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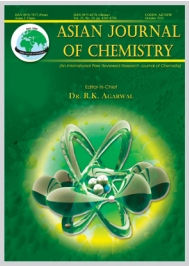

Preparation and Characterization of Florfenicol-Polyethyleneglycol 4000 Solid Dispersions with Improved Solubility

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Florfenicol/polyethyleneglycol 4000 solid dispersions (FF/PEG4000 SDs) was prepared by the melting and solvent-melting methods. Infrared spectrum and differential thermal analysis were employed to study the physical and chemical properties. Studies of dissolution rate and solubility of florfenicol from solid dispersions were carried out in comparison with corresponding physical mixtures and drug alone. The UV method was developed for determination the concentrations. It was found that the spectra of IR, DTA of the solid dispersions were remarkably different from the florfenicol and physical mixture. Solubility of florfenicol was enhanced for the formation of solid dispersions. The dissolution rate of solid dispersions prepared by solvent-melting method was higher than that of solid dispersion prepared by melting method. The calibration curve was linear with a correlation coefficient r = 0.9999 in the range of 50.0-350.0 μg/mL. PEG4000 is a potential carrier in enhancing the dissolution rate and solubility of florfenicol.

Key Words: Florfenicol, Polyethyleneglycol 4000, Solid dispersions, Dissolution rate, Solubility.

INTRODUCTION

Florfenicol (FF) chemically, R-(R*,R*)]-*N*-[1-(fluoromethyl)-2-hydroxy-2-(4-(methylsulforyl) phenyl)-ethyl]-2,2-dichloroacetamide, a member of chloramphenicol and thiamphenicol family is a broad spectrum antibiotics against many Gram negative and Gram positive microorganisms. Compared to thiamphenicol, florfenicol shows significant superiority in antibacterial spectrum, antibacterial activity and considerably lower side effect; its antibacterial potency is 10 times higher than that of thiamphenicol. Therefore florfenicol is widely used clinically for the treatment of respiratory tract infections, typhoid, intestinal infections and so on[1-4]. However, due to florfenicol relatively poor water-soluble and low dissolution in gastric fluids, the most common preparation of florfenicol is premix formulations in market. The solubility issue complicating the delivery of the drug also affects the bioavailability of florfenicol, it shows variation in bioavailability. A small number of water-soluble preparations were made by adding organic solvents, solubilizer or hydrotropy agent. But the preparations are less stable, toxic and stimulating. It is necessary to enhance the solubility and bioavailability of florfenicol through the preparation technology.

Solid dispersions technology is one of the effective and widely used techniques for dissolution enhancement in the field of pharmaceutical preparation technology[5]. Drugs in the solid dispersions systems may exist as an amorphous form in polymeric carriers and improve the solubility and dissolution rate compared with crystalline material. In case of this the increase in dissolution rate for solid dispersions can be attributed to a number of factors, which include reduction in particle size, absence of aggregation or agglomeration of fine crystallites of the drug, possible solubilization effect of the polymer, excellent wettability and dispersibility of the drug from solid dispersions and partial conversion of the drug into amorphous form[6-8]. The two basic procedures used to prepare solid dispersions are the melting and solvent-melting techniques. Both of these methods are very easy and less expensive for preparation of solid dispersions[9-11].

Polyethyleneglycol 4000 (PEG4000) is semicrystalline polymer that has been used extensively in the solid dispersions preparation[12]. The advantages of PEG4000 for the formation of solid dispersions are that it has good solubility in many organic solvents and lower melting point. Additional attractive features of PEG4000 include their ability to solubilize some compounds and improve compound wettability[13].

The purpose of this research was to choose PEG4000 as a suitable polymer for preparation the solid dispersions. Solid dispersions were then evaluated by dissolution rate, infrared spectroscopy and differential thermal analysis.

EXPERIMENTAL

Florfenicol of 98.5 % purity was kindly supplied by Yonghe Pharmaceutical Co. Ltd., Zhengzhou, China. PEG4000 and other reagents of analytical grade were purchased from Bafang Chemicals Co. Ltd., Zhengzhou, China.

Preparation of physical mixtures: Physical mixtures of florfenicol and PEG4000 at five different mass ratios (1:1, 1:3, 1:5, 1:7 and 1:10) were prepared in a glass mortar by simple blending for 20 min. The mixtures were passed through a 100-mesh sieve. They were then filled in glass bottles, sealed and stored in desiccators until further use.

Preparation of solid dispersions: FF/PEG4000 solid dispersions at five different mass ratios (1:1, 1:3, 1:5, 1:7 and 1:10) were prepared by the melting and solvent-melting methods, respectively. For melting method, the PEG4000 was placed in a porcelain dish and allowed to melt by heating up to 70 ºC. To the molten mass, an appropriate amount of florfenicol was added and stirred constantly until homogenous dispersion was obtained. The resultant solution was cooled in an ice bath and stored in desiccators for 24 h for rapid solidification, it was then scrapped, pulverized and passed through a 100-mesh sieve. For melting-solvent method, the PEG4000 was placed in a porcelain dish and allowed to melt by heating up to 70 ºC. florfenicol was dissolved in an appropriate amount of *N,N*-dimethylformamide to its saturation solubility. After complete dissolution of florfenicol, solution was added to the molten mass. The mixture was stirred constantly until homogenous dispersion was obtained. The resultant solution was removed and cooled in an ice bath and then it was stored in desiccators for 24 h for rapid solidification. The solid dispersions was then scrapped, pulverized and passed through a 100-mesh sieve. Then the two prepared solid dispersions were filled in glass bottles, sealed and stored in desiccators until further use.

UV absorption spectrophotometry: Spectrophotometry was performed with a UV-VIS scanning spectrophotometer (TU-1810PC, Beijing Purkinje General Instrument Co. Ltd., Beijing, China) to quantify florfenicol in its free and solid dispersions forms. Standard solutions of florfenicol ranging from 50 to 350 µg/mL were prepared in 99.5 % ethanol; complete spectrophotometric scans between 200 and 400 nm were performed to monitor any changes in the UV spectra of the florfenicol. The absorbance maximum 266 nm of florfenicol was selected to quantify its concentration; the certain absorbance value was regressed with the certain concentration to calculate the calibration equation.

Drug content: The drug content in each solid dispersions and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersions equivalent to 50 mg florfenicol were transferred to 50 mL volumetric flasks containing ethanol and dissolved, 5 mL solutions were transferred to another 25 mL volumetric flasks, the volume was made up to 25 mL with water and the final solutions were assayed spectrophotometrically at 266 nm, the contents of florfenicol were calculated from the regression equation generated from standard data.

Saturation solubility study: The saturation solubility studies of florfenicol, physical mixture, solid dispersions prepared by melting and solvent-melting methods were carried out in water at room temperature. Pure florfenicol (100 mg), a quantity of FF/PEG4000 solid dispersions and the physical mixtures(mass ratio 1:1, 1:3, 1:5, 1:7 and 1:10) equivalent to 100 mg of florfenicol were weighted into sealed vials and stirred vigorously in a water bath shaker (SHA-C, Jiamei Instruments Co. Ltd., Jintan, China) at 25 ± 0.5 ºC with water (10 mL) for 24 h. The samples were then centrifuged and filtered through 0.22 µm cellulose acetate membrane filters. After suitable dilution, the absorbance was assayed spectrophotometrically at 266 nm.

Dissolution rate studies: *In vitro* dissolution studies of florfenicol, FF/PEG4000 solid dispersions and the physical mixtures (mass ratio 1:1, 1:3, 1:5, 1:7 and 1:10) were carried out in a dissolution apparatus (ZRC-6FT, Tianjin Chuangxin Electronic Equipment Manufacture Co. Ltd., Tianjin, China) using the first method described in Chinese Pharmacopoeia at 37 ±0.5 ºC, rotating at 100 rpm. 200 mg of florfenicol or its equivalent in physical mixture or solid dispersions was added to 900 mL distilled water. 5 mL of dissolution medium was withdrawn at 2, 5, 10, 20, 30 and 45 min with a pipette. The samples were immediately filtered (0.22 µm pore size) and assayed spectrophotometrically at 266 nm. Equivalent amount of fresh water pre-warmed to 37 ± 0.5 ºC was replaced after each sampling. The cumulative percentage of florfenicol dissolved was calculated from the regression equation generated from standard data.

FT-IR study: FT-IR spectra were recorded using a Bio-Rad FT-IR Spectrophotometer (USA). The samples (FF, PEG4000, physical mixtures and solid dispersions) were previously ground and mixed thoroughly with potassium bromide. Sixteen scans were obtained at a resolution of 4 cm^{-1} from 4000 to 500 cm^{-1}.

Differential thermal analysis: DTA curves of florfenicol, PEG4000, physical mixtures and solid dispersions (mass ratio 1:5) were measured with a DTA instrument (CRY-32P. Shanghai Precision and Scientific Instrument Co. Ltd., Shanghai, China). Each sample (5 mg) was accurately weighed and heated in an hermetically aluminum pan at a rate of 10 ºC/min between 30 ºC and 300 ºC temperature range under an air flow. An empty aluminum pan was used as a reference. The DTA curves were compared with one another regarding to peak position, peak shifting and the presence or lack of peaks in certain temperature values.

RESULTS AND DISCUSSION

Preparation of solid dispersions: The described melting method and solvent-melting method in preparation of solid dispersions appeared to be suitable for improving florfenicol solubility. They are the common methods for preparation solid dispersions. The melting method consists of melting the carrier firstly and then the florfenicol was added to the molten PEG4000 followed by cooling and pulverizing of the resultant product. The key procedure was to ensure florfenicol powder dispersed uniformly. The solvent-melting method involves melting the carrier followed by addition of the florfenicol solution, evaporation of the solvent and cooling to obtain the product. The uniformity was influenced by the different ways of florfenicol adding to the PEG4000. Ultimately it affected the dissolution rate of florfenicol.

UV absorption spectrophotometry: The response fitted a linear regression model, the calibration equation is A = 0.0027C + 0.0073 in the concentration range of 50-350 μg/mL and the correlation coefficient is 0.9999. Additionally, the presence of PEG4000 did not interfere the UV absorbance of florfenicol at 266 nm.

Saturation solubility study: The solubility data showed that the PEG4000 enhanced the solubility of florfenicol in solid dispersions formulations. Solubility of florfenicol was 3.23, 2.96, 1.52 mg/mL from 1:10 (w/w) solid dispersions made with solvent-melting method, melting method and 1:10 (w/w) physical mixtures respectively. It was also proved that the solubility of florfenicol increased with the increment in ratio of PEG4000 in solid dispersions. The result indicated that PEG4000 as the carrier in solid dispersions leads to a considerable improvement in the solubility of florfenicol. The solubility increase observed for solid dispersions may be attributed to the presence of an optimum hydrophilic environment and finer distribution of florfenicol in PEG4000 as the solid dispersions corresponds to its eutectic composition. The solubility of solid dispersions prepared by solvent-melting method was higher than that of melting method.

Dissolution rate studies: It is interesting to compare the results of florfenicol dissolution tests from solid dispersions samples made with melting, solvent-melting method with those of the corresponding physical mixture. As shown in Fig. 1a-d, enhancement of florfenicol dissolution rate was achieved in all cases. The dissolution rate of florfenicol from the physical mixtures was improved as compared to that with crystalline florfenicol and can be ascribed to the solubilizing effect of PEG4000[14,15]. Furthermore, solid dispersions had faster dissolution rates than the pure drug and physical mixtures. At the end of 10 min, approximately 21.3, 50.8, 42.7, 54.3, 77.9, 78.6 and 87.7 % of florfenicol was released from crystalline florfenicol, 1:10 (w/w) physical mixtures, 1:1, 1:3 1:5, 1:7 and 1:10 (w/w) solid dispersions made with solvent melting method, respectively.

The improvement of drug dissolution from solid dispersions can be attributed to drug particle size reduction and possible amorphization within the dispersion, improved wetting of the drug, as well as a possible solubilization effect of the carrier and specific molecular interactions between the drug and polymer[16,17]. In addition, with the improved ratio of PEG4000 in solid dispersions, the dissolution of florfenicol from solid dispersions was obviously increased.

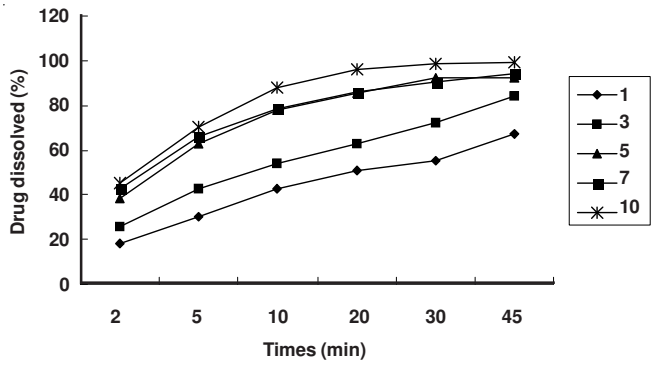

Fig. 1a. Solid dispersions made with solvent-melting method (mass ratio 1:1, 1:3, 1:5, 1:7 and 1:10)

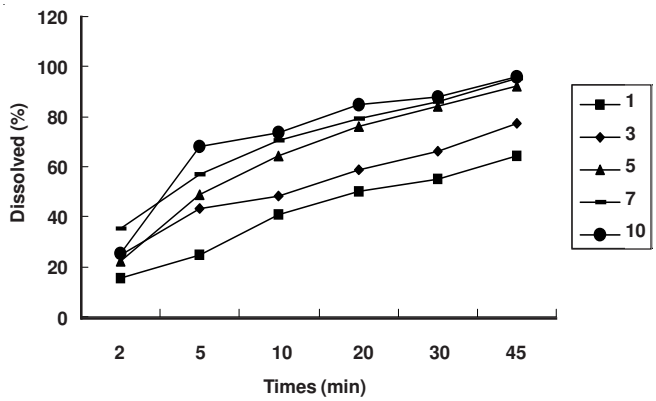

Fig. 1b. Solid dispersions made with melting method (mass ratio 1:1, 1:3, 1:5, 1:7 and 1:10)

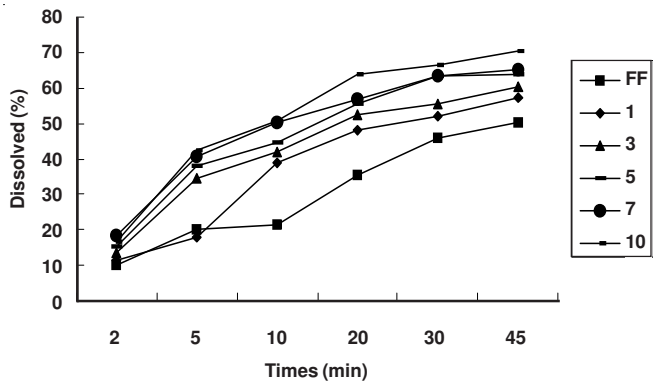

Fig. 1c. Physical mixtures (mass ratio 1:1, 1:3, 1:5, 1:7 and 1:10) and florfenicol (FF)

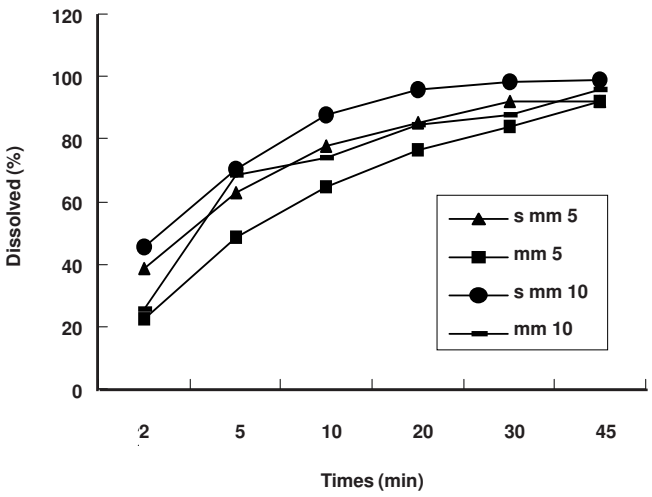

Fig. 1d. Solid dispersions made with solvent-melting method and melting method (mass ratio 1:5 and 1:10)

Dissolution curves of FF/PEG4000 solid dispersions samples made with solvent-melting method was higher than that of the samples made with melting method. The full mechanism behind the improved dissolution rates for amorphous drug compounds stabilized by a hydrophilic carrier is still not fully understood. Comprehensive reviews of the subject have been given by others, *e.g.* by Leuner, Dressman and Craig[6,16]. This dissolution has been suggested to either be carrier-controlled or drug-controlled. For the carrier controlled, the dissolution is dominated by the properties of the carrier, whereas for the

drug controlled, drug properties such as particle size and physical form can be linked to the dissolution rate. The possible reasons for solvent-melting method, synergistic effect of trituration and solubilization of used solvent reduces crystallinity leading to improvement in dissolution rate. The other reason may be due to availability of increased surface area of particles PEG4000 and disperseing uniformity.

FT-IR study: FT-IR is a powerful technique in detecting presence of interaction in drug-carrier solid dispersions. The appearance or disappearance of peaks and/or the shift of their positions are often an indication of interactions such as hydrogen bonding. In this case, any sign of interaction would be reflected by changes depending upon the extent of interaction. From the chemical structures, hydrogen bonding could be expected between the hydroxyl group of PEG4000 and carbonyl function of florfenicol and hydrogen bonding between hydrogen atom of the NH of florfenicol and one of the ion pairs of the oxygen atom[7] in PEG4000.

The FT-IR spectra of florfenicol, PEG4000, physical mixture (1:5) and solid dispersions (1:5) are presented in Fig. 2a-d. The spectrum of florfenicol showed stretching peaks at 3455 cm^{-1} and 1684 cm^{-1} for the hydroxy group and carbonyl group respectively. The peak at 1535 cm^{-1} was bending vibration for amino group and stretching vibration for nitrile group[18]. These intense bands are clearly present in the physical mixture of florfenicol and PEG4000; however, these bands are no longer apparent upon solid dispersions. The PEG4000 spectrum showed important peaks at 1114 cm^{-1} (C-O-C stretch) and at 2888 cm^{-1} (CH stretch). The spectrum of the solid dispersions appeared to be very similar to that of PEG4000. The spectra of solid dispersion and physical mixture did not indicate any well-defined interaction between florfenicol and PEG4000.

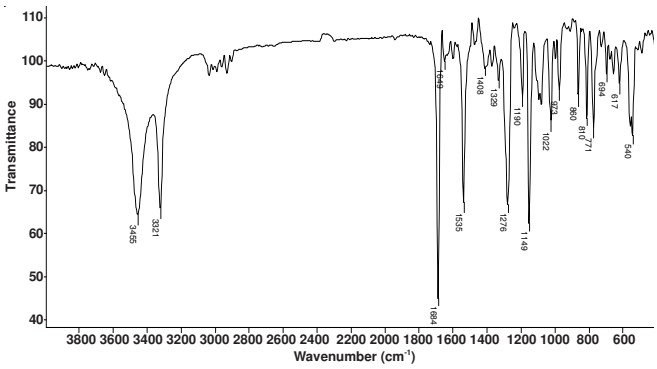

Fig. 2a. IR spectra of florfenicol

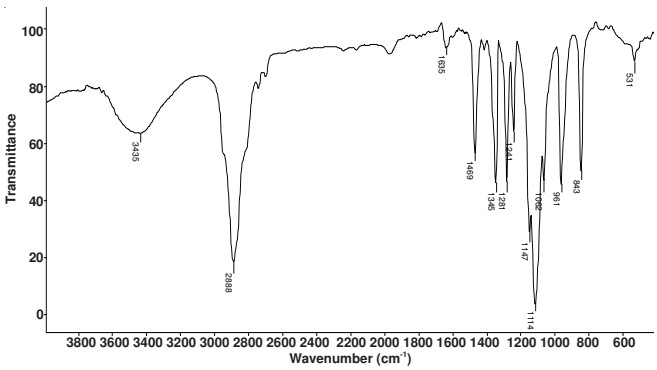

Fig. 2b. IR spectra of PEG4000

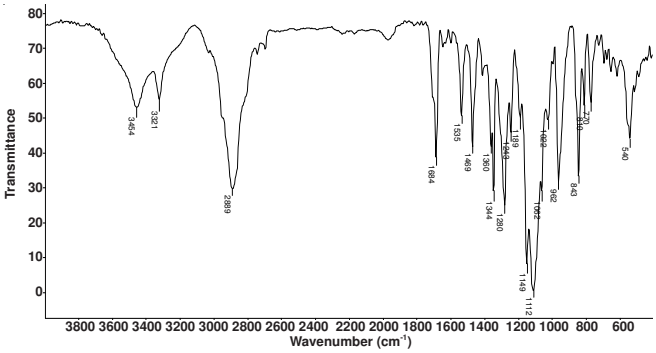

Fig. 2c. IR spectra of physical mixture

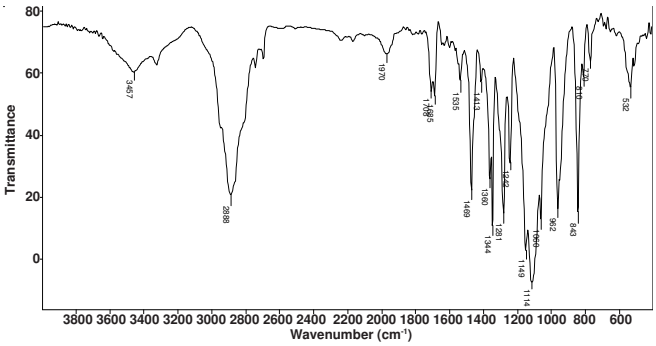

Fig. 2d. IR spectra of FF/PEG4000solid dispersions

Differential thermal analysis: DTA provided the evidence that solid dispersions were formed. When florfenicol changed into another crystal lattice, it's melting, boiling or sublimation point generally shifted to a different temperature or disappears within the temperature range where PEG4000 decomposes. The DTA thermograms of florfenicol, PEG4000, physical mixture and solid dispersions are shown in Fig. 3. The thermogram of florfenicol exhibited an endothermic reaction and its melting peak was at 154.2 ºC. The thermal behaviour of PEG4000 exhibited a sharp but slightly broad endothermic peak at 55.7 ºC owing to its amorphous nature. The DTA thermograms of physical mixture as well as solid dispersions showed identical peaks indicated the physical interaction between florfenicol and PEG4000. Complete disappearance of the florfenicol peak observed in both physical mixture and solid dispersions was attributable to complete miscibility of the drug in the melted carrier.

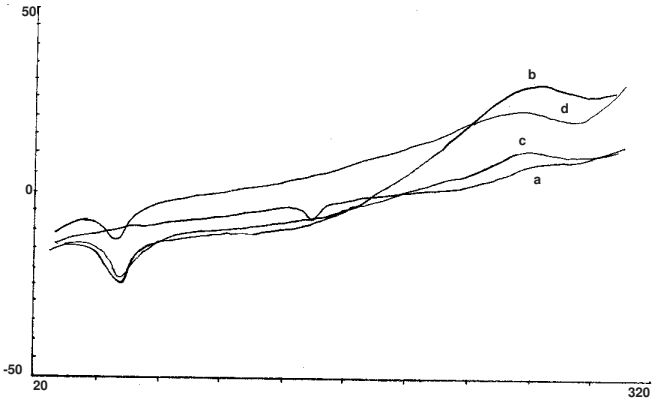

Fig. 3. DTA thermograms of the samples florfenicol (a), PEG4000 (b), physical mixture (c) and solid dispersions (d) of florfenicol with PEG4000

Conclusion

The results show that PEG4000 can be used as carrier in florfenicol/PEG4000 solid dispersions and that solvent-melting method and melting method are suitable for preparation of florfenicol/PEG4000 solid dispersions. The dissolution profile of florfenicol depends both on the mass ratio of florfenicol to the carrier and the preparation method. All the solid dispersions showed improved dissolution rate in comparison with starting material and physical mixtures of florfenicol and PEG4000. The improved dissolution rate of the solid dispersions was ascribed to the conversion of florfenicol into its amorphous form, the presence of polymer and the reduction in particle size. The characterization of samples by DTA and IR confirmed the amorphous state of florfenicol in solid dispersions.

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