Title: Study of the critical points in combined matrix tablets containing both inert and swelling excipients.

Author names and affiliations:

Ángela Aguilar-de-Leyva

Mª Dolores Campiñez

Flavia Jost

Miguel Gavira

Isidoro Caraballo

Department of Pharmacy and Pharmaceutical Technology. University of Seville,

C/Profesor García González 2. 41012, Seville, Spain.

Corresponding author:

Ángela Aguilar-de-Leyva

[a]Department of Pharmacy and Pharmaceutical Technology. University of Seville,

C/Profesor García González 2. 41012, Seville, Spain.

Telephone number: 954556136

FAX number: 954556085

e-mail address: aguilardeleyva@us.es

Declarations of interest: none

ABSTRACT

This work estimates for the first time critical points in combined matrices containing varying concentrations of the hydrophilic polymer Hydroxypropyl methylcellulose (HPMC) K100M CR in presence of a constant percentage of the inert matrix forming polymer Eudragit RS-PO as well as varying concentrations of the inert polymer in presence of a constant percentage of the hydrophilic excipient. Drug release assays, water uptake studies and calculation of the Exicipient Efficiency (*EE*) have been carried out to study the interaction between the polymers.

Surprisingly, an increase in the drug release rate occurs as the percentage of the hydrophobic polymer increases in the formulations. This fact is supported by the *EE* values which indicate a negative interaction between the two excipients. Moreover the HPMC percolation threshold estimated is higher than the one observed in pure HPMC matrices.

It can be concluded that the HPMC creates pores in the inert skeleton, destabilizing the system. Moreover, the inert excipient destabilizes the gel layer formed by HPMC, changing its critical point. This information is essential for a rational estimation of the Design Space of a formulation and provides new knowledge on the behavior of the polymers in combined matrices, which contributes to the science based design.

KEYWORDS

Critical points; Percolation Theory; Expert System SeDeM; Matrix Controlled Release Formulations; Interaction of Matrix Polymers; Science based design.

1. INTRODUCTION

Matrix tablets are the most widely employed controlled release dosage forms due to their low cost and ease of manufacture. In the last years increasing attention is being paid to the

employment of matrices containing both, inert and swellable matrix forming polymers [1–6]. One of the reasons for preparing these systems is to modify the release behavior of the matrices to achieve a specific release profile. The gel or colloid formed by the swellable polymer controls the drug release increasing the viscosity, so reducing the diffusion rate through the gel layer, whereas the inert or hydrophobic excipient reduces the release rate increasing the diffusion path, forcing the drug to diffuse through matrix pores [7].

Cellulose derivatives are the most employed polymers in the manufacture of hydrophilic matrix systems, being hydroxypropylmethyl cellulose (HPMC) the most frequently used due to its non-ionic structure, which may reduce the incompatibilities with other substances; its resistance to enzyme degradation; its stability at a broad pH range (3-11); and its gelation with water [8,9].

In the case of inert matrices, the drug is released by diffusion through the pores of the systems, including the initial porosity and the pores that are formed when the drug is dissolved [10]. Methacrylate copolymers such as Eudragit RL and RS are frequently employed as sustained drug release excipients. Both are water-insoluble copolymers of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and provide pH-independent permeability to the polymers [8].

Preformulation studies of the matrix forming polymers are necessary to determine their suitability to be employed in the manufacture of matrix tablets by direct compression. With this purpose an expert system called SeDeM was developed in 2005 by Suñé-Negre et al [11]. This method consists of a determination of a number of rheological parameters whose values are normalized in order to make possible the comparison of the results of the different assays and then classified in different groups, based on the property measured. This method allows the detection of the powder properties which are adequate and those which need to be improved in order to employ the direct compression technology [12,13].

On the other hand, the Excipient Efficency (*EE*) is a parameter that provides a rational basis to compare excipients to be employed in controlled release formulations since it measures the ability of an excipient to reduce the drug release rate. In this sense, both tools, the SeDeM expert system and the EE provide valuable knowledge for the selection of the most adequate excipients for a concrete controlled release formulation obtained by direct compression.

The application of the percolation theory to the study of pharmaceutical dosage forms allows knowing the internal structure of these systems in order to determine the existence of critical points. These critical points suppose discontinuities of the system that result from a geometrical phase transition of a component which changes its distribution pattern in the dosage forms. A critical point could be expected for each component of the matrix [14].

Percolation theory defines cluster as a group of neighboring particles of the same component. This cluster is infinite (in a theoretical infinite lattice), percolating or coherent when it extends from one side to the other sides of the system. Otherwise the cluster is finite or isolated. Percolation theory also defines the percolation threshold (p_c) as the concentration of a component at which there is the maximum probability of appearance of an infinite or percolating cluster of this component. At this concentration point this component starts having a greater influence on the system, so some properties change abruptly [8].

It is important to know the percolation thresholds in order to have a science-based knowledge of the structure of the system according to the principles of Quality by Design (QbD) presented in the guidelines of the International Conference on Harmonisation (ICH Q8) [15].

Furthermore, the knowledge of these areas of high variability is interesting because i) they correspond to discontinuities of the system, representing natural limits of the “Design

space" of the formulation, and ii) Avoiding these areas, more robust formulations will be obtained, reducing time and cost to market [16].

The main aim of this study is to estimate for the first time critical points in two types of combined matrices: i) matrices containing a constant concentration of the inert matrix forming excipient Eudragit RS-PO and varying concentrations of HPMC K100M CR and ii) matrices containing a constant concentration of the hydrophillic matrix forming excipient HPMC K100M CR and varying percentages Eudragit RS-PO.

2. MATERIALS AND METHODS

2.1 Materials

The following materials were employed in the manufacture of the matrix tablets: theophylline anhydrous (Acofarma, Spain) was employed as model drug, Eudragit RS-PO® (Evonik, Germany) was used as inert excipient and HPMC K100M CR® (Colorcon, (USA)) was employed as swelling matrix forming polymer.

2.2 Methods

2.2.1. Granulometric characterization

Granulometric characterization of the drug and polymers was carried out according to European Pharmacopoeia 9th Edition [17] employing sieves with different mesh sizes (45, 90, 180 and 355 μm). Sieves have been subjected to vibration for 10 min at a speed of 60 (Retsch, model AS 200, Germany). The mass fraction of each sieve was weighed (Ohaus, Explorer Pro, Switzerland) and the mean particle size was calculated according to the Eq (1):

$$\bar{x} = \sum_{1}^{i} \frac{\bar{x}_i * M_i}{100} \qquad \text{Eq (1)}$$

Where $\overline{x}$ is the mean particle size, $\overline{x}_i$ the average mesh size and M_i the mass fraction of the average mesh size.

2.2.2. Rheological studies

Rheological studies were carried out for theophylline and the polymers applying the SeDeM method. Whenever possible, the methods indicated in pharmacopoeias were applied. If not available, methods based on the usual practice in pharmaceutical technology research, specifically adapted for the SeDeM Diagram were employed [18].

The rheological parameters are classified in five different groups (see Table 1). The formula employed to calculate each parameter, the acceptable numerical limit values and the factor applied for the normalization of the values obtained into radii (r) values are also shown in table 1.

The radius values obtained are plotted in the SeDeM diagram (Fig. 1). The polygon drawn connecting the radius values with lineal segments illustrates the characteristics of the powder for direct compression. When all radii values are 10, the SeDeM Diagram takes the form of a circumscribed 12 side's regular polygon.

In order to determine the suitability of a powder for direct compression employing a numerical method, three indices based on the SeDeM diagram are also calculated:

Parametric index (IP) has been calculated according to Eq (2).

$$IP = \frac{N^{o}\,\rho \geq 5}{N^{o}.Pt} \qquad \text{Eq (2)}$$

where $N^{o}.\,\rho \geq 5$ indicates the number of parameters whose values are equal to or higher than 5. $N^{o}.\,Pt$: Indicates the total number of parameters studied. The acceptability limit would correspond to: $IP \geq 0.5$.

Parametric profile index (IPP) corresponds to the mean r value of all parameters. The acceptability limit would correspond to: IPP = mean r ≥ 5

Good compression index (IGC) is calculated applying Eq (3).

$IGC = IPP * f$ Eq (3)

where f is a reliability factor and is calculated with Eq (4).

f = polygon area/circle area Eq (4)

The acceptability limit corresponds to IGC = IPP * f $\geq$ 5

The reliability factor indicates that the reliability of the method is increased when more parameters are considered. Thus, when infinite parameters are studied (the polygon would be a circle, indicating maximum reliability), the reliability factor is 1. In the case of this paper, 12 parameters are analyzed obtaining a reliability factor of 0.952.

2.2.3. Morphological analyses

Morphological characterization of Eudragit RS-PO, HPMC K100M CR and theophylline was carried out employing a Scanning Electron Microscope (SEM) (Phillips, model XL30), connected to a picture analysis system to determine the size and shape of the particles of these materials.

The samples were prepared using a sputter coating machine (Edwards, Scancoat six, United Kingdom) that sprayed a thin gold layer over the powders.

2.2.4. Preparation of the matrix tablets

Eight batches of 50 tablets were prepared. Four batches contained different percentages of HPMC K100M CR (10, 20, 30 and 40% w/w) and a constant amount of Eudragit RS-PO (40% w/w) while the other four batches contained different concentrations of Eudragit RS-PO (10, 20, 30 and 40% w/w) and a fixed concentration of HPMC K100M CR (40%). The materials were blended for 5 minutes in a Turbula mixer (Willy A. Bachofem, Switzerland) and 250 mg tablets were manufactured by direct compression employing an eccentric tableting machine (Bonals A-300, Barcelona) with 9 mm punches. Table 2 shows the composition of the different batches.

2.2.5. Matrix tablet characterization

External aspect of the matrix tablets such as colour, shine, homogeneity and visible fractures or erosions were observed. The internal structure i.e. the distribution, shape and size of the components of the tablets were analyzed employing a scanning electron microscope (SEM) (Phillips XL-30 Eindhoven, Holland) connected to a picture analysis system. The preparation of the samples was carried out spraying the cross-section of the tablets with a thin gold layer with a sputter coating machine (Edwards, Scancoat six, United Kingdom).

Thickness and diameter of 10 matrix tablets of each batch was determined with a precision of ± 0.001 mm employing a 25-mm digital micrometer (Comecta, S.A.).

Mass uniformity was determined weighing 20 matrix tablets of each batch in an analytical balance (Ohaus, Explorer Pro, model EP214, Switzerland).

The initial porosity (ε_0) of the tablets was calculated according to Eq (5).

$$\varepsilon_0 \frac{V_{real} - V_{theor}}{V_{real}} \qquad \text{Eq (5).}$$

Where V_{real} is the real volume of the tablets and V_{theor}, is the theoretical volume of the tablet obtained as the sum of the volumes calculated dividing the mass of each component by their real density.

Total porosity (ε) was calculated applying Eq (6).

$$\varepsilon = \frac{V_{real} - V_{theor}}{V_{real}} \qquad \text{Eq (6)}$$

Where V_{real} is the real volume of the tablets and V_{theor} in this case is the theoretical volume excluding the volume corresponding to the soluble substances in the tablet, (theophylline) so it corresponds to the porosity of the matrix once the soluble components are dissolved.

The crushing strength of 10 tablets from each batch was measured employing a Sotax HT1 durometer.

Finally, the friability of 20 tablets from each batch was determined according to European Pharmacopoeia 9th edition [17] using a friability meter (Erweka, type TAR, Germany) and an analytical balance (Ohaus, Explorer Pro, model EP214, Switzerland).

2.2.6. Drug release studies

Drug release studies were carried out employing the paddle method according to European Pharmacopea 7th edition [17] for six tablets of each batch in a dissolution apparatus Sotax AT7 Smart (Allschwil, Switzerland). The dissolution media consisted of 900 ml of distilled water at 37±0.5ºC and a stirring speed of 50 rpm was employed. Five milliliters samples were withdrawn at 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 360 y 480 minutes. The content of theophylline was analyzed in an UV-Visible spectrophotometer Agilent 8453 (Agilent, California, USA) at a wavelength of 272 nm.

2.2.7. Water uptake studies

Water uptake studies were carried out in a modified Enslin apparatus [19].

This apparatus is equipped with a fritted and contains water that is in equilibrium with a water reservoir which is placed on the plate of a precision balance (Ohaus, Explorer Pro, model EP214, Switzerland). When the tablet is placed on the fritted, the water is absorbed from the reservoir. The amount of water uptaken by the tablet was measured as weight loss in the reservoir.

The rate of water penetration was expressed as the weight gain of the swelled matrix, in percentage w/w of penetrant fluid with respect to dry polymer.

The assay was performed for each batch during six hours.

2.2.8. Kinetics studies

Drug release data were analyzed according to Higuchi (1963) [20](Eq (7)), Korsmeyer et al. (1983) [21](Eq (8)), Zero order (Eq (9)) and Peppas and Sahlin (1989) [22](Eq (10)) kinetic models.

$$\frac{M_t}{M_\infty} = k_H \cdot t^{1/2}$$ Eq (7)

$$\frac{M_t}{M_\infty} = k_k \cdot t^n$$ Eq (8)

$$\frac{M_t}{M_\infty} = k_0 \cdot t$$ Eq (9)

$$\frac{M_t}{M_\infty} = k_d \cdot t^m + k_r \cdot t^{2m}$$ Eq (10)

where M_t/M_∞ is the drug released fraction at time t (M_∞ corresponds to the amount of drug released at infinite time), t is the release time, k_H is the Higuchi's release rate constant on Eq (7), k_k is the Korsmeyer's kinetic constant and n is the Korsmeyer's time exponent that depends on the release mechanism and the shape of the matrix tested on Eq (8), k_0 is the zero-order release constant on Eq (9) and k_d is the diffusional rate constant, k_r is the erosion/relaxation rate constant and m is the purely Fickian diffusion exponent (which depends on the geometrical shape of the delivery device through its aspect ratio) on Eq (10).

The optimum values for the parameters in each equation were determined by linear or nonlinear least squares fitting methods with Excel. The determination coefficient (r^2) was used to test the applicability of the release models.

2.2.9. Efficiency of the excipient

The parameter Excipient Efficency (*EE*) intends to quantify the ability of an excipient to reduce the drug release rate from a pharmaceutical formulation, allowing an easy comparison between different excipients and providing a rational basis for identifying the

most adequate excipients for a concrete formulation. This parameter was initially proposed by Caraballo [23] as the ratio between the total porosity of the system (ε) and the slope of the Higuchi's equation (k_H) (see Eq (11)). Two corrections of this parameter have been recently proposed by Casas et al. [24] considering the mean excipient particle size and the drug solubility (see Eq (12)), making possible the comparison of the EE in matrices prepared with different drugs and excipient particle sizes.

$$EE = \varepsilon / k_H \qquad \text{Eq (11)}$$

$$EE = \frac{\varepsilon}{k_H} \cdot \frac{1}{(1.43 - 0.00244d)} \cdot \frac{1}{(1.963 - 0.246 \ln C_s)} \qquad \text{Eq (12)}$$

Where EE is the efficiency of the excipient, ε is the total porosity, k_H is the Higuchi rate constant, d is the weighed mean particle size of the excipients and C_s is the drug solubility.

3. RESULTS AND DISCUSSION

3.1. Granulometric characterization

Granulometric studies were carried out to determine the particle size distribution and the mean particle size of the components employed in the manufacture of the combined matrices.

The mean particle sizes of theophylline, Eudragit RS-PO and HPMC K100M CR are 194.85, 219.91 and 173.04 μm, respectively. These values are similar, which is considered adequate to have homogeneous mixing of the components and to prevent segregation.

3.2. Rheological characterization

As it has been stated in a previous section, the SeDeM expert system has been applied in order to obtain information about the rheology of the powders studied and its ability to be processed by direct compression. Table 3 shows the results obtained for the parameters

studied. All the parameters have been calculated as the average of three determinations with the exception of the rest angle, which was measured in six replicates.

Employing these results, the SeDeM diagrams have been obtained for the three substances (see Fig. 2).

The values for the Parametric index (IP), Parametric profile index (IPP) and Good compression index (IGC) are shown in Table 4.

The results obtained confirm that the materials employed in the manufacture of the matrix tablets studied are above the acceptability limits except for the IGC of the HPMC K100 M CR.

3.3. Morphological characterization

Microphotographs of HPMC K100M CR, Eudragit RS-PO and theophylline anhydrous, obtained by SEM with a magnification of 350x, are shown in Fig. 3, 4 and 5.

It can be observed that HPMC K100M CR and theophylline particles are fibrous with an acicular shape. By contrary, Eudragit RS-PO particles have a more regular shape with smooth borders.

3.4. Tablet characterization

The results of the assays carried out for the tablet characterization are shown in table 5.

All the obtained tablets showed homogeneous white colour and smooth borders. No fissures could be observed. An adequate uniformity of weight has been obtained.

A satisfactory crushing strength from 166 to 225N was obtained for all the batches, indicating good compactibility. Moreover, the results of the friability assay are below 1% for all the batches, fulfilling the specifications of the European Pharmacopoeia 9th edition [17].

The thickness variability between batches is very low.

With respect to the initial porosity, it can be observed a decrease as the drug content rises. Obviously, the opposite behaviour, i.e., an increase with the drug content is observed for the total porosity.

It is clear that in the case of inert matrices an increase in the total matrix porosity leads to a faster drug release due to the fact that in this type of matrices the drug is released by diffusion through the pores of the system, including the initial porosity and the pores that are formed when the drug is dissolved [10].

On the other hand, in the case of hydrophilic matrices, the influence of the porosity is not so certain. Although it is necessary a level of initial porosity to form the gel layer that control the drug release, it seems that higher total porosities are causing a faster drug release [25].

Based on these arguments, a decrease in the theophylline release rate could be expected as the percentage of HPMC and Eudragit increases from batch 1 to batch 4 and from batch 5 to batch 8, respectively, due to the decrease in the total porosity of the system.

3.5. Release studies

The results of the dissolution assays are shown in Fig. 6. These results were surprising. On one hand, it can be observed that theophylline is released faster from the matrix tablets as the percentage of HPMC increases from batches 1 to 4. Initially, it was expected a better control and therefore a slower drug release rate with higher amounts of the controlling excipient. However, the obtained result can be explained taking into account that the hydrophilic HPMC would create pores in the inert skeleton of Eudragit RS-PO, since these matrices contain 40% of this inert polymer. These hydrophilic pores allow water penetration into the matrix. This effect is more evident for batch 4, suggesting that this batch is above the HPMC percolation threshold.

An anomalous behaviour can be observed for batch 1, which contains 10% of HPMC. This behaviour is due to the breaking of the inert skeleton of the Eudragit caused by the disintegrant effect of the HPMC which can be observed when this excipient is used at low concentrations [26,27] .

With respect to batches 5 to 8, an equivalent behavior has been observed: theophylline is released faster from tablets containing a higher amount of inert matrix forming excipient

Eudragit RS-PO (for example tablet containing 10% of Eudragit RS-PO releases 40% of theophylline within 8 hours while release is increased to 60% in presence of 40% Eudragit RS-PO), despite the fact that these batches have a lower drug load and lower total porosity.

Porosity does not seem to be a major factor. As it was previously mentioned, in the case of inert matrices, a drug is expected to be released faster from a matrix with higher porosity. This can be applied both to the initial and to the total porosity, the latter being the main contributing factor [28,29]. Recent studies show that pores in hydrophilic matrices favour the penetration of water resulting in faster drug release [25]. Contradictory results have been reported concerning interaction between a copolymer of hydroxypropil cellulose and methyl methacrylate and HPMC [1–3]. The results of the present study suggest a destabilization of the HPMC gel layer by Eudragit RS PO.

Drug release data have been analyzed according to different kinetic models: Zero order, Higuchi, Korsmeyer and Peppas&Sahlin. Table 6 shows the results of the fit of the data to these models. The time exponent *"n"*, indicative of the release mechanism in the Korsmeyer equation, was examined. Values near to 0.5 are indicative of a diffusion mechanism whereas higher values indicate a certain contribution of the erosion mechanism. Table 6 shows that the obtained time exponents of the Korsmeyer equation for all the batches are close to 0.5, indicating that drug release follows a diffusion kinetics, with a low contribution of the erosion mechanism. In addition, the results obtained applying the Peppas&Sahlin equation also indicate that the diffusion mechanism predominates over the erosion/relaxation with K_d values much higher than the values of K_r. Moreover, the release profiles of theophylline observed in Fig. 6 are consistent with this interpretation.

Finally, it can be observed that the Higuchi constant "k_H" increases from batches 2 to 4 and from batches 5 to 8 as the content of hydrophilic and inert excipient, respectively, rises in the matrix tablets. This is in agreement with a faster dissolution rate of theophylline with

higher concentrations of HPMC K100M CR and Eudragit RS-PO. Batch 1 constitutes the exception previously commented.

3.6. Water uptake studies

For batches 1 to 4 a slower water penetration can be observed as the percentage of HPMC increases in the matrix tablets. This result could be attributed to a higher viscosity. The disintegrant effect of the HPMC in batch 1 can also be clearly observed in this assay. A much slower water penetration is expected for batches 4 and 8 since these batches have only 20% of soluble substances. This fact is confirmed in Fig. 7. The other lots have an intermediate behaviour.

On the other hand, water uptake assays show a lower swelling capacity of matrix tablets when the concentration of Eudragit increases for batches 5 to 8 (see Fig. 7). This fact can be explained by a higher amount of inert and hydrophobic particles of Eudragit RS-PO creating a less hydrophilic environment in the tablet, which leads to a lower absorption of water.

It is interesting to note that for higher concentrations of Eudragit RS-PO the water penetration is slower but the drug release is faster. The only explanation for this paradoxical behaviour is the previously mentioned hypothesis of the destabilization of the gel layer.

A previous study of our team has confirmed the need of a coherent gel layer from the first minutes of the release process in order to control drug release from hydrophilic matrices [30].

3.7. Estimation of the HPMC K100M CR percolation threshold

Percolation threshold provides a rational basis for formulation and optimization of controlled release systems, according to the “Quality by Design” concept. Percolation threshold can be described as the concentration of a component for which there is a

maximum probability of appearance of an infinite or percolating cluster of this component that starts to percolate the system, acting as the outer phase of an emulsion [7,14].

The analysis of the kinetic data is in agreement with the percolation threshold estimated based on the drug release profiles. In Fig. 8 the Higuchi constant is plotted versus the % v/v of HPMC K100M CR. A clear increase in the value of the constant can be appreciated when batch 4, containing 38.07% v/v of HPMC is compared with batches 1, 2 and 3, containing 9.54%, 19.06% and 28.57% v/v of HPMC, respectively. The value of the constant is similar for these last three batches. This result is in concordance with the release profiles since a clear increase in the drug release rate is observed for batch 4 which releases 60% after 8 hours while batches 2 and 3 release less than 50% of theophylline in the same period of time.

According to previous studies, the HPMC percolation threshold is situated between 10–15% v/v in binary matrices [25]. Therefore, the result obtained in the present study indicates that the presence of a constant concentration of Eudragit RS-PO in the combined matrices results in an increase of the HPMC K100M CR percolation threshold. Above the HPMC K100M CR percolation threshold the hydrophilic polymer forms a percolating cluster that acts more evidently creating pores that destabilize the inert skeleton constituted by the Eudragit RS-PO leading to a faster drug release.

3.8. Estimation of the Eudragit percolation threshold

Tablet batches, which contain 11.20% and 22.09% v/v of Eudragit RS-PO release approximately 40% of theophylline after 8 hours. Tablets with 43.03% v/v of Eudragit RS-PO release approximately 60% after 8 hours. These results suggest that tablets containing 11.20% and 22.09% v/v of Eudragit RS-PO are below the percolation threshold of Eudragit RS-PO. Looking at the release profiles it can be deducted that batch 7, containing 32.70% v/v of Eudragit, is in the vicinity of the Eudragit percolation threshold. This fact can be confirmed by plotting the Higuchi constant of the different tablet batches versus the

percentage of the polymer contained in each batch. According to the Effective Medium Approximation theory (EMA), two linear regression lines could be drawn [31,32]. The intersection between these lines, which corresponds to a value of 26.44% v/v, is an estimation of the Eudragit RS-PO percolation threshold (see Fig. 9). Above the percolation threshold, Eudragit RS-PO acts as a percolating cluster, exerting a stronger influence on the properties of the gel layer and producing a stronger destabilization.

We conclude from this analysis that Eudragit RS-PO produces a destabilization of the hydrophilic gel layer, reducing the control on the drug release by the hydrophilic matrix forming polymer (HPMC). Below its percolation threshold, Eudragit RS-PO does not percolate the system and its influence on the gel layer is clearly lower. Therefore, the release of theophylline is more strongly controlled by HPMC, leading to a decrease in the drug release rate.

3.9. Calculation of the excipient efficiency

The values calculated for the *EE* of the Eudragit RS-PO and HPMC K100M CR in the matrices studied applying Eq (12) as well as the pure HPMC K4M and Eudragit RS-PM reported by Casas et al., [24] are shown in Table 7. It would be expected a higher value for batch 1 since the less HPMC contain the combined matrix tablet the better the drug release is controlled. However this high value for the *EE* is not observed because of the disintegrant effect of the HPMC observed at low concentrations.

To analyze the interaction between the inert and hydrophilic polymers employed in the manufacture of these combined matrices three patterns could be considered:

i) Collaboration between the excipients: the value of the *EE* is the weighted average of the *EE* of each individual polymer.

ii) Positive interaction: the value of the *EE* is higher than the weighted average of the *EE* of each individual polymer.

iii) Negative interaction: the value of the *EE* is lower than the weighted average of the *EE* of each individual polymer.

Despite the *EE* values have not been measured for pure HPMC K100M CR, we can expect that they will be higher than the one for HPMC K4M, which has a lower viscosity. The *EE* value for the HPMC K4M has been reported by Casas et al.,[24]. Taking this into account, the mean value obtained in this study for the *EE* for batches 1-4 and 5-8 are 11.80 and 13.53 $min^{1/2}\mu m^{-1}mg^{-1}ml$, respectively. These values are slightly lower than the corresponding to the weighted average of the two excipients employed (14.84 $min^{1/2}\mu m^{-1}mg^{-1}ml$), calculated based on the datum of *EE* of HPMC K4M. In case of pattern i), the real value of the weighted average is expected to be even higher.

Therefore, our results show that there is a negative interaction to control the drug release between the two matrix forming excipients which can be attributed to an effect of destabilization caused by the hydrophilic polymer HPMC through the inert skeleton formed by the Eudragit RS-PO in the case of matrices 1 to 4 and to the destabilization of the gel layer caused by the Eudragit RS-PO in the case of batches 5 to 8.

4. CONCLUSIONS

In this paper the percolation threshold of the hydrophilic polymer HPMC K100M CR and the inert excipient Eudragit RS-PO have been calculated for the first time in matrices containing a mixture of both polymers. On one hand, according to the study of the drug release and the analysis of the kinetic data of the release assay, the value of the HPMC K100M CR percolation threshold is estimated to be between 28.57 and 38.07% v/v. Therefore an increase in the value of this parameter has been observed compared with the percolation threshold of matrices containing only HPMC as matrix forming polymer. Moreover, it has been observed that an increase in the HPMC content supposes a faster drug release since the HPMC destabilize the inert skeleton constituted by the Eudragit RS-

PO. This result is supported by the *EE* value of the mixture of the two polymers employed in batches 1 to 4 which reflect a negative interaction between the two excipients.
On the other hand, according to percolation theory and EMA theory, the percolation threshold of Eudragit RS-PO is estimated to be between 22.09 and 32.70% v/v, concretely at 26.44% v/v. Above this concentration, Eudragit RS-PO begins to percolate the system. The hypothesis that an inert excipient can destabilize the gel layer built by HPMC has been confirmed considering the results of the drug release assay and those of the excipient efficiency. The results of the Excipient Efficiency also reflect this situation showing a negative interaction between the two polymers.

The surprising and unexpected behavior of combined (hydrophilic/inert) controlled release matrices has been explained for the first time according to the percolation theory. A quantitative and rational explanation has been obtained in contrast to qualitative answers provided by classical theories. This fact results essential according to the ICH Q8 Guideline that encourages the application of the Quality by Design concept in pharmaceutical formulations. To be able to design the quality it is crucial the knowledge of the percolation thresholds of the system and its related critical points since they are areas of great variability that must be avoided to obtain robust dosage forms. Percolation theory provides the rational basis for applying these concepts, being a fundamental part of industrial guidelines.

Acknoowledgements

Authors would like to acknowledge Joerg Huwyler for supporting the international collaboration making possible this work.

Funding

This work was supported by the Spanish Ministry of Economy and Business [project "MAT2012- 38,044-C03-02"].

REFERENCES

[1] Escudero JJ, Ferrero C, Casas M, Jiménez-Castellanos MR. Compaction properties, drug release kinetics and fronts movement studies of matrices combining mixtures of swellable and inert polymers. III: effect of polymer substitution type. Int J Pharm 2012;434:215–23. doi:10.1016/j.ijpharm.2012.05.027.

[2] Escudero JJ, Ferrero C, Jiménez-Castellanos MR. Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers. II. Effect of HPMC with different degrees of methoxy/hydroxypropyl substitution. Int J Pharm 2010;387:56–64. doi:10.1016/j.ijpharm.2009.12.001.

[3] Escudero JJ, Ferrero C, Jiménez-Castellanos MR. Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers: effect of HPMC of different viscosity grades. Int J Pharm 2008;351:61–73. doi:10.1016/j.ijpharm.2007.09.031.

[4] Boyapally H, Nukala RK, Douroumis D. Development and release mechanism of diltiazem HCl prolonged release matrix tablets. Drug Deliv 2009;16:67–74. doi:10.1080/10717540802586220.

[5] Saurí J, Millán D, Suñé-Negre JM, Colom H, Ticó JR, Miñarro M, et al. Quality by Design approach to understand the physicochemical phenomena involved in controlled release of captopril SR matrix tablets. Int J Pharm 2014;477:431–41. doi:10.1016/J.IJPHARM.2014.10.050.

[6] Naiserová M, Kubová K, Vysloužil J, Pavloková S, Vetchý D, Urbanová M, et al. Investigation of Dissolution Behavior HPMC/Eudragit®/Magnesium Aluminometasilicate Oral Matrices Based on NMR Solid-State Spectroscopy and Dynamic Characteristics of Gel Layer. AAPS PharmSciTech 2018;19:681–92. doi:10.1208/s12249-017-0870-6.

[7] Caraballo I. Critical points in the formulation of pharmaceutical swellable controlled release dosage forms-Influence of particle size. Particuology 2009;7:421–5. doi:10.1016/j.partic.2009.10.002.

[8] Aguilar-de-Leyva A, Campiñez MD, Casas M, Caraballo I. Critical Points and Phase Transitions in Polymeric Matrices for Controlled Drug Release. vol. 1. 2015. doi:10.1002/9781119041375.ch4.

[9] McCrystal CB, Ford JL, Rajabi-Siahboomi AR. Molecular interactions between water and HPMC polymers. Eur J Pharm Sci 1996;4:S174. doi:10.1016/S0928-0987(97)86526-8.

[10] Caraballo I, Fernández-Arévalo M, Holgado MA, Rabasco AM. Percolation theory: application to the study of the release behaviour from inert matrix systems. Int J Pharm 1993;96:175–81. doi:10.1016/0378-5173(93)90225-5.

[11] Suñé-Negre JM, Roig Carreras M, Fuster García R, Hernández Pérez C, Ruhí Roura R, García Montoya E, et al. Nueva metodología de preformulación galénica para la caracterización de sustancias en relación a su viabilidad para la compresión: Diagrama SeDeM. Cienc y Tecnol Pharm 2005;15:125–36.

[12] Campiñez MD, Ferris C, de Paz MV, Aguilar-de-Leyva A, Galbis J, Caraballo I. A new biodegradable polythiourethane as controlled release matrix polymer. Int J Pharm 2015;480:63–72. doi:10.1016/j.ijpharm.2015.01.011.

[13] Saurí J, Millán D, Suñé-Negre JM, Pérez-Lozano P, Sarrate R, Fàbregas A, et al. The use of the SeDeM diagram expert system for the formulation of Captopril SR matrix tablets by direct compression. Int J Pharm 2014;461:38–45.

doi:10.1016/j.ijpharm.2013.11.029.

[14] Caraballo I. Factors affecting drug release from hydroxypropyl methyl cellulose matrix systems in the light of classical and percolation theories. Expert Opin Drug Deliv 2010;7:1291–301.

[15] ICH Expert Working Group. Pharmaceutical Development Q8. ICH Harmon Tripart Guidel 2009;8:1–28.

[16] Leuenberger H, Lanz M. Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative. Adv Powder Technol 2005;16:3–25. doi:10.1163/1568552053166683.

[17] European Pharmacopoeia 9th Edition. European Directorate for the Quality of Medicines and HealthCare. 2017

[18] Pérez P, Suñé-Negre JM, Miñarro M, Roig M, Fuster R, García-Montoya E, et al. A new expert systems (SeDeM diagram) for control batch powder formulation and preformulation drug products. Eur J Pharm Biopharm 2006;64:351–9. doi:10.1016/j.ejpb.2006.06.008.

[19] Luginbühl R, Leuenberger H. Use of percolation theory to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures. Pharm Acta Helv 1994;69:127–34. doi:10.1016/0031-6865(94)90013-2.

[20] Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145–9.

[21] Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25–35. doi:10.1016/0378-5173(83)90064-9.

[22] Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int J Pharm 1989;57:169–72. doi:10.1016/0378-5173(89)90306-2.

[23] Caraballo I. Prices of the Controlled Release Society. In: Controlled Release Society,

editor. 28th Symp. San Diego, San Diego, Cal.: 2001.

[24] Casas M, Aguilar-de-Leyva Á, Caraballo I. Towards a rational basis for selection of excipients: Excipient Efficiency for controlled release. Int J Pharm 2015;494:288–95. doi:10.1016/j.ijpharm.2015.08.002.

[25] Aguilar-De-Leyva Á, Cifuentes C, Rajabi-Siahboomi AR, Caraballo I. Study of the critical points and the role of the pores and viscosity in carbamazepine hydrophilic matrix tablets. Eur J Pharm Biopharm 2012;80:136–42.

[26] Fuertes I, Miranda A, Millán M, Caraballo I. Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets. Eur J Pharm Biopharm 2006;64:336–42. doi:10.1016/j.ejpb.2006.05.009.

[27] Fuertes I, Caraballo I, Miranda A, Millán M. Study of critical points of drugs with different solubilities in hydrophilic matrices. Int J Pharm 2010;383:138–46.

[28] Bonny JD, Leuenberger H. Matrix type controlled release systems: I. Effect of percolation on drug dissolution kinetics. Pharm Acta Helv 1991;66:160–4.

[29] Bonny JD, Leuenberger H. Matrix type controlled release systems II. Percolation effects in non-swellable matrices. Pharm Acta Helv 1993;68:25–33. doi:10.1016/0031-6865(93)90005-Q.

[30] Mason LM, Campiñez MD, Pygall SR, Burley JC, Gupta P, Storey DE, et al. The influence of polymer content on early gel-layer formation in HPMC matrices: The use of CLSM visualisation to identify the percolation threshold. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Für Pharm Verfahrenstechnik eV 2015;94:485–92. doi:10.1016/j.ejpb.2015.06.019.

[31] Kirkpatrick S. The nature of percolation 'channels.' Solid State Commun 1973;12:1279–83. doi:10.1016/0038-1098(73)90865-X.

[32] Turban L. On the effective-medium approximation for bond-percolation conductivity. J Phys C Solid State Phys 2001;11:449–59. doi:10.1088/0022-3719/11/3/008.

Table 1

Formula, limit values accepted for the SeDeM Diagram parameters and factor applied to transform each parameter into radius values (r).

	Parameter	Symbol	Unit	Formula	Limit values	Factor applied to v
Dimensions	Bulk density	Da	g/ml	$Da = m/V_{bulk}$	0-1	10v
	Tapped density	Dc	g/ml	$Dc = m/V_{tapped}$	0-1	10v
Compressibility	Sponginess index	Ie	-	Ie = Dc-Da/Dc*Da	0-1.2	10v/1.2
	Carr index	IC	%	IC = (Dc-Da/Dc)100	0-50	v/5
	Cohesion index	Icd	N	~~{~~Experimental~~}~~	0-200	v/20
Flowability/ poder flow	Hausner ratio	IH	-	IH = Dc/Da	3-0	10-(10v/3)
	Rest angle	(α)	°	tg α = h/r	50-0	10-(v/5)
	Flowability	t''	s	Experimental	20-0	10-(v/2)
Lubricity/ stability	Loss on drying	%HR	%	Experimental	0-10	$10\text{-}v^a$
	Hygroscopicity	%H	%	Experimental	20-0	10-(v/2)
Lubricity/ dosage	Particles < 45µm	%Pf	%	Experimental	50-0	10-(v/5)
	Homogeneity index	(Iθ)	-	Iθ = Fm/100 + ΔFmn	0-0.02	500v

Table 2. Composition of the batches prepared.

	Batch 1		Batch 2		Batch 3		Batch 4		Batch 5		Batch 6		Batch 7		Batch 8	
	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)
Theophylline anhydrous	50	125	40	100	30	75	20	50	50	125	40	100	30	75	20	50
HPMC K100M CR	10	25	20	50	30	75	40	100	40	100	40	100	40	100	40	100
Eudragit RS-PO	40	100	40	100	40	100	40	100	10	25	20	50	30	75	40	100
Total	100	250	100	250	100	250	100	250	100	250	100	250	100	250	100	250

Table 3.

Experimental and radii values for the SeDeM parameters.

Parameter		Units	Theophylline		HPMC K100M CR		Eudragit RS-PO	
			Experimental value	r	Experimental value	r	Experimental value	r
Dimensions	Bulk density	g/ml	0.431±0.015	4.31	0.358±0.014	3.58	0.596±0.018	5.96
	Tapped density	g/ml	0.551±0.036	5.51	0.452±0.005	4.52	0.794±0.011	7.94
Compressibility	Sponginess	-	0.500±0.157	4.17	0.58±0.09	4.83	0.42±0.04	3.5
	index	%	21.489±6.222	4.30	20.76±2.31	4.15	24.97±1.35	4.99
	Carr index	N	221±13	10	344.2±21.74	10	122.6±9.46	6.13
	Cohesion index							
Flowability/	Hausner ratio	-	1.279±0.101	5.74	1.26±0.04	5.80	1.33±0.02	5.57
poder flow	Rest angle	º	49.2±0.7	0.17	37.34±1.58	2.53	24.41±5.12	2.26
	Flowability	S	∞±0.00	0.00	∞±0.00	0.00	∞±0.00	0.00
Lubricity/	Loss on drying	%	0.046±0.008	9.95	4.54±0.17	5.46	1.73±0.00	8.27
stability	Hygroscopicity	%	0.048±0.002	9.98	8.46±0.50	5.77	1.04±0.07	9.48
Lubricity/	Particles <	µm	1.287±0.010	9.74	12.38±1.31	7.52	0.063±0.093	9.99
dosage	45µm							
	Homogeneity	-	0.007±0.000	3.25	0.012±0.000	6.01	0.003±0.000	1.74
	index							

Table 4. Parametric index (IP), Parametric profile index (IPP) and Good compression index (IGC) of theophillyne, HPMC K100M CR and Eudragit RS-PO

	Theophillyne	HPMC K100M CR	Eudragit RS-PO
IP	0.5	0.50	0.58
IPP	5.59	5.02	5.72
IGC	5.32	4.77	5.45

Table 5. Tablet characterization.

	Weight (g)	Strength (N)	Diameter (cm)	Thickness (cm)	Initial Porosity (%)	Total porosity (%)	Friability (%)
Batch 1	0.242±0.002	171±10	0.908±0.010	0.299±0.022	5.73	50.37	0.281
Batch 2	0.235±0.006	166±9	0.908±0.008	0.298±0.072	7.70	42.64	0.213
Batch 3	0.240±0.003	168±7	0.906±0.009	0.307±0.036	8.39	34.38	0.195
Batch 4	0.238±0.002	173±8	0.904±0.012	0.312±0.022	10.22	27.19	0.217
Batch 5	0.246±0.002	225±10.7	0.909±0.013	0.293±0.024	4.65	51.54	0.257
Batch 6	0.245±0.002	213±18.1	0.909±0.008	0.301±0.053	5.72	42.28	0.186
Batch 7	0.245±0.001	203±5.5	0.909±0.010	0.309±0.018	7.28	34.20	0.211
Batch 8	0.245±0.002	188±13.8	0.907±0.011	0.320±0.010	8.79	26.03	0.259

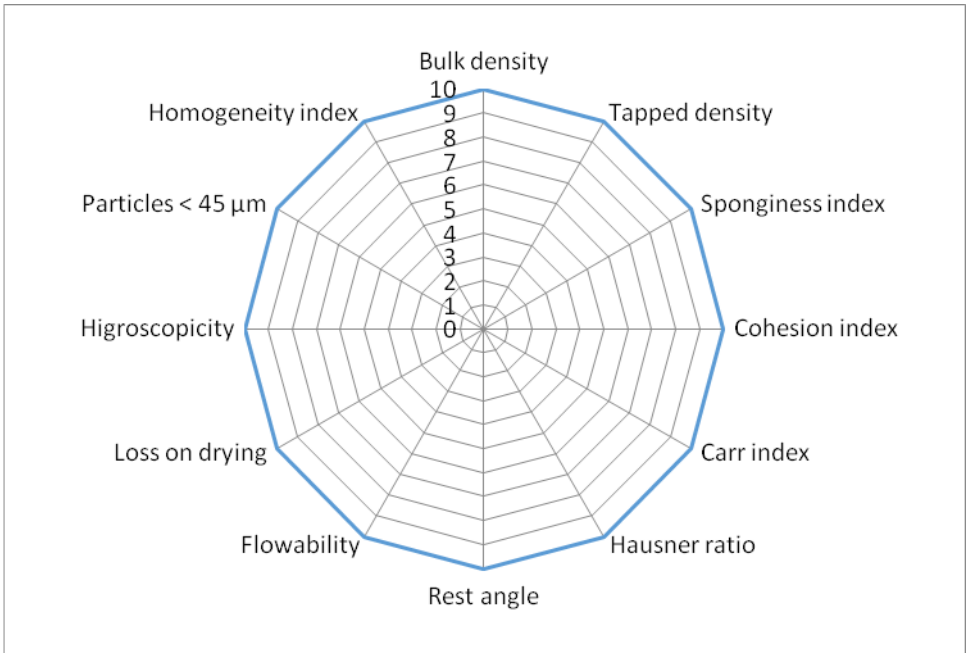
Table 6. Drug release kinetics from the different batches

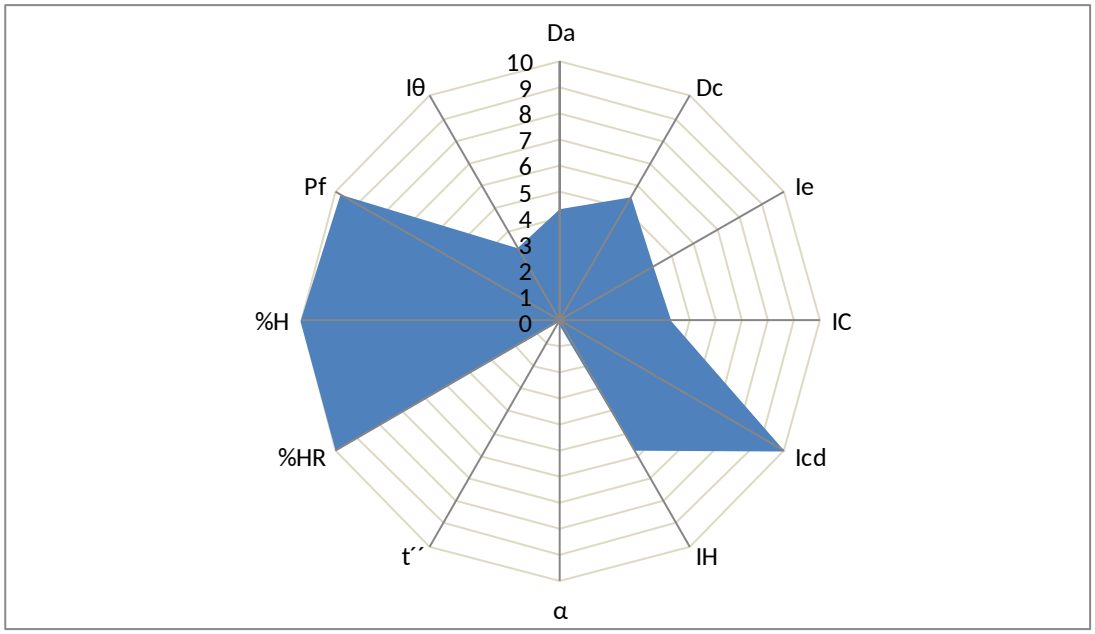
Batch	HPMC K100M CR (%)	Eudragit RS-PO (%)	Zero order		Higuchi		Korsmeyer-Peppas			Peppas y Shalin		
			K_o	R^2	K_H	R^2	K	n	R^2	K_d	K_r	R^2
1	10		0.0011	0.9671	0.0244	0.9508	0.0158	0.5452	0.9282	0.0100	0.0006	0.9799
2	20		0.0009	0.9439	0.0213	0.9702	0.0101	0.6159	0.9875	0.0143	0.0003	0.9793
3	30		0.0009	0.9160	0.0233	0.9488	0.0127	0.5908	0.9645	0.0215	0.0000	0.9493
4	40		0.0011	0.9586	0.0291	0.9860	0.0126	0.6303	0.9939	0.0252	0.0002	0.9875
5		10	0.0703	0.9940	0.0179	0.9855	0.5507	0.6738	0.9990	0.0079	0.0040	0.9990
6		20	0.0714	0.9930	0.0178	0.9703	1.0522	0.5633	0.9864	0.0042	0.0006	0.9953
7		30	0.0873	0.9770	0.0221	0.9903	0.8237	0.6480	0.9989	0.0147	0.0003	0.9953
8		40	0.1162	0.9822	0.0294	0.9929	0.8065	0.6607	0.9967	0.0186	0.0004	0.9989

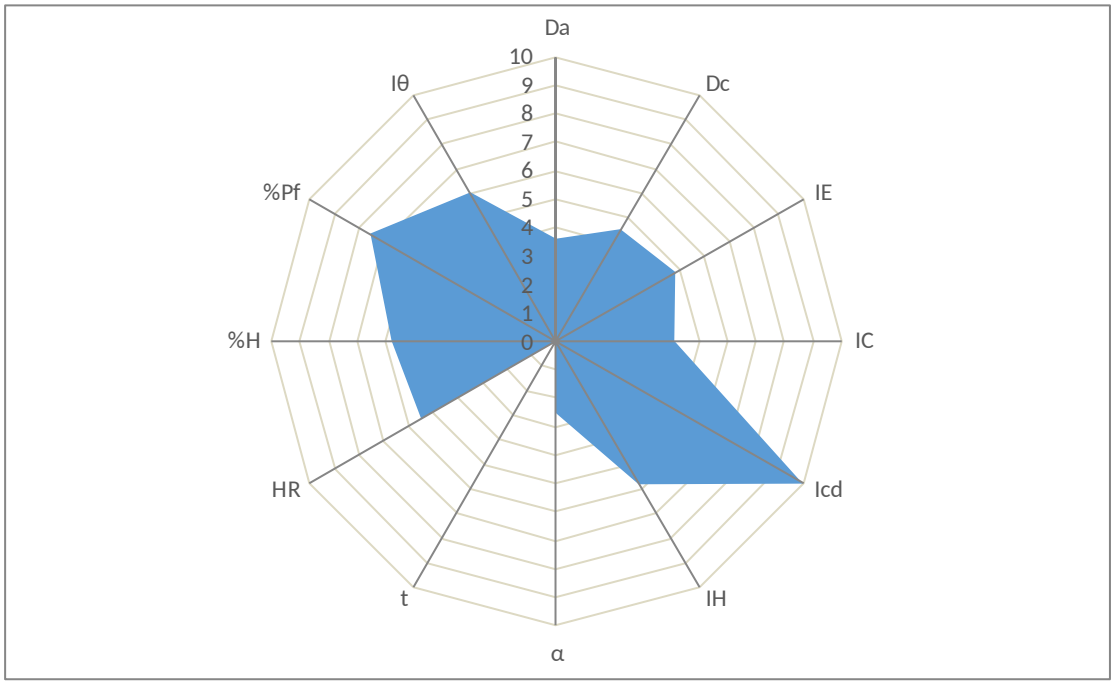
K_0: zero-order release constant (min^{-1})
K_H: Higuchi kinetic constant ($min^{-0.5}$)
K: Korsmeyer-Peppas kinetic constant (min^{-n})
n: Diffusion exponent
K_d: Diffusion kinetic constant ($min^{-0.5}$)
K_r: Relaxation kinetic constant (min^{-1})
R^2: Determination coefficient

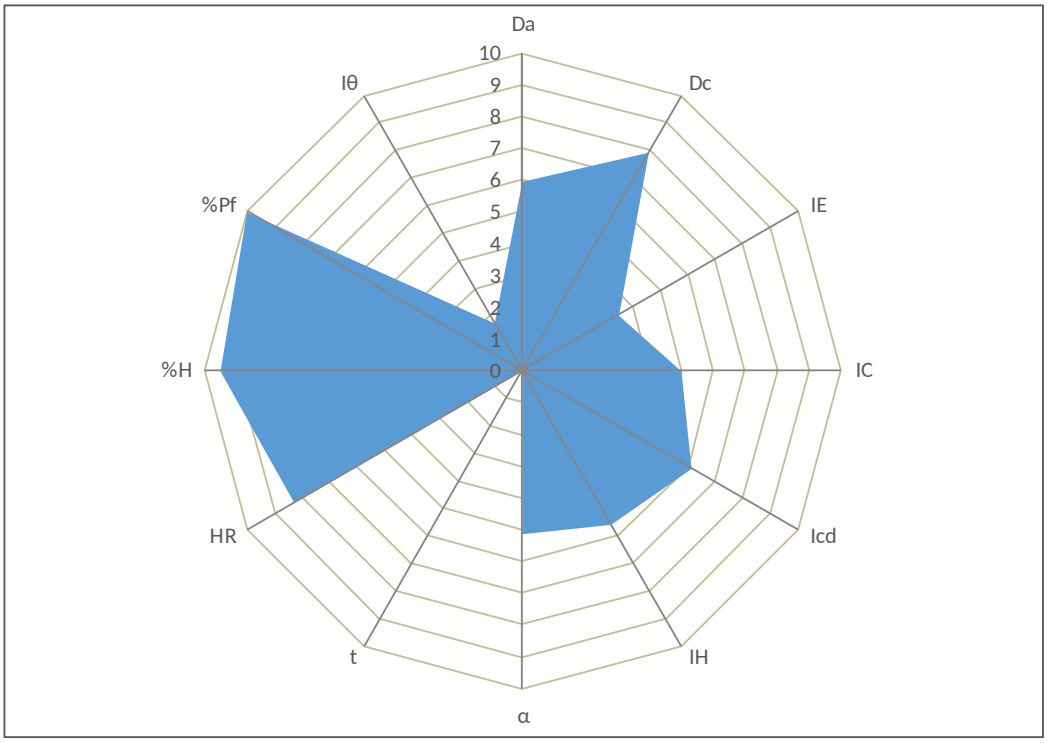
Table 7. *EE* for theEudragit RS-PO and HPMC K100M CR in the batches studied, and pure Eudragit RS-PM and HPMC K4M.

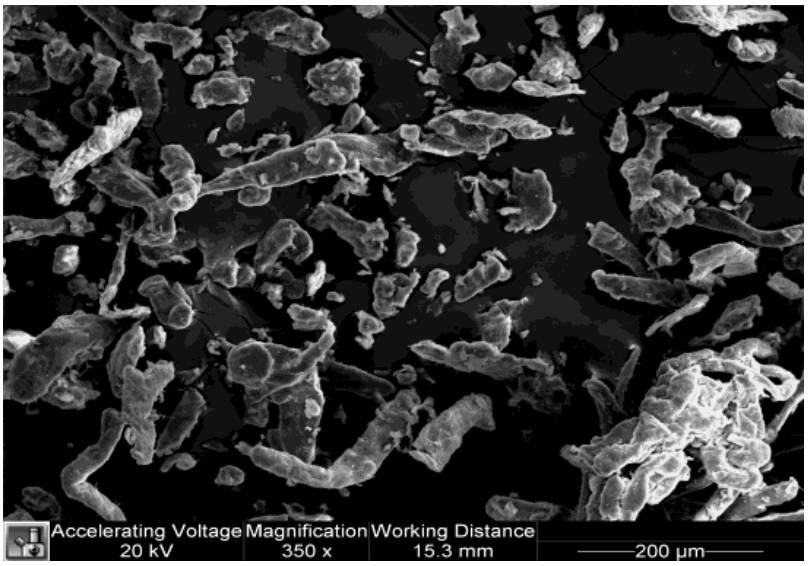
	Excipient Efficiency ($min^{1/2}\mu m^{-1}mg^{-1}ml$)
Batch 1	15,3056
Batch 2	14,5995
Batch 3	10,6366
Batch 4	6,6776
Batch 5	20,1993
Batch 6	16,6416
Batch 7	10,9653
Batch 8	6,3275
Methocel K4M	20.73
Eudragit RS-PM	5.59

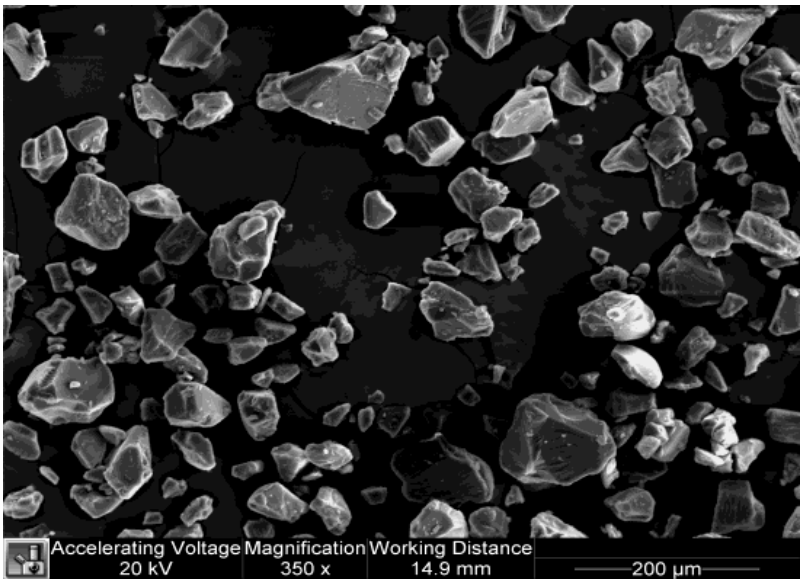

Bulk density
10
9
8
7
6
5
4
3
2
1
0
Tapped density
Sponginess index
Cohesion index
Carr index
Hausner ratio
Rest angle
Flowability
Loss on drying
Higroscopicity
Particles < 45 µm
Homogeneity index


Da
Dc
Ie
IC
Icd
IH
α
t´´
%HR
%H
Pf
Iθ
10
9
8
7
6
5
4
3
2
1
0

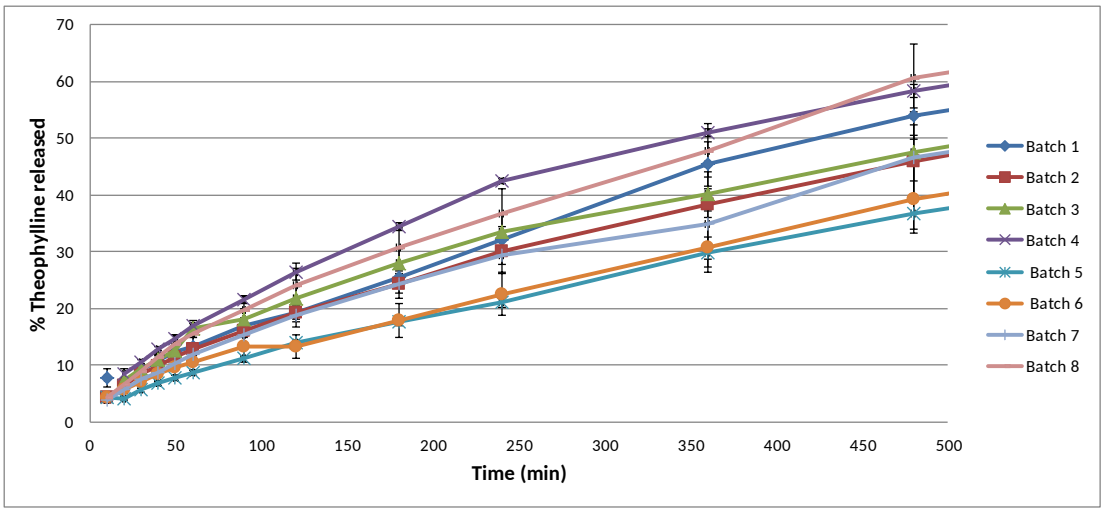

Da
Dc
IE
IC
Icd
IH
α
t
HR
%H
%Pf
Iθ
10
9
8
7
6
5
4
3
2
1
0

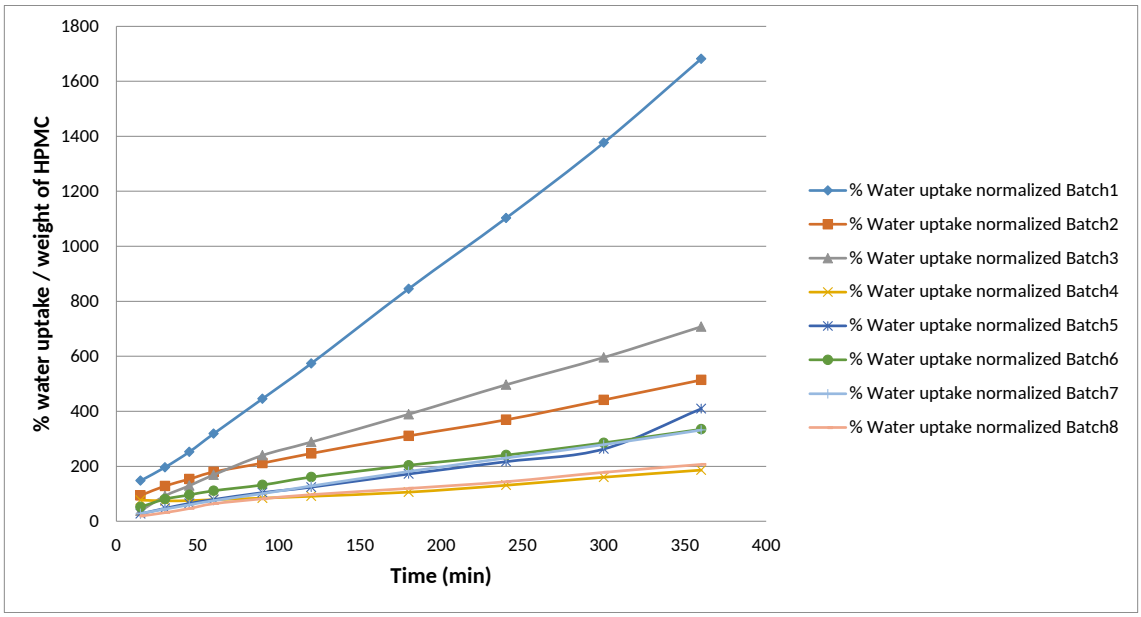

Da
Dc
IE
IC
Icd
IH
α
t
HR
%H
%Pf
Iθ
10
9
8
7
6
5
4
3
2
1
0

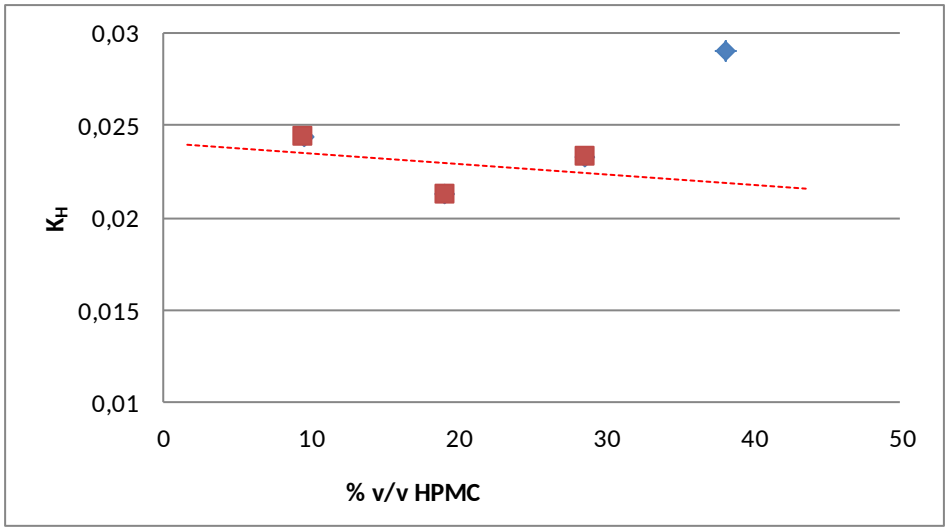

Accelerating Voltage
20 kV
Magnification
350 x
Working Distance
15.3 mm
200 µm


Accelerating Voltage
20 kV
Magnification
350 x
Working Distance
14.9 mm
200 µm


Accelerating Voltage
20 kV
Magnification
350 x
Working Distance
15.3 mm
200 µm


% Theophylline released
Time (min)
0
10
20
30
40
50
60
70
0
50
100
150
200
250
300
350
400
450
500
Batch 1
Batch 2
Batch 3
Batch 4
Batch 5
Batch 6
Batch 7
Batch 8


% water uptake / weight of HPMC
Time (min)
0
200
400
600
800
1000
1200
1400
1600
1800
0
50
100
150
200
250
300
350
400
% Water uptake normalized Batch1
% Water uptake normalized Batch2
% Water uptake normalized Batch3
% Water uptake normalized Batch4
% Water uptake normalized Batch5
% Water uptake normalized Batch6
% Water uptake normalized Batch7
% Water uptake normalized Batch8


0,03
0,025
0,02
0,015
0,01
K_H
0
10
20
30
40
50
% v/v HPMC

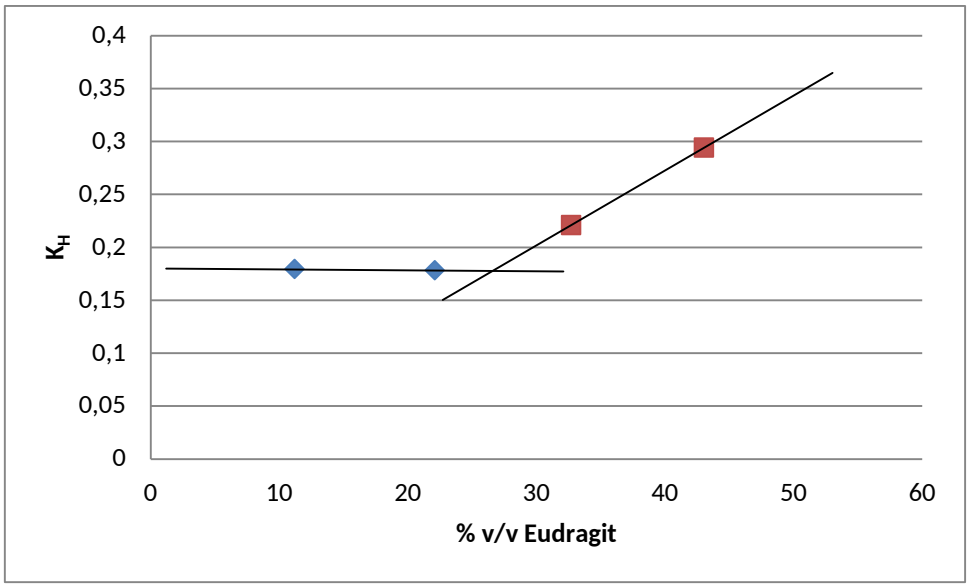

0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
K_H
0
10
20
30
40
50
60
% v/v Eudragit

Figure 1. SeDeM diagram containing the main rheological parameters.

Figure 2a. SeDeM diagram for theophylline

Figure 2b. SeDeM diagram for HPMC K100 CR

Figure 2c. SeDeM diagram for Eudragit RS-PO

Figure 3. SEM microphotograph corresponding to particles of HPMC K100M CR

Figure 4. SEM microphotograph corresponding to particles of Eudragit RS-PO

Figure 5. SEM microphotograph corresponding to particles of theophylline

Figure 6. Dissolution profiles for batches 1 to 8.

Figure 7. Water uptake profiles for batches 1 to 8.

Figure 8. Higuchi's kinetic constant versus the % (v/v) of HPMC K100M CR.

Figure 9. Higuchi's kinetic constant versus the % v/v of Eudragit RS-PO.

Conflict of interest

Declarations of interest: none