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Preparation of resveratrol-loaded nanoporous silica materials with different structures

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ABSTRACT

Solid, nanoporous silica-based spherical mesoporous MCM-41 and KIL-2 with interparticle mesoporosity as well as nanosized zeolite BEA materials differing in morphology and pore size distribution, were used as carriers for the preparation of resveratrol-loaded delivery systems. Two preparation methods have been applied: (i) loading by mixing of resveratrol and mesoporous carrier in solid state and (ii) deposition in ethanol solution.

The parent and the resveratrol loaded carriers were characterized by XRD, TEM, N2 physisorption, thermal analysis, and FT-IR spectroscopy. The influence of the support structure on the adsorption capacity and the release kinetics of this poorly soluble compound were investigated. Our results indicated that the chosen nanoporous silica supports are suitable for stabilization of *trans*-resveratrol and reveal controlled release and ability to protect the supported compound against degradation regardless of loading method. The solid-state dry mixing appears very effective for preparation of drug formulations composed of poorly soluble compound.

1. Introduction

Mesoporous silicas and zeolites are promising materials for various aspects of biomedical applications. The preparation of meso – and microporous silica delivery systems for drugs and bioactive molecules is based on the advantages of these materials – tunable pore size, controlled particle size and morphology, dual-functional surface (external and internal) and chemical composition [1–3]. Thus, their application as drug carriers can solve some problems associated with low stability and poor bioavailability of the active molecules.

Resveratrol (*trans*-3,4,5-trihydroxystilbene), (R) is a potential antioxidant with strong anti-inflammatory and antiproliferative properties, which can be found in grapes, nuts, fruits and red wine (Scheme 1). It is extremely photosensitive compound with low chemical stability, which limits its beneficial therapeutic effects [4]. Thus, loading of resveratrol in nanoporous silica systems can stabilize and protect it from degradation. In addition, the increased specific surface area of mesoporous silica particles could eventually improve its bioavailability.

It is well known that preparation method of drug formulations can influence the solubility of active substance, its loading degree and release profile. Most investigated methods regarding improvement of water solubility are surfactant solubilisation, complexation and micronisation of drugs. A more efficient method to increase drug solubility in water and dissolution velocity was developed at the beginning of the nineties by drug amorphization. A review of some nanotechnologies, commercialized to help deliver poorly water-soluble drugs is made by Kharb et al. [5]. Production of nanocrystalline particles has been attained by different milling techniques leading to amorphization and hence to drug solubility increase. Wet-milling technique [6], physical mixing (paste) [7], ball milling and high pressure homogenization in water [8,9], spray-drying of the drug dissolved in its amorphous/nanocrystalline state on the support [10] and even melt method [11], consisting in heating of a mixture of the drug (itraconazole or ibuprofen) with SBA-15 support have been developed for drug amorphization.

In this study a procedure for dry physical mixing of resveratrol and two types of supports has been applied. Solid nanoporous silica-based materials differing in morphology, topology and pore size distribution, such as mesoporous pure silica (spherical

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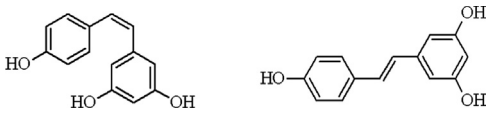

Scheme 1. *Cis*- and *trans*-resveratrol.

MCM-41 and KIL-2) and nanosized silica-alumina zeolite BEA have been used as carriers. Vibrational ball mill mixer was applied for simultaneous amorphization and loading of the poorly water-soluble drug. To the best of our knowledge, such type of mechanical deposition of resveratrol on the chosen silica nanomaterials has not been reported. This solid-state procedure for encapsulation has two important advantages. Dry mixing ensures partial amorphization of resveratrol crystallites, expected to increase its water solubility. The other priority is that the whole amount of added drug substance should remain on the carrier without any loss at preparation. The physico-chemical characteristics, the adsorption capacity and the drug-release kinetics of the formulations prepared by the solid-state method have been compared to their analogues obtained by the conventional method of encapsulation in solution.

2. Experimental

2.1. Synthesis of spherical MCM-41 silica material

MCM-41 with 100 nm particle size was prepared according to the procedure of Huh et al. [12]. This sol–gel procedure is carried out at 80 °C without co-solvent, in water solution and applying NaOH as a catalyst. The relative molar composition of the reaction mixture was: 1 TEOS:0.12C_{16}TMABr:0.31 NaOH:1190H_2O. The formed gel was aged at 80 °C for 2 h, then washed with distilled water until neutral pH, and dried at ambient. Template removal of MCM-41 materials was carried out in air up to 550 °C with 1 °C/min rate for 5 h.

2.2. Synthesis of nanosized KIL-2 material

Mesoporous disordered silicate KIL-2 [13] was prepared by two-step synthesis in molar ratio of 1 TEOS:0.5 TEA:0.1 TEAOH: 11H_2O. In the first step tetraorthosilicate (TEOS 98%, Acros) and triethanolamine (TEA 99%, Fluka) were stirred for 30 min. Then demineralized water was added to the above mixture, followed by the addition of tetraethyammonium hydroxide (TEAOH 20%, Acros). The solution was mixed with a magnetic stirrer to obtain a homogeneous gel. The final gel was aged overnight at room temperature and then dried in an oven at 50 °C for 24 h. In the second step the gel was solvothermally treated in ethanol in a Teflon-lined stainless autoclave at 150 °C for 48 h. Template was removed by calcination at 500 °C for 10 h in air flow.

2.3. Synthesis of nanosized BEA zeolite

Zeolite beta nanoparticles were synthesized according to Ref. [14]. In brief, the synthesis procedure includes the preparation of a precursor mixture with the following molar composition: 25.00 SiO_2:0.25 Al_2O_3:9.0 R:0.35 Na_2O:295.0H_2O, where R is the organic templating agent tetramethylammonium (TEA) (Sigma, 20% TEAOH in water). The silica source was derived from a colloidal silica suspension Bindzil 30/360 (Eka Nobel, Sweden) containing 31.1 wt% SiO_2 and 0.6 wt% Na_2O. The suspension was freeze-dried to powder. The aluminum source was aluminum isopropylate (Sigma). The obtained initial mixture was a clear homogeneous solution, which was subjected to hydrothermal treatment at 100 °C for 9 days. The crystalline nanoparticles were purified by three times centrifugation at 20,000 rpm for 1 h, followed by redispersion in distilled water using an ultrasonic bath to obtain a colloidal sol with a pH of about 9.5. The sample in its H-form, H-BEA, is used for further resveratrol loading and is designated as R/BEA.

2.4. Characterization

X-ray patterns were recorded by Philips PW 1810/3710 diffractometer with Bregg-Brentano parafocusing geometry applying monochromatized Cu $K\alpha$ (λ=0.15418 nm) radiation (40 kV, 35 mA) and proportional counter.

Nitrogen physisorption measurements were carried out at −196 °C using Quantachrome Autosorb 1C Gas Sorption Instrument. The BET surface area, the mean pore diameter, and the total volume of the samples was calculated and presented in Tables 1 and 2. The pore-size distributions were calculated from the desorption branch of the isotherms with the BJH method. Samples were pre-treated at 80 °C before measurements.

Thermogravimetric measurements (TG) were performed with a Setaram TG92 micro balance with a heating rate of 5 °C/min in air flow.

Attenuated total reflection infrared (ATR-FTIR) spectra were recorded by means of a Varian Scimitar 2000 FT-IR spectrometer equipped with a MCT (mercury-cadmium-tellur) detector and a single reflection ATR unit (SPECAC "Golden Gate") with diamond ATR element. In general, 128 scans and 4 cm^{-1} resolution was applied. For all spectra ATR-correction was performed (Varian ResPro 4.0 software).

2.5. Resveratrol loading and in-vitro release measurements

The powdered samples were loaded with resveratrol by two different methods: deposition by ethanol solution and by solid-state method. Ethanol was chosen as a solvent for drug loading because of high solubility of (R) in it. Deposition of resveratrol in solution was carried out by soaking the silica carriers, under continuous

Table 1
Textural and physico-chemical properties of the parent KIL-2 and MCM-41 mesoporous silica materials and their resveratrol-loaded formulations.

Samples	BET (m^2/g)	Pore diameter (nm)	Pore volume (cm^3/g)	Loaded resveratrol (wt%)*
MCM-41	1175	2.7	0.97	–
R/MCM-41(S)	320	2.5	0.26	39.8
R/MCM-41(SS)	306	2.5	0.27	46.6
KIL-2	664	15.2	1.28	–
R/KIL-2(S)	320	9.8	0.72	35.8
R/KIL-2(SS)	232	10	0.52	48.3

* Determined by TGA by heating from 180 °C to 600 °C.

Table 2
Textural and physico-chemical properties of the parent BEA zeolite and its resveratrol-loaded formulations.

Samples	BET (m^2/g)	Total pore volume (cm^3/g)	Mesopore volume	Micropore volume	Loaded resveratrol (wt%)*
BEA	761	0.46	0.34	0.12	–
R/BEA(S)	34	–	n.d.	–	48.4
R/BEA(SS)	18	0.04	n.d.	–	49.2

* Determined by TGA by heating from 180 °C to 600 °C.