DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 3(1), 1-21 (1977)

PERMEABILITY AND PENETRABILITY OF SOLID BEDS IN DOSAGE FORM DESIGN AND DEVELOPMENT

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ABSTRACT

The theory of fluid penetration in solid beds is presented; the relevance of liquid penetration measurements in dosage form design is stressed and a descriptiontion is offered of the influence of some common additives on the penetrability of tablets and capsules.

INTRODUCTION

The main aim of modern pharmaceutical technology is optimisation of the dosage form from the therapeutical standpoint. To achieve this objective bioavailability must be carefully studied as shown by many authors in the past few years. In this regard much more emphasis has been laid on the study of dissolution rates of solid dosage forms than on other physical factors which can influence them. Disintegration and deaggregation can be the steps limiting dissolution rates of tablets.

These factors may be of little interest to the quality controller, since dissolution rates are the result of many other factors and are the last step before absorption, but they must be taken into account by the dosage form designer who must know at what step to operate in order to remove possible formulation defects. Disintegration and deaggregation are in turn governed mostly by the penetration of body fluids (e.g. gastric or intestinal juice) into the solid dosage form. The formulator thus has to be familiar with the physical factors that can influence penetration.

This paper reviews the literature on this question, in order to show how the dosage form designer can work on the physical factors involved in penetration, and to outline an experimental approach that is efficacious both from a theoretical and practical point of view.

THEORETICAL CONSIDERATIONS

The model which best describes fluid penetration into a powder plug is based on the assumption that the solid bed consists of a system of small particles (drug and additives) interconnected by a network of fine, tortuous channels. Thus the motion of a fluid through a solid dosage form, such as a tablet, can be described as the flow of a fluid through a series of capillaries.

The rate of flow of a fluid, under laminar stationary flow conditions, through a capillary of circular cross-section is given, according to Poiseuille's law, by the following equation[1,2]:

$$Q = \frac{\pi}{8\eta} \left(\frac{\Delta p}{L}\right) r^4 \qquad (1)$$

where

Q = volume of water flowing per unit time

η = fluid viscosity

L = capillary length

Δp = pressure difference across length L

r = capillary radius

thus the velocity of the stream, u, is:

$$u = \frac{dL}{dt} = \frac{Q}{\pi r^2} = \frac{\Delta p}{L} \frac{r^2}{8\eta} \qquad (2)$$

If the capillary has a non-circular cross-section, the equation (2) becomes[3,4]:

$$u = \frac{dL}{dt} = \frac{m^2}{k_o \eta} \frac{\Delta p}{L} \qquad (3)$$

where:

m = hydraulic mean radius (ratio of the cross-sectional area of the capillary to its perimeter)

k_o = a constant depending on the shape of the cross-section of the capillaries.

The term p is related to the forces which cause motion of the fluid; they are essentially the solid-liquid interaction forces (capillary forces) and the "external" forces, such as gravimetric liquid pressure.[5]

Thus equation (2) becomes:

$$u = \frac{r^2}{8\eta} \frac{\Delta p \text{ total}}{L} = \frac{r^2}{8\eta} \frac{\Delta p \text{ capillary} + \Delta p \text{ external}}{L} \qquad (4)$$

The term p capillary, for capillaries of circular cross-section, is given by the following equation

$$\Delta p \text{ capillary} = \frac{2\gamma \cos \vartheta}{r} \qquad (5)$$

where:

γ = surface tension of liquid

ϑ = solid-liquid contact angle

r = capillary radius

The term Δp external, considering only the gravimetric pressure, is given by[6]:

$$\Delta p \text{ external} = g\ d\ L \sin \qquad (6)$$

where:

g = acceleration of gravity
d = density of liquid
L = length of capillary
a = inclination of capillary to liquid surface

Since tablet size is usually very small, it is reasonable to neglect the term p external due to gravimetric pressure. Thus, by considering negligible all possible external forces, the motion of fluid into powdered systems can be described by the following equation:

$$u = \frac{dL}{dt} = \frac{r\ \gamma\ \cos\vartheta}{4\ \eta\ L} \qquad (7)$$

which is derived by substituting equation (5) into equation (2). Integration of equation (7) with the boundary conditions L = 0 if t = 0, gives:

$$L^2 = \frac{r\gamma\cos\vartheta}{2\eta}\ t \qquad (8)$$

This is known as Washburn's equation (7) and it holds for capillaries of circular cross-section.
If capillaries are not circular, p capillary becomes[8]

$$\Delta p \text{ capillary} = \frac{\gamma\ \cos\vartheta}{m} \qquad (9)$$

where:

m = hydraulic mean radius

Substitution of equation (9) into equation (3), which

is also related to non-circular capillaries, gives:

$$u = \frac{dL}{dt} = \frac{m^2}{k_o \eta} \frac{\Delta p \text{ capillary}}{L} = \frac{m^2}{k_o \eta} \frac{\gamma \cos \vartheta}{mL} \tag{10}$$

Integration of equation (10) leads to:

$$L^2 = \frac{k \gamma \cos \vartheta}{\eta} t \tag{11}$$

where:

$$k = \frac{2m}{k_o}$$

From equation (11) it follows that the relation between the square of penetration length (L^2) and the time is linear. As the volume of penetrated liquid is directly proportional to penetration length, the relation between the square of volume (V^2) and the time is also linear, as shown by Washburn[7]:

$$V^2 = k_1 L^2 = k_2 t \tag{12}$$

where:

$$k_2 = k_1 \frac{k \gamma \cos \vartheta}{\eta}$$

Thus, if penetrability data are plotted, according to Washburn's equation, as the square of length of penetration (or volume) vs. time, the resulting graph should be a straight line (see Fig. 1). But equation (11) does not always hold, for certain solid/liquid systems some authors[5] find a linear relationship between L and time (see Fig. 2). An explanation of this apparent failure of equation (11) has been provided recently by Schicketanz[9], who claims that fluid penetration into powder can be described better, at least

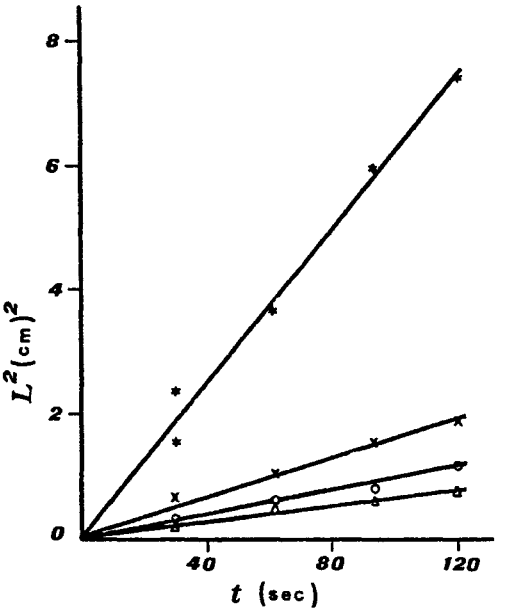

FIGURE 1.

Water penetration in packed powder beds. * = no lubricant, x = 1% magnesium stearate, o = 2% magnesium stearate, Δ = 5% magnesium stearate.

(According to Samyng and Yung)[10]

in the initial stage, by the following equation:

$$L = KV = 2\sqrt{\frac{\gamma \cos \nu^{l}}{d}}\, t \qquad (13)$$

This was first proposed by Kozeny[3], referring to a laminar non-stationary flow, where:

L = penetration length
V = penetration volume
γ = surface tension of liquid

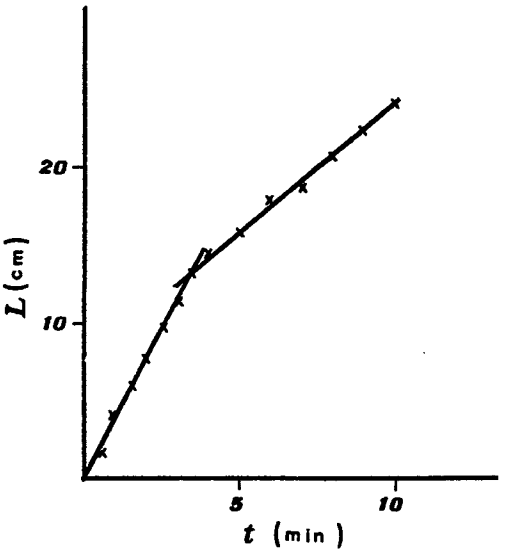

FIGURE 2.

Water penetration in quartz powder bed.
(According to Heertyes and Kossen)[5]

ϑ = solid/liquid contact angle
d = capillary diameter
s = liquid density

It is therefore better to use a more general expression underlining the variability of the penetration length (or volume) - time relationship:

$$V = K_1 \quad L = K_2 \; t^{m(t)} \tag{14}$$

where m can assume the value of 1 (short times, when equation (13) prevails), and finally decreases to 0, as saturation is reached. The logarithmic form of equation (14) is:

$$\log V = \log K_2 + m \log (t) \tag{15}$$

Thus, if penetrability data are plotted, according to equation (15), on a double-logarithmic graph, m can be calculated from the slope of the curve (see Fig. 3) for a given time interval, so that one can determine which equation best fits the penetration data, giving the operator the most correct as well as the most informative means of interpreting penetrability data.

MEASUREMENT TECHNIQUES

There are two basic types of experimental apparatus for evaluation of fluid motion through a bunch of capillaries: the permeameters and the penetrometers.

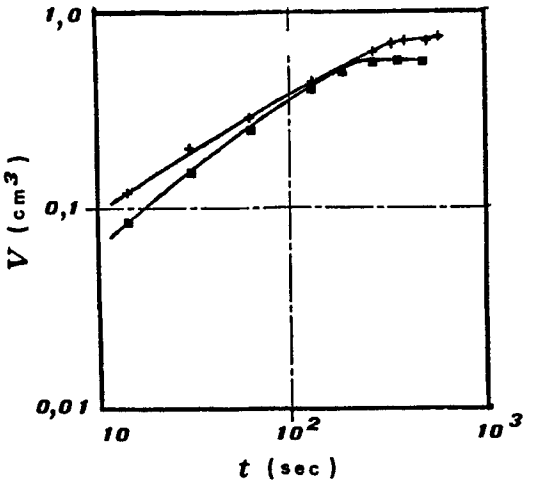

FIGURE 3.

Penetration of water in powder beds. ∪ = calcium carbonate, + = zinc oxide. The m values range from 0.75 ($CaCO_3$) and 0.6 (AnO) to zero, as penetration is reached.

(According to Schicketanz)[9]

The former[11,12] measure the flow rate of a fluid under a pressure head through a tube with a cell in which the powder bed has been placed; thus one measures the permeability, i.e. the resistance of the porous system to the flow of fluid; the fluid, when measurement starts, must already have filled all the open channels of the powder plug. The penetrometers[13,14,15] measure the rate at which the fluid, under no external pressure, penetrates the solid bed; in this case measurement starts when the fluid makes contact with the external surface of the porous system but has not yet wetted the inner open capillaries. The motion of fluid in both instruments can be described by equation (3), where the term p is related to the forces which cause motion of the fluid. In gas permeameters (Fig. 4) this p is essentially due to the pressure gradient across the cell in which the powder bed has been placed.

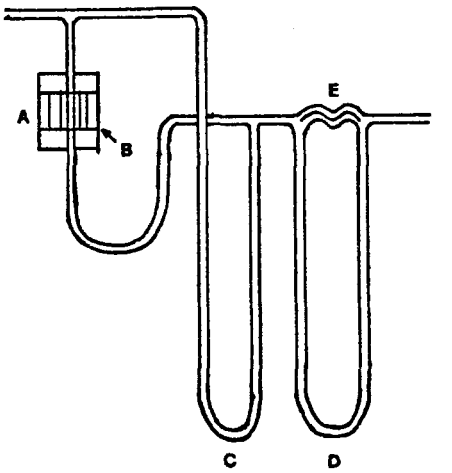

FIGURE 4. Gas permeator. A, sample cell; B, support gauze and filter; C, manometer for evaluation of Δp across Cell A; D, flowmeter with capillary tube bore E. (According to Gregg)[16]

In liquid permeameters (Fig. 5) Δp is given by hydrostatic pressure due to the height of the liquid column. Finally, in penetrometers (Fig. 6 and 7) Δp is only due to capillary forces, i.e. solid/liquid interactions equations (5) and (9). In both types of penetrometer the flow of liquid is due to capillary forces which draw the liquid into the powder plug capillaries, gravimetric pressure being negligible. Thus in measurements based on capillary penetration, the fluid enters the solid bed only by means of forces due to specific solid/liquid interactions[17]. On the other hand in permeability measurements the fluid is also subject to other external forces (hydrostatic pressure, gas pressure heads) which can mask possible behavioural differences between different solid/liquid systems. Great care must be taken in drawing conclusions about disintegration and deaggregation from gas permeability data, since the solid/gas interaction

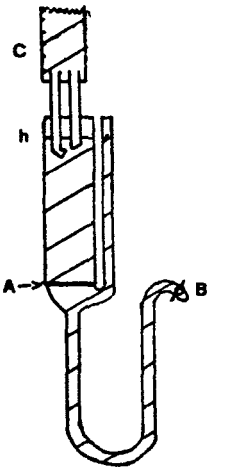

FIGURE 5. Liquid permeator. A, sample support gauze and filter; B, stopcock controlling the flow rate; C, graduated resevoir; h, constant level of liquid. (According to Allen)[12]

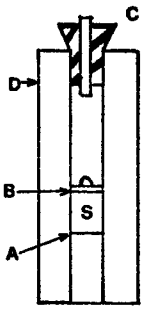

FIGURE 6. Liquid penetrometer for penetration length measurements. A, support gauze with filter; B, perforated platinum disc; C, one-hole rubber stopper; D, plexigas tube; S, sample. The rate of movement of liquid, added through C, in the sample is measured with a cathetometer. (According to Studebaker and Snow)[15]

forces can be very different from the solid/liquind ones. An example was given by Ganderton, who found that the addition of a hydrophobic lubricant such as magnesium stearate[18] or of a disintegranting agent such as starch[19,20], to magnesium carbonate tablets did not affect permeability, whilst it practically inhibited water penetration. The addition of binders to granule massing also had no apparent effect on permeability of the tablets[21], whilst the penetrability was notably altered. At any rate gas permeability data (especially air permeability) still retains some use-

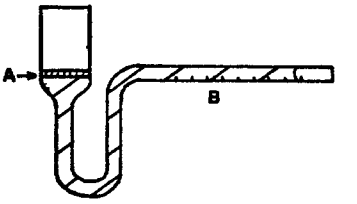

FIGURE 7. Liquid penetrometer for penetrated volume measurements. A, sample support gauze with filter; B, graduated tube, from which the withdrawal of liquid is measured. (According to Nogami)[13]

fulness, since the mean radius of solid bed capillaries (which influences penetration itself) can be derived from these data by appropriately rearranging equation (3).

Thus it is advisable for the formulator to measure the permeability of solid dosage forms in conjunction with the penetrability, in order to draw the most correct and informative conclusions.

FACTORS INFLUENCING PENETRABILITY

From the theoretical considerations it follows that liquid penetration into a pharmaceutical solid dosage form such as a tablet or a capsule is a function of the porous structure and wettability of the solid as well as of the surface tension and viscosity of the liquid. The first two properties may, in turn, be influenced by the formulation characteristics (presence of lubricants of disintegrating agents, granulation etc.). Thus it is of practical significance to go into details of how these factors can affect solid dosage form penetrability.

CHARACTERISTICS OF THE LIQUID

Viscosity: the greater the viscosity of the penetrating liquid, the slower the rate of penetration. This has been observed by Nogami[6], studying the penetration of 0.8% and 1% methylcellulose solutions in magnesium oxide tablets. The viscosity of a liquid may change during penetration because the wetted portion of the tablet can increase viscosity and slow down the penetration rate. This happens if the liquid is not capable of opening the tablet structure. If, on the other hand, the liquid opens the structure, it reduces the

viscous resistance of the wetted portion of the tablet and the penetration rate is not slowed down[18].

Surface tension: Nogami[6], studying water penetration into a magnesium oxide powder bed, reported that the addition of 0.02% and 0.2% of sodium dioctylsulfosuccinate to water slowed the penetration rate, while the addition of surfactant increased the penetration rate into an aspirin powder bed. These contradictory results might be explained, in Nogami's opinion, by the addition of surfactants to the penetrating liquid having opposite effects on the cosine of the solid/liquid contact angle and on the liquid surface tension: the former is increased, the latter decreased. Thus, if wettability (i.e., the cosine of contact angle) is already good, as in the case of magnesium oxide, addition of a surfactant primarily affects surface tension. If, on the other hand, wettability is poor, as in the case of aspirin powder, the addition of surfactant primarily influences the contact angle, reducing it and raising the penetration rate.

WETTABILITY

The penetration of liquids into a solid dosage form is dramatically influenced by the wettability of the components; generally, the better the wettability, the higher the penetration rate. Since surfactants are commonly used in formulation both as wetting agents and as sorption promoters, their influence on solid dosage form penetrability should be evaluated very carefully. Aoki[22] showed an increase of water penetration in tablets of poorly soluble drugs after wetting with a non ionic surfactant; Nogami[6] also claims greater penetration for aspirin tablets wetted with sodium dioctylsulfosuccinate. However, adding a surfactant to tablets with good overall wettability, may

be ineffective or negative by slowing the penetration rate. In fact, when wettability is good, the dissolution characteristics of the surfactant can play a decisive role, primarily affecting the liquid surface tension and its rheological properties. The different penetration rates found by Cooper[23] who added various succinic esters of a wetting agent to tablets, were attributed by Nogami to their different dissolution.

Another surfactant property which can affect penetration is HLB. This has been detailed Huttenrauch[24], using Tween 80 (HLB=15), Span 20 (HLB=8.6) and fatty acids (HLB=1). These substances were added either to starch powder, the penetration liquid being a carbon tetrachloride-paraffin mixture, or to sulphur powder, the penetration liquid being water. Huttenrauch's findings show that the addition of Span 20 to sulphur powder caused the greatest increase in water penetration, whereas the addition of Tween 80 was less effective.

In other words the graph of penetration volume vs. HLB, in the case of the sulphur/water system, showed a maximum in relation to an HLB in the range 7 to 9. For the starch/carbon tetrachloride-paraffin system, the penetration volume increased linearly as HLB increased (greatest penetration for Tween 80) with no maximum.

POROUS STRUCTURE

Nogami[6], studying the penetration of water into magnesium oxide and aspirin tablets, reported that the penetration rate increased with mean pore diameter.

In an interesting study on sucrose and lactose tablets, Ganderton[25] found a linear uptake of cyclohexane at lower porosity (20%), while at higher porosities (30%) penetration slowed. The percent cyclo-

hexane saturation of tablets (calculated from the penetrated volume and the void space) when penetration stopped increased at lower porosities.

At a given porosity the pore size distribution seems to play a decisive role; tablets having a coarse pore structure permit faster penetration than tablets with the same porosity but a more even pore structure. In the former, rapid penetration could isolate pores by trapping air, so that percent saturation could decrease.

Other authors who reported the possible occlusion of pores by air bubbles were Wurster[26], Wood[27], and Huttenrauch[28]. The latter has also given a further demonstration of the relevance of porous structure in penetrability; investigating water penetration in binary mixtures (aluminum oxide, zinc oxide, talc, kaolin) he found the relation between the penetration rate and the mixing ratios strictly parallel to the relation between porosity and the mixing ratios[29].

PARTICLE SIZE

The powder particle size, the granulation technique, the granule size and the compression force are undoubtedly factors that can markedly affect penetrability, since porous structure depends on them. In this regard the work of Ganderton et al[25, 30, 31] on lactose and sucrose tablets is fundamental. The revealed that granule porosity was greatly influenced by water massing concentration: as water concentrations increased, porosity changed up to 6% in the sucrose granulates and up to 10% in the lactose granulates. The porosity of sucrose tablets produced at any pressure level increased as the granule size and water massing concentration decreased. With lactose, on the

other hand, neither granule size nor water massing concentration affected the relation between porosity and compaction force.

The effect of sucrose granule properties on the mean pore radius can be summarized by saying that this radius increased as the massing water concentration increased and the granule size decreased. The effect of these two factors however on the intergranular mean pore radius is negligible at high compressional force; coarse granules, if compressed, also gave a poorly open structure.

The effect of compression on granule characteristics depended primarily on the granulation technique; highly porous and brittle lactose granules, made by dry granulation, fragmented greatly, giving tablets with a narrow pore size distribution range, while strong granules made by wet massing, led to a much wider pore size distribution.

Intragranular porosity is also influenced by the size of the powders used in massing. Ganderton et al [32, 33] reported higher porosity for granules made by net massing of lactose powder with finer particle size; however, the influence of particle size decreased as massing water content increased.

ADDITIVES

The influence of disintegrating agents and lubricants on solid dosage form penetrability has been thoroughly studied by many authors, whereas other adjuvants such as binders, diluents, stabilizing agents etc., which could markedly affect porous structure and penetrability, have been almost neglected.

Disintegrants. Starch is the one that has been studied most. Ganderton and Fraser[34] reported that addition of

starch to tablets of aspirin, calcium phosphate, lactose and magnesium carbonate, manufactured under high pressure, led to a higher penetration rate. They claimed that the tablet structure is more easily deformed, thus overcoming viscous resistance. On the other hand, with tablets made at lower pressure, starch had no significant effect on water penetration rate. This might be due to viscous resistance overcoming liquid uptake by the starch.

The same conclusion was drawn by Samyn and Yung[10], studying the penetrability of capsule powder blends with lactose and calcium phosphate as fillers; the addition of starch led to a decrease in water penetration rate.

In aspirin and magnesium oxide tablets, Nogami[35] reported, under particular conditions, a proportional increase in mean pore radius and porosity as the starch content increased. Although other authors[36,37] report similar results, there is little agreement in interpreting the starch effect on pore diameter. The hypothesis that penetration rate increases since further liquid uptake is promoted by starch grains is more widely accepted, and is supported by the work of Fraser and Ganderton[38] on various types of starch. The highest penetration rate was reported for magnesium carbonate tablets with potato starch; corn starch led to an intermediate rate, while rice starch gave the lowest rate.

Differences were also reported between starch and other disintegrating agents such as microcrystalline cellulose and ion-exchange resins[13,37]. Both the different intragranular porosity of the disintegrants[38] and the different cohesiveness of disintegrant parti-

cles were considered responsible for different effects on water penetration rates.

Lubricants. The marked effect of lubricants on penetrability is substantiated by much experimental data; e.g., a decrease in water penetration rate as magnesium stearate content increased was reported in magnesium carbonate tablets[25]. This inhibitory effect very much increased as the lubricant distribution in the tablet increased, the highest inhibition being found when magnesium stearate was added during wet massing.

This inhibitory effect has also been supported by studies on tablets with various drugs[39,40] and on capsule powder blends[10]; the mixtures containing magnesium stearate were poorly penetrated and tended to become a highly viscous slug; talc, too, had a negative effect on penetrability, though less.

CONCLUSION

This review demonstrates that liquid penetrability is more informative than gas permeability in preformulation studies and development of oral solid dosage forms.

It has been shown that penetrability is influenced by the nature of formulation components, by their ratio and by the manufacturing processes. It has also been shown that the same manufacturing techniques can have different effects on penetrability, depending on the type and ratio of constituents, and that at a given porosity, the penetration rate may differ.

If one considers that during the absorption process the first stage is contact of the drug with G.I. fluids, it is important to study the mechanism by which body fluids penetrate the solid dosage forms. Lastly, the penetration rate also depends on some physical

characteristics of the penetration liquid. This could be of interest in determining dosage regimens since it gives an indicator of how well defined physiological conditions (e.g., stomach contents) can affect penetration of G.I. fluids into the dosage form, thus modifying its disintegration and drug dissolution and hence bioavailability.

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