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Research paper

Design of silica carrier for controlled release of molsidomine: Effect of preparation methods of silica matrixes and their composites with molsidomine on the drug release kinetics in vitro

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ABSTRACT

Biodegradable, controlled-release carrier materials with non-toxic degradation products are very valuable for delivery of cardiovascular drugs. This study is a part of development of novel form of vasodilator molsidomine to improve pharmacokinetic and consumer properties of the drug. It focuses on the effect of preparation methods of the drug–silica composites on their release kinetics. Phenyl modified silica materials prepared by different ways were studied as potential carriers for molsidomine. The composites of molsidomine with the modified silica were synthesized via one-step sol–gel route and adsorption. The drug was adsorbed onto the phenyl modified silica prepared by co-condensation and grafting. Furthermore, the one-step sol–gel derived composites were prepared at pH 4.4 (the isoelectric point of the drug) and pH 6.3 (the zero point of charge of the silica). In vitro release kinetics of molsidomine from the synthesized composites in simulated gastric (pH 1.6) and simulated blood (pH 7.4) media was studied. Our findings demonstrate that the release of the drug can be controlled by manipulating the synthesis ways and changing the sol–gel pH. The comparative analysis of molsidomine release profiles from the composites prepared by one-step sol–gel synthesis at different pH and adsorption allows to reveal perspective composites which exhibit sustained release of molsidomine for about 36 h in acidic medium close to the zero order release kinetics.

1. Introduction

Efficiency of therapy depends on many factors, including patients' adherence to drug dosing. It is evident that single dose a day can ensure the best fulfillment of the drug dosing. Molsidomine is an active substance of a series of cardiovascular drugs which are widely used clinically. It acts via the metabolite SIN-1 through liberation of NO. The duration of effect of single oral dose of molsidomine is 2–3 h. This leads to necessity to take the drug at 3–4 times a day [1]. Therefore, development of controlled release form of the drugs is very important task.

In present time there are some approaches to improve pharmacokinetics of drugs and change duration of single drug dose. For example, ability of cyclodextrins to act as hosts in the formation of inclusion complexes has been extensively exploited in their use as sustained release drug carriers. Functionalized cyclodextrins have been proposed as sustained release carriers for molsidomine [2–4]. "Packing" of drug into special matrixes can ensure controlled release of drug and ability to be taken once daily but preserve the drug efficiency as in traditional formulations. The sustained release matrixes on the basis of various polymers and copolymers have been developed for molsidomine administration [5–7].

In this work mesoporous silica materials are offered as potential carriers for sustained release of molsidomine. It is well known that amorphous silica is nontoxic [8] and biodegradable [9,10]. In contrast to some polymers whose degradation can cause an inflammatory response which interferes with the intended therapy [11,12], silica materials are biocompatible [9,13]. Unlike cyclodextrins, silica particles due to their porous structure and high surface area are able to incorporate sufficiently greater drug amount and ensure high drug loading. In addition, silica materials have a higher mechanical stability and thermal stability than polymers and cyclodextrins. There are simple, reliable and inexpensive procedures of synthesis of silica materials having designed pore size

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and surface properties. Therefore, undoubtedly, amorphous silica is promising platform for development of controlled drug delivery matrixes.

In recent years, employing mesoporous materials for hosting and further delivering of a variety of drug molecules has been demonstrated [14–25]. It has been shown that molecular drugs can be easily accommodated within the mesopores and the pore size in the range of 2.5–5.0 nm is the most suitable for incorporation of small drug molecules [14,15]. However it is generally accepted that the drug delivery rate decreases with decreasing pore size. Therefore, in the present work the silica materials having the pore size of about 3 nm and narrow pores distribution are considered as the matrixes for molsidomine delivery systems.

Drug release rate for such mesoporous materials also depends on their surface chemical properties, i.e. nature of surface functional groups because this factor determines strength of drug–silica matrix interaction. Stronger interaction between naproxen and amino-modified SBA-15 results in the good control ability of the samples in comparison with the unmodified silica [17]. The same result was observed for release of sulfadiazine from the carboxylic-modified silica materials [18], emodin from amino-functionalized silica [19], etc. The results of some studied testify that drug release could be effectively controlled by introduction of hydrophobic groups on the mesoporous silica surface. The hydrophobic groups could delay the release fluid to penetrate into the mesopore channels and hence delay drug molecules to move out of the mesopore channels [20,21].

Our previous studies showed that the mesoporous silica functionalized by phenyl groups binds the largest amount of molsidomine and the drug–silica interactions are the strongest [22–25]. It has been established that π–π interactions between the heterocycle of molsidomine and the phenyl surface groups of the functionalized silica as well as hydrogen bonding between the N_6-exocyclic molsidomine groups and the silanols are responsible for the drug-matrix binding [22–25] (Structural formula of molsidomine is presented in Fig. 1). Therefore, the phenyl functionalized silica materials were chosen as the objects of this study.

Surface functionalization of mesoporous silica materials via covalent bonding of organic groups can be achieved by two methods: i.e., grafting and co-condensation [26]. The functionalized silica materials synthesized through these two methods have different surface properties [26–29], resulting in different drug loading and strength of interaction with the matrixes and hence, the drug release rate [28,29]. In the present work a comparative investigations of drug release properties of mesoporous materials whose surfaces are functionalized with chosen organic groups via post-grafting or co-condensation were carried out.

There are two routes of "packing" (or incorporation) of drug molecules into designed matrix: adsorption [15–25,28–30] and one-step sol–gel synthesis [30–32]. Properties of the silica–drug composites prepared by these methods differ from one another because they are formed by different ways. Consequently, the route of synthesis of the silica-molsidomine composites should affect the drug delivery rate. In addition, taking into account that hydrogen bonding plays the important role in molsidomine binding with the silica matrixes [22–25] and pH affects a state of the drug molecules in solution and surface chemistry of the adsorbents, the composite formation at the one-step sol–gel synthesis was carried out at pH 4.4 (molsidomine pI = 4.4 [25]) and 6.3 when the phenyl functionalized silica surface is uncharged [24].

Thus, the aim of this work was to study effects of preparation of phenyl functionalized mesoporous silica matrix as well as the silica-molsidomine composites on the drug release kinetics at pH 1.6 (stomach) and 7.4 (blood) because we conjecture that novel form of molsidomine may be destined both for oral and intravenous administration. The obtained results allowed to estimate a potential application of the composites for development of new sustained release form of molsidomine.

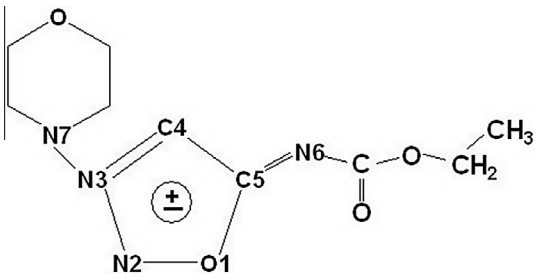

Fig. 1. Structural formula of molsidomine (N-(ethoxycarbonyl)-3-(4-morpholino)sydnonimine).

2. Experimental

2.1. Materials

Molsidomine ((N-(ethoxycarbonyl)-3-(4-morpholino)sydnonimine) (Aldrich), tetraethoxysilane (TEOS) (high purity grade, Russia), phenyltrimethoxysilane (PhTMOS) (Acros, 85%), D-glucose (ICN Biomedicals, >99% purity) were used without further purification. Sodium hydrogen phosphate and sodium dihydrogen phosphate (Russia, analytical grade) were used to prepare buffer solutions with pH 4.8 and pH 7.4. Glicine (Sigma–Aldrich, >99%), sodium chloride (Russia, analytical grade) and hydrochloric acid (HCl, 36–38%) were used to prepare buffer solution, pH 1.6.The buffer solutions were prepared using doubly distilled deionized water.

Potassium bromide (Acros, 99+%, IR grade) was dried at 250 °C before use.

2.2. Syntheses

2.2.1. Synthesis of unfunctionalized mesoporous silica (UMS)

The unmodified silica (UMS) was synthesized by sol–gel procedure using D-glucose as structure-forming agent and HCl as catalyst in the prehydrolysis followed by neutralization with NaOH for subsequent polycondensation in the presence of D-glucose as described in [33]. Removal of the template was carried out by water extraction. The sample was dried at 300 °C for 24 h.

2.2.2. Syntheses of phenyl functionalized mesoporous silica materials (PhMS)

The functionalized mesoporous silica (PhMS) was synthesized by two different routes: grafting and co-condensation. The procedures of syntheses have been described in detail early [22]. In brief, to prepare PhMS by grafting, PhTMOS was added to suspension of UMS in ethanol and stirred at room temperature for 20 h. The sample was finally centrifuged and washed two times in ethanol and dried. The resulted sample was denoted as PhMS-g.

The procedure of PhMS synthesis by co-condensation was similar to that described above for synthesis of UMS. The D-glucose solution was added to the prehydrolyzed and then neutralized PhTMOS and TEOS mixture (molar ratio 0.05: 0.95). The sample was washed by water three times and dried. The resulted sample was denoted as PhMS-c.

FTIR spectra showed the complete removal of glucose and successful introduction of the phenyl groups in silica matrix [22].

The parameters of porous structure of PhMS-g and PhMS-c have been obtained earlier and are presented in Table 1 .