ORIGINAL ARTICLES

DILTIAZEM-LOADED EUDRAGIT RS 100 MICROPARTICLES FOR DRUG DELIVERY: THE CHALLENGE OF VISCOSITY

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ABSTRACT

Strongly shape-dependent viscosity has been found in drug-loaded and “empty” polymeric microspheres (drug delivery systems) made of pharmacopoeial Eudragit RS 100 representative. The dramatically increased viscosity of a layer of spherical particles deposited on the gold electrode surface of quartz resonators from water suspension leads to a large dynamic resistance and inability to sustain stable oscillations in a frequency measuring circuit. The viscosity is also affected by loading the polymer matrix with Diltiazem. Its adverse impact is removed by exposing the deposited layer to acetone vapor leading to “dissolving” the investigated spheres and changing their shape to a thin-layered one.

Keywords: polymeric particles, QCM, viscosity

INTRODUCTION

In the recent decades, polymers have been used widely as key inert or active pharmaceutical materials (ingredients) due to their favorable properties such as good biocompatibility, easy design and preparation, a variety of structures and interesting biomimetic character. Especially in the field of smart drug delivery, polymers play a significant role because they can deliver therapeutic agents directly into the intended site of action with superior efficacy. Moreover, polymers provide controlled release of these agents in constant doses over long periods, cyclic dosage, and also tunable release of both hydrophilic and hydrophobic drugs. Modern advances in drug delivery are now concerned with the design of polymers tailored for specific cargo and engineered to exert distinct biological functions (1).

An important side of polymer-assisted drug delivery research has recently been focused on nanotechnology (2). In this newly emerging area two specific aspects are noticeable. One is the polymer-nanoparticle composites. For example, drug carriers that incorporate inorganic cores may serve as contrast agents for several imaging modalities such
as magnetic resonance imaging. The other aspect is drug carriers of natural, semi-synthetic, and synthetic polymeric nature in the nanoscale to microscale range. The polymeric particles are collectively classified as dense and hollow (with a “free” inner volume) semi-solid plastic-like materials. Most of the polymeric nanoparticles offer stability to various forms of active drugs and have useful to smart release properties.

Recently, we have focused on a specific case of this nanotechnological approach, involving microparticles of Eudragit RS 100, loaded with diltiazem. The ammonio methacrylate copolymer type B, also known as Eudragit® RS 100, has been used for targeting colon, stomach, dermal and mucosal drug delivery. Out of all available pharmacopoeial polymers, it demonstrates proven chemical, physical and microbiological intactness and capability to form stable porous microspheres (3). The uniqueness of this polymeric material has also been reflected in its ability to form pH-independent sustained release matrix formulations (predominantly microparticles with a “microspone” type architecture) with a non-collapsible, highly porous structure and an extremely high drug-loading efficacy. Diltiazem is used to treat high blood pressure and to control angina (chest pain). Diltiazem is in a class of medications called calcium-channel blockers. It works by relaxing the blood vessels so the heart does not have to pump as hard. It also increases the supply of blood and oxygen to the heart (4).

We developed a technique for constructing the polymer microparticles and loading them with the drug Diltiazem, and conducted a preliminary experimental assay of its efficiency by using the quartz crystal microbalance (QCM) method. This method allows measuring very small mass variations on the surface of a quartz resonator by monitoring the behavior of its resonant frequency. In addition, its dynamic resistance is indicative of the damping losses resulting from the viscosity of the attached layer. Thus, various processes involving the penetration of external agent molecules in a polymer matrix and the resulting change of its properties can be precisely followed. A particular research results on applying this method to the study of zeolite porosity by gas absorption has been recently published by us in (5). As a side effect of the present study, we found a dramatic increase of the viscosity of the microparticle layer residing on the resonator surface after the release of water from the previously deposited aqueous solution. This result seems to contradict the existing knowledge on this kind of phenomena and obviously needs to be announced and discussed yet at its premature state of appearance.

**MATERIALS AND METHODS**

All chemicals needed for the fabrication of nanoparticles were of analytical grade and were used as received from commercial sources without any further purification as follows: Diltiazem hydrochloride (99.9%, Puho Pharmaceuticals Co. Limited, China), Ammonio methacrylate copolymer (type B)- Eudragit® RS 100 (Evonik, Germany), Poly(vinyl alcohol) Mw 49 000 (Sigma Aldrich, USA), Sodium hydrogen carbonate (99.5%, Acros Organics), Potassium dihydrogen phosphate (≥99.5%, Fisher Chemical), Sodium hydroxide (≥97%, Fisher Chemical), and Disodium hydrogen phosphate (≥98%, Acros Organics). The solvents ethanol (anhydrous) and dichloromethane were received from Fisher Chemical.

The preparation of the microsized, polyporous polymeric particles (of microspongeous type) was realized applying the so-called Quasi-Emulsion Solvent Diffusion (QESD) method. First, 0.2 g of Diltiazem and 0.6 g of Eudragit® RS 100 were dissolved in 8.0 ml of dichloromethane (so-called “good” solvent) under vigorous magnetic stirring. Then, the organic solution was quickly moved into a 25 ml analogue volumetric burette equipped with a 25-gauge stainless steel needle on its orifice. The obtained organic phase has been slowly dropped (at a rate of about 2 ml/min) into a 100 ml well stirred (650 rpm) aqueous solution of polyvinyl alcohol (0.15% w/v). Having completed the addition of the aqueous PVA solution, the resulted suspension was stirred for additional 3 hours, and then degassed under dynamic vacuum for approximately an hour. The obtained organic phase has been slowly dropped (at a rate of about 2 ml/min) into a 100 ml well stirred (650 rpm) aqueous solution of polyvinyl alcohol (0.15% w/v). Having completed the addition of the aqueous PVA solution, the resulted suspension was stirred for additional 3 hours, and then degassed under dynamic vacuum for approximately an hour. The obtained microparticles have been isolated by centrifugation for 5 minutes at 4000 rpm, and then washed with distilled water by suction filtration. In the same conditions, a blank sample (unloaded with drug) was also prepared. The obtained filtrate has been concentrated to dryness under reduced pressure in a desiccator for 24 hours (yield = 93.0%).
Aqueous suspensions of the obtained microparticles have been prepared and thin layers have been coated on the central part of quartz resonators (10 MHz, gold electrodes, Quartz Design Bulgaria Ltd.) by drop casting with a micropipette. To release the water, the resonators have been heated at 80°C for appropriate intervals of time. A photograph of several samples is shown in Fig.1. Both free and drug loaded samples have been prepared. Then the resonators have been successively incorporated in a flow-gas chamber for measuring their resonant frequency as a function of mass loading additives. HCl carried by Argon has been used as a measure of the quantity of accepted drug through irreversible chemical reaction. The details of the experimental side are described in (5) and will not be discussed here.

The size and morphology of polymeric particles were studied by scanning electron microscopy (SEM, Tescan LYRA I XMU dual beam SEM/FIB system, equipped with Bruker EDX detector Quantax 200).

A major difficulty, which immediately arose at the very beginning of the experiments, was the inability of the oscillator circuit, implemented in the device, to provide a reliable signal. This has happened with all prepared samples including free and drug-loaded ones. It is well known that such a behavior can only be due to break-down of the oscillations from overloading the oscillator. In other words, the resonant acoustic loss in the resonators appeared too high for unexpected reasons. Let us just mention that such effects have been observed in our practice so far only in cases of large mass loading of the resonators through either thick polymer layer deposition or heavy gas irradiation, which obviously is not the present case. What follows next is a description of our first efforts to try to understand this unusual behavior.

**RESULTS**

We first found out that the normal oscillator performance was immediately restored upon exposition of the surface of the samples to acetone vapor. Then we continued in the same direction by replacing the aqueous suspensions with acetone ones. We met no further problems with exciting the samples and making all the necessary investigations concerned with the main topic – the drug absorption study. The results of this study are subject to a forthcoming publication.

The unanswered question, however, remained: what is this peculiarity due to, and how does the acetone help in resolving it?

As a first step we supplied various types of resonators to a network analyzer (250C Roditi Int. Co. Ltd.) to measure their dynamic electric impedance parameters. The results are summarized in Table 1.

Then the quality of the coated resonator’s surface was studied by SEM. Images thus obtained are given in Fig. 2. The polymer spheres are clearly seen, Fig. 2b, and the surface modification by drug loading too, Fig. 2c. The exposure to acetone vapor leads to dissolution of the microparticles, Fig. 2d.

![Fig. 1. Quartz resonators coated with dried microparticle films](image)

| Deposition method | Drug loaded | Basic frequency, kHz | Frequency after deposition, kHz | Dynamic resistance after deposition, ohms* |
|------------------|-------------|----------------------|-------------------------------|----------------------------------|
| Water suspension | no          | 9 995                | 9 997                         | 152                             |
| Water suspension | yes         | 10 020               | 10 050                        | 333                             |
| Water suspension, acetone vapor | yes | 10 077               | 10 060                        | 14                              |
| Acetone suspension | yes         | 10 026               | 10 017                        | 23                              |

*The resistance of the resonators prior to deposition was of the order of 10 ohms.
DISCUSSION

The inspection of Table 1 reveals that the deposition of the layers through water suspension with subsequent drying to release the water content results in a dramatic increase of the resonators’ motional resistance. This holds for both the drug-unloaded and loaded cases, the addition of the drug even enhances the effect (rows 1 and 2, respectively). Subsequent exposure to acetone vapors restores the normal value of the resistance (for such thin layers), and this is equally observed for layers obtained from pure acetone suspension. The high values of the resonator resistance give clear explanation of the observed inability of sustaining stable oscillator performance. It has been known that this parameter is directly related to the energy loss coming from viscosity of the attached material. It is not related to mass loading, all the more that in the present case this latter effect is insignificant in view of the small frequency downshift produced (rows 3 and 4). Another fact in support of the conclusion for high viscosity is the increase of the resonant frequency as seen from rows 1 and 2 again. This effect has been known to assist the increased layer viscosity in quartz resonators in specific cases (6).

An insight into understanding the peculiar viscosity behavior of the layers comes from observing the SEM images shown in Fig. 2. It is seen that the water suspension keeps the spherical shape of polymeric particles untouched because this kind of polymeric material possesses limited water solubility. As a result, spheres of about 50μm in diameter remain positioned on the surface after the release of its aqueous milieu. The exposure to acetone leads to their complete “dissolution” and transformation into thin layered drops, as seen from Fig. 2d. This morpholo-

Fig. 2. Sample surface micrographs after deposition from water suspension; a) and b) drug-free forms recorded at different magnifications – 49 x and 1.0 kx, respectively; c) drug-loaded form (1.0 kx) and d) drug-free form, exposed to acetone vapor (49 x).
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Energy change seems to have a dramatic effect on viscosity. It has been known that granular materials often exhibit non-newtonian viscosity behavior, where the viscosity increases with applied stress due to dilation (7). But this does not appear to be exactly the present situation because here the spheres are not packed enough to produce the said effect. More likely, the spheres are too large in diameter and heavily resist the sliding motion of the surface accompanying the oscillations of the resonator. When transformed into a thin layer, their usual viscosity behavior is restored and the resonator resistance shifts to the accepted values. This type of shape dependent viscosity has not, to our knowledge, been reported in literature so far and deserves further attention and study.

**CONCLUSIONS**

Shape-dependent viscosity has been found in layers of microparticles of polymer Eudragit RS 100 deposited on the gold electrode surface of quartz resonators from water suspension. The large viscosity obtained is also affected by loading the particles with diltiazem. Its impact on the resonant frequency measurements is removed by exposing the particle layer to acetone vapor leading to dissolving the spheres and reducing their shape to a thin layered one. Possible reasons for this unusual behavior of the polymer viscosity have been outlined.

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