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Percolation Theory: Applications in Pharmacy

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Percolation theory is a statistical theory applied to explain behaviour of disordered systems. It considers a system to be composed of an infinite lattice. Random site, random bond and site-bond percolation types are commonly observed. The article explains the concept of percolation theory and types. Leuenberger started the application of this concept in the field of pharmacy. Its applications in powder technology, sustained release matrix systems and emulsions are discussed. The percolation theory will be an important tool in the design of dosage forms.

Recently, the novel concept of fractal geometry and percolation theory has been utilized in various fields of research to elucidate the mechanisms of various biological and physical phenomena[1-5]. Percolation theory is a statistical theory presented by Broadbent and Hammersley[6] to explain the behaviour of disordered systems. In pharmaceutical technology it was introduced by Leuenberger et al[7]. in 1987. It was extensively applied in the field of powder technology, emulsion stability, polymers and controlled drug delivery systems[8-13].

CONCEPT AND TYPES OF PERCOLATION:

A percolation structure is considered to be an infinitely large periodic real or virtual lattice with sites which may or may not be occupied by units of the system. There are no special requirements concerning the type of lattice and the nature of items that occupy the sites. Percolation theory deals with the number and properties of clusters in this lattice. A cluster may be considered as the group of neighbouring items which may or may not be connected depending on the type of percolation. Depending on the nature of clusters, percolation phenomenon can be differentiated into[8].

Site or Random - Site percolation

Bond or Random - Bond percolation

Random - Site Bond percolation

In site percolation system, the items occupy sites in a lattice. As percolation progresses, more and more sites in the lattice are occupied i.e. the site occupation probability P increases with percolation. Once two neighbouring sites are occupied, it is assumed that there exists a bond connecting these sites. Therefore, a cluster in site percolation consists of a group of neighbouring sites occupied by the same component. Emulsion may be considered to observe site percolation.

A random bond percolation considers that all sites of a lattice are always occupied; but the bond may or may not exist between neighbours. As percolation proceeds the bonds are formed between neighbouring items. A cluster in bond percolation structure consists of a group of items forming bonds with the neighbours. If two neighbouring sites in a lattice are occupied by two particles then according to site percolation, the cluster size will be two. But if the bond percolation is considered, the cluster size will be one as only one bond is present between two particles[9].

Bond percolation has been observed in powder system. Since the material and volume of lattice both are predetermined and limited, the bond probability and bond strength between different components can play impor-

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tant role in determining the properties of percolation structure. But there is no special requirement for the nature of forces that are responsible for the bonds formed and the origin of the driving force that increases the site occupation or bond formation probability in the lattice[10].

In site-bond percolation, both types of percolation phenomena are followed in the lattice e.g. formation of the tablet.

Percolation threshold:

The percolation probability P is the fraction of sites occupied (site percolation) or the fraction of bonds formed (bond percolation). At P = 0, no site has been occupied or no bond has been formed; at P = 1, all sites or bonds have been occupied or formed, depending on the type of percolation.

The probability P where the component of the system just begins to percolate i.e. forms continuous structure throughout the length, breadth and height of the system is known as 'percolation threshold' and is denoted by P_c[11]. At $P = P_c$ a property of a body or a system as a function of a continuously varying parameter diverges, vanishes or just begins to be manifested. Such an effect which starts to occur close to P_c is usually called a 'critical phenomenon'. For example, the electrical conductivity of the tablet consisting of copper powder mixed with Al_2O_3 powder may be cited. The tablet conducts electricity only if the copper particles form an "infinite" cluster within the tablet, spanning the tablet in all three dimensions[8].

Since a percolation structure is considered to be infinitely large, the cluster at and above P_c is also infinitely large. Therefore, at and above P_c the cluster is referred to as an infinite cluster whereas below P_c it is a finite cluster. The cluster at P_c is sometimes referred to as an 'incipient infinite cluster'[11]. The percolation system is considered to be an infinite lattice, but when percolation threshold is determined in a finite system it is not sharply defined and referred to as effective P_c. The true P_c can be obtained by extrapolating the effective P_c. But effective P_c has more practical utility as opposed to true P_c.

The percolation thresholds for various well-defined geometrical packings of monosized spherical particles in a two or three dimensional lattice is shown in Table 1[9]. The exact value of P_c depends on type of percolation and type of lattice. In a real system, the geometrical packing is a function of particle size, particle size distribution and the shape of the particles.

TABLE 1 : PERCOLATION THRESHOLDS FOR TWO- AND THREE-DIMENSIONAL LATTICES

Lattice	Site	Bond
Honeycomb	0.69620	0.65271
Square	0.59275	0.50000
Triangular	0.50000	0.34729
Diamond	0.42800	0.38800
Simple cubic	0.31170	0.24920
Body-centered cubic	0.24500	0.17850
Face-centered cubic	0.19800	0.11900

The properties of the percolation structure will be affected by the co-ordination number. For the same geometry of the items it is dependent on the porosity and type of lattice. The mean coordination number (k), for different packings of monosized spheres are shown in Table 2 alongwith the porosity(ρ) of the packing[8].

TABLE 2 : COORDINATION NUMBERS OF ISOMETRIC SPHERICAL PARTICLES FOR DIFFERENT PACKING STRUCTURES

Lattice type	Co-ordination No.	Porosity
Diamond	4	0.66
Simple cubic	6	0.48
Body-centered cubic	8	0.32
Face-centered cubic	12	0.26

In three dimensional lattice of binary mixture, there are two percolation thresholds. To make this statement more clear, consider an example of formation of a sponge[9]. Below lower percolation threshold sponge does not exist. There are only isolated clusters of sponge material. At the 1st or lower P_c, sponge begins to form but pores also exist as infinite clusters. Thus two infinite clusters occur in system side by side which is peculiar to three dimensional systems in contrast to two dimensional. Above second percolation threshold, the pores do not exist as an infinite cluster. This is a peculiarity of three dimensional system.

TABLE 3 : PERCOLATION EXPONENTS FOR TWO DIMENSIONS, THREE DIMENSIONS AND IN THE BETHE LATTICE AND THE CORRESPONDING QUANTITY

Exponent	Lattice Type			Quantity/ Property
	2 dimension	3 dimension	Bethe	
α	-2/3	-0.6	-1	Total number of clusters
β	5/36	0.4	1	Strength of infinite network
γ	43/18	1.8	1	Mean size of finite clusters
ν	4/3	0.9	1/2	Correlation length
μ	1.3	2.0	3	Conductivity

The concept of percolation theory can be applied to binary component powder mixes and compacts. In binary mixtures two percolation thresholds P_{c1} and P_{c2} exist. At first percolation threshold, infinite clusters of one component are formed. As the concentration of second component increases, percolation proceeds and infinite clusters of second component are formed. This is the second percolation threshold P_{c2}.

The change in the system property (X), is a function of and percolation threshold, P_c. It can be described by power law equation (1), which is valid only close to the percolation threshold[10].

$$X = S/P\text{-}P_c/^q \quad \ldots\ldots\ldots\ldots \quad (1)$$

Where, S is proportionality constant (Scaling factor) and q is a critical exponent which is dependent on the property and type of lattice. The higher is the percolation threshold, lower is the value of q and vice versa. The q values for different properties for two, three and infinite (Bethe) lattice are given in Table 3. The equation is valid in the range of $\pm$ 0.1 P_c. But because of the finite size of a lattice, P_c may be slightly displaced and the system property X may show a less sharp transition at P_c.

Percolation threshold is determined by measurement of critical system property as a function of the component. The different system properties used include tensile strength of compact, resistivity of the compacts containing power conducting substance, tapped density and drug release parameters.

APPLICATIONS IN PHARMACY

Loose powder compacts:

Loose powder compacts may be considered as compacts which easily disintegrate into primary particles. Such type of system may exist in powders filled in hard gelatin capsules. In the loose powder compacts the compressional force applied is relatively low where brittle fracture or plastic deformation can not occur. But the relative density of compact is such that fine particles are bonded by weak interparticulate forces at the point of contacts in the powder bed. Thus a loose powder compact may be considered as a bond percolation structure. The formation probability is defined as the ratio of the number of bonds formed to the maximum number of bonds possible. But for a loose compact weak bond probability is considered which is the ratio of number of bonds formed to the number of bonds at relative density when brittle fracture or plastic flow occurs. Leuenberger *et al.* have also considered the case where due to non-homogeneity in stress distribution strong bonded regions exist in the loose powder compacts and expressed strong bond probability[8,10].

The equations for different percolation probabilities are as follows[8] :

Bond probability P' : $P' = (\rho_r\text{-}\rho_t)/(1\text{-}\rho_t)$ —(2)

Weak bond probability P" : $P'' = (\rho_r\text{-}\rho_t)/(\rho_r^*\text{-}\rho_t)$ —— (3)

Strong bond probability P* : $P^* = (\rho_r\text{-}\rho_s)/(1\text{-}\rho_s)$— (4)

where, ρ_t = Relative tap density and all possible bonds are formed. ρ_r^* = Relative density at brittle fracture or plastic flow. ρ_s = Relative density where within the loose powder bed locally strong agglomerates are formed due to the non-homogeneous distribution of compressional stress.

These probabilities may be useful in analysis of applied stress on the conditions of the powder bed especially in capsule filling, storage of bulk powders etc.

Tablet Compaction:

Tablet is formed by uniaxial compression of the powder mass. The powder/granules in the die cavity may be considered as a three dimensional lattice with lattice spacing equal to mean pore size. In the initial stages the bond percolation prevails as discussed for the loose powder compact. First the bond percolation threshold (P_{c1}), occurs at tapped relative density where particles are bonded by weak interparticulate bonds. As the process of compaction proceeds the number of vacant lattice sites are continuously reduced and relative density is attained at which particles can not be displaced. This is the site percolation threshold (P_{c2}). With further progress of compaction the pore volume is further reduced so that they cannot form a network. This is site percolation threshold of the pores (P_{c3}).

The percolation thresholds in tablets are not sharp due to effects of variables such as particle size, shape, nature of fracture and plastic deformation and finite size of the tablet. During compression the stress applied by the upper punch is transmitted through the powder mass. Similar to the transmission of electric current particle-particle contact is essential for transmission of stress. Therefore, stress transmission during compaction follows power law[8].

$$\sigma_c = \sigma_o (\rho_r - \rho_o) \tau \text{ — (5)}$$

where, σ_c = Compressional stress transmitted. σ_o = Scaling factor, ρ_o = tapped density and τ = Stress transmission exponent.

Caraballo *et al.*[13] demonstrated that multicomponent system can be reduced to binary system.

Holman *et al.*[11] have studied the compression characteristics of binary mixtures of directly compressible dicalcium phosphate (Emcompress) and microcrystalline cellulose (Avicel). The percolation threshold of Emcompress in the compact appears to be much higher as compared to that determined by tapped density studies. This indicates that bond forming potential of Emcompress is very low compared to that of Avicel. Avicel has low yield stress and is very ductile compared to Emcompress. Avicel readily deforms and coats the particles of Emcompress. So less bonding points are available on the surface of Emcompress particles for bonding and higher concentration is required to form an infinite cluster.

Tablet Properties:

The properties of the powder material such as compressibility and compactibility which are important in processing as well as determining the properties of the final tablet are studied in details. The relationships were established between different parameters by Cooper and Eaton[14], Kawakita[15], Athy[16] and Heckel[17] and Leuenberger[18]. By combining Heckel and Leuenberger equations the relationship was established to explain tablet properties such as deformation hardness (P) and tensile strength (σ_t)[19].

$$\sigma_t = S' (\rho_r - \rho_c) \text{ with, } S' = \sigma_{tmax}/1-\rho_c \text{ — (6)}$$

$$P = S (\rho_r - \rho_c) \text{ with, } S = P_{max}/1-\rho_c \text{ —— (7)}$$

where, S and S' are scaling factors, ρ_r is relative density and ρ_c is relative density which is bond percolation threshold at low pressures or site percolation threshold at intermediate pressures and pore site percolation threshold at very high pressures. σ_{tmax} and P_{max} correspond to maximum tensile strength and deformation hardness respectively.

In binary mixture compacts, consisting of a relatively hard and relatively soft material, the hardness is dominated by the harder substance as long as it percolates the compact despite the occurrence of percolating clusters of a softer material. The hardness is not only dependent on the presence of infinite clusters but also total number of bonds[11].

Luginbuhl and Leuenberger[20], have suggested that disintegration of tablet is mainly influenced by the number of isolated finite clusters of an optimal size formed by the particles of the disintegrant. The mean cluster size may be estimated by fundamental power law equation. At concentration of disintegrant below percolation threshold i.e. when isolated finite clusters exist, it increases wettability of the porous system resulting in higher water uptake and faster disintegration of the tablet. Above percolation threshold the pores start to close by the swelling disintegrant causing hindrance in water uptake. Drug percolation threshold was found to be unaffected due to presence of disintegrant[19].

Sustained Release Drug Delivery Systems:

Percolation theory has been applied for elucidation of release mechanisms and effect of different variables[21-26], where in some cases classical theory also failed to provide justification. The drug in controlled release matrix system may be considered as the ant trying to escape

from the labyrinth consisting of randomly distributed sites which may or may not be accessible by the solvent[12]. In a three dimensional lattice consisting of two components of soluble phase (drug and fillers) and insoluble phase (swelling and nonswelling polymers), the accessible sites are soluble phase particles forming the infinite cluster and its finite clusters connected to tablet surface. The inaccessible sites consist of insoluble phase and the finite clusters completely encapsulated in the insoluble phase.

The matrix containing finite cluster of nonswelling polymer shows faster drug release as compared to compacts having infinite clusters due to faster water uptake. Whereas, for swelling type of polymers, matrix containing infinite cluster shows faster water uptake as it can be considered as accessible site and therefore drug release is faster as compared to matrix with finite cluster.

Drug release was found to be higher in case of matrix prepared by using hydrophilic liquids for wetting as compared to hydrophobic ones. But the effect was observed only in the systems where infinite clusters of insoluble phase do not exist. If we consider a binary matrix consisting of low concentration of drug in polymer and almost zero porosity then two percolation thresholds are obtained. At lower percolation threshold (P_{c1}) where drug just percolates in the matrix, whereas at upper percolation threshold (P_{c2}), there is formation of discrete clusters of matrix material and disintegration of tablet takes place. Leuenberger *et al.*[27] observed that if P_s is the site occupation probability of drug, then amount of drug released from one tablet surface at any time t is proportional to t^k. The different release kinetics are followed under different conditions as given in Table 4[12].

Thus, it was observed that between two percolation thresholds, matrix diffusion is followed, whereas when there is saturation of drug into the aqueous filled pores of the matrices, kinetics is zero order.

As per Higuchi matrix model,

$$Q(t) = \sqrt{D\, C_s\, (2A-\varepsilon C_s)\, t} \quad \text{— (8)}$$

where, apparent diffusion coefficient, $D = D_o(\varepsilon/\tau)$

D_o is diffusion coefficient of drug in the diffusion medium, τ and ε indicate tortuosity and porosity of the tablet respectively.

According to percolation theory, Stauffer and Aharony[28] deduced the relationship applying power law as follows,

$$D = \chi D_o\, (\varepsilon-\varepsilon^c)^{\mu} \quad \text{— (9)}$$

Where χD_o represents scaling factor, ε_c is critical porosity (where the pore network formed due to initial pores and pores filled up by the drug begin to percolate the system), μ is conductivity exponent the value of which is 2 for three dimensional lattice and 3 for Bethe lattice. Relationship was observed between the bioavailability from matrix and ε. Therefore bioavailability from the dosage can be estimated without performing release test and a optimum formulation can be obtained at certain distance i.e. $(\varepsilon-\varepsilon_c)$, from percolation threshold[28].

The matrix will show zero order drug release when the water filled pores are completely saturated[29]. Onset of zero order release periods are dependent on drug loading and the distance to the percolation threshold. Soriano *et al.*[30], have proposed that mechanical properties of the excipients have very low influence on the drug percolation threshold but the results need further validation.

Emulsion System:

In o/w or w/o system[9], the lattice sites are occupied by oil or water droplets. The site occupation probability depends on the concentration of the two phases and

TABLE 4 : RELATIONSHIP BETWEEN PERCOLATION THRESHOLD AND RELEASE KINETICS

Site occupation probability (P_s)	Exponent value (k)	Release kinetics
$P_s < P_{c1}$	$k \approx 0$	Few particles connected to surface, amount released remains constant
$P_s \approx P_{c1}$	$k \approx 0.2$	Anamalous diffusion
$P_{c1} < P_s < P_{c2}$	$k \approx 0.5$	Matrix controlled diffusion
$P_{c2} < P_s$	$k \approx 1.0$	Zero - order

geometrical arrangement of the droplets. Consider an oil in water system, at low concentrations of oil there will be isolated clusters of oil. As concentration of oil increases an infinite cluster of oil is formed at the critical concentration. This is first percolation threshold. If concentration is increased further there will be isolated clusters of water in the continuous oil phase. This is second percolation threshold. Therefore, phase inversion occurs at second percolation threshold. Above first percolation threshold and below second percolation threshold oil and water droplets form a continuous network of clusters. Apart from this percolation theory is applied in the polymeric solutions for studies on gelling behaviour[31].

Limitations of Percolation Theory:

1. Percolation theory has been developed for binary mixtures but pharmaceutical systems generally contain more than two components. But Caraballo *et al*[21], have shown that the multicomponent system can be reduced to a binary one.

2. The basic assumption of a regular lattice is difficult to apply to the pharmaceutical systems as they generally consist of particles of different size.

Thus percolation theory is a tool with significant potential and is applied in the field of dosage form design, tableting properties and for simplification of many complex phenomena.

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