Table 1. Effects of FMLP and LTB_4 (isomer III) on the release of lysosomal enzymes from human polymorphonuclear leucocytes.

Final concn. of cytotaxin M	Release of enzyme: β-Glucuronidase FMLP	β-Glucuronidase LTB_4	Lysozyme FMLP	Lysozyme LTB_4
0	2·5 ± 1·0*		16·3 ± 1·6	
10^{-9}	4·9 ± 1·0*	4·9 ± 1·1*	32·3 ± 3·1*	18·0 ± 2·1*
10^{-8}	5·5 ± 1·7*	6·2 ± 1·8*	37·1 ± 3·3*	26·0 ± 2·0*
10^{-7}	27·0 ± 5·9*	8·3 ± 2·3*	62·0 ± 4·9*	28·0 ± 1·6*
10^{-6}	43·9 ± 1·4*	4·4 ± 0·5*	82·0 ± 1·8*	28·9 ± 2·0*

The results are expressed as percentages of the release induced by exposure of the cells to Triton X 100 and are given as the means ± standard error of at least 5 separate experiments.
* Student's t-test $P < 0.05$ from results of corresponding control experiments.

at concentrations up to 10^{-6} M. The amounts of β-glucuronidase and lysozyme released by FMLP (10^{-9} to 10^{-6} M) in the presence of LTB_4 (isomer III) (10^{-6} M) were found to be between 60 to 80% of the predicted value for a completely additive effect of the two cytotaxins. In all the experiments the release of the cytoplasmic enzyme lactate dehydrogenase, was always less than 10%.

Two conclusions may be drawn from the results of the present work. First, the equipotence of LTB_4 (isomer III) and other cytotaxins, FMLP and C5a, with respect to aggregating and chemokinetic effects on human peripheral PMNs (Smith 1981) does not apply to their effects on the release of lysosomal enzymes from this cell type. LTB_4 (isomer III) is relatively much weaker than FMLP in terms of enzyme release than as a chemokinesin (cf. Goetzl & Pickett 1980). Secondly, it has been reported that a lipoxygenase-derived product of arachidonic acid may be concerned in the stimulation of enzyme release from human and rabbit PMNs by FMLP (Smolen & Weissmann 1980; Naccache et al 1979). It appears from this work that a substance, other than LTB_4 (isomer III), may be active metabolite involved. The present results suggest that neither LTC_4 (see Goetzl & Pickett 1980) nor LTD_4 are likely candidates. It will be of interest to examine other lipoxygenase-derived metabolites particularly since neither 5-HETE nor a mixture of tri-HETEs exhibit such activity (Goetzl & Pickett 1980).

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A comparison of the behaviour of tablet and capsule formulations in vivo

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The behaviour of solid dosage forms in vivo can be studied by using a suitable radiolabelled formulation and monitoring externally using a gamma camera or a profile scanning technique (Alpsten et al 1976; Digenis et al 1976; Hunter et al 1980). The observations and gastric emptying curves of Hunter et al led to the postulation that the capsule, on entering the stomach, adhered to the stomach wall. From there, dispersion of the capsule contents could take place providing a meal had been consumed, or the capsule contents were emptied from the stomach undispersed if the capsule was administered after an overnight fast.

The lack of overall movement before emptying, noted both by Hunter et al, and Digenis et al, tends to support this postulate, and may lead to the proposition that adherance to the stomach wall is a function of the adhesive nature of the gelatin capsule. This communication presents a comparison of the gastric emptying of a tablet and a capsule formulation.

Model formulations were prepared from Amberlite resin IRA-410 (BDH Ltd), 690–850 μm size fraction, for the capsules, and Amberlite resin CG-400CL (BDH Ltd)

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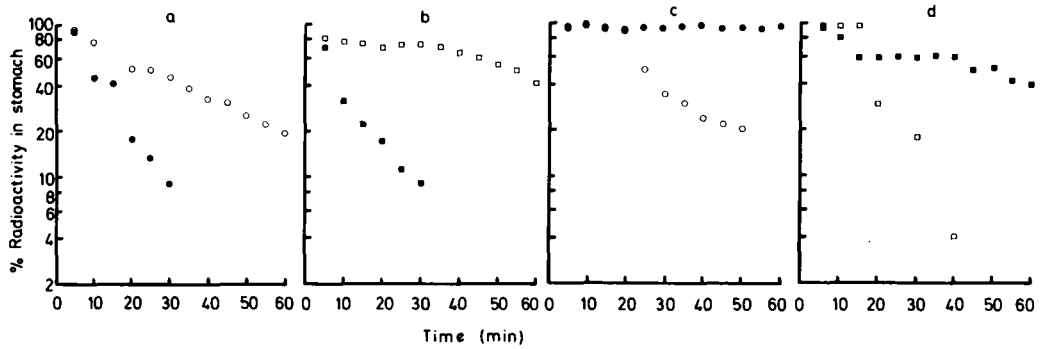

FIG. 1. Plots of % radioactivity in the stomach against time for subject 1(a + b) and subject 2(c + d). ● = tablet, fasting. ○ = tablet, after meal. ■ = capsule, fasting. □ = capsule, after meal.

milled to give a mean size of 9 μm, for the tablets. The resins were labelled with technecium 99^m as detailed by Hunter et al (1980). Samples of 0·1 g of the labelled resin were packed by hand into No 4 hard gelatin capsules. Tablets were prepared from 0·2 g samples (10% of which was unlabelled resin), compressed in a $^3/_8$" diameter flat faced punch and die set in a hydraulic press at a force of 30 KN. The average activity per tablet or capsule was 25 μCi. In vitro disintegration times (B.P. 1973) were 2–3 min for the capsule and less than 1 min for the tablet. In vivo experiments were on two male subjects, each of whom took a capsule or tablet with 100 ml of water after a night-long fast, or immediately after a standard breakfast of 200 ml milk, 40 g cornflakes and 6 g sugar. The subject was then placed supine to allow the upper abdominal region to be viewed by a gamma camera linked to an on-line computer (Med II, Nuclear Data Inc.). Data were accumulated at 1 min intervals for 60 min and stored. Gastric emptying curves were obtained by counting the total radioactivity (adjusted for decay) in the stomach in each 1 min period as a percentage of the initial 1 min count.

Curves of % radioactivity in the stomach against time are shown in Fig. 1. The similarity between the capsule and tablet formulations is seen. Subject 1 exhibited rapid gastric emptying when the dosage forms were taken on a fasting stomach. Observation of the dosage form on the oscilloscope display revealed that in both cases, the dosage forms passed out of the stomach as a whole. In the non-fasting subject, dispersion of both dosage forms took place and emptying followed a mono-exponential pattern.

No gastric emptying occurred during the period of the study, when the tablet was taken on a fasting stomach by subject 2. Dispersion of the dose form did not take place. Although the capsule exhibited some emptying from the stomach, indicating some degree of dispersion, visual observation showed most of the capsule to remain undispersed. In the non-fasting condition, both dosage forms exhibited dispersion, emptying occurring after a lag period.

The similarities in results from the two dosage forms suggest that they behave in a similar manner in the stomach. Thus disintegration and dispersion is dependent on the formulation of the dosage form and the physiological condition of the stomach. The gelatin shell of the capsule appears to play little part in controlling the behaviour of this dosage form in vivo.

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