パーコレーション理論とその製剤開発への新展開(第２回)―原文―

Introduction

In 2002 Dr. Ajaz Hussain, deputy director and Helen Winkle, director of the office of pharmaceutical sciences (OPS) of the Center for Drug Evaluation and Research (CDER) of FDA visited the laboratories of the Institute of Pharmaceutical Technology of the Department of Pharmaceutical Sciences of the University of Basel [1]. On July 1, 2005 the Head of the Institute of Pharmaceutical Technology was invited to give a presentation on his research activities in the area of PAT (Process Analytical Technology) at the FDA in Rockville,MD, which was also broadcasted to the FDA offices/labs in St. Louis MO. The PAT initiative of FDA created the basis for the subsequent requirements of "Quality by Design", i.e. to design the quality in an early stage of the formulation development and not to "test-in" the quality at later stage in order to eliminate samples, which are out of specifications. Needless to say, that an optimal Quality by Design leads to the concept of doing formulations experiments "Right, First Time" [2-4].

Due to this interest of FDA, respectively of the tripartite ICH (EU, Japan, USA) a series of PhD thesis topics of Basel PhD students in the area of Pharmaceutical Technology started to cover research work in the area of PAT (Process Analytical Technology), QbD (Quality by Design) including the requirement to explore the formulation design space according to ICH Q8. In this context, Go KIMURA covered the topic of "Design of pharmaceutical tablet formulation for a low water soluble drug : Search for the critical concentration of starch based disintegrant applying percolation theory and F-CAD (Formulation-Computer Aided Design)" [5].

It became soon evident, that it is important to keep in mind the impact of percolation theory on the properties of a dosage form when the formulation design space is explored according to ICH Q8. [6]. As the main part of his PhD thesiswill be translated into Japanese and publishedin this journal, an introduction of the essentials of percolation theory for a solid dosage form , i.e. a tablet formulation is presented in the following chapter.

The essentials of percolation theory

The standard text book for percolation theory in general is the "Introduction to Percolation Theory" written by Staufer and Ahorni [7]. The application of percolation theory touches key properties of pharmaceutical compacts [8-13] , taking into account complex interactions of different processes, which include disintegration of complex multi-particulate system, but also dissolution of soluble components and crack propagation in case of the tablet breaking test. It is well known that heterogeneous ensembles like pharmaceutical formulations of solid dosage forms represent disordered particulate systems. In such a case, it is necessary to take into account a geometrical description, i.e. a topological modelling. Geometrical phase transitions are independent of physical and chemical properties of the components.. Percolation theory is, in fact, the most suitable tool to predict and simulate the geometrical phase transitions in a complex multi-particulate system and allows finding the regions where the system undergoes transitional changes in its properties. Interestingly, it is possible to extend the concept of percolation theory to complex liquid dosage forms, assuming, that the pharmaceutical solution consist of solvents and solutes, which can be described as nano-sized particulate systems [14,15]

In terms of solid dosage form design, such regions usually are linked to extreme values of drug dissolution rate, tablet disintegration time, tablet water uptake [7,8]. According to percolation theory, a transitional change happens at a critical concentration of components in a system when one component forms an infinite cluster propagating through the entire system (i.e. percolates). This critical concentration, which is called percolation threshold pc, is attributed to the volumetric ratio (% v/v) of the percolating component. Percolation theory is linked to probability theory. In this context, there is a probability to form an infinite cluster of a certain component in an infinite lattice geometrically defined lattice. Node of a lattice is named "site". Each site is occupied or not by the component (molecule, atome, particle, droplet etc. Two types of percolation can be considered, as an infinite cluster is described by occupied sites (site percolation) or by bonds between two occupied sites (bond percolation). The value of percolation threshold p_c will be different for site (p_{cs}) and bond percolation (p_{cb}) for a given lattice at a given concentration of occupied sites. Percolation theory postulates that the probability of forming an infinite cluster spanning though the infinite lattice means that for any given concentration p of occupied sites or bonds, the probability to form an infinite cluster is either zero or one.

The lattice concept binds together the critical concentration at which the percolation event is happening with lattice geometry. It was proven that percolation threshold p_c depends on the lattice coordination number z which is an amount of contacts of any site with its neighbours. For example, the coordination number z is 3 for Bethe lattice (Figure 1).

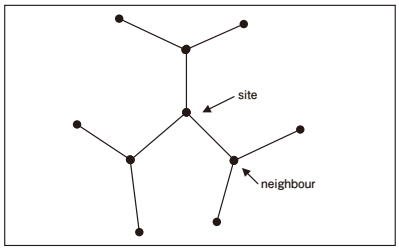

Figure 1 Example of Bethe lattice (Cayley Tree) with coordination number z=3.

The percolation threshold pc of a Bethe Lattice is equal to : $p_c = 1/(z-1)$ with z = Coordination number.

The advantage of a Bethe Lattice is the possibility to calculate analytically certain properties of a complex multi particulate system [16]. However, it has to be kept in mind, that such a calculation is an approximation due to the fact, that the Bethe Lattice does not make a difference between the site and bond percolation threshold. It is known, that the Bethe Lattice may be better used in case of high dimensional systems (D>6) [7]. However as the following table shows, if the coordination number is known, a rough estimate of the site percolation threshold in 3D can be obtained :

Table 1 Bond and site percolation thresholds of 3D lattices and Bethe lattice percolation threshold for different Coordination Numbers z

	Pc(bond)	Pc(site)	Coordinatio number, z	Bethe : 1/(z-1)
FCC	0.119	0.198	12	0.091
BCC	0.179	0.245	8	0.143
SC	0.247	0.311	6	0.20
Diamond	0.388	0.428	4	0.333
RCP		0.27	6	0.20

*FCC is face centered cubic, BCC is body-centered cubic, SC is simple cubic, and RCP is random close packed.

It is important to realize, that for 3D lattices the bond and site percolation threshold can only be calculated using numerical methods such as Monte Carlo methods or using Cellular Automata, which is a core module of the CINCAP software F-CAD (Formulation-Computer Aided Design). For this reason, a Bethe lattice approach cannot replace the use of F-CAD software. For three-dimensional lattices FCC (face-centered cubic), BCC (body-centered cubic), SC (simple cubic) and RCP (random close packed), the threshold values are known with quite high precision (Table 2).

Table 2 Critical parameters for bond and site percolation in case of 3D lattices (MCLachlan et al. [17])

Lattice*	Pcb	Pcs	Coordinatio number, z	Filling factor, v	zPcb	vPcs=øc
FCC	0.119	0.198	12	0.7405	1.43	0.147
BCC	0.179	0.245	8	0.6802	1.43	0.167
SC	0.247	0.311	6	0.5236	1.48	0.163
Diamond	0.388	0.428	4	0.3401	1.55	0.146
RCP		0.27	6	0.64	1.62	0.173
Average ± SD					1.5 ± 0.1	0.16 ± 0.01

As it can be seen in the Table 2, the threshold values for site and bond percolation (p_{cb} and pcs, respectively) are different for different lattice types. However, the product values of bond thresholds and coordination number (zP_{cb}) are remaining approximately in the same range (average $zP_{cb} \pm SD = 1.5 \pm 0.1$). This allows determination of bond percolation threshold in a compact by defining the lattice with a given coordination number. However, as it will be described further, the model proposed in this paper is based on site percolation in a multi-particulate system. The product of filling factor v and site percolation threshold, vPcs, are remaining approximately in the same range as well (average $vP_{cs} \pm SD = 0.16 \pm 0.01$). In a three dimensional multi-particulate system, the filling factor v represents the solid fraction of the volume. In system composed of spheres, all randomly packed in close contact (RCP sphere system), v can be expressed through the voids fraction of the volume (porosity ε) as $1-\varepsilon$. This shows a key dependency of percolation threshold on porosity, which is a function of the shape, size and size distribution of the particles involved in a powder system.

Another critical issue is the influence of the sample size on the probability of percolation. In an infinite system, the probability $\Pi(p,L)$ that a infinite

lattice (lattice size $L=\infty$) percolates at concentration p is 1 above the percolation threshold p_c and 0 below (solid line, Figure 2). However, for a finite system, the width of the transition region of the curve representing $\Pi(p,L)$ (dashed line, Figure 2) depends on the nature of the scaling function Φ, the lattice size L and the correlation length exponent ν : $\Pi = \Phi[(p-p_c)L^{1/\nu}]$

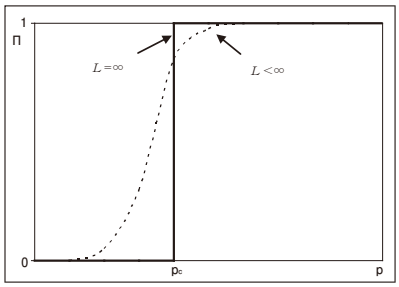

Figure 2 Schematic behaviour of the percolation probability Π for infinite and finite systems.

As a pharmaceutical compact has a finite sample size, it is evident that the lattice size L is not infinite ($L<\infty$) .Due to the finite sample size of the compact, the property X of the compact exhibits in the vicinity of the percolation threshold in a practical laboratory situation often a rather smooth, i.e. continuous change of the values (dashed line) and in general not a step function like in case of L is infinite. It has to be kept in mind, however, that a property X, e.g. the tensile strength of a tablet can show a step-like change, if the concentration p_A of a component A in the formulation, which is responsible for the tensile strength of the compact, is definitely lower, respectively definitely higher than the bond percolation threshold p_{bA} of the infinite lattice, the value of the tensile strength of a compact can show a step function.

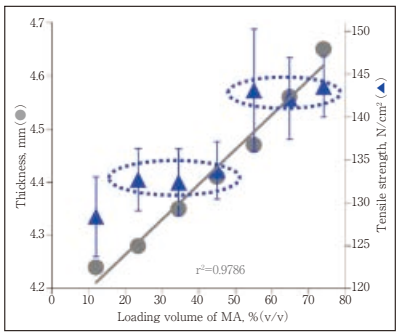

Figure 3 Thickness and tensile strength of tablets compressed at 7.0 kN from granules with increasing loading volume of Mefenamic acid.

Go KIMURA studied not only a binary, but a ternary system, where the tensile strength of the compact is determined by the drug substance MA = Mefenamic Acid and the excipients LA=Lactose and MS=Maize Starch. Compacts with a high concentration of MA and/or LA together with a low concentration of the disintegrant MS (i.e. below the bond percolation threshold p_{bMS} of MS) yield strong and brittle tablets with a higher tensile strength, than compacts, where the tensile strength is governed by a percolating network of the disintegrant MS forming weaker MS-MS bonds than MA-MA bonds respectively MA-LA and LA-MA bonds.

Table 3 Holistic investigation of characteristics of MA tablets for renormalized MS concentrations (Average±SD)

Composition (% v/v)				MS/(MS+MA)	7 kN		
					Porosity (% v/v)	TS (N/cm²)	TDis (sec.)
	MA	LA	MS		(n=6-7)	(n=6-7)	(n=3)
A	0	69.7	30.3	1	20.6±0.32	103±3.20	550±23
B	12	61.4	26.6	0.689	18.2±0.21	128±4.64	596± 8
C	23.5	53.4	23.1	0.497	17.0±0.28	133±3.60	616± 6
D	34.5	45.7	19.8	0.365	16.6±0.28	132±3.89	604±21
E	45.0	38.4	16.6	0.27	16.2±0.20	134±3.35	428±16
F	55.1	31.3	13.6	0.198	15.8±0.24	143±7.14	266± 8
G	64.8	24.6	10.6	0.141	15.5±0.14	142±4.76	453±24
H	74.1	18.1	7.8	0.096	16.4±0.37	143±3.52	758±15
I	0	84.8	15.2	1	20.6±0.16	97.6±2.71	379± 7
J	34.5	51.3	14.2	0.292	17.0±0.26	135±2.10	535±12
K	74.1	12.9	13.0	0.15	16.3±0.32	129±1.95	413± 8
L	0	78.8	21.2	1	19.7±0.15	118±1.96	373±36
M	74.0	7.7	18.3	0.198	16.2±0.11	131±2.17	290± 2
N	0	90.9	9.1	1	20.4±0.47	125±4.07	232±20
O	34.5	57.0	8.5	0.198	17.4±0.29	133±4.58	420± 9

TS : Tensile strength, TDis : Disintegration time

Instead of a step wise change of the property X, it is possible , that the property X is proportional to the first derivative of the function Π in Figure 3. In such a case the property X shows a minimum or maximum at the percolation threshold, corresponding to a Delta (δ) function. Due to the finite sample size of a compact the property X, e.g. disintegration time or uptake kinetics of water shows a minimum or maximum similar to the function of the disintegration time plotted below.

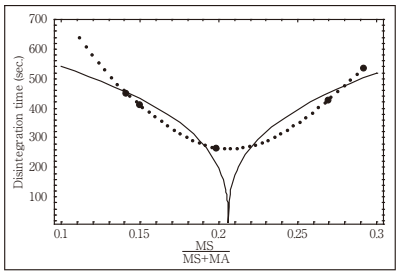

Figure 4 Results of fitting basic percolation equation for MA tablets compressed at 7 kN; figure shows fitting (—) with spline approximated data (dotted line) and raw experimental data (•).

Reading and studying the PhD thesis of Go KIMURA in the Pharm Tech Japan may rise more interest in the application of percolation theory in the area of pharmaceutical powder systems. In such a case, it is recommended to read and study the respective paper in the Journal Advanced Powder technology [18]. The author of this introductory paper is convinced, that the application of percolation theory and the future extension of in-silico experiments to the area of life sciences including clinical experiments will be extremely beneficial and will shorten substantially time to market [2].

Conclusions

According to the results of the PhD thesis of Go KIMURA [5] , it will be important that the pharmaceutical industry follows the concepts of Rapid Product Development, which is thanks to the pioneering work at Toyota the state of the art in the automotive industry with the focus on quality by design at lower costs. The replacement of expensive laboratory formulation experiments by F-CAD in-silico experiments is an important issue to reduce development costs and to comply with the requirements of ICH Q8 R2 exploring the design space with response surface methodology. It is important to keep in mind, that F-CAD is able to detect percolation thresholds, which can be a source of higher variability and which needs to be known in formulation science. The results of this thesis show clearly, that the application of percolation theory is a must in order to detect percolation thresholds. It is important to know the response surfaces close to the percolation threshold of sensitive tablet properties such as the disintegration time to get information about the robustness of the selected formulation. In this context one has to put the question forward, if the application of percolation theory should be an integral part of the guidelines of ICH Q8 exploring the formulation design space.

References :

[1] Leuenberger, H. ; Lanz, M. Pharmaceutical Powder Technology-from Art to Science : the challenge of FDA's PAT initiative. Adv. Powder Technol. 2005, 16, 1-36.

[2] Leuenberger, H. ; Leuenberger, M. N. ; Puchkov, M. Right First Time : Computer-Aided Scale-up for manufacturing solid dosage forms with a shorter time to market. SWISS PHARMA 2010, 32 (7-8), 3.13.

[3] Leuenberger, H. ; Leuenberger, M. N. ; Puchkov, M. Implementing virtual R & D reality in industry : In silico design and testing of solid dosage forms. SWISS PHARMA 2009, 31 (7-8), 18-24.

[4] Puchkov, M. ; Leuenberger, H. Computer-aided design of pharmaceutical formulations : F-CAD software and a mathematical concept. Glatt International Times 2011, 31, 2-6.

[5] Kimura G., "Design of pharmaceutical tablet formulation for a low water soluble drug : Search for the critical concentration of starch

based disintegrant applying percolation theory and F-CAD (Formulation-Computer Aided Design)" PhD thesis, Faculty of Science, University of Basel 2012.

[6] ICH Harmonized Tripartite Guideline : Pharmaceutical Development Q8 (R2), Current Step 4version : http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

[7] Stauffer, D. ; Aharony, A. Introduction to Percolation Theory, Revised 2nd edition. Taylor & Francis Group, 1994

[8] Luginbuehl R, Leuenberger H. Use of percolation theory to interpret water uptake,disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures. Pharm. Acta Helv. 1994 ; 69 (3) : 127-134.

[9] Caraballo I, Fernandez-Arevalo M, Holgado MA, Rabasco AM. Percolation theory : application to the study of the release behaviour from inert matrix systems. Int. J. Pharm. 1993 ; 96 : 175-181.

[10] Kimura G, Puchkov M, Betz G, Leuenberger H. Percolation theory and the role of maize starch as a disintegrant for a low water soluble drug. Pharm. Dev. Technol. 2007, 12, 11-19

[11] Leuenberger H, Ineichen L. Percolation theory and physics of compression. Eur. J. Pharm. Biopharm. 1997 ; 44 : 269-272.

[12] Leuenberger H, Rohera BD, Hass C. Percolation theory-a novel approach to solid dosage form design. Int. J. Pharm. 1987 ; 38 : 109-115

[13] Krausbauer, E. ; Puchkov, M. ; Leuenberger, H. Rational estimation of the optimum amount of nonfibrous disintegrant applying percolation theory for binary fast disintegrating formulation. J. Pharm. Sci. 2008, 97 (1), 529-541.

[14] Hernandez-Perni G, Stengele A, Leuenberger H : Detection of percolation phenomena in binary polar liquids by broadband dielectric spectroscopy.Int J Pharm ; 2005 Mar 3 ; 291 (1-2) : 197-209

[15] Hernandez-Perni, G. ; Leuenberger, H. The characterization of aprotic polar liquids and percolation phenomena in DMSO/water mixture. Eur. J. Pharma. Biopharma. 2005, 61, 201-213.

[16] Leuenberger, H., Bonny, JD., Kolb M., Percolation effects in matrix-type controlled drug release systems, Int. J. Pharm. 115 (1995) 217-224.

[17] MCLachlan DS, Blaszkiewicz M, et al: Electrical resistivity of composites. J. Am. Ceram. Soc. 1990 ; 73 (8) : 2187-2203.

[18] Leuenberger H. The application of percolation theory in powder technology. Adv. Powder Technol. 1999 ; 10 (4) : 323-353.