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STUDIES OF THE EFFECT OF POWDER MOISTURE CONTENT ON DRUG RELEASE FROM HARD GELATIN CAPSULES

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ABSTRACT

The in vitro dissolution of model formulations from hard gelatin capsules containing drug: diluent powder mixtures at different moisture levels has been studied. The capsules were filled to a constant porosity of 50% to contain either sodium barbitone or barbitone in 50:50 mixture with lactose or maize starch, the latter at one of three moisture levels. In addition, capsules containing drug alone were examined. The wettability and polarity indeces of the individual powders and binary mixtures, as well as the permeability and liquid penetration rates of powder beds were also determined.

The presence of either excipient was found to modify the time for 50% drug dissolution ($t_{50\%}$) compared with drug alone for all formulations examined, apart from the sodium barbitone: lactose capsules. The rate of drug dissolution was also dependent on the initial powder moisture content for the drug:starch formulations. Open storage of capsules at 20°/75% R.H. generally increased $t_{50\%}$ figures.

The findings are discussed in terms of the nature of the

surfaces of the powder particles, moisture sorption phenomena and factors such as powder bed permeability and water penetration rates.

INTRODUCTION

A number of studies have examined the formulation and processing variables associated with the production of hard gelatin capsules (1-5). Particle size of the drug, powder bed porosity, percentage of diluent and lubricant, together with production machine variables, were demonstrated to influence the properties and performance of the filled capsules. Variation in moisture content was not considered in these investigations although recent work has indicated that the physical stability and other properties of capsules and tablets can depend upon the moisture levels in constituent powdered drugs and excipients (6-9). It is also well recognised that changes in moisture content of solid dosage forms on storage can produce physical aging, the causes of which are not fully understood (6-7, 10-12). It was therefore thought appropriate to prepare several model capsule formulations and to study the effect of initial powder moisture content on in vitro drug release from capsules both initially and on storage. In addition relevant properties of the powder formulations, including moisture sorption isotherms, contact angles (13), permeability (3) and penetration rates (14), were examined. The powders selected were sodium barbitone and barbitone, as representative 'hydrophilic' and 'hydrophobic' drugs respectively, and lactose and maize starch as diluents.

MATERIALS

Sodium barbitone, barbitone, α-lactose monohydrate and maize starch were all B.P. grade. All other reagents used were of analar grade. Table 1 lists the mean particle volume-surface diameters, determined using a Fisher Sub-Sieve sizer (Kek Instru-

TABLE I - PARTICLE SIZE AND DENSITY OF EXAMINED POWDERS

	Mean volume - surface diameter (μm)	True particle density ($g.cm^{-3}$)
Sodium barbitone	44	1.57
Barbitone	44	1.24
Lactose	28	1.54
Maize starch	13	1.87

ments Ltd., Manchester, England), and true particle densities, estimated by the specific gravity bottle technique, of the four examined powders. Moisture contents were measured by drying samples to constant weight in a hot air oven at appropriate temperatures.

METHODS

Capsule preparation and storage

Single or mixed powders were filled into No. 1 clear, hard gelatin capsules (Eli Lilly & Co.,) in batches of sixty using a Feton hand capsule filler. Ten batches of capsules, B1 - B10 (see Table 4) were prepared to contain either sodium barbitone or barbitone in 50:50 mixture with lactose or maize starch, the starch at one of three moisture levels. The different moisture levels were achieved by storing the maize starch at 0%, 75% or 100% relative humidity. (This amount of diluent was selected since it has been shown that a level of 50% is required to modify drug release patterns (4)). The binary mixtures were prepared by tumbling constituent powders in a rotating cylinder until the coefficient of variation of five replicate samples was less than 5%. All capsules were filled to 50% porosity. The capsule shells used had previously been stored at 25°/75% R.H. and the prepared capsules were maintained at this storage condition.

Moisture sorption isotherms

Sorption and desorption isotherms at 25° were determined for sodium barbitone, barbitone, lactose, maize starch and the four possible binary mixtures containing 50:50 drug:diluent. Isotherms were also measured for the empty hard gelatin capsule shells. Samples were placed in shallow glass dishes inside desiccators containing appropriate saturated salt solutions to provide a range of relative humidities (15). The precautions indicated by Winston & Bates (16) were observed. Samples for moisture uptake studies were initially stored at 0% R.H. until equilibrated then placed in appropriate desiccators. Weight uptake was monitored until no further increase was observed. For moisture loss, samples were stored initially at 100% R.H. before transfer to desiccators.

Contact angle : index of polarity

These measurements were carried out as detailed by Lerk and others (13,17) and Zografi and Tam (18). Compacts were prepared by compressing powders in a 1.27cm diameter punch and die assembly in a hydraulic press using applied pressures in the range 50-100 kg/cm^2. Porosities were calculated from a knowledge of compact dimensions and weight. Presaturation without wetting the upper surface was achieved by placing the compacts on a porous disc partially immersed in the test liquid. (The two test liquids, double distilled water and tetraethylene glycol (Fluorochem Ltd., Glossop, England) were each saturated with respect to the component(s) of the particular compact under examination). As soon as compact saturation was achieved, the test solution was dropped slowly onto the compact surface and readings of drop height were taken with a cathetometer until additional drops caused no further increase in height. Single component compacts were prepared of sodium phenobarbitone, barbitone, lactose and maize starch, and 50:50 binary mixtures of sodium barbitone:lactose, sodium barbitone:maize starch,

barbitone:lactose and barbitone:maize starch. All measurements were performed at least in triplicate using the two test liquids. Reproducibility of contact angle was generally ± 1° except for compacts which exhibited swelling or softening when ± 3° was achieved. Densities and surface tensions of solutions were determined using specific gravity bottle and Du Nuoy tensiometer techniques respectively. Direct measurement of contact angle between the two test liquids and a paraffin sample (Parafilm, American Can Co., Greenwich, U.S.A.) was carried out using a cathetometer with protractor attachment. Liquid drops of about 0.05ml were placed on the paraffin surface and readings were made after 5 minutes following placement of drops, since advancing angles are independent of time after this time interval (19). Measurements were made at least in triplicate using new liquid and solid samples. Using these data and previously determined contact angles, indices of polarity, P_o, were then calculated using the technique of Zografi and Tam (18).

Dissolution testing

This was measured for filled capsules both initially and after open storage for 1 and 3 months at 25°/75% R.H. using a modified beaker technique (3) at a stirring rate of 50 rev./min. Individual capsules were held in a spiral of stainless steel wire attached above a circular loop of stainless steel wire placed centrally in the bottom of a 1L beaker containing 500ml of dissolution fluid maintained at 37°. The dissolution medium was HCl/KCl buffer at pH 2. During the test samples were withdrawn at known time intervals, filtered, diluted with buffer at pH 10 (boric acid/NaOH) and the amount of drug in solution was estimated using an ultraviolet spectrophotometer (Pye-Unicam SP 1800B, Pye-Unicam, Cambridge, England) at 240nm by reference to previously constructed calibration curves. Allowance was made for drug removed in the sample and results were calculated as a

percentage of the total drug originally present. The results are the mean of at least three replicate dissolution tests.

Permeability and penetration tests

Permeability coefficients of sodium barbitone:maize starch and barbitone:maize starch powder beds at 50% porosity and three moisture levels were estimated using a modified Rigden pressure decline apparatus with air as the permeating fluid and the relationships derived by Newton and Rowley (3). Liquid penetration rate measurements were also determined for these powder mixtures according to the method of Studebaker and Snow (20). Perspex tubes 1.25cm i.d. and 12cm long were filled with powder mixture to produce a bed 4cm thick at 50% porosity with the aid of a Fisher Sub-Sieve Size apparatus (14). Eight millilitres of water was added to the upper surface of the bed at zero time and the rate of movement of the water interface through the packed bed was measured against a millimetre scale attached to the outside of the perspex tube. Measurements for both tests were made at least in triplicate for each powder system examined.

RESULTS AND DISCUSSION

Sorption isotherms for maize starch and empty gelatin capsules are illustrated in Figures 1 and 2 respectively. Full sorption and desorption arms are shown and both materials exhibit hysteresis, confirming previous reports for these materials (15, 21-22). Barbitone and lactose did not show moisture sensitivity whilst moisture sorption at very high humidity levels (> 85% R.H.) was observed for sodium barbitone. Both drug:maize starch 50:50 mixtures exhibited a proportionally reduced area of hysteresis (see Figure 3).

Although several hypotheses have been proposed, a completely satisfactory theoretical explanation for the origin of hysteresis has not been made (23). Possible explanations consider such

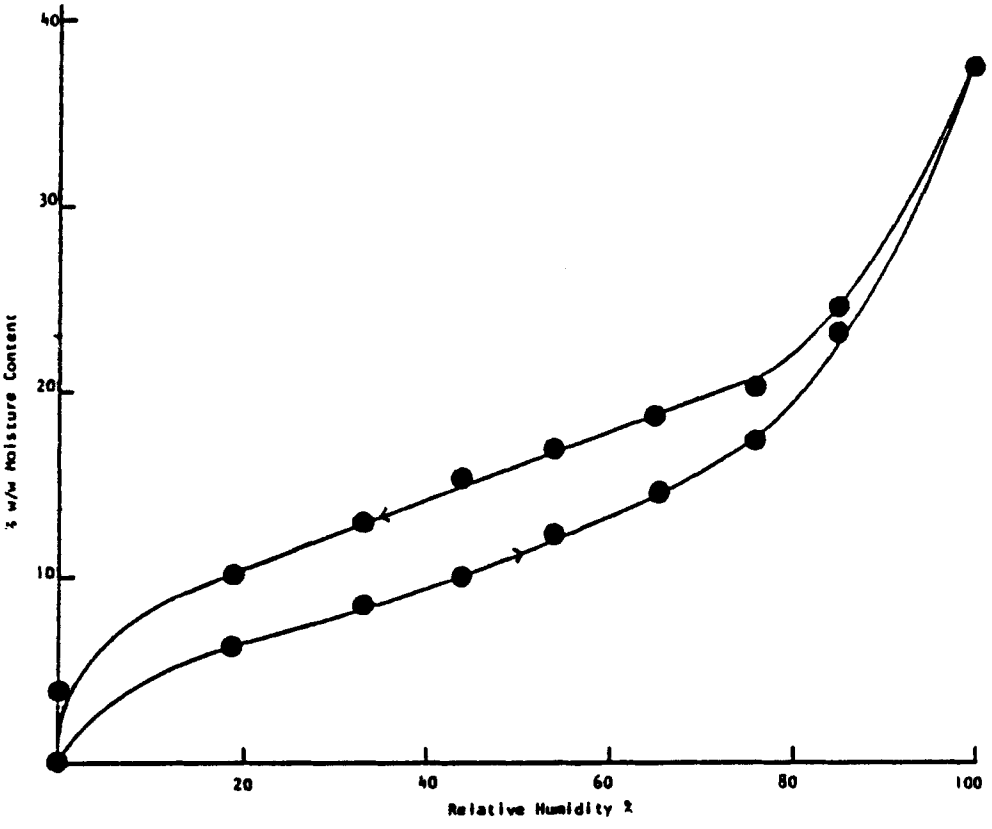

FIGURE 1

Moisture sorption and desorption isotherms for hard gelatin capsules at 25°C.

factors as differences in advancing and decreasing contact angles between adsorbent and adsorbate, the role of surface pore shape and volume, and the phenomenon of multilayer adsorption followed by capillary condensation in cylindrical pores (24). For biological materials, Young and Nelson (25-26) hypothesized that moisture can be held in three locations - a unimolecular layer bound to the surface of the material, multimolecular layers stacked on top of the first layer, and moisture held within the biological

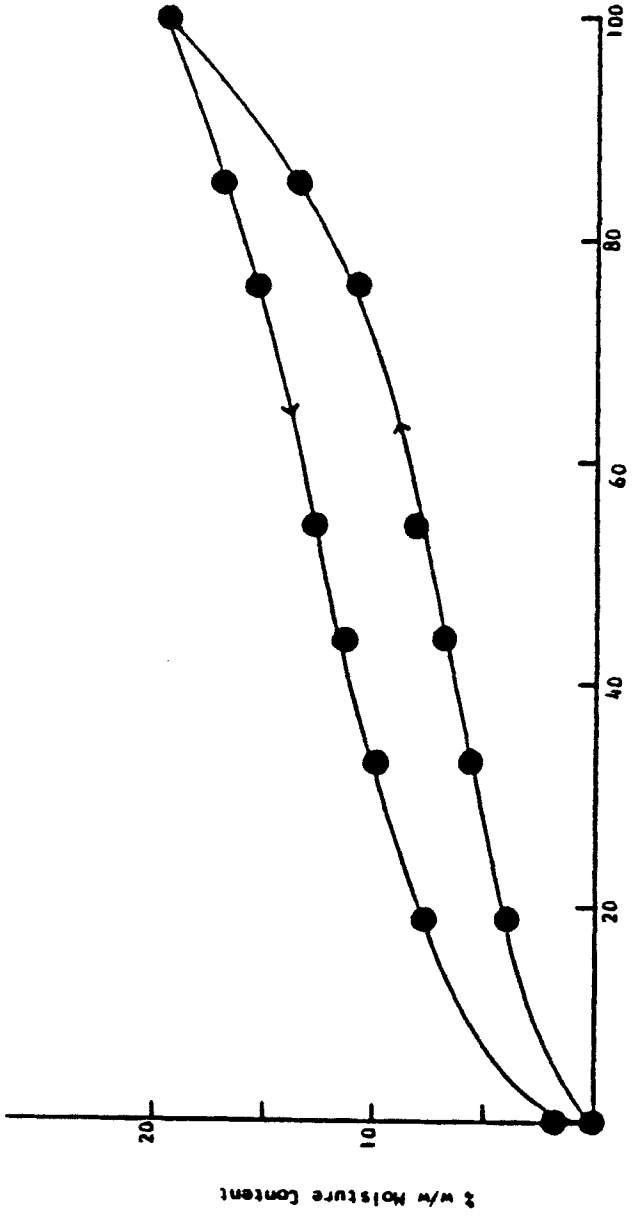

FIGURE 2

Moisture sorption and desorption isotherm for maize starch at 25°C.

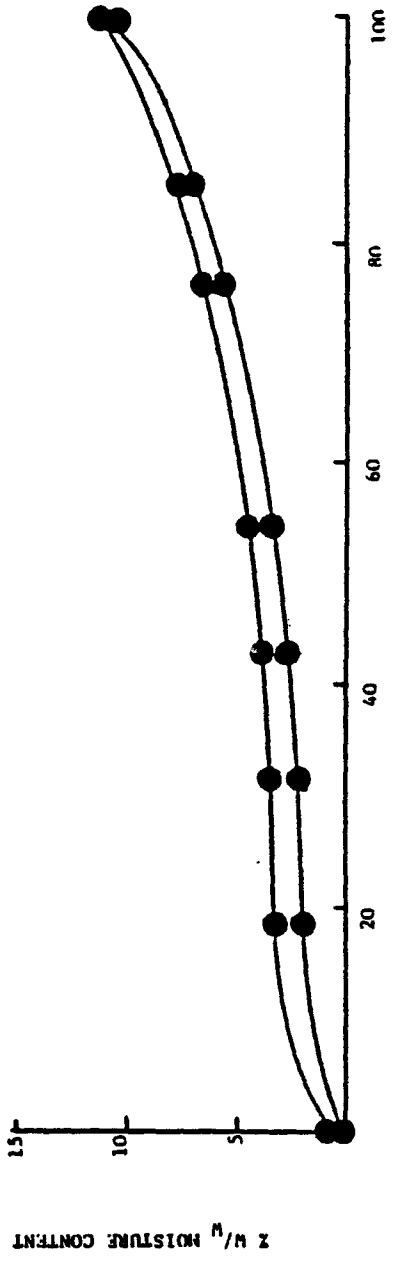

FIGURE 3

Moisture sorption and desorption isotherms for 50% sodium barbitone:50% maize starch mixture at 25°C.

material. Sorption hysteresis was explained by the fact that during sorption, the moisture molecules which initially build up the monomolecular layer are subjected to binding forces at the surface and weaker diffusional forces tending to cause transfer of moisture into the biological material. As more water molecules adhere to the surface, the diffusional forces exceed the binding forces tending to cause transfer of moisture into the biological material. During desorption, there is no force to pull the moisture out of the biological material until all the moisture has been removed from the surface. When this occurs, diffusional forces created by the concentration gradient cause moisture in the biological material to move out. Thus, a hysteresis effect occurs between the sorption and desorption curves.

Analysis of data of nitrogen adsorption onto powders has been widely used to estimate surface area and to interpret pore volume and size distribution (23). The use of moisture sorption isotherms, which has greater practical significance pharmaceutically, has not been extensively studied and caution should indeed be observed when using such data for specific surface estimation since rehydration of a surface, and penetration into the solid structure may take place.

The pharmaceutical significance of moisture sorption and hysteresis effects is exemplified by considering hard gelatin capsules. The capsule shells lose water under conditions of low humidity becoming brittle in nature, fracturing readily, whilst at high humidity conditions, they become sticky and difficult to handle. Consequently, hard gelatin capsules are generally filled with powder(s) under controlled humidity conditions within the range 30 to 50% R.H. However, if the powder formulation contains a moisture sensitive ingredient, such as starch, which has not been equilibrated under the specified humidity conditions, then moisture partitioning between capsule contents and shell with possible subsequent gain or loss in total moisture content can occur. Subsequent storage of such capsules at different humidi-

ties might also augment this effect, and bring about undesirable changes in the properties of the capsule. Recently, Chowhan & Amaro (27) have demonstrated the importance of moisture sorption studies when selecting appropriate drug species in formulations for capsules for powder inhalation aerosols.

The sorption of water molecules, and thereby the wetting of surfaces is clearly an important step in the process of drug dissolution both in vitro and in vivo. Many pharmaceutical powders do not wet readily due to their hydrophobic nature and surface active agents are often used to facilitate the wetting of such materials. In addition, it has been demonstrated that by increasing the hydrophilic nature of hydrophobic materials, by techniques such as granulating with a binder (28), spray drying with acacia (29), or coating with a hydrophilic polymer (17), improved dissolution characteristics are observed. For drug dissolution from capsule formulations however, conflicting evidence has been presented with respect to the importance of powder wetting, one of the parameters controlling liquid penetration (14,30).

Determination of contact angles of compressed powders gives a measure of their wettability (13,17). The technique involves measuring the maximum height of a drop of saturated test liquid formed on a presaturated compact of material. By using the equation of Paddday (31) and correcting for the porosity of the compact (13,32) contact angles for the two drugs, the two diluents and the four 50:50 drug:diluent mixtures against the two test liquids were calculated. Estimated values are listed in Table 2. For the contact angles determined using water, a high angle reflects a hydrophobic material, as examplified by barbitone, whilst a low angle is indicative of a hydrophilic easily wetted powder, for example lactose.

Surface free energies have been estimated for polymers of low surface energy (19, 33) and this technique has recently been extended to consider more polar surfaces (18). By estimating the contributions of non-polar γ_s^d, and polar, γ_s^p, components of the

TABLE 2 - CONTACT ANGLES, SURFACE FREE ENERGIES AND POLARITY INDICES OF THE POWDERS AND BINARY MIXTURES.

	Contact Angles		Surface Free Energies ($ergs/cm^2$)			Polarity Index P_o
	using water	using tetra-ethylene	γ_s^d non-polar component	γ_s^p polar component	γ_s	
Barbitone	70^o	49^o	22.2	12.3	34.5	0.36
Sodium barbitone	41^o	46^o	2.7	71.6	74.3	0.96
Lactose	30^o	31^o	5.2	72.8	78.0	0.93
Maize starch	(0)	(32^o)	1.2	106.3	107.5	0.99
50% barbitone: 50% lactose	33^o	28^o	7.6	63.4	71.0	0.89
50% barbitone: 50% maize starch	(2^o)	29^o	2.0	100.9	102.9	0.98
50% sodium barbitone: 50% lactose	30^o	41^o	1.7	87.8	89.5	0.98
50% sodium barbitone: 50% maize starch	(9^o)	37^o	0.6	111.3	111.9	0.99

(Values in brackets indicate systems causing experimental difficulty due either to very low angles or swelling and softening of compacts).

total surface free energy of a solid, γ_s, where ($\gamma_s = \gamma_s^d + \gamma_s^p$), a polarity index, Po, equal to $\frac{\gamma_s^p}{\gamma_s}$ can be derived.

Equation (1) was used to calculate values of γ_s^d and γ_s^p.

$$\gamma_L (1 + \cos\theta) = 2 [(\gamma_L^d \gamma_s^d)^{\frac{1}{2}} + (\gamma_L^p \gamma_s^p)^{\frac{1}{2}}] \quad (1)$$

where θ = contact angle

Since there are two unknowns, γ_s^d and γ_s^p, it was necessary to obtain contact angles on two test liquids with known values of γ_L and γ_L, respectively liquid surface free energy for the non-polar and polar components. The magnitude of γ_L^d and γ_L^p for the test liquids were estimated by measuring contact angles against paraffin which has γ_s^p equal to zero (33-34), and all derived values of γ_s^d and γ_s^p are fixed to this standard. To calculate γ_L for paraffin, γ_s^d was taken as 25.5 ergs cm^{-2} (33). Table 2 includes surface free energy terms and polarity indices for the powder systems examined, whilst Table 3 lists the contact angles and surface free energy terms for the test liquids against paraffin.

The hydrophobic nature of barbitone is confirmed by its polarity index of 0.36 whilst the hydrophilic features of the other systems is evidenced by polarity indices of 0.89 or greater.

TABLE 3 - CONTACT ANGLE, INTERFACIAL TENSION AND SURFACE FREE ENERGY TERMS FOR THE TEST LIQUIDS AGAINST PARAFFIN AT 25°C

	Interfacial tension (γ_L) (ergs/cm^2)	Contact angle	γ_L^d (ergs/cm^2)	γ_L^p (ergs/cm^2)
Water	71.8	103°	31.2	40.6
Tetraethylene glycol	49.0	49°	34.9	14.1

The results also clearly demonstrate that the presence of either diluent in 50:50 mixture with barbitone produced a hydrophilic system.

The generally higher values of γ_s observed for maize starch and drug : starch mixtures may be due in part to the adsorption of liquid vapour from the liquid to the solid surface, which has been assumed negligible in the derivation of equation (1).

The effect of wettability and degree of polarity on drug release from capsules can now be considered. The percentage drug released for the capsule formulations followed the same general pattern, approximating to an exponential decrease after a short lag phase and thus comparison of dissolution data was made by estimating the time required for 50% drug dissolution ($t_{50\%}$). Table 4 lists initial values of $t_{50\%}$ for the ten batches of

TABLE 4 - INITIAL POWDER MOISTURE CONTENT OF CAPSULE FORMULATIONS AND TIME FOR 50% DRUG DISSOLUTION ($t_{50\%}$).

Batch Number	Capsule Formulation	Powder Moisture Content (%w/w)	$t_{50\%}$ (minutes)
B1	Sodium barbitone	0.1	2.5
B2	50% sodium barbitone: 50% lactose	0.3	2.8
B3	50% sodium barbitone: 50% maize starch	1.2	9.3
B4	50% sodium barbitone: 50% maize starch	7.1	4.6
B5	50% sodium barbitone: 50% maize starch	13.5	4.9
B6	Barbitone	0.0	25.1
B7	50% barbitone: 50% lactose	0.3	4.8
B8	50% barbitone: 50% maize starch	1.2	28.3
B9	50% barbitone:50% maize starch	7.1	18.1
B10	50% barbitone:50% maize starch.	9.5	9.0

capsules together with the moisture content of the capsule contents. The data indicate that the presence of lactose in admixture with sodium barbitone does not modify the rapid $t_{50\%}$ compared with drug alone, which is consistent with the hydrophilic nature and aqueous solubility of the excipient and observed high polarity indices for the drug, and drug:lactose mixture. Figure 4 shows graphs of $t_{50\%}$ versus moisture content for the two series of drug:maize starch capsules. Figure 4 shows that the presence of maize starch with sodium barbitone decreases the rate of dissolution compared with drug alone. Considering the high Po values of both sodium barbitone, 0.96, and maize starch, 0.99, this result suggests that factors other than powder wettability and 'hydrophilic nature' are controlling the dissolution process.

The initial $t_{50\%}$ for barbitone capsules is significantly reduced when the drug is mixed 50:50 with lactose, with the mixed system providing a more hydrophilic environment (see Table 2). For the barbitone:maize starch mixtures increasing $t_{50\%}$ is again observed for decreasing initial moisture content (see Figure 4) although initial dissolution times for the 7.1% and 9.5% moisture levels are significantly less than for barbitone alone. The wettability and polarity factors again do not appear to be the sole factors controlling drug release from the barbitone:maize starch capsules. Other factors pertaining to starch in particular could include particle swelling, or alteration in pore structure of the powder bed (35). In general terms, other determining factors could be associated with permeability of the powder beds, liquid penetration and moisture distribution in the powder bed.

The penetration test data were plotted as the square of the distance of penetration against time of flow, in accord with the Washburn equation (36) (see Figure 5), and penetration rates were estimated from the slopes of the graphs. The values of penetration rates, together with calculated values of permeability coefficients are listed in Table 5. Figure 4 illustrates these data as a function of powder moisture content. For both

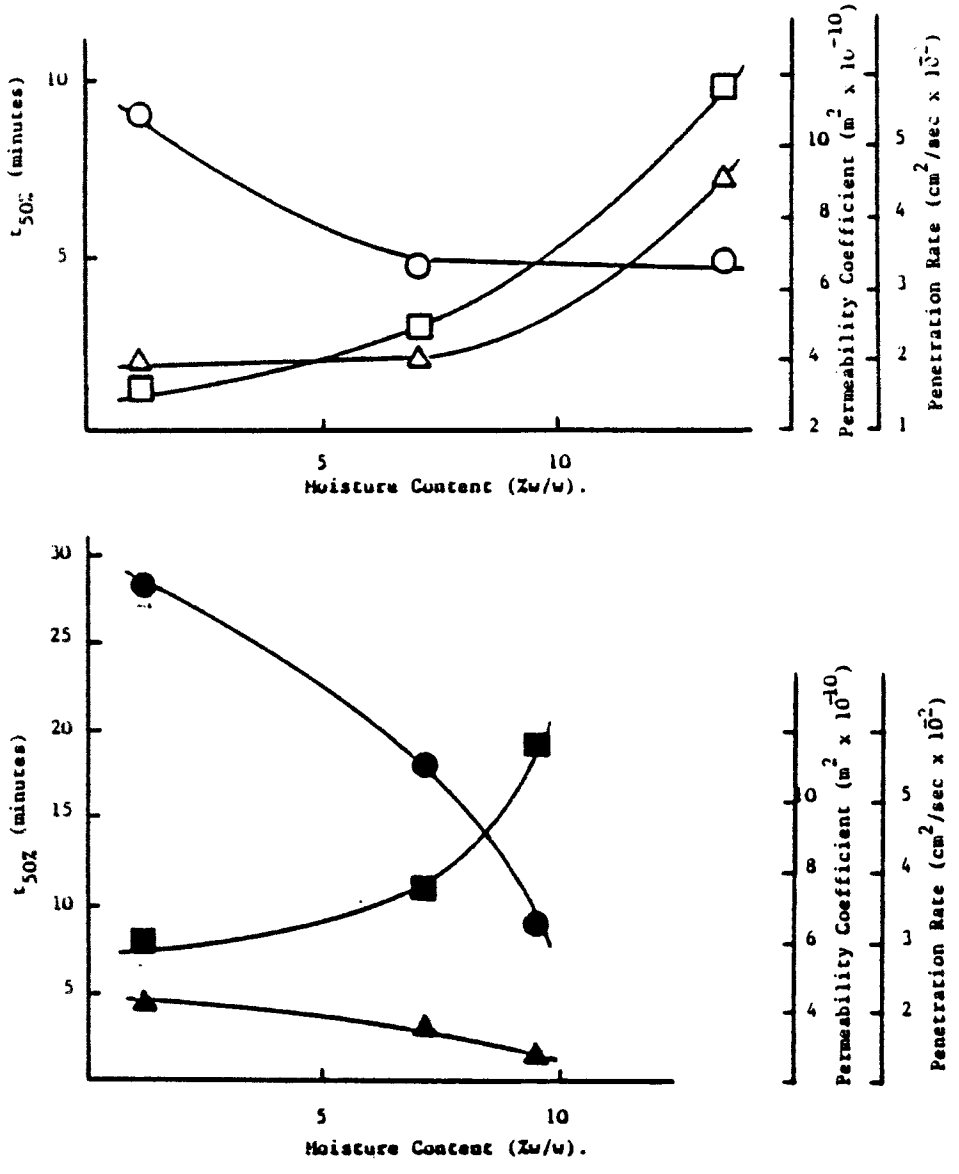

FIGURE 4

Graphs of $t_{50\%}$, permeability coefficient and water penetration rate versus moisture content for the drug maize starch systems at 50% porosity.

KEY ○ = $t_{50\%}$ for 50% sodium barbitone:50% maize starch capsules.
● = $t_{50\%}$ for 50% barbitone:50% maize starch capsules.
△ = permeability coefficient for 50% sodium barbitones:50% maize starch.
▲ = permeability coefficient for 50% barbitone:50% maize starch.
□ = penetration rate for 50% sodium barbitone:50% maize starch.
■ = penetration rate for 50% barbitone:50% maize starch.

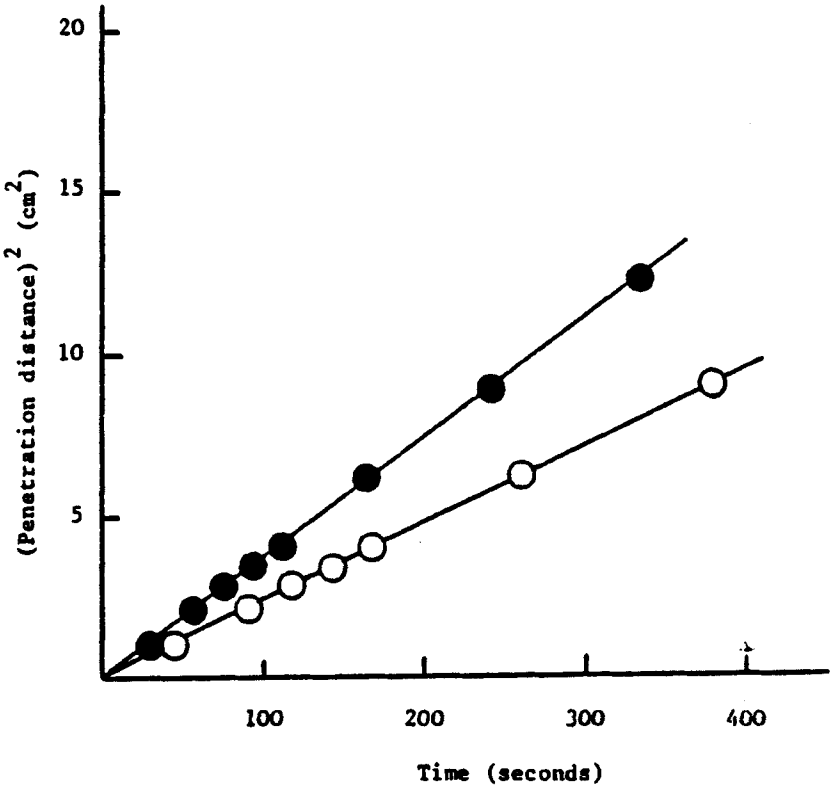

FIGURE 5

Representative graphs of the square of the distance of penetration versus time for 50% drug:50% maize starch powder beds at 50% porosity and 7.1% w/w moisture content.

KEY ○ 50% sodium barbitone:50% maize starch.
● 50% barbitone:50% maize starch.

drug:maize starch systems, water penetration rates increased as the moisture content of the powder bed was raised. Thus, water uptake into the powder filled capsules after rupture or dissolution of the gelatin shell, would be facilitated by increased powder moisture levels and drug dissolution promoted. This explanation is consistent with the fact that decreased $t_{50\%}$ figures are observed for increasing moisture content of the capsule contents.

TABLE 5 - PERMEABILITY COEFFICIENTS AND WATER PENETRATION RATES

	Powder Moisture Content (%w/w)	Permeability coefficient ($m^2 \times 10^{-10}$)	Water Penetration Rate ($cm^2/sec \times 10^{-2}$)
50% sodium barbitone: 50% maize starch	1.2	4.08	1.74
50% sodium barbitone: 50% maize starch	7.1	3.43	2.34
50% sodium barbitone: 50% maize starch	13.5	9.22	5.80
50% barbitone: 50% maize starch	1.2	4.35	3.00
50% barbitone: 50% maize starch	7.1	3.25	3.72
50% barbitone: 50% maize starch	9.5	2.35	5.80

Any increase in powder bed permeability might also be expected to contribute to improving drug dissolution. Whilst this is demonstrated for the sodium barbitone:maize starch mixtures, a corresponding increase in permeability is not observed for the barbitone:maize starch mixtures. Differences in the pattern of moisture distribution within the powder bed for the hydrophobic drug:maize starch mixture compared with the hydrophilic drug: maize starch system are likely to occur and might account for this finding.

Storage effects on $t_{50\%}$ are illustrated in Figures 6 and 7 for the sodium barbitone and barbitone systems respectively. For the sodium barbitone, sodium barbitone:lactose and barbitone: lactose systems, no significant aging effect is evident. However, the barbitone alone and both drug:maize starch capsules exhibit increased $t_{50\%}$ on storage. Similar aging on storage with respect to dissolution data has been reported for other capsule and tablet formulations (37-40) although such effects have not been fully

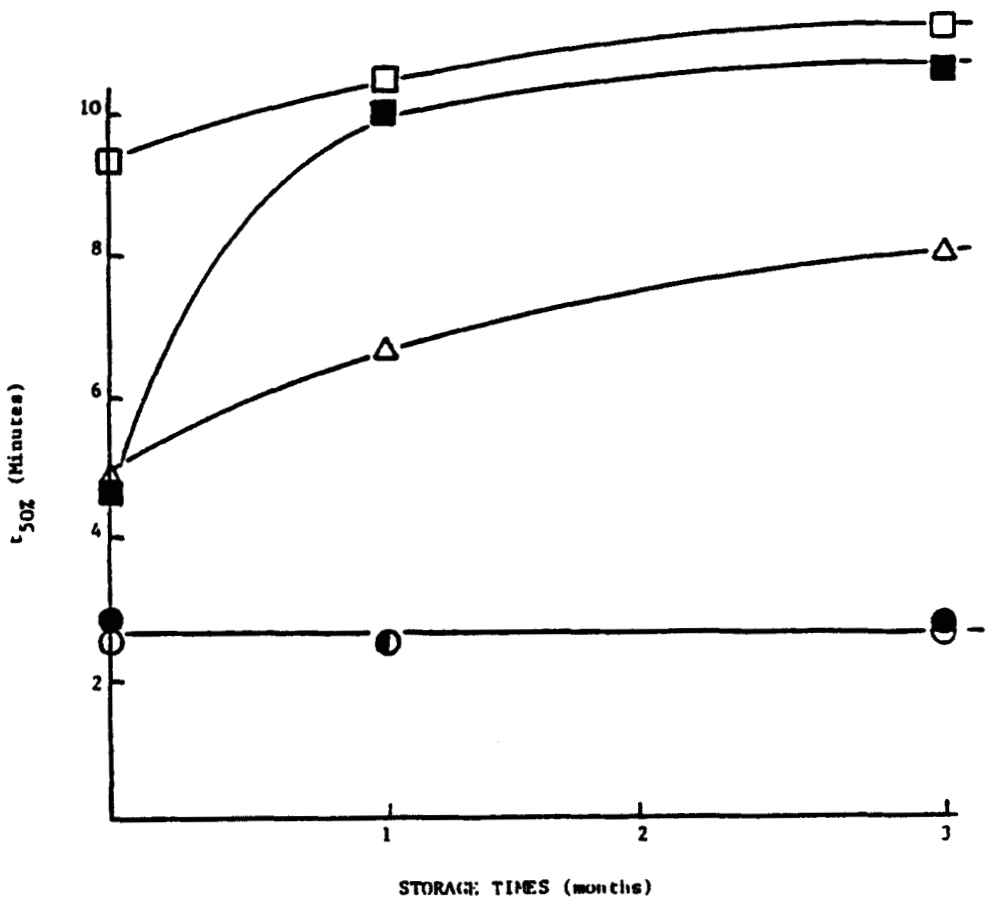

FIGURE 6

Graphs of time for 50% drug dissolution ($t_{50\%}$) versus storage time at 20°/75% R.H. from capsules containing sodium barbitone, and 50% sodium barbitone:50% diluent mixtures.

KEY ○ = sodium barbitone (m.c. = 0.1)
● = 50% sodium barbitone:50% lactose (m.c. = 0.3)
□ = 50% sodium barbitone:50% maize starch (m.c. = 1.2)
■ = 50% sodium barbitone:50% maize starch (m.c. = 7.1)
△ = 50% sodium barbitone:50% maize starch (m.c. = 13.5)

(m.c. = initial powder(s) moisture content % w/w)

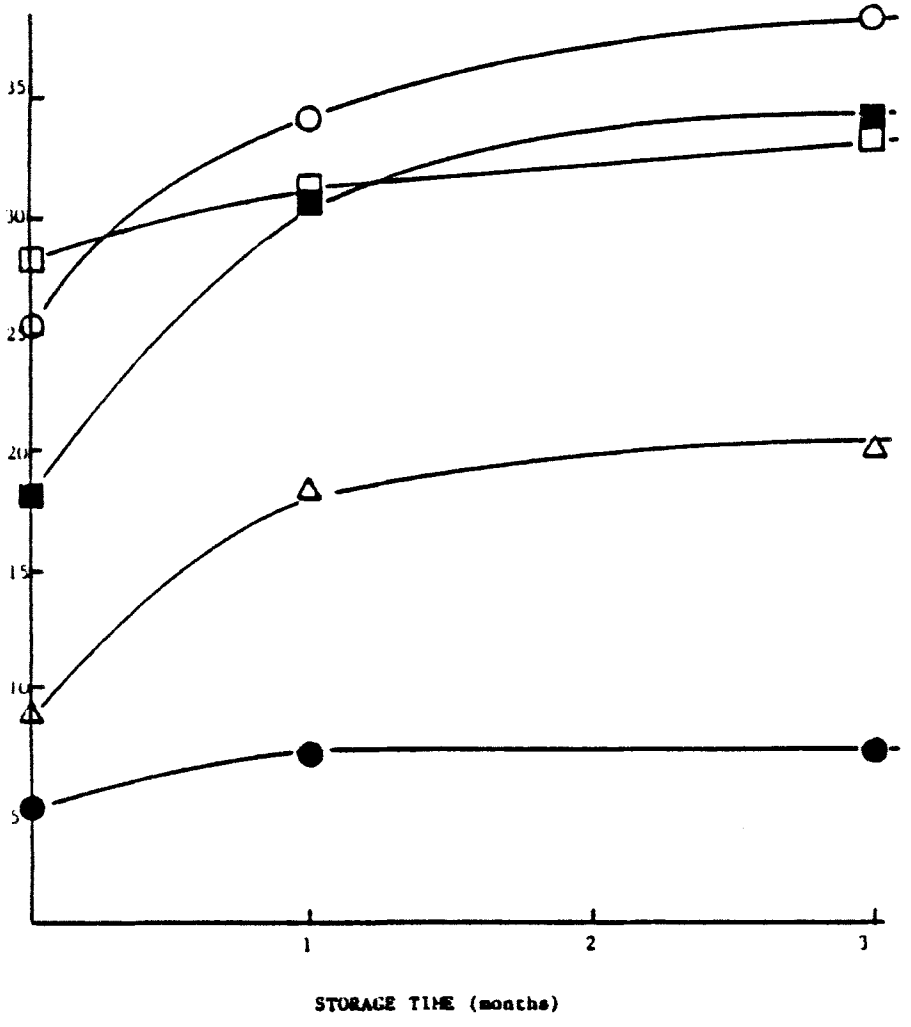

FIGURE 7

Graphs of time for 50% drug dissolution ($t_{50\%}$) versus storage time at 20°/75% R.H. from capsules containing barbitone, and 50% barbitone:50% diluent mixtures.

KEY ○ = barbitone (m.c. = 0.0)
● = 50% barbitone:50% lactose (m.c. = 0.3)
□ = 50% barbitone : 50% maize starch (m.c. = 1.2)
■ = 50% barbitone:50% maize starch (m.c. = 7.1)
△ = 50% barbitone:50% maize starch (m.c. = 9.5)

(m.c. = initial powder(s) moisture content % w/w)

explained. In the present study, possible reasons for decreased dissolution rates on storage include moisture partitioning effects between constituent powders and capsule shell, modification to the structure of the hard gelatin shell as well as factors related to the nature of particle surfaces and moisture distribution.

From a practical point of view, the dissolution results demonstrate that capsule formulations using lactose do not undergo aging effects under the conditions of the experiments which confirms its usefulness as a diluent. When maize starch is used however, significant aging is apparent suggesting that this material is less suitable as a diluent in capsule formulations. This may also apply to other moisture sensitive materials which exhibit moisture hysteresis.

CONCLUSIONS

The rate of dissolution of model capsule formulations prepared to contain 50:50 mixtures of either sodium phenobarbitone or barbitone and a diluent, lactose or maize starch, at a constant porosity of 50% was examined. For capsules containing maize starch the time for 50% drug dissolution ($t_{50\%}$) was found the decrease as the moisture content of the maize starch was raised. Sorption and desorption isotherms and polarity of the powders and their mixtures, and powder bed permeability and water penetration rates were considered as factors which were likely to contribute in producing this effect. Of the examined properties, changes in water penetration rate were found to reflect the changes in $t_{50\%}$. Aging with respect to drug dissolution after open storage at 25°/75% R.H. was observed for both drug:maize starch systems and the barbitone:lactose capsules.

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