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# Physicochemical characterization of solid dispersion of furosemide with TPGS

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**Abstract**

The D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) was used to increase the aqueous solubility and dissolution rate of furosemide. The solid dispersion of furosemide with TPGS was prepared by solvent method using methanol. The aqueous solubility and the dissolution rate of furosemide were rapid and markedly enhanced from the 1:2 furosemide–TPGS solid dispersion. The X-ray diffractometry showed that pure furosemide and furosemide contained within the physical mixture were crystalline in nature, whereas furosemide in the solid dispersion was not in crystalline form. The infrared spectroscopic analysis showed that an interaction, in the solid dispersion, such as an association between the functional groups of furosemide and TPGS might occur in the molecular level. The infrared spectroscopy and differential thermal analysis showed the physicochemical modifications of the furosemide from the solid dispersion. The solid dispersion technique with TPGS provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs.


*Keywords:* Furosemide; Solid dispersion; TPGS; Dissolution rate; Spectroscopic characterization

## 1. Introduction

One of the techniques that can potentially enhance the dissolution rate of hydrophobic drugs is the formation of the solid dispersion with pharmacologically inert, polymeric materials. A number of investigations demonstrate that the formation of solid dispersions or coprecipitates of relatively water insoluble drugs with various water-soluble polymers can increase significantly their in vitro dissolution rates and/or in vivo absorption.

In the previous studies, the dissolution rates of furosemide was enhanced markedly by formation of coprecipitates with inert, polymeric materials such as polyvinylpyrrolidone, polyethylene glycol (Shin, 1979a,b; Shin et al., 1976) or by cogrinding with chitin or chitosan (Shin et al., 1987).

TPGS is a water-soluble derivative of natural vitamin E, which is formed by esterification of vitamin E succinate with polyethylene glycol 1000 (Eastman Chemical Company, 1998). Several

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studies have demonstrated the effects of TPGS as an absorption enhancer (Bridges et al., 1998; Traber et al., 1986; Chang et al., 1996; Wu et al., 1996; Sokol et al., 1993; Agaro et al., 1992) conducted as a multi-center trial of TPGS for treatment of vitamin E deficiency in children with chronic cholestasis. These researchers reported that TPGS appeared to be a safe and effective form of vitamin E for reversing or preventing vitamin E deficiency during chronic childhood cholestasis.

TPGS has been utilized for numerous applications in pharmaceutical dosage forms. Its chemical structure contains both a lipophilic and a hydrophilic moiety, making it similar to a conventional surface-active agent. The chemical properties of this distinctive compound have suggested its use as a stabilizer, an emulsifier, an absorption enhancer, and as a water-soluble source of vitamin E. The TPGS has a melting point of approximately 38 °C and its degradation temperature has been reported to be 199.3 °C. These physical properties coupled with its chemical properties make TPGS a potential candidate for hot-melt extrusion applications (Repka and McGinity, 2000). TPGS is also used as an emulsifier to prepare the polymeric nanospheres for controlled release of paclitaxel (Mu and Feng, 2002).

The present investigation was focused on exploring D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) as a drug carrier to increase the drug solubility and the dissolution rate of hydrophobic drugs by formation of solid dispersions. In this study, the dissolution enhancement of furosemide was attempted using a solid dispersion technique with TPGS. The dissolution characteristics and physicochemical modification of the furosemide-TPGS solid dispersion were investigated by dissolution test, IR, X-ray diffractometry, and thermal analysis.

## 2. Materials and methods

### 2.1. Materials

Furosemide (Teva Middle East Pharm. and Chemical Work) and TPGS (Eastman Chemical Co., Kingsport, USA) were kindly supplied. All other chemicals were reagent grade and used as received.

### 2.2. Preparation of furosemide test system

The 1:2 (w/w) solid dispersion of furosemide and TPGS was prepared by solvent method (Shin, 1979a,b) using methanol. The same ratio physical mixture of furosemide and TPGS were mixed uniformly using 100-mesh sieve at cold room chamber with care to avoid any grinding action.

### 2.3. Dissolution test

The dissolution test of furosemide from the different test preparations was carried out in KP-6 disintegration medium No. 1 (pH 1.2) at 37 °C, 150 rpm. Each test preparation equivalent to 40 mg of furosemide, which is an excess amount of drug beyond its equilibrium solubility, was transferred into 500 ml of dissolution medium. 2.0 ml of sample solution was withdrawn at appropriate time intervals and filtered through a millipore filter (0.45 um) and immediately replaced with an equal volume of fresh dissolution medium. The amount dissolved was calculated by determining the absorbance of appropriately diluted solution at 274 nm.

### 2.4. Determination of equilibrium solubility of furosemide in water

An excess amount of furosemide was added slowly with stirring to water. The solution was shaken at room temperature for at least 24 h to achieve the equilibrium solubility. Samples were filtered and diluted with distilled water. The diluted samples were assayed for furosemide by UV spectroscopy at 274 nm.

### 2.5. Spectroscopic determination of furosemide–TPGS test preparation

Infrared spectra for the furosemide test systems were observed by potassium bromide disk method, with a double beam, Perkin–Elmer infrared spectrophotometer. Powder X-ray diffraction studies

were carried out by a Rigaku Geigerflex X-ray diffractometer. The target was Cu-tube (Ni-filter), 35 kV, 15 mA and the detector was a proportional counter at 1.7 kV for detector voltage. Thermograms were obtained using TG/DTA analyzing instruments (Seiko SSC 5200, Japan). Temperature was calibrated using indium (156.6 °C) as the standard. The operating conditions in an open-pan system were as follows: sample weight, 5–10 mg; heating rate, 10 °C $min^{-1}$ under $N_2$ purging at 90 ml $min^{-1}$. The temperature was increased from 20 to 660 °C then allowed to decrease to 20 °C.

## 3. Results and discussion

### 3.1. Dissolution rate studies

The effect of TPGS on the dissolution of furosemide was investigated for the furosemide test preparations. The dissolved amount of furosemide for the 1:2 furosemide–TPGS solid dispersion are shown in Fig. 1, while pure furosemide is included as a point of reference. The amount of furosemide in solution from the 1:2 furosemide–TPGS solid dispersion rapidly and markedly exceeded the pure furosemide.

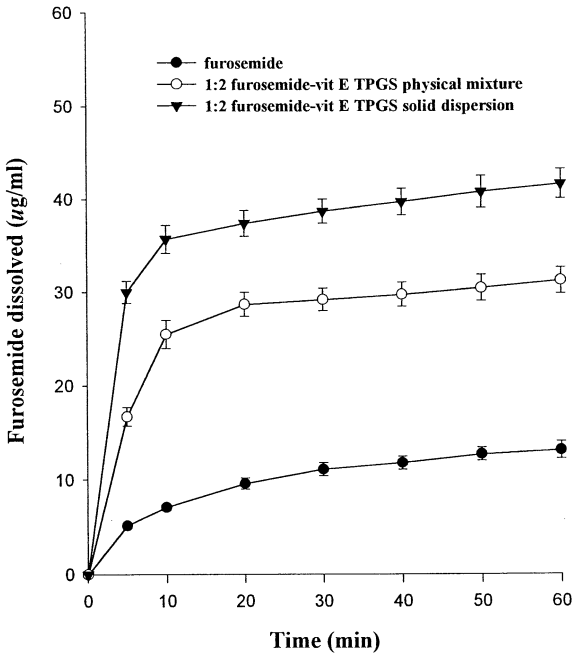


Fig. 1. Dissolution rates of furosemide in dissolution medium (pH 1.2) at 37 °C, 150 rpm ($n = 3$).

It is interesting to note that even though the particle size of the drug available for dissolution was the same, the dissolution rate of furosemide from the physical mixture was enhanced when compared with that of pure furosemide. This was supported by the observation that pure furosemide floats on the surface of the dissolution medium longer than the physical mixture. It is presumed that TPGS melts and dissolves in the dissolution medium of 37 °C quickly and acts as an emulsifier of hydrophobic furosemide particles (Mu and Feng, 2002). The increase noted in the rate of solution of furosemide from the physical mixture as compared with the pure drug is most likely due to the ability of the TPGS to enhance the wettability and emulsifying effects of the hydrophobic furosemide particles.

### 3.2. Equilibrium solubility of furosemide in water

The aqueous solubility of furosemide from the 1:2 (w/w) furosemide–TPGS solid dispersion was 345.75 μg $ml^{-1}$, and 133.65 ug $ml^{-1}$ from the same ratio physical mixture, whereas 18.25 ug $ml^{-1}$ from the pure furosemide.

The chemical structure of TPGS comprises both lipophilicity and hydrophilicity, resulting in amphiphilic properties. Moreover, its lipophilic alkyl tail (polyethylene glycol) and hydrophilic polar head portion (tocopheryl succinate) are bulky and have larger surface areas. Such characteristics make it a good emulsifier, which can emulsify a wide range of water–oil immiscible systems. The hydrophilic-lipophilic balance of TPGS is about 13.2. It melts at ~37–41 °C and is heat stable below temperature 200 °C (Mu and Feng, 2002). Ismailos et al. (1994) also reported on the enhancement of cyclosporin A solubility by TPGS.

The aqueous solubility of furosemide from the 1:2 furosemide–TPGS physical mixture increased about 7.3-fold compared with that of the pure furosemide. It is understandable, by the physical observation, that the increase in solubility of furosemide might be due to the physical properties of solubilizing and emulsifying ability of TPGS

(Ismailos et al., 1994). The equilibrium solubility of furosemide from the 1:2 furosemide–TPGS solid dispersion was increased dramatically about 19.84-fold compared with that of the pure furosemide. Equilibrium solubility studies suggest that there might be different phases of furosemide in the solid dispersion.

### 3.3. X-ray diffraction

Fig. 2 shows the X-ray diffractograms for the furosemide, physical mixture, and solid dispersion. The pure furosemide showed the same diffraction peaks at $2\theta$ of 18.0, 18.9, 24.7 and 28.6° etc., indicating the presence of crystalline furosemide. Interestingly, the physical mixture also showed crystallinity, probably due to the presence of crystalline furosemide. Thus, the mere presence of TPGS in the physical mixture should not interfere with the characterization of coexisting furosemide. On the other hand, the 1:2 ratio furosemide–TPGS solid dispersion (Fig. 2) did not show the crystallinity. This result implies that furosemide is present in an amorphous form in the 1:2 furosemide–TPGS solid dispersion.

According to these results, an amorphous property of furosemide in the solid dispersion is considered to be mainly responsible for the enhanced dissolution. Therefore, it is presumed that the solid dispersion shows an interaction between furosemide and TPGS in the molecular level and the crystallinity of furosemide was not shown by X-ray diffraction (Shin et al., 1987; Shin, 1979b; Shin et al., 1976).

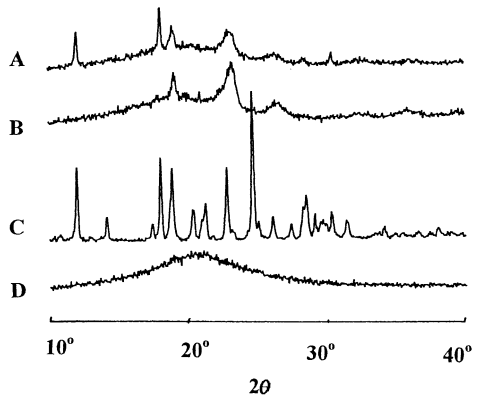


Fig. 2. X-ray diffractograms of 1:2 furosemide–TPGS test preparation. Key: A, pure furosemide; B, pure TPGS; C, physical mixture; D, solid dispersion.

### 3.4. Infrared spectroscopy

The pure furosemide and TPGS showed the crystallinity and the 1:2 ratio furosemide–TPGS physical mixture also showed the crystalline peaks of furosemide. In contrast, the 1:2 furosemide–TPGS solid dispersion did not show the crystallinity of furosemide. To elucidate further physicochemical properties, infrared absorption spectroscopy was carried out.

From the infrared spectrum of pure furosemide, an absorption band is observed at 3340 and 3260 $cm^{-1}$ in the region of 3500–3200 $cm^{-1}$, and a sharp band is observed at 1665 and 1560 $cm^{-1}$ in the region of 1700–1500 $cm^{-1}$ (Fig. 3). The 3340 $cm^{-1}$ band is assigned to the $NH_2$ stretching vibration of $Ar–NHCH_2$ and the 3260 $cm^{-1}$ band is assigned to stretching vibration of $SO_2NH_2$ and the 1665 $cm^{-1}$ band which appears at such high frequency region is assigned to the bending vibration of amino group. The 1560 $cm^{-1}$ band is due to the assymmetric stretching vibration of the carboxyl group and the 1318 $cm^{-1}$

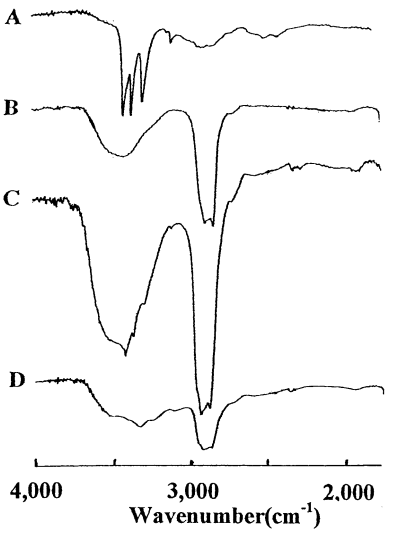


Fig. 3. Infrared spectrograms of 1:2 furosemide–TPGS test preparations. Key: A, pure furosemide; B, pure TPGS; C, physical mixture; D, solid dispersion.

band is assigned to the assymmetric stretching vibration of the sulfonyl group in the furosemide structure (Shin et al., 1987; Shin, 1979b; Shin et al., 1976). TPGS shows an absorption band at 3480 $cm^{-1}$ due to the hydroxyl group.

The stretching bands in the region of 3500–3200 $cm^{-1}$ assigned to the non-bonded aromatic imino group and sulfonylamide group in furosemide molecule was not shown in the spectrum of the solid dispersion, which was shown in the spectrum of the physical mixture. Therefore, it is presumed that the solid dispersion shows an interaction such as an association between the functional groups of furosemide and TPGS in the molecular level. An association between furosemide and TPGS is expected to be most probable between the imino group and sulfonylamide group of furosemide and the carboxyl group of TPGS (Shin et al., 1987; Shin, 1979b; Shin et al., 1976).

### 3.5. Thermal analysis

The thermograms for the furosemide test systems are shown in Fig. 4. TPGS exhibited a melting point of ~37–41 °C. The degradation that occurred at 199 °C indicates that TPGS has a good thermal stability under normal processing temperatures used for pharmaceutical application.

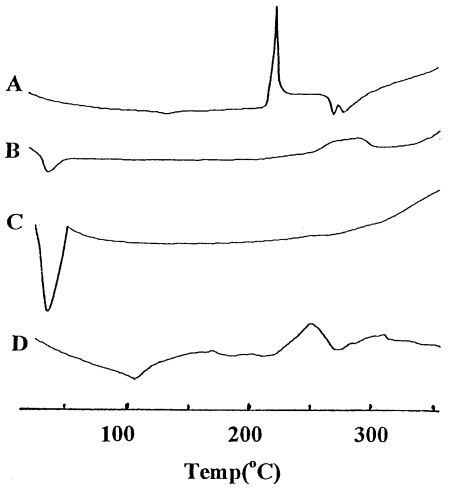


Fig. 4. Thermograms of 1:2 furosemide–TPGS test preparations. Key: A, pure furosemide; B, pure TPGS; C, physical mixture; D, solid dispersion.

Its low melting temperature and high degradation temperature suggest that TPGS is thermally stable and can be used in a melt granulation (Wu et al., 1996).

The pure furosemide was melted between 203 and 206 with decomposition (Shin, 1979a,b). The furosemide exhibited a single, sharp exothermic peak that resulted from the decomposition of furosemide at temperature of 220 °C, whereas the single exothermic peak of furosemide was not shown in the solid dispersion. A comparison of DTA curves of the physical mixture and the solid dispersion showed a slight transition peak. Their temperature range of transition appeared to be somewhat different from that of furosemide.

In conclusion, the relative enthalpy change may be considered to correspond to the disappearance of crystallinity. It may be said that the drug molecules are dispersed in the TPGS matrix of the solid dispersion and that the thermal property was changed.

## 4. Conclusions

The results of infrared spectroscopy, X-ray diffractometry, and thermal analysis indicate that the physico-chemical interaction such as an association between the functional groups of furosemide and TPGS might occur in the molecular level and does not show any crystallinity of furosemide in the solid dispersion, which increased the solubility and the dissolution of furosemide from the solid dispersion. The solid dispersion technique with TPGS provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs.

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