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The importance of intestinal residence time of absorption enhancer on drug absorption and implication on formulative considerations

Muhammad Baluom, Michael Friedman, Abraham Rubinstein [1,*]

The Hebrew University of Jerusalem, Faculty of Medicine, School of Pharmacy, P.O. Box 12065, Jerusalem 91120, Israel

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Abstract

Absorption enhancers are efficient in small body cavities such as the nasal and the rectum. However, in the gastrointestinal tract, where the volume and amount of liquids are large and motility is more profound, dilution may require a constant input of the enhancer with a poorly absorbed drug. Using a perfused rat model, the purpose of the present study was to verify that the synchronized administration of a poorly absorbed drug and an absorption enhancer is required for optimal drug absorption after oral administration. Sodium cefazoline (SCef) was used as the poorly absorbed drug probe and sodium decanoate (SD) as the absorption enhancer. A secondary goal was to examine an erodible matrix formulation as a potential drug carrier for the synchronized release of two probes of different water solubilities. It was found that higher SCef blood levels were obtained after 30 min of co-administration of 50 mM of SD, than after co-administration of 100 mM over 15 min. In both cases SCef blood levels declined within 15–30 min after cessation of enhancer perfusion, a finding which suggests that SCef requires a constant input of SD for its absorption which is more important than the concentration of SD administered. The feasibility of a hydroxypropyl methyl cellulose (HPMC) matrix for the synchronous release of two drug probes with different solubility properties was examined as a potential carrier to maintain constant levels of two drug probes over a predetermined period of time. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Absorption; Absorption enhancement; Cefazoline; EDTA; Ibuprofen; HPMC; In vivo analysis; Sodium decanoate; Sodium dodecyl sulphate; Synchronous release

Abbreviations: EDTA, ethylene diaminetetracetic acid, di-sodium salt; HPMC, hydroxypropyl methyl cellulose; Ib, ibuprofen; PBS, phosphate buffered saline, pH = 7.4; SCef, sodium cefazoline; SD, sodium decanoate; SDS, sodium dodecyl sulphate.

* Corresponding author. Tel.: +972 2 6758603; fax: +972 2 6436246; e-mail: avri@cc.huji.ac.il

[1] Affiliated with the David R. Bloom Center for Pharmacy at The Hebrew University of Jerusalem.

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1. Introduction

Oral delivery of poorly absorbed drugs has been the focus of many studies. While recent findings tend to look at brush border enzymes, such as P-glycoprotein and Cytochrome P-450, as a possible cause for low bioavailability following oral ingestion of drugs (Wacher et al., 1996; Hunter and Hirst, 1997), it is well documented that many molecules cannot pass the intestinal epithelial barrier because they are too polar or too large (Muranishi, 1990; Hochman and Artursson, 1994). The latter reasons require the use of absorption promoters to overcome epithelial barrier functions. Excluding toxicity problems, the use of absorption enhancers is rational only in small body cavities (e.g. nose or rectum) (Muranishi, 1985). This is because in these locations mixing is poor for a finite period of time after administration, dilution is minute and the drug molecules stay together with their promoter(s) until absorption is completed. In this regard the lumen of the rat intestine, in which the majority of studies that measure the effect of absorption enhancers on intestinal wall drug permeation have been performed, can also be considered as a small volume cavity. Since in many reported protocols short segments of the rat intestine—in which very low (if at all) flow rates (a classic value is 0.2 ml/min) are utilized (Muranishi, 1990; Baluom et al., 1997; Sintov et al., 1996)—are involved, these models can also be considered as closed compartments. In the human gastrointestinal (GI) tract (or the GI tract of large animal models), however, due to the much larger dimensions, motility, and pH gradients the situation is different and closed compartment conditions cannot be considered. That is, dilution is almost infinite (or in other words, close to perfect sink conditions). As a result, water soluble molecules (polar drugs) and the co-incorporated absorption enhancers may be diluted right after their administration. Moreover, if possessing different solubility properties, they may be diluted in different rates. Thus, it is reasonable to assume that after a short travel of a conventional oral dosage form (e.g. capsule or a fast disintegrating tablet), a drug whose absorption needed to be enhanced, may be 'left' without the enhancer. In the case of different water solubility properties the situation may even be worse if a delayed release dosage form, such as swellable matrix, is used. This type of delivery system would release the highly water soluble entity by diffusion and retard the release of the less water soluble entity.

In a previous study, we demonstrated that the simultaneous (synchronic) release of two different drug molecules with different water solubilities, sodium cefazoline (SCef) and ibuprofen (Ib), is achievable when formulated into erodible matrix tablets. The formulations used were based on mixtures of the two acrylic polymers Eudragit RL-100 and polycarbophil. It was shown that the rates of diffusional drug release and matrix erosion could be synchronized to give a simultaneous release of the two drugs over time (Tirosh et al., 1997). Synchronous release has been suggested also by Kimura and coworkers as a possible explanation for the improved insulin bioavailability they have observed after oral administration of insulin together with the protease inhibitors aprotinin or bacitracin, formulated in PVA spheres to diabetic rats (Kimura et al., 1996). Yet, a direct biological model is required to verify the hypothesis that synchronized release of absorption enhancer is advantageous in the oral delivery of poorly absorbed drugs.

The purpose of the present study was, therefore, to verify that a synchronized administration of a poorly absorbed drug and an absorption enhancer is required for optimal drug absorption and that a proper oral formulation can be developed to meet the synchronous concept. More specifically the study goals were: (a) to develop a perfused-intestine rat model which will be able to analyze the influence of co-administered absorption enhancer on the intestinal absorption of poorly absorbed drugs; (b) to check the model with SCef and a series of absorption enhancers and; (c) to check whether hydroxypropyl methyl cellulose (HPMC) can be formulated into erodible matrices to serve as synchronized release drug platforms.

2. Materials and methods

2.1. Materials

All materials were purchased from Sigma, St. Louis, MO, unless otherwise mentioned in the text. Water was double distilled. HPMC (Methocel K15M PREM) was purchased from the DOW Chemical Company, Midland, Michigan. All solvents were high performance liquid chromatography (HPLC) grade.

2.2. Animals, anesthesia and euthanasia

Male Sabra rats (200–250 g) were obtained from the Animal Farm of Hadassah Medical Center and The Hebrew University, kept under constant environmental conditions (22°C, 12 h light/dark cycles), and fed with standard laboratory chow and tap water. The rats were anesthetized by an intra-peritoneal injection of Equitensine solution (equivalent to 6 mg sodium pentobarbitone/100 g body weight). Six anesthetized rats were used in each perfusion study, at the end of which they were sacrificed by chest wall puncture. All animal studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication # 85-23, revised 1985). Protocols were reviewed by the mutual committee of Hadassah and the Faculty of Medicine for Animal Welfare.

2.3. Intravenous administration of sodium cefazoline (SCef)

A 1 cm incision was made in the neck of the anesthetized rat and the right vena cava was exposed and cannulated with 0.98 mm O.D. silastic tubing. A 300 ml blood sample was withdrawn through the venous catheter (time zero). Then, 100-mg/kg-body weight of SCef (Cefamezin, Teva, Israel) in saline was administered via the same catheter followed by a saline rinse (500 ml). Blood samples of 300 μl were withdrawn at 5, 15, 30, 60, 90, 120, 180 and 240 min. Clotting was avoided by the addition of 100 μl (50 U/ml) of heparin to each test tube. Plasma was separated by centrifugation and kept at −20°C until SCef analysis.

2.4. Enhancers comparative residual effect studies

The purpose of this step of the study was to identify an absorption enhancer with the least residual effect (damage) on the jejunal wall of the rat (Section 4).

The jejunum of the anesthetized rats was exposed through a midline incision. An L-shaped glass cannula was inserted and secured with a 3/0 silk suture 10 cm distal to the ligament of Treitz. A second cannula was placed, in the same manner, 15 cm distal to the first one. An open perfusion system was achieved by connecting the proximal glass cannula to probe solutions reservoir and the distal cannula to a glass collecting vessel. This experimental set-up allowed the use of a probe reservoir under changing conditions, i.e. for the duration of the study, different probes were perfused or the intestinal segment rinsed without the need to stop the perfusion system. A metering pump (FMI model RHSY, New York), operated at a rate of 2 ml/min, was used to push the perfused solution through the intestinal segment which was kept outside the rat body without disrupting blood flow. The temperature of the exposed tissue was kept at 37°C with a 60 W bulb, and a gauze sponge wetted with saline kept the tissue moist. Blood samples (300 μl) were withdrawn via a polyethylene (Intramedic® Becton Dickinson, MD) catheter previously implanted in the jugular vein of each anesthetized rat. The blood sampling schedule was 0, 15, 30, 60, 90, 120, 180 and 240 min.

In three different sets of in situ studies 5 mg/ml of SCef in phosphate buffered saline, pH = 7.4 (PBS) was perfused over 120 min through the jejunal loops of the anesthetized rat. In addition to the 120 min of SCef perfusion, the following enhancers solutions (taken from separate reservoirs) were simultaneously perfused in separate studies, over the first 60 min, at the same flow rate: (a) 50 mM of sodium decanoate (SD) in PBS; (b) 50 mM of ethylene diaminetetracetic acid, di-sodium salt (EDTA) in PBS; and (c) 50 mM of sodium dodecyl sulphate (SDS) in PBS. Each set of the three studies included six rats.

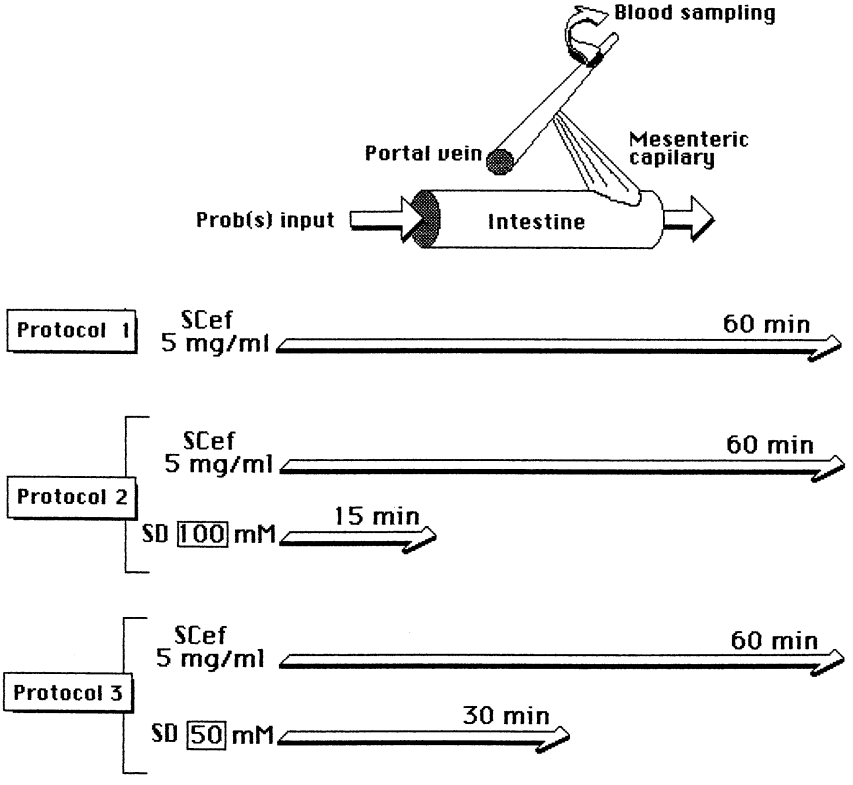
2.5. SCef dose-response residual effect studies

Three experimental protocols were conducted in this step of the study (Scheme 1). In all studies 5 mg/ml of SCef in PBS pH = 7.4 was perfused through a 15 cm long jejunal segment of the anesthetized rat preparation, under the same conditions described above, over 60 min. At the end of the SCef administration the jejunal segment was rinsed with PBS for an additional 30 min and kept inside the rat until the end of the study (cessation of blood sampling). In Protocol 1 no SD was added. In Protocol 2 100 mM of SD in PBS pH = 7.4 was perfused together with the SCef for the first 15 min of the study. In Protocol 3 50 mM of SD in PBS pH = 7.4 was perfused together with the SCef for the first 30 min of the study.

Prior to the initiation of the study a blood sample (300 μl) was withdrawn through the venous catheter (time zero). Blood samples (300 μl) were withdrawn at 15, 30, 60, 90, 120, 180 and 240 min and treated as described above. Six rats were included in each protocol.

2.6. Blood drug analysis

Samples of 100 μl of rat plasma was added to 100 μl of an ice-cold mixture of 0.1 M sodium acetate and methanol (ratio of 3:7). The mixture, which also contained 20 ml of cefoxitin (0.1 mg/ml) as an internal standard was vortexed for 30 s and incubated for 10 min at −20°C, after which it was centrifuged for 10 min at 3500 rpm.



Scheme 1. Schematic presentation of the experimental setup in which the residence time effect of the absorption enhancer SD was assessed in the jejunal loop of the anesthetized rat on the absorption of SCef. Protocol 1: SCef was perfused over 60 min; Protocol 2: SCef was perfused over 60 min. During the first 15 min 100 mM of SD was perfused together with the SCef and then stopped; Protocol 3: SCef was perfused over 60 min. A lower concentration of SD (50 mM) was perfused over a longer (30 min) period of time and then stopped. SCef concentration was 5 mg/ml and the perfusion rate was 2 ml/min.

Table 1
The composition of the matrix tablets used in the synchronized release study of SCef and IB

Formulation	HPMC K15M (mg)	Percentage	Mannitol (mg)	Percentage
A	420.0	84	—	—
B	350.0	70	70.0	14
C	280.0	56	140.0	28
D	210.0	42	210.0	42

HPLC (Hewlett Packard 1050 pumping system, Jasco 875 Intelligent UV/Vis detector) was used to assay SCef at a wavelength of 262 nm (column: Lichrospher 100, RP-18, 5 μ, 25 cm × 4 mm, Merck, Germany; flow rate: 1.0 ml/min; mobile phase: sodium acetate 0.01 M, pH = 5.2, 86%v/v, acetonitrile 13.6%v/v, methanol 0.4%v/v; R.T.: 6.3 min for cefazoline and 8.5 min for cefoxitin).

Pharmacokinetic parameters derived from the SCef plasma concentration were calculated by a computerized program (PC Nonline, Version 4.1, SCI Software, Clintrials, USA).

2.7. SCef-ibuprofen (Ib) tablet preparation and drug release studies

Four tablet formulations each containing equal amounts (40 mg) of SCef (highly water soluble) and Ib (poorly water soluble) with different erosion properties were prepared by incorporating increasing amounts of mannitol and reduced amounts of HPMC as specified in Table 1. The powdered mixtures were compressed (1 ton) into 500 mg tablets using a Perkin Elmer IR manual press. The average crushing strength (Dr K. Schleuinger, model 2E/205, Switzerland) of the tablets ranged from 6 to 9 kgP, depending on the relative contents of mannitol.

Drug release studies were performed in a U.S.P. Type II dissolution apparatus (Vankel VK 7000, USA) at 37°C, U.S.P. phosphate buffer, pH = 7.4, and 100 rpm, a revolving rate which is expected to correlate with the erosion rate taking place in the GI tract as analyzed in the dog (Shameen et al., 1995). At predetermined time intervals 5 ml samples were withdrawn for drugs analysis and replenished (to make up a volume of 1000 ml) with the same volume of fresh buffer solution.

2.8. Analysis of Ib and SCef in buffer solution

The samples withdrawn from the dissolution system were centrifuged to get rid of particulate debris. Ib was assayed by HPLC (same system mentioned above) at 273 nm (column: Lichrospher 100, RP-18, 5 μ, 25 cm × 4 mm, Merck, Germany; flow rate: 1.5 ml/min; mobile phase: diluted phosphoric acid, pH = 2.2, 50%v/v, acetonitrile 50%v/v; R.T.: 5.6). SCef was assayed separately as described above.

2.9. Statistical analysis of data derived from the rat studies

A Kruskal–Wallis test was performed to check whether the various groups of rats were from different populations. A difference was considered to be statistically significant when the p value was less than 0.05. When the difference between the groups was validated, a Mann–Whitney U test was used to analyze the significance of the differences between the obtained data ($p < 0.05$).

3. Results

SCef plasma concentrations after intravenous administration to the rat are shown in Fig. 1 and the derived pharmacokinetic parameters are summarized in Table 2. The $t_{1/2}\beta$ of this profile, as calculated by the PC Nonline program was 67 min. This relatively short elimination half life makes the system tested a convenient model for comperative residual effect measurements of various absorption enhancers on the jejunal wall. Any reduction or termination of the enhancement effect is immediately reflected in the SCef blood

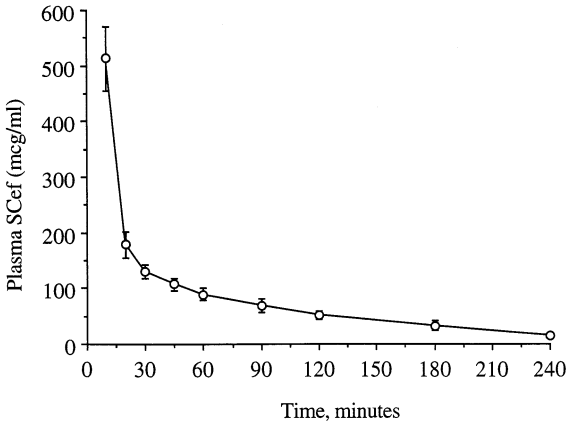


Fig. 1. Cefazolin plasma concentrations after intravenous administration of 100 mg/kg body weight of SCef in saline to six rats. Shown are the mean values ± S.D.

levels due to the rapid elimination proprties of the drug.

The pharmcokinetic profiles of SCef in the plasma of the rat after perfusion studies with the three absorption enhancers EDTA, SDS and SD are shown in Fig. 2A. The studies summarized in Fig. 2 were conducted to identify an absorption enhancer with the least membrane residual effect possible. The residual effect was assessed from the duration and nature of the plasma drug profiles after cessation of the enhancer administration (Section 4). It can be seen that the most profound enhancement effect was accomplished by SDS, which caused SCef plasma levels to elevate to 248 ± 23.0 mcg/ml. After cessation of the enhancer perfusion, plasma drug levels continued to elevate (at 90 min they reached 296 ± 22.5 mcg/ml). Much lesser plasma drug levels resulted from

Table 2
Pharmacokinetic parameters (mean values ± S.D.) of Cefazolin in the rat after intravenous administration of 100 mg/kg body weight of the drug (Fig. 1)

Pharmacokinetic parameter	Value
$t_{1/2}\alpha$ (min)	4.0 ± 0.07
$t_{1/2}\beta$ (min)	67.1 ± 15.5
CL (ml/min)	0.693 ± 0.24
MRT (min)	57.4 ± 19.1
Vss (ml)	41.0 ± 19.8

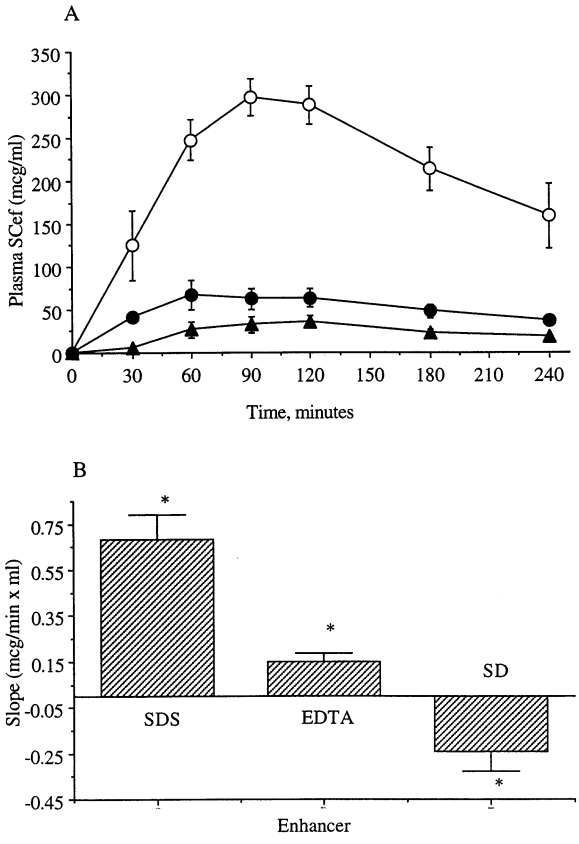


Fig. 2. Top: Plasma cefazolin levels after 120 min of intra-jejunal perfusion of 5 mg/ml of SCef together with: (a) 50 mM EDTA (filled triangles); (b) 50 mM SD (filled circles); and (c) 50 mM SDS (empty circles). All enhancers were perfused for the first 60 min only. Shown are the mean values of six rats ± S.E.M. Bottom: Slopes of the 60–120 min fractions (i.e. after the enhancers' perfusion was stopped) of the cefazolin pharmacokinetic profiles on top. Shown are the mean values of six rats ± S.E.M. * $p < 0.05$ when compared to each other.

the co-perfusion of EDTA (90 ± 13.2 mcg/ml at 60 min). Yet, as was observed in the case of the SDS, plasma drug levels continued to elevate following termination of EDTA perfusion (98 ± 17.2 mg/ml at 90 min). A reduced residual effect on the wall of the perfused gut of the rat was observed for SD. At 60 min SCef plasma levels reached 67.3 ± 17.0 mcg/ml. Right after cessation of SD perfusion the plasma drug levels decreased to 62 ± 12.0 at 90 min.

To emphasize the differences in the residual effect among the three absorption enhancers used,

the slope of each of the three pharmacokinetic curves was measured over 60 min, from the time of cessation of the enhancers' perfusion (60 min) until 120 min had elapsed. The values are summarized in Fig. 2B. SDS had the steepest slope (0.68 ± 0.1 mcg/min per ml). EDTA showed a significantly lower slope (0.15 ± 0.1 mcg/min per ml). SD had a negative slope (-0.24 ± 0.1 mcg/min per ml) meaning that SCef absorption was interrupted immediately after the termination of SD perfusion.

The effect of SD concentration and jejunal residence time on SCef absorption from the perfused jejunal loop is shown in Fig. 3. It can be seen that the highest plasma SCef levels (C_{max} 34 ± 4.3 mcg/ml, at t_{max} of 30 min) resulted from the co-administration of 50 mM of SD over 30 min (Fig. 3A). The co-administration of 100 mM of SD over 15 min resulted in lower SCef plasma levels (C_{max} 21 ± 2.2 mcg/ml, at t_{max} of 30 min). When no SD was used almost no SCef was absorbed. The relation between SD residence time and jejunal absorption of SCef is best shown in Fig. 3B, which demonstrates on a non-linear time scale, that within 15 min after the cessation of SD perfusion, plasma levels of SCef started to decrease.

The last part of the study checked whether synchronous input of two different probes is feasible by a matrix formulation of HPMC. The highly water soluble SCef and the poor water soluble Ib were formulated into HPMC tablets with increasing amounts of mannitol. The latter was aimed at increasing the erosion properties of the swelling polymer. Fig. 4 shows the cumulative release profiles of Ib and SCef from four types of HPMC tablets. Synchronization between the release rates of the two probes was accomplished only in Formulation D, where mannitol equaled the amount of HPMC.

4. Discussion

Using a common perfusion system, we were able to demonstrate that synchronous instillation of the absorption enhancer SD to the lumen of the rat jejunum was more important for the absorption of the poorly absorbed drug SCef than increasing the local concentrations of SD. Higher SCef blood levels were obtained after 30 min of co-administration of 50 mM of SD, than after co-administration of 100 mM over 15 min (Fig. 3). Moreover, since SD possesses short residual effect properties, in both experiments when SD perfusion stopped, a drop in the sCef plasma concentrations was observed.

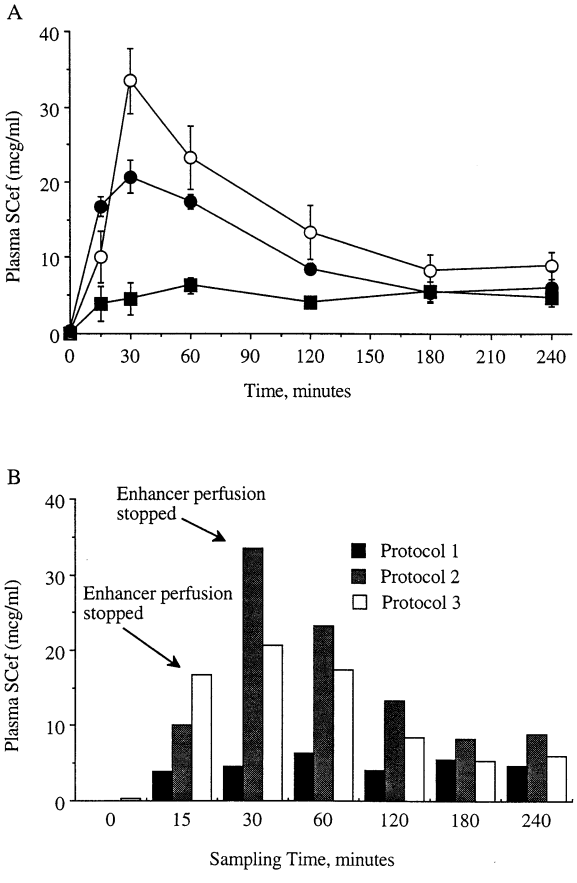


Fig. 3. Top: Plasma cefazolin levels after 60 min of intra-jejunal perfusion of 5 mg/ml of SCef in: (a) saline (filed squares), (b) saline with 100 mM of SD perfused during the first 15 min of the study (filled circles); and (c) saline with 50 mM of SD perfused during the first 30 min of the study (empty circles) (protocols 1, 2 and 3 respectively, see Scheme 1). Shown are the mean values of six rats $\pm$ S.E.M. Bottom: Non-linear columns plot of the above cefazolin pharmacokinetic plot, showing the effect of cessation of the enhancer's administration on the plasma levels of the drug.

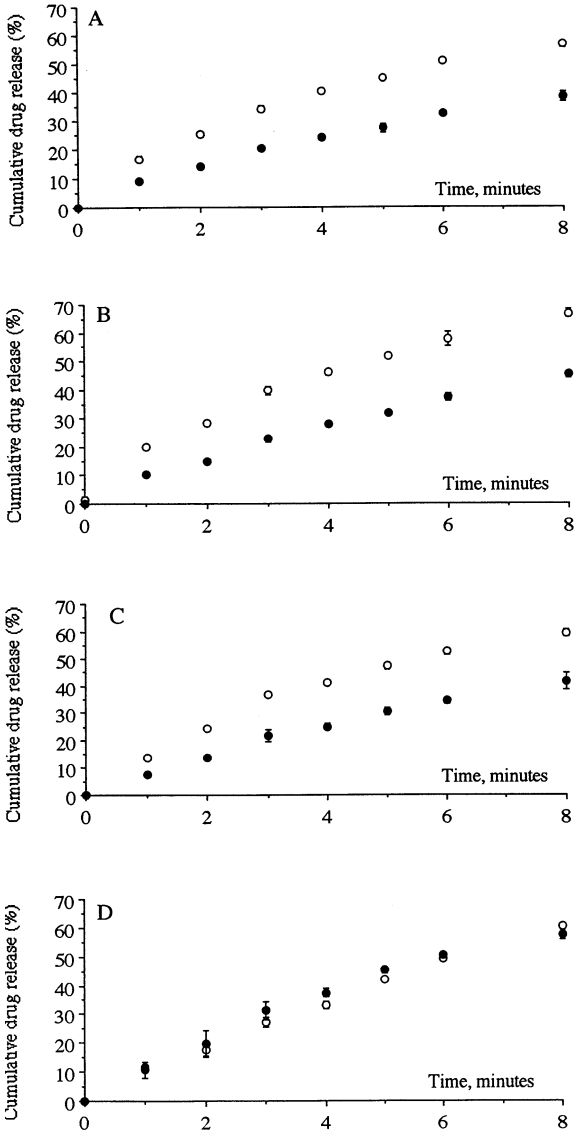


Fig. 4. The release kinetics of SCef (empty circles) and Ib (filled circles) from formulations A, B, C and D. Shown are the mean results of three tablets ± S.D.

The importance of the rate of delivery of an enhancer to the absorption of SCef in the rectum of the rat was previously reported by van Hoogdalem and coworkers (van Hoogdalem et al., 1988). They found that linear infusion of SCef together with a mixture of glycerol, octanoic acid and glyceryl mono-, di-, and tri-octanoate over half an hour, resulted in the complete absorption of the β-lactam, whereas bioavailability of only 60% (calculated from AUC/D measurements) was obtained following bolus (24 s) administration of the drug and the medium chain glyceride preparation. Kimura and coworkers (Kimura et al., 1996) have found that the most insulin absorption in the streptozotocin induced rat was in the colon and ileum and least was in the jejunum, after insulin was administered in PVA spheres which also contained the protease inhibitors aprotinin or bacitracin. They explained their findings by the prolonged residence time in the colon and by synchronous release of the peptide, which occurred together with the protease inhibitors.

This current study provides direct evidence for the need for simultaneous administration of an absorption enhancer, together with poorly absorbed drugs such as SCef. Apart from low toxicity (Yamamoto et al., 1996), an efficient enhancer should possess two important characteristics: rapid onset and low residual effect. Thus, upon removal from the surface of the epithelium, a fast recovery in both tissue integrity and epithlial transport properties, is expected. For example, Muranishi and coworkers have shown that the increased absorption of cefazoline, caused by oleic acid or n-lauryl-β-D-glucopyranoside, disappeared immediately after rinsing the treated epithelium with water (Muranishi, 1990). Swenson and coworkers also indicated that reversibility is an important parameter in the toxicity assessment of absorption enhancers (Swenson et al., 1994). In their comparative study which included a series of enhancers such as SDS, sodium taurocholate, polysorbate 80 and others, they found a correlation between the drop in the blood drug marker concentrations (phenol red) and tissue damage as assessed by biochemical markers (e.g. LDH). However, in the combinations they used the residual effect lasted 1–2 h. To demonstrate the synchronization effect, a much shorter reversibility is required. SD is an appropriate promoter for that purpose. As shown in Fig. 3, 15–30 min only were required for SCef blood levels to drop following cessation of SD co-administration, regardless of SD concentration. In other words, once the administration of SD was terminated, the absorption stopped, no matter what the concentration of

the enhancer was. To emphasize this point, Protocol 2 and Protocol 3 were designed so that the total amount (product of concentration by time) of SD perfused was equal in the two studies.

SD is known to act on calcium levels in tight junctions. It was suggested that it releases calcium from intracellular stores by activating phospholipase C in plasma membrane (Anderberg et al., 1993). This mode of enhancement, which does not cause direct insult to the enterocyte membrane may be the reason for its minor residual effect on the gut wall of the rat as observed in our study. However, SCef $t_{1/2}\beta$ which was calculated after intravenous administration (Table 2) is too long for such a system, and an alternative drug model is required to better highlight the synchronization effect.

Once the importance of synchronized release of a poorly absorbed drug and an absorption enhancer was demonstrated, a suggestion for a delivery system which is able to incorporate the parameters defined in the biological model is imperative. This is attainable by a simple formulative approach such as a matrix tablet. If properly designed, the release of the drug and the functional adjuvants do not depend upon intrinsic diffusion processes but are the result of the rate of the matrix erosion. By stripping off the erodible matrix layers in a well controlled manner, predetermined amounts of the drug and the absorption enhancer(s) can be delivered together, while travelling along the intestine. The successful functioning of the matrix tablets depends upon the ability to 'fine tune' its erosion rate. A suitable matrix would be one which erodes to release its drug load in a zero order kinetics, as already demonstrated by Colombo and coworkers (Colombo et al., 1987; Catellani et al., 1988). The next step would be the development of a matrix formulation, designed to synchronize the release rate of two probes, one driven by diffusion from the matrix, the other caused by erosion of the matrix. In a previous study (Tirosh et al., 1997), it was found that the similarity in the release rates, resulting from a controlled erosion process (governed by balancing the ratio of polycarbophil and Eudragit RL-100), yielded a synchronized release of SCef (highly water soluble) and ibuprofen (poorly water soluble). In this study, an alternative formulation was tested. Matrix tablets made of HPMC and increasing amounts of mannitol were prepared and tested. It was found that as the ratio of mannitol in the polymer–mannitol mix increased, the erosion properties of the tablets made of the mixtures increased as well. In those formulations where the relative amount of HPMC was high, release was governed by diffusion and synchronization was not achieved. Only when the amount of mannitol was equal to HPMC a degree of erosion was accomplished, so that the two drugs' molecules were released at similar rates. The in vivo performance of this type of tablet is currently being tested in our laboratory.

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