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COMMUNICATION

New Controlled-Release Ibuprofen Tablets

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ABSTRACT

Tablets containing two different doses of ibuprofen are realized. The first possesses very fast release kinetics, while the second has slow and linear release kinetics. This allows drug to produce a therapeutic effect quickly and to maintain it for a long time with only one administration unit. Such tablets are obtained by compression of a mixture of two very different kinds of granulates: an ibuprofen-starch granulate and an ibuprofen–Eudragit RS microsphere granulate. Specific proportions of mixtures of them give the described result after compression at particular tablet hardnesses.

INTRODUCTION

Ibuprofen is an analgesic, antipyretic, anti-inflammatory, nonsteroidal drug used very often in the pharmaceutical field. In fact, on the market there are many products from different pharmaceutical manufacturers that contain this drug. Particularly, tablets or (sugar) coated tablets having a dosage of ibuprofen ranging between 200 and 600 mg are more common.

The usual daily dose by mouth is 1.2 to 1.8 g divided in different administrations. The drug is readily absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 1 to 2 hr after ingestion (1). Unfortunately, ibuprofen has a plasma half-life of about 2 hr (1), and this necessitates repeated administration of the same single dose during 24 hr.

Many studies have been undertaken to obtain ibuprofen controlled-release systems, such as tablets (2–5), hard gelatin capsules (6), coated pellets (7), oral suspensions (8–10), and microspheres or microcapsules (11–18).

The aim of this work was to develop a new and versatile process that allows a tablet formulation in which every administration unit contains an ibuprofen fast-release dose (50%) and a prolonged-release second dose. These tablets should enable ibuprofen to reach plasma levels necessary to have a pharmacological response quickly and to maintain those levels constant as long as possible.

To obtain this complex pharmaceutical form requires the formulation of two kinds of granulates: the first with the tendency to speed up ibuprofen release, the second with the tendency to slow down it. So, a mixture of the two granulates was used for tablet preparations.

The second kind of granulate deserves particular attention because it is composed of microspheres of ibuprofen–Eudragit RS.

MATERIALS AND METHODS

Ibuprofen Granulate Preparation

For ibuprofen granulate preparation, 30 ml of a 10% (w/v) hydroxypropyl cellulose (Nuova Astrochimica, Milan, Italy) solution in ethanol-water 50:50 were added to 50 g of ibuprofen (ACRAF, Ancona, Italy). The wet mixture was granulated through a 1-mm grid of an oscillating granulator (Erweka AR 400). The granulate was then dried in an oven at 45°C for 1 hr.

Preparation of the Fast-Release Granulate

Ibuprofen-Starch 2:1 (w/w) Ratio

For the ibuprofen-starch 2:1 (w/w) ratio formulation, 27 ml of a 10% (w/v) hydroxypropyl cellulose solution in ethanol-water 50:50 were added to 40 g of ibuprofen and 20 g of starch (Chimisan, Rome, Italy), previously mixed. The wet mixture was granulated through a 1-mm grid of an oscillating granulator. The granulate was then dried in oven at 45°C for 1 hr.

Ibuprofen-Starch 1:1 (w/w) Ratio

For the ibuprofen-starch 1:1 (w/w) ratio formulation, 20 ml of a 10% (w/v) hydroxypropyl cellulose solution in ethanol-water 50:50 were added to 25 g of ibuprofen and 25 g of starch, previously mixed. The wet mixture was granulated through a 1-mm grid of an oscillating granulator. The granulate was then dried in oven at 45°C for 1 hr.

Preparation of Ibuprofen–Eudragit RS Microspheres

Weight Ratio 2:1

Ibuprofen (25 g) and Eudragit RS 100 (12.5 g) were first dissolved in 60 ml of CH_2Cl_2. This solution was then emulsified using Ultraturrax (IKA Labortechnik, Staufen, Germany) at 12,500 rpm in 600 ml of H_2O containing 2.4 g (0.4%) of tragacanth gum (Nuova Astrochimica, Milan, Italy). This emulsion was stirred at 60°C for 120 min to evaporate the inner organic phase completely. The solid microspheres consequently formed were then filtered under vacuum, resuspended twice in 200 ml H_2O (maintaining the solid under stirring for 5 min), and refiltered.

After this, the wet mass was easily disaggregated in clusters of microspheres, which were partially dried in an oven for 90 min at 45°C and granulated through a 1-mm grid of an oscillating granulator. The granulate was then dried in an oven at 45°C for an additional 90 min.

To recover free-flowing solid microspheres, it was necessary, after the first filtration under vacuum, to resuspend the solid for at least 8–10 times in 200 ml H_2O for 5 min minimum and to refilter each time. After the final filtration, the wet powder of microspheres was dried in an oven at 45°C for 90 min. Figure 1 shows the scheme of the process.

Weight Ratio 1:1

Ibuprofen (25 g) and Eudragit RS 100 (25 g) were first dissolved in 60 ml of CH_2Cl_2. This solution was then emulsified, using Ultraturrax at 12,500 rpm, in 600 ml of H_2O containing 2.4g (0.4%) of tragacanth gum. The rest of the process was the same as that described for the 2:1 weight ratio.

Scanning Electron Microscopy

A Stereoscan 360 electron scanning microscope (Cambridge Instruments Limited) was used to point out morphology and surface structure of the microcapsules obtained with the two different drug-polymer ratios.

Preparation of the Tablets with Only One Granulate

Ibuprofen Tablets

Ibuprofen granulate was compressed (Kilian rotary press) to obtain tablets of 400 mg and 4 or 8 kp hardness.

Ibuprofen-Starch Granulate Tablets

Ibuprofen-starch granulate (ratio 2:1) was compressed to obtain tablets of 4 or 8 kp hardness containing 400 mg of drug. The tablet weight was 600 mg.

Ibuprofen-Starch Granulate Tablets

Ibuprofen–Eudragit RS granulates (ratios 2:1 and 1:1) were compressed to obtain tablets of 4 or 8 kp hard-

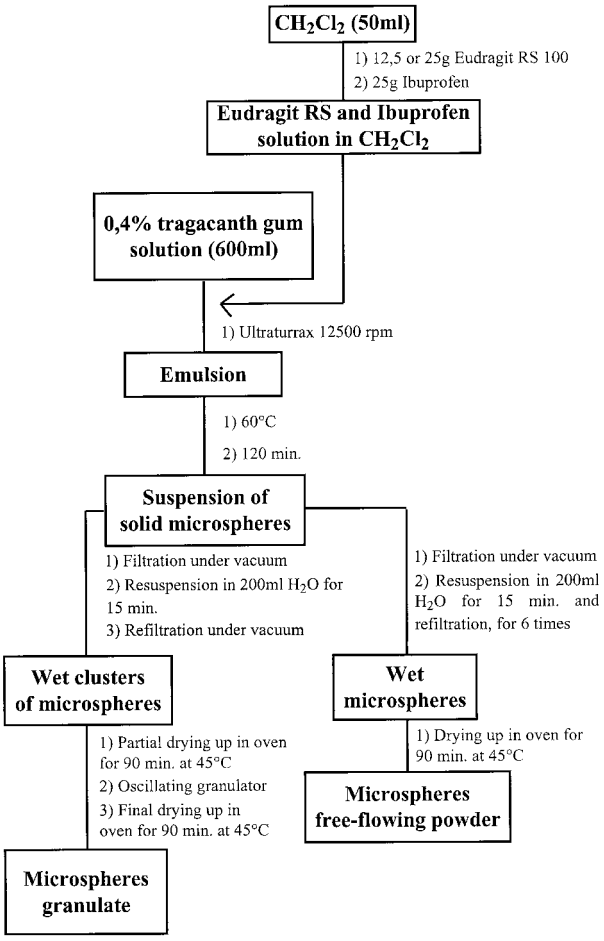

Figure 1. Scheme of the process for microsphere granulate preparation.

ness containing 400 mg of drug. The tablet weights were 600 mg for the 2:1 ratio and 800 mg for the 1:1 ratio.

Preparation of the Tablets with Two Kinds of Granulates

Ibuprofen–Eudragit RS (1:1 Ratio) and Ibuprofen-Starch (1:1 Ratio) Granulate Tablets

Tablets of 4, 6, and 8 kp hardness weighing 800 mg and containing 400 mg of drug were obtained from 50:50, 60:40, and 70:30 mixtures of the two granulates.

Ibuprofen–Eudragit RS (1:1 Ratio) and Ibuprofen-Starch (2:1 Ratio) Granulate Tablets

Tablets were formulated from 50:50, 60:40, and 70:30 mixtures of the two granulates. These tablets of 4, 6, and 8 kp hardness contained 400 mg of drug and weighed 700, 720, or 740 mg, according to the mixing ratio.

Ibuprofen–Eudragit RS (2:1 Ratio) and Ibuprofen-Starch (1:1 Ratio) Granulate Tablets

Tablets were formulated from 50:50, 60:40, and 70:30 mixtures of the two granulates. These tablets of 4, 6, and 8 kp hardness contained 400 mg of drug and weighed 700, 680, or 660 mg, according to the mixing ratio.

Ibuprofen–Eudragit RS (2:1 Ratio) and Ibuprofen-Starch (2:1 Ratio) Granulate Tablets

Tablets of 4, 6, and 8 kp hardness weighing 600 mg and containing 400 mg of drug were obtained from 50:50, 60:40, and 70:30 mixtures of the two granulates.

Ultraviolet Analyses

Granulates

An amount of each granulate corresponding to a theoretical ibuprofen content of 400 mg was crunched in a mortar and put into a 25-ml vessel, successively filled with ethanol, and stirred for 30 min. After filtration (if necessary), 1 ml of this solution was added to another 25-ml vessel, which was then filled with ethanol. Finally, this solution was assayed spectrophotometrically at 272 nm to determine the ibuprofen concentration.

Tablets

A tablet of each series was crunched in a mortar and put into a 25-ml vessel, successively filled with ethanol, and stirred for 30 min. After filtration (if necessary), 1 ml of this solution was added to another 25-ml vessel, which was then filled with ethanol. Finally, this solution was assayed spectrophotometrically at 272 nm to determine the ibuprofen concentration.

Dissolution Studies

The dissolution studies were performed in triplicate with an Erweka DT6 dissolution test in distilled water at 37°C using the paddle method at the rotation speed of 75 rpm (USP XXIII apparatus 2). Each tablet was put into a vessel with 1000 ml of water. At 10-min intervals, 3 ml of water were withdrawn, passed through a 0.45-μm membrane filter (Millipore) and assayed spectrophotometrically with a Cary 1E UV-Vis spectrophotometer

(Varian) at 272 nm to measure the concentration of drug present in the solution. The initial volume of the vessel was maintained by adding 3 ml of distilled water after each sampling.

RESULTS AND DISCUSSION

Ultraviolet Analyses

The ultraviolet (UV) analyses performed on the prepared granulates or tablets in all cases show a 100% drug content according to the theoretical composition.

Scanning Electron Microscopy

Figures 2 and 3 show images of microspheres with ibuprofen–Eudragit RS weight ratios of 2:1 and 1:1, respectively. Microspheres with a lower content of Eudragit RS (100 μm mean diameter) are bigger than the others (30 μm mean diameter). The surface morphologies of the two types of particles are also different. In fact, microspheres of ibuprofen–Eudragit RS at a 2:1 ratio have a spongelike structure with visible drug crystals; microspheres of ibuprofen–Eudragit RS at a 1:1 ratio are less porous, with a surface that is a little more smooth and drug crystals that are less visible.

Drug Release Kinetics

Figure 4 shows dissolution kinetics of the tablets obtained from ibuprofen, ibuprofen-starch granulates, and ibuprofen–Eudragit RS 1:1 (w/w) granulate. The ibuprofen tablets do not disintegrate, but are gradually eroded, so ibuprofen is released gradually, too. For this reason, it cannot be used for the double-dose tablet formulation. In contrast, ibuprofen-starch tablets possess very fast release kinetics.

If starch is substituted with Eudragit RS in the 1:1 (w/w) granulate formulation, drug release from the tablets becomes very gradual, and after 8 hours, only 60% of the ibuprofen dose is released. Also, the release kinetics, except for the first 30 min, is practically linear.

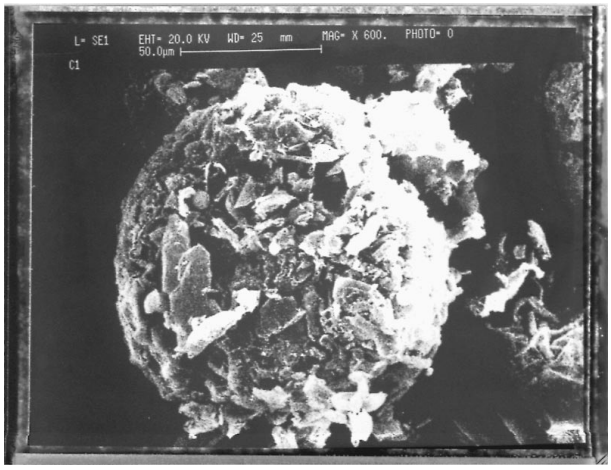

Figure 2. Ibuprofen–Eudragit RS 2:1 (w/w) microspheres (SEM).

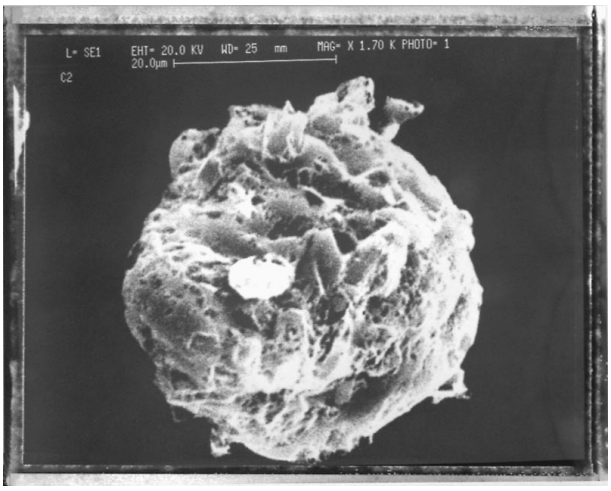

Figure 3. Ibuprofen–Eudragit RS 1:1 (w/w) microspheres (SEM).

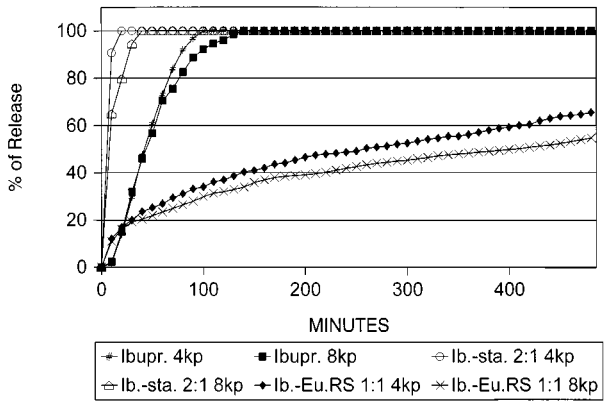

Figure 4. Dissolution curves of ibuprofen, ibuprofen-starch, and ibuprofen–Eudragit RS 1:1 tablets.

Table 1

Drug Release Times T_{50} and T_{80} *of the Tablets Containing the Ibuprofen–Eudragit RS 1:1 Granulate and Ibuprofen-Starch 1:1 or 2:1*

Granulates	Ratio	Hardness (KP)	T_{50} (min.)	T_{80} (min.)
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	4	<5	<10
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	6	<10	60
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	8	10	250
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	60:40	4	<10	15
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	60:40	6	10	40
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	60:40	8	110	>480
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	70:30	4	40	390
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	70:30	6	165	>480
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	50:50	4	15	40
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	50:50	6	20	60
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	50:50	8	40	180
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	60:40	4	20	40
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	60:40	6	40	190
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	60:40	8	110	440
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 2:1	70:30	4	140	>480

Table 1 shows the release time of 50% and 80% ($T_{50\%}$ and $T_{80\%}$) of the drug contained in the tablets obtained from the two granulates ibuprofen–Eudragit RS 1:1/ibuprofen-starch 1:1 in the proportions 50:50, 60:40, and 70:30 and in the tablets obtained from the two granulates ibuprofen–Eudragit RS 1:1/ibuprofen-starch 2:1 in the ratios 50:50, 60:40, and 70:30. For the ibuprofen–Eudragit RS 1:1/ibuprofen-starch 1:1 tablets with 50:50 and 60:40 proportions, only tablets of 8 kp hardness show good release kinetics, even if not perfect, because the first dose release (50% of the total) is too gradual, and for the 50:50 proportion, it is also too elevated. So, the formulation is still distant from the prefixed ideal conditions of the immediate release of 50% of the whole drug dose, with the rest released in a gradual and linear manner. In contrast, 4 kp hardness tablets obtained from the mixture of the two granulates in the 70:30 proportion release the drug with very good kinetics. Tablets of higher hardnesses slow ibuprofen release too much. The only drawback of these tablets is represented by the weight, which is a little too high. Further trials are planned to obtain the same results and reduce the tablet weight as much as possible.

For the ibuprofen–Eudragit RS 1:1/ibuprofen-starch 2:1 tablets, with the 50:50 proportion, drug release is too fast. At the 60:40 ratio at 8 kp tablet hardness, the drug dissolution is slowed, but the initial release is too gradual. In contrast, with the two granulates mixed in the proportion 70:30, tablets of 4 kp hardness had too slow release kinetics, so higher hardnesses were omitted from the study.

Figure 5 shows dissolution kinetics of tablets obtained from ibuprofen–Eudragit RS 2:1 (w/w) granulate compared with that of the 1:1 ratio. With this weight ratio

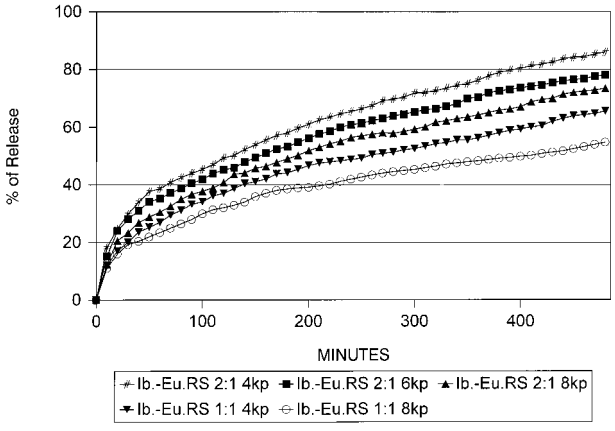

Figure 5. Dissolution curves of the tablets obtained from the ibuprofen–Eudragit RS 2:1 (w/w) granulate compared with those obtained from the ibuprofen–Eudragit RS 1:1 granulate.

Table 2

Drug Release Times T_{50} *and* T_{80} *of the Tablets Containing Ibuprofen–Eudragit RS 2:1 Granulate*

Granulate	Ratio	Hardness (KP)	T_{50} (min.)	T_{80} (min.)
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	4	5	18
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	6	18	50
Ibuprofen–Eudragit RS 1:1/ibuprofen–starch 1:1	50:50	8	35	90
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	60:40	4	5	18
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	60:40	6	13	30
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	60:40	8	20	50
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	70:30	4	12	30
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	70:30	6	15	60
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 1:1	70:30	8	45	190
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	50:50	4	<5	25
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	50:50	6	20	40
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	50:50	8	25	50
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	60:40	4	10	25
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	60:40	6	20	80
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	60:40	8	40	150
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	70:30	4	20	35
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	70:30	6	32	75
Ibuprofen–Eudragit RS 2:1/ibuprofen–starch 2:1	70:30	8	35	270

between the two molecules, it is possible to control drug release; further studies should be carried out to verify the possibility of using a mixture of this granulate and the ibuprofen-starch granulate to obtain the desired release kinetics.

Table 2 shows the release time of 50% and 80% ($T_{50\%}$ and $T_{80\%}$) of the drug contained in the tablets obtained from the two granulates ibuprofen–Eudragit RS 2:1/ibuprofen-starch 1:1 in the proportions 50:50, 60:40, and 70:30 and in the tablets obtained from the two granulates ibuprofen–Eudragit RS 2:1/ibuprofen-starch 2:1 in the ratios 50:50, 60:40, and 70:30. For the ibuprofen–Eudragit RS 2:1/ibuprofen-starch 1:1 tablets, the release kinetics are too fast, even for tablets of 8 kp hardness obtained by mixing the two granulates in the 70:30 ratio. For the ibuprofen–Eudragit RS 2:1/ibuprofen-starch 2:1 tablets, it can be clearly observed that drug release gradually slows from the 50:50 to the 70:30 ratio. Particularly for this last proportion of granulates mixture, tablets of 8 kp hardness possess exactly the ideal release kinetics, with fast initial dissolution of about 50% of drug content and the rest released in a gradual and linear way. Also, the tablet weight (600 mg) is surely acceptable.

CONCLUSION

Dissolution studies clearly demonstrate the versatility of the method. In fact, a variation of parameters, such as tablet hardness, granulate composition, and mixing proportion of the granulates, makes it possible to obtain a wide range of release kinetics. From these in vitro trials, it is pointed out that the use of the granulates ibuprofen–Eudragit RS 1:1 and ibuprofen-starch 1:1 mixed in a 70:30 proportion for the preparation of 4 kp hardness tablets or the use of the granulates ibuprofen–Eudragit RS 2:1 and ibuprofen-starch 2:1 mixed in a 70:30 proportion for the preparation of 8 kp hardness tablets gives a dosage form that incorporates in a single unit an immediate-release dose able to increase drug plasma levels quickly and a second dose, gradually released, that is able to maintain these plasma levels constant for several hours. Obviously, these in vitro trials should be followed by in vivo experiments.

From the technological point of view, the method used to obtain ibuprofen–Eudragit RS matrix microspheres enables the immediate granulation of them. Otherwise

obtaining a matrix granulate that is able to give the same drug release kinetics results is much more difficult.

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