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Dissolution Improvement of High Drug-loaded Solid Dispersion

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ABSTRACT

This study focused on an investigation of a high drug-loaded solid dispersion system consisting of drug, carrier, and surfactant. Solid dispersions of a water-insoluble ofloxacin (OFX) with polyethylene glycol (PEG) of different molecular weights, namely binary solid dispersion systems, were prepared at drug to carrier not less than 5:5. Polysorbate 80, a nonionic surfactant, was incorporated into the binary solid dispersion systems as the third component to obtain the ternary solid dispersion systems. The powder x-ray diffraction and differential scanning calorimetric studies indicated that crystalline OFX existed in the solid dispersions with high drug loading. However, a decreased crystallinity of the solid dispersions obtained revealed that a portion of OFX was in an amorphous state. The results indicated a remarkably improved dissolution of drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems. This was because of polysorbate 80, which improved wettability and solubilized the non–molecularly dispersed or crystalline fraction of OFX.

KEYWORDS: ofloxacin, ternary solid dispersion, polysorbate 80, dissolution, drug loading.

INTRODUCTION

Among numerous ways of enhancing drug dissolution, solid dispersion of drug in a water-soluble polymer is one of the promising techniques.[1,2] An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, ie, more than 50% to 80% wt/wt, was required to achieve the desired dissolution.[3-5] This high percentage of carrier causes consistency of product performance at the time of manufacturing. This is a major consideration in that the number of market products arising from this approach has been less than expected. Recently, combined carriers have been used and a higher increase in drug dissolution was reported.[6,7] However, those reported solid dispersions were still a very low percentage of drugs loading in the system, which required an extremely high amount of carrier. High drug-loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system is in complete crystal has high crystallinity. Therefore, the strategy of high drug-loaded solid dispersion systems with enhanced drug dissolution still needed to be improved.

In this study, drug concentration over 50% was loaded in solid dispersions. Ofloxacin (OFX) was used as a model drug. This drug is practically insoluble in water so that the dissolution from its dosage forms is too low and is a limiting step in the absorption process. It was reported that the dissolution of OFX could be improved to some extent by using urea as a carrier but such system needed more than 80% of carrier.[8] Moreover, the enhanced dissolution of this drug by water-soluble polymer has not yet been reported. In our present study, polyethylene glycols with different molecular weights have been used as they have shown strong enhancing power on the dissolution of several drugs.[9,10] The nonionic surfactant (Tween 80) was used as the third component in the ternary system.

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MATERIALS AND METHODS

Materials

Ofloxacin (OFX) was supplied by Daiichi Seiyaku Co Ltd (Tokyo, Japan). Polyethylene glycols (PEG) of various molecular weights (PEG 4000 and PEG 20000) were purchased from Fluka Chemika (Steinheim, Switzerland). Polysorbate 80 (Tween 80), a liquid nonionic surfactant with hydrophilic-lipophilic balance (HLB) of 15 was purchased from Merck (Darmstadt, Germany). Other chemicals were of analytical reagent grade. All materials were used as obtained.

High Drug-Loaded Solid Dispersion Preparation

OFX solid dispersions of both binary and ternary systems were prepared by conventional solvent method using PEG 4000 or PEG 20000 as a carrier. In the binary system, the solid dispersions of 5:5 and 7:3 wt/wt of drug to carrier were prepared. The mixture of drug and carrier was dissolved in chloroform. In the ternary system, the surfactant was added into the solution of drug and carrier to obtain the

final weight ratio of drug/carrier/surfactant of 5:5:1 and 7:3:1 wt/wt/wt. The solvent was evaporated under reduced pressure using a vacuum dryer at 40°C until complete evaporation. To ensure the residual solvent was completely removed, the solid mass was further dried in a vacuum oven at room temperature for 24 to 48 hours or until the weight constant was obtained. The resulting solid was pulverized and sieved. The particle fraction of 75 to 250 μm was used in the experiment.

The physical mixtures of binary system containing drug to carrier of 7:3 wt/wt were prepared by manually mixing the appropriate amount of 75- to 250-μm particle size fractions of OFX and carrier. In ternary physical mixtures, Tween 80 was gently mixed to the mixture of binary drug-carrier system to yield drug/carrier/Tween 80 of 7:3:1 wt/wt/wt.

Powder X-ray Diffraction

The powder x-ray diffraction (XRD) was performed by a Rigaku Denki 2027 diffractometer (Tokyo, Japan) using Ni-filtered, CuKα radiation, a voltage of 30 kV, and a current of 5 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of 4°/min over a 2θ range of 5° to 40°.

Thermal Analysis

A differential scanning calorimeter (DSC), model TA 9900 (Du Pont, New Castle, DE) was used under nitrogen gas flow of 60 mL/min at a heating rate of 5°C/min. The samples were sealed in an aluminum pan. A sample with accurate weight of ~2 to 3 mg was subjected to the DSC run over the temperature range of 40 to 300°C. The temperature was calibrated using pure indium with a melting point of 156.60°C. An empty pan was used as a reference.

Dissolution Study

The dissolution behavior of OFX from binary and ternary solid dispersions was investigated by using the modified USP paddle method at a rotating speed of 100 rpm. A powder sample containing 100 mg of OFX was compressed at 2 ton/cm^2 into a 10-mm diameter flat-face tablet. The tablet was fixed to the bottom of a beaker containing 1000 mL of distilled water as a medium at 37°C. The other end of the tablet except the top surface was sealed to allow only the top surface to contact the medium throughout the dissolution run. A 5-mL sample of the solution was taken out periodically, and the same amount of solvent at the same temperature was replaced. The sample solution was suitably diluted and the concentration of OFX was determined spectrophotometrically at 280 nm. The test was performed in triplicate.

Results and Discussion

Even though the melting method is suitable for drugs and ingredients for which melting is very easy, OFX physically decomposed when the temperature rose to ~150°C. The color of the OFX crystal gradually changed from white to yellowish from this point of temperature. At the melting point, a yellowish-brown liquid was observed. After quench-cooling, the yellow solid mass was obtained. The color of the solid mass of intact OFX after solvent evaporation was not changed. Therefore the solvent method was selected to prepare solid dispersions throughout this study. All of the ingredients used for the preparation of the binary and ternary systems were dissolvable in chloroform. The solvent was evaporated from the system until the weight of the remaining solid mass was constant. Consequently, the solvent was expected to be completely removed from the system.

The powder XRD patterns of OFX binary and ternary solid dispersions with PEG 4000 or PEG 20000 are shown in Figure 1 and Figure 2, respectively. Intact OFX, PEG 4000,

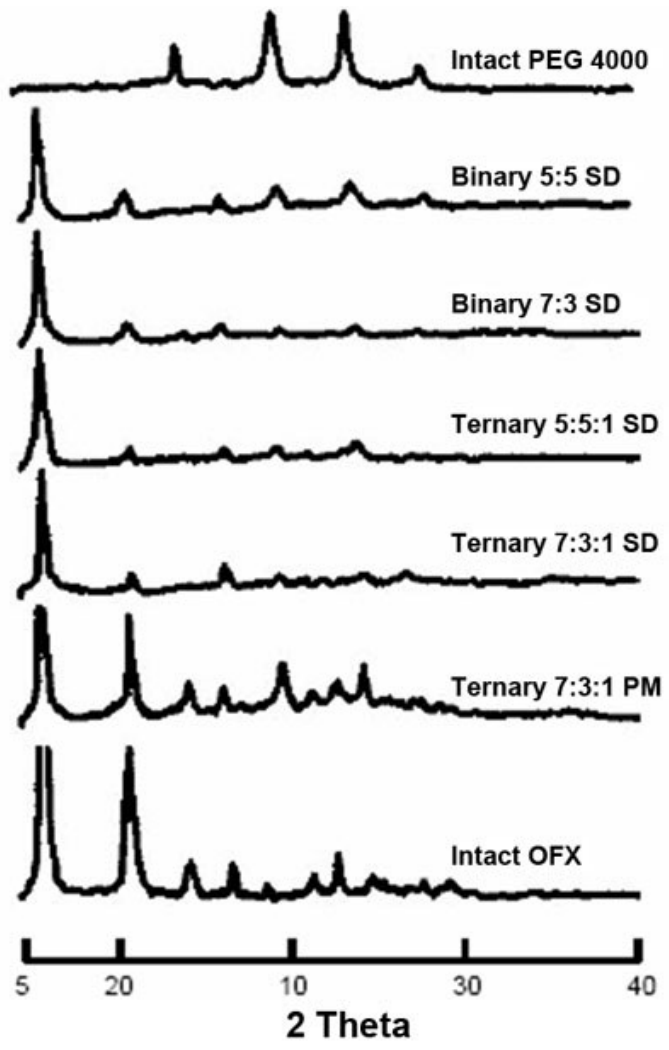

Figure 1. XRD patterns of OFX-PEG 4000 solid dispersion (SD) and physical mixture (PM).

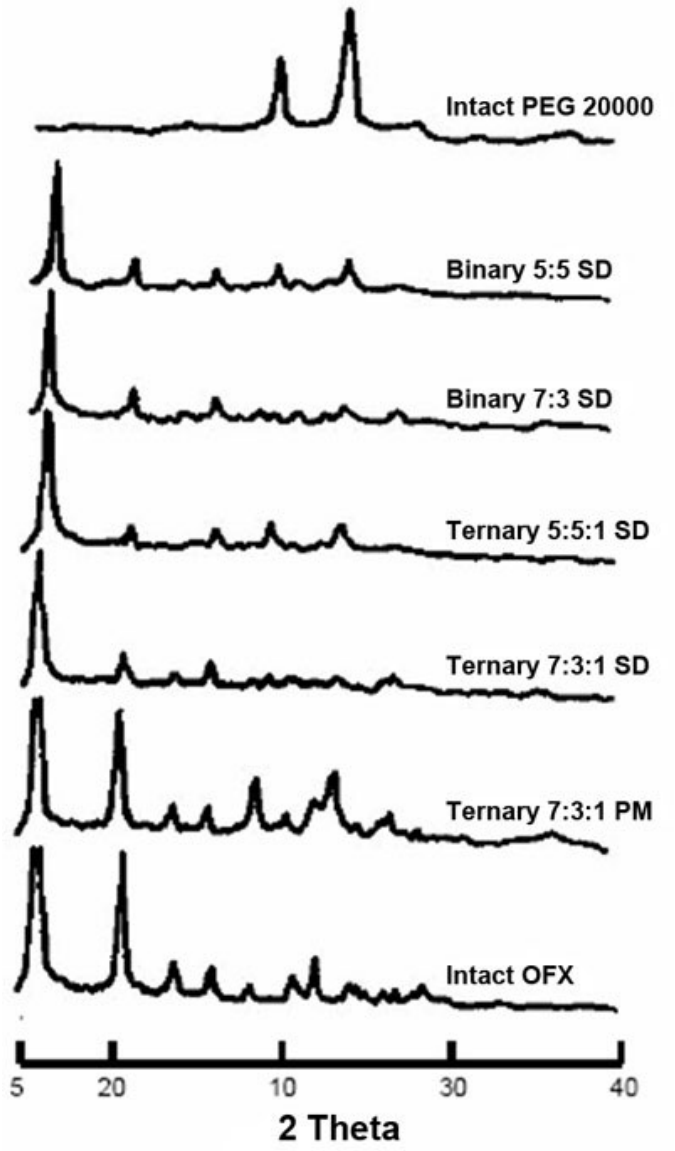

Figure 2. XRD Patterns of OFX-PEG 20000 SD and PM.

and PEG 20000 exhibited the internal crystalline characteristics and showed identical sharp XRD peaks at various 2θ. The XRD peaks of intact OFX crystals were observed at the same 2θ values in both binary and ternary physical mixtures. This indicated that the crystallinity of OFX did not change in the physical mixtures.

The XRD patterns of OFX binary solid dispersions with each carrier at both proportions demonstrated the crystalline diffraction peak of OFX. This suggested that OFX as crystalline state existed in the solid dispersion system. However, the intensity of crystalline peaks of OFX in the solid dispersions was significantly less than that of intact OFX, indicating lower crystallinity of OFX in the binary solid dispersion system. As OFX was highly loaded into the solid dispersion, a portion of OFX molecules was monomolecularly dispersed, some portion existed as an amorphous state, and a higher amount of OFX than its solubility in polymeric dispersion existed as a crystalline state.[11]

The XRD patterns of OFX ternary solid dispersions with each carrier were similar to those of the binary system. The incorporation of Tween 80 had no effect on XRD patterns of OFX in the solid dispersion system. It was considered that Tween 80 might exist in the amorphous region of both OFX and PEGs. This result was similar to the study of solid dispersion vehicle containing tween 80, which found that Tween 80 was incorporated into the amorphous region of the polymer solid structure.[12]

The results of the DSC study of OFX binary solid dispersions with PEG 4000 or PEG 20000 are shown in Figure 3 and Figure 4, respectively. The thermograms of intact OFX and carriers were also given for comparison purposes. The DSC curve of intact OFX exhibited a sharp endothermic peak at 275.1°C, which corresponded to its melting. The physical gradual change in color of OFX that was observed visually at the temperature of 150°C could not be detected in the DSC thermogram. This was considered that the energy change of this phenomenon might be less than the lower limit of DSC detection. Analogously, the thermal curves of PEG showed a single endothermic effect, with a peak at 56.9°C for PEG 4000 and 62.8°C for PEG 20000, corresponding to the melting point of the polymers. As the proportion of OFX decreased, the endotherm for the drug shifted toward lower than the melting point for intact OFX. Moreover, the peak corresponding to fusion of the drug was very small as compared with the peak exhibited by the pure OFX. The systems in which the drug was in low

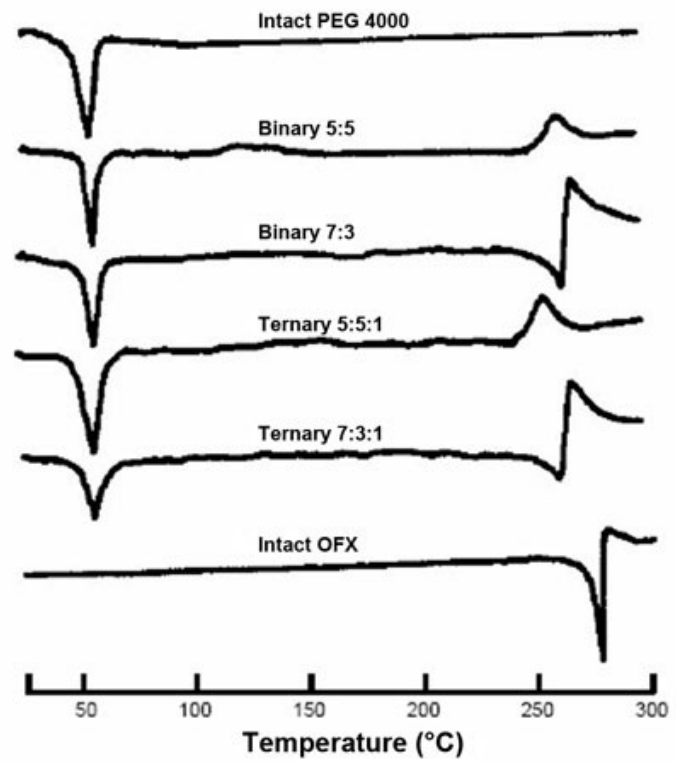

Figure 3. DSC thermograms of OFX-PEG 4000 SD.

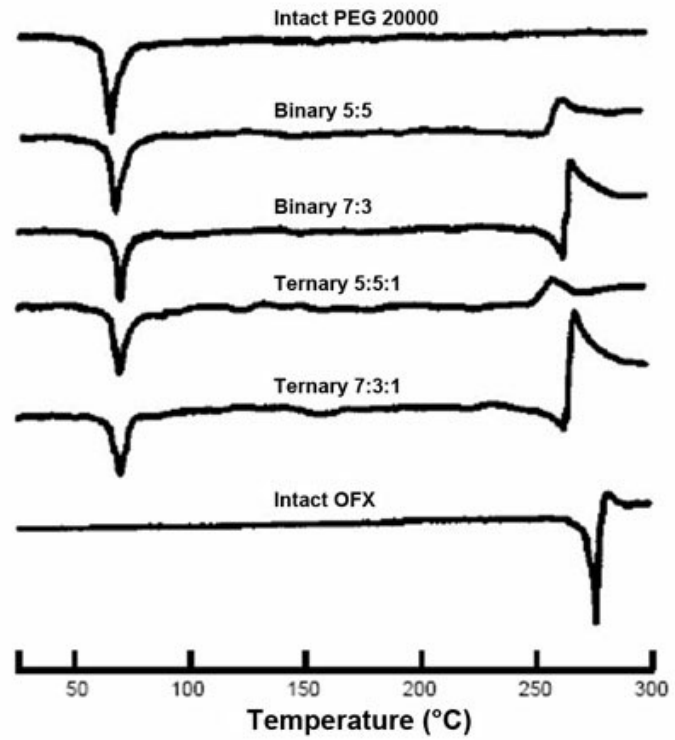

Figure 4. DSC thermograms of OFX-PEG 20000 SD.

proportion (drug to carrier of 5:5 wt/wt) displayed DSC with only one peak that corresponded to PEG fusion. The possibility of drug dissolution in the melting carrier on increased temperature has been reported.[13,14] Therefore, the DSC result suggested that microcrystalline OFX in the OFX-PEG solid dispersions were dissolved in the melting PEG during the DSC scans.

Tween 80 was liquid at room temperature, therefore it was not possible to record a DSC trace under the experimental conditions used. The thermal behavior of OFX in ternary systems was similar to that of binary systems. These results indicated that Tween 80 did not play a role in the thermal behavior of OFX.

The dissolution behavior of OFX from OFX binary and ternary solid dispersions with PEG 4000 or PEG 20000 in comparison with the intact drug was examined by plotting the percentage of drug released against time as shown in Figure 5 and Figure 6, respectively. The initial dissolution profile of the intact drug and solid dispersions obtained in the first 20 minutes was a linear relationship. The dissolution rate of the drug in the first 20 minutes was calculated from the slope of the regression line and listed in Table 1.

In all cases, solid dispersions exhibited faster dissolution rates than the intact drug. This was supposed to be due to the effect of molecular dispersion of drug in PEG, the decreased crystallinity of OFX existing in solid dispersions, and the effect of Tween 80 in the ternary system. The intact OFX demonstrated the slowest initial dissolution rate where

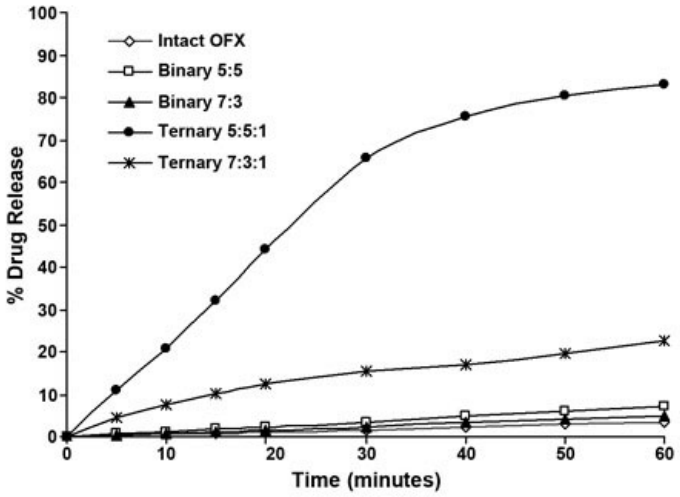

Figure 5. Dissolution profiles of OFX-PEG 4000 SD.

only ~1% of drug dissolved in the first 20 minutes. The dissolution rates presented in Table 1 indicated that OFX dissolution from solid dispersions was dependent on the relative concentration of drug and the molecular weight of PEG. The dissolution rates increased with the increment of the polymer proportions. These results demonstrated the carrier-controlled drug dissolution in solid dispersion systems.

It was noticed that the dissolution rate of OFX from the binary system was obviously lower than that from the ternary system. The enhancement of drug dissolution rate is only 2- to 2.6-fold for 1:1 binary system in PEG 4000 and PEG 20000 respectively. The result demonstrated the slightly higher drug dissolution of the binary system containing PEG 20000 than that of PEG 4000. This was considered that the hydrophobic molecule of OFX preferably interacted with PEG 20000. Hence drug molecular dispersion was slightly higher in this system. It was reported that molecular dispersion is one of the important roles of drug release from the

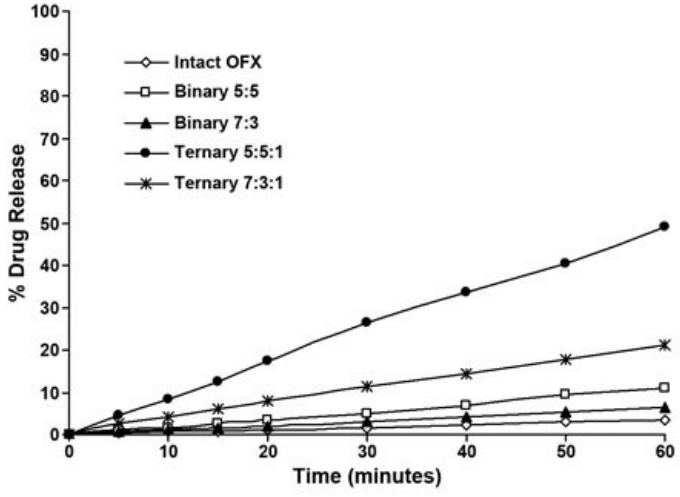

Figure 6. Dissolution profiles of OFX-PEG 20000 SD.

Table 1. Dissolution Rate of Ofloxacin from Different Solid Dispersion Systems

Solid Dispersion (SD) Systems	Ratio of Substances*		Initial Dissolution Rate, %/min	Intrinsic Dissolution Rate, mg/min/cm^2
	Binary SD	Ternary SD		
OFX:PEG 4000	5:5	—	0.12	0.39
	7:3	—	0.08	0.38
OFX:PEG 4000:Tween 80	—	5:5:1	2.18	7.57
	—	7:3:1	0.61	2.48
OFX:PEG 20000	5:5	—	0.16	0.52
	7:3	—	0.10	0.45
OFX:PEG 20000:Tween 80	—	5:5:1	0.86	2.48
	—	7:3:1	0.39	1.59
Intact OFX	—	—	0.06	0.38

*Weight proportion of drug/carrier in binary and drug/carrier/surfactant in ternary solid dispersion systems.

PEG-drug system.[15] Therefore, the slightly higher dissolution rate from PEG 20000 was considered to be due to the slightly higher molecular dispersion of OFX in this system.

In the ternary system, the dissolution results demonstrated a difference in enhancing power among each type of carrier used. At the same ratio of drug to carrier, PEG 4000, the polymer with lower molecular weight, caused the faster rate of drug dissolution. The higher molecular weight PEG 20000 caused enhancement of OFX dissolution but significantly less effect than PEG 4000. This was considered that upon exposure to the dissolution medium, Tween 80 was oriented onto the surface of OFX particles and decreased drug surface tension. This led to the extreme higher interaction of drug to Tween 80 and increased drug wettability.[16] During dissolution, the interfacial layer between the dissolving front and the dissolution bulk medium became rich of carrier since the drug was more rapidly dissolved. This led to the creation of a surface layer rich of carrier, another barrier for the drug to diffuse prior to release into the bulk phase. Soluble polymers with higher molecular weight gave more viscous of this barrier. This led to the decrease in the diffusion coefficient. Therefore, the dissolution rate of OFX from solid dispersions with PEG 20000, the higher molecular weight polymer, was shown to be relatively slower than that with PEG 4000 because of the diffusion coefficient effects. These results demonstrated the effects of Tween 80 and the difference in molecular weight of PEGs on the dissolution rate of OFX. In ternary solid dispersions, the OFX dissolution rate obtained was obviously higher than that obtained from binary solid dispersions. The fastest dissolution was observed from the ternary solid dispersion with PEG 4000 in the system of drug/carrier/Tween 80 of 5:5:1 wt/wt/wt. This proportional ternary solid dispersion provided the achievement of over 65% of drug dissolved within 30 minutes with an initial dissolution rate of 2.18%/min, above 36-fold increase in the dissolution rate of the intact drug. This obvious enhancement was also considered to be due to the solubilizing effect of Tween 80 existing in the solid dispersion system associated with the carrier. It was noticeable that the concentration of Tween 80 in the solid dispersion is high enough to make the diffusion layer surrounding solid dispersion surface in the dissolution medium higher than its CMC. Therefore, it was considered that the hydrophobic portion of OFX was also solubilized via surfactant micelles. These effects of Tween 80 and the desirable polymer of PEG 4000 in addition to the suitable proportional drug/carrier/surfactant of 5:5:1 wt/wt/wt gave extremely predominant increment dissolution rate of OFX.

Conclusion

The high drug-loaded OFX binary solid dispersion with different molecular weight PEGs exhibited faster but not obviously in drug dissolution characteristics than the intact OFX. The significant high drug-dissolution rate was achieved by a ternary solid dispersion system using Tween 80 as a third component. In the ternary system, the effect of the molecular weight of PEG and Tween 80 was obviously seen. The lower the molecular weight of PEG, the higher the dissolution rate. Tween 80 played an important role in drug dissolution from the ternary system by improving drug molecular dispersion in the polymer matrix as well as drug wettability and solubility. The fastest drug dissolution was obtained from a ternary solid dispersion containing OFX/PEG 4000/Tween 80 of 5:5:1 wt/wt/wt.

Acknowledgment

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