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A NEW IBUPROFEN PULSED RELEASE ORAL DOSAGE FORM

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ABSTRACT

Drug constant release is not always the desired solution for controlled drug administration; some therapeutic situations require consecutive pulses of active principle.

A biphasic oral delivery system able to release an immediate dose of therapeutic agent as well as a further pulse of drug after some hours could be interesting.

In order to obtain such desired releasing performances, a new system (three layer tablet) has been designed with the following characteristics:

- an energy source, able to deliver the two divided doses of drug

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- a control element, between the drug layers, able to delay the release of the second dose of drug. This control element acts as a barrier and is made with a mixture of water swellable polymers
- an outer film, which is made of water impermeable polymer, that covers the second dose of drug and the barrier.

The new system works through subsequent interactions with aqueous fluids of the three different layers of material in the following order:

1 - rapid interaction of the uncoated part of the system, and immediate disintegration of the first dose;
2 - slow interaction of the barrier and its gelation;
3 - interaction of the second drug layer and development of a force able to break the barrier thus promoting the release of the second dose of drug.

Preliminary *in vivo* experiments carried out on this biphasic pulsed release device containing Ibuprofen as a model drug, show two distinct peaks in plasma profiles thus indicating that the *in vitro* results are in good agreement with the *in vivo* blood levels.

INTRODUCTION

Some new oral drug delivery systems based on the powder compression techniques have been prepared in the past years by our group, namely :

i - a "reservoir" system consisting of a core containing the active principle and an external compressed polymeric layer (1,2).
ii - a multiple unit "hybrid" reservoir system consisting of minimatrices, whose drug release modulation is governed by the swellable properties of the polymeric core and by the thickness of the outer

permeable membrane obtained by surface cross-linking or by spray-coating (3,4,5,6).

iii - an *in vitro* programmable system, a matrix with a constant releasing area, which is the main control element of the drug release. In this system the kinetics of the release is also dependent on the swelling and dissolution characteristics of the polymeric material; the influence of the solubility of the active principle is also reduced (7,8).

A further development of this system has been the preparation of drug delivery systems whereby the releasing area exposed to the dissolution has been reduced by an impermeable partial coating. In this way the kinetics of release approximating zero order was achieved (9,10).

Frequently, the constant release of a drug from pharmaceutical dosage forms enables one to obtain a suitable pharmacological and therapeutic response. However, for therapy of certain pathologies i.e. some heart and rheumatic diseases, or in the utilization of some drugs like contraceptive steroids and antibiotics, it would be more useful to obtain different plasma levels of active principle at different times related to the painful symptoms, or circadian rhythms, etc.. . In these cases the desired therapeutic results can be usually obtained with frequent administration of conventional dosage forms which lead to a prompt absorption of the active principle. This kind of drug treatment is often compromised by lack of full compliance by the patient. Till now there are few systems that allow the release of the active principle in successive pulses at precise and well-controlled time periods (11,12).

Taking all these considerations into account, the aim of this work was to design and prepare a new pulsed release oral drug delivery system,

capable of releasing an immediate dose of drug as well as a further dose after some hours.

To obtain such a pulsed release pattern, a system based on a three-layer tablet with the following characteristics has been designed:

- two layers each containing a dose of the drug,
- an intermediate layer acting as a control element, which separates the drug layers. This control element, made by a mixture of water- swellable polymers, would act as a barrier in order to delay the release of the dose of the drug present in the second layer,
- an outer film made of an impermeable polymer (container), which coats the barrier and the second dose of the drug.
- an energy source, based on a fast swelling polymer, able to promote the delivery of the two doses of the drug.

Therefore, we prepared and tested cylindric compressed three-layer tablets, covered on all surfaces, except one part of the first dose, with an impermeable coating. We employed Ibuprofen as a model drug, hydroxypropylmethylcelluloses as components of the control barrier and some *superdisintegrants* as energy source (13).

The feasibility, the *in vitro* release profiles and the *in vivo* preliminary results of some of these systems are described and discussed.

EXPERIMENTAL

Materials and methods

- Ibuprofen (USP XXI grade - Francis, Milano, I),
- corn starch (USP XXI grade - C. Erba, Milano, I)
- methylcellulose (500-600 cps - BDH, Poole, UK)
- ethylcellulose (22 cps - BDH, Poole, UK)

- mannitol (USP XXI grade - C. Erba, Milano, I)
- talc (USP XXI grade - C. Erba, Milano, I)
- hydroxypropylmethylcellulose (Methocel K4M and Methocel K15M- Colorcon, Orpington, UK)
- polyvinylpyrrolidone (Plasdone K 29-32- GAF Corp., New York, USA)
- magnesium stearate (USP XXI grade - C. Erba, Milano, I)
- sodium starch glycolate (Primojel® -Avebe,Foxhol, The Netherlands)
- cross-linked polyvinylpyrrolidone (PolyplasdoneXL®-GAF Corp., New York, USA)
- castor oil (USP XXI grade - C. Erba, Milano, I)
- FD & C lake Yellow 6 (Eigenmann & Veronelli S.p.A. , Milano, I)

a) Preparation of Ibuprofen granulate (granulate A).

830 g of Ibuprofen and 170 g of corn starch were mixed (Erweka LK 5-Heusenstamm, FRG) and the resulting mixture was wetted with 200 ml of a 2.5% w/v methylcellulose aqueous solution. The wet mixture was forced through an 800 µm screen to obtain a granulate which, after partial drying at 40°C in an air circulating oven, was forced through a 420 µm screen.The dried granulate was then mixed in a Turbula apparatus (type T2A - Basel, CH) with corn starch (2%), sodium starch glycolate (2%), cross-linked polyvinylpyrrolidone (2%) and magnesium stearate (0.5%), to obtain the granulate A.

b) Preparation of barrier granulate (granulate B)

150 g of Methocel K15M , 50 g of Methocel K4M , 400 g of mannitol , 280 g of talc and 10 g of Yellow 6 lake were kneaded with 200 ml of a 10% w/v polyvinylpyrrolidone alcoholic solution and the wet mass was forced through a 420 µm screen.

The granulate was dried at 40°C and then was mixed with magnesium stearate (1%), to obtain the granulate B.

c) Preparation of the three-layer tablets.

The tablets were prepared using a multilayer tablet press having three loading stations (Manesty, Layer-press- Liverpool, U.K.) equipped with a punch set (13 mm diameter); the first and third loading stations were filled with the granulate A, the second one being filled with the granulate B. The die filling was adjusted to fill 400 mg of the granulate A (equivalent to 300 mg of Ibuprofen) from stations 1 and 3 and 100 mg of granulate B from station 2. The compression force of the final tabletting step was about 25 KN.

Operating as described, cylindrical three-layer tablets were prepared, weighing about 900 mg and having two layers of active substance separated by a barrier layer of water swellable polymer mixture (granulate B).

d) Film coating procedure.

A nude three-layer tablet was placed in a specially designed rotating bored holder so that only one of the drug layers was lodged into the holder itself, one portion of the tablet being exposed.

The exposed surface of the tablet (barrier plus the second drug layer) was then coated by spraying a 5% w/v methyl alcohol / dichloromethane 1:1 solution of ethylcellulose in order to obtain a film of thickness 0.20 ± 0.05 mm.

e) *In vitro* disintegration and release tests.

1 . The USP XXI disintegration method was used to control the finished systems; a modified apparatus (4000 ml beaker instead of 1000

ml low-form beaker) was used in order to improve observation of the whole system during the test which otherwise is compromised, during the initial phase, by the large amount of disintegrating particles.

2 . The systems were tested in 4000 ml of pH 7.2 phosphate buffer, at 37°C.

The Ibuprofen concentration was determined spectrophotometrically at 264 nm (SPECTRACOMP 602 - Advanced Products, Milan, I).

This procedure allowed us to determine by means of the same experiment :

i) the disintegration time of the immediate dose,

ii) the dissolution rate of the immediate dose,

iii) the dissolution rate of the remaining dose

and additionally to evaluate the resistance of both the barrier and the container.

f) *In vivo* experiments.

A preliminary study involving two healthy adult volunteers was carried out.

Each subject received a single oral administration of the following dosage forms:

a - conventional marketed plain tablets (300 mg of Ibuprofen),

b - conventional plain tablets prepared with the granulate A (300 mg of Ibuprofen); two preparations from different batches of Ibuprofen, having differing particle size distribution.

c - pulsed release system (2x300 mg of Ibuprofen).

Collection of blood samples (10 ml) was effected over 12 h following dosing. Plasma was separated by centrifugation and stored at -20°C until analyzed. Ibuprofen concentration was determined by HPLC using the method described in (14).

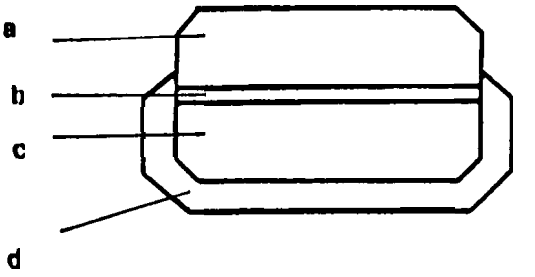

FIG. 1 : schematic representation of the prepared pulsed release system : (a) layer containing the immediately available dose of drug (first dose); (b) barrier of swellable polymeric material; (c) layer containing the second dose of drug, and (d) impermeable film container.

RESULTS AND DISCUSSION

a) Structural characteristics of the systems.

The system prepared is presented in Figure 1.

b) *In vitro* testing.

The system works as follows: upon contact with the dissolution medium, the uncoated layer (a) rapidly disintegrates leaving the remaining part of the system intact. The dissolution medium will then come into contact with the barrier (b) slowly interacting with it. The barrier delays the interaction between the dissolution medium and the second dose layer (c) for a time depending on its composition and thickness.

In fact as a result of medium/polymer interaction, the barrier slowly becomes viscous and its mechanical resistance decreases.

When a sufficient amount of water crosses the barrier, the disintegrants present in the layer (c) swell, thus developing a

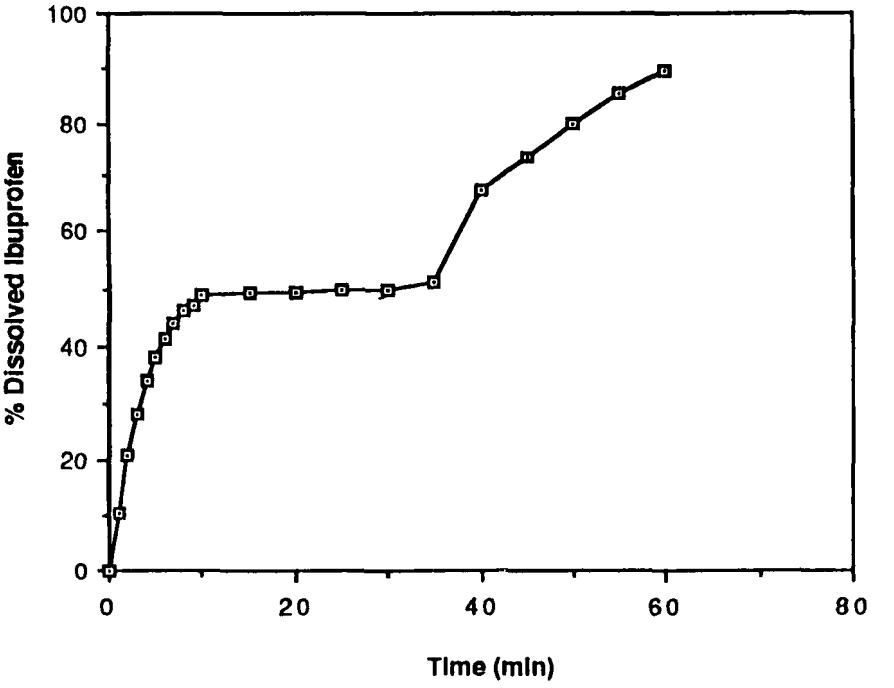

FIG. 2 : Dissolution profile of the system containing the two doses of Ibuprofen (pH 7.2 phosphate buffer,37° C, mean of six replicates)

disintegrating force. The barrier breaks and the disintegration of the third layer containing the second dose of Ibuprofen occurs.

The disintegrating force developed by the two doses of the drug upon contact with aqueous fluids, is the energy source for the delivery of active substance; it has been obtained using the so called *superdisintegrant* excipients (e.g. Poliplasdone XL®, Primojel®).

On *in vitro* testing when the pulsed release system is immersed in the dissolution medium, the following modifications can be observed: a) rapid disintegration of the uncoated part of the system (< 5 minutes) leading to a fast dissolution of the first dose; b) slow gelation of the

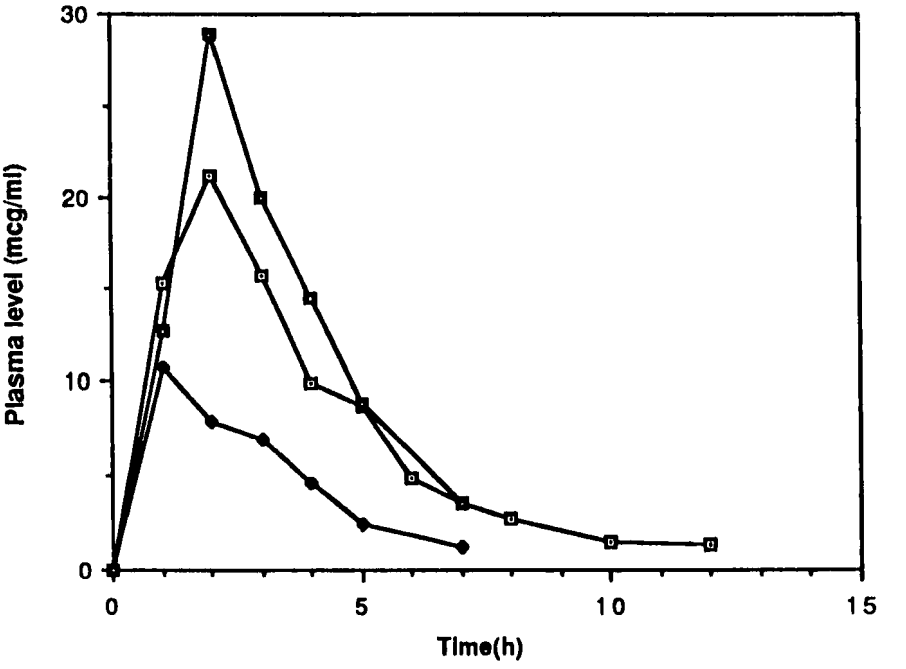

FIG. 3 : Ibuprofen plasma levels following administration of: ⊡ Ibuprofen 300 mg conventional marketed tablets; ◆ Ibuprofen (d_{VS}= 11.5 μm) 300 mg conventional tablets; ■ Ibuprofen (d_{VS} = 5 μm) 300 mg conventional tablets; each curve is the mean of the data from two subjects.

barrier; c) disintegration and dissolution of the second dose of the drug on breaking of the barrier.

Figure 2 shows the dissolution profiles of the system.

The lag-time evident in the dissolution profile of the second dose is determined by the progressive gelation of the intermediate barrier; in addition, since the dissolution medium permeates the barrier very slowly and wets the third layer, the disintegrant efficiency could be reduced thus resulting in a significant decrease of drug dissolution rate.

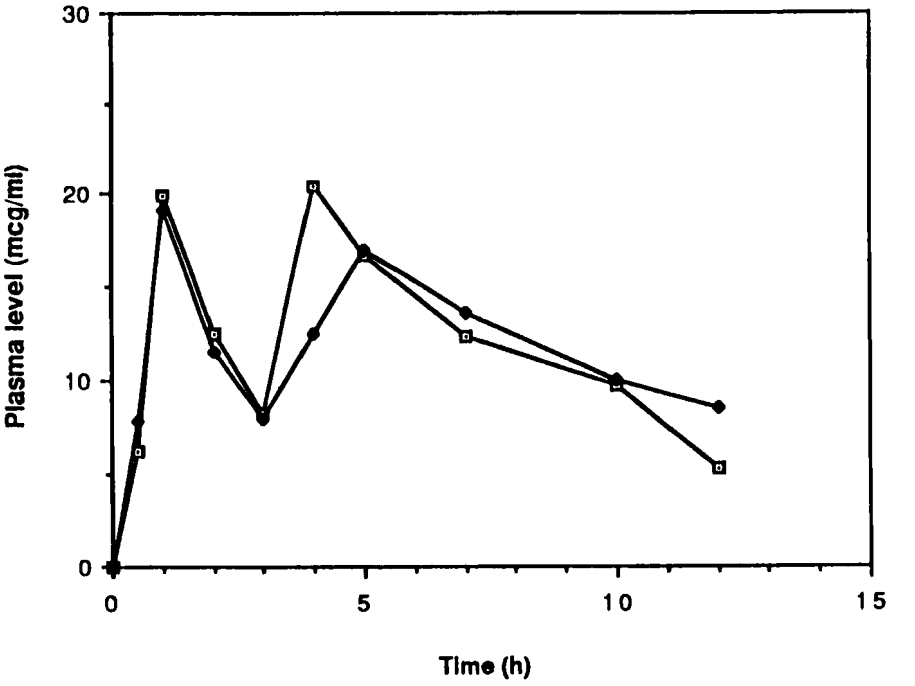

FIG. 4 : Ibuprofen plasma levels following administration of pulsed release system to two subjects. ◻ first subject; ● second subject.

c) *In vivo* experiments.

Preliminary plasma levels obtained in a few subjects in order to verify the dependence of the *in vivo* pattern on the structure of the whole system , on the type, amount and characteristics of the drug and the polymers used are very promising.

Figure 3 shows the plasma profiles obtained after oral administration of two plain tablets of 300 mg of Ibuprofen prepared with two different batches of active principle, having differing particle size distribution (d_{VS} of 11.5 µm and of 5 µm respectively), compared with a conventional marketed Ibuprofen tablet .

The plasma levels are strongly dependent on the specific surface area of the starting Ibuprofen powder.

The difference in bioavailability between the tablets prepared with the differing batches of Ibuprofen are clearly evident despite the fact that their *in vitro* dissolution profiles are pratically superimposed , when tested according to USP XXI Ibuprofen Tablets monograph.

Figure 4 shows an example of the plasma levels after administration of the pulsed release system to two volunteers.

As can be seen from Figure 4, in both cases there are two peaks. The first peak is 20 $\mu g.ml^{-1}$ after about 1hour, and the second is 16-20 $\mu g.ml^{-1}$ after 4.5-5 hours; there is an evident delay in the absorption of the second dose which appears to correlate quite well with the *in vitro* performance of the pulsed system.

CONCLUSIONS

The *in vitro* disintegration and dissolution tests of the pulsed system, obtained with a suitable blend of polymers and appropriate processing, are in good agreement with the *in vivo* blood levels and pattern.

Despite the problems posed by the pharmacokinetic and physico-chemical characteristics of Ibuprofen (small therapeutic window, erratic absorption due to its poor solubility etc...), this pulsed release system results in good separation of the two plasma peaks (indicating there is in fact a delayed release of the second drug dose) at the desired concentrations.

These preliminary results which substantiate the initial hypothesis, show the system to be very promising.

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