ORIGINAL ARTICLE

FORMULATION AND PREPARATION OF OMEPRAZOL AND KETOPROFEN BI-LAYER TABLETS BY DIRECT COMPRESSION METHOD

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Abstract

The aim of the study was to prepare and characterize bi-layer tablets containing ketoprofen and omeprazole in order to reduce the side effects of ketoprofen and to improve the therapeutic benefits and patients' compliance to treatment. Bi-layer tablets of ketoprofen 100 mg and 20 mg omeprazole (in form of enteric pellets) were prepared by direct compression technique using carbopol, sodium carboxymethyl cellulose, hydroxypropyl methylcellulose**,** Kollidon® as matrix-forming agents. These polymers have the ability to hydrate in digestive fluids and form a gel on the surface of the tablets undergoing erosion processes in time, in order to control the release of active drugs from compressed matrix tablets. Hardness, friability and release studies were performed on bi-layer tablets. The results have shown the influence of polymers over the physicochemical properties and the release profile of the active drugs.

Rezumat

Obiectivul studiului a fost prepararea şi caracterizarea unor comprimate dublu strat conţinând ketoprofen şi omeprazol cu scopul de a reduce reacţiile adverse la nivel gastrointestinal ale ketoprofenului şi de a îmbunătăţi beneficiile terapeutice şi complianţa pacientului la tratament. S-au preparat comprimate dublu strat ce conţin 100 mg ketoprofen şi 20 mg omeprazol (sub formă de pelete) prin metoda comprimării directe, utilizând ca polimeri formatori de matriţă carbopol, carboximetilceluloză sodică, hidroxipropilmetilceluloză, Kollidon® care au capacitatea de a se hidrata în lichidele digestive şi de a forma la suprafaţa comprimatelor un gel care suferă procese de erodare în timp, astfel încât vor controla eliberarea din matriţă a substanţelor medicamentoase. S-a determinat duritatea şi friabilitatea şi s-a efectuat testul de dizolvare pe comprimatele dublu strat. Rezultatele obţinute au arăt influenţa polimerilor asupra proprietăţilor fizico-chimice şi a profilului de eliberare a principiilor active.

Keywords: bi-layer tablets, ketoprofen, omeprazole, direct compression

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) hold an important place in current therapy having multiple indications in rheumatic diseases due to their analgesic and anti-inflammatory properties. Ketoprofen is one of them; its analgesic properties have been confirmed for degenerative diseases. Nevertheless, side effects are found in cases of long-term administration, especially at the level of gastrointestinal tract where ulcerations and bleeding are mentioned. In practice, in order to reduce these side effects, the association of a proton pump inhibitor is used, out of which the most widely used was omeprazole. This therapeutic association could be employed using new systems of modified release. Modified release tablets are coated or uncoated tablets that contain special excipients or they are prepared by special techniques, designed to modify the place or time of release of the active drugs. Bi-layered tablets perform this type of release due to the fact that each layer contains different active substances having different release profiles [4, 7].

Materials and Methods

Materials

In the study there were used: Ketoprofen supplied by Bidachem, Italy; omeprazole enteric-coated pellets (Antiobiotice SA); hydroxypropyl methylcellulose (HPMC) Methocel® K100 (Colorcon, United Kingdom); Kollidon® VA64 (BASF, Germany); carbopol 971 PNF (Lubrizol, USA); sodium carboxymethyl cellulose (CMC) (Ashland, USA); magnesium stearate - Kemilub® (Undesa, Spain).

Methods

Preparation of the ketoprofen layer. Seven formulations were prepared for the ketoprofen layer (Table I). Preparation was achieved by direct compression with direct compressible excipients.

The mixture was made in a mortar by adding components in the ascending order of quantities. Mixing was carried out for 10 minutes and in the end magnesium stearate was added and mixing continued for another 2 minutes. The final mixture for each formulation was compressed with a Korsch tablet equipment using 9 mm flat punches and a compression pressure of 25kN [4, 5].

Table I

Different formulas of the ketoprofen tablet layer

Components	Quantity (in mg)						
	K1	K 2	K 3	K 4	K 5	K 6	K 7
Ketoprofen	100	100	100	100	100	100	100
Carbopol 971 PNF	10	15	10	-	-	-	
Microcrystalline cellulose	-	-	-	50	50	65	65
Sodium carboxymethyl cellulose (CMC)	20	18	10	10	15	-	11
Hydroxypropyl methylcellulose (HPMC K100M)	46	43	56	16	11	11	-
Sorbitol	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Magnesium stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Total/tablet (mg)	180	180	180	180	180	180	180

Preparation of the omeprazole layer. Three formulations were prepared for the omeprazole layer (Table II). Omeprazole enteric-coated pellets (20 mg omeprazole *per* 60 mg pellets) were homogenized together with excipients for 7 minutes. In the end magnesium stearate was added and mixing continued for another 2 minutes. Omeprazole mixture was compressed under the same conditions as the mixture of ketoprofen. In the preparation of the layer containing pellets of omeprazole, excipients (microcrystalline cellulose, Kollidon®) were used, which produce sufficiently hard tablets at a low pressure. In this way the release of the active substance should not be affected [2, 3].

Table II

Different formulas of the omeprazole tablet layer

Components	Quantity (in mg)		
	O1	O2	O3
Omeprazole pellets	60	60	60
Kollidon VA 64	8.5	19	11
Microcrystalline cellulose	21	10.5	18.5
Magnesium stearate	0.5	0.5	0.5
Total (mg)	90	90	90

Evaluation of compressed ketoprofen and omeprazole layers. The prepared formulas were subjected to the following tests: hardness and friability. The hardness of 5 tablets from each of the prepared formulas was measured individually using a Pharma Test hardness tester**.** The friability test was performed using an EF-2 Electrolab Friabilator. The friability was calculated as a weight loss percentage after 100 revolutions of 20 tablets from each formula [7, 9].

Bi-layer tablets preparation. Ketoprofen K2 formula and omeprazole O2 formula were selected after hardness and friability tests and they were used to prepare bi-layer tablets (K2- O2). 180 mg of powder for ketoprofen layer was manually poured into the 9 mm die and mild compressed (40 kN). Over it, the amount of 90 mg of the physical mixture of pellets with omeprazole was poured and it was compressed at the same force for 10 seconds to form the bi-layer tablet.

Evaluation of pharmacotechnical properties of the bi-layer tablets. Measurements were made under the same conditions as mentioned above.

Bi-layer tablet's dissolution study. The *in vitro* study of active substances release from bi-layer tablets was carried out using a dissolution apparatus type 1 (basket) at 50 rpm. A hydrochloric acid solution 0.1 N (pH = 1.2, 900 mL) was used as a dissolution medium for the first two hours and then it was replaced by a phosphate buffer solution (pH = 6.8) for 8 hours, maintained at 37 ± 2ºC for the whole experiment. Samples (5 mL) were withdrawn at different time intervals and the drugs content in each sample was analysed using a spectrophotometer Jasco V-530 UV-VIS at λ = 255 nm for ketoprofen, and 302 nm for omeprazole, respectively [8, 9].

Results and Discussion

In the case of ketoprofen formulations, hydrophilic polymers were used as matrix-forming polymers that have the ability to hydrate in digestive fluids and to form a viscous gel on the surface of the tablet that finally dissolves in the biological fluids. The gel layer controls the diffusion and the release from the matrix of the dissolved drug substance [4, 6]. The association between CMC, HPMC and Carbopol determined superior results for K1, K2, K3 formulas regarding the hardness and the friability tests. K2 formula was selected for the preparation of the bi-layer tablets. The combination of these three polymers ensures binding properties for mixtures subjected to direct compression. In case of formulations containing omeprazole pellets, hardness and friability tests showed no significant differences between the three proposed formulas. We selected the O2 formula as it showed an improved hardness which provides a better stability in the gastric environment (Table III).

Table III

Evaluation of post compression parameters

Experimental formula	Hardness (N)	Friability (%)
K1	76	0.61
K2	80	0.6
K3	78	0.65
K4	75	0.9
K5	77	0.92
K6	75	1
K7	75	1
O1	75	0.98
O2	82	0.90
O3	78	0.96
K2-O2	85	0.80

Dissolution studies were carried out for the bi-layer tablets (Figure 1). It could be observed that both for ketoprofen and omeprazole, the content released after 10 hours is over 90%. It may be noted that the release of omeprazole from the bi-layer tablets occurs mainly in phosphate buffer solution (pH = 6.8), while its release in the acidic medium is minimal, complying with specific properties for enteric pellets. This release profile can be explained by the nature of polymers used, regarding their rate of hydration.

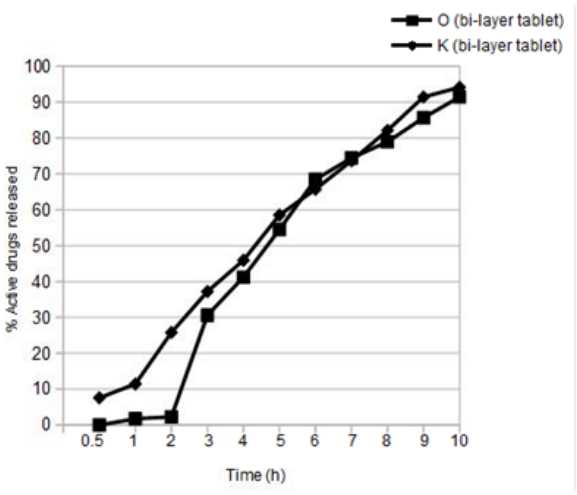

Figure 1.
Release profile of ketoprofen and omeprazole from bi- layer tablets

Conclusions

Bi-layer tablets have been formulated and prepared with a NSAID and a proton pump inhibitor using a hydrophilic matrix type that controls the release of the active substances through processes of erosion occurring over time. The formulations have been described in terms of pharmacotechnical properties by measuring the hardness and friability parameters. Formulations with optimal properties have been selected to obtain bi-layer tablets of adequate quality. The *in vitro* dissolution study of the prepared bi-layer tablets showed a controlled release of active drugs over a period of 10 hours.

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