

Solubility Enhancement of Oxcarbazepine by Melt Sonocrystallization Technique to Increase the Bioavailability

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ABSTRACT

Objectives: The present study aimed to enhance the solubility of Oxcarbazepine by melt sono crystallization technique as well as increase its bioavailability. **Materials and Methods:** Tablets of Melt Sonocrystallized Oxcarbazepine were prepared by the direct compression method. Compression was performed on a Remik mini-press tablet compression machine using an 8mm punch. The analytical method development was carried out in 20x10 and 10x10 twin trough chambers. The sample was spotted with a 100 μ l camas microliter syringe on silica gel aluminum plate 60 F₂₅₄ (20X10) and (10x10) plate; Merck using a CAMAG Linomat-5 sample applicator. **Results:** The Oxcarbazepine had better solubility in the ph 6.8 buffer. The mobile phase selected for HPTLC was Ethyl acetate: Methanol in the ratio (8:2 v/v) with the R_f value 0.582. The formulation F2 containing 5% SSG showed a release of 90.51% and was considered as an optimized formulation based on several parameters such as friability (0.21%), disintegration time(27.8 sec) and *in vitro* dissolution studies.

Key words: Melt sonocrystallized, Oxcarbazepine, Method development, HPTLC, Validation, Solubility Enhancement.

INTRODUCTION

Epilepsy is defined as having two or more unprovoked seizures. Seizures are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function. Seizures are expected in adults with the age group of 60 and above.¹ Oxcarbazepine is an antiepileptic drug generally used to treat generalized tonic-clonic seizures and partial seizures in humans.² Oral bioavailability of Oxcarbazepine is >95% and is not affected by food. By oral administration, Oxcarbazepine is completely absorbed and is converted into an active metabolite i.e. 10-monohydroxy metabolite (MHD).

The oral route of administration is the most convenient route of administration. The major problem faced during the oral administration of the active agent is the bioavailability factor, which ultimately depends on the solubility of the agent. Techniques for Solubility Enhancement include -Particle size reduction, Micronization, nanosuspension, Hydrotropy.³ Hot Melt Extrusion technique Steam aided granulation Floating granulation Sono crystallization Melt Sonocrystallization is a new particle design technology developed to modify the undesired properties of compounds such as poor flowability and solubility.⁴ This technique is an efficient tool to influence the external

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appearance structure of crystalline products, smaller crystal size compared with conventional crystallization and cost-effectiveness of apparatus. Ultrasonication energy has been used to achieve nucleation at moderate super saturation during the crystallization process to achieve de agglomeration and to obtain the desired crystal habit.⁵ In the melt sonocrystallization technique the drug is first melted in the heavy liquid paraffin bath and the liquid drug is added to deionized water. Simultaneously subjected to sonication. The resultant solution is filtered and dried at room temperature. High-Performance Thin Layer Chromatography is a powerful tool for qualitative and quantitative analytical tasks.⁶

MATERIALS AND METHODS

Oxcarbazepine was a gift sample from Vergo Pharma Research Laboratories Pvt. Ltd, Sodium Starch Glycolate, SLS, Talc, Magnesium stearate was procured from M/s Hi-Media Laboratories Pvt. Ltd, Microcrystalline Cellulose from M/s Ozone ® International, Mumbai, Pregelatinized Starch from Colorcon Pvt. Ltd and PVP K-30 from M/s Balaji Drugs.

Preformulation studies

Identification Tests

Melting point

The melting point of Oxcarbazepine was determined by an open capillary method using theils tube apparatus.

Lambda max (λ_{max})

The 100mg of drug dissolved in 10 ml of methanol in a 100 ml volumetric flask and the volume was made up to 100ml with phosphate buffer pH 6.8. Further 10ml was pipette and diluted up to 100ml using phosphate buffer pH 6.8 in a volumetric flask and the λ_{max} was scanned in the range of 200-400nm using a UV spectrophotometer

FT-IR

The FT-IR spectrum of Oxcarbazepine by potassium bromide method was carried out to confirm any changes in the purity of the drug

Standard Calibration Curve

The primary stock solution of Oxcarbazepine was prepared by dissolving 100mg of a drug in 10ml of methanol in a 100ml volumetric flask and sonicated for 4 min. The volume was made up to 100ml with pH6.8 buffer solution to get the concentration of 1000 μ g/ml. From this, an aliquot of 10ml was withdrawn and it was diluted to 100ml with the buffer solution to give a concentration of 100 μ g/ml. Again from the above solution, aliquots of 0.5, 1, 1.5, 2.0, 2.5, 3.0 ml were

pipette out into 10ml volumetric flask using phosphate buffer pH 6.8 to get the concentrations of 5 to 30 μ g/ml. The absorbance of this solution was measured at λ_{max} 256 nm using a UV spectrophotometer.

Method of Preparation of Melt Sonocrystallized Oxcarbazepine

1g of Oxcarbazepine was melted in a test tube of 10ml capacity by placing it on a heavy liquid paraffin oil bath at a temperature of 215°C. The molten mass was poured into deionized water maintained at a temperature of 50°C. The suspension was sonocrystallized using a probe tip solicitor at a frequency of 33 \pm 3 kHz and amplitude of 80% for 4 min with a cycle of 15sec ON and 15 sec OFF. After sonication, the content is filtered off using Whatman filter paper no.1. The filtrate is dried at an ambient temperature of 60°C for several hours to obtain a dry mass. The percentage of practical yield was calculated.

Solubility analysis

To select the best solvent, solubility studies were carried out by preparing a saturated solution of a drug by adding an excess of a drug into different buffer solutions. The prepared solution was subjected to constant stirring for 24 hr. After this, the solution was filtered and analyzed spectrophotometrically at wavelength 256nm with suitable dilutions.

HPTLC method development

The HPTLC is a widely used method of choice for the analysis of the substance. A CAMAG HPTLC was used for the estimation of Oxcarbazepine using the visioncats-software version 2.4.17207.2.

Method Validation

This includes the procedure of performing numerous assessments designed to verify that an analytical test system is suitable for its intended reason and is capable of providing beneficial and legitimate analytical data. The validation parameters included are Linearity, Limit of detection and limit of quantification, Precision, Specificity and Accuracy.

Compatibility studies

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) analysis was performed on a DSC60 detector (Shimadzu Co., Japan). Approximately 4mg of melt sonocrystallized Oxcarbazepine along with excipients was weighed in an aluminum pan and sealed hermetically. DSC scan was recorded from 30°C to 300°C at a heating rate of 10°C/min under a nitrogen purge, using an empty pan as reference.

Formulation of Melt Sonocrystallized Oxcarbazepine tablet

The 150 mg of drug was taken and mixed with directly compressible diluents and super disintegrate in mortar. Magnesium stearate was passed through sieve no. 60, mixed and blended with the initial mixture in the mortar followed by compression of the blend. Compression was performed on a Remik mini-press tablet compression machine using an 8mm punch by direct compression method (Table 1).

Evaluation of tablets

The angle of Repose (θ)

The angle of repose is the maximum angle formed between the freestanding surface of the powder heap and the horizontal plane.

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Bulk density and Tapped density

The weighed amount of the sample is taken in a 25ml measuring cylinder and the volume of the packing is recorded and tapped until no change in the volume was noted on the hard wooden surface

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Weight of powder}}{\text{Volume of packing}}$$

$$\text{TBD (Tapped bulk density)} = \frac{\text{Weight of powder}}{\text{Tapped Volume of packing}}$$

Compressibility Index and Hausner's Ratio

$$\text{Carr's Index \%} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's Ratio} = \frac{D_t}{D_b}$$

Post compression parameters

Drug Content Uniformity

Random 5 tablets were crushed and powder equivalent to 150 mg of the drug is dissolved in a minimum quantity of methanol in 100 ml volumetric flask and the volume was made up to 100 ml with a phosphate buffer of pH

6.8. The resultant solution was filtered and 10ml of it was withdrawn in 100 ml volumetric flask and volume was made with pH6.8 buffer solution and was analyzed spectrophotometrically at 256 nm.

In vitro Disintegration Time

The *in-vitro* disintegration time of tablets was determined using the disintegration test apparatus as per I.P. specification using 6 tablets in phosphate buffer pH 6.8 maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In-vitro Dissolution Studies

In vitro drug release of the formulation was carried out by the USP type II paddle apparatus with a rotating speed of 50 rpm at a temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The phosphate buffer of pH6.8 was used as a dissolution medium. 900ml of phosphate buffer was taken in the basket. The temperature was maintained at $37 \pm 0.50^{\circ}\text{C}$ with a stirring speed of 50 rpm. Sink condition was maintained throughout the study by adding 5ml of phosphate buffer was every time after the withdrawal of aliquots. The samples withdrawn were filtered through Whatman filter paper no. 1 and assayed spectrophotometrically at 256nm.

Short Term Stability Studies

The purpose of stability studies is to determine how the quality of formulation varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Short term stability studies for the formulation F2 was performed at both room temperature and accelerated temperatures as per ICH guidelines. The tablets were analyzed on the 15th, 30th, 45th day it's for appearance, disintegration time, drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

Melting point: The melting point of the drug was found to be between 215°C - 219°C . This indicates that the drug obtained was in pure form.

Table 1: Formulation of Melt Sonocrystallized Oxcarbazepine tablet.

Formulation ingredients	F1	F2	F3	F4	F5	F6
Msc oxcarbazepine	150 mg					
Sodium Starch Glycolate	3%	5%	7%	-	-	-
Pre gelatinized starch	-	-	-	3%	5%	7%
Microcrystalline cellulose	40.5mg	37.5mg	34.5mg	40.5mg	37.5mg	34.5mg
PVP K-30	1%	1%	1%	1%	1%	1%
SLS	1%	1%	1%	1%	1%	1%
Magnesium stearate	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%
Talc	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

Lambda max (λ_{max}): The lambda max of Oxcarbazepine pure drug was found to be 256 nm. This shows that the drug obtained was in pure form. Further, the absorbance of multiple concentrations of the oxcarbazepine is presented in Table 2 and Figure 1.

IR Spectroscopy: The IR spectrum of the pure drug was similar to that of Oxcarbazepine which indicates that the drug obtained is pure.

Absorbance data for standard calibration of oxcarbazepine

Solubility analysis

The solubility of Oxcarbazepine in a buffer solution of pH 1.2 was found to be 0.021 mg/ml, 0.0789 mg/ml in pH 6.8 and 0.072 mg/ml in pH 7.4. The solubility of melt sonocrystallized oxcarbazepine in a buffer solution of pH 1.2 was found to be 0.0712 mg/ml, 0.114 mg/ml in pH 6.8 and 0.085 mg/ml in pH 7.4. Results obtained by carrying out saturation solubility studies indicated that both oxcarbazepine and melt sonocrystallized oxcarbazepine had better solubility in pH 6.8 buffer.

X-Ray Powder Diffraction (XRPD)

The XRPD pattern of both OXC and MSCOXC showed characteristic diffraction peaks which were

also seen in the MSCOXC indicating no structural changes. The intensity of the peaks of MSCOXC was low as compared to the peaks of OXC indicating the difference in the particle size of the samples; presented in Figures 2 and 3.

Scanning Electron Microscopy (SEM)

The SEM of the pure Oxcarbazepine particles and MSCOXC particles are shown in Figures 4 and 5. The crystals of the original form of the drug i.e.

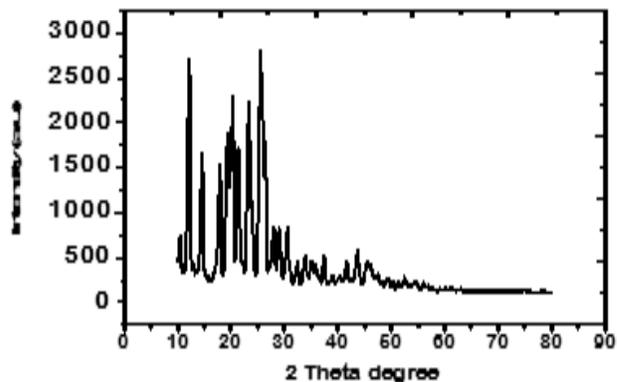


Figure 2: XRPD pattern of Oxcarbazepine (OXC).

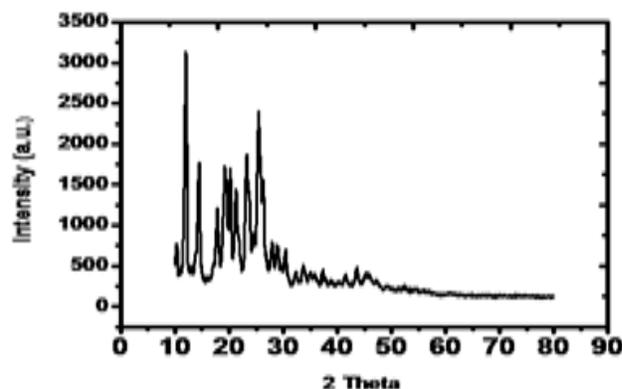


Figure 3: XRPD pattern of Melt sonocrystallized Oxcarbazepine (MSCOXC).

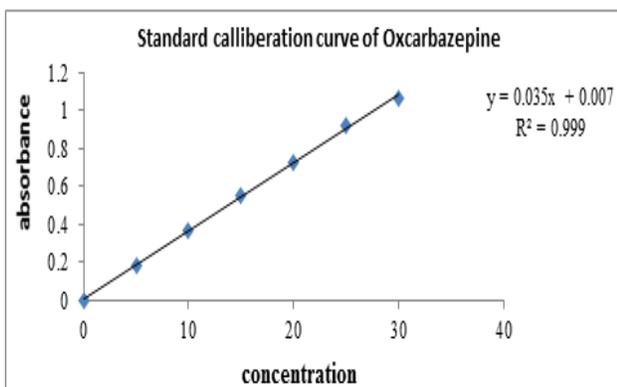


Figure 1: Standard calibration curve of Oxcarbazepine.

Table 2: Absorbance of multiple concentrations of Oxcarbazepine.

S. No.	Concentration ($\mu\text{g}/\text{ml}$)	Absorbance
1	0	0.00
2	5	0.188
3	10	0.370
4	15	0.550
5	20	0.727
6	25	0.918
7	30	1.070

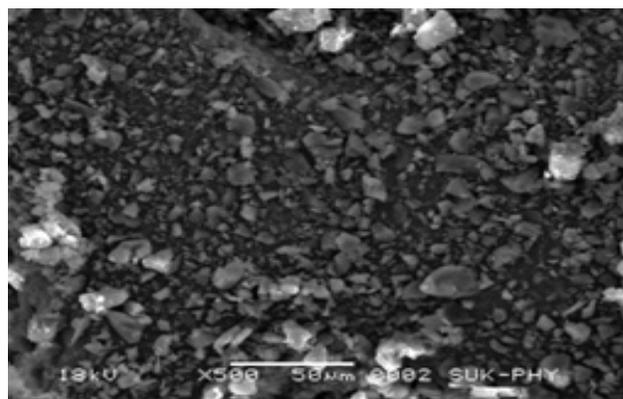


Figure 4: Scanning Electron Microscopy of Oxcarbazepine.

Oxcarbazepine were large with defined boundaries whereas the MSC form shows smaller particles.

Differential Scanning Calorimetry (DSC)

The melting point of oxcarbazepine pure drug was found to be in the range of 215-219°C. DSC peak of oxcarbazepine was found to be 217.74°C. Similarly, melt-sonocrystallized oxcarbazepine showed a peak of 217.74°C. This indicates that no modification has occurred during the melt sonocrystallization technique; Figure 6 and 7.

Compatibility studies

Differential Scanning Calorimetry (DSC)

The DSC peak of melt sonocrystallized oxcarbazepine with excipients was seen at 214.99°C. Peaks obtained indicate that the drug was found to be compatible with the excipients; Figure 8.

Evaluation of Tablets

Precompression studies

The angle of repose for powder was found to be in the range of 18°-25°. Bulk density was found to be 0.4g/

ml-0.39g/ml and tap density was found to be in the range of 0.414g/ml to 0.490g/ml. Hausner's ratio was found to be in the range of 1.04-1.22. The percentage compressibility range was found to be 5.70%- 18.36%. The average weight of tablets prepared was in the range of 200±0.63 mg to 199±0.33 mg. The hardness of tablets was found to be in the range of 3±0.02 to 3±0.003 kg/cm². Thickness was found to be in that range of 4±0.03 to 4±0.05 mm. The diameter was uniform and found to be 8mm. Friability was below 1%.

Drug content

Absorbance was measured at 256 nm. The percentage of drug content was found to be in the range of 96.38% - 98.54%.

In vitro drug release

This test was performed as triplicates for each batch of the formulation; pure drug and marketed formulation. The results are given in Figures 9-11.

Selection and optimization of mobile phase

The mobile phase selected was Ethyl acetate: Methanol in the ratio (8:2 v/v) as it showed the best

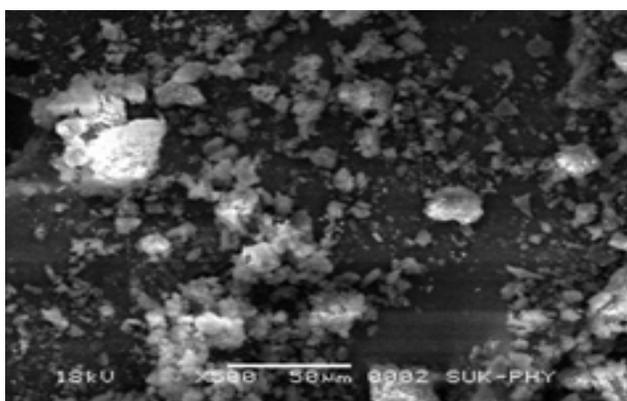


Figure 5: Melt sonocrystallization Oxcarbazepine.

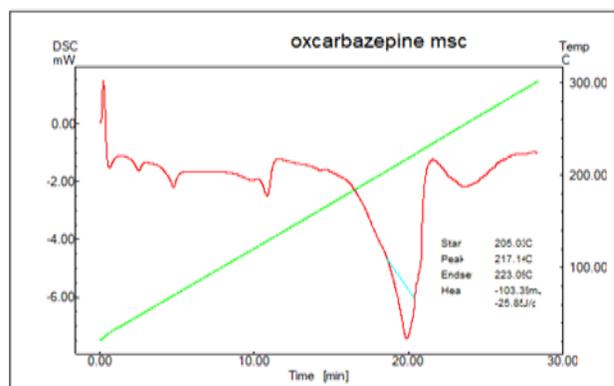


Figure 7: DSC peak of melt-sonocrystallized oxcarbazepine.

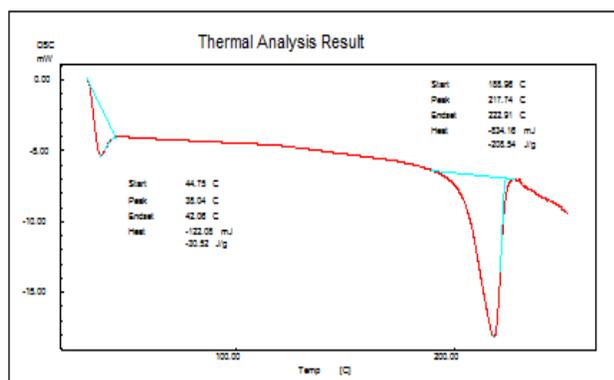


Figure 6: DSC peak of oxcarbazepine pure drug.

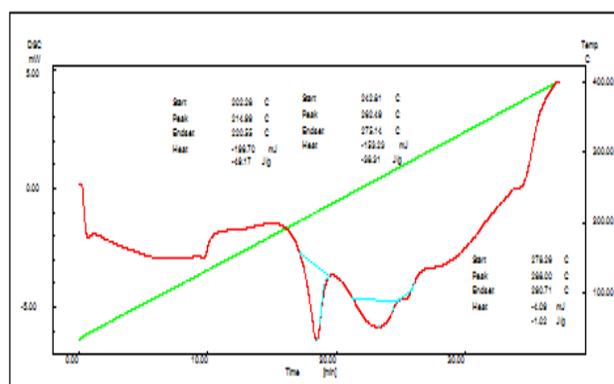


Figure 8: DSC peak of melt-sonocrystallized oxcarbazepine with excipients.

separation, compact spots at the R_f 0.582. The R_f value was reproducible at room temperature.

The optimization of chromatographic conditions

To optimize the mobile phase various mixtures of mobile phases and flow rates were previously tested on the standards. The best results were obtained with a mixture of ethyl acetate and methanol (8:2 v/v). The

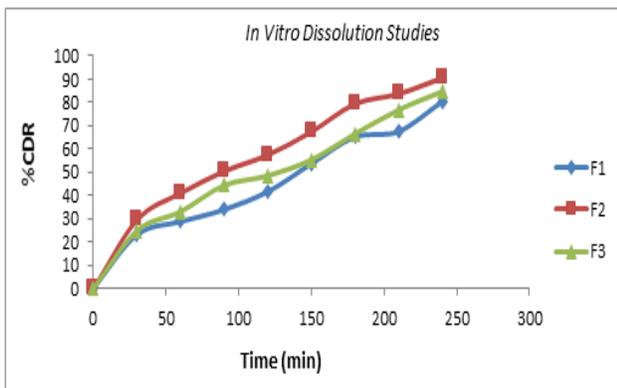


Figure 9: Comparison of the *in vitro* dissolution release of melt sonocrystallized oxcarbazepine tablets F1, F2, F3 (SSG).

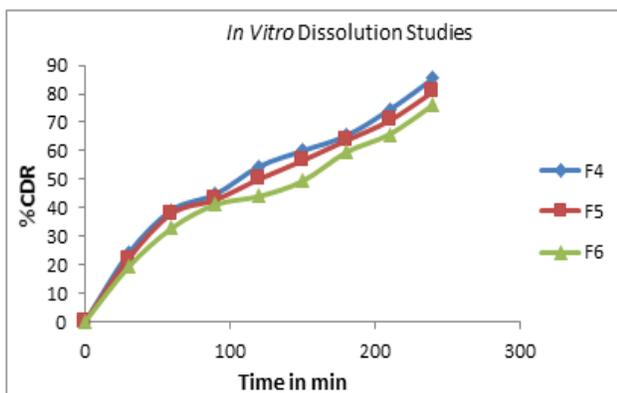


Figure 10: Comparison of the *in vitro* dissolution release of melt sonocrystallized oxcarbazepine tablets F4, F5, F6 (PGS).

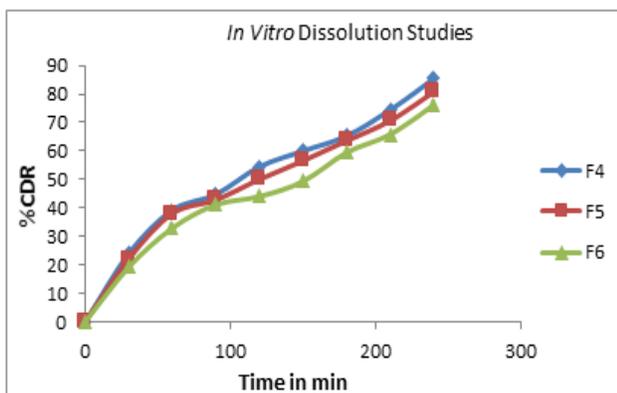


Figure 11: Comparison of the *in vitro* dissolution release of melt sonocrystallized oxcarbazepine tablet F4, F2 with marketed tablets of oxcarbazepine i.e. Trioptal and Pure drug.

densitometry scanner CAMAGTLC SCANNER 4 was used. It was observed that analyses showed the best peak resolution at 259 nm.

Chromatographic Development

The chromatographic development pattern is shown in Figures 12 and 13 and validation parameters for HPTLC analytical method development and validation are summarized in Table 3 and 4.

Linearity

Linear regression data showed a good linear relationship over a concentration range of 150 to 350 $\mu\text{g/ml}$ with an equation of $y = 9.263 \times 10^{-9} x + 2.668 \times 10^{-3}$ and the correlation coefficient is $R = 99.830\%$ (Figure 14).

Limit of Detection and Limit of Quantification

LOD and LOQ were calculated by standard calibration method. LOD for oxcarbazepine was found to be 18 μg and LOQ for Oxcarbazepine was found to be 54.8 μg .

Precision

Intra-day precision was carried out twice on the same day (replicate of 6 times). An inter-day precision study was carried out on two different days (replicate 6 times).

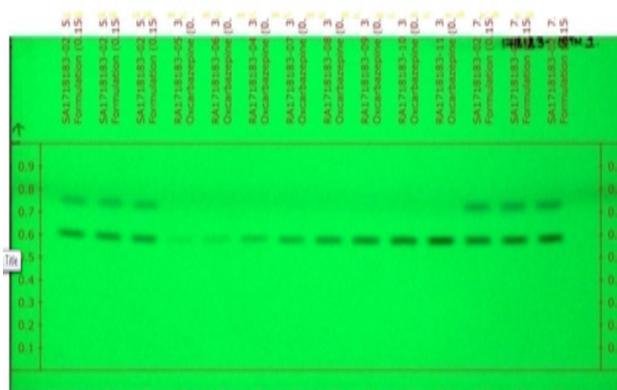


Figure 12: Detection of the developed TLC plate at 254nm.

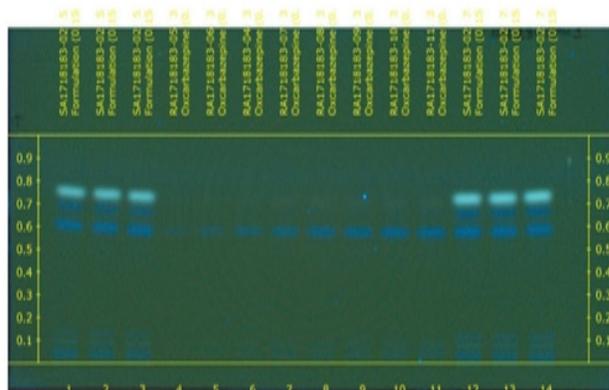


Figure 13: Detection of the developed TLC plate at 366nm.

The %RSD values for intra-day and inter-day precision less than 5% (Table 4) were considered as an acceptance criterion.

Accuracy

Accuracy of Oxcarbazepine was carried out in triplicate by comparing the areas of spiking the pure drug of Oxcarbazepine with the formulation (Melt sonocrystallized Oxcarbazepine) at three different levels (80%, 100% and 120%) with the area obtained by spiking the formulation with the pure drug. Acceptance criteria; % recovery should be within the range of 80-115%.

Specificity

Specificity was carried out by application of the standards, formulation, mobile phase and diluent. The R_f value of Oxcarbazepine the standard was found to be 0.602. The R_f value of Oxcarbazepine from the formulation was found to be 0.587, further, the mobile phase and diluents did not show any peaks at the R_f of the standards confirming the method are specific (Figure 15-18).

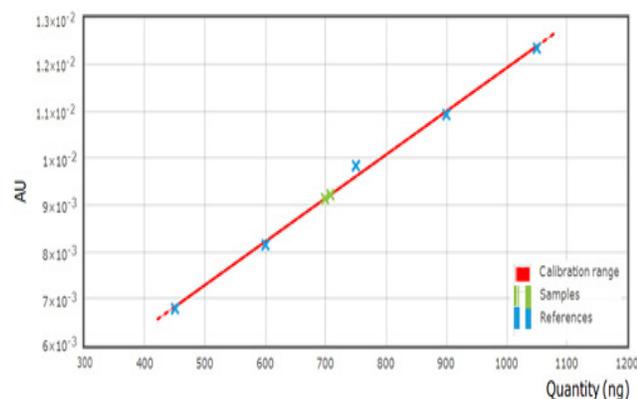


Figure 14: Calibration Curve of Oxcarbazepine by HPTLC.

Table 5: Results of intra-day precision studies of Oxcarbazepine.				
	1		2	
Concentration (µg/spot)	Mean peak area (n=6)	% RSD	Mean peak area (n=6)	% RSD
100	0.0042	2.636	0.0044	2.515
			Average	0.0043
			% RSD	2.57

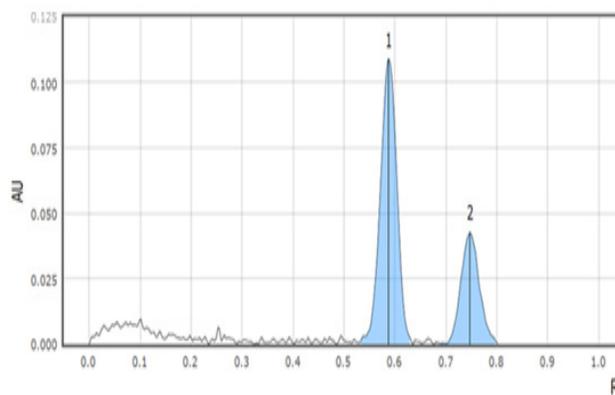


Figure 15: Chromatogram for Specificity of Oxcarbazepine in the formulation.

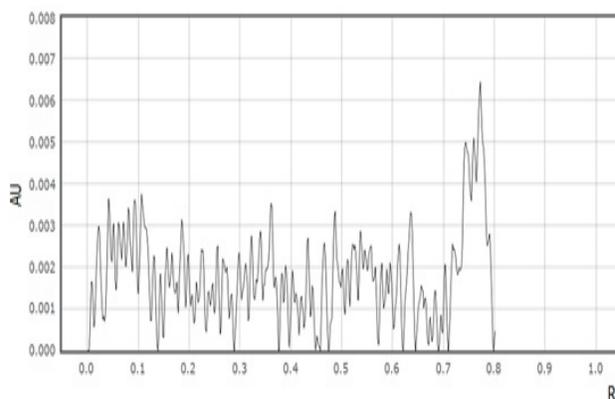


Figure 16: Chromatogram for Specificity of Diluent.

Table 3: HPTLC Analytical Method Development and Validation.

Evaluation Parameters	Optimized formulation F2						
	Initial day	15 th day		30 th day		45 th day	
		RT/65% RH	40°/75% RH	RT/65% RH	40°/75% RH	RT/65% RH	40°/75% RH
Disintegration time(sec)	27.8	28.02	27.60	27.33	28.01	27.30	28.03
Drug content (%)	98.54%	98.41%	98.40%	98.36%	98.39%	98.28%	98.12%
%CDR on the 4 th hr	90.54%	90.53%	90.60%	90.52%	90.02%	90.49%	90.28%

Table 4: Validation parameters.

Sample	Theoretical concentration mg/spot	Observed concentration mg/spot	Amount obtained mg/tablet	%content	%RSD
Oxcarbazepine	0.150	0.140	140	93.33%	0.89%

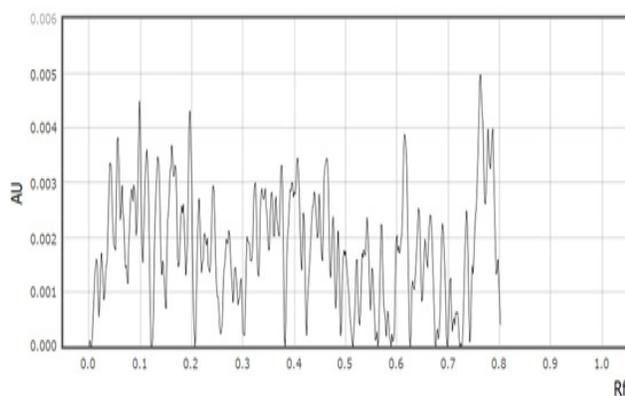


Figure 17: Chromatogram for Specificity of Mobile Phase.

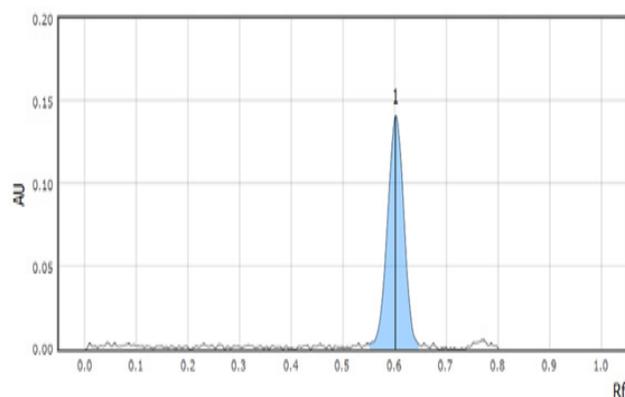


Figure 18: Chromatogram for Specificity of Oxcarbazepine.

CONCLUSION

The melt sonocrystallization technique enhanced the solubility of the Oxcarbazepine and the saturation solubility revealed it. XRPD, SEM, DSC is the preferred analytical method for the characterization of the MSCOXC. The direct compression method is the preferred method for the formulation of melt sonocrystallized Oxcarbazepine tablets. FTIR and DSC is the preferred analytical method for the compatibility studies. The formulation and post-compression studies were found in the limit. The optimized formulations have a high dissolution profile as compared to the pure drug and marketed formulation and were stable in the 45 days stability studies HPTLC method is developed on

the Optimized formulation i.e. F2 melt sonocrystallized Oxcarbazepine for the estimation of the drug in the formulation. The Assay showed 93.3% of the drug content which was within a limit i.e 90%-110% as per I.P. with % RSD less than 2.00%. The developed method is validated and found to be a linear, precise, accurate and specific method.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DSC: Differential scanning calorimetry; **FT-IR:** Fourier-transform infrared spectroscopy; **HPTLC:** High-Performance Thin Layer Chromatography; **SEM:** Scanning Electron Microscopy; **XRPD:** X-Ray Powder Diffraction.

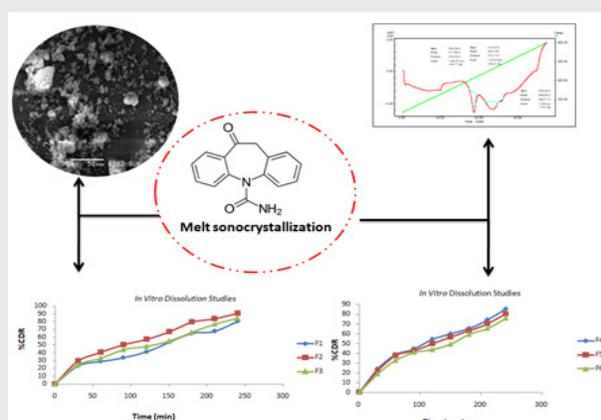
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SUMMARY

The present study reveals that the application of the melt sonocrystallization technique to BCS class II drug Oxcarbazepine has resulted in the enhancement of solubility. The study has demonstrated the role of ultrasonic energy in particle size reduction and change in crystal habit. Melt sonocrystallized Oxcarbazepine was prepared from a pure drug of Oxcarbazepine using the sonocrystallization technique where the melt form of the drug is sonocrystallized using probe tip sonicator. The saturation solubility revealed that the solubility of Melt sonocrystallized Oxcarbazepine (0.114mg/ml) was higher than the pure Oxcarbazepine (0.078mg/ml) in the buffer solution of pH 6.8. The characterization of the Melt sonocrystallized Oxcarbazepine was done by carrying out XRPD, SEM and DSC analysis. XRPD analysis revealed that the MSCOXC drug was showing low-intensity peaks which indicates that the change in crystal habit has occurred and the particle size has been decreased. SEM analysis revealed that the application of ultrasonic energy has resulted in the formation of a porous surface on the drug particles which contributes to the solubility enhancement. DSC showed no change in the melting point of the MSCOXC indicating no modification on the melting properties of the drug. Preformulation studies were performed to examine the compatibility between the drug melt sonocrystallized Oxcarbazepine and polymers. The IR spectra revealed that functional group peaks of Oxcarbazepine, Melt Sonocrystallized Oxcarbazepine and MSCOXC with excipients were found to be in the given limit and the DSC thermogram showed no change in the melting point of the drug. This indicates that there was no interaction between the polymer and drug and hence they are compatible. Directly compressible tablets of Melt Sonocrystallized Oxcarbazepine were prepared for oral delivery. Tablets prepared were of uniform size and shape. The percentage drug content of all the prepared formulations lied in the range of 95 to 105% respectively. The disintegration time was less than 15 min which is the limit for the uncoated tablet. The percentage cumulative drug released of formulations prepared was found to be in the range of 90.51% - 76.11% at the end of 4 hr. The formulation F2 containing 5% SSG showed a release of 90.51% and was considered as an optimized formulation based on several parameters such as friability (0.21%), disintegration time (27.8 sec) and *in vitro* dissolution studies. Stability studies were carried out on F2 batch for 45 days as per ICH guidelines in normal conditions and accelerated conditions. Tablets were found to be stable at the end of the 45th day. Thus, it can be concluded that Melt Sonocrystallized Oxcarbazepine was proven to be a suitable candidate for formulating oral tablets by direct compression method to achieve enhanced solubility and better patient compliance. In the present work, the mobile phase selected was Ethyl acetate: Methanol in the ratio (8:2 v/v) with the R_f value 0.582 and the chromatographic conditions was optimized. The amount of Oxcarbazepine present in the formulation was calculated and the % Drug Content was found to be 93.33% with 0.89% RSD. Validation parameters like Linearity, Accuracy, Precision, Assay and Specificity were carried out. Linearity was found over a concentration range of 150-350 µg/ml with an equation of $y = 9.263 \times 10^{-3}x + 2.668 \times 10^{-3}$ and Correlation coefficient (R²) 0.998 for Oxcarbazepine. LOD for Oxcarbazepine was found to be 18µg and LOQ for Oxcarbazepine was found to be 54.8 µg. Intra-day precision and Inter-day precision were found to be < 5.0 % which confirmed that the method developed for Oxcarbazepine was precise. The mean recovery for Oxcarbazepine was 90.023%. The % recovery was within the acceptance limits of 80-115% hence the method was found to be accurate. It was concluded that the developed HPTLC method is simple, rapid, accurate, precise, economical, specific and reproducible for the qualitative and quantitative determination of Oxcarbazepine with good resolution and high sensitivity.

PICTORIAL ABSTRACT



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