Full Length Research Paper

Preparation and characterization of toltrazuril polyethyleneglycol 6000 solid dispersions with improved solubility

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The current study investigated toltrazuril /polyethyleneglycol 6000 solid dispersions (toltrazuril/PEG6000 SDs) with improved solubility. The SDs were prepared by solvent-melting method with PEG 6000 as carrier. It was validated by differential thermal analysis (DTA) and cumulative dissolution rate. The solubility of toltrazuril, physical mixture and SDs were measured. The ultra violet (UV) spectrophotometer method was developed for the determination of toltrazuril. It was found that the spectra of cumulative dissolution rate, DTA of the SDs were different from the toltrazuril and physical mixture. Solubility of toltrazuril was enhanced for the formation of SDs. The calibration curve was linear with a correlation coefficient \( r = 0.9998 \) in range of 4.0~20.0 \( \mu \)g/mL. The method was simple and practical in preparation and determination the toltrazuril SDs.

Key words: Toltrazuril, polyethyleneglycol 6000, solid dispersions, solubility.

INTRODUCTION

Toltrazuril chemically, 1-methyl-3-[3-methyl-4-[4-(trifluoromethylthio)phenoxy]phenyl]-1,3,5-triazinane-2,4,6- trione, is a symmetrical triazinetrione broad-spectrum anticoccidial and antiprotozoal agent (Figure 1). It is widely used in poultry and swine for the prevention and treatment of coccidiosis. Toltrazuril may have clinical application in the treatment of Neospora caninum and other protozoal infections in cattle (Dirikolu et al., 2009; Martinez-Villalb et al., 2010). Toltrazuril is effective in vivo against Eimeria species in avians, in vitro against Toxoplasma gondii, and in vivo against intestinal and hepatic coccidiosis in rabbits (Peters and Geeroms,1986; Chapman,1987; Ricketts and Pfefferkorn,1993; Reynaud et al., 1999; Ai et al., 2011). However, due to toltrazuril’s relatively poor water-soluble and low dissolution in gastric fluids, it is not well absorbed from the preparations. It shows variation in bioavailability. It is necessary to enhance the solubility and bioavailability of toltrazuril 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 (Win and Sidney, 1971; Nemanja, 2012). Drugs in the SDs systems may exist as an amorphous form in polymeric carriers, and improve the solubility and dissolution rate compared with crystalline material. The basic procedure used to prepare SDs is solvent- melting techniques. It is very easy and less expensive for preparation of SDs (Hao et al., 2009).

Polyethyleneglycol 6000 (PEG6000) is semicrystalline polymer that has been used extensively in the SDs preparation (Craig, 1990). The advantages of PEG6000 for the formation of SDs 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 (Madhuri et al., 2008).

The purpose of this research was to choose PEG6000 as a suitable polymer for the preparation of toltrazuril polyethyleneglycol 6000 SDs. SDs were then evaluated by dissolution rate and differential thermal analysis (DTA).

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MATERIALS AND METHODS

Toltrazuril was purchased from Zhengzhou Vet Chempharm CO., Ltd, Zhengzhou, China. PEG6000 and other reagents of analytical grade were purchased from Aoboxing Chemicals Co. Ltd, Beijing, China. The instruments employed were Spectrophotometer (Shimadzu UV-1800, Kyoto, Japan), dissolution apparatus (ZRC-6FT, Tianjin Chuangxin Electronic Equipment Manufacture, Tianjin, China) and DTA instrument (CRY-32P, Shanghai Precision and Scientific Instrument Co. Ltd, Shanghai, China).

Preparation of SDs

Toltrazuril/PEG6000 SDs 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 80°C. Toltrazuril was dissolved in an appropriate amount of diethyl carbonate to its saturation solubility. After complete dissolution of toltrazuril, solution was added to the melted 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 SDs were then scrapped, pulverized and passed through a 100-mesh sieve. Then the prepared SDs were filled in glass bottles, sealed and stored in desiccators until further use.

Preparation of physical mixtures

Physical mixtures of toltrazuril 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 Shimadzu UV-1800 spectrophotometer. Standard solutions of toltrazuril was prepared with acetonitrile/water (60/40); working solutions were prepared by diluting stock solutions with acetonitrile/water (60/40). Calibration standard solutions were prepared at concentrations of 4.0, 8.0, 10.0, 12.5, 15.0 and 20.0 µg/mL for toltrazuril and assayed in replicates of three. Complete spectrophotometric scans between 200 and 400 nm were performed to monitor any changes in the UV spectra of the toltrazuril. The absorbance maximum 243 nm of toltrazuril 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 SDs and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of 50 mg sample was transferred to 100 mL volumetric flasks containing water and dissolved, the solution was filtered, diluted and assayed spectrophotometrically at 243 nm, the contents of toltrazuril were calculated from the regression equation generated from standard data.

Saturation solubility study

The saturation solubilities of toltrazuril, physical mixture, SDs were carried out in water at room temperature. Pure toltrazuril (25 mg), a quantity of toltrazuril/PEG6000 SDs and the physical mixtures (mass ratio 1:10, 1:15 and 1:20) equivalent to 25 mg of toltrazuril were weighted into sealed vials and stirred vigorously in a water bath shaker at 25± 0.5°C with water (10 mL) for 24 h. The samples were then centrifuged and filtered through 0.45 µm cellulose acetate membrane filters. After suitable dilution, the absorbance was assayed spectrophotometrically at 243 nm.

Dissolution rate studies

In vitro dissolution studies of toltrazuril, SDs 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°C, rotating at 50 rpm. Hundred (100) mg toltrazuril or its equivalent in physical mixture or SDS was added to 900 mL-distilled water, 5 ml dissolution medium was withdrawn at 5.0, 10.0, 20.0, 30.0, 45.0 and 60.0 min with a pipette. The samples were immediately filtered (0.45 µm pore size) and assayed spectrophotometrically at 243 nm. Equivalent amount of fresh water pre-warmed to 37±0.5°C was replaced after each sampling. The cumulative percentage of toltrazuril dissolved was calculated from the regression equation generated from standard data.

Differential thermal analysis

DTA curves of toltrazuril, PEG6000, physical mixtures and SDs (mass ratio 1:10) were measured with a DTA instrument. Each sample (10mg) was accurately weighed and heated in an hermetically aluminum pan at a rate of 10°C /min between 40 and 300°C 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

UV absorption spectrophotometry

The response fitted a linear regression model, the calibration equation is $A = 0.0466C - 0.0485$ in the concentration range of 4.0~20.0µg/mL and the correlation coefficient is 0.9998. Additionally, the presence of PEG6000 did not interfere the UV absorbance of toltrazuril at 243 nm.
Table 1. The results of solubility test (mg/mL).

<table>
<thead>
<tr>
<th>NO</th>
<th>Toltrazuril</th>
<th>1:10</th>
<th>1:15</th>
<th>1:20</th>
</tr>
</thead>
<tbody>
<tr>
<td>toltrazuril</td>
<td>0.0041</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>physical mixture</td>
<td>-</td>
<td>0.0054</td>
<td>0.0054</td>
<td>0.0058</td>
</tr>
<tr>
<td>SDs</td>
<td>-</td>
<td>0.7914</td>
<td>0.8153</td>
<td>0.8601</td>
</tr>
</tbody>
</table>

**Saturation solubility study**

The solubility data were presented in Table 1. It showed that the PEG6000 enhanced the solubility of toltrazuril in SDs formulations. Solubility of toltrazuril was 0.0041, 0.8601, 0.0058 mg/mL from toltrazuril, 1:20 (w/w) SDs and 1:20 (w/w) physical mixtures, respectively. It was also proved that the solubility of toltrazuril increased with the increment in ratio of PEG6000 in SDs.

**Dissolution rate studies**

The dissolution rate tests are shown in Figure 2, enhancement of toltrazuril dissolution rate was achieved. The dissolution rate of toltrazuril from the physical mixture was improved as compared to that with crystalline toltrazuril and can be ascribed to the solubilizing effect of PEG6000 (Doshi et al., 1997; Moneghini et al., 2001). Furthermore, SDs had faster dissolution rates than the pure drug and physical mixture. For example, at the end of 60 min, approximately 8.90, 37.86, 56.74, 58.03, 85.25, 91.78 and 97.87% of toltrazuril was released from crystalline toltrazuril, physical mixtures and SDs (mass ratio 1:10, 1:15 and 1:20), respectively.

**Differential thermal analysis**

The DTA thermograms of toltrazuril, PEG6000, physical mixture and SDS are shown in Figure 3. The thermogram of toltrazuril exhibited an endothermic reaction and its melting peak was at 193.5°C (a). The thermal behavior of PEG6000 exhibited a sharp but slightly broad endothermic peak at 65.7°C owing to its amorphous nature (b). The DTA thermograms of physical mixture exhibited the comprehensive characteristic of toltrazuril and PEG6000. Complete peaks appearance of toltrazuril and PEG6000 were observed in physical mixture (c). The peaks disappearance of toltrazuril and PEG6000 observed in SDs indicated the interaction between toltrazuril and PEG6000, and it attributable to complete miscibility of the drug in the melted carrier (d).

**DISCUSSION**

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

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

Enhancement of toltrazuril 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 (Leuner and Dressman, 2000). 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.

DTA provided the evidence that SDs were formed. When toltrazuril 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.

ACKNOWLEDGMENT

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REFERENCES


