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European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 95–100
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit® RS PO hot-melt extrudates

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Received 5 November 2002; accepted in revised form 5 March 2003

Abstract

The purpose of this study was to investigate the properties of methylparaben as a solid-state plasticizer for Eudragit® RS PO during a hot-melt extrusion process. Extruded matrices containing different levels of methylparaben and Eudragit® RS PO, were prepared by feeding the powder blend through a hot melt extruder. The melt viscosity of the polymer blends was assessed by torque rheometry using a Brabender Plasticorder. The physicochemical properties of the extruded methylparaben-containing polymer matrix were characterized by differential scanning calorimetry and X-ray diffraction. Solid state nuclear magnetic resonance spectroscopy (NMR) was used to study the possible interaction between methylparaben and Eudragit® RS PO polymer. The results demonstrated that the glass transition temperature of the Eudragit® RS PO decreased with increasing levels of methylparaben in the extrudate, due to an increase in the chain mobility of Eudragit® RS PO. The crystallinity of methylparaben was absent following hot-melt processing. At increasing levels of methylparaben in the extrudates, a decrease in the melt viscosity was seen due to a plasticization of the polymer. Rheological properties of the extrudates containing methylparaben were compared with the extrudates containing conventional plasticizers. It was found that methylparaben was as effective as triethyl citrate (TEC) in reducing torque during the extrusion process. Solid state NMR spectra indicated a change in the chemical shift of Eudragit® RS PO plasticized with methylparaben, which could be ascribed to an interaction between the hydroxyl group of the methylparaben and the ester group of the Eudragit® RS PO polymer. The results of this study demonstrated that methylparaben could be used as a solid-state plasticizer for the Eudragit® RS PO polymer when a hot melt extrusion technique was employed in the preparation of sustained release tablets.

Keywords: Acrylic polymer; Eudragit® RS PO; Hot melt extrusion; Methylparaben; Plasticization

1. Introduction

The hot melt extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. A major advantage of hot-melt extrusion is that several production steps may be condensed into one continuous process. Other advantages of the hot melt extrusion technique include solvent free processing, no requirement on compressibility of materials, and it is an elegant and economical way of manufacturing controlled release drug delivery systems.

The use of hot melt extrusion to achieve sustained drug release is receiving more attention in the scientific literature. Aitken-Nichol et al. [1] applied the technique to fabricate a solvent free lidocaine hydrochloride film based on the Eudragit® E 100 resin. El-Egakey [2] used epoxy resins and poly(vinyl acetate-co-methyl methacrylate) as polymer materials. Follonier and co-workers [3,4] extruded diltiazem hydrochloride pellets with poly(ethylene-co-vinyl acetate), polymethacrylate, and cellulose derivatives without causing significant degradation of the drug. Repka and co-workers [5] reported on the influence of both plasticizers and drugs on the physical–mechanical properties of

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doi:10.1016/S0939-6411(03)00035-3

hydroxypropylcellulose films by using hot melt extrusion technology. Zhang and McGinity [6] investigated the mechanism of release of chlorpheniramine maleate from hot-melt extruded matrix tablets containing polyethylene oxide as the polymeric carrier.

To control and modulate the release of drugs from polymer-based extrudates, plasticizers are necessary to facilitate the thermal process. However, most pharmaceutical grade plasticizers are in a liquid state and a homogeneous blend of the plasticizer with a powder blend containing the active ingredient must be obtained before the solid mass is added to the extruder. An incomplete mixing of a polymer powder with a liquid additive has been shown to result in an unstable mass flow when feeding the mixture into the extruder [7]. Several reports have focused on the evaporation and loss of plasticizer, during a high temperature operation, thus causing stability problems in the finished dosage forms [8–10]. Methylparaben is a solid powder and can be readily mixed with other powder ingredients, which reduces blending time within the extruder and avoids subjecting the polymer and drug to high temperatures for extended periods of time. Previous studies have demonstrated that methylparaben can exert a plasticization effect on film coatings composed of either polymers or proteins [11–14]. Most recently, other solid-state plasticizers for acrylic polymer including ibuprofen and chlorpheniramine maleate, were reported for both coating and hot melt processes [15,16].

The objective of the current study was to investigate the properties of methylparaben as a solid state plasticizer for Eudragit® RS PO during a hot-melt extrusion process and to characterize the physicochemical properties of the extruded methylparaben-containing polymer matrix. Eudragit® RS PO is a thermally stable pharmaceutical grade polymer that can be processed at a relatively low temperature. The glass transition temperature of Eudragit® RS PO polymer was investigated as a function of the methylparaben concentration in the powder blend. The plasticization efficiency of methylparaben was compared to that of traditional plasticizers. Wide angle X-ray diffraction was used to characterize the crystallinity of Eudragit® RS PO extrudates, and solid-state NMR was used to study the possible interaction between Eudragit® RS PO and methylparaben.

2. Materials and methods

2.1. Materials

Eudragit® RS PO polymer (molecular weight 15,000) was provided by Röhm Inc. (Darmstadt, Germany). Methylparaben was purchased from Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate (TEC) and dibutyl sebacate (DBS) were donated by Morflex, Inc. (Greensboro, NC).

2.2. Preparation of extrudates

Eudragit® RS PO and methylparaben were dried in an oven at 40 °C for 24 h prior to processing to minimize degradation due to absorbed moisture. These powders were blended and extruded through a single screw Brabender extruder (C.W. Brabender Instrument Inc., S. Hackensack, NJ). The extruder was driven by a Plasti-Corder (Model EPL-V5501) electronic torque rheometer unit. The operating temperatures for the four zones in the extruder were 90, 105, 110 and 115 °C. The screw rotation speed was 20 rpm. The *L/D* ratio of the barrel with two heating zones was 15:1. A rod-shaped die was attached to the end of the barrel. The dwell time of the polymer inside the barrel was about 2–3 min. The extrudates were cooled down to room temperature and then stored over a silica gel desiccant at 0% RH and 25 °C prior to further testing.

For preparation of extrudates containing TEC or DBS, all procedures were the same as the methylparaben-containing extrudates, except the TEC and DBS were sprayed onto the Eudragit® RS PO powder instead of blending the polymer with the plasticizers.

2.3. Measurement of melt viscosity

The rheological properties of each sample were assessed by torque rheometry using a Brabender Plasticorder operated at 100 °C and 30 rpm with a 50-ml mixing bowl. Torque readings were measured continuously and provided a measurement of the melt viscosity for these materials.

2.4. Thermal analysis of films

The thermal properties of the extruded mass were determined using a differential scanning calorimeter (Modulated DSC, TA Instruments, Inc. New Castle, DE). The modulation was set at 1.0 °C for every 60 s. Extrudate samples of 10–15 mg were accurately weighed into aluminum pans and then sealed. The samples were tested under a nitrogen atmosphere at a heating rate of 10 °C/min, over a temperature range of −20–100 °C. The samples were cycled twice to remove thermal history. The glass transition temperature was measured in the second cycle as the step transition in the plot of reversible heat flow versus temperature.

2.5. X-Ray diffraction analysis

The powder X-ray diffraction profiles were determined using a Philips vertical scanning diffractometer (type 42273, Philips Electronic Instrument, Mount Vernon, NY). The samples were exposed to CuKα radiation under 35 kV and 20 mA over the 2-theta range from 10 to 50° at increments of 0.5°. The diffraction patterns for methylparaben, Eudragit® RS PO, methylparaben–polymer mixtures and methylparaben plasticized polymers were obtained. The

extrudates were ground into fine powder before analysis. Physical mixtures of methylparaben (15%) and Eudragit® RS PO (85%) were prepared by grinding the polymer with methylparaben.

2.6. Solid state nuclear magnetic resonance spectroscopy

Solid state ^{13}C cross-polarization, magic-angle spinning (CP/MAS) NMR spectra were measured with a Bruker CMX-300 NMR spectrometer which operated at 75.33 MHz with a CP/MAS accessory at 25 °C. Approximately 200 mg of the sample was placed in a cylindrical ceramic rotor. The contact time was 5 ms and the spectral width was 30.03 kHz. ^{13}C chemical shifts were calibrated with reference to the higher field adamantane peak 29.5 ppm relative to tetramethylsilane ($(CH_3)_4Si$). More than 1000 scans were acquired for each resulting spectrum.

3. Results and discussion

A plasticizer is essential to lower the extrusion temperature as well as to soften a brittle polymer to form a continuous strand during extrusion. The data in Fig. 1 show the influence of methylparaben levels on the glass transition temperature (T_g) of Eudragit® RS PO polymer extrudates following processing in a hot-melt extruder. The T_g of the polymer decreased with increasing levels of methylparaben in the extrudates. With 15% methylparaben in Eudragit® RS PO extrudate, the T_g was reduced from 55 to 32 °C, which was due to an increase in chain mobility of the polymer molecules when methylparaben was incorporated in the polymer matrices. These results demonstrated that methylparaben was an effective plasticizer for the acrylic resin copolymer. Since the molecular weight of methylparaben (152 MW) is significantly lower than that of Eudragit® RS PO (150,000 MW), the presence of the smaller molecules of methylparaben within the polymer was

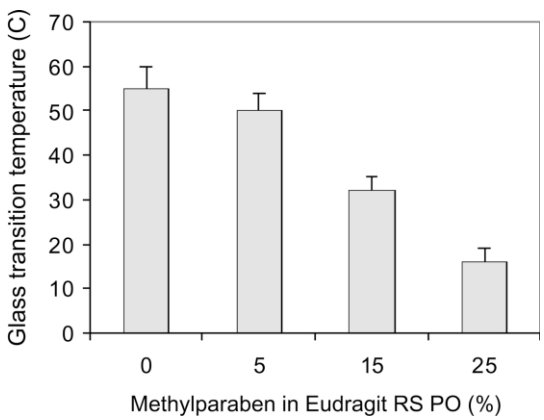

Fig. 1. Glass transition temperatures of Eudragit RS PO polymer extrudates containing different level of methylparaben as a solid state plasticizer ($n = 6$).

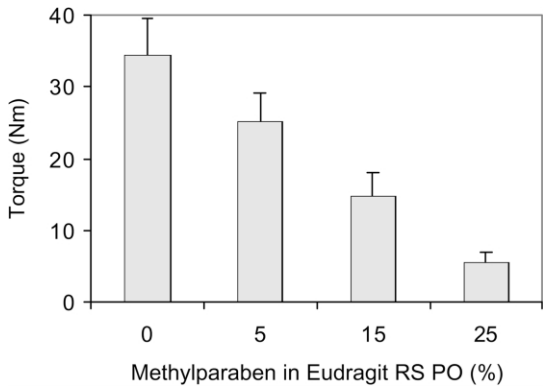

Fig. 2. Influence of methylparaben levels on the melt viscosity of Eudragit RS PO. Rheological properties of each sample were assessed by torque rhemetry using a Brabender Plasticorder operated at 100 °C and 30 rpm with a 50-ml mixing bowl ($n = 6$).

found to dilute and weaken the cohesive interactions between the Eudragit® RS PO chains. This reduced the friction and entanglement by increasing the free volume in the polymer matrix. This finding was in agreement with previous reports by the authors [13,14] on the plasticization of Eudragit® RS 30 D films containing methylparaben. In order to obtain good compatibility between two components, Sears and Touchette [17] reported that the solubility parameters should be very similar and differ by less than 6.3 $(MPa)^{1/2}$. The solubility parameters for Eudragit® RS PO and methylparaben, 19.2 and 24.1 $(MPa)^{1/2}$, respectively [13], indicate that Eudragit® RS PO had good miscibility with methylparaben as a plasticizer.

The melt viscosity of a polymer at a given temperature is a measurement of the rate at which chains can move relative to each other. This is controlled by the ease of rotation of the backbone bonds, i.e. the chain flexibility, and the degree of entanglement. The melt viscosity determines whether a polymer can be melt-processed under specific conditions for the desired pharmaceutical product. If the melt viscosity of a polymer is high, a plasticizer must be added to process the material. The data in Fig. 2 show the influence of methylparaben levels on the melt viscosity of Eudragit® RS PO. The torque during mixing is a measure of the viscosity and it is a good parameter for evaluating the processability of the polymer systems. The torque on Eudragit® RS PO decreases almost linearly with the addition of methylparaben. With increasing methylparaben concentration in Eudragit® RS PO polymer from 0 to 25%, the torque values were reduced from 35 to 5 Nm, which could be ascribed to the reaction between the polymer and methylparaben. These results demonstrated that the melt viscosity of the Eudragit® RS PO polymer can be reduced significantly, thus the processibility of the polymer can be improved by blending methylparaben with the polymer prior to thermal processing.

Fig. 3 shows the melt viscosity of the Eudragit® RS PO polymer containing 15% w/w of either methylparaben,

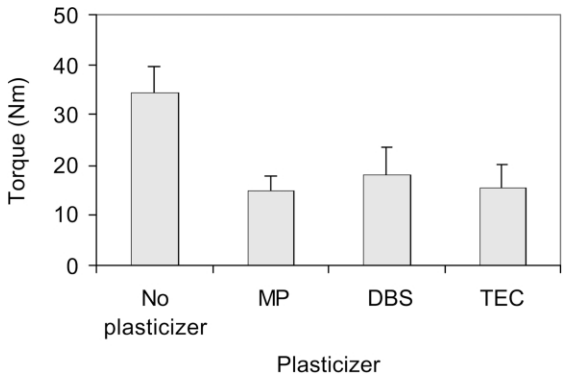

Fig. 3. Influence of 15% different plasticizers on the melt viscosity of Eudragit RS PO. Rheological properties of each sample were assessed by torque rhemetry using a Brabender Plasticorder operated at 100 °C and 30 rpm with a 50-ml mixing bowl ($n = 6$).

triethyl citrate (TEC), and dibutyl sebacate (DBS). The torque values of plasticized Eudragit® RS PO were significantly lower than the values of Eudragit® RS PO without plasticizers. This finding can be explained by the fundamental nature of the plasticizers, since plasticizers enhance the motions of the polymer chain segments and increase the backbone flexibility. The increased flexibility results in a reduction in both chain stiffness and viscosity, leading to an enhancement of non-Newtonian behavior and consequently a further reduction in melt viscosity under high shear conditions. The extent of torque reduction of the polymer blend containing methylparaben as the solid-state plasticizer was similar to that of the polymer with TEC and higher than that of the polymer when plasticized with DBS. These results demonstrated that methylparaben was an effective plasticizer to reduce the melt viscosity of the Eudragit® RS PO polymer.

The profiles in Fig. 4 illustrate the X-ray diffraction patterns for the Eudragit® RS PO polymer, methylparaben, a physical mixture of Eudragit® RS PO with methylparaben, as well as the methylparaben-containing extrudate. The Eudragit® RS PO polymer is amorphous due to the absence of complete stereoregularity and the presence of bulky side groups. The crystallinity of methylparaben is clearly demonstrated by its unique X-ray diffraction pattern. The diffraction pattern from a physical mixture of 15% methylparaben with pure polymer contained sharp diffraction peaks corresponding to the crystallinity of methylparaben in the mixture. The diffraction patterns from extruded Eudragit® RS PO polymer containing 15% methylparaben exhibited no peaks associated with the methylparaben and were identical to those of the pure polymer, suggesting that the methylparaben was either dissolved in the polymer or dispersed as an amorphous material within the polymeric matrix. No recrystallization of methylparaben in the film was seen on storage.

An active ingredient can be present in an extrudate in the form of either crystalline particles embedded in the hardened polymer phase or in the amorphous state, where the molecules dissolve in the polymer during the hot melt process and remain in the molecular state in the final product. The crystalline form is more common. In the current study, the extrudates were transparent strands since no embedded crystals of active drug were present to refract light, which further demonstrated that the methylparaben had dissolved in the Eudragit® RS PO polymer.

The plasticization of Eudragit® RS PO with methylparaben can be measured using NMR, which is a powerful technique for probing the molecular level interactions between the polymer and plasticizer. A ^{13}C cross-polarization, magic-angle spinning (CP/MAS) NMR spectrum for Eudragit RS PO in the solid state is shown in Fig. 5A. The chemical shift region for the polymer was approximately 10–90 ppm, which is indicative of a polyacrylate polymer [18]. The observed resonance signals were assigned as follows: aliphatic methyl group carbons and those corresponding to the quaternary ammonium function resonate between 15 and 22 ppm; quaternary substituted carbons appear at 46 ppm; α-acyl ester carbons appear at 52.5 ppm; and carbonyl carbons appear at 177.2 ppm. Similarly, a ^{13}C CP/MAS spectrum for methylparaben was obtained in order to identify the chemical shift regions attributable to this molecule (Fig. 5B). Chemical shift assignments for methylparaben were consistent with the previously published CP/MAS NMR data [19]. The aromatic carbons were of interest, since these carbons are particularly sensitive to aromatic ^{13}C shielding originating from local group effects or microenvironment effects. The carbons of benzene itself resonate and substitution into the ring creates a range of ^{13}C shielding from 115 to 140 ppm. This range particularly enables an investigation of the interaction between

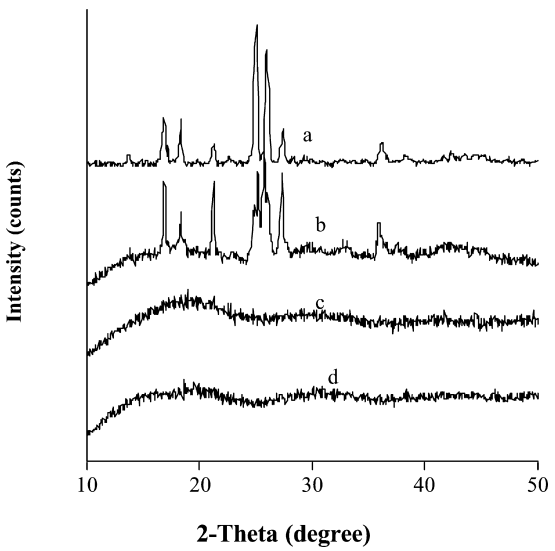

Fig. 4. X-Ray diffraction patterns of methylparaben and Eudragit RS PO. (a) Methylparaben; (b) mixture of methylparaben and Eudragit® RS PO; (c) extrudate from methylparaben and Eudragit® RS PO; and (d) Eudragit® RS PO.

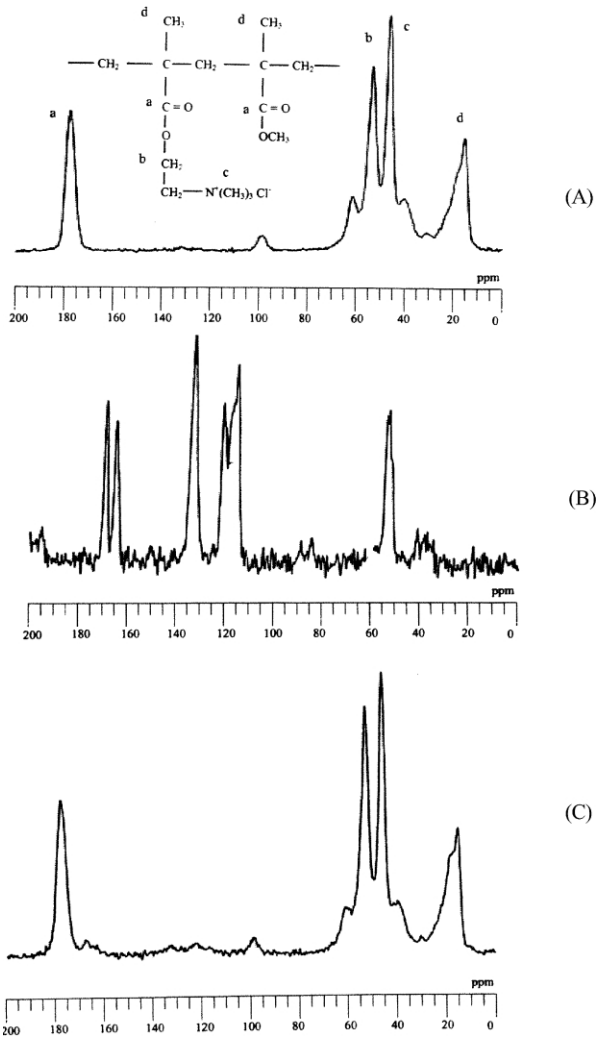

Fig. 5. ^{13}C CP/MAS NMR spectrum of (A) Eudragit RS PO; (B) methylparaben; and (C) Eudragit RS PO plasticized with methylparaben (15% w/w).

methylparaben and Eudragit® RS PO polymer since Eudragit® RS PO displays no resonance activity in this region.

In the absence of molecular interaction, the ^{13}C-NMR spectrum for the methylparaben–polymer matrix is expected to be the result of the superposition of the spectra of the two components separately. The methylparaben-Eudragit® RS PO spectra in Fig. 5C show that the spectroscopic behavior of the Eudragit® RS PO extrudates plasticized by methylparaben is virtually identical to that of the pure Eudragit® RS PO. The broad peaks due to the aromatic carbon of methylparaben did not appear in the plasticized Eudragit® RS PO polymeric matrix.

Table 1 lists ^{13}C chemical shifts experimentally determined for the methylparaben plasticized Eudragit® RS PO polymer matrix, as well as for those corresponding to pure Eudragit® RS PO. Data were obtained under the same conditions for comparison purposes. The chemical shifts of plasticized Eudragit® RS PO carbons in the polymer matrix were similar to those found in pure Eudragit® RS PO except for carbons at positions 'a' and 'b'. The carbon in position 'a' appeared at a lower chemical shift from 177.2 to 176.7 ppm under plasticization, which implies that the ^{13}C shielding component changed. This could be due to the hydrogen-bond interaction between the (–OH) group of methylparaben and the >C=O group of Eudragit® RS PO.

In conclusion, addition of methylparaben to the Eudragit® RS PO polymer resulted in an increase in the polymer chain mobility during hot-melt extrusion and reduced both the glass transition temperature and the melt viscosity of the polymer. X-Ray diffraction studies demonstrated that methylparaben was dissolved in the polymer and then became incorporated within the polymeric network, functioning as an effective plasticizer for the Eudragit® RS PO. The solid state NMR spectra showed changes in chemical shift of the Eudragit® RS PO plasticized with methylparaben and these changes were ascribed to the interaction between the hydroxyl group of methylparaben and the ester group of the Eudragit® RS PO polymer. Methylparaben has shown to be an effective plasticizer for Eudragit® RS PO when a hot-melt extrusion technique was employed for developing sustained release tablets containing this polymer.

Table 1
C-NMR chemical shifts of MP, Eudragit® RS PO, and MP plasticized Eudragit® RS PO samples

Carbons	^{13}C-NMR chemical shifts (ppm)	
	Eudragit® RS PO	MP plasticized Eudragit® RS PO
a (C=O)	177.2	176.7
b (α-acyl ester)	52.5	52.3
c (quaternary substituted carbons)	46.0	45.9
d (aliphatic methyl group)	15.5	15.4

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