The effect of addition of lactose on the oral absorption of a highly lipid soluble drug

Davies & Fell (1973) reported that addition of lactose to phenobarbitone increased the rate of dissolution *in vitro*, suggesting the possibility that this would improve the rate of oral absorption. During a study on the oral absorption of the highly lipid soluble narcotic analgesic, Ro 03-4661, (±)-α[1-(3,4-dihydro-6,7-dimethoxy-1-methyl-2-(1H)-isoquinolyl)-methyl]-3′-methyl butyl-3,4-dimethyl benzylacetate hydrochloride (Osbond & Fothergill, 1971), we have found that admixture of the drug with starch or lactose increased the rate of *in vitro* dissolution. This led to more rapid absorption which resulted in increased bioavailability *in vivo*.

Ro 03-4661 is a comparatively strong base of very low aqueous and high lipid solubility. The partition coefficients of the drug between heptane and 0·1 M acetate buffer at pH 5·01 and 4·13 were 135·5 and 17·5 respectively. It was not possible to determine the pKa accurately due to slow hydrolysis of the acetate group at pH $> 7{\cdot}0$, but the pKa for the corresponding carbinol ($8{\cdot}7 \pm 0{\cdot}1$) was measured by the solubility method (Albert & Serjeant, 1971) in tris buffer. Samples were diluted with 0·1N H_2SO_4 (2 vol) and the drug in solution was determined by fluorescence analysis (excitation 280, emission 320 nm) using a Farrand Mark 1 Spectrophotofluorimeter.

In vitro dissolution was measured by the method of Potter (1971). Two forms of Ro 03-4661 were tested:

(1) Powdered (non-micronized) drug, passed through a 60 mesh sieve. (2) Micronized drug, mean volume surface diameter 1·30 μm; specific surface area 3·94 $m^2\ g^{-1}$ as determined by a Fisher Sub-Sieve Sizer.

Samples (39 mg) were loosly packed by hand into three No. 2 gelatin capsules, either alone or after mixing with Hopkins and Williams potato starch or Analar lactose (5 parts by weight) on a Denley blood mixer for 3 h. The volume of the dissolution medium (2 litres), temperature (37°) and stirring speed (60 rev min^{-1}) were kept constant for 2 h. Tween 80 (0·5 ml) was then added and the stirring speed was increased to complete the dissolution. Drug in solution was determined from the ultraviolet absorption (285 nm). The percentages of the powdered form which had dissolved in 2 h were: alone, 29; plus starch, 69; and mixed with lactose, 80%. The dissolution was hindered rather than improved by micronization so that only 3% dissolved in 2 h without the additives, and 29% when the drug was mixed with starch.

To determine whether these results would be reflected in the rates of oral absorption five Beagle dogs were dosed, after an overnight fast, with the powdered drug (10 mg kg^{-1}) on a cross-over basis as: (1) an aqueous ethanolic solution (9:1 v/v) (5 animals); (2) drug alone in a No. 2 gelatin capsule (3 animals); (3) drug mixed with lactose (5 parts by wt) in a No. 2 gelatin capsule (2 animals).

Blood samples (10 ml) were collected at 0·5, 1, 2, 4, 6 and 24 h after dosing and were stored frozen. Aliquots (4 ml) were buffered with 0·1M phosphate, pH 7·4 (1 ml) and extracted with heptane/ethyl acetate ($4{\cdot}5 + 0{\cdot}5$ ml). The organic layer (4·0 ml) was back extracted with 0·1N sulphuric acid (2·5 ml) and the fluorescence in the aqueous phase was determined. Comparison of the mean blood concentrations for the different doses (Table 1) showed that the most rapid and complete absorption was obtained when the drug was given in solution, but both the rate of absorption and the proportion of the dose reaching the general circulation was much increased by the addition of lactose to the capsules. Thus peak blood concentrations were found at 0·5–1 h after administration in solution, 1–2 h when the drug was mixed with lactose, and 2–4 h when the compound alone was given. Also, when the drug alone was administered the area under the blood concentration/time curve was only 30% of the

Table 1. *Mean blood concentrations (μg ml^{-1}) of 'drug' at various times after oral administration to beagles of Ro 03-4661 in different forms.*

	n = 3		n = 2	
Time (h)	Solution	Capsule (drug alone)	Solution	Capsule (drug and lactose)
0·5	0·25	<0·02	0·42	0·08
1	0·47	0·06	0·47	0·27
2	0·32	0·17	0·23	0·35
4	0·26	0·07	0·14	0·15
6	0·11	0·06	0·11	0·08
24	<0·02	<0·02	<0·02	<0·02

n = No. of animals.

corresponding solution value, whereas almost complete absorption (88·5%) was found for the samples mixed with lactose. These figures do not, however, represent true bioavailability values, as neutralization and back extraction of the acid solutions followed by t.l.c. analysis (Allen & Haigh, 1975) showed that small amounts of more polar metabolites were also present.

The reason for the increase in dissolution rate has not been determined but visual examination indicated that addition of the carbohydrate diluent improved the "wetability" of the drug, possibly by dissipating electrostatic surfaces charges. These results do indicate, however, that addition of carbohydrate might improve the absorption and bioavailability of lipid soluble drugs undergoing pharmacological testing and toxicity trials.

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