# Synchronized Release of Sulpiride and Sodium Decanoate from HPMC Matrices: A Rational Approach to Enhance Sulpiride Absorption in the Rat Intestine

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***Purpose.*** (a) To improve the absorption of sulpiride (SP) through the intestinal wall by incorporating it together with sodium decanoate (SD) into erodible matrices, designed to synchronize the release of SP and SD over different periods of time; (b) to test, *in vivo* the hypothesis that this simultaneous release increases SP absorption from the intestinal lumen.

***Methods.*** Matrix tablets, possessing different erosion rates, were prepared by changing the ratios between SD and hydroxypropyl methylcellulose (HPMC). The amounts of HPMC varied from 2.5% to 17% w/w. Double layer tablets, containing similar amounts of SP, SD, and HPMC were used as nonsynchronous controls. The erosion kinetics of the tablets was assessed gravimetrically *in vitro* in USP basket dissolution apparatus and *in vivo* in the intestine of the anesthetized rat after intra-intestinal administration. SP absorption was studied after intra-intestinal administration of the different kinds of tablets to anesthetized rats, by monitoring SP blood levels. SP and SD levels in the withdrawn samples from the dissolution systems and blood were analyzed by HPLC.

***Results.*** The controlled erosion of the tablets resulted in equal release rates of SP and SD during the initial linear phase of the process. This synchronized release lasted over different time periods depending on the relative amount of HPMC in the formulations (from 1 hour to 4 hours for 2.5 and 17 % w/w of HPMC, respectively). The synchronous matrices increased SP bioavailability after intra-intestinal administration. The increase varied from 1.4 to 2.3-fold for the slow and the fast release formulations, respectively (compared with the nonsynchronous, SD containing control formulations), indicating the ability to control both erosion rate and length of intestinal segment in which absorption is taking place.

***Conclusions.*** SP bioavailability after intestinal administration can be improved only if SP is released together with SD along the entire intestinal route. This can be accomplished by the design of synchronous matrices capable of concomitant release of SP and SD despite the differences in their water solubility. The ability to manipulate and control the duration of the synchronous phase of the matrices makes it possible for SP to be absorbed at different parts of the intestine.

**KEY WORDS:** synchronized release; hydroxypropyl methylcellulose (HPMC) matrices; sulpiride; sodium decanoate (SD); intestinal absorption enhancement; rat.

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## INTRODUCTION

To increase the oral availability of poorly absorbed drugs, co-administration of absorption adjuvant should be performed at the same site in the gastrointestinal (GI) tract. This was demonstrated with insulin which was administered to easily accessible organs such as buccal tissue of the dog and rectal cavity of the rat (1–3). In this context, it was reported that oleic acid was able to increase the intestinal absorption of sulpiride in the rabbit intestine only when a burst concomitant release of the two was accomplished (4). The rectum is an optimal location for such coadministration because it contains a low amount of fluid and hence dilution is minor, as was demonstrated with mixed micelles (5). The properties of the rectum can be viewed as "closed compartment" conditions. Similar conditions take place in experimental models, such as everted sacs or perfused rat intestine, in which short segments of the intestine are exposed to the influence of enhancers with minimal mixing (6,7).

The physiological conditions are different in the human intestine. Motility is intensive and the amounts of secreted fluid and mucus turnover are profound in the small intestine (8,9). Under such circumstances—"open compartment" conditions with rapid dilution—the drug and its absorption adjuvant(s) may separate right after administration. If possessing different solubility properties, dissolution will occur at different rates and the concomitant administration may be useless. It is obvious that immediate release dosage forms cannot be used in such cases. Yet, if sustained release dosage forms are to be used, they must be carefully designed. For example, swellable matrices would release the highly water-soluble entity by diffusion while, retarding the release of the one that is less water soluble.

In a previous study (10), we demonstrated that in the rat intestine, a constant input rate of the absorption enhancer sodium decanoate (SD) was more important for sodium cefazoline (SC) absorption than SD concentration in the perfused solution. It was concluded that a rational oral dosage form of poorly absorbed drug would be one which is designed to release both the drug and its absorption enhancer at similar rates (synchronized release). This concept was tested with sulpiride in the present study.

Sulpiride (SP), a substituted benzamide, is a specific antipsychotic drug used for the treatment of depression, schizophrenia, migraine, vertigo, and gastrointestinal disorders. Sulpiride absorption is slow and erratic, follows zero-order kinetics and is highly dependent on formulation factors (11,12). The oral bioavailability of sulpiride is 30% in man and 15% in the rat (11,13). The absorption of SP in the human intestine after oral administration may be improved if an absorption enhancer is used. Yet, if administered together with a highly water-soluble enhancer such as SD in a bolus form (immediate release formulation), an enhancement effect will not be accomplished as explained above because of the poor water solubility of SP. SD is a well-recognized absorption enhancer whose transient dilation effect on the paracellular pathway has been extensively documented using cell line (14,15) and *in situ* rat models (10).

The overall goal of the present study was to develop an oral platform for SP with improved intestinal absorption properties. More specifically, the study objectives were: (a) to



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develop an erodible matrix made of hydroxypropyl methylcellulose (HPMC) that will release both SP and SD in a synchronous manner; (b) To characterize the simultaneous release of the two probes *in vitro* and (c) to test (rat) the hypothesis *in vivo* that synchronous matrices are superior to nonsynchronous ones in increasing SP oral bioavailability.

## MATERIALS AND METHODS

All materials were purchased from Sigma, St. Louis, MO., unless otherwise mentioned in the text. Water was double-distilled. Hydroxypropyl methylcellulose (Methocel - K15M PREM) was purchased from Dow Chemicals, Midland, IL. 2-(4-aminophenyl)-6-methylbenzothiazole (AMZ) was recrystallized from chloroform. All solvents were HPLC grade. Sabra rats (16) were used in the study. All animal studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication #85-23, revised 1985). The mutual committee of Hadassah and the Faculty of Medicine reviewed protocols for animal welfare. Euthanasia of the anesthetized rats was carried out by chest-wall puncturing.

### Matrix Formulations and *In Vitro* Dissolution and Erosion Studies

Three types of matrix tablets with increasing amounts of HPMC (S-1, S-2, and S-4) were prepared. Their serial numbers indicate their overall erosion time (1, 2, and 4 hours, respectively) as measured *in vitro*. Each tablet contained 16 mg of SP and 34 mg of SD. The dose was designed in accord with the limited water solubility of SP and after preliminary perfusion studies (not shown), which verified that the amount of SD incorporated was within the liner fraction of the response (enhancement) curve (10). Control tablets without SD were prepared. C-2 and C-4 contained the same amounts of HPMC as formulations S-2 and S-4, respectively. Formulation CI-0 did contain SD and served as a control to S-1 to emphasize the difference between an immediate release formulation (CI-0) and a rapid synchronous release formulation (S-1) (Table 1). Similar erosion times of the control tablets C-2 and C-4 to the corresponding test formulations were accomplished by the addition of mannitol, and by altering the amount of HPMC (Table 1). Drug release and erosion rates were studied in U.S.P. phosphate buffer pH = 7.4, were performed in a USP Type I dissolution apparatus (Vankel VK 7000, USA), equipped with small sample (100 ml) adapters at 20 r.p.m. at 37°C. This stirring rate was selected due to preliminary studies in which the erosion rates *in vitro* were correlated with the *in vivo* conditions. At predetermined time intervals, samples (1.5 ml) were withdrawn and replenished with the same volume of fresh buffer solution to make up a volume of 100 ml. Samples were kept at −20°C until analysis. Erosion kinetics of the tablets was measured gravimetrically at separate studies under the same conditions. At 30, 60, 90, 120 minutes, and 4 hours the tablets were taken from the dissolution baskets and dried at 45°C until there was no further weight loss. Each study was performed in triplicate.

**Table 1.** The Composition of the Two SP-SD Synchronous Release Matrices (S-4 and S-2), Their Controls Without SD (C-4 and C-2), the Synchronous Release Matrix, S-1, the Immediate Release Matrix, CI-0 and the SP-SD Nonsynchronous Release Layered Matrices, NS-2 and NS-4. Each of the Two Layers Contained Either SP or SD with Different Release Rates. They Were Attached Together to Allow Release Initiation at the Same Locations of the Rat Intestine

| Formulation | HPMC (%) | HPMC (mg) | Mannitol (mg) | SP (mg) | SD (mg) |
|---|---|---|---|---|---|
| S-4 | 17 | 10 | — | 16 | 34 |
| C-4 | 15 | 8.8 | 34 | 16 | — |
| S-2 | 9 | 5 | — | 16 | 34 |
| C-2 | 10 | 5.5 | 34 | 16 | — |
| S-1 | 2.5 | 1.3 | — | 16 | 34 |
| CI-0 | 0 | — | — | 16 | 34 |
| NS-2 1st layer | 9 | 5 | 34 | 16 | — |
| NS-2 2nd layer | 9 | 3.5 | — | — | 34 |
| NS-4 1st layer | 17 | 10 | 34 | 16 | — |
| NS-4 2nd layer | 17 | 7 | — | — | 34 |

A second set of two formulations containing 9% (NS-2) or 17% (NS-4) of HPMC was prepared. This set of tablets was composed of two layers each (Table 1). One layer contained SP and the other contained SD; they were designed so that a nonsynchronous release rate of SP and SD would be accomplished. That is, SD diffused faster than did SP, which was released as a result of the matrix erosion. In all cases mannitol was required to control the release of SP which is sparingly water-soluble.

All tablets were 5 mm in diameter. They were compressed in a Perkin Elmer IR manual press at a compression of 1 ton and the resulted crushing strength (Dr. K. Schleuinger and Co., model 2E/205, Switzerland), excluding CI-0, was 5 to 6.5 KgP.

### SP and SD Analysis in Buffer Solutions

SP concentrations in the withdrawn samples were measured spectrophotometrically (Uvikon 933, Kontron Instruments, Switzerland) at $\lambda = 240$ nm. SD concentrations in the withdrawn samples were measured by HPLC, using octanoic acid (OA) as an internal standard as described below.

### Derivatization of OA

1.2 g of OA (8.33 mmol) was mixed with 1.71 g (8.28 mmol) of dicyclohexylcarbodiimide (DCC) in chloroform. After 15 minutes, 2g (8.32 mmol) of AMZ was added. The mixture was stirred for additional 3 hours at 37°C, after which chloroform was evaporated. Crystals of Oct-AMZ were collected as dry powder. NMR (Varian VXR-300 S) was used to verify the formation of Oct-AMZ.

### HPLC Analysis of SD

0.2 ml taken from the withdrawn dissolution sample was mixed with 0.5 ml of 1N HCl, 1 ml of chloroform, and 0.5 ml of Oct-AMZ (0.2 mg/ml in chloroform). The mixture was centrifuged for 5 minutes. 0.5 ml of the chloroform phase was withdrawn and placed in a glass vial into which 0.5 ml of AMZ in chloroform (1.4mg/ml) and 0.5 ml of DCC (1.2 mg/ml in chloroform) were added. The mixture was shaken for 3 hours at 37 °C after which it was centrifuged for 5 minutes at 3,500 rpm and 1μL of the chloroformic phase was injected into the HPLC. The HPLC used was HP 1050, equipped with Shimadzu RF551 fluorometric detector. Excitation and emission were set at 343 and 423 nm, respectively. The column was Lichrospher 100, RP-18, 5 μ, 25 cm X 4 mm, Merck, Germany. The flow rate was 1.0 ml/min and the mobile phase was

triethylamine 1%v/v, acetonitrile 90%v/v, $H_20$ 9%v/v. Retention times obtained were 4.8 minutes for Oct-AMZ and 7.1 minutes for Dec-AMZ.

### *In vivo* Erosion Studies

Erosion times of the tablets were measured in the jejunum of anesthetized rats. The study was performed with the control matrices C-2 and C-4 as follows: 2 cm segment of the jejunum of the anesthetized (Equitensine, equivalent to 2% w/v pentobarbital) fed rats was exposed through a midline incision. The tablets were administered through a 5 mm cut, 5 cm distal to the ligament of Treitz. After administration was completed, the cut was ligated immediately as well as the abdominal wall. At 30, 60, 90, 120 minutes, and 4 hours the rats were sacrificed. The small intestine was then separated and cut wide open after which the tablets were located and their distance from the site of administration was measured. They were dried at 45°C until there was no further weight loss. At least four rats were used for each time point. Figure 1 displays the linear nature of the tablets' erosion.

### SP Absorption Studies in the Rat

Tablets were administered directly into the jejunum of the anesthetized rats as described above. Blood samples (500 μL) were withdrawn through a polyethylene catheter (Intramedic®, Becton Dickinson, MD, USA) previously implanted in the jugular vein of each anesthetized rat and exteriorized from the back of their neck. Plasma was separated by centrifugation and stored at –20°C until analysis.

### Blood SP Level Analysis

Duplicates of 100 μL of the withdrawn plasma samples were mixed with 200 μL of carbonate buffer (pH = 9.8, 0.2 M), followed by the addition of 600 μL of chloroform. The mixture was vortexed for 30 seconds and then centrifuged for 5 minutes at 3500 r.p.m. 500 μL of the chloroform phase was evaporated and reconstituted with 200 μL of methanol out of which 100 μL was injected into the HPLC. The pump, detector, column and flow rate were similar to those described above. Excitation and emission were set at 300 and 345, nm respectively. The mobile phase consisted of 0.01 N phosphoric acid and 0.1% triethylamine 73 %v/v, acetonitrile 19 %v/v, and methanol 8%v/v. Retention time obtained was 4.4 minutes.

A computerized program (PC Nonline, Version 4.1, SCI Software, Clintrials Inc., USA) was used to calculate the pharmacokinetic parameters derived from the SP plasma concentration.

### 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 ($p < 0.05$).

## RESULTS

By changing the balance between erosion and swelling properties of the three types of synchronous release formulations tested in this study, we were able to accomplish simultaneous release of SP and SD over different durations. In the rat intestine formulations S-1, S-2, C-2, S-4, and C-4 eroded within 1, 2, 2, 4, and 4 hours, respectively and the immediate release formulation, CI-0, eroded within 15 minutes. Figure 2 shows the *in vitro* release kinetics of SP and SD from two formulations: the immediate release CI-0, out of which an instantaneous release occurred, and the fast synchronous matrix S-1 out of which the two probes were released within 1 hour. The *in vitro* similar release profiles of SP and SD from

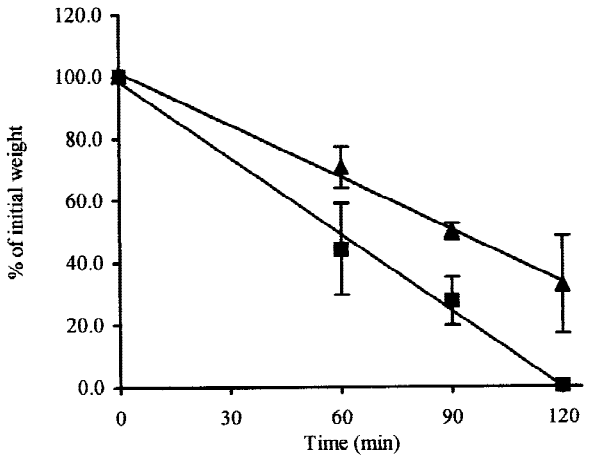


**Fig. 1.** The *in vivo* erosion kinetics of formulations C-4 (triangles) and C-2 (squares) in the rat intestine. Shown are the mean values of 4 studies ± S.E.M.

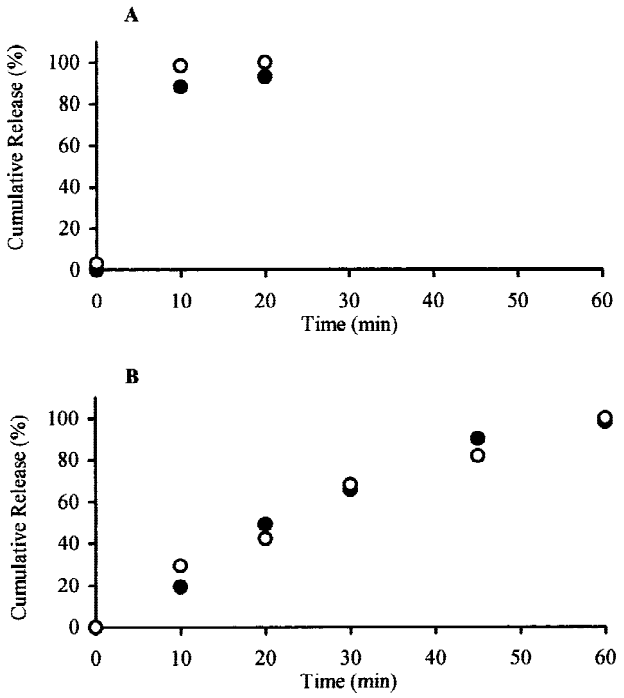


**Fig. 2.** The *in vitro* release kinetics of SP (filled circles) and SD (open circles) from the CI-0 (A) and S-1 (B) formulations. Shown are the mean values of 3 studies.

the synchronous formulation S-2, which was designed to complete its *in vivo* erosion within 2 hours, is shown in Figure 3. This figure also shows the different release profiles of SP and SD from the nonsynchronous control formulation NS-2. The *in vitro* release kinetics of SP and SD from the synchronous formulation S-4, which was designed to complete its *in vivo* erosion within 4 hours, and from its nonsynchronous control formulation, NS-4, is shown in Figure 4.

The effect of simultaneous release of SD on the intestinal absorption of SP is shown in Figure 5, which shows the SP plasma levels in the rat after intra-intestinal administration of formulations CI-0 and S-1. This figure demonstrates that SP requires an absorption enhancer to increase its bioavailability. Moreover, it demonstrates that the absorption enhancers' supply must be synchronized with drug input in the lumen, since CI-0 also contains SD. Once formulation S-1 was completely eroded (designed to do so within 1 h), SP absorption stopped. The $AUC_{0-6}$ of SP after S-1 administration was two-fold larger than the $AUC_{0-6}$ after CI-0 administration. SP Cmax was 21.5 mcg/ml after 1 hour for S-1 and 9.4 mcg/ml after 1 hour for CI-0 (Table 2).

Similar observations were obtained for those formulations that were designed to erode more slowly. Figure 6 demonstrates that SP requires a constant supply of SD for its intestinal absorption. The $AUC_{0-6}$ values were 3-fold higher after S-2 administration compared with C-2 administration. The corresponding Cmax values were 9.0 and 3.9 mcg/ml for S-2 and C-2, respectively. As for the less erodible formulations, the $AUC_{0-6}$ values were two-fold higher after S-4 administration compared with C-4 administration. The corresponding Cmax values were 4.5 and 2.2 mcg/ml for S-4 and C-4, respectively (Table 2). SP plasma levels after the administration of the nonsynchronous formulations (NS-2 and NS-4) were low and close to those obtained after the administration of the formulations without SD (C-2 and C-4). The corresponding Cmax were 3.1 and 1.4 mcg/ml for NS-2 and NS-4, respectively.

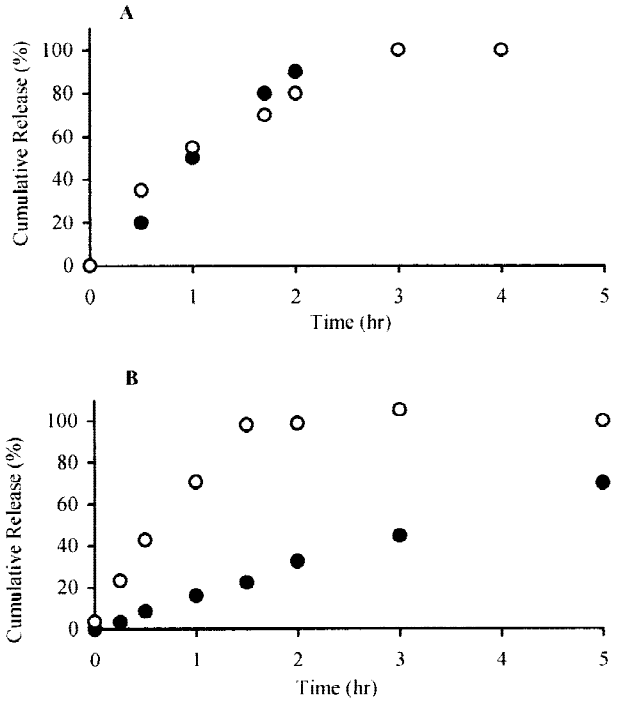


**Fig. 3.** The *in vitro* release kinetics of SP (filled circles) and SD (open circles) from the synchronous formulation S-2 (A) and the nonsynchronous formulation NS-2 (B). Shown are the mean values of 3 studies.

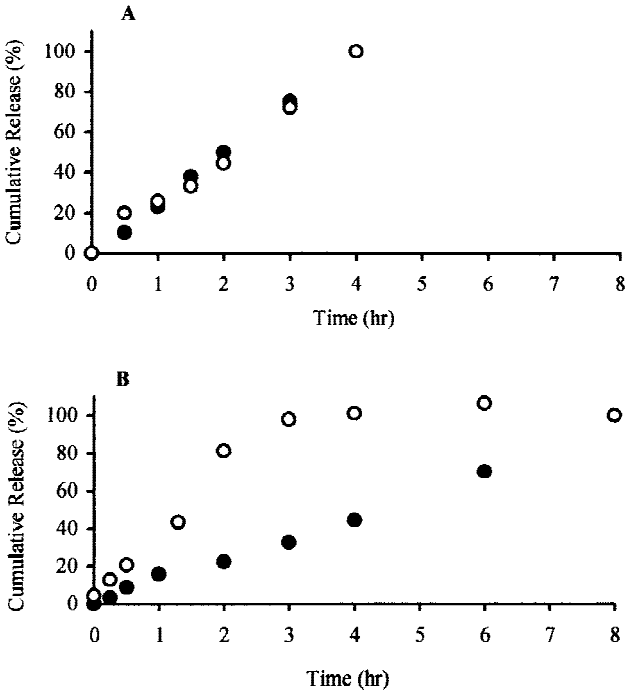


**Fig. 4.** The *in vitro* release kinetics of SP (filled circles) and SD (open circles) from the synchronous formulation S-4 (A) and the nonsynchronous formulation NS-4 (B). Shown are the mean values of 3 studies.

## DISCUSSION

In this study we have demonstrated that the intestinal absorption of the poorly water-soluble and poorly absorbed drug, SP, can be enhanced if formulated, together with SD,

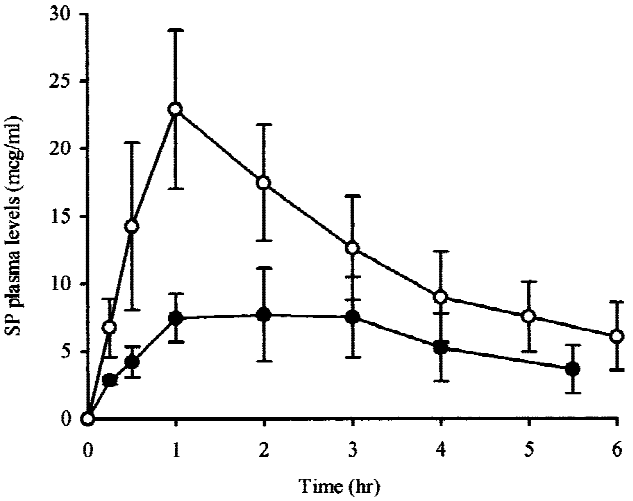


**Fig. 5.** Plasma levels of SP after intra-intestinal administration of formulations S-1 (open circles) and CI-0 (closed circles) in the rat. Shown are the mean values of 4 studies ± S.E.M.

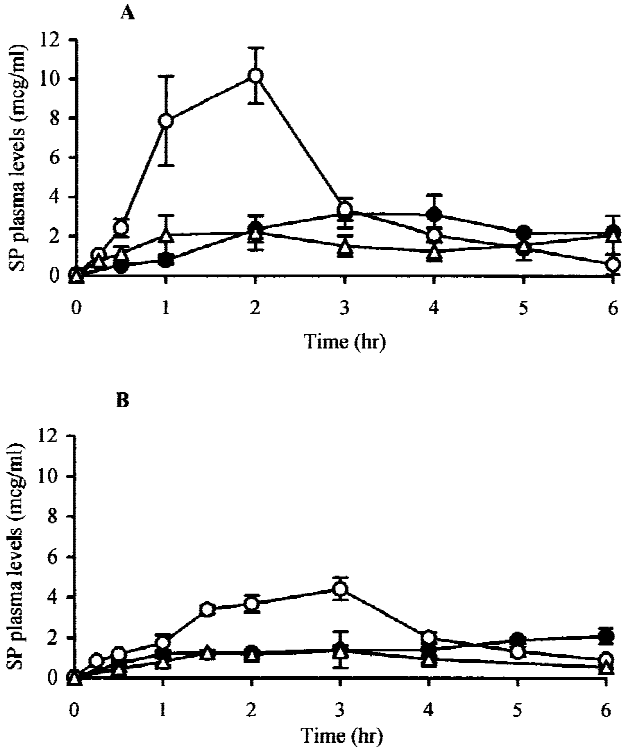


**Fig. 6.** Plasma levels of SP after intra-intestinal administration of (A) S-2 (open circles), C-2 (closed circles) and the nonsynchronous formulation NS-2 (open triangles) and (B) S-4 (open circles), C-4 (closed circles) and the nonsynchronous formulation NS-4 (open triangles). Shown are the mean values of 4 studies ± S.E.M.

into a drug platform which is capable of synchronizing their release rates. SD induces tight junctions opening in the intestinal epithelium by activating phospholipase C which, in turn, causes calcium release from intracellular stores (15,17). Yet, its most important property in the context of this study is its rapid onset and short residual effect (10,14). This property contributes to the safety of SD. It also makes it possible to illustrate, experimentally, the need for a concomitant delivery in the intestine for the purpose of absorption enhancement. Van Hoogdalem and co-workers have already shown that under closed compartment conditions (rectum) the enhancement of sodium cefazoline absorption, caused by medium chain glyceride preparation is improved when the administration is slow (18). That is, the rate of delivery is as important as the concentration and residence time of the enhancer used (19). Prolonged residence time of PVA spheres in the lower intestine, and the synchronous release of insulin and protease inhibitors from those spheres were suggested as an explanation for the improved bioavailability of insulin administered (20). We showed that in long jejunal segments (open compartment), the exposure time of the mucosa to SD is even more important than the enhancer's concentration, because of its rapid on (2 min)–off (15 min) effect (10,21). The above findings bring into question whether an oral delivery system, capable of placing discrete amounts of absorption enhancer and poorly absorbed drug along the intestinal lumen is attainable and whether it will improve oral absorption. The findings of this study suggest that erodible matrices could serve that purpose over a predetermined time slot (the linear phase of the erosion process). The matrices used were made of physical mixtures of HPMC, mannitol, SD (highly water-soluble) and SP (poor water-soluble). Based on the hydrophobicity and hydrophilicty of the various components, they were designed to release both SD and SP at similar rates (synchronous release) over 1, 2, or 4 hours. Prolongation of the erosion was obtained by increasing the relative amount of HPMC in the matrices (Table 1). Four hours is a typical value for overall small intestine transit time in man. Since the release of SD was governed by diffusion and the matrice's erosion-governed SP release, the overall release kinetics was dictated by the matrices' erosion. More specifically, the overall kinetics was probably governed by the distance between the diffusion and erosion fronts, as was shown by Colombo and Peppas for three different drug probes when analyzed separately for their release kinetics from matrices made of the more soluble polymer PVA (22). Synchronized release of drugs with different water solubilities can also be accomplished by different polymer combinations such as by polycarbophil and Eudragit RL-100, as has been shown previously (23).

**Table 2.** Area Under the Curves of SP Blood Concentration versus Time Plots During the First Six Hours ($AUC_{0-6}$) Following Intestinal Administration of Synchronous and Nonsynchronous Formulations to the Rat, and the Derived Absolute Bioavailability Values (F). Shown are the Mean Values of 4 Studies ± SEM

| Formulation | Tmax (hr) | Cmax (mcg $ml^{-1}$) | $AUC_{0-6}$ (mcg $ml^{-1}$ $hr^{-1}$) | F[a] (%) |
|---|---|---|---|---|
| S-4 | 2.7 ± 0.4 | 4.5 ± 0.5 | 12.6 ± 1.1 | 7.8 ± 0.7* |
| C-4 | 3.7 ± 1.4 | 2.2 ± 0.5 | 8.2 ± 1.7 | 5.1 ± 1.0 |
| NS-4 | 2.5 ± 1.5 | 1.4 ± 0.2 | 9.1 ± 2.3 | 5.7 ± 1.5 |
| S-2 | 1.7 ± 0.4 | 9.0 ± 0.5 | 25.8 ± 3.7 | 16.0 ± 2.3** |
| C-2 | 3.0 ± 1.0 | 3.9 ± 0.7 | 10.6 ± 2.4 | 6.6 ± 1.5 |
| NS-2 | 2.7 ± 1.5 | 3.1 ± 0.4 | 13.9 ± 5.5 | 10.8 ± 3.4 |
| S-1 | 1.2 ± 0.3 | 21.5 ± 10.3 | 73.3 ± 13.5 | 45.8 ± 8.0*** |
| CI-0 | 1.7 ± 0.4 | 9.4 ± 2.7 | 31.9 ± 11.1 | 19.8 ± 6.9 |

[a] F was calculated after intravenous administration of 0.18 mg/200 g rat body weight of SP. At this dose the $AUC_{0-6}$ was found to be 1.8 ± 0.3 mcg $ml^{-1}$ $hr^{-1}$.

* $P < 0.05$ compared with C-4 and compared with NS-4.

** $P < 0.05$ compared with C-2 and compared with NS-2.

*** $P < 0.05$ compared with CI-0.

To emphasize the importance of synchronous release on absorption enhancement, we also prepared nonsynchronous double layer control matrices (formulations NS-2 and NS-4, Table 1). These double-layer tablets contained, in each layer, either SD or SP. They differed from the synchronous release formulations (S-1, S-2, and S-4, Table 1) by their inability to cause a concomitant release of SP and SD. They were layered into single units to allow the release of SD and SP to start at the same time in the intestine of the rat, which was used in the *in vivo* section of the study. Indeed, it was found that formulations NS-2 and NS-4 were unable to increase SP absorption (Figure 6), probably because SD was released earlier in the rat bowel, while SP was released much later, when SD was no longer available for enhancement (24).

The erosion properties of the synchronous tablets were also measured *in vivo* directly in the intestine of the anesthetized rat. The tablets were administered to the rat intestine in order to account for the net intestinal transit time. The direct measurements verified the linear nature of the erosion kinet-

ics (Figure 1). In these studies, the distance of the tablets from the site of administration was also measured. It was found that the distance the tablets passed was proportional to their erosion properties. The faster erosion observed the longer distance the tablets passed while being eroded (data not shown). The large distance the fast eroding tablets (S-1, see Table 2) passed in the intestine could explain the observation that the larger improvement in SP bioavailability was accomplished with these types of tablets. Because it has already been reported that SP is best absorbed in the upper part of the intestine of the rabbit (12), the results obtained for formulations S-1 and CI-0 should be discussed separately. The F value obtained for the immediate release formulation CI-0 verifies the findings of Kohri and co-workers. The high F values obtained for S-1 can then be explained by a combinatory effect: the relative fast release in the upper intestine of the rat together with the concomitant fast spreading over large surface area of the intestine due to rapid transit of this specific formulation.

The simultaneous release of two probes from a single dosage form is important for dosage forms undergoing significant stirring and erosion. However, while this is true for the gastrointestinal tract of a model animal such as the dog, this may not be the case for humans as was indicated by Katori and coworkers, who reported that in man, the hydrodynamic flow around a dosage form could be much slower (25).

The observation that synchronized release of an absorption enhancer is important for SP oral availability was mentioned by Kohri and coworkers who used sodium oleate together with SP in enteric-coated capsules. However, while able to demonstrate a concomitant release of sodium oleate and SP at pH 6.8, the authors failed to use a proper oral formulation. The enteric coating capsule used by them resulted in colonic absorption of the drug, probably because of its ability to arrive at the colon of the rabbit (being protected by the coat) and release SP together with the enhancer in that location for a prolonged time (12). The erodible system suggested in our study enables a synchronized release of SP and SD in the small intestine, which allows improved bioavailability of SP. This simple formulative approach may be useful for other drug molecules and absorption adjuvants that are currently under study in our laboratory.

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