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ORIGINAL ARTICLE

Chitosan–polycarbophil interpolyelectrolyte complex as a matrix former for controlled release of poorly water-soluble drugs I: in vitro evaluation

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Abstract

Purpose: It was previously shown in our laboratories that the interpolyelectrolyte complex between chitosan and polycarbophil has promise as a matrix former to control the release of water-soluble drugs. This study further investigates the applications of this polymeric complex to produce controlled release matrices for poorly water-soluble drugs. *Methods*: The swelling, erosion, and drug release performance of matrix-type tablets containing the chitosan–polycarbophil complex as matrix former was compared to those consisting of hydroxypropylmethylcellulose and a simple mixture of chitosan and polycarbophil powders. *Results*: The chitosan–polycarbophil complex matrices showed good swelling with relatively low erosion and slower drug release compared to those prepared from other polymeric materials. They also exhibited release exponent (*n*) values closer to unity and therefore to zero-order release compared to the other matrices. *Conclusions*: The chitosan–polycarbophil complex formed matrix-type tablets that controlled the release of poorly water-soluble drugs approaching zero-order kinetics. The mechanism of drug release was mainly diffusion from swollen systems.

Key words: *Chitosan; controlled release; interpolyelectrolyte complex; matrix system; polycarbophil*

Introduction

A great deal of attention is currently focused on the development of novel and controlled release drug delivery systems to provide a long-term therapeutic effect of drugs at the site of action following a single dose[1,2]. Many formulation techniques have been used to provide a barrier mechanism within solid oral dosage forms to produce slow release of the maintenance dose. These techniques include the use of coatings, microencapsulation, chemical binding to ion-exchange resins, osmotic pump systems, and embedding of the drug in a waxy, polymeric, or plastic matrix[3]. Monolithic matrix systems are amongst the most popular technologies to control drug release because of the simplicity of formulation, ease of manufacturing, low cost, and applicability to drugs with wide range of solubility[4,5].

Although drug release from polymeric matrix systems can be influenced by different factors, the physicochemical properties of the matrix-forming polymer play the primary role[5]. Hydroxypropylmethylcellulose (HPMC) is one of the most important and frequently used hydrophilic carrier materials used for oral drug modified delivery systems[6,7]. It is generally recognized that drug release from HPMC matrices occurs by means of two mechanisms, namely drug diffusion through the swelling gel layer and erosion of the swollen layer[8–12]. The advantages of this combination of drug release mechanisms (i.e., swelling and erosion) in HPMC-based matrix drug delivery systems are a low incidence of burst-release effect, the release rate of drugs with different physicochemical properties approaches a constant value, and the possibility to predict the effect of design parameters (e.g., shape, size, and composition of the matrices) on the drug release rate[6,7].

Interpolyelectrolyte complexes (IPECs) are formed by mixing two oppositely charged polyelectrolytes in an aqueous solution and have been used as a new class of

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polymer carriers for creating novel drug delivery systems[13–16]. Chitosan is a positively charged deacetylated derivative of the natural polysaccharide, chitin[17], and has been used to form complexes with natural anionic polymers such as carboxymethylcellulose, alginic acid, dextran sulfate, carboxymethyl dextran, heparin, carrageenan, pectin, methacrylic acid copolymers, and xanthan[14,18–20].

As the IPEC between chitosan and polycarbophil showed high potential as a matrix former[21–23], it is important to investigate different applications of this polymeric complex such as the release behavior of drugs with different physicochemical properties from matrix systems containing this polymeric complex. The aim of this study was to determine the in vitro swelling, erosion, and dissolution behavior of monolithic matrix systems containing poorly water-soluble drugs (hydrochlorothiazide and ketoprofen, respectively) prepared with the chitosan–polycarbophil IPEC as matrix former. The results obtained for these matrix systems were compared to that obtained for HPMC (i.e., K100M and K100LV, respectively)-based matrix systems.

Materials and methods

Materials

Chitosan (Warren Chem Specialities, Johannesburg, South Africa, deacetylation degree = 91.25%), polycarbophil (Noveon, Cleveland, OH, USA), HPMC (Methocel K100M, K100LV Premium, Colorcon Limited, Kent, UK), ketoprofen (Changzhou Siyao Pharma, Changzhou, China), hydrochlorothiazide (Huzhou Konch Pharmaceutical Co., Ltd., Huzhou, China), microcrystalline cellulose (Avicel, pH101, FMC Corporation NV, Brussels, Belgium), and sodium carboxymethyl starch (Explotab, Edward Mendell Co., Inc., New York, NY, USA) were used. All other chemicals were of analytical grade and used as received.

Preparation of the chitosan–polycarbophil IPEC

Both chitosan (30 g) and polycarbophil (30 g) were each dissolved in 2% (v/v) acetic acid solutions (1000 mL each). The chitosan solution was slowly added to the polycarbophil solution under homogenization (5200 rpm, Ultra-TURRAX T50, IKA-WERKE GmbH Co., Staufen, Germany) over a period of 20 minutes. The mixture was then mechanically stirred for a period of 1 hour at a speed of 1200 rpm (Heidolph RZR2021, Heidolph Instruments GmbH, Schwabach, Germany). The gel formed was separated by centrifuging for 5 minutes at 1207 × *g* and then washed several times with a 2% (v/v) acetic acid solution to remove any unreacted polymeric material. The gel was freeze-dried for a period of 48 hours (Jouan LP3, Thermo Scientific, Saint-Herblain, France) and the resultant lyophilized powder was screened through a 300-μm sieve.

Characterization of the chitosan–polycarbophil IPEC

Both DSC thermograms and Fourier transform infrared (FTIR) spectra of chitosan alone, polycarbophil alone, and the chitosan–polycarbophil IPEC were obtained as previously described[21,22] to confirm formation of a complex between the two polymers.

Preparation of matrix-type tablets

Monolithic matrix-type tablets containing hydrochlorothiazide or ketoprofen as the model drug were prepared by direct compression of a mixture of the ingredients as shown in Table 1. Different matrix-type tablets containing the chitosan–polycarbophil IPEC or a chitosan–polycarbophil physical mixture or K100M HPMC or K100LV HPMC as matrix formers were therefore prepared. The ingredients of the different formulations were each manually mixed in a 1000-mL glass beaker for 30 minutes. After the addition of magnesium stearate (0.5%, w/w), the powder mass was further mixed for 10 minutes. The powder mixture was then compressed using a rotating tablet press (Cadmach, Ahmedabad, India) fitted with round, shallow punches to produce matrix-type tablets with a 6 mm diameter.

Table 1. Composition of the different matrix-type tablet formulations.

	Concentration (%, w/w) of ingredients in the different formulations							
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Hydrochlorothiazide	5	5	5				5	
Ketoprofen				5	5	5		5
IPEC between chitosan and polycarbophil	95			95				
HPMC K100M		95			95			
HPMC K100LV			95			95		
Physical mixture (1:1) of chitosan and polycarbophil							95	95

Physical properties of the matrix-type tablets

The weight variation of the matrix-type tablets from each formulation was tested by weighing 20 randomly selected tablets individually, then calculating the average weight, and comparing the individual tablet weights to the average. The specification for weight variation is 10% from the average weight if the average weight is <0.08 g[24].

The hardness of 10 randomly selected matrix-type tablets from each formulation was determined using a hardness tester (TBH 220 ERWEKA®; Hausenstamm, Germany). The force (*N*) needed to break each tablet was recorded.

The thickness of each of 10 randomly selected matrix-type tablets from each formulation was measured with a vernier caliper (accuracy = 0.02 mm). The thickness of the tablet should be within 5% variation of the average value.

A friability test was conducted on the matrix-type tablets using an Erweka Friabilator (TA3R). Twenty matrix-type tablets were randomly selected from each formulation and any loose dust was removed with the aid of a soft brush. The selected tablets were weighed accurately and placed in the drum of the friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets before they were weighed again. The friability limit is 1%[24] and was calculated using the following equation:

$$F(\%) = \frac{W_{\text{before}} - W_{\text{after}}}{W_{\text{after}}} \times 100,$$

where F is the friability, W_{before} is the initial weight of the matrix-type tablets, and W_{after} is the weight of the matrix-type tablets after testing.

Swelling and erosion of the matrix-type tablets

Three matrix-type tablets were randomly selected from each formulation and weighed individually before they were placed in 900 mL phosphate buffer (pH 7.4) at 37.0 ± 0.5°C. The medium was stirred with a paddle at a rotation speed of 50 rpm in a USP dissolution flask. At different time points, the tablets of each formulation were removed from the dissolution flask and gently wiped with a tissue to remove surface water, weighed and then dried at 60°C until constant weight was achieved. The mean weights were determined for the three tablets at each time interval. The data obtained from this experiment were used to calculate both the swelling index and the percentage mass loss (indication of erosion) as explained below.

Swelling index

The swelling index (or degree of swelling) was calculated according to the following equation:

$$SI(\%) = \frac{W_s - W_d}{W_d} \times 100,$$

where SI is the swelling index, W_s is the weight of the swollen matrix-type tablet, and W_d is the weight of the dry matrix-type tablet at the different time points.

Percentage of matrix erosion

The percentage matrix erosion was calculated using the dry weight of the matrix-type tablets at the specific time points in relation to the initial dry weight according to the following equation:

$$\text{Erosion}(\%) = \left(1 - \frac{W_{dt}}{W_{id}}\right) \times 100,$$

where W_{dt} is the dry weight of the matrix-type tablets at the different time points and W_{id} is the initial dry weight of the matrix-type tablets.

Content assay of the matrix-type tablets

The drug content of the matrix-type tablets was determined by crushing 10 randomly selected tablets from each formulation in a mortar and pestle. Approximately 80 mg powder from the hydrochlorothiazide- or ketoprofen-containing matrix tablets was weighed accurately and individually transferred into 200-mL volumetric flasks, which were then made up to volume with phosphate buffer solution (pH 7.4). This mixture was stirred for 30 minutes to allow complete release of the drug from the powder. After filtration through a 0.45-µm filter membrane, the solution was assayed using ultraviolet (UV) spectrophotometry (Helios α, Thermo Scientific, Cambridge, UK) at a wavelength of 271 nm for hydrochlorothiazide and 261 nm for ketoprofen. The assay for drug content was performed in triplicate for each formulation and the percentage drug content (%, w/w) of the tablets was calculated.

Dissolution studies

The USP[24] dissolution apparatus 2 (i.e., paddle) was used to determine the in vitro drug release from the different formulations of matrix-type tablets. The dissolution medium (900 mL) consisted of phosphate buffer solution (pH 7.4) at 37 ± 0.5°C and a rotation speed of 50 rpm was used. Three hydrochlorothiazide or ketoprofen matrix-type tablets from each formulation were introduced into each of three dissolution vessels,

respectively (i.e., dissolution for each formulation was done in triplicate) in a six-station dissolution apparatus (TDT-08L; Electrolab®, Mumbai, India). Samples with a volume of 5 mL each were withdrawn at predetermined time intervals, and 5 mL of preheated dissolution medium was replaced immediately. The samples were filtered through a 0.45-μm membrane and the hydrochlorothiazide or ketoprofen content in the solution was determined using UV spectrophotometry at a wavelength of 271 and 261 nm, respectively.

Drug release kinetic analysis

Drug release from simple swellable and erosion matrix systems may be described by the well-known power law expression and is defined by the following equation[25,26]:

$$\frac{M_t}{M_\infty} = K_1 t^n,$$

where M_t is the amount of drug released at time t, M_∞ is the overall amount of drug released, K_1 is the release constant, n is the release or diffusional exponent, M_t/M_∞ is the cumulative drug concentration released per time unit (or fractional drug release).

The release exponent (n) is used for the interpretation of the release mechanism from polymeric matrix-controlled drug release systems[27]. For cylindrical-shaped systems $n \leq 0.45$ corresponds to Fickian diffusion release (or Case I), $0.45 < n \leq 0.89$ corresponds to anomalous release (or non-Fickian), $n = 0.89$ to zero-order release (or Case II), and $n > 0.89$ to super Case II release/transport[25].

The dissolution data obtained for the different formulations were modeled by using the Power law equation with graphs analysis software (Origin® Scientific Graphing and Analysis software, Version 7; OriginLab Corporation, Northampton, MA, USA) using the Gaussian–Newton (Levenberg–Hartely) approach.

Adjusted mean dissolution time (MDT_{ad})

Mean dissolution time (MDT) is a statistical moment that describes the cumulative dissolution process and provides a quantitative estimation of the drug release rate[28,29]. Unfortunately, the use of MDT was limited in this study because not all the formulations released the total drug dose within the time period of the dissolution test. Therefore, an adjusted MDT value was calculated, which considers the dissolution up to an extrapolated time of 100% drug release[21]

$$\mathrm{MDT_{ad}} = \sum_{i=1}^{n} t_i \frac{M_t}{M_\infty} + \frac{t_{100\%} + t_n}{2} \times \left(1 - \left[\frac{M_n}{M_\infty}\right]\right),$$

where $\mathrm{MDT_{ad}}$ is the adjusted MDT, M_t is the amount of the drug released at time t, t_i is the time (minutes) at the midpoint between i and $i-1$, M_∞ is the overall amount of the drug released, $t_{100\%}$ is the calculated time (minutes) of 100% drug release, t_n is the time at the nth minute (last sample withdrawn), and M_n is the amount of drug released at time n.

Results and discussion

Characterization of the chitosan–polycarbophil IPEC

The formation of a separate chemical compound that is distinctive from the starting polymers was confirmed with both DSC and FTIR in the same way as previously described[21,22]. As explained before, the peak that appeared at 1561 cm^{-1} on the FTIR spectrum (data not shown) of the chitosan–polycarbophil IPEC may be assigned to the carboxyl groups of polycarbophil that formed ionic bonds with the protonated amino groups of chitosan, which is schematically illustrated in Figure 1.

Physical characteristics and drug content of matrix-type tablets

As summarized in Table 2, the different matrix-type tablets showed good thickness uniformity, which ranged between 3.40 ± 0.04 and 4.12 ± 0.04 mm for the tablets made from different formulations. The weight of the different matrix-type tablet formulations varied between 73.3 ± 2.4 and 87.9 ± 4.0 mg, whereas the weight variation within each formulation was low and within the USP specification (<10% from the average weight). Hardness of the different matrix-type tablets ranged between 68 ± 14 and 94 ± 12 N. All the matrix-type tablets complied to the specification for friability (<1%) and the drug content of all formulations ranged from 4.60 ± 0.65% to 5.01 ± 0.11% (w/w) for the different formulations.

Swelling and erosion of the matrix-type tablets

Figures 2 and 3 illustrate the water uptake (or swelling index) profiles and percentage erosion of the different matrix-type tablets. From these results it is clear that the matrix-type tablets prepared from the IPEC between chitosan and polycarbophil (formulations F1 and F4) have superior water uptake properties compared to those made of HPMC (formulations F2 and F5 for K100M and formulations F3 and F6 for K100LV) or the mixture of chitosan and polycarbophil powders (formulations F7 and F8). Furthermore, use of the chitosan–polycarbophil IPEC as matrix former led to matrix-type tablets with much lower erosion compared to those made from HPMC or the chitosan–polycarbophil powder mixture. Of importance is the relatively fast erosion

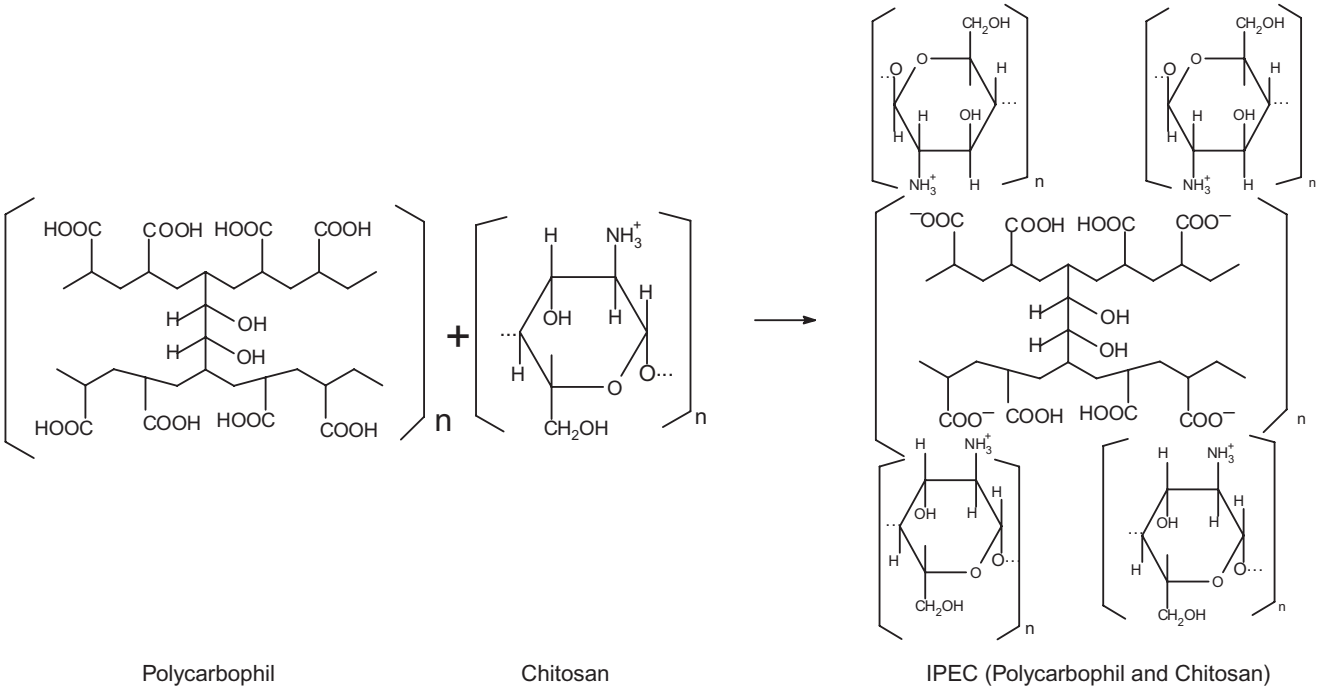

Figure 1. Proposed ionic interaction as the mechanism for interpolyelectrolyte complex (IPEC) formation between chitosan and polycarbophil.

Table 2. Physical characteristics and drug content (%, w/w) of the different matrix-type tablet formulations.

Formulation	Thickness (mm), $n = 20$	Hardness (N), $n = 10$	Friability (%), $n = 20$	Weight (mg), $n = 20$	Drug content, $n = 3$
F1	4.12 ± 0.04	73 ± 10	0.15	78.2 ± 1.3	4.90 ± 0.12
F2	3.66 ± 0.04	71 ± 11	0.19	73.3 ± 2.4	4.88 ± 0.15
F3	3.52 ± 0.08	69 ± 8	0.21	74.8 ± 2.9	4.92 ± 0.12
F4	3.50 ± 0.04	75 ± 14	0.11	73.5 ± 2.8	4.90 ± 0.09
F5	3.46 ± 0.04	71 ± 12	0.25	75.9 ± 3.2	4.95 ± 0.35
F6	3.46 ± 0.04	68 ± 14	0.15	74.1 ± 2.4	4.89 ± 0.45
F7	3.67 ± 0.04	91 ± 11	0.20	87.9 ± 4.0	4.60 ± 0.65
F8	3.40 ± 0.04	84 ± 8	0.26	75.8 ± 2.3	5.01 ± 0.11

of the matrix-type tablets prepared with a mixture of chitosan and polycarbophil powders (formulations F7 and F8), which were completely disintegrated within 3 hours. These results show that the IPEC between chitosan and polycarbophil acts differently as matrix-forming excipient in matrix-type systems than just a physical mixture of the two polymer powders. It further indicates that the polymeric complex probably did not dissociate during water uptake and this prevented the erosion of the matrix systems as opposed to those made of the simple polymeric powder mixture.

Drug release

The drug release profiles of hydrochlorothiazide and ketoprofen from the different formulations of matrix-type tablets are presented in Figures 4 and 5, whereas the MDT and drug release kinetics are presented in Table 3.

All the formulations investigated in this study showed controlled release of the model drugs except for those prepared from the chitosan–polycarbophil powder mixture (formulations F7 and F8), which exhibited complete release of the entire dose after only 4 hours. This was expected based on the relatively fast erosion and complete disintegration of the matrix-type tablets prepared from the chitosan–polycarbophil powder mixtures.

For hydrochlorothiazide, the formulation containing HPMC K100M (formulation F2, MDT_{ad} = 587.40 ± 2.27 minutes) as matrix former exhibited the slowest release rate followed by the formulation containing the chitosan–polycarbophil IPEC (formulation F1, MDT_{ad} = 435.11 ± 6.55 minutes) as matrix former, which was

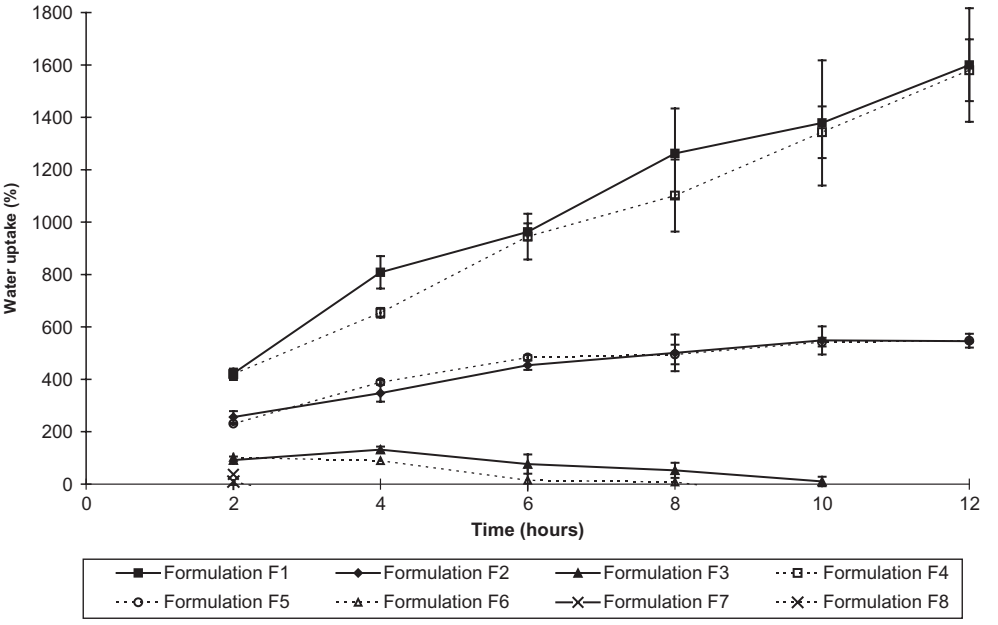

Figure 2. Water uptake (%) or swelling index profiles of the different matrix-type tablet formulations at pH 7.4.

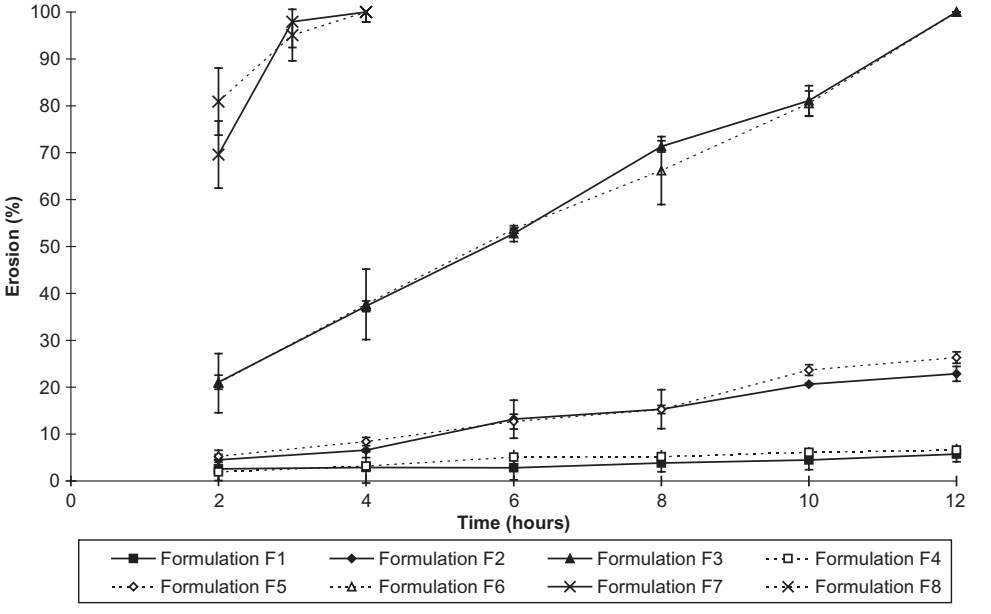

Figure 3. Erosion profiles of the different matrix-type tablet formulations at pH 7.

slower than that of the matrix-type tablet formulation containing HPMC K100LV (formulation F3, MDT_{ad} = 301.85 ± 17.82 minutes) as matrix former. However, for ketoprofen, the matrix-type tablet formulation containing the chitosan–polycarbophil IPEC (formulation F4, MDT_{ad} = 650.09 ± 35.12 minutes) showed the slowest drug release, which was followed by those made from HPMC K100M and K100LV (formulation F5, MDT_{ad} = 413.51 ± 39.70 minutes, and formulation F6, MDT_{ad} = 254.20). This slower release from the chitosan–polycarbophil IPEC-based matrix-type tablets compared to that of HPMC is in conjunction with previous findings, which were obtained for highly soluble drugs[22].

According to the drug release exponent (n) values, it is clear that the matrix-type tablets prepared from the chitosan–polycarbophil IPEC approached zero-order release for hydrochlorothiazide (formulation F1, n = 0.89) and super Case II for ketoprofen (formulation F4, n = 0.99).

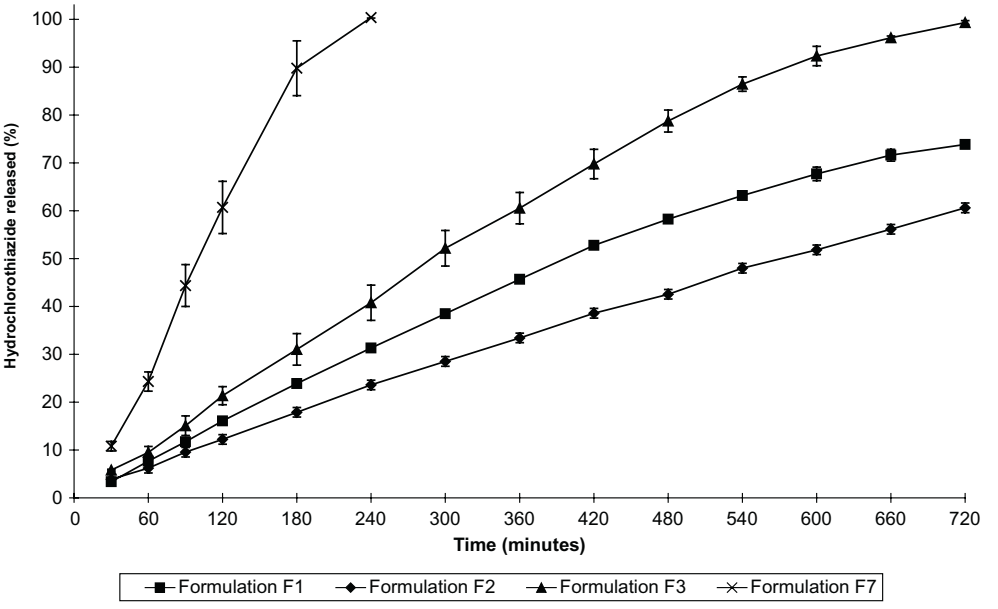

Figure 4. Hydrochlorothiazide release profiles from the different matrix-type tablet formulations at pH 7.4.

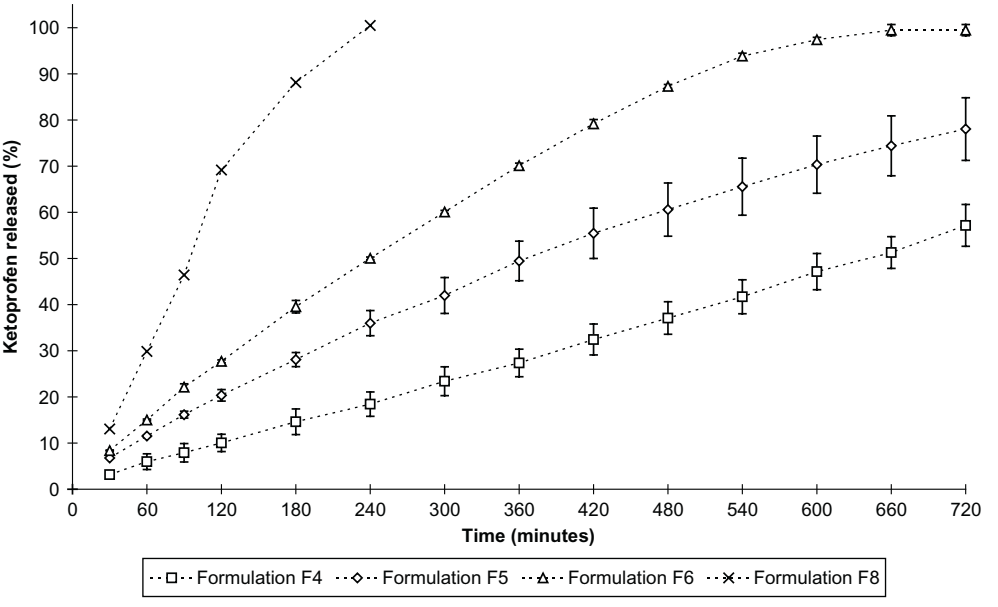

Figure 5. Ketoprofen release profiles from the different matrix-type tablet formulations at pH 7.4.

In contrast, the matrix-type tablets made from the chitosan–polycarbophil powder mixture exhibited Fickian diffusion for both model drugs investigated in this study (formulation F7 for hydrochlorothiazide with n = 0.37 and formulation F8 for ketoprofen with n = 0.34). This can be explained by the relatively fast disentanglement of the polymeric chains during water uptake into the matrix systems when the polymers are not cross-linked with each other, which results in surface erosion and relatively fast drug release.

Conclusions

The rate and extent of the release of hydrochlorothiazide and ketoprofen from matrix-type tablets prepared from the IPEC between chitosan and polycarbophil exhibited similar and, in certain cases, improved results compared to those made from the well-known polymeric matrix formers HPMC K100M and HPMC K100LV. The results from this study therefore showed the high potential of the chitosan–polycarbophil IPEC as a matrix-forming

Table 3. Release kinetics and MDT_{ad} values of the different matrix-type tablet formulations.

Formulation	MDT_{ad} (minutes)	Release constant (K_1)	Release exponent (n)	Correlation coefficient (R^2)
F1	435.11 ± 6.55	0.33 ± 0.06	0.89 ± 0.03	0.993
F2	587.40 ± 2.27	0.19 ± 0.01	0.88 ± 0.01	1.000
F3	301.85 ± 17.82	0.41 ± 0.08	0.85 ± 0.03	0.992
F4	650.09 ± 35.12	0.08 ± 0.01	0.99 ± 0.02	0.999
F5	413.51 ± 39.70	0.62 ± 0.06	0.74 ± 0.01	0.998
F6	254.20 ± 7.18	0.83 ± 0.15	0.75 ± 0.03	0.992
F7	105.88 ± 7.74	9.88 ± 4.53	0.37 ± 0.08	0.774
F8	100.40 ± 3.67	11.56 ± 4.78	0.34 ± 0.10	0.779

excipient for controlled release of poorly soluble drugs from matrix-type tablets capable of performing zero-order drug release kinetics. It was also shown that the matrix-type tablets prepared from the chitosan–polycarbophil IPEC released the drug mainly through the mechanism of diffusion from swellable systems with very low erosion. These systems are therefore less complex with potential higher predictability and repeatability of drug release behavior.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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