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Arti Mohan
RGR Siddhanti College of Pharmacy Bolten Road, Opposite Tivoli Cinema, Secunderabad, Telangana, India

M. Madhavi
RGR Siddhanti College of Pharmacy, Bolton Road, Secunderabad, Telangana, India

P. Jyosthna
RGR Siddhanti College of Pharmacy, Bolton Road, Secunderabad, Telangana, India

Correspondence:
Arti Mohan
Professor & Principal,
RGR Siddhanti College of Pharmacy Bolten Road,
Opposite Tivoli Cinema,
Secunderabad, Telangana, India

Preparation, *in vitro* and *in vivo* characterization of solid dispersions of Oxcarbazepine using melting technique

Arti Mohan, M. Madhavi, P. Jyosthna

Abstract
Oxcarbazepine is one of the newer antiepileptic drugs and low aqueous solubility of Oxcarbazepine is responsible for its poor dissolution and delayed onset of action. The purpose of the present investigation is to increase the dissolution rate of Oxcarbazepine by preparing its solid dispersions with PEG 6000 using melting technique and subjecting the prepared solid dispersions to drug-carrier interaction, dissolution and stability studies and it was found that the dissolution rate was improved for Oxcarbazepine in its solid dispersion. As indicated from XRD and DSC studies, Oxcarbazepine was in the amorphous form in the solid dispersions, which confirmed the better dissolution rate of prepared stable solid dispersions. Pharmacokinetic profiles of Oxcarbazepine and solid dispersion were compared by one way ANOVA followed by a Dunnett Post Hoc test which indicated higher attainable plasma concentrations. Solid dispersion showed a difference with the pure drug in its pharmacokinetic profile which may be attributed to better dissolution rate of Oxcarbazepine from its solid dispersion.

Keywords: Oxcarbazepine, Solubility, Physical Mixture, Solid dispersions, Solvent evaporation, Pharmacokinetic.

1. Introduction
Oxcarbazepine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder [1]. Oxcarbazepine also acts as a mood stabilizer [2]. Oxcarbazepine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The Common oral dosage is 150 mg/day (dose/solubility ratio ≥250 ml; class II drug according to the BCS). Peak plasma concentrations occur anywhere from 1 to 2 hours following drug administration. This delay in the onset of action in spite of good bioavailability is because of its low aqueous solubility which is only 0.30 g/litre. The most promising method for promoting dissolution is the formation of solid dispersion in a proper hydrophilic polymeric carrier [3-4]. Poly ethylene glycol (PEG) is amongst the most frequently investigated hydrophilic polymeric carriers [5–6]. The purpose of the present investigation is to increase the solubility and dissolution rate of Oxcarbazepine by preparing its solid dispersions with poly ethylene glycol (PEG) 6000 using melting technique.

2. Material and Methods
Oxcarbazepine was a gift sample from Jubiliant Organosys Ltd, Noida, U.P, India and Polyethylene Glycol 6000 was purchased from Oxford Laboratory, Mumbai, India. All other chemicals and reagents used were of analytical grade.

2.1 Phase solubility studies
Solubility measurements were performed according to the method reported by Higuchi and Connors [7]. Both PEG 4000 and 6000 were assessed for solubility enhancement. Various (1%, 2%, 5% and 10% w/v) aqueous solutions of PEG 6000 and PEG 4000 were prepared and transferred to volumetric flasks. An excess amount of drug was added to each flask. The contents of each flask (10 ml) were equilibrated by shaking for 48 hours in a thermostatically controlled water bath at 37±0.1 ^{0}C. After 48 hours, samples were analyzed at 256 nm for Oxcarbazepine. Solubility studies were performed in triplicate (n=3).

2.2 Preparation of Physical Mixtures and Solid Dispersions
For Oxcarbazepine, the physical mixtures (PM) were prepared and the solid dispersions were

prepared by melting technique in three different ratios by using PEG 6000 as a hydrophilic carrier. The following combination of the drug and carrier were used. PEG 6000 was chosen as it was found to give a better dissolution profile of Oxcarbazepine.

Table 1: Ratio of drug and carrier used for the preparation of solid dispersion

Code	Quantity of Drug	Quantity of carrier (PEG 6000)	Ratio (Drug: Carrier)
SD1	150 mgs	150 mgs	(1:1)
SD2	150 mgs	300 mgs	(1:2)
SD3	150 mgs	750 mgs	(1:5)

Preparation of Physical Mixture

The Physical Mixture were prepared by mixing the required quantity of drug and PEG 6000 in a glass container until a homogenous mixture was obtained, which was sieved through an 80 mesh screen. Packed in double polythene covers and stored in dessicator till further estimation.

Preparation of solid dispersions by Melting method

PEG 6000 was melted in a beaker on a water bath maintained at 50-60 ^{0}C. Required amount of drug was then added to molten PEG 6000 and mixed thoroughly for 5 minutes. The molten mixture was cooled rapidly by placing it in an ice bath for about 5 minutes and solidified. The hardened mixture was powdered, sieved through an 80-mesh screen and packed till further use.

2.3 Characterization of physical mixture and solid dispersions of Oxcarbazepine [8]

Fourier transforms infrared spectroscopy (FTIR)

Fourier transform infrared spectra were obtained using Thermo Nicolet 380 FTIR. The scanning range was 40 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetric (DSC)

The DSC thermograms of samples were recorded on a DSC (SISI Nanotech). The samples (6.5-10 mg) were heated under nitrogen atmosphere in hermetically sealed aluminium pans over a temperature range 20 ^{0}C to 350 °C at a constant rate of 20 °C/min under nitrogen purge (10 ml / min).

Powder X-ray diffraction (PXRD)

The powder X-ray diffraction patterns were determined. The scanning rate was 1°/min over a 2 θ range of 1-50 °C.

2.4 Dissolution studies

The *in vitro* dissolution for the solid dispersions (equivalent to 150 mg of OX) were carried out using USP Paddle Type II apparatus (Paddle method). The dissolution medium used was 1% Sodium Lauryl Sulphate [9] 900 ml, maintained at 37±0.5 ^{0}C and paddles rotated at 75 rpm. 10 ml of samples were withdrawn every 10 minutes, filtered through a membrane filter (pore size 0.45 µm) and analyzed at 256 nm for Oxcarbazepine. Similarly, the pure drug (150 mg) and the PM were subjected to *in vitro* drug release studies and the release profile was compared with selected formulation.

2.5 Accelerated stability studies for solid dispersions

Accelerated stability studies were performed according to ICH guidelines at 40 ^{0}C±2 ^{0}C, 75±5% RH for a 6 months period. Solid dispersions were removed at the end of three and six months and evaluated for drug release. A paired 't' test was applied to solid dispersion dissolution studies initial and after 6 months results, in order to study the effect of storage on the solid dispersion.

2.6 Comparison of oral absorption between Oxcarbazepine pure drug and solid dispersions

The *in vivo* absorption studies of pure Oxcarbazepine and solid dispersions were carried out using male Wistar rats (250-300 g). The animals were fasted for 12 hours prior to commencement of the study as well as during the study and had access to water *ad libitum*. The institutional animal ethical clearance was obtained from (**Reg. No. CPCSEA/MRCP/ 2008/1217**) before conducting the studies. Animals were divided into three groups (six in each group); Control group, Pure drug, Solid dispersion. The plasma concentration of the drug was determined by High Performance Liquid Chromatography (HPLC) [10].

2.7 Pharmacokinetic Studies

The animals were fasted overnight (water given ad libitum) and then given a drug (10 mg/Kg) Oxcarbazepine [10] and Oxcarbazepine solid dispersion [11] suspended in 1% solution of carboxymethyl cellulose. Blood samples were collected through the lateral tail vein of rats before dosing and at 10, 20, 30 minutes, followed by 1, 1.5, 2, 3, 4, 6 and 24 hours after dosing. The blood samples were centrifuged at 3000 rpm for 10 mins and 100 µl of plasma samples were stored at -20 ^{0}C until analysis. The results obtained were analyzed for various non-compartmental pharmacokinetic parameters using PK functions.

HPLC Analysis

The HPLC system consisted of a system controller (M-721), a data module (M-730), a solvent delivery pump (M-501), an auto sampler (WISP-712) and a variable wavelength U.V. detector (M-481). Chromatographic separations were performed using a symmetry C_{18} stainless steel column (150 × 3.9 mm i.d., 5 µm). A mobile phase consisting of 0.01 M potassium phosphate–acetonitrile–methanol (70:20:10% v/v/v) at a pH adjusted to 6.7 was used using a flow rate of 1.3 ml/min and monitored at 214 nm with a sensitivity of 0.01 absorbance units full scale (AUFS) and a chart speed of 0.5 cm/min

Statistical analysis

Results are expressed as mean ± S.D. ANOVA was used to test the statistical significance of

Differences among groups. Statistical significance in the differences of the means was determined by Dunnett Post Hoc test for multiple comparison.

3. Results

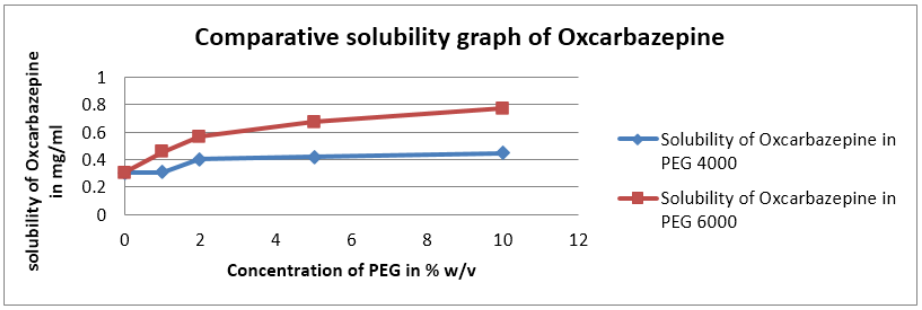

Fig 1: Effect of PEG on the solubility of Oxcarbazepine

The results of the phase solubility as seen from Figure 1 revealed that PEG 6000 has a more pronounced effect on increasing the solubility of Oxcarbazepine as compared to PEG 4000. The aqueous solubility of Oxcarbazepine was found to be 0.30 mg/ ml. The solubility of the drug was increased up to 35 fold in 10% w/v PEG 6000 aqueous solution at 25 °C as compared to pure drug. This may be attributed to more number of ether linkages in case of PEG 6000 and hence greater solubility.

The infrared spectra of the solid dispersions are shown in Figure 2 together with those for Oxcarbazepine alone and PEG 6000 alone as references.

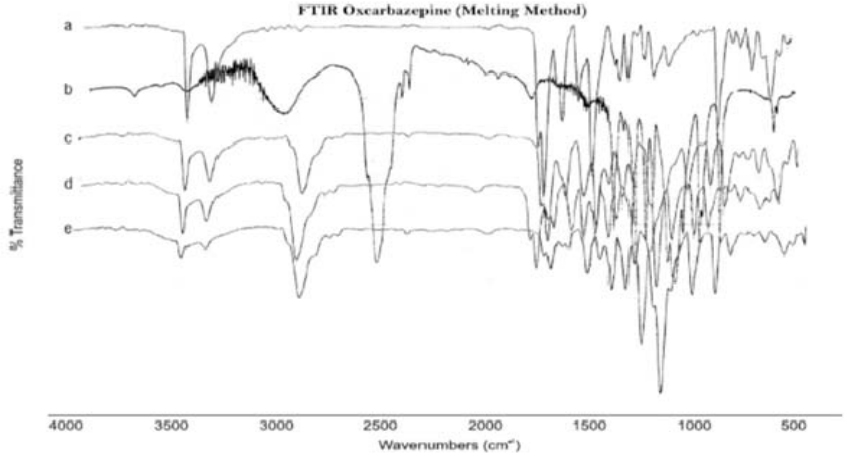

Fig 2: FTIR Curves a) Pure Drug Oxcarbazepine b) PEG c) SD1 d) SD2 e) SD3

As seen from Figure 2, the spectrum of Oxcarbazepine is characterized by the presence of a strong absorption band at 3451 cm^{-1}, 3318 cm^{-1} and 3267 cm^{-1}, which are all indicative of amines (-NH- group). The carbonyl-stretching mode appears as a very strong doublet at 1600 cm^{-1} (C=O stretching) and at 800 cm^{-1}, which was indicative of the presence of aromatic rings. The spectra of PEG 6000 are characterized by the C-H stretching vibrations at 2883 cm^{-1} and C-O (ether) stretching at 1105 cm^{-1}. The careful observation of the IR spectra reveals that all the major peaks of the pure drug and PEG 6000 appear with negligible variation in the IR spectrum of the solid dispersion, indicating that there is no chemical interaction between the drug and polymer.

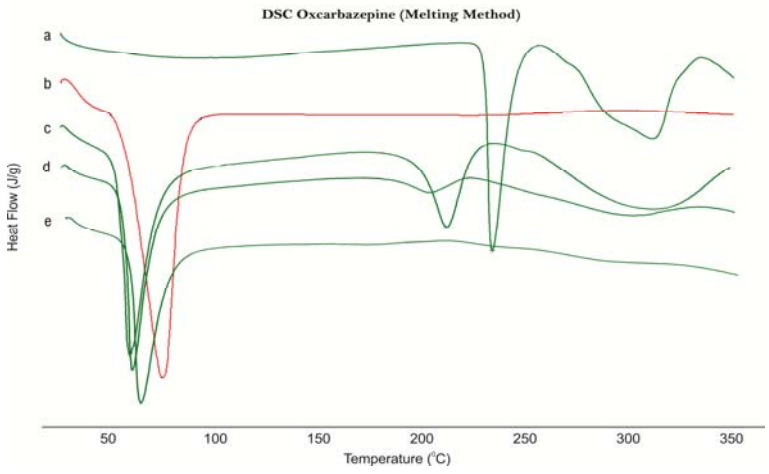

Fig 3: DSC Thermogram a) Pure Drug Oxcarbazepine b) PEG c) SD1 d) SD2 e) SD3

The DSC curve of pure drug Oxcarbazepine shows an endothermic peak at 224.76 ^{0}C indicating that it has a sharp melting point, whereas PEG 6000 displays a peak at 74.79 ^{0}C (Figure 3). In the melting method both the drug as well as the polymer shows a slight shift and broadening in the peaks indicating amorphization of the drug in the polymer [12] which may be helpful in increasing the solubility of pure drug in the formulation [12].

The solid state crystallinity of Oxcarbazepine, PEG 6000 & formulations prepared by melting method were studied by PXRD technique illustrated in Figure 4.

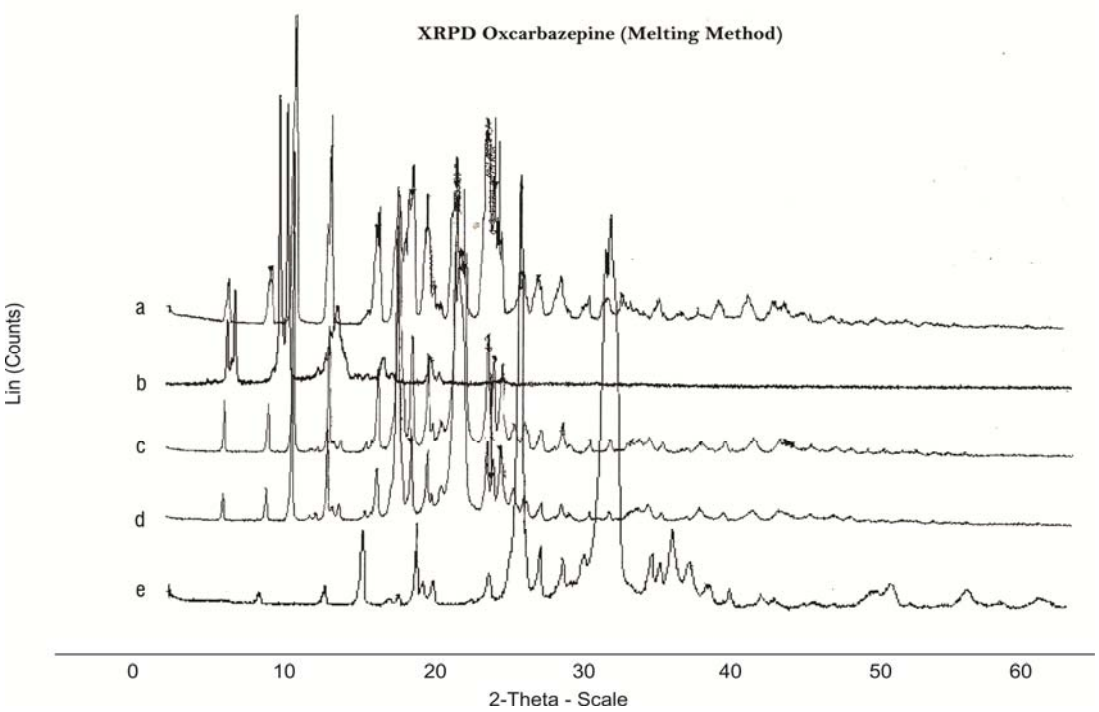

Fig 4: PXRD a) Pure Drug Oxcarbazepine b) PEG c) SD1 d) SD2 e) SD3

The reduction in crystallinity of Oxcarbazepine in the formulations was observed and it was also noted that the crystallinity was decreased with increase in concentration of PEG 6000 (1:1, 1:2, 1:5).

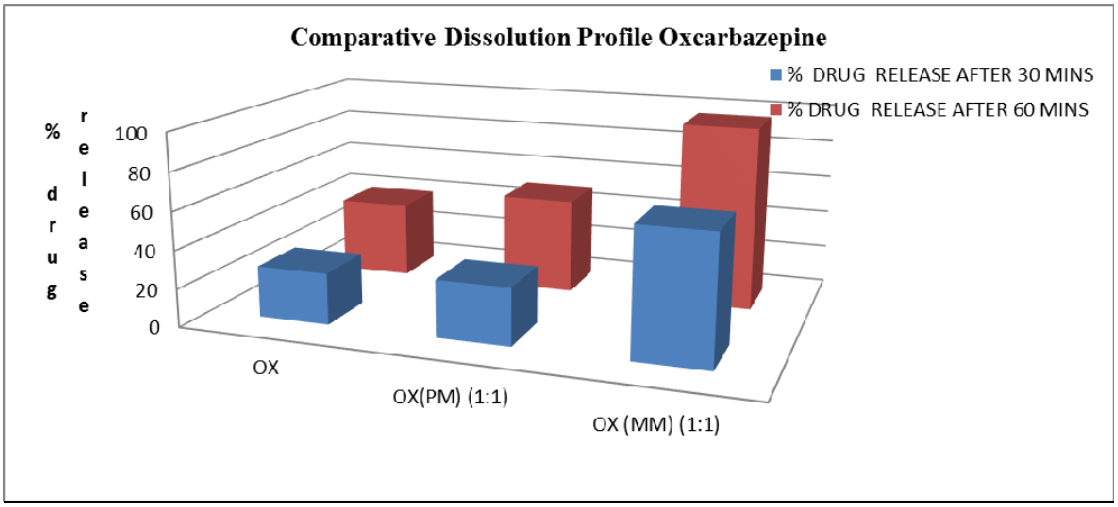

Fig 5: Comparative Dissolution Profile Oxcarbazepine

LM- Oxcarbazepine Pure drug; PM- Physical Mixture; SE- Solvent Evaporation Method; MM – Melting Method.

From Figure 5, it is evident that the dissolution rate of Oxcarbazepine has improved in the case of solid dispersion and the best dissolution profile was obtained when the drug and the carrier were combined in 1:1 ratio in the melting method. Solid dispersions and physical mixtures prepared in 1:2 and 1:5 ratio did not give a comparable release profile.

Table 2: *In vitro* cumulative % drug release at 40 ± 2 ^{0}C, 75 ± 5% RH for Oxcarbazepine

Time In Minutes	Cumulative Percentage Drug Release		
	Initial N=3, EAN±S.D.	After 3 Months N=3, Mean±S.D.	After 6 Months N=3, Mean±S.D.
4	72.64 ± 0.4	72.44 ± 0.5	72.82 ± 0.33
8	82 ± 0.3	83 ± 0.5	82 ± 0.4
12	85 ± 0.3	85.5 ± 0.7	85.23 ± 0.5
16	92.72 ± 0.3	92.62 ± 0.8	93.47 ± 0.4
20	98.72 ± 0.3	98.62 ± 0.8	98.47 ± 0.4

Accelerated stability studies dissolution data when subjected to paired 't' test shows that the effect of storage was insignificant at 5% level of F {t stat (0.0128) < t critical (2.3060)} and it can be conclusively stated that the dissolution studies show compliance with the ICH guidelines demonstrating shelf life through curve fitting at 95% confidence limit.

Table 3: Pharmacokinetic parameters of solid dispersions of Oxcarbazepine

Pharmacokinetic Parameters	Pure drug	Solid dispersion (SD1)
Peak plasma concentration C_{max} (µg/ml)	80.44	200.87
Time to reach peak plasma concentration T_{max}(hr)	1.5 hrs	0.5 hrs
Biological half lifet $^{1/2}$(hr)	24.54	24.55
Elimination rate constant Ke (hr^{-1})	0.0282	0.028
Area under the curve AUC $_{(0-t)}$ (Total) (µg/ml* hr)	251.45	740

The average peak plasma concentration obtained from the drug and solid dispersion, indicated an increase in the extent of absorption (AUC_{0-t}). The decrease in the t_{max} values indicated faster absorption from the solid dispersions and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug.

ANOVA followed by Post Hoc Dunnett t3 test indicated that prepared solid dispersion and the pure drug showed a significant difference in their pharmacokinetic profiles. This difference may be attributed to better dissolution rate of Oxcarbazepine from its solid dispersion.

4. Conclusion

Solid dispersions prepared from hydrophilic polymers using the melting technique were effective in improving drug dissolution. The above studies indicated that PEG 6000 inhibited the crystallization of drugs, resulting in the amorphous state form of the drug in solid dispersion. Accelerated stability studies of solid dispersion show compliance with the ICH guidelines demonstrating shelf life through curve fitting at 95% confidence limit. Prepared solid dispersion and the pure drug showed a significant difference in their pharmacokinetic profiles which may be attributed to better dissolution rate of Oxcarbazepine from its solid dispersion. Thus the solid dispersion technique with PEG 6000 as a carrier provides a promising way to enhance the solubility and dissolution rate of Oxcarbazepine.

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