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Evaluation of the drug release kinetics in assembled modular systems based on the Dome Matrix technology

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ABSTRACT: Mathematical models are an important tool in pharmaceutical formulations development, to evaluate *in vitro* and *in vivo* drug release processes and to optimize the design of new systems. Dome Matrix technology allows the combination of modules with different types of drugs, doses, and releases kinetics. This work aimed to design drug release systems based on Dome Matrix technology, with different swelling and erosion properties, to obtain complex drug release profiles and analyze them with simple mathematical models. Most of the release profiles followed a sigmoid curve, with an inflection point corresponding to a change in the release rate behavior. The experimental data were fitted with a simple model recently developed, named the Dual Release model, which consists in the combination of a modified Korsmayer-Peppas model from the beginning to the inflection point and the Lumped model from there until the end. This approach allowed determining relevant pharmaceutical parameters, such as the maximum release rate and the dissolution efficiency, among others. The use of the Dual Release model and the pharmaceutical parameters that characterize the different Dome Matrix modules allows optimizing the choice of the composition and the configuration during the development of a drug delivery system.

Keywords: release rate; mathematical models; dual release model; drug delivery.

INTRODUCTION

In 2006, Colombo and collaborators developed an innovative modular technology platform suitable for assemblage into drug delivery systems. Each module consists of a cylindrically shaped tablet, with one of the bases concave and the other convex[1,2]. Since the axial section of the modules appears as a cupola, such modular technology platform was named Dome Matrix. The individual modules are designed to allow the convex base of one module to be inserted into the concave base of another. This modular technology platform allows modifying the kinetics of drug release through the assembly of the modules containing the drug(s), constituting a single system for controlled drug release for oral administration (Figure 1)[2,3].

//Insert Fig. 1//

A single Dome Matrix module has a comparable surface area to that of a flat-based conventional tablet[2]. The shape of the modules facilitates the assembly of two or more units by stacking, thus obtaining multiple module systems. When the convex face of one module is stacked into the concave face of the adjacent one, the piled configuration is obtained; while the void configuration consists of a peculiar assembly formed by stacking two modules through their concave bases (Figure 1). This latter configuration is characterized by an inner space, providing the assembly with the potential to work as a floating drug delivery system and thus providing, after administration, gastroretention and site-specific drug release, assuring drug absorption in the upper part of the gastrointestinal (GI) tract. On the other hand, the assembly of two modules formulated as hydrophilic matrices, in a piled configuration reduces the available surface area for drug release more than the void configuration if compared to the surface area of the two separated modules[2]. This implies that the piled configuration is potentially useful as a sustained-release drug vehicle, whereas the void configuration can be applied as a buoyant gastro-retentive dosage form. The void space in the assembly generates buoyancy forces that can keep the matrix afloat for as long as 8 hours; then, erosion or disintegration process supersedes the floating behavior[4,5]

Dome Matrix technology shows definite advantages as a drug delivery system when compared to traditional controlled-release tablets. It is such a versatile system that allows the combination of modules loaded with different types of incompatible drugs, different doses, and even providing multiple release kinetics in a single unit. The planned therapeutic regimen and the drug release kinetics can be adapted according to the disease status and the convenience of healthcare/patient

management simply by changing the number and type of modules constituting the personalized system[5-7].

Mathematical models are an important tool to evaluate drug release processes both *in vitro* and *in vivo* and, in general, to optimize the design of new pharmaceutical drug delivery systems[8]. They also allow determining some important parameters related to the physicochemical phenomena (for example, drug diffusion coefficient)[9] and of pharmaceutical relevance (such as the dissolution efficiency). It is very important to know how to use these equations to understand the different factors that affect the dissolution rate and how dissolution behaviors can vary and influence the efficiency or therapeutic regimen of patients.

Since the Higuchi model[10,11], various mathematical models were proposed to fit data from drug release profiles[12], such as the semiempirical equation, called the power-law model, presented by Peppas and Sahlin[13], or other models developed for specific drug delivery system geometries[14-17]. However, these models are usually useful to fit only the data up to 60% of the drug released over time. We recently developed a mathematical model, named the Lumped model, based on second-order kinetics, that groups different transport steps involved in the drug release processes[18,19]. Although the Lumped model fits properly *in vitro* experimental data across the entire drug release profile, neither this nor the other models can fit data following sigmoid profiles, where the release rate increases over time up to an inflection point and decreases thereafter. In this regard, the cumulative Weibull function model[20,21] was used to describe sigmoidal profiles of drug release over time, among other types of observed complex phenomena. However, important differences were observed in several studies between the experimental data and the values estimated by the Weibull function, mainly at the beginning (up to 10% of drug released) and at the end (after 70% of drug released) of the release profile. Considering this limitation, we developed a new model, named Dual Release model, able to fit experimental data from sigmoid profiles of the cumulative amount of drug release versus time with very low standard error (s≈1%) and correlation coefficient higher than 0.99[22]. Moreover, the Dual Release model can be used to fit peculiar cases, such as experimental release data from profiles where the release rate increases constantly with respect to time until total drug release.

Dome Matrix modules have been usually manufactured by tableting using cellulose derivatives or polyethylene oxide polymers[4,5], since they form a monolithic system when the drug is dispersed into them and the powder tableted. Among cellulose derivatives, hypromellose or hydroxypropylmethylcellulose (HPMC) is used from 10% up to 80% w/w for controlled drug release in solid dosage form, and as a coating for tablets and pellets[23-25]. When in contact with the dissolution medium, HPMC matrix hydrates and swells forming a gel layer on the surface that

moves towards the core[26-28]. Gel erosion takes place thereafter and may occur simultaneously with the subsequent phases of hydration and swelling of the matrix[28]. The swelling and erosion properties of a solid matrix made of HPMC have a strong influence on its drug release kinetics.

In this work, HPMC matrices were designed based on Dome Matrix technology containing riboflavin as a hydrophilic model drug. By varying the ratio of two HPMCs with different molecular weights and viscosities, modules with dissimilar swelling and erosion properties were obtained. Also, the release behavior of matrices of single configuration was compared with the presented by matrices of piled and void configurations prepared with two modules. In this way, complex drug release profiles were achieved, which were analyzed with simple mathematical models that allow to predict their behavior and explain the phenomena involved in the release process.

MATERIALS AND METHODS

Materials

Riboflavin (Rb) (Universal®, Roche, batch number: UQ11022019), Methocel® (HPMC) CR premium K100LV and K15M with molecular weights of approximately 25 and 120 kDa[29], respectively (Colorcon, Orpington, Eng, batch numbers: MM90041321K and NH16012N11), Lactose Spray Dried (90 – 150 µm, Chiesi, Parma, It.), Polyethylenglicol (PEG) 6000 (Hoechst AG. Werk Gendorf, Ger.), Kollidon® K25 (BASF, Ger, batch number: 09-8760) and magnesium stearate (Eigemann & Veronelli Spa., Mi, It., batch number: 24762) were used for matrices preparation. All other reactive and solvent used were p.a. quality and water and ethanol distilled.

Manufacturing of Dome Matrix modules

Five types of modules were prepared by direct compression using different mixtures of HPMC K15M and HPMC K100LV. Table 1 shows the percentage composition of the five modules types. Briefly, powders ground in a mortar and sieved through a 125 µm sieve were mixed in a Turbula mixer (WAB, Basel, Switzerland) for 30 min without lubricant. Then magnesium stearate was added and mixed for 5 min. The matrices were obtained by automatic direct compression in a single punch tableting machine (EKO Kosch, Berlin, Germany) provided with a special set of cylindrical punches of 7.4 mm diameter having the upper punch a convex surface and a lower concave punch. The compression force was between 20 and 30 kN in all cases. The final weight of the modules was 110±5 mg containing 10 mg of riboflavin.

Dome Matrices in piled and void configurations were prepared by assembling two modules. The piled configuration was obtained by inserting the convex base of one module into the concave base

of the adjacent one and welding by ultrasound. To obtain a floating system, the void configuration was prepared by welding two modules with the concave bases facing each other[2]. In both cases, the welding of the assembled modules was performed using a Branson ultrasound machine (Branson Ultraschall, Dietzenbach, Germany) consisting of a concave punch shaped titanium sonotrode probe and a cylindrical die holding the matrices. The modules were stacked on the die and the resulting system was pressed with the sonotrode at 100-110 N, using the Time mode for 0.55 s (energy: 40-70 J). Twenty soldered systems of each formulation were tested for resistance using the friabilometer operating at 25 rpm for 4 min, complying with the pharmacopoeial specification which accepts a maximum mean weight loss lower than 1.0%[30].

//Insert Table 1//

In vitro drug release studies

The riboflavin release studies from the single modules and the two assembled configurations were performed in a USP dissolution apparatus 2 (Erweka DT6R, Heusenstamm, Germany) with paddle rotation at 75±1 rpm, using 900 ml of degassed simulated gastric fluid without pepsin (pH 1.2±0.5) as dissolution medium, at 37.0±0.5°C. The released riboflavin was quantified spectrophotometrically at 267 nm, using the corresponding calibration curve.

Mathematical modeling of drug release profiles

Riboflavin release profiles were analyzed by the Dual Release model, which allows fitting experimental data following sigmoid curves[22]. It consists of dividing the curve into two parts at the characteristic inflection point and applying a modified Korsmeyer-Peppas like model (Eq. 1) in the first part and a modified Lumped model (Eq. 2) in the second one. This model will be retaken and discussed in depth in the results and discussion section.

$$M_t\%_1 = c + d \times t^n \quad (1)$$

where c (%), d (% min^{-n}) and n, are the model parameters and t (min) is the time.

$$M_t\%_2 = \frac{a\times(t-t_L)}{1+b\times(t-t_L)} \quad (2)$$

where a (% min^{-1}) and b (min^{-1}) are the characteristic parameters of the model and t_L is the lag time, which is the value of time obtained by extrapolation of the model for $M_t\%_2 = 0$.

Using the mathematical equations proposed by the models it was possible to calculate different parameters of pharmaceutical relevance, such as the maximum release rate (RR_{max}), the time needed to release the 80% of the drug ($t_{80\%}$), the dissolution efficiency (*DE*), and the mean dissolution time ($MDT_{X\%}$), which are useful to compare the different release profiles[31,32].

Data analysis

Assays were performed by triplicate and data are presented as the mean ± the standard deviation (*s*). Regression and statistical analysis of the data were performed using Polymath 6.0 software (Polymath Software, Connecticut, USA).

RESULTS AND DISCUSSION

Mathematical modeling of drug release profiles

The riboflavin release profiles from the Dome Matrix modules manufactured with different compositions (C1-C5) based on different HPMC proportions are shown in Figures 2a, 2b, and 2c, for the single modules, piled and void configurations, respectively. From the release profiles, it can be observed that an increasing proportion of the HPMC K15M allows for a prolongation of the drug release in all the cases.

//Insert Fig. 2//

Mathematical equations enable the quantitative interpretation of the values obtained from a drug release assay. They are important tools that allow to explain the behavior of drug formulations and to evaluate and compare them through by determining different pharmaceutical parameters.

The steps in the process of drug release from a formulation based on a swellable polymer involve first the fluid absorption and matrix swelling; the subsequent drug dissolution and diffusion through the matrix, its erosion and finally the transfer of the drug from the drug dosage form surface of the form to the surrounding solution. During the first steps, the matrix absorbs the liquid solution and swells, opening its structure and therefore increasing the diffusivity as a function of time. The drug release rate increases with time until swelling and dissolution rates are of the same order of magnitude, after which the release rate begins to decrease. Therefore, the drug release profile will be different, depending on the rate of each step.

The profiles of the percentage of riboflavin released versus time clearly showed an inflection point (t_i) corresponding to a change in the release rate behavior, except maybe the ones belonging to the C1 composition, for which the t_i could be identified after the 95% of drug release. Since most of the

presented drug release profiles from the Dome Matrix assemblies follow a sigmoid curve, the possibility of analyzing the data with cumulative Weibull function was studied. However, this mathematical function did not present a good fitting for these curves, and even in some cases, the calculated data were far from those determined experimentally (the results obtained from the application of the Weibull function to the riboflavin release profiles are shown in the Supplementary Material).

Rothstein *et al.* proposed a model that describes the drug release mechanism of a water-soluble agent from a spherical matrix[16]. The authors solved the differential equation using the finite element method. The solution of this complex mechanism for a 2:1 blend of 7.4 kDA PLGA and 60 kDA PLA shows a sigmoid profile of cumulative released fraction over time. However, it was not possible to obtain a simple analytical equation.

In 2009 Lao *et al.* presented an analytical expression for the fraction of drug released as a function of time, based on a three-step mechanism[15]. The model equation is given by the sum of the solution of each step. The authors found a good correlation coefficient for the release of the hydrophobic drug paclitaxel release from bulk-degrading PLGA 53/47 films, which exhibits a sigmoid profile. However, the models based on multiple release mechanisms are very complex, many parameters need to be estimated beforehand and some programming skills are necessary to fit the model equation to experimental data. Furthermore, care must be taken in each particular case in the valid range of parameter values.

Accounting for this situation, the Dual Release model, recently developed by our research group[22] can fit experimental data from release profiles following sigmoid curves (*s* in the order of 1% and correlation coefficients better than 0.995). Also, this model can fit experimental data from concave release profiles as shown by modules based on C1 composition. The sigmoid profiles have an inflection point where the first derivative respect to time (release rate) is maximum, and therefore, it is important to determine the inflection point time, which is possible with the proposed model.

If the fluid uptake and swelling of the matrix are fast compared to the other steps, then the drug release profile will be a continuous curve with a maximum release rate at the initial time. The swelling phenomenon will not have any influence on the dissolution rate and the modified Lumped model (Eq. 2) will fit the experimental data with $t_L = 0$. On the other hand, if fluid absorption and swelling play a major role in the process, the profile will have an inflection point where the mechanism of the drug release process changes. In the first part, the drug release rate increases up to the inflection point (Eq. 1) and then begins to decrease following the modified Lumped model (Eq. 2).

Therefore, the full range of experimental data is covered by the Dual Release model, which is the combination of two equations given by Eq. 1 from the beginning of the drug release process to the time of the inflection point and by Eq. 2 from there to t_F. It should be noted that the percentage of drug release at t_F achieved in this study is 95% or higher.

Table 2 shows the results obtained from the fitting of the experimental data using the Dual Release model proposed, and the theoretical release curves of the model can be observed in Figure 2 for the three configurations (continuous lines interpolating release profiles).

Table 2 shows the values of the model parameters, the correlation coefficient (R^2), and the standard deviation (*s*) for each case, which is defined by Eq. 3:

$$s = \sqrt{\frac{(SSD)}{(n-1)}} \tag{3}$$

where *SSD* is the sum of the squares of the differences between the experimental value and the one calculated by the model, and *n* is the number of samples taken in an experimental run.

The correlation coefficient values (from 0.9901 to 0.9999) and standard deviations (from 0.08 to 1.95) suggested a good fitting of the experimental data and supported the accuracy of the model.

//Insert Table 2//

The experimental data of the riboflavin release profiles following an inflection point were fitted by the modified Korsmayer-Peppas model[13,33-35], described by Eq. (1), from the first experimental point up to the inflection point, with exponential parameter *n* higher than one. The mathematical fitting was made from the first experimental point taken (5 minutes in all cases) since either the release does not occur as soon as the matrix is contacted with the fluid because a lag period is required before the release process begins, or the concentration is too low to be detected by analytical methods. The exponent n is related to the release mechanism[36]. While values of 0.5 indicate pure Fickian diffusion, values between 0.5 and 1 are considered anomalous transport. On the other hand, exponent values greater than one indicate a Fickian release with a diffusion coefficient that changes over time.

Besides, this model allows fitting the experimental data obtained from profiles that comply with the power law, in which a concave curve is followed over the entire time range, such as that observed for the Dome Matrix modules based on the composition C1 which have only HPMC K100LV. These modules presented a profile in which the first derivative respect to time increases until total

release. This behavior is probably because, in the initial dissolution phase, the pores closest to the matrix surfaces can be quickly filled with water. In this way, rapid drug release can occur because the process of swelling and gelation of the matrix is very slow. Continuous hydration of the matrix is accompanied by dilution of the polymer chains in the gel layer, which leads to a continuous increase in the drug release rate. The modified Korsmeyer-Peppas model accounts for the mechanism of swelling, diffusion, and erosion of the matrix along with the entire range of the drug release profile. Losi *et al.* studied the swelling behavior of Dome Matrix drug delivery modules by high-resolution X-ray computed tomography[37]. For this purpose, they prepared Dome Matrix tablets by direct compression of particles of near 130 μm size at 200 MPa. The authors observed that the expansion of the structure due to swelling caused the detachment of particles from the matrix with time, and therefore the release rate increased constantly until finally, the module disintegrated completely. This phenomenon is expected to occur faster in matrices prepared with low viscosity HPMC, such as the based on the C1 composition, and agrees with their observed drug release profile.

On the other hand, when the amount of HPMC K15M increases in the composition of the Dome Matrix modules, visual observations of the modules based on C2, C3, C4, and C5 composition evidenced a noticeably thick and viscous gel layer with a slow erosion and a diffusion front near the swelling front. Although the more hydrated the gel, the less resistant it is to drug diffusion, this would also lead to an increase in the diffusion distance of the drug through the gel with a consequent deceleration in the drug release process, after an increase in the drug release rate before the inflection point. It is known that a rapid hydration rate is necessary followed by rapid gelation and a polymer/polymer coalescence so that a rate-controlling polymer forms a protective gelatinous layer around the matrix. This prevents the tablet from disintegrating immediately, resulting in the premature release of the drug.

Release rate

Useful information to evaluate the behavior of different systems in general, and of the Dome Matrix modules in this case in particular, is provided by the release rate (*RR*) and the maximum release rate (RR_{max}). Considering the release profiles following a sigmoid curve, the release rate initially increases continuously until reaching the time corresponding to the inflection point where it is maximum. Since the Dual Release model fits very well with the experimental data from these profiles, it is possible to evaluate the rates and their maximum values in each case.

From the beginning of the drug release until the inflection point, the data are fitted by Eq. 1, and then, the *RR* is given by Eq. 4:

$$RR = d \times n \times t^{(n-1)} \quad (4)$$

From the inflection point until t_F, Eq. 2 is valid and the *RR* can be calculated from Eq. 5:

$$RR = \frac{a}{(1+b\times(t-t_L))^2} \quad (5)$$

Taking into account Eq. 5, the RR_{max} is found for the time corresponding to the inflection point (Eq. 6):

$$RR_{max} = \frac{a}{(1+b\times(t_i-t_L))^2} \quad (6)$$

The values of RR_{max} calculated for the different Dome Matrix configurations and compositions are shown in Table 3. In the case of the profiles corresponding to the Dome Matrix modules based on the C1 composition, which do not present an inflection point and the whole range of experimental data is fitted by Eq. 1, since the *RR* increases continuously, the RR_{max} was determined for the time corresponding to a 95% of drug released.

As it can be observed in Table 3, when the proportion of HPMC K15M is increased in the module's composition, the RR_{max} decreases for all the configurations studied, probably because its higher viscosity makes the structure more rigid. On the other hand, the Dome Matrix configuration influence the RR_{max}, being almost double for the single configuration compared to the void one, and even lower when the modules are assembled in the piled configuration, regardless of the composition. This behavior may be explained by the fact that the single module has almost twice the transfer surface area per unit volume than the other two assembled modules. The initial surface-exposed area per unit volume of the modules developed in this study were 17.40 and 10.95 cm^{-1} for the single unit and the piled configuration, respectively, while it was 10.90 cm^{-1} for the void configuration, excluding the volume inside the assembled modules. The difference of RR_{max} between the two assembled configurations is explained because the void configuration has an empty volume inside the two units while the piled one is formed by a compact body of the two units. Furthermore, the single module and the piled configuration have one convex and one concave surface exposed, while the void configuration has two convex surfaces exposed. Caccavo *et al*. showed that the erosion rate of convex surfaces is slightly higher than the concave surfaces because the first one is more accessible by the agitated medium[38].

//Insert Table 3//

Parameters of pharmaceutical relevance

Taking into account the good fitting of the model, several useful parameters that characterize the profiles of drug release platforms were estimated. These parameters allow a comparison between the formulations of a drug and to evaluate the influence of different variables on the release profiles. One of the most used and simple parameters is the time required to release a certain percentage of the drug ($t_{X\%}$), which is usually determined for 80% of the drug released ($t_{80\%}$).

Another characteristic parameter of a pharmaceutic form is its dissolution efficiency (*DE*), which is defined by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as the ratio between the area under the release profile up to a certain final time (t_F), and the area of the rectangle described by 100% release at the same t_F (Eq. 7).

$$DE = \frac{\int_0^{t_F} M_{t\%}\ dt}{100 \times t_F} \times 100 \tag{7}$$

For profiles presenting an inflection point and, therefore, a lag time, *DE* is given by Eq. 8:

$$DE = \frac{\int_{t_1}^{t_i} M_t\%_1 \times dt + \int_{t_i}^{t_F} M_t\%_2 \times dt}{t_F} \tag{8}$$

Here, t_1 is the time corresponding to the first experimental sample taken during the release study (5 min in all cases).

Replacing Eq. 1and 2 in Eq. 8 and solving the integrals, the *DE* can be calculated from Eq. 9:

$$DE = \frac{c \times (t_i - t_1) + \frac{d}{(n+1)} \times \left(t_i^{(n+1)} - t_1^{(n+1)}\right) + \frac{a}{b^2} \times \left[b * (t_F - t_i) - ln\frac{1 + b \times (t_F - t_L)}{1 + b \times (t_i - t_L)}\right]}{t_F} \tag{9}$$

In the case of the C1 modules based on HPMC K100LV, since the Eq. 1 fits the whole profile of the drug release, the *DE* is calculated from Eq. 10, which is obtained from Eq. 8 canceling the term of the integral of $M_t\%_2$.

$$DE = \frac{c\times(t_F - t_1) + \frac{d}{(n+1)}\times\left(t_F^{(n+1)} - t_1^{(n+1)}\right)}{t_F} \quad (10)$$

Finally, another interesting parameter that allows comparing release profiles is the mean dissolution time ($MDT_{X\%}$). According to the independent statistical methods[35], the following expression can be used to calculate the $MDT_{X\%}$ (Eq. 11):

$$MDT_{X\%} = \frac{\sum_{j=1}^{n} t_{jm}\times \Delta M\%}{\sum_{j=1}^{n} \Delta M\%} \quad (11)$$

where $t_{jm} = (t_j + t_{j-1})/2$, is the midpoint time between two samples and $\Delta M\%$ is the additional amount of drug release between t_j and t_{j-1}. However, as we pointed out previously since the Dual Release model fits very well the experimental values, the $MDT_{X\%}$ can be calculated from Eq. 12, which becomes Eq. 13 for the profiles that present t_i and t_L.

$$MDT_{X\%} = \frac{\int_0^{M\%_j} t \times dM\%_j}{\int_0^{M\%_j} dM\%_j} \quad (12)$$

$$MDT_{X\%} = \frac{\int_{t_1}^{t_i} t\times dM_t\%_1 + \int_{t_i}^{T_{X\%}} t\times dM_t\%_2}{M_t\%(t_{X\%})} \quad (13)$$

where $M_t\%(t_{X\%})$ is the percentage of drug released at time $t_{X\%}$.

Solving Eq. 13 by taking into account Eq. 1 and 2, $MDT_{X\%}$ can be calculated from Eq. 14:

$$MDT_{X\%} = \frac{\frac{d\times n}{(n+1)}\times\left(t_i^{(n+1)} - t_1^{(n+1)}\right) + \frac{a}{b^2} ln\frac{[1+b\times(t_{X\%}-t_L)]}{[1+b\times(t_i-t_L)]} - \left(\frac{a\times t_L}{b} - \frac{a}{b^2}\right)\times\left[\frac{1}{1+(t_{X\%}-t_L)} - \frac{1}{1+(t_i-t_L)}\right]}{M\%(t_{X\%})} \quad (14)$$

In the case of Dome Matrix based on C1 composition, the $MDT_{X\%}$ is given by Eq. 15:

$$MDT_{X\%} = \frac{\frac{d*n}{(n+1)}\times\left(t_{X\%}^{(n+1)} - t_1^{(n+1)}\right)}{M\%(t_{X\%})} \quad (15)$$

The values of these parameters of pharmaceutical relevance are shown in Table 4. It can be observed that as the proportion of HPMC K15M polymer increased in the Dome Matrix composition, the release of the drug became more sustained over time, regardless of module

configuration (single, void, or piled). Values of $t_{80\%}$ of 154 min were found for modules based on pure HPMC K100LV with a single configuration and as high as 1190 min for pure HPMC K15M and piled configuration. The highest values of $t_{80\%}$ were obtained for the piled configuration, followed by the void configuration and were lower for the single one, regardless of the composition. On the other hand, the $t_{80\%}$ value increases when the HPMC K15M is in a higher proportion in the composition of the module. As expected, the *DE* decreased and the $MDT_{X\%}$ increased continuously as the amount of HPMC K100LV in the Dome Matrix composition was smaller, following the same behavior.

//Insert Table 4//

CONCLUSIONS

A general Dual Release model that fits the experimental data of the release profiles of riboflavin from delivery systems based on the Dome Matrix technology was presented. This model is valid for a wide range of variables, such as different configurations of Dome Matrix modules and proportions of HPMC of different viscosity and swelling properties. This model is based on the combination of the modified Korsmeyer-Peppas like the model from the process beginning to the inflection point of the drug release profile, and the modified Lumped model from the inflection point time up to the final process time, reaching values of percentage of drug release higher than 95%. The entire Dual Release model fit very well the experimental data from drug release profiles that followed sigmoid shaped curves with standard error near 1% and the regression coefficient higher than 0.995. Besides, it can also fit the drug release concave profile of modules prepared with low viscosity HPMC. The model proposed describes better the release profile than the cumulative Weibull function, which is analyzed in the Supplementary Materials. The Dual Release model allows obtaining a simple analytical equation of the release rate and can be used to analyze the effect of the different Dome Matrix configurations.

The use of the Dual Release model and the pharmaceutical parameters that characterize the different Dome Matrix modules allows adapting the choice of the composition and the configuration to meet the requirements in the release performance of a drug delivery system. Therefore, mathematical evaluation of drug release kinetics adds value, ensuring the optimal design of pharmaceutical formulations as well as understanding release mechanisms through experimental verification.

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Figure Legends:

Fig 1. Dome Matrix modules of riboflavin prepared by direct compression: single modules (a), piled (b) and void (c) configurations of two modules.

Fig 2. Release profiles of riboflavin in simulated gastric fluid from Dome Matrix modules based on different HPMC proportions for single module (a), piled (b), and void (c) configurations. Symbols are the mean value of the experimental data and lines represent the theoretical release predictions, corresponding the dotted line to Eq.1 and the continuous line to Eq. 2.

Table 1. Formulations composition (mg)

Components	C1	C2	C3	C4	C5
Riboflavin	10.0	10.0	10.0	10.0	10.0
HPMC K15M	0	10.0	20.0	30.0	40.0
HPMC K100LV	40.0	30.0	20.0	10.0	0
Lactose	49.8	49.8	49.8	49.8	49.8
PEG 6000	5.0	5.0	5.0	5.0	5.0
PVP K25	5.0	5.0	5.0	5.0	5.0
Mg Stearate	0.2	0.2	0.2	0.2	0.2

Table 2. Dual Release model parameters, inflection point (t_i), lag time (t_L), correlation coefficients (R^2) and standard deviation (s) for each Dome Matrix module configuration and the different compositions studied

	Modified Korsmeyer-Peppas model					***Lumped model***					
	c *(%)*	d *(%/min^n)*	*n*	R^2	*s*	*a* *(%/min)*	*b* *(1/min)*	t_i *(min)*	t_L *(min)*	R^2	*s*
Single configuration											
C1	-0.672	0.25974	1.1375	0.9996	0.43	--	--	--	--	--	--
C2	2.2827	0.03057	1.4877	0.9982	0.54	1.24734	0.00876	120	75	0.9936	1.95
C3	1.0524	0.07848	1.1856	0.9999	0.08	0.50186	0.00306	120	65	0.9994	0.61
C4	1.3972	0.02816	1.3502	0.9997	0.17	0.36761	0.00239	180	72	0.9971	1.18
C5	3.3304	0.03672	1.2643	0.9994	0.14	0.24068	0.00126	140	37	0.9982	1.07
Void configuration											
C1	-2.620	0.13082	1.1421	0.9985	1.19	--	--	--	--	--	--
C2	1.5773	0.03926	1.2476	0.9992	0.67	2.59601	0.02248	420	336	0.9901	1.04
C3	0.5711	0.03320	1.2610	0.9995	0.22	0.19968	0.00065	233	50	0.9940	1.82
C4	-0.228	0.04573	1.1696	0.9993	0.26	0.15168	0.00043	267	42	0.9985	0.85
C5	1.7399	0.02366	1.2305	0.9989	0.13	0.11354	0.00029	180	42	0.9973	1.47
Piled configuration											
C1	-1.907	0.25817	1.0356	0.9994	0.71	--	--	--	--	--	--
C2	0.9904	0.04198	1.2073	0.9971	0.87	0.57202	0.00461	360	200	0.9983	0.57
C3	0.1708	0.03552	1.2254	0.9977	0.48	0.17296	0.00068	241	47	0.9972	1.16
C4	0.8731	0.01926	1.2738	0.9996	0.16	0.12462	0.00039	295	50	0.9994	0.52
C5	2.9303	0.04036	1.0999	0.9996	0.12	0.08550	0.00023	271	0	0.9999	0.22

Table 3. Maximum release rate (RR_{max}) for the different configurations and compositions of Dome Matrix modules

Dome Matrix composition	RR_{max} *(%/min)*		
	Single	**Void**	**Piled**
C1	0.604[a]	0.340[a]	0.328[a]
C2	0.642	0.311	0.190
C3	0.368	0.159	0.135
C4	0.232	0.126	0.104
C5	0.189	0.105	0.076

[a] For 95% of drug released

Table 4. Characteristic pharmaceutical parameters for the different configurations and compositions of the Dome Matrix modules

Dome	**Single**			**Void**			**Piled**		
Matrix composition	$t_{80\%}$ ***(min)***	DE^a ***(%)***	$MDT_{80\%}$ ***(min)***	$t_{80\%}$ ***(min)***	DE^a ***(%)***	$MDT_{80\%}$ ***(min)***	$t_{80\%}$ ***(min)***	DE^a ***(%)***	$MDT_{80\%}$ ***(min)***
C1	154	43.8	81.4	285	20.5	157.8	260	25.5	134.9
C2	222	57.9	114.9	437	27.6	239.3	593	28.0	282.3
C3	377	39.4	178.3	592	23.7	289.5	724	20.6	340.0
C4	530	30.7	238.7	725	19.6	352.5	905	15.5	433.5
C5	608	27.9	266.3	928	15.6	448.5	1190	14.8	545.3

[a] For C2, C3, C4, and C5 D*E* were calculated for t = 350 min, while for C1, it was calculated for t = 180 min.