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Research paper

Tapioca starch graft copolymers and Dome Matrix® modules II. Effect of modules assemblage on Riboflavin release kinetics

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ABSTRACT

This paper studies the Riboflavin release from systems made of assembled modules of Dome Matrix® technology using tapioca starch-ethylmethacrylate (TSEMA) and tapioca hydroxypropylstarch-ethylmethacrylate (THSEMA) graft copolymers produced by two different drying methods. Two different shape modules were manufactured for this study, i.e., female and male modules, in order to facilitate their assemblage in "void configuration", a system with an internal void space. Drug release studies on void configurations based on THSEMA show faster releases than TSEMA; HPMC systems used as a comparative reference showed intermediate release. Moreover, using void configurations made with one module of TSEMA and the other of THSEMA is possible to average the drug release, without difference between the drying methods used for the polymers. With respect to the floatation characteristics, all the void configurations floated immediately and, due to the mass center of the system, the floatation position of the system was always axial with the female module up and the male down. The drug release studies performed with a sinker to force the immersion of the systems in the medium did not show differences with respect to the dissolution test without a sinker. The combination of floatation capability of the assembled modules and the prolonged drug release provided with the graft copolymers make these assembled modules candidates as controlled release gastro-retentive dosage forms.

1. Introduction

There are drugs that have poor oral bioavailability because of incomplete absorption and/or degradation in the gastrointestinal tract. Narrow absorption window (NAW) in the upper part of the intestinal tract characterized several of these drugs. Despite the absorption capability of the duodenum and jejunum, their extent of absorption at these sites is reduced in case of rapid transit [1].

Prolonging the gastric residence time of NAW drugs may significantly improve the extent of their intestinal absorption. A variety of products have been developed to extend gastric residence time, such as, bioadhesive [2] and floating systems [3], high density dosage forms [4], concomitant administration of substances affecting gastrointestinal motility [5] and dosage form swelling to a large size to prevent emptying through pylorus [6].

Prolonged release dosage forms have been used to improve therapy with many important drugs. However, in the case of NAW drugs, this pharmaceutical approach requires colonic absorption of the drug. On the contrary, incorporation of the drug in a prolonged release gastro-retentive dosage form could allow the complete absorption over time [1].

A new platform for oral controlled release drugs, defined module assemblage technology or Dome Matrix®, has been introduced by Colombo and co-workers [7]. This technology was based on release units or modules made by hydrophilic polymers (matrix) having the shape of a disc with one convex and one concave base. The dome shape made straightforward the assembling of two or more modules by stacking. In this basic assembly, the concave base of one module was stack on the convex base of a second one in such a way that a firm pile of modules could be obtained (stacked configuration). By sticking two modules concave base against concave base produced a system with an internal void space. This assembly, named void configuration, was characterized by an immediate floatation of the system when plunged in water [3].

In a previous paper [8], two tapioca starch graft copolymers, i.e., tapioca starch-ethylmethacrylate (TSEMA) and tapioca hydroxypropylstarch-ethylmethacrylate (THSEMA), both dried by vacuum oven (OD-) or freeze-drying (FD-), were studied for manufacturing female and male Dome Matrix® modules performing as inert matrices. The modules have been designed for concave-to-concave assemblage by interlocking a protrusion on the rim of concave base

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of the male module with the concave base of female module. These modules made of tapioca starch graft copolymers showed different drug release behaviour depending on polymer and module shape.

In this paper, we studied the drug release kinetics from systems assembled with inert modules of tapioca starch graft copolymers. The two module shapes (male and female) were assembled in void configuration in order to have floating behaviour [3]. The aim was to introduce flexibility in the Riboflavin prolonged release in floatation conditions by means of the assemblage of different composed inert matrix modules. Nine void configurations have been prepared by different combining polymers and module shapes. To study these assembled systems for the application as controlled release gastro-retentive dosage forms, Riboflavin (NAW) [9,10] has been used as model drug.

2. Materials and methods

2.1. Materials

The copolymers were synthesised by free radical copolymerisation of ethylmethacrylate (EMA) and different starches (tapioca starch – TS and hydroxypropyl tapioca starch – THS) [11,12]. After polymerisation, the graft copolymers (TSEMA and THSEMA) were dried by drying in a vacuum oven (0.5 Pa) at 50 °C until constant weight (OD-TSEMA and OD-THSEMA) or by freeze-drying (freeze process at −80 °C for 48 h and sublimation process at 0.1 Pa) until dry product was obtained (FD-TSEMA and FD-THSEMA). OD-TSEMA and FD-TSEMA were crushed at 10,000 rpm in a knives mill (Retsch, Haan, Germany) to obtain powdery samples. On the other hand, OD-THSEMA and FD-THSEMA were not crushed as were obtained as powder.

Hydroxypropylmethylcellulose (HPMC) (Methocel® K15M, batch NH16012N11 Colorcon, Gallarate, Italy), Riboflavin (Riboflavin Universal®, batch UQ11022019, Roche, Brussel, Belgium), lactose (size 90–150 μm, Chiesi, Parma, Italy), PEG 6000 (HOECHST A.G., Werk Gendorf, Germany), Kollidon® K25 (batch 09–8760, BASF, Germany) and magnesium stearate vegetable (batch 24762, Eigemann & Veronelli S.p.A., Milan, Italy) were used for the preparation of modules.

The formulation is reported in Table 1.

2.2. Methods

2.2.1. Preparation of matrix modules

All the materials listed in Table 1 were mixed in a Turbula mixer (WAB, Basel, Switzerland) for 30 min. The modules were made by direct compression with a single punch tableting machine (EKO Korsch, Berlin, Germany) equipped with a special set of cylindrical punches of 7.4 mm diameter having appropriately designed tip surface to make female and male modules. A quantity of powder (105 mg) was weighed and manually fed into the die. The radial crushing strength of the modules was kept between 15 and 20 N.

The modules were assembled in void configuration as reported in Table 2.

The centre of mass and geometric center of void configuration were calculated using the programme Solid edge v.17.

Table 1
Composition of the modules using hydroxypropylmethylcellulose (HPMC K15M) or graft copolymers: oven-dried tapioca starch-ethylmethacrylate (OD-TSEMA), freeze-dried tapioca starch-ethylmethacrylate (FD-TSEMA), oven-dried tapioca hydroxypropylstarch-ethylmethacrylate (OD-THSEMA) and freeze-dried tapioca hydroxypropyl-starch-ethylmethacrylate (FD-THSEMA).

	mg per tablet
Riboflavin	5.0
Polymer	
HPMC K15M	40.0
OD-TSEMA	
FD-TSEMA	
OD-THSEMA	
FD-THSEMA	
Lactose	49.8
PEG 6000	5.0
PVP K25	5.0
Magnesium stearate	0.2
Total weight	105

2.2.2. Drug release study

Riboflavin release studies were performed using USP apparatus 2 (Erweka DT6R, Heusenstamm, Germany) with paddle rotation of 75 rpm, in 900 ml of simulated gastric fluid without pepsin [13] at 37.0 ± 0.5 °C, minimizing the exposure to visible light. Filtered samples were withdrawn at specified time intervals via a peristaltic pump and quantified with a validated UV spectrophotometer (Jasco V530, Tokyo, Japan) at the wavelength 267 nm. Linearity between 0.5 and 5.0 μg/ml: $r^2 = 0.99987$; Precision RSD (%) values: around 5%. The test was carried out for 24 h, and at the end of the study, a photograph of the system was taken in order to record the final shape of the system.

In a second series of experiments, in order to evaluate the influence of the floatation of void configuration, release studies were performed placing the assembled modules in a sinker, according to Japanese Pharmacopoeia [14].

2.2.3. Analysis of drug release

Drug release data were analysed according to Korsmeyer et al. [15] Eq. (1) and Peppas and Sahlin [16] Eq. (2):

$$\frac{M_t}{M_\infty} = k' t^m \tag{1}$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \tag{2}$$

where M_t/M_∞ is the fraction of drug released, k' is the kinetic constant characteristic of the drug/polymer, 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 which exhibits controlled release. Eqs. (1) and (2) were used to fit released data in the range 5–60%.

Moreover, release profiles were compared using similarity factor, f_2, calculated by the following Eq. (3):

$$f_2 = 50 \cdot \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\} \tag{3}$$

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles [17].

3. Results and discussion

The four copolymers, OD-TSEMA, OD-THSEMA, FD-TSEMA and FD-THSEMA, were used to construct both male and female modules. In the previous paper [8], we studied the influence of module shape on drug release. Now, female and male modules were assembled in void configuration by interlocking the protrusion of the concave base rim of the male module within the concave base of female module (Fig. 1). In order to reduce the number of combinations, assembled modules containing only polymers dried with the same method were studied. Male and female modules of

Table 2
Combinations studied using hydroxypropylmethylcellulose (HPMC K15M), tapioca starch-ethyl methacrylate (TSEMA) and tapioca hydroxypropylstarch-ethyl methacrylate (THSEMA) polymers.

Combination	Female	Male	Void configuration
1	HPMC	HPMC	HPMC & HPMC
2	OD-TSEMA	OD-TSEMA	OD-TSEMA & OD-TSEMA
3	FD-TSEMA	FD-TSEMA	FD-TSEMA & FD-TSEMA
4	OD-THSEMA	OD-THSEMA	OD-THSEMA & OD-THSEMA
5	FD-THSEMA	FD-THSEMA	FD-THSEMA & FD-THSEMA
6	OD-TSEMA	OD-THSEMA	OD-TSEMA & OD-THSEMA
7	OD-THSEMA	OD-TSEMA	OD-THSEMA & OD-TSEMA
8	FD-TSEMA	FD-THSEMA	FD-TSEMA & FD-THSEMA
9	FD-THSEMA	FD-TSEMA	FD-THSEMA & FD-TSEMA

HPMC, used as reference, were also interlocked in void configuration. Then, nine different assembled systems in void configuration have been prepared (Table 2). Assembled male and female modules made with the same polymer constituted the first group of combinations (1–5 in Table 2) whereas modules made with different polymers characterized combinations 6–9 (see Table 2). In particular, OD-TSEMA female and OD-THSEMA male modules gave combination 6, while combination 7 was reversed, i.e., OD-THSEMA female module and OD-TSEMA male one. Combinations 8–9 were similar but employing FD copolymers. In the code for the void assembled systems, the first name corresponds to the female module polymer and the second to the male module polymer.

During the dissolution test carried out in simulated gastric fluid without enzymes, all void combination systems exhibited an instantaneous floatation in the medium that lasted until 24 h, the end of release experiment. Losi et al. [7] and Strusi et al. [3] observed similar behaviour, using swellable polymers in void configurations (HPMC K100M). According to these authors, the instantaneous floating is due to the positive resultant-weight value at time zero, owing an empty space inside of the system.

Fig. 2 shows Riboflavin fraction released of void configurations with male and female modules manufactured with the same polymer (combination 1–5). HPMC assembled modules, that is the reference system, showed linear release reaching 60% of drug released at 660 min. Also, these assembled HPMC modules were completely eroded/dissolved at the end of the experiment (24 h).

The graft copolymers assembled systems presented a non-linear drug release. OD-TSEMA or FD-TSEMA assembled systems showed release profile slightly slower than HPMC, with 30–40% of Riboflavin released at 660 min. These assembled systems remained intact after 24 h (Fig. 4a) when 60% of drug was released. Assembled modules containing tapioca hydroxypropylstarch graft copolymers (OD-THSEMA or FD-THSEMA) showed release profile higher than HPMC modules, with a difference between the two copolymers dependent on the drying method (f_2 = 37.17). In fact, FD-THSEMA released 100% of Riboflavin in 660 min, whereas OD-THSEMA released 80%. Moreover, both systems presented surface erosion after 24 h, but the shape of the assembled void system remained.

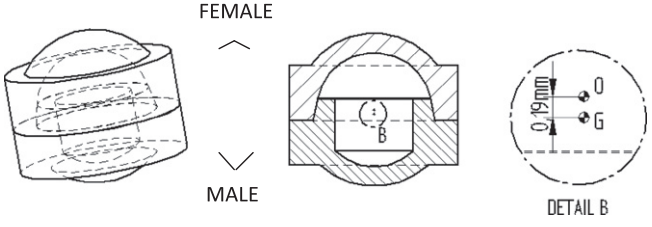

Fig. 1. Dome Matrix® assembled modules (female and male) in void configuration with the center of mass (G) and geometric center (O).

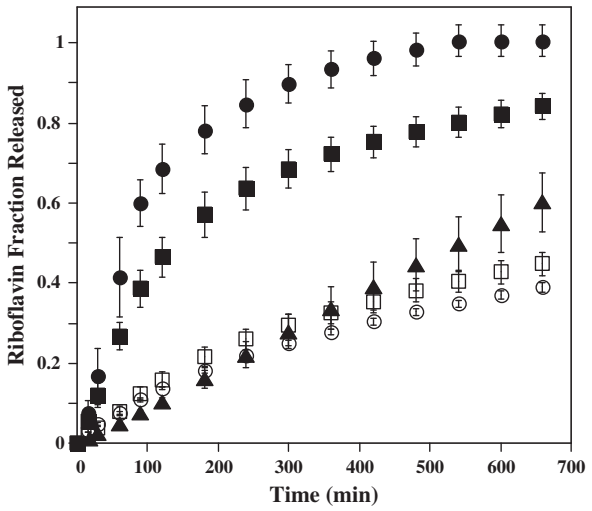

Fig. 2. Riboflavin fraction released versus time of Dome Matrix® 1–5 void configurations: HPMC & HPMC (▲); OD-TSEMA & OD-TSEMA (□); FD-TSEMA & FD-TSEMA (○); OD-THSEMA & OD-THSEMA (■); FD-THSEMA & FD-THSEMA (●) (mean ± standard deviation, n = 3).

In spite of the different hydrodynamic conditions of floatation, all dissolution profiles were in agreement with results obtained for the single modules studied in the previous paper [8]. So, using HPMC K15M modules as reference, the tapioca THSEMA modules released the drug faster while the TSEMA modules drug released profiles were slower compared to the reference. In summary, the relationship between the erosion of the systems and the drug release profiles observed with individual modules was confirmed despite that the concave faces of the modules were hidden to the medium in the void assemblage. In fact, OD-TSEMA and FD-TSEMA assembled modules behave as inert matrices and their dissolution profiles were slower than OD-THSEMA and FD-THSEMA void configurations that presented an erosion phenomena leading to a higher drug release profiles.

For the assembled systems with modules containing different copolymers (combinations 6–9), we interlocked one OD-TSEMA or FD-TSEMA module with one OD-THSEMA or FD-THSEMA module, respectively. Riboflavin release was averaged by the individual contribution of the two different modules (Fig. 3). In fact, all assembled modules made with different polymers released 50–60% of the drug at 660 min.

In order to study the influence of the male or female polymer composition on drug release, we have compared assembled systems having interchanged composition. In case of oven-dried copolymers (combinations 6–7), the assembled systems displayed superposed profiles of drug release. On the contrary, the combination 8 (FD-TSEMA & FD-THSEMA) compared to the combination 9 (FD-THSEMA & FD-TSEMA), in which the polymers in the male and female module were exchanged, shows different release profiles (f_2 = 49.47). This was due to the contribution of FD-THSEMA male module that, as previously seen, released faster than the corresponding female module [8]. So, in this case the male or female position in the configuration had a certain influence on the drug release when using THSEMA polymer. Moreover, in void configurations, that combined one module of TSEMA and the other one with THSEMA, it could be observed the erosive behaviour of THSEMA module. It can be seen that the module manufactured with TSEMA remained intact while the module with THSEMA (OD or FD) eroded (Fig. 4b).

During dissolution test, we have observed a peculiar position of the void configuration during floating in the dissolution medium. The void assembled modules floated in such a way that the

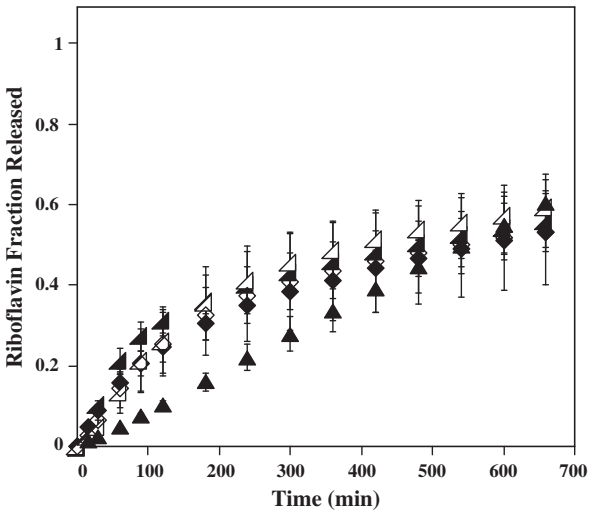

Fig. 3. Riboflavin fraction released versus time of Dome Matrix® 6–9 void configurations: HPMC & HPMC (▲); OD-TSEMA & OD-THSEMA (◇); OD-THSEMA & OD-TSEMA (♦); FD-TSEMA & FD-THSEMA (◿); FD-THSEMA & FD-TSEMA (◢) (mean ± standard deviation, $n = 3$).

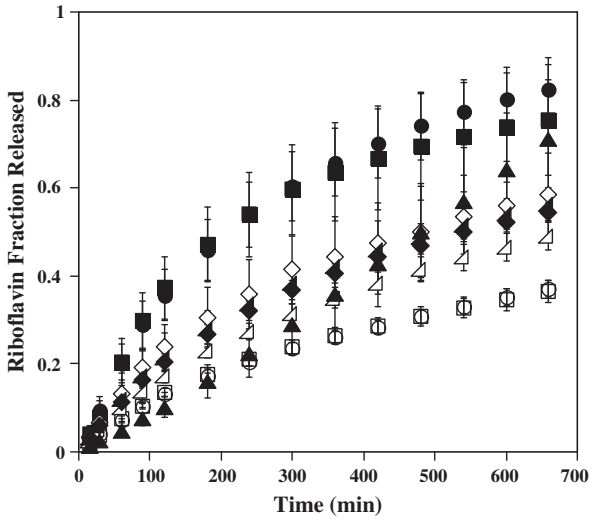

Fig. 5. Riboflavin fraction released versus time of Dome Matrix® assembled modules with sinker: HPMC & HPMC (▲); OD-TSEMA & OD-TSEMA (□); FD-TSEMA & FD-TSEMA (○); OD-THSEMA & OD-THSEMA (■); FD-THSEMA & FD-THSEMA (●); OD-TSEMA & OD-THSEMA (◇); OD-THSEMA & OD-TSEMA (♦) ; FD-TSEMA & FD-THSEMA (◿); FD-THSEMA & FD-TSEMA (◢) (mean ± standard deviation, $n = 3$).

assembled system was always axially aligned in the medium. In particular, we have observed that the assembled modules floated with the female module towards the medium surface and the male one towards the bottom. This was due to the not-centred mass distribution of the assembled modules. We have determined the center of mass (G) and geometric center (O) of void configuration (Fig. 1). As it can be seen, the center of mass was placed on the perpendicular axis of the system in the male module at 0.19 mm below the assembly geometric centre. Since the geometry is nearly spherical, the void configuration assumes a position where its center of mass is as lowest level. This behaviour could be considered for applications increasing the flexibility of drug release from assembled systems.

In order to evaluate the influence of the floatation of assembled system in dissolution results, release studies were also performed sinking the assemblage in a sinker [14]. Fig. 5 shows the drug release of all combinations using graft copolymers (combinations 2–9) with sinker. Sinked assembled modules showed, in general, similar results to the floating assemblages, except for the case of FD-THSEMA assembled modules (combination 5), in which drug release profile of sinked system was lower ($f_2 = 30.80$). This could be due to the hydrodynamic effect at the surface of the vessel that promotes a higher erosion of the structure of FD-THSEMA modules without sinker and, consequently, higher drug release than that for sinked system. Drug release profiles of sinked assembled modules did not show a higher percentage of Riboflavin released as expected because of the exposition to the medium. It has been concluded that the portion of the assembled system at the surface of the medium did not influence the drug release.

Release data were analysed according to Korsmeyer et al. [15] and Peppas and Sahlin [16] equations. The main parameters are listed in Table 3. Peppas [18] claimed that Eq. (1) could adequately describe the release of solutes from slabs, spheres, cylinders and discs (tablets), regardless of the release mechanism. Conscious of the fact that n is dependent on the shape of the matrix, the diffusional exponent n values were calculated as well (Table 3). In relation to Peppas and Sahlin equation, as the modules under study presented an aspect ratio ($2a/l$, where $2a$ is the diameter and l is the thickness of the device), the m value was 0.44 [16].

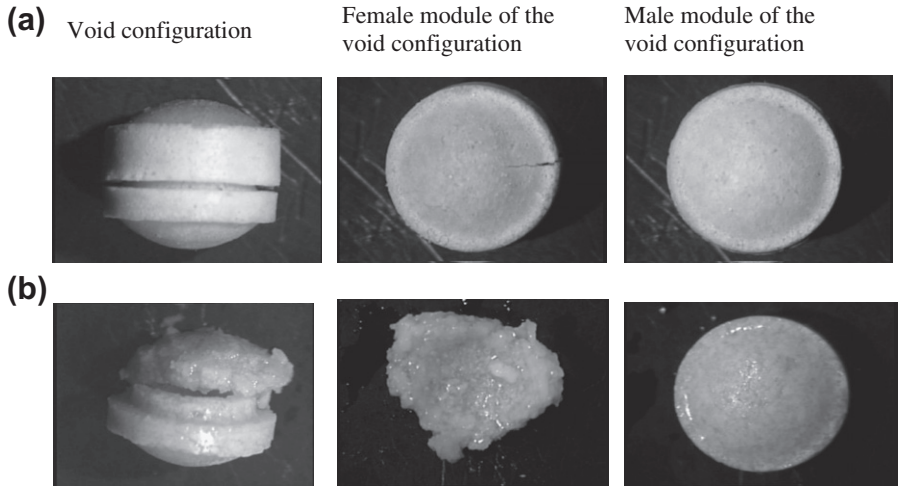

Fig. 4. Photographs of Dome Matrix® assembled modules after 24 h of dissolution: (a) void configuration FD-TSEMA & FD-TSEMA (combination 3) and (b) void configuration FD-THSEMA & FD-TSEMA (combination 9).

Table 3
Mathematical modelling and drug release kinetics from Dome Matrix® assembled modules.

	Void Combinations	Korsmeyer equation		Peppas and Sahlin equation		
		$n \pm 95\%$ CI	r^2	k_d	k_r	r^2
1	HPMC & HPMC	1.029 ± 0.039	0.9979	-1.3×10^{-2}	5.4×10^{-3}	0.98505
2	OD-TSEMA & OD-TSEMA	0.798 ± 0.011	0.9816	1.2×10^{-2}	8.7×10^{-4}	0.98521
3	FD-TSEMA & FD-TSEMA	0.658 ± 0.026	0.9938	1.5×10^{-2}	3.7×10^{-4}	0.98568
4	OD-THSEMA & OD-THSEMA	0.966 ± 0.100	0.9790	9.6×10^{-3}	5.3×10^{-3}	0.97209
5	FD-THSEMA & FD-THSEMA	1.173 ± 0.119	0.9961	-2.9×10^{-2}	1.6×10^{-2}	0.99657
6	OD-TSEMA & OD-THSEMA	0.722 ± 0.119	0.9431	2.7×10^{-2}	3.1×10^{-4}	0.96349
7	OD-THSEMA & OD-TSEMA	0.603 ± 0.044	0.9741	2.6×10^{-2}	2.9×10^{-4}	0.98606
8	FD-TSEMA & FD-THSEMA	0.825 ± 0.091	0.9743	2.6×10^{-2}	5.9×10^{-4}	0.95433
9	FD-THSEMA & FD-TSEMA	0.651 ± 0.125	0.8709	3.9×10^{-2}	-4.2×10^{-4}	0.96684

The determination coefficient (r^2) was used to test the applicability of the release models.

In the case of HPMC void configuration, n value of 1.029 indicates a case II transport with kinetic close to zero order ($n = 1.0$) [19], in agreement with the linear release profile. On the other hand, the negative value of k_d and high value of k_r of binomial equation reveal a drug release mechanism controlled by polymer relaxation or erosion [20].

In contrast, observing the Korsmeyer equation n parameters of the graft copolymers assembled modules (configurations 2–9), the values would indicate anomalous (non-Fickian) transport ($0.45 < n < 0.89$) [21] for all configurations except for the case of the erosive systems, OD-THSEMA & OD-THSEMA and FD-THSEMA & FD-THSEMA. Respect to the Peppas and Sahlin equation binomial equation, the combination of k_d over k_r in all configurations reveals a drug release mechanism predominantly controlled by drug diffusion. Only in the case of FD-THSEMA & FD-TSHEMA, the negative value of k_d and the higher value of k_r indicated a drug release mechanism predominantly erosive. The k_d values using or not using the sinker confirm the similar release profiles observed in Fig. 2 (data not shown). The high k_r values for OD-THSEMA & OD-THSEMA and FD-THSEMA & FD-THSEMA respect to other combinations are in agreement with their faster releases showed in Fig. 2.

4. Conclusions

The Dome Matrix® module void configurations made with inert polymers show the possibility to prolong the floatation conditions and drug release of Riboflavin for a long time. Moreover, using void configurations with one module of TSEMA polymer and the other one with THSEMA, it was possible to modulate the drug release. Furthermore, the non-disintegration behaviour of TSEMA modules and the erosion supported by THSEMA individual modules were also presented in void configurations.

Respect to the floatation behaviour, the apparent density lower than water for the assembled modules, deriving from their composition and the void space created between modules, produced an immediate floatation of all void configurations studied that lasted depending on the type of modules and polymers used. Moreover, the positioning of the void configuration floating in the medium, with the female module towards the surface and male module submerged, provides future applications in drug delivery control.

The kinetic analysis of systems in void configuration revealed that drug release was controlled mainly by diffusion for all graft copolymers, except for the systems made with the FD-THSEMA & FD-THSEMA combination where erosion of polymer predominated.

The floatation capability of the assembled modules and the prolonged drug release provided with the graft copolymers make these assembled modules candidates as controlled release gastroretentive dosage forms.

References

[1] A. Hoffman, D. Stepensky, E. Lavy, S. Eyal, E. Klausner, M. Friedman, Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms, Int. J. Pharm. 277 (2004) 141–153.
[2] M.R. Jiménez-Castellanos, H. Zia, C.T. Rhodes, Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application, Int. J. Pharm. 105 (1994) 65–70.
[3] O.L. Strusi, F. Sonvico, R. Bettini, P. Santi, G. Colombo, P. Barata, A. Oliveira, D. Santos, P. Colombo, Module assemblage technology for floating systems: in vitro flotation and in vivo gastro-retention, J. Control. Release 129 (2008) 88–92.
[4] N. Rouge, E. Allemann, M. Gex-Fabry, L. Balant, E.T. Cole, P. Buri, E. Doelker, Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multipleunit capsule and an immediate-release tablet containing 25 mg atenolol, Pharm. Acta Helbetiae 73 (1998) 81–87.
[5] J.M. Greiff, D. Rowbotham, Pharmacokinetic drug interactions with gastrointestinal motility modifying agents, Clin. Pharmacokinet. 27 (6) (1994) 447–461.
[6] A.A. Deshpande, C.T. Rhodes, N.H. Shah, A.W. Malick, Controlled-release drug delivery systems for prolonged gastric residence: an overview, Drug Dev. Ind. Pharm. 22 (1996) 531–539.
[7] E. Losi, R. Bettini, P. Santi, F. Sonvico, G. Colombo, K. Lofthus, P. Colombo, N.A. Peppas, Assemblage of novel release modules for the development of adaptable drug delivery systems, J. Control. Release 11 (1–2) (2006) 212–218.
[8] M. Casas, O.L. Strusi, M.R. Jiménez-Castellanos, P. Colombo, Tapioca starch graft copolymers and Dome Matrix® modules assembling technology. I. Effect of module shape on drug release, Eur. J. Pharm. Biopharm. 75 (2010) 42–47.
[9] J. Goole, J. Hamdani, F. Vanderbist, K. Amighi, In vitro and in vivo evaluation in healthy human volunteers of floating riboflavin minitablets, J. Drug Deliv. Sci. Technol. 16 (5) (2006) 351–356.
[10] L. Kagan, A. Hoffman, Biopharmaceutical aspects of gastro-retentive dosage form: the gabapentin paradigm, J. Drug Delv. Sci. Technol. 19 (4) (2009) 233–239.
[11] M. Casas, C. Ferrero, M.R. Jiménez-Castellanos, Synthesis and characterization of new copolymers of ethyl methacrylate grafted on tapioca starch as novel excipients for direct compression matrix tablets, Eur. Polym. J. 45 (2009) 1765–1776.
[12] M. Casas, C. Ferrero, M.R. Jiménez-Castellanos, Graft tapioca starch copolymers as novel excipients for controlled-release matrix tablets, Carbohyd. Polym. 2009 (80) (2010) 71–77.
[13] USP 29, Webcom Limited, Toronto, 2006, pp. 3168–3179.
[14] The Japanese Pharmacopeia, 14th ed., Society of Japanese Pharmacopeia, Tokyo, Japan, 2001.
[15] R.W. Korsmeyer, K. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[16] N.A. Peppas, J.J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, Int. J. Pharm. 57 (1989) 169–172.
[17] Guidance for industry "Dissolution testing of immediate release solid oral dosage forms", US Department of Health and Human Services, CDER, August 1997.
[18] N.A. Peppas, Analysis of Fickian and non Fickian drug release from polymers, Pharm. Acta Helv. 60 (1985) 110–111.
[19] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices, J. Control. Release 5 (1987) 37–42.
[20] P. Colombo, R. Bettini, P.L. Catellani, P. Santi, N.A. Peppas, Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropylmethyl cellulose matrices containing a soluble drug, Eur. J. Pharm. Sci. 9 (1999) 33–40.
[21] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release. I. Fickian and anomalous release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Control. Release 5 (1987) 23–36.