International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(1): January-February 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 23-01-2015; Revised: 28-01-2015; Accepted: 29-01-2015

COMPARATIVE EVALUATION OF NEWER GRANULATION TECHNOLOGY ON PROPERTIES OF TABLET DOSAGE FORM

Ranju R. Kondekar*[1], Vinita V. Kale[2]

1. HI-Tech College of Pharmacy, Chandrapur
2. Gurunanak College of Pharmacy, Nagpur

Keywords:

Freeze Granulation, Foam Granulation, Moisture activated dry Granulation, Steam Granulation, thermal adhesion

For Correspondence:

Ranju R. Kondekar

HI-Tech College of Pharmacy, Chandrapur

E-mail:

ranjukon12@gmail.com

ABSTRACT

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity, and reduced down time. Pharmaceutical products are processed all over the world using the direct-compressing, wet-granulation, or dry granulation methods. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied. The objective of present article was to focus on the novel granulation technology and comparative study.

INTRODUCTION

Granulation is a size enlargement (agglomeration) operation, by which fine powders are agglomerated into larger granules engineered to a specific size and shape. Granulation can result in improved flow ability and appearance and improve other properties such as dissolution rate, bulk density, reduced caking formation and granule strength. [1] Granulation is the process of collecting particles together by creating bonds between them. [2] It is an important technique to improve powder handling, especially for fine powders, which are difficult to handle because of their cohesiveness and low flow ability. Granulation technology has a wide spectrum of applications ranging from pharmaceutical, food, fertilizer, and detergent to mineral, ceramic, waste processing, and advanced materials. [2] Granulation method was selected not only on the basis of individual properties of the ingredients like their flow property, compressibility, eject-ability, and disintegrate-ability but also on the basis of compliance of the regulatory requirement for the product and employed technologies Pharmaceutical industry was very conservative with respect to application of new applications and new technologies associated with their required regulatory compliances with respect to the reproducibility of the process. Depth knowledge in the GT was essential to adopt proper granulation process during development stage of product to get a targeted granulation and final product parameters. [3] Both dry and wet processes can achieve granulation. Many conventional granulators, such as pan granulators, inclined disc agglomerates, pelletizes, spray dryers, drums, extrusion processes, fluidized beds and roll compactors for compaction of dry materials are employed.[4]

In wet granulation, usually called binder granulation, a liquid binder such as a solution or a melt is pumped, poured or atomized into an agitated bed of powders contained in a granulator whose main role is to provide shearing forces to the powder mass. Binders are used for generating cohesiveness to agglomerating powders. Consolidation by shear forces and drying result in solvent evaporation from the binder or melt thickening as a result of which, interparticle bridges strengthen, powder particles stick together, and larger granules of the original powder are formed. In many cases, binders left in the granules have some undesirable effects on the granule properties, like solubility reduction, too much strength to disintegrate etc. [4] Wet granulation methods, such as fluid bed granulation, extrusion granulation, foam granulation, melt granulation etc. utilize liquid to bind primary particles together to produce porous granules for various applications. The granulation process can be either very simple or very complex depending on material characteristics, the target quality of

the final granules and the equipment available. [5,7] Granulation process research is important for several reasons. Process improvement in production scale ensures the quality of granules. Also, with good process control it is possible to minimize time consuming size classification processes, such as sieving. [6]

MATERIAL AND METHODS

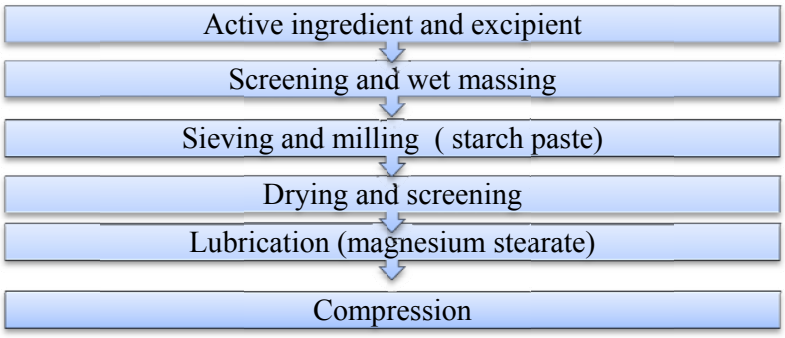
Diclofenac obtained as gift sample from zim laboratory, Hydroxy propyl cellulose, Lactose monohydrate, Magnesium stearate etc supplied from the Himedia. All chemical used were of pharmaceutical/analytical grade. Methods used for granulation technology are as follows.

A. Wet Granulation
B. Foam Granulation
C. Melt Granulation
D. Steam Granulation
E. Pelletization

Procedure for the preparation of granules by different granulation technology

1) Wet Granulation:

The most widely used & most general method of tablet preparation is the wet granulation method. The active ingredient, diluents were mixed or blend well. Solution of the binding agent was added to the mixed powder with the stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow. If the granulation was over wetted the granules will be hard, if not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication. The wet mass was forced through a 16 or 22 mesh (Mesh no. is the number of wires passing through an inch) screen or several mills can be used. Moist material from wet milling steps were placed on large tray and placed in a drying chamber with a circulating air current. Commonly used dryer are tray dryer, fluidized bed dryer. After drying, the granules were reduced in particle size by passing the smaller mesh screen. Followed by addition of the lubricant or glidants is added as fine powder to promote flow of granules. These granules then compressed to get tablet.



2) Foam Granulation

Foam granulation is a new granulation technology, now days this method is prefer over wet granulation technology. In this process the foam of binder was added as binder. The procedure of granulation was given below.

- All ingredient were accurately weighed such lactose and Diclofenac sodium and mixed in mortar.
- Binder solution was added (binder solution was prepared by dissolving HPC in water and for the generation of the foam air was blow into the beaker containing solution with help of compressor)
- The dough formed was passed through sieve no 16 and 22 and dried the granules in oven at 60^0c for 10 min (In wet granulation time required for drying is more) Then pass the granules from sieve no 80, add required quantity of fines (2%) then add lubricant and compressed to get tablet.

3) Melt Granulation

Melt granulation is new granulation technique. In this technology, generally hydrophilic or hydrophobic polymers are used. In some formulation wax is used, this method is generally suitable for preparation of sustained release formulation. In present formulation HPC is use as binder. The procedure for granulation is given below.

1) Weigh the entire ingredient, mixed the powder into mortar.
2) Then transfer into china dish and melt the powder up to the melting point of the HPC.
3) Then the powder was pass through the sieve no 22 & 30, lubricate with the magnesium stearate, then compressed into a tablet.

4) Steam Granulation

Steam granulation is new granulation technology. It modified process of wet granulation. As the title indicated steam is used as a binder instead of water. In this method, the granules are formed by the injection of the required amount of liquid in the form of steam. This type of steam injection method discharges steam at a temperature of about 150^o c tends to cause local overheating and excessive wetting of the particle in the vicinity of the stem nozzles, thereby leads to formation of lumps in the granulated product. General procedure for steam granulation is given below.

1) Weigh all the ingredient (drug, diluents, and binder) mixed well.
2) Steam was pass in the powder, then mixed the powder and dump mass was formed.

3) This mass was passing through the sieve no 16 or 22; granules were kept for the drying into the dryer.
4) Then granules was lubricated with the magnesium stearate and then compressed into the tablet.
5) Pelletization process

Extrusion/Spheronization is a multistep process used to make uniformly sized spherical particles. Pellet or granules were prepared in the Extrusion Spheronizer. From the above granulation technology we were selected one granulation technology i.e. Foam granulation technology**.** Reason behind the selection of the foam granulation technology was due to some drawback and due to difficulties in the processing in lab scale. Along with foam granulation technology we used wet granulation technology for the comparison of results of these two processes and also for knowing the better process among these two processes.

EXPERIMENTAL WORK

Analytical Method For The Determination of Diclofenac Sodium

To analyze the developed formulation of Diclofenac sodium and to determine drug content UV spectrophotometric method was adopted for the analysis of drug in the formulations.the calibration curve was prepared in water and in phosphate buffer for determination by UV spectrophotometry.

UV Spectrophometric Analysis of Diclofenac Sodium:

About 100 mg of Diclofenac sodium was weighed accurately and then dissolved in of water/ phosphate buffer in 100 ml volumetric flask to prepare stock solution having concentration 1000ug/ml. From this 1 ml solution was pipette out and diluted 10 ml using water/ phosphate buffer to form solution having concentration 100 µg/ml.

Preparation of Working Standard Solution: About 1, 2,3,4,5 and 6 ml of aliquots were taken from stock solution and diluted with water in 10 ml volumetric flasks to prepare the series of working standard solutions in concentration range of 10 to 60 ug /ml respectively.

Analysis of Working Standard Solution:

The absorbance of working standard solutions of Diclofenac sodium was taken at 276nm. Calibration curve was constructed by plotting absorbance against the concentration of drug in µg/ml. the linear relationship was evaluated by calculation of the regression line by the method of least squares.

Compatibility Study: Using Infrared Spectroscopy

The Fourier transform infrared analysis was conducted for the structural characterization. FTIR of pure drugs and polymer were recorded. Sample of 0.1g was mixed with 1gm of KBr, in mortar. Part of this mix was introduced in a cell connected to a piston of a hydraulic pump giving a compression pressure of 15kPa / cm^2. The mix was converted to solid disc then it was transfer to the FTIR analyzer was obtained showing the wave lengths of the different functional groups in the sample which were identified by comparing these value with those in the literature.

Precompression Evaluation:

Measurement of flow ability and density:

Bulk Density (pb) = Weight/ Bulk volume Equation (1)

Tapped Density (pt) = Weight/ Tapped volume Equation (2)

Carr's Index= [(pt- pb)/pt] × 100 Equation (3)

Hausner's ratio = (pt/pb) Equation (4)

Compressibility Index= V_o- V_t/ V_o× 100 Equation (5)

Where, V_t is the tap volume and V_o is the Bulk volume.

Angle of repose (˚) = Tan^{-1}(h/r) Equation (6)

Porosity (θ) = (1- Pr)×100 Equation (7)

Where pr is the relative density and θ is the porosity.

Moisture content : Granules need to retain certain amount of moisture after drying to obtain tablets of good quality (less 2% moisture is required for tablet formulation). Too dry granulation yield friable tablets. Granulation that too wet cause sticking, picking of tablets.

It was determined by using a moisture balance or analyzer. It has heat source for rapid heating scale calculated as % MC or % LOD. Weighed samples were placed on the balance and allow to dry at particular temperature and time.

Sieve analysis or Particle size distribution:

Sieving is one of the fundamental methods for the classification of particulars, and it is the method of choice for determining the size distribution of granules, 12gm of granules sifted into a sieve shaker where a series of sieve were placed. The machine was run for 5 min. All the meshes were taken out and retained granules collected by respective mesh and % retention was calculated.

Post Compression Evaluation

General Appearance

The general appearance of tablet, its identity and general elegance is essential for consumer acceptance, for control of low to low uniformity and tablet to tablet uniformity. The control

of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

Size & Shape

It can be dimensionally described & controlled. The thickness of tablet is only variables. Tablet thickness was measured by screw gauge in micrometer. Tablet thickness was controlled within a±5% variation of standard value. [40]

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using "Monsanto hardness tester." It is expressed in kg/cm^2. Hardness for compressed tablet in 5 to 8 kg

Friability

Friability of a tablet was determined in laboratory by Roche Friabilator. This consists of a plastic chamber that revolves at 25 rpm, dropping the tablets through a distance of six inches in the Friabilator, which was then operating for 100 revolutions. The tablets were reweighed. Compress tablet that loose less than 0.5 to 1.0 % the tablet weigh were consider acceptable [41, 42]

Weight variation test

20 tablets were taken and weighed individually. Average weight calculated and individual tablet weight was compared to the average weight. The tablet passes USP test because not more than two tablets were found outside the percentage limit.

Disintegration test

The U.S.P. device to test disintegration uses 6 glass tubes, to test the disintegration time, one tablet was placed in each tube and the basket rack was positioned in a beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0 C such that the tablet remain 2.5 cm below the surface of the liquid on their upward movement. and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablet was prevented by placing perforated plastic disc on each tablet. According to the test the tablet must disintegrate and all particles must pass through 10 mesh screen in time specified.If any residue remains,it must have soft mass. [43]

In-vitro drug release study

The drug release study for the prepared tablets was carried out using USP Dissolution test apparatus-II (Electro lab) paddle method in 900 ml water maintained at 37 ± 0.5^oC, at 50 rpm.

The sample was filtered through what man filter paper. The fresh dissolution medium replaced every time with same amount of sample. The collected sample suitably diluted and absorbance was measured Spectrophotometrically at 276 nm. The percentage of Diclofenac sodium release at various time intervals was calculated and plotted against time.

Assay of Diclofenac sodium

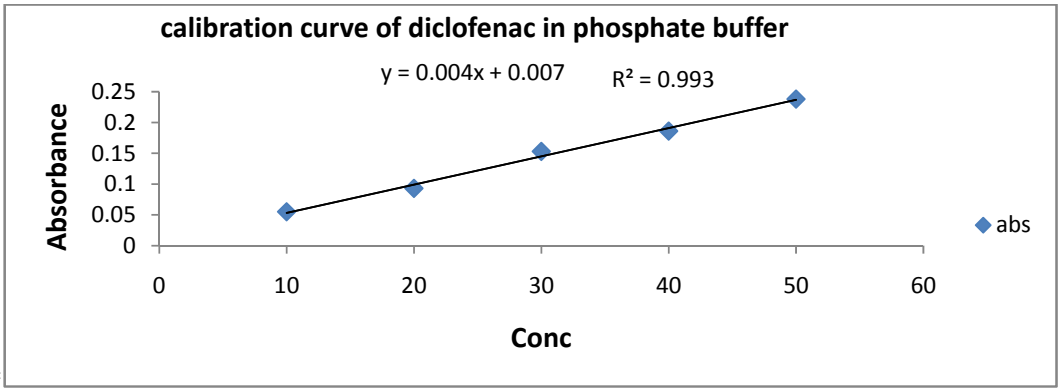
Weigh and powder 20 tablets accurately a quantity of powder equivalent to 50 mg of Diclofenac sodium, shake with 60 ml of methanol in 200 ml volumetric flask and dilute to volume with methanol. Dilute 5 ml of this solution to 100ml with methanol and measure the absorbance of the resulting solution at maximum at about 276 nm.

Stability study:

Accelerated stability study carried out to observe the effect of temperature and humidity on tablet formulation by keeping at 40^{o}C±2 in air tight high density polyethylene pauch for one month, at RH 75± 5%. The samples were subjected to physical evaluation, drug content, and invitro release study at each month.

RESULT AND DISCUSSION

Spectrophotometric Analysis of Diclofenac Sodium



=

Fig 1: Calibration curve of Diclofenac sodium in phosphate buffer at 276.4 nm

Compatibility Study

FTIR of Diclofenac Sodium:

FTIR of Diclofenac Sodium is shown in following graph. From the spectral study following significant peaks were observed which given in following table;

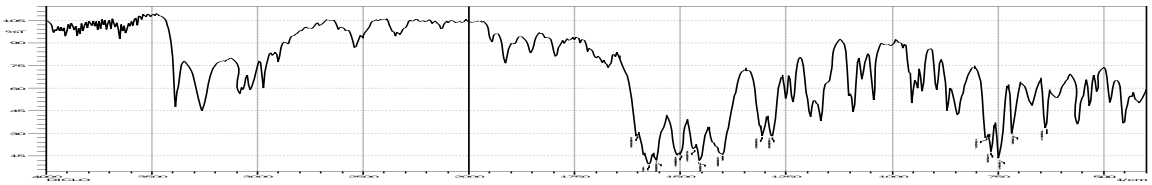


Fig 2 : FTIR of Diclofenac Sodium

FTIR of Drug & Excipients

FTIR of pure drug & mixture of drug & excipients are shown in following graph. From the spectral study it was observed that there was no significant change in the peaks of pure drug & drug excipients mixture. Hence, no specific interaction was observed between the drug & the excipients used in the formulations.

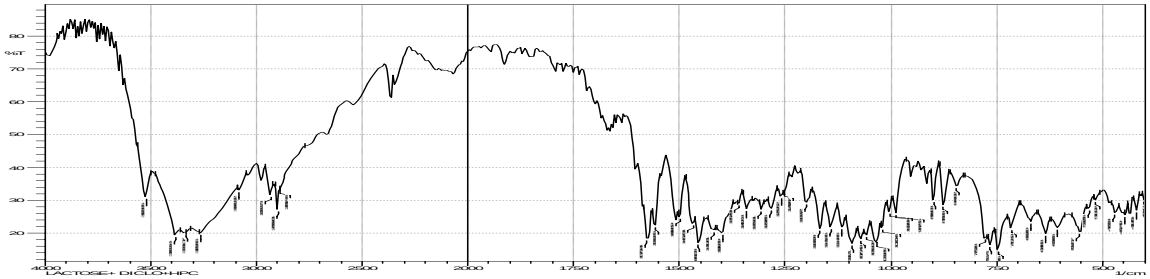


Fig 3: **FTIR of Drug & Excipients**

PRECOMPRESSION EVALUATION

Table 1: Precompression Parameter of Diclofenac sodium tablets prepared by different granulation technology: (10% Binder)

Test	Formulation code				
	WG	FG	MG	SG	PG
Bulk D.	0.464±0.031	0.473±0.042	0.766±0.02	0.500±0.023	0.782±0.031
Tapped D	0.582±0.039	0.544±0.041	1.022±0.02	0.661±0.019	0.812±0.024
Carr's Index	20.27±0.041	13.05±0.032	25.04±0.031	24.34±0.024	3.69±0.021
Hausner's ratio	1.25±0.03	1.15±0.021	1.334±0.019	1.32±0.021	1.038±0.019
Angle of repose	36.12±0.13	27.05±0.012	35.39±0.021	34.82±0.034	28.03±0.021

POST COMPRESSION EVALUATION

Table 2: Post compression Parameter of Diclofenac tablet Prepared by Different Granulation tech. (10%Binder)

Test	Formulation Code				
	WG	FG	MG	SG	PG
Hardness (kg/cm^2)	6.25±0.24	3.5±0.67	8.45±0.49	6.5±1.04	3.8±0.46
% Friability	0.65±0.12	0 .57±0.38	0.89±0.36	0.83±0.96	2.69±0.62
Disintegration (min)	15.12±1.1	12.32±0.45	25 ±0.39	45±0.62	20±0.30

In-Vitro dissolution study:

The different formulations prepared by different granulation technology were subjected to in-vitro drug release studies. The in vitro drug release study was carried in 0.1N HCL for 2 hr and then In 6.8 phosphate buffer for 1 hr. from the table it was observed that the 60.56 % drug was release by foam granulation. It was found that tablet prepared by foam granulation had more release as compare to other granulation technique.

Table 3 : In-vitro dissolution study of Diclofenac tablet (prepared by diff. G. tech.) 10% binder

Time	Formulation code				
	WG	FG	MG	SG	PG
1hr	10.62±0.23	11.36±0.32	4.03±0.41	5.8±0.086	4.76±0.31
2hr	18.68±0.22	21.25±0.083	10.62±0.039	11.36±0.41	9.52±0.066
15min	22.72±0.09	33.34±0.056	14.29±0.42	17.95±0.039	14.29±0.045
30min	31.37±0.062	43.60±0.049	15.75±1.12	23.08±0.054	19.42±0.094
45min	37.37±0.056	52.03±0.069	21.25±0.54	28.95±0.099	25.28±0.42
60min	49.83±0.087	61.56±0.067	27.85±0.18	31.51±0.99	28.58±0.15

Table 4: Precompression Parameter of Diclofenac sodium tablets prepared by different granulation technology: (5 % Binder)

Test	Formulation code				
	WG	FG	MG	SG	PG
Bulk D.	0.424±0.51	0.438 ± 0.31	0.629±0.52	0.489±0.39	0.762±0.42
Tapped D.	0.512±0.12	0.496±0.39	0.826±0.16	0.638±0.12	0.796±0.31
Carr's Index	17.18±0.32	11.69±34	23.84±0.12	23.35±0.38	4.27±0.12
Hausner's ratio	1.207±0.13	1.132±0.12	1.313±0.12	1.304±0.18	1.044±0.13
Angle of repose	29.13±0.53	28.82±0.55	35.49±0.36	37.09±0.39	28.19±0.42

.Table 5 : Post compression Parameter of Diclofenac tablet Prepared by Different Granulation tech. (5 %Binder)

Test	Formulation Code				
	WG	FG	MG	SG	PG
Hardness (kg/cm^2)	4.9±0.31	4.2±0.26	7.8±0.69	7.2±0.18	5.6±0.23
% Friability	0.62±1.12	0.53±0.96	1.16±0.13	0.92 ±082	1.93±0.92
Disintegration Time (min)	12.26±0.61	8.62±0.86	22.42±0.78	39.42±0.31	17.18±0.91

Table 6 : In-vitro dissolution study of Diclofenac tablet (prepared by diff. G. tech.) 5 % binder

Time	Formulation code				
	WG	FG	MG	SG	PG
1hr	9.82±0.53	15.13±0.42	6.21±0.21	6.98±0.116	5.96±0.31
2hr	17.98±0.25	22.61±0.083	11.42±0.039	13.49±0.41	11.52±0.066
15min	35.49±0.19	37.27±0.156	15.79±0.48	19.95±0.069	15.91±0.085
30min	45.07±0.062	51.15±0.049	17.28±1.12	27.42±0.154	21.62±0.114
45min	52.49±0.056	58.93±0.069	23.48±0.54	34.18±0.099	29.49±0.12
60 min	59..91±0.097	71.28±0.097	32.16±0.18	41.98±0.99	36.23±0.15

Precompression Evaluation (Foam Granulation):

Table 7 : Precompression Parameter of Diclofenac sodium Tablet (Foam granulation)

TEST	FORMULATION CODE					
	F1	F2	F3	F4	F5	F6
Bulk D.	0.462±0.16	0.474±0.23	0.464±0.36	0.482±0.45	0.468±0.39	0.464±0.46
Tapped D.	0.502±0.23	0.538±0.29	0.513±0.41	0.516±0.98	0.529±0.56	0.524±0.49
Carr's In.	7.96±0.12	11.8±0.25	9.55±0.41	5.69 ±0.68	11.53±0.12	11.45±0.25
Hausner's ratio	1.086±0.34	1.13±0.099	1.105±0.29	1.05±0.57	1.13±0.53	1.12±0.19
Angle of Repose	26.69±0.12	29.15±0.39	27.89±0.62	25.36±0.14	28.48±0.12	29.49±0.86
Moisture content	1.78±0.49	1.62±0.99	1.82±0.58	1.81±0.48	1. 86±0.12	1.68±0.23

Table 8 : Precompression Parameter of Diclofenac sodium Tablet (Wet Granulation)

TEST	FORMULATION CODE					
	W1	W2	W3	W4	W5	W6
Bulk D.	0.464±0.13	0.484±0.98	o.441±0.49	0.474±0.53	0.416±056	0.469±0.86
Tapped D.	0.513±0.39	0.528±0.98	0.498±0.86	0.516±0.65	0.492±0.49	0.529±0.68
Carr's In.	9.55±0.92	8.33±0.36	11.4±0.54	8.35±0.89	15.44±0.86	11.34±0.89
Hausner's Ratio	1.105±1.12	1.09±0.43	1.12±0.43	1.65±0.69	1.182±1.43	1.12±0.12
Angle of Repose	30.01±0.98	28.13±0.24	29.18±0.41	29.50±0.89	29.29±1.14	27.79±0.49
Moisture Content	2.02±1.14	1.65±0.12	1.68±0.32	1.59±1.02	1.87±0.89	1.82±1.12

Sieve Analysis/Particle Size Distribution

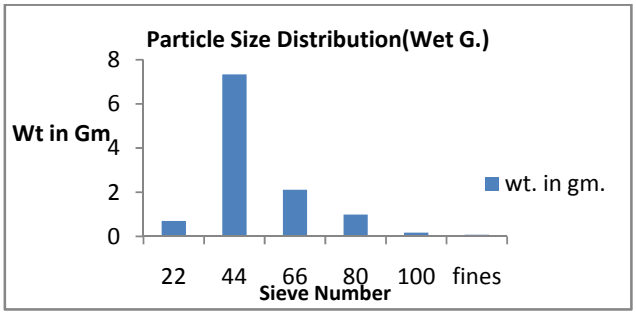


Fig 4: Particle size distribution (wet G.)

Upon sieve analysis, granules showed a random size distribution. 85-90% of granules were found to be greater than 44 mesh (0.42mm or 420 µm). Optimum size distribution was obtained which resulted in good flow properties.

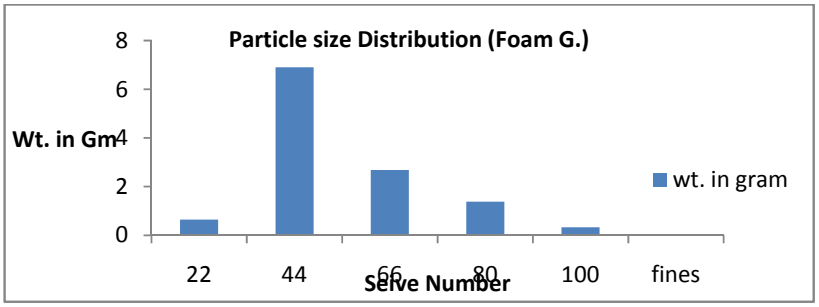


Fig 5 : Particle size distribution (Foam G.)

Upon sieve analysis, granules showed a random size distribution. 85-90% of granules were found to be greater than 44 mesh (0.42mm or 420 µm). Optimum size distribution was obtained which resulted in good flow properties

Table 9 : Solubility

Component	Solubility of drug(mg)
Pure drug+ phosphate buffer	50.18
Granules (Foam)+ phosphate buffer	62.407
Granule (Wet) + phosphate buffer	55.23
Pure drug+ 1.2 PH HCL	0.071
Granule(foam) + 1.2 PH HCL	0.114
Granule(Wet) + + 1.2 PH HCL	0.097

Solubility study was done to know the increase in solubility by foam granulation. From the above table we observed that granules prepared by foam granulation shoes increase in solubility in phosphate buffer and 0.1 N HCl.

Table 10: Post Compression Evaluation of Diclofenac Tablet :(Foam Granulation)

Formulation code	Hardness Kg/cm^2	Friability % weight loss	Disintegration time (min)	Weight variation	Thickness (mm)
F1	4.8±0.43	0. 93±0.54	8.23±0.98	Within limit	0.25±0.16
F2	4.9±0.12	0.76±0.69	8.12±0.43	Within limit	0.29±0.23
F3	5.5±0.39	0.51±0.82	9.34±0.12	Within limit	0.31±0.26
F4	4.1±0.46	0.81±0.41	6.48±0.59	Within limit	0.24±0.21
F5	5.8±0.12	o.49±0.45	10.09±0.62	Within limit	0.33±0.25
F6	5.8±0.86	0.52±0.91	9.54±0.54	Within limit	0.36±0.12

Table 11 : Post Compression Evaluation of Diclofenac Tablet: Wet Granulation

Formulation code	Hardness Kg/cm^2	Friability % weight loss	Disintegration time (min)	Weight variation	Thickness (mm)
W1	4.3±1.12	0.59±0.46	12.23±0.87	Within limit	0.31±0.24
W2	5.2±0.98	0.43±0.67	12.39±0.82	Within limit	0.26±0.16
W3	5.8±0.56	0.48±0.49	13.56±0.67	Within limit	0.31±0.31
W4	5.42±0.49	0.67±0.48	10..59±0.52	Within limit	0.26±0.23
W5	6.2±0.89	0.51±0.87	14.02±0.12	Within limit	0.39±0.27
W6	5.2±0.49	0.59±0.96	12.34±1.34	Within limit	0.36±0.16

Table 12 : DRUG CONTENT: F4 and W4 Formulation

Sr. no	Diclofenac sodium (f4)	Diclofenac sodium(w4)
1	99.13	96.39
2	98.7	97.12
3	99.56	97.48
Avg.	99.13	96.99
SD	±0.431	±0.55

Drug content of tablet formulation (f4) was found to be 99.13±0.431. so the drug content was found to be within limits.

In-Vitro Drug Release

Table 13 : Drug Release Study of Diclofenac Sodium by Foam Granulation:

Time (min)	Formulation code					
	F1	F2	F3	F4	F5	F6
1hr	7.69±0.24	14.29±0.39	14.29±0.42	19.05±0.86	10.62±0.51	13.92±0.32
2hr	17.95±0.43	21.62±0.78	22.72±1.12	35.18±0.67	21.25±0.82	25.28±0.87
15	30.04±0.62	36.27±0.86	39.57±0.13	48.00±0.43	31.88±0.67	31.88±0.56
30	36.27±1.06	49.83±0.49	52.03±0.54	65.59±0.43	42.50±0.34	38.47±1.12
45	48.37±1.16	57.9±0.65	61.93±0.47	73.65±0.45	53.13±0.13	50.93±0.98
60	59.73±0.98	69.26±0.12	77.68±0.78	89.05±0.67	63.76±0.65	68.16±0.86
90	72.55±0.86	85.75±0.62	87.21±0.98	94.91±0.23	74.39±0.87	86.48±0.86

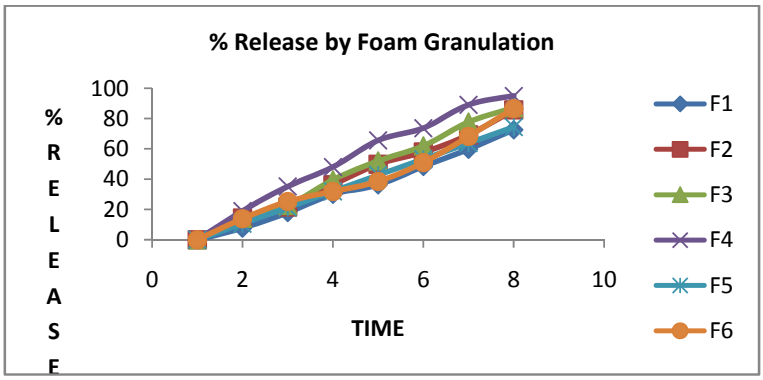


Fig 6: Graph showing in-vitro drug release of formulation F1 to F6

Table 14: Drug Release Study of Diclofenac by Wet Granulation

Time (min)	Formulation code					
	W1	W2	W3	W4	W5	W6
1 hr	7.69±0.15	9.52±0.49	13.92±0.86	15.75±0.34	10.62±0.56	12.82±0.84
2 hr	13.19±0.37	17.59±0.49	17.95±0.89	34.44±0.78	16.85±0.49	24.91±0.34
15	29.68±0.59	35.91±0.68	28.95±1.12	41.04±0.87	23.82±0.42	35.54±0.42
30	43.60±0.89	45.07±0.89	38.84±1.09	52.03±0.67	31.51±0.31	44.34±0.65
45	50.93±1.12	55.70±0.65	48.37±0.98	61.19±0.59	39.94±0.63	50.57±0.12
60	54.60±1.06	59.73±0.12	63.03±0.45	68.16±0.53	50.93±0.23	60.09±0.87
90	65.59±0.98	78.42±0.65	76.22±0.12	86.48±0.62	63.03±0.34	79.15±0.42

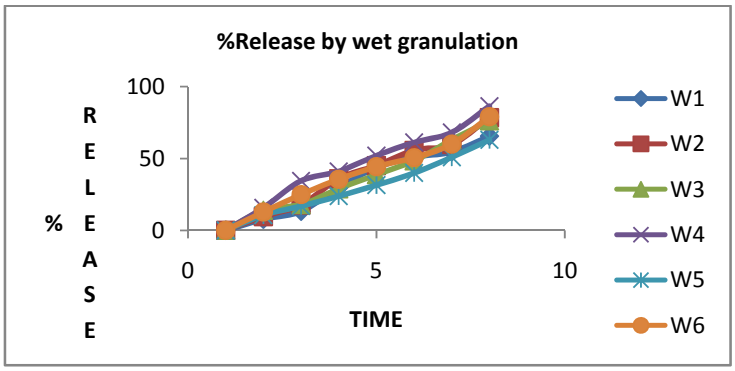


Fig 7: Graphical representation of drug release by wet granulation

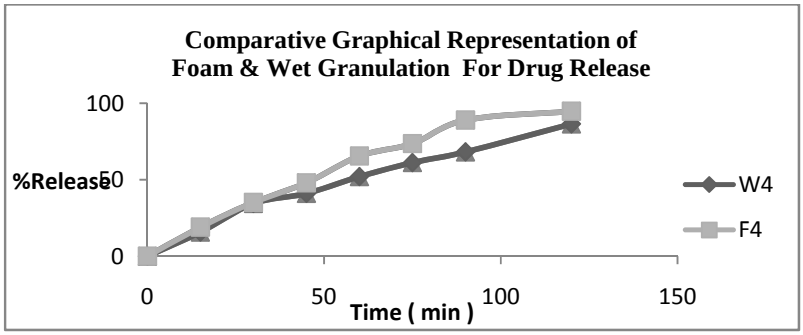


Fig. 8 : Comparative Graphical Representation of Foam & Wet Granulation

From the above graph of formulation F4 & W4 it show that their more release of drug from the F4 formulation as compare to the W4 formulation. From the dissolution study it was found that there is a increase in the release rate of Diclofenac sodium by foam granulation process.

Stability Study:

Stability studies on tablet formulation were carried out as per ICH Guidelines for 1 month and evaluated for drug content and drug release. There was no significant change was observed in drug content and in % release and also no significant change in the appearance of the tablet.

Table 15 : Stability study of Optimized F4 & W4 Diclofenac tablet

Storage condition	Room Temperature		40^0C/75%RH	
Period ⟹	Initial		1 Month	
Formulations ⟹	F4	W4	F4	W4
Parameter ⇩	Observations			
Assay	99.13±0.431	96.99±0.55	98.89±0.54	96.76±0.36
Dissolution	94.91±0.23	86.48±0.62	94.23±0.41	87.94±0.52

SUMMARY AND CONCLUSION

Granulation is a size enlargement (agglomeration) operation, by which fine powders are agglomerated into larger granules engineered to a specific size and shape. Granulation can result in improved flow ability and appearance and improve other properties such as dissolution rate, bulk density, reduced caking formation and granule strength. Granulation is the process of collecting particles together by creating bonds between them. It is an important technique to improve powder handling, especially for fine powders, which are difficult to handle because of their cohesiveness and low flow ability. Granulation method was selected not only on the basis of individual properties of the ingredients like their flow property, compressibility, eject-ability, and disintegrate-ability but also on the basis of compliance of the regulatory requirement for the product and employed technologies Pharmaceutical industry was very conservative with respect to application of new applications and new technologies associated with their required regulatory compliances with respect to the reproducibility of the process. In the present study, Different granulation technology was used for the formation of granules, technology like wet granulation, foam granulation, melt

granulation, steam granulation, Pelletization. HPC was used as a common binder. Common binder was used for the comparison of granulation technology. Granules growth was depended on the binder availability at the surface. If too much liquid is added or the evaporation of the liquid is not adequate then this results in an increase of the powder bed moisture content and ultimately affected on powder flow property. Granules were prepared by different granulation methods and their flow properties were evaluated by using HPC as binder at 5% and 10 % concentration. No major differences in the granules property by changing the binder concentration were observed within individual methods of granulation.

The Carr's index value provided some indication of the flow of behavior of the various granulations obtained during this investigation. Granule having high Carr's index values shows the relatively poor flow than the lower the Carr's index. This was also observed and proved by measuring the angle of repose of different granulations. Observation showed the difference in the values of angle of repose and Carr's index. The Foam granulation (FG) and granulation by Pelletization showed the lower value for angle of repose and Carr's index at 5% and 10% binder concentrations. Wet granulation (WG) at 10% binder concentration showed optimum values for Carr's index and angle of repose. Resulting in better flow compared to other methods of granulations. The Hausner's Ratio gives a measure of the packing of the granules. Smaller granules tend to have greater cohesiveness due to high surface-to-mass ratio and result in greater bulk density. Therefore, the Hausner's index tends to increase with smaller granule size. Hausner's indices lower than 1.16 was considered to be acceptable, because the granules are then considered to be free-flowing.

Among formulations melt granulation (MG) and steam granulation (SG) methods showed extensive sticking and layer separation problem. During compression blend materials blocked the feed frame perhaps due to high moisture content. So, formulations of wet granulation (WG), foam granulation (FG) and Pelletization granulation (PG) were undertaken for further studies such as hardness, friability test, DT and dissolution. Formulations of wet and foam granulation methods showed optimum value of successful operation and to meet good tablet properties. The formulation of Pelletization granulation showed high friability value.

SCOPE OF PROPOSED WORK

Granulation is one of the most important unit operations in the production of Tablet dosage form. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. This would result in improved yields, reduced tablet defect, increased productivity, modify

the release property and reduced down time. Tablets are processed using the direct-compressing, wet granulation, or dry granulation methods. The choice of method depends on the ingredients individual characteristics and ability to property flow, compresses eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. The study of these parameters helps in choice of proper granulation process.

From the results of granules property and tablet properties for formulation of tablet containing Diclofenac Na using HPC as binder foam granulation and wet granulation method was most effective. Thus these two methods were used for further optimization of tablet.

Abbreviations:

WG- wet granulation

FG-foam granulation

MG-melt granulation

PG- pelletization

SG- steam granulation

D-density

In- index

REFERENCES

1. Bale, “Book of pharmaceutics – formulation and processing of conventional dosage form”, Chapter no-2, page no.32-34.
2. Michael D. Tousey, “The granulation process 101” Basic technology for tablet making, Page no. 10-13.
3. Malcom Summers, Michael Aulton, “Granulation” Dosage form design and manufacture, page no. 365-378.
4. Mahammad Athas, A. Saikh, International Journal of Pharmaceutical Sciences & Research, “A Technical note on granulation technology: A way to optimize Granules”.
5. Kristensen H G, Schaefer T. Granulation, a review on wet granulation. Drug Dev. Ind. Pharm. 1987; 13(4&5): 803-872.
6. Solanki H. K., Patel C. A. “Recent advances in granulation technology”, review article, International journal of pharmaceutical sciences. Volume-5, issue-3 Nov. page no.48-54.
7. Leon Lachman, Herbert A. Liberman, Joseph L. Kanig, ”Tablets”, The Theory and Practice of Industrial Pharmacy**,** 3rd edition, Varghese publishing house, Bombay, 1991: 314-317.

8. Das S. and Jarowski, C.I. (1979) Effect of granulating method on particle size distribution of granules and disintegrated tablets. Drug Dev. Ind. Pharm., 5, 47.
9. Agrawal R., Yadav N., "Pharmaceutical processing- A Review on wet granulation technology," IJPER, April-June 2011; 1(1), 65-83.
10. Chokshi R, Zia H. Hot melt extrusion technique: a review, Iranian J Pharm Res. 2004;3:3
11. Research journal of Klucel™ hydroxyl propyl cellulose physical and chemical properties.
12. Research article of ASHLAND- from matrix to film coating, pharmaceutical technology resource.