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Solubility and Dissolution enhancement of Carbamazepine by Melt-Sono-crystallization Technique

Chaitali Khemchand Gunjal[1], Jyotsna Pandit Khedkar[2], Snehal Jagan Takate[2], Niket S. Kankariya[3], Renuka subhash Hazare[2], Salva Midat[3] and Sumitra Mane[3]

[1]Department of Pharmaceutics Shri Gulabrao Devkar College of Pharmacy, Shri Gulabrao Deokar College of Pharmacy, Mohadi Shivar, Shirsoli Road, Jalgaon - 425001 (India)
[2]Department of Pharmaceutics, Gangamai College of Pharmacy Nagaon, Dhule - 424002 (India)
[3]Department of Pharmaceutics, Government College of Pharmacy Osmanpura, Aurangabad - 431005 (India)
Corresponding Mail: bkjyotsna108@gmail.com

Abstract

The present work aimed at the Solubility and Dissolution Enhancement of Carbamazepine by Melt-Sono-Crystallization Technique. Immediate Release Tablet was successfully prepared by Melt Sono crystallization Technique into different ratios. The Prepare ratio was evaluated according to the selected conditions. The successful preparations were compared with raw tablets as well as with marketed tablets in these selected conditions. The 32 factorial design was Performed by Selecting Gelucire 48/16 and Sonication Time As the independent variable and %DR as the Dependent Variable. The optimized formulation shows a %DR of 80.72% & 90.23% in the selected Conditions. Based on Evaluation the drug release of the F9 batch with sonication showed a release of 80.72% in water and 90.23% in HCL in 40 mins. Compared to the F3 batch without sonication showed 69.70 % in water and 75.17% in HCL. Solubility And Dissolution Enhancement of Carbamazepine by Melt-Sono-Crystallization Technique Was done successfully.

Key words : Carbamazepine, Melt-Sono-Crystallization Technique, Immediate Release, Tablet.

Routes of Administration

Because of patient compliance and convenience, the majority of medications are taken orally. It is simple and common to take medication by swallowing a dosage form.

Hence, compliance of patient and drug treatments are classically more efficient with orally given medication than other drug administration routes.[6]

Problems with poorly water-soluble drug:

Poor solubility is a problem for over 90% of pharmaceuticals. 40% of active pharmacological compounds found through combinatorial screening processes run by numerous pharmaceutical corporations are thought to be inadequately water-soluble. When medications are taken orally, they dissolve in the stomach and/or intestinal fluids before diffusing through the gastrointestinal tract's membranes and entering the bloodstream.[4] Therefore, poorly water-soluble drugs naturally show dissolution-controlled absorption, and drugs with low membrane permeability usually show permeation-controlled absorption. Therefore, a major focus of pharmaceutical research is improving the oral bioavailability of drugs [6,4]

- Improving the solubility and rate of dissolution of medications that are not very soluble in water.
- Improving the permeability of poorly permeable drugs.[4]

Immediate Release :

The medication is released from immediate-release tablets when they dissolve and disintegrate rapidly. A suitable, pharmaceutically acceptable diluent or carrier that doesn't appreciably slow down the drug's rate of release and/or absorption can offer immediate release.[3]

Solubility :

The degree to which a substance dissolves in a particular solvent at a specific temperature and pressure is known as its solubility. One of a specified molecule's intrinsic material properties is its solubility in different solvents. The highest concentration of a given solute that can dissolve in a given solvent to create a homogenous single-phase system is another definition of solubility. A set temperature, often a little over room temperature, is used to assess a solute's solubility in a given solvent.[9, 14]

Methods of preparation of Solid Dispersion[11,5]

Fusion method:

The fusion process was used to create the first solid dispersions for use in medicinal applications. This process involves dissolving a medication and carrier mixture in a metal container that has been heated in a bath. Pour the sample onto a metal plate submerged in freezing water as soon as it has thawed. Spray solidification from a modified Spr. dry on a cold metal surface is one example of a process modification. Decomposition should be prevented and is influenced by cooling rate and dissolving time.

Lyophilization technology :

Freeze-drying has been seen as a method of molecular mixing. To create a lyophilized molecular dispersion, the drug and carrier are dissolved in a common solvent, frozen, and then sublimed.

Melt Agglomeration method [10] :

Sites inside the binder that will act as support were prepared using this method. Preparations have also been created by heating the drug, binder, and excipients to a temperature higher than the binder's melting point or by heating the drug's dispersion in the molten binder using a high-shear mixer. Carried out by misting the excipient. An alternate melt agglomeration device that was suggested was a rotary processor. Because it is easier to manage the temperature and integrate a larger binder content into the agglomerate, a rotary processor might be appropriate for high melting point agglomeration. Additionally, the medication is uniformly distributed throughout the aggregates as a result of the melting process. While finer particles result in perfect adherence, larger particles cause agglomeration densification. The dispersion and coalescence of the fir particles are what causes the lumps to cluster together as soon as they melt.

Kneading method :

In a glass mortar, a carefully weighed mixture of medication and carrier is thoroughly kneaded for a while after being wetted with solvent. After drying, the resultant paste is sieved.

Melt Sono-crystallization[1,8]:

Ultrasound energizes liquids through acoustic cavitation. This phenomenon is due to the formation and collapse of gas bubbles induced by expensive, compressible sound waves radiated into the liquid.

A compound can use this energy

i) Cause a chemical reaction between reactants: this is sonochemistry.

ii) Influencing the crystal growth of the product: this is ultrasonic crystallization

Material : The carbamazepine drug used in the study is generous compliments from Glenmark Pharmaceuticals, Nashik.

Preparation[2, 13]:

a) Fusion Method :

The ratios of medication to carrier were measured at 1:1, 1:2, and 1:1.5. In this case, 100, 200, and 150 mg of Gelucire were combined with 100 mg of the medication,

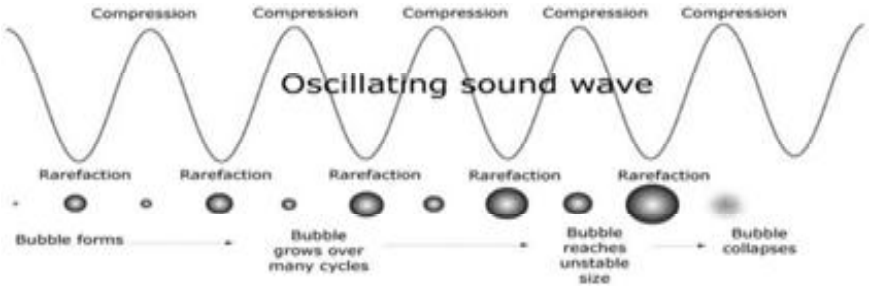

Figure 1. Indicating Melt Sono-Crystallization[1, 8]

heated in a water bath until a molten mixture of each ratio was formed, and then allowed to cool to form a solid mass that was later scraped out with a spatula to create a powder that was used to make tablets using the direct compression method.

b) Melt-sono crystallization Method :

Using different ratios of 1:1, 1:2, and 1:1.5, the three groups each contained a mixture of drug and carrier mixture. 100, 200, and 150 mg of Gelucire were taken, combined with 100 mg of the drug, and heated in a water bath until the molten mixture of each ratio was formed. The mixture was then allowed to cool to form a solid mass, which was later scraped out with a spatula to form a powder. Three milliliters of ethanol were added to this powder, and the mixture was allowed to be sonicated using an ultrasonicator at intervals of five and ten minutes. To evaporate the ethanol, the mixture was then poured into a petri dish, and the solid mass that resulted was scraped out and used for direct compression to create tablets and performance on two different media.

Preparation of Preliminary batches with Solid dispersions :

Table-1. Carbamazepine IR tablets primary batch

Tablet Formulation code	B1	B2
Drug	100	100
Gelucire	100	200
Cross PVP	40	40
Talc	4	4
MCC	156	106
TOTAL	400	400

Optimization by 3^2 Factorial Design :

A 32 factorial design was used in order to systematically examine the factors. The equation illustrates how the replies are assessed using a static model that combines interactive and polynomials. The formula is Y-b0-b 1 x 1 + b 2 X 2 + b 1 2 X 1 X 2 + b 1 2 X 1 2 + 622X22…(1).

Where b1 and b2 are the estimated coefficients of the independent parameters X1 and X2, respectively; Y is the dependent variables, which are hardness and disintegration time; and b2 is the bin arithmetic mean response of the nine runs. The main effects (X1 and X2) reprise the average result of changing one factor at a time from its low to high value. The interaction term (XI, X2) shows how the response changes when 2 factors simultaneously changed. The polynomial terms (X12 and X22) are including investigation non-linearity. Different groups, each consisting of formulations, undertook the optimization. The disintegration time of the produced formulations was assessed. Hardness and drug release. The optimized amount of the independent factors (amount of excipient and sonication time) incorporated in the tablet, which also served as the checkpoint of the regression analysis model, was used to target the disintegration time and hardness after the factorial design was applied and with the aid of the obtained polynomial terms. Table-2 displays the groups tabulated below the actual formulation design of the Carbamazepine immediate-release tablet based on the full factorial design.

Table-2. formulation design of the Carbamazepine immediate-release tablet

Factors	Unit's	Level 1(-1)	Level 2 (0)	Level 3(+1)
Gelucire 48/16	mg	100	150	200
Sonication time	min	0	5	10

Table-3. Formulation of Optimized Batches of Carbamazepine IR tablets with Water:

Ingredients	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG	100	100	100	100	100	100	100	100	100
GELUCIRE	100	150	200	100	150	200	100	150	200
CROSS PVP	40	40	40	40	40	40	40	40	40
TALC	4	4	4	4	4	4	4	4	4
MCC	156	106	56	156	106	56	156	106	56
SONICATION TIME	0	0	0	5	5	5	10	10	10
TOTAL (wt.)	400	400	400	400	400	400	400	400	400

B. Pre-formulation Evaluation Parameters[7,15]:

Angle of Repose :

The Angle of repose was determined by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table and the height and radius of the pile were measured. The angle of repose of the blend was calculated using the formula: tan θ = (h/r) θ = tan" (h/r)

Table-4. Specifications of Angle of Repose

Angle of repose	Type of flow
<25	Excellent
25-30	Good
30-40	Passabe
>40	Very poor

Bulk Density :

The blend was poured into a graduated cylinder to measure the apparent bulk density (pb). The powder's weight (M) and bulk volume (Vb) were calculated. The formula was used to get the bulk density.

Bulk density (pb) = mass / bulk volume

Tapped Density :

Using a tapped density instrument, the measurement cylinder containing a known mass of blend was tapped 100 times. Following tapping, the blend's weight (M) and constant minimum volume (Vt) in the cylinder were measured. The formula was used to determine the tapped density (pt).

Tapped Density (pt) = mass/ tapped volume

Carr's *Index :*

A powder inclines to compress. For 500, 750, and 1250 taps, it is measured using tapped density equipment; the discrepancy

should not exceed 2%. Dahlinder (1982). The following formula was used to calculate the blend's percentage compressibility based on the apparent bulk density and tapped density.

Carr's index = Tapped Density-Bulk Density/ Bulk density*100

Table-5. Specifications of Carr's Index

Carr's Index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's *ratio :*

(HR) serves as a proxy for powder flow easiness. This formula was used to calculate it.

Hausner's ratio (H) = pt/ pb

Where pt is tapped density and pb is bulk density.

Table-6. Specifications of Hausner's Ratio

Hausner's Ratio	Type of Flow
<1.25	Good flow
1.25-1.5	Moderate
>1.5	Poor flow

Drug content uniformity :

A 100volumetric flask was filled with solid carbamazepine dispersions from a batch. Dissolved in an adequate amount of 1% SLS. After removing roughly 10 millilitres of the solution from the volumetric flask, the absorbance at 284 nm was measured. For every batch of tablets 27, this test was conducted six times (n=3). The table shows the estimated amount of carbamazepine from various batches.

Drug Release studies from Solid Dispersions

Using 900 ml of water and 0.1 N HCL as a medium, dissolution tests on solid dispersions were carried out in a calibrated eight-stage dissolution rate test apparatus with paddles. Throughout the experiment, the temperature was kept at 37±0.5°C and the paddles were run at 50 rpm. Throughout the experiment, samples were taken out at 5, 10, 20, 30, 40, 50, and 60 minutes and refilled with equal volumes to keep the dissolution medium's volume constant. Following appropriate sample dilutions, the drug concentration of the samples was measured at 284 nm using a SHIMADZU double-beam UV visible spectrophotometer. Three separate trials of the drug release from solid dispersions were carried out.

C. *Post-Formulation evaluation Parameters*[12]:

1. General appearance :

Consumer acceptance is largely dependent on a tablet's overall look, visual identity, and "elegance." This covers the tablet's dimensions, form, colour, flavour, texture, physical defects, order, and so on.

2. Weight uniformity :

Twenty tablets were randomly selected and weighed from each batch. After determining the average weight, each tablet was weighed separately, and its weight was recorded. Next,

the weights of each tablet were compared to the previously determined average weight. The weight of each tablet was compared to the average weight to see if there was any variation. This test highly describes that all tablets of a particular batch should be uniform in weight. If any weight variation is there, that should be within the LP limits. The test was considered correct if not more than two tablets fell outside the LP limits out of twenty tablets taken for the test. The weight ranges of different batches of tablets were depicted in tables.

3. Hardness :

A Monsanto tablet hardness tester was used to measure the tablets' hardness. The indicator's reading is set to zero when the test tablet is held between a fixed and moving jaw. The screw knob was then moved forward to progressively increase the force applied to the tablet's edge until it shattered. The scale, which shows the pressure needed in kg/cm^2 to shatter the tablet, was used to record the reading. Tables showing the hardness of various tablet batches were provided. The weight of the material used, the distance between the upper and lower punches during compression, and the pressure utilized during compression all affect how hard the tablet is.

4. Friability :

The Roche friability was used to conduct the friability test. A batch of twenty tablets was weighed, put in a friability chamber, and rotated for 100 revolutions. These tablets are dropped six inches apart to experience shock throughout each turn. Tablets were weighed once more after 100 revolutions, and the weight decrease suggested friability. Weight loss should not exceed 1.0% of total body weight. The purpose of this test was to assess the tablets' resistance to abrasion during handling, packing, and transportation. Tables with these friability values were provided.

5. Wetting time :

Ten millilitres of water in clean, dry Petri dishes were filled with a double-folded piece of tissue paper. The tablet was set on paper, and the number of seconds it took for the tablet to completely wet was recorded.

6. Water absorption Ratio :

Twice A piece of folded tissue paper was placed in a small petri dish (5.5 cm in diameter) with roughly 10 ml of water to evaluate the water absorption ratio. On the tissue paper, a tablet was placed and left to get fully saturated. After that, the wet tablet was weighed again. The following formula was used to calculate the water absorption ratio or R:

$$R=100 \times Wa-Wb/ Wb$$

Where Wa = weight of the tablet after water absorption and

Wb-weight of the tablet before water absorption

7. Disintegration time :

Three pills were added to 900 millilitres of water and swirled until they were evenly distributed. According to European Pharmacopoeia 5.0, 2005, the maximum disintegration time for Immediate Release was three minutes. For each formulation, the

disintegration time was recorded, and the findings were displayed in tables.

8. Drug content uniformity :

20 tablets of Carbamazepine weighed and powdered. Dissolved in sufficient quantity of 1% SLS. About 10ml of the solution from the volumetric flask was taken then the diluted and the absorbance was measured at 284 nm. The amount of Carbamazepine estimated from different batches was depicted in tables.

9. In vitro Dissolution study :

A calibrated eight-stage dissolving rate test apparatus with paddles was used to conduct dissolution tests on each tablet formulation using 900 millilitres of water and 0.1N HCL. Throughout the experiment, the temperature was kept at 37±0.5°C and the paddles were run at 50 rpm. Throughout the experiment, samples were taken out at 5, 10, 20, 30, 40, 50, and 60 minutes and refilled with equal volumes to keep the dissolving medium volume constant. Following appropriate sample dilutions, the drug concentration of the samples was measured at 284 nm using a SHIMADZU double-beam UV visible spectrophotometer.

10. Mathematical modeling of release kinetics :

To examine the release mechanism, the dissolution data findings were fitted to a number of kinetic equations. All of the formulations' n values were found to be more than 0.5, suggesting that the drug release mechanism was non-firkin.

Analysis of drug release data :

DD Solver was used to analyze the mechanism of drug release from the in situ gelling system using the in vitro Version 2.08

Table-7. Evaluation of Optimized Batches of Carbamazepine IR tablets:

Formulation code	Weight vari-ation (Mean SD)	Hard ness (Kg/ cm^2)	Fria-bility (%)	*In vitro* DT Water (sec)	*In vitro* DT0.1 Hcl (sec)	Drug con-tent (%)	Water absor-ption ratio(%)	Wetting-time (sec)	% DR
Pure Drug	190	7	0.62	51	53	90	57	53	49.84
Marketed	195	6	0.50	74	75	99	60	55	70.60
F1	180	6	0.52	55	66	98	50	51	76.12
F2	183	6.5	0.62	59	60	90	51	52	86.06
F3	190	7	0.50	57	60	97	59	50	95.19
F4	183	6.5	0.61	51	53	99	55	54	72.65
F5	190	6	0.52	57	66	90	57	52	80.08
F6	180	6.5	0.61	55	55	98	50	52	91.81
F7	180	7	0.60	51	66	98	55	50	81.69
F8	190	7	0.62	51	53	90	57	53	93.95
F9	183	6.5	0.52	55	60	99	59	54	105.08

software. The dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method, and Korsemeyer-Peppas model. The model with the highest correlation coefficient was deemed the best model. The following is the Korsemeyer-Peppas equation :

$$Mt/M = Ktn$$
$$Log = \log K + n \log$$

Where Mt/M is the fraction of drug released at time t, k is the release rate constant, and When n is equal to 0.5, the drug release is with a Fickian-diffusion mechanism (Higuchi n is the diffusion exponent indicating the release mechanism. model). If 0.5 <n> 1 this indicates anomalous or non-fiction release, while if n = 0.89 this indicates zero order release.

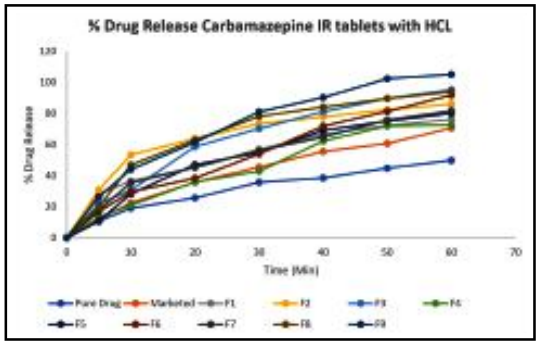

Figure 2. % Drug release carbamazepine IR tablets with HCL

Table-8. Kinetics model of drug release for optimized batches:

Code	Zero-order	R^2 1st Order	Hig-uchi	Hexon-Crowell	Kors-meyer's-Peppas	n	K	Best Fit Model
F1	0.9923	0.9290	0.9683	0.9723	0.9099	0.5996	18.0862	Zeroorder
F2	0.9418	0.9550	0.9875	0.9118	0.9977	0.8762	15.7069	Pappas
F3	0.9237	0.9508	0.9454	0.9620	0.9804	0.8998	12.7456	Pappas
F4	0.9066	0.9780	0.9809	0.9289	0.9721	0.6845	12.1357	Higuchi
F5	0.9312	0.9612	0.9312	0.9707	0.9875	0.8865	13.7400	Pappas
F6	0.9781	0.9323	0.9703	0.9780	0.9960	0.8910	9.7646	Pappas
F7	0.9467	0.9117	0.9267	0.9967	0.9347	0.8930	20.1137	Hixon Crowell
F8	0.9909	0.9447	0.9701	0.9849	0.9764	0.5303	21.4791	Zero order
F9	0.9805	0.9758	0.9980	0.9486	0.9975	0.8960	14.1132	Pappas

• The kinetic model shows mainly Korsmeyer's - Pappas model for media.

Table-9. Factors in water

ANALYSIS OF DATA BY DESIGN EXPERT SOFTWARE (Full Factorial Design):

Factor	Name	Units	Type	Sub Type	Minimum	Maximum	Mean
A	Gelucire 48/16	Mg	Numeric	Continuous	100.00	200.00	150.0
B	Sonication time	Mg	Numeric	Continuous	0.0000	10.00	5.00

Table-10. Responses in water

Response	Name	Units	Observations	Minimum	Maximum	Mean
R1	DR in 60 min	%	9.00	68.82	102.84	84.15

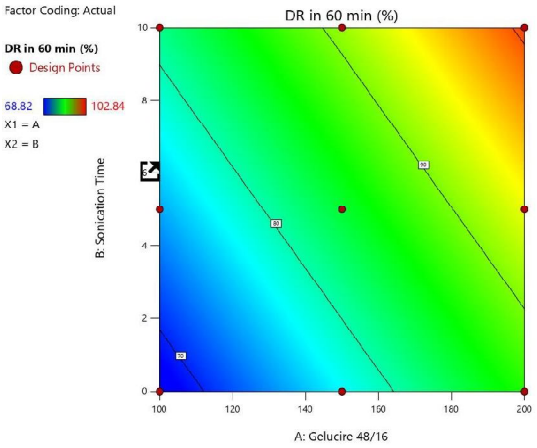

Figure 3. Contour plot of drug release in water

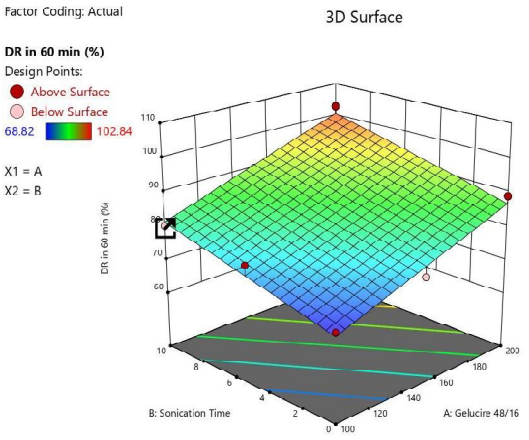

Figure 4. 3D surface response of drug release in water

Table-11. Factors in HCL

Factor	Name	Units	Type	Sub Type	Minimum	Maximum	Mean
A	Gelucire 48/16	mg	Numeric	Continuous	100.00	200.00	150.00
B	Sonication Time	mg	Numeric	Continuous	0.0000	10.00	5.00

Table-12. Responses in HCL

Response	Name	Units	Observations	Minimum	Maximum	Mean
R1	DR	%	9.00	65.01	95.08	77.22

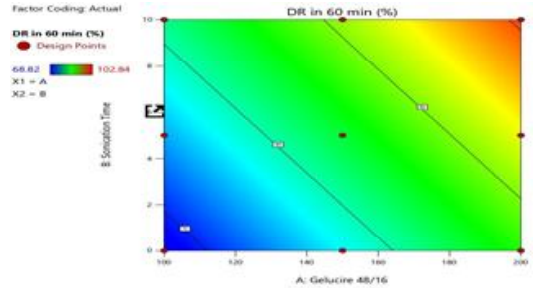

Figure 5. Counter plot showing percent drug release in HCL

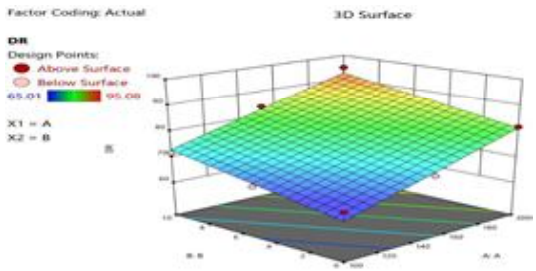

Figure 6. 3D surface response of drug release in HC

7.14. ANOVA STUDY
Response 1: DR in 60 min

Table-13. ANOVA for the linear model in water

Source	p-value	
Model	< 0.0001	significant
A-Gelucire 48/16	< 0.0001	significant
B-sonication time	0.0005	significant

Fit Statistics in water :

Table 14: ANOVA for linear model in HCL

R^2	0.9574
Adjusted R^2	0.9433
Predicted R^2	0.9028
Adeq Precision	22.9232

Table-15. Response 1: DR

Source	p-value	
Model	< 0.0001	significant
A-Gelucire 48/16	< 0.0001	significant
B-Sonication Time	0.0007	significant

Factor coding is **coded**.
The sum of squares is **Type III - Partial**

Table-16. Fit Statistics in HCL

R^2	0.9650
Adjusted R^2	0.9533
Predicted R^2	0.9041
Adea precision	24.8154

1) The final equation for % drug release for wate

%drug release=+48.45+0.192 *A+1.375*B

2) The final equation for % drug release for HCL

% drug release = +41.95 +0.197*A+1.127*B

- **From the above % Drug Release equation this is found that both the X1 and X2 factors show positive effects in the study**

Study of evaluation of carbamazepine solid dispersion: Preparation with Neusilin US retains the Dissolution property of a drug MCC as compared to the Neusilin US. Thus, we can conclude that MCC is the better choice for the preparation of solid dispersion. The preliminary batch study shows us that both the ratio of 1:1 and 1:2 drug and Gelucire 48/16 Shows better dissolution properties in both water as well as HCL. Hence, we can conclude that the Gelucire 48/16 shows good dissolution properties and can be efficient not only in Gastric media but also shows better dissolution in the presence of water. The drug release of the F9 batch with sonication showed a release of 80.72 % in water and 90.23 % in HCL in 40 mins. Compared to the F3 batch without sonication showed 69.70 % in water and 75.17 % in HCL. Thus, we can conclude that the increase in sonication time results in better dissolution of the drug. According to official media as per USP it was 1% SLS+water for dissolution but from the study it was found that Gelucire 48/16 shows good results as compared to the marketed preparation even in the absence of SLS. The results of the ANOVA analysis demonstrated that the drug release pattern is positively impacted by both Gelucire and sonication time. We can therefore conclude that better dissolution is achieved with higher Gelucire 48/16 concentrations and longer sonication times.

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