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Experimental modelling of drug absorption and drug absorption interactions

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Summary

Five experimental models of drug absorption were evaluated using chloroquine and phenobarbitone as tracer drugs. Their absorption was followed at different pH values and in the absence and presence of the interactants kaolin and activated charcoal. The experimental models tested were: an in vivo buccal partitioning technique, an in situ rat intestine technique, an everted rat intestine method, the Sartorius absorption simulator and a centrifugation method in which adsorption of drug to an interactant was measured. Qualitatively similar results were obtained using all five techniques. The data, however, indicated that the buccal partitioning and the in situ intestinal models were superior to the other techniques. Chloroquine and phenobarbitone appeared to be adsorbed to the Sartorius membrane, the amount of drug absorbed using everted rat intestine was small while the centrifugation method does not involve an absorption phase.

Introduction

Drug interactions take place at many different sites in the body, e.g. in the liver, kidney, at plasma and tissue protein binding and at drug receptor sites. An important site of interaction, however, is at the site of absorption of orally administered drugs in the gastrointestinal tract. Mechanisms of altered drug absorption due to drug interaction include adsorption, pH changes and changes in the rate of gastric emptying. Since it is difficult to produce an experimental model of gastric emptying, research has been concentrated on adsorption interactions and also those involving changed pH since both mechanisms may be involved in a drug–antacid interaction. In this drug absorption modelling a method conceived by Swintosky uses an organic solvent to represent a lipid membrane (Doluisio and Swintosky, 1964, 1965; Perrin, 1967). The method has a usefulness in depicting graphically the rates of the passive drug transfer process; and in illustrating prior to in situ or in vivo studies, what may be the consequences on the rates of drug transfer when, for example, the pH of the media is changed and when various additives are present in the media. More commonly either synthetic or animal membranes are used to study drug transfer, simulating the drug absorption process. Probably the most common animal intestinal methods used in drug bioavailability studies are the everted rat intestine technique (Wilson and Wiseman, 1954) and the in

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situ rat intestine technique conceived by Swintosky and developed by him and his colleagues (Doluisio et al., 1969a). Techniques involving the in situ stomach of the dog (Shore et al., 1957) and a dog intestinal loop in vivo model (Taylor et al., 1981) have also been described. More recently a buccal partitioning model involving human volunteers has been used to examine drug absorption interactions (McElnay and Temple, 1982; McElnay and Mooney, 1983). In certain cases if adsorption is thought to be the only mechanism involved in an interaction, then a simple centrifugation technique (e.g. Bainbridge et al., 1977) will suffice and can be used to separate and therefore allow quantitation of unadsorbed drug.

The aim of the present study was to compare the more commonly used drug absorption techniques using both phenobarbitone and chloroquine. The two model drugs were chosen since one drug is a weak acid, the other is a weak base, and both drugs are easily quantified.

Materials and Methods

All chemicals used were analytical reagent grade. Chloroquine was used as the diphosphate salt (Sigma Chemical Co.) and phenobarbitone was used in the form of the sodium salt (Sigma Chemical Co.). A modified isotonic Britton Robinson type buffer was used when pH control was required. The experimental techniques used are described in the following section while specific details of drug concentrations and pHs used in individual experiments are given in the experimental procedures section.

Description of models used

(i) Buccal partitioning model

Three male volunteer subjects, who were familiar with the buccal absorption technique, took part in each set of experiments. The experimental protocol was as follows.

(a) A buffer solution (20 ml, pH of the test solution) containing no drug was placed in the mouth and circulated for 30 s to rinse the mouth and adjust the pH. This was discarded.

(b) During experiments determining the rate of drug absorption 20 ml of the buffered drug solution (test solution) was circulated in the mouth for 1, 2, 3, 4 and 5 min intervals on separate days and collected. In all other cases the 5-min contact time alone was used.

(c) After this drug absorption phase the mouth was then rinsed with a further aliquot of drug free buffer (20 ml at the same pH as the test solution) for 10 s and the aliquot collected. The samples collected in steps (b) and (c) were analyzed to determine the amount of drug disappearing from the buccal cavity into the buccal membranes.

(ii) Everted rat intestine

Albino Wistar male rats (Charles River CDI strain) weighing 180–240g were used as the source of everted intestine segments. The rats were fasted for 18–24 h prior to the experimentation, but with water allowed ad lib. The rats were killed by an overdose of anaesthetic ether; each rat was then immediately transferred to a cork-dissecting board where the small intestine was exposed via a midline incision. The intestine was then bisected at the ileocecal junction, at the pyloric junction and removed from the abdomen before placing in an isolated tissue bath containing buffer solution at 37°C. The initial 15 cm portion of the proximal end of the intestine was discarded, to ensure the use of the jejunum and to prevent the inclusion of the entrance of the bile duct in the segments being used. The intestine was everted using a glass rod (approximately 3 mm in diameter and 20 cm long). The proximal end of the everted intestine was tied, using a linen thread to the top plastic cannula while the distal end was attached to the bottom cannula to complete the tubular system in the first perfusion chamber (Fig. 1). The consecutive segment of the everted intestine was cannulated to complete the perfusion system in the second chamber. Boiling tubes A and B at this stage contained 100 ml of buffer solution at 37°C.

The apparatus (Fig. 1) was adjusted to expose 7.5 cm of the everted intestine in all cases. Volumes of 20 ml of the buffer were then flushed through each segment using the perfusion pumps, to wash and inflate the segments. The segments were allowed to stand for a further 5 min and then

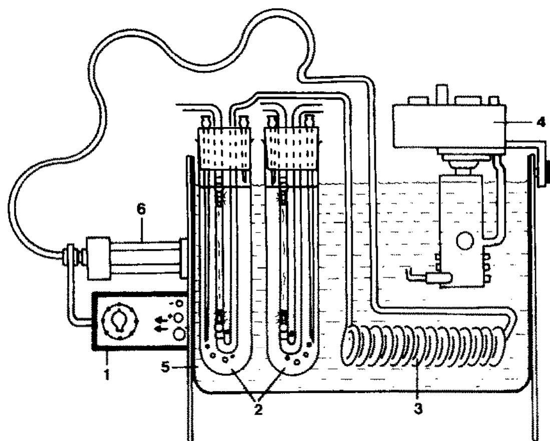

Fig. 1. Schematic representation of the intestinal perfusion apparatus. (1) perfusion pump; (2) boiling tubes (intestinal perfusion chambers); (3) heating coil; (4) thermostated heating unit; (5) water bath; (6) 50 ml syringe filled with buffer.

flushed again with 10 ml of the buffer solution. This ensured that any intestinal contents were removed from the system. The segments were next transferred to fresh boiling tubes which contained drug solutions and a stopwatch was started. In interaction experiments tube A contained drug solution alone while tube B also contained the possible interactant under investigation. The mucosal solutions at all stages were continuously gassed with an oxygen–carbon dioxide mixture (95 : 5) through an 18-gauge blunt needle that extended to the bottom of the tubes. The rate of bubbling of the gas in the two separate tubes was adjusted to the same rate (two bubbles per second). Evertion of the intestine permitted the epithelial cells of the mucosal surface to be exposed directly to the oxygenated mucosal fluid. This was necessitated by the very high oxygen requirements of the epithelial cells (Wiseman, 1961).

Drug transferred across the intestinal segments was collected by the perfusion of 10 ml buffer samples at pH 7.4 through the segments using the infusion pumps. The samples were collected every 10 min for a total experimental time period of 60 min.

(iii) In situ perfused rat intestinal method

The Swintosky Method was used as described by Doluisio et al. (1969a) and Swintosky and Pogonowska-Wala (1982).

Albino Wistar male rats (Charles River CDI strain) weighing 260–295 g were fasted for 16–24 h, but were allowed water ad lib. The rats were anaesthetized by intraperitoneal injection of pentobarbitone (60 mg/kg).

Each anaesthetized rat was then transferred to a cork dissecting board; the intestine was exposed by a midline abdominal incision, and two L-shaped glass cannulae were inserted through small slits at the duodenal and ileal ends, as illustrated on Fig. 2. Care was taken to handle the small intestine gently and to reduce surgery to a minimum in order to maintain an intact blood supply. The cannulae were secured by ligation with linen sutures, and the intestine was returned to the abdominal cavity. Segments of 4 cm plastic tubing were attached to the exposed ends of both cannulae; a 20 ml syringe fitted with a three-way stopcock and containing perfusion fluid warmed to 37°C, was attached to the duodenal cannula. As a means of clearing the gut of food remnants, perfusion fluid was then passed slowly through it, out of the ileal cannula until the effluent solution was clear. The remaining perfusion fluid in the segment was carefully expelled by means of air

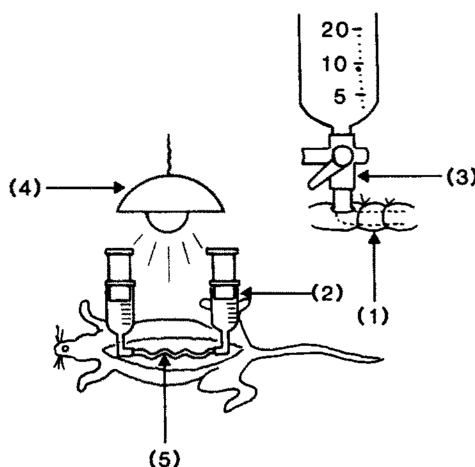

Fig. 2. Diagrammatic representation of the in situ rat intestine preparation. (1) L-shaped cannulas; (2) syringe (20 ml); (3) three way stopcock; (4) heating lamp; (5) in situ intestinal segment. (Redrawn from Swintosky and Pogonowska-Wala, 1982.)

pumped through from the syringe. The ileal cannula was connected to another 20 ml syringe which was clamped in an upright position. A sample of the drug solution (10 ml) was then introduced into the intestinal segment using the syringe connected to the duodenal cannula, and a stopwatch started. This arrangement allowed the operator to transfer the drug solution into either the ileal or duodenal syringes, remove aliquots (1 ml) and return the remaining solution into the intestine within 10–15 s. To assure uniform drug solution concentrations throughout the gut segment, aliquots were removed from the two outlet points alternately. One millilitre of fresh drug solution was added in each case to replace the sample withdrawn, which is a slight departure from the Swintosky in situ method. This additional amount of drug was accounted for in all calculations. A heating lamp was used to maintain the body temperature of the anaesthetized rat throughout the experiment.

(iv) The Satorius absorption simulator cell

The artificial intestinal membranes used in this part of the study were prepared using commercially available Sartorius kits. Care was taken in handling the membranes to avoid mechanical damage. Two such prepared membrane barriers were placed between the two outer diffusion chambers and the middle chamber of a Sartorius absorption simulator cell. The plates were tightened together using the screws (Fig. 3). The outer chambers were interconnected using suitable tubing and connectors to form a single compartment. A peristaltic pump was used to circulate drug solution (100 ml) in the centre chamber while plasma simulating buffer (100 ml) was circulated through the outer chambers. After circulation the solutions were returned to their respective bulk containers (stirred beakers). Both the plasma simulating solution and the drug solution were warmed to 37°C by passing through glass coils placed into a thermostated bath. The assembled diffusion cell was also placed in the water bath. The peristaltic pumps were operated at the steady rate of 10 ml/min. A stopwatch was started and serial samples were withdrawn from the plasma simulating fluid and immediately replaced with an equal volume of buffer at 10 min intervals over the experimental time period. The amount of drug withdrawn in each sample was accounted for in all calculations. The membrane used had a pH toler-

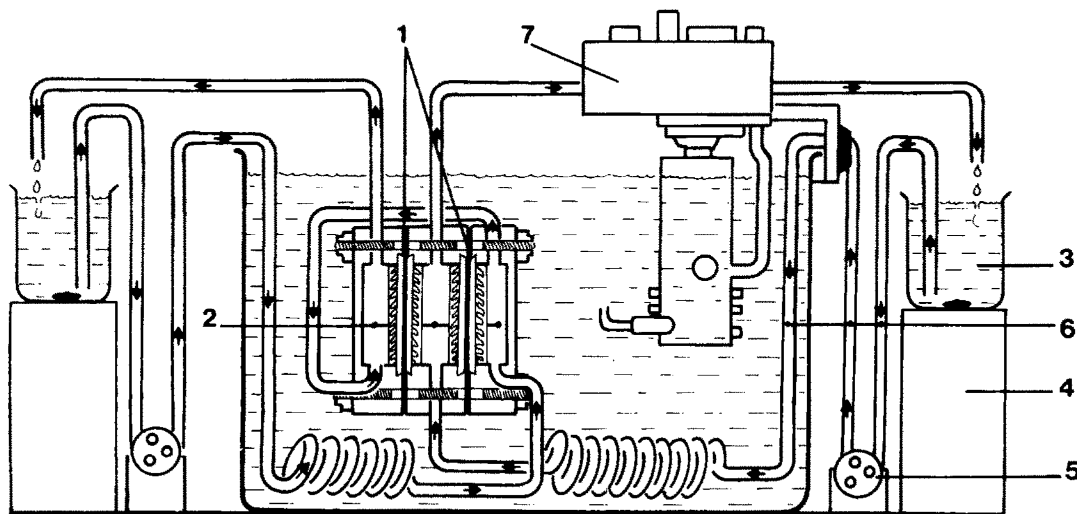

Fig. 3. Schematic representation of the Sartorius simulator apparatus used in the present study. (1) artificial intestinal lipid barriers; (2) diffusion chambers; (3) 100 ml glass beaker; (4) magnetic stirrer; (5) peristaltic pump; (6) connecting tubing with glass heating coils; (7) thermostat controlling water bath temperature.

ance range between pH 1 and pH 7.6. The total membrane surface area available for drug transfer was 80 cm^2.

(v) Centrifugation method for measurement of drug adsorption to an interactant

The method was used to assess the percentage of drug absorbed to the interactant. Solutions (50 ml) of the drug were added to a known quantity of the adsorbent and shaken together continuously in a glass conical flask for 5 min. The mixture was then allowed to stand for one hour at 37°C. After centrifugation, the supernatant was assayed for drug content and compared with control solutions which were treated similarly, but contained no interactant. This model was only used in the interaction part of the study (experimental procedure iv).

Experimental procedures

(i) Influence of concentration on the transfer of chloroquine and phenobarbitone

The ability of each model to show increased absorption as drug concentration was increased was assessed in order to choose the appropriate concentrations for experimentation. This was achieved by using three different concentrations for each of the two model drugs. The transfer of chloroquine phosphate doses of 0.2, 0.4 and 0.6 mg placed in the appropriate amount of buffer were assessed using the buccal partitioning and the in situ perfused rat intestine models. Absorption in both methods was found to increase uniformly with increased dose. A dose of 0.4 mg chloroquine phosphate was found to yield sample concentrations that were easily measurable and it therefore was chosen for further experiments. Corresponding doses of 2, 4 and 8 mg phenobarbitone sodium were found suitable for the buccal and in situ models and therefore a dose of 4 mg was used in all further experiments.

For the everted rat intestine and the Sartorius absorption techniques, much higher doses were required in order to obtain measurable concentrations of the transferred drugs. Chloroquine phosphate was tested at doses of 8, 16 and 24 mg. The 16 mg dose of chloroquine phosphate was chosen for further experimentation. The corresponding doses of phenobarbitone sodium were 40, 80 and 120 mg. Again the middle dose was chosen for further phenobarbitone experimentations. All experiments were carried out in triplicate.

(ii) Influence of pH on the transfer of chloroquine and phenobarbitone

The models were first compared by assessing their ability to show changed drug absorption over a range of pH values. Transfer of both drugs at pH 4, 5, 6, 7.5, 8.5 and 9.5 was examined using buccal partitioning, the in situ method and the everted rat segment method. In the Sartorius absorption cell, the limited pH tolerance of the synthetic membrane prevented its use above pH 7.6. The absorption tests were carried out over a total contact time of 5 min for buccal partitioning, 60 min in case of the in situ and the everted segments, and 120 min for the Sartorius absorption simulator. All experiments were carried out in triplicate.

(iii) Rate of drug transfer and the shape of the absorption curve

Using fixed pH conditions (pH 8.5 for chloroquine and pH 5.0 for phenobarbitone), drug transfer rate across the various membranes was studied. Sampling was as described earlier for all models; for example, in the case of the buccal partitioning technique, the absorption rate was assessed by sampling at 1, 2, 3, 4 or 5 min on 5 separate days. All experiments were carried out in triplicate. A decreased experimental time period of 60 min was used for the Sartorius absorption method during this part of the study.

(iv) Use of the experimental models to assess drug transfer while in the presence or absence of interactants

The effect of kaolin on the transfer of chloroquine and that of activated charcoal on the transfer of phenobarbitone were both examined using the four absorption models, while the centrifugation method was also used to assess drug adsorption to the interactants. The chloroquine:kaolin weight ratio used in the test solution was 1 : 4 in all cases, i.e. similar to their usual therapeutic dose ratio. The phenobarbitone:activated charcoal

weight ratio was also 1 : 4. The chloroquine/kaolin interaction was evaluated at pH 8.5 for all methods except for the Sartorius absorption simulator which, due to membrane instability at high pH, was examined at pH 7.5. For the phenobarbitone/activated charcoal interaction combination, all studies were performed at pH 5. All experiments were carried out in triplicate.

(v) Drug assays

Phenobarbitone was assayed spectrophotometrically ($\lambda = 250$ nm) while chloroquine was assayed spectrofluorometrically (Rubin et al., 1965). For chloroquine an excitation wavelength of 335 nm and an emission wavelength of 400 nm were used after prior buffering of the final solutions to pH 9.5.

Results and Discussion

All the methods examined were straightforward and gave rise to few difficulties during usage. An organic extraction of both chloroquine and phenobarbitone from the aqueous samples was required to remove biological substances from saliva and intestinal perfusates before assay.

(i) Influence of concentration on the transfer of chloroquine and phenobarbitone

The transfer of chloroquine and phenobarbitone was in all cases found to be concentration dependent indicating that the passive diffusion processes did not become saturated. The concentrations of drug chosen for later studies together with the transfer data are shown in Table 1.

TABLE 1

EFFECT OF DRUG CONCENTRATION ON THE TRANSFER OF CHLOROQUINE AND PHENOBARBITONE USING FOUR ABSORPTION MODELS

Model	Drug	pH	Dose used (mg)	Dose transferred (mg)
Buccal partitioning (5 min absorption)	Phenobarbitone sodium	5.0	2.0	0.54
			4.0 *	1.19
			8.0	2.24
	Chloroquine phosphate	8.5	0.2	0.15
			0.4 *	0.29
			0.6	0.46
In situ rat intestine (60 min absorption)	Phenobarbitone sodium	5.0	2.0	1.74
			4.0 *	3.53
			8.0	6.48
	Chloroquine phosphate	8.5	0.2	0.17
			0.4 *	0.33
			0.6	0.48
Everted rat intestine (60 min absorption)	Phenobarbitone sodium	5.0	40.0	0.66
			80.0 *	1.24
			120.0	1.38
	Chloroquine phosphate	8.5	8.0	0.12
			16.0 *	0.24
			24.0	0.32
Sartorius absorption Simulator (120 min absorption)	Phenobarbitone sodium	5.0	40.0	8.22
			80.0 *	16.90
			120.0	25.30
	Chloroquine phosphate	7.5	8.0	0.80
			16.0 *	1.73
			24.0	2.52

* Dose chosen for all further studies.

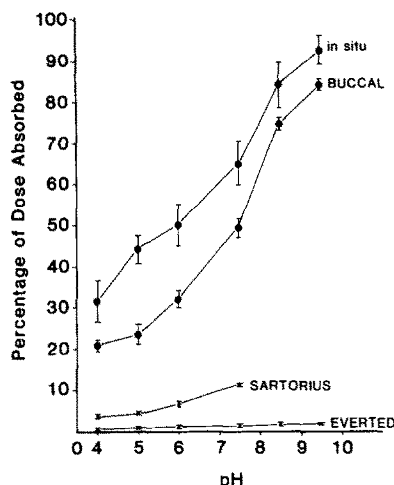

Fig. 4. Chloroquine pH/absorption profiles obtained using the four drug absorption models. Each point represents the mean (±S.E.) result of 3 experiments.

As mentioned earlier, larger doses of drug were required in particular for the everted rat intestine system due to the small surface area available for absorption.

(ii) Influence of pH on the transfer of chloroquine and phenobarbitone

With chloroquine all four absorption models yielded increased transfer of chloroquine with increase in the pH of the absorption medium. The converse was true for phenobarbitone. The profiles obtained for the two drugs are shown on Figs. 4 and 5. Data are presented as a cumulative percentage of the initial dose which was transferred over the allocated experimental time period for each technique. Such a normalization is necessary since different doses and different time schedules were used depending on the method. With both drugs maximal absorption was obtained using the in situ rat intestine model followed in decreasing order by the buccal and Sartorius methods. The everted rat intestine, although reflecting the expected changes in absorption versus pH (i.e. decreased absorption when the pH favoured drug ionization) was insensitive when compared with the other methods.

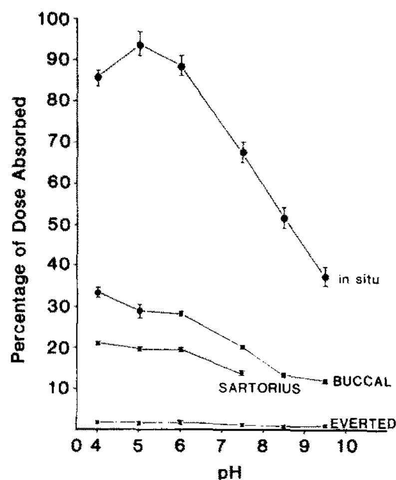

Fig. 5. Phenobarbitone pH/absorption profiles obtained using the four drug absorption models. Each point represents the mean (±S.E.) results of 3 experiments.

(iii) Rate of drug transfer and the shape of the absorption curve

The buccal method showed a high absorption rate in the first minute of contact time for both drugs. This led to a more sharply curved graph than expected from a passive first-order absorption process (Figs. 6 and 7). This was not entirely surprising since Beckett and Moffat (1970) obtained a non-linear relationship when plotting absorption (at pH 4.0) of ten acids against buccal contact time on semi-log paper. They concluded that buccal absorption was not a simple first-order process and they attributed this to saliva production which, by increasing both the volume and pH of the absorption solutions, led to the reduction in the concentration of the unionized drug and consequently the rate of absorption decreased with time. Dearden and Tomlinson (1971) attributed the initial high absorption rate to protein binding in the buccal cavity.

The in situ model gave rise to a typical first-order absorption curve for phenobarbitone, but not for chloroquine. The rate of chloroquine absorption across the in situ segment was high in the first 10 min and then equilibrated. Chloroquine is known to bind strongly to tissue proteins and this initial rapid absorption may be due to the uptake and binding of the drug by the in situ segment. These data are in agreement with those obtained by Doluisio et al. (1969b) with salicylic acid (acidic) and haloperidol (basic).

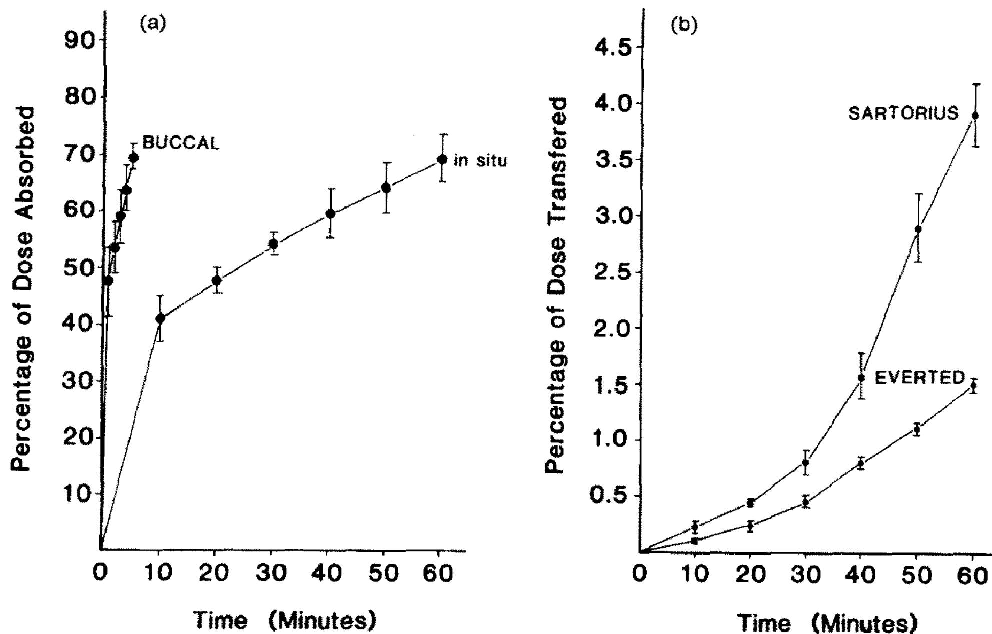

Fig. 6. (a) Cumulative chloroquine transfer using the buccal partitioning and in situ models (pH 8.5); and (b) the Sartorius cell (pH 7.5) and everted rat intestine models (pH 8.5). Each point represents the mean (±S.E.) result of 3 experiments.

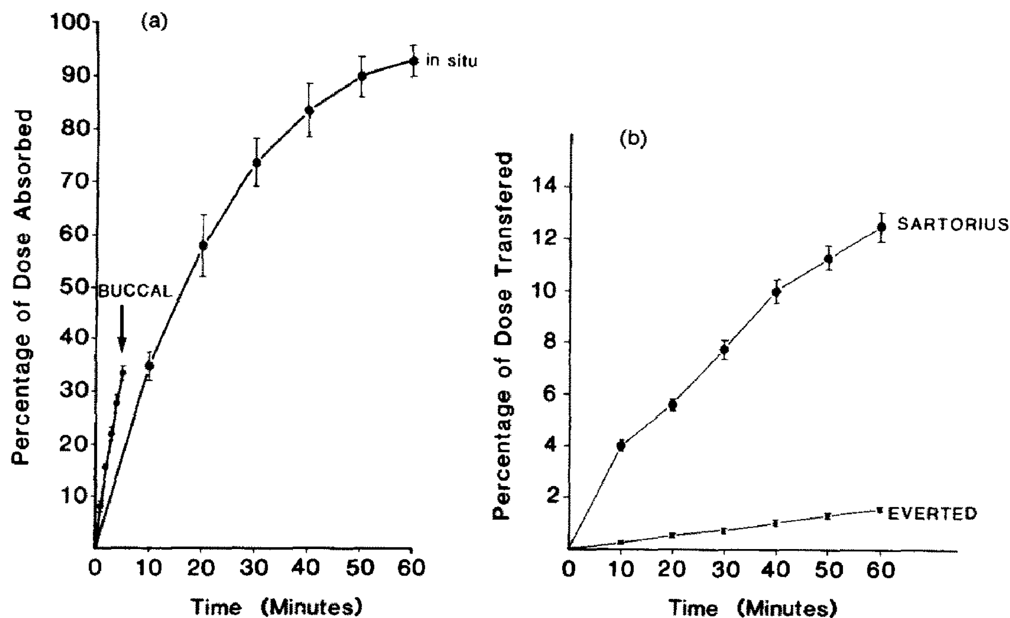

Fig. 7. (a) Cumulative phenobarbitone transfer using the buccal partitioning and in situ models; and (b) the Sartorius cell and everted rat intestine models. All work was carried out at pH 5.0 and each point represents the mean (±S.E.) of 3 experiments.

The everted rat intestine model and the Sartorius absorption simulator showed lag phases in their chloroquine absorption/time curves (Fig. 6); this was not evident in their phenobarbitone absorption/time curves (Fig. 7). Doluisio et al. (1969a) have suggested that the lag phase in transfer of the drug across the everted segment is because the drug has to cross the mucosa and in addition to that, the smooth muscle, connective tissue, and finally the sparingly permeable serosa, before reaching the serosal solution. With the Sartorius synthetic membrane, the lag phase may have been caused by adsorption of both drugs onto the membrane and/or other parts of apparatus. The known high affinity of chloroquine for adsorption onto the surface of the apparatus (data not reported) is the most plausible explanation for the prolonged lag phase.

(iv) Efficacy of the models in screening drug absorption interactions

Two known interaction combinations were used to test the ability of the absorption models to quantify drug interactions. McElnay et al. (1982) have shown that the absorption of chloroquine in healthy volunteers is significantly decreased when given concomitantly with kaolin. Activated charcoal is known to be a powerful adsorbent for barbiturates (indeed it is used as an effective antidote for barbiturate poisoning as an aqueous suspension for stomach lavage or in hæmoperfusion dialysis cartridges to remove barbiturate from the blood in overdosage).

All four models showed that kaolin interacted with chloroquine leading to a significantly decreased absorption ($P < 0.05$). The percentage reduction varied slightly between the different methods, the average decrease being 25.7% (Table 2).

The result of the centrifugation technique for measuring adsorption of chloroquine to kaolin showed that approximately 12% of the dose was adsorbed. This accounted for about 50% of the reduction in drug transfer seen with the absorption models, indicating that the interaction was not only due to adsorption of chloroquine onto kaolin. Kaolin may have also impaired mucosal efficiency by forming a coating layer, an effect which is also likely to take place in the in vivo situation.

The data obtained from the four absorption models also showed that activated charcoal significantly reduced the absorption of phenobarbitone. The extent of this reduction (mean 56.8%) was in agreement with the result obtained by using the simple centrifugation technique (Table 2). The reduction obtained using the Sartorius model, however, was somewhat lower than for the other methods (46.2%); adsorption of phenobarbitone by the Sartorius membrane may have been involved in this effect. All models were therefore capable of quantifying both these known interactions.

(v) The present results in the context of other published work

The everted gut technique has been successfully

TABLE 2

REDUCTION OF CHLOROQUINE AND PHENOBARBITONE TRANSFER IN THE PRESENCE OF THE INTERACTANTS USING THE FIVE EXPERIMENTAL MODELS

		Buccal absorption model	In situ rat intestinal model	Everted rat intestine model	Sartorius Absorption Simulator	Adsorption/ centrifugation technique
Chloroquine + kaolin	pH	8.5	8.5	8.5	7.5	8.5
	Experimental time (min)	5	60	60	120	60
	Mean reduction % (±S.E.)	22.4 ± 2.6	22.1 ± 5.3%	29.8 ± 3.1%	28.5 ± 5.0%	12.1 ± 0.6%
Phenobarbitone + activated charcoal	pH	5	5	5	5	5
	Experimental time (min)	5	60	60	120	60
	Mean reduction % (±S.E.)	70.4 ± 3.2%	57.3 ± 3.2%	53.5 ± 2.7%	46.2 ± 5.9%	63.8 ± 0.6%

used in the past to screen for drug absorption interactions and was found to give reliable predictions (D'Arcy et al., 1976; McElnay et al., 1979a and b; McElnay, 1980). The technique both then, and in the present comparative studies, was found to suffer from some disadvantages. These included leakage due to mechanical damage during the evertion process, and during attachment to the cannulae. The segments' lack of a blood supply also led invariably to loss of structural integrity of the mucosal surface. Perrier and Gibaldi (1973) carried out experiments comparing everted and in situ rat intestine models. They found that the in situ model showed rank-order agreement with in vivo absorption in human volunteers while the everted intestine model did not. They attributed this to the fact that transfer of drug in the everted segment was not physiologically realistic because of the presence of unnatural absorption barriers in the mucosal/serosal transfer. Much earlier Crouthamel et al. (1971) had found that the transfer of ions occurred more readily in in vitro preparations than in in vivo situations.

The present work showed that only a small fraction of drug was transferred in both everted and Sartorius models. This is in part was explained by the small surface area available for absorption (in comparison with other methods), and the absence of a vascular system to remove drug penetrating the membrane. The lower absorption made it necessary to use more concentrated drug solutions to attain sample drug concentrations that could be conveniently assayed. This, however, brought the risk of saturation of the absorption potential of the membranes rendering them insensitive to small fluctuations in free drug concentration in solution. Using the Sartorius model, it was found that the drugs examined were adsorbed by the apparatus. The manual provided with the instrument, suggested that, this difficulty could be overcome either by reducing the surface area of the membrane or by increasing the initial drug concentration in the test solutions. These measures, it suggested, might limit the sensitivity of the model, and might also be insufficient to overcome the problem. Although Stricker (1971) found good agreement between in vitro and in vivo absorption rates for a variety of neutral, acidic and basic compounds there has not been a widespread usage of the model.

In the present study, the absorption rates and extents were high when using the in situ method. This was attributed to the large surface area available for absorption. An intact blood supply also allowed rapid removal of the drugs transferred across the segment thus maintaining sink conditions. In this model the blood supply maintains the high metabolic requirements of the segment thus ensuring its structural integrity during the experiment. The technique also showed little in-use problems and the data obtained were reproducible. For these reasons together with the good experimental/clinical correlation obtained by Doluisio et al. (1969a), the in situ rat intestine model was considered superior to the everted rat intestine and the Sartorius models.

A disadvantage, however, of the in situ method was water absorption from the drug solution. Although isotonic drug solutions were used to minimize this effect, with these particular drugs and buffer a 20–30% reduction in drug solution occurred at the end of each experiment and had to be accounted for in the calculations. Generally the results obtained from individual models were reproducible, however, as expected in different groups of experiments in different volunteer subjects and animals, slight variations did occur. Differences were greatest for chloroquine but rarely exceeded 10%.

Conclusions

The buccal partitioning model was considered very valuable for our purposes. Like the in situ model it showed a high rate and extent of drug absorption due to the large surface area available for drug transfer. The results were reproducible and the same volunteer subjects could be used for control and test measurements thus allowing crossover studies to be carried out. The technique was found to be simple, convenient and the time spent on individual experiments was short. The method also had the advantage of generating absorption data in human subjects. This is not to infer that buccal absorption can always be equated

with intestinal absorption. The only major disadvantage with the technique is that it can only be used for agents with minimal toxicity; for example, in recent studies on melphalan and chlorambucil absorption in these laboratories, the in situ rat intestinal model has been used in preference over the buccal partitioning method.

Although simple to use the everted rat intestine and Sartorius absorption models were considered to be poor methods because drug transfer across the membranes was slow. Drug binding to the apparatus was also a problem with the Sartorius method. The simple centrifugation method suffered from the absence of an absorption phase, which appeared to be important in the case of the chloroquine/kaolin interaction. It could obviously not be used to examine drug pH/absorption profiles or absorption vs time curves.

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