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Percolation Theory, Fractal Geometry, and Dosage Form Design

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Introduction

Percolation theory [1] and fractal geometry [2] are attracting an increasing number of scientists from various research fields. Through the application of percolation theory and the concept of fractal geometry it is possible to gain new insights into well-known problems of pharmaceutical technology, such as dosage form design, characterization of dosage forms, unit operations in production and drug release properties of matrix systems.

What is Percolation Theory?

Percolation theory deals with the number and properties of clusters of occupied sites in a real or virtual lattice. There are two main kinds of percolation–site and bond–and several variations of these two types [3, 4]. A cluster is defined differently for each kind of percolation. In site percolation a cluster is defined as a group of neighbouring occupied sites. The sites in the lattice are considered to be occupied with a probability p (or unoccupied with a probability 1-p). In bond percolation all sites in a lattice are occupied. Bonds may or may not be formed between two nearest neighbours. The connecting bond is formed with a probability p (or not formed with a probability 1-p). A cluster in bond percolation is thus defined as a group of neighbours connected by bonds.

When clusters are isolated, they are termed finite. On the other hand, when a cluster percolates a lattice, i.e. when a cluster spans the length, breadth and height of a lattice, it is considered infinite because in percolation theory the lattices are considered to be infinitely large. The probability at which a cluster just percolates a system is termed percolation threshold, p_c. The probability for site percolation corresponds to ca. 60% of occupied sites in a two-dimensional square lattice. The exact value for p_c depends on the geometrical arrangement, i.e. lattice type and topological dimension.

In Figure 1a two rather big-sized clusters are shown which, however, do not span the whole lattice, i.e. at a probability p = 0.50 of occupied sites, no "infinite cluster" is formed.

According to *Stauffer* [1] Figures 1a and 1b could describe a forest where each occupied site of the virtual lattice represents a tree. In case of a forest fire only clusters of trees may burn down. Thus, the diffusional spreading of a forest fire can be amply described by percolation theory.

Figure 1a

Example for percolation on a 60×60 square lattice for p = 0.50 [1]. Occupied sites are shown as ""; empty sites are ignored. Two clusters are marked by bonds*

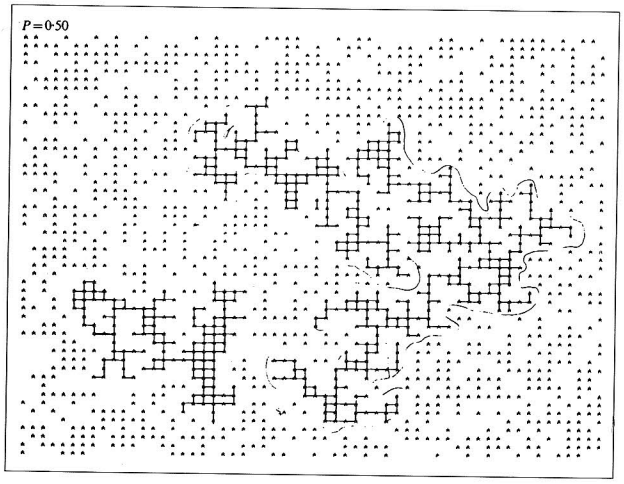
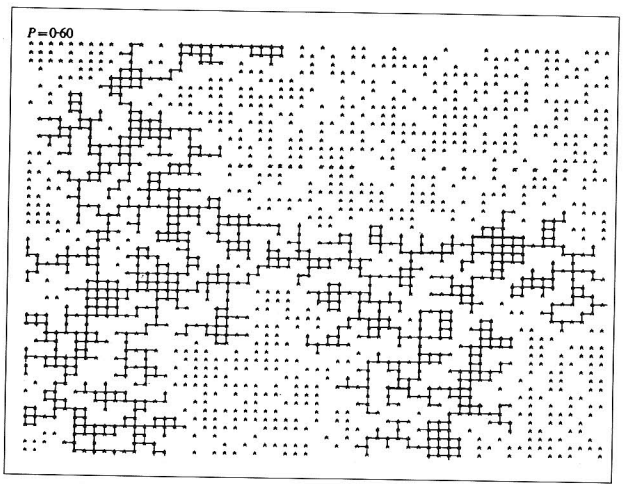


Figure 1b

Example for percolation on a 60×60 square lattice for p = 0.60 [1]. The "infinite cluster" is marked by bonds



In a crystal, lattice sites are occupied by different atoms, vacancies, defects, etc., whereas in a pharmaceutical dosage form, e.g. a tablet, "lattice sites" are occupied by pores or particles. The solid particles may be lubricants, disintegrants, fillers, etc.
Figure 1b could, as an example, describe a two-dimensional cross section of a continuous pore network in a tablet, whereas Figure 1a shows only isolated pores. If the "infinite" network in Figure 1b is interpreted as bonds between particles compressed in a tablet, the percolation threshold p_c indicates the formation of a tablet with zero strength.

Site and Bond Percolation

In case of site percolation the cluster size of two occupied sites is equal to two, whereas in bond percolation only one bond is formed between the two occupied sites, i.e. the cluster size is equal to one (Fig. 2). As a consequence, the percolation thresholds p_c, i.e. critical probabilities or critical concentrations depend on the type of lattice and on the type of percolation (Table 1). In a three-dimensional lattice there are two percolation thresholds, which may be illustrated by imagining a sponge type system. Below the lower percolation threshold the sponge does not exist, there are only isolated clusters of sponge material. Above the first (i.e. lower) percolation threshold a sponge is formed which spans the whole three-dimensional lattice. The pore cluster still exists as an infinite cluster. Thus, two infinite clusters simultaneously occur side by side in the system. This is a pecularity of a three-dimensional system in contrast to a two-dimensional system.
If more sites are increasingly occupied by sponge material, isolated pores are finally formed, i.e. above the second percolation threshold the pore system no longer forms an "infinite network".

Figure 2

Site and bond percolation: definition of cluster size

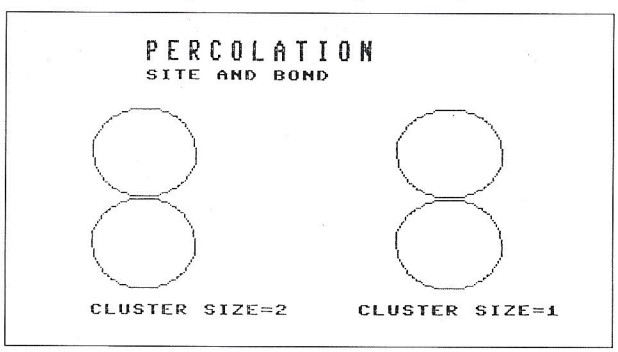


Table 1

Percolation thresholds for two- and three-dimensional lattices. "Site" refers to site percolation and bond to bond percolation [1]

Lattice	Site	Bond
Honeycomb	0·6962	0·65271
Square	0·59275	0·50000
Triangular	0·50000	0·34729
Diamond	0·428	0·388
Simple cubic	0·3117	0·2492
BCC	0·245	0·1785
FCC	0·198	0·119

Site Percolation in an Oil-in-water (o/w) System

In case of an o/w or w/o system the "lattice sites" are occupied by oil or water droplets. The probability for an o/w or w/o system depends on the volume concentration of oil and water as well as on the geometrical arrangement of the oil or water droplets. In case of low concentration of oil in the system, the oil droplets form isolated clusters in a continuous phase of water. With increasing amount of oil, the oil droplets form an infinite cluster. The infinite cluster formation takes place at a critical volume to volume ratio of the oil in water. The critical volume to volume ratio of oil corresponds to the first percolation threshold. When the concentration of oil is further increased, a point is reached where the water droplets form isolated clusters in a continuous phase of oil. This concentration is the second percolation of the system. Above the first percolation threshold and below the second percolation threshold oil and water droplets form a continuous network (case of a "sponge"-like system) of clusters.
According to *Mandelbrot* [2], Figure 3 represents a description of the holes in a Swiss cheese (Emmentaler) with the fractal dimension of D = 1.9. How-

Figure 3

Cross section through a Swiss cheese (Emmentaler) [2] or micrograph of an oil-in-water emulsion?

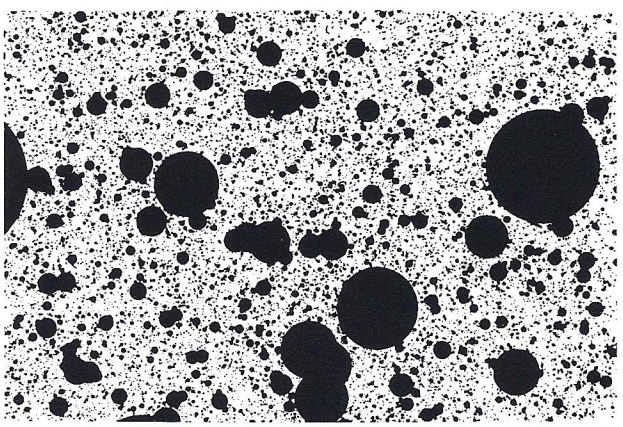
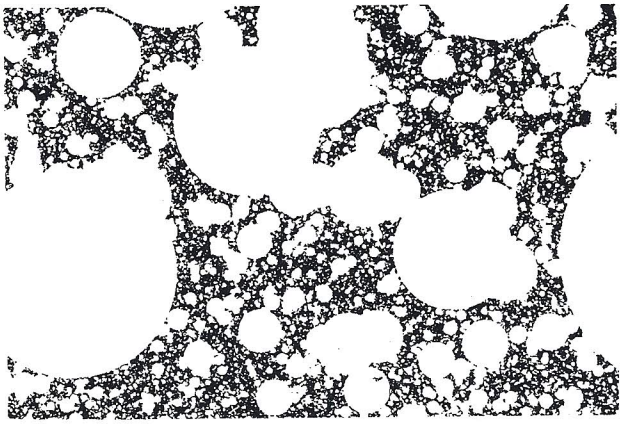


Figure 4

Micrograph of a foam [2]



ever, Figure 3 illustrates as well an oil-in-water emulsion. The geometry of a system can be considered as an ideal fractal only when the system exhibits similar geometry at all magnifications. Such a system is said to manifest self-similarity.

Figure 4 characterizes another percolating system which can be described as a foam. The fractal dimension is D = 1.75 and is less than that for the o/w system described in Figure 3, where the water phase covers nearly completely the surface with its physical dimension d = 2.

Bond Percolation in a Powder System

A typical bond percolation problem is the formation of a tablet on the basis of the compaction of a powder system [5]. The first percolation threshold, p_c, corresponds to the formation of an "infinite network of bonds" between the particles compacted. The value of this threshold, p_c, corresponds to the relative density of the compact, where the tablet is just formed, but shows approximately zero strength. At high relative densities, i.e. high compaction pressure and low porosities, the pore system does not form a continuous network but isolated clusters. This relative density corresponds to the second percolation threshold. Depending on dosage form design important changes in mechanical and biopharmaceutical properties of the tablet occur at the percolation threshold [6].

Figure 5

Semilogarithmic plot of Brinell Hardness versus normalized solid fraction p of acetylsalicylic acid and microcrystalline cellulose 8 : 2 (w/w) compacts. The second percolation threshold p_c corresponds to p = 0.89

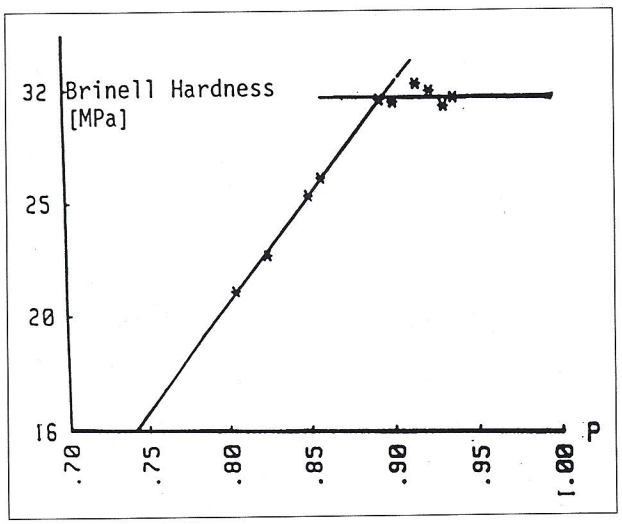
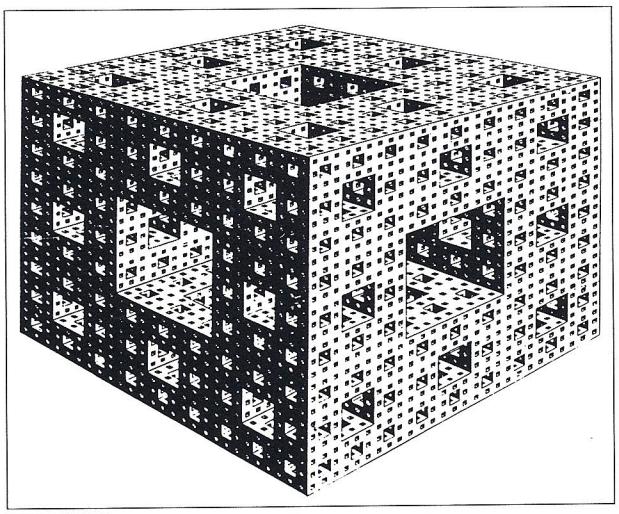


Figure 6

An idealized three-dimensional network of a pore system (Menger sponge) with the fractal dimension of D = 2.72 [2]



Ants in the Labyrinth

Molecules of an active substance, which are enclosed in a matrix type controlled release system, may be called ants in a labyrinth [1] trying to escape from an ordered or disordered network of connected pores. The random walk distance R of such an ant is related to time as follows: $R^2 = Dt$, where D is equal to the diffusivity. Close to the percolation threshold, where the pores start to form isolated clusters, this diffusion law is not valid. In this case the value of D varies proportionally to $(p-p_c)^{\mu}$, where μ is the conductivity exponent and R is proportional to t^k with k = 0.27. This process is called anomalous diffusion.

Generally, in percolation theory, system properties can be described by a power law which relates the property and $(p-p_c)^{\alpha}$. Critical phenomena in thermodynamics are also adequately described by this power law.

The question arises how to describe a network of connected pores. The following figures show models based on the concept of fractal dimension. Figure 6

Figure 7

Idealized description of a bronchial tree with fractal dimension D = 2.9 [2]

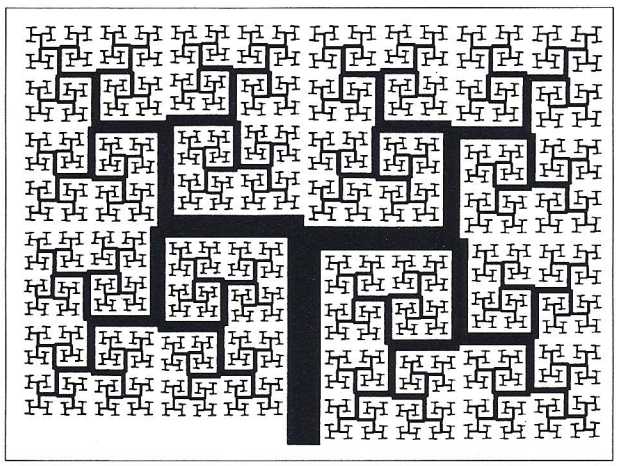
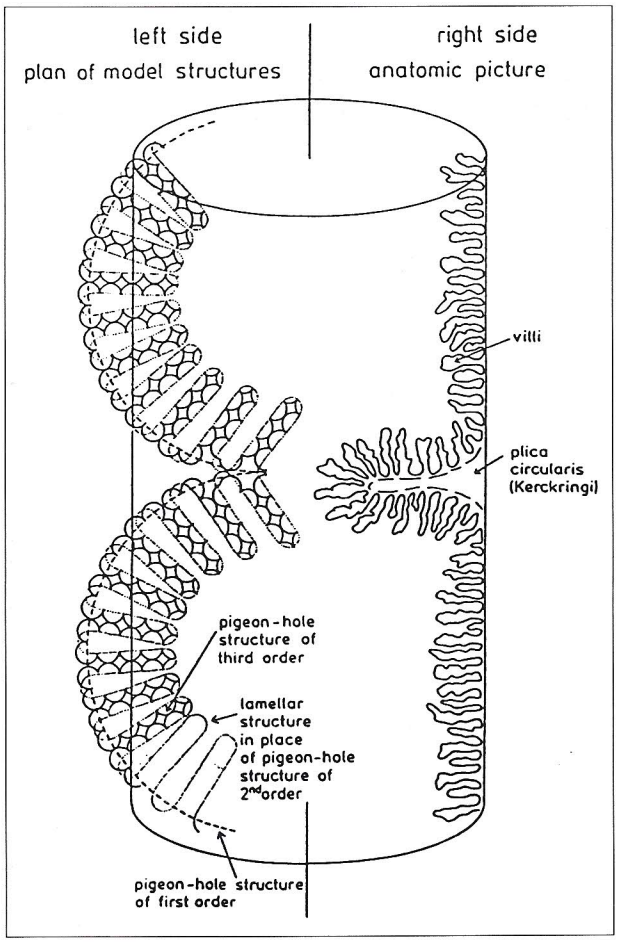


Figure 8

Mathematical modelling of a cross section through the small intestine using pigeonhole model [7]



represents an idealized three-dimensional network of a pore system (Menger sponge) where the size and geometry of pores are self-similar. This labyrinth has a very high internal surface and a fractal dimension D = 2.72.

The lungs (Fig. 7) can be described as another idealized self-similar network, with an extremely high internal surface and a fractal dimension D = 2.9, which is close to the volume filling physical dimension D = 3. *Pape* et al. [7] used the pigeonhole model to describe the large surface area of the intestine (Fig. 8).

Fractals and Coastline of Britain Problem

The reciprocal of the exponent k (see preceding chapter) is sometimes called the fractal dimension of the ant's walk. This fractal dimension is different from the fractal dimension of the cluster on which the walk takes place. Considering the surface structure of a pore system, a certain roughness of the surface has to be expected. This roughness is related to the surface structure of the particles and granules compacted and depends on the compaction process. Applying the concept of fractal dimension [2], the surface roughness or in the linear case the irregularity of a coastline, i.e. "the Coastline of Britain Problem" can be quantitatively solved.

The "Coastline of Britain Problem" originates from the fact that the length of the coastline as well as the length of many border lines, e.g. frontiers, depend on the resolution power, i.e. the unit length applied as a yardstick. A log-log plot of length of the border line versus unit length yields in general a slope proportional to (1-D). The plot is called Richardson plot (Fig. 9).

Using the method of polygon approximation, linear fractal dimensions of lactose and dicalciumphosphate granules have been estimated by us to be D (lactose) = 1.091 ± 0.007 and D (dicalciumphosphate) = 1.064 ± 0.002 (Fig. 10).

In case of isotropic growth of these lactose granules it is possible to give an estimate of the surface rough-

Figure 9

Richardson plot for coastlines and boundary lines of different countries [2]

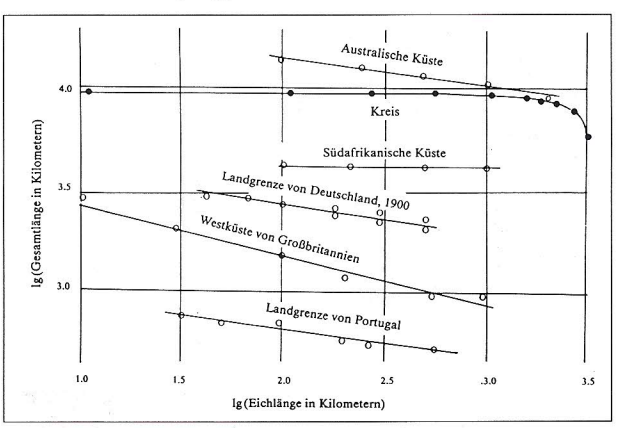
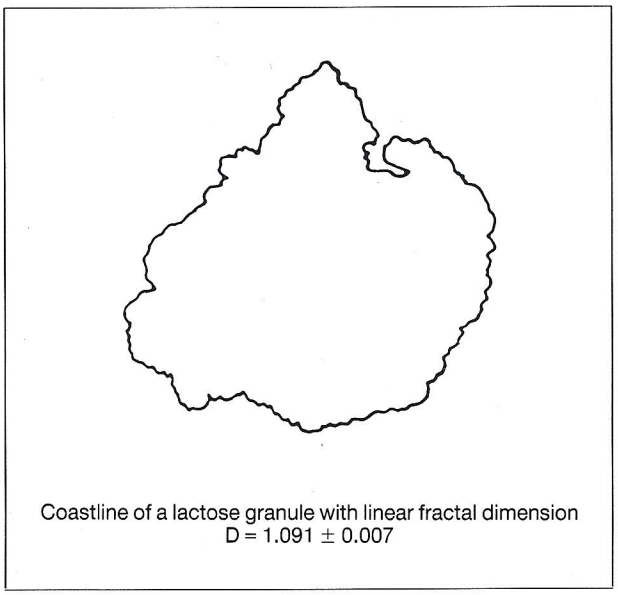


Figure 10

An outline of the surface roughness of a lactose granule



Coastline of a lactose granule with linear fractal dimension D = 1.091 ± 0.007

Figure 11

Mathematical simulation of coastlines with fractal dimensions D = 1.47, 1.26, and 1.16

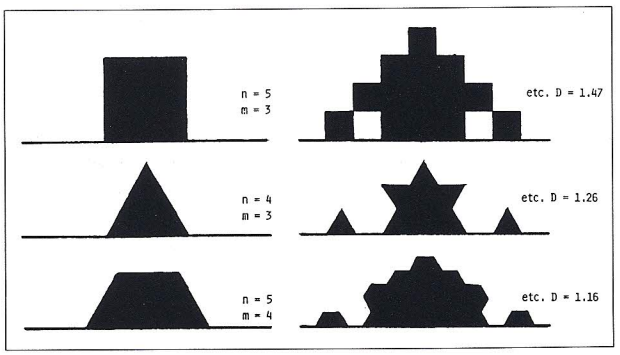
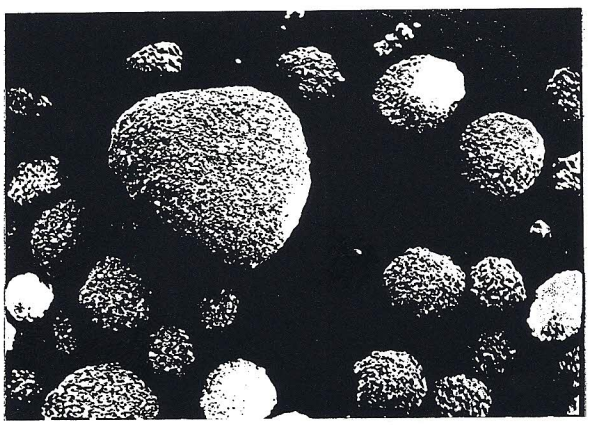


Figure 12

Scanning electron micrograph of the surface of lactose granules



ness, i.e. surface fractal dimension D (surface) = D (linear) + 1. Surface fractals have a dimension between 2 and 3. Depending on the individual lactose granule batch and experimental method to determine fractal dimension, linear fractals between D = 1.091 ± 0.007 and D = 1.19 ± 0.08 have been found.

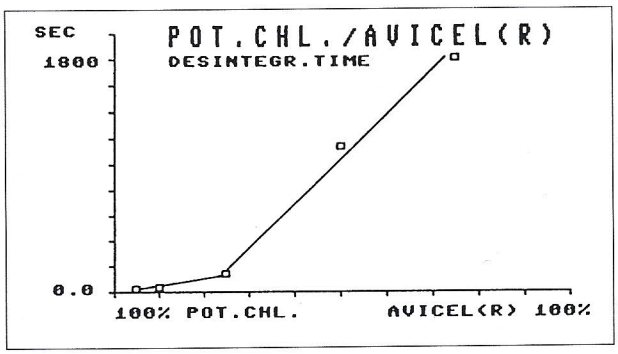
Figure 11 shows a mathematical simulation of a self-similar linear (fractal) coastline with different D values. The surface roughness of lactose granules is qualitatively described by a scanning electron micrograph in Figure 12.

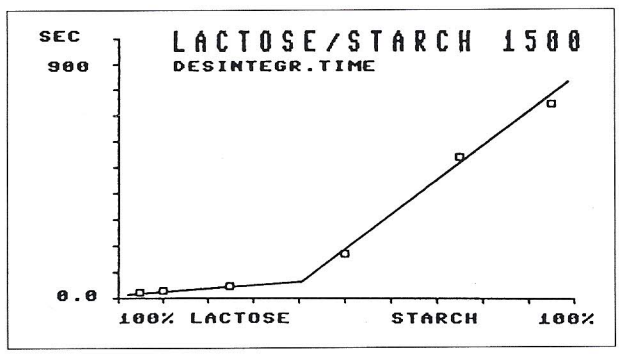
Dosage Form Design

A dosage form usually consists of an active substance and different excipients. In general, the material used is dispersed in a finely divided state in the dosage form. If one varies the proportions of the constituents in the formulation, important changes in the properties of the dosage form have to be expected as soon as one of the excipients involved forms an infinite cluster at the percolation threshold [5, 6]. For example the following properties of a tablet may change: crushing strength, friability, disintegration time, release properties, etc. (Fig. 13a and 13b).

Figure 13a and b

The disintegration time as a function of compositions of binary component compacts [6]
a) Potassium chloride/Avicel®
b) Lactose/Starch Rx 1500®





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