Intradermal dextran in ASH rats (doses between 100 μg and 1 mg) produced a dose-dependent increase in dye leakage, but again PS in doses up to 50 μg failed to enhance these responses. In NR rats, dextran alone was 250 times weaker than in ASH rats and PS was ineffective. In this type of experiment, as in the paw experiments, only the *effects* of released amines on vascular permeability are being measured.

Thus, PS potentiates the action of dextran on isolated mast cells of ASH rats but does not enhance its action in the skin or subcutaneous tissues where enough PS may be normally present for the dextran reaction to occur. When mast cells are isolated for experimental work, a necessary factor for the dextran reaction may be lost, and the experiments with blood and plasma indicate that this factor is not contained in these intravascular fluids. However as PS does not potentiate dextran in isolated cells of NR rats, a deficiency of PS is unlikely to be the cause of failure of these animals to respond to dextran.

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The influence of starch and lactose on the release rates of drugs from hard gelatin capsules

The influence of additives on the rates of release of drugs from hard gelatin capsules has been studied by Samyn & Jung (1970) and Newton, Rowley & Törnblom (1971a, b). Newton & others (1971b) examining the effect of a diluent, lactose, a lubricant, magnesium stearate, and a wetting agent, sodium lauryl sulphate, on the release of the hydrophobic drug, ethinamate, found the effect produced by each additive was dependent on the presence, and level, of the other two additives. If the diluent only was considered, a level of 50% was required to increase the drug release rate, lower levels being presumably insufficient to change the hydrophobic nature of the powder bed.

We have examined the effect of two commonly used diluents, lactose and starch (potato) on the release of a hydrophobic drug, phenobarbitone, and a hydrophilic drug, phenobarbitone sodium. Experiments were made with a single size fraction, 75–104 μm, of both drugs and diluents to eliminate the influence of particle size (Newton & Rowley, 1970). No 5 hard gelatin capsules were used and were hand filled to a constant weight of 100 mg $\pm$ 5 mg.

Dissolution testing was by the beaker method of Levy & Hayes (1960) adapted for capsules as described by Newton & Rowley (1970), using a stirrer speed of 80 rev min^{-1}. The dissolution fluid was distilled water (1900 ml) maintained at 37°. During a test, samples were taken at regular time intervals, filtered through a No. 5 sintered glass filter, and the amount of drug in solution estimated immediately by ultraviolet spectroscopy at 253 nm after suitable dilution to 0·1 N with sodium hydroxide solution.

Table 1. *The effect of different concentrations of starch and lactose on the release rates of phenobarbitone and phenobarbitone sodium.*

	Phenobarbitone								Phenobarbitone sodium			
	Diluent concentration %											
	0		10		25		50		0		50	
	t_{50}*	SD†	t_{50}	SD	t_{50}	SD	t_{50}	SD	t_{50}	SD	t_{50}	SD
Starch ..	29	2·4	28	2·4	23	2·0	23	2·1	4·6	1·4	4·1	1·6
Lactose ..	29	2·4	31	2·2	17	1·8	13	2·3	4·6	1·4	4·5	1·4

* t_{50} = time in minutes for 50% drug release.

† SD = geometric standard deviation = $\frac{\text{time for 50\% release}}{\text{time for 16\% release}}$ or $\frac{\text{time for 84\% release}}{\text{time for 50\% release}}$.

Allowance was made for the drug removed during sampling. Four replicate experiments were carried out for each combination.

The results, interpreted according to Wagner (1969), formed straight lines when plotted on log probability paper, and the times for 50% release, and the geometric standard deviations are given in Table 1.

The following points are of interest:—

(*a*) Lactose enhances the release of phenobarbitone at the two higher concentration levels. This is similar to the effect noted by Newton & others (1971a and b) and may be related to the need for a high concentration of lactose to alter the hydrophobic nature of the powder bed.

(*b*) Starch also enhances the release of phenobarbitone at the two higher concentrations, but not to the same extent as lactose. The use of starch as a disintegrant in tablets is widespread, but its mechanism of action is not fully understood. In the present case, grain swelling (Patel & Hopponen, 1966) would presumably need to be extensive to disrupt a loose powder bed, and alterations in the pore structure of the bed (Ingram & Lowenthal, 1968) on the addition of starch have been minimized by using equivalent particle sizes. Starch absorbs large amounts of water (Shotton & Harb, 1965) and this could create a hydrophilic environment enhancing drug release.

(*c*) The presence of large quantities of diluent do not inhibit the release of the water-soluble phenobarbitone sodium.

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