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Improvement in Solubility by Solid Dispersion Techniques via Freeze Drying method of Antiepileptic Drug.

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ABSTRACT

Present studies demonstrated that solid dispersion prepared by freeze drying method improves the carbamazepine solubility and tablets prepared from such solid dispersion achieves faster dissolution. Solid dispersions were prepared by Neusilin US2 and Pluronic F68 carrier. The developed solid dispersion's were then subjected to characterization includes micromeritics, rheological properties and Drug content. The friability, hardness, in-vitro dissolution and disintegration time of carbamazepine tablets were also examined prepared by the direct compression method. The experimental design of the Carbamazepine solid dispersions shows the effects of the Neusilin US2 and Pluronic F-68 on the drug content and the dissolution profile. It shows that when the concentration of the both the excipients is at lower and higher side according to the design given by design expert software, the drug content and dissolution profile getting poor. But when concentration of the both excipients was at optimum level (middle level) then prepared solid dispersion gives good dissolution profile and higher drug content. Optimized formulation F-4 shows enhanced solubility of drug, 92% of the drug content and dissolution of the drug from solid dispersion in 30 minutes goes to 98%. Conclusively, solid dispersion formulation with Neusilin US2 as a high specific surface area adsorption carrier and Pluronic F68 as an amphiphilic polymer was successfully used to improve solubility of Carbamazepine. From the present study, it can be concluded that the solid dispersion prepared by freeze drying technique shows the good increase in solubility, better dissolution profiles, when compared with the pure drug.

Keywords: Carbamazepine, Solid dispersion, Neusilin US2, Pluronic F68, Freeze drying, physical characterization.

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INTRODUCTION

Epilepsy is the tendency to have recurrent nonprovoked seizures. A seizure is a short, excessive burst of electrical activity in the brain that causes transitory behavioural changes. Neurons communicate with one another by chemical and electrical impulses, and they create networks with other neurons. Most seizures are caused by a limited number of aberrant neurons that generate alterations in other nearby or networked neurons.(1)

Epilepsy represents a varied set of illnesseswith diverse aetiologies, electrographical and behavioural seizure patterns, and pharmacological sensitivities. As there are several causes of epilepsy, the primary issue is caused by aberrant synchronous impulses of a network of neurons. Epilepsy can be induced by either aberrant ionic conductance or other changes in neuronal membranes, or by a balance of excitatory and inhibitory forces. Serotonin (5-HT) receptors are expressed on a variety of neurons, including cortical and/or GABAergic or hippocampal glutamatergic neurons or terminals, which include at least 5-HT1A, 5-HT2A, 5-HT2C, 5-HT1B, and 5-HT7 receptors in the CNS.G-protein-coupled 5-HT receptors and the ligand-gated ion channel 5-HT3 receptor can affect ionic conductance and/or concentration inside cells, resulting in hyperpolarization or depolarization of neurons. Based on these findings, serotonin can produce a considerable change in excitability in the majority of epilepsy-related networks.(2) Carbamazepine works pharmacologically by binding to the inactivated state of the voltage-gated sodium channel and stabilising it.

Carbamazepine exerts their pharmacologic effect by binding to and stabilizing the inactivated state of the voltage-gated sodium channel. This inhibits the channel from returning to its relaxed state, which would then be vulnerable to depolarization and subsequent repeated neuronal firing.(3)Carbamazepine, which displays dissolution dependent oral bioavailability, is an antiepileptic drug of 'Class II' in the Biopharmaceutical Classification System with polymorphs and low solubility in water (113μg·ml−1,25°C) exhibiting slow and irregular gastrointestinal absorption. Considerable variability in carbamazepine plasma concentration has also been reported.(4)

In compared to a chemical technique, solid dispersion is a simple and suitable method for improving the solubility of weakly water soluble medicaments. Chiou stated that "Solid dispersion is the dispersion of one or more active substances in an inert carrier matrix at solid-state generated by various techniques such as solvent, melting (fusion), or melting-solvent technique."Solid dispersions are also known as solid state dispersions (5). It is, for example, medicament's molecular mix and a hydrophilic polymer in which the dispersed chemicals can exist as solitary entities or in clusters. Chemical techniques will involve the production of salts and the synthesis of prodrugs.(6)

Carbamazepine (CBZ) is practically insoluble in water and shows instability in GI tract & CBZ belongs to Biopharmaceutical Classification System (BCS) class II drug having low aqueous solubility. Therefore, the present research is aimed to design and develop Solid Dispersion of CBZ with a view to improving its oral bioavailability. In the present study, Pluronic F68 and Neusiline US2 were used to enhance the solubility of carbamazepine by solid dispersion method. Further, tablets were formulated by tablet compression machine and evaluated by various parameters such as hardness, friability disintegration time, *invitro* dissolution testing.

MATERIALS AND METHOD

Carbamazepine was supplied as gift sample by U-medica Labs Mumbai, India, Neusiline US2 was supplied by Gangwal chemicals Mumbai, India, Pluronic F68was supplied by FMC Biopolymer Bangalore, India, Magnesium Stearate, Cross carmellose, Potassium hydrogen phosphate, Sodium hydrogen phosphate, Mannitolwere obtained from LobaChemie Pvt Ltd, Mumbai, India), Hydrochloric acid purchased from S.D. Fine chemicals Mumbai, India, Lactose monohydrate, Ethanol, Methanol were purchased from Merck Pvt. Ltd., Mumbai, India.

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Method

Preparation of Carbamazepine solid dispersion using freeze drying technique

Carbamazepine (API) was accurately weighed and dissolved in methanol. Neusilin US2 was correctly weighed and added to the same vessel. In another vessel accurately weighed Pluronic F68 was added in appropriate amount of methanol and continuously stirredit on magnetic stirrer to get clear solution. To obtain a clear solution, the API and Neusilin US2 solutions were added to the Pluronic F68 solution while stirring continuously. The prepared final solution stirred for additional 15 min on magnetic stirrer to ensure complete coating of polymer on the API. The methanol in the solution was evaporated using the Rotary evaporator (bekman)at 93 mBar and 35^{0}C. The dried film obtained on the wall of the container of the rotary evaporator was hydrated with purified water. Accurately weighed quantity of Mannitol (Cryo-protectant) was added to the above solution and kept in deep freezer overnight. The solution of solid dispersion in water was dried in freeze dryer (at -72^{0}C and vacuum pressure of 20 Pa) (Vertis Benchtop K). After drying,the prepared solid dispersion was passed through 30 mesh and stored in closed vials until further characterization.(7)

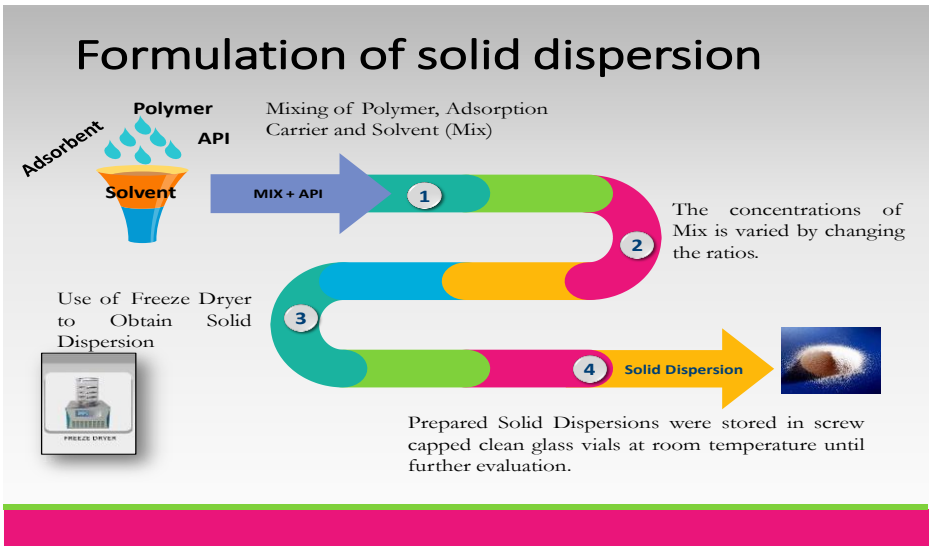

Fig. 1 Diagramatic representation of Formulation

Preformulation Studies

FTIR Spectroscopy

IR grade KBr was combined separately with the improved batch formulation. Trituratein a 1:100 ratio, and equivalent pellets were prepared in a hydraulic press under 10 metric tonnes of pressure. The pellets were analysed in FTIR instrument with wave range of 4000-400cm^{-1}. (Shimadzu, Japan).(14)

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) of pure carbamazepine and solid dispersions of optimized batch were conducted using differential scanning calorimeter (Mettler Toledo, US) at heating rate of 10^{0}C/min over a temperature range of 40 to 350^{0}C under an inert atmosphere flushed with nitrogen at a speed of 10 ml/min.(15)(16)

Characterization of Solid dispersions of Carbamazepine

Solubility measurement of solid dispersion

Carbamazepine solid dispersion of an excessive amount was added to 10 ml of distilled water into the test tubes. This mixture is then mixed by using vortex mixture for 5-10 min at 1400 rpm. The test tubes then kept in orbital shaker for 7 days. These test tubes were centrifuged for 5 minutes at 6000 rpm

after 7 days.The upper layer of the water of nearly 5 ml decanted and diluted with 20 ml of distilled water. The diluted solution was analyzed under UV at 287 nm and the concentration of the carbamazepine was calculated.(18)

Physical characterization of solid dispersions

Angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index were all used to evaluate carbamazepine solid dispersions.(8)

Powder X-ray diffraction study (PXRD)

PXRD patterns in transmission mode were recorded using Bruker advance diffractometer equipped with focusing Ge-crystal primary monochromator that generates CuKα1 radiation (λ=1.541Å), within 4-450 2θ range in steps of 0.050 and scanning time of 12 sec per step.(17)

Percentage yield

The dried solid dispersion was carefully collected and weighed. The % yield was calculated by using following (9)

$$\% \text{ Yield} = \frac{\text{mass of solid dispersion}}{\text{Total weight of drug+polymer}} \text{ x } 100$$

Drug Content

Drug content of solid dispersion was determined by extracting it with 100ml of methanol. The solid dispersions equivalent to exactly 100mg of pure drug was accurately weighed, groundedand transferred into a 100ml volumetric flask containing 100 ml of methanol and the mixture was stirred for complete extraction of drug. The solution was filtered through a 0.45 µm filter paper, diluted with appropriate amount of methanol and spectrophotometrically measured at 287 nm.(10)

Particle size analysis

The particle size distribution of solid dispersions was evaluated by sieve analysis. 5-6 gm of the solid dispersions was sieved through a nest of sieves on a vibratory sieve shaker (Lab India, India) for 20 min.(11)

Particle morphology analysis (Optical Microscopy)

Motic digital microscope was used to determine morphology of optimized solid dispersion and drug. (Motic, china).(12)

***In vitro* drug dissolution study**

Carbamazepine dissolution rates from the pure drug sample and prepared solid dispersions were tested using rotating paddle apparatus (Electrolab, India). pH 1.2 HCl buffer (900ml) was used as dissolution medium, since carbamazepine exhibits pH-independent solubility so distilled water can also be used as dissolution medium for the same. The test was performed with paddle rotation speed of 50 rpm. The experiment employed a quantity of solid dispersion samples corresponding to a single therapeutic dosage of Carbamazepine of 200 mg. 5 ml aliquots were collected at predefined intervals (5, 10, 15, 20, and 30 minutes), after that replace the media with the same volume of fresh media. Withdrawn aliquots were screened through a 0.45 m membrane filter, and the quantity of dissolved carbamazepine was measured by UV Spectrophotometry at a wavelength of 287 nm using a UV-Vis spectrophotometer. (Shimazdu, Japan).(13)

Formulation of Tablets from Solid Dispersions of Carbamazepine

Trial batches were carried out to develop and standardize the formula of tablet containing 200 mg Carbamazepine and the match the dissolution profile with marketed drug products.

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Manufacturing procedure

The Manufacturing procedure to formulate tablet 200mg consists of the following steps:

Calculated and weighed amount of Solid dispersion containing 200mg of Carbamazepine based on its potency and all other ingredients. Shift the solid dispersion, lactose monohydrate through 30 #, magnesium stearate and cross carmellose sodium through 60 mesh. Mix all the above ingredients with solid dispersion and blend for 10 min to get uniform mixing. Lubricated blend was compressed in tablet compression machine with 12 mm punches.(19)

Experimental design for Carbamazepine solid dispersion

Various batches of Carbamazepine solid dispersion were prepared based on the Central Composite Design which was employed in design expert to design batches as follows:

Table 1: The independent variables and dependent variables.

Independent Variables (Factors)	Dependent Variables(Responses)
X_1 = Conc. of Neusilin US2 (%)	Y_1 = Drug content (%)
X_2 = Conc. of Pluronic F-68 (%)	Y_2 = Drug Release in 30min Q30 (%)

Table 2: The independent variables and their level for Central Composite Design:

Independent Variables Factors	Low Level	Middle Level	High Level
(X_1) Conc. of Neusilin US2 (%)	40	50	60
(X_2) Conc. of Pluronic F-68 (%)	10	15	20

Table 3: The investigated factors with their coded and actual values

Formulation	X1 Actual value	X1 Code value	X2 Actual value	X2 Code value
F1	**40**	**-1**	**10**	**-1**
F2	**50**	**0**	**15**	**0**
F3	**60**	**+1**	**20**	**+1**
F4	**50**	**0**	**15**	**0**
F5	**50**	**0**	**22.07**	+1.2
F6	**64.14**	+1.2	**15**	**0**
F7	**35.86**	-1.2	**15**	**0**
F8	**50**	**0**	**15**	**0**
F9	**50**	**0**	**7.93**	-1.2
F10	**60**	+1	**10**	**-1**
F11	**40**	**-**1	**20**	**+1**

Optimization data analysis and model-validation

ANOVA was used to establish the statistical validation of the polynomial equations generated by Design Expert® software (version 8.0.1, Stat-Ease Inc).

In the model analysis, the responses: the drug content and drug release in 30 min (Q30) of all model formulations were treated by Design Expert® software. On the basis of comparisons of several statistical parameters, including the coefficient of variation (CV), the multiple correlation coefficient (R2), adjusted multiple correlation coefficient (adjusted R2), and the obtained by the Design Expert® software, the best fitting mathematical model was chosen. The desirability technique was then utilised to determine the best parameters for the formulas.(20)

Comparison of dissolution profile of optimized batch with pure drug batch

The in vitro dissolution profile is the most important consideration when comparing two drugs, formulations, or dosage forms.The USFDA emphasises similarity and difference aspects when comparing in vitro dissolution profiles.

Similarity factor (F2)

It stress on the comparison of closeness of 2 comparative formulations. Similarity factor in range 50-100 is acceptable according to USFDA.

Eq- **$50 \log \{[1+(1/n)\Sigma t=1 (Rt - Tt)2]-0.5 \times 100\}$**

n is the no. of dissolution sample times.

The similarity factor should be between 0 and 100. It is 100 when two comparative gp's of reference and test are identical and approaches 0 as dissimilarity increases.

Difference Factor (F1)

It focused on the difference in % dissolved between reference and test at various time intervals. It can be mathematically computed by using

$F1 = \{[St=1 (Rt- Tt)] / St=1 Rt]\} \times 100$

The optimized batch and pure drug was compared by calculating F1 and F2 values.

Formulation of the solid dispersions using a central composite design

Various batches of Carbamazepine solid dispersion were prepared based on the Central Composite Design. Central Composite Design was used in design expert to design batches. The independent variables and dependent variables were Neusilin US2 concentration (%) (X_1) and Pluronic F68 concentration (%) (X_2). Drug content (%) (Y_1) and Drug Release in 30 min (Q30) (%CDR) (Y_2) were taken as response parameters as the dependent variables. The results of the given batches are summarized in following table.

Table 4: Optimization Data Analysis and Model-validation

Batch	Factors (Independent Variables)		Responses (Dependent variables)	
	Neusilin US2 (X_1) (%)	Pluronic F-68 (X_2) (%)	Drug Content (Y_1) (%)	Drug Release Q30min (Y_2) (%)
F1	40	10	90.95	89.64
F2	50	15	93.64	98
F3	60	20	88.65	87.24
F4	50	15	93.65	98
F5	50	22.07	92.54	86
F6	64.14	15	88.87	72
F7	35.86	15	94.57	94
F8	50	15	93.64	98
F9	50	7.93	92.54	89
F10	60	10	91.84	80.23
F11	40	20	90.07	85

Fitting of Data to the Model

The central composite rotational design (**CCRD**) - Response surface model (**RSM**) methodology offers to investigate a high number of variables at different levels with limited number of experiments. A

mathematical relationship between factors and variables was generated by response surface regression analysis using Design-Expert® (version 8.0.1, Stat-Easc, Inc., Minneapolis, MN, USA)software. To fit the data, a quadratic model was chosen as the best model. Additionally, analysis of variance (ANOVA) results were calculated by this software.

The two factors with lower, middle and upper design points in coded and uncoded values are shown in Table 4. All the responses observed for eleven formulations prepared were fitted to various models using Design- Expert® software. It was observed that the best-fitted models were linear for Y_1 and Y_2 is Quadratic. The results of ANOVA in **Table 5, 6** for the dependent variables demonstrate that the model was significant for all the response variables.

Regression equations of the fitted quadratic and model:

$$Y1 = +9.61 - 0.81*A - 0.98*B$$

$$Y2 = +87.77 - 0.40*A + 1.43*B + 0.16*A*B - 3.21*A^2 - 0.39*B^2$$

Model Assessment for the Dependent Variables

After putting the data in Design Expert software, Fit summary applied to data in that quadratic model had been suggested by the software for all the responses. The statistical evaluation was performed by one-way ANOVA.

Table 5: ANNOVA for Response Surface Quadratic model, Response 1 : Drug content

Source	Sum of Squares	Df	Mean Sq	F value	p-value Prob>F	inference
Model Quadratic	45.56	1	11.64	6.99	0.0192	Significant
A –Neusilin US2	9.23	1	9.23	5.54	0.0568	
B – Pluronic F-68	15.09	1	15.09	9.05	0.0237	
A^2	6.74	1	6.74	4.05	0.0910	
B^2	20.49	1	20.49	12.30	0.0127	
Residual	10.00	6	1.67			
Cor total	56.55	10				

Where df = Degree of Freedom; F = Fischer's Ratio.

The Model F-value of 6.99 implies the model is significant. There is only a 1.92% chance that an F-value this large could occur due to noise. Model terms with P-values less than 0.0500 are significant. B and B2 are important model terms in this scenario. The model terms are not important if the value is bigger than 0.1000.Model reduction may improve your model if there are many inconsequential model terms (not including those required to support hierarchy).

Table 6: ANNOVA for Response Surface Quadratic model, Response 2 : %Drug Release

Source	Sum of Squares	Df	Mean Sq	F value	p-value Prob>F	inference
Model Quadratic	59.57	5	11.91	11.84	0.0084	Significant
A –Neusilin US2	4.91	1	4.91	4.87	0.0783	
B – Pluronic F-68	5.32	1	5.38	5.34	0.0688	
AB	25.10	1	25.10	5.34	0.0041	
A^2	11.70	1	11.70	24.94	0.0190	
B^2	5.63	1	5.63	5.59	0.0644	
Residual	5.03	5	1.01			
Lack of fit	4.57	3	1.52	6.65	0.1336	Not Significant
Cor total	64.60	10				

The Model F-value of 11.84 implies the model is significant. There is only a 0.84% chance that and F-value is large which could occur due to noise.

Model terms with P-values less than 0.0500 are significant. AB and A2 are important model terms in this situation. The model terms are not important if the value is bigger than 0.1000.Model reduction may improve your model if there are many inconsequential model terms (not including those required to support hierarchy).

Response Surface Plot Analysis

Figures show three-dimensional response surface plots created by Design Expert® software for the examined responses, namely drug content (Y1) and drug release in 30 minutes (Y2).Figure 2 depicts response surface plot of Neusilin US2 concentration (A) and Pluronic F68 effect i.e. when increased A from low to high the value of Y_1 decreased and when B increased from low to high the value of Y_1 also decreased. Factor amount of A had lower values of "F" than B which indicated that factor amount of A more significantly affect response variable then B factor as shown in Table 5. Figure 3 represents response surface plot of the effect of A and B on Drug Release in 30 min (Y_2) which shows quadratic model. Optimum range of A and B combine increases the drug release. Factor amount of A had lower values of "F" than B which indicated that both factors amount of Aand B more significantly affect response variable as shown in Table 6.

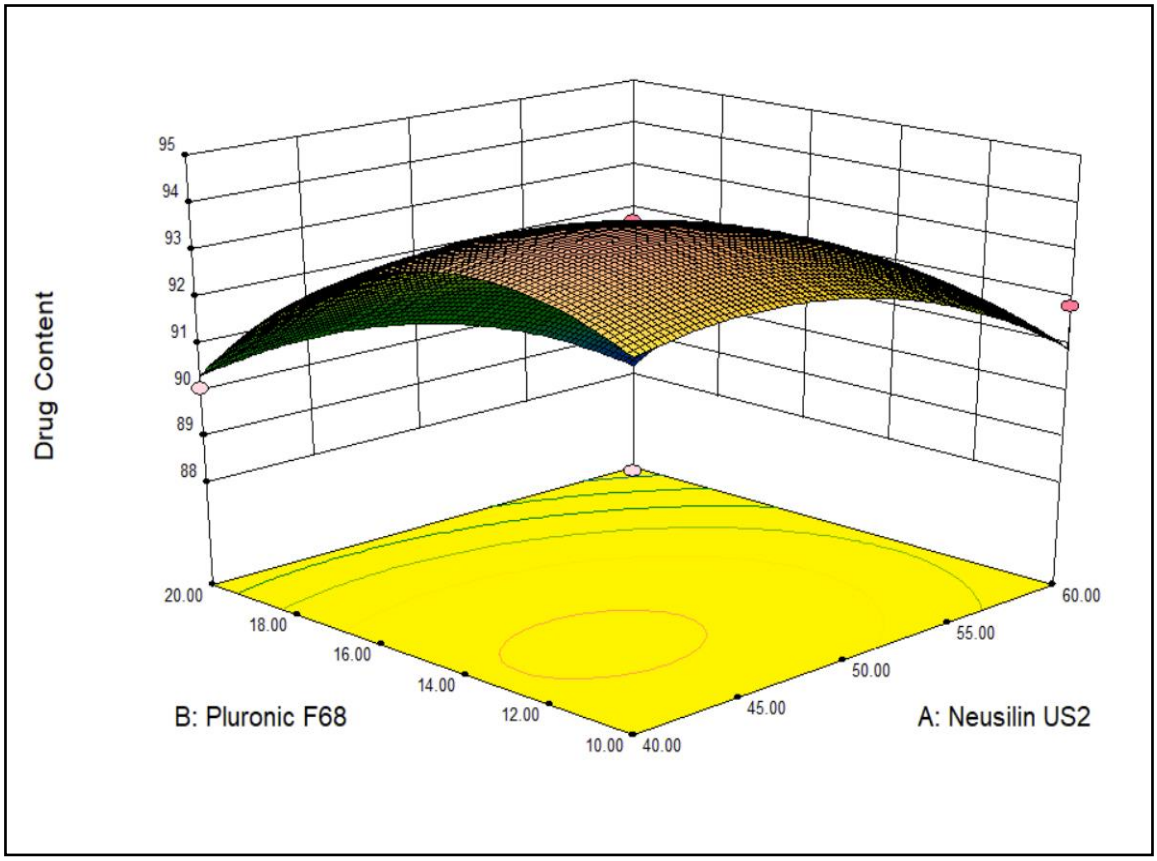

Fig No 2: Response surface plots for the A and B on Drug content(Y_1), Where A = Neusilin US2 concentration and B = Pluronic F-68 concentration.

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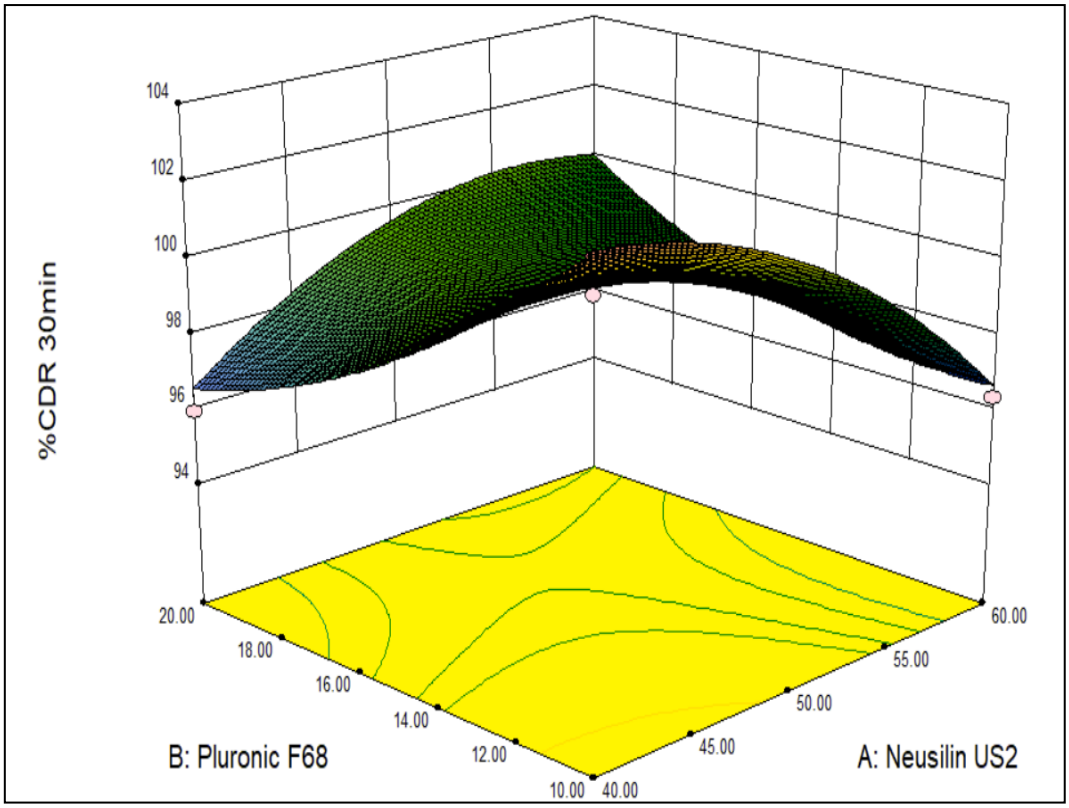

Fig No. 3 Response surface plots for the Drug Release in 30 min (Y_2),

Where A = Neusilin US2 concentration and B = Pluronic F-68 concentration

Optimization of Result

The optimization was performed on the basis of response surface modelling by using the numerical and graphical optimization method. Desirability is an objective function with a value of one at the goal and 0 outside of the limits. The numerical optimization identifies a position where the desirability function is maximised. Adjusting the weight or priority of a goal might change its qualities. All goals are merged into one for a variety of reactions and variablesdesirabilityfunction. The goal of optimization is to find a good set of conditions that will meet all the goals.

Optimized formulation containing 50% Neusilin US2 concentration, 15% Pluronic F-68 concentration fulfilled all the criteria set from desirability.

Evaluation of Pre-compression parameters of drug and powder blend

Physical parameters of drug

Tablet powder blend was subjected for evaluation of various micrometrics properties such as angle of repose, Carr's index and Hausner'sratio.

Bulk Density and Tapped Density

The volume (Vp) was measured after an accurately weighed quantity of powder (W) was carefully poured into a 100 ml graduated cylinder.The graduated cylinder was secured to the bulk density instrument with a lid. The density apparatus was set to (500, 750, or 1250 tapping) until no further volume reduction was seen or the difference in percentage was less than 2%. The volume (Vt) occupied by the powder blend was measured after tapping. The formula was used to compute the bulk density and tapped density.(21)

$$Bulkdensity = \frac{\text{MassofPowder}}{\text{Bulk Volume of powder}}$$

$$Tappeddensity = \frac{\text{MassofPowder}}{\text{Tapped Volume of powder}}$$

Compressibility index

It is also one of the approaches for evaluating granule flow properties by comparing bulk and tapped densities. Carr's compressibility provides a valuable empirical reference. The drug's packing ability was assessed based on changes in volume caused by packing rearrangement during tapping. Carr's compressibility index was determined using equation,(21)

$$Carr'sIndex = \frac{\text{Tapped Density} - \text{Bulk Density}}{Tapped\ Density} \times 100$$

Hausner's ratio

It is measurement of fractional resistant of drug. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$Hausnersratio = \frac{\text{Tapped Denbsity}}{Bulk\ Density}$$

Angle of repose

The angle of repose was determined by fixed funnel method. A glass funnel was held in place with a clamp on a ring support over a horizontal surface. The powder blend was accurately weighted and placed into the funnel, with the opening of the funnel blocked by the thumb.As the thumb was removed the powder blend was allowed to flow through the funnel freely on to the surface. The pile's height (h) and base radius (r) were measured, and the angle of repose was computed using the equation below.(21)

$$\textbf{Tan } \theta = \frac{h}{r}$$

Where; **h** and **r** are the height and radius of the powder cone.

Post-Compression parameters of Tablet

General appearance

The general appearance and elegance of the tablet were visually identified, which included tablet size, shape, colour, scent presence or absence, and surface texture.(21)

Weight variation test

Twenty tablets were chosen at random from each batch and weighed individually. We determined the average weight and standard deviation of 20 pills. If not more than two of the individual tablet weights deviate from the average weight by more than the percentage provided in table 25, and none deviate by more than twice the percentage shown, the batch passes the weight variation test.(21)

Uniformity of thickness (Felix E. Fernandez et al 1995)

Ten tablets were picked from formulations randomly and thickness was measured individually using "Vernier-caliper (Mitutoyo, Japan)". It is expressed in (mm) and average was calculated.

Hardness test (Jain S., et al., 1999)

Tablets must have a specific level of strength or hardness in order to survive mechanical shocks during production, packaging, and delivery. The "Monsanto Hardness tester (Vinsyst Technologies)" was

used to determine the hardness of the tablets. It is expressed in kilo pound (kp). Tablets were randomly picked from batch and hardness of the same tablets was determined. Most commonly used apparatus for hardness is electronically operated hardness tester Criteria: Tablet hardness should lies between 5 to 10 kg/cm^3.(22)

Friability test

Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing; handling and transporting. The friability of the tablets was determined using Roche Friabilator. It is expressed in percentage (%).Initially, ten tablets were weighed and placed in the friabilator. For 4 minutes, the friabilator was spun at 25 rpm. The tablets were weighed again after 4 minutes. The formula was then used to calculate the friability.

$$\textbf{Friability}\ (\%) = \frac{\text{Initialweight} - \text{finalweight}}{\text{Initialweight}}$$

% Friability of tablets less than 1.0% are considered acceptable.(22)

Disintegration time

Complete disintegration of a tablet is defined as any residue of the unit remaining on the screen of the test instrument or sticking to the lower surface of the disc, excluding insoluble coating particles. The disintegration time was calculated using a USP equipment that includes a basket-rack assembly and an 800 mL low-form beaker device for lifting and lowering the basket in the immersion fluid at a constant frequency rate of 29 to 32 cycles per minute.The Basket contained 6 glass tubes whichare 3 inches long, openedat one end and held against 10 mesh screen at the bottom end of basket rack assembly. One tablet was placed in each tube and the basket was placed in an 800 ml beaker of water at a temperature of 370C 20C to test disintegration time. The basket assembly was moved up and down by a typical motor-driven system. All tablets must disintegrate and all particles must pass through the 10 mesh in the time specified to meet the USP criteria.(22)

***In vitro* dissolution test**

Dissolution study of tablet performed in USP II (Paddle) dissolution test apparatus (Electrolab, India) using 900 ml of pH 1.2 HCL buffer as a dissolution media. Throughout the investigation, the tablet was placed into each vessel of the dissolution equipment, and the temperature of the dissolution media was maintained at 370°C 0.50°C with a stirring speed of 50 rpm. At intervals of 5, 10, 15, 20, 30, 45, and 60 minutes, aliquots of dissolving media containing 5 ml of samples were taken, and 5 ml of new dissolution media kept at the same temperature was reintroduced. UV analysis of the samples was used to calculate the amount of drug released and the percentage cumulative drug release at various time intervals.(22)

Dissimilarity factor ƒ1 and Similarity factor ƒ2

Dissimilarity factor (ƒ1)

It was calculated in the comparison with reference or innovator product with in house product to know the dissimilarity.

The dissimilarity factor (ƒ1) should be always less than 10 (f1<10).

Dissimilarity factor (ƒ1) =

$$\frac{\sum Rt - Tt}{\sum Rt} \times 100$$

Similarity factor (ƒ2)

The similarity factor (ƒ2) was defined as the 'logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products'.

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This was calculated so that the test could be compared to reference release profiles. The similarity factor (2>50) must always be more than 50.

When more than three or four dissolution time points are available, the approach is more appropriate for comparing dissolution profiles, and it can only be used if the average difference between Rt and Tt is less than 100.If this difference is higher than 100, normalization of data is required. Similarity factor between in house tablet and reference product was calculated by following formula.

$$\text{Similarity factor } (f2) = 50\times\log 10\times\frac{1}{\sqrt{1+\frac{1}{n}}}$$

Where, n = No. of sampling points.

RESULT AND DISCUSSION

The preformulation studies results the confirmation of the drug test performed by the melting point determination, infrared spectroscopy, and differential scanning calorimetry, from that data it was found that drug has melting point of 192^{0}C, and characteristics peaks showed on the spectroscopic graph shows the presence of the peaks 3462, 1569, 1672, etc. are same when compared with standard spectroscopic graph of CBZ. Carbamazepine shows peak absorbance at 287nm and shows linear graphs in the methanol, water, pH 1.2, 7.4, etc.

The solubility of the Carbamazepine in water was reported to be 0.018mg/ml, which was increased to the 1.747 mg/ml i.e. increase in the solubility to 97.101 times that of the original solubility of the drug. Increase in the solubility of the carbamazepine is due to the addition of the adsorption carrier Neusilin US2 and Polymer Pluronic F-68.The concentration of Neusilin US2 and Pluronic F-68 of 50:15 was selected as best through design expert software which was effective for solubility enhancement of drug. The technique of solid dispersions by freeze drying technique enhanced the drug solubility in water by ninety seven folds.

Overlay Spectra of FTIR includes spectra of drug with optimized batch. The spectra of physical mixes, all of the drug's characteristic peaks appear at the same wave number, showing that there is no modification or interaction between the drug and the polymers. Hence, it can be stated that our prepared solid dispersion did not have any impact on the drug properties so as to ensure its biological activities.

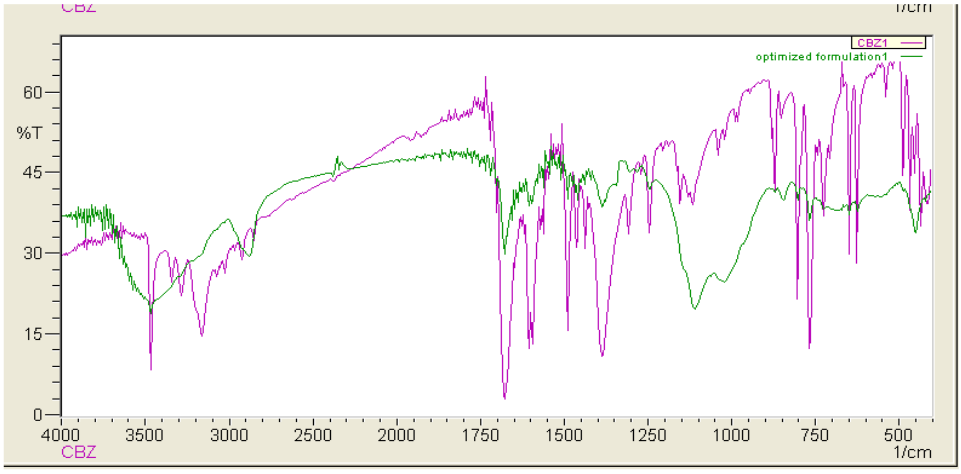

Fig No. 4 Overlay Spectra of FTIR includes spectra of drug with optimized batch

In the above overlay DSC Graph the endothermic peak of pure drug, optimized batch and excipients shows no shift in their position of Melting Point. This shows that there is no change in thermal properties of drug and excipients and no change in Melting point.

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DSC thermogram of carbamazepine showed two characteristic endothermic peaks separated by one exothermic peak. The melting of CBZ polymorph form III correlates to the first endothermic peak at 1780C, confirming that CBZ raw material has this polymorphic form, which is the only one permitted by the Pharmacopeia. DSC analysis revealed that CBZ was present in crystalline form in all solid dispersion samples examined. Because of the polymorphic form of CBZ changing due to heating during analysis.As a result of this, the polymorphic form of CBZ was identified utilising the PXRD approach.

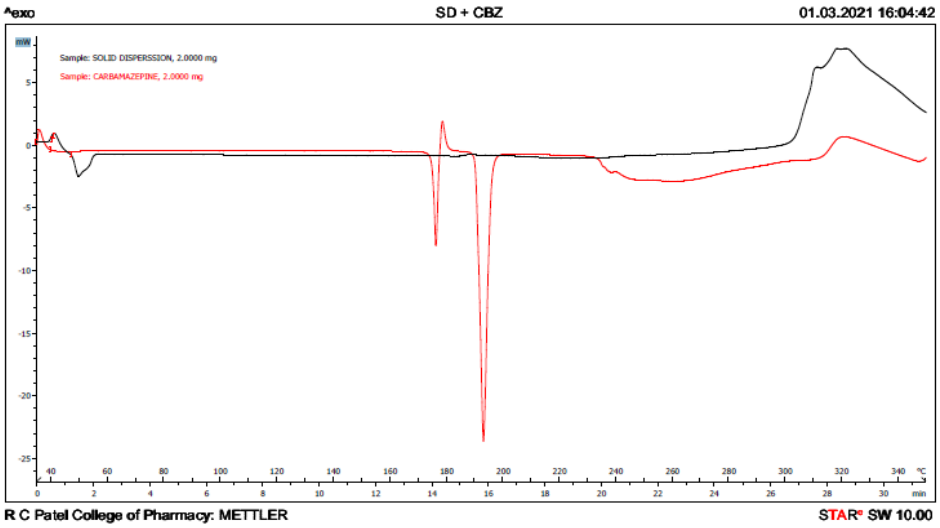

Fig No. 5 Overlay of DSC graph of pure drug with optimized batch

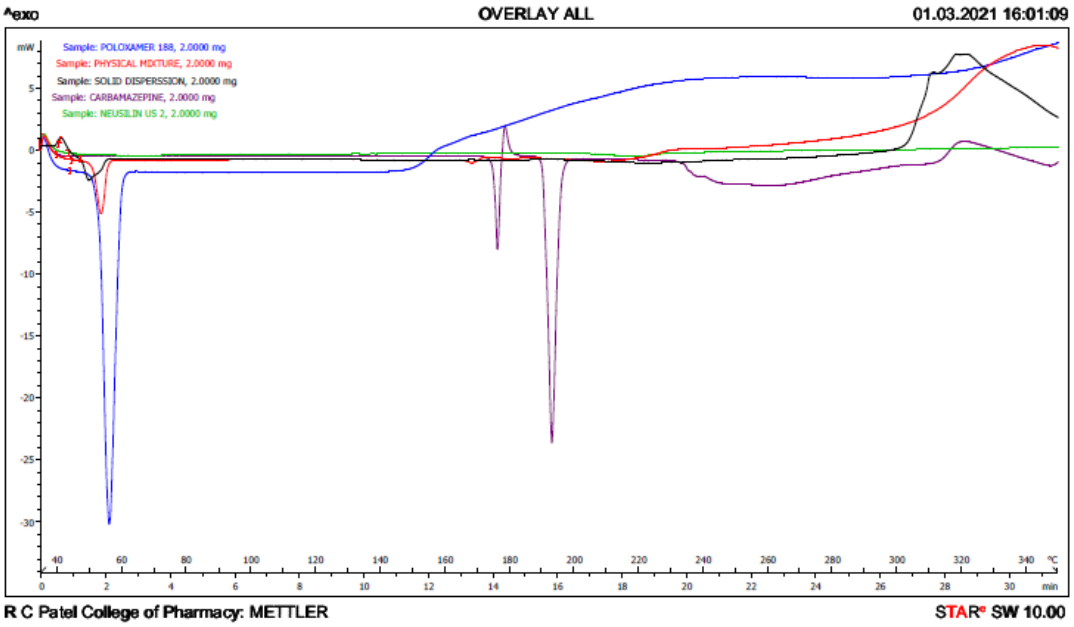

Fig. No. 6 Overlay of DSC graph of pure drug, physical Mixture, optimized batch and polymers.

The PXRD pattern of pure CBZ had peaks at 13.15o, 14.25o, 15.36o, 15.9o, 19.55o, 23.5o, and 27.7o 2, which corresponded to the PXRD pattern of polymorphic form III of CBZ previously reported.Diffractogram of optimized formulation indicates that CBZ in this formulation partially transformed into amorphous form. Position of three distinguishable peaks on the diffractogram of this formulation (13.2°, 23.95°, 25.05° 2θ) is in close agreement with the diffractogram of polymorphic form III, indicating absence of polymorphic transition during preparation of this sample.

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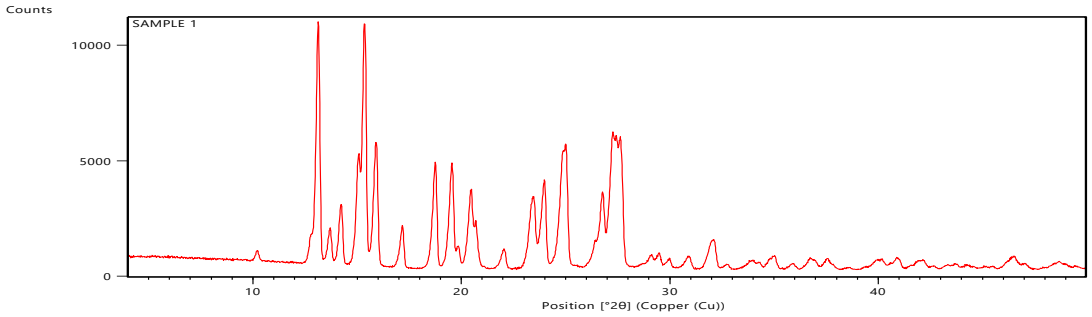

Fig No. 7 PXRD image of pure drug Carbamazepine

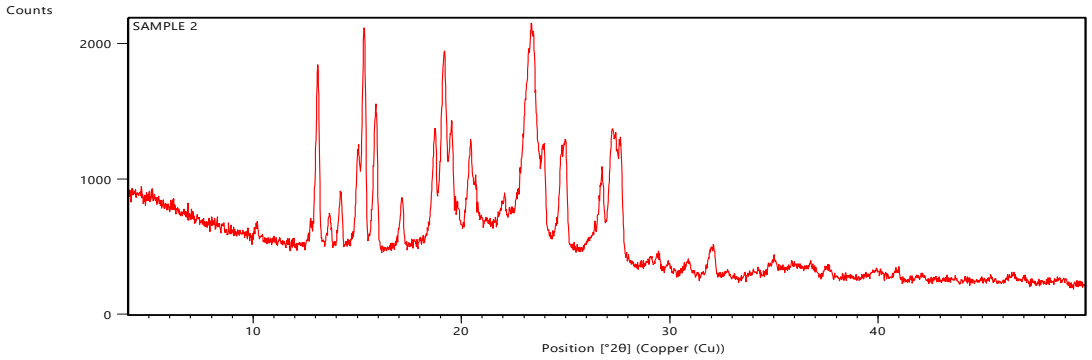

Fig No. 8 X-ray diffractogram of optimized batch of Solid dispersions.

The experimental design of the Carbamazepine solid dispersions shows the effects of the Neusilin US2 and Pluronic F-68 on the drug content and the dissolution profile. It shows that when the concentration of the both the excipients is at lower and higher side according to the design given by design expert software, the drug content and dissolution profile getting poor. But when concentration of the both excipients is at optimum level (middle level) then prepared solid dispersion gives good dissolution profile and higher drug content.

Table 7: Physical Properties of Batches.

Batch	Angle of Repose	Bulk Density	Tapped Density	Carr's Index
1	29.98±0.081	0.83±0.11	0.922±0.21	15.69±1.2
2	27.43±0.21	0.612±0.32	0.739±0.24	13.04±1.54
3	26.55±0.44	0.910±0.42	0.971±0.26	15.78±1.43
4	**29.11±0.56**	**0.82±0.53**	**0.88±0.76**	**19.98±1.21**
5	25.87±0.22	0.923±0.45	0.987±0.54	13.17±1.23
6	27.38±0.14	0.955±0.35	0.996±0.76	12.56±1.02
7	24.27±0.58	0.865±0.35	0.934±0.32	13.17±1.23
8	29.11±0.56	0.82±0.53	0.88±0.76	19.98±1.21
9	28.64±0.65	0.865±0.42	0.911±0.11	12.78±0.72
10	27.16±0.73	0.637±0.48	0.769±0.47	11.41±0.88
11	24.87±0.22	0.953±0.45	0.977±0.54	13.19±1.23

* Values expressed as Mean ± SD, n=3

All the batches show angle of repose between 25 - 30° and Carr's index near to 15%. The results of Bulk and Tapped Density were satisfactory. **Flow property was found to be "passable.**

Development of trial batches

Trial batches carried out to developed and standardize the formula to formulate tablet containing 200 mg drug and to matches the dissolution profile with marketed drug product.

Physical Evaluation Parameter of Tablets

Physical evaluation of powder blend of the solid dispersion batches was mentioned in the above section no. F4 batch from the solid dispersion batches was taken as optimized batch and used for the preparation of tablets, because the drug content in this found to be 93.65% and the % drug release in 30 min from solid dispersion was 98%.ence, this optimized batch of solid dispersion was used to prepare tablets. Batches taken for tablets are mentioned as B1-B6 respectively (Batches for solid dispersion mentioned as F1-F11.

Table 8: Post-Compression parameter of different batches

Sr. No.	Average wt. (mg)	Thickness (mm)	Hardness (N)
Specification	**241-279 (targeted wt. 270mg)**	**5.15mm -5.45mm**	**7-9 kg/cm^3**
B1	262	5.20	6
B2	265	5.16	7
B3	272	5.23	6
B4	267	5.18	8
B5	267	5.21	7
B6	**275.86**	**5.24**	**8**

Optimized batch **B6** is compared with the **Marketed** batch with the 0.1 N HCl medium.

The formulation batch **B6** shows better results. When compared with the marketed formulation which shows release of 98.6% release in 30 min, our test product shows 97% of the drug release in 30 min which is present in given limits and same as the marketed product with minor deviations.

The release of drug from other batches hampered due to low concentration of disintegrant and high hardness. These formulation problems were resolved to get optimized batch by changing the concentration of binder, disintegrant and lubricant.

Table 9: Production Yield and Drug Content of all Batches.

Batches	%Production Yield (%)	Drug Content (%)
1	80	90.95
2	85.23	93.64
3	75.86	88.65
4	**91.25**	**93.64**
5	85.24	93.64
6	78.65	88.87
7	79.36	94.57
8	91.25	93.64
9	85.36	92.54
10	87.00	91.84
11	86.47	90.07

* Values expressed as Mean ± SD, n=3

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The Neusilin US2 used as adsorption carrier and Pluronic F68 was used as Surfactant to increase the solubility of the Carbamazepine. Firstly when API adsorbed on the Neusilin US2, the Pluronic F-68 coats the adsorbed drug. When the concentration of Neusilin US2 is increased at the highest concentration according to the Design expert software, the solubility and dissolution of the carbamazepine increased to maximum level and again goes to the lower level again after addition of the Neusilin US2.

The Pluronic F-68 concentration also affects the solubility of the carbamazepine. When the concentration of Pluronic F-68 increased upto middle level according to the design expert software data, the concentration increases, but further addition of Pluronic F-68 decreases the solubility as well as dissolution of the Carbamazepine.

Table 10: Particle shape analysis parameters determination

Batch	Aspect ratio	Pellips	Roundness	Circularity
1	1.25	0.764	1.029	0.959
2	1.92	0.88	1.058	0.969
3	2.025	1.04	1.001	0.989
4	1.21	0.68	1.073	0.711
5	1	0.70	1.035	0.728
6	1.11	0.472	1.092	0.827
7	1.12	0.87	1.063	0.911
4	1.21	0.68	1.073	0.711
9	1	0.92	1.044	0.814
7	1.13	0.86	1.054	0.864
8	1.66	1.27	1.023	0.895

The aspect ratio, circularity, particle size and pellips are important parameters in solid dispersion which determine its ideal characteristics. The aspect ratio, particle size, pellips, and circularity of solid dispersions was analyzed by using optical microscope. The solid dispersions of each batch were placed on glass plate and observed under 10X. Mostly all batches were observed spherical but batch 7th showed all values of aspect ratio, roundness and circularity close to standard values as 1.12, 1.063, 0.911, respectively.

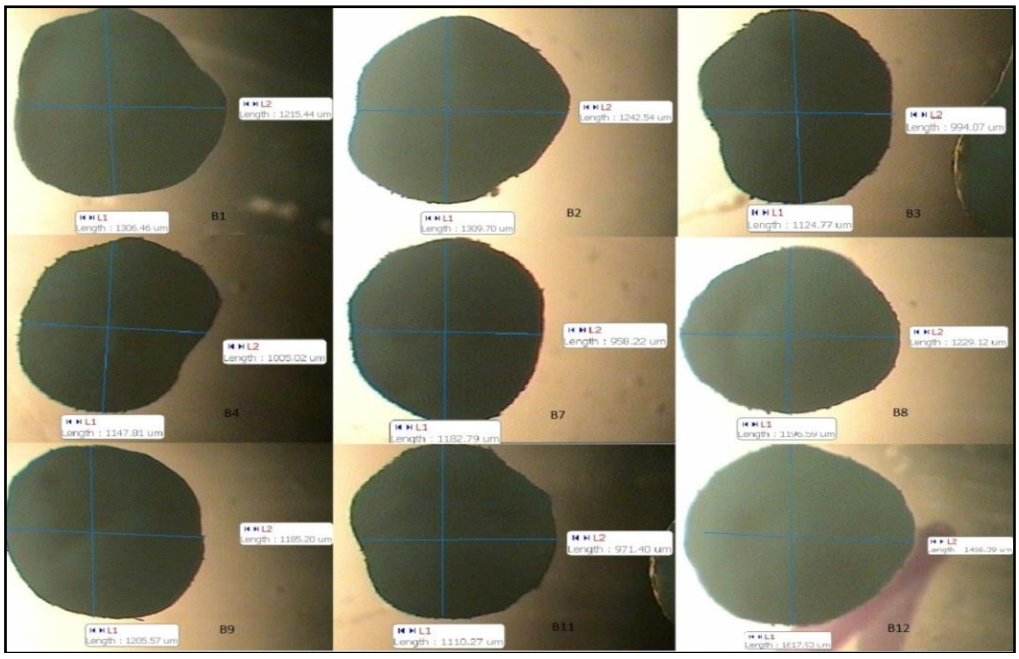

Fig No.9 Optical microscopic image for determination of aspect ratio

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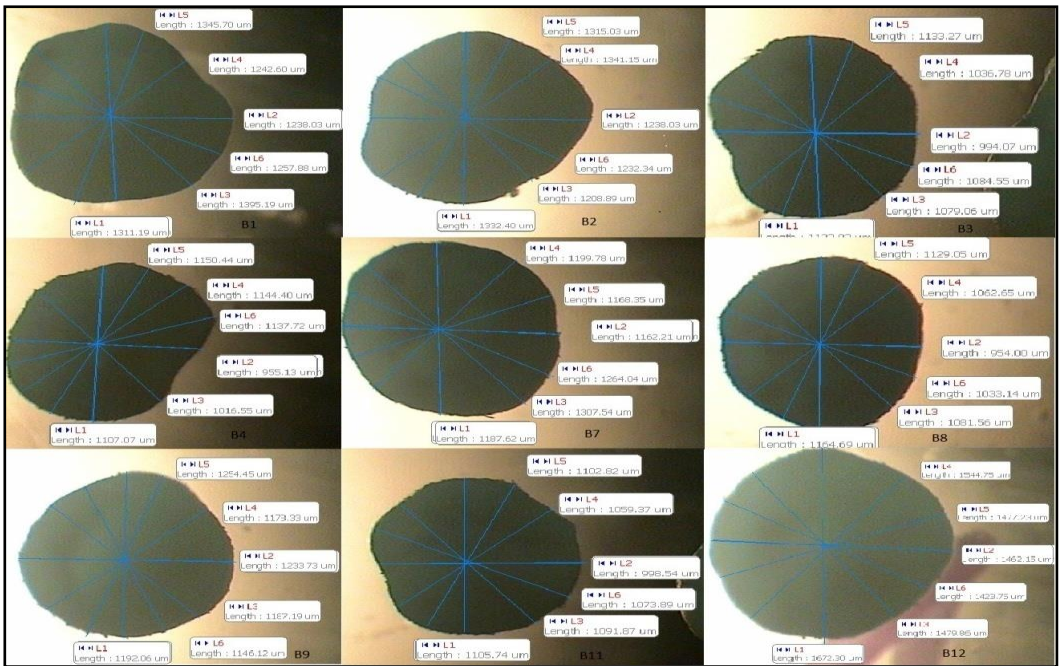

Fig no. 10 Optical microscopic image for determination of Particle size.

Table 11: Cumulative drug release from Optimized batch & Pure drug

TIME (min)	%CDR of optimized batch	Pure drug % CDR
0	0	0
5	41.41±0.69	9.89 ± 0.91
10	56.11±1.52	17.27±1.33
15	65.38±0.65	25.17±0.76
20	87.77±1.25	37.23±1.24
30	98±1.42	45.23±1.62

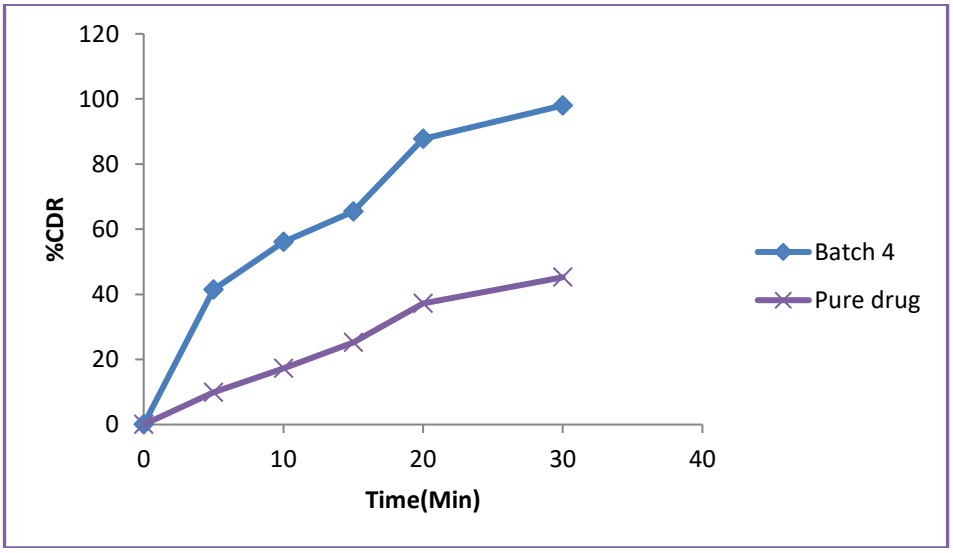

Fig.11: Comparison of dissolution profile of optimized batch (Batch 4) with pure drug

Dissolution profiles of CBZ from pure the samples of pure drug and prepared formulation are shown Pure CBZ dissolves slowly and incompletely, with less than 45 percent of the dissolved drug after 30 minutes of testing, according to the dissolution profiles reported. In comparison to pure CBZ, CBZ dissolution from all created dispersions was faster. Formulation F4 had the fastest CBZ dissolution rate, with 98 percent of the CBZ dissolved after 30 minutes of testing. Within the first 10 minutes, nearly 17% of the pure CBZ was dissolved from the pure drug samples. From the contour plots; it shows that lowest CBZ dissolution rate is characteristic for formulation that contains only CBZ and Neusilin US2. On the other hand, the fastest CBZ dissolution was observed when CBZ proportion is on upper limit of the studies range, with presence of 10-15% of PluronicF68. The plots showed that the most pronounced effect of changing in the concentration of Pluronic F68, where the quantity of dissolved CBZ increases upto some optimal concentration of PluronicF68, than reach plateau and start to decrease. Neusilin US2 negatively affect CBZ dissolution rates, i.e. quantity of dissolved CBZ decreases with increasing proportion of this adsorption carrier.

CONCLUSION

Carbamazepine is an drug indicated for the treatment of epilepsy, trigeminal neuralgia, bipolar disorder and acute mania, is characterized by low and erratic absorption. In order to overcome the low solubility problem, our aim is to increase the solubility of the CBZ by incorporating it into the polymer by the solid dispersion technology. In the present work the Solid dispersions of Carbamazepine were prepared by using Neusilin US2 and Pluronic F-68 and with central composite design by Lyophilization method. The Neusilin US2 used as adsorption carrier and Pluronic F68 was used as Surfactant to increase the solubility of the Carbamazepine. Firstly when API adsorbed on the Neusilin US2, the Pluronic F-68 coats the adsorbed drug. When the concentration of Neusilin US2 is increased at the highest concentration according to the Design expert software, the solubility and dissolution of the carbamazepine increased to maximum level. In this investigation, the important parameters like physic-chemical characterization, solubility studies and in-vitro drug release studies were done and found to be improvement in solubility. Formulation F-4 shows the 97 times increase in the solubility of the drug, as well as this formulation of solid dispersion shows 92% of the drug content and dissolution of the drug from solid dispersion in 30 minutes goes to 98%.

The solid dispersion prepared by this method shows increased solubility and good drug release.

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