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Assembled modules technology for site-specific prolonged delivery of norfloxacin

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ABSTRACT

The aim of this research was to design and study norfloxacin (NFX) release in floating conditions from compressed hydrophilic matrices of hydroxypropylmethylcellulose (HPMC) or poly(ethylene oxide) (PEO). Module assembling technology for drug delivery system manufacturing was used. Two differently cylindrical base curved matrix/modules, identified as female and male, were assembled in void configuration by friction interlocking their concave bases obtaining a floating release system. Drug release and floatation behavior of this assembly was investigated.

Due to the higher surface area exposed to the release medium, faster release was observed for individual modules compared to their assembled configuration, independently on the polymer used and concentration. The release curves analyzed using the Korsmeyer exponential equation and Peppas & Sahlin binomial equation showed that the drug release was controlled both by drug diffusion and polymer relaxation or erosion mechanisms. However, convective transport was predominant with PEO and at low content of polymers. NFX release from PEO polymeric matrix was more erosion dependent than HPMC. The assembled systems were able to float in vitro for up to 240 min, indicating that this drug delivery system of norfloxacin could provide gastro-retentive site-specific release for increasing norfloxacin bioavailability.

1. Introduction

Modified-release formulations are valuable developments in pharmaceutical industry since, compared to the new drug application cost, product innovation remains affordable. Among the different approaches adopted for oral prolonged-release dosage forms, hydrophilic matrices are the most used delivery systems, due to the simple technology and manufacturing (Colombo et al., 2009; Omidian and Park, 2008; Fichtner et al., 2007; Siepmann and Peppas, 2001). An innovative drug delivery platform based on hydrophilic matrices, named module-assembling technology (Dome Matrix®), has been recently presented (Losi et al., 2006). In this technology, release modules made as swellable polymeric matrices are fixed together in a firm structure constituting the drug delivery system. The individual modules in their typical shape are cylindrical tablets having one concave and one convex base, designed for allowing their assembling by inserting the convex into the concave base. In dependence on modules assemblage, different system configurations can be made. Piled configurations are obtained by stacking two or more modules convex base into concave base. A peculiar assembly obtained by sticking the concave base of one module to the concave base of another module made feasible the construction of floating systems. This configuration, named "void", is characterized by an inner empty space that makes buoyant the assembly (Strusi et al., 2008). Referring to the module assembling for delivery system manufacturing, two differently shaped matrix/modules, identified as female and male, have been recently constructed (Strusi et al., 2010). The friction interlocking of the complementary concave bases of these modules drives their assemblage in void configuration.

Using this technology, the individual dose administered can be easily adjusted or, if the composition of modules is different, multiple release kinetics can be achieved. In addition, module assemblage can allow the delivery of two drugs in a single unit at a specific time and at a proper rate and duration, characterizing the flexibility of the Dome Matrix® technology.

Norfloxacin (NFX) is a synthetic broad-spectrum antibacterial drug firstly selected for the treatment of diseases caused by *Campylobacter*, *E. coli*, *Salmonella*, *Shigella* and *V. cholera* (Emmerson and Jones, 2003; Van Bambeke et al., 2005). The drug is used for the treatment of urinary tract infections (Emmerson and Jones, 2003). Development of bacterial resistance to currently available antibiotics due to the lack of patient compliance suggests an appropriate dosing of antibacterial drugs, such as quinolone drugs (Alexiou

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et al., 2007; Isturiz, 2008; Sheng et al., 2002; Taubes, 2008; Martinez et al., 2009). NFX is very slightly soluble in water; however, its solubility increases sharply at pH below 4.0 and above 10.0, due to its amphoteric nature (Mandell et al., 1988; Dua et al., 2007). The recommended dosage is 400 mg twice daily. The half-life of NFX in serum is 3–4 h; only approximately 30–40% of an oral dose is absorbed and the fecal recovery accounts for 30% of the administered dose (Mandell et al., 1988).

Since NFX is more soluble in acidic media a prolonged gastric residence of dose form is expected to lead to an increased in vivo dissolution rate. Dome Matrix® modules assembled in void configuration floated for up to 4 h on gastric content (Strusi et al., 2008). Then, the development of a gastro-retentive site-specific drug delivery system of NFX could improve the drug bioavailability and simplify the administration schedule. This intends to favor the patient convenience and compliance resulting in less erratic absorption and hampering bacterial resistance development.

Thus, the aim of this work was to design and study a floating norfloxacin prolonged-release delivery system manufactured with Dome Matrix® modules. In this paper, the formulations and the performances of the NFX non-assembled modules made with two different polymers (HPMC and PEO) at two concentrations (20 and 30%, w/w) and the corresponding void configurations have been examined. In vitro studies on floatation behavior and the release profile of the system have been carried out.

2. Materials and methods

2.1. Materials

Norfloxacin was purchased from Zhejiang Neo-Dankong Pharmaceutical (Zhejiang, China). Hydroxypropylmethylcellulose (Methocel K4M, viscosity 2% (w/v) solution 4000 mPa s) and poly(ethylene oxide) (Polyox N60K, MW 2 × 106 Da, viscosity 2% (w/v) solution 3060 mPa s) were kindly donated by Colorcon (Gallarate, Italy). Magnesium stearate (Eigemann & Veronelli S.p.A., Milan, Italy), colloidal silicon dioxide (Aerosil®, Evonik Degussa S.p.A., Ravenna, Italy), and talc (A.C.E.F., Fiorenzuola D'Arda, Italy) were pharmacopoeia grade. The compatibility of NFX with excipients was described elsewhere (Oliveira et al., 2009). NaCl anhydrous (A.C.E.F., Fiorenzuola D'Arda, Italy), HCl 37% and NaOH anhydrous (Carlo Erba S.p.A., Milan, Italy) were used to prepare the simulated gastric fluid.

Table 1
Composition of the norfloxacin male and female modules.

Composition	Polymer 20% (mg)	Polymer 30% (mg)
Norfloxacin	100	100
Methocel K4M or Polyox N60K	20	30
Talc	4.8	5.2
Magnesium stearate	1.2	1.3
Colloidal silicon dioxide	0.6	0.7
Total weight	126.6	137.2

2.2. Methods

2.2.1. Matrix modules preparation

NFX, hydrophilic polymer and talc were blended in a Turbula® mixer (WAB, Basel, Switzerland) for 15 min, followed by the addition of magnesium stearate and colloidal silicon dioxide with a further 5 min mixing. The modules composition and weight is reported in Table 1. Male and female modules having the same weight were prepared by direct compression in a single punch tableting machine (EKO Korsch, Berlin, Germany) equipped with special sets of cylindrical punches of 7.4 mm diameter, having the tip surface concave or convex. In the assembling procedure, one male and one female module were manually interlocked concave-to-concave bases to give rise to a void configuration system (Fig. 1). The modules had a diametral crushing strength of 22.0 ± 2.1 N (mean value ± standard deviation) for male modules and of 20.0 ± 2.1 N for female modules.

2.2.2. Floatation behavior

The floatation characteristics of the void assembled modules were assessed using an apparatus constructed according to Timmermans and Moes (1990). A digital camera pictured the swollen system during the immersion in the medium for determining the volume of the floating object. The resultant-force due to the sinking of the system in simulated gastric fluid without enzyme (USP 29) at 37 ± 0.5 °C was measured during time by the weighing part of the apparatus (precision 0.1 mg). The resultant-force is the difference between the buoyancy and gravity forces both act-

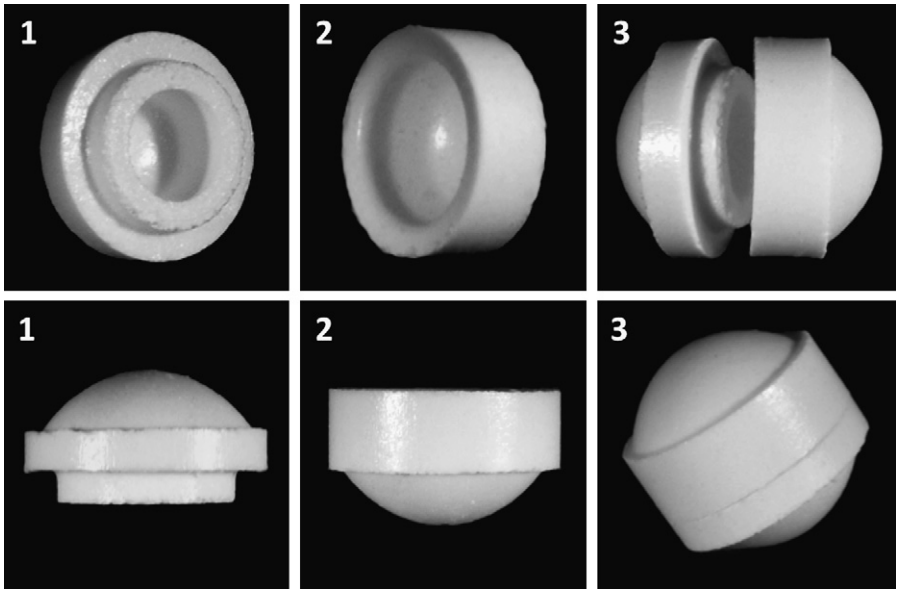

Fig. 1. Norfloxacin Dome Matrix® modules and assemblage: 1, male; 2, female; 3, void configuration assembled modules.

ing on the system submerged in water, according to the following equation Eq. (1):

$$F_{\text{result}} = (d_f - d_s)gV \quad (1)$$

where F_{result} is the resultant force, d_f is the density of the medium in which the object is sunk, d_s is the apparent density of the solid, g is the gravity acceleration and V is the volume of the object. This force was measured as weight by the balance inserted in the apparatus.

2.2.3. In vitro drug release

Drug release studies were performed using USP apparatus II (Erweka DT6R, Heusenstamm, Germany) with paddle rotation of 50 rpm, in 900 ml of simulated gastric fluid without pepsin (USP 29) at 37.0 ± 0.5 °C. At specified time intervals, 5 mL samples were withdrawn, filtered and quantified by a validated UV spectrophotometric method (Jasco V530, Tokyo, Japan) at the wavelength 278 nm.

Drug release data were analyzed according to Korsmeyer equation (2) (Korsmeyer et al., 1983) and Peppas and Sahlin equation (3) (Peppas and Sahlin, 1989):

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \quad (3)$$

where M_t/M_∞ is the fraction of drug released, k is the kinetic constants characteristic of the drug/polymer combination, n is the diffusional exponent for drug release, k_d and k_r are diffusion and relaxation rate constants, respectively, and m is the purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release. The value of 0.425 was used in this analysis according to the aspect ratio of the matrix. These mathematical models are capable of describing the solute release kinetics and mechanism from polymeric hydrophilic matrices and were used to fit release fractions in the range of 5–60%. The Peppas and Sahlin equation allows the calculation of the fraction of drug released due to Fickian mechanism, F, as in Eq. (4):

$$F = \frac{1}{1 + k_r/k_d t^m} \quad (4)$$

Release curves were compared using difference factor f_1 and similarity factor f_2, calculated by Eqs. (5) and (6), respectively (Moore and Flanner, 1996; FDA, 1997):

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad (5)$$

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\} \quad (6)$$

where R_t and T_t are the percentages released at each time point. f_1 value up to 15 (0–15) and f_2 value between 50 and 100 implies similarity between two release profiles.

3. Results and discussion

3.1. In vitro drug release from modules and assemblies

The cylindrical tablet modules of norfloxacin have been designed to allow their assemblage by interlocking the curved bases. Two differently shaped Dome Matrix® modules were manufactured in this study to obtain NFX prolonged release floating drug delivery systems, i.e., "female" module and "male" module (Fig. 1). In particular, the protrusion on the concave base rim of male module fit the concavity on concave base of the module without protrusion on the rim, i.e., female. Thus, facing the concave base of male module to the concave base of female one and exerting a light pressure, the two modules interlock giving rise to one-piece assembled system characterized by the presence of an empty internal space. The modules contained 20 or 30% of HPMC or PEO polymers (calculated on the drug present) and approximately 70% of norfloxacin on the total tablet weight.

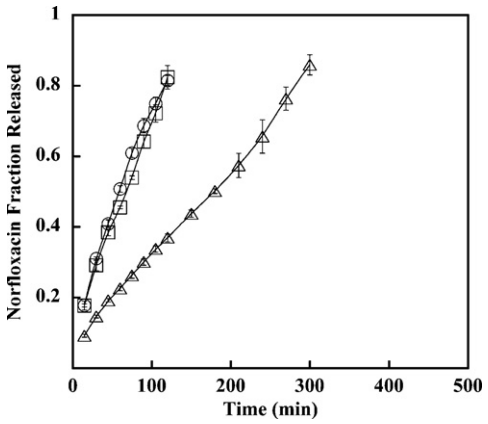

Fig. 2. Norfloxacin fraction released vs. time of Dome Matrix® modules containing 20% of HPMC: female module (○); male module (□); void configuration (△) (mean values ± standard deviation, $n = 6$).

The norfloxacin release profiles of the Dome Matrix® modules and their assemblies are shown in Figs. 2–5. The release of NFX observed for the female modules, independently on the polymer used and its concentration, was faster compared to the male modules. However, the curves were found pretty similar based on the difference (f_1) and similarity (f_2) parameters calculated (Table 2). This difference between the two module shapes was already observed with other drugs having solubility different from NFX and formulated as hydrophilic matrices with HPMC (Strusi et al., 2010; Casas et al., 2010). Moreover, even when inert polymers were used to obtain the modules, such as Tapioca starch derivatives (Casas et al., 2010), the female module showed faster release than the male. Apart from the different initial surface area, the release difference has to be assigned to the swelling kinetics of the two modules. The male and female modules have different concavity size due to the protrusion on the rim of male concave base. We observed that NFX module swelling determined the filling-up with jellified polymer of the concavity of the male module but not of the female module that had a larger concavity. As a consequence, the

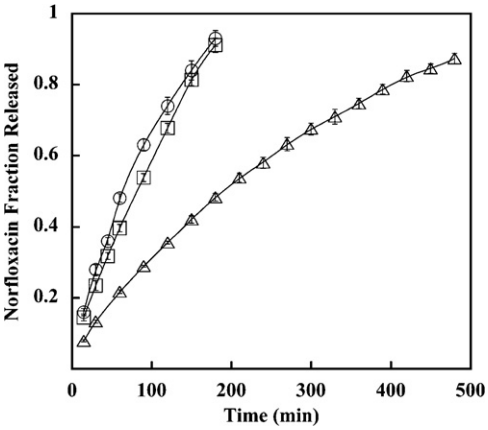

Fig. 3. Norfloxacin fraction released vs. time of Dome Matrix® modules containing 30% of HPMC: female module (○); male module (□); void configuration (△) (mean values ± standard deviation, $n = 6$).

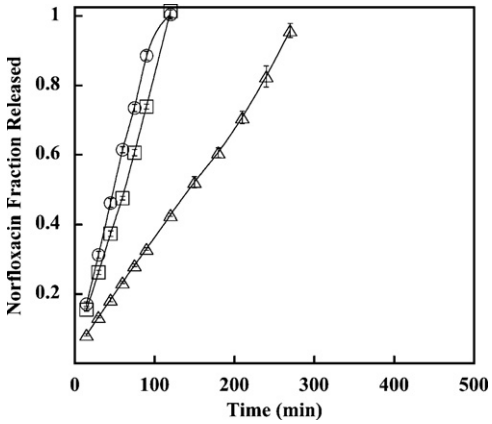

Fig. 4. Norfloxacin fraction released vs. time of Dome Matrix® modules containing 20% of PEO: female module (○); male module (□); void configuration (△) (mean values ± standard deviation, $n = 6$).

female module eroded/dissolved more quickly than the male one. Finally, the individual modules exhibited no floatation.

The release studies of the void configuration showed that NFX release rate was significantly slowed down in comparison to individual modules, independently on the polymer type and concentration. The void assembled modules containing 20% HPMC, released about 80% of drug in 270 min (Fig. 2), maintaining the floatation up to 240 min. In correspondence of this time, these assembled modules in part disintegrated with the consequent impairment of floatation capacity. This phenomenon was also revealed by the release profile that between 200 and 250 min had an evident increase of release rate. The standard deviation increase of the NFX release values after 200 min reflected the variability of void configuration disintegration. The floating capability of the Dome Matrix® in void configuration was already studied in humans, showing that the system remained in the stomach after a light standard meal for 214.5 ± 54.2 min (Strusi et al., 2008). The prolonged gastric residence could be beneficial for NFX absorption that, due to the favored dissolution in acid, can be promptly absorbed in stomach or in the first intestinal tract (Arora et al., 2005; Iannuccelli et al., 2004).

The assembled modules containing 30% HPMC had a different performance in terms of release and floatation. The void configuration system remained floating until 480 min, which is the end of the release experiment (Fig. 3). At 210 min, which corresponded to the time of void configuration gastro-residence (Strusi et al., 2008), about 55% of NFX was released. The 80% release was achieved at

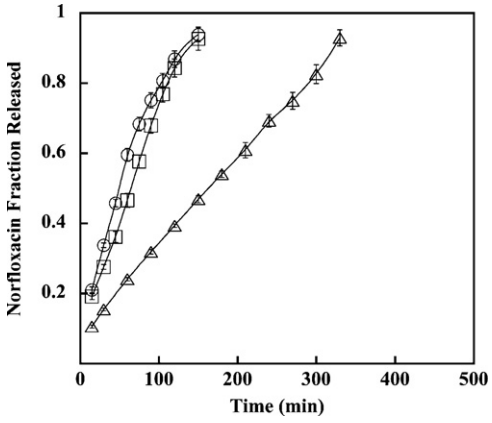

Fig. 5. Norfloxacin fraction released vs. time of Dome Matrix® modules containing 30% of PEO: female module (○); male module (□); void configuration (△) (mean values ± standard deviation, $n = 6$).

Table 2
Difference factor (f_1) and similarity factor (f_2) calculated for the male and female modules.

Formulation	f_1	f_2
HPMC K4M 20%	4.84	71.41
HPMC K4M 30%	6.37	64.96
PEO N60K 20%	13.86	50.18
PEO N60K 30%	7.54	58.54

about 400 min; at this time, the system could still be in the stomach if additional foods were taken.

High molecular weight poly(ethylene oxide) have been proposed as an alternative to HPMC. The choice of this hydrophilic polymer molecular weight and quantity in the matrix formulation can provide an appropriate combination of swelling, dissolution or erosion mechanisms to control drug release kinetics (Maggi et al., 2000; Heller et al., 2002; Lopes et al., 2005; Jamzad and Fassihi, 2006). For the norfloxacin formulations containing PEO, the drug release rate of individual modules was faster than the correspondent modules made with HPMC. The same was observed with the void configurations in comparison to the release of the HPMC assembled modules (Figs. 4 and 5).

However, similarly to HPMC system, the void assembled modules made with 20% PEO maintained the floating up to 240 min. After this time, assembled systems disintegrated at a level impairing the floating capacity. Despite the different polymer, also in this case the disintegration of the assembled system was reflected by an evident slope increase in the fraction released profile after 200 min (Fig. 4). Similarly, the increase in standard deviation of NFX release values due to the variability of disintegration can be observed. The floatation time corresponded to about 80% of NFX released.

Compared to HPMC composition, the Dome Matrix® modules containing 30% PEO (Fig. 5) showed faster release rate than the assembly. The floating time was prolonged until 330 min by the higher polymer concentration. At 210 min, about 60% of NFX was released and the 80% release was achieved at about 300 min.

3.2. Analysis of drug release from modules and assemblies

The release profiles of norfloxacin were analyzed with the Korsmeyer exponential equation up to 60% of drug released (Korsmeyer et al., 1983). Release data analysis was carried out also with the Peppas and Sahlin equation in order to calculate the Fickian fraction released of each system (Peppas and Sahlin, 1989). Parameter values are listed in Table 3. Calculation of the diffusional exponent n identifies the prevalent mechanism of release. For planar systems, $n = 0.5$ indicates diffusion-controlled (Fickian) drug release and $n = 1.0$ indicates swelling/erosion-controlled drug release (Case-II transport). Values of n between 0.5 and 1.0 can be regarded as a superposition of both phenomena, indicating that the drug release was not controlled only by diffusion, but also significantly by polymer relaxation or erosion mechanisms (anomalous non-Fickian transport). In general, the data of all release systems studied provided good fit to the different models (Table 3), supporting the adaptability of both models to fit the release data with the systems and polymers studied.

In the case of HPMC modules, the n values from Korsmeyer equation were in the range 0.686–0.767 indicating an important anomalous non-Fickian transport as evidenced by the quasi–linear release profiles. The k_d and k_r values for male and female modules revealed the relevance of drug diffusion or polymer relaxation and erosion. Calculations showed that the fraction of drug released due to the Fickian mechanism was the lowest for the female module compared to the male module and void assembly (Fig. 6). Fickian fraction released was very similar for modules containing 20

Table 3
Drug release kinetics parameters from Dome Matrix® modules and assemblies obtained from Korsmeyer and Peppas–Sahlin equations (mean values ± SD; $n = 6$).

Modules	Korsmeyer equation		Peppas and Sahlin equation		
	$n \pm 95\%$ CI	r^2	$k_d \times 10^3$	$k_r \times 10^3$	r^2
HPMC K4M 20%					
Male	0.686 ± 0.044	0.9994	29 ± 7.6	9.1 ± 1.2	0.9992
Female	0.758 ± 0.021	0.9996	17 ± 3.6	13 ± 0.8	0.9995
Void	0.688 ± 0.011	0.9986	14 ± 3.4	4.5 ± 0.5	0.9996
HPMC K4M 30%					
Male	0.767 ± 0.040	0.9983	16 ± 6.9	9.4 ± 1.3	0.9999
Female	0.732 ± 0.049	0.9998	15 ± 5.6	12 ± 1.2	0.9981
Void	0.718 ± 0.014	0.9998	14 ± 1.8	4.2 ± 0.3	0.9995
POE N60K 20%					
Male	0.841 ± 0.025	0.9977	−4.8 ± 3.4	16 ± 0.7	0.9979
Female	0.921 ± 0.029	0.9995	−17 ± 5.2	22 ± 1.0	0.9993
Void	0.816 ± 0.014	0.9993	−0.4 ± 2.0	7.4 ± 0.3	0.9997
POE N60K 30%					
Male	0.679 ± 0.015	0.9911	18 ± 3.4	11 ± 0.7	0.9940
Female	0.742 ± 0.024	0.9975	15 ± 6.1	15 ± 1.3	0.9983
Void	0.670 ± 0.013	0.9982	15 ± 1.4	4.9 ± 0.2	0.9996

and 30% of HPMC assembled in void configuration. This result fits with the similar n exponents obtained with Korsmeyer equation (Table 3). The contribution of Fickian diffusion to NFX release was around 50% for the assembled system at the beginning of the release experiment and tended to slowly decrease with time. The percentages of drug released by Fickian mechanism for individual modules were lower than 40% with the exception of the male module containing 20% of HPMC that behaved similarly to the assembled system. Considered that the difference between the assembled system and the individual modules is the non-accessibility of the concave bases to the release medium after the assemblage, it seems straightforward to consider that solvent penetration, chain disentanglement, build-up of gel-layer thickness and erosion of the matrix occurred differently affecting the balance between Fickian and relaxation release mechanisms. These results corresponded to a relevant anomalous non-Fickian release typical of swellable matrices (Colombo et al., 1999) due to an important contribution of the polymer swelling and erosion mechanisms to drug delivery.

In the case of PEO polymer, n diffusional exponents for the PEO concentration of 20% were in the range 0.816–0.921, indicating a release mechanism very close to Case II transport. The negative values of k_d and the high values of k_r in Peppas and Sahlin equation indicate that the drug release was predominantly controlled by polymer relaxation or erosion. Due to the negative values of k_d obtained, the Fickian release fractions were not calculated in this case. Likely, the PEO gel layer was weaker in comparison to HPMC and could be more rapidly removed by the dissolution medium; therefore, NFX/PEO matrix system was more susceptible to the erosion process. In general, PEO polymer is considered more soluble than HPMC (Maggi et al., 2002).

For the 30% PEO concentration, the diffusional exponents between 0.670 and 0.742 indicated anomalous non-Fickian transport profiles with lower erosion contribution than 20%. The k_d and k_r values revealed that the drug release control was mainly driven by polymer relaxation or erosion mechanisms, in particular for the female module; in fact Fig. 7 showed that the fraction of drug released due to pure diffusive mechanism was very low for the female module. Comparing the relaxation coefficient (k_r) of male and female modules made with the two polymers, one can notice that the values were significantly higher when the polymer used was PEO.

For void configuration Fickian fraction release values with PEO were very similar to those obtained for 20 and 30% of HPMC assembled in the same configuration. The same was observed for the n diffusional exponents obtained (Table 3). As for HPMC, the NFX release from PEO systems due to Fickian contribution initially was about 50% and decreased with time (Fig. 7). It was impressive to see the linearity of the release profiles obtained with PEO polymer considered that a quasi–linear dissolution profile (Figs. 4 and 5) could be observed up to 80% of NFX released. The linearity of the release was the goal of several oral drug delivery system and has been accomplished by designing reservoir devices or osmotic pumps. The advantage of this release kinetics is to obtain constant plasma

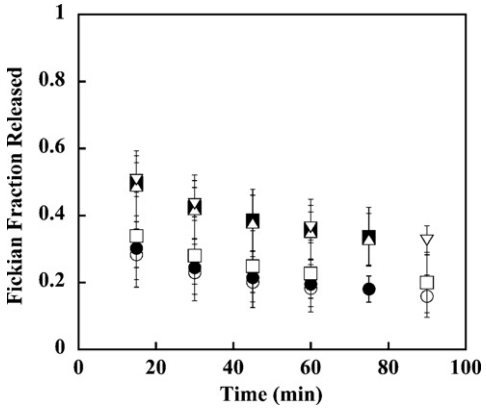

Fig. 6. Norfloxacin Fickian released fraction vs. time of Dome Matrix® modules containing 20% of HPMC: female module (●); male module (■); void configuration (△) and 30% of HPMC: female module (○); male module (□); void configuration (▽) (mean values ± standard deviation, $n = 6$).

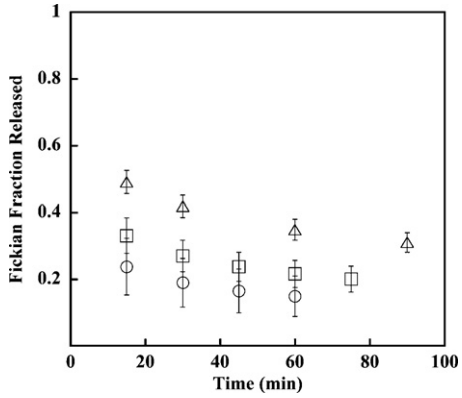

Fig. 7. Norfloxacin Fickian released fraction vs. time of Dome Matrix® modules containing 30% of PEO: female module (○); male module (□); void configuration (△) (mean values ± standard deviation, $n = 6$).

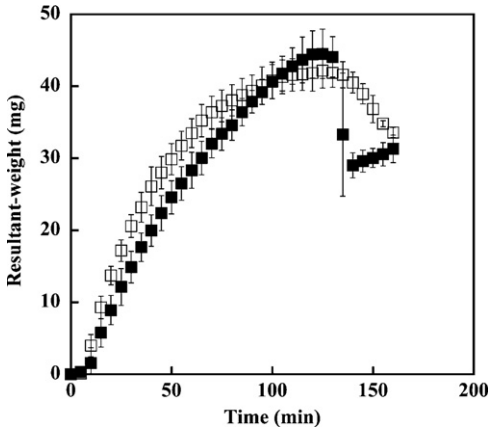

Fig. 8. Resultant weight vs. time of Dome Matrix® 20% HPMC K4M (□) and 20% PEO N60K (■) modules assembled in void configuration (mean values ± standard deviation, $n = 6$).

levels of the drug. In the case of matrices the release kinetics are not expected to be linear, but appropriate combinations of swellable polymers and drug make feasible quasi–linear profiles also with this kind of controlled drug delivery systems.

3.3. *In vitro floatation behavior of assembled modules*

Originally, the dome-shaped modules were designed for facilitating their assemblage by insertion of the convex base into the concave in the aim to build up a pile. The possibility to proceed to a different module assembly between the flat surfaces of the concave base rims held in contact was discovered later, but glue or ultrasounds were used to firmly link the modules. In this study, two new types of dome modules described elsewhere (Strusi et al., 2008), having the rim of concavity modified in order to favor a firm concave-to-concave assembly by simple interlocking, were used (see Fig. 1). The floatation behavior of the void assembled NFX system, made of two swellable modules, was studied in vitro. In particular, it was determined that the force required to hold the system submerged in water and its variation over time (Timmermans and Moes, 1990). The individual male and female modules never floated.

Based on the floating time observed in the release experiments of void configurations, two formulations, i.e., 20% HPMC and 20% PEO were selected for this study. The floatation behavior, expressed as resultant-weight variation versus time, is shown in Fig. 8. The profiles show that the systems did not float immediately but they started to float between 5 and 10 min after submersion in medium; at 10 min a positive resultant-weight of approximately 4 and 2 mg was measured for PEO and HPMC, respectively. Then, the resultant-weight values increased attaining peak values of approximately 42 mg for HPMC and 45 mg for PEO, both at 125 min. After this peak, the resultant-weight had a continuous slow decrease for HPMC, while an abrupt decrease was observed for PEO. This PEO behavior anticipated the beginning of system disintegration manifested by a partial exit of air bubbles from the inside of the void system. This phenomenon did not affect the floatation of the residual part of the system. The buoyancy variation during time is explained as the volume and weight change of the immersed system due to water uptake and swelling (Strusi et al., 2008). Therefore, the augmentation of resultant-weight over time was due to the swelling of the system that reinforced the capability of system to float. The gastric residence time previously demonstrated in vivo (214.5 ± 54.2 min) with a floating system made of HPMC 80% and calcium phosphate 20% was derived from an experiment after a standard meal without any additional food (Strusi et al., 2008). In cases where a longer gastric residence time is requested and the food intake after drug administration is allowed, a more durable Dome Matrix® system could be constructed. In this case, formulations containing higher amount of polymers (HPM, PEO or different polymers) have to be studied.

4. Conclusion

This study discovered a prolonged linear release of norfloxacin in simulated gastric fluid when the drug is formulated in Dome Matrix® modules with hydroxypropyl-methylcellulose but, in particular, with poly(ethylene oxide). Two modules, “male and female”, have been manufactured and interlocked to form a “void” configuration system. This assembly exhibited in vitro floatation up to 240 min, while the individual male and female modules never floated.

The mechanism of drug release from norfloxacin modules and void assemblies was mainly governed by the swelling and/or erosion of the polymer matrix. The diffusive contribution to drug release was less than 50% and decreased during release time. The release relaxation mechanism was more important for modules containing PEO in comparison with those with HPMC. In conclusion, a site-specific prolonged drug delivery system of norfloxacin was achieved by assembling the modules in void configuration; the release kinetics was strongly linear. However, in vivo studies are necessary to confirm the possibility for this linear release gastroretentive system to increase norfloxacin bioavailability and reduce dose administration.

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