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Research Article

FORMULATION AND EVALUATION OF FLURBIPROFEN TABLET USING SPHERICAL CRYSTALLIZATION FOR SOLUBILITY ENHANCEMENT

ARUN RAJ R*, MEENAKURUP

Department of Pharmaceutical Sciences, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India, [2]Department of Pharmaceutical Sciences, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.

Email: arunraj2486@gmail.com

ABSTRACT

Objective : The present study deals with spherical crystallization of Flurbiprofen crystals in order to improve its flow properties, compressibility and enhancement of dissolution characteristics of drug crystals. **Methods:** Spherical agglomerates of Flurbiprofen prepared by different techniques. Selection of Neutralization technique based on the better percentage yield, drug content, and SEM analysis. Optimization of Flurbiprofen spherical agglomerate was done. Optimized formulation of spherical agglomerate was chosen for preparation of tablet. Response surface methodology using Factorial design was chosen for the optimization of spherical agglomerates. Preparation and evaluation of spherical agglomerate tablet and comparing its dissolution characteristics with conventional as well as marketed product. **Results :** The micromeritic properties, solubility, In-vitro drug release of spherical agglomerates were evaluated. Spherical agglomeration enhances the micromeritic and dissolution properties of Flurbiprofen. The drug release mechanism from the tablets was found to be case II transport kind of diffusion. **Conclusion :** It can be concluded that the spherical crystallization technique is an effective approach for the dissolution rate improvement of Flurbiprofen.

Keywords : Flurbiprofen, Solubility enhancement techniques, Factorial design, Optimization, Spherical Agglomerate tablets.

INTRODUCTION

The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. It also governs the possibility of parenteral administration of a drug and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an equilibrium measure but also the dissolution rate at which the solid drug or drug from the dosage form passes into solution is critically important when the dissolution time is limited[1].Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action [2].Oral bioavailability of a drug depends on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms, aqueous solubility and drug permeability are also important parameters attributed to oral bioavailability [3]. In drug discovery, the number of insoluble drug candidates has increased in recent years, with almost 70% of new drug candidates showing poor water solubility [4].

The spherical crystallization has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid. With decreasing amount of bridging liquid in the three-solvent system, the median diameter of agglomerated crystals increased, having a wider size distribution. The spherical crystallization technique has already been successfully applied to improve the micromeritic properties of several drugs. Besides modifying the size and shape, flowability, packability and bulk density of the particles, this technique can also be exploited to increase solubility, dissolution rate and hence, bioavailability of poorly soluble drugs [5].

METERIALS AND METHODS

Materials

The following materials were used (Grade-LR): Flurbiprofen -API (Yarrowchem Products, Mumbai), HPMC $K_{15}M$ (Sance Laboratories Pvt. Ltd., Pala), Dimethyl sulphoxide, Sodium hydroxide, Acetone, Chloroform, Hydrochloric Acid (Spectrum Reagents and Chemicals, Cochin).

METHODS

Preformulation Studies

Preformulation studies were performed on the drug (API), which included solubility, melting point determination and compatibility studies.

Solubility [6]

Solubility of Meloxicam was observed in different solvents such as water, acetone, dichloromethane, diethylether, dimethylsulphoxide, chloroform, ammonia and water.

Melting point Determination [7]

Melting point of the drug was determined by melting point apparatus.

Compatibility Studies [8]

IR spectral analysis of pure drug and polymer was carried out as physical mixtures. Observation was made whether changes in the chemical constitution of drug occurred after combining it with the polymer. The absorption maxima in spectrum were compared with the reference spectrum.

PREPARATION OF SPHERICAL AGGLOMERATES

Selection of Method

In order to select the best method for obtaining spherical agglomerates, spherical crystallization was carried out mainly by the following three techniques:

a) **Solvent exchange method [9]**: Drug is dissolved in dimethylsulphoxide, this solution is added to a solution of polymer HPMC in distilled water and stirred at different rpm. Hexane which acts as bridging liquid is added drop wise.

b) **Neutralization method [10]** : Drug is dissolved in 0.1N NaOH and heated till it dissolves and this drug solution was quickly poured into a solution of 0.1N HCl with continuous stirring at different rpm and bridging liquid hexane is added drop wise.

EVALUATION OF SPHERICAL AGGLOMERATES [11]

Percentage Yield

The prepared agglomerates were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds which were used for preparation.

$$\% \text{ Yield} = \frac{\text{Weight of Spherical Agglomerate}}{\text{Weight of Starting Material}}$$

Drug content

An amount of prepared spherical agglomerate equivalent to a theoretical content of 100 mg drug was accurately weighed and dissolved in 100 ml phosphate buffer pH 7.4, then suitable dilution was done and the absorbance of solution was measured spectrophotometrically at wave length 247 nm using phosphate buffer as blank.

SEM Analysis

The obtained agglomerates were subjected to Surface Electron Microscopy (SEM) analysis in order to check whether the obtained crystal had become spherical in shape [12].

OPTIMIZATION OF MELOXICAM SPHERICAL AGGLOMERATES

Spherical agglomerates were prepared and optimized by factorial design.

Preparation of different formulations of spherical agglomerates by neutralization technique

Flurbiprofenspherical agglomerates were prepared by Neutralization technique and process variables like agitation speed and agitation time were optimized [13, 14].

Characterization of spherical agglomerates

Angle of repose [15]

The angle of repose of pure drug and agglomerates was determined by the funnel method. The accurately weighed agglomerates were passed through a funnel. The agglomerates were allowed to flow through the funnel freely onto the surface until the base of the cone formed reaches the desired radius. The height of the agglomerates cone was measured and angle of repose was calculated using the following equation [51].

$$\theta = \text{Tan}^{-1} h/r$$

Where, h and r are the height and radius of the agglomerates cone respectively.

Dissolution rate [16]

In-vitrodissolution of flurbiprofen spherical agglomerates (equivalent to 100mg of flurbiprofen) was carried out using USP dissolution apparatus. The dissolution medium was 0.1 N HCL at 37±0.5ºc stirred at 100 rpm. The samples were withdrawn at predetermined intervals and replaced with fresh medium. Collected samples were filtered and assayed spectrophotometrically at λmax247nm using 0.1 N HCL as blank.

Solubility Analysis [17]

An excess quantity of Flurbiprofen agglomerates was added to the 10 ml of distilled water in a flask and placed in rotary shaker at room temperature for 24 hrs. The solutions were then filtered through No. 41 whatman filter paper and the filtrate was suitably diluted and analyzed spectrophotometrically at 247 nm.

DEVELOPMENT OF THE OPTIMUM BATCH

Based on the statistical evaluations the software suggested one optimum batch. This batch of formulation was used for the further studies

EVALUATION OF OPTIMIZED SPHERICAL AGGLOMERATE

Angle of repose [15]

The angle of repose of optimized batch was determined by the funnel method.

Dissolution rate [16]

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Particle shape and surface morphology- Scanning Electron Microscopy [12]

The surface morphology and particle size of agglomerates were determined by Scanning Electron Microscopy using a JEOL JSM-6390 scanning microscope. Dry agglomerates were placed on an electron microscope brass stub and coated with platinum in an ion sputter. Picture of agglomerates were taken by random scanning of the stub.

Powder X-ray diffraction [18]

X-ray powder diffraction is an important technique for establishing batch-to batch reproducibility of a crystalline form. The form of crystals in agglomerates was determined by using this technique. An amorphous form does not produce a pattern. The X-ray is made to scatter in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound.

PRECOMPRESSIONAL ANALYSIS [15]

Bulk density

Accurately weighed agglomerates from each formulation were lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the agglomerates was measured, which gave bulk volume. The bulk density of agglomerates was determined using the following formula.

$$\text{Bulk density} = \frac{\text{Total weight of agglomerates}}{\text{Total volume of agglomerates}}$$

Tapped density

An accurately weighed quantity of crystals from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted, which gavethe tapped volume. The tapped density was determined by the following formula.

$$\text{Tapped density} = \frac{\text{Total weight of agglomerates}}{\text{Tapped volume}}$$

Hausner's ratio

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.5 shows poor flow of agglomerates.

Carr's compressibility index

In theory, the less compressible a material the more flowable it is. The compressibility index of the agglomerates was determined using following formula. Carr's index below 15% indicates good flow properties and above 25% indicates poor flow properties.

Carr's compressibility index

$$= \frac{[(\text{Tapped density} - \text{Bulk density}) X\ 100}{\text{Tapped density}}$$

Compression behavior

Good compatibility and compressibility are essential properties of directly compressible crystals. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. It is estimated that the surfaces are freshly formed by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation, compared to that of single crystals .

In-vitro Dissolution rate of Spherical agglomerate [16]

The dissolution rate, bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the agglomerated crystals. It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases. Comparative study of dissolution behavior between agglomerated crystals and pure Flurbiprofen was done. In vitro dissolution of Flurbiprofen and its spherical agglomerates (equivalent to 100mg of Flurbiprofen) was carried out using USP dissolution apparatus. The dissolution medium was 0.1 N HCL at 37±0.5ºC stirred at 100 rpm. The samples were withdrawn at predetermined intervals and replaced with fresh medium. Collected samples were filtered and assayed spectrophotometrically at λmax247 nm using 0.1 N HCL as blank.

PREPARATION OF TABLET [19]

Tablets of Flurbiprofen agglomerates were prepared by direct compression technique. Tablets of plain Flurbiprofen were also prepared using same quantity of excipients for comparison. Flurbiprofen or Flurbiprofen agglomerates (equivalent to 100 mg Flurbiprofen/tablet) was mixed with excipients in a tumbler type mixer for 15 min. The obtained mixture was compressed on a rotary punching machine.

EVALUATION OF TABLETS [19]

Thickness and diameter

The thickness and diameter of the prepared tablets were measured using Vernier Callipers.

Hardness

Hardness of tablets was measured with Pfizer hardness tester. The tablet was placed between the holding anvil and the piston for the compression. The holding anvil and piston were connected to a force reading gauge, which read the force for compression.

Friability

The friability values of the tablets were determined using Roche friabilator. Accurately weighed twenty tablets were placed in Roche friabilator and were rotated at 25 rpm for 4 minutes. After the process, these tablets were de-dusted and reweighed. Percentage loss of tablet weight was calculated and reported as friability.

Weight variation

Twenty tablets were selected and weighed together to calculate the average weight then each tablet was weighed individually. Individual weights were subtracted from average weight and reported as weight variation.

Drug content

Ten tablets were collected and grounded using a glass mortar and pestle to obtain a fine powder. Accurately weighed powdered sample equivalent to 50 mg of drug was transferred to 50ml volumetric flask. About 15ml methanol and 2 ml of 0.1M sodium hydroxide solution was added to added to extract and dissolve the drug. The mixture was sonicated for 15 min to ensure complete extraction and the final volume was made up to the mark with methanol. From this 1ml was taken in 100 ml volumetric flask and made up to the mark with pH 7.4 phosphate buffer. The absorbance of this solution was measured using phosphate buffer as blank. The samples were analyzed for Flurbiprofen using double beam spectrophotometer) at 247 nm. The drug content was obtained from calibration graph.

***In-vitro* Dissolution studies [16]**

In-vitro dissolution studies of tablets were carried out using USP apparatus II paddle method. Tablets were placed in 900 ml of 0.1N HCL at 37+0.5°C stirred at 100 rpm. Samples of 1 ml were withdrawn at different time intervals. An equal volume of fresh dissolution medium was immediately replaced. The samples were filtered and analyzed spectrophotometrically at 247 nm.

Comparison of prepared flurbiprofen spherical agglomerate tablet with marketed tablet

The Flurbiprofen tablet obtained as a result of spherical crystallization was compared with tablet prepared using pure drug. The dissolution release profiles of both the tablet were compared with marketed product.

KINETICS OF IN VITRO DRUG RELEASE [15]

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer-Peppas as log %drug released Vs log time and Hixson-Crowell as (% drug retained)$^{1/3}$ Vs time. By comparing the r-values obtained, the best-fit model was selected.

STABILITY STUDY [20]

Stability study for the optimized spherical agglomerates of Flurbiprofen tablets was carried. The samples were stored in amber colored screw capped glass bottles at room temperature for a period of 60 days. Samples were withdrawn periodically and were visually examined for any physical change. The samples were analyzed for thickness, hardness, drug content and the dissolution studies.

RESULTS AND DISCUSSION

Preformulation Studies

The solubility of the received sample of Flurbiprofen was examined in various solvents (aqueous and organic). The results observed were as follows:

Table 1: Solubility of samples in various solvents

SL.NO	SOLVENT	SOLUBILITY
1	Water	Practically insoluble
2	Ethanol	Freely soluble
3	Chloroform	Freely soluble
4	Methanol	Freely soluble
5	Hexane	Freely soluble
6	Ammonia water	Practically insoluble
7	Dimethyl sulphoxide	Soluble

Melting point of the drug was found to be 116 ^{0}C, which was in conformity with the reported range.

The major peaks observed in drug spectrum were also observed in spectrum of drug with polymer was within the characteristic peaks range

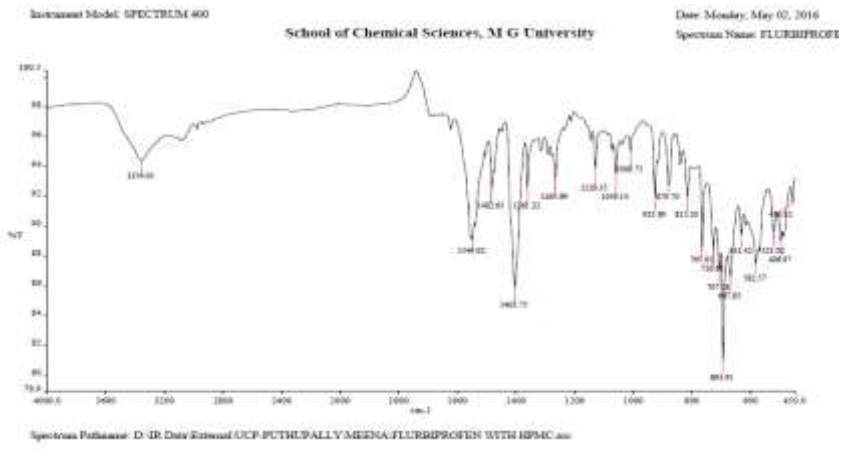


Fig. 1: IR Spectrum of Flurbiprofen-HPMC

PREPARATION OF SPHERICAL AGGLOMERATES

Table 2: Formulation Code for Spherical Agglomerates

CONTENTS AND PARAMETERS	FORMULATIONS					
	SOLVENT EVAPORATION			NEUTRALIZATION TECHNIQUE		
	SA1	**SA2**	**SA3**	**SA4**	**SA5**	**SA6**
Flurbiprofen(mg)	100	100	100	100	100	100
Rotation speed(rpm)	400	600	800	400	600	800
Agitation time(min)	20	30	40	20	30	40
Dimethyl Sulphoxide (ml)	20	27	25	-	-	-
HPMC solution (ml)	8	15	10	-	-	-
Hexane(ml)	4	8	6	4	6	8
0.1N HCl(ml)	-	-	-	25	30	32
0.1N NaOH(ml)	-	-	-	10	15	20

EVALUATION OF SPHERICAL AGGLOMERATES

Percentage yield

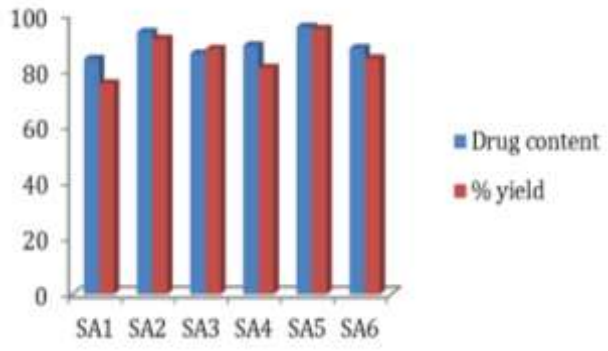
The percentage yield of the prepared spherical agglomerates of flurbiprofen was in the range of 75.22 % to 94.66 % being the highest for the formulation SA5 which was prepared by Neutralization method and the lowest for the formulation SA1 which was prepared by solvent exchange method.

Drug content

The percentage drug content of prepared spherical agglomerates of flurbiprofen was in the range of 83.97 % to 95.46 % being the highest for formulation SA5 which was prepared by Neutralization technique and the lowest for the formulation SA1 which was prepared by solvent exchange method. (Graph 1)

SEM Analysis

The obtained agglomerates were subjected to Surface Electron Microscopy (SEM) analysis in order to check whether the obtained crystal had become spherical in shape. (Figure 2-3)



Graph 1: Percentage yield and drug content

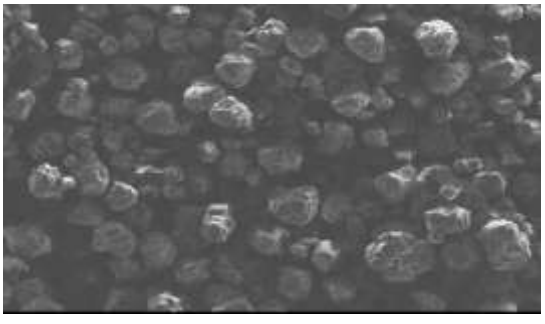


Fig. 2: SEM of SA2 (Solvent exchange method)

Fig. 3: SEM of SA5 (Neutralization Technique)

From the above SEM analysis of the spherical agglomerates, it was found that the spherical crystals obtained by Solvent exchange method (SA2) was least spherical in shape whereas the spherical agglomerate (SA5) obtained by Neutralization technique showed a convincing shape which was selected for further studies.

OPTIMIZATION OF FLURBIPROFENSPHERICAL AGGLOMERATES

Spherical agglomerates were optimized by Factorial design.

Preparation of different formulations of spherical agglomerates by neutralization technique

Since the SEM analysis showed a considerable spherical shape, Flurbiprofen spherical agglomerates were prepared by Neutralization technique and variables like agitation speed and time of agitation were optimized.

OPTIMIZATION BY FACTORIAL DESIGN

The experiment runs with independent variables and the observed responses for the 9 formulations and characterization of spherical agglomerates are shown in the Table 3

Table 3: The Factors and Responses for 9 Formulations

Formulation code	Factor 1 X1Agitation speed rpm	Factor 2 X2 Agitation time Min	Response 1 Angle of repose °	Response 2 Cumulative drug release %	Response 3 Solubility enhancement ratio Fold
F1	400	20	25.74	85.37	07
F2	400	30	29.05	86.24	09
F3	400	40	28.36	85.38	08
F4	600	30	27.75	87.98	12
F5	600	20	27.14	87.12	10
F6	600	40	27.14	89.71	11
F7	800	40	25.46	97.49	14
F8	800	30	24.94	99.22	15
F9	800	20	26.56	96.62	13

Contour plots are two dimensional representations of the responses for the selected factors. Three dimensional surface plots for the obtained responses were drawn based on the model polynomial functions to assess the change of response surface. The contour plot and the response surface plots of the significant interaction terms of the factors were given below,

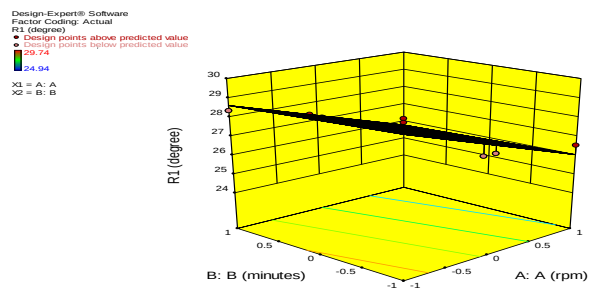


Fig. 4: Response surface plot for the effect of rotation speed and agitation time on angle of repose

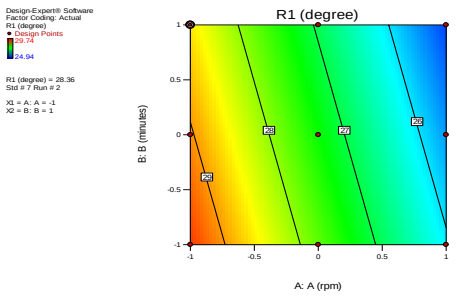


Fig. 5: Contour plot for the effect of rotation speed and agitation time on angle of repose.

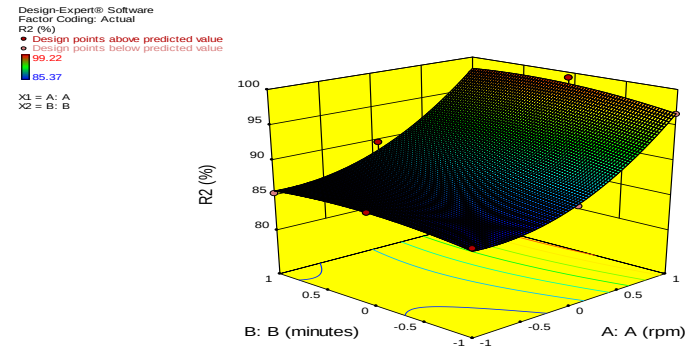


Fig. 6: Response surface plot for the effect of rotation speed and agitation time on dissolution at 60th minute.

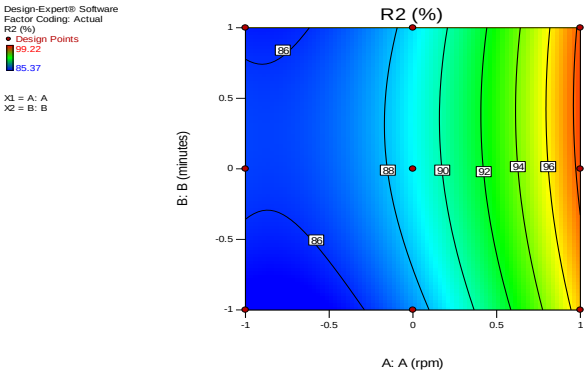


Fig. 7: Contour plot for the effect of rotation speed and agitation time on dissolution at 60th minute.

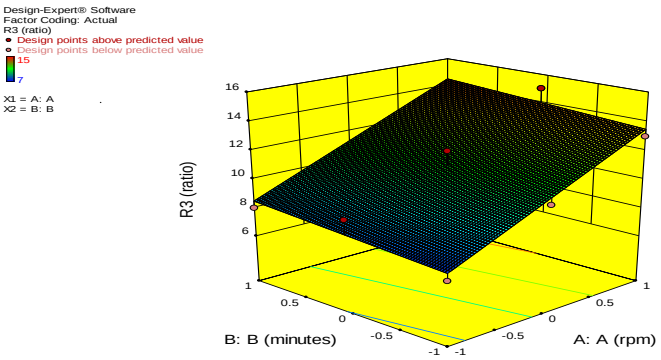


Fig. 8: Response surface plot for the effect of rotation speed and agitation time on solubility enhancement ratio.

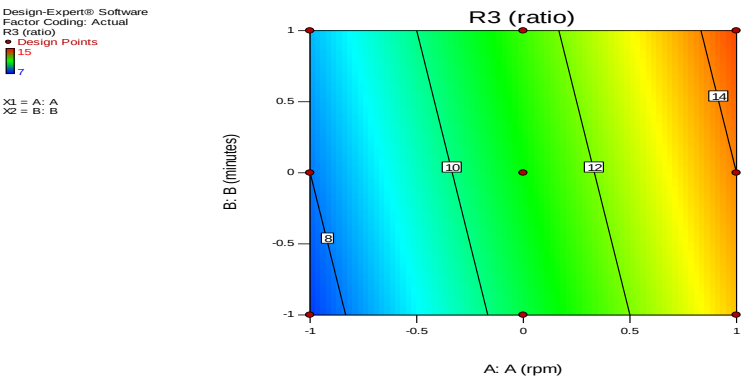


Fig. 9: Contour plot for the effect of rotation speed and agitation time on solubility enhancement ratio.

The relationship between factors and the responses were further studied by using contour plot and the 3D response surface plot. It is evident from the plot that angle of repose decreased as the agitation speed and time increased. Similarly dissolution and solubility enhancement ratio increased as the agitation speed and time increased.

DEVELOPMENT OF THE OPTIMUM BATCH

Based on the statistical evaluations the software gave a solution for obtaining maximum dissolution and solubility enhancement ratio, also the minimum angle of repose of the formulation. The formula opted for the further studies were given along with angle of repose, dissolution and solubility enhancement ratio.

Table 4: Formula for Optimum Batch Based on Statistical Evaluations.

Number	Rotation Speed (rpm)	Agitation time (min)	Angle of repose (degree)	Dissolution at 60th min (%)	Solubility enhancement ratio
1	800	40	25.44	98.40	14

EVALUATION OF OPTIMIZED SPHERICAL AGGLOMERATES

The spherical agglomerates were evaluated for Drug content, Percentage yield, Dissolution at 60th min, SEM, FTIR, Powder X-ray diffraction, Solubility analysis. The evaluation is depicted in Table 5.

Table 5: **Evaluation of Optimized Formulation of Spherical Agglomerates**

Parameter	Result
Angle of repose	25.46
Dissolution at 60^{th} min	98.38
Solubility enhancement ratio	14

Particle shape and surface morphology- Scanning Electron Microscopy

The SEM photographs of pure Flurbiprofen and the formulation which gave the smoothest sphere (OF) is given in figures 10 and 11. This proves that, fine crystals of Flurbiprofen can be effectively converted to larger, spherical agglomerates by the process of spherical crystallization. The smooth surface and spherical shape of the agglomerates impart good flowability, solubility and enhanced dissolution rate.

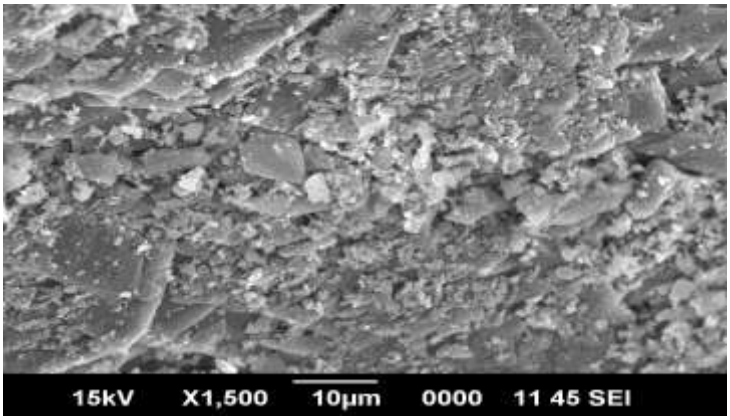


Fig. 10: SEM photograph of pure Flurbiprofen

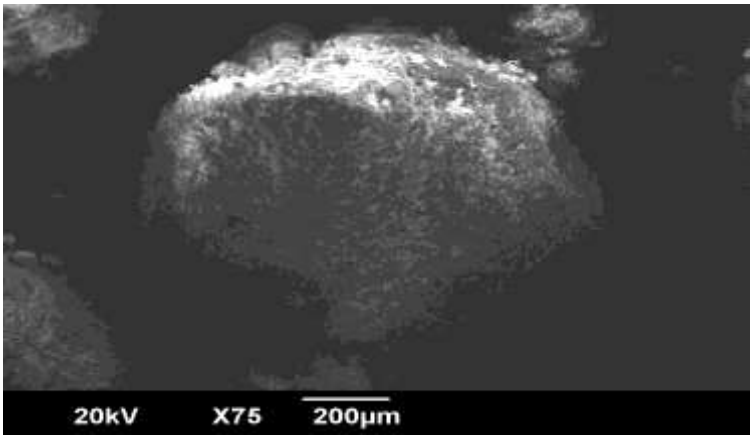


Figure 11: SEM photograph of spherical agglomerate of (OF) 3.5.2. Powder X-ray diffraction

The diffraction angles are similar as far as both X-ray diffraction patterns are concerned. Only a decrease in reflection intensities can be pointed out for the spherical crystal sample and they exhibited a halo pattern. This suggests that crystallinity of the agglomerates could be inferior compared to the pure drug. This slightly amorphous nature is thought to enhance the solubility of Flurbiprofen.

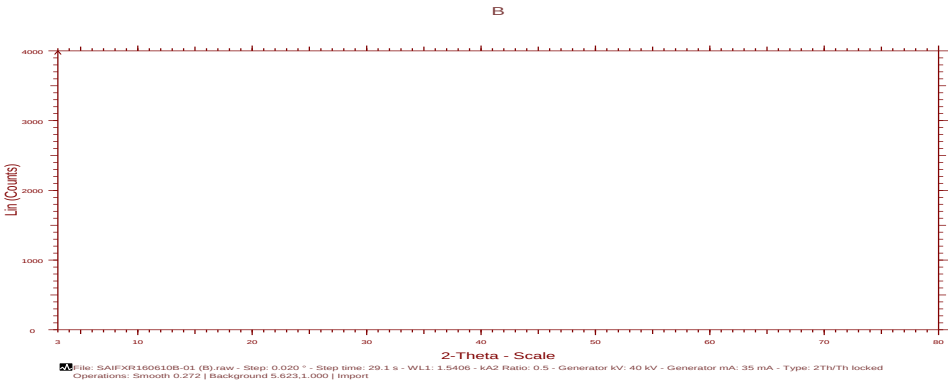


Fig. 12: Powder X-ray Diffraction pattern of pure Flurbiprofen

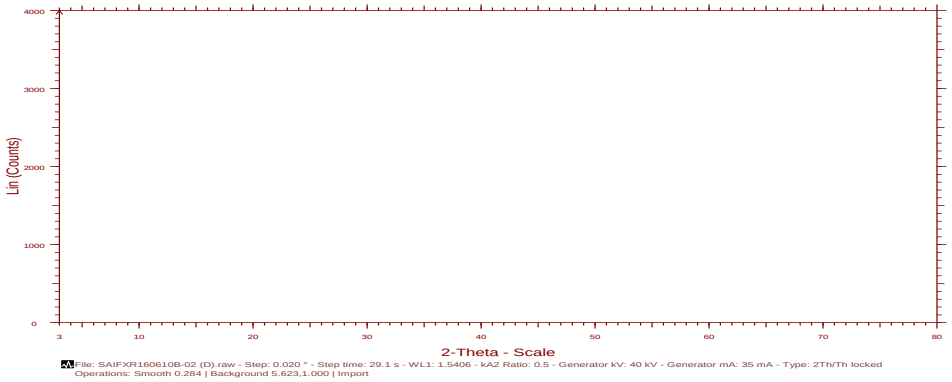


Fig. 13: Powder X-Ray Diffraction pattern of Spherical agglomerate (OF)

PRECOMPRESSIONAL ANALYSIS

The optimized agglomerates were subject to analysis of their micromeritic properties.

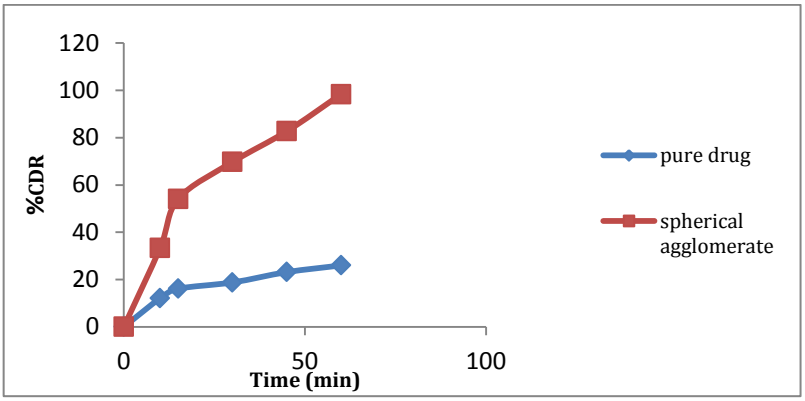
Table 6: Micromeritic Properties of Flurbiprofen Pure Drug and Spherical Agglomerates

Formulation	Bulk densityg/ml	Tapped densityg/ml	Hausner ratio	Carr's index%
Pure drug	0.3125	0.5263	1.6841	40.62
Spherical agglomerates	0.3846	0.4347	1.1302	11.52

The bulk density of agglomerates was found to be 0.3846 g/ml and bulk density of pure drug was found to be 0.3125 g/ml, which indicate good flow property. The tapped density of agglomerates was found to be 0.4347 g/ml and tapped density of pure drug was found to be 0.5263 g/ml, which indicate good flow property. Hausner ratios of pure Flurbiprofen and spherical agglomerates are given in Table 6. Pure drug Flurbiprofen exhibited a Hausner ratio of 1.6841, which shows poor flow characteristics. While spherical agglomerates showed good flow properties with Hausner's ratio below 1.1302. Carr's index of Flurbiprofen was very high- 40.62%. Spherical agglomeration of the drug led to a reduction in Carr's index of the drug. Spherical agglomerate showed Carr's index value 11.52, which is less than 15%, this shows that the formulation exhibited a good flow property. For compressibility analysis, plain Flurbiprofen and spherical agglomerates was selected. Pure Flurbiprofen powder was very difficult to compress into a solid mass. This was due to very poor cohesion and compressibility of Flurbiprofen whereas Spherical agglomerates of Flurbiprofen could be compressed directly to solid pellets. Spherical agglomerate exhibited better compressibility than Flurbiprofen in pure form, thereby proving that spherical agglomeration is an effective tool for improving compressibility of poorly compressible powders like Flubiprofen.

In-vitro Dissolution study

Dissolution profiles of agglomerated crystals and pure Flurbiprofen are given in graph 2. The release percentage of Flurbiprofen pure crystals after 60 minutes was found to be about 25.97% whereas the spherical agglomerate showed about 98.38 %. This shows that spherical agglomeration lead to a faster release of drug.



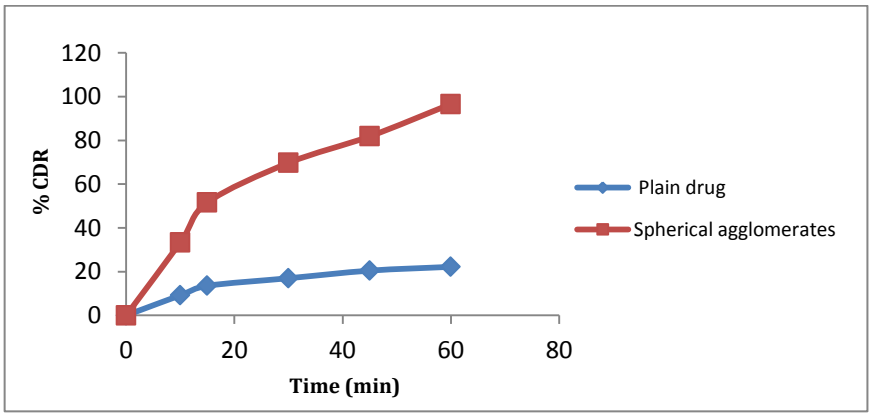
Graph 2: Dissolution profiles of agglomerated crystals and pure Flurbiprofen

EVALUATION OF TABLETS

Average thickness of the tablets was found to be 4.80 ±0.23 mm. Average diameter of the tablet was found to be 7.01±0.39 mm. Average hardness of the tablets was found to be 4.7±0.03 Kg/cm2. n=3, which was found to be with in the IP limit. Friability of the tablets was found to be 0.39%. The weight variation of the tablet was found to be 200.8±0.77, n=10.The percentage content of formulation was found to be 98.1±0.03%.n=3.

COMPARISON OF PREPARED FLURBIPROFEN SPHERICAL AGGLOMERATE TABLET WITH PURE DRUG TABLET

Dissolution profiles of Flurbiprofen tablet prepared from spherical agglomerate and pure drug is given in Table 6.27 and depicted on Graph 3.The release percentage of Flurbiprofen tablet prepared from spherical agglomerate was found to be 96.62% whereas the tablet prepared from pure drug showed only about 22.21 %. This shows that the tablet prepared from spherical agglomerate leads to a faster release of drug within 1 hours when compared with pure drug formulation.



Graph 3: Comparison of dissolution profile of tablet prepared from Spherical agglomerate with pure drug

KINETICS OF IN VITRO DRUG RELEASE

The R2 values suggested that the drug release from the system predominately followed Higuchi's square root of time kinetics as the values for Q vs. t1/2 was always higher. The slope of KorsmeyerPeppas plot (n value) was found to be 1.1231 which lies in range of ≥1. This is an indication that the tablets follow case II transport.

STABILITY STUDIES

Thickness, hardness, drug content and dissolution rates of the tablets before and after 60 days of stability study are given in Table 8. It can be seen that there is no considerable change in these parameters. Thus it is proved that the tablets prepared from spherical crystallization of Flurbiprofen were found to pass 60 days of stability studies.

Table 8: Stability Studies

Parameters	Before Stability	After Stability
Thickness(mm)	4.80	4.78
Hardness(Kg/cm^2)	4.7	4.5
Drug content (%)	98.1	96.9
Dissolution (%)	96.62	95.31

CONCLUSION

Spherical agglomerates of Flurbiprofen were prepared by Neutralization technique. This method was selected, since the SEM analysis showed a considerable spherical shape, also the percentage yield and drug content was found to be satisfactory when compared to other techniques. Optimization of Flurbiprofen spherical agglomerate was done. SEM analysis of the agglomerates confirmed their spherical shape. Surface of the agglomerates were found to be smooth. The smooth spherical surface of the agglomerates can be thought to impart excellent flow properties to them. Solubility of Flurbiprofen spherical agglomerate was enhanced to that of pure Flurbiprofen in phosphate. The improvement in solubility may be due to changing the crystal forms and/or surface modifications. Micromeritic properties such as Angle of repose, Carr's index and Hausner ratio of spherical agglomerate of Flurbiprofen was improved. It was found that compressibility of Flurbiprofen improved by spherical agglomeration. *In-vitro* dissolution studies of prepared agglomerates showed that spherical agglomeration enhances the dissolution properties of Flurbiprofen. Optimized formulation of spherical agglomerate was chosen for preparation of tablet. The tablet prepared from spherical agglomerate leads to a faster release of drug when compared with marketed formulation. The drug release mechanism from the tablets was found to be case II transport kind of diffusion. Stability studies of prepared tablets

confirm that the agglomerates remain stable throughout the period of study.

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