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Controlled release of metoprolol tartrate from nanoporous silica matrices

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ABSTRACT

A series of nanoporous silica matrices (a silica gel matrix and two ordered mesoporous silica) have been investigated as potential carriers for the controlled release of metoprolol tartrate a selective β1 receptor blocker used in the treatment of several diseases of the cardiovascular system. Particular attention was devoted to the optimisation of a reproducible and fast synthetic procedure. The textural properties, structure and chemical nature of the porous surfaces were characterised by N_2 physisorption, X-ray diffraction, HR-TEM and FTIR analyses. The delivery profiles were collected in vitro in physiological solution at pH 7.4.

It has been possible to observe a close correlation between the drug release kinetic and the textural properties of the carriers.

1. Introduction

The realisation of a new pharmaceutical form involves several steps, among which the selection of the excipients (stabilizing agents, lubricating, binding agents, sweetening, colouring, aromatizing, ...) that both improve and favour the acceptability of the final product by the patient. The choice of the carrier is of fundamental importance as in most cases it affect the transfer modality of the drug to the organism. With traditional formulations the delivery of the active agent is total and immediate: it reaches a maximum value that could be out of the therapeutically range. In the last years many efforts have been devoted to the development of new formulations that can control both rate and period of drug delivery. Using controlled drug delivery systems (DDS) designed for long-term administration, the drug level in the blood is kept constant for long time between the desired maximum and minimum value. Other important advantages of using controlled-delivery systems can include: (i) the need for fewer administrations, (ii) optimal use of the drug at issue, and (iii) increased patient compliance.

An inert, biocompatible and stable matrix has to be adopted in the design of an ideal DDS. The traditional carriers currently employed are either natural or synthetic polymers (such as microcapsules, cells, lipoproteins, liposomes, ...), but an increasing number of studies is actually addressed to the development of alternative supports, such as silica-based materials that have attracted a lot of interest [1–8]. Silica matrices show high biocompatibility–biodegrability [1,9] (these materials are biodegradable to monosilicic acid (in the long run) in the intestine) and resistance to microbial attack; these systems exhibit higher mechanical strength, enhanced thermal stability, and negligible swelling in organic solvents if compared to most organic polymers. Moreover, physico-chemical and textural properties of silica can be modulated *ad hoc* by the choice of a tailored synthetic approach. Among the different techniques adopted for silica preparation, the sol–gel process is particularly attractive, as it permits to control the physico-chemical features (textural properties, hydrophilic–hydrophobic character) of the material simply through the proper choice of the synthesis parameters (such as composition of precursors mixture, catalysts, pH range, ageing). The relatively mild processing conditions allow the incorporation of the bioactive molecule into the matrix in a one-step process [10,11]. In the case of silica-based delivery systems, the kinetic release of the drug is ruled by several factors and an important key-role is played by both physico-chemical nature of silica surface and the interaction between the carrier and the active molecule. These interactions can be of different nature: chemical interaction (hydrogen or electrostatic bond) and/or steric interaction related with the texture of the carrier. This last interaction is very marked in the case of ordered nanoporous silica, like MCM-41, SBA-15 and so on.

Recently we have studied several silica systems as carrier for sustaining the drug release of ibuprofen. We have investigated the behaviour of methyl-modified silica matrix prepared by a sol–gel approach or ordered silica matrices pure and modified with aminopropyl groups [12–14].

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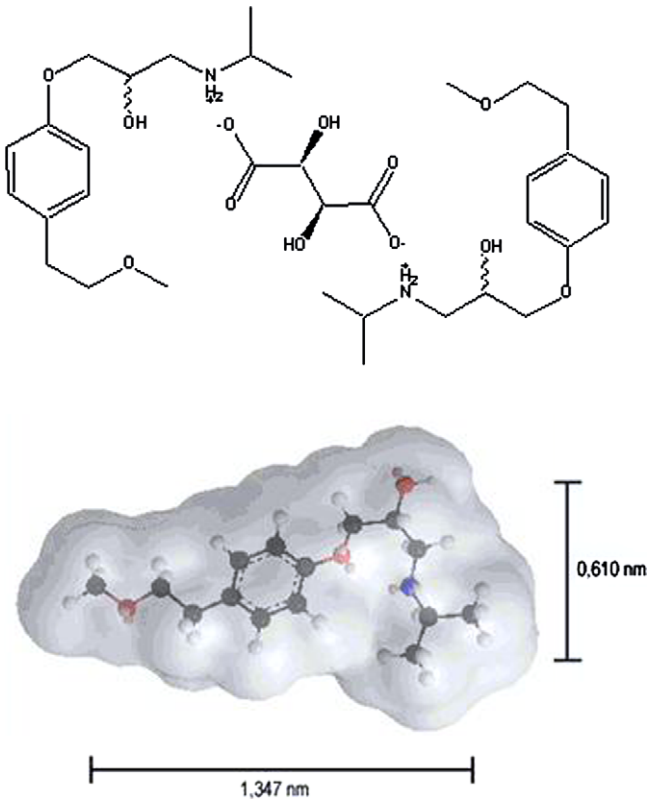

Fig. 1. Molecular model of metoprolol tartrate.

In the present work we have focused the attention on both synthesis and characterisation of silica carriers for the controlled release of metoprolol tartrate (MPT) (see Fig. 1). Several points of novelty are presented in this paper, as reported in the following:

(i) For the first time, MPT has been used as drug model to develop a DDS by using silica as carrier. Metoprolol is frequently employed to alleviate several diseases of the cardiovascular system and its administration by means of a prolonged DDS is desirable, as confirmed by the controlled release formulations of metropolol present on the market.
(ii) Two innovative and reliable techniques have been optimised for the synthesis of the investigated drug-silica systems: a one-pot sol–gel approach and an incipient wetness impregnation method. The drug is usually adsorbed on the (silica) carrier by post-synthesis wet impregnation.
(iii) A thorough comparison between a silica gel and two mesoporous carriers is here reported.

Aim of our work has been the investigation of the effect of both textural and physico-chemical properties of the carriers on the drug delivery behaviour. The target has been pursued through a depth analysis and comparison of three different silica matrices.

2. Experimental

2.1. Materials

Tetraethoxysilane (TEOS) (Aldrich, 98%), NaOH (Fluka, 97%), EtOH (Fluka, 99%), Tris Buffer Saline (Fluka), HCl (Fluka, 37%), Cetyltrimethyammonium bromide (CTA-Br) (Fluka, 99.5%), Pluronic 123 (Aldrich), Metoprolol Tartrate (MPT, 99%). All reagents have been used as received.

2.2. Synthesis

In order to ensure the drug stability after adsorption, all the MPT/Silica composites were prepared by using mild synthesis conditions (room temperature, gentle stirring...) as described in detail in the following sections.

2.3. Silica gel

Drug/silica composites were synthesised by a one-step sol–gel process. In a typical procedure, the silica precursor (TEOS) was combined with ultra pure water (acidified with the addition of a few drops of HCl 0.01 M) in the opportune molar ratio (1TEOS: $5H_2O$) and the mixture was homogenised by sonication. A water (milliQ water) solution of metoprolol tartrate (40 g/L) was added to the obtained sol under continuous stirring in order to favour the homogeneous dispersion of the drug in the final material. Each individual sample (silica + MPT) was obtained by dispensing 1 mL of the sol into a polyethylene cylindrical vial (diameter: 1.2 cm, thickness: 1 cm) the monolithic and homogeneous tablets were left to age in a closed environment at room temperature for one day, in order to ensure the complete reticulation of the gel and to reach a constant weight. Each tablets (diameter: 1.0 cm; thickness: 0.5 cm) contains 80 mg of MPT (real amount). The MPT real content was verified by means of TG analyses (TG analyses were performed in the 25–600 °C interval using a NETZSCH STA 409 instrument in flowing air with temperature ramp set at 10 °C/min).

2.4. Mesoporous samples

MCM-41 and SBA-15 matrices were synthesised as reported in a previous work [15].

The drug was embedded on the as-synthesised carriers by incipient wetness impregnation. In a typical synthesis, an opportune amount of metoprolol tartrate is dissolved in ethanol. Then the drug-containing solution is added to the silica support containing the same pore volume as the volume of solution that was added. Capillary action draws the solution into the pores. The drug/silica composite was then dried at 50 °C for 12 h to drive off the volatile components within the solution. The silica/drug samples (MCM-41 + MPT or SBA-15 + MPT) were conformed (pressure 2.5 Ton for 5 min) as 0.3 g capsules (diameter 1.0 cm; thickness: 0.5 cm, MCM-41 + MPTp and SBA-15 + MPTp).

All the capsules contain 80 mg of MPT.

This method was used to adsorb MPT also in a commercial silica (Akzo, 329 m^2/g) used as reference frame.

2.5. Delivery release (in vitro study)

In vitro study of metoprolol release from the substrates was performed as follows.

In a typical experiment, a capsule was soaked in the opportune volume (10 mL) of a saline solution (Tris Buffer Saline Solution) at pH 7.4 and maintained at 37 °C. Samples of 1 mL were removed at predetermined times and replaced by the same volume of the fresh medium. The drug concentration in the liquid phase was evaluated by UV spectrometry at 274 nm (Perkin–Elmer λ40 instrument). Calibration curve of metoprolol was determined by taking absorbance vs. metoprolol concentration between 0 and 2000 ppm as reference parameters. The effective concentration in solution was calculated on the basis of the following equation [16]:

$$C_{eff} = C_{app} + \frac{v}{V}\sum_{1}^{t-1} C_{app}$$