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Original Article

IN VITRO-IN VIVO EVALUATION OF FAST-DISSOLVING TABLETS CONTAINING SOLID DISPERSION OF OXCARBAZEPINE

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ABSTRACT

Objective: Investigation of *in vitro*/*in vivo* behaviour of fast-dissolving tablets containing solid dispersions of oxcarbazepine is the focus of the present research work.

Methods: The effect of various hydrophilic polymers on the aqueous solubility of oxcarbazepine was studied. Polyethylene glycol 6000 carrier was selected and solid dispersions were prepared by various methods. A total of nine formulations were compressed into fast-dissolving tablets using avicel PH 102 as a directly compressible filler and ac-di-sol, sodium starch glycolate and crospovidone as super disintegrants and evaluated for pre and post compression parameters and *in vitro* drug release. *In vivo* studies of the pure drug, optimized formulation and marketed formulation were carried out on male Wistar rats and pharmacokinetic parameters were calculated using the pk function for Microsoft excel.

Results: Mathematical analysis of *in vitro* data suggested that the first order was the most suitable mathematical model for describing the optimized formulation. The first-order plot was found to be fairly linear for optimized formulation as indicated by its high regression value. Stability studies indicated that the effect of storage was insignificant at 5% level of confidence. The optimized formulation has shown T_{max} of 0.5 h, which was highly significant ($P<0.05$) when compared with pure drug and marketed formulation.

Conclusion: Therefore, the solid dispersions prepared by melting method using polyethylene glycol 6000 as hydrophilic carrier can be successfully used for the improvement of dissolution of oxcarbazepine and resulted in faster onset of action as indicated by *in vitro* and *in vivo* studies.

Keywords: Dissolution profile, Hydrophilic carrier, Melting method, Solubility, Solid dispersion

INTRODUCTION

Oxcarbazepine is an antiepileptic and mood stabilizing drug, used primarily in the treatment of epilepsy and bipolar disorder. Oxcarbazepine is 10, 11–dihydro-10–oxo-5H-dibenz (b, f) azepine-5-carboxamide, [1] structural derivative of carbamazepine, [2] adding extra oxygen to dibenzepine ring.

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/d (dose/solubility ratio ≥250ml; class II drug according to the BCS). Peak plasma concentrations occur anywhere from 1 to 2 h 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/l. This may result in the delayed onset of action because of sub-therapeutic plasma drug levels and may also lead to therapeutic failure.

Hence there is an urgent need to increase the aqueous solubility of the drug. Solid dispersions [3, 4] refer to a system in which hydrophobic drug is dispersed in a hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In solid dispersion, a drug can exist in an amorphous or crystalline form in hydrophilic polymeric carriers [5, 6] such as polyethylene glycols, polyvinyl pyrrolidone K30 and urea etc. which results in improved solubility and dissolution rates.

The objective of the present research work was to formulate fast dissolving tablet of oxcarbazepine using a solid dispersion method in order to improve its aqueous solubility.

For this two hydrophilic carriers were evaluated to determine their effect on the solubility of oxcarbazepine; different methods were then evaluated to select the best method of preparation of solid dispersions and the solid dispersion was formulated into fast-dissolving tablets and effect of formulation on the T_{max} of oxcarbazepine was studied.

Oxcarbazepine is having low solubility many techniques have been tried in the past in order to improve its solubility and dissolution. According to the method developed by the authors in the above text direct compression was used for the preparation of fast dissolving tablets which is superior to wet granulation technique used earlier due to convenience in processing and three different methods evaluated for the formulation of solid dispersions as compared to previously reported works. According to previously reported literature superdisintegrant method used in the above text was found to be superior to the other methods of improving the dissolution of poorly soluble drugs.

MATERIALS AND METHODS

Materials

Oxcarbazepine was a gift sample from Jubiliant Organosis Ltd (U. P, India) and polyethylene glycol 6000, polyethylene glycol 4000 and polyvinyl pyrrolidone K30 were purchased from Oxford laboratory (Mumbai, India). All other chemicals and reagents used were of analytical grade. In order to conduct *in vivo* studies the institutional animal ethical clearance (vide letter no. CPCSEA/MRCP/1217/2008/) was obtained before conducting the studies. The results obtained were analyzed for various non-compartmental pharmacokinetic parameters using pk functions of Microsoft excel. Furthermore, the pharmacokinetic data were analyzed statistically [7] by one way ANOVA ($P<0.05$) followed by Dunnett post hoc test for multiple comparisons.

Screening of appropriate carrier for oxcarbazepine solid dispersion using solubility studies

Solubility measurements were performed according to the method reported by Higuchi and Connors [8]. Both polyethylene glycol 4000 and polyethylene glycol 6000 were assessed for solubility enhancement. Various (1%, 2%, 5% and 10% w/v) aqueous solutions of polyethylene glycol 4000 and polyethylene glycol 6000 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 h in a thermostatically controlled water bath at 37±0.1 °C. After 48 h, samples were

analyzed at 256 nm for oxcarbazepine. Solubility studies were performed in triplicate (n=3).

Preparation of physical mixtures and solid dispersions

For oxcarbazepine solid dispersions were prepared by three different methods viz. kneading method, melting method and solvent evaporation method in three different ratios by using polyvinyl pyrrolidone K30 and polyethylene glycol 6000 as hydrophilic carriers as shown in table 1.

Kneading method [9]

A mixture of oxcarbazepine and polyvinyl pyrrolidone K30 was wetted with water and kneaded thoroughly for 30 min, the paste formed was dried under vacuum for 24 h. Dried powder was passed through sieve no.60.

Melting method [10]

Polyethylene glycol 6000 was melted in a beaker on a water bath maintained at 50-60 °C. The required amount of oxcarbazepine was then added to melted polyethylene glycol 6000 and mixed thoroughly for 5 min. The molten mixture was cooled rapidly by placing it in an ice bath for about 5 min and solidified. The hardened mixture was powdered, sieved through an 80-mesh screen.

Solvent evaporation method [11]

Accurately weighed the quantity of polyethylene glycol 6000 was dissolved in 10 ml of acetone. To these solutions, accurately weighed quantities of oxcarbazepine was added and allowed to dissolve. The solution was transferred to a petri dish and the solvent was allowed to evaporate at room temperature for 1 h and then was kept in a desiccator for 48 h.

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

Code	Quantity of drug	Quantity of carrier	Ratio (Drug: carrier)
SD1	150 mg	150 mg	(1:1)
SD2	150 mg	300 mg	(1:2)
SD3	150 mg	750 mg	(1:5)

Evaluation of solid dispersions [8]

Fourier transforms infrared spectroscopy (FTIR)

Fourier transform infrared spectra were obtained by potassium bromide (KBr) disc method using Shimadzu FTIR-8700 spectrophotometer (Tokyo, Japan). The scanning range was 40 to 4000/cm and the resolution was 4/cm.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using DSC (SISI Nanothec) on 6.5-10 mg samples of pure oxcarbazepine, polyethylene glycol and oxcarbazepine-polyethylene glycol 6000 solid dispersions. Samples were heated in an open aluminium pan at a constant rate of 20 °C/min over a temperature range 20 °C to 350 °C under nitrogen purge (10 ml/min).

Powder x-ray diffraction

The powder x-ray diffraction patterns were determined for oxcarbazepine, polyethylene glycol and oxcarbazepine–polyethylene glycol 6000 solid dispersions using x-ray diffractometer (Bruker, Germany, D8 advance) ceramic x-ray, cu anode, voltage 2.2 KV, Detector-lynx eye detector (silicon strip detector technology). The scanning rate was 1 °/min over a 2 θ range of 1-50 °C.

***In vitro* dissolution**

The *in vitro* dissolution for the solid dispersions (equivalent to 150 mg of the oxcarbazepine) was carried out using USP Paddle type II apparatus (Paddle method). The dissolution medium used was 1% sodium lauryl sulphate [12] 900 ml, maintained at 37±0.5 °C and paddles rotated at 75 rpm. 10 ml of sample was withdrawn every 10 min, 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 physical mixture were subjected to *in vitro* drug release studies and their release profiles were compared.

Preparation of oxcarbazepine fast dissolving tablets

The solid dispersion (SD1) having the maximum solubility and dissolution rate was selected for the preparation of fast dissolving tablets according to the formula and 150 mg oxcarbazepine equivalent was incorporated into each tablet. All the ingredients (except magnesium stearate) were mixed homogeneously and co ground in a mortar and pestle. Finally, magnesium stearate was added and mixed for 5 min and the powder blend was evaluated for flow properties such as tapped density, bulk density, Hausner's ratio, compressibility index and angle of repose. The mixed blend of drug and excipients was compressed using cadmach 16 station tablet punching machine using 10 mm punches to produce flat faced tablets weighing 400 mg each for oxcarbazepine as shown in table 2.

Table 2: Formulation of fast dissolving tablets of oxcarbazepine

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Amount of complex equivalent to 150 mg of Oxcarbazepine (1:1)	300	300	300	300	300	300	300	300	300
2	Mannitol	58	50	46	58	50	46	58	50	46
3	Ac-di-sol	12	4	0	12	4	0	12	4	0
4	Sodium starch glycolate	0	24	16	0	24	16	0	24	16
5	Crosspovidone	8	0	16	8	0	16	8	0	16
6	Magnesium stearate	4	2	3	2	3	4	3	4	2
7	Aerosol	2	4	3	4	3	2	3	2	4
8	Aspartame	16	16	16	16	16	16	16	16	16

Evaluation of prepared tablets

The tablet hardness [13] and friability [14] were determined using monsanto tablet hardness tester and friabilator (Roche), respectively. The disintegration time [15] was measured by using tablet disintegrator (Electrolab, India). Wetting time [16] was determined by well-reported method. A tissue paper was folded double and placed in a petri dish (internal diameter 10 cm) containing 10 ml of eosin dye solution. The tablet was carefully placed on the surface of tissue paper. The time required for the tablet to get colored completely red was noted as wetting time. Tablets were also evaluated for parameters such as weight variation [17], content uniformity [18] and water absorption ratio [19].

***In vitro* release studies of oxcarbazepine tablet**

The release rate of tablets containing a solid dispersion of oxcarbazepine (SD1) and marketed formulation (containing

equivalent of 150 mg of the oxcarbazepine) (n=6) was determined using USP Type II apparatus (Paddle method). The dissolution medium used was 900 ml of 1% sodium lauryl sulphate maintained at 37±0.5 °C and paddles rotated at 75 rpm. 10 ml of sample was withdrawn after every 1 min, filtered through a membrane filter (pore size 0.45 µm) and analyzed at 256 nm for oxcarbazepine.

Mathematical analysis of *in vitro* data

The data obtained from *in vitro* release studies were analyzed by the curve fitting method to various models viz., zero, first-order kinetics, Higuchi and Korsmeyer-peppas model [20]. In order to evaluate the similarity between the optimized formulation and marketed formulation, the *in vitro* dissolution profiles of both were compared [21].

***In vivo* studies**

The bioavailability studies for pure oxcarbazepine, tablets with solid dispersion of oxcarbazepine (F4), and marketed formulation (Oleptal DT^{R}) were carried out using male wistar rats (200-250 g). The animals were maintained in a clean room at a temperature between 20-25 °C with 12-hour light and dark cycles and controlled relative humidity. The animals were fasted for 12 h prior to the commencement of the study as well as during the study and had access to water *ad libitum*. The institutional animal ethical clearance (vide letter no. CPCSEA/MRCP/1217/2008/) was obtained before conducting the studies. They were divided into four groups (six in each group); group I served as a control group, whereas other three groups were treated with pure drug oxcarbazepine suspended in 1% solution of carboxy methyl cellulose [19], marketed formulation and tablets with solid dispersion of oxcarbazepine (F4) respectively. Tablets with a dose of 30 mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe [22].

Blood samples were collected from the lateral tail vein [23] of rats at 10, 20, 30 min, followed by 1, 1.5, 2, 3, 4, 6 and 24 h after administration. The blood samples were centrifuged at 3000 rpm for 10 min and 100 µl of plasma samples were stored at-20 °C until analysis. The plasma concentration of the drug was determined by high performance liquid chromatography. The high performance liquid chromatography system consisted of a system controller (M-721), a data module (M-730), a solvent delivery pump (M-501), an autosampler (WISP-712) and a variable wavelength U. V. detector (M-481) using a symmetry C_{18} stainless steel column (150 × 3.9 mm i.d., 5 µm) and 0.01 M potassium phosphate–acetonitrile–methanol (70:20:10% v/v/v) (PH 6.7) using a flow rate of 1.3 ml/min as a mobile phase at 214 nm.

The results obtained were analyzed for various non-compartmental pharmacokinetic parameters using pk functions. Furthermore, the pharmacokinetic data were analyzed statistically [24] by one way ANOVA followed by Dunnett post hoc test for multiple comparisons.

Stability studies

Accelerated stability studies [25] were carried out for optimized formulation (F4) as per ICH guidelines. The optimized formulation (F4) was sealed in high density polyethylene bottles and stored at 40±2 °C/75±5 % relative humidity for 6 mo period. Samples were withdrawn at the end of three and six mo and evaluated for *in vitro* drug release pattern, hardness and disintegration time. A paired test was applied to tablet dissolution initially and after 6 mo results, in order to study the effect of storage.

RESULTS AND DISCUSSION

Screening of appropriate carrier for oxcarbazepine solid dispersion

Preliminary solubility analysis was carried out to screen the most appropriate carriers wherein polyethylene glycol 4000 and polyethylene glycol 6000 were used. The results of the phase solubility revealed that both polyethylene glycol 4000 and polyethylene glycol 6000 enhance the solubility of oxcarbazepine significantly. More pronounced and linear results were obtained for solubility analysis from polyethylene glycol 6000 and hence it was selected as the carrier for the preparation of solid dispersion of oxcarbazepine (fig. 1).

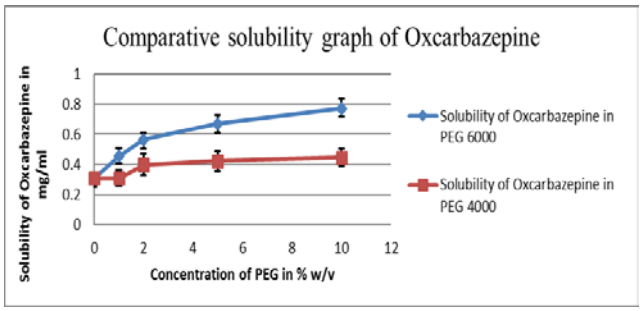

Fig. 1: Effect of carriers on the solubility of pure oxcarbazepine, mean±SD, n=3

Preparation of solid dispersions

For oxcarbazepine solid dispersions were prepared by three different methods viz. kneading method, melting method and solvent evaporation method in three different ratios by using polyvinyl pyrrolidone K30 for the kneading method and polyethylene glycol 6000 as hydrophilic carriers for both melting method and solvent evaporation method as shown in table 1.

The physical observation of solid dispersion prepared by both melting method and solvent evaporation method indicated that the solid dispersion prepared by melting method and solvent evaporation was free flowing in nature, whereas the solid dispersion prepared by kneading method was sticky in nature and not used for further studies and hence, it was concluded that polyethylene glycol was the most suitable polymeric carrier.

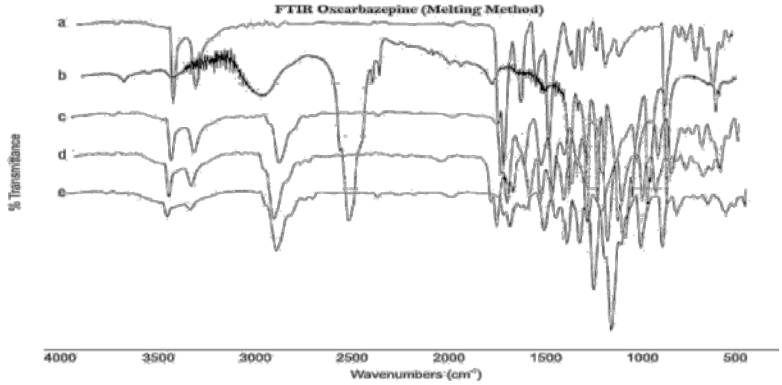

Fig. 2: FTIR curves melting method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

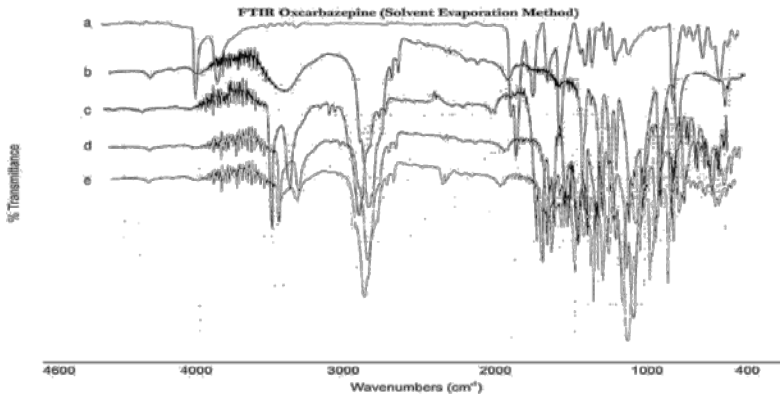

Fig. 3: FTIR curves solvent evaporation method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

Evaluation of solid dispersions

Fourier transform infrared spectroscopy

The spectrum of the oxcarbazepine is characterized by the presence of a strong absorption band at 3344 cm^{-1} and 3466 cm^{-1} which are all indicative of amines (-NH-group). The carbonyl-stretching mode appears as a very strong doublet at 1685 cm^{-1} and 1654 cm^{-1} (C=O stretching) and at 1563 cm^{-1} and 1481 cm^{-1} which were indicative of the presence of aromatic rings. All the characteristic peaks of the drug and polymer appear in the spectra of solid dispersion of oxcarbazepine (prepared by melting and solvent evaporation method) indicating no interaction between the drug and carrier. (fig. 2 and 3).

Differential scanning calorimetry

The thermogram of solid dispersions showed a shift in the endothermic peaks of both drugs as well as polymer. This data suggests the complete amorphization of drug in the polymer which may be helpful in increasing the solubility of pure drug in the formulation (fig. 4 and 5).

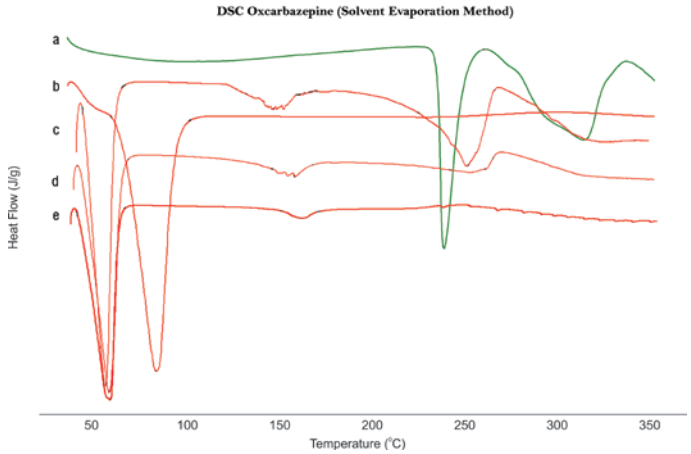

Fig. 4: DSC Thermogram melting method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

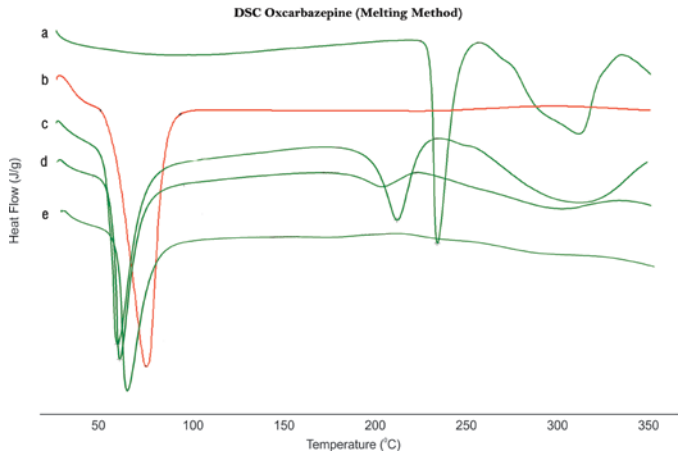

Fig. 5: DSC Thermogram solvent evaporation method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

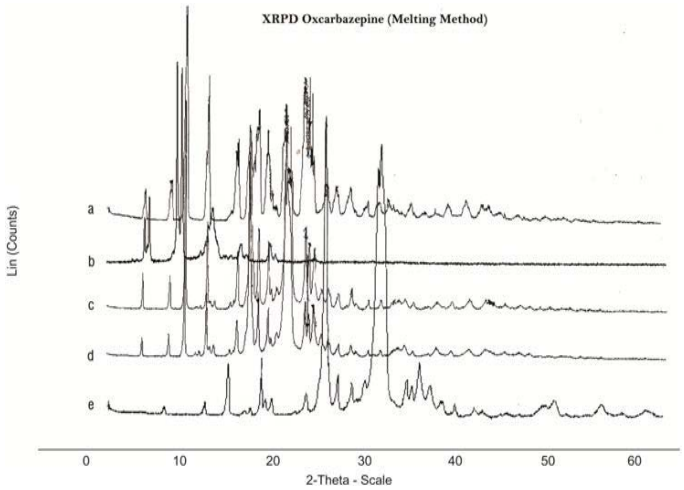

Fig. 6: PXRD melting method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

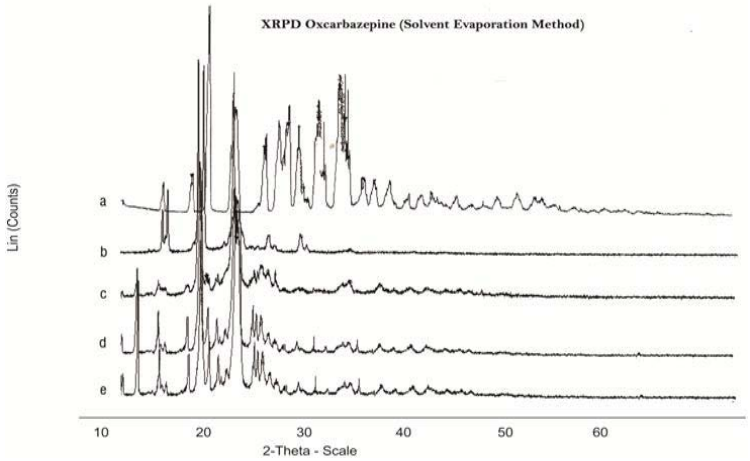

Fig. 7: PXRD Solvent evaporation method a) Pure drug oxcarbazepine b) Polyethylene glycol c) SD 1:1 d) SD 1:2 e) SD 1:5

X-ray powder diffraction

The diffraction pattern of the solid dispersions was simply the superimposition of those of the pure components. In case of solid dispersions, there was a reduction in the intensities of the drug peaks indicating the formation of amorphous compound (fig. 6 and 7).

Dissolution rate studies

The dissolution profiles of pure oxcarbazepine, physical mixture and solid dispersions (prepared by melting and solvent evaporation method) in (1:1) ratio are shown in (fig. 8). Oxcarbazepine has shown the release of 40.03±1.38 % after 1 h reflecting its low solubility. Oxcarbazepine when combined with polyethylene glycol 6000 in 1:2 or 1:5 ratio did not give a satisfactory drug release. It was also observed that the release profile of solid dispersion was dependent on the method of preparation. The dissolution from the physical mixture showed an improved drug release profile of 50.16±1.79 %, whereas in the solid dispersions, 78.94±2.55 % and 96.23±3.05 % for formulations (1:1) prepared by solvent evaporation and melting method, respectively, were observed. This enhancement of dissolution of oxcarbazepine from solid dispersion may be due to several factors. The presence of amorphous nature increased wettability and dispersibility, and particle size reduction are the important factors for dissolution rate enhancement. Moreover, other factors such as absence of aggregation and/or re-agglomeration phenomenon during dissolution and particle size reduction could be attributed to the better dissolution profile. Based on the drug release profile, the solid dispersion SD1 containing oxcarbazepine and polyethylene glycol 6000 in 1:1 ratio prepared by melting method was selected for the formulation of fast dissolving tablets.

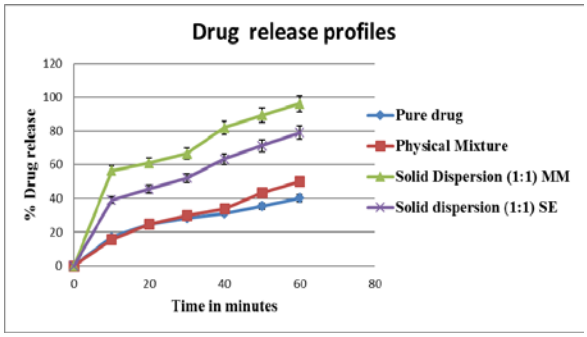

Fig. 8: Drug release profile of oxcarbazepine, physical mixture, solid dispersion prepared by solvent evaporation method (SE) and melting method (MM), mean±SD, n=3

Preparation and Evaluation of pre compression parameters

The pre compression characteristics of all the nine formulations of oxcarbazepine were evaluated for flow properties such as tapped density, bulk density, Hausner's ratio, compressibility index and angle of repose as shown in table 3.

Table 3: Powder characteristics of oxcarbazepine

Formulation	Tapped density g/cm³ (t) [a]	Bulk density g/cm³ (b) [a]	Hausner's Ratio h=t/b[a]	Carr's index c= 100 * (1-1/h) [a]	Angle of repose (θ) tan⁻¹=h/r. [a]
F1	0.45±0.02	0.40±0.02	1.13±0.01	12±0.03	29±1
F2	0.47±0.03	0.41±0.01	1.15±0.03	13±0.02	30±3
F3	0.47±0.01	0.40±0.02	1.18±0.01	15±0.02	27±2
F4	0.41±0.02	0.37±0.01	1.11±0.05	10±0.04	28±2
F5	0.47±0.01	0.42±0.02	1.12±0.01	11±0.05	26±3
F6	0.44±0.02	0.39±0.01	1.13±0.01	12±0.04	29±2
F7	0.46±0.02	0.36±0.02	1.28±0.04	22±0.02	32±4
F8	0.48±0.01	0.32±0.01	1.50±0.01	33±0.01	33±1
F9	0.49±0.01	0.31±0.01	1.58±0.01	37±0.01	34±1

[a]mean±SD, n=3

The pre compression characteristics of all the nine formulations of oxcarbazepine indicated that the tapped density, bulk density, Hausner's ratio, compressibility index and angle of repose for all the formulations was within the acceptable range barring F8 and F9 which did not give good results.

Evaluation of post compression parameters

All the tablet parameters were measured six times and the mean reported with standard deviations. The prepared tablets were spherical and white in colour. The mean weight, content uniformity and friability of all the 9 formulations were within the acceptable range. The hardness range for the fast dissolving tablets should be between 2-4 kg/cm² and friability readings should be below 1%. Fast dissolving tablets are required to disintegrate within 2 min. The wetting time for the tablets is used as an indicator of the ease of tablet dissolution in the buccal cavity. Hydrophobicity of the compound, as well as the inner composition of the tablet has an effect on the wetting time of the tablet as shown in table 4.

Table 4: Evaluation of oxcarbazepine tablets

S. No.	Weight variation (mgs) [a]	Content uniformity (%) [a]	Hardness (kg/cm²)[a]	Friability (%) [a]	Disintegration time (s) [a]	Wetting time (s)[a]	Water absorption Ratio [a]
F1	400±0.3	98.21±.31	2.5±0.1	0.84±0.02	16.37±0.5	46.54±1.00	43.49±0.4
F2	400±0.2	97.26±2.68	2.5±0.1	0.82±0.01	17.28±0.4	50.01±2.11	42.17±0.5
F3	400±0.1	99.47±1.45	2.5±0.0	0.83±0.03	18.45±0.1	47.66±2.51	43.62±0.5
F4	400±0.5	96.37±1.76	2.5±0.0	0.84±0.03	16.45±0.4	48.42±.51	44.15±0.3
F5	400±0.7	96.11±2.55	2.5±0.1	0.85±0.02	16.38±0.6	49.99±.28	43.56±0.4
F6	400±0.8	95.54±3.01	2.5±0.0	0.88±0.02	16.34±0.4	50.66±2.51	42.91±0.5
F7	400±0.1	97.36±1.65	2.5±0.1	0.83±0.03	17.63±0.4	48.98±2.43	43.75±0.3
F8	400±0.6	98.52±1.99	2.5±0.0	0.84±0.04	18.21±0.2	49.96±2.33	44.24±0.5
F9	400±0.3	99.1±0.1	2.5±0.1	0.85±0.04	16.30±0.2	48.87±2.11	43.62±0.5

[a]mean±SD, n=3, The post compression parameters of the tablets were also found to be acceptable and satisfactory.

Dissolution studies of prepared formulation

From the dissolution analysis, it was clear that optimized formulation (F4) showed an enhanced dissolution rate as compared to pure oxcarbazepine and marketed formulation. The maximum % of drug release was observed with the formulation F4 containing ac-di-sol and crospovidone combination for oxcarbazepine. The increase in dissolution from formulation containing ac-di-sol and crospovidone may be due to the wetting and solubilizing effect of these superdisintegrants which could reduce the interfacial tension between oxcarbazepine and the dissolution medium. Percent of drug released from optimized formulation and marketed formulation have followed similar pattern and they are very close to each other in our study.

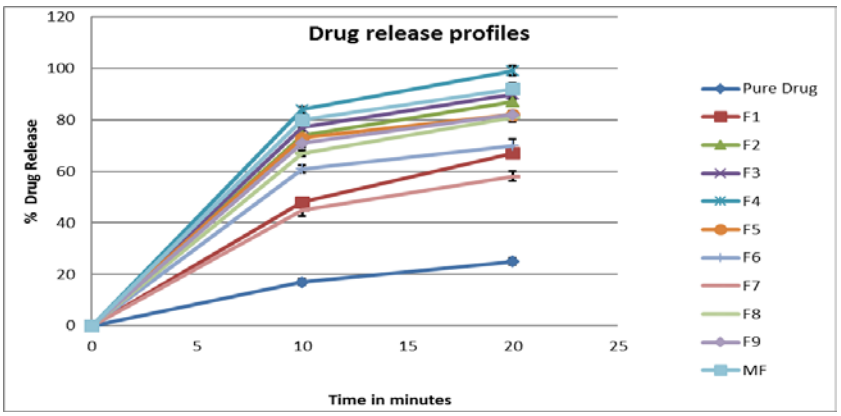

Fig. 9: The drug release profiles of oxcarbazepine pure drug, oxcarbazepine all formulations and marketed formulation, mean±SD, n=3

Mathematical analysis of *in vitro* dissolution of prepared formulations

The first-order plots were found to be fairly linear for optimized formulation as indicated by their high regression values. Korsmeyer peppas "n" values less than 0.5 for all the formulations suggest that the release of oxcarbazepine from fast dissolving tablets followed fickian diffusion mechanism.

***In vivo* studies for oxcarbazepine**

The linear regression analysis of oxcarbazepine was constructed by plotting the peak–area ratio of drug versus analyte concentration in spiked plasma samples. The average regression equation and correlation coefficients were calculated. r^2 = 0.999 for oxcarbazepine showed a good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 **µ**g/ml for determination of oxcarbazepine in plasma. The limit had been sufficient for pharmacokinetic studies of the oxcarbazepine. From the pharmacokinetic analysis, it can be concluded that the *in vivo* studies mimic the *in vitro* results. The average peak plasma concentration obtained from the optimized and marketed formulation indicated an increase in the extent of absorption (AUC_{0-t}). Optimized and marketed formulation showed C_{max} values of 135.45±2.63 µg/ml and 130.45±2.68 µg/ml respectively. A difference of almost half an hour was observed between the T_{max} values of pure drug and optimized or marketed formulation. (fig. 10), **(**table 5).

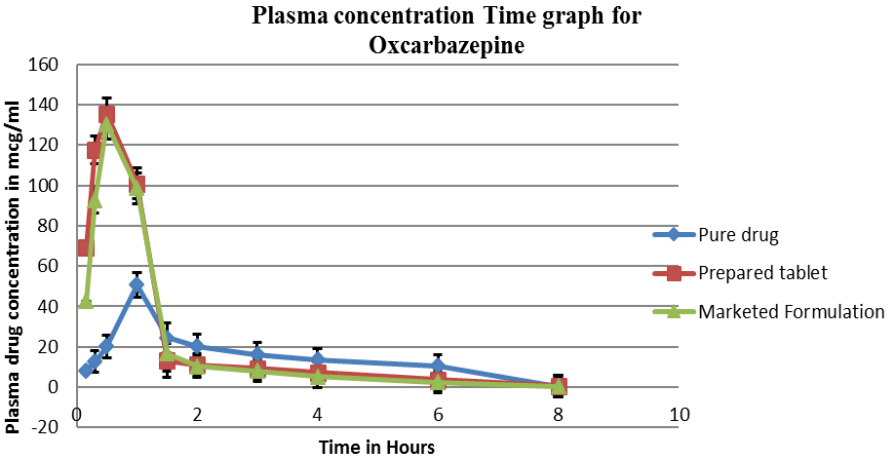

Fig. 10: The plasma concentration time graph for pure drug, optimized formulation (F4) and marketed formulation, mean±SD, n=3

Table 5: Pharmacokinetic parameters of pure drug, optimized formulation (F4) and marketed formulation

Pharmacokinetics parameters	Pure drug	Optimized formulation	Marketed formulation
Peak plasma concentration C_{max} (µg/ml)	50.73±2.45	135.45±2.63	130.45±2.68
Time to reach peak plasma concentration T_{max} (h)	1±0.172	0.5±0.09	0.5±0.072
Biological half life t ½(h)	2.02±1.5	1.080±1.2	1.03±0.98
Elimination rate constant Ke (h^{-1})	0.3428±0.068	0.6412±0.033	0.6668±0.026
Area under the curve AUC (Total) (µg/ml h)	120.82±8.4	165.38±7.9	150.51±7.7

ANOVA followed by Dunnett post hoc t3 test for oxcarbazepine indicates that optimized formulation and the marketed formulation do not show a significant difference, whereas a significant difference is observed between optimized formulation and pure drug pharmacokinetic profiles. Mean area under the plasma concentration-time curve (AUC) for marketed formulation versus optimized formulation indicates that optimized formulation has similar bioavailability to the marketed formulation (Oleptal®). The higher values of pharmacokinetic parameters (AUC_0-t, C_{max}, Tmax, and $t_{1/2}$) show enhancement in bioavailability of a drug by formulating fast dissolving tablets. Thus, it was concluded that the optimized formulation is capable of delivering higher plasma concentrations of drug within a shorter span of time as compared to pure drug, although not much difference was seen between the optimized and marketed formulation.

Stability studies

Stability studies showed no remarkable changes in the physical properties of the tablets as well as no change in drug content and release profile. According to T test results F {t stat (-0.0366)<t critical (2.3060)} showing negligible effect of storage on the formulated tablet dissolution properties. Hence 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 as shown in table 6 and 7.

Table 6: Accelerated stability studies on oxcarbazepine

Parameters	Initial[a]	3 mo[a]	6 mo[a]
Wt of tab (mg)	400±0.2	400±0.1	400±0.1
Hardness (kg/cm^2)	2.6±0.1	2.5±0.1	2±0.03
Friability (%)	0.84±0.03	0.84±0.01	0.84±0.02
Wetting Time (s)	45±1	46±2	46±2.2
Content Uniformity (%)	98±0.1	97.9±0.1	97.8±0.1
Disintegration (s)	16±1	18±1	16±2

[a]mean±SD, n=3

Table 7: *In vitro* cumulative % drug release at 40±2 °C/75±5% relative humidity for oxcarbazepine

Time in mins	Cumulative percentage drug release		
	Initial[a]	After 3 mo[a]	After 6 mo[a]
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

[a]mean±SD, n=3

Oxcarbazepine is having low solubility many techniques have been tried in the past in order to improve its solubility and dissolution. Malke *et al.* prepared fast dissolving tablets of oxcarbazepine in the year 2007 using wet granulation technique and the prepared tablets reported a disintegration time of 28±5 secs [12]. According to the method developed by the authors in the above text direct compression was used for the preparation of fast dissolving tablets which is superior to wet granulation technique due to convenience in processing and tablets prepared using optimized formulation (F4) reported the disintegration time of 16.45±0.4 secs. Moreover, three different methods evaluated for the formulation of solid dispersions as compared to previously reported work of Kalia *et al.* in the year 2009 [26] wherein only one method was used for the preparation of solid dispersions. According to previously reported literature by Neduri *et al.* who studied different techniques to enhance the dissolution rate of poorly soluble drugs [27] superdisintegrant method used in the above text was found to be superior to the other methods in improving the dissolution of poorly soluble drugs [28].

CONCLUSION

Therefore, the solid dispersions prepared by melting method using polyethylene glycol 6000 as hydrophilic carrier can be successfully used for the improvement of dissolution of oxcarbazepine and resulted in faster onset of action as indicated by *in vivo* studies.

CONFLICTS OF INTERESTS

All authors have nothing to declare

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