Diffusion cell with cellulose acetate membrane—donor solutions (a) and (b), receptor fluid phosphate buffer pH 6·3. After reaching steady state, samples were analysed hourly for 6 h to calculate apparent permeability coefficients. (4) Sartorius Absorption Simulator with artificial intestinal wall—donor solutions (a) and (b), receptor (representing plasma) buffer pH 7·5. Samples analysed hourly for 6 h to calculate Sartorius diffusion rate constant.

Table 1.

Method	*In vivo* perfusion			Everted gut			Diffusion cell	Absorption simulator
Parameter	% App. Absorption			Serosal conc (μg)			Pa ($cm^2\ s^{-1}$)*	kd ($cm\ min^{-1}$)
No. of Replicates	20			12			15	5
Time (min)	20	40	60	20	40	60		
Tetracycline (TC)	17·2 ±1·2**	30·3 ±1·3	43·3 ±1·4	18·1 ±1·7	77·2 ±7·0	202 ±10	$3{\cdot}2 \times 10^{-9}$	$4{\cdot}6 \times 10^{-4}$
TC + Mucin	8·2 ±0·7	16·1 ±0·9	24·1 ±1·2	20·2 ±1·6	45·1 ±2·1	88·8 ±7·2	$2{\cdot}4 \times 10^{-9}$	$2{\cdot}4 \times 10^{-4}$
% Reduction	52	47	45	—10	42	56	23	49

* Pa = Apparent Permeability Coefficient; kd = Sartorius Diffusion Rate Constant.
** Value quoted with error of mean.

The everted gut method was easy, reliable and cheap, but absorption rates were unnaturally slow due to lack of blood supply and other factors, complications not present in the *in situ* rat intestine perfusion method. When using artificial membranes drug transfer rates depend mainly upon the drug partition coefficient between solvent and membrane. The physiological significance of the results can be increased by using the most suitable membrane and conditions e.g. in the Sartorius Absorption Simulator.

If the gel nature of natural mucin arises from overlapping rigid rods of protein-carbohydrate then at low concentrations (little interlocking), the mobile suspension provides little viscous resistance to drug passage. Thus the reduced bioavailability of tetracycline (Table 1) may be due to hydrogen bonding to the mucin e.g. at the many possible sites on the carbohydrate side chains, or to solubilization of the drug in the lipophilic portions of the macromolecule.

The effect of food on the *in vivo* release of propranolol from a PVC matrix tablet in the dog

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Plastic matrix tablets have been used extensively as sustained-release formulations for drugs (Graffner & Sjögren, 1971; D'Arcy, Griffin & others, 1971). Various factors affecting release of drugs from these tablets have been reported (Sjögren, 1971). This communication reports studies carried out to examine the effect of food on the *in vivo* release of propranolol from a sustained-release matrix tablet.

The matrix tablet consisted of propranolol hydrochloride, (Inderal; 125 mg), embedded in an insoluble matrix of Pevikon D–42–P (polyvinyl chloride, 273 mg). This tablet was of sufficient hardness to survive passage through the alimentary tract of a dog intact and released approximately 50% of the dose in 3 h, as measured using the USP dissolution apparatus at 100 rev min^{-1}. Measurement of β-blockade in dogs (using isoprenaline challenge), demonstrated a considerable prolongation of activity compared with a standard propranolol tablet. A single 125 mg matrix tablet maintained greater than 50% blockade over a period of about 24 h.

Tablets administered to dogs under different feeding conditions were recovered from the faeces after transit through the alimentary canal. Drug content of recovered tablets was analysed and the results are summarized in the table.

Feeding conditions	No. of dogs	Approx. transit time (h)	Propranolol (%, recovered ± s.d.)
1. No food ± 24 h of dose	4	44 ± 9	2 ± 1
2. No food 16 h before dose	7	28 ± 9	28 ± 11
3. Dosed 1 h after ~100 g food (light feed)	5	28 ± 3	35 ± 9
4. Dosed 1 h after ~800 g food (full feed)	4	25 ± 3	53 ± 12

The results indicate a dependence of the amount of drug retained in the matrix on the feeding conditions before its administration. Condition 1 demonstrates almost complete release of drug from the matrix; thereafter, as the amount of food present at the time of dosing is increased, there is a corresponding increase in the amount of drug which is *not* released *in vivo*. This is probably due to the tablet becoming embedded in the food mass, which affects the penetration of water into the pores of the matrix, and thus inhibits dissolution and hence release of drug.

This effect could introduce a large degree of variability into blood levels achieved with such a tablet, and is apparently a restriction on the use of this type of sustained-release formulation.

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The renal clearance of practolol in man

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Practolol is a potent β-blocking drug which is not protein bound and which is not metabolized to any extent (Scales & Cosgrove, 1970; Bodem & Chidsey, 1972). This communication reports on the renal clearance of practolol in man, comparing the renal clearance of practolol to glomerular filtration rate (GFR) measured by inulin clearance and examining the effect of frusemide on GFR and practolol clearance.

The results are presented in Table 1. Practolol clearance was, on average, less than GFR, but not significantly so (Group 1). Administration of frusemide caused a fall in GFR and in practolol clearance measured over the following 3 h in normal volunteers (Group 2) and practolol clearance in patients (Group 3) also fell on administration of frusemide (Group 4). Aspirin did not produce a significant fall in practolol clearance in normal volunteers.

It is concluded that practolol is eliminated largely by filtration at a rate approximately equal to GFR, and that factors which alter GFR will cause a parallel change in body clearance of practolol.

Table 1. *Renal clearance of practolol and inulin (GFR) in man; results are mean ± s.e.m. of (N) observations.* The groups are defined in the text. a; less than group 1, $P<0.05$; b; less than group 1, $P<0.02$, greater than practolol clearance at same time, $P<0.05$; c: less than group 3, $P<0.05$.

Group	1	2	3	4
Practolol clearance	105·4 ± 9·4 (20)	81·9a ± 7·2 (29)	103·6 ± 14·4 (8)	83·0c ± 14·4 (8)
GFR	123·9 ± 9·6 (20)	102·5b ± 5·8 (29)	—	