ASIAN JOURNAL OF PHARMACY & LIFE SCIENCE

ENHANCEMENT OF SOLUBILITY OF PACLITAXEL BY SOLID DISPERSIONS TECHNIQUES

J.K. BADJATYA*[1], R. B. BODLA[1], SHAILENDRA SOLANKI[2], D. KUMAR[3]

1. **Shri Jagdish Prasad Jhabarmal Tibrewala University, Chudela, Jhunjhunu, Raj. India**
2. **College of Pharmacy, IPS Academy, Rajendra Nagar, Indore, India.**
3. **Vinayaka College of Pharmacy, Kullu, India.**

Abstract:

Paclitaxel is an anti cancer drug shows poor water-solubility; in order to improve solubility and dissolution rate; solid dispersions of Paclitaxel were prepared and evaluated. Solid dispersions of Paclitaxel were prepared using PEG 6000 and Poloxamer 407. Dissolution studies indicated significant enhancement in dissolution of Paclitaxel when dispersed in PEG 6000 and Poloxamer 407. Solid dispersions containing Paclitaxel / Poloxamer 407, 1: 8, showed a 14-fold increase in dissolution after 60 min (D60) and another dispersion containing Paclitaxel /PEG 6000, 1:10, showed an 8-fold increase in dissolution rate. Lyophilized solid dispersions also enhanced dissolution of Paclitaxel significantly. X-ray diffraction and FT-IR were performed to determine the physicochemical properties of the solid dispersions in comparison with the pure drug. Lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Paclitaxel.

Keywords: *Paclitaxel, Lyophilized, Solid dispersions, Dissolution.*

*Corresponding Author's E-mail: - jeeutbadjatya@gmail.com

Received: 27/05/11 Accepted: 09/07/11

INTRODUCTION

Poor water-solubility of drugs has been one of the major problems in drug formulation and drug absorption these drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds; several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers to enhance solubility of such drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole [1-4]. Lyophilization has also been employed largely for the preparation of lyophilized molecular dispersion [5]. Application of paclitaxel in cancer therapy has been limited by its low water solubility (0.3 µg/ml), thus Paclitaxel was chosen as a water-insoluble model drug, and Poloxamer 407 and PEG 6000 were employed as carrier material for the formulation of solid dispersion with model drug. The results of this study suggested that lyophilization of solid dispersions is ideal for poorly water soluble drugs.

MATERIAL AND METHODS

Apparatus and chemicals

Poloxamer 407 (Pluronic F127) was obtained from BASF (Mount Olive, NJ, USA). PEG 6000 was purchased from Sigma Aldich. Other excipients used were of analytical grade. All chemicals were used as received.

Composition of Solid Dispersion

Single component solid dispersions contained 2, 4, 6, 8 or 10 parts by weight of Poloxamer 407 or PEG 6000 and 1 part of Paclitaxel. (**Table 1).**

Preparation of solid dispersions

The fusion (melt) method

Accurately weighed amounts of carrier(s) were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of drug was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature

Lyophilization of solid dispersions

The selected solid dispersions were dissolved in a minimum amount of Chloroform. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in Methanol bath at 50°C. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under pressure of 8-10 mmHg and condensed. Lyophilized preparations were stored in desiccators at room temperature.

Dissolution rate determination

An Electrolab dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the Paclitaxel. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2^0C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace with the same amount of fresh dissolution media so as to maintain sink condition. The samples were filtered through 0.2µm filter and diluted, and then these samples were assayed by HPLC. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

FT-IR Studies

FT-IR spectra of prepared Lyophilized solid dispersion were recorded on Shimadzu FT IR – 8400

spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1}.

RESULTS AND DISCUSSION

In Vitro Dissolution Study of Solid Dispersion

The dissolution rate of Paclitaxel from all the physical mixtures was significantly higher than Paclitaxel alone. The dissolution profiles of solid dispersions prepared using Poloxamer 407 exhibited significant increase in rate of dissolution. The dispersion prepared with 10 parts of PEG 6000 had the highest dissolution at 60 min (D60) of 95%, which is significantly greater than the other dispersions. Dispersions containing 8 parts of Poloxamer 407 were found to be the best preparation, showing a D30 value of 55.2% and D60 value of 99.6%, which is about 17- and 18-fold increase, respectively, compared with Paclitaxel alone. Solid dispersions prepared with 10 parts of PEG 6000 and 8 parts of Poloxamer 407 were chosen for lyophilization because these dispersions provided the best dissolution profiles. The rate and extent of dissolution increased with all the lyophilized solid dispersions. Dissolution of solid dispersions at 60 min (D60) is shown in **Fig. 1 & 2.**

All the lyophilized solid dispersions showed significant increase in D60 values compared with their respective plain solid dispersions. The dissolution of the drug from the solid dispersion is also affected by the method of preparation of the solid dispersion. It also depends on the proportion and properties of the polymer carrier used in the composition of solid dispersion [6]

Solid dispersions containing Poloxamer 407 and PEG 6000 showed higher dissolution rates compared with Paclitaxel alone. Physical mixtures also exhibited higher dissolution rates as compared with Paclitaxel alone. The process of lyophilization occurs in three stages: freezing, primary drying (ice sublimation) and secondary drying (water desorption) [7]. The freezing process largely determines the physical traits of the dried solid product [8]. The resultant dried mixture was porous and fluffy this increases the surface area and surface free energy; resulting in enhancement of dissolution rate. The faster dissolution rate merely based on the particle size without anything to do with energy changes. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and drug; and thus enhance dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which may facilitates faster dissolution [9].

FT-IR Study

State of drug molecule with the different polymers and surfactants was determined using FT-IR. IR-spectra of Paclitaxel and solid dispersion are exactly same, and there is no shift of peaks after absorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into melt granules.

X-RAY Diffraction Study

X-Ray Diffraction study showed Lyophilized solid dispersions of Paclitaxel with PEG 6000 and Poloxamer 407 (Fig. 3). Paclitaxel crystals showed various diffraction peaks due to its crystalline structure however, the solid dispersion shows a loss of drug crystallinity due to drug loading onto polymers and surfactants surface.

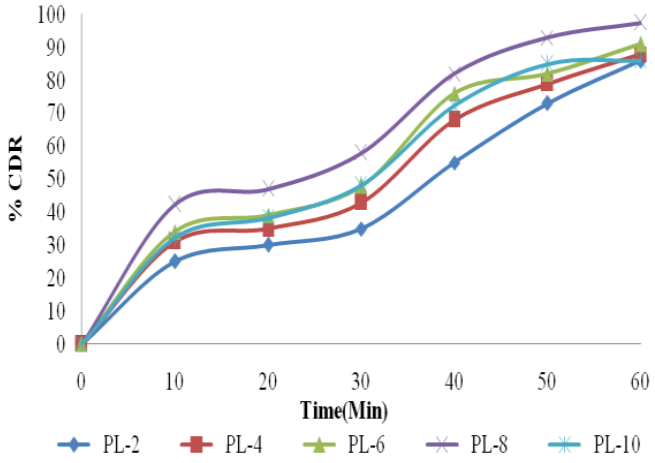

Fig. 1. In vitro dissolution of solid dispersions (Ploxamer 407) at 60 mins.

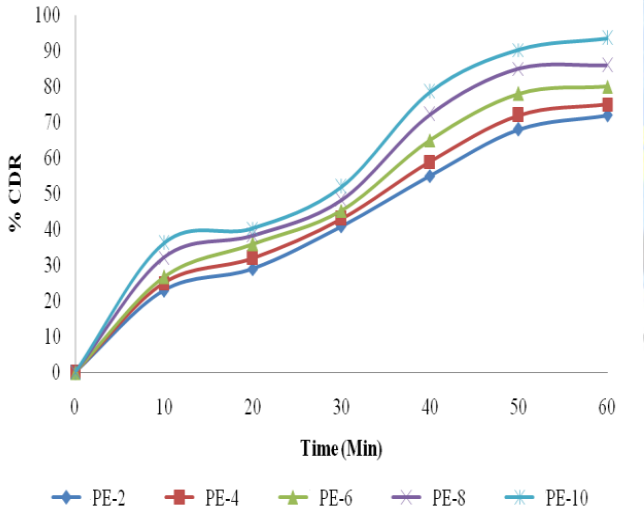

Fig. 2. In vitro dissolution of solid dispersions (PEG 6000) at 60 mins.

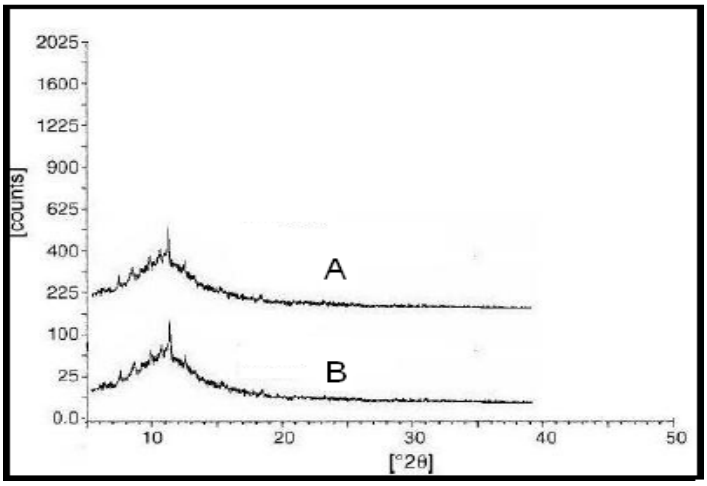

Fig 3. X-Ray Diffraction of lyophilized solid dispersions of drug with PEG 6000 (A) and Poloxamer 407 (B)

Table 1: Composition of Solid dispersion

Carrier	Drug: Carrier ratio	Formulation code
Poloxamer 407	1:2	PE- 2
	1:4	PE- 4
	1:6	PE- 6
	1:8	PE- 8
	1:10	PE- 10
PEG 6000	1:2	PE- 2
	1:4	PE- 4
	1:6	PE- 6
	1:8	PE- 8
	1:10	PE- 10

Conclusion:

In conclusion solid dispersions and lyophilized solid dispersions were found to have responsible for the enhancement in dissolution of Paclitaxel. Lyophilized

solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Paclitaxel. The results of this study clearly suggested that lyophilization of solid dispersions is ideal for poorly water soluble drugs. The adsorption of Paclitaxel does not leave any residual solvent in the final formulation because of elimination of use of solvent from the preparation of solid dispersion. Crystallinity of the solid dispersion was reduced due to drug excipients interaction in formulation obtained using lyophilization technique without any chemical interaction.

References:

1. Sekiguchi, K. and Obi, N. Studies on absorption of eu-tectic mixture. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man, Chem. Pharm. Bull., 1961; 9: 866-872.
2. Yalkowsky, SH. Solubility and solubilization in aqueous media. American Chemical Society; Washington, D.C.: 1999.
3. Löbenberg, R.; Amidon, GL.; Vierira, M. Solubility as a limiting factor to drug absorption. In: Dressman, JB.; Lennernäs, H., editors. Oral Drug Absorption. Prediction and Assessment. Marcel Dekker; New York: 2000; 137-153.
4. Müller, RH, Böhm, RH. Benita, S, Böhm, Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs. Medpharm Scientific Publishers; Stuttgart: 1998. 149-174.
5. Lin, Y.E. and Wilken, L.O. Some effects of a modified lyophilization procedure on dissolution and other properties of Digoxin powders and tablets. M.S. Thesis. Auburn University, AL, 1980; 63.
6. Corrigan, O.1., Mechanisms of dissolution of fast release solid dispersions. Drug Dev. Ind. Pharm., 1985; 11: 697-724.
7. Pikal, M.J., Shah, S., Senior, D. and Lang, J.E. Physical chemistry of freeze-drying: measurement of sublimation rates for frozen aqueous solutions by a microbalance technique. J. Pharm. Sci., 1983; 72: 635 650.
8. MacKenzie, A.P. Principles of freeze-drying Transplant Proc., 8 (Suppl. l) 1976; 181 188.
9. Sekikawa, H., Naganuma, T., Fujiwara, J.E., Nakano, M. and Arita, T., Dissolution behaviors and gastrointestinal absorption of phenytoin in phenytoin-polyvinylpyrrolidone coprecipitate. Chem. Pharm. Bull., 1979; 27: 1223-1230.