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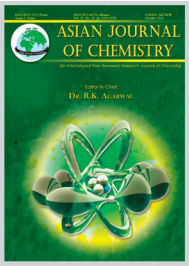

Study on Diclazuril Polyethylene Glycol 6000 Solid Dispersions with Improved Solubility

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Present study investigated diclazuril/polyethyleneglycol 6000 solid dispersions (diclazuril/PEG6000 SDs) with improved solubility. The solid dispersions were prepared by solvent-melting method with PEG 6000 as carrier. It was validated by differential thermal analysis and cumulative dissolution rate. The solubility of diclazuril, mixture and solid dispersions were measured. The UV spectrophotometer method was developed for determination diclazuril. It was found that the spectra of cumulative dissolution rate, differential thermal analysis of the solid dispersions were different from the diclazuril and physical mixture. Solubility of diclazuril was enhanced for the formation of solid dispersions. The calibration curve was linear with an correlation coefficient r = 0.9997 in range of 5-20 μg/mL. The method was simple and practical in preparation and determination the diclazuril solid dispersions.

Key Words: Diclazuril, Polyethyleneglycol 6000, Solid dispersions, Solubility.

INTRODUCTION

Diclazuril chemically 2,6- dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzene-acetonitrile, is a broad-spectrum anticoccidial and antiprotozoal agent. It is widely used in chickens, turkeys, pigs and cattles for prevention and treatment of coccidiosis. For example, diclazuril has proven efficacy against intstinal *Eimeria* species in avian coccidiosis, intestinal and hepatic coccidiosis in rabbits and against toxoplasmosis in mice and so on. It showed that diclazuril was also be a potentially important therapentic agent for use in the treatment of equine protozoal myeloencephalitis[1]. However, due to relatively poor water-solubility of diclazuril and low dissolution in gastric fluids, it is not well absorbed from the preprations. It shows variation in bioavailability. It is necessary to enhance the solubility and bioavailability of diclazuril through the preparation technology.

Solid dispersions (SDs) technology is one of the effective and widely used techniques for dissolution enhancement in the field of pharmaceutical preparation technology[2]. 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. The basic procedures used to prepare solid dispersions is solvent- melting techniques. It is very easy and less expensive for preparation of solid dispersions[3].

Polyethylene glycol 6000 (PEG6000) is semicrystalline polymer that has been used extensively in the solid dispersions preparation[4]. The advantages of PEG6000 for the formation of solid dispersions are that it has good solubility in many organic solvents and lower melting point. Additional attractive features of PEG6000 include their ability to solubilize some compounds and improve compound wettability[5].

The purpose of this research was to choose PEG6000 as a suitable polymer for preparation the solid dispersions. Solid dispersions were then evaluated by dissolution rate and differential thermal analysis.

EXPERIMENTAL

Diclazuril was kindly supplied by Zhongzhou Pharmaceutical Co. Ltd., Zhengzhou, P.R. China. PEG6000 and other reagents of analytical grade were purchased from Aoboxing Chemicals Co. Ltd., Beijing, P.R. China.

The instruments employed were spectrophotometer (TU-1810PC, Beijing Purkinje General Instrument Co. Ltd., Beijing, P.R. China), dissolution apparatus (ZRC-6FT, Tianjin Chuangxin Electronic Equipment Manufacture, Tianjin, P.R. China) and DTA instrument (CRY-32P. Shanghai Precision and Scientific Instrument Co. Ltd., Shanghai, P.R.China).

Preparation of solid dispersions: Diclazuril /PEG6000 solid dispersions at three different mass ratios (1:10, 1:15 and 1:20) were prepared by solvent-melting methods. the PEG 6000 was placed in a porcelain dish and allowed to melt by heating up to 70 ºC. Diclazuril was dissolved in an appropriate amount of *N,N*-dimethylformamide to its saturation solubility. After complete dissolution of diclazuril, solution was added to the melted mass. The mixture was stirred constantly until homo-

genous 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 were then scrapped, pulverized and passed through a 100-mesh sieve. Then the prepared solid dispersions were filled in glass bottles, sealed and stored in desiccators until further use.

Preparation of physical mixtures: Physical mixtures of diclazuril and PEG6000 at three different mass ratio (1:10, 1:15 and 1:20) 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.

UV absorption spectrophotometry: Spectrophotometry was performed with a UV-VIS scanning spectrophotometer. Standard solutions of diclazuril was prepared in *N,N*-dimethyl formamide and methanol; working solutions were prepared by diluting stock solutions with methanol. Calibration standard solutions were prepared at concentrations of 5.0, 10.0, 12.5, 15.0 and 20.0 μg/mL for diclazuril and assyed in replicates of three. Complete spectrophotometric scans between 200 and 400 nm were performed to monitor any changes in the UV spectra of the diclazuril. The absorbance maximum 277 nm of diclazuril was selected to quantify its concentration and 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 100 mg sample was transferred to 100 mL volumetric flasks containing water and dissolved, the solution was filtered, diluted and assayed spectrophotometrically at 277 nm, the contents of diclazuril were calculated from the regression equation generated from standard data.

Saturation solubility study: The saturation solubilities of diclazuril, physical mixture, solid dispersions were carried out in water at room temperature. Pure diclazuril (100 mg), a quantity of diclazuril/PEG6000 solid dispersions and the physical mixtures (mass ratio 1:10, 1:15 and 1:20) equivalent to 100 mg of diclazuril were weighted into sealed vials and stirred vigorously in a water bath shaker at 25 ºC ± 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 277 nm.

Dissolution rate studies: *In vitro* dissolution studies of diclazuril, solid dispersions and the physical mixtures (mass ratio 1:10, 1:15 and 1:20) were carried out in a dissolution apparatus using the second method described in Chinese Pharmacopoeia at 37 ± 0.5 ºC, rotating at 50 rpm. One hundred milligrams of diclazuril or its equivalent in physical mixture or solid dispersions was added to 900 mL distilled water. Five milliliters of dissolution medium was withdrawn at 5, 10, 20, 30, 45 and 60 min with a pipette. The samples were immediately filtered (0.22 μm pore size) and assayed spectrophotometrically at 277 nm. Equivalent amount of fresh water pre-warmed to 37 ± 0.5 ºC was replaced after each sampling. The cumulative percentage of diclazuril dissolved was calculated from the regression equation generated from standard data.

Differential thermal analysis: Differential thermal analysis curves of diclazuril, PEG6000, physical mixtures and solid dispersions (mass ratio 1:10) were measured with a DTA instrument. Each sample (10 mg) was accurately weighed and heated in an hermetically aluminum pan at a rate of 10 ºC/min between 30 ºC and 360 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

UV absorption spectrophotometry: The response fitted a linear regression model, the calibration equation is A = 0.0376C + 0.04 in the concentration range of 5-20 μg/mL and the correlation coefficient is 0.9997. Additionally, the presence of PEG6000 did not interfere the UV absorbance of diclazuril at 277 nm.

Saturation solubility study: The solubility data were presented in Table-1. It showed that the PEG6000 enhanced the solubility of diclazuril in solid dispersions formulations. Solubility of diclazuril was 0.00069, 0.2107, 0.0015 mg/mL from diclazuril, 1:20 (w/w) solid dispersions and 1:20 (w/w) physical mixtures, respectively. It was also proved that the solubility of diclazuril increased with the increment in ratio of PEG6000 in solid dispersions.

TABLE-1
RESULTS OF SOLUBILITY TEST (mg/mL)

NO	Diclazuril	1:10	1:15	1:20
Diclazuril	0.00069	-	-	-
Physical mixture	-	0.0014	0.0014	0.0015
Solid dispersions	-	0.1011	0.1516	0.2107

Dissolution rate studies: The dissolution rate tests were shown in Fig. 1, enhancement of diclazuril dissolution rate was achieved. The dissolution rate of diclazuril from the physical mixture was improved as compared to that with crystalline diclazuril and can be ascribed to the solubilizing effect of PEG6000[6,7]. Furthermore, solid dispersions had faster dissolution rates than the pure drug and physical mixture. For example, at the end of 30 min, approximately 5.85, 30.26, 35.87, 38.79, 48.93, 74.43 and 78.68 % of diclazuril was released from crystalline diclazuril, physical mixtures and solid dispersions (mass ratio 1:10, 1:15 and 1:20), respectively.

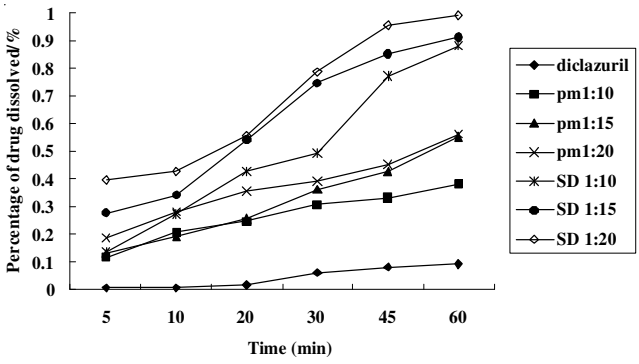

Fig. 1. Dissolution curves of diclazuril, solid dispersions and physical mixtures (mass ration 1:10, 1:15 and 1:20)

Differential thermal analysis: The DTA thermograms of diclazuril, PEG6000, physical mixture and solid dispersions are shown in Fig. 2. The thermogram of diclazuril exhibited an endothermic reaction and its melting peak was at 269.9 ºC (a). The thermal behaviour of PEG6000 exhibited a sharp but slightly broad endothermic peak at 65.7 ºC owing to its amorphous nature (d). The DTA thermograms of physical mixture exhibited the comprehensive characteristic of diclazuril and PEG6000. Complete peaks appearance of diclazuril and PEG6000 were observed in physical mixture (b). The peaks disappearance of diclazuril and PEG6000 observed in solid dispersions indicated the interaction between diclazuril and PEG6000 and it attributable to complete miscibility of the drug in the melted carrier (c).

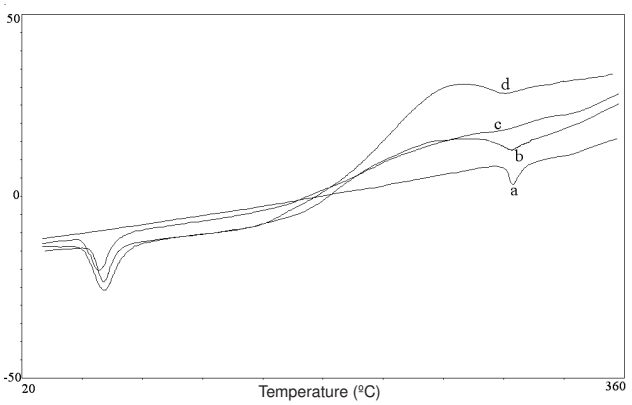

Fig. 2. DTA thermograms of diclazuril (a), physical mixture (b), diclazuril /PEG6000 solid dispersions (c) and PEG6000 (d)

The described solvent-melting method in preparation of solid dispersions appeared to be suitable for improving diclazuril solubility. It's the common method for preparation solid dispersions. The method involves melting the carrier followed by addition of the diclazuril solution, evaporation of the solvent and cooling to obtain the product. The uniformity was influenced by the different ways of diclazuril adding to the PEG6000. Ultimately it affected the dissolution rate of diclazuril.

The solubility study indicated that PEG6000 as the carrier in solid dispersions leads to an improvement in the solubility of diclazuril. The solubility increase observed for solid dispersions may be attributed to the presence of an optimum hydrophilic environment and finer distribution of diclazuril in PEG6000 as the solid dispersions corresponds to its eutectic composition.

Enhancement of diclazuril dissolution rate was achieved, but 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[8]. 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 PEG6000 and dispersing uniformity.

Differential thermal analysis provided the evidence that solid dispersions were formed. When diclazuril 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 PEG6000 decomposes.

Conclusion

The results show that PEG6000 can be used as carrier in diclazuril/PEG6000 solid dispersions and that solvent-melting method is suitable for preparation of diclazuril/PEG6000 solid dispersions. The dissolution profile of diclazuril depends on the mass ratio of diclazuril to the carrier. The solid dispersions shown improved dissolution rate in comparison with starting material and physical mixtures of diclazuril and PEG6000. The characterization of samples by DTA confirmed the amorphous state of diclazuril in solid dispersions.

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