SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE FLURBIPROFEN BY CRYALLO-CO-AGGLOMERATION APPROACH

Rothe Kanchan. R[1(Correspondence Author)] Dabhade M. P[2]

[1] Research Scholar DEPARTMENT OF PHARMACEUTICS S.N.D. COLLEGE OF PHARMACY, BABHULGAON,

[2]Assistant Professor DEPARTMENT OF PHARMACEUTICS S.N.D. COLLEGE OF PHARMACY, BABHULGAON.

ABSTRACT:

The crystal-co-agglomerate technique has been performed as promising valued particle design technique for enhancing SLty and DisL rate, compressibility and micrometric properties. "Crystallo-co-agglomeration is an extension of spherical crystallization technique,which enables simultaneous crystallization and agglomeration of two or more drugs or crystallization of a drug and its simultaneous agglomeration with another drug or excipient." The selected drug was characterized and identified by melting point SLty, partion coefficient, IR, DSC, XRD. and for analysis of drug uv spectroscopy is done . For crystal-co-agglomerates polymers and solvent system are selected and used with different concentration. Crystal-co-agglomerates are obtained with help of polymer, bridging liquid good solvent, bad solvent etc. Initial batches of crystal-co-agglomerates were obtained of different concentration of Peg6000 and pvpk30. SLty data was obtained in triplicate of preliminary batches. Optimization is done by applying 3^2 factorial design 9 batches where obtained and further evaluated SLty of it. Out of 9 optimized batches F9 batch was further used for study depending on SLty data. Crystal-co-agglomerate showed enhancement in physicochemical and micrometric properties. From the above optimized crystal-co-agglomerate batch Fast dissolving tablets were formulated by using various concentration of super-disintegrants by direct compression method and different batches were studied for DisL study and disintegration time. From above discussion it was concluded that Fast dissolving tablet were prepared by direct compression method exhibited disintegration time 42 sec and improved DisLrate

KEYWORDS: Polyethylene glycol/effects. Flurbiprofen/solubility. Flurbiprofen/dissolution rate. Drugcarrier compatibility/study. Dissolution efficiency.

I. INTRODUCTION:

In the pharmaceutical formulation the major challenge is to be the oral formuation because of there solubility and dissolution barriers instead of these there are the many techniques that can be increses the solubility and dissolution of the poorly water soluble drug and on of them are Crystallo-co-agglomeration (CCA) is an inventive strategy created with the aim to furnish the medications with great micromeritic and mechanical attributes.[1] The cycle of CCA includes crystallization followed by synchronous agglomeration of the medication with the guide of a decent dissolvable or potentially a connecting fluid and an awful dissolvable. This cycle empowers planning of circular agglomerates containing low portion drugs which are inadequately flowable and compressible. The CCA require less preparing time and may diminish the assembling just as handling time during pressure. The crystallo-co-agglomeration strategy might be used to improve the micromeritic properties of powder materials used in direct pressure. The resultant tablets may show improved squashing, pressure, deterioration and disintegration profile when contrasted and the tablet using other ordinary strategies[2]

I.I FACTORS AFFECTING CRYSTALLO-CO-AGGLOMERATION TECHNIQUE[3]

1. Solvent system

The range of the solvent system depends upon the stability and SLty characteristics of the drug. The physical form of the final product can be controlled by the correct assortment of solvent proportions. Typically of the drugs are soluble in organic solvent due to this organic solvents are chosen as a good solvent or bridging liquid while water is used as a poor solvent. The bridging liquid must wet the crystals to form liquid bridges during the process. The good solvent should be volatile and non-miscible with poor solvent to evade drug loss due to co-solvency.

2. Diluent Selection.

Diluents are utilized for size expansion of drugs having a low dose. It must be physiologically and physicochemically inert and cheap. It must be agglomerates insoluble in water to avoid the damages. It is reported by various researchers that talc is used as a fruitful original diluent in crystallo-co- agglomeration process

3. Intensity and Mode of Agitation.

Agitation is essential to support the process of dispersion of the internal phase into the external phase. High-speed agitation is essential to disperse the bridging liquid throughout the system. Any alteration in the speed of agitation would disturb the shape, size, and strength of agglomerate. High-speed agitation rises sphericity but decreases the strength of agglomerates.

4. Batch Processing Time

The completion of the process depends upon the agitation time. Insufficient agitation may cause imperfect growth of agglomerates since improper mixing of constituents. It can also cause imperfect evaporation of an organic solvent from a vessel. The endpoint of the agglomeration process can be determined by the clarity of the supernatant, attainment of proper size agglomerates and remaining organic solvent.

5. Temperature

The temperature has also a substantial effect on the shape, size, and strength of agglomerates since temperature straight affects the solubility of the drug.

I.II BENEFITS OF CRYSTAL-CO-AGGLOMERATION TECHNIQUE

1. As it is a single step process it is profitable in terms of processing cost.

2. The spherical agglomerates gained can be used as directly compressible tablet intermediates and/or spansules having improved micrometric properties (flowability, packability), mechanical properties (friability, crushing strength, and tensile strength, etc) compressibility and compactibility.

3. It is a single-step process, carried out in a closed system, preventing adulteration, and dust generation, thus guarantying exercise of GMP.

4. Controlled drug release can be attained with the help of certain polymers used through the agglomeration process.

5. Less amount of organic solvent is used as a good solvent also works as bridging liquid.

6. It includes continuous stirring of drug/s and excipients in a liquid medium, Uniform drug content distribution.

7. The large surface area presented by spheres outcomes in uniform distribution throughout gastrointestinal tract (GIT) chief to a reduction in the localized toxicity. Besides, this uniform distribution may expand the absorption and bioavailability of drugs.

8. The crystallized drug forms minuscular form hence may progress Dissolution

9. Since low surface-area-to-volume ratio likened to powder or granules, they can be measured as an outstanding coating substrate.

10. Spheres display enhancement in the therapeutic qualities of dosage form due to good dosing and handling properties.[4]

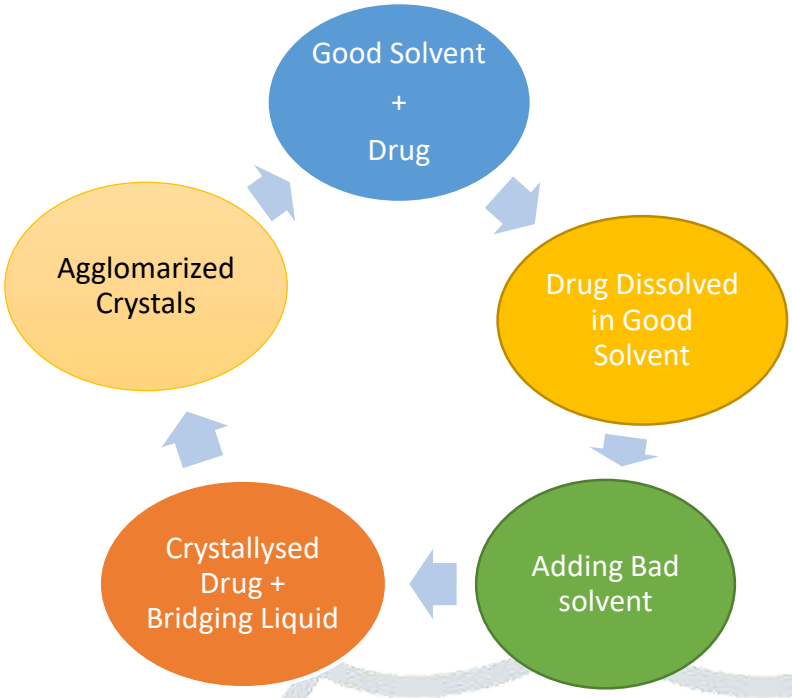

Figure 1: Mechanism of Cryallo-Co-Agglomeration

II. MATERIALS:

Flurbiprofen was kindly gifted FDC Ltd., (Mumbai, India). PEG 8000 and PEG 10000 were gift samples from Central Drug House Pvt. Ltd., (Delhi, India). Polyethylene glycol 6000, Hydroxypropyl methylcellulose (HPMC), Polyvinylpyrrolidone k 30, Croscarmellose Sodium, Micrcrystalline Cellulose, Magnesium Sterate All other chemicals and reagents were purchased from S.D. Fine Chemicals, (Mumbai, India).

III. METHOD:

III.I Preparation of Crystallo-co-agglomerates

FLp and HPMC were dissolved in Acetone (good solvent) and Hexane(bridging liquid) and talc were uniformly dispersed in it. The resultant solution was then poured into water containing PEG6000 and PVP K30 with stirring at 800 rpm. The stirring was continued to obtain agglomerates, which were filtered and dried overnight. After drying these crystal-co-agglomerates were collected and stored to appropriate condition and then subjected to their characterization by melting point, FT-IR, DSC, XRD, SLty determination etc.[5]

III.II Formulation development by direct compression method

The formula for direct compression was designed and different batches were prepared by varying concentration of super disintegrant agreeing to following procedure. Accurately weighed quantity of crystal-co-agglomerates equivalent to drug dose was mixed with other ingredients for 20 min in self sealing pouch. The resulting blend was passed through sieve no.80 and directly compressed using 8 mm punch plain round standard concave D tooling on Cad Mac rotary multi station tablet compression machine.[6]

Four batches were prepared F1, F2, F3 and F4 according to formula given in (**Table 1**). The batch size selected of 10 tablets in per batches.

Table 1. Formula

Sr.No	Ingredients	Batch F1	Batch F2	Batch F3	Batch F4
1	FLp	108	108	108	108
2	Crosscarmellose sodium	4	4	4	4
3	Magnessium Streate	4	4	4	4
4	Mannitol	20	20	20	20
5	Talc	4	4	4	4
6	Microcrystalline cellulose	q.s	q.s	q.s	q.s

IV. EXPERIMENTAL WORK:[7]

IV.I Selection of Drug candidate (API):

A drug candidate for crystallo-co-agglomeration is selected by considering various physicochemical parameters of a drug such as poor water SLty ,poor flow property, etc which can be overcome by crystallo-co-aggomeration approach..

IV.II Selection of Method:

A wide range of SLty enhancement techniques is available like salt formation, hydrotrophy, co-crystallization, co-solvency, etc. Crystallo-co- agglomeration is a technique for improvement of SLty of poorly soluble drugs and also improvement of micrometric property of the drug. Therefore crystallo-co- agglomeration technique was selected which overcomes the drawbacks of other techniques.

IV.III Selection of Polymer and Solvent:

After wide literature review polymers and solvent were selected. Polymers were selected permitting to their properties and to result in pharmaceutical acceptance of the product. The selection of solvent was based on the SLty behavior of the solvent. Therefore polymer and solvent in this investigation were selected from to literature i.e Polymer: HPMC, PEG6000, PVP K30, and Solvent: Acetone(good solvent) , Hexane (bridging liquid), and water (bad solvent).

IV.IV Physicochemical Characterization of Drug(API):[8]

1. Saturation Solubility:

The saturation SLty is used to predict the SLty of the drug. The saturation SLty of FLp was determined in water. The Saturation SLty studies were conducted according to the method given by Higuchi and Connors in triplicate. To determine saturation SLty, an excess amount of FLp was added to vials having 10 ml of distilled water. The vials are subjected to rotary shaking for 6 hours and then allowed to stand for equilibrations for 24 hrs, after that samples were filtered through Whatman filter paper and remainder was analyzed by UV Spectrophotometer after appropriate dilutions.

2. Partition coefficient:

The partition coefficient for the drug was determined in Octanol and Water and it was taken each 5ml and 10mg of the drug was added and the mixture was shaken for 5-6 hrs and then kept for 24 hrs for equilibrium. From the mixture, octanol was separated and then absorbance of the remaining mixture is taken and the partition coefficient was calculated.

Log P = log C (organic) /C (aqueous) Equation 1: Partition coefficient

Where, C (organic) = Concentration in organic solvent C (aqueous) = Concentration in aqueous solvent

3. Melting Point:

The melting point of FLp was determined by the Digital melting point apparatus (LAB TRONICS Ltd). The capillaries filled with powder were placed in the Melting point apparatus containing liquid paraffin. The melting point of the drug powder was noted. Each observation was made in triplicate determination.

4. FT-IR Spectroscopy:

Shimadzu FTIR spectrometer Prestige 21 with DRS assembly was used in Diminished total reflectance (ATR) mode for collecting FT-IR spectra of FLp and polymer. The spectra were collected over the range of 4000-400 cm-1 in 45 scans, with a resolution of 5 cm-1 for each sample.

5. Differential Scanning Calorimetry (DSC):

Thermal analysis of the FLP and CCA was performed using a differential scanning calorimeter SHIMADZUDSC 60 PLUS. The sample powders (7mg) were placed in aluminum pans, sealed hermetically, and then these hermetically sealed aluminum pans were heated at a scanning rate of 10°C/min from 50° to 250°C under constant purging dry nitrogen flow (100 mL/min). Empty aluminum pan was used as a reference.

6. X-Ray Diffraction:

In this technique, a powder sample is exposed to a beam of monochromatic X-ray radiation using a Bruker D8 Discover, which is diffracted and recorded by an X-ray detector. The diffracted data is processed and an X-ray powder pattern is plotted. XRD of pure drug and CCA was exploited to test the ability of a novel method to effectively reproduce crystallo-co-agglomerates.

IV.V UV-Spectrophotometric analysis of FLp (Analytical Method Development):

1. Construction of calibration curve:

A series of dilutions from standard solution in the range 5-30µg/ml were prepared and a calibration curve was constructed in a wavelength range of 200- 400 nm and a wavelength maximum were selected.

IV.VI Preparation of Crystallo-co-agglomerates:

FLp and HPMC were dissolved in Acetone (good solvent) and Hexane(bridging liquid) and talc were uniformly dispersed in it. The resultant solution was then poured into water containing PEG6000 and PVP K30 with stirring at 800 rpm. The stirring was continued to obtain agglomerates, which were filtered and dried overnight. After drying these crystalco-agglomerates were collected and stored to appropriate condition and then subjected to their characterization by melting point, FT-IR, DSC, XRD, SLty determination etc.[9]

IV.VII Optimization of crystal-co-agglomerates:

Optimization of crystal-co-agglomerate is done with design software version 11.which shows the predicted and practical data of SLty gives SLty responses and optimized batch for further formulation studies.[10,11]

V. Characterization of Crystallo-co-agglomerates:[12,13]

1. **Saturation Solubility of CCA:**

The saturation Solubity of crystallo-co-agglomerate was determined by the method given using Crystallo-co-agglomerates as a sample.

2. Melting point determination:

The melting point of CCA was done by the same procedure carried out for melting point determination of drug and CCA given in point.

3. FT-IR spectroscopy:

The FT-IR of co-crystals were done by the same procedure carried out for FT-IR determination of drug and CCA given in point

4. Differential Scanning Calorimetry (DSC):

The DSC of CCA was done by the same procedure carried out for DSC determination of drug and CCA given in point

5. X-ray diffraction:

The X-ray diffraction of CCA was done by same procedure carried out for X-ray diffraction determination of drug and CCA given in point

6. Pre-formulation characterization of Crystallo-co-agglomerates:[14,15]

After crystallo-co-agglomeration was performed the pre-formulation characterization of CCA and their comparison with FLp was done. The pharmaceutical processing properties i.e. angle of repose, bulk density; tapped density, Carr's index and Hausner's ratio were studied in comparison to pure FLp.

7. Process yield and Drug content:

For determination of drug content in agglomerates were powdered from which eqvivalent to 100 mg of FLp was weighed and added in solvent hexane and then filtered through whatman filter paper and drug solvent was determined spectrophotometrically at 247 λ .The percentage drug content was calculated using following formula.[16,17]

Percent yield and percentage drug content =

Percentage yield= total weigh of agglomerates / total weigh of drug+excipient × 100

Percentage drug content = practical drug concentration / theoretical drug concentration × 100

8. Formulation of Immediate release tablet by using selected Crystalco-agglomerates:

8.1 Formulation development by direct compression method:

The formula for direct compression was designed and different batches were prepared by varying concentration of super disintegrant agreeing to following procedure. Accurately weighed quantity of crystal-co-agglomerates equivalent to drug dose was mixed with other ingredients for 20 min in self sealing pouch. The resulting blend was passed through sieve no.80 and directly compressed using 8 mm punch plain round standard concave D

tooling on Cad Mac rotary multi station tablet compression machine. Four batches were prepared F1, F2, F3 and F4 according to formula given in (Table 5). The batch size selected of 10 tablets in per batches.[18,19]

Table 2: Formulae for Immediate release Tablet of different batches

Sr.No	Ingredients	Batch F1	Batch F2	Batch F3	Batch F4
1	FLp	108	108	108	108
2	Crosscarmellose sodium	4	4	4	4
3	Magnessium Streate	4	4	4	4
4	Mannitol	20	20	20	20
5	Talc	4	4	4	4
6	Microcrystalline cellulose	q.s	q.s	q.s	q.s

8.2 Evaluation of Prepared Immediate Release Tablets.

8.2.1 Thickness

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a VernierCalliper. Three tablets from each batch were used.[20]

8.2.2 Weight variation test I.P.

The procedure mentioned in I. P. was selected for uniformity of weight. Ten tablets were selected randomly and weighed. Average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined. The limits of weight variation test according to I.P.[21,22]

8.2.3 Friability

Friability is the measure of tablet strength. In this test whole tablets corresponding to about 6.5 gm subjected to combined effect of shock abrasion by utilising a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester (Veego Instruments Ltd. Mumbai). This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined. Friability = (W1 - W2)/ W1 X 100 Equation 9 : % Friability

Where,W1 = weight of the tablets before test, W2 = weight of the tablets after test

8.2.4 In vitro Disintegration time

The disintegration time of Immediate Release tablets was determined in conventional disintegration test apparatus in agreement with the official European Pharmacopoeia monograph Immediate Release tablets.The in-vitro disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±20C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded.[23,24]

8.2.5 In vitro DisL test

DisL profiles of Immediate release tablets were determined using the USP Method II with paddle speed at 50 rpm. DisL was performed in 900 ml of 0.1N hydrochloric acid maintained at 37 ± 0.5°C. 5 ml of samples were withdrawn at specified time intervals. The volume of DisL fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1N hydrochloric acid solution, pre- warmed at 37±0.5°C. Samples were withdrawn and analyzed at 247nm, using UV spectrophotometer (SHIMADZU 1800). The data presented is the average of 3 individual determinations.[25]

V. RESULT AND DISCUSSION

V.I Selection of Drug (API), polymers and Method.

V.I.I Selection of Drug

FLp was selected as a model drug of choice for crystal-co-agglomeration from the review of literature and also there were few problems were associated it which can be resolved by crystallo-co-agglomeration. Such problems were enumerated follows;

- Poor soluble in water.
- Poor compressibility
- Poor flow property

V.I.II Selection of Method

Crystallo-co-agglomeration technique was chosen according to literature review and also few issues related to other methods of SLty enhancement which can be resolved by crystallo-co-agglomeration

- Less unit operation are essential.
- Processing cost is economic.
- Capability to generate spherical agglomerates in a single step.
- Less man power prerequisite.
- Proper GMP consideration

V.I.IV Selection of polymer and solvent

According to literature survey the selection of polymers were carried out with. The polymers selected were Hydroxy propyl methyl cellulose, polyethylene glycol 6000, polyvinylpyrolidone- k30.

Hexane (bridging liquid) , acetone (good solvent) and water as (bad solvent) was selected on the basis of SLty behavior and formation of agglomerates .other bridging liquid like chloroform, benzene, toluene SLty and agglomerates were not observed

Table 3 Solubility of FLp in solvents

Solvent	**SLty mg/ml**
Chloroform	**0.02678**
Acetone	**0.05890**
Toluene	**0.02545**
Hexane	**0.07894**

Table. 4 Selection of bridging liquid

Solvent	**Agglomerates**
Chloroform	No agglomeration
Benzene	No agglomeration
Toulene	No agglomeration
Hexane	Agglomerates were observed

V.II Drug- Excipient Compatibility Study

V.II.I DSC data for drug excipient compatibility study

1. DSC of FLp and HPMC

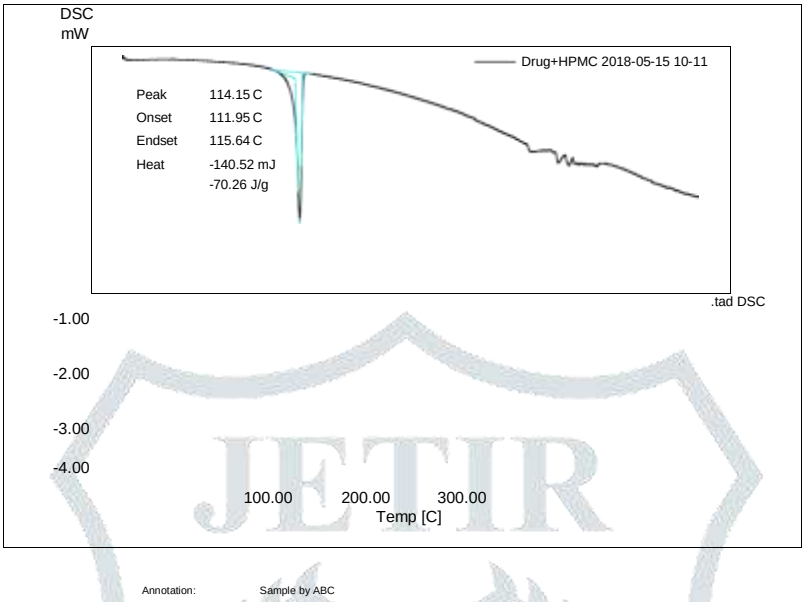

Figure 2. DSC Thermogram of FLp and HPMC

FLp and HPMC were mixed in 1:1 ratio and kept for 1 month .Further sample were analyzed by DSC which does not show any interaction in DSC Thermogram of FLp and HPMC.

2. DSC of FLp and PEG6000

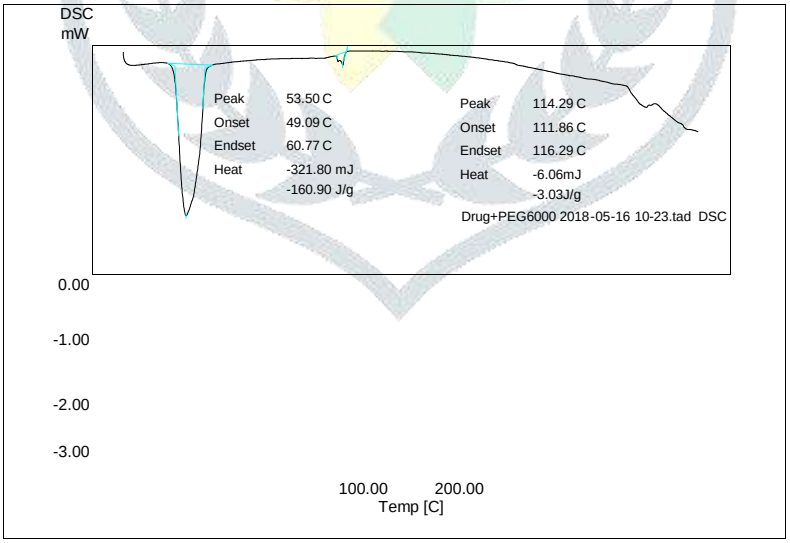

Figure 3: DSC thermogram of FLp and PEG6000

FLp and PEG6000 were mixed in 1:1 ratio and kept for 1 month .Further sample were analyzed by DSC which does not show any interaction in DSC Thermogram of FLp and PEG6000.

3. DSC of FLp and PVPk30

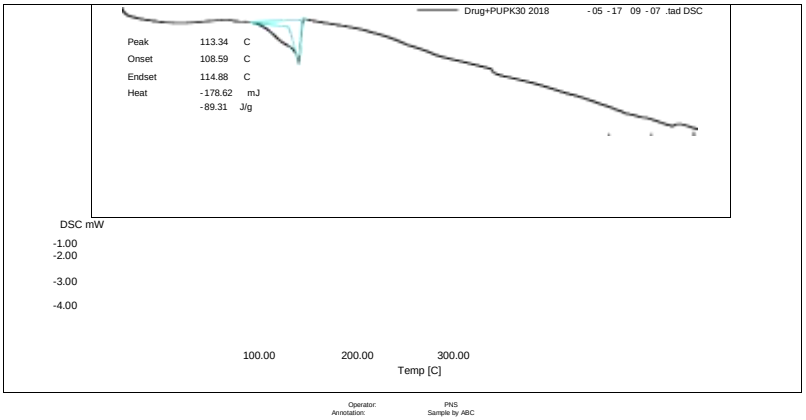

Figure 4: DSC of FLp and PVP K30

FLp and PVP K30 were mixed in 1:1 ratio and kept for 1 month as per ICH. Further samples were analyzed by DSC which does not show any interaction in DSC Thermogram of FLp and PVP K30.

V.III Characterization of Drug

1. Saturation Solubility

The saturation SLty of FLp was determined in water and results was as shown in Table

Table 5 : Saturation Solubility of FLp in water

Sr.No	Solvent	Solubility(mg/mL)	Reported Solubility(mg/mL)
1	Water	0.0243 ±0.75	0.0249mg/mL

2. Partition Coefficient

Table 6: Partition Coefficient of FLp

Sr.No	Solvent	LogP	Reported LogP
1	Octanol/water	4.15±0.15	4.16

Log P value for Octanol/Water was 2.57. It indicates that F Lp is lipophilic in nature it might be the reason for its poor aqueous SLty.

3. Melting point

The melting point of FLp was found to be **110-111^{0}C** which is within the standard range of 110-111^{0}C.

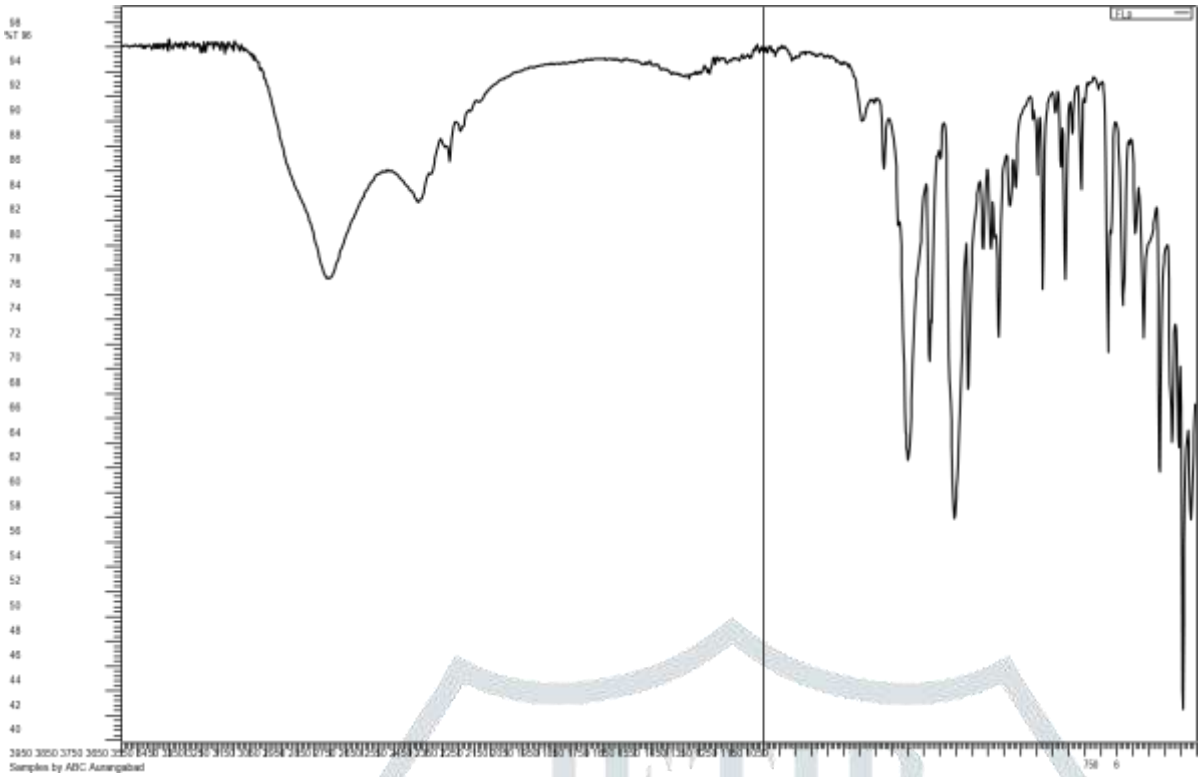

Figure 5: FT-IR spectrum of FLp

Table 7: FT-IR frequency of FLp data correlated with reported frequency

Functional Groups	Reported Value	Observed Value
Fuorine	1360-1000 cm^{-1}	1323 cm^{-1}
Acid C=O	1750-1690 cm^{-1}	1694 cm^{-1}
=C-H alkyl stretching	2950-3050 cm^{-1}	2723 cm^{-1}
C-H aromatic	3030cm^{-1}	2972cm^{-1}

The data obtained by FT-IR of FLp was matches with reported values which were reported in literatures of FLp. The principal peaks corresponding to FLp were obtained and matches with reported values.

(Differential Scanning Calorimetry (DSC) of FLp

Thermal analysis by DSC of the FLp was performed using a *SHIMADZU DSC 60 PLUS(MIT)A'BAD.* Thermal analysis by DSC of the FLp

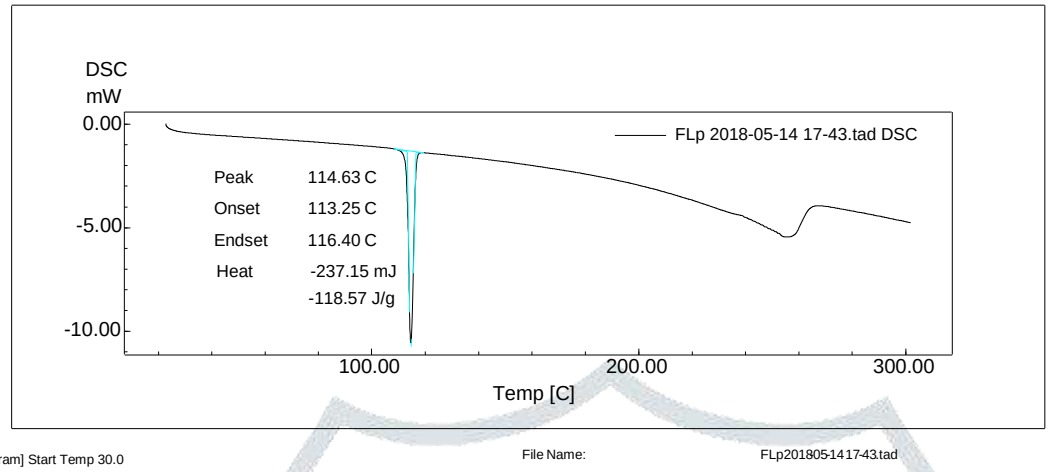

Figure 6: DSC thermogram of FLp

Indicates the DSC of the FLp and the indicates the reported melting point of the FLp and observed by DSC matches with reported melting point. From DSC data we found peak at 114.63^{0}C with the heating rate at 10^{0}C/min.

Table 8: DSC data for FLp

Sr.No	Theoratical Melting Point	Reported Melting Point
1	110-111^{0}C	114.63^{0}C

4 UV- Spectrophotometric estimation of FLp.

The UV scan for FLp in 7.4 phosphate buffer solution between 200 – 400 nm showed the absorption maxima at 247nm and It was found that no change in wavelength observed that of reported.

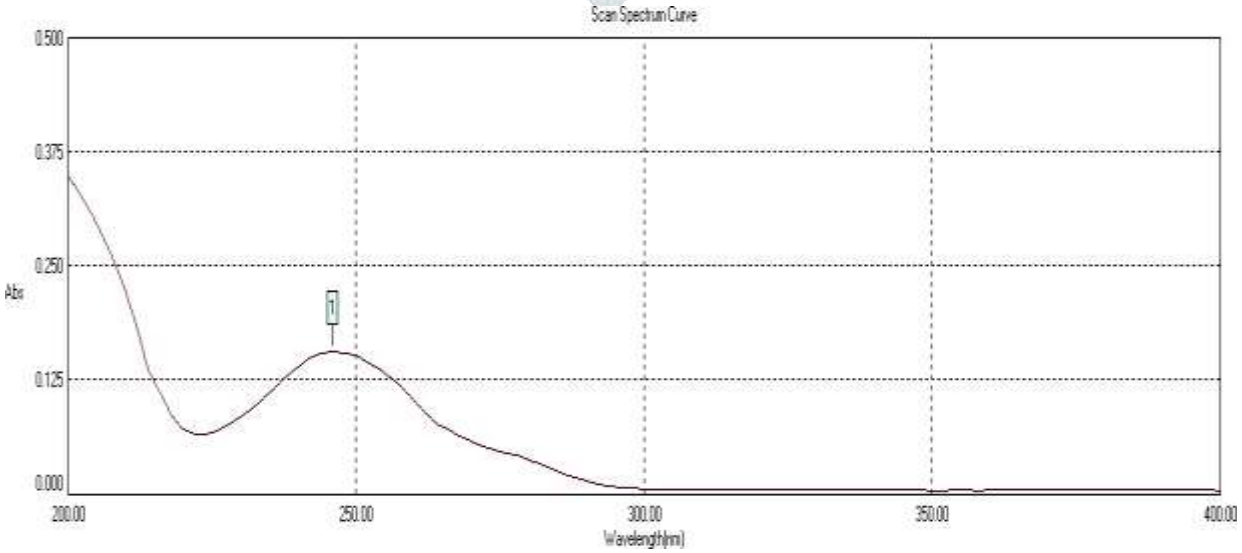

Figure 7: UV Spectrum of FLp in 7.4 PBS

3.1.Calibration curve of FLp in 7.4 Phosphate buffer solution.

The calibration curve of FLp was taken in 7.4 Phosphate buffer solution and the absorbance was measures at 247nm by UV spectrophotometer and results and (**Figure 9**).

Table 9: Data showing Concentration vs. Absorbance of FLP in 7.4 PBS.

Concentration (µg/ml)	Absorbance
5	0.236
10	0.489
15	0.657
20	0.868
25	1.101
30	1.313

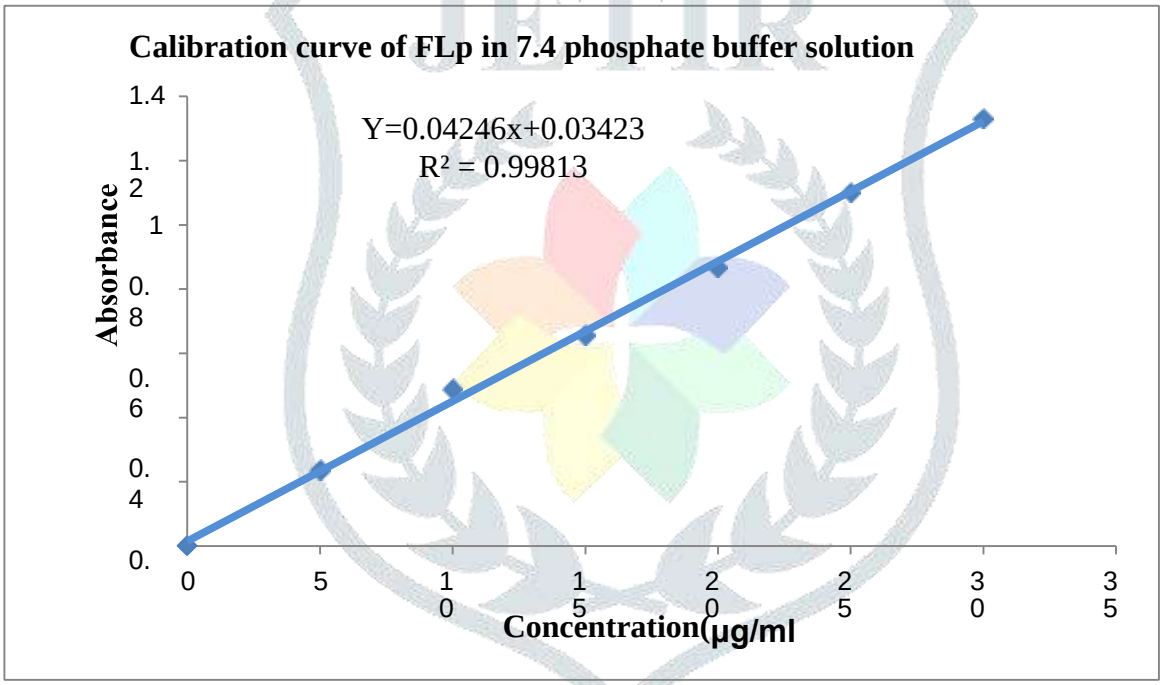

Figure 8: Calibration curve of FLp in 7.4 PBS

V.IV Preparation of Crystal-co-agglomerates

V.IV.I Crystallo-co-agglomeration.

1. Preparation of preliminary batch of cystallo-co-agglomerates.

Table 10: Preparation of preliminary batches of Crystallo-co-agglomerates

Sr. no	Batch code	Drug	Talc	PEG6000	HPMC	PVP K30	Acetone	Hexane	Water
1	FP1	100 mg	100 mg	10mg	12mg	0.25 mg	6ml	4ml	10 ml
2	FP2	100	100	12	12	0.5	6	4	10
3	FP3	100	100	14	12	0.75	6	4	10
4	FP4	100	100	16	12	0.90	6	4	10
5	FP5	100	100	18	12	1.15	6	4	10
6	FP6	100	100	20	12	1.40	6	4	10
7	FP7	100	100	22	12	1.60	6	4	10
8	FP8	100	100	24	12	1.90	6	4	10

The crystal-co-agglomerates were prepared of FLp with different polymer concentration were prepared by solvent change method FLp and HPMC were dissolved in Acetone (good solvent) and Hexane (bridging liquid) and talc was dispersed uniformly. The resultant solution was poured in water containing PEG6000 and PVPk30 with stirring rate 800 rpm.

2. Evaluation of preliminary batch of crystallo-co-agglomerates.

The saturation SLty of prepared crystal-co-agglomerates is given in (**Table15**). **Table 11:** Solubility Data of Preliminary Batches in Triplicate

Sr.no	Batch code	SLty (N=3) (µg/ml)		
1	FP1	127.830	126.808	127.207
2	FP2	180.727	179.834	180.350
3	FP3	2O2.348	202.389	202.384
4	FP4	208.733	208.373	208.733
5	FP5	210.470	210.590	210.740
6	FP6	213.782	213.827	213.873
7	FP7	214.833	214.835	214.834
8	FP8	222.322	222.343	222.234

It indicates that the SLty of FLp crystal-co-agglomerate formed with polymer PEG6000, HPMC,PVP K30 showed increase in SLty maximum SLty was observed in FP 8 batch.

V.IV.II Optimization by 3^2 factorial design.

Table 12: Optimization of variables by 3^2 factorial design.

Coded values	Actual values(mg)	
	X1(Polymer PEG6000)	X2(PVP K 30)
-1	10	0.35
0	15	0.85
+1	20	1.5

The amount of polymer PEG6000(X1) and PVP K30 (X2) were selected as independent variables and each factor being studied at -1 ,0,+1 level.

V.IV.III Full factorial Design Layout

Table 13: Variables level of factorial design

Formulation Batch	Variables Level Coded values	
	X1(PEG6000)	X2(PVP K30)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 14: Saturation Solubility of factorial design Crystal-co-agglomerates

Batch	PEG6000(X1)	PVP K30 (X2)	SLty data (mcg)
F1	10	0.35	162.079
F2	10	0.85	163.280
F3	10	1.5	173.088
F4	15	0.35	178.214
F5	15	0.85	194.420
F6	15	1.5	203.098
F7	20	0.35	207.023
F8	20	0.85	211.453
F9	20	1.5	237.931

From the factorial design of 3^2 crystal-co-agglomerates of 9 batches were obtained and saturation SLty is determined from the observed data of SLty results batch F9 was found to be optimized batch showing maximum SLty .

Figure 9: Crystall-co-agglomerates of optimized batch.

V.V EXPERIMENTAL DESIGN

The optimization of crystallo-co-agglomerates was performed factors were concentration of PEG6000 and PVP K30 . in this optimization the concentration of PEG6000 and PVP K30 are used as factors with 10 mg,15mg,20mg concentration and PVP K30 at 0.35mg,0.85 mg, 1.5 mg concentration are optimized with design expert optimization with 1 respone i.e SLty **1.** ANOVA for Solubility

The quadratic model was tested, using Design Expert 11.0 trial version of ANOVA and the results were showed in (**Table 19**).

The P-values were used as a tool to check significance of each coefficient, which also indicated interaction strength of each parameter-value indicate statistical significance of obtained model.

7.5.2.3.1 Response: Solubility

Table 15: ANOVA of SLty with (X1) PEG6000 and (X2)PVP K30.

Sr.no	Source	Sum of Squares	Df	Mean Square	F-Value	P-Value	
1	**Model**	0.0050	5	0.0010	8.59	0.0063	**Significant**
2	A-PEG6000	0.0042	1	0.0042	159.47	0.0011	
3	B-PVP K 30	0.0007	1	0.0007	28.52	0.0128	
4	AB	0.0001	1	0.0001	3.80	0.1465	
5	A_2	6.384E-07	1	6.384E-07	0.0245	0.8856	
6	B_2	0.0000	1	0.0000	1.14	0.3640	
7	**Residual**	0.0001		0.0000			
8	**Cor Total**	0.0051	8				

The **Model F-value** of 38.59 implies the model is significant. There is only a 0.63% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 16: Statistics of Standard deviation and r^2

Std. Dev.	0.0051	**R^2**	0.9847
Mean	0.1923	**Adjusted R^2**	0.9592
C.V. %	2.66	**Predicted R^2**	0.8673
		Adeq Precision	17.9685

The **Predicted r^2** of 0.8673 is in reasonable agreement with the **Adjusted r^2** of 0.9592; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 17.968 indicates an adequate signal. This model can be used to navigate the design space.

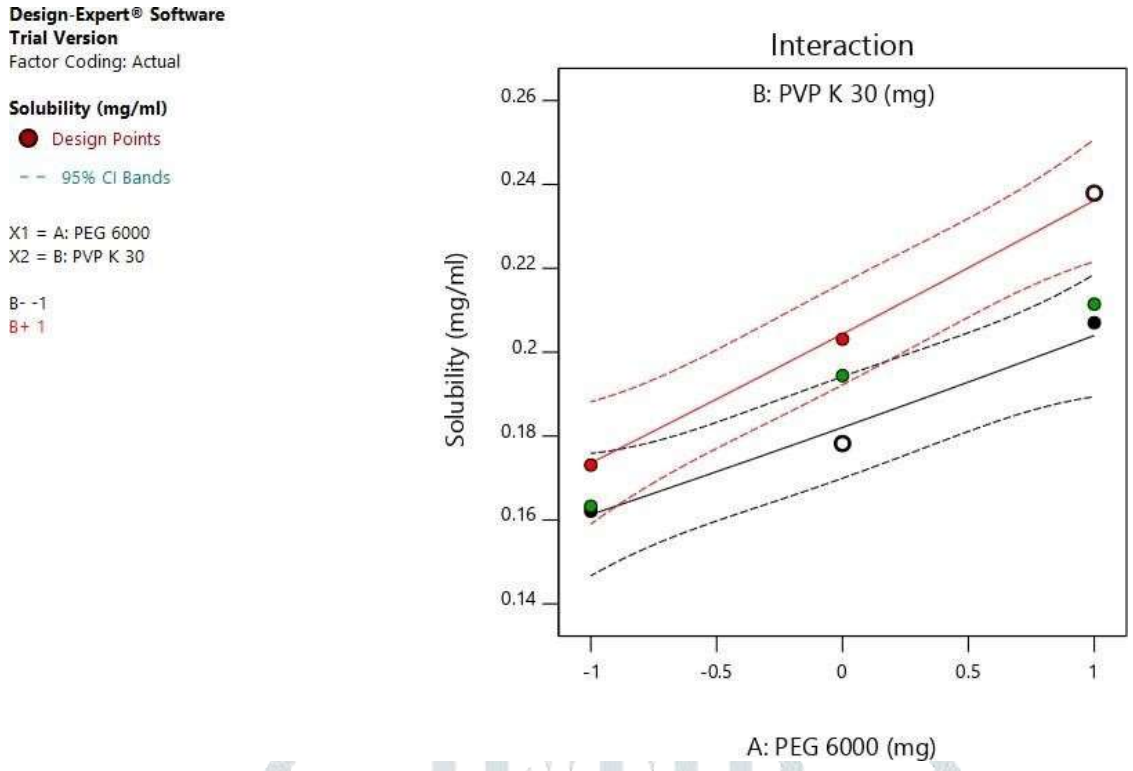

Figure 10: Interaction of PEG6000 and PVPK30

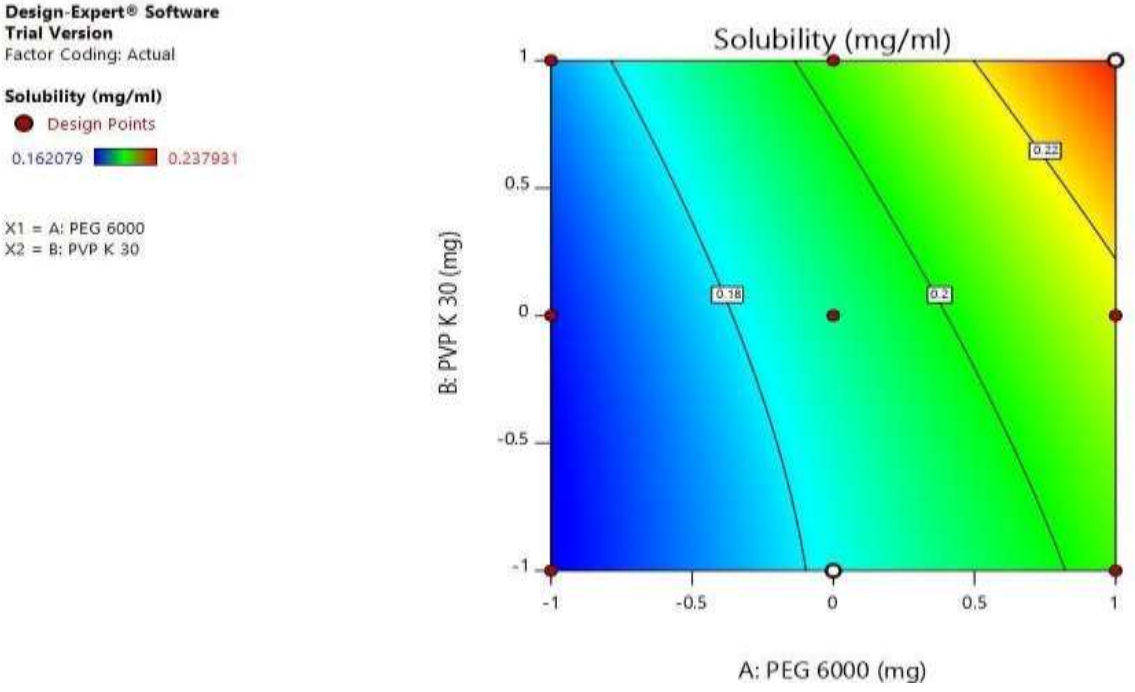

Figure 11: Contour plots of SLty data based on conc. of PEG6000 and PVPK30

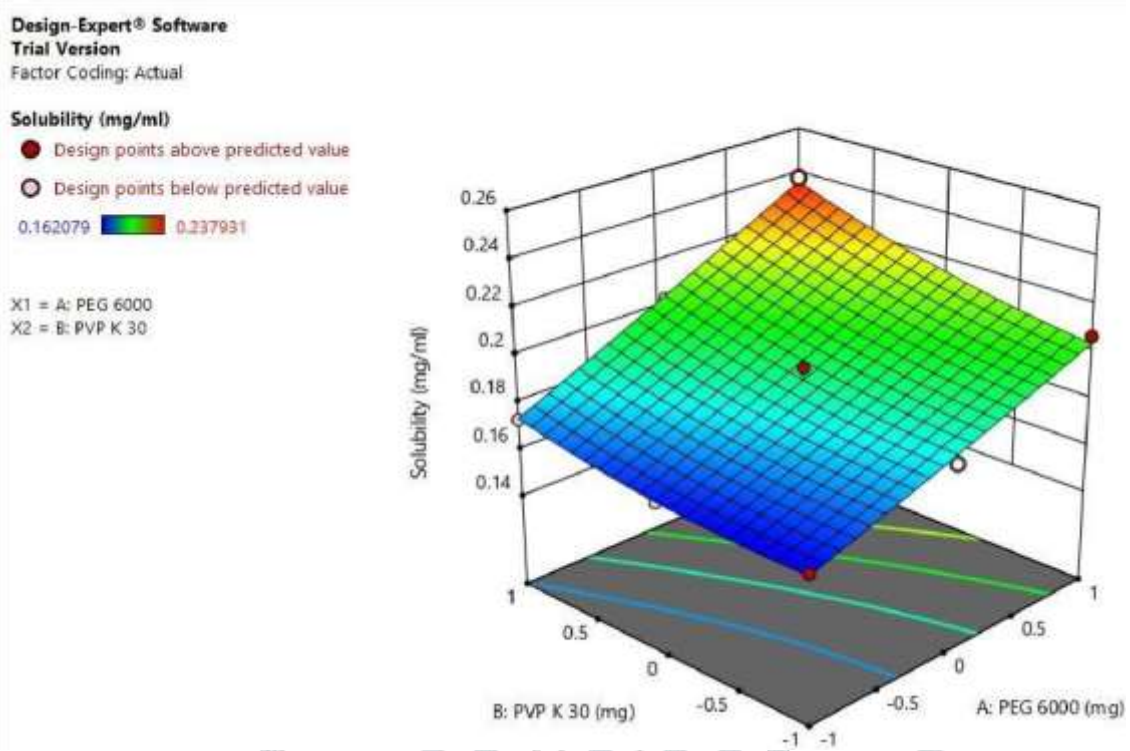

Figure 12: 3D Surface Response of X1 PEG6000 and X2 PVP K30 on SLty.

2 Point Prediction

Two-sided Confidence = 95% Population = 99%

Table 17: Point prediction of SLty data

Solution of 100 nse	Predicted Mean	Predicted Median	bserved	Std Dev	SE Mean	95% low for Mean	95% high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
SLty	0.1761 03	0.1761 03		0.00510 663	0.0034 7 6 46	0.16 50 39	0.1871 66	0.1295 12	0.2226 93

Point prediction uses model fit during analysis and factor setting specified on factors tools to compute the point prediction and interval estimate the predicted

3. Confirmation

Confirmation is intended to be used to confirm that model can predict actual outcomes at optimal settings determined from analysis.

Two-sided Confidence = 95%

Table 18: Confirmation table

Solution 1 of 100 Response	Predicted Mean	Predicted Median	served	Std Dev	n	SE Pred	95% PI low	Data Mean	5% PI high
Solubility	0.18934 1	0.18934 1		0.005106 63	1	0.006369 09	0.16907 2		0.2096 1

Process parameters revealed that factors like concentration of(X1) PEG6000 and (X2) PVP K30 at 3 level depicted significant influence on SLty behavior of crystal- coagglomerate of FLp .Hence they were utilized for further formulation studies.

V.VI. Characterization of crystallo-co-agglomerates.

1. FT-IR spectroscopy of crystal-co-agglomerates.

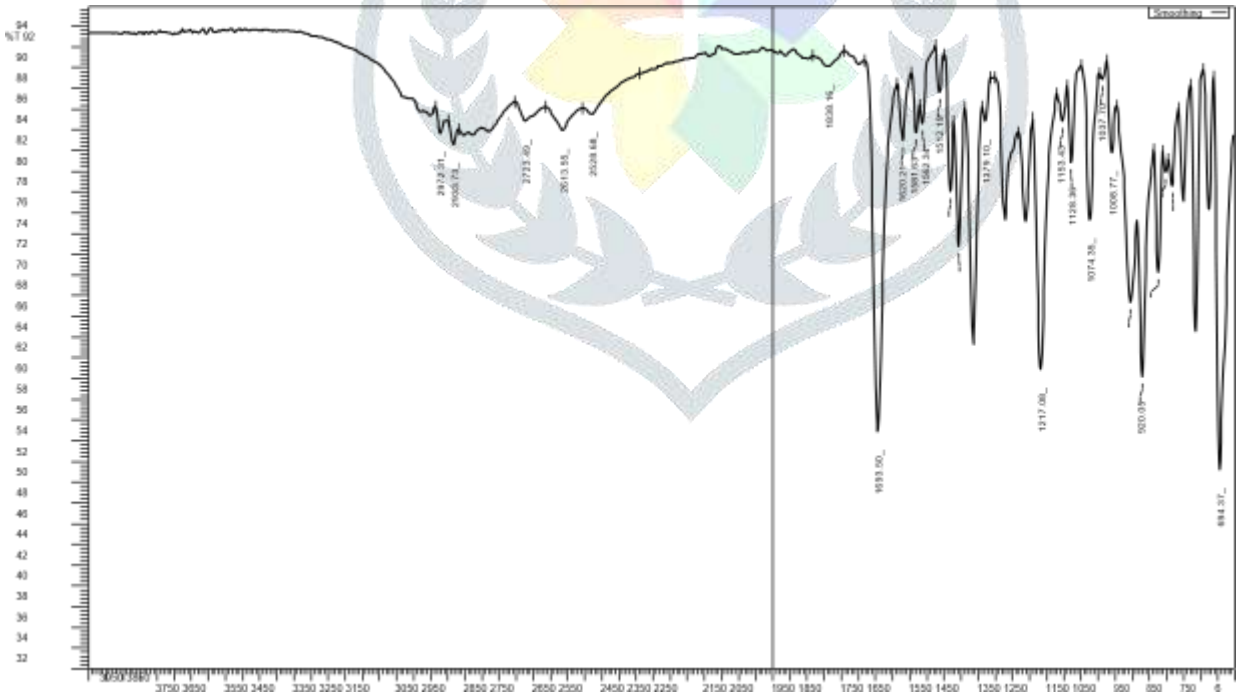

Figure 13: FT-IR spectroscopy of crystal-co-agglomerates.

Table 19: Crystal-co-agglomerate IR interpretation data.

Functional group	Reported value(cm^{-1})	Observed value(cm^{-1})
Fluorine	1360-1000	1323
Acid C=O	1750-1690	1694
Alkyl C-H Streching	2950-2850	2723
Aromatic C-H	3030	2972

The spectra of crystal-co-agglomerate shows nearly same peaks as that of FLp. There may be new bond due to crystallization and agglomeration of FLp with polymers.

2. Differential Scanning Calorimetry (DSC)

Thermal analysis by DSC of FLp crystal-co-agglomerates

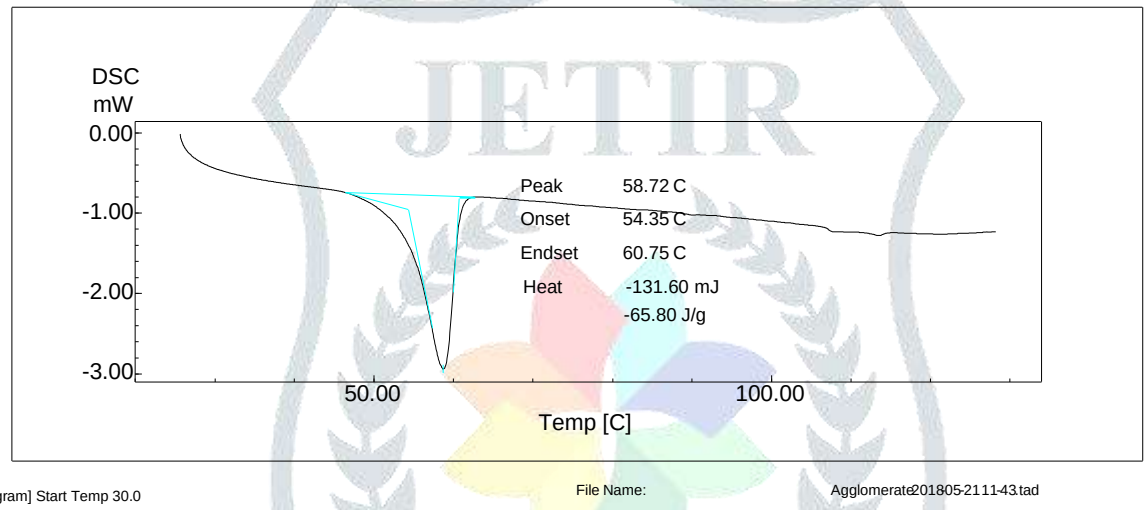

Figure 14: DSC thermogram of FLp crystallo-co-agglomerate.

From results of DSC study, crystal-co-agglomerate formation can be confirmed for those formulations which show characteristic change in the melting behavior. There is dras C

Table 20: DSC thermogram of FLp crystal-co-agglomerates

Sr.no	DSC	Theoretical M.P	Practical M.P
1	FLp	- C	C
2	Crystal-co-agglomerate		C

3. Pre-formulation characteristics of crystal co-agglomerates

After the crystallo-co-agglomerates the pre-formulation characterization of CCA were performed and its comparison with FLp is given in (**Table 25**).

Table 21: Preformulation characteristics of FLp and Crystal-co-agglomerate

	Bulk Density (gm/cm^3)	**Tapped Density (gm/cm^3)**	**Carr's ndex (%)**	**Hausner's Ratio**	**Angle of Repose (^{0})**
Pure Drug	0.3241g/ml	0.4514g/ml	40.81%	1.7824	46^0 '
Crystal-co agglomerate	0.37845g/ml	0.5313g/m	12.52%	1.1578	25^0 4 '

The results achieved shown that by Crystallo-co-agglomeration technique the pharmaceutical processing properties i.e. angle of repose, bulk density, tapped of FLp.

The crystal-coagglomerates of FLp showed good pre-formulation properties. The preformulation characteristics of drug and co-crystals are summarized in (**Table 29)** which gives a clear idea about improvement in the processing characters of the crystal-coagglomerate over a pure drug FLp.

V.VII Formulation development

The immediate release tablet was selected as dosage form for development using Optimized batch of FLp crystal-co-agglomerate. Immediate release tablet was prepared by direct compression method using 8mm die on 13 stage rotary tablet machine.

1. Evaluation of Different batches

Table 22: Evaluation parameters of immediate release tablets batch codes (F1-F4)

Parameters	F1	F2	F3	F4
Weight Variation(mg)	199±1.2	198±1.5	201±1.0	200±1.0
Hardness(kg/cm^3)	4.5±0.2	4.6±0.2	4.6±0.1	4.5±0.2
Thickness(mm)	0.5±0.05	0.6±0.05	0.6±0.05	0.5±0.05
Friability%	0.83±0.61	0.75±0.37	074±0.87	0.66±0.66
Disintegrating Time(sec)	72±1.5	63±1.8	51±1.5	42±1.2
Drug Content	97.16 ±0.65	98.78 ±0.65	98.02 ±0.57	98.85 ±0.56

VI. SUMMARY

1.The crystal-co-agglomerate technique has been performed as promising valued particle design technique for enhancingSLty and DisL rate, compressibility and micrometricproperties.

2. "Crystallo-co-agglomeration is an extension of spherical crystallization technique,which enables simultaneous crystallization and agglomeration of two or more drugs or crystallization of a drug and its simultaneous agglomeration with another drug orexcipient."
3. Theselecteddrugwascharacterizedandidentifiedbymeltingpoint
4. , SLty,partioncoefficient,IR, DSC, XRD. and for analysis of drug uv spectroscopy is done .
5. For crystal-co-agglomerates polymers and solvent system are selected and used with differentconcentration..
6. Crystal-co-agglomerates are obtained with help of polymer,bridgingliquid
7. , goodsolvent, bad solvent etc.
8. Initial batches of crystal-co-agglomerates were obtained of different concentration of Peg6000 and pvpk30.
9. SLty data was obtained in triplicate of preliminarybatches.
10. Optimization is done by applying 3^2 factorial design 9 batches where obtained and further evaluated SLty ofit.
11. Out of 9 optimized batches F9 batch was further used for study depending on SLtydata.
12. Crystal-co-agglomerate showed enhancement in physicochemical and micrometricproperties.
13. From the above optimized crystal-co-agglomerate batch Fast dissolving tablets were formulated by using various concentration of super-disintegrants by direct compression method and different batches were studied for DisL study and disintegration time.
14. From above discussion it was concluded that Fast dissolving tablet were prepared by direct compression method exhibited disintegration time 42 sec and improved DisLrate.

VII. CONCLUSION

1. FLp ,a non-steroidal anti-inflammatory and analgesic ,antipyretic drug , was successfully used to form crystal-co-agglomerates by crystallo-co- agglomerationtechnique.
2. FT-IR,DSC and XRD technique were utilized to study bonding between drug and polymers which are used to predict crystal-co-agglomerateformation.
3. Crystal-co-agglomerates were prepared by solvent change method .this method was selected due to it is economic ,less unit operation,less man power ,etc.
4. Optimization of FLp wasdone
5. SLty of FLp crystal-co-agglomerates was enhanced to that of pure form ofFLp.
6. The improvement in SLty may be due to changing crystal forms and /or surfacemodifications.
7. Micrometric properties such as angle of repose,carr's index and hausner's ratio of crystal-coagglomerates of FLp was improved by crystallo-co- agglomerationtechnique.
8. In –vitroDisL studies showed that it enhances DisLproperties
9. Further tablets where prepared of optimized batch by direct compression method leads to faster release of drug

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