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ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 68 (2008) 303–309
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

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

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Received 21 March 2007; accepted in revised form 4 June 2007
Available online 12 June 2007

**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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doi:10.1016/j.ejpb.2007.06.004

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 $g^{-1}$).