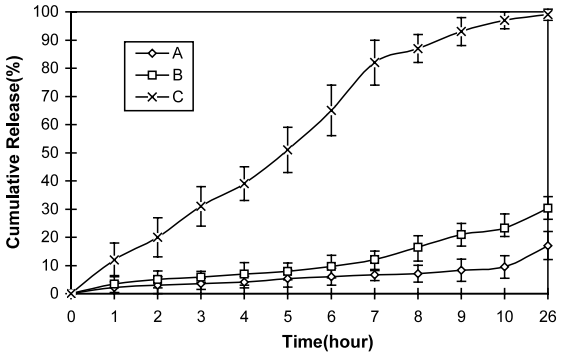

Fig. 3. The cumulative fraction of DFNa release from the polymeric discs prepared in three different compositions (in intestinal fluid).

25% from poly(HEMA) and poly(HEMA–DMAEMA) discs (Fig. 3). This result was expected and was in harmony with the swelling studies and it showed that DFNa release depended upon the swelling behavior of the polymeric structure.

While orally administered tablet passes from stomach to intestine, it faces with media having pH-values between 1 and 7. Therefore, the residence time of tablet at different pH-values has a considerable effect on the bioavailability of the drug. That is why it was decided that in vitro release studies should have done in media having different pH-values. By considering the residence time of the drug in stomach, release studies were carried out in simulated gastric fluid (pH 1.2) for 3 h followed by simulated intestinal fluid (pH 7.5). In release studies, the effects of the disc thickness, amount of DFNa loaded and the concentration of AA in polymeric structure were investigated. Depending on the diffusional transport mechanism, release rate decreased as the disc thickness increased but it reached approximately to the same percentage cumulative release value at 10th hour (Fig. 4).

Release studies were conducted by 5, 18 and 33 mg DFNa-loaded poly(HEMA–AA) discs. Comparison of release curves given in Fig. 5 indicates that the rate and extent of drug release at 10th hour increases in relation to the increasing initial drug loading. The difference is more clear between 5 and 18 mg. This result was attributed to the increasing driving force for drug diffusion and an increase in the porosity of the polymer matrix. However, raising the amount of drug over 18 mg did not significantly affect release rate.

In this study, polymeric matrices were prepared by changing the AA content. Fig. 6 shows the effect of AA percentage on the release rate of DFNa. As seen here, the drug release rate from the matrix which has high AA content is significantly higher than that obtained from the matrix including less AA. This result can be explained by high swelling ability of gels as due to the ionizable monomer content.

The release data of the monolithic systems were substantiated by fitting the cumulative fraction

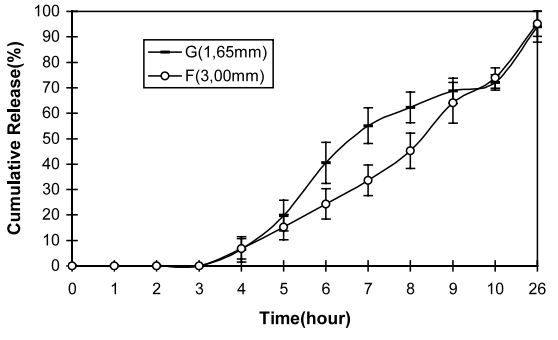

Fig. 4. The cumulative fraction of DFNa release from the polymeric discs as a function of disc thickness (first 3 h in gastric fluid and then in intestinal fluid).

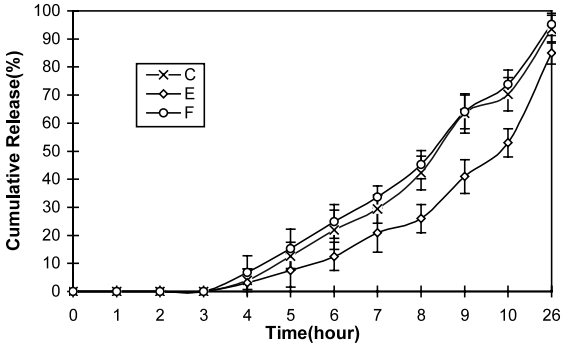

Fig. 5. The cumulative fraction of DFNa release from the polymeric discs as a function of drug loading capacity (first 3 h in gastric fluid and then in intestinal fluid).

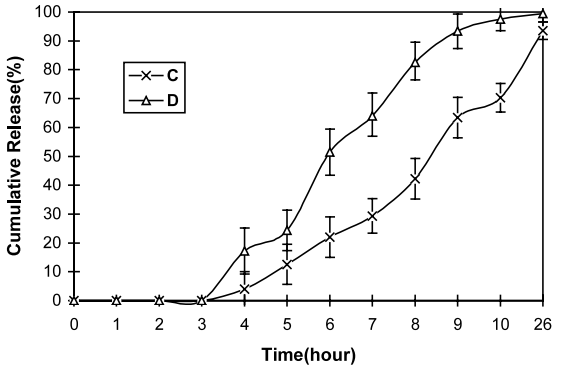

Fig. 6. The cumulative fraction of DFNa release from the polymeric discs as a function of AA content in polymer composition (first 3 h in gastric fluid and then in intestinal fluid).

release data, M_t/M_∞, to an empirical equation (Ritger and Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n, \tag{2}$$

where t is the release time, k is a constant characteristic of the system, and n is an exponent which characterizes the diffusional release kinetic mechanism.

The n- and k-values determined from the initial portion of ($M_t/M_\infty \leq 0.6$) log–log plots of M_t/M_∞ vs time are presented in Table 3 together with the regression coefficients. In the case of cylinder geometry, n-values between 0.45 and 0.89 show non-Fickian diffusion, while n is equal to 0.45 for Fickian diffusion. As could be seen in Table 3, calculated n-values ranging between 0.71 and 0.97 indicate that the release deviates from the Fickian mode.

Table 3
Estimated values of k, n and regression coefficient for various devices from Eq. (2)

Device	k (10^2)	n	r^2
A	0.02	0.77	0.99
B	0.03	0.71	0.93
C	0.11	0.97	0.99
D	0.17	0.95	0.92

The values of k depend upon characteristics of the polymer network and the active agent. Since drug loading was kept constant for the devices indicated in Table 3, i.e. A, B, C, and D, here k-values are only function of polymeric composition and the effect of AA content is more noticeable. Presence of AA in the polymeric formulation increases k-values approximately five times.

New formulations of DFNa are available in the market as Voltaren SR® and Voltaren Retard® commercial names. Release studies of these commercial forms of DFNa were performed in the same conditions with the polymeric discs having different AA concentrations. Similar release behavior was observed for the commercially available forms and the proposed systems (Fig. 7).

Similar polymeric composition had been used by other researchers for the development of oral drug release systems. Van den Mooter et al. (1995) investigated the release of a model compound ibuprofen from capsules coated with terpolymer, poly(HEMA–MMA–AA). An azoreductase substrate was also used in that polymeric formulation. Their in vitro studies conducted in simulated rat cecal content-releasing medium exhibited that significant drug release occurs 8–10 h after initiation of release study and total release was achieved by 18 h.

Ende and Peppas (1997) investigated the release of ionizable drugs, i.e. theophylline, oxprenolol

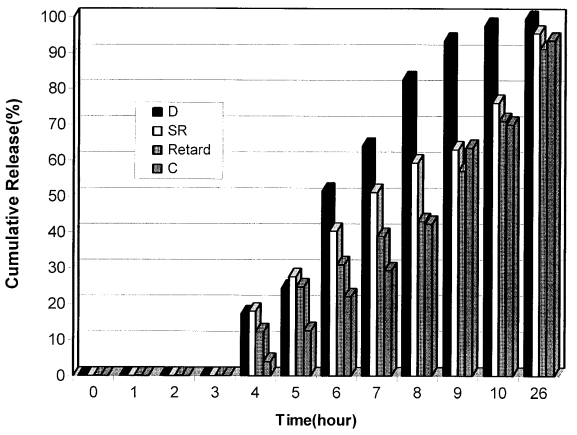

Fig. 7. Comparison of release kinetics of proposed monolithic systems with commercially available systems (first 3 h in gastric fluid and then in intestinal fluid).

HCl and proteins including insulin, lysozyme, albumin and fibrinogen from the poly(HEMA–AA) hydrogel formulation.

4. Conclusion

This paper summarizes the preparation and in vitro drug release studies of acrylate-based pH-sensitive monolithic devices loaded with, anti-inflammatory agent, DFNa. Release rates can be readily varied by changing the type of ionizable comonomer, i.e. AA or DMAEMA, disc thickness, initial drug loading and the pH of releasing medium, i.e. pH 1.2 or 7.5. In conclusion, the monolithic system which was composed of HEMA and AA (20%, v/v) can be proposed as a good candidate for the release of DFNa, since its release characteristics are comparable to commercially available tablet forms.

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