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On the release of drug from hard gelatin capsules

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The effect of particle size and packing on the *in vitro* release of a water-insoluble hydrophobic drug from hard gelatin capsules has been related to the liquid permeability of powder beds of similar porosities. Drug release and permeability decrease with a decrease in particle size and porosity of the powder bed. A simple moist granulation process transforms a non-permeable powder bed, which allows low drug release, into one with high permeability and high drug release.

The review of the release of drugs from solid dosage forms by Wood (1967), shows that few investigations have been made of the factors affecting the release of drugs from hard gelatin capsules. Differences in biological availability of drugs from capsules, reported by Brice & Hammer (1969) and Glazko, Kinkel & others (1968) can be ascribed to differences in the physical chracteristics of the drug; e.g. crystal form, particle size and the method of formulation. The last effect was demonstrated by Aguiar, Wheeler & others (1968) who were also able to correlate *in vivo* plasma levels of chloramphenicol, administered in capsules of differing formulations, with the results from an *in vitro* dissolution test. Withey & Mainville (1969) reported that differences in the particle size of chloramphenicol altered its release *in vitro* from capsules and they discussed the influence that wetting, deaggregation and packing might have on the drug release. The present report contains details of an investigation of some factors which influence the release of a water-insoluble, hydrophobic drug, ethinamate from hard gelatin capsules and shows one way in which drug release can be improved.

EXPERIMENTAL

Materials

Ethinamate (1-ethynylcyclohexyl carbamate) U.S.N.F., from a single batch of material was graded into size fractions by sieving. A quantity of the unfractionated drug was subjected to fluid energy milling. The resulting powder had a mean particle diameter of 8·3 μm calculated from its specific surface area as determined by the air permeability method of Lea & Nurse (1939). Granules of this micronized ethinamate were prepared by wet granulation with isopropanol. All other chemicals used were of reagent grade.

Methods

Capsule filling. Size No. O hard gelatin capsules (Lilly) were filled using a CAP III capsule filling machine (Tevopharm-Schiedam N.V.). The lowest fill weight for each particle size fraction corresponded to the amount of powder which would occupy the volume of the capsule body without applied pressure. To increase the fill weight for a given size fraction, known weights were applied to the pressure plate to compress the

powder within the capsule body. Each loading was followed by a levelling off with powder until no more powder could be filled into the capsule. By increasing the loading weight, a range of capsules of increasing fill weights was obtained for each size fraction. The capsules were weighed and only those within $\pm 5\%$ of the average fill weight for the filling conditions were retained. The porosity of the bed of powder within the capsule, was calculated as the ratio of the volume of voids to the total capsule volume, assuming that the powder was distributed evenly throughout the capsule shell.

Dissolution testing. This was by the beaker method of Levy & Hayes (1960) at a stirring rate of 45 rev/min. The capsule was held in a spiral of stainless steel wire (0·86 mm d), 5 cm long, 0·8–1·0 cm d with approximately 5 coils per 2 cm. This was held horizontally, 1 cm above a circular loop (5 cm d) of stainless steel wire (1·0 mm d), which was placed centrally at the bottom of a wide necked, round bottom flask containing 1 litre of distilled water. During the test, samples were taken at known time intervals, filtered and the ethinamate in solution determined by refluxing for 2 min with 1% sulphuric acid and estimation of the ammonium salt formed with Nessler's reagent. Allowance was made for the drug removed in the sample volume and results were calculated as a percentage of the total drug originally present. The results are the mean of 8 replicate dissolution tests. The percentage in solution–time curves followed the same general pattern (approximating to an exponential decrease in amount of release with time), hence comparison of different capsules was made at a constant time of 30 min.

Disintegration time of capsules. This was determined by the B.P. disintegration test, but using single capsules, the results being the mean of 5 replicates.

Permeability. The permeability of powder beds of different porosities was measured by the pressure decline method of Dodd, Davis & Pigdeon (1951). A saturated aqueous solution of ethinamate was used as permeating liquid to prevent changes in bed structure due to ethinamate dissolving. It was not possible to obtain a bed of micronized ethinamate through which the liquid would readily permeate without forming channels.

The Kozeny (1927) equation as used by Carman (1937) relates the flow rate of a fluid through a bed of powder, to the characteristics of the bed and the permeating fluid, and can be expressed as

$$Q = \frac{1}{k}\frac{A}{\eta So^2}\frac{\epsilon^3}{(1-\epsilon)^2}\frac{\rho g h}{L} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where Q = volume rate of flow of liquid through the bed; k = dimensionless constant, known as the Kozeny constant and taken as 5; A = cross sectional area of the powder bed; η = viscosity of the permeating fluid; So = specific surface area per unit volume; ϵ = fractional porosity of the packed powder bed; ρ = density of the permeating fluid; g = acceleration due to gravity; h = drop in fluid head across the powder bed; L = depth of powder bed.

Equation (1) may be written in the form

$$Q = K \rho h \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

where

$$K = \frac{1}{k}\frac{A}{\eta So^2}\frac{\epsilon^3}{(1-\epsilon)^2}\frac{g}{L} \quad .. \quad .. \quad .. \quad .. \quad (3)$$

Equation (1) may also be arranged in a form equivalent to Darcy's law for isothermal

liquid streamline flow through a porous media as

$$Q = B_0 \frac{A}{\eta} \frac{\rho g h}{L} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where B_0 = the "permeability coefficient" or permeability. Comparison of equation (2) with equation (4) yields the relation

$$B_0 = \frac{\eta K L}{A g} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (5)$$

In terms of experimental work B_0 can be calculated by employing the values of K, as determined by the method of Dodd and others (1951), in the equation (5).

RESULTS AND DISCUSSION

The percentage of drug released into the solution from the capsule after 30 min is shown as a function of the porosity of the bed of material within the capsule shell in Fig. 1A. The relation obtained is dependent on the particle size of the drug. If dissolution is compared at the same porosity, a larger percentage of drug is released from capsules containing the larger particle size fractions. The larger particle size fractions are not greatly influenced by the packing within the capsules, but as the particle size of drug decreases, packing larger quantities of material into the capsule causes a marked decrease in the percentage of drug released. For the smallest particle size fraction tested, the decrease in drug release took place over a small porosity range and thereafter decreasing porosity had little effect on drug release.

Within the conditions of filling, a larger range of porosities can be obtained as the particle size decreases because of the higher initial voidages associated with finer particles. Reducing the particle size will also decrease the size of pores between the particles which will reduce the ease of access of dissolution media to the powder mass. If this is a significant restriction, the release of drug will be reduced. To obtain a measure of the effect of particle size and packing on the access of dissolution medium to

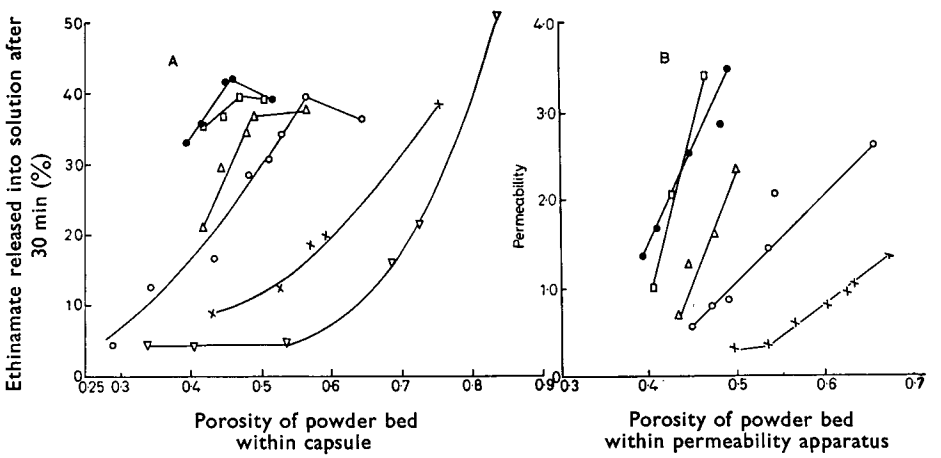

FIG. 1. A. The percentage of drug released after 30 min from capsules containing different particle size fractions of ethinamate packed to give different porosities. B. The liquid permeability ($m^2 \times 10^{11}$) of equivalent particle size fractions at known porosities. ●——● 251–420 μm. □——□ 177–251 μm. △——△ 152–177 μm. ○——○ 125–152 μm. +——+ 66–76 μm. ▽——▽ 8·3 μm.

the powder bed, we applied the liquid permeability method of Dodd & others (1951). The results for the same powders, under packing conditions as near as possible to those within the capsule, are shown in Fig. 1B. The results relate qualitatively to the dissolution results, the larger the particle size and the higher the porosity, the greater is the permeability of the bed: there is not, however, complete correlation. The larger particle sizes show more rapid change in permeability with porosity than the smaller particle sizes, whilst in certain regions of porosity, the reverse is true of drug release. This difference can be attributed to the fact that permeability is not the only factor involved in the dissolution process, the disintegration of the capsule, and the characteristics of the resultant powder mass being also important. The disintegration time of capsules containing 251–420 μm particles is lower than those containing smaller particle sizes and is less influenced by packing (Table 1). Thus, the larger size particle

Table 1. *Porosity of capsule fill (ϵ) and disintegration time (D) of capsules of ethinamate of different particle size fractions*

Particle size fraction							
251–420 μm		251–420 μm (granules)		124–152 μm		8·3 μm	
ϵ	D (min)	ϵ	D (min)	ϵ	D (min)	ϵ	D (min)
0·515	5·7	0·763	2·7	0·646	7·3	0·833	18·4
0·459	4·6	0·678	3·6	0·531	4·5	0·726	13·75
0·416	4·5	0·604	3·7	0·511	7·75	0·686	17·1
0·403	4·75	0·514	5·0	0·484	6·1	0·485	>30·0
				0·435	5·9		
				0·290	10·6		

systems break up and form a powder mass on the bottom of the beaker which probably has a higher porosity than the powder mass within the capsule. The smaller particles with extended disintegration times, however, do not break up readily and in extreme cases remain virtually in the same structure as that within the capsule. When the mass does not disintegrate readily, permeability will more nearly parallel dissolution, although in extreme cases the very low permeability will only allow dissolution to take place from the outermost surface of the capsule-shaped powder mass which often remains. In these cases increasing the quantity of drug within the capsule will not affect dissolution, e.g. the dissolution results for capsules containing micronized material.

The results from the permeability experiments can be used to determine the specific surface area of different size fractions, under similar packing conditions to those within the capsule, see Table 2. Comparison of these results with those for dissolution leads to the conclusion that, although the specific surface area increases with decrease in particle size, it is not available for dissolution. Studies on the dissolution rates from powdered drugs by Finholt, Kristiansen & others (1966), illustrated that granulation of powders increased the availability of the surface as indicated by dissolution. We prepared granules from micronized material which when dried, were sieved to give the same particle size as the largest individual size fraction of crystals tested, i.e. 251–450 μm. The dissolution and permeability of these two types of material are compared in Fig. 2. The results show the advantage of granulating the

Table 2. *Specific surface area per unit volume (So), of ethinamate size fractions as determined by liquid permeability at different porosities (ϵ)*

Size fraction μm	ϵ	So cm²/cm³	Size fraction μm	ϵ	So cm²/cm³	Size fraction μm	ϵ	So cm²/cm³
251–420	0·491	514	125–152	0·655	1348	251–420 Granulated	0·583	336
	0·482	543		0·543	872		0·565	360
	0·448	484		0·490	1029		0·537	330
	0·409	491		0·471	986		0·523	376
	0·398	490		0·448	1034		0·507	416
177–251	0·468	463		0·674	2070			
	0·428	484		0·633	1914			
	0·408	627		0·626	1940			
152–177	0·501	660	66–76	0·601	1866			
	0·475	701		0·564	1799			
	0·446	676		0·536	2026			
	0·435	880		0·497	1815			

micronized drug. Again, there is a clear relation between dissolution and permeability. The ranges of porosity used in the dissolution tests are higher than those of the permeability tests because the liquid pressure head in the permeability apparatus causes initial compaction of the powder bed. Thus permeabilities of powder beds of granules within the capsules will be even higher than those in Fig. 2. Because there is not a parallel increase in the rate of release of drug from capsules containing granules, we must again conclude that permeability alone does not control dissolution. The similarity of the specific surface areas of crystalline and granulated ethinamate, as determined by liquid permeability (Table 2) again indicates a lack of correlation

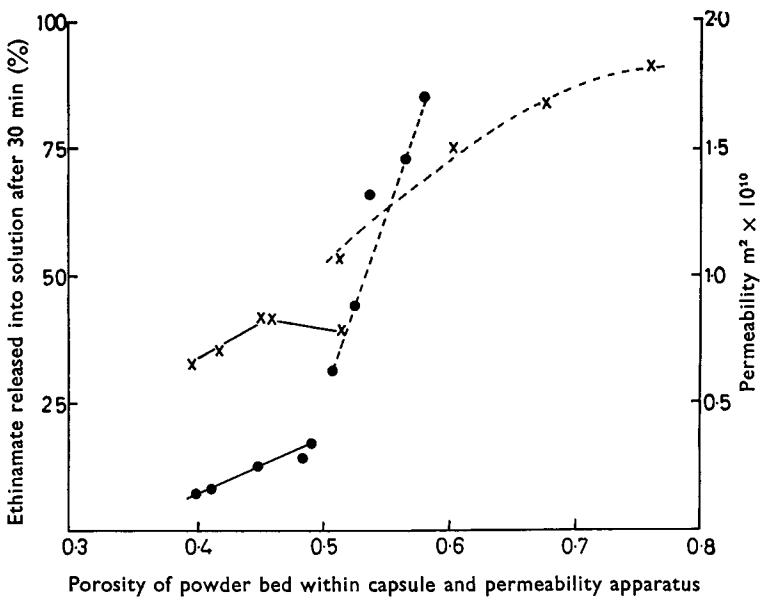

FIG. 2. A comparison of percentage of drug released after 30 min from capsules containing 251–420 μm crystals and 251–420 μm granules of micronized ethinamate, packed to give different porosities, and the liquid permeability of beds of the same samples. —— 251–420 μm crystals. ------ 251–420 μm granules. ● Liquid permeability. × Dissolution.

between permeability and dissolution. As noted previously, the time taken for the capsule to disintegrate under standard conditions does not solely control drug release. The capsules containing the granulated drug had similar disintegration times to those containing crystals of same particle size range see Table 1.

In the presentation of water insoluble hydrophobic drugs in capsules, it is important to ensure that a water permeable mass exists within the capsule and we have demonstrated one method whereby this may be achieved. This is based on capsules filled by one particular process. Capsules filled by alternative processes, especially those in which a slug is formed, may require different formulation methods. To ensure adequate drug release, however, penetration of liquid into the powder mass and its break up into readily available particles is essential.

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