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Metolose–PEG interaction as seen by positron annihilation spectroscopy

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Abstract

The plasticizing effects of poly(ethylene glycol) (PEG 400) on methylcellulose (Metolose) cast films were studied by conventional physico-chemical methods and positron annihilation spectroscopy. The PEG concentrations relative to the total polymer content were varied within the range 0–75% (w/w). At low concentrations (below 33.3%, w/w), the plasticizer was found to build in into the methylcellulose structure. On the other hand, at higher concentrations (above 50%, w/w), it formed small separate phases in the films.

Positron annihilation spectroscopy (PALS) was applied to track the Metolose–PEG interaction. Controlled ageing of Metolose–PEG films at room temperature and at 75% RH revealed a significant difference between the ageing processes of the monophase and those of the separate phase films. The ageing involves two steps in both cases: a fast and a slow one. The PALS measurements demonstrated that the slow process is hindered in the phase-separated samples.

Keywords: Deformation process; Thermal behaviour; Positron annihilation spectroscopy

1. Introduction

Different polymers are frequently used in the course of the formulation of various dosage forms in the pharmaceutical and food industries. Most of these applications require long-term stability. Amorphous polymers, such as methylcellulose, are not in equilibrium below their glass transition temperature (T_g), and these polymers therefore usually undergo spontaneous, though slow, transformations towards low-energy equilibrium states (Guo, 1994). This physical ageing is usually manifested in the relaxation phenomena (volume and enthalpy) (Chapman et al., 2001; Cowie and Ferguson, 1993; Gomez Ribelles et al., 1990), indicating considerable structural changes in the material. The plasticization effects of residual solvents, absorbed water, plasticizers and other additives can affect the long-term performance and stability of amorphous polymers in pharmaceutical dosage forms (Hodge et al., 1996; Hancock and Zografi, 1993, 1994, 1997; Hancock et al., 1995; Oksanen and Zografi, 1990; Süvegh and Zelkó, 2002; Süvegh et al., 1998). The plasticizer applied can modify the structure of a polymer film, causing significant changes in the mechanical properties of a polymeric binder or a coating. Even the viscoelastic state of a polymer is sometimes changed by the long-term physical ageing (Sakellariou et al., 1986).

The viscoelastic properties of amorphous solids differ significantly below and above glass transition temperature. Thus, the apparent state of the applied polymer might affect the activity of the drug present in the dosage form. As a result of these changes the stability of the final dosage form (the hardness of the tablets, the disintegration time and the drug release characteristics) can be seriously modified (Zelkó et al., 2000; Zelkó and Süvegh, 2004).

Sakellariou et al. (1986) studied the interactions between ethylcellulose and hydroxypropyl methylcellulose, hydrox-

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ypropyl cellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and poly(ethylene glycol) 6000 (PEG 6000) by a dynamic mechanical testing method, and the results were related to the transport mechanisms in the controlled release dosage forms. They established the limit of PEG 6000 in hydroxypropyl methylcellusose (HPMC). The objective of the present work was to study the influence of a poly(ethylene glycol), applied as plasticizer, on the deformation and thermal behaviour of free films of methylcellulose, and the related structural changes. The effects of the plasticizer on the structure and the viscoelastic properties of the polymer were studied by conventional physicochemical methods and positron annihilation spectroscopy. This latter method provides information on the size of free volume holes in an amorphous material, and thus on the plasticizer-induced structural changes of the polymers.

2. Experimental

2.1. Materials

Metolose is a non-ionic, water-soluble cellulose ether which is prepared from cellulose. The cellulose is processed with caustic soda and then treated with an etherification reagent such as methyl chloride, propylene oxide or ethylene oxide. Metolose is classified into three types, i.e. SM, SH and SE, according to the kind of etherification reagent used.

Plasticizers have the capacity to alter the physical properties of a polymer film. PEGs belong in the group of polyols. The PEG grades 200–6000 are generally used as plasticizers. In this work, Metolose SM-4 (Methylcellulose, Lot No. 406555, ShinEtsu Chemical Co. Ltd., Tokyo, Japan) was used as film-forming polymer and PEG 400 (Ph. Eur.) was used as plasticizer.Characteristic data of Metolose SM-4 are the followings:

viscosity: 3.0–5.6 mPa s (2%, w/w, aqueous solution);
methoxyl content: 27.5–31.5%;
degree of substitution: 1.8.

It can be used as gastrosoluble coating material or binder in wet granulation.

2.2. Compositions

The film-forming liquid contained Metolose SM-4 in a concentration of 2% (w/w) and also the plasticizer (PEG 400) in 0, 0.25, 0.5, 1, 2, 3, 4, 5 and 8% (w/w) concentrations. The PEG concentrations related to the total polymer content were 0, 11.6, 20, 33.3, 50, 60, 66.6, 71.4 and 75% (w/w), respectively. This latter concentration scale is used below because it reflects the construction of the studied films. The solvent applied for the preparation of the film-forming liquid was distilled water (Ph. Eur.). The free films were prepared by pouring approximately 20 g solution onto a Petri dish 7 cm in diameter. The solution was dried at room temperature (22 ± 1 °C) for 72 h. The deformation behaviour of the cast films was tested 1 day after preparation. Two to 5 mg samples of the cast films obtained were used for DSC analysis.

2.3. Deformation process and moisture content

A modified breaking hardness tester (Chinoin Chemical and Pharmaceutical Works Ltd., Budapest, Hungary) was used. The apparatus was connected to a computer, and software developed at the Department of Pharmaceutical Technology (University of Szeged) was utilized to evaluate the deformation (breaking) process of the free films. The tests were carried out under ambient circumstances (22 ± 1 °C/65% RH).

The moisture content of the free films was determined with a moisture analyzer (HR73 Halogen Moisture Analyzer, Mettler-Toledo GmbH, Greifensee, Switzerland). The standard drying program was used and the drying temperature was 105 °C. This program is set in the factory and is suitable for most samples. The sample is heated to the drying temperature and held constant at this temperature.

2.4. Differential scanning calorimetry (DSC)

The DSC examinations of the free films were made with a Mettler-Toledo DSC 821^e instrument. The start temperature was −40 °C, the end temperature was 200 °C and the heating rate was 5 °C min^{-1}. An argon atmosphere and aluminium pans were used.

To the calibration indium and zinc were used. To check the temperature and heat flow accuracy of a DSC modules indium (for the low temperature) and zinc (for the high temperature) were selected. Checks were within the defined limits:

Indium:
onset temperature: 156.6 ± 0.3 °C;
heat flow: 28.45 ± 0.6 J/g.
Zinc:
onset temperature: 419.6 ± 0.7 °C;
heat flow: 107.5 ± 3.2 J/g.

2.5. Positron annihilation spectroscopy

2.5.1. Principle of positron annihilation spectroscopy

Positrons are the antiparticles of electrons. When a positron meets with an electron, they undergo mutual annihilation and provide information on the surroundings of the annihilating pair. As the probability of such a meeting depends on the electron density in materials, positrons are exceptionally sensitive to free volumes, i.e. to the electron density. In polymers, a large proportion of the injected positrons form a bound state with electrons before their annihilation (Süvegh et al., 1999). One of the bound states, the *ortho*-positronium atom or *o*-Ps, has a "long" lifetime: in polymers it lives for 1–10 ns. This lifetime is long enough for positronium atoms to scan their surroundings and, fortunately, it is long enough to be observed easily. Moreover, according to a simple model, the lifetime of an *o*-Ps atom depends on the size of the free volume in which it is located (Deng and Jean, 1993):

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \quad (1)$$