Expert Opinion

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Factors affecting drug release from hydroxypropyl methylcellulose matrix systems in the light of classical and percolation theories

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Importance of the field: Hydroxypropyl methylcellulose (HPMC) is a versatile polymer widely used in the preparation of pharmaceutical dosage forms. The behavior of this polymer is a key factor in designing a variety of controlled release systems, especially hydrophilic matrices in which HPMC can be the only substance responsible for controlling the release rate of the drug.
Areas covered in this review: A new approach, proposed in 2004, based on percolation theory to explain the influence of the main formulation factors on drug release from HPMC matrices has been analyzed, paying attention to the advantages with respect to previous theories.
What the reader will gain: The influence of especially important factors such as polymer concentration and particle size is now much better known thanks to these new theories.
Take home message: To formulate a HPMC matrix, the system must be above the polymer's critical point, that is, allowing HPMC to act as outer phase. In this way, a coherent gel layer will be obtained because the first moment and the drug release will be controlled by this layer. Furthermore, knowing the critical points allows the vicinity of these points to be avoided, which are regions of high variability. In this way, robust dosage forms can be obtained.

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1. Introduction

As is well known, controlled release systems provide slow release of drugs to reduce the fluctuation of drug concentration in plasma in order to improve patient compliance, to increase the efficiency of treatment and/or to reduce adverse effects. The key factor identifying controlled release systems is the fact that, using these dosage forms, the time between doses can be increased with respect to conventional dosage forms.

Hydroxypropyl methylcellulose (HPMC), whose International Nonproprietary Name (INN) is hypromellose, short for hydroxypropyl methylcellulose, is a polymer widely used as pharmaceutical excipient and also as a food ingredient, receiving FDA approval as GRAS (generally recognized as safe) in 2006. Chemically it is a 2-hydroxypropyl methylether of cellulose of empirical formula $[C_6H_7O_2(OH)_x(O\text{-}CH_3)_y(OCH_2CHOHCH_3)_z]_n$, where $x = 3 - (z + y)$, $(z + y)$ being the degree of substitution, z the molar substitution of hydroxypropyl and y the molar substitution

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Article highlights.

- The article summarizes the new concepts applied since 2004 to the design of HPMC matrices, based on percolation theory.
- These concepts are compared with previous theories discussing the practical and theoretical consequences.
- The influence of formulation factors such as polymer and drug content, polymer viscosity, polymer blends, drug solubility and particle size on the drug release from HPMC matrices is discussed.
- A HPMC matrix must be formulated above the polymer's critical point, allowing HPMC to develop a coherent gel layer.
- The influence of particle size is connected to the polymer content. Now we know why.
- The new models provide a scientific basis that will fulfil future requirements of the regulatory authorities on science-based formulation and 'quality by design'.

This box summarizes key points contained in the article.

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of methoxy. The main physicochemical properties of the commercially available HPMC grades have been reported in previous papers [1,2].

HPMC is a very versatile polymer, able to develop different roles depending on its concentration, its viscosity level and its distribution in a dosage form. For example, when it is mixed with ethyl cellulose for film coating, HPMC increases the drug release rate, breaking the structure of the ethyl cellulose film [3]. Even mixing it directly with the drug to make a tablet (in an approximately random distribution), HPMC can exert two opposite behaviors, acting as disintegrant when it is incorporated in low concentration (5% w/w in **Figure 1**), whereas for high concentrations it shows an opposite behavior, developing a high-viscosity hydrated layer able to control the drug release, acting as a hydrophilic matrix-forming polymer [4,5].

Hydrophilic matrices represent one of the most used controlled release system nowadays. They basically consist of a dispersion of a drug in a hydrophilic excipient, which, in contact with water, swells, forming a gel or a colloid of high viscosity. More excipients as lubricant aids or solubility enhancers, including water-soluble or water-insoluble fillers and/or pH modifiers, are usually added [6,7].

HPMC is probably the most used polymer for the preparation of hydrophilic matrices. This may be because of its low sensitivity to pH and ionic strength and to its acceptable compressibility and compactibility properties. HPMC can also be used in the development of bioadhesive and floating formulations [8,9].

2. Factors affecting drug release from HPMC matrices

Drug release kinetics from hydrophilic matrices depends on several processes, such as swelling of the polymer, penetration of water through the matrix, dissolution of the drug, transport of the drug through the swelled material and erosion of the matrix. Obviously some of the above processes take place simultaneously [9-13].

Owing, on the one hand, to the large number of processes involved in the drug release and, on the other hand, to the complex and disordered structure of hydrophilic matrices, their study is a difficult task. For this reason, a large number of publications deals with the study of the mechanisms of drug release from hydrophilic matrices [2,10-14]. The most used models to study the release behavior of hydrophilic matrices are summarized by the following equations [4]:

Zero-order equation: (1)

$$Q = k_0 t$$

Higuchi (1963) equation [15]: (2)

$$Q = k_H t^{1/2}$$

Korsmeyer–Peppas (1983) equation [16]: (3)

$$Q = k t^n$$

Peppas and Sahlin (1989) equation [17]: (4)

$$Q = k_d t^m + k_r t^{2m}$$

where: Q is the amount of drug remaining at time t; k_0 is the zero-order release constant; k_H is the Higuchi rate constant; k is the Korsmeyer–Peppas kinetic constant; n is the exponent indicative of the release mechanism; for matrix tablets, an n value of 0.5 indicates diffusion control and an n value of 1.0 indicates erosion or relaxation control [18], intermediate values suggest that at least two processes contribute to the overall release mechanism; k_d is the diffusion rate constant; k_r is the relaxation rate constant; and m is the purely Fickian diffusion exponent for a device of any geometrical shape that shows controlled release.

Numerous formulation factors, such as, for example, drug loading, polymer concentration and distribution, polymer viscosity, mixtures of polymers, drug solubility, drug and excipient particle sizes, pH of the matrix and compression pressure, have been reported to influence the drug release from HPMC matrices [1,2,6,19]. Despite the fact that the individual influence of most of these factors is more or less predictable, it is very difficult nowadays to predict, for a new formulation, what its release behavior will be, that is, which factor or combination of factors will exert a higher influence and will govern the release kinetics from the matrix.

Since 2004 [20], percolation theory has been applied to the study of the release behavior of hydrophilic matrix systems. Most of the systems studied were obtained using HPMC as a matrix-forming polymer. Despite these studies being relatively new and more research needing to be done, this new model is helping to explain on a scientific basis the release behavior of HPMC-based controlled release dosage forms. This would be in accordance with the new requirements

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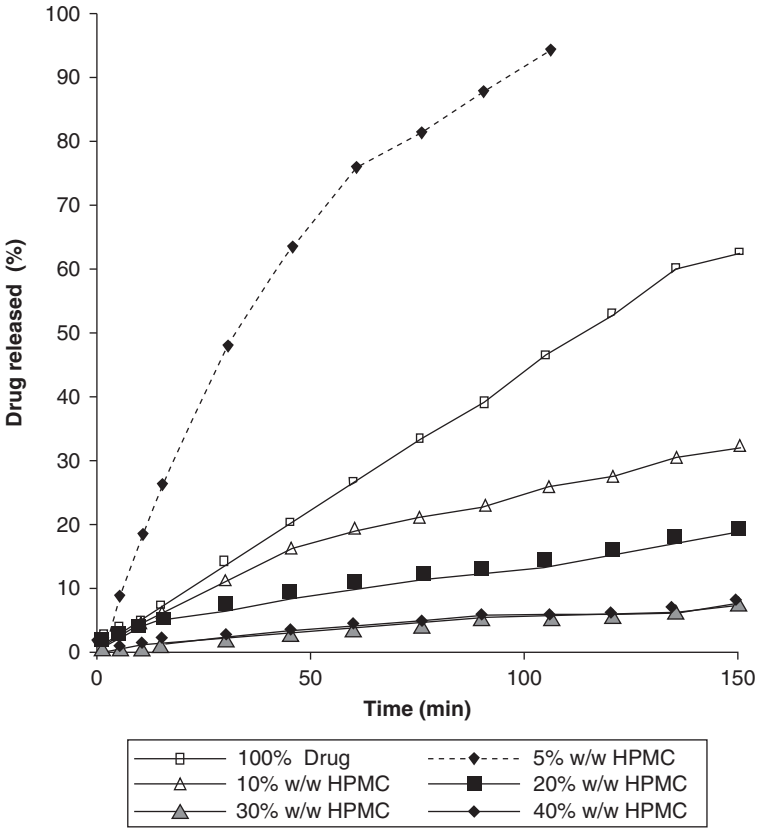

Figure 1. Release profiles illustrating the behavior of HPMC as disintegrant for low concentration (5% w/w, dashed line), whereas for higher concentrations it behaves as a release controlling agent. Note that the drug release profile corresponding to 5% w/w HPMC (dashed line) is clearly above the profile corresponding to a tablet containing 100% of drug.

of regulatory authorities on science-based formulation and quality by design.

Therefore, in the following sections, the model proposed by percolation theory to explain the influence of formulation factors such as polymer and drug content, polymer viscosity, polymer blends, drug solubility and particle size on the drug release from HPMC matrices will be discussed and compared with the proposed 'classical theories'.

The term 'classical theories' is used here to denote the models that work with the Euclidean space and with systems having a fixed structure, whereas percolation theory works with the Euclidean or fractal space and considers that the structure of the system is unknown [21]. The objective is to take into account all the possible configurations of the system, applying the principles of statistical physics and working with the occupation probability, which refers to the probability of a point being occupied by one component [6,21-27].

For example, considering a process as the movement of a molecule of solute through a system, when the system has a structure that allows the molecule to percolate, that is, to move randomly through the whole system, the solute follows a diffusion process, which can be studied using Fick's law of diffusion and the later derived equations based on this law, such as, for example, Higuchi's equations [15]. Nevertheless, these equations do not take into account that in some cases the structure of the system does not allow the solute to move freely through the whole system, changing significantly the kinetic of the process. For example, in an inert matrix below the drug percolation threshold, the drug molecules cannot diffuse through the whole system, being limited to a space region owing to the lack of connectivity of the water-filled pores through the matrix. As a consequence, an important fraction of the drug will remain encapsulated in the matrix. This supposes an important change in the release behavior of the system that is not taken into account by the equations derived from Fick's law.

Opposite to 'classical theories', percolation theory takes into account all the possible structures of the system as a function of the concentration of the components and tries to estimate their influence on the process studied [6,21,22]. For example, the equations derived by Leuenberger and co-workers consider the variations of the diffusion coefficient as a function of the distance to the percolation threshold in inert matrices [26,27]. These equations take into account that the structure of the system is expected to change as a function of the concentration of the components, and this change in

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the structure of the system will influence the diffusion process. According to percolation theory, in an inert matrix below the drug percolation threshold the soluble substances do not percolate through the matrix and only the groups of drug particles in contact with the outer faces of the matrix will be released [26,27].

2.1 Polymer concentration

On the basis of classical theories, the influence of polymer concentration on the drug release should be exerted in a continuous way. For example, according to classical theories the influence on the drug release rate of an increase of 10% in the polymer concentration for matrices containing 10% HPMC would be expected to be similar to matrices containing 20, 30, 40, 50, 60, …% HPMC.

Nevertheless, following percolation theory a different behavior is expected. Percolation theory predicts the existence of critical points that suppose a discontinuity in the properties of the system. Therefore, different structures of systems will be obtained below the critical point than above the critical point.

Percolation theory was introduced into the pharmaceutical field by Leuenberger and co-workers [22-27]. According to this theory, a cluster is defined as a group of neighboring particles of the same component. A cluster is considered to be infinite, coherent or percolating when it extends from one side to the other sides of the system, that is, it percolates through the whole system [21,22]. Otherwise, it is considered a finite or isolated cluster. When a component percolates through a system, it behaves in a similar way to the outer phase of an emulsion, having much greater influence on the properties of the whole system. An important parameter of percolation theory is the percolation threshold, which corresponds to the concentration of one component for which there is a maximum probability of appearance of an infinite or percolating cluster of this component [21].

In the author's case, the system could be a HPMC matrix, for example a matrix tablet. When a component, for example the polymer (HPMC), is percolating through the system, that is, acting as the outer phase, the properties of the matrix will be governed much more clearly by HPMC.

According to percolation theory, a critical point could be expected for each component of the matrix. This critical point supposes a discontinuity of the system, resulting from a geometrical phase transition of this component leading to a different distribution.

The existence of these critical points was first demonstrated in inert matrices [26-28]. To formulate an inert matrix, the excipient must be above its percolation threshold, that is, acting as an outer phase of insoluble excipient, which forms a skeleton controlling the drug release and avoiding disintegration of the matrix.

It has to be emphasized that in solid forms more than one component can act as outer phase. As **Figure 2** shows, the percolation thresholds in solid dosage forms are usually < 50% v/v, therefore in a binary mixture there is a concentration range, between the two percolation thresholds, where a bicoherent system is obtained, that is, both components, drug and excipient, are percolating through the system. In fact, in the case of inert matrices where the matrix-forming excipient is insoluble, the system must be formulated above the drug percolation threshold in order also to have the drug acting as outer phase; otherwise an important fraction of the drug would remain unreleased, embedded by the insoluble excipient [26-28].

In 2004, critical points were reported for the first time in hydrophilic matrices by Caraballo and Leuenberger, studying the water uptake properties of HPMC K15M matrices, using potassium chloride as model drug [20]. Since then, the author's research group has been applying percolation theory to study the release and hydration behavior of swellable matrices [4,6,19,29-37]. According to percolation theory, the critical points observed in the drug release and water uptake studies can be attributed to the percolation thresholds of the components of the matrix, especially to the matrix-forming excipient.

Opposite to inert matrices, in which the most important critical point corresponds to the drug percolation threshold, in the case of hydrophilic matrices the main critical point corresponds to the polymer percolation threshold. The percolation thresholds have been estimated in hydrophilic HPMC matrices, studying the behavior of the kinetic parameters (Higuchi's slope 'b', normalized Higuchi's slope 'b/% (v/v) of HPMC', relaxation constant of Peppas–Sahlin 'k_r') with respect to the volumetric fraction of each component [4,29].

In agreement with percolation theory, these parameters behave as critical properties, showing a sudden change in the neighborhood of the percolation threshold [33]. As stated before, this change is very clear for the polymer (HPMC) percolation threshold. Nevertheless, it is very slight for the percolation threshold of the drug, in most cases being difficult to appreciate. This can be because there is no need of a percolating cluster of drug in order to have complete drug release in hydrophilic matrices. In these matrices the polymer will swell and will favor water penetration throughout the whole system, despite a percolating cluster of soluble substances not being present [29].

The importance of the polymer critical point has also been confirmed in ternary [34,36] and multicomponent [33,37] HPMC hydrophilic matrices. Above the excipient percolation threshold, the matrices contain a coherent cluster of HPMC, which controls the hydration and release rate. The polymer swells in contact with a liquid and forms a gel layer, which spreads over the whole tablet, controlling the drug release rate.

Below the HPMC percolation threshold, the polymer would not percolate through the matrix, leaving important 'holes' that allow water penetration. The subsequent swelling of HPMC cannot avoid a rapid erosion of the matrix, leading in most cases to its disintegration. In these cases the tablet behaves as a conventional dosage form instead of a controlled

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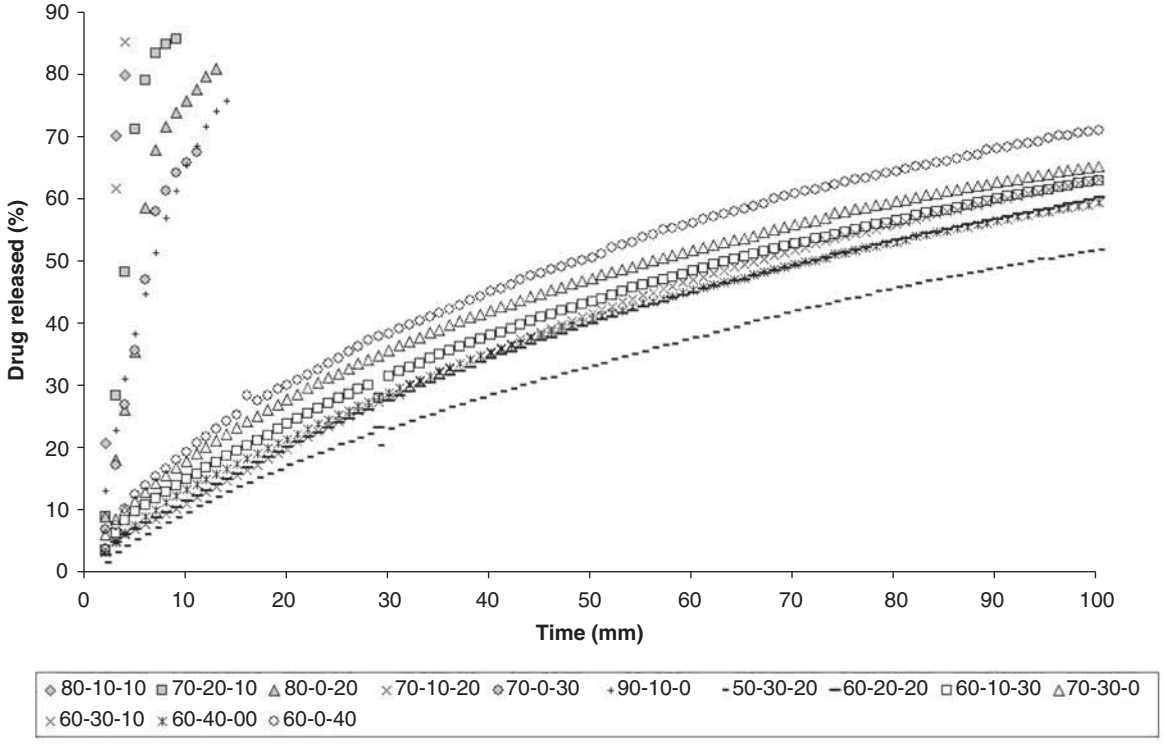

Figure 2. Representation of the three possible structures of the system in binary solid forms as a function of the percentage of the components A and B (typically drug and excipient). When the drug concentration is below the drug percolation threshold, only the excipient (B) is percolating the system, whereas the drug particles will form isolated (finite) clusters. Between the two percolation thresholds both components are percolating the system, which is called a bicoherent system. Finally, the third possibility is that the drug concentration is so high that it does not allow the excipient to percolate the system, only isolated (finite) clusters of excipient will be found, whereas the drug will be acting as the outer phase (percolating the system).

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release matrix. Therefore, knowledge of the percolation threshold of HPMC would result in a clear improvement of the design of hydrophilic matrix tablets based on this polymer. It is important to note that the percolation thresholds correspond to volume fractions because the ability of the particles to contact with neighboring ones depends on their volume instead of on their weight [21].

Another point that should be taken into account is the fact that, as will be commented on in Section 2.6, the percolation threshold of a component depends on its relative particle size.

2.2 Polymer viscosity

Depending on the degree of substitution of HPMC, different viscosities can be obtained. There are commercially available hydroxypropyl methylcelluloses with several viscosity levels [2]. The viscosity values are usually reported as the viscosity shown by an aqueous dispersion containing 2% w/w of the polymer.

Polymer viscosity is one of the better known factors affecting drug release from hydrophilic matrices. Obviously, an increase in the viscosity level of the polymer will result in a decreased diffusion rate, affecting both water uptake and drug transport. Therefore, a decrease in the release rate can be expected.

It was not so clear whether the polymer viscosity would affect the critical point of the polymer or whether this critical polymer concentration would remain unchanged even if different viscosity levels were used. The question was whether a change in the polymer viscosity would change the release profiles of all the formulations, keeping the same values of critical concentration of the polymer (hypothesis A), or, on the contrary, the critical point would also change as a function of the polymer viscosity (hypothesis B).

It is interesting to remember that the critical point or critical concentration of the polymer is a concentration showing a sudden change in the release properties of the matrix. According to percolation theory, this change is due to the polymer percolation threshold, that is, to the fact that the distribution of the polymer is changing at this point, passing from being isolated and surrounded by the other components of the formulation, that is, acting as the inner phase of an emulsion, to a different distribution in which the polymer will be percolating the whole matrix (acting as the outer phase).

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Following percolation theory, the behavior described in hypothesis A was expected, taking into account that the polymer distribution inside the matrix will not be modified by varying the polymer viscosity level. Therefore, the polymer percolation threshold would remain at the same concentration.

Despite more data being needed, preliminary results of the authors' research group [38] support hypothesis A, and therefore the interpretation proposed by percolation theory.

2.3 Polymer blends

Blends of HPMC with different cellulosic and non-cellulosic polymers have been widely used in the formulation of controlled release hydrophilic matrices [36], in order to obtain the required release properties. Typically HPMC has been mixed with sodium carboxymethyl cellulose (NaCMC) as a strategy to find zero-order drug release or better drug release properties [39].

As indicated in previous sections, the percolation theory has been applied since 2004 to explain the behavior of binary hydrophilic matrix systems [4,20,29]. Percolation theory was initially developed for binary systems, whereas most pharmaceutical formulations include more than two components. In previous work [40] dealing with carteolol hydrochloride inert matrices, multicomponent systems were simplified to binary systems based on a common property. On the other hand, Caraballo and co-workers [41] described the existence of a 'combined percolation threshold' on inert ternary matrix systems, defining the combined percolation threshold of two components as the volume fraction at which there is maximum probability that these components, jointly considered, start to percolate the sample.

In a recent study [36], experimental ternary matrices were performed using mixtures of two matrix-forming hydrophilic polymers, HPMC and NaCMC, and using potassium chloride as the model drug, with the purpose of studying for the first time the effect of one hydrophilic excipient on the critical point of the other, and to investigate the presence of a combined percolation threshold of both excipients. The release profiles of these matrices (see **Figure 3**) showed very clearly two release behaviors, revealing which matrices contained a continuous and consistent gel layer controlling the drug release from the first moment. As can be appreciated from **Figure 3**, the matrices can be easily classified according to their release profiles in a group showing diffusion-controlled drug release (which obviously is expected to correspond to the matrices formulated above the polymer percolation threshold) and a second group (below the polymer percolation threshold) showing a release behavior similar to conventional dosage forms.

The kinetic analysis of the release data [36] confirms this assumption. Nevertheless, in the ternary systems studied the concept of being above the excipient percolation threshold is not as simple as in the binary systems: when a matrix is observed to show controlled release of the drug, it can be argued, according to the concepts of percolation theory, that a continuous gel layer has been obtained. Nevertheless, it is difficult to know which polymer or polymers are forming this gel layer.

Therefore, in a three-component plot, representing simultaneously the percentage of KCl, HPMC and NaCMC, a critical excipient barrier instead of a critical excipient concentration would govern the release properties of the system. This critical excipient barrier was located in the range 54 – 61% v/v (60 – 70% w/w) KCl [36].Therefore, above this critical barrier a percolating cluster of excipients leads to the formation of a gel layer from the first moment and the matrices show controlled drug release.

The following question studying these tablets concerns the composition of this gel layer. As mentioned previously, the existence of a 'combined percolation threshold' was described in 1996 [41] on inert ternary matrix systems. A combined percolation threshold for HPMC and NaCMC would mean a common percolation threshold, that is, a fraction of polymer that can be reached using one of the polymers or any combination of both excipients. Therefore, the concept of combined percolation threshold, as described by Caraballo *et al.* [41], implies that this critical excipient concentration can be reached using HPMC as the only polymer (binary mixtures drug/HPMC), and can also be reached using only NaCMC (mixtures drug/NaCMC).

As can be observed in the work by Contreras-Cháves *et al.* [36], this seemed not to be the case, HPMC and NaCMC having different ranges for the drug percolation thresholds with a very small overlapping region. The excipient percolation thresholds for the binary mixtures were estimated based on the water uptake and especially on the release behavior of the matrices. For the binary KCl–HPMC matrices the HPMC percolation threshold was situated between 29 and 41% (v/v) HPMC, whereas the excipient percolation threshold for the binary KCl–NaCMC hydrophilic matrices was estimated between 39 and 54% (v/v) NaCMC.

Therefore, there was little possibility of these two excipients showing a combined percolation threshold. Nevertheless, the question of the possible influence of each excipient on the ability of the other polymer to form a percolating gel layer was not answered. To investigate it in more detail, two opposite patterns were considered.

(1) *Pattern 1.* The excipients are interchangeable. In this case both excipients show full collaboration in order to create the gel layer controlling the drug release. This behavior implies that the concentrations of the hydrophilic polymers HPMC and NaCMC will be fully additive, that is, the value of Higuchi's slope b will be the same whenever the sum of the concentrations of both excipients is the same, independent of the individual concentration of each of the excipients.

(2) *Pattern 2.* The excipients behave independently of each other. This hypothesis supposes that at least the critical

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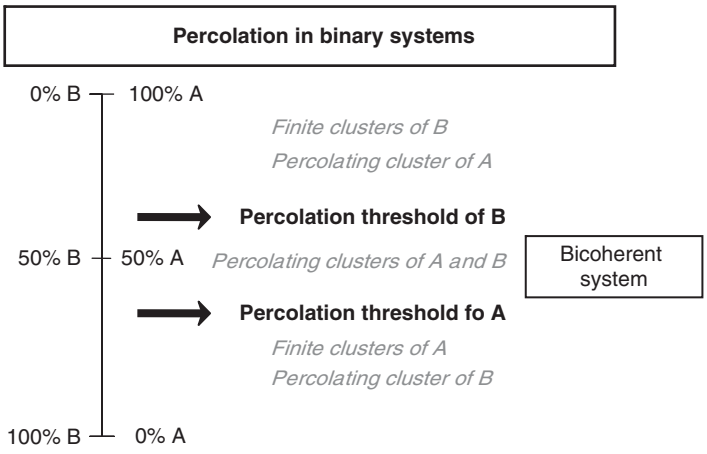

Figure 3. Dissolution profiles of ternary and binary hydrophilic matrix systems. The key indicates the weight in weight concentration of the three components (KCl-HPMC-NaCMC).

concentration of one of the excipients (HPMC or NaCMC) has to be reached in order to obtain the gel layer controlling drug release, independently of the concentration of the other polymer.

These two patterns were applied to the data obtained [36] to study their validity. Pattern 1 failed to explain the release behaviors of lots containing very similar volume percentages of polymers (adding HPMC + NaCMC) and release rates almost three times larger for one than for the other. On the other hand, pattern 2 did not explain the behavior of the data either. For example, matrices containing almost the same percentage volume in volume of HPMC showed Higuchi's slopes varying > 22 times.

Therefore, this study concluded that the behavior of the polymers was intermediate between the two extreme situations, that is, there is some collaboration between HPMC and NaCMC in order to form the gel layer controlling the release rate from hydrophilic matrices. Nevertheless, the effect of these polymers is not additive. A possible explanation could be the existence of interactions between chemical groups of the polymers that avoid a complete collaboration between them.

In this sense, another study by the author's group dealing with HPMC matrices containing verapamil·HCl as drug and microcrystalline cellulose (MCC) as filler reported a possible collaboration between MCC and HPMC to establish the gel layer, resulting in lower values for the HPMC percolation thresholds [33].

2.4 Drug content

Despite the fact that the concentration of drug substance or the concentration of soluble substances is fundamental to explaining the release behavior of inert matrices, this factor has shown little influence on the behavior of hydrophilic matrices [29,31]. The main difference is that in inert matrices water has to enter through soluble substances (the drug and soluble excipients, if any), otherwise the drug will remain encapsulated by the excipient. Nevertheless, in hydrophilic matrices water can enter the system through the hydrophilic polymer, hydrating the molecules, and also through the pores created as a consequence of the swelling process. Therefore, the existence of a percolating cluster of soluble substances at the onset of the release process is not very important, taking into account that during the release process water will percolate through the whole system [29].

This was found in the release behavior of the HPMC matrices containing a model drug (potassium chloride) [19,29], as well as real drugs [30], showing in most cases very few differences between matrices formulated above the drug percolation threshold (where the drug substance is acting as outer phase) and matrices in which the drug particles are isolated by the other components of the formulation (acting as inner phase).

2.5 Drug solubility

Most studies in the field assume that *in vitro* release of water-soluble drugs is controlled mainly by diffusion out of the gel layer, whereas release of poorly soluble drugs is likely to be controlled by polymer relaxation-erosion [42,43]. This is attributed to the following three main reasons.

(1) Poorly soluble drugs normally have low diffusion rates, owing to the fact that the dissolution rate is usually low, because of the low solubility. Therefore, the drug release rate following this mechanism would be low for poorly soluble drugs.
(2) Poorly soluble drugs are usually hydrophobic substances. Therefore, their inclusion in a hydrophilic matrix results in the creation of regions of hydrophobic (at least not hydrophilic) nature. Furthermore, these substances usually remain as solid particles for a long period of time. These regions are considered to reduce the entanglement of the polymer chains and the gel strength, facilitating its

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erosion and therefore favoring the release of the drug through this mechanism [43].

(3) Substances with high solubility enhance the osmotic stress and accelerate water penetration into the matrix, resulting in a higher degree of polymer swelling and formation of more microcavities. This increases the diffusion mechanism for highly soluble drugs [44].

From the point of view of percolation theory, it would be interesting to know whether the drug solubility affects only the release mechanism, keeping unchanged the critical points of the excipient or, on the contrary, a different concentration of polymer will be needed to obtain a gel layer able to control the drug release. In other words, it would be interesting to know whether the drug solubility affects the critical points of the matrix (mainly the excipient critical point), changing the percolation threshold of the polymer.

This question has been investigated in a recent paper [32] that prepared HPMC K4M hydrophilic matrices containing acetaminophen, theophiline and ranitidine·HCl. The results were compared with a previous paper dealing with similar HPMC K4M matrices containing acyclovir [4]. The results obtained were in agreement with previously exposed theories, showing the drugs with lower solubilities and slower and more linear release profiles, as a result of erosion-driven release processes. Release of intermediate and highly soluble drugs (acetaminophen and ranitidine·HCl) was faster and purely Fickian (exponent n close to 0.5).

The matrices were also characterized from the point of view of percolation theory, estimating their polymer percolation thresholds based on their release and water uptake behavior (measured using the Enslin modified method). Plotting the results obtained versus the drug solubility, no relationship was found between the polymer percolation threshold and drug solubility, even when correcting the percolation thresholds with the relative particle size to avoid the masking effect of the different particle size [32]. The effect of particle size is explained in the following section.

On the other hand, multicomponent HPMC hydrophilic matrices containing verapamil·HCl and carbamazepine have also been studied by the author's group [37]. The HPMC percolation thresholds for these matrices, containing drugs with very different water solubilities, were estimated and compared, and showed no significant influence of drug solubility on the HPMC critical concentration (excipient percolation threshold). This supports the validity of the percolation threshold as a preformulation parameter and is also indicative of the robustness and broad functionality of the HPMC hydrophilic matrices [37].

2.6 Particle size

It is well known that the particle size of the polymer influences the release behavior of hydrophilic matrices [45-47]. In the light of 'classical' theories, the increase in drug release rate observed when coarser polymer particles are used is attributed to the fact that coarser polymer particles need a longer time for water to penetrate in order to swell, that is, before the particles bind together and form a stable gel barrier. Furthermore, the gel layer obtained shows larger pore size when coarser HPMC particles are used.

It is important to emphasize that most authors reported that the previously described effect of particle size seemed to disappear for matrices containing high polymer concentrations [45-47]. For example, Heng *et al.* reported in 2001 [48] a significant increase in the release rate from HPMC K15M/Aspirin matrices when the particle size of the polymer was > 113 µm. These authors also indicated that this effect was dependent on polymer concentration. The explanation proposed by classical theories fails to explain the dependence between the influence of the particle size and the polymer concentration.

On the basis of percolation theory, the percolation thresholds show a linear dependency on particle size. This relationship was discovered by Caraballo *et al.* [49] in inert matrices. Subsequent studies [4,19,33,50,51] have shown that this dependence can also be extended to hydrophilic matrices and that the factor responsible for the change of the percolation threshold is the relative particle size of this component, that is, the result of dividing the mean particle size of this component by the mean particle size of the other components of the formulation.

In this way, the percolation theory approach can explain that the particle size influences the release rates: as stated in previous sections, hydrophilic matrices must be formulated above the polymer percolation threshold. The effect of particle size indicates that higher polymer percolation thresholds will be obtained for higher relative particle sizes of the polymer, owing to the lower ability to percolate the tablet of the coarser particles. For a given polymer percentage, as the percolation threshold increases for coarser particles, the distance to the percolation threshold will be reduced. This would be especially significant if the studied matrix were formulated very close to the polymer percolation threshold or even below this threshold. In the first case the formulation can experience a significant change in the release properties. In the second case (below the threshold), the formulation will fail to control the drug release.

Nevertheless, if the studied formulation is far above the polymer percolation threshold, even using coarser particles (which cause the excipient percolation threshold to rise) this formulation will fall far enough from the percolation threshold to avoid a significant change in the release properties.

Equation 5 is known as the fundamental equation of percolation theory [4,6,21,22]:

$$X \propto S\,(p - p_c)^q$$

where: X is the studied property; S is a constant; p is the occupation probability, which corresponds to the volumetric fraction of the component; p_c is the percolation threshold; $(p - p_c)$ is the distance to the percolation threshold; and q is a critical exponent.

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According to this equation, the critical properties depend exponentially on the distance to the percolation threshold; so this dependence is clearly significant only close to the percolation threshold (10% above or below the percolation threshold [21]). This is the reason why the matrices with a high concentration of polymer do not experience the effect of the particle size of the polymer, as correctly reported by previous authors [48].

3. Conclusions

The behavior of HPMC is still far from completely known, especially when it enters into contact with aqueous fluids, leading to hydration of the polymer chains, changing the structure of the polymer. This process is very useful in pharmaceutical technology, especially for increasing the viscosity of a system and for controlling drug release.

The interpretation proposed in 2004, based on percolation theory, shows significant advantages to have a better understanding of the influence of the main formulation factors on the behavior of HPMC. For example, this approach provides a scientific explanation for the existence of a critical polymer concentration, as well as for the influence of the particle size on the release behavior of HPMC matrices.

Furthermore, for practical purposes, knowledge of the critical points of the system will allow us to avoid formulating in the vicinity of these points, which are regions of high variability. In this way, robust dosage forms can be obtained.

4. Expert opinion

HPMC is a polymer that has wide use in pharmaceutical formulation. Furthermore, its important advantages (safety, availability, compatibility with tissues, versatility, etc.) foretell increasing use of this polymer in the future.

Nevertheless, the behavior of this polymer is not well known, especially when it is hydrated, undergoing conformational changes in its molecule. Therefore, there is a need for new knowledge, especially when HPMC is included in solid dosage forms, where the hydration process and the following conformational changes will condition their function. Perhaps the most typical example of these dosage forms is the HPMC hydrophilic matrices, in which the glassy–rubbery transition is a key factor influencing the water uptake and release kinetics of these controlled release systems.

As has been detailed in this paper, percolation theory has provided, since 2004, a more scientific basis for the study of these systems, anticipating the existence of a critical point of HPMC governing the behavior of the matrices or explaining, for example, what would be the effect of particle size and why this effect seems to disappear (as reported by previous authors) when the matrix contains a high concentration of HPMC.

Despite these being important findings, more research is needed to determine the influence of the formulation factors on the critical points of the system. There are still important factors whose influence on the percolation thresholds and therefore on the corresponding critical points is not yet well known. This may be owing to the difficulty in estimating the percolation thresholds based on experimental measures. On some occasions the error in the estimation can make it difficult to obtain significant results. The positive point in this sense is that, as the number of experiments increases, better statistical significance will be obtained, leading to better knowledge of these parameters. Obviously an improved method to estimate the critical points will be a very important help to go faster to valid conclusions. In this sense, a method for fast estimation of the critical points in inert matrices was developed by Espina and Caraballo in 2004 using wet conductometry [52]. Now there is a need for a method that facilitates the estimation of the critical points in hydrophilic matrices.

One of the main questions concerning the application of percolation theory in pharmaceutical technology is the degree of universality of the percolation thresholds. For the moment only one factor has shown a clear influence on the percolation thresholds. This factor is the relative particle size of the component, that is, its mean particle size divided by the mean particle size of the other components of the formulation. This factor shows the advantage that its influence is linear, so it can be easily corrected in order to estimate the percolation threshold for a given system.

If the percolation thresholds were universal, that is, the same for a given component independently of the formulation factors of the system in which the component is included (except the mean particle size), it would not be necessary to calculate it for each new system. The dream is that the percolation thresholds could be used in the future as preformulation parameters; therefore, knowing the percolation threshold of each component of the formulation, the critical points governing the behavior of the system could be anticipated before performing experimental assays.

This will undoubtedly lead to a science-based formulation, accomplished with the new trends of the regulatory agencies and improving the quality of the dosage forms, applying the concept of 'quality by design' [53].

On the other hand, it is important to emphasize that knowledge of the percolation thresholds and the corresponding critical points of the system is very important for the right application of one of the most usually used optimization techniques, as the factorial design or experimental design. This method deals with factors having a continuous influence on the response variable; nevertheless, the critical points represent discontinuities of the system. Therefore, including in the study points below and above the percolation thresholds is not consistent with the method and can lead to erroneous results (such as, for example, including

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some water-in-oil emulsions in a design intended to optimize oil-in-water emulsions).

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