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Silica coatings on clarithromycin

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Abstract

Pre-crystallized clarithromycin (6-*O*-methylerythromycin A) particles were coated with silica from the tetraethyl orthosilicate (TEOS)–ethanol–aqueous ammonia system. The coatings had a typical thickness of 100–150 nm and presented about 15 wt.% of the silica-drug composite material. The properties of the coatings depended on reactant concentration, temperature and mixing rate and, in particular, on the presence of a cationic surfactant (cetylpyridinium chloride). In the presence of cetylpyridinium chloride the silica coatings slightly decreased the rate of pure clarithromycin dissolution.

Keywords: Clarithromycin; 6-*O*-methylerythromycin A; Silica; Coated drugs; Dissolution

1. Introduction

There are several benefits for using controlled drug delivery systems over the conventional tablets or capsules: reduction in drug plasma level fluctuations, reduction in adverse side effects and improvement in tolerability, patient comfort and compliance and, finally, reduction in healthcare costs. The existing oral controlled-release systems comprise coating of tablets or granules, matrix systems, slowly eroding devices and osmotically controlled devices. In this work we present a novel approach in which single drug particles—rather than compressed tablets—are coated with a thin layer of silica with the aim to decrease the rate of drug release.

Formation of silica coatings with selected properties has been studied mostly in systems with inorganic substrates. Examples are silica coatings on hematite (Ohmori and Matijević, 1993) and on titania particles (Lin et al., 2002). Only very recently, Škapin and Matijević (2004) have succeeded to prepare silica and, also, alumina coatings on water insoluble drug particles such as loratadine and danazol. The same

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idea was followed in this work, but with two modifications: (i) the method proposed here is applicable also to water-soluble drug particles, and (ii) the concentration of drug in the reactant mixture is much higher (by up to one order of magnitude) thus being more appropriate for potential use on industrial scale. An additional novelty is the use of special additives (cationic polyelectrolytes) to control both the charge of drug particles and the charge of silica and, hence, to control the deposition process. As a model drug compound, recrystallized clarithromycin (6-*O*-methylerythromycin A) was used in this study.

2. Materials and methods

2.1. Materials

Clarithromycin (6-*O*-methylerythromycin A) was received from Lek Pharmaceuticals d.d., Slovenia. Before use, clarithromycin particles were prepared by pre-crystallization: 10 g of clarithromycin was dissolved in 400 g of water–ethyl alcohol (96%) mixture and then evaporated at 50 °C. Tetraethyl orthosilicate (TEOS, Aldrich Cat. No. 13,190-3), ethyl alcohol (Merck Cat. No. 1.00983.1000), cetylpyridinium chloride monohydrate (CPC, Aldrich Cat. No. 85,556-1), and ammonium hydroxide were of the highest purity grade and used as-received.

2.2. Sample preparations

Preparation of silica coatings on clarithromycin particles was derived from the Stöber process originally developed for preparation of silica particles (Stöber et al., 1986). The procedure consists of hydrolysis and condensation of tetraethyl orthosilicate in ethyl alcohol in the presence of water and ammonia. In the modified procedure used in the present work, clarithromycin particles—in equilibrium with the corresponding amount of dissolved clarithromycin—were present in the reactant solution. Specifically, 4.8 g of clarithromycin particles were dispersed in 62 cm^3 of ethyl alcohol containing 0.48 mol of water and 0.016 mol of ammonia in an ultrasonic bath for 30 min at room temperature. In some experiments, 70 μmol of CPC was added into reactant mixture. Then, 0.04 mol of TEOS were admixed at a rate of 0.34 mmol min^{-1} to this dispersion and aged at 25 °C for 3 h. The system was slowly mechanically stirred during the entire process. The resulting solids were finally separated by sedimentation and drying at 60 °C. For comparison, blank silica suspensions with no clarithromycin particles were prepared by a similar procedure and washed via centrifugation and re-dispersion in water three times.

2.3. Characterization methods

In order to determine the clarithromycin fraction in silica-coated samples, we carried out thermogravimetric analyses (TGA) in air atmosphere using TG 951 and DSC 910 modules (TA Instruments, USA). The particles were examined by scanning electron microscopy (SEM) using a JEOL 220T Microscope (Jeol, Japan). X-ray powder diffraction (XRPD) patterns of all samples were collected on a Siemens D-5000 diffractometer using Cu Kα radiation in the 2θ range from 5° to 35° in steps of 0.04° with a sampling time of 1 s per step. In vitro dissolution studies of pure and coated drug were performed according to USP 24, Apparatus 1 (Basket, Vankel dissolution tester 7000, USA) in 0.1 M Na acetate buffer pH 5.0 and temperature 37 °C. Three hundred milligrams of the sample was suspended into 900 ml of a solvent. At fixed time intervals the samples were withdrawn with a syringe and filtered (filter pore size 0.2 mm) and assayed with high performance liquid chromatography (HPLC) system consisting of a Knauer (Germany) pump K501, a Knauer UV detector and a Knauer 5197 manual injector. A stainless steel analytical column (5 mm × 100 mm) packed with C18 material (Millipore Water Inc., Milford, MA) was used for the chromatographic analysis. The column was kept at room temperature. The mobile phase consisted of a Me:H_2O (0.067 KH_2PO_4) mixture (600/400, v/v) having a pH of 4. The flow rate was adjusted to 1 ml/min. The detection wavelength was 210 nm. Peak detection and integration was done using a BDS 1,26A chromatographic software (Barspec Systems Inc., Israel).

2.4. Statistical evaluation of dissolution profiles

To prove the similarity of dissolution profiles we used the method of calculating the similarity factor as

defined in the following equation:

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [\bar{R}(t) - \bar{T}(z)]^2}{n}}} \right] \quad (1)$$

where f_2 is the similarity factor, n the number of time points, $\bar{R}(t)$ the mean percentage of a dissolved reference drug, and $\bar{T}(z)$ is the mean percentage of dissolved test drug. The evaluation of similarity is based on the conditions of: (i) a minimum of three time points (zero excluded), (ii) 12 individual values for every time point for each formulation, (iii) not more than one mean value of >85% dissolved for each formulation, (iv) that the standard deviation of the mean of any product should be less than 10% from second to last time points, (v) an f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. In cases where more than 85% of the drug are dissolved within 15 min, dissolution profiles may be accepted as similar without further mathematical evaluation (Committee for Proprietary Medicinal Products, 2001).

3. Results and discussion

Silica coatings were directly deposited on clarithromycin particles from the TEOS–ethanol–aqueous ammonia system. As clarithromycin particles are soluble in water, we had to add large quantities of this substance to the reaction mixture to keep a significant amount undissolved and use it as a substrate for deposition. Before use, the original clarithromycin obtained from the producer was pre-crystallized to obtain well defined crystallites as shown in Fig. 1, having crystalline form I. Their crystal structure was determined by comparing the acquired X-ray powder diffraction pattern with literature (Liu et al., 1999; Sohn et al., 2000). The use of such well-defined and rather uniform crystallites facilitated observation of their interaction with silica.

It is well known that in absence of clarithromycin, hydrolysis and consequent condensation of TEOS lead to formation of spherical silica particles. An example of such a material prepared at conditions used in the present work is shown in Fig. 2. In the presence of clarithromycin particles (and, also, the corresponding amount of dissolved clarithromycin in reaction solution), however, silica is deposited onto the surface of clarithromycin particles in a form of a thin layer (Fig. 3). It is worth noting that the crystal structure of clarithromycin did not change during the process of silica deposition (Fig. 4).

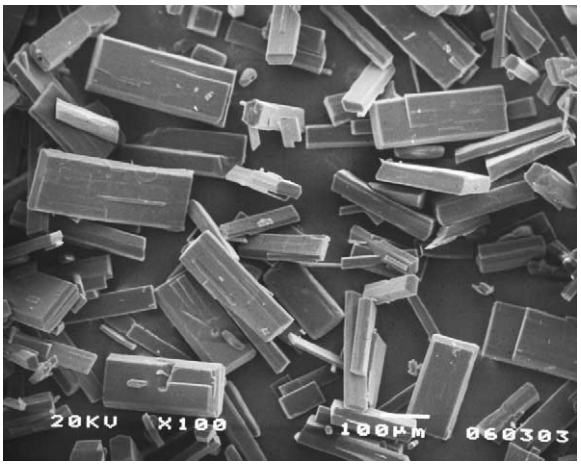

Fig. 1. SEM micrographs of pre-crystallized clarithromycin particles.

Careful examination of Fig. 3 and many other similar SEM micrographs showed that the side planes of clarithromycin particles were not covered with silica. The reasons for this rather surprising effect were unclear. We assumed that it could be due to the

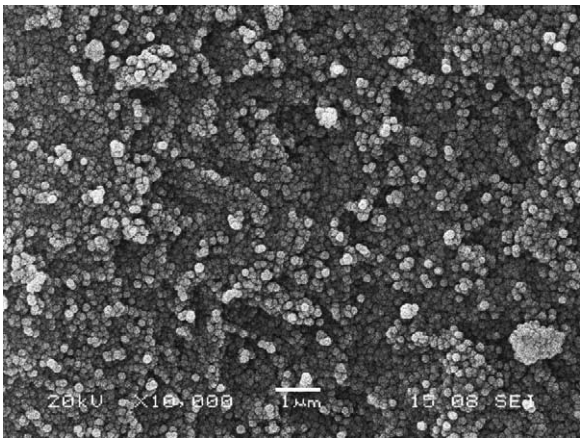

Fig. 2. SEM micrographs of spherical silica particles obtained by hydrolysis and condensation of TEOS without clarithromycin particles in the reactant solution.

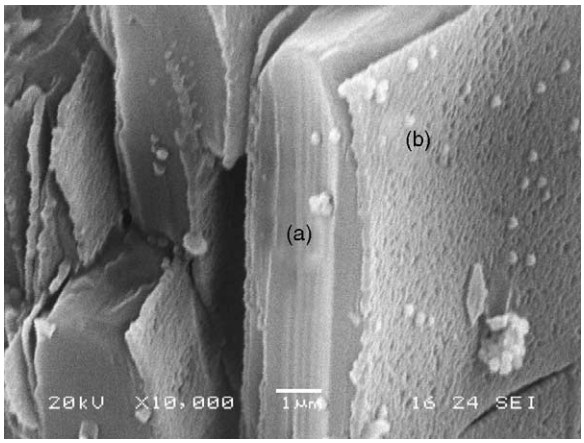

Fig. 3. SEM micrographs of silica-coated clarithromycin particles.

electrostatic repulsion between the negative surface charge dominating the side planes of clarithromycin and the negative charge on silica nanoparticles (nucleoli) due to presence of silanol groups. If so, we further speculated that addition of an appropriate counter-charged substance should decrease the negative charge on both materials' surfaces and thus

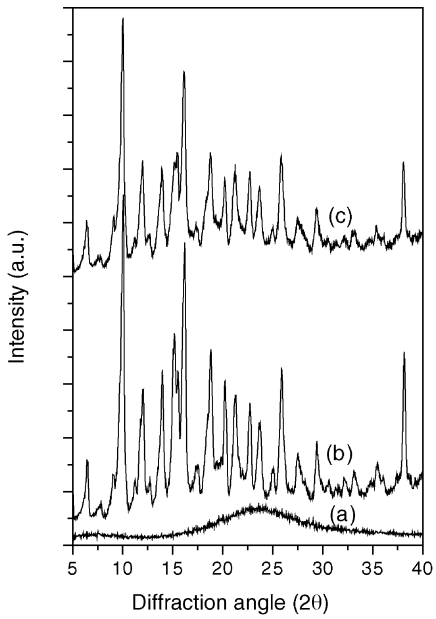

Fig. 4. X-ray powder diffraction patterns of amorphous spherical silica particles (a), pre-crystallized clarithromycin particles (b) and silica-coated clarithromycin particles (c).

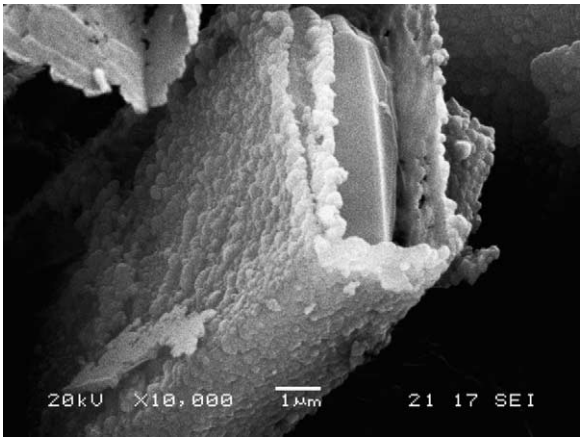

Fig. 5. SEM micrographs of silica-coated clarithromycin particles with CPC in the reactant mixture.

improve the deposition of silica on clarithromycin. To check this assumption, we added a cationic surfactant (cetylpyridinium chloride monohydrate, CPC) into the reactant mixture. Indeed, the SEM micrographs in Fig. 5 show that addition of CPC increases the amount of deposited silica both on the base plane (probably due to smaller silica–silica particle repulsion) and on the side planes (smaller repulsion forces between these planes and silica particles).

In order to study the properties of silica coatings in more detail we dissolved the clarithromycin from the core to obtain pure silica shells as shown in Fig. 6. We have found that the shells are actually monoparticle-arrays (sheets) of silica spheres with a

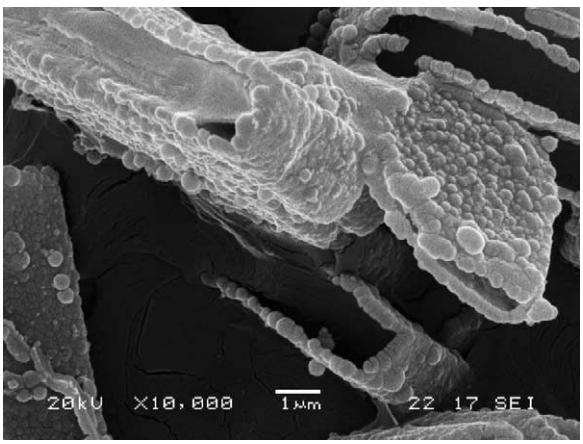

Fig. 6. SEM micrographs of silica coatings after dissolution of clarithromycin core.

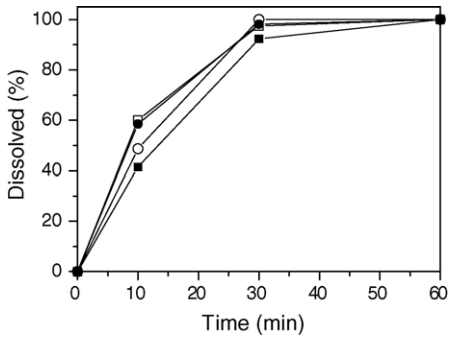

Fig. 7. Dissolution of clarithromycin particles (open circles), clarithromycin particles with 0.4 wt.% CPC (open squares), silica-coated clarithromycin particles (solid circle) and silica-coated clarithromycin particles with CPC in the reactant mixture (solid square).

diameter between 100 and 150 nm. When using CPC as surfactant, an additional layer of silica spheres was deposited on top of such a silica monolayer.

Further experiments showed that the properties of silica coatings were strongly dependent on the preparation conditions, such as the concentration of reactants, temperature and mixing rate. The weight fraction of silica in the final samples was determined by thermogravimetric analysis. The mass remaining after heating to 650 °C was between 14 and 16 wt.% in all samples.

Dissolution profiles of clarithromycin samples are summarized in Fig. 7. Statistical evaluation of dissolution profiles was made with an f_2 test. According to this test no significant differences were found between the samples tested. However dissolution of clarithromycin coated with silica in the presence of CPC differs more while the other profiles are very similar. CPC alone in the formulation with clarithromycin slightly increases dissolution of the drug. This effect is well known and can be explained by improved wettability of the drug in the presence of the surfactant. The decrease of the drug dissolution from the formulation with silica and CPC in comparison with the other samples can be explained by assuming that the coatings formed in the presence of CPC are much less permeable for clarithromycin, either due to the inherent smaller porosity and observed increased thickness of the coating or due to better coverage of the side planes of clarithromycin particles. Incomplete coverage of the drug particles and porosity of the coating may be the main reasons for relatively small differences in dissolution profiles between the samples tested. However, the results are encouraging for further investigations of using this simple precipitation technology for coating of drugs with a purpose to change their dissolution kinetics.

4. Conclusion

It is possible to prepare silica coatings on particles of water-soluble drugs (clarithromycin was used as a model substance). The coatings are thicker and more compact if formed in the presence of a cationic surfactant, which (partially) neutralizes the repulsion forces between silica and the drug but also between the silica particles themselves. Silica-coated clarithromycin in presence of CPC dissolves at a distinctly slower rate than pure clarithromycin.

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