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Research paper

Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin

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Abstract

The low bioavailability and short half-life of metformin hydrochloride (MH) make the development of sustained-release forms desirable. However, drug absorption is limited to the upper gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit. This study was undertaken to develop a MH sustained-release formulation in compliance with these requirements. The strategy proposed is based on direct-compressed matrix tablets consisting of a combination of MH with the hydrophobic triacetyl-β-cyclodextrin (TAβCD), dispersed in a polymeric material. Different polymers were tested as excipients, i.e. hydroxypropylmethylcellulose, xanthan gum, chitosan, ethylcellulose, Eudragit®L100-55, and Precirol®. Compatibility among the formulation components was assessed by DSC analysis. All the tablets were examined for drug release pattern in simulated gastric and jejunal fluids used in sequence to mimic the GI transit. Release studies demonstrated that blends of a hydrophobic swelling polymer (hydroxypropylmethylcellulose or chitosan) with a pH-dependent one (Eudragit®L100-55) were more useful than single polymers in controlling drug release. Moreover, the main role played by the MH–TAβCD system preparation method (i.e. grinding or spray-drying) in determining the behaviour of the final formulation was evidenced. In fact, for a given matrix-tablet composition, different sustained-release effects were obtained by varying the relative amounts of MH–TAβCD as ground or spray-dried product. In particular, the 1:1 (w/w) blend of such systems, dispersed in a Eudragit–chitosan polymeric matrix, fully achieved the prefixed goal, giving about 30% released drug after 2 h at gastric pH, and overcoming 90% released drug within the subsequent 3 h in jejunal fluid.

Keywords: Metformin hydrochloride; Triacetyl-β-cyclodextrin; Sustained release; Matrix tablets

1. Introduction

Metformin hydrochloride is a highly water-soluble anti-hyperglycaemic agent used in the treatment of type II non-insulin-dependent diabetes mellitus. Its relatively low (50–60%) bioavailability together with its short and variable biological half-life (0.9–2.6 h) [1–4] require repeated administrations of high doses to maintain effective plasma concentrations, thus reducing patient compliance and/or enhancing the incidence of side-effects. Sustained-release systems of metformin, developed in order to overcome these problems, were however still less bioavailable than conventional immediate-release tablets [5–7]. Moreover, gastric-retentive swelling tablets of metformin showed only a 15% increase of bioavailability with respect to the immediate-release tablets [8]. These results could be attributed to a lack of correspondence between the time of transit of the drug delivery system across the upper part of the gastrointestinal (GI) tract and the time necessary for complete drug release and/or absorption. In fact, many studies have reported that the oral absorption of metformin is mainly confined to the small intestine, i.e. duodenum and jejunum and, to a lesser extent, ileum [3,9,10]. Therefore, a more effective rationalisation of the drug release pattern is clearly needed. This could be attained through the development of suitable drug delivery systems able to initiate release in the stomach

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and almost complete it in the jejunum, so that the time for total drug release nearly coincides with that of transit of the system through the upper GI tract. A site-specific controlled release of metformin was recently achieved by using a somewhat elaborate method based on tablets prepared by compression of drug-polymer granules, previously obtained by solid dispersion at 85 °C, and then coated on one face with a pH-dependent polymer [11]. Moreover, it has been reported that pellets of metformin adsorbed on talc, coated by centrifugal granulation with two different pH-dependent polymers, enabled a restricted delivery of the drug to the small intestine and resulted in increased relative bioavailability with respect to a commercial immediate-release tablet [12]. These results confirmed the actual effectiveness of the upper-GI-tract-limited sustained-release approach for improving the therapeutic efficacy of metformin.

A study was thus undertaken aimed at developing a metformin sustained-release formulation in compliance with the above "site-specific delivery" requirements, but using a simpler and easier to scale up formulation strategy. In a previous report [13] the suitability of a hydrophobic cyclodextrin, i.e. the triacetyl-β-cyclodextrin (TAβCD), as a carrier for obtaining a slow-dissolving profile of metformin, was demonstrated. Therefore, in the present work we considered it worthy of interest to use a combination of the drug with such a hydrophobic carrier and disperse it in a suitable polymeric material for preparing matrix tablets able to provide appropriate modulation of the metformin release profile, according to the rationale stated above. Matrix tablets were chosen as formulation approach since their preparation involves few processing variables and they can be easily manufactured by direct compression with conventional tableting facilities. Various kinds of polymers, with different chemical–physical properties, were tested (both alone and in mixtures at different (w/w) ratios) as candidate matrix-forming excipients to reach the prefixed goal. Among them, hydroxypropylmethylcellulose, xanthan gum and chitosan were selected as hydrophilic and swellable excipients, ethylcellulose was chosen as an inert and insoluble material, Eudragit®L100-55 as a pH-dependent polymer and Precirol® (glyceryl palmito-stearate) as a lipophilic material. After verification of the compatibility among the formulation components, matrix tablets were prepared by direct compression of the powder mixtures, by keeping both the total amount of drug and the drug-to-polymer ratio constant. All the tablets were then examined for drug release pattern and mechanism in simulated gastric and jejunal fluids used in sequence to mimic the GI transit.

2. Materials and methods

2.1. Materials

Metformin hydrochloride (MH) was kindly supplied by Menarini (Firenze, Italy) and triacetyl-β-cyclodextrin (Cavasol®W7TA, TAβCD) was kindly donated by Wacker-Chemie GmbH (Germany). Chitosan (Mw 150 kDa, deacetylation degree 75–85%, CS), ethylcellulose (Ethocel®, EC), hydroxypropylmethylcellulose (Methocel®K4M, HPMC) and xanthan gum (XG) were obtained from Sigma (Italy). Methacrylic acid copolymer (Eudragit®L100-55, EU) was gifted by Rofarma Italia S.r.l. (Milano, Italy) and glyceryl palmito-stearate (Precirol®Ato5) was kindly supplied from Gattefossé Italia S.r.l. (Milano, Italy). All other chemicals and solvents were of reagent grade.

2.2. Preparation of solid binary systems

MH–TAβCD equimolar systems were obtained from the individual components previously sieved (75–150 μm): (a) by ball-milling physical mixtures in a high vibrational micro-mill for 30 min at 24 Hz (ground systems, GR); (b) by dissolving physical mixtures in an 8:2 (v/v) ethanol:water solution and then spray-drying (IRA Mini-Spray Ho, Italy) (spray-dried systems, SP).

2.3. Preparation of matrix tablets

Matrix tablets containing 50 mg of MH, or its equivalent as equimolar ground (GR) or spray-dried (SP) product with TAβCD, mixed with the polymeric material (using each polymer alone or in binary 1:1 or 1.5:0.5 (w/w) mixtures), were prepared by direct compression process using a Perkin-Elmer hydraulic press equipped with a 10 mm flat faced punch and die set. The compression force and compression time were 3 ton and 2 min, respectively. The mixtures were checked for blend uniformity prior to tableting (coefficient of variation (C.V.) of the mixing index $<5\%$). For each batch, 5 randomly drawn tablets were checked for weight uniformity (Mettler AE-50 electronic balance). All the preparations were stored in airtight containers at room temperature for further study. The composition of the examined tablets is given in Table 1.

2.4. Compatibility studies

The possibility of drug-excipient and/or cyclodextrin-excipient interactions before and after compression was investigated by differential scanning calorimetry (DSC) analysis using a Mettler TA4000 Star^e software apparatus (Mettler Toledo, Switzerland) equipped with a DSC 25 cell. Thermal curves of pure drug, carrier and polymers and of their different examined mixtures before and after compression (in the same w/w ratios as in the final tablets, according to Table 1) were recorded. Samples of about 5–10 mg accurately weighed (Mettler MX5 microbalance) were sealed in pierced Al pans and analysed under static air at a heating rate of 10 °C/min over a temperature range of 30–300 °C. The instrument was calibrated using indium as a standard (99.98% purity; melting point 156.61 °C; fusion enthalpy 28.71 J g^{-1}).

Table 1
Composition of the examined metformin hydrochloride (MH) matrix tablets

Components	Milligrams per tablet												
	A	B	C	D	E	G	H	I	L	M	N	O	P
MH–TAβCD[a]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]	660[b]
Chitosan	165	–	–	–	–	–	41.3	–	41.3	–	82.5	–	82.5
Ethylcellulose	–	165	–	–	–	–	–	123.7	123.7	–		82.5	82.5
Xanthan gum	–	–	165	–	–	–	–	–	–	–		–	–
Eudragit	–	–	–	165	–	123.7	123.7	–	–	82.5	82.5		
HPMC	–	–	–	–	165	41.3	–	41.3	–	82.5		82.5	–

[a] As equimolar ground or spray-dried product, or their (w/w) mixtures.
[b] Equivalent to 50 mg of pure drug.

2.5. Release experiments

In vitro drug release studies from the prepared matrix tablets were performed according to the USP paddle method (Apparatus II) using 500 mL of pH 1.1 HCl solution, simulating the gastric fluid (SGF) or pH 6.5 phosphate buffer, simulating the jejunal fluid (SJF) thermostated at 37 ± 0.1 °C and stirred at 100 rpm. SGF and SJF were used in sequence (2 h the first and 3 h the second one) to simulate the tablet transit from stomach to jejunum. At time intervals of 30 min samples were withdrawn with a syringe filter (pore size 0.45 mm) and replaced with an equal volume of fresh medium. The drug content was spectrometrically determined (UV/vis 1600 Shimadzu spectrophotometer, Tokyo, Japan) at 232.2 nm. The UV spectrum of MH in about neutral aqueous solutions (such as the simulated jejunal fluid) shows a maximum of absorption at this wavelength. Therefore, samples in pH 6.5 phosphate buffer were directly assayed; on the contrary samples in pH 1.1 acid solution were previously neutralized by adding a proper amount of solid disodium hydrogen phosphate dehydrate. Blank runs showed the absence of interferences with the spectrophotometric assay. The cumulative percent of drug released was calculated and plotted versus time. Three replications were made for each tablet batch (coefficient of variation <5%). In order to gain insight into the drug release mechanism from the examined tablets, release data of selected formulations were examined according to the zero-order, first-order and Higuchi's square root of time mathematical models and the release exponent n was calculated according to the following equation [14,15]:

$$W = kt^n \quad (1)$$

where W is the percent of drug released at time t, k is a kinetic constant incorporating the structural and geometric characteristics of the tablet and n is an exponent which characterizes the mechanism of release. A n value 0.5 is considered consistent with a diffusion-controlled release, whereas a value of 1.0 indicates a zero-order release behaviour, and intermediate values ($0.5 > n > 1.0$) are defined as anomalous non-Fickian transport mechanism [14].

3. Results and discussion

The present study was aimed at developing a novel formulation for a rational prolonged release of MH allowing a synchronization between the time required for complete drug release and the transit time of the delivery system across the upper part of the GI tract, where drug absorption occurs and where sites of MH glucose-lowering action are located, which contribute to the overall pharmacodynamic effect [16].

The proposed formulation strategy was based on the preparation of matrix tablets simultaneously exploiting the use of a drug combination with a hydrophobic carrier, such as TAβCD, and its dispersion into a proper polymeric matrix. MH–TAβCD equimolar ground and spray-dried systems were selected on the basis of previous results [13] as the most effective products for reducing the drug dissolution rate. The prefixed goal was the obtainment of a drug release profile in compliance with the above-described requirements, i.e. able to ensure a MH release not higher than 40% of the initial dose during the first 2 h in gastric fluid, and to allow achievement of at least 90% of release within the subsequent 3 h in jejunal fluid.

4. Compatibility studies

First of all, the occurrence of any interaction between the formulation components, mixed in the same w/w ratios as in the corresponding examined matrix tablets (see Table 1 for their composition), was assessed by DSC analysis. The thermal curves of pure components and of selected complete mixtures, before and after compression, are shown in Fig. 1a and b. The thermal curve of pure MH exhibited an initial flat profile followed by a sharp endothermic effect, with a T_{onset} at 229.7 °C and a T_{peak} at 231.0 °C and an associated fusion enthalpy of 292.2 J g^{-1}, indicative of its anhydrous crystalline state. The thermal behaviour of commercial TAβCD showed an initial broad endothermic band, attributed to the loss of the weakly hydrogen-bonded water, followed by the fusion peak at 191.8 °C of a low-melting anhydrous polymorph which then recrystallizes into a higher-melting form, whose fusion

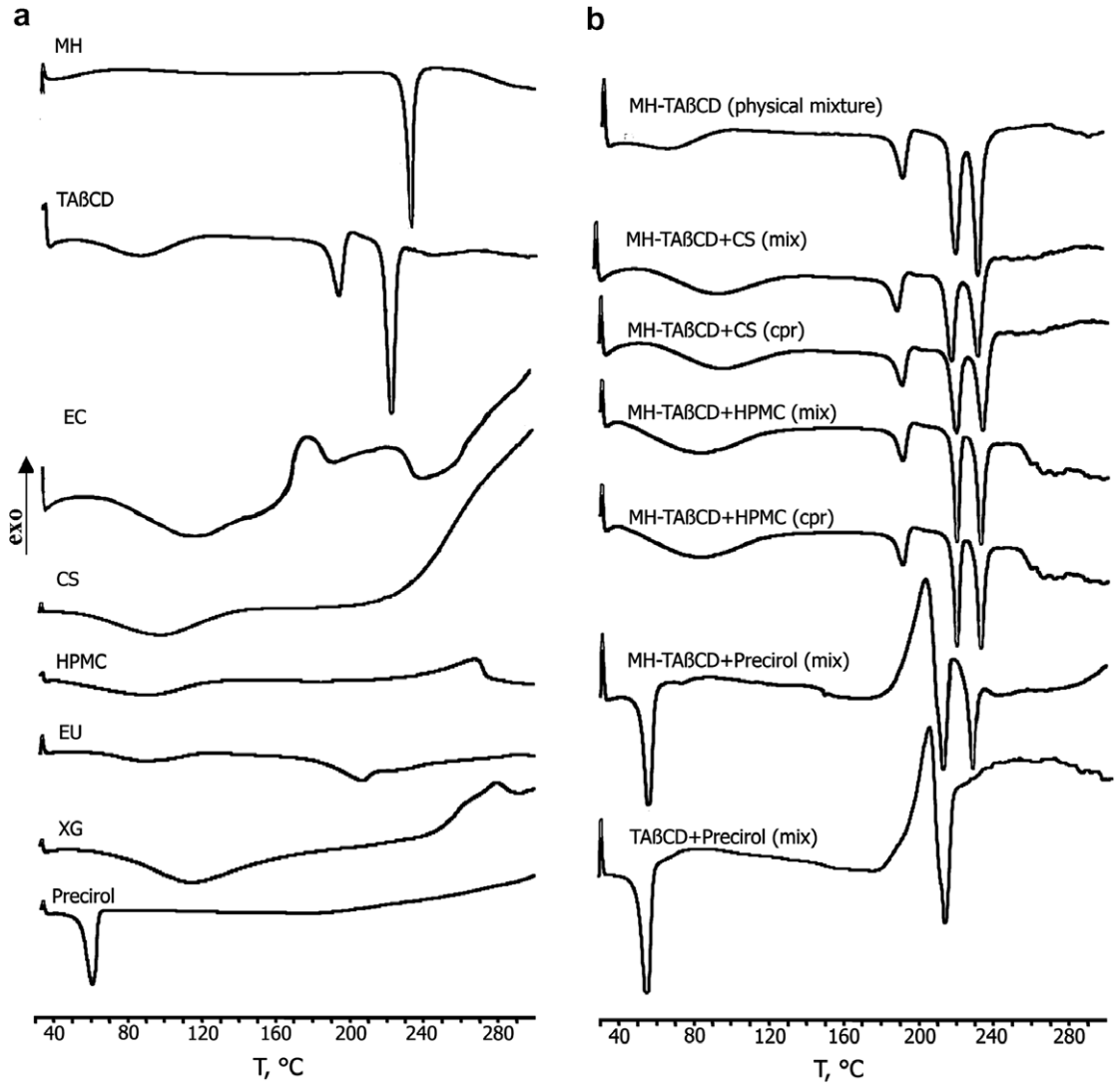

Fig. 1. DSC curves of (a) pure components (MH, metformin hydrochloride; TAβCD, triacetyl-β-cyclodextrin; XG, xanthan gum; CS, chitosan; EC, ethylcellulose; HPMC, hydroxypropylmethylcellulose; EU, Eudragit®L100-55; Precirol®), and (b) equimolar mixtures of MH–TAβCD (1:1 mol/mol) with HPMC, or CS or Precirol®.

endotherm peaked at 219.8 °C [17]. The DSC profiles of chitosan, ethylcellulose, hydroxypropylmethylcellulose, and xanthan gum were typical of amorphous substances, all showing a large dehydration band in the 50–120 °C temperature range. Eudragit-L100-55 showed a broad endothermic band ranging between 50 and 100 °C, due to the polymer dehydration, followed by a second endothermic effect at higher temperature, attributable to the melting of its crystalline portion, whereas the thermal behaviour of Precirol® indicated its crystalline anhydrous nature, only exhibiting a sharp melting peak at about 60 °C. The thermal profiles of the physical mixtures of drug and TAβCD with the different examined excipients (except the case of blends with Precirol®) nearly corresponded to the superimposition of those of the single components, as it is shown, for example, in Fig. 1b for the system with chitosan or HPMC, indicating the absence of solid-state interactions and allowing assessment of compatibility in all the examined formulations. As a further confirmation of the absence of incompatibility problems, no appreciable differences in the DSC curves of the mixtures were observed after their tableting and subsequent powdering.

On the contrary, the thermal curve of the mixture containing Precirol® (Fig. 1b) showed the disappearance of the fusion peak of the low-melting polymorphic form of TAβCD and the appearance of an exothermal effect, peaked at about 220 °C, not present in the thermal profiles of pure components. In order to gain insight into this unexpected behaviour, the curves of the related binary mixtures were then recorded. The DSC curve of the Precirol®–drug binary mixture (not shown) was the simple superimposition of those of pure components. On the contrary, the thermal curve of the binary Precirol®–TAβCD mixture (Fig. 1b) showed the same effects observed in the complete final blend, thus supporting in the interpretation of its thermal profile. In fact, the appearance of the exothermal band

and the concomitant disappearance of the TAβCD fusion peak at lower temperature can both be explained by the presence of an amorphous form of the CD, formed during mixing with Precirol®, which recrystallizes, during the DSC run, into the more stable higher-melting crystalline form. A similar thermal behaviour has been described for pure TAβCD after grinding or kneading with water–ethanol of the commercial sample [13]. Moreover, comparable thermal profiles have been reported also for X-ray amorphous TAαCD (obtained by microwave-drying) and TAγCD (obtained by spray-drying of acetone/water solutions) and attributed to the tendency of the samples to recrystallize by heating [18]. It can be therefore concluded that the changes noticed in the DSC curve of the Precirol®–MH–TAβCD mixture are related to a modification of the solid-state properties of TAβCD as a consequence of mixing with the excipient and, consequently, they are not indicative of incompatibility with the drug. Nevertheless, it was considered opportune to eliminate Precirol® from the list of possible excipient candidates for the production of the MH–TAβCD sustained-release matrix tablets.

4.1. Development and evaluation of matrix-tablet formulations

Preliminary release experiments performed with matrix tablets containing MH alone in mixture with each of the selected polymers showed that, as expected, because of the high water solubility of the drug, none of the polymers used was able to adequately control and/or reduce drug release rate in agreement with the prefixed goals.

A first series of matrix-tablet formulations was therefore prepared, by using the drug as equimolar co-ground system with TAβCD, and mixing it with the different individual polymers, always keeping the total drug amount and the complex-to-polymer (w/w) ratio constant (see Table 1, tablets A–E). As can be observed in Fig. 2, where the drug release profiles from such tablets are presented, the presence of the hydrophobic carrier TAβCD was very effective in slowing down the drug release rate with respect to the corresponding previous formulations with drug alone. However, none of these matrix-tablet formulations allowed achievement of the prefixed targets for drug release behaviour, even though clearly different release profiles were obtained with the various examined excipients. In fact, tablets with hydrophilic swelling polymers such as HPMC, CS and particularly XG clearly overcame the prefixed 40% limit value for gastric release and reached 100 % release in less than 3 h. On the contrary, both the water insoluble EC and the pH-dependent EU accomplished the above requirement, exhibiting a percent of drug released lower than 30% after 2 h; however, they gave rise to an excessive reduction in drug release rate, reaching less than 60 % of release after 5 h.

Therefore, in the attempt to obtain the desired synchronization of the drug release rate, the effect of using suitable mixtures of the examined polymers, by combining a faster-release one (such as HPMC or CS) with a slower-release one (such as EC or EU), was investigated. With this aim, a new series of matrix tablets containing the equimolar physical mixture MH–TAβCD and mixtures of EC–CS, EC–HPMC, EU–CS and EU–HPMC in the 1:1 or 1.5:0.5 (w/w) ratios was prepared (always keeping the complex-to-polymer (w/w) ratio constant) (see Table 1, tablets G–P). Fig. 3 shows the drug release profiles from such tablet formulations. The use of the examined polymeric mixtures enabled a better modulation of the drug release rate with respect to formulations with individual polymers. In particular, combinations with CS were more effective in reducing the drug release rate than the corresponding ones with EC, and the 1.5:0.5 (w/w) polymer-to-polymer ratio was better than the 1:1 one. In fact, the best results were obtained with EU–HPMC and EU–CS 1.5:0.5 (w/w) mixtures, which

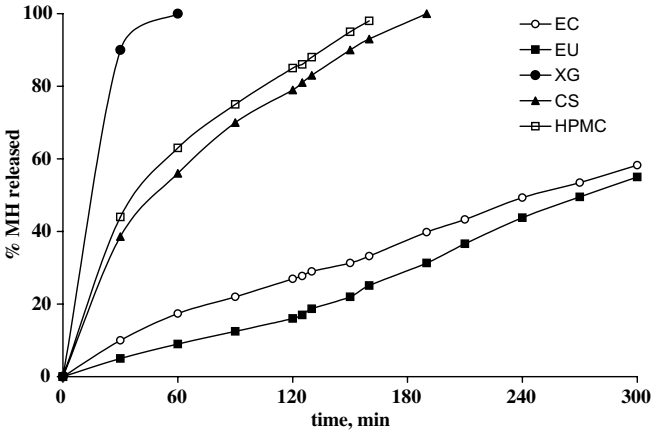

Fig. 2. Drug release profiles from matrix-tablet formulations containing MH–TAβCD ground product dispersed in xanthan gum (XG), hydroxypropylmethylcellulose (HPMC), chitosan (CS), Eudragit®L100-55, ethylcellulose (EC) (see Table 1 for tablet composition).

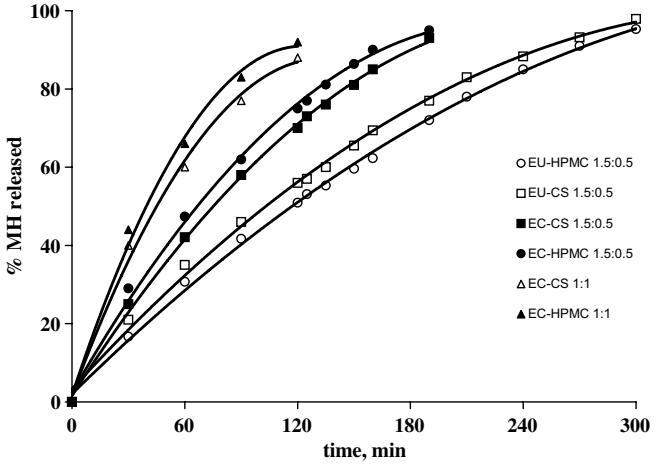

Fig. 3. Drug release profiles of formulations containing MH–TAβCD ground product dispersed in ethylcellulose–hydroxypropylmethylcellulose (EC–HPMC), ethylcellulose–chitosan (EC–CS), Eudragit®L100-55–chitosan (EU–CS), Eudragit-L100-55–ethylcellulose (EU–EC) 1:1 and 1.5:0.5 (w/w) mixtures (see Table 1 for tablet composition).

allowed achievement of 100% drug release within the target time of 5 h. However, the prefixed goal was not completely reached, since the drug amount released after 2 h (about 50–55%) was still higher than the target 40% value.

In order to further reduce the initial drug release rate, a new series of matrix tablets based on the selected EU–HPMC or EU–CS mixtures were then prepared, where the drug–CD co-ground product was replaced by the corresponding spray-dried one (Table 1, new tablets G–P). In fact, according to our previous studies [13], spray-drying was absolutely the most successful technique in bringing about strong drug–carrier interactions, and, consequently, in reducing the drug dissolution rate. Unexpectedly, however, as can be observed in Fig. 4, the use of the MH–TAβCD spray-dried system gave rise to an excessive decrease of the drug release rate, leading to a percent of drug released lower than 40% after 5 h, independent of both the type (EU–HPMC or EU–CS) of polymeric mixture and the relative ratio between the components (1:1 or 1.5:0.5 (w/w)).

Taking into account the very different performance displayed by the MH–TAβCD system when used as co-ground or as spray-dried system, we considered it interesting to evaluate the effect of their combined use in the tablet formulations. Thus, a further series of matrix tablets was prepared by using the EU–CS 1.5:0.5 (w/w) mixture, selected as polymeric matrix, and blends, in the 1:1 or 1:2 (w/w) ratios, of MH–TAβCD as co-ground or spray-dried product. Fig. 5 shows the drug release profiles from the new formulations, together with those from the corresponding tablets containing the drug–CD co-ground or spray-dried product, separately. As can be seen, the proposed strategy was successful in adequately modulating the drug release rate, giving rise to very regular almost linear release profiles. In particular, the matrix-tablet formulation containing the 1:1 (w/w) blend of MH–TAβCD as co-ground and spray-dried system fully achieved the prefixed goal, giving about 30% released drug after 2 h at gastric pH, and overcoming 90% released drug within the prefixed interval time of 5 h.

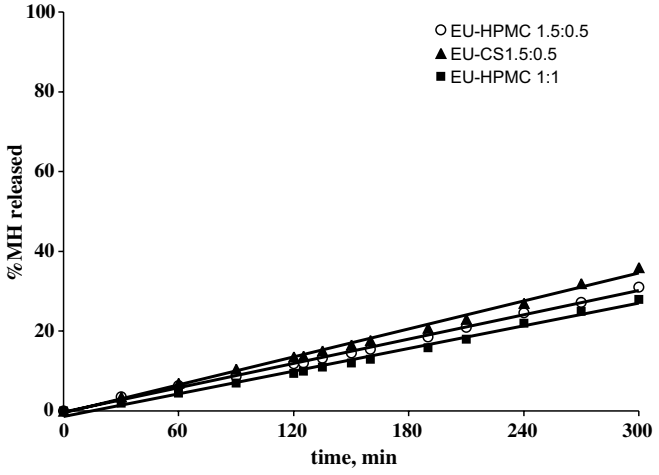

Fig. 4. Drug release profiles of formulations containing MH–TAβCD spray-dried product dispersed in Eudragit®L100-55–chitosan (EU–CS), Eudragit®L100-55–hydroxypropylmethylcellulose (EU–HPMC) 1:1 or 1.5:0.5 (w/w) mixtures (see Table 1 for tablet composition).

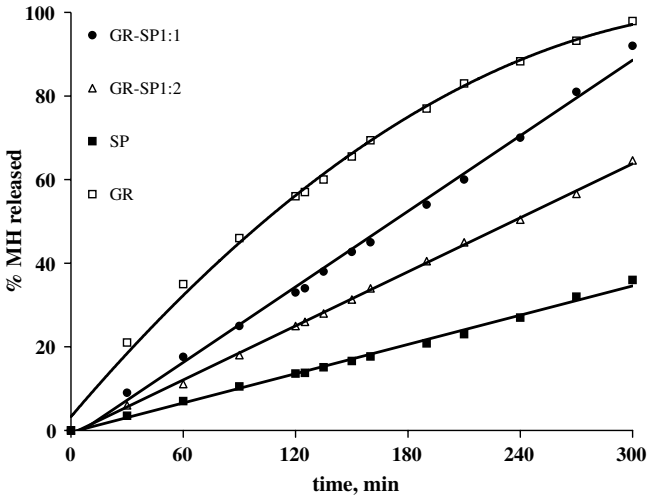

Fig. 5. Drug release profiles of formulations containing MH–TAβCD ground and spray-dried product (at 1:1 and 1:2 (w/w) ratios) dispersed in Eudragit®L100-55–chitosan (EU–CS) 1.5:0.5 (w/w) mixtures (see Table 1 for tablet composition).

In order to gain more insight into the role of the use of MH–TAβCD, as co-ground or as spray-dried product, separately or in different (w/w) combinations, on the drug release mechanism, release data from this series of selected matrix tablets were analysed according to the zero-order, first-order and Higuchi's square root equations (Table 2). It can be observed that the Higuchi equation was the most suitable mathematical model for describing experimental data only for formulations containing drug–CD ground alone, indicating that diffusion through the matrix was the main factor in controlling the drug release rate from such tablets. This was also evidenced by the value of the release exponent n (0.651), which was rather near to the theoretical one expected for a Fickian diffusion-controlled release mechanism ($n = 0.5$), even though a contribution of the hydrophobic carrier in influencing drug release rate has to be considered.

Interestingly, all formulations containing the drug–CD spray-dried product, alone or in combination with the co-ground one, showed an almost zero-order release, as indicated by the highest correlation coefficient values obtained according to this kinetic model, and as confirmed by the release coefficient exponent n, which was in all cases about

Table 2
Correlation coefficients and release exponent n according to the different kinetic equations used for describing metformin hydrochloride (MH) release behaviour from Eudragit®L100-55–chitosan matrix tablets containing the drug as equimolar ground (GR) or spray-dried (SP) product with triacetyl-β-cyclodextrin (TAβCD) or their 1:1 or 1:2 (w/w) mixtures (see Table 1 for tablet composition)

MH–TAβCD	Zero-order	First-order	Higuchi's equation	n
GR	0.9579	0.8546	0.9853	0.651
SP	0.9951	0.9056	0.8872	1.040
GR-SP1:1	0.9962	0.9169	0.8995	1.004
GR-SP1:2	0.9991	0.8864	0.8825	0.996

1. This indicated that in the presence of the slow-dissolving spray-dried product, the drug dissolution rate from the drug–CD complex, and not the diffusion through the matrix, becomes the predominant element in determining the drug release kinetic. Such an important finding underlines the prevalent role of the drug–TAβCD complex and of its preparation method on the performance of the final formulation. A further powerful advantage deriving from this finding is that the drug release from these formulations, mainly depending on the slow dissolution rate of its complex with the pH-independent hydrophobic CD, is scarcely influenced by pH variations.

5. Conclusion

The proposed strategy of simultaneously exploiting the combination of the drug with a hydrophobic cyclodextrin, such as TAβCD, and its dispersion in a suitable polymeric matrix, was effective in adequately modulating the drug release rate.

Release experiments demonstrated that blends consisting of a hydrophobic swelling polymer (such as HPMC or chitosan) with a pH-dependent one (such as Eudragit-L100-55) were more useful than single polymers in controlling drug release.

Moreover, the crucial role played by the drug–TAβCD system preparation method (as co-ground or as spray-dried product) in determining the behaviour of the final matrix-tablet formulation was also evidenced. In fact, it has been shown that, for a given matrix-tablet composition, different sustained-release effects can be obtained by simply varying the relative amounts of MH–TAβCD as co-ground or spray-dried product. In particular, the 1:1 (w/w) blend of such systems, dispersed in a Eudragit–chitosan polymeric matrix, was able to provide the desired rationalisation of the drug release pattern, allowing an effective delivery of the drug restricted to the gastric and jejunal tract. Moreover, the zero-order release kinetic obtained from this formulation was mainly driven by the slow dissolution rate of the MH–TAβCD complex, and then poorly sensitive to the environmental pH. This should make the *in vivo* drug release profile almost independent from the ample physiological variations observed for gastric pH (either on the different individuals and, for a given individual, on fasted or fed conditions) and thus enable a more predictable behaviour with respect to a common pH-dependent matrix-tablet formulation.

Therefore, it can be reasonably hypothesized that the obtained formulation could provide a satisfying agreement between the time for complete release and that for the transit of the system through the upper part of the GI tract, thus allowing an improvement of drug bioavailability and therapeutic efficacy as well as better patient compliance compared to immediate-release formulations. *In vivo* studies on human volunteers with the selected tablet formulations are currently under investigation, in order to evaluate their actual better therapeutic effectiveness in comparison with an immediate release formulation.

Acknowledgement

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