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Review article

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.

Contents

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, which 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.

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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 such as Raman spectroscopy, 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. The lattices which best describe a pharmaceutical tablet are the *body centered cubic lattice* (site percolation threshold: 24.64) and the simple cubic lattice (site percolation threshold: 31.16) [6] 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 [7].

Many researchers have successfully estimated the percolation thresholds of drug products and excipients, confirming changes in mechanical or rheological properties, conductivity, water uptake, dissolution rate, etc. [5,8–15]. 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.

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, being the particle size the formulation factor showing a clearer influence in solid dosage forms.

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 formulations. 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 [16].

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 [17]. 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 pre-formulation 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 [18]. 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 [7].

Before the application of percolation theory, several authors had reported an increase in the drug release rate when coarser polymer particle sizes where employed in the case of hydrophilic matrices [19] [20]. The explanation given was that coarser polymer particles form a gel layer with larger pore size that also need a longer time to be established. 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 [21].

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 [22].

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