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IMPROVEMENT IN BIOAVAILABILITY OF OXCARBAZEPINE USING SPHERICAL AGGLOMERATION

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Keywords:

Spherical agglomerates, Crystallo-co-agglomeration, Oxcarbazepine, Factorial design, Dissolution, Micromeritic properties

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ABSTRACT: Spherical agglomeration technique enables simultaneous crystallization and agglomeration. Oxcarbazepine spherical agglomerates were prepared by crystallo-co agglomeration technique. Acetone acted as a good solvent, aqueous solution of PEG 6000 served as a bad solvent, and dichloromethane was used as bridging liquid. The optimization was carried out using 2^3 factorial design, where the factors were rotation speed, polymer-drug ratio and amount of bridging liquid. The responses evaluated were % drug release, mean yield pressure (MYP), and carr's index. The optimized agglomerates and oxcarbazepine were evaluated by powder x-ray diffractometer (PXRD) and scanning electron microscopy (SEM). The agglomeration improved the micromeritic properties of oxcarbazepine. PXRD showed reduction in crystalline nature of oxcarbazepine, and SEM demonstrated a spherical and smooth surface. *In-vitro* dissolution increased by 10-fold. The AUC (35.19%), C_{max} (23%), and t_{max} (reduced by 1h) also recorded improvement. From the results, spherical agglomerates are a suitable method and can be used to design immediate-release formulations.

INTRODUCTION: Oxcarbazepine is an anticonvulsant medication primarily used in the treatment of epilepsy and as an add-on therapy for bipolar disorder. It is a BCS Class II drug, which means poor water-soluble drugs. Oxcarbazepine also has poor micrometric properties. Particle engineering techniques enable a formulator to improve dissolution as well as flow and compression characteristics of a substance. This improves therapeutic efficacy and makes it amenable to large scale manufacture of solid dosage forms. Spherical crystallization is one of the techniques of particle design.

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The spherical crystallization (SC) technique has shown promising results in the improvement of particle size, flowability, and compression characteristics of active pharmaceutical agents. A near-saturated solution of the drug in a good solvent is poured into a poor solvent. The poor and good solvents are freely miscible, and the affinity between the solvents is stronger than the affinity between drug and good solvent, leading to precipitation of crystals immediately. Under agitation, the bridging liquid (the wetting agent) is added, which is immiscible with the poor solvent and preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid adheres the crystals to one another resulting in the formation of larger size agglomerates [1-3].

The present work describes the formation of agglomerates of oxcarbazepine to enhance flow, compression, and dissolution properties. A 2^3

factorial design was employed where stirring speed, polymer-drug ratio, and volume of bridging liquid were optimized to achieve the agglomerates that will have required flow, compression, and drug release properties.

MATERIALS AND METHODS:

Materials: Oxcarbazepine was supplied as a gift sample from Micro Labs Limited, Bangalore. Polyvinyl pyrrolidone (PVP K30) was obtained from BASF, Polyethylene glycol 6000 (PEG 6000) was obtained from Clariant India Ltd. Starch was obtained from Roquette. Solvents used were of analytical grade.

Method:

Crystallo-Co-Agglomeration Technique: Oxcarbazepine was dissolved in good solvent (acetone) and was added to the aqueous polymeric solution (3g PEG 6000 in 30 ml bad solvent, i.e., water) with stirring. The bridging liquid dichloromethane (DCM) was added to obtain spherical crystals [4]. The temperature of the crystallization system was maintained at 5 °C, and stirring was performed for about 15 min. The obtained agglomerates were filtered and dried over-night. A 2^3 factorial design containing 8 experimental runs to evaluate three variables viz. polymer: drug ratio, stirring speed, and amount of bridging liquid at 2 levels was employed to determine their effect on three responses *i.e.*, minimum yield pressure (MYP), dissolution, Carr's index, and their interaction. The layout of the experimental design is shown in **Table 1**.

TABLE 1: BATCHES FOR OPTIMIZATION

Formulation code	Stirring speed (rpm)	Polymer: Drug Ratio (g)	Amount of Bridging Liquid (ml)
1	400	0.5:1	2
2	400	1.5:1	2
3	700	0.5:1	2
4	700	1.5:1	2
5	400	0.5:1	1
6	400	1.5:1	1
7	700	0.5:1	1
8	700	1.5:1	1

Evaluation of Crystallo Co-agglomerates:

Determination of Drug Content: Drug content was determined by dissolving samples of agglomerates (10 mg) in 10 ml of acetonitrile. The solution was filtered through Whatman filter paper no. 41 and was suitably diluted, the absorbance was measured [5].

Micromeritic Studies: [6, 7]

Angle of Repose: The angle of repose was determined by the fixed funnel method, whereas Carr Index and Hausner ratio were calculated from bulk density and tapped density using methods described in the literature.

Heckel Analysis: The Heckel analysis was performed on bulk drugs and agglomerates using discs prepared at a compaction pressure of 2, 4, 6, 8, 10, 12 tonnes in KBr press (techno search instruments, Model-M-15) using 13.00 mm flat faces punches, the diameter, height, and weight of the tablets was measured, and Heckel analysis was performed by plotting log relative density vs. pressure [8].

***In-vitro* Studies:** The dissolution rate studies were conducted in 900 mL of 0.3% sodium lauryl sulphate at 60 rpm maintained at 37±0.5 °C in a dissolution apparatus (Model TDT-08L, Electrolab) using the basket type. 150 mg of drug and agglomerates of PVP and PEG 6000 equivalent to 150 mg of the drug was added to the dissolution medium, and the samples were withdrawn at appropriate time intervals. The samples were immediately filtered through a 0.45 μm membrane filter, suitably diluted, and analyzed spectrophotometrically at 290 nm [9].

Saturation Solubility Studies: Saturation solubility studies were performed in phosphate buffer pH 7.4 in triplicate according to the method reported by Higuchi and Connors. Excess of Oxcarbazepine (50 mg) and agglomerates equivalent to 50 mg of the drug was added to 20 mL of phosphate buffer pH 7.4 taken in the screw cap tube and shaken for 24 h in rotary flask shaker at 37 ± 0.5 °C to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatman filter paper no. 41 and analyzed spectro-photometrically at 290 nm. The results obtained from saturation solubility studies were statistically validated [4].

Powder X-ray Diffractometer (PXRD): The PXRD data of agglomerates of optimized batch and oxcarbazepine were recorded on a Bruker PXRD (Model: D 8 Advance) with the copper target. The conditions were: 40 kV voltages; 40 mA current; at room temperature. The samples were loaded on to

the diffractometer and scanned over a range of 2θ values from 10 to 800 at a scan rate of 0.050 /min [10].

Scanning Electron Microscopy (SEM): The surface morphological properties of agglomerates of optimized batch and oxcarbazepine was investigated by scanning electron microscopy (SEM-Jeol Instruments, JSM-6360, and Japan).

Preparation and Evaluation of Oxcarbazepine Tablet Using Agglomerates: The optimized oxcarbazepine agglomerates were subjected to direct compression after the addition of different excipients in **Table 2**. Evaluation of tablets such as thickness and diameter, hardness, friability, weight variation, disintegration time, and dissolution were carried out by using methods reported in literature [11].

TABLE 2: FORMULA FOR PREPARATION OF TABLETS

S. no.	Ingredient	Amount (mg)
1	Oxcarbazepine spherical agglomerates	80.0
2	Starch	4.5
3	Sodium Lauryl Sulfate	3.0
4	Povidone K-30	12.0
5	Talc	3.0
6	Lactose	q.s.

Total weight of the tablets was kept 150 mg

The powder blend was evaluated for angle of repose, compressibility index, and Hausner's ratio. Standard 10.5 mm concave punches were used for direct compression of tablets on the rotary tablet compression machine (Rimek Mini Press II MT).

***In-vivo* Pharmacokinetic Analysis:**

Preparation of Calibration Curve: The calibration standards were obtained by spiking 0.2 ml of rat blank plasma with appropriate dilutions of the stock solution (0.1 ml of working standard solutions) of Oxcarbazepine which was mixed with 0.1 ml stock solution of Clonazepam (20 µg/mL, IS) and vortex mixed. The extraction procedure of plasma samples was performed by solid-phase extraction using a 24-tube vacuum manifold. The Strata C18-E (55 um, 70A) columns were conditioned with 2 × 1 mL methanol (MeOH) followed by 2 ×1 mL ultrapure water and 2 ×1 mL MeOH: Water (35:65, v/v) mixture. After the sample deposit, the columns were washed with 2 × 1 mL MeOH: Water (35:65, v/v) mixture, then the elution was performed using 250 µL of pure MeOH twice. After evaporating, MeOH elutes to dryness under a stream of nitrogen at ambient temperature followed by reconstitution with 1 mL of the mobile phase, 20 µL of each aliquot was injected in the chromatographic system. The peak area ratios of Oxcarbazepine and Clonazepam were calculated, and the calibration curve was plotted of response factor against the concentration of the drug.

Collection of Blood Samples and Pharmacokinetic Analysis: Blood samples (1 ml) were collected in EDTA coated bottles through the retro-orbital route during a dosing interval at the following times: 0 (prior to drug administration), 0.5, 1, 2, 4, 6, 10, 12, and 24 h post-dose. Samples were centrifuged for 15 min at 1500 rpm to collect plasma and then frozen at −20 °C until analysis. Plasma samples were analyzed for Oxcarbazepine concentrations by H.P.L.C. under the above-mentioned conditions.

RESULTS AND DISCUSSION: Absorbance of various standard concentrations of Oxcarbazepine solutions were read at 290 nm. λ_{max} and calibration curve was plotted using an average of 3 determinations.

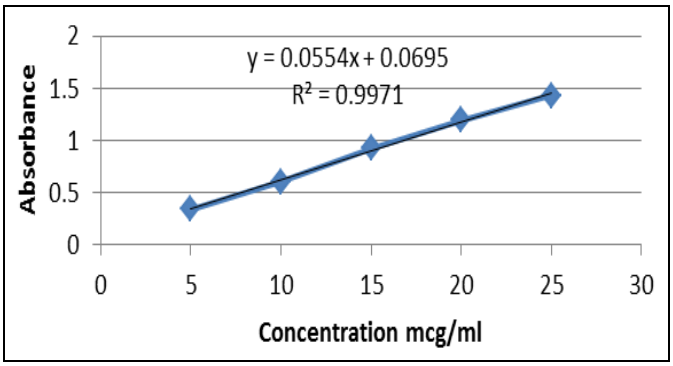

FIG. 1: CALIBRATION CURVE FOR OXCARBAZEPINE BY UV SPECTROPHOTOMETRY

TABLE 3: PARAMETERS FOUND IN CALIBRATION CURVE

S. no.	Parameters	Results
1	Detection wavelength (λ_{max})	290 nm
2	Regression Equation	y = 0.0554x + 0.0695
3	Correlation Coefficient	0.997

Spherical Agglomeration Technique: Oxcarbazepine is an anticonvulsant drug that is poorly water-soluble and possesses poor compaction and flow properties. The agglomerates of Oxcarbazepine were prepared using a spherical agglomeration

technique. Oxcarbazepine was crystallized from the acetone-water-DCM system and agglomerated with hydrophilic polymer PEG 6000. Oxcarbazepine is freely soluble in acetone but practically insoluble in water. Also, it is soluble in DCM (bridging liquid). Hence, this solvent system was selected for the present study. In this process, the crystallization of drug was performed by the addition of the anti-solvent phase (water) to drug solution. The addition of bridging liquid (DCM) promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of the dispersed crystals [12].

Drug Content: Oxcarbazepine shows poor aqueous solubility (0.08 mg/ml). The spherical agglomeration technique shows significant improvement in the aqueous solubility of Oxcarbazepine. Incorporation of hydrophilic polymers PEG 6000 enhances the wettability of Oxcarbazepine by the process of hydrophilization, which may increase the aqueous solubility of Oxcarbazepine [13]. Also, it may increase due to increased surface area, wettability, changes in the crystal forms, structure, and surface modification with hydrophilic Polymer [14]. There was (0.08 to 0.66 mg/ml) *i.e.,* 8.04 fold increase in the aqueous solubility of Oxcarbazepine from the spherical agglomerates.

Micromeritic Studies: The micrometric properties of spherical agglomerates are shown in **Table 4**. It shows that the flowability of spherical agglomerates represented in terms of the angle of repose, Carr's index and Hausner's ratio was much improved compared to those of the original drug. Oxcarbazepine crystal has a significantly higher angle of repose (>40) in comparison with the spherical agglomerates. **Table 4**, which could be due to the irregular shape of the crystals, which hindered the uniform flow of crystals. The reason for the excellent flowability of the agglomerate is the significant reduction in the interparticle friction because of the perfect spherical shape and the larger size of the crystals [15]. Carr's index and Hausner's ratio values also corroborate the above findings. The dissolution profile is evident that the spherical-agglomerates have improved the dissolution rate of Oxcarbazepine significantly compared to oxcarbazepine. The enhancement in the dissolution rate was observed up to 89.26%. This faster drug dissolution can be linked to the increase in surface area, wetting, and the porous internal structure [16].

Heckel Analysis: Heckel analysis has been used to classify powder compaction behavior and for the interpretation of the mechanism of bonding. MyP is the pressure required to de forma powder or granules and to obtain compacts and is defined as the inverse of the slope of the linear portion of the Heckel plot. The slope (k) is an indication of the deformation behavior of the material. With low values of Py, the amount of plasticide formation increases. And when high values of Py is an indication of the materials compressing behavior is mainly fragmentation. The values obtained from Heckel equation as shown in **Table 4** indicated significant low yield pressure (MYP) of spherical agglomerates (2.7-3.5 ton) than Oxcarbazepine (5.95 tonns) indicating improvement in compaction behavior of spherical Agglomerates [15, 16].

Optimization using Design Expert, Stat-Ease, Minneapolis, MN. The experiments were designed to study the effect of three independent variables, namely speed of rotation, polymer concentration, and amount of bridging liquid at two levels on MYP, % Dissolution, and Carr index. The traditional approach to developing a formulation is to change one variable at a time, but this method is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variable.

TABLE 4: OPTIMIZATION RESULTS FOR OXCARBAZEPINE

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	Drug
Polymer: Drug Ratio (X1)	0.25:1	0.25:1	0.25:1	0.25:1	0.75	0.75	0.75	0.75	-
Speed (X2)	400	700	400	700	400	700	400	700	-
Bridging Liquid (X3)	1	1	2	2	1	1	2	2	-
Dissolution (%) (R1)	80.2	87.36	85.2	92.43	86.2	83.92	80.29	82.53	8.10
Carr Index (R2) (%)	17.8	14.8	12.5	14.8	10.4	13.7	12.5	10.5	60
MyP (R3)	2.29	2.78	3.12	2.96	3.08	3.35	3.14	3.01	5.38
Hausner's Ratio	1.13	1.1	1.12	1.16	1.13	1.09	1.08	1.11	1.6

Among all the DOE methods, 2^3 factorial design reduces the number of experiments in a3-experimental factor design and requires fewer runs. Factorial designs (FD, full or fractional), also known as experimental designs for the first- degree models, are the most popular response surface designs. Full factorial designs involve studying the effect of all factors (n) at various levels (X), including the interactions [16, 17].

Factorial designs have maximum efficiency in estimating main effects in the absence of interaction, they reveal and identify interactions, and conclusions apply to a wide range of conditions.

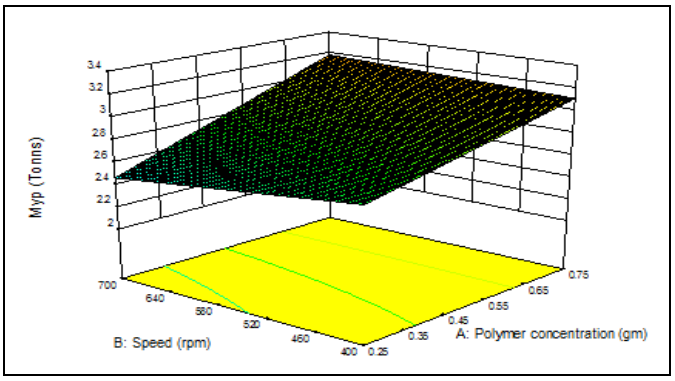

FIG. 2: EFFECT OF STIRRING SPEED AND POLYMER CONCENTRATION ON MyP

The design expert software yielded the following equations

$$MYP = 0.28 - 0.041X_1 - 8.75\ X_2 - 0.03\ X_3 + 0.076 - 0.061 - 0.23 + 0.13_{ABC} \text{ ------- (1)}$$

$$\text{Carr index} = 10.75 + 1.86X_1 - 1.50X_2 + 1.09\ X_3 - 0.65X_1X_2 + 0.71X_1X_3 - 0.41X2X_3 \text{ ---- (2)}$$

$$\text{Dissolution} = 33.85 - 7.87A - 0.80B + 1.21C - 6.26AB + 0.44AC + 9.42 - 3.50_{ABC} \text{ ---- (3)}$$

The mean yield pressure values of spherical agglomerates were found to be higher at high polymer and high bridging liquid concentration, whereas at low values of polymer the increase in bridging liquid reduced MYP sharply which may be due to porous agglomerates whereas PEG beings of plastic in nature give better compressibility to the formed agglomerates as it undergoes plastic deformation [18]. The combination of low bridging liquid and high, stirring speed reduced the MYP as the particle collisions increase at high speed, which resulted in smaller particle size and smaller MYP. The binary combination of variables, as well as all the three, demonstrated a good effect on reducing the MYP **Fig. 2**.

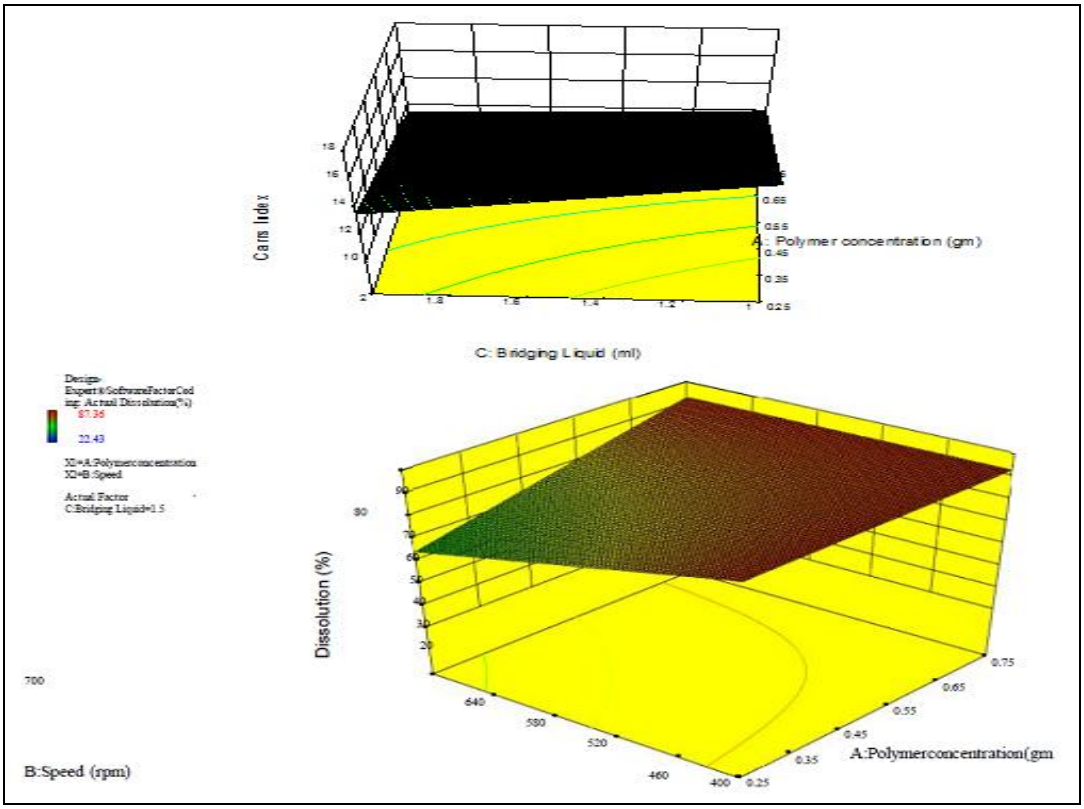

FIG. 3: RESPONSE SURFACE PLOT FOR CARR'S INDEX AND DISSOLUTION STUDIES

Carr Index: Carr index was reduced by increasing the polymer and increased to some extent by stirring speed. It was highly influenced by bridging liquid; the values of products from trial runs ranged between 8.33-14.8%. High values were seen at high, stirring speeds and bridging liquid combination and declined with the decrease in either of the variables. Whereas low polymer and high bridging liquid combinations exhibited good Carr index **Fig. 3**.

The dissolution is the most coveted characteristic of a drug material; dissolution of Oxcarbazepine was highly reduced by increasing polymer content as agglomerates formed were sticky in nature.

The low, stirring speeds which produce bigger agglomerates may also reduce the dissolution. The higher polymer: drug ratio and low bridging lead to a significant reduction in dissolution. High bridging liquid and high, stirring speeds increase in dissolution. Also, a combination of low polymer: drug ratio and high, stirring speed lead to an increase in dissolution. Incorporation of PEG causes faster consolidation and yields particles with lower tortuosity, and hence batches containing PEG at higher levels exhibit slow release of drugs [19].

The formulations prepared as per the experimental design were evaluated, and the analysis of experimental results was done by using the Design Expert. The ANOVA, P-value, and model F-value for the Carr index, % Dissolution and MYP were obtained.

F value for models was found to be high, which indicated that the model was significant. A P-value of less than 0.05 indicated that the model terms were significant. High R^2 value indicated good agreement between formulation variables and response parameters. Thus, the models can be used to predict the values of the response parameters at selected values of formulation variables within the design space.

The solution provided by the Design-Expert software on the basis of desirability function was, polymer: drug ratio concentration (0.5:1), speed of rotation (700 rpm) and amount of bridging liquid (2 ml) and had desirability value of 1 to obtain optimum parameters for the preparation of spherical agglomerates. The percentage drug content of spherical agglomerates of optimized formulation was found to be 98.5% **Fig. 3**.

TABLE 5: ANOVA OUTPUT OF THE 2^3 DESIGN FOR OPTIMIZATION OF SPHERICAL AGGLOMERATES

Outcome	Carr's Index %	Dissolution %	MYP Tonne
F value	85.23	54.31	66.39
P value	0.0096	0.0001	0.0092
R^2 value	0.993	0.981	0.973

TABLE 6: PROPERTIES OF SPHERICAL AGGLOMERATES (n=3)

System/ parameters	Hausner ratio	Carr's Index	% dissolution	MyP tone
Oxcarbazepine	1.6	60	8.1	5.74
Spherical agglomerates	1.2	16.07	89.26	3.58

PXRD: The PXRD scan of plain Oxcarbazepine showed intense peak so of crystallinity, whereas the XRD pattern of agglomerates exhibited halo pattern with less intense and denser peaks Compared with plain Oxcarbazepine indicating the decrease in crystallinity or partial Amorphization of the drug in its agglomerated form.

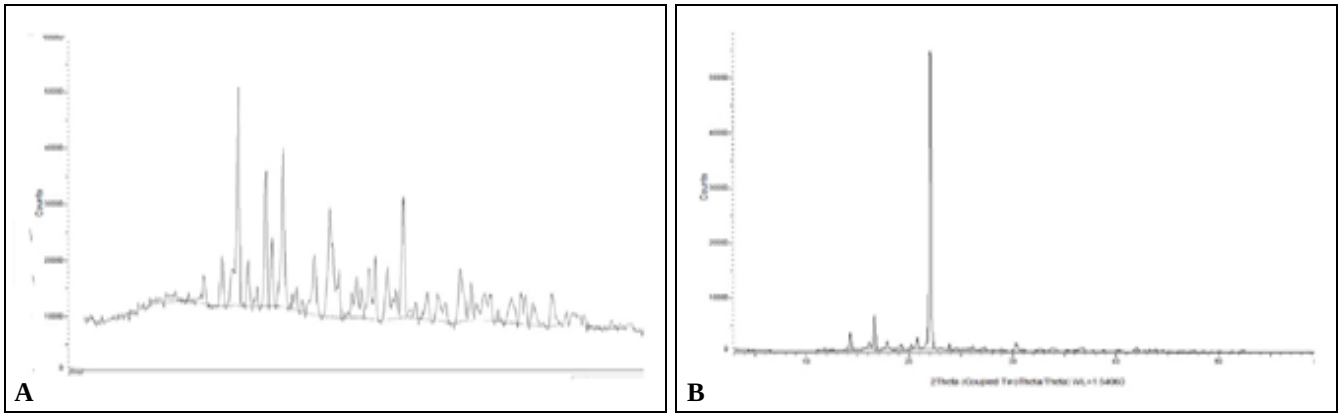

FIG. 4: POWDER X RAY DIFFRACTOGRAM FOR A) OXCARBAZEPINE AND B) SPHERICAL AGGLOMERATES PREPARATION AND EVALUATION OF OXCARBAZEPINE TABLET USING AGGLOMERATES

The tablets were compressed using the optimized spherical agglomerates by direct compression, the hardness was found to be 4.33 kg/cm^2, disintegration time was found to be 13.39 minutes and the friability was found to be 0.543%. The Oxcarbazepine particles in the physical mixture were irregular, and the shape of prepared agglomerates was uniform and spherical, which is the reason behind the improved flow of agglomerates [20, 21].

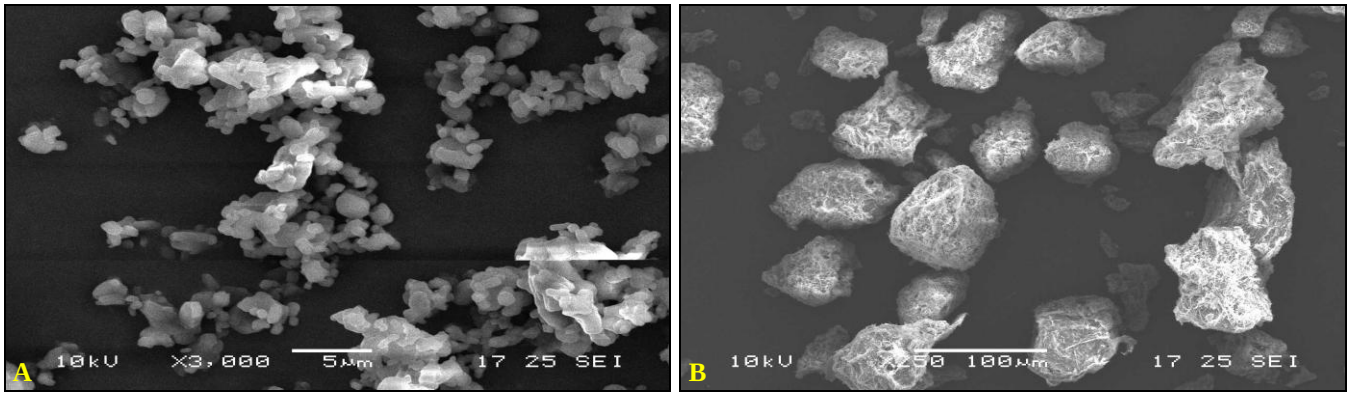

FIG. 5: SCANNING ELECTRON MICROSCOPIC IMAGES OF A) OXCARBAZEPINE AND B) SPHERICAL AGGLOMERATES

***In-vivo* Pharmacokinetic Analysis of Prepared Spherical Agglomerates:**

Calibration Curve Data For Oxcarbazepine In Plasma: The peak area ratios of Oxcarbazepine and Clonazepam were calculated, and the calibration curve was plotted of response factor against the concentration of the drug. The calibration curve was found to be linear in the range of 0.1 µg/ml to 10 µg/ml, and the equation was Y = 0.2526X + 0.0252.

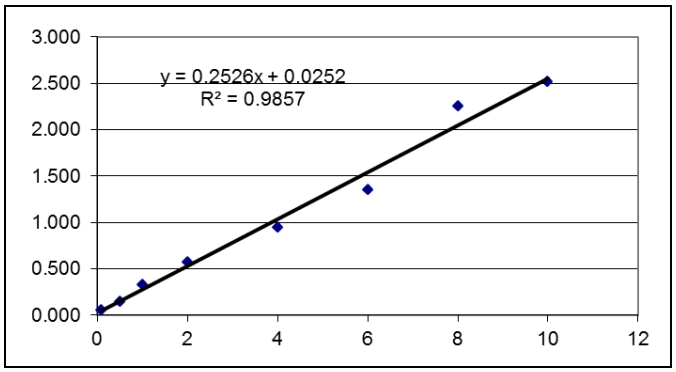

FIG. 6: CALIBRATION CURVE FOR OXCARBAZEPINE IN PLASMA

Pharmacokinetic Analysis: Plasma samples were collected and analyzed at dosing intervals of 0, 0.5, 1, 2, 4, 6, 10, 12, and 24 h post-dose for Oxcarbazepine concentrations by HPLC.

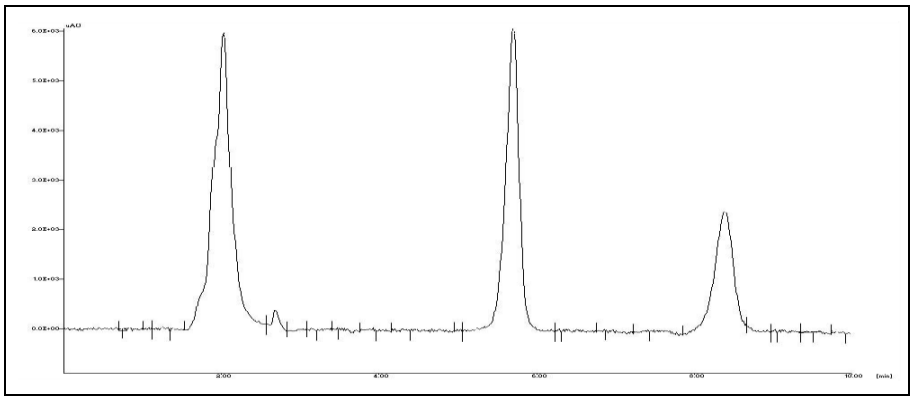

FIG. 7: REPRESENTATIVE CHROMATOGRAPH FOR PLASMA SAMPLE AT 1 h (AGGLOMERATES) RETENTION TIME OXCARBAZEPINE – 5.820 min AND CLONAZEPAM – 8.352 min

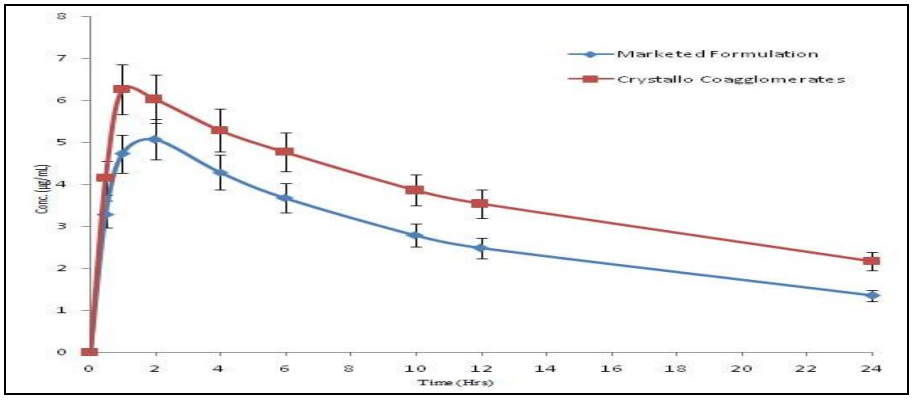

FIG. 8: PLASMA CONCENTRATION TIME PROFILE FOR OXCARBAZEPINE SPHERICAL AGGLOMERATES AND MARKETED FORMULATION

Fig. 8 shows significant improvement in C_{max}, $t_{max,}$ and AUC from spherical agglomerates, the values are summarized in **Table 7**. This depicts 123.52 % improvement in C_{max}; 135.19 % improvement in AUC (0-24h) of Oxcarbazepine in Crystallo Coagglomerates as compared to its Marketed Formulation **Fig. 8**. There is a marked increase in AUC (24 µg/mL/h) with a significant decrease in t_{max}. Also, there is an increase in C_{max} value indicate crystallo agglomeration has improved the formulation in terms of fast action.

TABLE 7: SUMMARY OF PHARMACOKINETIC ANALYSIS

Pharmacokinetic Parameters	Marketed Formulation	Crystallo-Co-Agglomerates	% Increase
C_{max} (mcg/mL)	5.063	6.254	23.52
AUC mcg/mL*h (0-24h)	103.56	139.995	35.19
t_{max} (h)	2.0	1.0	

CONCLUSION: Oxcabazepine agglomerates were successfully prepared by spherical agglomeration using PEG. Spherical agglomerates exhibited improved micrometric properties compared to pure drug. Optimized formulation shows a better result with respect to percent drug release MYP value and Carr's index when compared to other formulation. Hence this technique can be used for the formulation of tablets of Oxcabazepine by direct compression with directly compressible excipients.

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CONFLICTS OF INTEREST: The author(s) declare no conflict of interest.

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