J. Pharm. Pharmacol. 1989, 41: 145–148
Received December 23, 1987

Solid State Adsorption of Antibiotics onto Sorbitol

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Abstract—The ability of two types of sorbitol, instant and crystalline, to hold antibiotics permanently after mixing has been assessed by an air sieving technique. Sorbitol instant was found to have a greater adsorption capacity and binding strength than crystalline sorbitol. The six antibiotics studied were found to fall roughly into two groups of different adsorption capacities: (1) pivampicillin, cephalexin monohydrate and erythromycin ethylsuccinate, and (2) ampicillin trihydrate, amoxycillin trihydrate and cloxacillin sodium. The former have slightly higher levels of adsorption than the latter. A negative linear relationship was found between the amount of antibiotic adsorbed onto dry sorbitol and that originally added to sorbitol. When adsorption is expressed as the weight of drug adsorbed per unit weight of sorbitol, an 'apparent' Langmuir isotherm results. This suggests that there are a number of adsorption sites available for holding drug particles, these sites being different for the different antibiotics.

Hersey (1975) defined 'ordered' mixtures as those formed between a fine cohesive powder and a coarse free flowing powder, when the fine particles are attracted to the surface of the coarse particles. The homogeneity of these mixtures has been reported to be very good and providing there is sufficient attraction between the two components, their physical stability is also satisfactory (Hersey 1975; Crooks & Ho 1976). However, it has been found that the last property varies considerably, depending on the physicochemical properties of the powders, their processing history and moisture content (Travers 1975; Staniforth & Rees 1982; Nikolakakis & Newton 1988).

Practical examples of two component powder mixtures where 'ordered' mixing may be involved, are the dry blends of sucrose and antibiotics which can be reconstituted with water to provide antibiotic syrup formulations. The replacement of sucrose with sorbitol offers an opportunity for preparing sucrose-free formulations which are now being advocated to avoid the risk of tooth decay (Cornick & Bowen 1972). Sorbitol is an acceptable sugar for this use and the new sorbitol instant is thought to have improved binding capacity, to enable mixtures of good physical stability to be prepared (Schmidt & Benke 1985). The ability of instant and crystalline sorbitol to adsorb antibiotics has been investigated.

Materials and Methods

The six fine antibiotic powders used: ampicillin trihydrate, amoxycillin trihydrate, cloxacillin sodium, pivampicillin, cephalexin monohydrate and erythromycin ethylsuccinate, were sieved on an Alpine air jet sieve to remove all particles >90 μm, and the two coarse powders used: sorbitol instant and sorbitol crystalline, were sieved on a vibration sieve (Fritsch Analysette, W. Germany) to obtain the size fractions >250 μm and <840 μm (mean diameter $d=500$ μm). The particle densities of the powders were determined with an air comparison pycnometer (Beckman Model 930). Values of the mean particle diameters and particle densities of the experimental materials, and further details are given in Table 1. All the powders were dried in a vacuum oven at a temperature between 50 and 60°C to constant weight and then stored over silica gel until required for use.

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Mixing and adsorption

A 40 g sample of the appropriate proportion of antibiotic and sorbitol was placed in a 230 mL glass vessel and then blended on a Turbula blender (W. A. Bachofen Basle) for 30 min. During blending fine powder was adsorbed on the surface of sorbitol. The sample was next placed on a 90 μm Haver Boacker sieve attached to an Alpine air jet sieve and was subjected to sieving for 15 min, at a fixed pressure of 60 mm water (unless otherwise stated). Thus, any drug not firmly adsorbed onto sorbitol during blending was separated. The weight of the powders remaining on the sieve, i.e. sorbitol plus adsorbed antibiotic was measured and the quantity of antibiotic adsorbed calculated by difference.

Results and Discussion

The percentage of drug in the mixture after sieving as a function of the percentage in the mixture before sieving is given in Fig. 1. The % in the final mixture increases with the quantity of drug present, reaches a plateau and eventually, in all but two cases, decreases. In general, the antibiotics appear to fall into two groups: (1) pivampicillin, cephalexin monohydrate and erythromycin ethylsuccinate, and (2) ampicillin trihydrate, amoxycillin trihydrate and cloxacillin sodium, the latter group showing less adsorption than the former. For the first five antibiotics listed in Table 1, this appears to be related to the particle size, since ampicillin amoxycillin and cloxacillin with an average diameter $d=20$ μm, are in group (2) and pivampicillin, cephalexin with $d=10$ μm are in group (1). However, group (1) also includes erythromycin with a mean particle diameter significantly greater than other antibiotics in this group (see Table 1). Therefore while particle size will certainly influence the extent of adsorption, the nature of the adsorbate will also be important such that adsorption will not always be equivalent for the same particle size of different adsorbents.

Fig. 2 provides a comparison between the adsorption

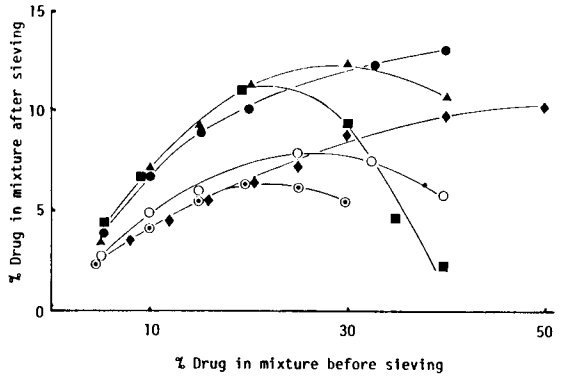

FIG. 1. Percentage of six antibiotics in their mixtures with sorbitol instant after sieving versus % before sieving. Key: ⊙ Ampicillin trihydrate. ○ Amoxycillin trihydrate. ◆ Cloxacillin sodium. ■ Pivampicillin. ▲ Cephalexin monohydrate. ● Erythromycin ethylsuccinate.

Table 1. Details of antibiotics.

Antibiotic	Average diameter* of size fraction μm	Particle density g cm^{-3}
Ampicillin trihydrate	20[a]	1·34
Amoxycillin trihydrate	20	1·39
Cloxicillin sodium	20	1·43
Pivampicillin	10	1·30
Cephalexin monohydrate	10	1·40
Erythromycin ethylsuccinate	35	1·20
Sorbitol instant	500[b]	1·46
Sorbitol crystalline	500	1·46

*[a] median projected area diameter.
[b] mean diameter from sieving data.

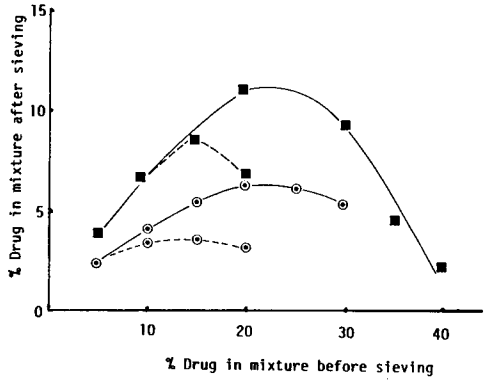

FIG. 2. Comparison between the adsorption capacities of sorbitol instant (solid lines) and sorbitol crystalline (broken lines) for ampicillin trihydrate and pivampicillin. Key as in Fig. 1.

capacities of sorbitol instant and sorbitol crystalline for ampicillin and pivampicillin. It can be seen that over the entire range of initial % drug used, the amount of drug retained by the crystalline sorbitol is much less than that retained by the instant form (Schmidt & Benke 1985).

The effect of the operating pressure of the air jet sieve on the % ampicillin and pivampicillin left in the mixture after sieving a mixture which initially contained 20% antibiotic is shown in Fig. 3. There is a small linear decrease in the final percentage of drug adsorbed as pressure increases in the case of the instant form, but there is a sharp drop with the crystalline form. This indicates that antibiotic particles are held firmly on the surface of the former but rather loosely on the surface of the latter. Since both sorbitols were dry and had the same mean particle size d = 500 μm, the greater capacity and binding strength of the instant form Figs 2, 3 can be related to the greater rugosity and porosity of the surface of its particles, cf. Fig. 4. This enables them to form a large number of contacts with antibiotic particles (Nikolakakis & Pilpel 1985).

The results can be transformed to express the percentage drug which has been held onto sorbitol instant as a function of the initial proportion added—Fig. 5a, b. This method of presentation clearly shows that as the proportion of drug in the mixture increases, there is a linear decrease in the relative quantity held (for pivampicillin, Fig. 5a, this applies only for initial proportions <ca 25%). Now it was previously seen (Fig. 1) that the antibiotics fall into two groups of different adsorption capacities.

A further method of expressing the results is as 'apparent' adsorption isotherms in Fig. 6. It can be seen that the amount adsorbed per unit weight of sorbitol, x/m, increases with increasing equilibrium concentration C of the non-adsorbed drug, reaches a plateau and in the cases of ampicillin trihydrate, amoxycillin trihydrate, pivampicillin and cephalexin monohydrate, eventually decreases (cf. Fig. 1). The final decrease of the curves in the last four cases is believed to be due to drug aggregates being formed when large proportions of drug are blended, that is, when C is high (Figs 1, 6). Under these conditions free drug particles can be preferentially adsorbed onto the drug aggregates rather than onto the sorbitol particles. Nevertheless, before the decline of the curves, the shape of the isotherms is equivalent to the classical Langmuir type I isotherm (Florence & Attwood 1981) and adsorption can be assumed to occur entirely on the surface of sorbitol (for cloxacillin sodium and erythromycin

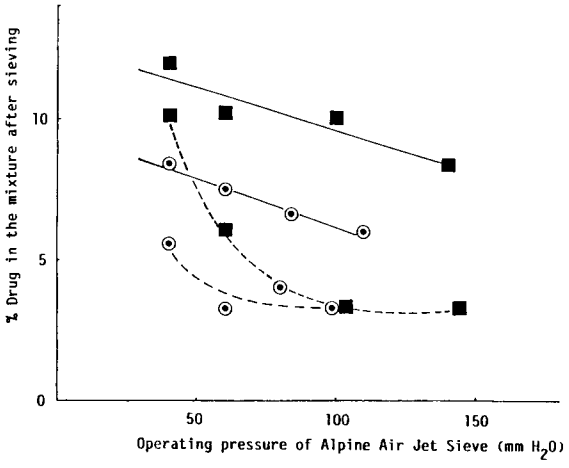

FIG. 3. Effect of the operating pressure of the air jet sieve on the % of ampicillin trihydrate and pivampicillin left in the mixture after sieving a standard 20% mixture with sorbitol instant (solid lines) and sorbitol crystalline (broken lines). ⊙ Ampicillin trihydrate. ■ Pivampicillin.

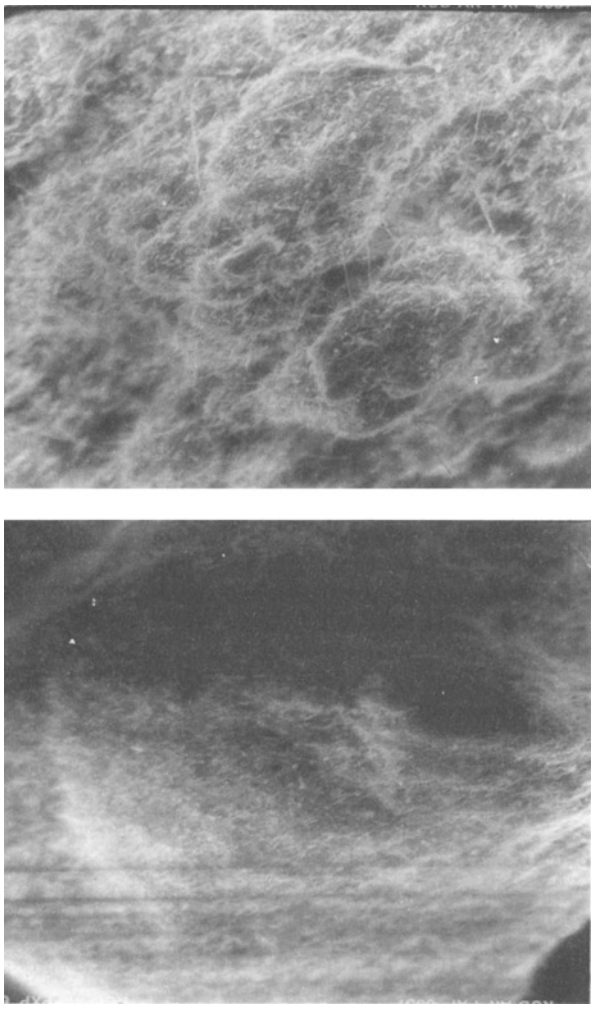

FIG. 4. (top). Scanning electron micrograph of sorbitol, instant form; magnification × 500. (bottom). Scanning electron micrograph of sorbitol, crystalline form; magnification × 500.

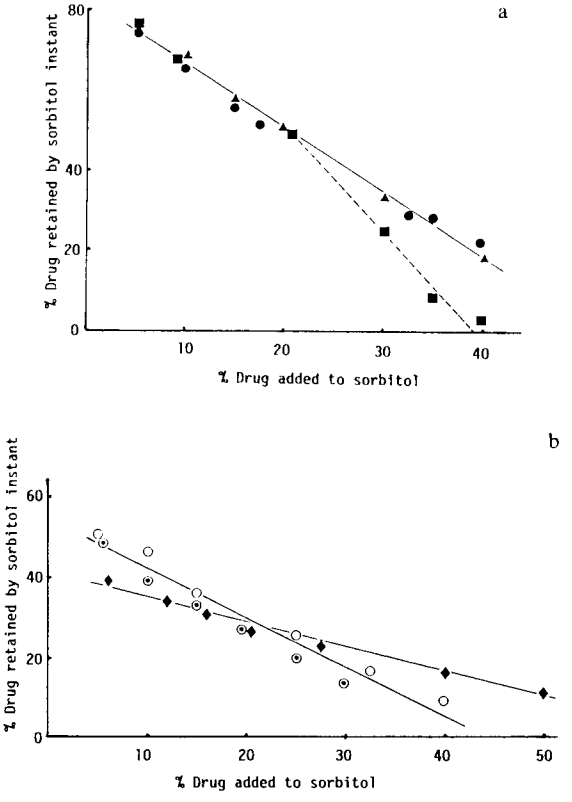

FIG. 5. a. Adsorption of pivampicillin, cephalexin monohydrate and erythromycin ethylsuccinate on sorbitol instant. ■ Pivampicillin. ▲ Cephalexin monohydrate. ● Erythromycin ethylsuccinate. b. Adsorption of ampicillin trihydrate, amoxycillin trihydrate and cloxacillin sodium on sorbitol instant. ⊙ Ampicillin trihydrate. ○ Amoxycillin trihydrate. ◆ Cloxacillin sodium.

ethylsuccinate this applies to the whole curve) This is confirmed in Fig. 7 where the plot of C/(x/m) versus C is seen to be a straight line, described by the equation

$$C(x/m) = 1/ab + C/a \quad (1)$$

C is the % of free drug at the end of the mixing process, x is the amount of drug adsorbed by mass m of sorbitol instant, b is a constant related to the enthalpy of adsorption and a is another constant whose physical significance is explained below. Again, as was the case before (Fig. 5a, b), the results of the better adsorbed group (1) of antibiotics can be reasonably represented by a straight line with equation

$$C/(x/m) = 5{\cdot}93C + 25{\cdot}2 \quad (2)$$

correlation coefficient 0·998, and the results of the lesser adsorbed group (2) can be represented by another line with equation

$$C/(x/m) = 6{\cdot}86C + 96{\cdot}14 \quad (3)$$

correlation coefficient 0·958.

The parameter a in equation 1 is the quantity of antibiotic particles per unit weight of sorbitol required to form a monolayer on the surface of sorbitol particles, and can be taken as a measure of the adsorption capacity of sorbitol for the particular drug (Florence & Attwood 1981). For antibiotic group (1), combination of equations 1,2 gives $a = 16{\cdot}86 \times 10^{-2}$, $b = 23{\cdot}56 \times 10^{-2}$ and for group (2) combination of equations 1,3 gives $a = 14{\cdot}58 \times 10^{-2}$ and

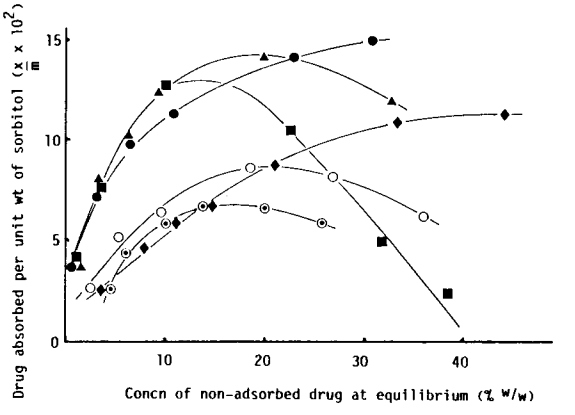

FIG. 6. Adsorption isotherms for the adsorption of six antibiotics on sorbitol instant. Key as in Fig. 1.

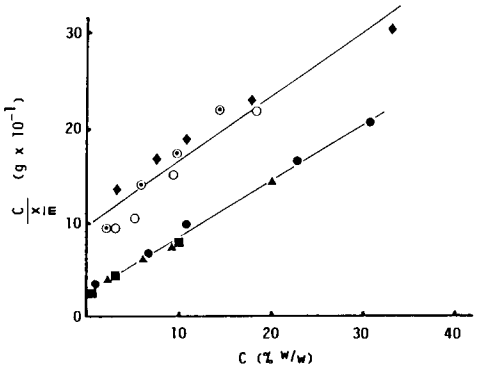

FIG. 7. Langmuir plots for the adsorption of six antibiotics on sorbitol instant. Key as in Fig. 1.

$b = 7{\cdot}14 \times 10^{-2}$. The above experimental values of a can now be compared with those predicted, a_{PR}, assuming monolayer coverage of the sorbitol particles by the drug particles.

The monolayer coverage, a_{PR} per unit weight of sorbitol may be defined by:

$$a_{PR} = n\ Wa/Ws = n\ d^3Pa/D^3Ps \quad (4)$$

where Wa, d, Pa are the weight, diameter and density of an antibiotic particle and Ws, D, Ps are the corresponding parameters for a sorbitol particle: n is the number of small particles forming a monolayer on a large particle and assuming that the drug particles are spherical and close packed in an hexagonal arrangement (Jones & Pilpel 1965),

$$n = 3{\cdot}63(D+d)^2/d^2 \quad (5)$$

Combining equations 4 and 5 we have

$$a_{PR} = 3{\cdot}63d\ (D+d)^2Pa/D^3Ps \quad (6)$$

and substituting values of d, Pa, D, Ps from Table 1 into the last equation values of a_{PR} can be obtained. These are listed in Table 2 for the different materials, together with the corresponding experimental values derived from equations 1-3, as described above. The last column of Table 2 gives the ratios a/a_{PR} which express the fraction of the surface covered, or the number of adsorbed layers formed on a sorbitol particle. It can be seen that ampicillin, amoxycillin and cloxacillin closely approximate to a monolayer, pivampicillin and cephalexin form more than two layers and erythromycin covers a fraction of the particle surface.

Table 2. Values of the constants a from Langmuir adsorption isotherms and a_{PR} from equation 6.

Drug	$a \times 10^2$	$a_{PR} \times 10^2$	a/a_{PR}
Ampicillin trihydrate	14·58	14·93	0·98
Amoxycillin trihydrate	14·58	14·93	0·98
Cloxacillin sodium	14·58	14·93	0·98
Pivampicillin	16·86	6·99	2·41
Cephalexin monohydrate	16·86	6·99	2·41
Erythromycin ethylsuccinate	16·86	23·91	0·71

Conclusion

The admixture of fine and coarse particles which forms the basis of ordered mixing has been shown to be represented by the classical Langmuir isotherm for certain proportions of mixtures of antibiotics and sorbitol instant. Thus the system can be quantified in terms of adsorption performance. The type and extent of particle coverage can be shown to be dependent on the size and physicochemical nature of the particles. Formation of the sorbitol as the 'instant' rather than the crystalline form is shown to improve the adsorption capacity.

Acknowledgments

The authors wish to thank Dr A. Basedow of E. Merck and Mr S. Burgess of BDH for the samples of sorbitol and for helpful discussions.

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