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Research paper

Formulation of biphasic release tablets containing slightly soluble drugs

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Abstract

A new biphasic release system for slightly soluble drugs has been proposed. To enhance the dissolution rate, the drug was milled with a superdisintegrant. Then, double-layer tablets were prepared. One layer was formulated to release the drug in a very short time (fast-release). The other consisted of an extended-release hydroxypropylmethylcellulose (HPMC) matrix. Different HPMC concentrations (10, 16 and 22%) and viscosity grades (Methocel K4, K15 and K100M) were used to obtain different release rates of the drug from the extended-release layer, ketoprofen and praziquantel were used as slightly soluble model drugs.The in vitro dissolution tests of the prepared double-layer systems, showed the desired biphasic behaviour: the drug contained in the fast releasing layer dissolved within the first 15 min, while the drug contained in the prolonged-release layer was released at different times, depending on the formulation of the hydrophilic matrix. In particular, an increase in the percentage and viscosity grade of HPMC, in the extended release layer, leads to a decrease in the drug delivery rate and produces a wide range of different release rates from only a few hours up to 24 h.

Keywords: Biphasic release; Slightly soluble drug; Ketoprofen; Praziquantel, Hydroxypropylmethylcellulose matrix

1. Introduction

In many therapies, extended-release preparations are considered desirable but, for many drugs, significant daily variations in pharmacokinetics and/or drug effects have been demonstrated on human beings [1,2]. Moreover, for some drugs (such as NSAIDs, antihypertensive, antihistaminic, antiallergic agents) a prompt disposition of a fraction of the dose should be reached in the shortest time possible to relieve the symptoms of the disease and then the continuation of the drug effect should be prolonged for some hours to optimize the therapy. For these types of drugs, extended release formulations generally lead to a delayed appearance of effective plasma levels and they can not provide a prompt disposition of the dose immediately after administration. To fulfil the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients [3].

On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-layer tablet [4], in which the first layer is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a prolonged-release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time.

The combination of a fast release pulse with a slow release pattern could allow for an easier and more flexible optimization of the fast and slow dose fractions as a function of the pharmacokinetics and metabolism of the drug.

In this study we considered two drugs for which this fast/slow delivery system could be particularly suitable, praziquantel and ketoprofen. Praziquantel is an antihelmintic drug with a plasmatic half life of 1.5–2.0 h [5]. It is used for the treatment of neurocysticercosis (parasitic infection of the human central nervous system). The recommended oral dosage is 1500–3000 mg divided into three doses for 15 days [6] and is subject to a saturable metabolism process [7]. In this case a fast release would saturate drug metabolism and thus increase the amount of unchanged drug reaching the blood circulation, which will be delivered during the following slow-release phase.

Ketoprofen is an analgesic and anti-inflammatory drug with a plasma elimination half life of 1–3 h [8] the oral dose is 50–100 mg/twice daily [9]. A fast/slow drug delivery is particularly suitable for the formulation of analgesic anti-inflammatory drugs to relieve the painful symptoms as fast as possible after administration, but, to avoid repeated daily

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Table 1
Composition (%) of the fast-releasing layers, KET-FR and PZQ-FR.

Materials	Composition (%)
Drug (PZQ or KET)	35.6
Sodium starch glycolate (intragranular)	35.6
Corn starch	17.8
Methylcellulose	0.4
Sodium lauryl sulphate	1.8
Cross-linked PVP	3.5
Sodium starch glycolate (extragranular)	3.5
Magnesium stearate	1.4
Colloidal silicon dioxide	0.4

administration, an extended release phase is needed at the same time.

These two drugs are characterised by low water solubility, for this reason both active ingredients were previously milled with a swellable polymer used commonly as a disintegrant, cross-linked sodium starch glycolate. The presence of this polymer enhances the dissolution rate of the drugs in the fast releasing layer [10,11] and helps to control the delivery process from the hydrophilic matrix (extended-release layer). In fact, cross-linked swellable polymers can be used to increase the eroding characteristic of hydrophilic matrices [12] and thus, by synchronising the matrix swelling and erosion processes, to reach nearly constant release rates for a programmable period of time [13].

The aim of the present study is the design and preparation of an oral dosage form able to deliver a first impulse of the dose in the shortest time possible (a few min) and a second fraction of the dose in a prolonged time at a constant rate.

Table 2
Composition (%) of the extended-release layers (plus 4.5% of binder, polyvinylpyrrolidone, 1.0 % of magnesium stearate and 0.5 % of silicon dioxide)

Code	Drug primojel (%)	HPMC (%)	Mannitol (%)
		Methocel K4M	
PZQ 10% K4M	31.5 : 31.5	10	21
PZQ 16% K4M		16	15
KET 16% K4M		16	15
PZQ 22% K4M		22	9
KET 22% K4M		22	9
		Methocel K15M	
PZQ 16% K15M	31.5 : 31.5	16	15
KET 16% K15M		16	15
PZQ 22% K15M		22	9
KET 22% K15M		22	9
		Methocel K100M	
PZQ 10% K100M	31.5 : 31.5	10	21
PZQ 16% K100M		16	15
KET 16%K100M		16	15
PZQ 22% K100M		22	9
KET 22%K100M		22	9

2. Materials and methods

2.1. Materials

Two slightly soluble drugs were used, praziquantel (PZQ) (Therapicon, Milan, I) and ketoprofen. (KET) (S.I.M.S., Reggello, Florence, I). The particle size distribution of the active compounds was measured with the Coulter Counter (Multisizer II, Coulter, Luton UK), the mean diameter (d_{vs}) is 7.8 μm for PZQ and 6.9 μm for KET. Cross-linked sodium starch glycolate (PJ) (Primojel®, AVEBE, Veendam, NL) was used for the preparation of the drug:Primojel systems.

For the preparation of the prolonged-release layers three different viscosity grades of hydroxypropylmethylcellulose (HPMC) were chosen: 4,000 mPa s (Methocel® K4M) 15 000 mPa s (Methocel® K15M), 100 000 mPa s (Methocel® K100M), (Colorcon, Orpington, UK) (viscosity values stated by the supplier on 2 wt.% water solutions, 20°C).

Additionally the following excipients were used, methylcellulose (Methocel A4C, Orpington, UK), colloidal silicon dioxide, (Syloid® 244, Grace GmbH, Worms, D) cross-linked polyvinylpyrrolidone, (Polyplasdone XL®, ISP, Wayne, USA) mannitol, corn starch, and magnesium stearate (Carlo Erba, Milan, I).

2.2. Drug Primojel system preparation

The drug and Primojel in a 1:1 weight ratio were milled in a hard porcelain mortar grinder for 30 min (RM0, Retsch, Haan, D), 90 rev/min, batch size 20 g. The product obtained was calibrated through a 200 mesh sieve (75 μm). Two drug:Primojel systems were obtained: KET: PJ and PZQ: PJ.

2.3. Tablet preparation

Table 1 shows the composition (%) of the fast release formulation KET-FR and PZQ-FR.

The drug-Primojel system (KET:PJ or PZQ:PJ) and corn starch (diluent) were mixed and moistened with a 1% methylcellulose aqueous solution. The wet mass was forced through a 25 mesh sieve (710 μm). The granules were dried at 40°C until a constant weight is achieved, and then calibrated through the same sieve. A further amount of disintegrants was used to improve drug disposition from the fast-releasing layer, cross-linked polyvinylpyrrolidone and sodium starch glycolate were added to the dry granules, and mixed with magnesium stearate and colloidal silicon dioxide for 15 min in a Turbula mixer (Type T2A, Bachofen, Basel, CH).

The formulations of the extended release layers, contain-

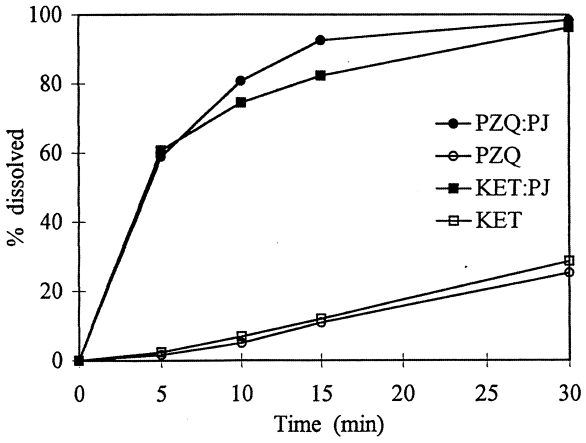

Fig. 1. Dissolution rate of drug primojel systems and drugs alone.

ing PZQ:PJ system or KET:PJ system, were prepared using different concentrations of HPMC and different viscosity grades to obtain different release rates (Table 2). HPMC concentrations were varied by changing the relative amounts of HPMC and mannitol, in order to keep the matrix weight and surface area constant.

For the preparation of the prolonged release matrices, drug Primojel systems were mixed with HPMC and mannitol and then moistened with a 10% povidone ethanol solution, granulated and dried at 40°C until constant weight is achieved. Magnesium stearate and colloidal silicon dioxide were added to the dry granules and mixed for 15 min in a Turbula apparatus.

For each formulation, single-layer tablets were prepared with 100 mg of the drugs' content, (Korsh EK0, Berlin, D, 11 mm flat punches) to evaluate the dissolution profile of the formulation of each layer separately.

The double-layer tablets weighed 600 mg and contained a total amount of 200 mg of drug (ketoprofen or praziquantel), 100 mg in the fast-releasing layer and 100 mg in the extended releasing layer.

For the preparation of the two-layer tablets the die of the tableting machine was progressively filled by hand with the weighed amounts of the fast and the prolonged released granulates. As the prolonged release formulations containing the lower amount of HPMC tend to disintegrate, only the formulations containing the higher concentration of HPMC were used for the preparation of the double-layer tablets (16 and 22%). The crushing strength of the tablets was kept in the range 100–200 N.

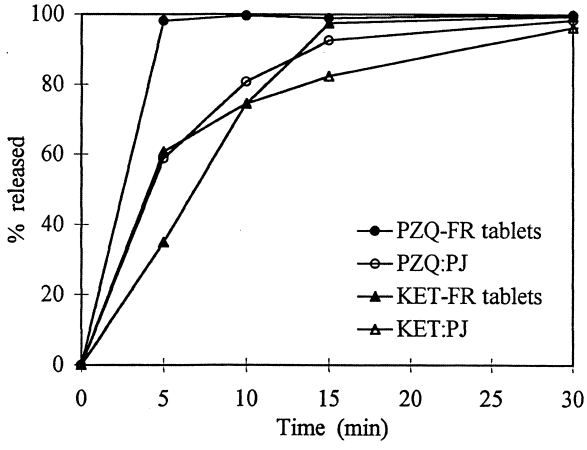

Fig. 2. Comparison of the dissolution profiles of the drug primojel systems and the fast-releasing tablets.

2.4. Dissolution Studies

The aqueous solubility of the two drugs had been previously tested. For ketoprofen the solubility in distilled water (37°C) was 100 mg/l and 400 mg/L for praziquantel in the same conditions.

The samples (six replicates for each formulation) were placed into 5000 ml of distilled water, 37°C, using a modified USP no. 2 apparatus (paddle at 100 rev./min) to maintain the sink conditions. The drug concentration was measured spectrophotometrically at 261 nm for ketoprofen and 217 nm for praziquantel. (Spectracomp 602, Advanced Products, Milan, I). The dissolution tests were carried out on PZQ and KET alone (100 mg), on the drug primojel systems (KET:PJ and PZQ:PJ, corresponding to a drug content of 100 mg) and on single-layer tablets containing 100 mg of drug each, and on double layer tablets with a total drug content of 200 mg. The results were reproducible (SD < 3 percent released) and the mean values have been plotted versus time.

3. Results

Fig. 1 shows the dissolution rates of the drugs alone (praziquantel and ketoprofen) and of the drug:Primojel systems (PZQ:PJ and KET:PJ). Both drug primojel systems have shown an improvement in drug dissolution rate compared to the drug alone. In fact, 100% of praziquantel present in PZQ:PJ is dissolved within 30 min, while in the same time, less than 30% of the drug alone is dissolved. The same result was observed for the KET:PJ system and ketoprofen alone.

The dissolution profile of the fast-release tablets containing PZQ shows a further improvement in the dissolution rate of the drug, compared to the drug primojel systems, due to the presence of other disintegrants and a surfactant agent in the fast-releasing formulation (Fig. 2). In fact, praziquantel is released within 5 min from this type of prompt release tablet. In contrast, the dissolution rate of ketoprofen from the fast-releasing tablets was not improved by the presence of other disintegrants.

Fig. 3 shows the release profiles of prolonged-release matrix tablets containing PZQ and 10% of HPMC. The single-layer devices containing the lowest percentage of HPMC (10%) generally show a partial disintegration at the beginning of the dissolution test. If the disintegration process is too extensive, it may prevent the formation of a continuous gel layer, which is responsible for the modula-

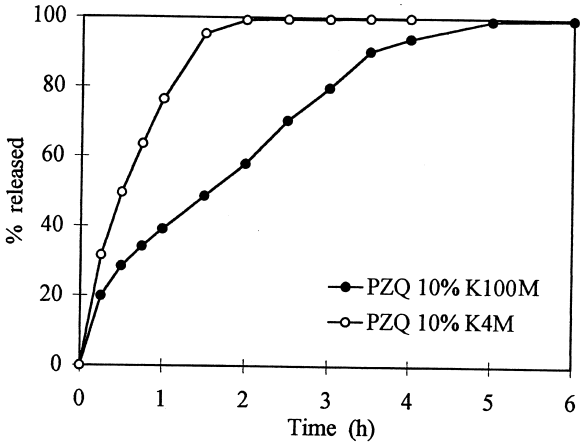

Fig. 3. Comparison of the release profiles of the single-layer tablets containing 10% of HPMC.

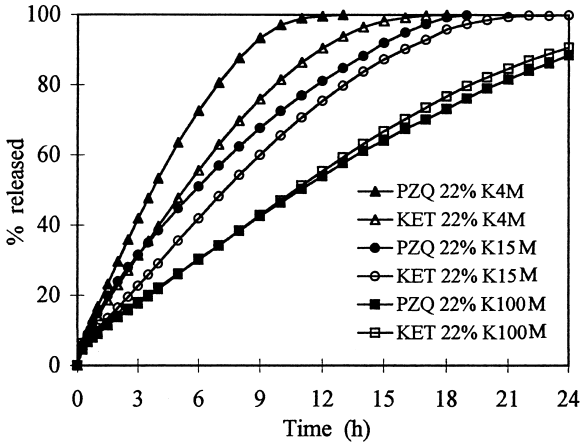

Fig. 5. Comparison of the release profiles of the single-layer tablets containing 22% of HPMC.

tion of the release process [14]. In these cases, drug release takes place in quite a short time. The matrix disintegration is certainly enhanced by the presence of sodium starch glycolate; the disintegrant swells very quickly when in contact with water, and this effect may prevent the formation of a coherent and effective gelled structure on the surface of the matrix, which is able to restrain water penetration and drug diffusion.

On the other hand, matrix tablets containing higher percentages of HPMC (i.e. 16 and 22%) were able to keep their integrity and therefore they showed a good control of drug dissolution process with slower release rates for longer periods of time (Figs. 4 and 5).

In fact, the tablets containing 16 and 22% of HPMC are able to deliver the drug at different rates, depending on the amount and viscosity grade of polymer used. Although the tablets did not disintegrate, erosion was observed during the whole dissolution process and at the end of the test, the systems were completely dissolved.

In Fig. 4 the release profiles of the tablets containing 16% of HPMC are shown. For PZQ, 16% K4M, the whole dose was released within 6 h, while more extended release profiles are obtained for matrices containing the same polymer concentration but higher viscosity grades. In fact PZQ, 16% K15M released the entire dose in about 8 h while 15 h were required for the complete release from PZQ, 16% K100M.

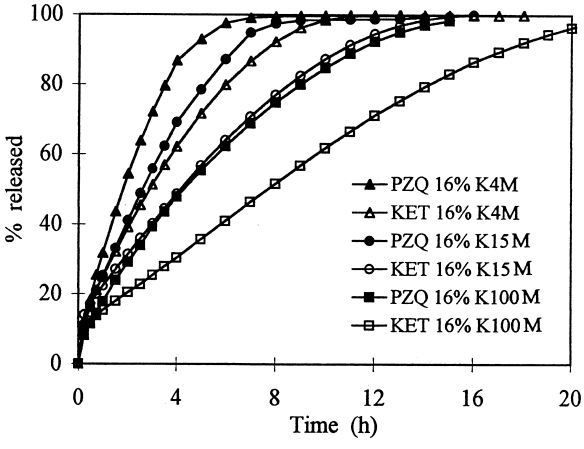

Fig. 4. Comparison of the release profiles of the single-layer tablets containing 16% of HPMC.

Slower release rates have generally been obtained from the matrices where praziquantel was replaced by ketoprofen (less soluble drug). For example, the release process of the KET, 16% K4M tablets containing ketoprofen is completed in 9 h rather than 6 h needed for the corresponding matrix formulation containing praziquantel. The matrices containing a higher viscosity HPMC grade, (Methocel K100M), but the same concentration (16%), showed a greater difference between the release rate of the two different drugs, praziquantel was released in about 15 h while the tablets containing ketoprofen needed about 20 h to deliver the whole dose.

A different behaviour was observed for matrices prepared with the highest HPMC concentration, 22%. Although the release profiles of praziquantel and ketoprofen from identical formulations containing 22% K4M are different, the systems containing K15M show comparable behaviour in dissolution (Fig. 5) and, in the case of Methocel K100M, the release profiles are superimposed despite the presence of the two drugs of different solubility. This result suggests that, in these conditions, for the formulations containing the higher concentration and viscosity grade of HPMC, the release rate is not influenced by the drug any more.

Fig. 6 shows the release rate (mg dissolved per h) of praziquantel and ketoprofen from matrices containing 22% of Methocel K100M. Although a burst effect can be evidenced during the first hour, quite constant release rates can be obtained for both drugs.

During the dissolution test, the matrices were subjected to two simultaneous processes, the formation of a gel layer and its progressive erosion. Although matrix erosion is generally influenced by the hydrodynamic conditions, in this case the

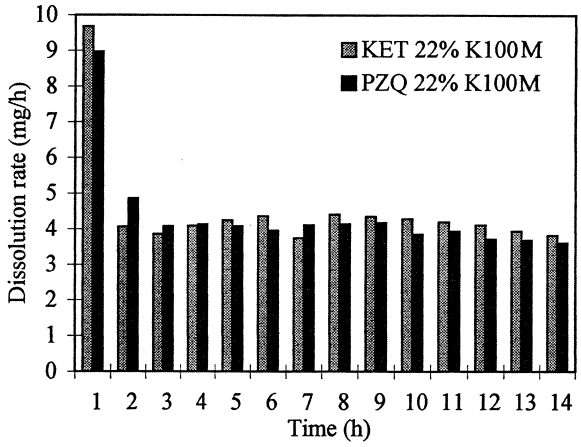

Fig. 6. Dissolution rate of the single-layer tablets containing 22% of Methocel K100M.

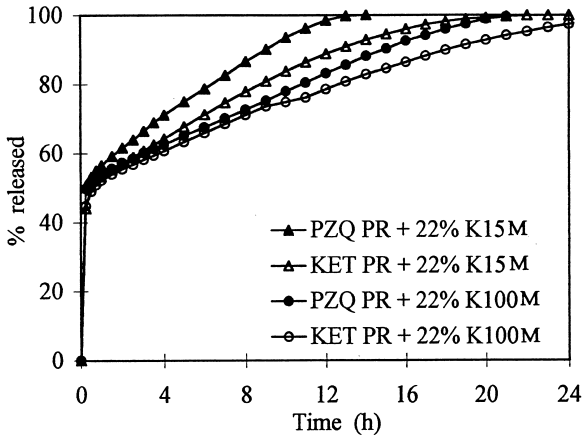

Fig. 8. Comparison of the release profiles of the double-layer tablets containing 22% of HPMC.

synchronisation of the two processes led to a nearly constant dissolution rate, particularly for tablets prepared with 22% of Methocel K100M.

From double-layer systems, praziquantel and ketoprofen are released in two clearly distinct phases (Figs. 7 and 8): In the first phase, the first fraction of the dose is dissolved within less than 15 min, due to the prompt disintegration of the fast-releasing layer and to the enhanced dissolution rate of the drug primojel systems. This behaviour is identical for all formulations, as evidenced in Fig. 7. After this main releasing phase, the dissolution profiles are dependent of the composition of the prolonged release layer and, in particular, the percentage and viscosity grade of the HPMC (Figs. 7 and 8).

In all cases, a wide range of dissolution rates at a fairly constant rate can be obtained.

4. Discussion

The combination of a disintegrant and HPMC for the preparation of the matrix tablets containing the drugs of low solubility (praziquantel or ketoprofen) allows for a fine tuning of their release profiles to be achieved, from a few hours to 24 h.

As seen for conventional HPMC matrices, the drug release depends on the concentration and viscosity grade of the polymer used, but the presence of the superdisintegrant may enhance the matrix erosion process and, by synchronizing the gelling and erosion rates, quite constant release profiles can be obtained.

The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program, the two different release phases can be easily adjusted in a wide range of variation and in terms of both delivery rate and ratio of the dose fractions, on the basis of the pharmacokinetics and therapeutic needs, to perform the desired 'in vivo' profile. This device can be a useful tool for the formulations of those active ingredients for which specific delivery patterns and/or input rates are needed or will be needed in the future when more accurate pharmacokinetics and clinical trials will be developed.

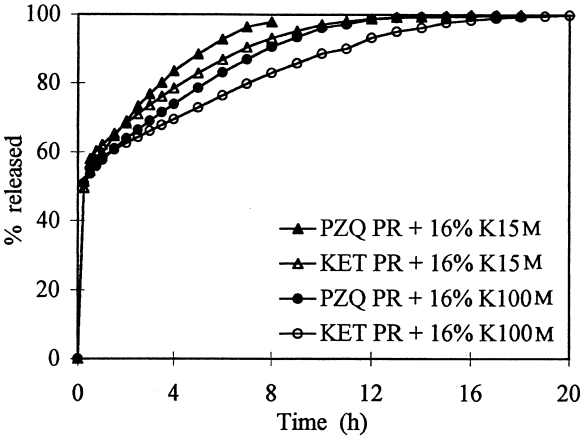

Fig. 7. Comparison of the release profiles of the double-layer tablets containing 16% of HPMC.

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