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Press-coated tablets for the sequential pulsed administration of two different drugs

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Summary

The most common risk connected with non-steroidal anti-inflammatory drugs (NSAIDs) oral administration is represented by their local irritation effects on the mucosa of the gastro-intestinal tract. To prevent NSAID-induced mucosal lesions and ulcer formation or exacerbation a new dosage form was designed for the administration in sequential pulses of a mucosal protective agent firstly and then NSAID. The active substances are formulated in a press-coated tablet in which the inner core contains sodium diclofenac and the outer shell sucralfate. The shell composition includes rapidly disintegrating agents for the prompt release of the mucosal protective agent. Diclofenac release from the core starts only when the outer layer has completely disintegrated. In vitro release of the anti-inflammatory drug is not influenced by the sucralfate delivery impulse. Preliminary in vivo studies confirm that the presence of sucralfate does not prevent diclofenac absorption from the GI tract.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) include a wide variety of active substances often characterized by similar mechanisms of action and, consequently, similar side effects. The most common risk connected with NSAIDs oral administration is represented by their local irritation effect on the gastro-intestinal mucosa (Rainsford et al., 1988; Altman et al., 1990). This risk is particularly high when the drug elimination half-life is low, and repeated daily administrations are needed to maintain therapeutic plasma levels.

In the treatment of rheumatic disease, peptic ulceration associated with NSAIDs therapy can be a serious problem and sometimes limits the usefulness of these agents mainly in the cronic treatment of this disease. For this reason, some protective agents for the prevention of NSAIDs induced gastro-duodenal mucosal injury have been evaluated (Stiel et al., 1986). In particular sucralfate, a well-known and effective agent for the treatment of gastro-duodenal ulcer disease, has a protective effect on the gastric mucosa when administered before the drug with gastrolesive properties (Maclaurin et al., 1985; Kounterek et al., 1986; Stern et al., 1987). In these

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studies the two drugs are administered separately, in different dosage forms and a time interval occurs between sucralfate and NSAID administration. However, the evaluation of a potential interaction between sucralfate and NSAID, from both a pharmaceutical and biopharmaceutical point of view, remains a prerequisite for the application of this useful association (Lau et al., 1986).

In this paper, as a further development of previous works (Italian Patent, 1983; European Patent, 1987), a new device is proposed and described for the administration in a single dosage form of two different drugs. The unit is prepared by a double-compression technique. The tablet consists of a center core containing sodium diclofenac which is coated by a sucralfate shell. The system is able to deliver in sequential pulses firstly sucralfate, and then NSAID.

Sodium diclofenac was chosen as the NSAID model drug. It has analgesic, antipyretic and anti-inflammatory properties and is generally used in the treatment of rheumatic and other inflammatory disorders. The drug is absorbed from the gastro-intestinal tract and is subject to hepatic first-pass effect. After ingestion of enteric coated tablets, peak plasma concentrations occur about 1–4 h after administration; the plasma half-life is about 1–2 h; for this reason, the usual oral dosage, 75–150 mg daily, is administered into divided doses. Even if diclofenac is well tolerated the most recurrent side effects are gastro-intestinal disturbances (Todd and Sorkin, 1988).

Sucralfate is a basic aluminium salt of sucrose octasulphate. In vitro, aluminium hydroxide ions dissociate in acid leaving negatively charged molecules of sucrose octasulphate which polymerize into a viscous paste, which is the active form of the drug. The negatively charged molecules of paste then bind to positively charged protein, mucosa and white cells in the ulcer base. This adherent complex may be a barrier against acid, pepsin and bile salts (Brogden et al., 1984). The drug has no systemic effects in man because of the very poor absorption.

In the dosage form proposed the sucralfate dose can exert its protective and healing properties because it is promptly and completely delivered from the system just before the NSAID release begins. For this reason the active substances are formulated in a press-coated tablet in which the inner core contains sodium diclofenac and the outer shell a sucralfate dose (Fig. 1). The shell composition includes rapidly disintegrating agents that, in contact with aqueous fluids, result in the prompt disintegration of the outer layer (which contains sucralfate). Only when the core is completely cleared of the shell does the release of the second drug commence (Fig. 1). The core, on the other side, can be formulated in order to exhibit different extents of release, ranging from few minutes to some hours (prolonged or modified release formulations).

The advantage of the new therapeutic devices consists of a single dosage form comprising the two drugs and also a built-in administration pro-

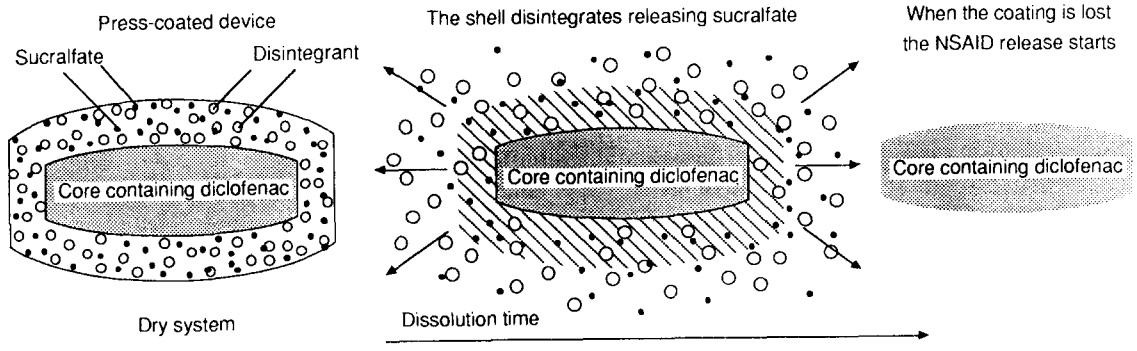

Fig. 1. Schematic representation of the behaviour of the sucralfate-coated device.

gramme in sequential pulses. In fact, the interaction between the drug delivered by the core with the gastro-intestinal (GI) environment can start only when the outer layer has completely disintegrated.

A preliminary in vivo study was carried out to verify whether the presence of sucralfate that forms a protective lining on the gastric and duodenal mucosa could prevent diclofenac absorption from the GI tract.

Experimental

Materials

The active ingredients and the excipients used were: sucralfate (D.R., Milan, Italy), sodium diclofenac (Secifarma, Milan, Italy), sodium starch glycolate (Explotab®, E. Mendell Co. Inc., Carmel, NY, U.S.A.), polyvinylpirrolydone (Plasdone® K29-32, Gaf Corp., Wayne, NY, U.S.A.), hydroxypropylmethylcellulose (Methocel® K4M and Methocel® E5, Colorcon, Orpington, U.K.), Aluminum lake red (E120, Colorcon, Orpington, U.K.), colloidal silicon dioxide (Syloid® 244, Grace Gmbh, Worms, Germany); corn starch, talc and magnesium stearate, all of USP grade, were supplied by C. Erba, Milan, Italy.

Methods

Two different diclofenac formulations were tested: the first, D1, is designed as a rapidly erodible core while the second, D2, is intended to be a sustained release formulation characterized by a slower delivery pattern. D1 and D2 core compositions are reported in Table 1.

TABLE 1

Core compositions (mg)

	D1	D2
Sodium diclofenac	50.0	50.0
Corn starch	25.0	25.0
Hydroxypropylmethylcellulose	15.0 [a]	25.0 [b]
Polyvinylpirrolydone	3.0	3.0
Magnesium stearate	1.0	1.0
Colloidal silicon dioxide	0.5	0.5

[a] Methocel® E5.
[b] Methocel® K4M.

TABLE 2

Shell compositions (mg)

	S1	S2
Sucralfate	200.0	300.0
Corn starch	100.0	150.0
Sodium starch glycolate	25.0	37.5
Polyvinylpirrolydone	15.0	22.5
Aluminum lake red	0.1	0.1
Talc	4.0	6.0
Magnesium stearate	2.0	3.0

For the preparation of both granulates, the same procedure was employed: sodium diclofenac, hydroxypropylmethylcellulose and corn starch were mixed (Erweka LK5, Heusenstamm, Germany) for 20 min and then wetted with a 10% (w/v) solution of polyvinylpirrolydone in ethanol. The wetted mass was forced through a 710 μm screen. The granules obtained were dried in a circulating air oven and calibrated through a 420 μm screen. Magnesium stearate and colloidal silicon dioxide were added to the granules and mixed for 15 min in a Turbula apparatus (type T2A, Basel, Switzerland).

The shell compositions are reported in Table 2 Two coating thicknesses were tested, S1 and S2 containing, respectively, 200 or 300 mg of sucralfate.

For the preparation of the shell granulate, sucralfate and corn starch were wetted with a 10% (w/v) solution of polyvinylpirrolydone in ethanol. The wetted mass was forced through a 710 μm screen, the granules being dried and calibrated through the same screen. The extragranular disintegrant, sodium starch glycolate, was added to the dry granules at the end of the preparation with talc and magnesium stearate and mixed in the Turbula apparatus for 15 min.

To produce the press-coated devices (Fig. 1) a suitable equipment (Dry-Cota, Manesty, Liverpool, U.K.) is used. In this machinery two rotary-presses are coupled: the first one produces the cores, and a connecting device transfers and places the cores in the dies of the second press that provides for the dry coating of the tablets.

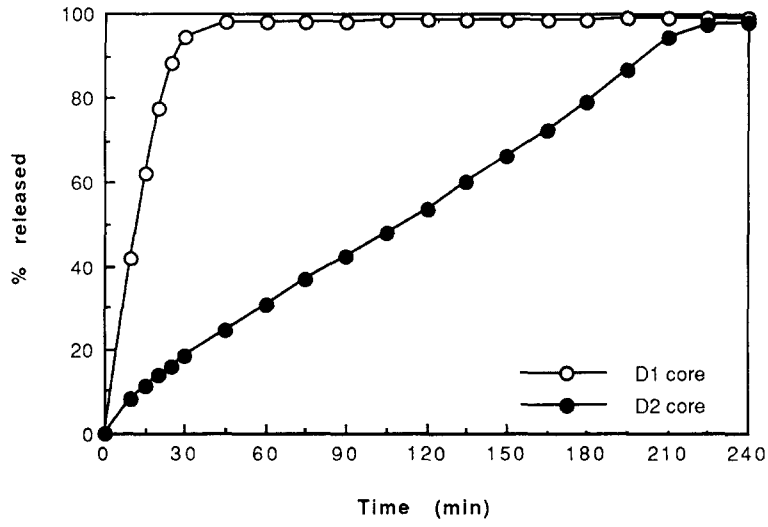

Fig. 2. Dissolution profiles of the D1 (fast release) and D2 (slow release) uncoated cores.

Concave punches of 8 mm in diameter (curvature radius = 10.0 mm) were used for the preparation of the cores, while 12 mm concave punches (curvature radius = 10.0 mm) produced the final coated devices.

For each core composition, D1 and D2, two batches of coated tablets were prepared with, respectively, 200 or 300 mg of sucralfate in the shell.

In vitro test

In order to verify whether the presence of the sucralfate shell interferes with NSAID release from the core, the in vitro release behaviour of the devices was tested on both the uncoated cores and press-coated systems. The tests were carried out in 1 l of distilled water, at 37°C, using the dissolution test apparatus 1, basket (USP XXII), 100 rpm, six replicates. Diclofenac release was

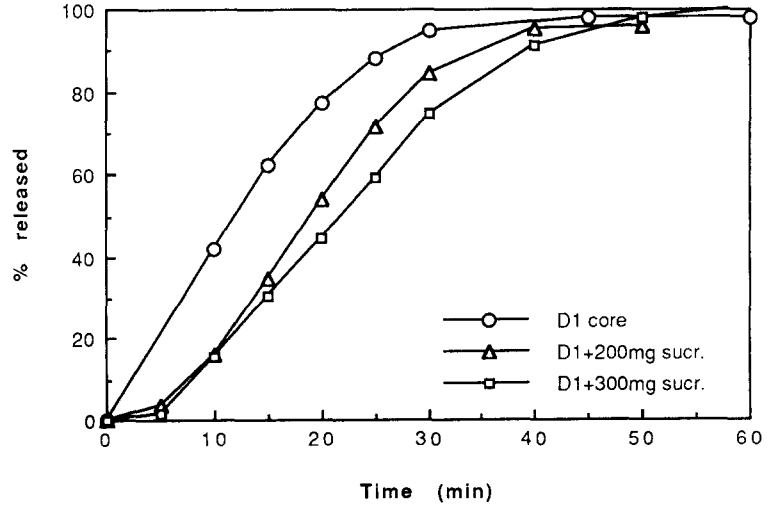

Fig. 3. Comparison of the diclofenac release profiles from the D1 uncoated cores (fast release) and from the press-coated devices containing 200 or 300 mg of sucralfate.

spectrophotometrically determined at 276 nm (Spectracomp 602, Advanced Products srl, Milan, Italy) and a personal computer, connected on-line, provided for data recording and treatment.

The amount of sucralfate delivered by the system (the active substance is insoluble in the dissolution medium) was measured by a HPLC system (Perkin-Elmer-10, Beaconsfield, U.K.) equipped with a refractive index detector (Perkin-Elmer LC-30) according to the procedure described in the Pharmacopoeial Forum (1992).

In vivo test

The preliminary in vivo study involved four unfasted and informed healthy volunteers. The study was carried out under medical supervision.

Blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8 and 12 h after the administration of the D1/S1 press-coated device; the diclofenac concentration was determined using a HPLC method (Blagbrough et al., 1992).

Results and Discussion

In vitro

In Fig. 2 the release profiles of the uncoated diclofenac cores of the two formulations are compared. The cores of the rapid release formulation (D1) deliver the dose in 30–40 min, while the cores designed as a sustained release formulation (D2) predictably show a more prolonged delivery pattern and zero-order kinetics is closely approached: the total drug content is released in 4 h.

The sucralfate shells of the dry-coated devices disintegrate within a few minutes, after immersion in the dissolution medium, and the sucralfate is released in less than 5 min. The presence of the coating does not significantly alter the core dissolution profiles of both formulations D1 (Fig. 3) and D2 (Fig. 4).

During dissolution the press-coated tablets show only a slight delay at the beginning of diclofenac release: a few minutes are needed for the complete disintegration of the coating, whether the thicker or thinner shell is applied (200 or 300 mg of sucralfate).

In vivo

The preliminary in vivo study was carried out to verify whether the presence of sucralfate could alter the absorption rate or bioavailability of diclofenac. The 1D/S1 formulation was chosen for this evaluation since, by providing rapid release of diclofenac, drug absorption is less influenced

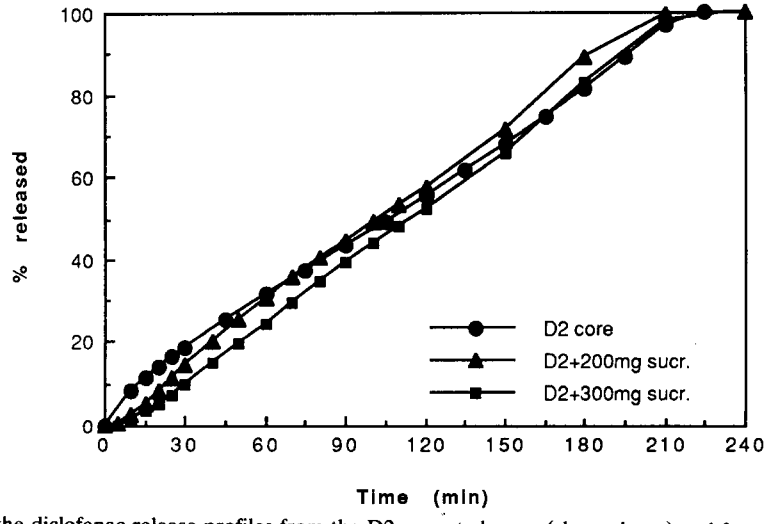

Fig. 4. Comparison of the diclofenac release profiles from the D2 uncoated cores (slow release) and from the press-coated devices containing 200 or 300 mg of sucralfate.

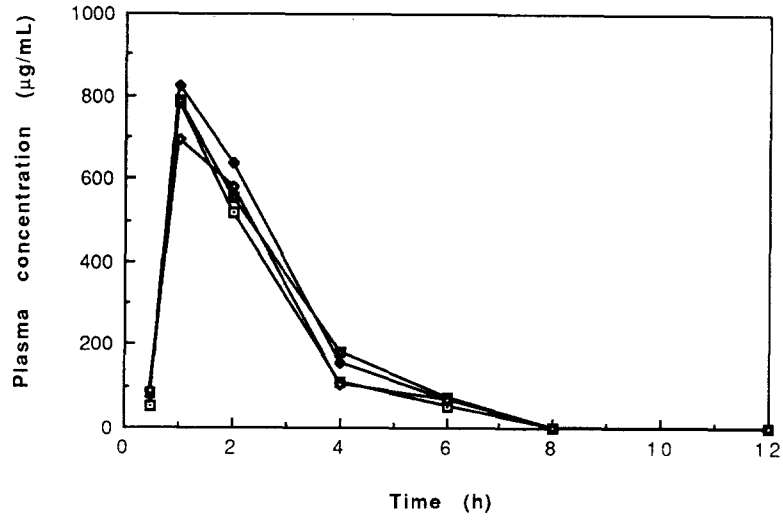

Fig. 5. Plasma concentration-time profiles of four subjects after administration of the sucralfate-coated diclofenac dosage form D1/S1.

by the release pattern from the dosage form and a potential interaction with sucralfate could readily be detected.

The concentration-time profiles obtained after the administration of the sucralfate-coated devices to the four subjects involved in the study are reported in Fig. 5.

Bearing in mind that diclofenac release from the D1/S1 dosage form is completed in about 40 min, the drug appears to be rapidly and readily adsorbed by the GI tract. The reproducibility of the results obtained is excellent. The mean plasma levels (±S.D.) vs time are reported in Fig. 6.

The tolerability was positive: no adverse reac-

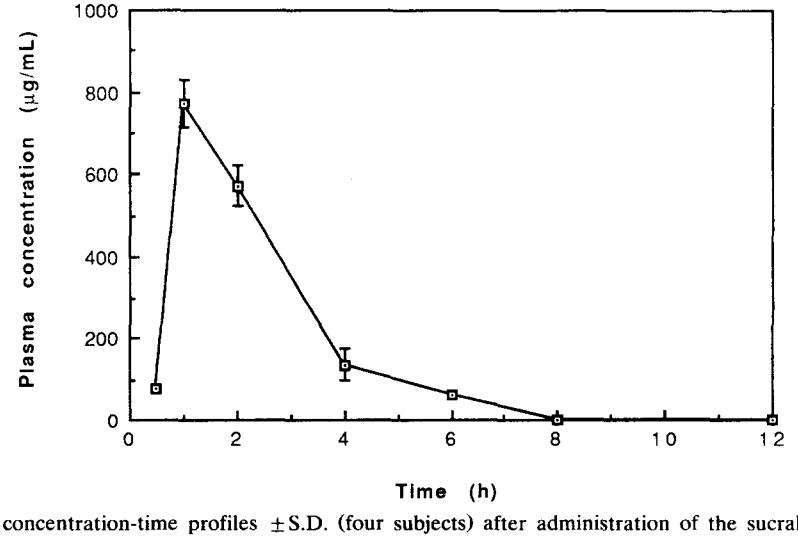

Fig. 6. Mean plasma concentration-time profiles ±S.D. (four subjects) after administration of the sucralfate-coated diclofenac dosage form D1/S1.

tions or any kind of disturbance (mainly gastric desease) ascribed to the active ingredients administered were reported by any of the subjects treated.

These results are in accordance with a study carried out by Feletti et al. (1991), who compared a similar press-coated device, containing 50 mg of ketoprofen in the core (fast release) and 200 mg of sucralfate in the shell, to a conventional formulation containing only ketoprofen (same dosage). 15 subjects were involved in the study in a cross-over evaluation. The results showed that the presence of sucralfate caused a short delay in ketoprofen absorption, however, the delay was also detectable in the elimination constant. In spite of this short delay in the peak plasma appearance, total ketoprofen bioavailability was not significantly different from that of the reference dosage form.

Conclusions

The presence of the sucralfate shells in the dry-coated devices does not appear to modify the dissolution patterns of the two diclofenac formulations tested. Only a short time lag can be detected in both in vitro diclofenac release and in vivo drug absorption.

The results obtained from the preliminary in vivo study confirm that diclofenac absorption is not prevented by the concomitant administration of sucralfate.

The new delivery system for the administration of drugs in sequential pulses appears effective and versatile; in particular, it can be advantageously employed to prevent gastro-intestinal adverse effects when a chronic therapy with non-steroidal anti-inflammatory drugs is required.

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