DESIGN SPACE AND CRITICAL POINTS IN SOLID DOSAGE FORMS

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Abstract

The current regulatory environment based on the ICH guidelines encourages a systematic and science-based approach in the pharmaceutical development, required by the "Quality by design" concept. This methodology implies that the quality of a product must be designed instead of assayed in the final dosage form. For this purpose, a deep knowledge of the factors affecting the quality of the product is needed to establish the Design Space. This Design Space is limited by critical points of the formulation whose knowledge is essential in order to develop a robust dosage form. This papers deals with the main critical points that must be taken into account in the design of solid dosage forms such as inert and hydrophilic matrices as well as controlled released systems based in new biopolymers. The influence of factors such as the particle size or the rheology of powders in these critical points has been analysed. Moreover, *in silico* simulation software has been employed to elucidate the release mechanism leading to unexpectedly low critical points in sustained release matrices prepared with two new polyurethanes.

Keywords

Critical Points; Design Space; Percolation Theory; Quality by Design (QbD); Matrix systems.

1. PAT, Design Space and critical points

In 2002 the FDA identified a significant number of ongoing problems in pharmaceutical manufacturing, revealing the need of a rigorous science-based approach for the design of formulations and processes. The number of defects was enormous comparing with other sectors as the chip industry that had achieved to reduce errors in the manufacturing process to ≤ 2 ppb, seeking the "six sigma" objective, while pharmaceutical manufacturing performance was only about two sigma, equivalent to 46,000,000,000 ppb [1]. For this reason, the Agency launched a new initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" in order to facilitate industry application of modern quality management techniques, including implementation of quality systems approaches. So, the concept of quality by design (QbD), firstly outlined by Juran in 1992 [2], was introduced in pharmaceutical industries to enhance robust manufacturing process and to facilitate product quality. [3]. Following this approach, the quality of a product has to be ensured since its design, instead of measuring it in the final dosage form.

In order to reduce the variability of most pharmaceutical processes, the FDA developed the Guidance for Industry: Process Analytical Technology (PAT), a framework for innovative pharmaceutical development, manufacturing, and quality assurance. PAT is considered to be a system for designing, analyzing, and in-process controlling manufacturing through measurements of critical quality and performance attributes of materials and processes, with the goal of ensuring the desired quality [4]. In this way, the industries are making a great effort to invest in PAT tools as RAMAN, Near Infrared spectroscopy or terahertz pulsed imaging to obtain continuous "real time" assurance of quality.

The deep knowledge gained from pharmaceutical studies provides a scientific basis to an adequate establishment of the Design Space, which ensures that the manufacturing process leads to a product that meets the Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs).

Design Space is defined in the ICH Q8 directive as the multidimensional combination and interaction of input variables and process parameters that have demonstrated to provide

assurance of quality. Working within the Design Space is not considered as a change from the regulatory point of view, since this provides a final product of the same quality [4].

In order to have a solid and robust understanding of the behavior of a pharmaceutical system, it is necessary to know those critical points related to the formulation that can affect the CQAs. These points make the drug product fall outside the acceptable range for that attribute and, therefore, they constitute natural limits of the Design Space [5]. According to the percolation theory, these critical points are usually related to a change in the distribution pattern of the components of the system known as percolation threshold. Percolation theory is a statistical discipline that studies the distribution of disordered systems, in which the components are randomly distributed in a network, as well as their relationship with the behavior of their macroscopic properties. This theory defines a cluster as a group of neighboring sites occupied by the same component in a real or virtual lattice. A cluster is considered infinite, coherent or percolating when it extends from one side to the other sides of the system, i.e. it percolates through the whole system. The minimum concentration of a component at which there is expected to appear an infinite or percolating cluster of this material, is called the percolation threshold. When a component reaches its percolation threshold, the system undergoes a geometrical phase transition and this component starts to extend over the whole system, exerting a higher influence on the properties of the system, acting in a similar way than the outer phase of an emulsion. This concentration is usually related to a critical point, because close to this point important changes in the properties of the system can occur [6].

Many researchers have successfully estimated the percolation thresholds of drug products and excipients, confirming changes in different properties such as mechanical or rheological properties, conductivity, water uptake, dissolution rate, etc. [5,7–14]. From all above, it is clear that the pharmaceutical systems do not meet the required robustness conditions of the Design Space close to the critical points, which can be considered as natural limits of the Design Space.

Therefore, in order to properly apply the QbD approaches, it is very convenient to estimate the percolation thresholds of the systems and the related critical points. In this sense, it is important to know the factors that influence the critical points in a pharmaceutical formulation. At the

moment, the formulation factor showing a clearer influence on the critical points of solid dosage forms is the particle size.

2. Critical points and particle size

Different studies have been carried out to study the effect of the particle size of the components in different pharmaceutical formulation. The first one of these studies reported the influence of the drug particle size on the drug percolation threshold in inert matrices. This study was performed preparing matrix tablets with KCl as model drug, employing five different KCl particle size fractions and Eudragit RS-PM® as matrix forming excipient, keeping constant its particle size. The study showed that drug particles of a bigger size have a low efficiency to percolate the system and a linear relationship between the drug particle size and the drug percolation threshold was found [15].

A later study employing seven different particle size fractions of KCl and four granulometric fractions of Eudragit RS-PM® showed that what really influences the drug percolation threshold is the relative and not the absolute drug particle size i.e., the ratio between the mean drug and excipient particle sizes [16]. This finding could be explained according to percolation theory and it was an important milestone since it provided the possibility to employ the percolation threshold of a component as a preformulation parameter to improve the design of solid dosage forms.

A few years later the effect of the relative particle size was investigated in hydrophilic matrices, in order to determine if the linear dependence observed in inert matrices could also apply for this type of systems [17]. In this case, six different excipient/drug particle size ratios (ranging from 0.42 to 4.16) were employed to prepare matrix tablets containing KCl and Lobenzarit disodium as drugs and HPMC K4M as matrix forming excipient. A linear relationship between the polymer percolation threshold and its relative excipient/drug particle size was found when adding the initial porosity of the matrix to the excipient volumetric fraction in the calculation of the percolation threshold of the hydrophilic polymer. Moreover, this study showed that this relationship is independent on the drug contained in the matrix and on the type of system, since

the regression line obtained for hydrophilic matrices was very similar to that obtained for inert matrices.

The effect of the particle size on the drug or polymer percolation threshold can be explained taking into account that coarse particles can be considered as clusters with 100% density of the same component. It is well known that a much lower occupation density, -around 50%- is sufficient to give rise to a cluster of the similar dimensions and similar ability to percolate the samples. Therefore, the component whose particles are coarser need a higher concentration to reach its percolation threshold, whereas particles of smaller size have a higher efficiency to percolate the system [6].

Before the application of percolation theory, several authors had reported an increase in the drug release rate when coarser polymer particle sizes where employed [18][19]. The explanation given was that coarser polymer particles form a gel layer with larger pore size that also need a longer time to be stablished. Furthermore, these authors indicated that this effect seems to disappear when matrices contain high polymer concentrations, nevertheless they did not provide a rational explanation to this fact [20].

According to percolation theory this phenomenon is due to the fact that particle size has only a moderate influence on the percolation thresholds -in the previously reported studies, the maximum change obtained in the percolation thresholds was around 20%, changing ten times the relative particle size-. Therefore, in case of standard changes in the particle size, this effect is only clear when the system is relatively close to the percolation threshold, whereas for systems formulated far away from the critical point, the effect is almost negligible [21].

A study dealing with clozapine matrix pellets [22] illustrates very well this phenomenon. As Figure 1a shows, a clear influence of the clozapine particle size in the release behavior was observed for batches A and B, formulated in the neighborhood of the drug percolation threshold. However, this effect was less evident when the drug content in the pellets is higher, i.e., in batches C and D that have been formulated at a higher distance from the percolation threshold (see Figure 1b).

The effect of the particle size on the percolation threshold, which was first investigated in the pharmaceutical area, has transcended this field, being currently applied to different areas of research as for example the behavior of semiconductors [23].

3. Critical points and rheology of powder blends

The deep understanding of the internal structure of powder blends is necessary to properly apply the QbD approach [5]. SeDeM methodology is being proposed since 2006 as a new Expert System which provides information about the suitability of powder blends for direct compression [24]. The SeDeM methodology is based on the evaluation of several rheological parameters of substances in powder form and the normalization of the results to values from 0 to 10. According to this approach, the powder blend is acceptable for direct compression when the mean of the normalized values is higher than 5. The expert system also provides quantitative information about the amount of excipient that must be added to the powder blend to obtain a formulation suitable for direct compression [25]. The SeDeM methodology makes this estimation based on the assumption of a continuous behavior of the system. According to percolation theory, powder blends behave as non-linear systems whose properties are expected to change near to geometrical phase transitions of the components of the formulation.

In 2016, the evolution of SeDeM parameters in drug/excipient powder blends has been analyzed for the first time from the percolation theory point of view [5]. Powder blends of lactose and theophylline with varying concentrations of the model drug have been prepared and the SeDeM analysis has been applied to each blend in order to monitor the evolution of their properties. Twelve rheological parameters were studied. The results showed a nonlinear behavior as a function of the percentage of drug. Plotting these results versus % v/v of drug, two discontinuities in the rheological behavior of blends were observed. For example flowability factors showed three linear regions: (i) for low drug concentrations (0–31% v/v of theophylline) blends show good flow properties, (ii) for medium theophylline content (37–61% v/v theophylline) they have a fair behavior and (iii) with high theophylline content (74–100% v/v

theophylline) poor flow properties are observed. Figure 2 shows the normalized values of rest angle for the different blends studied where the three regions can be observed.

These results show the influence of the two percolation thresholds, corresponding to the geometrical phase transitions of each component of the blends, reflected as discontinuities in the evolution of the rheological properties. The first threshold was between 31 and 37% v/v of theophylline and the second one was between 61 and 74% v/v of theophylline, corresponding to the percolation thresholds of the drug and the excipient, respectively. Critical points were calculated applying the method developed by Fuertes et al. [26], as the intersection between the two regression lines reflecting the trend of a property before and after the critical region, as a function of the % v/v of drug.

As Figure 2 shows, blends with concentrations below the drug percolation threshold –estimated at 35.3% v/v of drug- show better rheological behavior, especially affecting its flow capacity, due to the predominant effect of the excipient. On the other hand, blends with more than 71.3% v/v of drug, where the excipient does not percolate, show higher compressibility values and poor flowability.

In relation with the quantity of excipient necessary to improve the rheological behavior of the drug, the SeDeM method proposed the following equation (Eq. 1), based on the SeDeM radius regarded as the minimum necessary for each incidence parameter in order to ensure successful compression.

$$CP = 100 - {}^{(RE - R)}/_{(RE - RP)} \times 100 \qquad \text{Eq. 1}$$

where CP is the percentage of corrective excipient; RE is the mean-incidence radius value of the corrective excipient; R is the mean-incidence radius value to be obtained in the blend and RP is the mean-incidence radius value of the API to be corrected.

The higher difference in the rheological behavior between the API and the excipient studied was found for flowability, where theophylline had a radius value of 1.97, while lactose showed 6.09. Eq. (1) was applied using these values, in order to obtain R = 5, as the minimum value to achieve good compression. The obtained result indicates that the percentage of lactose needed to

correct this API was 74% w/w, which means a maximum content of 26% of theophylline. However, based on percolation theory, below the percolation threshold of drug at 33% w/w theophylline, this component cannot percolate the system, exerting a lower influence in the blend. In fact, good flow results were found for blends with 33 % w/w of drug. Therefore, there is a d of about 7% w/w of excipient that would be added in excess, following the SeDeM equation. So, calculations based on percolation theory have shown to be more accurate.

In conclusion, there is a general agreement between the solutions proposed by the SeDeM method and the Percolation theory, which in this case has provided a more accurate estimation of the Design Space.

4. Design Space in matrix systems:

4.1. Inert matrices

As it was stated before, when a component of a dosage form reaches its percolation threshold it starts percolating the system and, consequently, this component will have a higher influence on the general behaviour of the system when it is formulated at this or higher concentrations.

From the point of view of the drug content, which can be described as a Critical Quality Attribute (CQA) according to the ICH Q8 [4], to assure the complete release of the drug dose it is necessary that the drug plus the initial pores percolate the system. Otherwise, isolated drug clusters remain encapsulated inside the dosage form, leading to a therapeutic failure, since only the drug fraction contained in the clusters that connect with the surface is released. On the other hand, it is also required that the inert polymer percolates the matrix, forming a skeleton controlling the drug release and avoiding a quick release of the drug as a consequence of matrix disintegration. For these reasons inert matrices must be formulated as bicoherent systems to achieve an optimal release profile, i.e., both the drug and the inert polymer must percolate the matrix. This type of system can be obtained in solid dosage forms as the percolation threshold of their components is typically around 25-35% v/v, so more than one component can reach this concentration [27]. Profuse research has been made in order to investigate the percolation

ranges for drug and excipient in inert matrices [28][29][30][31][32]. The knowledge of these ranges and the related critical points leads to an important decrease in the costs of the optimization process and in the time to market [1].

From a science-based approach, it is important to know the different factors that influence critical points in inert matrices. Several studies have been carried out in order to address this issue, applying the concepts of percolation theory. The main factors studied have been:

a) Mechanical properties of polymers

This factor seems not to have influence in the critical points of inert matrices. Soriano et al. [33] revealed that in spite of the different mechanical behaviour showed by Eudragit RS-PM®, a rigid polymer, and Ethocel® 100, a much more plastic excipient, inert matrices prepared with both excipients did not show significant differences in their drug percolation threshold.

b) Drug and excipient particle size

The influence of the particle size in the critical points has been discussed in a previous section. Therefore, it has to be taken into account that an increase in the drug particle size leads to an increase in the drug percolation threshold. Moreover, in a binary system, the effect of an increase in the drug particle size is equivalent to a reduction in the excipient particle size, resulting in a decrease in the excipient percolation threshold.

c) Solubility of the filler

The influence of the presence of an hydrophilic filler such as lactose in the release behaviour of poor soluble drugs in inert matrices prepared with Ethocel® 7 FP and carbamazepine was studied by Cifuentes et al. [34]. An important change in the release behaviour of carbamazepine between batches below and above the lactose percolation thr[8]eshold is appreciated in this study, indicating that the percolating cluster of lactose favours water penetration into the matrix, increasing as a result the carbamazepine release rate, but keeping unchanged its percolation threshold.

d) Tablet porosity

The influence of the percentage of initial porosity was also studied in Ethocel® 7 FP / carbamazepine inert matrices by Cifuentes et al. [34]. A percolation threshold of the pores around 16% was observed. This result is in agreement with the obtained by Caraballo et al. in ultrasound compacted tablets [35].

The parameter *Excipient Efficiency* (EE), proposed by Caraballo to calculate the capability of an excipient to control the drug release, correcting the influence of the porosity, has been recently reformulated adding two correction factors for the excipient particle size and for the drug solubility, so that EE can be applied to systems with different drugs and varying granulometry. Equation 2 shows the current formula of EE [36].

$$EE = \frac{\boxtimes}{b} * \frac{1}{1.43 - 0.00244d} * \frac{1}{1.963 - 0.246lnCs} \qquad \text{Eq. 2}$$

Where $\boxtimes$ is the total porosity of the matrices, b is the Higuchi's release rate constant, d is the mean particle size of excipient (μm) and Cs is the drug solubility in mg/ml.

EE provides a rational basis to compare and select the more adequate excipients for the development of a controlled release formulation, moving one step further in the application of the "quality by design concept". Nevertheless, it has to be taken into account that for a correct comparisson both, drug and excipient must be above their critical points in the system [36].

4.2. Hydrophilic matrices

Hydrophilic matrices are one of the most employed sustained drug delivery systems, which consist of a dispersion of drug particles in one or more hydrophilic excipients, which swell after contact with water, generating a gel or a high viscosity colloid. Among the advantages of these systems, their low cost and simple manufacture, flexibility to obtain a desirable drug release profile and the existence of a wide variety of excipients with low toxicity can be highlighted.

Drug release kinetics from these systems depend on several factors such as rate of polymer swelling, rate of penetration of water through the matrix, rate of dissolution of the drug in the medium, rate of diffusion of the drug through the swelled polymer and erosion of the swelled

matrix. Due to the complexity of mechanisms involved in the release process from these systems, there is a high number of publications that investigate drug release from hydrophilic matrices [37–39]. Factors such as polymer concentration, polymer properties, drug content, drug and excipient relative particle size, and compression pressure, have been demonstrated to influence drug release [27].

The percolation theory has been applied to the study of swellable matrices, being critical points in hydrophilic matrices reported for the first time by Caraballo and Leuenberger in 2004 [40]. Since then, an important number of papers dealing with the application of the percolation theory to the study of the release and the water uptake behavior of these systems have been published. Percolation thresholds have been estimated in hydrophilic HPMC matrices, plotting the kinetic parameters (Higuchi's slope 'b'; normalized Higuchi's slope 'b/% (v/v) of HPMC'; relaxation constant of Peppas-Sahlin 'k_r') as a function of the volumetric fraction of each component [41–43].

The presence of critical points is related to a discontinuity of the system due to the geometrical phase transition that takes place. This leads to a different distribution of the components of the system. In the case of swellable matrices, critical points can be expected for each one of the components of the formulation. Nevertheless, it has been found that the polymer critical point plays the most important role in these systems. Therefore, the knowledge of the polymer percolation threshold is essential in order to formulate controlled release hydrophilic matrix systems employing the quality by design approach, since above the polymer percolation threshold this excipient, in contact with the biological fluids, forms a coherent gel layer that controls the drug release rate. On the contrary, below the polymer percolation threshold, polymer is distributed in isolated clusters which do not produce a continuous gel layer. This leads to the erosion of the polymer and in the majority of the cases to the disintegration of the matrix, with the subsequent abrupt release of the drug in a similar way as a conventional dosage form [21].

With respect to the drug percolation threshold, this critical point shows much less influence on the behavior of hydrophilic matrices when compare to inert matrix tablets. This is attributed to

the fact that in swellable matrices the existence of an infinite cluster of drug is not necessary to obtain its complete release. In these systems the polymer swells and enables the water penetration through the whole systems without the need of a percolating cluster of soluble substances. As a result, little differences have been found between matrices formulated below and above the drug percolation threshold.

The influence of factors such as drug solubility, relative particle size, tablet initial porosity and polymer viscosity on the critical points has also been studied in hydrophilic matrices, concluding that the percolation threshold only shows a clear dependency on the relative particle size [44][8][17] .

Recently, a work performed in collaboration between our group at the University of Seville, and the group of Colin Melia, at the University of Nottingham, has studied the pattern of polymer hydration and gel layer growth during early gel layer formation in hydrophilic matrices by confocal laser scanning fluorescence microscopy (CLSM) [9]. The study examined how early gel layer formation depends on polymer content, with the aim to provide direct physical evidence of the influence of the percolation threshold in the control of the drug release. The correlation between percolation thresholds estimated from dissolution and imaging techniques suggests that confocal imaging may provide a fast method to predict and confirm critical points and provides new insights into existing technologies, facilitating the rational design of hydrophilic matrices at lower polymer contents with minimal risk of dose dumping.

As a conclusion it can be stated that the application of the percolation theory to the design of hydrophilic matrices has shown to be an essential tool to establish the design space of the formulation according to the current regulatory environment.

5. SR-systems obtained with new biopolymers

The rational design of polymers for the development of novel biomedical applications is being a hot topic in the synthesis of new materials. In the last years, a wide range of natural and synthetic polymers with particular biomedical applications, capable of undergoing degradation by hydrolytic or enzymatic mechanism, have been synthesized [45].

Among the synthetic materials used in biomedicine, polyurethanes (PUs) are being widely investigated due to their low toxicity, potential biodegradability, biocompatibility, and versatile structures [46–48]. Numerous articles and reviews have reported exhaustive studies on degradability of polyurethanes, mainly processes involving hydrolytic, enzymatic, and oxidative pathways [49–53]. Furthermore, the introduction of hydrolysable linkages besides the urethane bonds leaded to an improvement in the degradation rates of the materials [54,55]. For instance, the introduction of disulfide bonds into polyurethane skeletons makes these linkages prone to a rapid cleavage in a reductive environment by the action of the natural tripeptide glutathione (γ-glutamylcysteinylglycine, GSH) [52,56,57].

In the latest years, thanks to the collaborative work between a research group of the Department of Organic and Pharmaceutical Chemistry of the University of Seville leaded by J.A Galbis and our research team, new polyurethanes have been synthesized and studied to be employed as matrix forming excipients for oral sustained drug delivery [58–60]. The results have shown a noticeable reduction of the drug release rate just employing 20% w/w (or even 10% w/w of polymer) [58,59]. This fact is very important in order to design a controlled release system because these dosage forms usually contain a high drug load. Furthermore, reduction of the total amount of excipient administered to the body reduces the potential risk of negative effects.

In addition, new functionalized polyurethanes for site-specific drug release in the gastrointestinal tract have been developed and characterized [61]. The results obtained have shown a good ability of the polymers to control the drug release. Even, in the case of PU(dithiodiethanol-DTDI), a clear increase in the release rate has been observed when the formulation is subjected to colon simulating conditions.

5.1. In silico modelization, image analysis and release mechanism

A study of the drug release mechanism from sustained release matrices prepared with two new polyurethanes have been carried out thanks to a collaborative research work between the University of Basel, Switzerland, the University of Applied Sciences Northwestern Switzerland,

Muttenz, Switzerland and the University of Seville, Spain [62] in order to explain the surprisingly high ability of these polymers to control the drug release.

For this purpose, F-CAD software, which is an innovative formulation tool based on cellular automata, was used to simulate *in silico* the drug release profile of binary matrix tablets of theophylline and the polyurethanes and to compare it with the experimental results. A good agreement was found between in silico and in vitro release profiles.

Additionally, polymer distributions in the tablets were imaged by scanning electron microscopy (SEM) and the tortuosity was quantified using experimental data.

A particular behavior of the polymers with no swelling or erosion was deducted from the in silico simulation. Moreover, an increase in the tortuosity was detected, which could explain the high ability of the polymers to control the drug release according to classical theories. However, it was found that the drug release was controlled thanks to a special geometrical arrangement of the excipient particles, creating an almost continuous barrier surrounding the drug particles in a very effective way, comparable to lipid or waxy excipients, decreasing the percolation threshold and the corresponding critical point likewise a continuous system from the point of view of percolation theory.

As in previous works, F-CAD has demonstrated to be a tool capable of replacing expensive laboratory work by performing in silico experiments for the exploration of the formulation design space according to ICH Q8 guideline [63] .

In summary, the theories derived from statistical physics provide a rational basis for the design of an increasing number of pharmaceutical formulations. The knowledge of the geometrical phase transitions occurring at the percolation thresholds and the related critical points, is essential to accomplish the pharmaceutical development according to the requirements of ICH Q8 guideline [4]. As it has been described in the different sections of this review, critical points are very important tools to properly define the design space of a formulation.

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Figure captions

Fig. 1.a: Percentage of clozapine released versus time of batches A and B, contaning 20% of drug. Batch B contain the coarsest particles of clozapine.

Fig. 1.b: Percentage of clozapine released versus time of batches C and D, containing 30% of clozapine. Batches D contain the coarsest particles of clozapine.

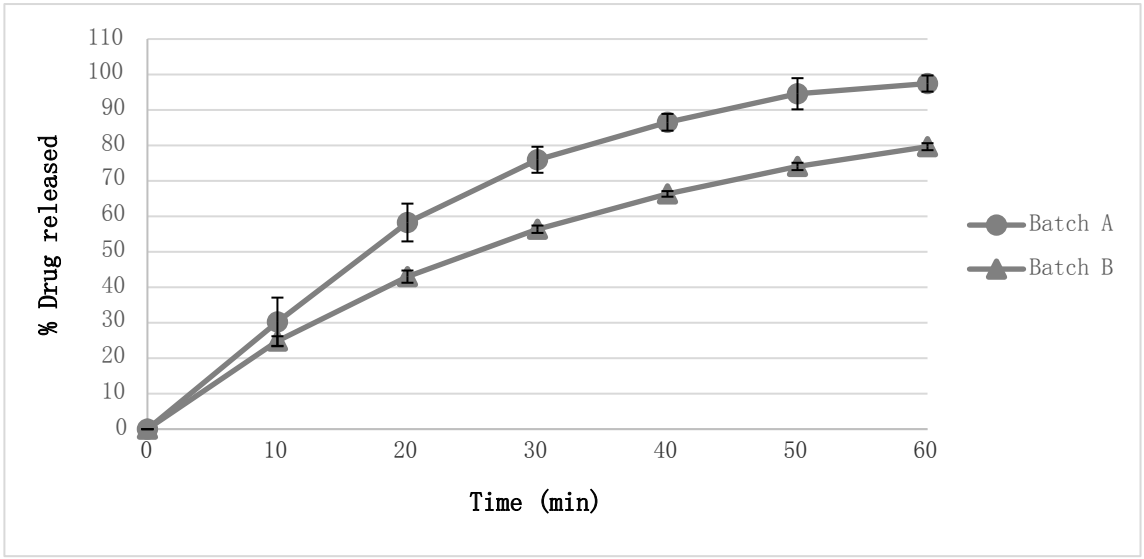
Fig. 2a: Normalized values of rest angle for powder blends of lactose and theophylline expressed in %v/v.

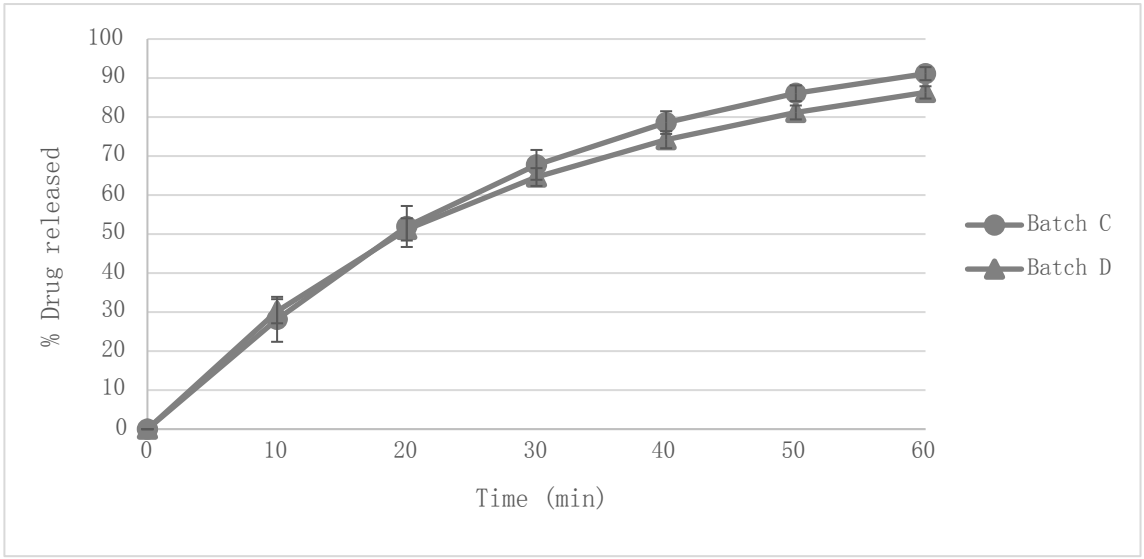
Fig. 2b: Normalized values of rest angle for powder blends of lactose and theophylline expressed in %w/w.

Fig. 3: Confocal imaging of HPMC matrices swelling in aqueous Congo Red 0.008% w/v at 37 C. Images are coded for fluorescent intensity (highest, white; lowest, black) in a continuous grayscale as above. White dashed line denotes the dry matrix boundary at t = 0. Ex 488/Em > 510 nm. Scale bar = 500 lm. (from Mason et al. [10] with permission of Elsevier).

Fig. 4: Microphotograph of a tablet with 40% PTU (DTT-HMDI) and 60% theophylline. Darker particles correspond to theophylline and light gray indicates polymer (from Campiñez et al. [63] with permission of Elsevier).

Fig. 5: Intrinsic dissolution profiles. Experimental (*filled figures*) and simulated release profiles (*open figures*) (from Campiñez et al. [63] with permission of Elsevier).


110
100
90
80
70
60
50
40
30
20
10
0
% Drug released
0
10
20
30
40
50
60
Time (min)
Batch A
Batch B


100
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% Drug released
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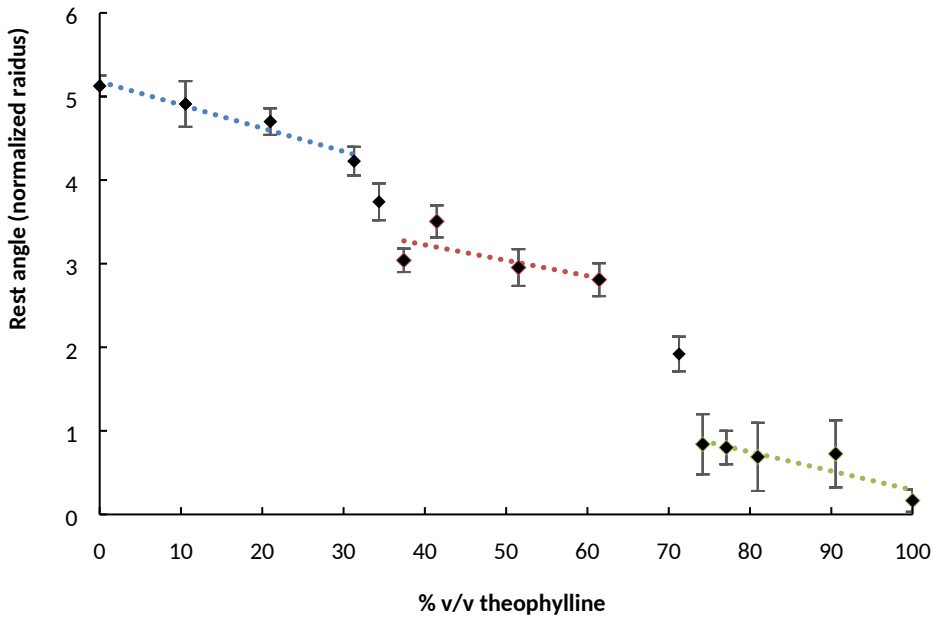
Time (min)
Batch C
Batch D


Rest angle (normalized raidus)
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5
4
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0
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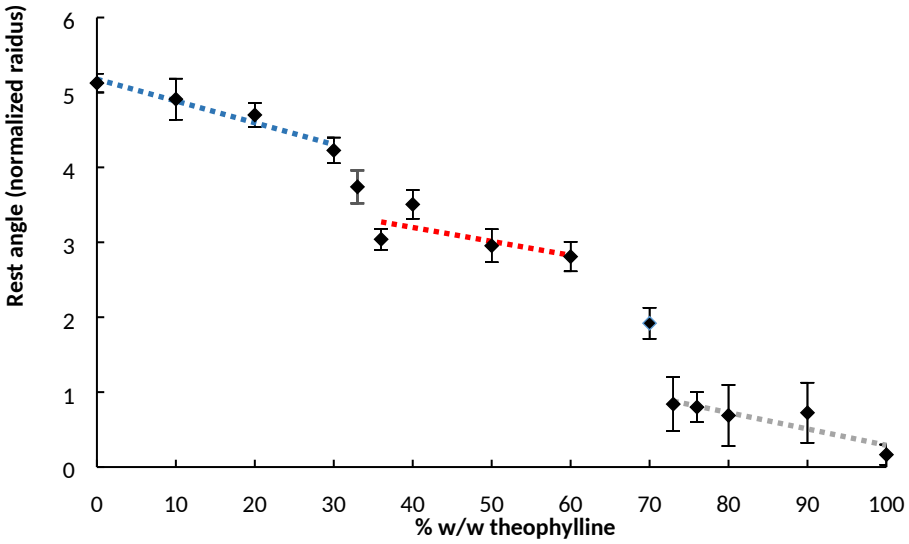
100
% v/v theophylline


Rest angle (normalized raidus)
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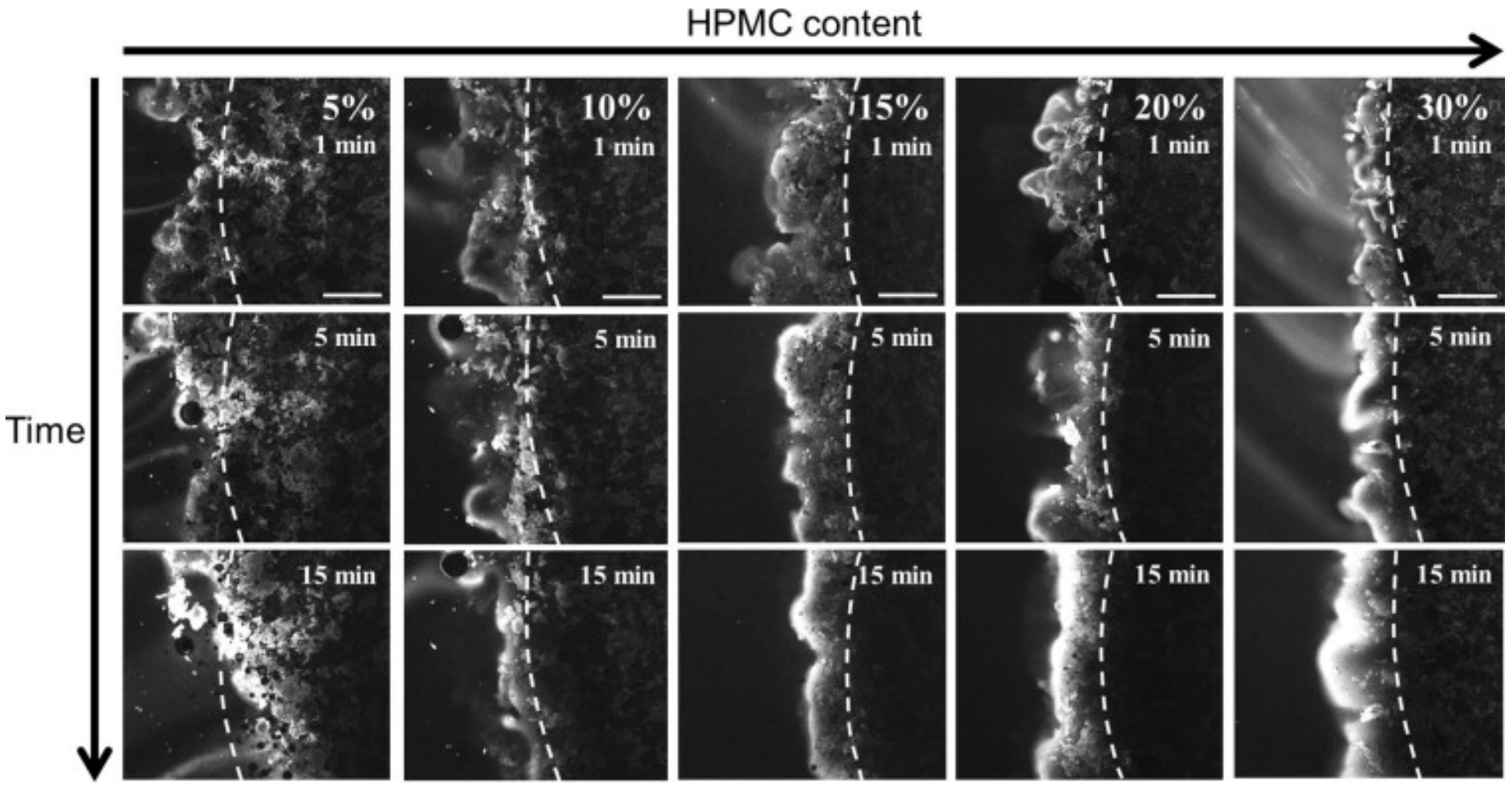
HPMC content
Time
5%
1 min
10%
1 min
15%
1 min
20%
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30%
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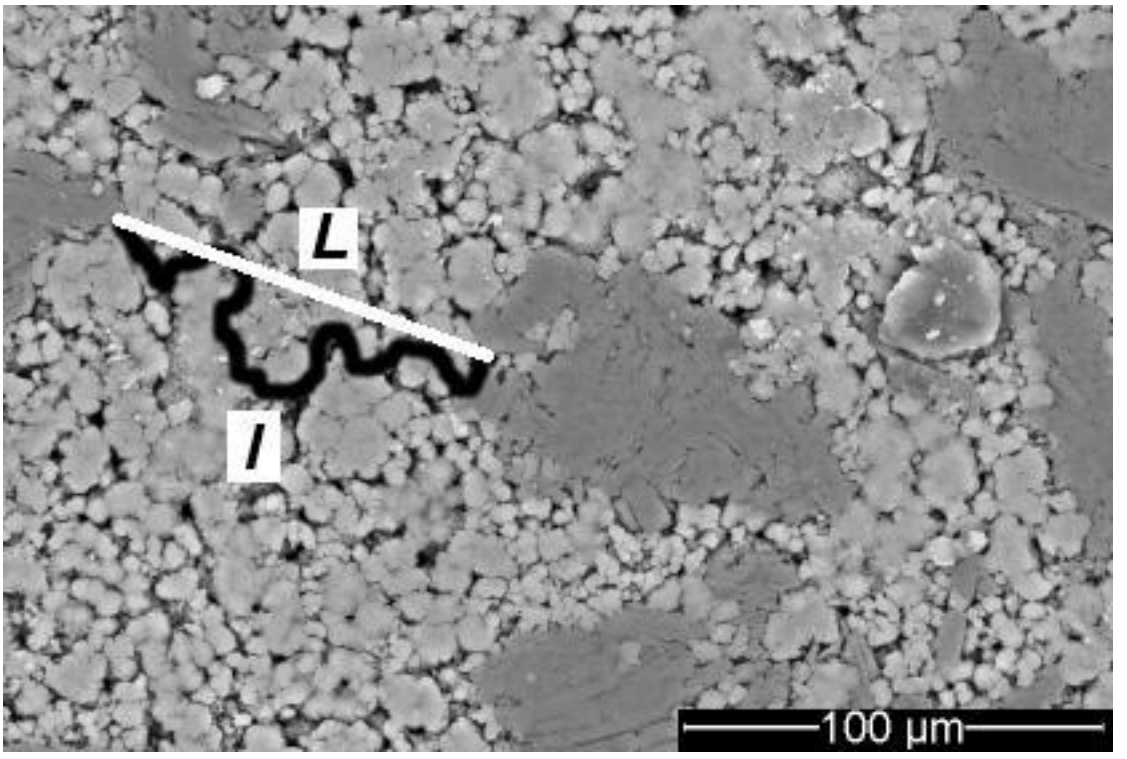
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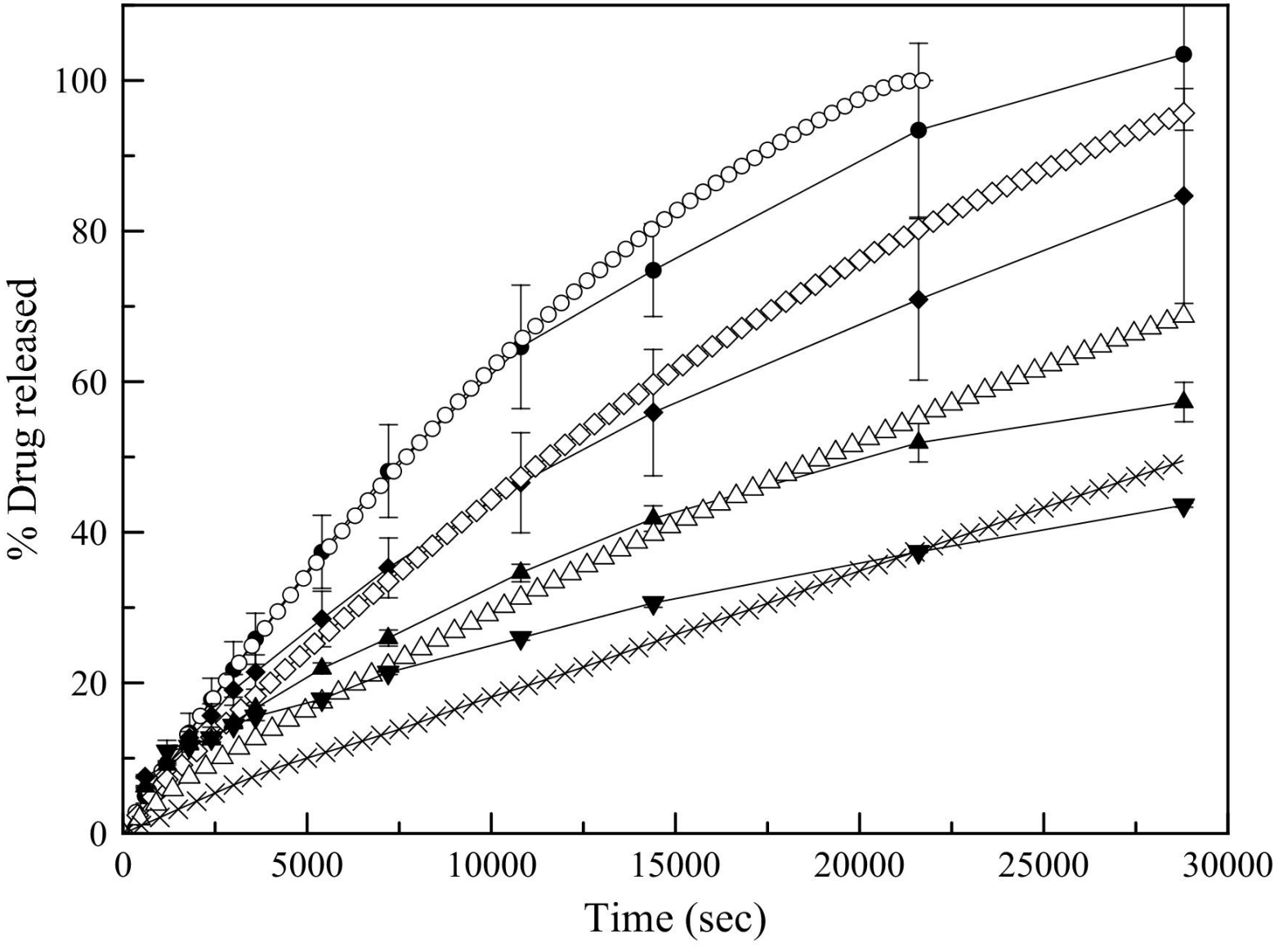
100 µm


% Drug released
Time (sec)
0
20
40
60
80
100
0
5000
10000
15000
20000
25000
30000