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Characterization of ethylcellulose free films by positron annihilation spectroscopy and mechanical testing

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ABSTRACT

The distribution of the plasticizer triethyl citrate between the chains of the polymer ethylcellulose was determined in order to explain the mechanical properties. A knowledge of these properties is indispensable for preformulation studies. As preformulation, the relationship between the mechanical properties and the distribution of the plasticizer was studied. The distribution was investigated with positron annihilation lifetime spectroscopy, and the mechanical properties with breaking hardness tests. Two kinds of ethylcellulose were used. The best film-former with plasticizer was chosen with the optimal concentration. Selection of the optimum type and concentration of the plasticizer is essential in the formulation of pellets and coated dosage forms.

1. Introduction

Film coating is a method widely used for the development of solid dosage forms. In the process of film coating, a thin stable polymer film coat is created on the surface of a solid dosage form, such as tablets, capsules, pellets or crystals.

The numerous polymers available for coating ensure different dissolution profiles. Cellulose esters, cellulose acetatephthalate and hydroxypropylmethylcellulose phthalate are enteric polymers used to form colonic drug delivery systems [1]. Methylcellulose, hydroxyethylcellulose and some polymethacrylate products (e.g. Eudragit® E) are polymers that dissolve in the gastric juice [2]. We earlier studied Eudragit® L 30D-55, an aqueous dispersion of anionic polymers with methacrylic acid functional groups [3].

Acryl-Eze, an aqueous system, which contains a 1:1 copolymer of methacrylic acid and methyl methacrylate, is often used for the enteric coating of dosage forms [4–6].

In the present study, ethylcellulose was used as film former. Ethylcellulose is an ideal polymer for the formation of products allowing modified drug release. It is insoluble at any pH that occurs in organism, but in the presence of the gastric juice it undergoes swelling. It is then permeable for water and permits extended modified drug release [7–10]. This makes it suitable for improved patient compliance. Only a small number of ethylcellulose polymers have been approved for general pharmaceutical application and are used in extended release solid dosage formulations. Several types of such ethylcellulose exist, e.g. Ethocel 4, Ethocel 10 and Ethocel 45, which differ in the length of the polymer chains, the rate of dissolution, and the viscosity of their solution.

The purpose of the polymer film is to form a uniform and continuous coat on the surface of the core, and it must therefore have appropriate elasticity. In most cases, films prepared from a film-forming polymer alone are rigid and break easily, and the use of a plasticizer is therefore indispensable to increase the elasticity of the coat. The quantity and quality of plasticizers can be determined by means of various physical–chemical investigations [11].

Before the film coating, preformulation studies are necessary in order to study the physicochemical and thermal properties of the free films, e.g. the glass-transition temperature, the minimum film-forming temperature, the surface properties, the breaking strength and deformability and the structure of the film-former polymer. The thermal behaviour of ethylcellulose free films was studied earlier [12]. Ethocel 45 films proved to be more stable than Ethocel 10 films during storage. In our previous work [13], we made use of FT-IR spectroscopy, to study the structure of free films containing ethylcellulose, and the effects of the plasticizer on the structure and surface characteristics of the films. The results indicated that only a limited amount of plasticizer can be incorporated into the structure of the polymer film through physical–chemical binding,

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the proportion basically determining some of the main properties of the product. The mechanical properties of the resulting film depend on the distribution of the plasticizer. It is necessary to know its breaking strength, because the film is exposed to intense mechanical stress during the technological process.

In the present work, the distribution of the plasticizer and the supramolecular structure of free films were studied by means of positron annihilation lifetime spectroscopy (PALS), which furnishes direct information about the dimensions and contents of free-volume holes in amorphous materials. The magnitude of the free volume can be measured with the aid of PALS as electron density changes in the lifetime of the ortho-positron depend on the free volume of the polymer [14–16]. This method is most commonly applied to study polymers. Investigation of cellulose-based polymers by PALS has revealed that substitution on cellulose has little effect on the lifetime, but a major effect on the probability of formation of the ortho-positron (o-Ps) [17,18].

2. Experimental

Two different forms of ethylcellulose were used in the experiments: Ethocel Standard Premium 10 and Ethocel Standard Premium 45 (Colorcon Ltd, Dartford, England). Triethyl citrate was used as a plasticizer (Ph. Eur.).

2.1. Preparation of free films

The free films were prepared by spraying, as described previously [13]. The temperature of the drying air was set at the minimum film-forming temperature. The process parameters of the spraying are given in Table 1.

2.2. Positron lifetime measurements

PALS measures the time for which a positron can exist in a material. This lifetime depends on the properties of the particular material. The method is based on the fact that electrons and positrons annihilate each other to form photons. The properties of the resulting radiation correspond exactly to the relevant properties of the electron and the positron preceding the annihilation. PALS is an important method in the structural characterization of polymers, and its role is currently increasing in pharmaceutical technology [19–21]. Together with other properties, this method measures the size distribution of free-volume holes in polymers.

The use of positrons in polymers is based on the formation of the positronium, a bound state of an electron and a positron, in which the role of the positron resembles that of the proton in a hydrogen atom. The lifetime of the positronium before its annihilation is determined by the properties of the material in which it is formed. The exact dependence can be approximated by means of a simple model. The free-volume model regards the free volume in polymers as formed of uniform spherical voids [21]. Although the model is simple, it provides a possibility to derive a connection between the measured lifetime and the size distribution of the free-volume holes:

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

Table 1
Process parameters for preparation of free films.

Parameter	Value
Rotation rate of vessel (rpm)	22
Rate of liquid feeding (ml/min)	5
Pressure of spraying air (bar)	1.5
Diameter of nozzle (mm)	0.8

where τ is the lifetime of the ortho-positronium in nanoseconds, R is the radius of the voids in Angströms, and ΔR is a constant. This formula indicates that τ increases with R. On a molecular scale, the R values correspond well with the BET and neutron scattering results.

The positron source applied for the measurements was made of carrier-free ^{22}NaCl with an activity of 10^5 Bq, sealed between two very thin Kapton foils. The source was placed between two pieces of polymeric mixture previously treated identically. Positron lifetime spectra were recorded by a conventional fast–fast coincidence system based on BaF_2/XP2020Q detectors and Ortec electronics.

Spectra were recorded in 4096 channels of a computer-based multichannel analyser card (Nucleus). The time resolution of the spectrometer was ~220 ps. Each spectrum related to 1.5×10^6 annihilation events. Samples were measured repeatedly and the data given below are averages of the repeated measurements.

2.3. Mechanical properties of free films

The breaking strength of the films was tested with an indentation hardness tester. This device and the software were developed in our institute. The tester contains a special specimen holder and a jowl. The loading indicates stress in the sample and it can deform. These devices are connected with a computer through an interface. Thus, not only can the ultimate deformation force be measured, but also the process (force–time and force–displacement curves) can be followed. The specimen, and hence the free film is located horizontally in the holder and the jowl moves vertically. The measuring range was 0–200 N, the speed of the stamp was 20 mm/min, the sampling rate was 50 Hz, the output was 0–5 V, and the sensitivity was ±0.1 digit. The sensor was a Unicell force-measuring instrument, calibrated with the C9B 20 kN cell.

3. Results

3.1. Positron lifetime measurement

The PALS results revealed that there was no significant difference between the two types of ethylcellulose samples (Fig. 1), which were influenced very similarly by the plasticizer. A significant difference was observed only at the highest concentration of the plasticizer.

The positron lifetime initially decreased slightly at the lowest plasticizer concentration. This is a consequence of the distribution of the plasticizer molecules between the polymer chains, filling the free-volume holes, occupying sites formerly available for the positronium atoms, providing a higher electron density. The lifetime of the positronium

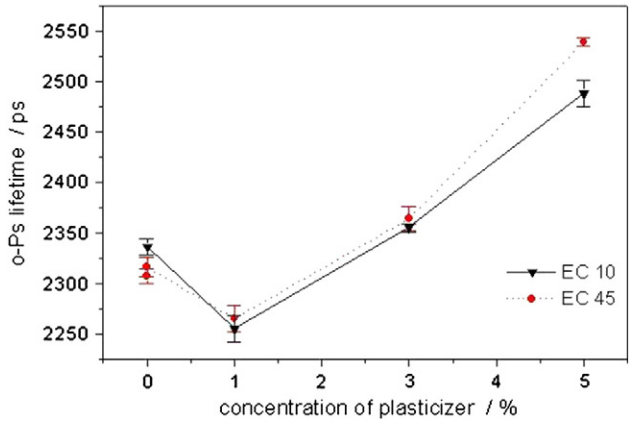

Fig. 1. Positron lifetime plotted against concentration.