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SHORT COMMUNICATION

The dissolution of paracetamol tablets and the *in vitro* transfer of paracetamol with and without sorbitol

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MANY adjuvants such as sorbitol, glucosamine hydrochloride and sodium hexametaphosphate, have been added to oral dosage forms to improve the absorption of drugs, but Wagner (1961) emphasizes that the attribution of beneficial results to them is not always unequivocal. With sorbitol in paracetamol tablets, it has been suggested that the improved absorption is due to the sorbitol acting on the metabolism of paracetamol and as a dispersing agent (Gwilt, Robertson & others, 1963). The combination of paracetamol and sorbitol provides a readily assayable system with which to examine the role of the adjuvant.

I have examined the effect of sorbitol on the aqueous solubility and partitioning of paracetamol and have studied the dissolution rate of paracetamol from commercial tablets containing paracetamol with or without sorbitol with the aim of evaluating the effect of the adjuvant on the availability of the drug.

EXPERIMENTAL

Materials. *p*-Acetamidophenol (B.D.H. Laboratory Reagent). n-Octanol (B.D.H. Laboratory Reagent). Sorbitol (Kerfoot Biochemical Reagent).

Proprietary tablets A and B containing paracetamol; A with, B without sorbitol, and tablet C, paracetamol tablets B.P. 0·155M buffer solutions, pH 2·0 were made from A.R. potassium chloride and hydrochloric acid, those of pH 7·4 from A.R. potassium dihydrogen phosphate and sodium hydroxide. pH was measured with a Pye Dynacap pH meter.

Solubility of paracetamol in sorbitol solutions. Water (10 ml) containing 0, 0·5, 1·0, 2·0, 4·0 and 8·0% sorbitol was added to excess (250 mg) paracetamol in 50 ml Quickfit flasks which were shaken (24 hr) at 25°. Aliquots were filtered through 13 mm 0·45 μ pore diameter Millipore membrane filters, diluted, and the concentration of paracetamol in solution measured at 243 mμ. Paracetamol in water or 0·1N HCl had λ_{max} 243 mμ and within the concentration range 0–16 μg/ml the solutions obeyed Beer's Law. The regression line equation was used to determine the concentration present.

Partition coefficients. n-Octanol (20 ml) was added to separate weighed quantities (6–20 mg) of paracetamol in Quickfit flasks and 20 ml of one of the following: water, water containing sorbitol 1/5th of the weight of paracetamol, buffer solutions pH 2·0 and pH 7·4 was added to successive duplicate flasks. The flasks were shaken at 25° for 24 hr. The absorption of the diluted aqueous phases was measured at 243 mμ and the apparent partition coefficients (Reese, Irwin & others, 1964) calculated.

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Transfer in three-phase model. A model similar to that described by Perrin (1967) was used at 25°. Buffer (500 ml; pH 2·0) containing paracetamol (100 mg) with and without sorbitol (20 mg) was placed in compartment A and buffer (500 ml; pH 7·4) in compartment C. n-Octanol (350 ml) was layered onto the aqueous phases. All aqueous phases were pre-saturated with n-octanol and the octanol with the pH 7·4 buffer. 1·6 ml samples of the aqueous phases were removed at intervals, suitably diluted with 0·1N HCl and assayed at 243 mμ. The volumes were kept constant by replacement with 1·6 ml of fresh buffer solutions.

Tests made on tablets included: (*a*) Assay for paracetamol (B.P. 1963) (*b*) Disintegration at 37° (B.P. 1963) (*c*) Dissolution as follows: 500 ml 0·1N HCl in a 600 ml beaker was equilibrated in a water bath at 37°. A stainless steel stirrer with 4 blades of 3·5 cm diameter was rotated at 113 rev/min at a depth of about 8·2 cm. Two tablets were placed in a tube, as used for the B.P. disintegration test, and this was moved vertically as for the B.P. test. 2 ml samples of the 0·1N HCl solution were removed at intervals by means of Luer syringes and the solutions filtered through Millipore HA membrane filters in Swinnex-13 holders. The extinction of the diluted filtrates was measured at 243 mμ. The total amount of drug in solution at each sampling time was calculated after taking into consideration the increase in volume due to disintegration and dissolution (about 1·3 ml), the decreasing volume of the dissolution medium after each sample was removed, and the amount of drug removed in each sample.

RESULTS AND DISCUSSION

The solubility of paracetamol in solutions containing 0–8% sorbitol was 1·43% (standard deviation 0·025). The mean partition coefficients were as follows: n-octanol–water, 2·03; n-octanol–water containing sorbitol (1/5th of the quantity of paracetamol), 2·02; n-octanol–buffer (pH 2·0), 2·00; and n-octanol–buffer (pH 7·4), 2·06. At equilibrium in the three-phase model the value for n-octanol–buffer solutions was 2·01. Equilibrium distribution of paracetamol was attained slowly (about 50 hr) in this system (Fig. 1). The results both with and without sorbitol were in close agreement and an analysis of variance showed that there was no significant difference ($P = 0{\cdot}05$). Distribution curves comparable with those in Fig. 1 have been obtained with barbitone (Doluisio & Swintosky, 1965) and salicylic acid (Khalil & Martin, 1967). The mean apparent rate constants for the transfer from A during the first 7 hr were calculated from the first-order equation:

$$k = \frac{2{\cdot}303}{t} \log \frac{C_o - C_\alpha}{C_t - C_\alpha}$$

where C_o and C_t are the concentrations at zero time and after time t and C_α the concentration at equilibrium. The value of k hr^{-1} for paracetamol in the absence of sorbitol was 0·259 and in the presence of sorbitol, 0·257,

The mean disintegration times for tablets A, B and C were 4·3, 2·8 and 7·75 min whereas the $t_{0{\cdot}9}$ (time for solution of 900 mg of drug) read from

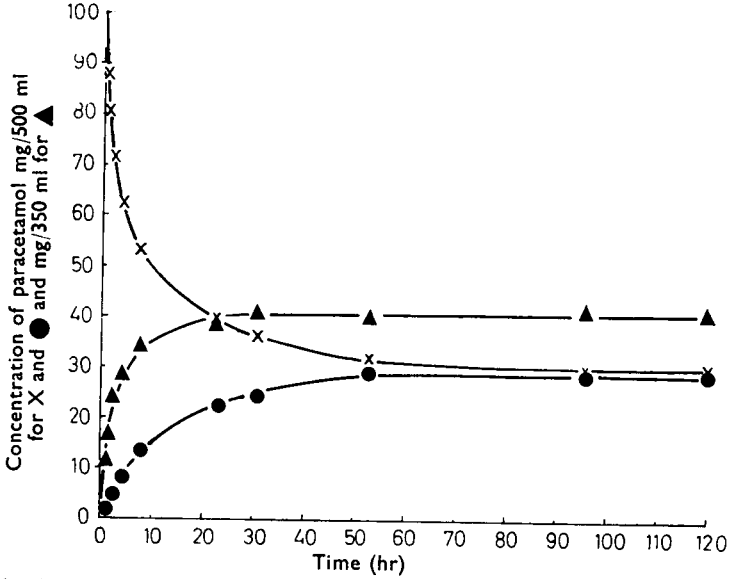

FIG. 1. Transfer of paracetamol from pH 2·0 buffer (×) through n-octanol (▲) to pH 7·4 buffer (●) at 25°.

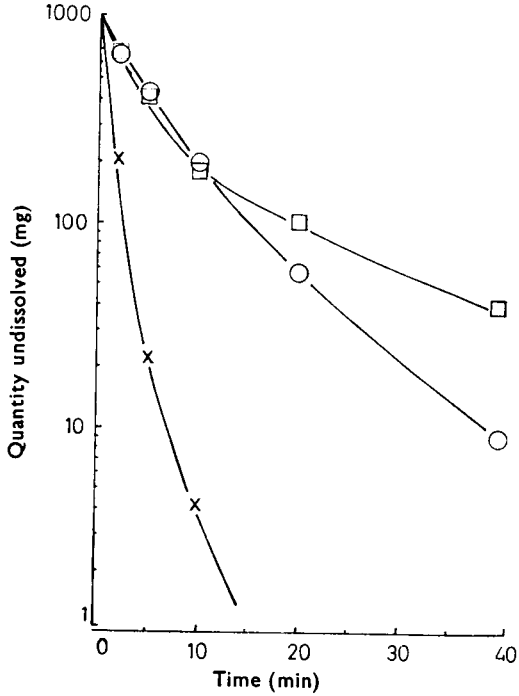

FIG. 2. Log paracetamol undissolved with time from commercial tablets (2) of paracetamol + sorbitol (×), paracetamol (○) and paracetamol tablets B.P. (□). Dissolution medium: 500 ml 0·1N HCl at 37°. (The points are the means of three replicates).

the dissolution rate curves (Fig. 2) were 3, 14·25 and 19 min, using the mean assay figures of 493·2, 505·0 and 502·2 mg paracetamol per tablet respectively. An analysis of variance showed that there was no significant difference between replicate dissolution tests ($P = 0{\cdot}05$). In agreement with the results of Levy & Hayes (1960) and Brudney, Stewart & Eustace (1964), the disintegration times did not correlate with the dissolution times. Varying degrees of correlation have, however, been claimed (Middleton, Davies & Morrison, 1964; Schroeter, Tingstad, & others, 1962; see also Morrison & Campbell, 1965; Wood, 1967). The characteristics of the material passing through the sieve during disintegration differed according to the source of the tablet. Tablets A and C appeared as a dispersible powder with more fine granules from the latter tablets, whereas tablet B disintegrated into aggregates smaller than 10-mesh sieve size which sedimented rapidly.

The results indicate that sorbitol does not form an absorbable complex with paracetamol. The improved absorption, claimed by Gwilt & others (1963), of paracetamol from tablets containing paracetamol and sorbitol (tablet A) may result from their higher dissolution rate. This rate is a function of formulation and of compression force (Levy & Gumtow, 1963; Ganderton, Hadgraft, & others, 1967; Marlowe & Shangraw, 1967; Polderman & Braakman, 1968) and these factors need to be standardized, leaving the presence or absence of sorbitol as the sole variable, before any improved *in vitro-in vivo* effects can be attributed to it.

References

Brudney, N., Stewart, D. J. & Eustace, B. T. (1964). *Can. med. Ass. J.*, **90**, 980–981.
Doluisio, J. T. & Swintosky, J. V. (1965). *J. pharm. Sci.*, **54**, 1594–1599.
Ganderton, D., Hadgraft, J. W., Rispin, W. T. & Thompson, A. G. (1967). *Pharm. Acta Helv.*, **42**, 152–162.
Gwilt, J. R., Robertson, A., Goldman, L. & Blanchard, A. W. (1963). *J. Pharm. Pharmac.*, **15**, 445–453.
Khalil, S. A. & Martin, A. N. (1967). *J. pharm. Sci.*, **56**, 1225–1233.
Levy, G. & Hayes, B. A. (1960). *New Engl. J. Med.*, **262**, 1053–1058.
Levy, G. & Gumtow, R. H. (1963). *J. pharm. Sci.*, **52**, 1139–1144.
Marlowe, E. & Shangraw, R. F. (1967). *Ibid.*, **56**, 498–504.
Middleton, E. J., Davies, J. M. & Morrison, A. B. (1964). *Ibid.*, **53**, 1378–1380.
Morrison, A. B. & Campbell, J. A. (1965). *Ibid.*, **54**, 1–7.
Perrin, J. (1967). *J. Pharm. Pharmac.*, **19**, 25–31.
Polderman, J. & Braakman, D. R. (1968). *Ibid.*, **20**, 323–324.
Reese, D. R., Irwin, G. M., Dittert, L. W., Chong, C. W. & Swintosky, J. V. (1964), *J. pharm. Sci.*, **53**, 591–597.
Schroeter, L. C., Tingstad, J. E., Knoechel, E. L. & Wagner, J. G. (1962). *Ibid.*, **51**, 865–874.
Wagner, J. G. (1961). *Ibid.*, **50**, 359–387.
Wood, J. H. (1967). *Pharm. Acta Helv.*, **42**, 129–151.