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DESIGN AND DEVELOPMENT OF FLUID BED GRANULES OF PARACETAMOL AND DICLOFENAC SODIUM

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Abstract: The purpose of this research was to prepare the granules of Paracetamol and Diclofenac Sodium using fluidized bed processor and to formulate a tablet containing Paracetamol and Diclofenac sodium. Drug exhibits poor flow properties, and poor compression ability which creates issues in tablet formulation which can be overcome by Fluidized bed processor. The Granules was prepared by Fluidized Bed Processor method. Paracetamol and Diclofenac sodium granules were prepared by using propylene glycol as an anti-capping agent, Microcryastalline cellulose as a diluent, P.V.P.K-30 and Starch as a binder, sodium starch glycolate as a superdisintegrants. The drug excipient compatability study was carried out with FTIR study indicates any no interaction found with another. The granules were evaluated for flow properties parameters like angle of repose, bulk density, tapped density and compressibility index showed satisfactory good flow. The tablets were evaluated with regard to weight variation, hardness, friability, content uniformity, disintegration time, *in-vitro* drug release. Optimized formulation F7 showed satisfactory physical parameters like hardness, % friability and disintegration time and desired drug release profile. The selected formulation (F7) was found to be stable at 40 ± 0.5 °C and 75 ± 5% RH during the test period of 1 month which showed no remarkable change on drug content as well as on drug release profile. It can be that, development of Fluidized bed granules is a good approach to enhance the flow properties, productivity and in process parameters of Paracetamol and Diclofenac sodium. From the results, it can be concluded that Fluidized bed granules for Paracetamol and Diclofenac sodium with desired characteristics could be prepared using fluidized bed processor.

Keywords: Fluidized bed processor, Flow properties, Paracetamol, Diclofenac sodium

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INTRODUCTION

Granulation is defined as "any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified." In simple words, granulation is the generic term used for particle agglomeration processes, in which fine powder solids are agglomerated together with a liquid/melt binder to form larger aggregates. Granulation, a technique of particle enlargement by agglomeration, is one of the most significant unit operations in the production of pharmaceutical dosage forms, mostly tablets and capsules. However, it should be noted that although agglomeration and granulation are defined similarly, they are different terms. Agglomeration refers to the buildup of small particles into larger aggregates without the addition of a binding agent or use of mechanical force, while granulation refers to the buildup of small particles into larger aggregates with the aid of a binding agent or mechanical force, water, starch paste roller compaction, etc. Thus, agglomeration often occurs without intention during such manufacturing operations as dense powder conveying, sieving, sifting, mixing, and grinding.

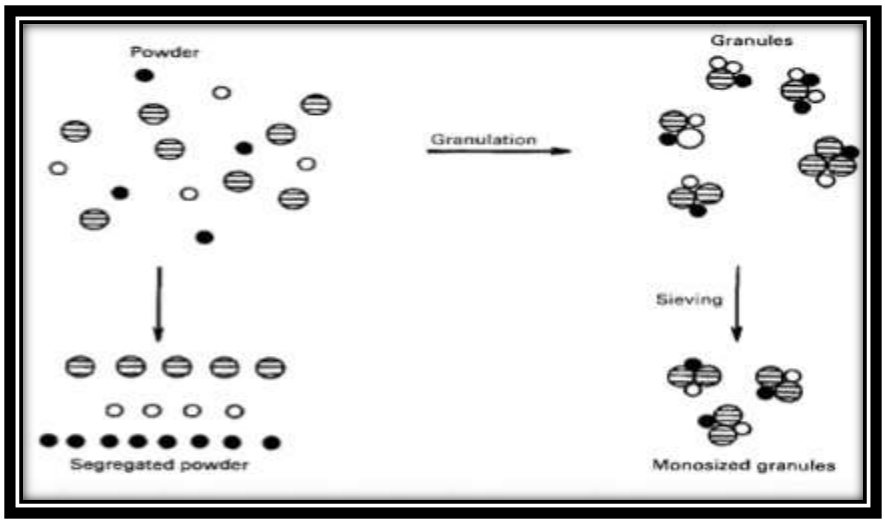

Figure 1 : Granulation to prevent powder segregation

Introduction to fluidized bed technology

FLUIDISATION is a process in which a bed of small solid particles is suspended and agitated by a stream of gas/air, which enables a through solid-gas contact throughout the bed. Fluid bed technology has found enhanced use in pharmaceuticals for **drying, granulation, palletizing** and **coating.** The formulation development is the key step in the success of a formulation to sustain in the present day market. Such formulation development is emerging new technologies for the development of products via innovative techniques, of which Fluid Bed Technology is one important and successful technique widely being used in the pharmaceutical industries

now a days. The principle involved in fluidized bed processor (FBP) and the latest equipment available in market working on the principle of FBP. The main principle involved in the FBP is the air suspension in which the material to be coated is suspended in the coating material with the help of air stream. Fluid bed process involves three principles viz. Top spray, bottom spray and tangential spray (Fig.2). The FBP has a wide range of applications such as drying, granulation powder or particle coating and pelletizing.

- Types of fluid bed processing systems:

1. Drying
2. Granulation
3. Coating

- Types of FBP according to the position of the spray gun:

a. Top spray
b. Bottom spray
c. Tangential spray

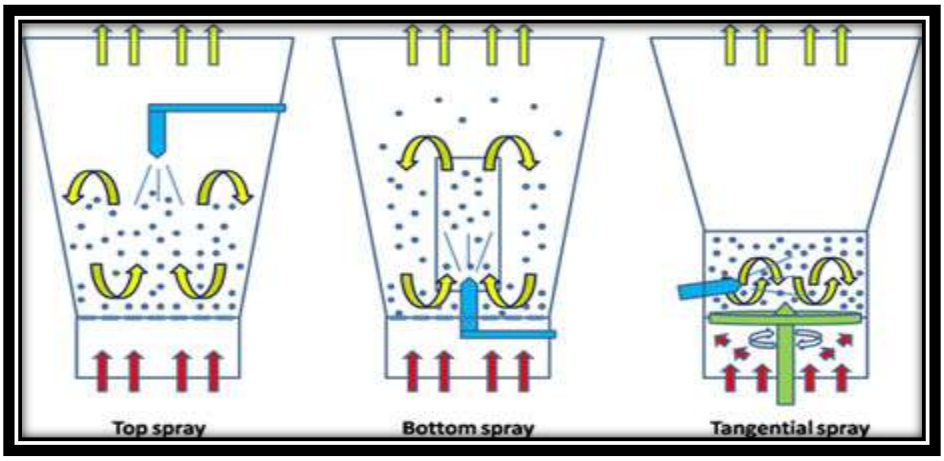

Figure 2: principles of fluid bed process

Fluidization is the operation by which fine solids are transformed into a fluid like state through contact with a gas or air. At certain gas velocities the fluid will support the particle giving them freedom of mobility without entrainment such fluidized bed resembles a vigorously boiling fluid with solid particles undergoing extremely turbulent motion which increases with gas velocity or sir velocity. Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed.

Fluidized bed granulation is a process, which forms small particles into aggregates or granules using a liquid binder sprayed onto the fluidized bed or particles.

Granulation is one of the key processes in pharmaceutical solid dosage form production. Among the various granulation techniques, fluid bed granulation (FBG) is one of the most widely used. One benefit of FBG is that mixing, granulation and drying all occur in the same equipment. The main quality targets for the final granules in pharmaceutical process are usually

1) Uniform drug substance content,

2) Good process ability, and

3) Desired drug release profile.

Fluidized bed granulation is used much less extensively than high shear granulation within the pharmaceutical industry. In fluidized bed granulation, the powder particles are fluidized by air and the liquid binder is sprayed from an atomizing nozzle onto the powder bed. The fluidized air is typically heated and/or filtered. Heated and filtered air is blown or sucked through the bed of unmixed powders to fluidize the particles and mix the powders; fluidization is actually a very efficient mixing process. Granulating fluid is pumped from a reservoir through a spray nozzle positioned over the bed of particles. The fluid causes the primary powder particles to adhere when the droplets and powders collide.

The escape of powder from the unit is prevented by exhaust filters, which are periodically agitated to reintroduce the powder to the bed. Sufficient liquid is sprayed to produce granules of satisfactory size, at which point spray is stopped but the fluidizing air stream remains engaged in order to dry the granules. Fluidized bed granulation has many advantages over conventional wet granulation. All the granulation processes mixing, granulation, and drying that normally require separate pieces of equipment are performed in the same unit. This consolidation saves labour costs, transfer losses, and time. Fluidized bed granulation has many advantages over conventional wet massing. All the granulation processes, which require separate equipment in the conventional method, are performed in one unit, saving labor costs, transfer losses and time, Complies with GMP (closed system), Easy automation, Short processing time, Efficient heat and mass transfer. Another advantages is that the process can be automated once the conditions affecting the granulation have been optimized.

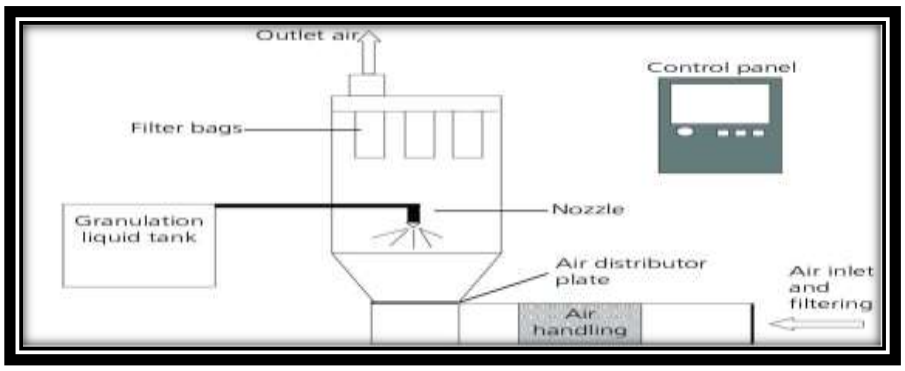

Figure 3: Typical fluidized bed granulator set-up

Materials and Methods

Paracetamol and Diclofenac sodium was received as gift from Lincoln pharmaceutical Ltd. Inactive ingredients like Microcrystalline cellulose, Maize Starch, Talc, Magnesium stearate, Sodium Starch Glycolate, PVP K 30 also received from Lincoln pharmaceutical Ltd.

Formulation of Paracetamol and Diclofenac sodium tablets

Sifting: Paracetamol and Diclofenac sodium tablet were prepared by fluid bed granulation method. Paracetamol were passed through 16# mesh sieve. And Diclofenac sodium, MCC plain were passed through 40# mesh sieve.

Mixing: Load the above sifted material to clean FBP and mix for 10 Minutes.

Binding Solution Preparation: Take purified water in Paste kettle. Heat the purified water till 70° C. & 70° C temperature maintain during entire process. Take PVP K 30 & Propylene glycol in above step at 70° C temperature & stir until it gets clear. Take hot purified water and add maize starch & make slurry. Then add maize starch slurry in 2nd step of binding solution preparation with continuous stirring for 15 minutes.

Binding: Add binder Paste in FBP by peristaltic pump keep parameters like Set inlet temperature, bed temperature, outlet temperature, Air pressure, Atomization Air Pressure, Pump speed, Gun size, Blower Speed etc.

Final Drying: Dry the granulated mass in Fluid Bed Processor for 2 to 5 min at 40°C±5°C. Check loss on drying (L.O.D) of the granules using halogen moisture analyzer.**Sifting and Milling:** Pass the dried granules through a CO-mill using 2.0 mm sieve at fast speed knife forward. Then transfer the material into octagonal blender by vacuumed machine.

Mixing: Put all the sieved dried granules of above step in octagonal Blender.

Lubrication: Sift the Purified talc and Sodium Starch Glycolate(TYPE-A) Through 40 mesh sieve on vibrator sifter. then load the above sifted material in to clean Octagonal Blender and mix for 10 minutes at slow speed. Sift the Magnesium Stearate through 40 mesh sieve on vibrator sifter. Load the above sifted material of step 2nd in Octagonal Blender and mix for 5 minutes at slow speed.

Preliminary batches

Table 1:- Preliminary batches

Sr. No.	Ingredients (in mg)	Batch F1	Batch F2	Batch F3	Batch F4
1	Paracetamol	500	500	500	500
2	Diclofenac Sodium	50	50	50	50
3	M.C.C PH-101	21.5	21.5	34	29
4	Maize Starch	17	-	12	12
5	P.V.P.K- 30	-	17	5	10
6	Propylene glycol	0.50	0.50	0.50	0.50
7	Purified water	Q.S.	Q.S.	Q.S.	Q.S.
8	S.S.G (TYPE-A)	22	22	22	22
9	Purified Talc	8	8	8	8
10	Magnesium Stearate	5	5	5	5
	Total weight	**636.50 mg**	**636.50 mg**	**636.50 mg**	**636.50 mg**

Table 2:- Preliminary batches

Sr. No.	Ingredients (in mg)	Batch F5	Batch F6	Batch F7	Batch F8
1	Paracetamol	500	500	500	500
2	Diclofenac Sodium	50	50	50	50
3	M.C.C PH-101	24	28	23	18
4	Maize Starch	12	18	18	18
5	P.V.P.K- 30	15	5	10	15
6	Propylene glycol	0.50	0.50	0.50	0.50
7	Purified water	Q.S.	Q.S.	Q.S.	Q.S.
8	S.S.G (TYPE-A)	22	22	22	22
9	Purified Talc	8	8	8	8
10	Magnesium Stearate	5	5	5	5
	Total weight	**636.50 mg**	**636.50 mg**	**636.50 mg**	**636.50 mg**

Pre compression parameters of powder blend

Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. The bulk density was calculated as following equation 1.1 It is expressed in gm/ml.

Bulk density = Weight of powder / Bulk volume ---------- Equation 1.1

Tapped density : It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder and the tapped volume was noted. It is expressed in gm/ml and is given by the following equation 1.2.

Tapped Density = Weight of powder / Tapped volume ---------- Equation 1.2

Carr's index : Percentage carr's index was calculated as 100 times the ratio of the difference between the tapped density and bulk density to the tapped density .One of the important measures that can be obtained from bulk and tapped density determinations was the percent compressibility or the Carr's index, which was determined by the following equation 1.3

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100 \quad \text{----------Equation 1.3}$$

Table 3 : Carr's as an indication of powder flow

Carr's Index (%)	Type of Flow
5 –15	Excellent - free flowing granules
12 – 16	Good - free flowing powder granules
18 – 21	Fair powder granules
23 –28	Poor – very fluid powders
28 –35	Poor – fluid cohesive powder
35 – 38	Very poor - fluid cohesive
>40	Extremely poor – cohesive powder

Hausner's ratio : Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. Tapped density and bulk density are measured and the Hausner's ratio was calculated using the equation 1.4

Hausner's ratio = Tapped density/Bulk density ----------Equation 1.4

Table 4: Effect of hausner's ratio on flow property

Hausner's ratio	Flow property
Less than 1.25	Good flow
1.25 – 1.5	Moderate
More than 1.5	Poor flow

Angle of repose :This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. Angle of repose was calculated by the following equation 1.5

$$\tan\theta = h/r \quad \text{or} \quad \theta = \tan^{-1}(h/r) \quad \text{---------- Equation 1.5}$$

Where, θ = angle of repose,

h = height of the heap,

r = radius of the base of pile

Table 5: Effect of angle of repose on flow property

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Evaluation of tablet

Thickness and diameter

The thickness and diameter of the tablet were measured using Vernier callipers. Three tablets were selected randomly from individual formulations, thickness and diameter was measured using Vernier callipers. It was measured in mm. results shown in table.

Hardness

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in kg/cm^2.

Weight variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown.

Friability

Friability of the tablet determined using Friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablet was placed in the loss in the weight of tablet is the measure of friability and is expressed in % as,

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{final weight of the tablet}}{\text{Initial weight of tablet}} \times 100$$

Disintegration test

The in vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus with lid on upper side and the time (seconds) taken for complete disintegration of the tablet in water at 37±0.5 °C with no palatable mass remaining in the apparatus was measured.

Assay:

Instrument: HPLC

Preparation of buffer: Dissolve 90 mg of disodium hydrogen orthophosphate in 250 ml of distilled water.

Preparation of mobile phase: Mix well 250 ml of buffer and 900 ml of methanol. Adjust pH 4.0 with orthophosphoric acid. Degas the mobile phase for 15 minutes and filter through 0.22µ filter.

Chromatographic conditions:

Column : Symmetry C_{18} (250 mm X 4.6 mm), 5µ **OR** Equivalent

Column temperature : Ambient

Wavelength : 278 nm

Injection volume : 20µL

Flow rate : 1.0 ml/minute

Standard preparation: Weigh accurately about 500 mg of Paracetamol WS and 50 mg 50 mg of Diclofenac sodium WS in 100 ml volumetric flask, add about 50 ml of mobile phase to dissolve with the aid of ultrasound for about 5 minutes with occasional shaking and make volume 100 ml with mobile phase. Transfer 5 ml of this solution to 50 ml volumetric flask and make volume with mobile phase.

Sample preparation: Crush the content of 20 Tablets to a fine powder and weigh accurately about 1 average weight (equivalent to 500 mg of Paracetamol and 50 mg of Diclofenac sodium) to 100 ml volumetric flask, add about 50 ml of mobile phase to dissolve with the aid of ultrasound for about 20 minutes with occasional shaking and make volume 100 ml with mobile phase. Filter the solution through 0.45-µm nylon syringe filter. Discard first 5 ml of the filtrate. Transfer 5 ml of this solution to 50 ml volumetric flask and make volume 50 ml with mobile phase.

System suitability requirement : Inject 20µl of standard preparation.

1. **Tailing factor**: Not more than 2.0 for Paracetamol and Diclofenac sodium peaks.
2. **Theoretical plates**: Not less than 2000 for Paracetamol and Diclofenac sodium peaks.
3. **Relative standard deviation**: Not more than 2.0% for Paracetamol and Diclofenac sodium peaks.

Calculation:

Calculate the amount of Paracetamol using following formula:

mg of Paracetamol per tablet =

Spl. Area Std. wt 5 ml 100 ml 50 ml Avg. wt.

(in mg)

..... X ..... X ..... X ..... X ..... X % Assay of Paracetamol X .....

Std. Area 100 ml 50 ml Spl. wt 5 ml on 'as is' basis of 100

(in mg) paracetamol WS

% of Paracetamol per tablet =

Mg of paracetamol per tablet X 100

.....

Claim (500 mg)

Calculate the amount of Diclofenac Sodium using following formula:

Mg of Diclofenac Sodium per tablet =

Spl. Area Std. wt (in mg) 5 ml 100 ml 50 ml %Assay of Avg.Wt.

..... X ..... X ..... X ..... X..... X Diclofenac sodium X .....

Std.Area 100 ml 50 ml Spl. wt 5 ml on "as is basis of 100

(in mg) Diclofenac Sodium

% of Diclofenac Sodium per tablet =

Mg of Diclofenac Sodium per tablet X 100

.....

Claim (50 mg)

***In-vitro* drug release study :(By HPLC)**

The *in-vitro* dissolution study was carried out using dissolution medium consisted of 900ml Phosphate Buffer pH 6.8 using apparatus-2 USP (Paddle) for 45 mins. Temperature maintained at 37±0.5°C.

Apparatus : Dissolution test apparatus.

Instrument : HPLC

Note : Buffer preparation, Mobile phase preparation and Chromatographic condition as per Assay.

Preparation of Phosphate Buffer pH 6.8 : Weigh accurately about 6.8 gm of potassium dihydrogen orthophosphate in 1000 ml beaker, Add sufficient water to dissolve and make up the volume with water. Adjust pH 6.8 with 1 M sodium hydroxide.

Dissolution conditions :

Dissolution medium : Phosphate Buffer pH 6.8

Volume of dissolution medium : 900 mL

Apparatus 2 : Paddle

RPM : 100 RPM

Time point : 60.0 minutes

Bowl temperature : 37.0°C ± 0.5°C.

Standard preparation : Weigh accurately about 555 mg of Paracetamol WS and 55 mg of Diclofenac Sodium WS in 100 ml volumetric flask, add about 50 ml of dissolution medium to dissolve with the aid of ultrasound for about 10 minutes with occasional shaking and make volume with dissolution medium. Transfer 5 ml of this solution to 50 ml volumetric flask and make volume with dissolution medium. Further transfer 5 ml of this solution to 50 ml volumetric flask and make volume with mobile phase.

Procedure: Select six tablets for the test and add one tablet to each of the six bowls containing 900 ml phosphate buffer ph 6.8 maintained at 37.0°C. At the end of the specified time, withdraw 20 ml of the solution from the zone midway between the surface of the dissolution medium and top of the paddle, not less than 1cm from the vessel wall. Filter through 0.45-µm nylon syringe filter. Discard first 5 ml of the filtrate. Transfer 5 ml of this filtrate to 50 ml volumetric flask and make volume with mobile phase.

Calculation:

Calculate the amount of Paracetamol dissolved using following formula:-

mg of Paracetamol dissolved per tablet =

Spl.Area Std.wt(in mg) 5 ml 5ml 900 ml 50 ml 1

---------- × ---------- × ------ × ----- × -------- × ------ × % Assay of × ------

Std. Area 100 ml 50 ml 50 ml 1 5 ml Paracetamol on 100

On "as is" basis of

Paracetamol WS

% of Paracetamol dissolved per tablet =

mg of Paracetamol dissolved per tablet × 100

Claim (500 mg)

Calculate the amount of Diclofenac Sodium dissolved using following formula:-

mg of Diclofenac Sodium dissolved per tablet =

Spl.Area Std.wt(in mg) 5 ml 5ml 900 ml 50 ml % Assay of 1

---------- × ---------- × ------ × ----- × -------- × ------ × Diclofenac Sodium × ------

Std. Area 100 ml 50 ml 50 ml 1 5 ml On "as is" basis of 100

Diclofenac Sodium WS

% of Diclofenac Sodium dissolved per tablet =

mg of Diclofenac Sodium dissolved per tablet × 100

Claim (50 mg)

Drug excipients compatibility study

By FTIR spectroscopy

IR spectra of pure drug Paracetamol and Diclofenac sodium and physical mixture of drug with excipients are shown in fig. The pure drug Paracetamol and Diclofenac sodium exhibited various peaks due to presence of specific functional groups. It was observed that there were no changes in these major peak in the IR spectra of a mixture of drug and excipients.

Stability studies of the optimized formulation

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess drug and formulation stability, short-term stability studies were done for 1 month. The stability studies were carried out on the most satisfactory formulations (batch F7). The most satisfactory formulations were sealed in aluminium packaging and kept in a humid chamber maintained at 40 ± 2°C/75 ± 5% relative humidity (RH) for 1 month. The optimized formulation sealed in aluminium foil was also kept at room temperature and humid condition. At the end of the storage time, the samples were analyzed for drug content, *in-vitro* disintegration time, hardness, friability, and physical appearance.

RESULT AND DISCUSSION

Table: Pre compression parameters

Table 6: Data for pre compression parameters of tablet formulations (F1-F4)

Parameters	F1	F2	F3	F4
Bulk Density (g/ml)	0.480±0.003	0.476±0.003	0.471±0.004	0.462±0.001
Tapped Density (g/ml)	0.615±0.004	0.602±0.001	0.590±0.004	0.570±0.003

Carr's index (%)	21.95±1.71	21.05±0.99	20.17±1.14	18.94±0.91
Hausner's ratio (%)	1.38±0.03	1.26±0.02	1.25±0.01	1.23±0.02
Angle of repose (θ)	42.80±1.15	41.87±1.99	40.32±0.58	38.79±1.66

Table 7: Data for pre compression parameters of tablet formulations (F5-F8)
(Mean ± S.D., n=3)

Parameters	F5	F6	F7	F8
Bulk Density (g/ml)	0.462±0.001	0.480±0.002	0.46±0.004	0.470±0.006
Tapped Density (g/ml)	0.562±0.002	0.586±0.001	0.518±0.007	0.534±0.002
Carr's index (%)	7.442±0.94	18.2±0.66	10.01±1.64	13.0±1.64
Hausner's ratio (%)	1.21±0.01	1.23±0.01	1.10±0.01	1.15±0.04
Angle of repose (θ)	37.70±0.91	38.90±1.43	29.78±1.01	33.10±0.73

Post compression Parameters of Formulations:

Table 8: Result of post compression parameter of batch F1 to F4

(Mean ± S.D., n=3)

Name of Parameter	F1	F2	F3	F4
Diameter (mm)	12.71 ± 0.03	12.70 ± 0.02	12.70 ± 0.04	12.72 ± 0.03
Thickness (mm)	4.29±0.03	4.28±0.05	4.32±0.02	4.30±0.03
Hardness (Kg/cm^2)	6 ± 0.400	10 ±0.200	2 ±0.416	3 ±0.350

Friability (%)	0.9±0.02	0.7±0.06	0.9±0.01	0.8±0.05
Disintegration time (min)	5 ±2.09	10±2.51	3±1.70	6±1.56
Weight variation (mg)	630±1.15	636.500±1.20	633±0.60	637±0.57

Table 9 : Result of post compression parameter of batch F5 to F8

(Mean ± S.D., n=3)				
Name of Parameter	**F5**	**F6**	**F7**	**F8**
Diameter (mm)	12.72 ± 0.06	12.70 ± 0.03	12.70 ± 0.01	12.71 ± 0.02
Thickness (mm)	4.31±0.09	4.28±0.01	4.30±0.02	4.30±0.02
Hardness (Kg/cm2)	7±0.305	6±0.250	10±0.420	15±0.350
Friability (%)	0.4±0.01	0.5±0.03	0.2±0.01	0.2±0.02
Disintegration time (min)	11±3.10	7±3.40	6±2.21	12±1.90
Weight variation (mg)	632±0.58	634±1.52	635±0.50	637±1.15

In fluidized bed processor bacth F1 to F6 show improvement in flow properties but not upto satisfactory level than batch F7 and F8 show good flow properties but F7 batch granules formed show very good flow properties and compressibility. so, formulation F7 was final optimized formulation having good compressionparametrs with minimization of problem like sticking, caping.

Assay of tablet:

Table 10: Assay of Tablet.

Batch	% Paracetamol (n =3)	% Diclofenac sodium (n =3)
R1	93.20 ±1.30	94.40 ±1.10
F1	95.50 ±2.38	93.60 ±4.05

F2	101.25 ± 1.75	96.20 ±3.76
F3	97.00 ±1.56	94.30 ±1.64
F4	100.23 ± 1.98	95.20 ±2.89
F5	100.31 ± 1.08	99.20±0.92
F6	98.20 ± 2.58	97.50 ± 2.31
F7	99.73 ± 1.16	103.03 ± 0.80
F8	98.40 ± 2.14	98.80 ± 4.35

✓ Tablets were passed the both assay test.

***In-vitro* drug release profile:**

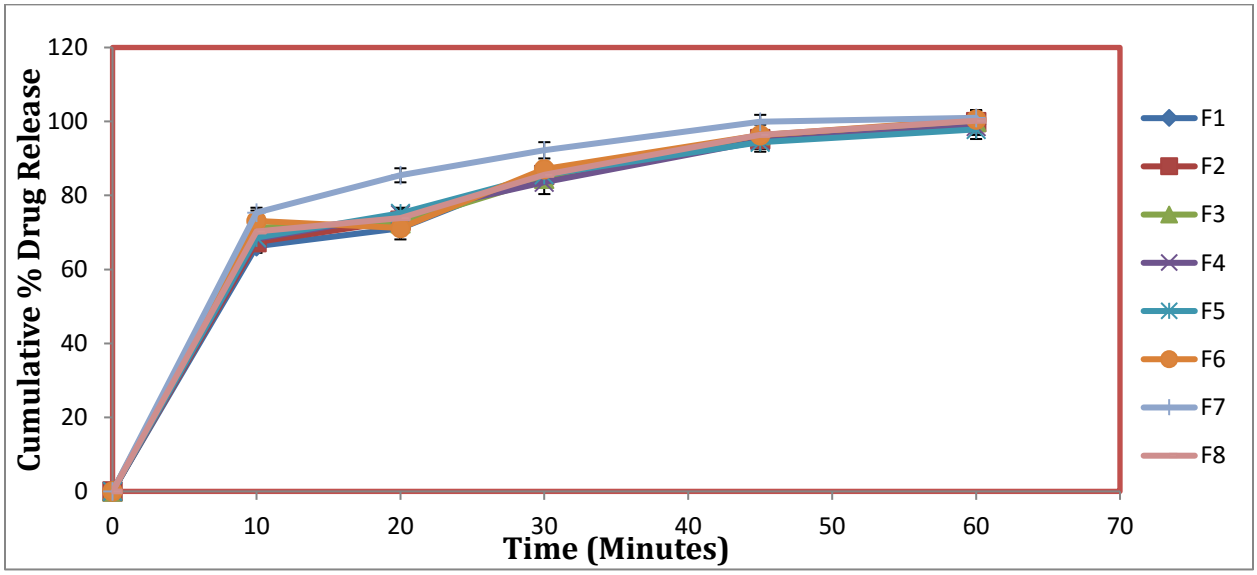

Figure : 2 In vitro drug release profile of preliminary batch PB1-PB10

Table 7*:- In vitro* drug release profile

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
10	66.29±1.8	67.45±1.1	71.3±1.1	68.3±1.9	68.65±0.6	73.12±1.3	75.39±2.8	70.29±1.1
20	71.16±1.5	73.23±1.9	72.54±1.9	74.89±1.8	75.16±1.1	71.22±1.9	85.45±3.1	73.88±1.6
30	86.56±2.1	85.54±2.3	84.57±2.1	83.57±3.2	85.75±2.2	87.15±2.2	92.21±0.2	85.57±2.6
45	94.83±3	95.23±0.9	96.27±0.5	94.72±1.3	94.37±1.8	96.33±1.9	99.90±0.8	96.37±3.5
60	99.23±2.2	99.86±2.3	99.96±2.5	98.66±1.2	97.86±2.3	100.53±2.1	101±1.6	100.2±2.8

STABILITY STUDY OF OPTIMIZED FORMULATION

The stability studies were carried out on the most satisfactory formulations (Batch F7) as per ICH guidelines Q1C. The stability studies were performed at 40 ± 2 °C / 75 ± 5 % RH conditions for 1 month. At the end of studies, samples were analyzed for the drug content, in vitro drug release, hardness, friability, and physical appearance.

Table 11:- *In vitro* drug release profile of batch F7 after stability study and comparison with initial

Time (min)	CPR	CPR after storage at 40^0C ± 2^0 C/ 75±5 % RH)
0	0	0
10	75.39	74.80
20	85.45	84.60
30	92.21	91.75
45	99.90	98.40
60	101	100.70

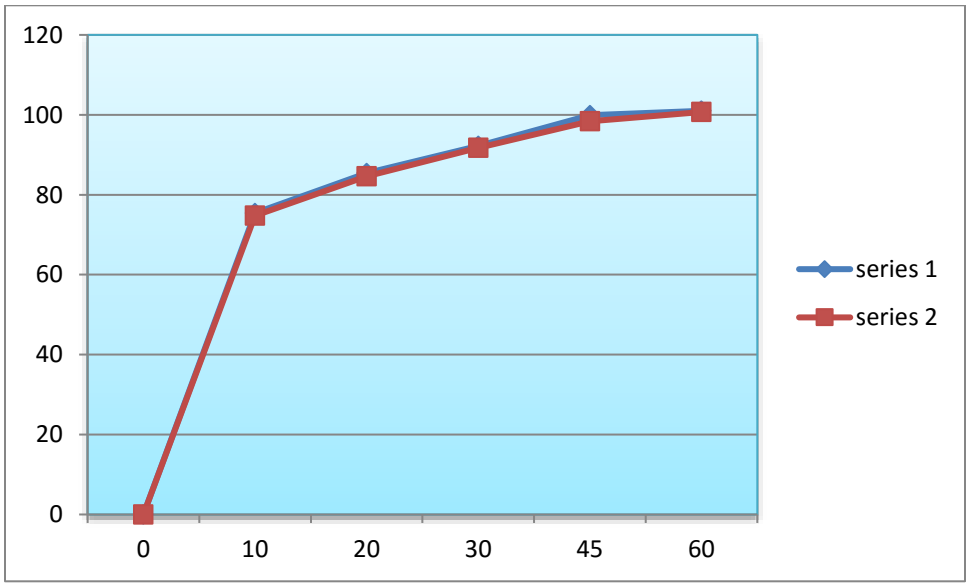

Figure:4 In vitro drug release profile of optimized batch after stability study and compare with initial

Table 12:- Evaluation of batch F6 after stability study and comparison with initial

	Hardness	Friability	Disintegration time (min)	% Drug content	
				paracetamol	**Diclofenac sodium**
Initial	10±0.420	0.2±0.01	6±2.21	99.73 ± 1.16	103.03 ± 0.80
After stability	9±0.150	0.3±0.02	5±1.10	99.20±0.50	100.70±1.10

The optimized formulations (Batch F6) stored at 40 ± 2 °C / 75 ± 5 % were found stable. After storage at 40±2°C/ 75 ± 5 % cumulative percentage drug release, Friability, Hardness, Disintegration time, % drug content were nearly similar to the initial results. So, it was clear that drug and formulation were thermally stable as well as not affected by high humidity at 40 ± 2 °C / 75 ± 5%.

Fourier transforms infrared spectroscopy

The peak of Paracetamol as shown in figure 5 and table 6 matches with the peaks mentioned in the literature, which conforms identification group.

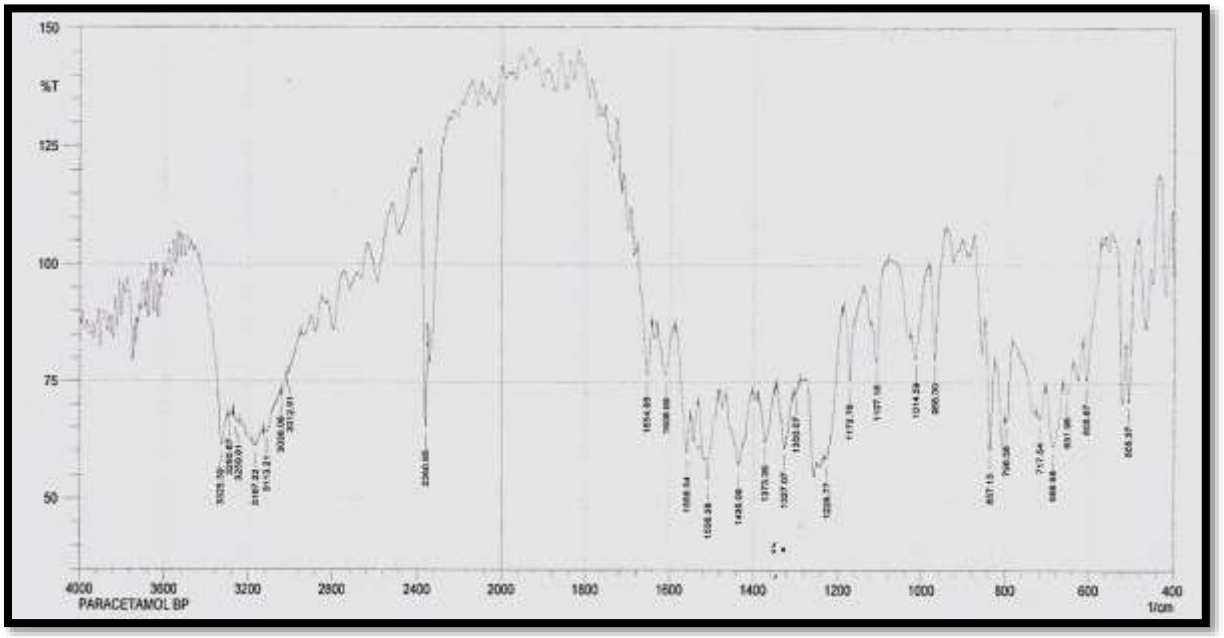

Figure:- 5 FTIR spectrum of Paracetamol

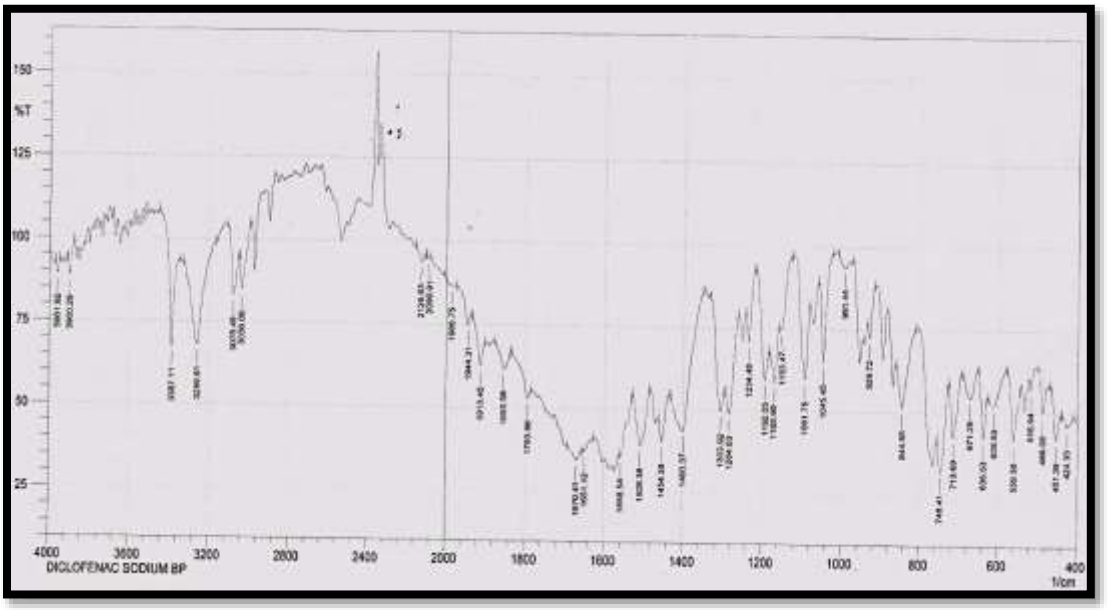

Figure:- 6 FTIR spectrum of Diclofenac sodium

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