European Journal of Pharmaceutics and Biopharmaceutics 77 (2011) 297–305

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

# Ethylene vinyl acetate as matrix for oral sustained release dosage forms produced via hot-melt extrusion

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ARTICLE INFO

*Article history:*
Received 23 June 2010
Accepted in revised form 6 December 2010
Available online 17 December 2010

*Keywords:*
Hot-melt extrusion
Ethylene vinyl acetate
Sustained release
Multiple-unit dosage form
Matrix system
Metoprolol tartrate

ABSTRACT

Different ethylene vinyl acetate grades (EVA9, EVA15, EVA28 and EVA40 having a VA content of 9%, 15%, 28% and 40%, respectively) were characterized via differential scanning calorimetry. Glass transition temperature ($T_g$), polymer crystallinity, melting point and polymer flexibility were positively influenced by the vinyl acetate content. The processability of EVA-based formulations produced by means of hot-melt extrusion (2 mm die) was evaluated in function of VA content, extrusion temperature (60–140 °C) and metoprolol tartrate (MPT, used as model drug) concentration (10–60%). Matrices containing 50% MPT resulted in smooth-surfaced extrudates, whereas at 60% drug content severe surface defects (shark skinning) were observed. Drug release from EVA/MPT matrices (50/50, w/w) was affected by the EVA grades: 90% after 24 h for EVA15 and 28, while EVA9 and EVA40 formulations released 80% and 60%, respectively. Drug release also depended on drug loading and extrusion temperature. For all systems, the total matrix porosity (measured by X-ray tomography) was decreased after dissolution due to elastic rearrangement of the polymer. However, the largest porosity reduction was observed for EVA40 matrices as partial melting of the structure (melt onset temperature: 34.7 °C) also contributed (thereby reducing the drug release pathway and yielding the lowest release rate from EVA40 formulations).

The Simulator of the Human Intestinal Microbial Ecosystem (SHIME) used to evaluate the stability of EVA during gastrointestinal transit showed that EVA was not modified during GI transit, nor did it affect the GI ecosystem following oral administration.



## 1. Introduction

Hot-melt extrusion (HME) is a well-known technique in the field of polymer science, and it has proven to be a useful tool for pharmaceutical purposes to develop immediate- or sustained-release formulations. Compared with other techniques, HME has a lower environmental impact (absence of solvents) and reduced costs (few processing steps, continuous operation) [1–3]. As sustained release dosage forms have an important role to improve the life quality of chronic and poly-medicated patients by reducing their daily intake of dosage forms, considerable research efforts have been directed towards the use of polymers that provide practical, safe and controlled long-term delivery of drugs. Several polymers, suitable for pharmaceutical HME applications have been identified (ethylcellulose, polymethacrylate, hydroxypropylcellulose, polyethylene oxide, polyvinylalcohol, etc.) [4–7], but the majority of them require a plasticizer to improve the elasticity and flexibility of the polymers [8–11]. This results in several restrictions related to polymer/plasticizer miscibility, plasticizer concentration, interactions with drug and polymer. In contrast, ethylene vinyl acetate (EVA) does not require a plasticizer to obtain good quality extrudates.

EVA is a copolymer of ethylene and vinyl acetate (VA). While polyethylene is a semicrystalline polymer with alternating crystalline lamellae (with different types of crystals) and amorphous domains, the incorporation of VA co-monomer units (typically the VA content varies between 9% and 40%) into a polyethylene backbone chain induces differences in crystallinity and crystalline structure, melting point, solubility, density and glass transition temperature, affecting the flexibility and thermoplastic characteristics of EVA [12,13]. Therefore, the versatility of EVA for hot melt processing resulted in a wide spectrum of applications [14]. In the pharmaceutical field, it has been specifically used for the development of films

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doi:10.1016/j.ejpb.2010.12.004

[15,16], stent coatings [17], implantable devices [18], vaginal rings [19], etc.

The purpose of this study was to evaluate the potential of EVA as a matrix carrier for oral sustained release dosage forms produced via hot-melt extrusion, and to characterize the different aspects of EVA copolymers. Metoprolol tartrate was embedded as model drug in the EVA matrices.

As the stability of EVA matrices after oral intake when exposed to the gastrointestinal fluids and its effects on the gastrointestinal microbiota have not been described, the effect of the polymer on the gastrointestinal ecosystem and vice versa was evaluated using a Simulator of the Human Intestinal Microbial Ecosystem (SHIME).

## 2. Material and methods

### 2.1. Materials

Different ethylene vinyl acetate (EVA) grades (Elvax® 40w, 260, 550 and 750 with a vinyl acetate (VA) content of 40, 28, 15 and 9 wt.%, respectively) were kindly donated by Dupont (Geneva, Switzerland) and used as hydrophobic carrier. Metoprolol tartrate (MPT) (10 μm) (EQ Esteve, Barcelona, Spain) was selected as model drug.

### 2.2. Hot-melt extrusion: production of the mini-matrices

EVA powder and physical mixtures of metoprolol tartrate and EVA (homogenized using mortar and pestle) were fed into a co-rotating twin-screw mini-extruder (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany), operating at different screw speeds (40, 60 and 90 rpm) and processing temperatures (60, 80, 90, 100, 110, 120, 130 and 140 °C) in order to evaluate the processability of these formulations via hot-melt extrusion. The extruder was equipped with a pneumatic feeder, two archimedes screws and a cylindrical die of 2 mm. The extrudates were cooled down to room temperature and manually cut, using surgical blades, into mini-matrices of 2 mm length.

### 2.3. Extrudate characterization

The extrudates were visually inspected for surface defects (e.g. shark skinning). The deformation due to cutting and the presence of cracks were evaluated using a KH-7700 digital microscope (Hirox, Japan), equipped with a high resolution zoom lens (MXG-10C model, using co-axial vertical lighting for high-level optical observation) and an OL-70 II objective lens with a magnification capacity of 70–700×. The imaging system had a 2.11 mega-pixel CCD sensor and a maximum pixel resolution of 30 mega-pixels (i.e. 6400 horizontal lines and 4800 vertical lines). To visualize the surface morphology photomicrographs were taken with a field emission gun scanning electron microscope (SEM, type Quanta 200F, FEI, Eindhoven, Nederland). The pressure in the chamber was 100 Pa, and a large field detector was used.

### 2.4. X-ray diffraction

The crystallinity of powdered EVA grades and EVA samples extracted from the intestinal passage experiment was investigated by means of X-ray diffraction. The X-ray patterns were determined using a D5000 Cu Kα diffractor ($\lambda$ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

### 2.5. Raman spectroscopy

The MPT crystallinity and distribution of and the EVA40 solid state were evaluated in EVA matrices containing 50% MPT via Raman microscopy. A RamanRxn 1 Microprobe (Kaiser Optical systems, Ann Arbor, USA) equipped with an air-cooled CCD detector (back-illuminated deep depletion design) was used to inspect MPT crystallinity in the tablets. Using a 10× long working distance objective lens (spot size of 50 μm), 10 spectra were collected on a vertical cross-section of the tablets. To evaluate the MPT distribution on the vertical cross-section, three areas ($2200 \times 1200\ \mu m^2$) (two at the edges and one in the middle of the mini-tablet) were scanned in a point-by-point mapping mode with a step size of 50 μm in both $x$ and $y$ directions. The laser wavelength during the experiments was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded at a resolution of 4 $cm^{-1}$ using a laser power of 400 mW and a laser light exposure time of 20 s per spectrum. Before data analysis, spectra were baseline-corrected (Pearson's method). Data collection and analysis were done using the HoloGRAMS™ data collection software package, the HoloMAP™ data analysis software package and the Matlab® software package (version 6.5).

### 2.6. Thermal analysis

Thermogravimetric analysis (Hi-res TGA 2950, TA instruments, Leatherhead, UK) was employed to investigate the thermal stability of EVA, MPT and extruded EVA/MPT samples (50/50 ratio, w/w). Samples (±15 mg) were equilibrated at 50 °C and heated to 500 °C at a heating rate of 10 °C/min while recording the weight loss.

Glass transition temperature ($T_g$), crystallization temperature ($T_c$), melting point ($T_m$) and heat of fusion ($\Delta H$) of pure components (EVA40, EVA28, EVA15, EVA9 and MPT), physical mixtures and extruded samples were analyzed by differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC). The DSC instrument used was a Model 2920 from TA Instruments (Leatherhead, UK) running in standard mode and equipped with a refrigerated cooling system (RCS). Samples (±10 mg) were run in closed aluminium pans; the mass of each empty sample pan was matched with the mass of the empty reference pan to ±0.10 mg. Depending on the samples and the determined parameters, the experimental method consisted of a single heating cycle (heating rate of 20 °C/min from −100 to 180 °C) or a three-phase analysis with consecutive heating, cooling and heating cycles. All samples and starting materials were analyzed in triplicate.

MDSC measurements were carried out using a Q2000 Modulated DSC (TA, Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the DSC cell. The amplitude of the temperature was 0.3 °C, the period was 50 s and the underlying heating rate was 2 °C/min. The samples were evaluated according to the three cycle analysis (heating, cooling and heating) from −100 to 180 °C.

All results were analyzed using the TA Instruments Universal Analysis 2000 software.

### 2.7. In vitro drug release

Drug release from the EVA-based matrices was determined using USP apparatus 1 (baskets), in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA). The mini-tablets (eight tablets of 2 mm length) were placed in demineralized water (900 ml, at a temperature of 37 ± 0.5 °C), while the rotational speed of the baskets was 100 rpm. Samples of 5 ml were withdrawn at 0.5, 1, 2,