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Freeze Drying Method for Enhancement of Solubility and Dissolution Rate of Poorly Aqueous Soluble Drug Paliperidone In Vitro–Evaluation

Sameer H. Lakade[1*], M R Bhalekar[2]

1. *Karpagam University, Coimbatore (T.N) India and Sinhgad Institute of Pharmaceutical Sciences Lonavala Pune 410401.*

2 AISSMS College of Pharmacy Kennedy road Pune 411001.

ABSTRACT

The main objective of the study is to enhance the dissolution rate and solubility of paliperidone by using the solid dispersion technique which were wildly used in pharmaceutical company because of its less cost. Paliperidone is antipsychotic classes of drug that can be used for the treatment of schizophrenia. Initially preformulation studies were conducted to check the incompatibilities of drug substance. Initially phase solubility studies were performed with respect to different molar ratio. Drug polymer interactions were investigated using differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). As indicated from XRD and DSC data, paliperidone was in the amorphous form, which explains the better dissolution rate of then drug from its solid dispersion. Solid dispersion of paliperidone were prepared to check the solubility of paliperidone because of its poor solubility issue by using the different polymer and to find out the effect of various solubilizer on its solubility and dissolution rate.

Keywords: Solid Dispersion, Solubilizer, Paliperidone, Dissolution Enhancement.

*Corresponding Author Email: sameer_patil97@rediffmail.com

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INTRODUCTION

Antipsycotic drugs are able to reduce psychotic symptoms in a wide variety of conditions, including schizophrenia, bipolar disorder, psychotic depression, senile psychoses, various organic psychoses, and drug- induced psychoses. They are also able to improve mood and reduce anxiety and sleep disturbances, but they are not the treatment of choice when these symptoms are the primary disturbance in nonpsychotic patients[1].The manifestations of the disease include two types of symptoms positive and negative symptoms are characterized by delusion(often paranoid in nature) illusion, auditory hallucinations(usually in the form of voices), thought disorders with irrational conclusions, garbled sentences and stereotyped or at time aggressive behavior[2].Most psychoses are functional rather than organic. The current understanding of schizophrenia suggests that it has metabolic, genetic and psychosocial components. It is now believed that noradrenaline, and dopamine in particular are involved in the schizophrenic process, and the imbalance between the two is associated with the disease. Recently a correlation has been demonstrated between the therapeutic potencies of number of antipsychotic drugs and their ability to block dopaminergic receptors in vitro. This blocked produces a number of effects in the CNS including extrapypamidal disorders in man and catalepsy in animal[3].An additional factor indicating heterogeneity among schizophrenic patient is the presence or absence of anatomic changes[4]. The aim of the present study was to enhance the dissolution rate of paliperidone using solid dispersion technique with various hydrophilic polymers. The melt method, solvent evaporation method, and freeze drying method was used to prepare solid dispersion particles of Paliperidone. Solid dispersion systems and physical mixtures of Paliperidone were prepared with polyethylene glycol 6000 (PEG6000/4000/1500) each in 1:1, 1:3 and 1:5 ratios. The selection of different ratios of polymers was purely on random basis. The solid-state properties of these binary systems were studied by Fourier transformation infrared spectroscopy, X-ray powder diffractometry and differential scanning calorimetry.

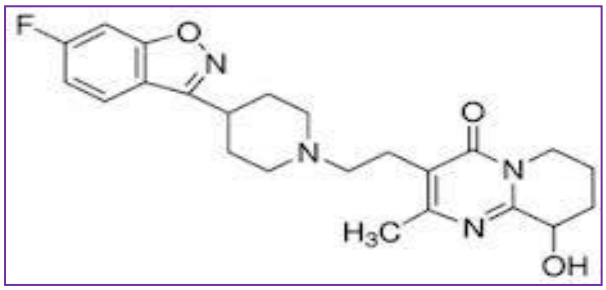


Figure 1 Chemical structure of paliperidone

Chemical Name: (±) - 3 - [2 - [4 - (6 - fluoro - 1,2 - benzisoxazol - 3 - yl) - 1 piperidyl]ethyl] –

6,7,8,9 - tetrahydro - 9 - hydroxy - 2 - methyl - 4H - pyrido[1,2 - a]pyrimidin - 4 – on

Molecular Formula: $C_{23}H_{27}FN_4O_3$

MATERIALS AND METHOD

PPD was obtained from Alkem Lab Mumbai, PEG 6000, PEG 4000, PEG 1500 used were of analytical grade.

Preparation of the physical mixture

Physical mixtures (PM), PPD-PEG (1:1) were prepared by simple blending in a glass mortar.

Preparation of solid Dispersion[5,6,7]

a) Melt Method b) Solvent evaporation c) Freeze–Drying Method

Evaluation of Solid Dispersion

Drug solid dispersion equivalent to 10 mg of drug was stirred with 100 ml of methanol. From this the concentration of 10 µg/ml was prepared and the drug content was determined spectrophotometrically at 227 nm using methanol as blank.

Dissolution study

Dissolution studies were performed in 900 ml 0.1 N HCl at 37 ± 0.5^{o}C, using 6-station USP Electro Lab Tablet Dissolution Test Machine with paddle rotating at 50 rpm. Dissolution studies were performed on pure drug and the solid dispersion containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (5mL) were analyzed spectrophotometrically at 227 nm, and were replaced with an equal volume of plain dissolution medium.

Physicochemical characterization

Fourier transforms infrared spectroscopy

The FTIR spectral measurement were taken at ambient temperature using shimadzu spectrophotometer. Sample were prepared by mixing in KBr powder and FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer[8].

X-Ray diffraction (XRD) study:

X-Ray diffraction patterns were obtained on a siemans kristalloflex D-500 diffractometer with Ni-filtered CuKα radiation at a goniometer speed of 1^0 (2ø)/min and a chart speed of 1cm/ min.[9]

Differential scanning calorimetry

Heat of fusion determinations were made by a DSC 20 (Mettler Switzerland). The sample weight was 5 mg in all samples. A heating rate of 10^0C/ min and the result presented are mean value of at least four determination.[10]

RESULTS AND DISCUSSION

All the Solid dispersions (SDs) were found to be free flowing under dry conditions. The dissolution of paliperidone was rapid and higher from all the SDs when compared to paliperidone pure drug, i.e. the dissolution rates are in the order: SD> PM> Pure drug. The increased solubility of SDs was due to reduction in the particle size and / or the presence of drug in the form of solid solution in a water-soluble carrier in molecular form. There is a significant improvement in solubility and dissolution rate of poorly soluble drugs by using different drug-polymer ratios and preparing SDs by different methods like PM, solvent evaporation and freeze drying. The dissolution rate of drug increased with increase in polymer concentration and it is dependent on the method of preparation. In PEG 1500/ 4000 and PEG 6000 drug and polymer solid dispersion, broadening and smoothing of C-OH stretch vibrations occurred between 3300 - 3250 cm^{-1} indicates conversion of free OH group into bonded form. sp^3 C-H stretch, sp^2 C-H stretch between 2850 – 3010 cm^{-1}, C=O (carbonyl group) at 1633 cm-1, C – F stretch at 1112, C – O stretch at 980 are prominently decreased in a 1: 5 ratio than other 1:1 and 1:3 ratio. Better SD of PEG–1500/ 4000 /6000 (1:5) may indicate increase in solubility. There is no formation of extra peak indicate no chemical interaction.

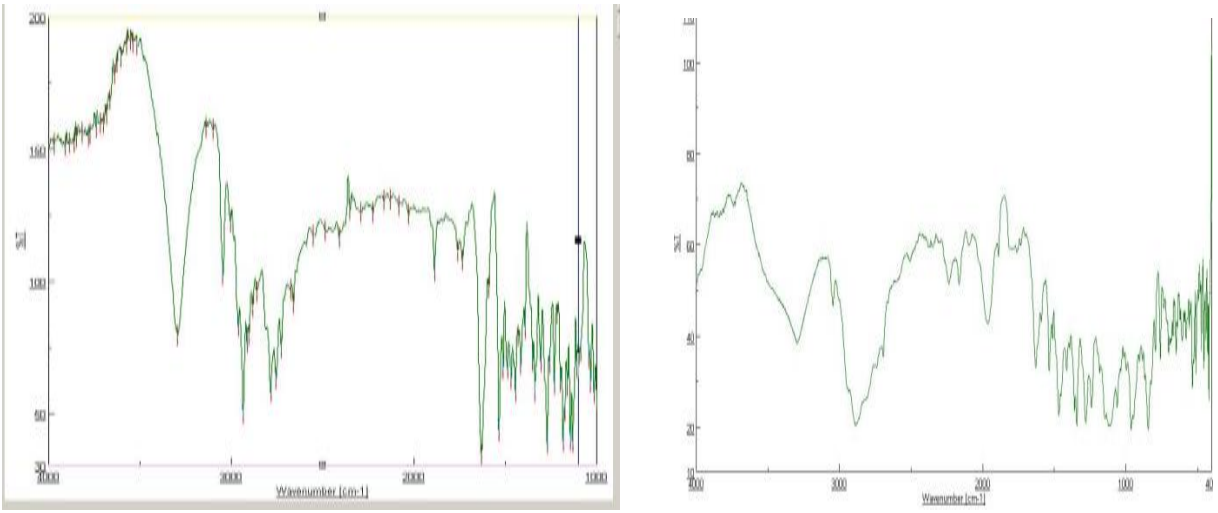


Figure 2 FTIR spectra of drug and solid dispersion

X-ray powder diffraction analysis

Paliperidone crystals show various diffraction peaks due to its crystalline structure. However, the lyophilized solid dispersion shows a loss of drug Crystallinity due to drug loading onto polymers surface. In optimized lyophilized solid dispersion, a few less intense and wide diffraction peaks of Paliperidone was observed, which may be attributed to the adsorption process in which some

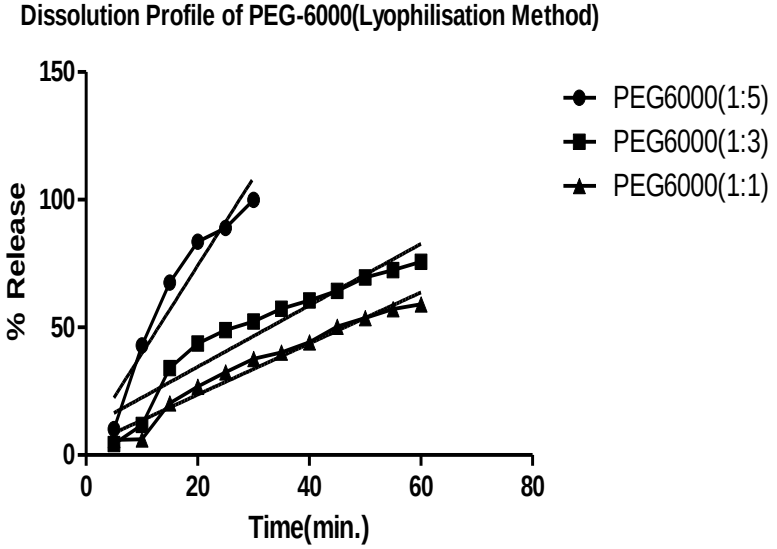
of amorphous drug may have crystallized due to higher temperature. The sharp drug peaks corresponding to drug are absent in the lyophilized solid dispersion.

Differential Scanning Calorimetry

DSC curves of paliperidone for all solid dispersion were obtained by a differential scanning calorimeter DSC 20 (Mettler Switzerland) at a heating rate of 10°C/min from 30°C to 300°C in nitrogen atmosphere. The DSC thermogram of paliperidone alone showed endothermic Tmax of 180.05°C, corresponding to the melting point of crystalline form of the drug paliperidone. Considering the melting point of polymer. Curing curve for both polymer at melt method was observed at 180^{o}C it may be due to the cross linking of polymer molecule with drug. It was usually appeared soon after the glass transition temperature. There was an complete disappearance of drug peak at both system suggesting that there was solubilization of drug in polymeric matrix and change in crystallinity of paliperidone i.e conversion of drug to its amorphous form.

Dissolution study

The dissolution rate of pure paliperidone was very poor and during 60 min a maximum about 28% of the drug was released. The reason for the poor dissolution of pure drug could be poor wettability and/or agglomeration or particles size. It was found that the dissolution rate of the drug increased according to increasing amount of hydrophilic carrier in solid dispersion batches. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particles.



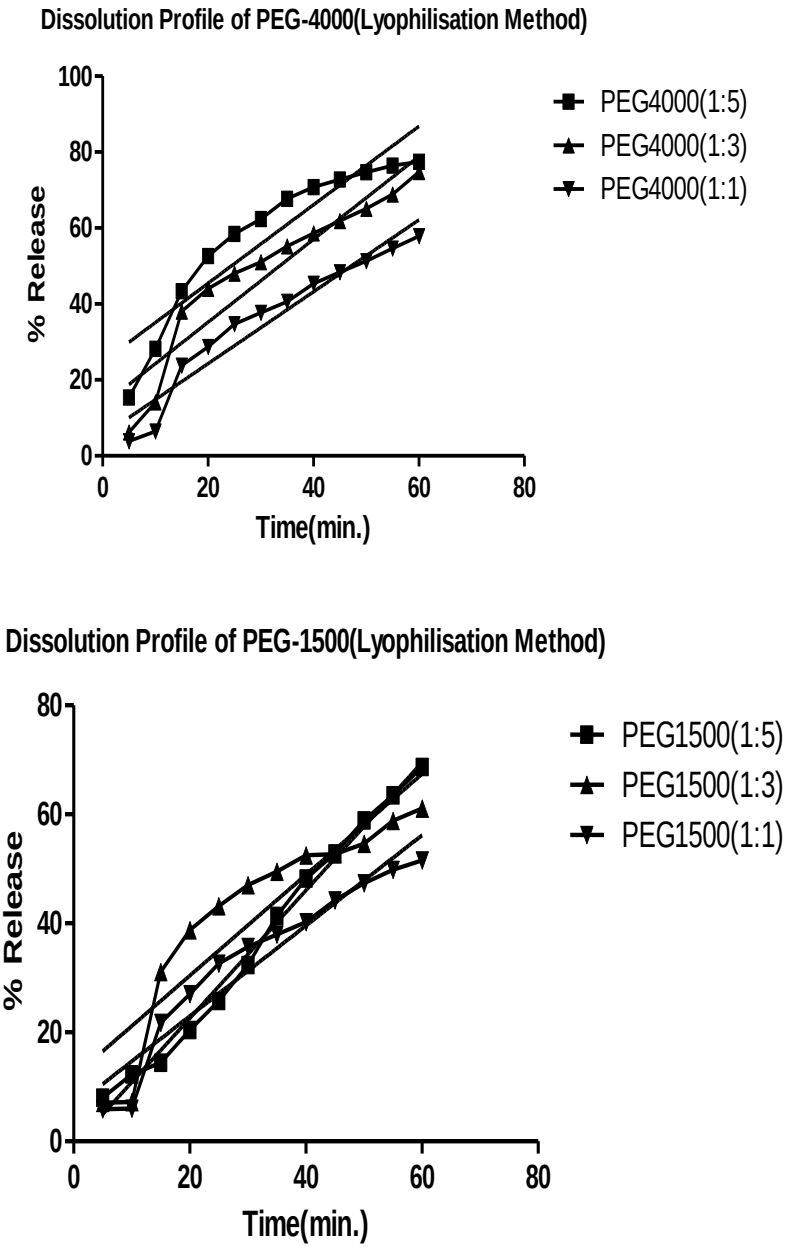


Figure. 3 *In-vitro* release of solid dispersion

The greater hydrophilicity and surfactant property of polymers results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. The percentage drug dissolved from the solid dispersions of Paliperidone-PEG 6000-/PEG-4000-/PEG-1500 was compared with that dissolved from an equal amount of pure Paliperidone. In all cases, increasing the proportion of carrier resulted in the enhancement of the dissolution rate. This extent of enhancement was markedly greater for the melted products of both polymer. It is evident that the solid dispersion of lyophilization of 1: 5 w/w ratios have the fastest dissolution rates. Dissolution was greatly enhanced during the initial

20 min of the dissolution profiles. This rapid release was attributed to the presence of drug in a very fine state of subdivion. This is mainly due to the significant reduction of the drug particles size in addition to the solubilizing and wetting effect of the carrier. The release rate by PEG-6000-98.65% , peg-4000-77.47% and peg-1500-68.68. %.

CONCLUSION

Finally it can be concluded that freeze drying technique of SD may be considered as good technique to increase the dissolution property of poorly soluble drug like paliperidone. Freeze drying method of polyethylene glycol 6000 and drug at all ratios was found to be effective in increasing the release of the drug. Especially the drug polyethylene glycol ratio of 1:5 was found to be successful mostly.

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