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Research Article

**OPTIMIZATION OF GRANULATION TECHNIQUES FOR  
DEVELOPMENT OF TABLET DOSAGE FORM****V. B. Khot\*<sup>1</sup>, D.A. Bhagwat<sup>2</sup>, J. I. D'Souza<sup>2</sup>, S. S. Shelake<sup>3</sup>, S. V. Patil<sup>4</sup>**<sup>1</sup> Mandar Education Society's, College of Pharmacy, Pedhambe, Ratnagiri, MS, India.<sup>2</sup> Department of Pharmaceutics, Tatyasaheb Kore College of Pharmacy, Warananagar, MS, India.<sup>3</sup> Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, MS, India.<sup>4</sup> Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, MS, India.**Abstract:**

*The purpose of this study was to optimize the best granulation techniques for development of tablet dosage form. The present study explains comparative study of different wet granulation techniques including Planetary mixer granulation, Rapid mixer granulation, Fluid bed granulation with Direct compression method. Similar formulations were used to evaluate Planetary mixer granulation, Rapid mixer granulation and Fluid bed granulation method. The granules prepared by different techniques were evaluated for particle size distribution, porosity, sphericity, bulk density, flow property and compressibility, compatibility and tablet properties of Diclofenac sodium tablet. The fluid bed granulation technique had superior flow properties, compressibility, compactibility measured by Kawakita, Hekel, Walker and Leuenberger equation. The granules prepared by Fluid bed granulation showed better tablet properties (weight uniformity, hardness, friability and disintegration, drug content, dissolution) and accelerated stability study compared to other granulation techniques so finally, it was concluded that Diclofenac sodium tablets prepared by using fluid bed granulation which meets the required specification compared to other wet granulation techniques and direct compression method.*

**Key words:** Granulation technique, Flowability, compressibility, compactibility, Diclofenac sodium tablet.**Corresponding author:****V. B. Khot,**

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**INTRODUCTION:**

Most product formulators see wet granulation technology as a universally applicable means of tablet processing. The wet granulation techniques to be most preferred due to various advantages including improving flow property, compression characteristics, better distribution of colour and reduces dust hazards. So that to optimize the best wet granulation technology is important for development of tablet dosage form. Direct compression is one of the popular methods for preparation of tablet. However, it is often necessary to improve poor content uniformity, flowability, compression and compactibility to produce tablet of adequate quality. These properties are commonly enhanced by wet granulation.[1] Wet granulation is widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass. The wet mass is dried and then sized to obtain granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates.[2] This can be achieved by using Planetary mixer granulation, Rapid mixer granulation and Fluid bed granulation. Fluid bed granulation has some advantages compared to other granulation methods. Fluid bed granulation method is selected for production of porous and free-flowing granules, which enables to form tablets with high mechanical strength at low compression pressure. Simultaneous granulation and drying removes the need for additional drier and all granulation process performed in one unit so saving time, transfer losses and labour costs.[3]

Kawakita analysis revealed improved flowability for formulations prepared by direct compression and wet granulation technique. Compressibility is the powder's ability to deform under pressure, and compactibility is the ability to form mechanically strong compacts. Compressibility is often described by the change in the relationship between relative density, porosity and applied pressure represented by Heckle and Walker models. [8] Compactibility is nonlinear plot of tensile strength with respect to product of compaction pressure and relative density represented by Leuenberger equation. Literature addresses each type of granulation process individually and in detail.[5] Comparison was found between a low shear, high shear, and fluid bed granulation during low dose tablet process development.[6] A comparison was also found between the different granulation techniques for Lactose Monohydrate.[7] Another reference compared impact of wet and dry granulation versus a direct tableting mixer and a compressibility and compactibility study of real tableting mixtures.[8]

The purpose of study was to investigate the effect of planetary mixer granulation, Rapid mixture granulation and Fluid bed granulation on granulation properties like particle size distribution, porosity, sphericity, bulk density, flow property and compressibility, compatibility, tablet properties and accelerated stability study of Diclofenac sodium tablet and based on above evaluation parameter to optimize the best granulation techniques for development of tablet dosage form.[9,10,11]

**1. MATERIALS AND METHODS:****1.1 Materials**

The mixture consisted of Diclofenac sodium (model drug, Neon labs Ltd Palghar, India), 40% (W/W); lactose monohydrate (Filler, Pharmatose 350M for wet granulation, 41.3% (W/W); lactopress spray dried-250 for direct compression, 43.12 % (W/W); DFE Pharma India, LLP, Bangalor), microcrystalline cellulose (Filler/ dry binder, Avicel PH 101, VerGo Pharma Research Laboratories Pvt. Ltd, Goa) 13.7% (W/W); polyvinylpyrrolidone (binder, Povidone K90, BASF India Ltd., Navi Mumbai) 2.5% (W/W); Crosspovidone (disintegrating agent, Research Fine Lab, Mumbai) 2% (W/W); and magnesium stearate (Lubricant, BASF India Ltd., Navi Mumbai) 0.5% (W/W) etc. [All chemicals used were of analytical grade.]

**2.2 Characterization of Diclofenac sodium**

The organoleptic properties of drug were determined including nature, color, solubility. Melting point: The melting point was determined by using open capillary method.

**2.3.2 FTIR Spectroscopy****IR Spectrum interpretation**

The infrared absorption spectrum of pure Diclofenac sodium was recorded on FT-IR Spectrophotometer (Model- Agilent) and the spectrum analysis was done for functional groups.[12]

**2.3.3 X-ray Diffractometry**

The X-ray diffraction patterns of drug were determined using a Bruker D2 Phaser powder X-ray diffractometer. Samples were irradiated with monochromatized CuK alpha radiation (1.542 Å) and analyzed between 10 and 70 (2θ) at a scan rate of 0.1° 2θ per min. [12]

**2.3.4 Drug - Excipients compatibility studies of physical mixture**

The infrared absorption spectrum of pure Diclofenac sodium and physical mixer of drug and excipients was recorded on FT-IR Spectrophotometer (Model- Agilent) The IR spectroscopy was used to investigate and predict

any physiochemical interaction between drug and different excipients.

### 2.3.5 X-ray diffractometry of drug, excipients and formulation

The X-Ray diffraction study was conducted for evaluation of change in crystalline nature of pure drug by process or addition of other polymers. The sample was analyzed by using Brooker D2 Phaser powder X-Ray Diffractometer and was scanned from 10° to 70° 2θ.

### 2.4 Preparation of granules

Granules were prepared according to the procedures enumerated and described below. Before preparation of granules, all materials were sieved manually through a sieve with a mesh size of 0.8 mm. The weighted amounts of powders were the same for all mixtures: Diclofenac sodium (100gm), Pharmatose 350M (103.5gm), Avicel PH-101 (34.25gm), PVP K-90 (6.25gm), Crosspovidone (5gm).[8]

#### 2.4.1. Planetary mixer granulation (PMG)

Weighted powders without PVP-K 90 were mixed in a mixing bowl of planetary mixer granulator (Kenwood, Kolkata, India). All ingredients were mixed at low speed then 5% binder was added then mixture was mixed at high speed. With the help of wet mass consistency and physical properties of granules end point of granules was determined. Wet granules were sieved using a sieve with a mesh size 16#. Then granules were transferred to the fluid-bed dryer and dried at an inlet air temperature 60°C and air flow of 60 rpm. Drying lasted for 40 min. after that dried granules were sieved using a sieve with a mesh size of 30#.

#### 2.4.2. Rapid mixer granulation (RMG)

Weighted powders were mixed with a Rapid mixer granulator for 2 min at an impeller speed of 150 rpm. 4.5 % binder was added into the mixed ingredients and then granulate was kneaded for 180 s. at an impeller speed of 250 rpm and the chopper speed of 2500 rpm. With the help of wet mass consistency and physical properties of granules end point of granules was determined. Wet granules were sieved using a sieve with a mesh size 16#. Then granules were transferred to the fluid-bed dryer and dried at an inlet air temperature 60°C and air flow of 60 rpm. Drying lasted for 40 min. Dried granules were sieved using a sieve with a mesh size of 30#.

#### 2.4.3. Fluid bed granulation (FBG)

Weighted powders without PVP-K-90 were mixed in a fluid bed processor (Pam glatt, Mumbai) The parameter was set like process time-420 min, pause time-40 sec, shaking time-10 sec, shaking speed-500 msec. Then 8.33% (w/w) aqueous solution of PVP-K-90 was sprayed. After that the parameter

was set like Inlet temperature 50°C, Product temperature 40°C, exhaust temperature 50°C, atomization air-1.1 bar, blower drive speed-14%, air flow 130 cfm, spray pump speed 14 rpm and spray rate 10 gm/min. At the end point the product temperature was 54°C and inlet air temperature was 70°C. The moisture content of granules during the operation was continuously monitored. The operating conditions such as inlet air temperature and airflow rate were controlled during granulation. Then the granules were passed through 30# and lubricated with Mg-stearate.

#### 2.4.4. Mixture for direct tableting (DC)

Weighted Diclofenac sodium(100gm), Lactopress spray dried- 250 (107.8gm), Avicel PH 101(35.95gm), Crosspovidone (5gm) were mixed for 10min. Magnesium stearate (1.25gm) was added then mixing for 2 min was performed.

### 2.5 Evaluations of granules

#### 2.5.1 Moisture content

Five grams (5g) of each powder sample was accurately weighed and dried at 105°C in the oven to constant weight. The sample was reweighed and weight loss calculated.[13]

#### 2.5.2 Particle size distribution

The particle size distribution for all mixtures (50 g sample) was determined by sieve analysis using vibrating shaker using the following sieves size (µm): 500, 355, 250, 180and 150. The sieving lasted for 10 min. Results was represented as particle size distribution and also as the particle size at which 50% (w/w) of particles were below the given size denoted as median particle diameter d50.[7,8,15]

#### 2.5.3 Span value of granules [14]

Span value determined by using sieving method. Span value was calculated by using d10, d50 and d90 values

$$\text{Span} = \frac{d90 - d10}{d50}$$

Where, d90 =90% of particles are below the particle diameter

d10 = 10% of particles are below the particle diameter

d50 = median particle diameter

#### 2.5.4 Particle shape [5,7]

Motic microscope (Optical microscope with cammera motic image plus version, 2.0 MI) was used to determine the shape of granule. By using Motic microscope radius, perimeter and area of granule was determined. The Form factor was used to determine the sphericity of granules. Form factor was calculated by using following formula

$$\text{Formfactor} = \frac{4\pi(\text{area})}{(\text{perimeter})^2}$$

### 2.5.5 Bulk and tapped densities

Bulk Density and Tap Density were subjected to Bulk and Tap density determination. Tapping cylinder method was used for determining bulk and tap density of granules were taken in 10 ml measuring cylinder. Initial volume (Bulk volume) and the volume after 100 tapings (Tap volume) were measured. From the results of Bulk and Tap densities, the Hausner's ratio and Carr's Index were calculated.[7]

### 2.5.6 Flow properties of tableting mixture [16,18]

The flowability was determined by measuring the Carr's index, and Hausner's ratio, angle of repose, flow time.

The bulk and tapped densities were used to determine the Carr's index, and Hausner's ratio. The Carr's index and Hausner's ratio were calculated according to following equations

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

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

1. Angle of repose: The end of a funnel was placed 2 cm above a flat base. Powder was filled into the funnel, so that after releasing the powder out of the funnel the top of the resulting cone reached the end of the funnel. The powder was released from the funnel. From the height of the cone ( $h$ ) and the diameter at the base ( $d$ ) the angle at the base, the angle of repose, ( $\alpha$ ) was determined.

$$\tan \alpha = \frac{2h}{d}$$

2. Flow rate: 10 gm of granule was placed in funnel and time was measured to flow of granules from the funnel. Flow rate were determined as the ratio of mass (g) to time (seconds) using a steel funnel with an orifice diameter of 10 mm.

$$\text{Flowability} = \frac{\text{Flowing time}}{\text{Mass}}$$

### 2.5.7 Bulkiness [17]

Bulkiness is determined by using specific bulk volume or bulk density. Bulkiness determined by using following formula

$$\text{Bulkiness} = \frac{1}{\text{Bulk density}}$$

### 2.5.8 Porosity of granules [17]

Porosity is the ratio of void volume to the bulk volume. The void volume is calculated by using following formula

$$\text{Void volume (v)} = v_{\text{bulk (untapped)}} - v_{\text{true (tapped)}}$$

Porosity is expressed in percentage so the porosity was calculated by using following formula

$$\text{Porosity } (\epsilon) = \frac{\text{Void volume}}{\text{Bulk volume}} \times 100$$

### 2.5.9 Kawakita plot

Flowability was determined using the Kawakita analysis.

The formulation (10) gm was poured into a 50 ml glass measuring cylinder. The heaped particles in the cylinder were then levelled off horizontally and the bulk volume  $V_0$  was accurately measured. Tapping was afterwards initiated mechanically and the change in volume of the powder column  $V_N$  was noted after  $N$  no. of tap. The Kawakita equation is given by:

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab}$$

Where  $a$  and  $b$  are constants;  $a$  describes the degree of volume reduction at the limit of tapping and is called compactibility;  $1/b$  is called cohesiveness,  $C$ , the degree of volume reduction is calculated from the initial volume  $V_0$  and tapped volume  $V_N$  as

$$C = \frac{(V_0 - V_N)}{V_0}$$

Numerical values for constants  $a$  and  $1/b$  was obtained from the slope, of plots of  $N/C$  versus number of taps  $N$ .<sup>18</sup>

### 2.6 Formulation of Diclofenac sodium tablet

1. Wet granulation method: The granules were mixed with 0.5% Mg-stearate
2. Direct compression method: Mixture for direct tableting was used

## 2.7 Compaction studies [8]

### 2.7.1 Heckel plot

Preparation of compacts: 250mg Diclofenac sodium tablet were made using 10Kg/cm<sup>2</sup> to 120Kg/cm<sup>2</sup> compression pressures in KBr pellet press machine. Compacts were made at each compression level. Before compression, the die and the flat-faced punches were lubricated Mg-stearate. The hardness, dimensions and weight of compacts were determined. The relative density was calculated as the ratio of apparent density of the compact to the true density of the powder. The data obtained using this 'ejected tablet method' was used to obtain Heckel plots.

#### Heckel Analysis:

The Heckel model was based on the assumption that the process of pore reduction during compression. The degree of compact densification with increasing compression pressure is directly proportional to the porosity as follows:

$$-\ln \varepsilon = \ln \frac{1}{(1-D)} = KP + A$$

Where, D is the relative density of the compact, P is applied pressure, K (slope; Heckel coefficient), K is the slope of the straight portion of the graph, reflects the reduction in porosity or the resistance to volume reduction of granules and A (y-intercept) are regression coefficients of the linear portion of the curve, and  $\varepsilon$  is porosity. Yield pressure (Py), which is the reciprocal value of the slope (K) of the Heckel plot was a measurement of the material's compressibility. Greater slopes indicate a greater degree of plasticity hence better compressibility of the material.

### 2.7.2 Walker plot

The Walker equation plots the specific volume of the powder compact against the logarithm of the axial pressure applied

$$V' = w' \log P + V'_{sp}$$

where V' is the specific volume of a tablet and w' is the Walker coefficient expressing the volume reduction corresponding to one decade change in pressure P obtained by linear regression analysis, and V' sp is the specific volume at pressure 1.

### 2.7.3 Leuenberger Equation

The compression susceptibility parameter for compact formed by direct compression and wet granulation technique indicated that the maximum crushing strength is reached faster at lower pressure of compression

For compactability assessment, tensile strength of the compacts was calculated by the following

equation where x is hardness (in kg/cm<sup>2</sup>) and d and t are the diameter and thickness of the compacts (in mm), respectively.

$$\sigma_x = \frac{2x}{\pi dt}$$

Leuenberger analysis was performed by fitting the data in the following equation. A nonlinear plot of tensile strength with respect to product of compaction pressure P and relative density  $\rho_r$  was obtained.

$$\sigma_x = \sigma_{xmax} (1 - e^{-\rho_r \gamma x p})$$

Where,  $\sigma_{xmax}$  is maximum tensile strength (kg/cm<sup>2</sup>), p will be infinite and  $\rho_r$  will be equal to 1, and  $\gamma$  is compression susceptibility.[18]

## 2.8 EVALUATION OF TABLETS

### 2.8.1 Thickness

Thickness of tablet was determined using calibrated Vernier caliper.[20]

### 2.8.2 Hardness

For each formulation, the hardness of six tablets was determined using the Pfizer hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm<sup>2</sup>. Then constant force was applied by rotating the knob until the tablet fractured. The optimum hardness regarded for uncoated tablet is 4-6 kg/cm<sup>2</sup>. [19]

### 2.8.3 Weight variation test

Randomly selected twenty tablets were weighed individually and together. Average weight was calculated. Each individual tablet weight was compared against the calculated average.[19]

### 2.8.4 Friability test

The friability of a sample of 6 tablets was measured using a Roche friabilator (Remi electronics, Mumbai). 6 previously weighed tablets were rotated at 25 rpm for 4 min. The tablets were dedusted and again weighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability was calculated as follows

$$\% F = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

### 2.8.5 Drug content

The tablets were finely powered and a quantity of powder equivalent to 100mg of diclofenac sodium were accurately weighed and transferred to 100ml volumetric flasks containing approximately 50ml of buffer solution (pH6.8) and analysed for the content of diclofenac sodium using UV-visible

spectrophotometer at 276nm. The drug content of each sample was estimated.[20]

### 2.8.6 Disintegration test

The disintegration time of the uncoated tablet was performed with help of disintegration test apparatus using phosphate buffer (pH 6.8) media at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . The time taken for six randomly selected tablets to disintegrate in each case was recorded.[21]

### 2.8.7 In-vitro drug release studies

*In-vitro* drug release study of Diclofenac sodium was done by using USP dissolution test apparatus II. The study was conducted at 50 rpm using 900 ml of pH 6.8 phosphate buffer maintained at  $37^{\circ}\text{C} - 0.5^{\circ}\text{C}$  by using a constant temperature bath. The 5 ml sample was withdrawn from the dissolution apparatus at 10 min time intervals up to 60 min. the sample were replaced with fresh dissolution medium and then absorbance was measured by using UV-visible spectrophotometer at  $\lambda_{\text{max}}$  of 276 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The graphs of % cumulative release Vs time were plotted.[21]

### 2.9 Stability study of tablets

Samples of Diclofenac sodium tablets were blister packed in aluminum foil. These samples were then subjected for stability study according to ICH guidelines where zone II was selected as storage conditions (ICH 2003). Tests were conducted at

room temperature (RT) and accelerated stability conditions. The samples were designated as time 0, 3, 6, 9, 12, 18 and 24 months for RT and 0, 1, 2, 3 and 6 month for accelerated studies. Samples designed for RT storage were kept at  $25 \pm 2^{\circ}\text{C}$  and  $60 \pm 5\%$  relative humidity (RH). The samples in the accelerated stability study were kept at  $40 \pm 2^{\circ}\text{C}$  and  $75 \pm 5\%$  RH in humidity chamber. Samples were tested for its appearance, disintegration, dissolution and assay using the previously described procedure to evaluate the stability of tablets. The percent dissolution, assay, appearance and hardness of the tablets stored at room temperature for 24 months.[21]

## 3. RESULT AND DISCUSSION:

### 3.1 Characterization of drug

The powder was found to be White to slightly yellowish, slightly hygroscopic, crystalline powder. Diclofenac sodium is soluble in ethanol, methanol and water. The melting point was found in the range of  $284-285^{\circ}\text{C}$ . All observed parameters was found to be similar and complies with the standard specifications. Hence the drug sample was considered as a pure.

### 3.1 FTIR Spectroscopy

The IR spectrum (Figure 1) of the Diclofenac sodium showed similar characteristics peaks to that of reported spectra of Diclofenac sodium. From the FTIR study the sample of Diclofenac sodium was identified.

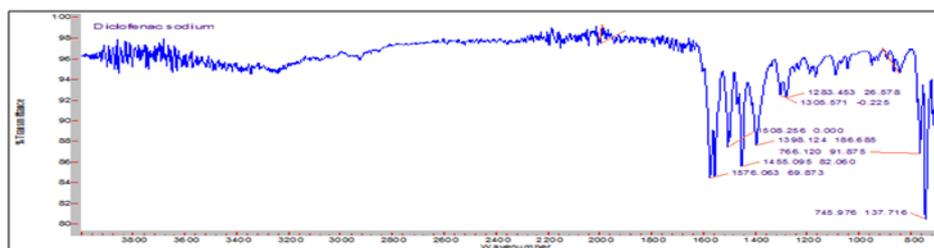


Fig. 1: FTIR Spectra of Diclofenac sodium

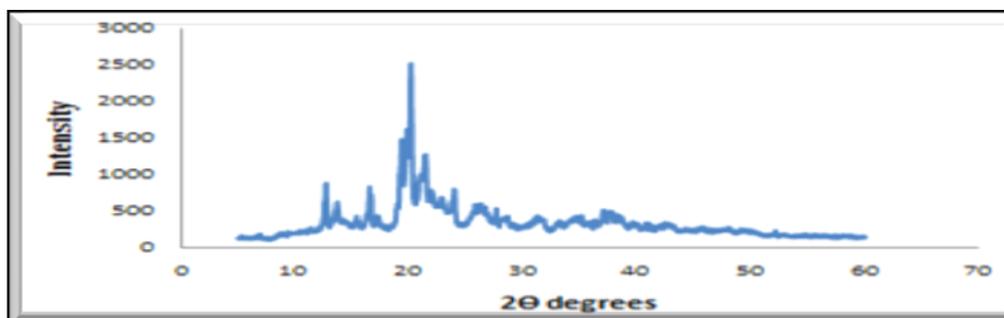


Fig. 2: XRD of pure Diclofenac sodium

### 3.2 X-ray diffractometry:

The X-Ray diffraction patterns of pure Diclofenac sodium were illustrated in Figure 5. The 79.8% of drug was found to be in crystalline form. 20.2% was in amorphous form.

The characteristic peaks of Diclofenac sodium appeared at a diffraction angle of  $20.18^\circ$  at maximum intensity of 2527 and several sharp diffraction peaks suggesting that the drug is present in crystalline form.

### 3.3 Drug and polymer compatibility

#### 3.1.1 FTIR spectroscopy

The IR spectra of drug and physical mixture show similar characteristic functional peaks. This similarity in peaks indicates the compatibility of Diclofenac sodium with the excipients.

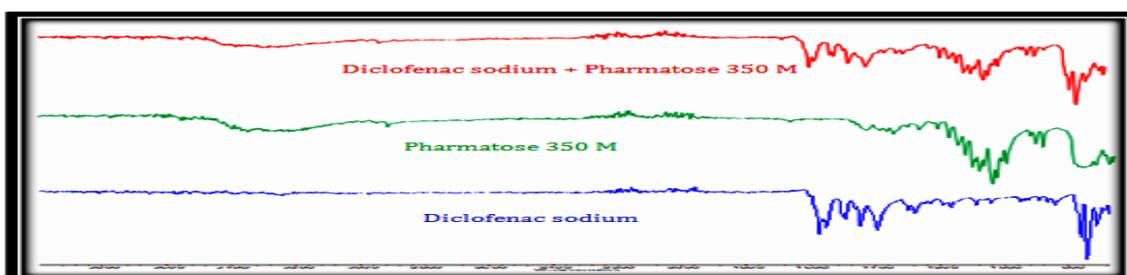


Fig.3: IR spectra of drug and physical mixture of pharmatose 350M

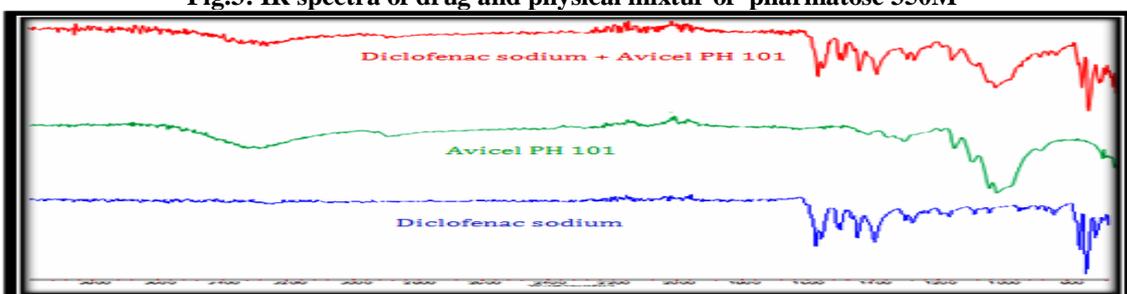


Fig. 4: IR spectra of drug and physical mixture of Avicel PH 101

#### 3.1.2 X- ray diffractometry of drug, excipient and formulation

The Figure 8, 9 shows non-interactive peaks of pure drug, excipients like Pharmatose 350M, Avicel PH

101 and formulation was showed characteristic sharp peak in the range of  $2\theta$  scattered. The decrease in the peak intensity was observed in formulation.

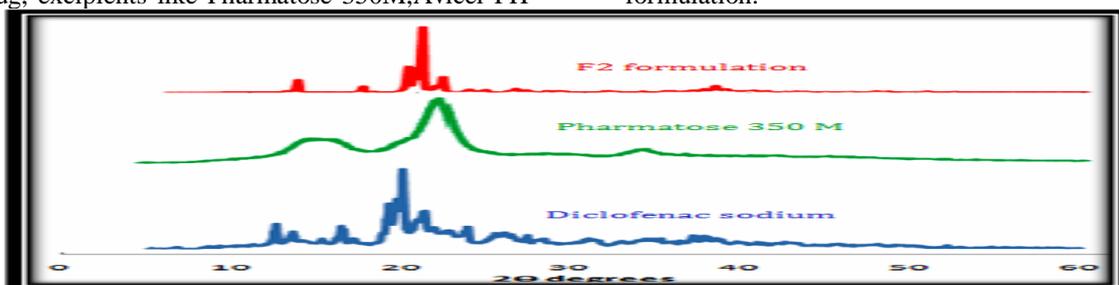


Fig. 5: XRD of Diclofenac sodium, Pharmatose 350M and F2 formulation

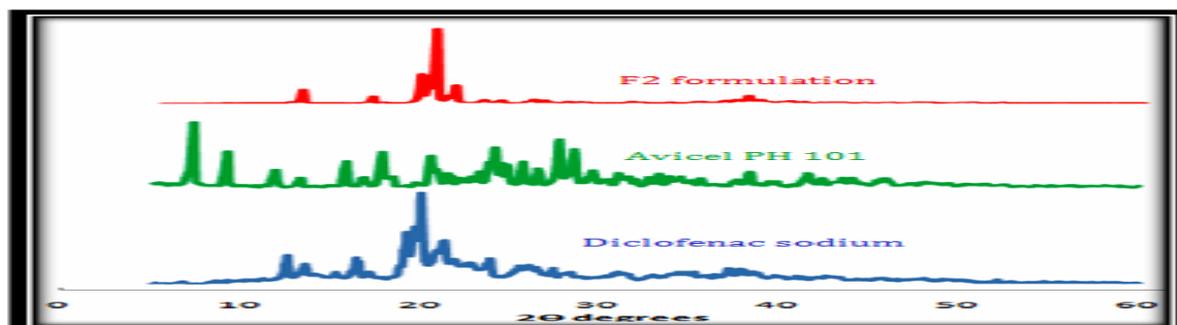


Fig. 6: XRD of Diclofenac sodium, Avicel PH 101 and F2 formulation

### 3.4 Formulation of granules

Wet granulation method was used for preparation of granules. PMG, RMG and FBG were used for preparation of granules.

### 3.5 Evaluation of granules

#### 3.5.1 Moisture content

Loss on drying is known that the moisture content in granules or powders can influence the hardness and therefore compactibility of the tablets produced. Therefore, all tableting mixtures produced were dried to an approximately equal moisture level. It was established that the loss on drying (LOD) values of the tableting mixtures produced were the following: PMG 1.50%, RMG 1.75%, FBG 1.65%, and DC 1.25%. All LOD values are within the range of 1.25–1.75% and may be considered comparable or approximately equal because it is known that moisture content is difficult to control during drying

processes of pharmaceutical materials, especially when drying wet granules in narrow ranges such as  $\pm 0.1\%$ . Similar batch-to-batch variability in LOD values are commonly observed for regular pharmaceutical intermediate products such as granulates and tableting mixtures.

#### 3.5.2 Particle size distribution

Tableting mixtures were prepared using different granulation methods PMG, RMG, FBG and DC. The particle of PMG(P2), RMG(R2), FBG(F2) mixtures were considerably d50 values of around 342 $\mu\text{m}$ , 350 $\mu\text{m}$ , 409 $\mu\text{m}$ , respectively and particles of the DC (D1) mixtures were considerably smaller, with d50 values of around 93.75 $\mu\text{m}$ . Larger particles in the size range of 125–1250  $\mu\text{m}$ . The larger particle size of agglomerates compared with the DC mixture is expected due to the granulation process.

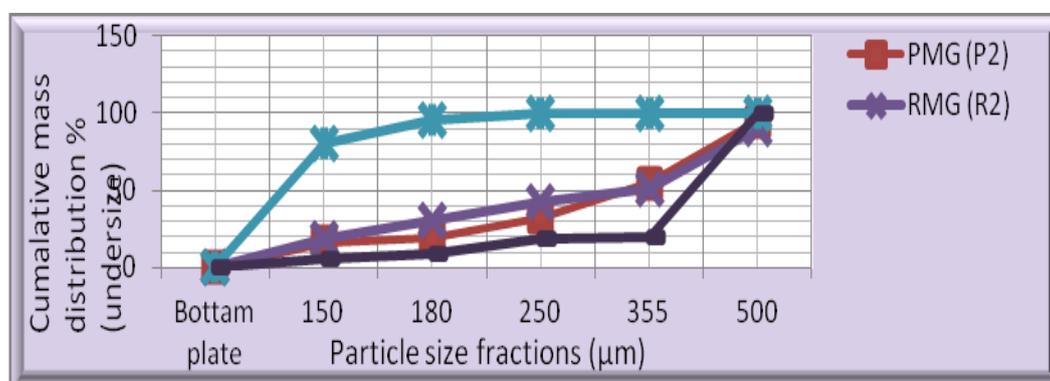


Fig.7: Cumulative mass distribution of compression mixtures

A good powder formulation has a uniform particle size distribution. If the particle size distribution was not uniform, the powder can segregate according to the different particle sizes. A uniform particle size distribution insures uniform dissolution rate, compaction process and flowability, so it was important to evaluate these parameters. Thus, in order to compare the mixtures,

a numerical particle size was given as the median particle diameter d50.

#### 3.5.3 Span value of granules:

Lowest span value shows the narrow particle size distribution. Here FBG showed lowest span value so the FBG showed narrow particle size distribution compare with PMG, RMG and DC method.

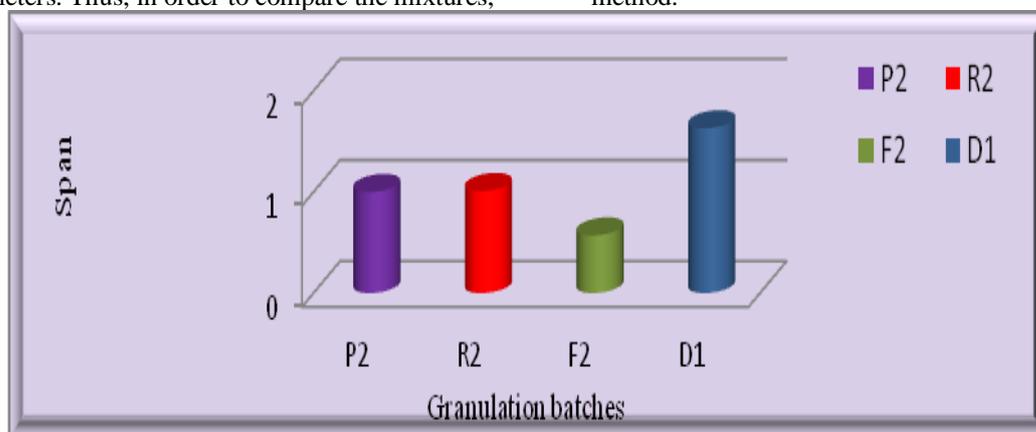


Fig. 8: Span value of granules

**Form factor of granules:**

Formfactor gives a measure of sphericity and a perfect sphere has a formfactor value of unity. FBG showed formfactor value of unity so that FBG have high sphericity compare to the RMG, PMG and DC method. If the particles have more sphericity then flow rate of granule decreases. FBG showed the less flow rate because the sphericity of granules.

**Table 1: Form factor of granules**

Granulation batches	P2	R2	F2	D1
Form factor	0.6866	0.5929	1.000	0.999

In case of direct compression have also same formfactor value of unity because lactopress spray dried-250 a direct compressible vehicle present in to DC method.

**Bulk density**

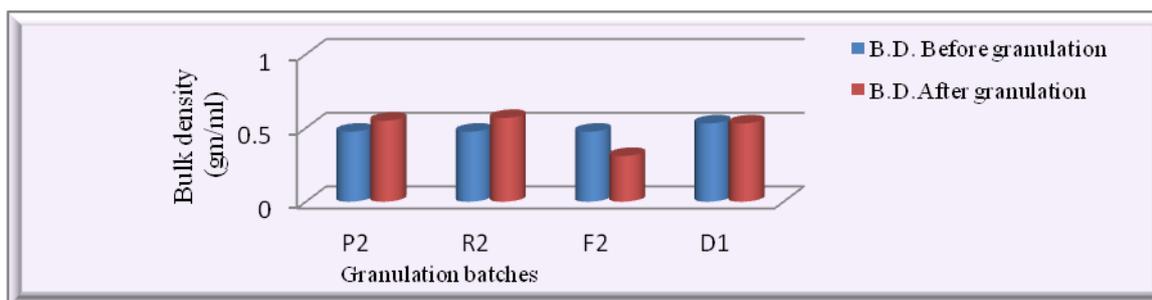
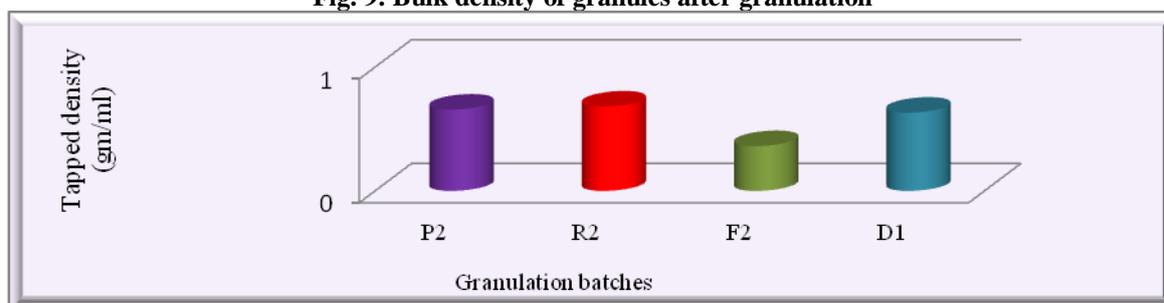
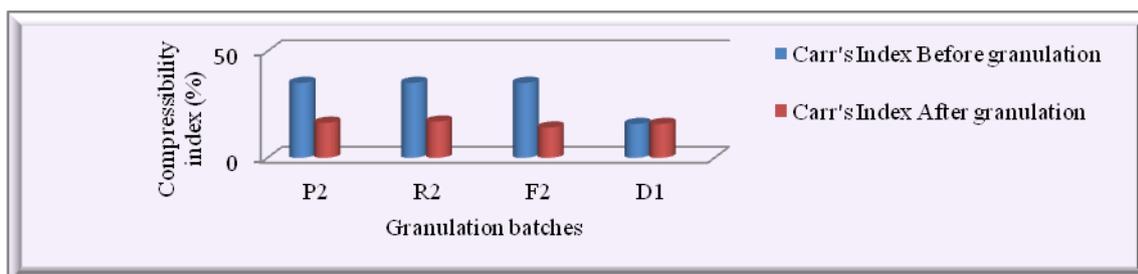
After granulation bulk density of FBG was decreased compare to RMG, PMG and DC method. FBG showed decreases in bulk density with increase in granule voidage but in case of RMG bulk density increase during kneading step. The void between granules was compressed and granule densify. PMG cannot compress the voids between

granules so that bulk density of PMG was intermediate in value between those of FBG and RMG. PMG produce fluffier, more porous granules than RMG. The bulk density of fluid bed granulation is decrease compare to direct compression.

Tapped density of FBG was less compare to RMG, PMG and DC method. The tableting mixture density obviously plays an important role in powder compressibility.

**3.5.6 Flow properties of tableting mixture**

The flow properties results are shown in Table 6, 7 and 8. The flow properties as dictated by the Carr index, the Hausner ratio, Angle of repose and the flow time are entirely consistent with one other. In general, flow properties of wet granulated mixtures are superior to other mixtures. FBG shows excellent flow property. The RMG, PMG and DC method shows good flow property. DC mixture shows good flow properties due to the usage of directly compressible main component of the formulation.

**Fig. 9: Bulk density of granules after granulation****Fig. 10: Tapped densities of granulation batches****Fig. 11: Carr's Index of granules**

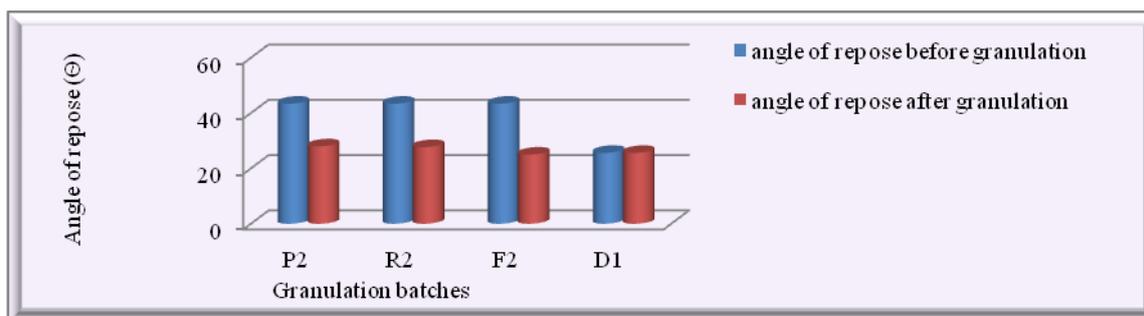


Fig. 12: Angle of repose of granule after granulation

### 3.5.7 Bulkiness

Granules prepared by FBG have higher bulkiness compare to the RMG, PMG and direct compression method. It may be due to the large amount of voidage is present in FBG.

Table 2: Bulkiness of granules

Granulation batches	P2	R2	F2	D1
Bulkiness	1.549	1.760	<b>3.225</b>	1.883

### 3.5.8 Porosity of granules

Granules prepared by FBG was porous than that of PMG and RMG. It may be due to the consolidation time was limited to granule drying time, which was of order of second, rather than minutes. Thus process changes that reduce drying time (higher bed temperature, lower liquid flow rate, and smaller drop size) will decrease granule density (increase granule porosity). Granules prepared by RMG showed lower porosity results in increased granule strength.

Table 3: Porosity of granules

Granulation batches	P2	R2	F2	D1
Porosity (%)	16.4	15.9	<b>17.3</b>	15.9

### 3.5.9 Kawakita Plot

The value of 'a' was least, and 'b' was maximum indicating good flowability. The value of 'a' indicated compressibility or densification due to tapping and 'b' as rate of achieving final packing. Figure 21 showed the kawakita plots for Diclofenac sodium granules containing selected diluents and PVP as binder, where a fairly linear relationship between N/C and N is obtained at all compression pressures used with correlation coefficient  $\geq 0.99$  for all the formulations, and hence, the equation can be used to predict the densification mechanisms. Values of  $1/b$  and  $1/ab$  were obtained from the slope and intercept of the plots respectively. It was observed from Table 11 (which showed the Kawakita constants) that values of 'a' were smaller in the formulations with FBG than in the formulations with DC, PMG and RMG implying that the better the fluidity of the FBG.

From Kawakita analysis, it was found that FBG granules densified the least (small compressible value) but attained the final packing state more slowly than DC formulation. The lower values of a and  $1/b$  for the FBG granule formulation indicate better flowability and lesser cohesiveness than the direct compression formulation.

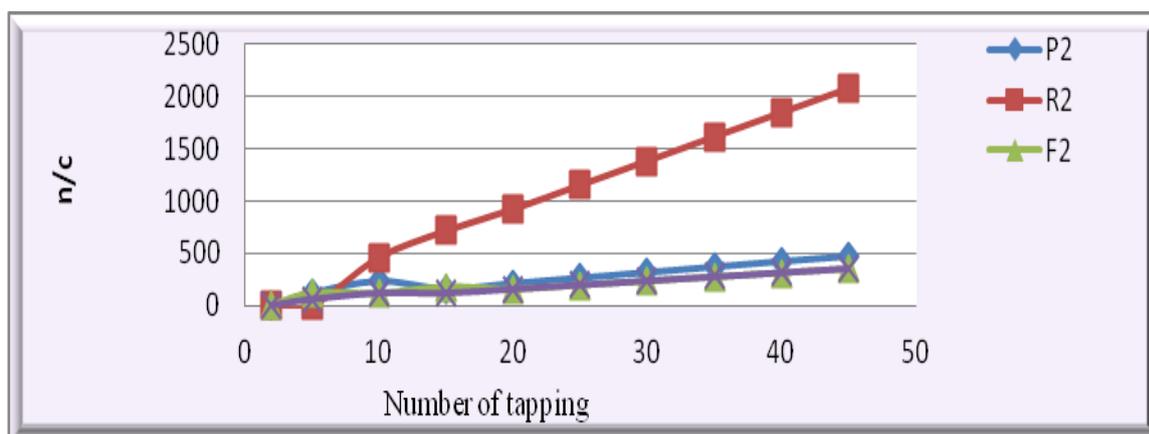


Fig. 13: Kawakita plot

### 3.6 Formulation of Diclofenac sodium tablet

Tablets were prepared by addition of 0.5% Mg-stearate into the prepared granules. Tablets were prepared by wet granulation method and direct compression method.

### 3.7 Compaction Studies

Heckel and walker plot was used to determine the compressibility of granules.

#### 3.7.1 Heckel plot

K represents the Heckel coefficient (slope of the Heckel plot) and  $mPy$  represents yield pressure as its inverse value. A (y-intercept) are regression coefficients of the linear portion of the curve. The FBG mixture is most compressible, with  $Py$  (for F2) 1.1748 followed by the PMG, RMG and DC mixtures have  $Py$  2.0967, 2.1610, 1.7921 respectively, Low value of  $py$  indicates faster onset of plastic deformation.

Heckel data for DC formulation and granule show no linearity at the early stages of compression due to particle rearrangement and the initial fragmentation. The higher value of intercept (A) for granules implies a higher degree of fragmentation than for DC formulation. When the

compression pressure was increased, the granules showed plastic deformation. Materials with higher  $k$  values undergo more plastic flow and such materials often form strong tablets at relatively low compaction force. Crushing strength of tablets correlated with the values of  $k$ ; Increased the slope value increased degree of plasticity and better compressibility formed. Here FBG have higher  $k$  values compare to the PMG, RMG and DC method. FBG mixture has excellent compressibility it may be due to its higher porosity to compare PMG, RMG and direct compression method. It was evident that the achieved linearity of the Heckel curves was satisfactory, as demonstrated by high values of  $R^2 \geq 0.971$ . The best linearity was observed in the FBG mixture. The FBG mixture was most compressible.

The tableting mixture density obviously plays an important role in powder compressibility. Usually, powders were more porous are considered more compressible. For instance, if the porosity of two mixtures of the same material is equal the mixture with lower bulk and/or tapped density was likely to be more compressible. This positive relationship was observed between the tapped densities and the Heckel coefficients of the mixtures studied.

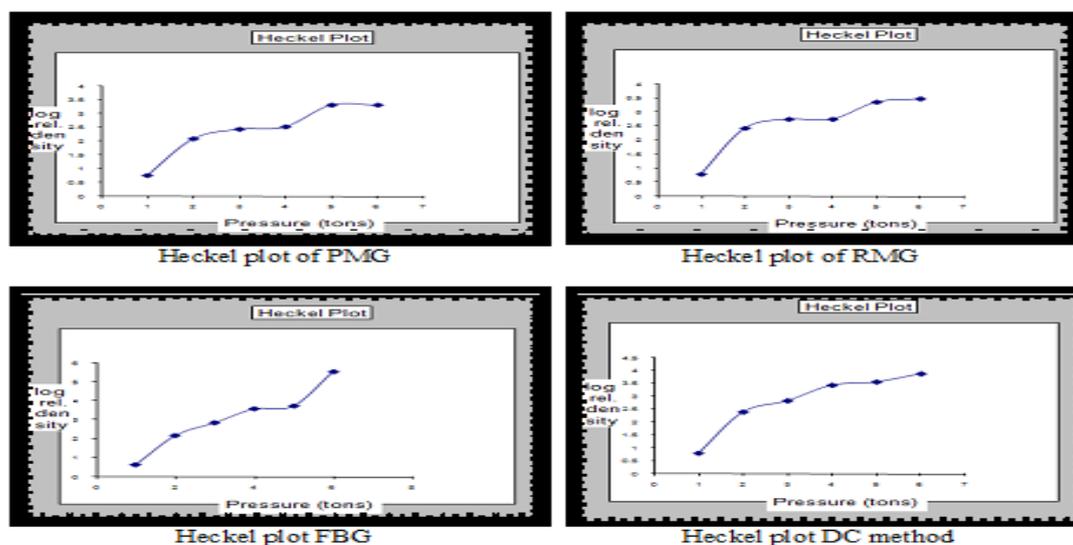


Fig. 14: A positive correlation between the tapped densities of tableting mixtures and their Heckel coefficients (K).

#### 3.7.2 Walker plot:

The Walker plots of compression for the respective mixtures showed even better linearity compared to the Heckel plot. The Walker model once again proved that FBG was most compressible mixture with  $w$  of 24.9 PMG, RMG and DC mixtures considerably lower compressibility measured.

These results demonstrate exactly the same order of compressibility as the Heckel model and the positive correlation between these two methods that was observed. It was important to emphasize the Walker model's slightly better discriminative power over the Heckel model to differentiate tableting mixture compressibility.

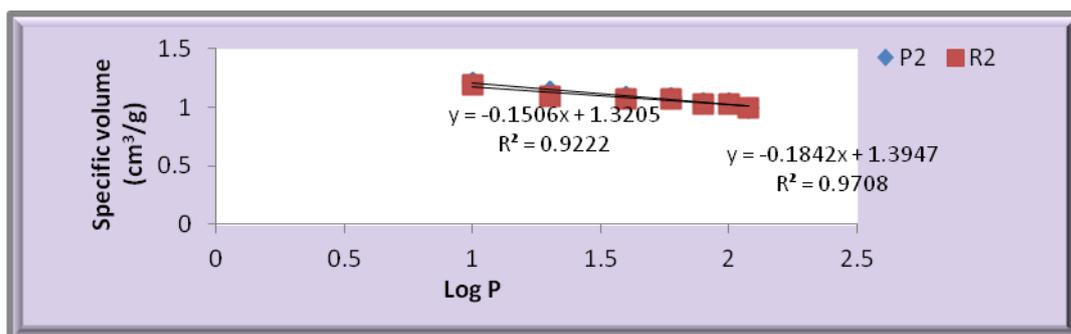


Fig. 15: A typical Walker plot: PMG mixture prepared by PMG and RMG mixture prepared by RMG

### 3.8 Evaluation of tablets:

Tablet for all the formulation were evaluated for parameter such as thickness, hardness, weight variation, drug content and friability. Results are summarised in Table 4.

#### 3.8.1 Thickness

Thickness of tablet within the prescribed limit.

#### 3.8.2 Hardness

FBG higher hardness compare to the RMG, PMG and DC method. FBG shows higher hardness at low compression force compare to RMG, PMG and DC method but all hardness of tablets are within the prescribed limit.

#### 3.8.3 Weight variation test

In weight variation test used to show the content uniformity of drugs. Average weight in mg (within the limit  $\pm 5\%$ ). Average percentage deviation of all formulations was found to be within limit and hence, all formulations passed the test for uniformity of weight as per official requirement.

#### 3.8.4 Friability test

Friability of FBG was less than RMG, PMG and DC method. DC method shows higher friability

compare to the wet granulation method. But percentage friability for all formulation was below 1%, indicating that friability was within the prescribed limits.

#### 3.8.5 Drug content

All formulation showed good uniformity in drug content among different formulations of tablet and percentage of drug content was within the prescribed limit.

#### 3.8.6 Disintegration test for tablet:

Here In wet granulation method FBG tablet disintegrate fast in phosphate buffer pH 6.8 compare to tablet produced by the RMG and PMG. But direct compression method shows faster disintegration compared to the wet granulation method.

All the tablet formulation showed acceptable properties and complied with specification for weight variation, drug content, hardness, friability and disintegration.

#### 3.8.7 In- vitro drug release studies:

Direct compression shows fast release compare to wet granulation method. In wet granulation FBG showed fast release compared to PMG and RMG.

Table 4: Evaluation of tablet parameters

Sr. No.	Parameter	PMG	RMG	FBG	DC
1	Thickness* (mm) $\pm$ SD	4 $\pm$ 0.05	4.1 $\pm$ 0.04	4 $\pm$ 0.01	4.2 $\pm$ 0.04
2	Hardness*(Kg/cm <sup>2</sup> ) $\pm$ SD	4.8 $\pm$ 0.115	4.6 $\pm$ 0.115	5.0 $\pm$ 0.115	4.8 $\pm$ 0.115
3	Average weight* (mg) $\pm$ SD	Within the limits ( $\pm 5\%$ )			
4	Friability* (%) $\pm$ SD	0.53 $\pm$ 0.05	0.68 $\pm$ 0.02	0.46 $\pm$ 0.01	0.78 $\pm$ 0.02
5	Drug content* (%) $\pm$ SD	98.73 $\pm$ 1.96	99.27 $\pm$ 08	100 $\pm$ 0.66	98.48 $\pm$ 2.44
6	Disintegration test (min) (Average time taken)	15	14	13	12
7	Dissolution test	Mean cumulative % release within 60 minutes (92.2%)	Mean cumulative % release within 60 minutes (90.0%)	Mean cumulative % release within 60 minutes (96.7%)	Mean cumulative % release within 60 minutes (97.0%)

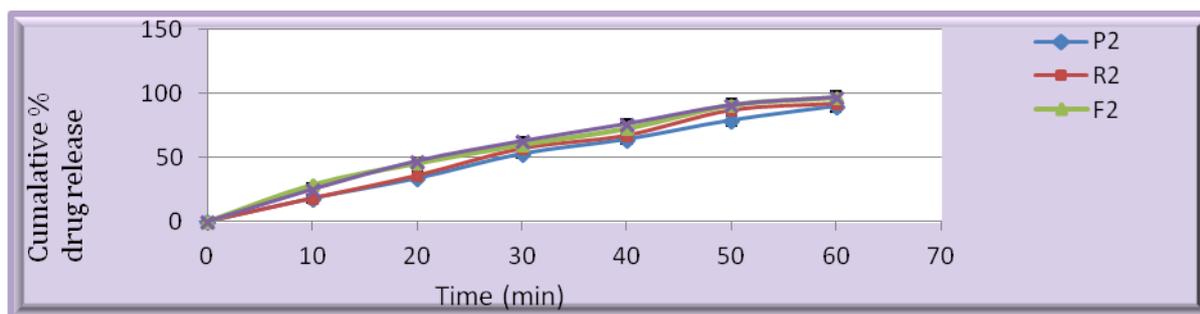


Fig.16: Dissolution profile of formulation P2, R2, F2 and D2

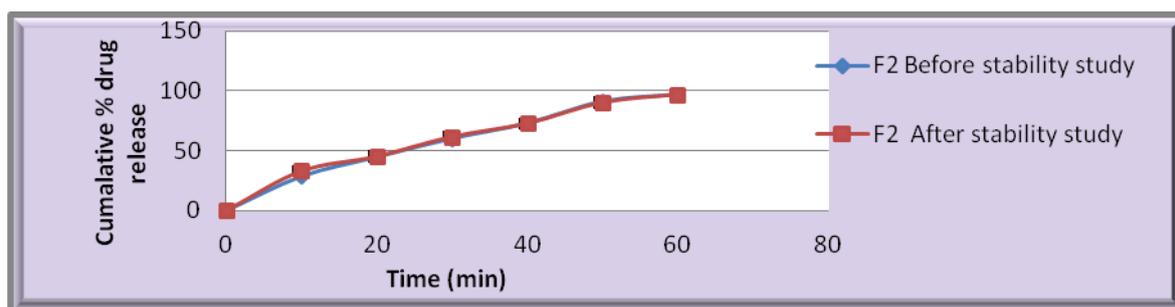


Fig. 17: Dissolution profile of stability study of F2 batch

### 3.8.8 Drug Release Kinetic

All the formulation were studied for kinetic release like different mechanisms first order, Higuchi, Hixon crowell, zero order or Korsmer- Peppas model. From this study it was observed that from all formulation batch showed more best fitted model was Korsymer- Peppas model except DC method

### 3.9 Accelerated Stability Study

Table 36 showed that there was no considerable change in thickness, hardness and drug content of F2 formulation before and after accelerated stability study. Also there was no significant difference found between dissolution profile of F2 formulation before and after stability. Hence tablet prepared by wet granulation to be stable.

### CONCLUSION:

Various powder agglomeration processes have a great impact on the tablet compaction process. In order to investigate the loss on drying, particle size distribution, porosity, sphericity, bulk density, flow property and compressibility, compatibility, tablet properties (weight uniformity, hardness, friability and disintegration, drug content, dissolution) and accelerated stability study of Diclofenac sodium tablet for that complex tableting mixtures of Diclofenac sodium were precisely characterized. FBG show loss on drying within prescribed limit. Fluid bed granulation processes resulted in the formation of narrower particle size distribution, high porosity, sphericity, lower bulk density compared to PMG, RMG in which a higher amount

of fines 29.12% was produced, something that is typically observed in PMG processes. The flow properties of Fluid bed granulated mixtures were superior shown by the kawakita equation; however, all tableting mixtures had acceptable flow properties for tablet production on a KBr tablet press machine. Tablets produced from Fluid be granulated mixtures had lower friability at all compression pressures. The results of compressibility studies using Walker and Heckel analyses show that the FBG mixture has the best compressibility and Leuenberger equation show that FBG mixtuer has the best compactibility followed by the PMG, RMG and DC mixtures, which are comparable to each other. All the tablet formulations showed acceptable properties and complied with specification for weight variation, drug content, hardness, friability and disintegration. Fluid be granulated mixtures had lower friability compare to the other batches. In case of *in-vitro* drug release for wet granulation techniques FBG showed faster drug release compare to the RMG and PMG. But *in-vitro* drug release for FBG compare with DC method. The DC method showed faster drug release compare to the FBG. In case of Accelerated stability study of FBG there was no considerable change in physical appereance, thickness, hardness, drug content and *In-vitro* drug release. Finally by evaluation of different granulation properties and tablet properties, it was conclude that FBG is best wet granulation method compare to RMG, PMG and DC method.

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