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Research paper

Assemblage of drug release modules: Effect of module shape and position in the assembled systems on floating behavior and release rate

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ABSTRACT

The aim of this work was to study the clindamycin release kinetics from floating delivery systems consisting of two modules assembled in void configuration, according to the modified release technology platform known as Dome Matrix®. Two modules differently shaped, i.e., female and male, formulated as swellable matrices and containing clindamycin, were assembled by friction interlocking. Then, by stacking additional female modules without drug on the assembled two-module floating system, modulation of clindamycin release rate and kinetics was attained. The additional modules stacked on the assembled system acted as a transient barrier to clindamycin release from the void configuration. Inertness, dissolution/erosion or swelling behavior characterized their performance as matrices in simulated gastric fluid.

In particular, we found that stacking additional barrier modules on the bases of void configuration, the drug release rate and kinetics of the assembled system were modified in dependence on the composition of module added. In particular, the quickly soluble module exerted an influence on the release rate in the late time of delivery. The swellable module produced a significant reduction in release rate of void assembly, but the release mechanism remained the same. Finally, the inert module led to a substantial linearization of the release profile with a minimal reduction in release rate.

1. Introduction

In the last few decades, several oral prolonged release formulations have been developed to decrease dosing frequency and to enhance patient compliance [1,2]. Drug bioavailability of prolonged release oral systems is influenced by the gastrointestinal (GI) transit time of the dosage form. Gastro-retentive drug delivery systems offset this problem since a more predictable GI transit can be expected by prolonging the residence time in the stomach. Beside the effects related to local drug delivery, prolonged gastric residence increases the bioavailability of drugs having absorption window in the upper intestinal tract and improves the release of those that are less soluble in neutral pH environment [3–5].

The retention of a drug delivery system in the stomach can be based on several approaches. They may be classified into high-density (sinking) or low-density (floating) systems, expandable or super-porous hydrogel systems, mucoadhesive or magnetic systems [6–8]. In this work, we studied a floating drug delivery system obtained from release modules, consisting in tablets having concave/convex bases assembled by friction interlocking to form a firm structure [9–12]. This allows to build up a time and space modified release system combining different drugs in one "pill", having versatility in drug release kinetics and modulation of dose administered [13].

Assembling concave-to-concave bases of two differently shaped modules, male and female, a "void configuration" assembly was obtained. Systems in this configuration were immediately floated in water and provided in humans a gastro-residence up to 4 h [11]. Several modules containing the same or different drugs could be assembled to construct differently shaped systems.

In a previous paper, the release rate and behavior of male and female modules containing clindamycin and their assemblage in floating void configuration have been studied [14]. It would be now interesting to study the drug release kinetics from void assemblage of clindamycin modules in which the releasing area of the system has been modified by permanent or non-permanent presence of additional modules.

Therefore, the aim of this research was to study the clindamycin release kinetics from swellable floating delivery systems made with two Dome Matrix® modules assembled concave-to-concave bases. We attempted to modify the drug release kinetics by

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stacking, on one or both convex bases of void configuration, additional modules without drug. The intention was to create a barrier capable to introduce a geometric control on drug release kinetics. Hence, modules without drug and formulated using swellable, inert or soluble components were manufactured. These "barrier modules" stack on the void configuration could affect its swelling and release rate, thus modulating drug delivery. The objective was to change the external surface of the void configuration in such a way to reduce the releasing surface in a permanent or transient manner. The effect of these additional modules on the clindamycin release rate from void configuration was studied.

2. Materials and methods

2.1. Materials

Clindamycin phosphate (batch n. 29100804, Lisapharma, Erba, Italy) was chosen as model drug; hydroxypropylmethylcellulose (HPMC, Methocel® K100M, Colorcon, Gallarate, Italy), cellulose acetate propionate (CAP 482-20, Eastman Kodak, batch BP 978213) and mannitol (Lisapharma, Erba, Italy) were used as swellable, inert and soluble excipient, respectively, to prepare the drug-free barrier female modules. Dicalcium phosphate (Merck, Germany), polyvinylpyrrolidone (PVP, Kollidon® K30, BASF, Dortmund, Germany), magnesium stearate (ACEF, Fiorenzuola, Italy, batch C1402005) and talc (ACEF, Fiorenzuola, Italy, batch C5239004) were used for manufacturing the modules. Sodium chloride anhydrous (ACEF, Piacenza, Italy) and hydrochloric acid 37% (v/v) were used to prepare the simulated gastric fluid corrected at pH 1.2 with sodium hydroxide (Carlo Erba S.p.A., Milan, Italy). All other chemicals were HPLC grade.

2.2. Methods

2.2.1. Manufacturing of female and male modules containing clindamycin

Swellable matrix tablets containing clindamycin were made by conventional wet granulation and tabletting methods. Drug and HPMC were kneaded using a 10% (w/v) PVP K30 solution in ethanol:water (50:50). After granulation through a 0.8-mm mesh, the granules were dried for 6 h (50 ± 3 °C) in a static oven at 5% RH. The moisture content of granules, evaluated by Karl Fischer titration (Crison Instrument, S.A., Barcelona, Spain), was 5.4%. The granules were blended in a Turbula equipment (WAB, Basel, Switzerland) with magnesium stearate and talc and compressed in a single-punch tabletting machine (EKO Korsch, Berlin, Germany) using 7.4 mm diameter having appropriately designed tip surface for manufacturing convex or concave faces. Two different modules were manufactured for void configuration, using female or male module punch sets. For each module, 120 mg of mixture was weighed and manually introduced into the die. The radial crushing strength of the compressed modules was kept between 15 and 20 N. The assemblage (void configuration) was obtained by manual friction interlocking of two modules with the concave bases facing each other, creating a void space inside the system. A sinkable assembled system was obtained by filling the internal void space with glass beads. The composition of female and male modules containing clindamycin is summarized in Table 1.

2.2.2. Manufacturing of swellable, inert and erodible female modules without drug

An inert polymer, a swellable polymer and soluble/erodible substances were used to produce the three different female barrier modules. All excipients were weighed accurately and mixed in the Turbula mixer for 20 min. One hundred and twenty milligrams of powder was weighed and then directly compressed using a 7.4-mm female module punch set. The composition of the female barrier modules is detailed in Table 1.

Table 1
Composition of the male and female clindamycin modules and inert barrier modules.

Composition	Male or female module (mg)	Female barrier module (mg)
Clindamycin phosphate	80	–
PVP K30	3.3	–
HPMC K100 M	27	67.0[a]
Mannitol (soluble)	–	67.0[b]
Cellulose acetate propionate (inert)	–	67.0[c]
Dicalcium phosphate	–	48.0
Talc	3.6	3.6
Magnesium stearate	1.1	1.2
Dye (yellow Lake)	–	0.2
Residual water	5.0	–
Total weight	120	120

[a] Swellable module.
[b] Soluble module.
[c] Inert module.

2.2.3. Drug release rate determination

The drug release test was performed using the USP apparatus 2 (Erweka DT6R, Heusenstamm, Germany) with paddles rotating at 50 rpm. The dissolution medium consisted of 900 ml of simulated gastric fluid (SGF) without enzymes (pH 1.2) maintained at 37 ± 0.5 °C. Experiments at pH 3.0 were performed as well for approaching fed conditions. Samples (5 ml) were withdrawn at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480 min and replaced by an equivalent volume of fresh dissolution medium. Pictures of assembled systems were taken at fixed times during release experiments. The release studies were conducted in triplicate. Samples were filtered through a 0.45-μm membrane and analyzed by HPLC. The HPLC assay was performed using a mixture of 0.01 M potassium phosphate monobasic and methanol (40:60 v/v) as mobile phase, pumped at a flow rate of 1.0 ml/min by a LC-10AS pump system (Shimadzu, Japan). The stationary phase was a C18 column (3.9 × 300 mm, Waters Corp., Milford, MA, USA) kept at room temperature. The injection volume was 50 μl. UV absorbance was measured at 210 nm by an UV–Vis detector (SPD-10A, Shimadzu, Japan). The analytical method used for the assay of clindamycin phosphate was validated with respect to precision (repeatability, reproducibility), accuracy, specificity, linearity and range. Linearity of the response was confirmed in the concentration range 0.019–0.562 mg/ml. None of the excipients interfered with drug quantification, proving the specificity of the method. The values of relative standard deviation for repeatability and reproducibility were less than 2% (for $n = 6$ injections).

The Peppas and Sahlin binomial equation (Eq. (1)) was used to fit drug release data in range 5–60% [15]:

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \quad (1)$$

where M_t/M_∞ is the fraction of drug released, t is the release time, k_d the constant of diffusion contribution, k_r the constant of relaxation contribution and m is the Fickian diffusion exponent. In this study for the analysis of the void configuration with one or two additional barrier modules, the diffusional coefficient m [16] was set to 0.44 in dependence of the matrix aspect ratio. Eq. (1) allows to calculate the fraction of drug released due to Fickian mechanism (F) according to Eq. (2):

$$F = \frac{1}{1 + \frac{k_r}{k_d} t^m} \quad (2)$$

2.3. Data analysis

In this study, all the numerical results were showed as mean value ± standard deviation. The similarity test was used for assessing the relevance of the differences between release curves. Release profiles were compared using similarity factor, f_2, calculated according to the following Eq. (3):

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

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

Male and female Dome Matrix® swellable modules of clindamycin similar as composition to the clindamycin prolonged release modules previously studied for malaria combination product were prepared [14]. Briefly, each module contained 80 mg of clindamycin phosphate. The male and female module shapes differed for the annular protrusion present on the rim of the concave base of the male module (Fig. 1a and b). Both the convex and concave bases of these modules were complementarily designed in order to assemble them by interlocking of the appropriate bases. In the present study, we focused on the void configuration assembly obtained by friction interlocking of the concave base of one male with the concave base of one female module (Fig. 1c). This assemblage had an apparent density lower than the dissolution medium due to the presence of an internal empty space. As a consequence, the void assembly floated immediately after introduction in the medium, releasing the drug content during floatation.

The floating behavior of the assembled system and the in vitro drug release profiles of the non-assembled modules have been described in previous papers [11,14]. In the present paper, the release of clindamycin from the void configuration system (Fig. 2) was approximately 80% after 8 h in SGF pH 1.2. The release profiles of this floating system and of a same one but sinkable in the medium were compared. The part of the system remained during floatation non-surrounded by the medium produced a slightly lower release profile of the floating system in the dissolution paddle apparatus. In fact, the f_2 factor determined comparing the two clindamycin profiles was 44.5 indicating a borderline similarity. The release of

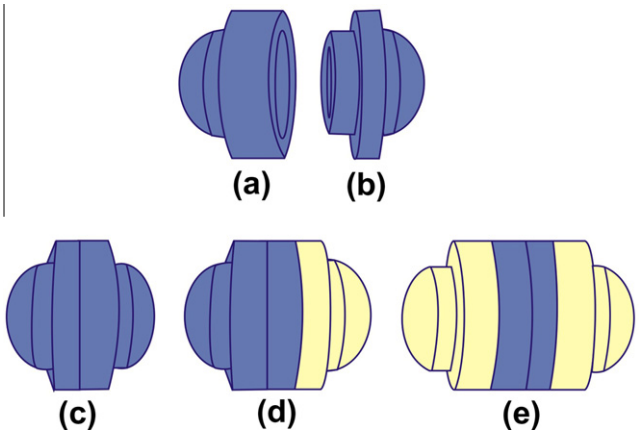

Fig. 1. Schematic of female module (a), male module (b), void configuration assembly, made by sticking male and female modules concave base to concave base (c). Assembled systems with additional barrier module to one (d) or both (e) convex bases of void configuration.

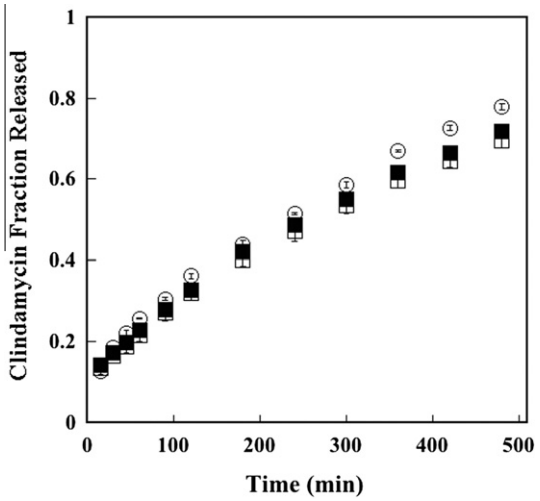

Fig. 2. Clindamycin fraction released from the void configuration system (○), with one (□) and two (■) additional soluble barrier modules (mean ± SD, $n = 3$).

clindamycin floating system was also determined at pH 3.0 in order to account for dissolution in gastric fed state conditions. The release profile at pH 3.0 was superposed to the one obtained at pH 1.2, likely due to the high solubility of clindamycin and non-sensitivity of HPMC to pH.

Then, we studied the effect on clindamycin release rate of additional modules stacked on this void configuration assembly. These not containing drug modules were added in order to obtain a more linear drug release profile from the void configuration, introducing in the assembly a transient barrier effect on drug release. Since the void configuration was obtained by assembling concave-to-concave bases of a male and a female module, two convex bases remained unengaged in this assembly (Fig. 1c). Thus, one or two additional female modules could be stacked on these convex bases of the void configuration, altering the geometry of the system. The new female modules without drug were stacked by clicking their concave base on the convex bases of void assembled system; in this way, part of the release surface of the void assembly exposed to the medium was masked by the presence of the additional barrier module on one (Fig. 1d) or both (Fig. 1e) convex bases. The size of the assembly was smaller than a CONI_SNAP 00 gelatin capsule (Capsugel, B) that could contain until six assembled modules.

In detail, three types of barrier module were prepared, each one characterized by a different behavior in the dissolution medium, namely swellable, inert and dissolving. The first type of barrier module was prepared with HPMC and the module behaved as a swellable matrix. The second barrier module, formulated with cellulose acetate propionate (CAP) polymer, had the characteristics of an inert matrix, whereas the third type made of mannitol rapidly dissolved.

Differently from the immediately floating two-module system in void configuration, the systems comprising the additional modules sank in dissolution vessel. However, after a period of time that varied between 5 and 50 min in dependence of the type of module added, the system regained floatation. Clearly, the buoyancy force provided at the beginning by the void configuration system was not enough to bear the weight of the additional modules on water surface. Recovery of buoyancy was due to the change in the structure and density of the assemblage during immersion in medium.

In the systems obtained by stacking soluble barrier modules on one or both convex bases of the void configuration, these additional modules dissolved in the SGF in less than 15 min. Thus, the soluble barrier modules remained on the surface of the void configuration system for a short time. The result was that they

exerted small influence on drug release rate in the early time of delivery, although lower release profiles at times longer than 300 min were observed (Fig. 2). In fact, at 8 h, the amount released from the simple void configuration was around 80%, whereas this percentage was reduced to 74% and 70% with one or two additional soluble barrier modules, respectively. However, the difference between one and two additional modules was not highly significant (void configuration versus void configuration with one additional module $f_2 = 64.08$; void configuration versus void configuration with two additional modules $f_2 = 70.02$). To identify the release mechanism, we used the Peppas–Sahlin binomial equation, allowing the determination of contribution of diffusional and relaxational mechanisms to clindamycin release. Knowing the coefficients k_d and k_r (Table 2), the Fickian fraction released was calculated. The result showed that drug release kinetics with additional soluble modules was less Fickian compared to the void configuration (Fig. 3). Finally, quickly soluble modules did not provide a relevant influence on clindamycin release rate and mechanism compared to the void configuration system. This has a practical consequence: no change of release rate from the void configuration should be expected in case of addition of a module containing an immediate release drug dose. However, the possibility exists to control the dissolution rate of soluble modules in order to modulate the drug release from the void configuration.

After stacking swellable barrier modules on one or both bases of void configuration, the assembled systems started to float with a delay of 5 and 10 min, respectively. The swellable barrier modules remained stacked on the void system until the end of the release test. In fact, these additional swellable modules were merged in the whole swollen assembled system that kept its integrity during drug release. The entanglement between the swollen polymer chains of additional module and the polymer chains of void configuration was responsible of this behavior (see Fig. 6). The release profiles of clindamycin from the system bearing the HPMC barrier modules are presented in Fig. 4. By stacking the concave base of one barrier module on one convex base of the void assembly, a three-module system was constructed. Now, in comparison with the two-module void configuration, a significant reduction in clindamycin release rate was achieved. After stacking a second barrier module on the other convex base of void assembly, the four-module system obtained exhibited further decrease in clindamycin release rate. The rate of drug release was modified because the added modules maintained covered part of the releasing surface area [18–20]. The analysis of release profiles for similarity using the f_2 parameter revealed that the release profiles of the system bearing one or two additional modules were significantly different from void configuration. Therefore, one or two additional swellable barrier modules clicked on the convex bases of void configuration determined a reduction in release rate directly related to the number of additional barrier modules. The consequence was the

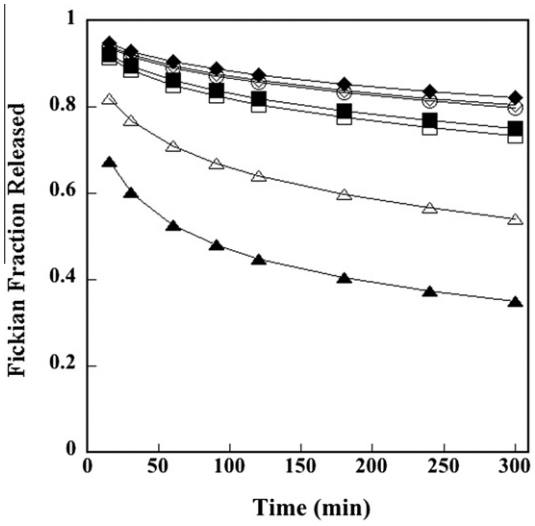

Fig. 3. Clindamycin Fickian fraction released from void configuration system (○); void configuration with one (◇) and two (◆) swellable barrier modules; void configuration with one soluble module barrier (□) and two (■) soluble barrier modules; void configuration with one (△) and two (▲) inert barrier modules. (The Fickian fraction released values have been calculated from the equation average parameters reported in Table 2.)

prolongation of the drug release time. Despite the reduction in release rate with the modules added, no difference in release kinetics was observed. This was demonstrated by the analysis with the Peppas and Sahlin equation, showing that the fraction of clindamycin released based on a Fickian mechanism from the systems with additional swellable barrier modules remained unchanged compared to void configuration (see Fig. 3). However, an evident biphasic release was determined by the addition of the swellable barrier modules. The explanation of the rate slow down in the second phase could be deducted from the picture in Fig. 6, where the swollen polymer of the barrier module extended on the release surface of the void configuration.

Using the inert type of additional modules, the assembled systems with one and two barrier modules took longer time to floatation (30 min and 50 min, respectively) in consequence of the reduced swelling of the void configuration part of the system. However, the novel result was that the additional inert modules did not remain stuck to the void assembled system during swelling of the latter, but were pushed away from the bases of void configuration after about 120–150 min. This unexpected detachment reconstituted the original delivery surface of the void assembly containing clindamycin that had been masked by the presence of the inert module. In the inert module, the polymer did not swell,

Table 2
Mathematical modeling of drug release kinetics of modules and assembled systems using Peppas and Sahlin equation. Data are expressed as mean ± standard deviation, $n = 3$.

Modules and assemblages	Peppas–Sahlin equation parameters		
	$k_d \pm$ SD	$k_r \pm$ SD	r^2
Female	$6.9 \pm 1.5 \times 10^{-2}$	$1.2 \pm 0.2 \times 10^{-3}$	0.9690
Male	$6.6 \pm 0.1 \times 10^{-2}$	$0.24 \pm 0.3 \times 10^{-3}$	0.9918
Void configuration	$3.5 \pm 0.3 \times 10^{-2}$	$0.68 \pm 0.2 \times 10^{-3}$	0.9993
Void configuration + one swellable barrier	$2.9 \pm 0.2 \times 10^{-2}$	$0.5 \pm 0.1 \times 10^{-3}$	0.9955
Void configuration + one soluble barrier	$3.0 \pm 0.06 \times 10^{-2}$	$0.8 \pm 0.5 \times 10^{-3}$	0.9973
Void configuration + one inert barrier	$2.3 \pm 0.2 \times 10^{-2}$	$1.5 \pm 0.1 \times 10^{-3}$	0.9940
Void configuration + two swellable barriers	$2.4 \pm 0.2 \times 10^{-2}$	$0.4 \pm 0.1 \times 10^{-3}$	0.9938
Void configuration + two soluble barriers	$3.1 \pm 0.04 \times 10^{-2}$	$0.8 \pm 0.3 \times 10^{-3}$	0.9965
Void configuration + two inert barriers	$1.4 \pm 0.07 \times 10^{-2}$	$2.0 \pm 0.5 \times 10^{-3}$	0.9863

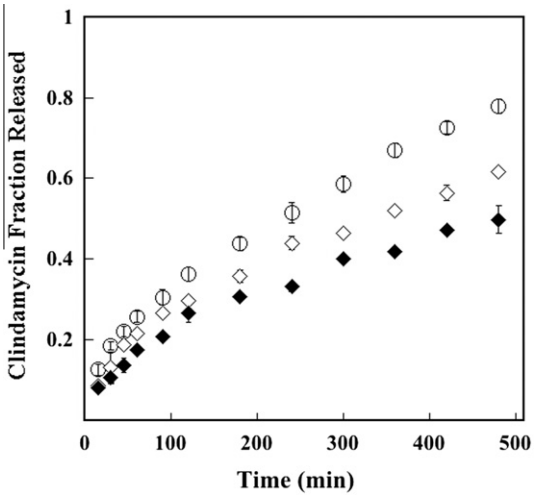

Fig. 4. Clindamycin fraction released from void configuration system (○) compared to void configuration systems with one (◇) or two (◆) additional swellable barrier modules (mean ± SD, $n = 3$).

without entanglement with the adjacent hydrated HPMC polymer chains. Therefore, the swelling pushed away the solid inert module. This phenomenon had a relevant effect on the release kinetics of clindamycin and on this result has to be focused the use of inert modules. In fact, examining the dissolution profiles obtained, the system assembled with inert barrier modules showed a drug release rate characterized by two delivery phases (Fig. 5). In the first phase, corresponding to the period of time during which the inert module was stuck to the void configuration, drug release rate was significantly slowed down compared to the void configuration. As a consequence, the typical drug burst release of swellable matrix systems was substantially reduced. Clearly, at the beginning, the swelling of void assembly was affected by the presence of the barrier module. The inert modules physically hindered the hydration process of void configuration by temporary covering its bases during release. When the added inert module(s) eventually detached after 120–150 min, drug release rate was sustained by the recovery of the whole surface of clindamycin-loaded modules. After the inert barrier modules were pushed away, the swelling of void assembled system recovered and sustained drug

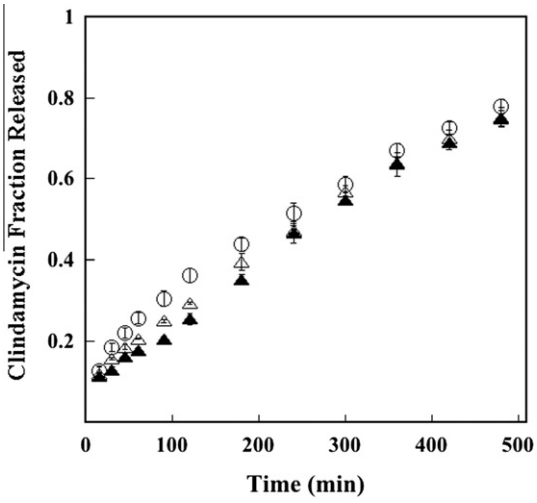

Fig. 5. Clindamycin fraction released from the void configuration system (○) compared with void configuration systems with one (△) and two (▲) additional inert barrier modules (mean ± SD, $n = 3$).

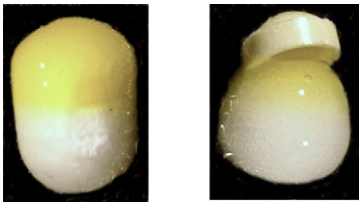

Fig. 6. Pictures of void configuration system with one additional module: (a) one swellable barrier module on the top (real thickness 14 mm); (b) one inert barrier module on the top (real thickness 14 mm). (Note: the yellow dye diffused from the barrier module to the adjacent module of the void configuration.)

release to a linear trend. In conclusion, considering the overall profile obtained, the release of clindamycin phosphate from the floating systems assembled with additional inert module(s) was remarkably linearized.

In summary, looking at the mechanism, clindamycin release from the assembled systems was predominantly under Fickian diffusion control when the additional modules were soluble or swellable. In the case of inert modules, their detachment after the first 2 h of dissolution promoted further swelling of the void configuration matrix and reduced the Fickian released fraction, driving clindamycin release towards linearity.

In the absence of in vivo data for the correlation with the in vitro rate and linearity, the release profiles of the void system and of systems with two swellable or inert barrier modules have been used for simulating the attainable plasma curves. PK parameters taken from literature [21] were employed using Stella simulation program [22]. The results show that the release profile obtained with the two swellable additional barriers provided a peak time shift of 2 h compared with the simulated plasma curve of the void configuration. The linear kinetic release profile of two inert barrier module assembled systems did not differentiate significantly from the void assembly in the plasma curve simulation.

4. Conclusions

In this study, assembled void configuration systems of female and male Dome Matrix® swellable modules made of HPMC and containing 80 mg clindamycin phosphate per module were successively reassembled by adding barrier modules without drug. This alteration of the geometry and composition of void configuration system proved to be able to modify the system typical drug release rate.

Additional female modules behaving as soluble, swellable or inert matrices, clicked on the base of void configuration, reduced the release surface and controlled the swelling phenomenon with consequent modification of drug release. This was particularly relevant when such additional modules were made of swellable or inert polymers. In contrast, an additional barrier module made of a soluble material did not substantially modify the release behavior of the void configuration, if the dissolution is fast.

When the dissolution profiles of the assembled systems with barrier modules were compared, the slowest drug release occurred in the assembled system with one or two additional barrier modules made of HPMC. The release kinetics of the system assembled with the inert additional modules showed a unique behavior: the inert modules were pushed away from the void assembly at a certain time, resulting in a subsequent acceleration of the drug release rate. The result was a quasi-constant release rate for at least 80% of drug released.

Hence, drug release from an assembled system in void configuration could be modulated by adding extra modules (one or two)

that interact differently with the void assembly. These additional modules might also contain other drugs.

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