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European Journal of Pharmaceutics and Biopharmaceutics 49 (2000) 237–242

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Melt extrusion – an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate

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Received 4 May 1999; accepted in revised form 9 February 2000

Abstract

17β-Estradiol hemihydrate (17β-E2) is a poorly water-soluble drug. Physical methods for improving the solubility and dissolution rate, e.g. micronization, have certain inherent disadvantages. The method of choice in this study, melt extrusion, proved to overcome many of the shortcomings of conventional methods. Different compositions of excipients such as PEG 6000, PVP (Kollidon® 30) or a vinylpyrrolidone-vinylacetate-copolymer (Kollidon® VA64) were used as polymers and Sucroester® WE15 or Gelucire® 44/14 as additives during melt extrusion. The solid dispersions resulted in a significant increase in dissolution rate when compared to the pure drug or to the physical mixtures. For example, a 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17β-E2, 50% PVP and 40% Gelucire® 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets. The USP XXIII requirement for estradiol tablets reaching greater than 75% drug dissolved after 60 min was obtained in this investigation.

Keywords: Solid dispersions; Melt extrusion; Tablets; 17β-Estradiol hemihydrate; Polymers; Poorly soluble drugs

1. Introduction

Physical methods for enhancing the dissolution rate of a sparingly water soluble drug, such as micronization, or traditional methods for the preparation of solid dispersions, such as the melt or solvent method, have several disadvantages.

Micronized powders/drugs can be difficult to handle because of air adsorption, high dust formation and low apparent densities. Lin et al. reported that although a reduction in particle size may be easy, the anticipated increase in bioavailability may not be achieved because of aggregation or agglomeration resulting in poor powder wettability [1].

The preparation of solid dispersions by melt or solvent methods is an alternative way to enhance the solubility of a sparingly water soluble drug. This concept was introduced by Sekiguchi and Obi [2] and has been studied and reviewed extensively [3–5]. The melt method often requires relatively high temperatures (more than 100°C), which may lead to thermal degradation of the drug. Problems with the solvent method include environmental aspects due to the use of organic solvents and health concerns because of residual solvents. In addition, solvent methods are time-consuming and expensive because of long processing and drying times.

The use of polymers for the manufacture of solid dispersions, such as PEG 6000, PVP or PVA 64 [6], have been described comprehensively. Additives like Gelucires® [7,8] or Sucroester® [9,10] have been used recently to improve the dissolution behavior of model compounds. To date, few formulations have been described utilizing polymers and additives as excipients.

The objective of this study was to investigate the melt extrusion technique using polymers and additives to prepare solid dispersions in order to enhance the drug dissolution rate of the model drug, 17β-E2 as an alternative to the traditional methods. Melt extrusion has been described primarily as a method for the preparation of sustained release preparations [7,11,12], but not for the enhancement of the dissolution rate.

In addition, only limited information is available on the processability of solid solutions/dispersions into the final dosage form. Special emphasis was, therefore, placed on the development of a single unit dosage form (e.g. tablets) taking into consideration industrial requirements, such as

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0939-6411/00/$ - see front matter
PII: S0939-6411(00)00077-1

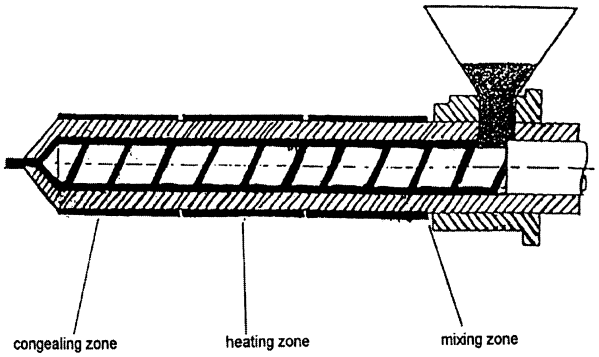

Fig. 1. Schematic of a single screw melt extruder.

easy and fast handling, while avoiding organic solvents and thermal stress on the drug.

2. Materials and methods

2.1. Materials

17β-E2 (Schering AG, Berlin/Bergkamen, Germany; non-micronized with a mean diameter of 187 μm, data for the water solubility of Estradiol (0.2–5 μg/ml) were taken from the literature [13,14], the solubility of the drug in 0.3% SDS is about 60 mg/ml), PEG 6000, PVP (Kollidon® 30: vinylpyrrolidone, PVA 64 (Kollidon® VA64, vinylpyrrolidone/vinylacetate–Copolymer 6:4) (BASF AG, Ludwigshafen, Germany), Sucroester® WE15 (saccharose-monopalmitate, HLB value of 15, melting point 60°C), Gelucire® 44/14 (mixture of 30% glycerolester and 70% PEG-ester with fatty acids; the first number in the designation of a Gelucire® product indicates its melting point, the second its HLB value) (Gattefossé, Weil am Rhein, Germany), microcrystalline cellulose (Avicel® PH101, FMC, Philadelphia, USA), corn starch (Roquette, Lestrem, France) and magnesium stearate (Faci Carasco, Italy).

2.2. Melt extrusion

An 18-mm single screw (metal, 30 cm, stepwise reduction of threads) extruder with a single rod die (Allrounder 100U, Arburg, Loβburg, Germany) was employed for carrying out the melt extrusion. It has three heating zones (two cylinder heating zones and one die heating zone), where only the middle zone was used (Fig. 1).

The drug and excipients were mixed using a mortar and pestle, even the treatment of Gelucire® was possible. The middle heating zone was heated to 60°C, while the mixing zone was cooled by water. The extrusion temperature was well below the drug's melting point of 175°C and also below its decomposition temperature. Once the extrusion temperature was reached, the melt extrusion with a screw rotation of 50 rev./min was started. The extruded and cooled product had a 'spaghetti-like' shape and was then crushed with a mortar and pestle and the particle size fraction of <0.1 μm and >0.4 μm was used for further experimentation.

The formulations of the melt-extruded solid dispersions are shown in Table 1. Physical mixtures containing the same ratio of carrier and drug as the melt-extruded batches were prepared for comparison.

2.3. Preparation of the tablets

Eighty milligram tablets each containing 2 mg 17β-E2 were prepared on an instrumented single punch press (EK0, Korsch, Berlin, Germany) with 6 mm punches. The extruded solid dispersions were crushed with a mortar and pestle and sieved (∅ 0.315 mm), as were the other excipients (microcrystalline cellulose, corn starch and magnesium stearate). All ingredients of the tablet formulation except magnesium stearate were mixed for 15 min at 400 rev./min in a ploughshear blender (MTI Type M3, Lage, Germany). After the addition of magnesium stearate, the blend was mixed again for 1 min at 400 rev./min.

A typical tablet formulation containing 2 mg 17β-E2 consisted of 8.3% solid dispersion, 45.6% microcrystalline cellulose, 45.6% corn starch and 0.5% magnesium stearate.

The tablet hardness was determined by diametrical compression on a motorized tablet hardness tester (Model 6D; Schleuniger, Jugenheim, Switzerland). The target tablet hardness was 50 N.

2.4. Dissolution tests

In vitro dissolution studies on tablets or bulk solid dispersion containing 2 mg of 17β-E2 were performed using the USP XXIII paddle dissolution apparatus (Dissolutiontester CD6, Janke und Kunkel, Staufen i.Br., Germany) with either 900 ml 0.1 N HCl or 500 ml 0.3% sodium dodecyl sulfate aqueous solution, 100 rpm, and at 37 ± 0.5°C in triplicate. Samples were withdrawn after 5, 10, 30 and 60 min, filtered (∅ 0.45 μm, regenerated cellulose) and assayed using a validated HPLC method at 242 nm (Gynkotek GINA 160, UVD 160, Germering, Germany) with a C_{18}-reversed phase column and a mixture of acetonitrile, water, methanol and tetrahydrofuran as mobile phase. Data acquisition and evaluation was performed with the Access*Chrom software package (PE Nelson, Cupertino, USA). Although sink conditions could only be maintained in the dissolution experiments with 0.3% SDS, nevertheless, HCl was used

Table 1
Composition of the melt-extruded solid dispersions

Drug or excipient	Composition of the solid dispersion
17β-Estradiol-hemihydrate	10 or 30%
Polymer (PEG 6000, PVP, PVA 64)	50 or 30%
Additive (Sucroester® WE15, Gelucire® 44/14)	40%

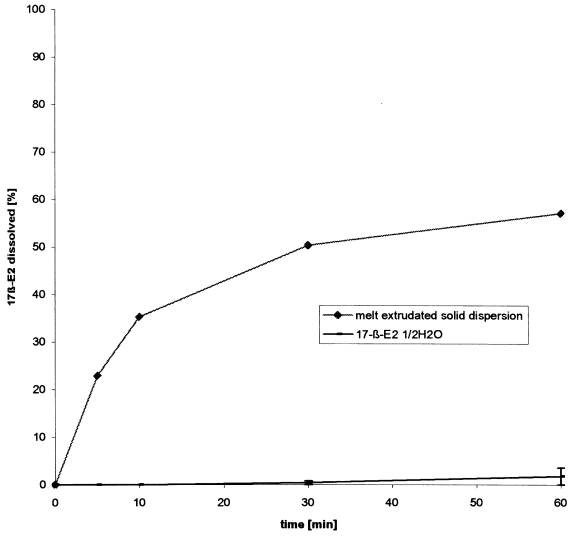

Fig. 2. Dissolution of a melt extruded solid dispersion and pure 17β-E2 (dissolution media: 0.1 N HCl).

as discriminating dissolution medium, since differences could be recognized in a better way.

2.5. X-ray powder diffraction (XRPD)

Data collection was carried out in transmission mode on an automated STOE Powder Diffractometer STADIP (STOE, USA) using germanium-monocromatized CuKα1-radiation ($\lambda = 1.5405989$ Å). The X-ray tube with a copper anode was operated at 40 kV and 30 mA. The 2θ scans were performed using the small linear position sensitive detector with an angular resolution of 0.08° between $3° \leq 2\theta \leq 40°$ (stepwidth 1°). The samples were enclosed between two polyacetate films held together by double sided adhesive tape. Data acquisition and evaluation was performed using the version 2.75 of the Stoe Visual-Xpow software package.

3. Results and discussion

Before determining the dissolution rate of the different batches, the content of 17β-estradiol in each melt extruded batch was assayed by the same HPLC method as was used for the dissolution test. The assay values were between 95 and 100% of theoretical. No additional peak, indicating decomposition, appeared.

The amount of drug release in 0.1 N HCl from a solid dispersion containing 10% 17β-E2, 50% PVP and 40% Gelucire® 44/14 was significantly higher when compared to the pure, non-micronized drug (Fig. 2). While less than 2% of the non-micronized drug was dissolved after 60 min, about 57% of the drug was released from the solid dispersion. This is approximately a 32-fold difference between the two formulations. The importance of the choice of carrier materials on the performance of solid dispersions has been reported extensively [4,5]. Polymers primarily enhance the solubility and/or the rate of dissolution of sparingly water soluble drugs. PVP has been reported to prevent possible drug recrystallization [15]. The amount of PVP and PVA 64 in the formulation was limited due to their relatively high melting points (>150°C) (formulations B–E) and resulting extruder clogging at higher polymer concentrations.

Low melting additives had to be included in the formulation in order to facilitate processing. A minimum amount of 40% additives, which melt at the extrusion temperature of 60°C, was necessary. Sucroester® WE15 and Gelucire® 44/14 were used because of their low melting points (<60°C), their amphiphilic character and their possible ability to prevent drug recrystallization during storage.

The preparation of melt-extruded solid dispersions clearly resulted in an increase in drug release when compared to the pure drug (Table 2). A 10–32-fold improvement in dissolution in 0.1 N HCl was obtained with the melt-extruded formulations. Although Sucroester® WE15 had an advantageous influence on the drug dissolution, its effect was less when compared to the other additives. The batch with 90% Sucroester® (formulation H) led to only a 10-fold increase in dissolution after 60 min and could not reach the results obtained from the other batches containing Sucroester® WE15 in combination with a polymer (formulations C, E and G). Because of its low melting point (44°C) and pasty character, Gelucire®; 44/14 could not be used by itself, but only in combination with a polymer (formulations B, D and F).

The effect of different polymers (PEG 6000, PVP, PVA 64) on the release of 17β-E2 from solid dispersions containing 10% 17β-E2, 40% Gelucire® 44/14 and 50% polymer (formulations B, D and F) is illustrated in Fig. 3. PVP exhibited the best dissolution enhancement and was, therefore, selected as the polymer for the preparation of tablets. The dissolution of 17β-estradiol in PVP is probably better than its dissolution in the other polymers.

Table 2
Amount of 17β-E2 dissolved after 60 min in 900 ml 0.1 N HCl from different melt-extruded formulations

	Formulation	% 17β-E2 dissolved	Standard deviation (%)
A	17β-E2	1.8	1.6
B	10% 17β-E2, 50% PVP, 40% Gelucire® 44/14	57.2	1.8
C	10% 17β-E2, 50%, PVP 40% Sucroester® WE15	39.7	3.4
D	10% 17β-E2, 50% PVA 64, 40% Gelucire® 44/14	37.7	0.7
E	10% 17β-E2, 50% PVA 64, 40% Sucroester® WE15	32.0	2.6
F	10% 17β-E2, 50% PEG 6000, 40% Gelucire® 44/14	38.1	2.1
G	10% 17β-E2, 50% PEG 6000, 40% Sucroester® WE15	38.7	1.8
H	10% 17β-E2, 90% Sucroester® WE15	17.3	1.9

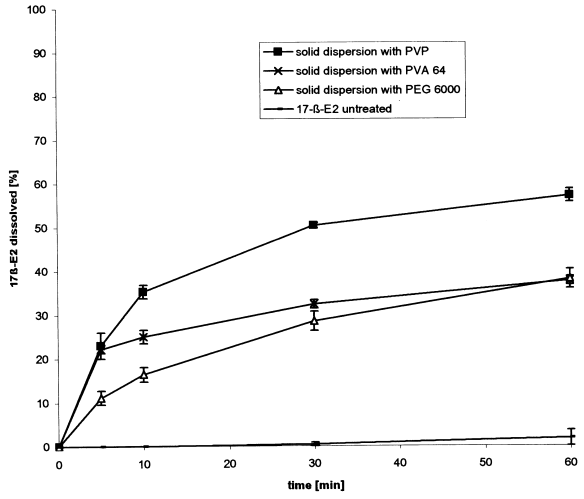

Fig. 3. Effect of polymer on the dissolution behavior (dissolution media: 0.1 N HCl).

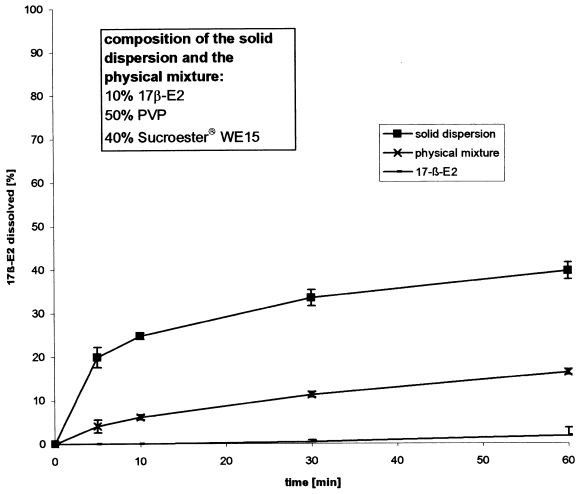

Fig. 5. Comparison of a melt extruded solid dispersion with a physical mixture and pure 17β-E2 (dissolution media: 0.1 N HCl).

In order to investigate the effect of particle size on dissolution behavior of the solid dispersion (formulation G), the melt extrudate was ground with a mortar and pestle and sieved into two different fractions (e.g. >0.4 mm, <0.1 mm). Although the smaller size fraction (<0.1 mm) had a higher initial dissolution rate, particle size of the solid dispersion had only a minor influence on the amount of drug released after 1 h (Fig. 4). These results suggest that the drug was homogeneously dispersed in the carrier. The dissolution of the drug from the solid dispersion was not only higher than the dissolution of the pure, non-micronized drug but was also higher than the release from a physical mixture (Fig. 5). The physical mixture was prepared by intimately mixing the drug and the excipients with a mortar and pestle. Comparing the dissolution profile of a physical mixture vs. the melt extruded solid dispersion, 16% 17β-E2 was released from the physical mixture after 60 min while almost 40% was released from the solid dispersion. The release from the physical mixture was also faster than the dissolution of the pure drug, possibly due to improved wetting of the drug particles.

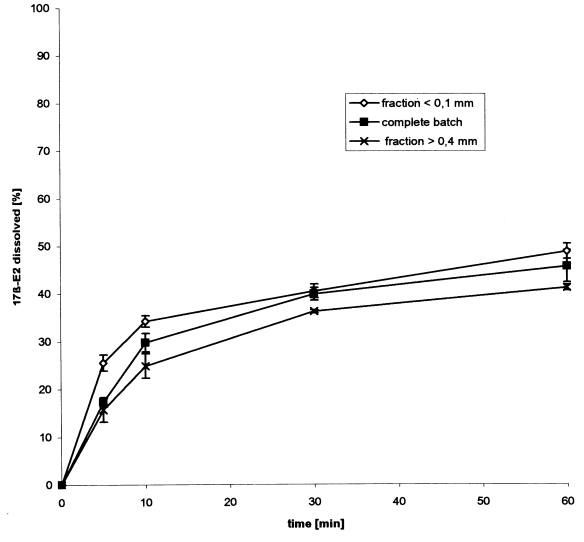

Fig. 4. Effect of particle size of the solid dispersion on the drug release (dissolution media: 0.1 N HCl).

These results suggest that melt extrusion is a suitable process for the preparation of solid dispersions and for the enhancement of the dissolution of a poorly water soluble drug.

Several theories have been proposed to explain the enhancement in dissolution rate from solid dispersions. Corrigan proposed that the increase in dissolution rate resulted from the formation of high energy, metastable, amorphous phases [16]. This theory could not be applied in the present system. The X-ray diffraction pattern of the pure drug and the solid dispersion indicated that there was crystalline 17β-E2 in the melt extruded material (Fig. 6). Better results concerning the dissolution rate may be expected with amorphous material. However, problems concerning stability might be reduced, since recrystallization may be minimal. Some additional peaks were observed with the melt extruded batch, which could be assigned to Sucroester® WE15.

The reason for the higher dissolution rates in this study was probably the improved wettability of the drug [17]. In contrast to the physical mixture, the dispersed drug particles in the solid dispersion are surrounded by the water-soluble carrier polymer, and also by amphiphilic additives facilitating drug release. The polymer/additives dissolve/disperse readily in contact with the release medium and therefore result in a better wetting of the drug particles by the medium. Therefore, melt extrusion leads to a better mixing of drug and excipients or a better embedding of the drug in the carrier, respectively.

The melt-extruded dispersions were incorporated into tablets as the final dosage form with the objective to eluci-

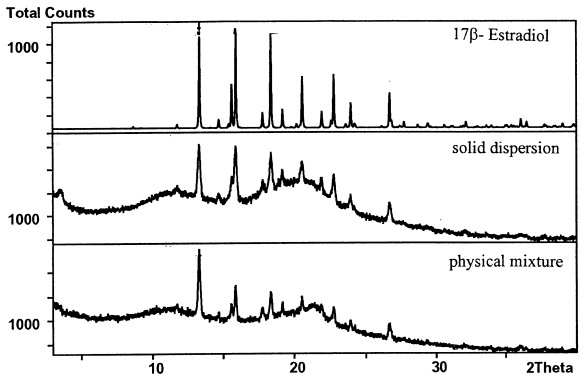

Fig. 6. X-ray diffractogram of bulk drug in comparison with a solid dispersion (10% 17β-E2, 50% PVP, 40% Sucroester® WE15).

date whether the enhancement in the dissolution rate could be maintained with the tablets. In order to allow the easy manufacturing of the tablets, the amount of solid dispersion per tablet was reduced by preparing solid dispersions with a higher drug loading of 30% 17β-E2 in order to improve flowability of the tablet mass and to reach content uniformity more easily. Before tableting, it was assured by conducting dissolution tests that there was no difference between the 10%- and the 30%- drug-loaded solid dispersions. A content of 8.3% of solid dispersion per 80 mg-tablet was sufficient to obtain tablets containing 2 mg 17β-E2.

Solid dispersions with Gelucire® 44/14 were pasty and difficult to handle, especially with regard to the flowability of the tablet mass and the uniform filling of the dies. Therefore, a solid dispersion with 30% 17β-E2, 30% PVP and 40% Sucroester® WE15 as the melting agent was manufactured.

The dissolution test was conducted according to the USP XXIII monograph for estradiol tablets in 500 ml 0.3% sodium dodecyl sulfate in water [18]. All tablets containing

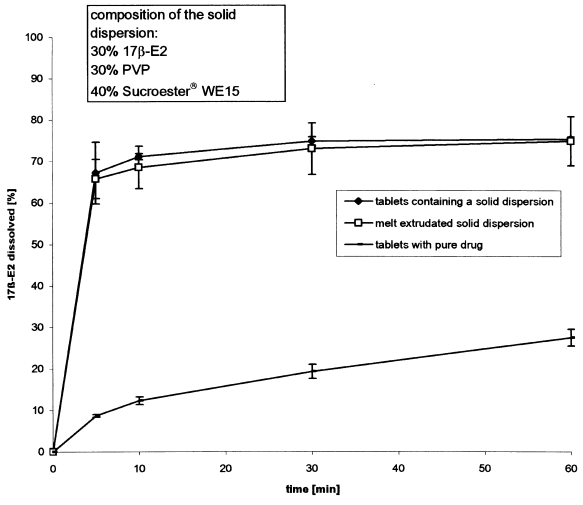

Fig. 7. Drug release from solid dispersions and tablets containing pure drug or a solid dispersion (dissolution media: 0.3% aqueous SDS-solution).

the solid dispersion met the USP requirement of 75% dissolved in 60 min (Fig. 7). The drug dissolution from the tablets containing melt-extruded 17β-E2 was also compared with a tablet containing the pure drug and the same excipients (polymer and low melting additive). An increase in drug dissolution from approximately 27% for tablets containing pure drug to more than 75% for tablets containing the solid dispersions could be demonstrated. These results correspond to results which were shown for the release from the solid dispersion in comparison to the physical mixture (Fig. 5). The release from the melt-extruded solid dispersion was not affected by the tabletting process, as shown by almost overlapping release curves for the powdered melt extrudate and the tabletted melt extrudate (Fig. 7). Standard deviations for the melt extruded solid dispersion was much higher than for the tablets.

In conclusion, melt extrusion is a suitable process for the preparation of solid dispersions in order to improve the dissolution rate of a sparingly water soluble drug. It is an attractive alternative to micronization or traditional methods for the preparation of solid dispersions, because it is a fast and simple one-step-process avoiding the use of organic solvents and high production temperatures. The skillful choice of excipients, i.e. the combination of polymers and additives, can contribute to a more desirable dissolution rate profile and the potential of the development of a superior single dosage unit.

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