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Research paper

Tapioca starch graft copolymers and Dome Matrix® modules assembling technology. I. Effect of module shape on drug release

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ABSTRACT

This paper studies the Riboflavin release from compressed disc modules of Dome Matrix® technology using tapioca starch–ethylmethacrylate (TSEMA) and tapioca hydroxypropylstarch–ethylmethacrylate (THSEMA), graft copolymers produced by two different drying methods. The comparison with the release behaviour of similar HPMC modules was performed. Two different shape modules have been made, identified as female and male modules, in order to obtain their assemblage by interlocking the disc bases. HPMC matrices showed quasi-linear Riboflavin release in case of both female and male modules, with faster drug release than TSEMA modules. In the case of THSEMA modules, a faster release was observed compared to HPMC modules. Furthermore, matrices obtained with TSEMA copolymers remained nearly intact after dissolution process, while matrices containing HPMC experimented a complete dissolution of the modules. Combining these results with the release curve analysis using the Korsmeyer and Peppas exponential equation, HPMC modules controlled the drug release by polymer relaxation or erosion. For TSEMA and THSEMA, the drug release mechanism was controlled mainly by drug diffusion. The pronounced faster releases for the matrices containing THSEMA copolymers compared with the ones with TSEMA were due to a more important erosive support; however, the main structure of the matrix remains coherent. Porosity and tortuosity values and the shape of the modules explained the drug release observed.

1. Introduction

In last years, graft copolymers based on starch have shown potential application in matrix construction. Depending on the type of carbohydrate and monomer used, the properties of the copolymer obtained changed [1,2]. Tapioca starch is different from other starches because of the low level of residual materials, lower amylose content (17%) and high molecular weights of amylose and amylopectin. These properties make tapioca a good native starch for direct use in industrial applications and a starting material for physical and chemical modifications [3]. Atichokudomchai et al. [4] modified native tapioca starch showing that these new products were useful as diluents in direct compression tablet preparation. Recently, graft copolymers combining natural or semi-synthetic (tapioca starch derivatives) and synthetic (ethyl methacrylate – EMA) polymers have been prepared [5]. The polymers tapioca starch–ethylmethacrylate (TSEMA) and tapioca hydroxypropylstarch–ethylmethacrylate (THSEMA) were obtained by two different drying methods. The adequate crushing strength of tablets obtained using lower compression force, and the high disintegration times observed and the suitability for use as direct compression diluents make TSEMA and THSEMA potential excipients for prolonged-release matrices [5].

Modified-release dosage forms prepared with various technologies have gained widespread importance in recent years with the aim to adapt the release rate to a particular therapeutic target [6–8]. Among the different approaches for oral prolonged-release dosage forms, matrix tablets have been the most widely used because of the simple and low-cost manufacturing process [9,10]. A new oral drug delivery platform, defined module assemblage and characterized by release flexibility, has been recently presented by Colombo and coworkers [11]. This technology, named Dome Matrix®, was based on release units, i.e. modules, to be assembled in drug delivery systems. Basically, the release units are matrices obtained by compression, having shape of a disc with curved bases, one convex and the other concave. The module protuberance and concavity made straightforward to stack two or more modules in a pile.

Until now, only hydroxypropylmethylcellulose (HPMC), as a rate-controlling polymer in matrix tablets, has been studied to make drug delivery system based on Dome Matrix® technology

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[11]. Due to previously described favourable direct compression properties of the tapioca starch graft copolymer powders [5], in this work, these new materials were used in Dome Matrix® module construction with the objective to compare the drug release kinetics from the tapioca derivatives copolymers with HPMC modules.

Two different types of modules designed for constructing assembled drug delivery systems by interlocking have been prepared. Their shape is essentially cylindrical, but the presence of different protrusions and recessions on the bases of cylinder suggested different water uptake behaviour and, as consequence, different release of drug. Thus, the influence of the module shape and composition on drug release rate and dosage form performance was studied. Riboflavin (vitamin B_2) has been used as model of narrow absorption window drug.

2. Materials and methods

2.1. Materials

Copolymers were synthesised by free radical copolymerisation of ethylmethacrylate (EMA) and different starches: Tapioca starch (TS) (Tapioca Starch, batch MCB 3053) and hydroxypropyl tapioca starch (THS) (Tapioca Textra, batch 8010) were kindly supplied by National Starch & Chemical (Manchester, UK) [5]. The products were obtained (TSEMA and THSEMA) by drying using two different methods: in a vacuum oven (0.5 Pa) at 50 °C until constant weight (OD-copolymers) or freeze-drying (freeze process at −80 °C for 48 h and sublimation process at 0.1 Pa) until a powder product was obtained (FD-copolymers). The starch-based copolymers (TSEMA) were milled at 10,000 rpm in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Hydroxypropylmethylcellulose (HPMC) (Methocel® K15M, batch NH16012N11 Colorcon, Gallarate, Italy) was used as reference swellable polymer.

Riboflavin (Riboflavin Universal®, batch UQ11022019, Roche, Brussel, Belgium) was chosen as model drug.

Lactose (micron 90–150, Chiesi, Parma, Italy), PEG 6000 (HOECHST A.G., Werk Gendorf, Germany), Kollidon® K25 (batch 09–8760, BASF, Germany) and magnesium stearate vegetale (batch 24762, Eigemann & Veronelli S.p.A., Milan, Italy) were used for the preparation of modules according to the composition reported in Table 1.

NaCl anhydrous (Acef, Piacenza, 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 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 hydroxypropylstarch–ethylmethacrylate (FD-THSEMA).

Composition	For one module (mg)
Riboflavin	5.0
Polymer HPMC K15M OD-TSEMA FD-TSEMA OD-THSEMA FD-THSEMA	40.0
Lactose	49.8
PVP K25	5.0
PEG 6000	5.0
Magnesium stearate	0.2
Total weight	105

Before the use, the materials were stored at constant relative humidity (40%) and room temperature (20 °C).

2.2. Methods

2.2.1. Preparation of matrix modules

All the materials were mixed in a Turbula mixer (WAB, Basel, Switzerland) for 30 min. The matrices were manufactured by direct compression in 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 surfaces. A fixed amount of powder (105 mg) was manually fed into the die. The radial crushing strength of the modules was kept between 15 and 20 N.

2.2.2. Drug release study

Riboflavin release rate 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 [12] 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 observe the final shape of the system.

2.2.3. Analysis of drug release

Drug release data ($M_t/M_\infty \leqslant 60\%$) were analysed according to Korsmeyer et al. [13] (1) and Peppas and Sahlin [14] Eq. (2):

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

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

where M_t/M_∞ is the fraction of drug released, k' is the kinetic constants 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 that exhibits controlled release. The equations 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 equation:

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

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 [15]. Therefore, only one more point after the 85% of drug has released, and it was used for the equation.

The tortuosity was calculated using the Higuchi equation [16]:

$$Q = \left[\frac{D\varepsilon C_s}{\tau}(2A - \varepsilon C_s)\right]^{1/2} \tag{4}$$

where Q is the quantity of drug released per exposed area at time t, D is the effective diffusion coefficient of drug in dissolution medium, ε is the porosity of the matrix and τ the tortuosity, C_s is the solubility of drug in the dissolution medium and A is the initial concentration of drug in the matrix. The approximate values for the apparent diffusion coefficient D', expressed as D/τ, were calculated.

2.2.4. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. An adequate number of modules ($n = 5$) per formulation were tested. Working pressures covered the range 0.1–60,000 psi, and the mercury solid contact angle and surface tension were considered to be 130° and 485 nM m^{-1}, respectively. Total porosity and pore size distribution were determined for each module tested.

3. Results and discussion

3.1. Drug release of modules

Two differently shaped Dome Matrix® modules were manufactured in this study: a "female" module (F) and "male" module (M) (Fig. 1). The modules have been designed to obtain their assemblage by interlocking the disc bases. As the picture shows, the protrusion on the concave base rim of one module, identified as male, was designed in order to fit the concavity on the base of a module without protrusion on concave base rim, identified as female. Facing the concave base of a male module to concave base of a female one and exerting a light pressure, the two modules interlock by clicking giving rise to an assembled system characterized by the presence of an empty internal space. In this paper, only non-assembled modules have been studied.

The Riboflavin-released profiles of female and male modules containing HPMC or tapioca starch copolymers oven-dried (OD-TSEMA) or freeze-dried (FD-TSEMA) are reported in Fig. 2. The release studies were performed over 24 h. Faster release of the drug was observed for the modules containing HPMC, compared to the modules of TSEMA. Moreover, both shaped HPMC matrices showed linear release of Riboflavin, and the drug release from female modules was faster than from the male ones ($f_2 > 50$).

Modules of TSEMA were associated with slower drug release rate and different mechanism of delivery by comparing with the modules containing HPMC. Using f_2 analysis, significant biopharmaceutical differences were found between the two polymer modules (female HPMC/female OD-TSEMA $f_2 = 34.33$; male HPMC/male OD-TSEMA $f_2 = 31.98$; female HPMC/female FD-TSEMA $f_2 = 27.99$; male HPMC/male FD-TSEMA $f_2 = 28.89$).

This difference was due to the swelling characteristics of hydroxypropyl methylcellulose, determining the formation of a gel non-enough resistant to prolong drug release for the duration provided by the graft copolymer matrices. In fact, matrices made of TSEMA copolymers (Fig. 4a and c) remained nearly intact during release process, while matrices of HPMC showed complete dissolution. The non-disintegrating behaviour and slow drug release of

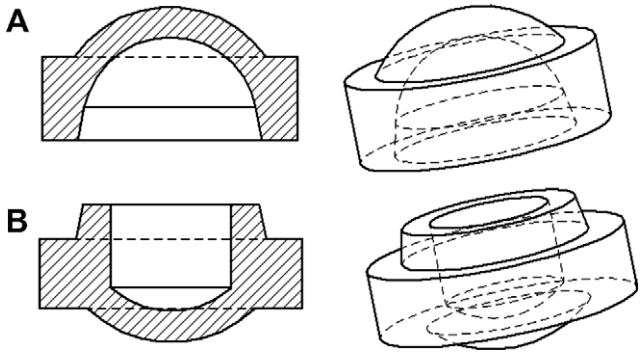

Fig. 1. Dome Matrix® modules designed for concave-to-concave assembling. The protrusion on the rim of concave base of the module B (male) interlocks inside the concave base of module A (female).

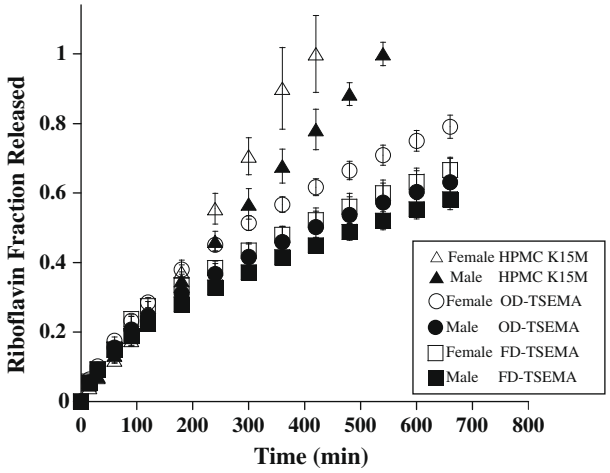

Fig. 2. Riboflavin fraction released versus time of Dome Matrix® modules using HPMC K15M, OD-TSEMA or FD-TSEMA (mean ± standard deviation, $n = 3$).

OD-TSEMA and FD-TSEMA modules lead to consider that the small particles of these tapioca starch copolymers have important binding properties. No swelling or erosion was observed (the module diameter remained fairly constant) (Fig. 4a and c). The inert behaviour of both module shapes was also supported by the hydrophobic character of these copolymers [5].

Considering the different module shape, a faster drug release for HPMC and TSEMA female modules in comparison with male ones was found, but the differences were not biopharmaceutically relevant. The higher release rate of Riboflavin from the female modules of tapioca polymers compared with the males was related to their higher porosity, different matrix shape and surface area (female: 185 mm^2; male: 182 mm^2).

With respect to the drying methods used for copolymer preparation, TSEMA copolymers dried in vacuum oven (OD) showed a slightly faster release than freeze-dried ones (FD), but in this comparison, the f_2 values indicated similarity between release profiles of female and male modules.

Fig. 3 illustrates the Riboflavin fraction released from modules containing THSEMA copolymers based on tapioca hydroxypropyl-starch. Drug release profiles of both oven-dried (OD-THSEMA) and freeze-dried (FD-THSEMA) until 60% of drug released were steeper than the reference HPMC matrix profiles illustrated in Fig. 2. This was totally different from the performance of TSEMA matrices that showed release profiles significantly lower than HPMC matrices. Therefore, matrices made with THSEMA copolymers in comparison with the matrices containing TSEMA (see Fig. 2), for the corresponded drying method and shape, exhibited a largely significant faster release. The differences of drug release from THSEMA and TSEMA copolymers, both male and female modules, were biopharmaceutically relevant (female OD-THSEMA/female OD-TSEMA $f_2 = 47.67$; male OD-THSEMA/male OD-TSEMA $f_2 = 21.14$; female FD-THSEMA/female FD-TSEMA $f_2 = 23.22$; male FD-THSEMA/male FD-TSEMA $f_2 = 13.67$).

These significant differences were the consequence of the erosive behaviour of THSEMA modules as evidenced from the pictures taken after 24 h (Fig. 4b and d). Erosion tendency of THSEMA with respect to TSEMA suggests a less efficient inert matrix formation. Actually, the THSEMA modules have been prepared with copolymer powders exhibiting larger particle size (d_{50}OD-TSEMA = 138 μm; d_{50}FD-TSEMA = 125 μm; d_{50}OD-THSEMA = 346 μm; d_{50}FD-THSEMA = 377 μm) [5] so reducing the efficiency of the compaction level in making a resisting matrix for the release process. For inert matrices, the compressibility and the size of particles of matrix forming polymer are relevant parameters because of their influence on

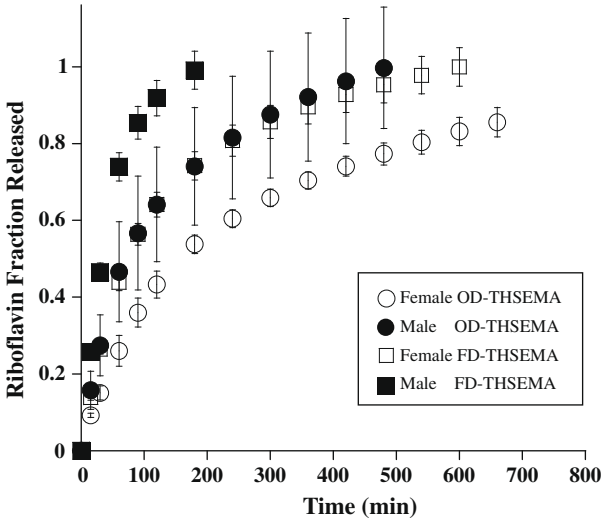

Fig. 3. Riboflavin fraction released versus time of Dome Matrix® modules using OD-THSEMA or FD-THSEMA (mean ± standard deviation, $n = 3$).

porosity and tortuosity of the matrix. This worst compressibility behaviour of THSEMA polymer in comparison to TSEMA was already noticed in a previous paper [5]. For hydrophilic swellable matrices, these parameters have less importance, whenever the pressure is enough to avoid matrix disintegration.

Different from the female modules prepared with TSEMA that released the drug faster than the male modules, female modules of THSEMA showed a release rate slower than the corresponding male ones. This could be attributed to the structure and shape of matrix in relation with its erosive behaviour. A more significant difference between the OD and the FD polymers than the one observed with TSEMA was also showed. Freeze-dried copolymer modules were more sensitive to erosion, and the release profiles were steeper. These differences in drug release for the FD and OD polymer male and female matrices were biopharmaceutically relevant.

3.2. Analysis of drug release

Release data analysis was carried out according to Korsmeyer–Peppas [13] and Peppas and Sahlin [14] equations. Parameter values are listed in Table 2. Peppas [17] claimed that the Eq. (2) 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 of the shape of the matrix, the diffusional exponent n values were calculated (Table 2). In relation with Peppas 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) around 3, the m value used was 0.44 [14]. The determination coefficient (r^2) was used to test the fitting of the release models.

In general, the data of all matrices provided good fit to the different models (Table 2). In the case of HPMC modules, the n values from Korsmeyer equation (female $n = 0.924 \pm 0.005$, male $n = 0.840 \pm 0.105$) indicate anomalous (non-Fickian) transport as evidenced by the linear release profiles [18,19]. The negative values of k_d and the high values of k_r in Peppas–Sahlin equation confirm the drug release mechanism controlled by polymer relaxation or erosion [20]. Moreover, the release parameters are according with the shape of profiles showed in Fig. 2 and the complete dissolution of the HPMC at the end of the study.

In the case of TSEMA graft copolymer, n diffusional exponents were in the range 0.608 ± 0.038 and 0.699 ± 0.032, indicating a pseudo-Fickian transport [18,19]; while in the THSEMA copolymer modules, the diffusional exponents between 0.726 ± 0.109 and 0.854 ± 0.104 indicated a more anomalous Fickian transport. However, we observed a less accurate fit to Korsmeyer equation than to binomial model. So, the higher accurate fit to Peppas equation is due to the better adaptability of the binomial equation to fit the release data. The prevalence of k_d over k_r revealed that the drug release mechanism was controlled mainly by drug diffusion in case of tapioca starch copolymers. However, in case of HPMC modules, the k_r was one order of magnitude higher than the THSEMA and TSEMA copolymer modules, supporting the quasi-linear release profiles. The higher k_d values of THSEMA respect to TSEMA were in accordance with the profiling of the respective release curves.

The methodology for the application of Peppas equation [14] proposes the determination of R/F (relaxation/diffusion ratio) parameter. However, due to the negative values of k_d or k_r obtained in some cases, this datum was not calculated. Ford et al. [21] and Ferrero et al. [22] have also obtained negative values for k_r in tablets prepared with HPMC and promethazine hydrochloride and methyl methacrylate copolymers with theophylline, respectively, and considered that the relaxation transport, instead of being additive term, was inhibiting the drug release.

3.3. Mercury porosimetry measurements

The pore size distribution profiles of the matrices prepared with the two copolymers were unimodal for all cases. Other authors have also detected unimodal distributions for matrices prepared

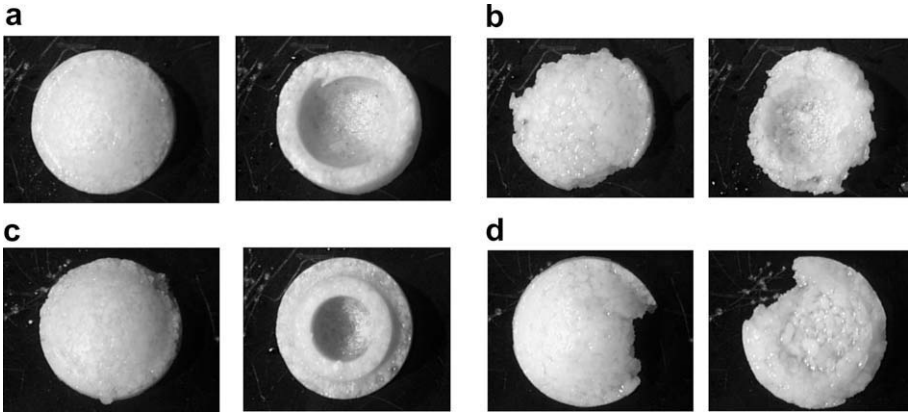

Fig. 4. Photographs of Dome Matrix® modules after 24 h of dissolution: OD-TSEMA female (a) and male (c); OD-THSEMA female (b) and male (d).

Table 2
Mathematical modelling and drug release kinetics from Dome Matrix® modules using Peppas and Sahlin equation with $m = 0.44$.

Modules	Korsmeyer et al. equation		Peppas and Sahlin equation		
	$n \pm 95\%$ confidence interval	r^2	k_d	k_r	r^2
HPMC					
Female	0.924 ± 0.005	0.9859	-5.5×10^{-2}	8.1×10^{-3}	0.9943
Male	0.840 ± 0.105	0.9947	-1.4 x 10^{-2}	4.6×10^{-3}	0.9998
OD-TSEMA					
Female	0.699 ± 0.032	0.9980	3.6×10^{-2}	9.2×10^{-4}	0.9985
Male	0.642 ± 0.106	0.9947	3.7×10^{-2}	2.5×10^{-4}	0.9999
FD-TSEMA					
Female	0.650 ± 0.064	0.9871	4.4×10^{-2}	-2.9×10^{-5}	0.9966
Male	0.608 ± 0.038	0.9958	2.9×10^{-2}	3.8×10^{-4}	0.9999
OD-THSEMA					
Female	0.729 ± 0.028	0.9963	5.7×10^{-2}	9.9×10^{-4}	0.9951
Male	0.726 ± 0.109	0.9906	13.4×10^{-2}	-2.6×10^{-3}	0.9911
FD-THSEMA					
Female	0.784 ± 0.222	0.9894	11.1×10^{-2}	3.1×10^{-4}	0.9999
Male	0.854 ± 0.104	0.9999	17.7×10^{-2}	-3.4×10^{-3}	0.9999

from acrylic polymers [5,9,23,24]. Confronting the porosity (Table 3) of the matrices with the release rate, a difference in behaviour between the male and female modules could be observed. In order to illustrate the relationships among the polymer type, drying method of copolymers and module shape, we constructed a graph (Fig. 5) in which the experimental points have been placed in the design space delimited by the time of 50% of drug release (T50%) and total porosity. According with the results observed in dissolution tests, THSEMA modules (female and male) are in the lower part of the design space, the HPMC modules in the middle and the TSEMA modules in the upper part of the plot. However, although it could be expected a correlation between T50% and porosity (low T50% when increase the porosity), this behaviour was only observed in the case of FD respect to OD-THSEMA female modules and OD respect to FD-TSEMA female modules. On the contrary, in case of male modules, the situation was reversed, in the sense that higher porosity entailed higher T50% (OD respect to FD-THSEMA and FD respect to OD-TSEMA male modules). As deduced by this discussion, the relationship between release rate and porosity was complex due to the shape and to the described erosive behaviour of certain modules, and it was not possible to draw a general correlation.

So, to interpret the release rate and kinetics, Table 3 shows the approximate values for the apparent diffusion coefficient D', obtained from Higuchi rate constant. D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium. High apparent diffusion coefficient values (D') correspond to small matrix tortuosity. This parameter was in agreement with drug release, considering that the disintegrating OD-THSEMA and FD-THSEMA modules showed the lowest tortuosity values. Also, the highest tortuosity in OD respect to FD-THSEMA and FD respect to OD-TSEMA male modules was consistent with the lowest release of these matrices.

Table 3
Porosity (%) of Dome Matrix® modules calculated by mercury intrusion–extrusion porosimetry and apparent diffusion coefficients (obtained from Higuchi rate constant) for drug release studies and time for 50% of drug released calculated with Korsmeyer equation. Values in brackets represent the standard deviation ($n = 2$).

Modules	Porosity (%)	$D' \times 10^{-3}$(cm^2/min)
HPMC		
Female	33.26 (0.73)	3.34
Male	13.58 (0.67)	8.03
OD-TSEMA		
Female	35.00 (0.58)	2.08
Male	11.87 (0.76)	4.40
FD-TSEMA		
Female	25.35 (0.56)	1.95
Male	24.77 (0.70)	1.67
OD-THSEMA		
Female	9.30 (0.81)	15.60
Male	15.59 (0.77)	25.19
FD-THSEMA		
Female	28.24 (0.68)	12.88
Male	14.02 (0.63)	86.44

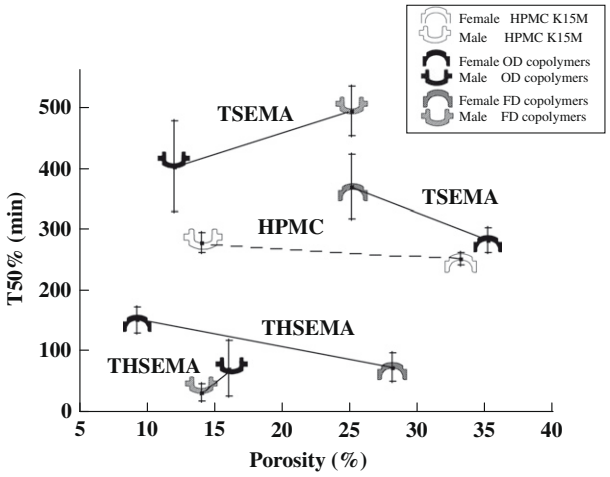

Fig. 5. Time of 50% Riboflavin released versus total porosity of Dome Matrix® modules using HPMC K15M or graft copolymers (mean ± standard deviation, $n = 3$).

Consequently, the combination of porosity and tortuosity data explained the drug release observed.

4. Conclusions

This study demonstrates the possibility to manufacture Dome Matrix® modules with inert polymers characterized by low content in the composition of the modules. The use of tapioca starch copolymers allowed to obtain different drug release rate related to the type of polymers contained in the modules. Using the hydroxypropylmethylcellulose K15M modules T50% as reference, the tapioca THSEMA modules released the drug faster, while the TSEMA modules drug released rate was slower compared to the reference. The HPMC showed a released behaviour between the two tapioca copolymers studied.

Different drug release mechanisms between the HPMC or new graft copolymers matrix/modules were demonstrated: HPMC clearly controlled the drug release by polymer swelling, whereas with TSEMA and THSEMA, the drug release mechanism was mainly controlled by drug diffusion.

The module shape or copolymer drying method affected the drug release mechanism and rate: in the case of the THSEMA, erosive male modules, in spite of their lower surface, showed a faster release than female ones; in this case, the freeze-dried copolymer determined faster release than oven-dried ones. On the contrary, in the case of TSEMA modules, female modules had faster release rate than male ones, and the oven-dried copolymer was associated with faster release rate. Both situations were linked to porosity and tortuosity values of the matrices.

This paper indicates that tapioca starch copolymers can modulate in a significant range the Riboflavin release in Dome Matrix® modules manufactured by direct compression, opening interesting perspectives in case of module assemblage.

In a future paper, the interlock of these female and male modules to make the void configuration with flotation characteristics will be studied in order to know the impact of the module assemblage on controlled release gastro-retentive dosage forms.

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