

Polymer Percolation Threshold in Multi-Component HPMC Matrices Tablets

Maryam Maghsoodi*, Leila Barghi

School of Pharmacy and Drug applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article Type:
Research Article

Article History:

Received: 21 May 2011

Accepted: 5 July 2011

ePublished: 20 July 2011

Keywords:

Percolation theory

HPMC

Phenobarbital

Percolation threshold

ABSTRACT

Introduction: The percolation theory studies the critical points or percolation thresholds of the system, where one component of the system undergoes a geometrical phase transition, starting to connect the whole system. The application of this theory to study the release rate of hydrophilic matrices allows to explain the changes in release kinetics of swellable matrix type system and results in a clear improvement of the design of controlled release dosage forms. **Methods:** In this study, the percolation theory has been applied to multi-component hydroxypropylmethylcellulose (HPMC) hydrophilic matrices. Matrix tablets have been prepared using phenobarbital as drug, magnesium stearate as a lubricant employing different amount of lactose and HPMC K4M as a filler and matrix forming material, respectively. Ethylcellulose (EC) as a polymeric excipient was also examined. Dissolution studies were carried out using the paddle method. In order to estimate the percolation threshold, the behaviour of the kinetic parameters with respect to the volumetric fraction of HPMC at time zero, was studied. **Results:** In both HPMC/lactose and HPMC/EC/lactose matrices, from the point of view of the percolation theory, the optimum concentration for HPMC, to obtain a hydrophilic matrix system for the controlled release of phenobarbital is higher than 18.1% (v/v) HPMC. Above 18.1% (v/v) HPMC, an infinite cluster of HPMC would be formed maintaining integrity of the system and controlling the drug release from the matrices. According to results, EC had no significant influence on the HPMC percolation threshold. **Conclusion:** This may be related to broad functionality of the swelling hydrophilic matrices.

Introduction

A matrix tablet is the simplest and most cost-effective method to develop and manufacture an extended release (ER) dosage form. Hydrophilic matrices are flexible technologies to obtain desired release profiles for a wide range of drugs, with cellulose ethers, and in particular hydroxyl propylmethylcellulose (HPMC) being the polymers of choice for their formulations. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading.¹ The percolation theory studies the critical points or percolation thresholds of the system, where one component of the system undergoes a

geometrical phase transition, starting to connect the whole system. These percolation thresholds are critical concentrations where some tablet properties (percentage of drug released, release rate, mechanical properties, etc.) may undergo sudden changes.² Percolation theory represents a powerful concept which covers a wide range of applications in pharmaceutical technology. The knowledge of the percolation threshold of the components of the matrix formulations contributes to improve their design. First, in order to develop robust formulations, i.e., to reduce variability problems when they are prepared at industrial scale, it is important to know the concentrations corresponding to the

* **Corresponding author:** Maryam Maghsoodi (PhD), School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.

E-mail: mmaghsoodi@gmail.com Tel: (+98) 411-3392593, Fax: (+98) 411-3344798

percolation thresholds. The percolation thresholds correspond to formulations showing a high variability in their properties as a function of the volume fraction of their components. Therefore, in order to increase the robustness of the formulation, the nearby of the percolation thresholds should be avoided. Second, the excipient percolation threshold is the border between a fast release of the drug (below the threshold) and a drug release controlled by the formation of a coherent gel layer (above the excipient percolation threshold). Therefore the knowledge of this threshold will allow us to avoid the preparation of a number of unnecessary lots, ring the development of a pharmaceutical formulation, resulting in a reduction of the time to market.

The percolation theory has been applied to describe controlled release inert matrix systems.^{3-5, 6, 7-9}

In recent studies¹⁰⁻¹⁴ the existence of critical points affecting the water uptake and the release behavior of hydrophilic matrices has been observed. Nevertheless, these works have been performed employing binary systems, i.e., tablets composed solely with the hydrophilic polymer and the drug. However, typical ER matrix formulations consist of a drug, release retardant polymer and one or more excipients. Additives such as fillers or polymeric excipients may be included to improve or optimize the release performance of the formulation system. Previous works have demonstrated experimentally the influence of the particle size of the components on the percolation threshold in hydrophilic matrices, as well as the importance of the initial porosity in the formation of the gel layer.^{12, 13}

The objective of the present paper is to study in multi-component ER formulations, the existence of critical points governing drug transport inside hydrophilic matrix systems prepared from HPMC. Various ER formulations of phenobarbital were prepared using lactose as a filler and magnesium stearate as a lubricant. Ethyl cellulose (EC) as a polymeric excipient was also examined in this study. Then the percolation theory was applied to these multi-component hydrophilic matrices.

Materials and methods

Materials

HPMC K4M (Colorcon, UK), EC (Colorcon, UK), Phenobarbital (Merck, Germany), magnesium stearate (BDH Chemicals Ltd, Poole, Dorset, UK) and lactose monohydrate (Merck, Germany) were used.

Matrix preparation

Table 1 lists the formulations used in this study. Initially, all materials, with the exception of magnesium stearate, were blended for 10 min in a Turbula mixer (type S27, Erweka, Apparatebau, Germany). Magnesium stearate was then added and blended for an additional period of 5 min. The mixtures (total weight 300 mg) were directly compressed at the maximum compression force accepted by the formulation (10 KN) with a hydraulic press (Riken Seiki Co, Japan) fitted with a 10-mm diameter flat punch.

Table 1. The composition and concentration of materials used in matrix formulations

batch	Phenobarbital (mg)	HPMC (mg)	Lactose (v/v)	Mg St (mg)	EC (mg)	EC (v/v)
HPMC ₁ /lactose	100	25	9.2	172	3	-
HPMC ₂ /lactose	100	50	18.1	147	3	-
HPMC ₃ /lactose	100	75	26.8	122	3	-
HPMC ₄ /lactose	100	100	35.3	97	3	-
HPMC ₁ /EC ₃ /lactose	100	25	8.6	97	3	75
HPMC ₂ /EC ₂ /lactose	100	50	17.3	97	3	50
HPMC ₃ /EC ₁ /lactose	100	75	26.2	97	3	25

Dissolution studies

The dissolution kinetics of the tablets was monitored using a tablet dissolution tester (8ST, Caleva, England). The USP paddle –type apparatus was used. Rotation speed was 50 rpm and dissolution medium was 900 ml distilled water¹⁵, maintained at 37 °C. At each sampling interval, 5 ml of the dissolution medium was withdrawn and an equal volume of fresh distilled water was replaced. Phenobarbital was determined at 240 nm using an ultraviolet spectrophotometer (Shimadzu 120A, Japan). Experiments were performed for three tablets for each formulation and mean and standard deviation values were obtained. The release rates from controlled release polymeric matrices can be studied using the zero-order model (Eqs. (1) and (2) proposed by Higuchi¹⁶, Eq. (3) proposed by Korsmeyer et al.¹⁷, and Eq.(4) proposed by Peppas and Sahlin.¹⁸ Linear and non-linear least squares fitting methods were used to determine the optimum values for the parameters present in each equation:

$$Q = kt \quad (1)$$

$$Q = b\sqrt{t} \quad (2)$$

$$Q = k_1 t^n \quad (3)$$

$$Q = k_d t^m + k_r t^{2m} \quad (4)$$

Where Q is the amount of drug remaining at time t ; k is the zero order release constant on Eq.(1), b is the Higuchi rate constant on Eq.(2), k_1 is the Korsmeyer–Peppas kinetic constant; n is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested.¹⁹ For thin slabs, values of $n = 0.5$ indicate Fickian release, values of $0.5 < n < 1.0$ indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of $n = 1.0$ indicate a case II (purely relaxation controlled) drug release. k_d is the diffusional constant; k_r is the relaxational constant and m is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.

Estimation of the percolation threshold

In order to estimate the percolation threshold, the behavior of the kinetic parameters (Higuchi's slope "b", relaxational constant of Peppas–Sahlin "k_r") with respect to the volumetric fraction of HPMC at time zero, were studied.¹¹⁻¹⁴ According to the fundamental equation of percolation theory (Eq. (5)), if these parameters behave as critical properties, we can expect that

$$X \propto (p - p_c)^q \quad (5)$$

Where X is the studied property; S is a constant; $(p - p_c)$ is the distance to the percolation threshold and q is a critical exponent.²⁰

Results and discussion

Study of release profile and release kinetics

The dissolution studies for the HPMC/lactose systems are shown in Figure 1.

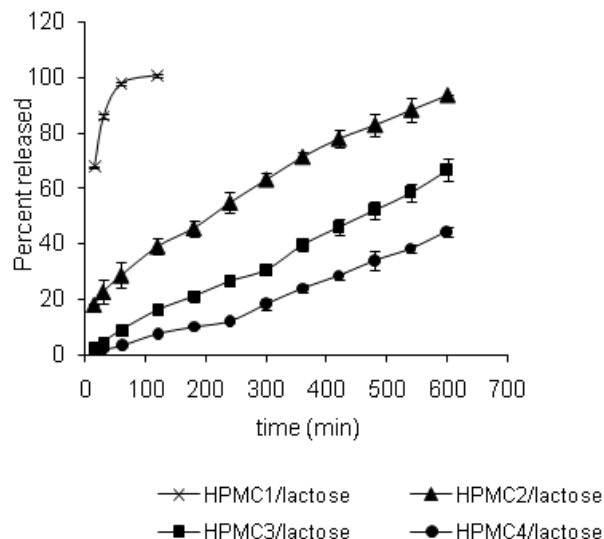


Figure 1. Dissolution profiles for HPMC/lactose matrices

The drug release profiles were evaluated both visual and mathematically, taking into account the kinetic parameters obtained from the fitting of the obtained data to the main kinetic models. According to Figure 1 an important change in the drug release profiles between HPMC₁/lactose and HPMC₂/lactose can be appreciated. The tablets containing lower than 50 mg HPMC allow the free dissolution of the drug when they are exposed to the dissolution medium due to the fact that the gel layer is not established since the first moment and, in these conditions, this structure cannot control the drug release. The kinetic analysis of the release data confirms this change. Table 2 shows the values obtained from Higuchi's, zero order, Korsmeyer and Peppas–Sahlin models. As it can be observed, the Korsmeyer's release rate (0.059 -0.344% minⁿ) and the Higuchi's slope, b (0.037 -0.076% min^{-1/2}) increase between HPMC₂/lactose and HPMC₁/lactose. For these matrices, according to Higuchi ($r^2 > 0.98$) and Peppas–Sahlin ($K_r < K_d$) equations, drug release is governed by the diffusion process. In the matrices that release the drug at slow rates (above 50 mg HPMC), the release was controlled by the fully hydrated gel layer. For these matrices, the erosion of the hydrophilic gel structure has shown an important influence on the drug release. This indicates a change in the drug release mechanism from diffusional to a relaxation or erosion controlled release.

Table 2. Kinetic parameters of drug release from the matrix tablets

Batch	Zero order equation		Higuchi equation		Korsmeyer equation			Peppas Sahlin equation			
	%(W/W) HPMC	K_0 (%t ⁻¹)	r^2	b (%t ^{-1/2})	r^2	K (%t ⁿ)	n	r^2	K_d (%t ^{-m})	K_r (%t ^{-2m})	r^2
HPMC ₁ /lactose	9.2	0.0064	0.94	0.0760	0.98	0.344	0.260	0.99	0.2510	-0.0145	0.99
HPMC ₂ /lactose	18.1	0.0013	0.98	0.0374	0.99	0.059	0.396	0.99	0.0412	0.0006	0.99
HPMC ₃ /lactose	26.8	0.0011	0.99	0.0301	0.95	0.002	0.877	0.99	0.0002	0.0019	0.99
HPMC ₄ /lactose	35.3	0.0007	0.99	0.0203	0.92	0.001	0.957	0.97	-0.0012	0.0012	0.98
HPMC ₁ /EC ₃ /lactose	8.6	0.0058	0.98	0.0685	0.99	0.320	0.252	0.99	0.2350	-0.0114	0.99
HPMC ₂ /EC ₂ /lactose	17.3	0.0012	0.98	0.0364	0.99	0.024	0.548	0.99	0.0266	0.0011	0.99
HPMC ₃ /EC ₁ /lactose	26.2	0.0011	0.99	0.0302	0.95	0.001	1.383	0.98	-0.0075	0.0023	0.98

This is indicated by the better fit of the drug release kinetics to the zero-order equation and increasing the n value of Korsmeyer–Peppasequation from 0.26 to 0.96 with increasing HPMC amount from 25 to 100 mg. Furthermore, the values of the Peppas and Sahlin constants confirm this change on the drug released mechanism. The diffusional constant, k_d decreases (0.251 to -0.001 % min^{-m}) whereas the relaxational constant, k_r increases from negative value to 0.001 % min^{-2m}.

Therefore, the results obtained from the kinetics analysis are in agreement with the release profiles, indicating a clear change in the release rate and mechanism between matrices by increasing HPMC. From the point of view of percolation theory, this means that above 50 mg HPMC K4M, the existence of a network of HPMC (able to form a hydrated layer from the first moment) controls the drug release.

Figure 2 shows the release profile of drug from HPMC/EC/ lactose matrices. According to this figure, drug release increased as the portion of HPMC replaced by EC in these matrices. These results confirmed the finding of Ford et al.²¹ who investigated the effect of replacement HPMC by diluents and reported that replacement of portions of HPMC within the matrices by diluents increased the release rate of promethazine hydrochloride, irrespective of whether the diluents were water soluble or water insoluble.

As Takka et al.²² - HPMCK100: Eudragit S-, Lotfipour et al.²³ - HPMC K4M: Eudragit RSPO- and Escudero et al.²⁴-HPMC: hydroxyl propylcellulose-methyl methacrylate (HCMMA)-, it is observed that the amount of HPMC played a dominant role, affecting the drug

release in these mixtures. The profiles were more similar to HPMC/ EC mixtures in function of predominant polymer.

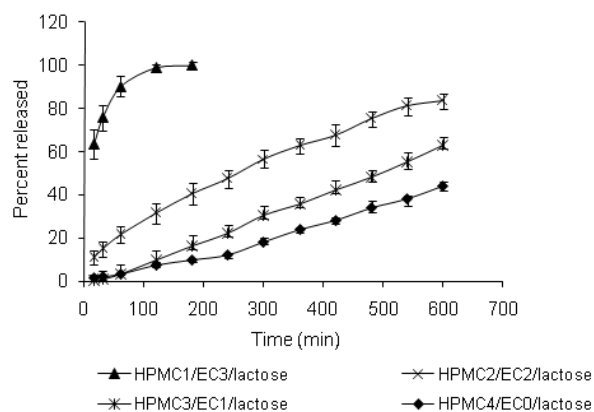


Figure 2. Dissolution profiles for HPMC/EC/lactose matrices. In Figure 2, two kinds of behaviours can be clearly appreciated. The first one, corresponding to batch HPMC₁/EC₃/lactose shows a fast drug release, whereas the second one (HPMC₂/EC₂/lactose and HPMC₃/EC₁/lactose) shows a modified drug release. In the case of batch HPMC₁/EC₃/lactose, as it can be observed in Table 2, the studied kinetic constants, i.e., the kinetic constant b from Higuchi's model, k from Korsmeyer's model, and the diffusional constant k_d showed higher values compared to the batches HPMC₂/EC₂/lactose and HPMC₃/EC₁/lactose. This means that the drug release from this batch is governed by diffusion mechanisms.

The kinetic analysis of the release profiles from batches HPMC/EC/lactose (see Table 2) shows increasing the values of the relaxational constant k_r and decreasing the diffusional constant k_d in the Peppas and Sahlin with increasing HPMC concentration. Furthermore, increasing the n value of Korsmeyer equation from 0.25 to 1.3 confirms the change on drug release mechanism to an erosion/relaxation controlled release of the drug. Finally, the analysis of the release profiles obtained from the studied HPMC/EC/lactose and HPMC/lactose matrices indicates clearly the existence of a critical behaviour in these matrices systems.

Estimation of HPMC percolation thresholds

The excipient percolation threshold is one of the main factors governing the gel layer formation and the control of the drug release from hydrophilic matrices. Above the excipient percolation threshold, a percolating cluster of this component exists and the gel layer is formed from the first moment, which is able to control the hydration and drug release rate. Below the excipient percolation threshold, the excipients do not percolate the system and the drug release is not controlled by the gel layer, resulting in a faster release rate. In order to estimate the percolation threshold, the evolution of the measured kinetic parameters (“ b ” slope of Higuchi, “ k_r ” relaxational constant of Peppas–Sahlin) as a function of the volumetric fraction of HPMC at time zero were studied¹¹⁻¹⁴ and the results are shown in Figure 3 and Figure 4. As the theory of percolation predicts (Eq. (5)), the kinetic parameters studied show a non-linear behaviour as a function of the volumetric fraction of HPMC. The results show that HPMC percolation threshold for HPMC/lactose matrices is between 9.2 and 18.1% (v/v) of HPMC. This fact indicates that above this range an infinite cluster of HPMC has been formed, which controls the release of drug from these systems. The differences between the critical points obtained in this work for multi-component systems, and the results from previous works using binary systems (polymer and drug), points out the possibility that the lactose used as a soluble filler, may help to establish the gel layer. This is attributable to this fact that lactose decreases the concentration of polymer in gel layer and consequently diffusion of water into the table is facilitated. If this hypothesis is confirmed by further studies, the presence of lactose would be responsible for the low values obtained for HPMC percolation threshold in the matrices, expressed as HPMC volume fraction.

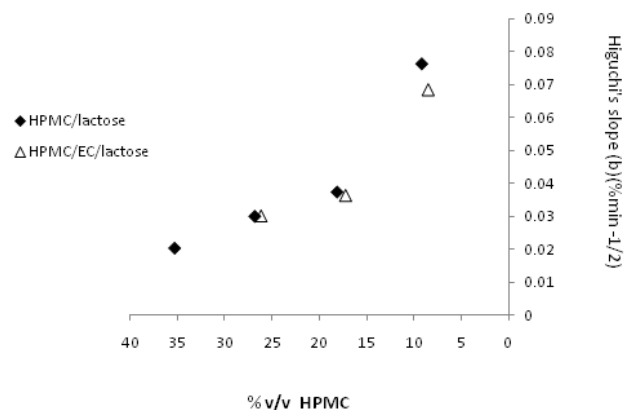


Figure 3. Higuchi's slope vs. percentage of the HPMC volumetric fraction

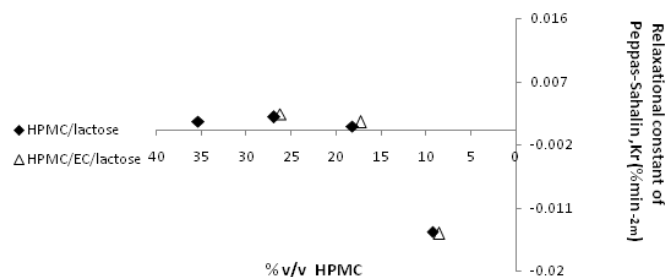


Figure 4. Relaxation constant of Peppas-Sahlin vs. percentage of the HPMC volumetric fraction

Figure 3 and Figure 4 also show the evolution of measured kinetic parameters for HPMC/EC/lactose matrices with constant total polymer content. For these systems, it could be observed a change between the batches HPMC₁/EC₃/lactose and HPMC₂/EC₂/lactose. In order to analyze these figures, two opposite patterns can be considered.^{25, 26} Pattern 1: Interchangeable polymers. This hypothesis supposes a full collaboration of both polymers in order to create the gel layer controlling the drug release from the matrices. In this case the concentrations of the polymers HPMC and EC will be fully additive, i.e., the value of the Higuchi's slope, b , will be the same whenever the sum of the concentrations of both excipients will be the same, independent of the individual concentration of each one of the excipients. For example, we could expect the same release behaviour for matrices containing same total polymer content (such as HPMC₁/EC₃/lactose and

HPMC₂/EC₂/lactose). Pattern 2: Independent excipients. This hypothesis supposes that at least the critical concentration of one of the excipients has to be reached in order to obtain the gel layer controlling the drug release, independently of the concentration of the other excipient.

Looking at Figure 3 and Figure 4, we can observe for example the behavior of batches HPMC₁/EC₃/lactose and HPMC₂/EC₂/lactose. Despite the total polymer content is close to 37% (v/v) for both batches (see Table 2), their Higuchi's slope values are 0.068 and 0.036 respectively. Therefore, matrices having same total polymer content, show very different drug release mechanism. These data do not fulfill the hypothesis depicted in Pattern 1, indicating that the excipients are not interchangeable. In order to check the second hypothesis, which we have named by similar HPMC concentrations, the value of the Higuchi's slope is almost similar for HPMC/lactose and HPMC/EC/lactose matrices with the same HPMC concentration (see Table 2). Therefore, it could be concluded that collaboration does not exist between HPMC and EC and the HPMC can be considered as acting independently of EC. A possible explanation can be the absence of interactions between chemical groups (hydrophilic groups of HPMC and hydrophobic groups of EC) of the polymers that avoids collaboration between them to establish the gel layer controlling the drug release, which has been also shown by other researchers.^{27,28}

Conclusions

Applying the concepts of the percolation theory to HPMC/lactose and HPMC/EC/lactose matrices, the existence of critical points related to HPMC percolation threshold has been confirmed. The excipient percolation threshold for HPMC/lactose matrices can be located between 9.2 and 18.1% (v/v) of HPMC. Above 18.1% (w/w) HPMC, an infinite cluster of polymer would be formed, controlling the hydration, gel formation and the drug release. The percolation threshold for HPMC/EC/lactose matrices is similar to that for HPMC/lactose matrices. This indicates the acting HPMC independently of EC as a consequence of the absence of collaboration between HPMC and EC. The knowledge of this critical barrier will be useful in order to optimize the design of the multi-component hydrophilic matrix systems. First, reducing the time to market and second, increasing their robustness when they are prepared at industrial scale, avoiding the formulation in the nearby of the percolation threshold.

Conflict of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgments

Authors wish to thank Tabriz Medical Science University for financial support of the study.

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