Microwave-Induced Enhancement of the Dissolution Rate of Poorly Water-Soluble Tibolone from Poly(ethylene glycol) Solid Dispersions

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ABSTRACT: In this study, solid dispersions of poorly water-soluble Tibolone in a poly(ethylene glycol) matrix were prepared with conventional melt mixing and microwave irradiation. The results of the assay content, LC–MS, and ^{1}H-NMR indicated that microwave irradiation did not affect drug stability when a relatively low irradiation power (440 W) was used. Fourier transform infrared spectroscopy indicated that there were no hydrogen bonds formed between Tibolone and poly(ethylene glycol), and this affected the drug's crystallinity and its particle size distribution. The dissolution rate of the drug was slightly higher in the case of dispersions prepared by microwave irradiation. This enhancement of the drug dissolution rate was probably due to the lower size of the Tibolone particles in the dispersions prepared by microwave irradiation. The application of microwaves represents a promising alternative to conventional preparative methods of drug dispersions. The main advantage in comparison with conventional melt mixing is that solid dispersions can be prepared in much shorter times. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 1249–1258, 2008

Key words: dispersions; drug delivery systems; irradiation

INTRODUCTION

Microwave irradiation is electromagnetic irradiation located between the infrared and radio frequencies in the range of 0.3–300 GHz, which corresponds to wavelengths of 1 cm to 1 m. To avoid disruptions with radar and telecommunications, all domestic and industrial microwave devices operate at a frequency of 2.45 GHz (corresponding to a wavelength of 12.25 cm). Microwave-assisted organic chemistry has received considerable attention during the last decade, and nowadays more and more research chemists are applying microwave technology to organic reactions, especially for drug synthesis on a small or kilolab scale and for polymer synthesis.[1–5] Microwaves can be directly converted into heat inside the material. Therefore, it is possible to achieve rapid and uniform heating even in materials exhibiting low heat conductivity, such as polymers, because the transfer of energy does not rely on heat diffusion. This is very important in the preparation of drug formulations because many excipients are polymers.

Except for drug synthesis, other potential uses of microwaves in the pharmaceutical industry are still in early stages of development but are attracting growing interest. The ability of microwave irradiation to successfully dry treated samples is well known in many disciplines, including pharmaceutical technology.[6–9] Wet granulation techniques are often employed for the preparation of free-flowing granules. The drying process of the granules can have an impact on the quality of the final product, such as its drug-release properties. The use of microwaves in dry granules containing a moisture-sensitive drug, such as acetylsalicylic acid, does not induce drug degradation and is considered to be a promising alternative to the conventional drying processes.[10] Microwave irradiation has also been used to induce changes in physicochemical or chemical properties of drug carriers such as starch[11] and gelatin.[12] With microwaves, the use of toxic agents, such as aldehydes and other bifunctional agents, to crosslink gelatin is avoided.

Another major application of microwaves in pharmaceutical technology concerns the use of microwave irradiation to alter the dissolution rate of drugs, an application on which the current study focuses. The first attempt in this area was probably the dissolution rate enhancement of felodipine from

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solid dispersions by the heating of physical mixtures of the drug and carrier (amorphous silicon dioxide) either in a vacuum dryer or in a microwave oven.[13] Bergese et al.,[14] with the long-term aim of increasing the bioavailability of several insoluble drugs, developed a microwave-induced diffusion method for generating activated drug/three-dimensional matrix nanocomposites. Microwaves have also been applied to induce changes in drug carriers that would retard drug release with alginate chitosan, bovine serum albumin, and pectin as matrices.[15–17]

One of the most promising microwave applications is the improvement of the dissolution rate of poorly water-soluble drugs. It is estimated that around 35–40% of all drugs are poorly water-soluble, and the improvement of their dissolution rate could open new opportunities for the effective use of these drugs. Thus, in this study, microwaves were applied for the preparation of solid dispersions of the poorly water-soluble drug Tibolone [Tibo; i.e., (7a,17a)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one] in poly(ethylene glycol) (PEG). The morphology, physicochemical characteristics, and drug-release properties of the microwave-prepared solid dispersions were investigated and compared to those of solid dispersions prepared by the respective conventional melting method to evaluate the effect of microwave irradiation

EXPERIMENTAL

Materials

Crystalline Tibo with an assay of 99.59% (90% of the drug passed through a 50-μm sieve) was supplied by Zhejiang Xianju Junye Pharmaceutical Co, Ltd. PEG, with a molecular weight of 3898 g/mol (as calculated by OH end groups), a melting temperature of 54°C [differential scanning calorimetry (DSC) analysis], a moisture content less than 0.5% (thermogravimetric analysis), and a viscosity at 20°C and 50% relative humidity of 118 mPa s, was obtained from Clariant (Germany). Absolute ethanol was obtained from Merck. All the other materials and reagents were of analytical grade and purity.

Preparation of the solid dispersions

Conventional melt mixing

For the preparation of PEG/Tibo solid dispersions, physical mixtures of Tibo/PEG (10/90, 30/70, and 50/50 w/w) were placed in reaction tubes (50 mL) and heated at 140°C under an argon atmosphere. Each mixture was held at this temperature for 15 min under gently stirring for the drug to completely melt, and a homogeneous solution of the drug was obtained in PEG. Then, the tubes were immersed in a water bath to quench the melt. All solid dispersions were stored at 25°C in a desiccator.

Microwave-assisted melt mixing

Similar mixtures of Tibo/PEG were placed in reaction tubes (50 mL) and inserted into the microwave apparatus (NNS255WB, Panasonic, Tokyo, Japan; 50 MHz, maximum of 1100 W) at 440 W until PEG melted (ca. 1 min). After that, the samples were removed and kept at room temperature for 30 s under gentle stirring (100 rpm) to improve the dispersion of Tibo into the PEG melt and to avoid overheating. The procedure was repeated several times until the drug completely melted, and then the samples were quenched in cold water. The time needed for the melt to become transparent, which was an indication that Tibo was completely dissolved in the PEG melt, was recorded.

Microwave stability studies of Tibo

To study the effect of microwave irradiation on Tibo's stability, three samples of the pure drug were placed in small vials and treated for up to 1, 3, and 5 min at a microwave power output of 440 or 600 W. To avoid the effect of heating that was generated during the microwave treatment, irradiation was stopped every 30 s, and the samples were maintained at room temperature to allow sufficient cooling. An assay of the samples was carried out with a Shimadzu model LC-20AD high-performance liquid chromatograph (Tokyo, Japan) using UV detection at a wavelength of 205 nm.[18] LC–MS analysis of pure and irradiated Tibo was carried out with a similar technique reported by Steckelbroeck et al.[19] ^{1}H-NMR spectra of the samples were obtained with a Bruker AMX 300 spectrometer operating at a frequency of 300 MHz for protons. Deuterated chloroform ($CDCl_3$) was used as a solvent to prepare 5% (w/v) solutions. The number of scans was 10, and the sweep width was 6 kHz.

DSC

Thermal analysis of the samples was carried out with a PerkinElmer Pyris-1 differential scanning calorimeter (Shelton, CT). The calorimeter was calibrated with indium and zinc standards. For each measurement, a sample of approximately 6 mg was used, placed in an aluminum seal, and heated up to 200°C at a heating rate of 20°C/min. The sample remained at that temperature for 1 min and was quenched to 0°C. A second thermograph was recorded for each sample with the same heating rate.

Wide-angle X-ray diffraction (WAXD)

WAXD was used for the identification of the crystal properties of the pure materials and dispersions. The WAXD study was performed over the 2θ range of 5–50°C with a Philips PW 1710 diffractometer (Eindhoven, The Netherlands) with Bragg–Brentano geometry (θ, 2θ) and Ni-filtered Cu Kα radiation.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were obtained with a PerkinElmer Spectrum 1000 FTIR spectrometer. A small amount of each material was mixed with KBr (1 wt % drug content) and compressed into tablets. The IR spectra of these tablets were obtained in the absorbance mode and in the spectral region of 450–4000 cm^{-1} with a resolution of 4 cm^{-1} and 64 coadded scans.

Scanning electron microscopy (SEM)

The morphology of the prepared solid dispersions was examined with an SEM system (JMS-840, JEOL, Tokyo, Japan). The samples were covered with carbon coating to increase the conductivity of the electron beam. The operating conditions were an accelerating voltage of 20 kV, a probe current of 45 nA, and a counting time of 60 s.

Release profile

Drug dissolution from the solid dispersions was investigated with a Pharma Test type PTWS III apparatus. Samples from the solid dispersions were obtained and used in the release experiments without further processing; that is, no compression was applied to the samples before dissolution testing. The paddle method was used, with the paddles rotating at 100 rpm. Samples from the solid dispersions, corresponding to a drug content of around 10 mg, were added to the vessels containing 1 L of a 1% (w/v) solution of sodium dodecyl sulfate in water at 37°C. At predetermined time intervals, 1-mL samples were withdrawn, filtered (0.22-μ Millex-GV, Millipore), and assayed for the drug spectrophotometrically at 205 nm. Samples were replaced by fresh dissolution medium. The data represent the mean values of three separate experiments.

RESULTS AND DISCUSSION

Effect of microwave irradiation on drug stability

Before the preparation and study of the solid dispersions, the effect of microwave irradiation on the drug's stability was evaluated. Tibo was irradiated with power levels of 440 and 600 W for several time periods. The drug content assay results, as measured by high-performance liquid chromatography, showed that the use of microwave irradiation did not significantly affect the stability of Tibo. No other peaks were identified, except for the characteristic peak of Tibo at 205 nm. Furthermore, no Tibo assay reduction was observed even after prolonged irradiation (5 min) at the low irradiation power (440 W). However, at the higher irradiation power of 600 W, the stability of Tibo was slightly reduced with increasing irradiation time. The recovery fell from 99.59 ± 0.002 to 98.68 ± 0.012% after 5 min of irradiation (Table I).

TABLE I
Tibo Assay of Microwave-Irradiated Samples

Sample	Assay	Standard deviation	Relative standard deviation (%)
Pure Tibo (not microwaved)	99.59	0.0024	0.5611
Tibo after 1 min at 440 W	99.65	0.0095	1.2379
Tibo after 3 min at 440 W	99.56	0.0121	1.3285
Tibo after 5 min at 440 W	99.49	0.0097	1.3961
Tibo after 1 min at 600 W	99.43	0.0065	1.3031
Tibo after 3 min at 600 W	99.15	0.0136	2.8119
Tibo after 5 min at 600 W	98.68	0.0116	2.3957

Tibo degradation products, possibly formed during microwave irradiation, were investigated with liquid chromatography-mass spectroscopy (LC–MS). The retention times of the recorded peak in all studied samples were almost identical, and it was impossible to detect some degradation products. A single peak was detected in all chromatograms that was also found in mass spectrometry analysis and attributed to Tibo. From the mass spectrum of pure Tibo, it became clear that Tibo formed adducts with the used solvents [$MH^+ + 2CH_3OH + H_2O$; m/z = 393], whereas the ion mass of Tibo was detected at MH^+ (m/z = 313). Additionally, by the loss of —OH and —CH_3 groups, an ion mass at MH^+ (m/z = 281) was recorded, which was the basic peak of the mass spectra; after that, it lost the —C≡CH group, with the remaining Tibo molecule corresponding to an ion mass at MH^+ (m/z = 256). The mass spectra of irradiated Tibo were similar (Fig. 1).

The ^{1}H-NMR spectra of irradiated samples at 440 and 600 W for 5 min were the same as the spectrum of pure (nonirradiated) Tibo (Fig. 2). From a first view of these spectra, it can be seen that there are no additional peaks or any significant shifts of existing peaks, and this would indicate the formation of degradation products in the irradiated samples. On the basis of the drug content assay results, this was expected for the samples irradiated with 440 W but not for those irradiated with 600 W. Examining more carefully the ^{1}H-NMR spectrum of irradiated samples at 600 W, we observed an additional curve with low intensity at 1.96 ppm, at which the proton of the hydroxyl group was absorbed. This was an indication

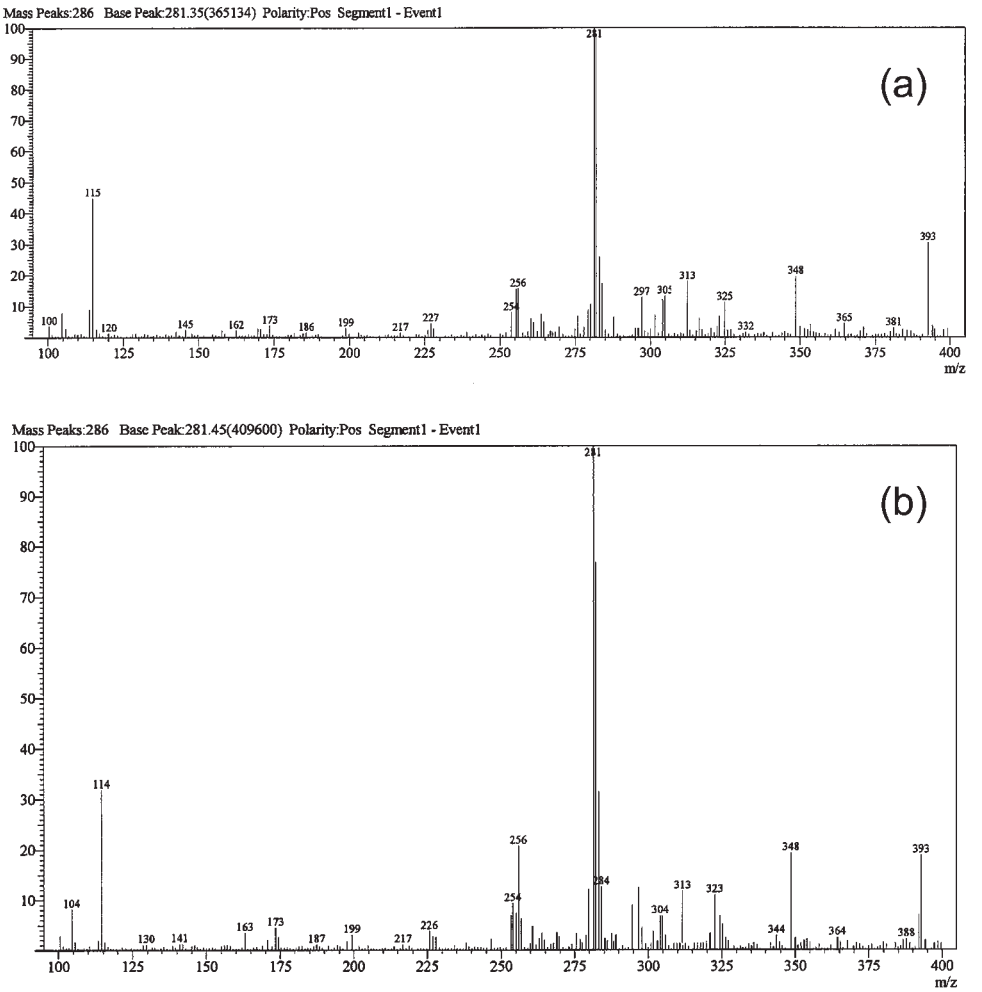

Figure 1 Mass spectra of (a) pure Tibo and (b) Tibo after microwave irradiation for 3 min at 440 W.

that during irradiation at the high microwave power, some small alterations occurred in the drug molecule, most likely the dehydration of the hydroxyl groups, confirming the assay analysis of the irradiated sample.

From the investigation of Tibo stability against microwave irradiation, as discussed previously, it can be concluded that microwave irradiation at 440 W does not aversely affect drug stability, even after prolonged irradiation times (5 min), whereas prolonged irradiation at 600 W appears to cause a slight degradation of the drug. For this reason and to prevent drug degradation during the preparation of the solid dispersions, all solid dispersions were prepared at an irradiation power of 440 W.

Effect of microwave irradiation on the time needed to prepare the solid dispersions

A study was conducted to find the time needed for complete Tibo dissolution in the PEG melt during microwave irradiation. As can be seen in Figure 3, the time necessary for the complete melting of microwave-irradiated PEG was short, less than 1 min even at the lowest power of 250 W, whereas the time needed for PEG melting under conventional heating at 140°C was more than 5 min. This directly affected the necessary time for complete drug dissolution into the PEG melt, which in the case of microwave irradiation ranged from 90 to 140 s (Fig. 3). Additionally, the time needed for Tibo to dissolve in the melted PEG (and form a transparent melt) decreased with increasing irradiation power. Thus, the samples containing 10 wt % Tibo (90/10 w/w PEG/Tibo sample) became transparent in 90 s at the lowest microwave power (250 W) and in only 60 s at 600 W. The time for Tibo dissolution in the melt was a little higher for the samples containing 30 wt % Tibo (70/30 w/w PEG/Tibo), ranging from 90 to 140 s at the different irradiation powers used. However, for the samples containing 50 wt % Tibo (50/50 w/w PEG/Tibo), complete dissolution was not achieved even after prolonged irradiation (200 s), as was evident from the nontransparency of the resulting

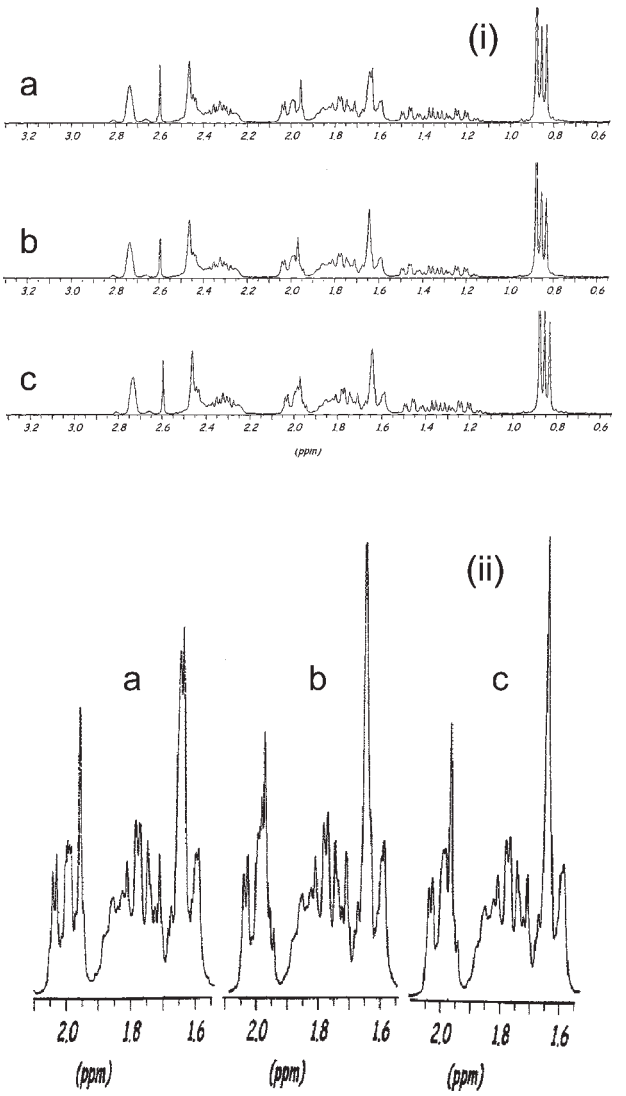

Figure 2 (i) ^{1}H-NMR spectra of (a) pure Tibo, (b) Tibo irradiated at 400 W for 5 min, and (c) Tibo irradiated at 600 W for 5 min and (ii) expanded regions of the hydroxyl group of Tibo for the same samples.

melts. It seems that Tibo was only partially dissolved, the rest of it remaining suspended in the melt because of PEG saturation with the drug. Total transparency of the 50/50 (w/w) PEG/Tibo samples was not observed when the conventional hot-melt method was also used, and this supports the aforementioned consideration.

The time needed for Tibo dissolution in the PEG melt under microwave irradiation was much shorter than that needed under the conventional method of melting by heat application (>15 min). Microwaves are a type of electromagnetic field, so they are made of perpendicular electric and magnetic waves. There are two mechanisms associated with microwave heating: ionic conduction and dipole rotation, which is mainly responsible for the heating in the studied solid dispersions. Polar groups such as —OH, —COOH, —NH_2, and >C=O, which exist in most molecules, tend to align by rotation with the applied oscillating electric field. In the case of PEG, such groups are the ether and hydroxyl end groups. If the applied frequency is too low, all the molecules will move precisely (align and realign) in time with the field, and no heating will result. If the frequency of the field is too high, the molecule will not have time to respond. This is the usual case in the operating frequency of microwave ovens and laboratory instruments (2.45 GHz), and the molecules will lag behind the field. This lag causes them to dissipate microwave energy in the form of heat. Thus, the main advantage of microwaves is that microwave energy can be converted into heat directly inside the material. Therefore, it is possible to achieve rapid and uniform heating even with materials showing low conductivity, such as polymers (e.g., PEG used in this study), because the transfer of energy does not rely on heat diffusion. This is very important in drug formulations because many of the formulation excipients are polymers. Furthermore, microwaves heat the contents directly, allowing the temperature to rise much faster. With conventional heat sources, the energy must first conduct through the walls of the vessel containing the reactants. For this reason, PEG needs only a few seconds to be melted by microwaves and more than 5 min with conventional heating. Thus, it may be concluded that microwave-induced preparation of solid dispersions of drugs is a much shorter (and therefore more efficient) process compared to the conventional methods of solid dispersion preparation, such as melt mixing through a heat supply.

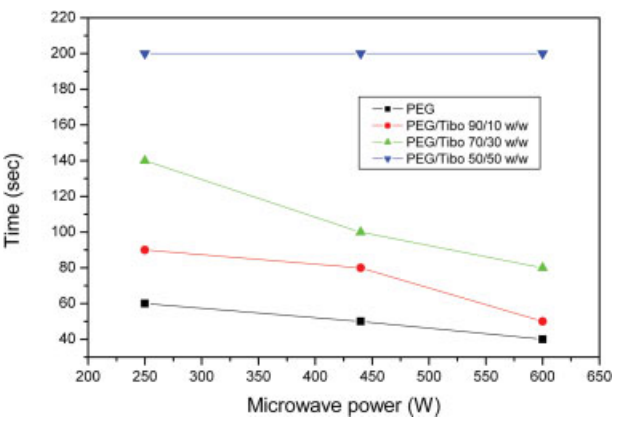

Figure 3 Irradiation time needed for the melting of PEG and Tibo dissolution at different microwave output powers (the melt solution was not clear). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

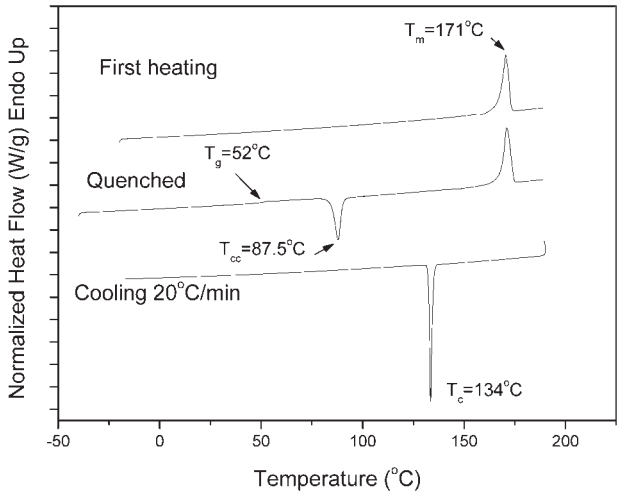

Figure 4 DSC thermograms of Tibo during heating in several procedures (T_c = crystallization temperature; T_{cc} = cold crystallization temperature; T_g = glass-transition temperature; T_m = melting temperature).

Physical characterization of the solid dispersions

DSC

To evaluate how the methods used to prepare solid dispersions impinged on the physical properties of the drug, DSC was used for all the prepared materials. Tibo is a crystalline compound with a melting point of 169–173°C and a maximum at 171°C. After quenching, it can be made completely amorphous, with a glass-transition temperature at 52°C (Fig. 4). During heating above the glass-transition temperature, it crystallizes at a cold crystallization temperature of 87.5°C, whereas its melting point remains identical to that previously reported for pure Tibo. Additionally, the shape of the melting peak remains the same, without the existence of other peaks, and this indicates that the thermal treatment does not affect the form or purity of Tibo. When it is cooled with a slow cooling rate from its melt, it crystallizes rapidly at 134°C.

The thermograms for the two different series of solid dispersions were recorded and are presented in Figure 5. PEG is a semicrystalline polymer that exhibits a very low melting point, so it can be used to prepare solid dispersions by the melt method.[20] Besides, because of its low melting point, after it melts, it dissolves drugs before reaching their melting temperatures, which may be much higher. In all the solid dispersions, the melting point of PEG predominated, whereas the melting point of Tibo was hardly detectable. Especially in samples containing 10 or 30 wt % Tibo, no melting point of the drug was observed. However, this is not evidence that the drug is dispersed in an amorphous state. From our previous study, it was found that when PEG is used as a drug carrier, because of its low melting point, drug particles (felodipine and hesperetin) can easily dissolve in the polymer melt at temperatures before their melting points.[21] Thus, the crystalline drug could not be detected with DSC in the solid dispersions. In such systems, thermal analysis is an inappropriate technique and must always be used in combination with SEM or X-ray diffraction. For this reason, the melting point of the drug could be detected only in the samples containing 50 wt % Tibo, independently of their preparation by melt mixing or microwave irradiation. In the case of microwave-prepared solid dispersions, the melting point was recorded at 152°C, which is exactly 19°C lower than that of the neat drug, whereas in the melt-mixing sample, this peak was recorded at 157°C. This shift may prove the already mentioned hypothesis that the drug dissolves in the melt of

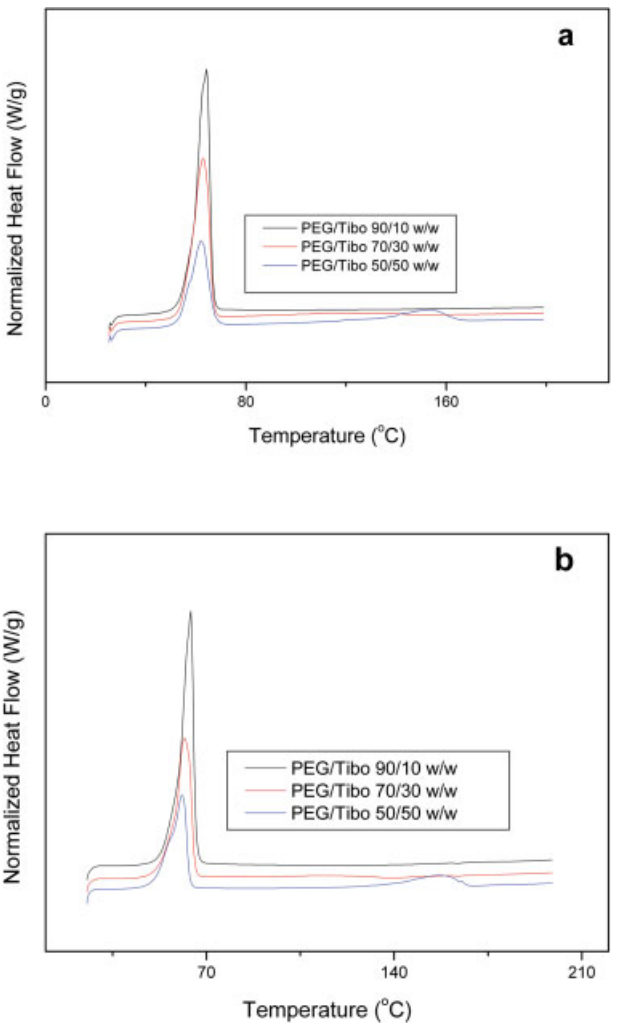

Figure 5 DSC thermograms of (a) PEG/Tibo solid dispersions prepared with microwaves and (b) PEG/Tibo prepared by conventional melt mixing. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

PEG. However, examining the melting point of PEG, we can see that with an increase in the amount of the drug, this melting point shifts to lower temperatures, from 64°C in the samples containing 10 wt % Tibo to 63 and 62–60°C for the samples with 30 and 50 wt % Tibo, respectively (Table II). The fact that a change in the melting temperature of PEG was observed leads us to hypothesize that a binary system of the drug and matrix was created but with few interactions between them. It seems that a small amount of the drug is interpenetrated in the PEG phase, and the formed crystals are of lower perfection and thus exhibit a lower melting point. Furthermore, as can be seen in Table II, in the irradiated samples, PEG has a slightly higher melting enthalpy than the samples prepared with the conventional method (melt mixing). This higher crystallinity of PEG may be related to the alignment of —OH groups of PEG during irradiation. This can cause a better alignment of PEG macromolecules during cooling and thus a higher degree of crystallinity.

WAXD was also used as a complementary method to study the crystal state of the drug.

WAXD

The WAXD pattern of Tibo showed that the drug was in a crystalline state with characteristic diffraction peaks at 2θ values of 14.15, 15.3, 16.31, 17.71, 18.65, 20.73, 21, 23.74, 24.32, 27.67, 23.6, and 35.37°, which corresponded to the crystalline form known as form II (Fig. 5). In the case of PEG/Tibo dispersions, all samples exhibited diffraction peaks in their WAXD graphs that were characteristic of both PEG and the drug [Fig. 6(a,b)]. The intensities of the peaks assigned to the drug increased as the drug content of the solid dispersion increased, indicating that a higher amount of the drug was in a crystalline state. Examining the diffraction patterns, we can see that for the samples containing up to 30 wt % Tibo, the crystal form remained the same as the initial drug. It appears, therefore, that melt mixing with either microwaves or conventional heating does not affect the crystalline form in dispersions containing a relatively low amount of the drug. However, in the PEG/Tibo dispersions containing 50 wt % drug, the second polymorph structure of Tibo was formed in both formulations [Fig. 6(a,b)]. This polymorph is known as form I[22] and has characteristic peaks at 2θ values of 13.74, 15.26, 16.1, 17.45, 17.81, 18.4, 19.34, 20.32, 21.23, 21.67, 23.88, 28.07, 33.56, and 37.37°. It seems that the preparation of an oversaturated solution affected the capacity for drug crystallization in the second polymorph. Similar degrees of crystallinity were calculated for the PEG/Tibo dispersions prepared by microwave-induced melting and those prepared by conventional melting, without any clear differences being found. From the calculated values, it was observed that the crystallinities ranged from 12 to 14%, from 40 to 42%, and from 66 to 70% for the solid dispersions containing 10, 30, and 50 wt %

TABLE II
Melting Temperature (T_m) and Melting Enthalpy (ΔH_m) Values of PEG/Tibo Solid Dispersions

Sample	ΔH_m (J/g)	T_m (°C) PEG	T_m (°C) Drug
PEG	200	54	
Tibo			171
Microwave samples			
90/10 (w/w) PEG/Tibo	199.5	63.2	—
70/30 (w/w) PEG/Tibo	184.3	60.56	—
50/50 (w/w) PEG/Tibo	176.4	60	152
Melt-mixing samples			
90/10 (w/w) PEG/Tibo	198.7	64.1	—
70/30 (w/w) PEG/Tibo	175.4	61.67	—
50/50 (w/w) PEG/Tibo	169	60.86	157

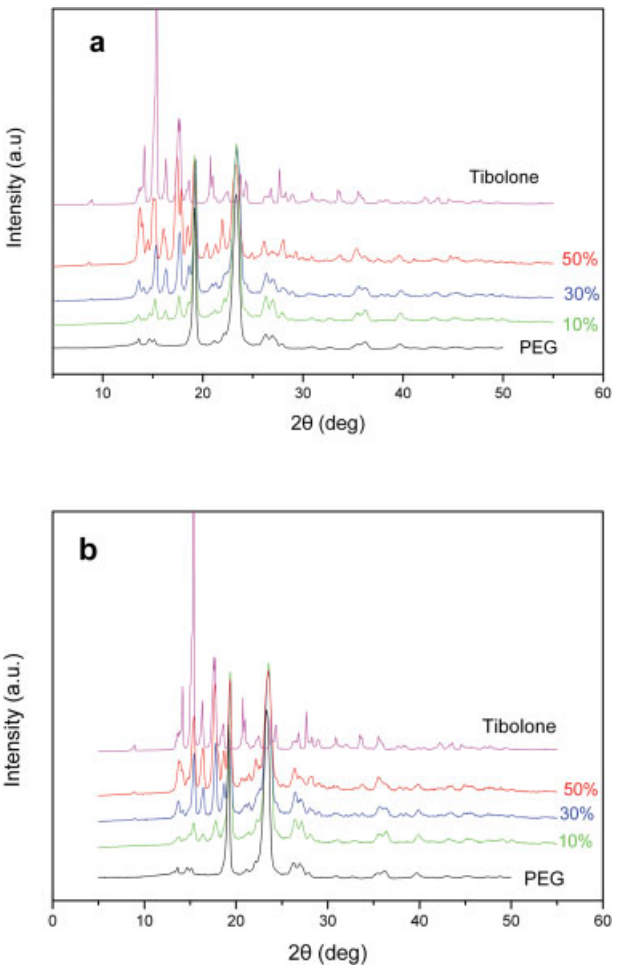

Figure 6 WAXD patterns of PEG/Tibo solid dispersions prepared with melt mixing with (a) microwave irradiation and (b) conventional heating. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

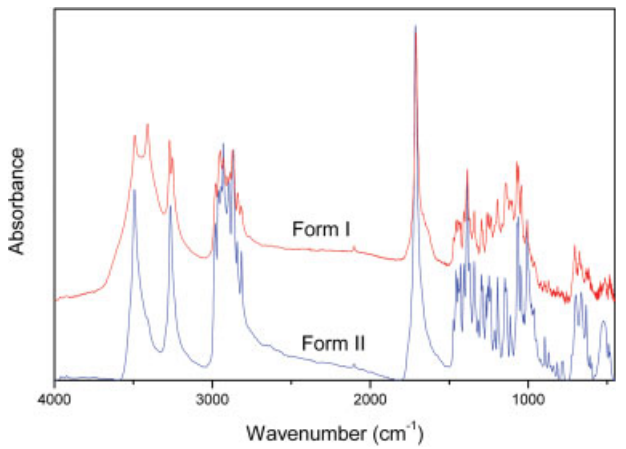

Figure 7 FTIR patterns of Tibo crystal form II and Tibo crystal form I. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Tibo, respectively. These crystallinities are the mean values of five different measurements. Therefore, in the case of melt mixing, microwave irradiation does not promote the amorphization of Tibo.

FTIR spectroscopy

The nature of the interactions between the drug carriers and Tibo was investigated with FTIR spectroscopy because any kind of physicochemical interactions that may take place, such as the formation of hydrogen bonds between the carrier and drug, will automatically lead to frequency shifts or splitting in absorption peaks. The Tibo spectrum showed some characteristic peaks. At 1714 cm^{-1}, the stretching of the carbonyl group of Tibo appeared. The —OH stretching frequencies gave a single absorption band at 3492 cm^{-1} in the case of crystallized Tibo in initial crystal form II and a double absorption band at 3492 and 3410 cm^{-1} in the case of crystal form I (Fig. 7).

In the spectra of the solid dispersions produced either by melt mixing with the conventional heating method or after microwave irradiation, all the characteristic peaks of Tibo were at the same positions as those in the spectrum of Tibo (form I or form II). Furthermore, no shift of the absorbance of the carbonyl group was observed, and this was an indication that hydrogen bonds were not formed between the carbonyl groups of Tibo and the hydroxyl end groups of PEG or its backbone oxygen groups. Additionally, the double absorption band of —OH of Tibo appeared only for the 50/50 (w/w) samples [Fig. 8(a,b)]; this is in agreement with the results of the WAXD experiment, indicating that in this sample Tibo was transformed only to crystalline form I, whereas in the samples containing 10 and 30 wt % Tibo, the crystal form remained the same as that of the initially used Tibo, that is, form II. Also, in the FTIR spectra of the region of hydroxyl groups, it is obvious that the intensity of the characteristic peak at 3410 cm^{-1} changed according to a comparison of 50/50 (w/w) samples for both preparation methods. In case of the sample prepared with the conventional method, the spectra tended to resemble the spectra of form I, and this indicated that the drug crystals appeared mainly in this form rather than form II. On the contrary, in the spectra of the sample prepared with the use of microwave irradiation, this characteristic peak at 3410 cm^{-1} appeared with a lower intensity with respect to the absorption band at 3492 cm^{-1}, an indication of the existence of both crystalline structures, forms I and II, of the drug in this sample.

SEM

In the micrographs of all PEG/Tibo dispersions [Fig. 9(a,b)], regardless of the drug content, drug crystals

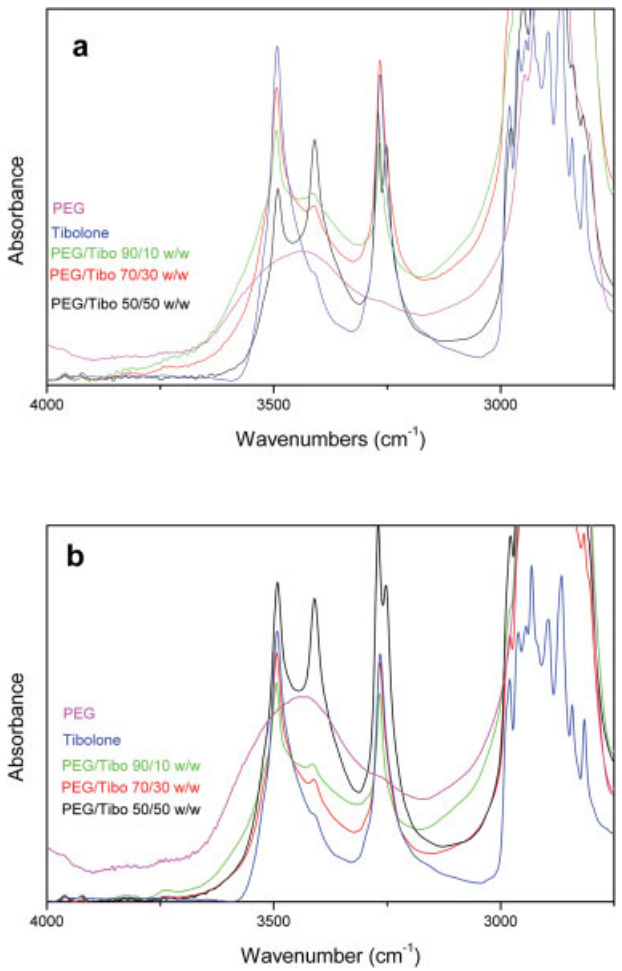

Figure 8 FTIR spectra of PEG/Tibo solid dispersions prepared by (a) conventional melt mixing and (b) microwave irradiation. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

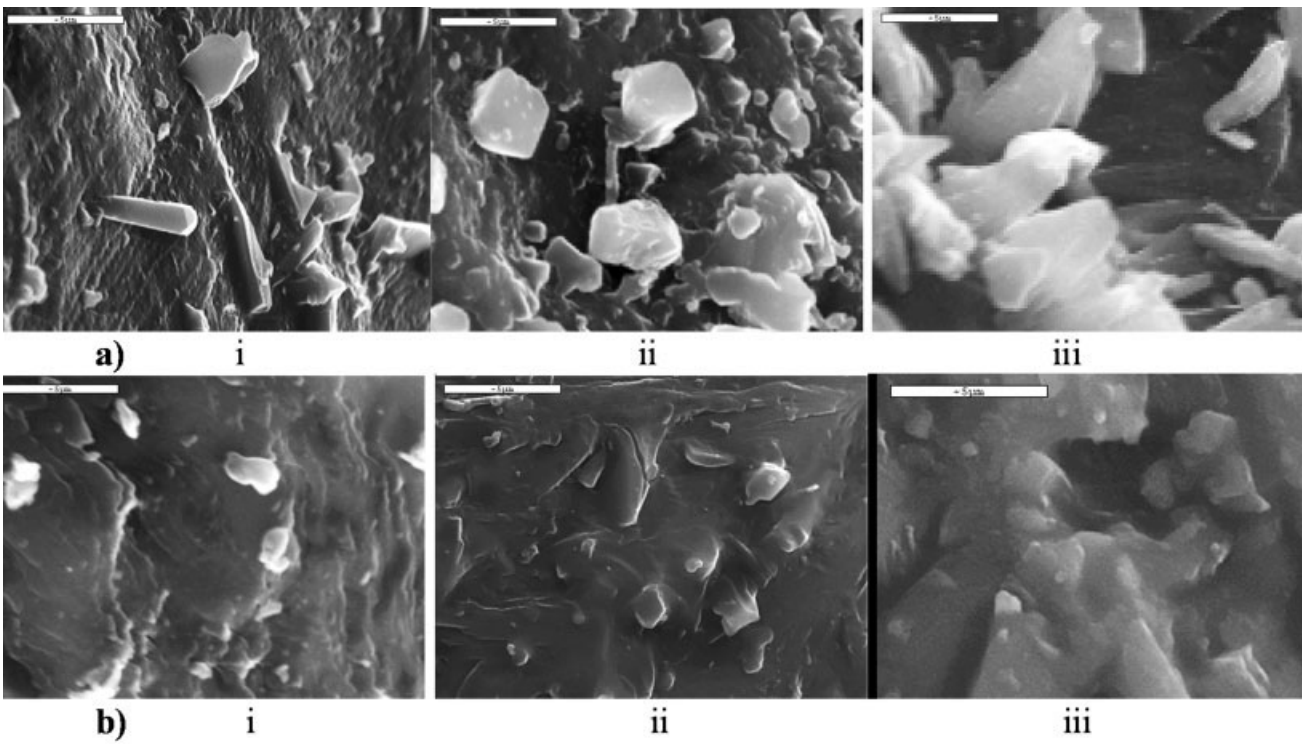

Figure 9 SEM micrographs of PEG/Tibo solid dispersions prepared by (a) conventional melt mixing and (b) microwave irradiation: (i) 10, (ii) 30, and (iii) 50 wt % Tibo.

were present, in accordance with WAXD data, which indicated that in all PEG/Tibo samples, the drug was in a crystalline state (Fig. 6). The absence of interactions between the reactive groups of Tibo and the hydroxyl groups of PEG permitted the crystallization of Tibo in the PEG matrix. With an increase in the relative proportion of drug, the size of the crystalline particles appeared to increase. SEM also revealed that the polymer matrix in the PEG/Tibo dispersions prepared by conventional melting seemed to extract the drug from the interior to the surface, creating a binary system with two different phases [Fig. 9(a)]. Most importantly, the size of the crystalline particles in the dispersions prepared by microwave irradiation was lower in all samples compared with the samples prepared by conventional melt mixing [Fig. 9(b)]. It seems that microwave irradiation created a finer dispersion of the drug in the polymer matrix, and this could have a positive effect on the rate of drug release from the solid dispersions prepared by microwave irradiation.

Release profile

The enhancement of dissolution profiles for poorly water-soluble drugs has become in recent years a great challenge for scientists who work on pharmaceutical technology. As can be seen in Figure 10, the dissolution enhancement of Tibo was achieved in all solid dispersions in comparison with pure Tibo, whose dissolution did not exceed 20%. PEG has frequently been applied for the enhancement of drug dissolution from solid dispersions, with the improvement of drug dissolution being attributed to improved wettability and dispersibility as well as particle size reduction and a decrease in the crystalline fraction of the drug.[23–25] This was also achieved in our studied samples containing Tibo, and in the

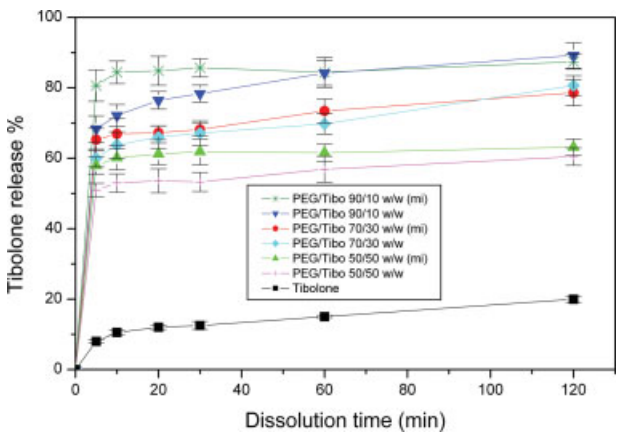

Figure 10 Release profiles of PEG/Tibo solid dispersions prepared by melt mixing with microwave irradiation and the conventional method. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

sample containing 10 wt % Tibo, almost the whole amount was released in the first 10 min. Furthermore, an increase in the relative proportion of Tibo in the dispersion caused a reduction of the drug's dissolution rate (Fig. 10), which could be attributed to the decreased hydrophilicity and reduced wettability of the dispersions with an increasing content of hydrophobic Tibo.[26,27]

The application of microwave irradiation to the preparation of the solid dispersions led to a slight increase in the Tibo dissolution rate (i.e., an increase in the fraction of the drug dissolved at a certain time) compared with that of the conventional melt-mixing method. The enhancement of the drug dissolution rate by microwave application can be attributed to the lower size of the Tibo particles in the dispersions prepared by microwave irradiation, as was evident from SEM (Fig. 9). The release profile appears to have two different phases of dissolution. The first, with a high slope, in the first minutes is a fast dissolution of small drug particles, and the second is a slow dissolution. During the second phase of the dissolution of the drug from the polymer matrix, it seems that bigger crystals have the determining role in the dissolution profile. Apparently, the microwave energy applied to the dispersions results in a finer distribution of the drug in the PEG melt than conventional melt mixing and, consequently, in smaller drug crystals upon drug recrystallization. It is well known that in poorly water-soluble drugs, amorphization or drug crystal reduction can cause a substantial increase in the drug dissolution rate.[24–29] The generation of a finer drug distribution in the PEG melt in the case of microwave-processed formulations can be attributed to the enhancement of drug diffusion in the polymer melt by microwave irradiation (microwaves' lower diffusion activation energy[14]).

CONCLUSIONS

The time needed for Tibo dissolution in a PEG melt under microwave irradiation was much shorter than that needed in the conventional method of melting by heat application (>15 min). Thus, it may be concluded that microwave-induced preparation of solid dispersions of drugs is a much shorter (and therefore more efficient) process compared to the conventional methods of solid dispersion preparation, such as melt mixing or solvent evaporation through heat application.

The application of microwaves during the preparation of solid dispersions of Tibo in PEG results in different crystal sizes of the drug in the dispersion in comparison with the solid dispersions prepared by conventional methods. As a result of the different drug properties, the dissolution rate of the drug is higher in the case of dispersions prepared by microwave irradiation.

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