An Attempt to Calculate *In Silico* Disintegration Time of Tablets Containing Mefenamic Acid, a Low Water-Soluble Drug

GO KIMURA,[1,2] MAXIM PUCHKOV,[1,3] HANS LEUENBERGER[1,3,4]

[1]Division of Pharmaceutical Technology, University of Basel, Basel CH-4056, Switzerland

[2]Oral Formulation Department, Formulation and Packaging Development Center, CMC Development Laboratories, Shionogi & Company, Ltd., Hyogo 660-0813, Japan

[3]CINCAP GmbH, Pfeffingen CH-4148, Switzerland

[4]IFIIP GmbH, Pfeffingen CH-4148, Switzerland

Received 8 January 2013; revised 2 March 2013; accepted 15 March 2013

Published online 23 April 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23541

ABSTRACT: Based on a Quality by Design (QbD) approach, it is important to follow International Conference on Harmonization (ICH) guidance Q8 (R2) recommendations to explore the design space. The application of an experimental design is, however, not sufficient because of the fact that it is necessary to take into account the effects of percolation theory. For this purpose, an adequate software needs to be applied, capable of detecting percolation thresholds as a function of the distribution of the functional powder particles. Formulation-computer aided design (F-CAD), originally designed to calculate *in silico* the drug dissolution profiles of a tablet formulation is, for example, a suitable software for this purpose. The study shows that F-CAD can calculate a good estimate of the disintegration time of a tablet formulation consisting of mefenamic acid. More important, F-CAD is capable of replacing expensive laboratory work by performing *in silico* experiments for the exploration of the formulation design space according to ICH guidance Q8 (R2). As a consequence, a similar workflow existing as best practice in the automotive and aircraft industry can be adopted by the pharmaceutical industry: The drug delivery vehicle can be first fully designed and tested *in silico*, which will improve the quality of the marketed formulation and save time and money. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2166–2178, 2013

Keywords: formulation; powder technology; compaction; disintegration time; percolation theory; *in silico* modeling; Quality by Design (QbD); solid dosage form

INTRODUCTION

Quality by Design and Development Costs

For the pharmaceutical formulation design and process development, the scientific understanding of those attributes that influence their quality should be provided while taking into account for Quality by Design (QbD) in International Conference on Harmonization (ICH) guidance Q8 (R2).[1] The use of scientific approaches for the understanding of quality attributes, such as statistical design of experiment (DOE), response surface methodology (RSM), optimization modeling, multivariate data analysis, and chemometrics in combination with the knowledge management system is required.

Any pharmaceutical formulation for solid dosage forms could be classified as complex and heterogeneous disordered particular system, that is, multiparticulate and multicomponent. Such class of systems is naturally prone to feature nonlinear effects and nonmonotonous (i.e., critical) behavior. Topology-based assessment is often necessary to take into account a critical behavior caused by geometrical phase transition, known as percolation event. Percolation theory is, in fact, one of the suitable topological modeling tools to predict and simulate the geometric phase transitions in complex system such as a tablet formulation. Thus, percolation theory allows finding the regions where the system undergoes sharp property

Correspondence to: Go Kimura (Telephone: +81-6-6401-8332; Fax: +81-6-6401-4593; E-mail: go.kimura@shionogi.co.jp)

Journal of Pharmaceutical Sciences, Vol. 102, 2166–2178 (2013)

change. It happens at critical concentration of the components where a component percolates (percolation threshold or p_c). In terms of tablet formulation design, such regions usually linked to external value of properties such as water uptake, disintegration time (t_{dis}), and dissolution rate.

Nowadays, because of advances in combinatorial chemistry and high throughput screening, the number of drug candidates has increased tremendously. However, more than 40% of newly discovered drugs are poorly water soluble. This significantly increases the challenge for formulation scientist as it has to be kept in mind that up to now there is no universal science-based formulation design for low water-soluble drugs. In many cases, disintegration is a limiting factor on the dissolution process of tablet. Disintegrant is used to aid the disintegration of tablets. Determination of the critical concentration of disintegrant is important parameter for a tablet formulation design, especially for low water-soluble drugs. In our laboratory, the percolation theory has applied to determine the critical concentration of disintegrant in a binary mixture of tablet.[2–6] However, the further investigation is needed to determine the critical concentration of disintegrant not only for the binary tablets but also for multicomponent tablets to design a pharmaceutical tablet formulation based on the scientific approach.

Mefenamic acid (MA) is used as a model substance of a low water-soluble drug. Fifteen types of granules and tablets are prepared at different loading volume of MA (0%–74.1%, v/v) in exchange of lactose (LA; 7.7%–90.9%, v/v) as a filler and maize starch (MS; 8.5%–30.3% v/v) as a disintegrant forming a truly ternary tablet formulation.

Finding the ruling principles for pharmaceutical tablet formulation design is necessary from the point of view of development costs and fulfilling the requirements of QbD. In this context, the application of the best practice—such as in automative and aircraft industry, that is, to design the delivery vehicle *in silico*—is of primary importance. The costs of corresponding laboratory experiments are much too high. This may be one of the reasons, why in an early development a little attention is paid to use an optimized drug-delivery vehicle but a simple service dosage form such as capsule.

ICH Guidance Q8 (R2) and Critical Parameters on Three-Dimensional Lattices from the Percolation Theory Point of View

International Conference on Harmonization guidance Q8 (R2) demands in an early phase of development to explore the design space of a formulation using RSM. RSM can be best carried out by using the tools of experimental design, that is, full factorial designs, fractional factorial designs, central composite designs, and so forth. However, it is important to keep in mind that such designs are appropriate to give only a rough picture of the response surfaces—that is, providing no details, which may be important. A full factorial design delivers as a response surface an approximation, which can be compared with Taylor expansion of a function $f(x,y,z)$ of, for example, three or more factors, taking into account main effects and important interactions. In case of a central composite design, the approximation is taking into account also quadratic terms of the Taylor expansion, yielding a second-order response surface, which is a nice tool suited for optimization purposes. The main problem of such approximations is the fact that the true reality is just approximated and that major changes in a property of a system cannot be detected because of a lack of resolution. This problem needs special attention, if the response surface close to a p_c should be evaluated.

The main postulate of percolation theory is the probability (p) of forming an infinite cluster spanning through the infinite lattice (Eq. 1). As a small isolated cluster grows, there will be a point, when for the first time it spans throughout the system. The p_c is a borderline concentration at which the probability to form an infinite cluster is nonzero any longer. At or near the p_c, important property changes of the system occurs[7] as a consequence of the property of the component that starts to percolate and to "dominate" the system.

$$X = S|p - p_c|^q \tag{1}$$

where X is a system's property, S is a proportionally constant (= scaling factor), p is an occupation probability, p_c is a critical concentration (= percolation threshold), and q is a critical exponent, close to the p_c. Please note that the difference (p–p_c) in Eq. 1 is considered as an absolute value, that is, there are no negative values.

A typical example of dramatic change can be seen in a particle mixture containing electrically conductive particles and insulator particles on simple cubic (SC) lattice. It is known that site p_c on SC lattice is 0.311608.[8] If an electrically conductive/insulator particle system is composed into a tablet, the tablet becomes electrically conductive only at the concentration of conductive component above p_c.[7,9]

Three-dimensional lattices should be considered while designing a pharmaceutical tablet. Critical parameters on three-dimensional lattices are summarized in Table 1. For face-centered cubic (FCC), body-centered cubic (BCC), SC, diamond, and random close packed (RCP) lattices, the threshold values have been calculated.[10–13] The threshold values for bond (p_{cb}) and site (p_{cs}) percolation are different from the different lattices (nonuniversality).[8]