Rajveer Bhaskar. *et al*. / *International Journal of Biological & Pharmaceutical Research.* 2014; 5(6): 516-526.

e- ISSN 0976 - 3651
Print ISSN 2229 - 7480

International Journal of Biological & Pharmaceutical Research
Journal homepage: www.ijbpr.com

IJBPR

FORMULATION AND EVALUATION OF IR IBUPROFEN TABLET BY USING (APOC) GRANULATION TECHNIQUE

Rajveer Bhaskar, Monika Ola, Manoj Patil*, P.H. Patil, H.S.Mahajan

Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Educational and Research, Shirpur. Dist. Dhule, Maharashtra, India.

ABSTRACT

Agglomerative phase of comminution (APOC) is a relatively newer granulation cum particle size reduction technique in which agglomeration of the fine coherent particles take place into loose granular structure. Agglomeration of the fine cohesive particles produced during grinding particularly with rotating or oscillating ball mills. Reduction of particle size during prolonged grinding by a ball mill has been used as a novel means of producing a pharmaceutical granulation. When compared with conventional granulation methods, this method produced mechanically stronger tablets with a higher dissolution rate than those compacted from granules made by a conventional wet granulation method. It is suggested that binderless tablets may be prepared by using this method, thus simplifying tablet formulation and enhancing stability. A possible mechanism for the increased dissolution rate is the increased internal surface area of the particles produced by the prolonged grinding method. As the comminution proceeds, agglomeration commences and eventually a wide size range of particles is produced consisting essentially of very coarse and very fine particles. This system eventually comes to an equilibrium situation, where coarse particles are milled to produce fine powder which, in turn, coheres to form coarse granules. Increased homogeneity and bioavailability characteristics can be obtained both by of this granulation technique.

Key Words: Agglomeration, Granulation, particle size, Bioavailability, Dissolution, Ball mill.

INTRODUCTION

Granulation Technique

A tablet with good characteristics is not made on a tablet press; it is made in the granulation process. Joining particles within a given 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, increase productivity, and reduced down time. The objective of the process is to combine ingredients to produce a quality tablet (Tousey MD, 2002).

Different existing granulation techniques use for the preparing form such as tablets, capsule, and pellets are following-

1. Wet granulation
2. Dry granulation
3. Direct compression
4. Agglomerative phase of comminution (APOC)

Agglomerative phase of comminution (APOC)

A newer technology called as agglomerative phase of comminution (APOC) was found to produce mechanically stronger tablets with higher dissolution rates than those of made by wet granulation. A possible mechanism is increased internal surface area of particles produced by APOC method. A successful processing for the agglomeration of primary particles depends on proper control of the adhesional forces between particles, which encourage agglomerate formation and growth and provide adequate mechanical strength in the product.

Corresponding Author

Manoj Patil
Email: mbpatil12@gmail.com

Agglomeration refers to a phenomenon where small particles dispersed to form relatively permanent larger particles. Usually the sizes and shape of the original particles can still be distinguished. Agglomeration is a common phenomenon within a wide variety of industries that deal with solid particles. These industries include fields like minerals processing pharmaceutical, agriculture, chemicals and fertilizers, food, biological materials and ceramics. In industries production agglomeration can be either or desired. As points out, size classification, comminution and conveying are examples of unit operations where agglomeration undesired. Furthermore, agglomerates may entrap mother liquor and impurities, thus preventing efficient washing of the product. The properties of single particles usually improve when the particle size becomes smaller. These include properties like homogeneity, strength and bioavailability. However, as the particle size gets reduced, the tendency of the particles to form agglomerate during operation further increases, (Rumpf H, in Knepper WA, 1962). Also, processing fine powders in general is problematic. A powder takes a lot of space, create dust and it can be improve handling properties of both the products and the intermediates.

Agglomeration of the fine cohesive particles produced during grinding, particularly with rotating oscillating ball mills, has long been recognized as an end point of the comminution operation. There is considerable literature on the use of grinding aids to prevent or delay the onset of agglomeration during the comminution of a wide variety of materials.

A typical grinding operation leading to subsequent agglomeration to exist in three separate stages. The first (Rittinger's stage) is the first stage which is normal comminution operation carried out, where the energy input (or grinding time) is directly proportional to the size reduction produced. During the second or coating stage, particles adhere to the milling and grinding media due to the presence of unsaturated bonds caused by crystal lattice distortion produced during prolonged milling. This phase can be delayed or eliminated by adding surface-active grinding aids to neutralize the free bonds forces. The final or agglomeration stage follows on prolonged milling and is largely unaffected by the presence of grinding aids, (Rumpf H & Knepper WA, 1962) have discussed the mechanisms and forces necessary to produce granulation. These include molecular (London or Van der Waal's forces), electrostatic forces, melting, chemical interaction, recrystallization or mechanical interlocking. Many or all these forces may be employed in the agglomerative phase of comminution. Despite the extensive literature on the agglomeration of a wide variety of materials produced by prolonged grinding operation, few reports are available on the applicability of this technique as a granulation operation. Such a granulation technique could offer advantages in that during preparative stage, fine particles are employed. Thus increased homogeneity and bioavailability characteristics may result from the use of this granulation technique.

MATERIALS AND METHODS

Materials

Ibuprofen procured by Concept Pharma Ltd. Hydroxypropyl cellulose and Crossmellose sodium procured by Basf, Germany, Microcrystalline Cellulose procured by N B Entrepreneurs and Magnesium stearate.

Equipments

Ball mill, DSC, U.V Spectroscopy, IR, Zeta particle size analyser, Dissolution Apparatus, Disintegration test Apparatus, Table compression machine (10 stations), weighing balance.

Preformulation studies

The preformulation studies include the physicochemical characterization of the drug and excipients which are useful in formulation the dosage form.

Organoleptic characters

This includes recording of colour, odor and taste of the drug, record of color is very useful in establishing appropriate of batches.

Density

Powder flow, compressibility, dissolution and other properties may dependent on density.

Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. Initially the weight of the measuring cylinder was tarred. Then, 4 gm presieved (40#) bulk drug were poured into the measuring cylinder using a funnel. Then volume of the powder was taken. Bulk density of the granules was calculated using following formula.

Bulk density = Weight of powder / Volume of powder.

Tapped density

Tapped density is determined by placing a graduated cylinder containing same mass of powder used for B.D. on a mechanical tapper apparatus which is operated for a fixed number of taps (approx500) until powder bed volume has reached a minimum.

$$\text{Tapped density} = \frac{\text{Weight of powder / min.}}{\text{Volume of powder}}$$

Carr's Index (CI)

Tapped and bulk density measurements can be used to estimate the carr's index of a material.

Carr's index was determined by,

Carr's index (%) = [(Tapped density – bulk density)/tapped density] * 100

Hausner's ratio (HR)

It is stated by Hausner. It was calculated as follow:

Hausner ratio = Tapped density / Bulk density

Angle of repose (Tan θ)

Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. It can be obtained between the freestanding surface of the powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface. Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel.

Solubility studies

Aqueous solubility of NSAID as a function of pH was determined in different physiological media. Solubility of drug was studied at different pH range i.e. water, Methanol, pH 1.2 (0.1 N HCL), pH 6.8 (Phosphate Buffer), pH 7.4 (Phosphate Buffer).

Analysis of drug

UV Spectrophotometric Analysis

Drug was dissolved in 100ml of 7.2 pH buffer, stirred for 15 min, sonicated and filtered through membrane filter paper. 5ml aliquot of this sample was diluted to 10 ml and UV absorbance was analyzed for λ max.

Linearity

10 mg of drug was dissolved in 100 ml of 7.2 pH buffer solution, stirred for 5 minutes, sonicated, filtered through membrane filter paper to prepare a solution having concentration of 100µg/ml and this solution was serially diluted to get a range of concentration from 1 to 10µg/ml. The absorbances of these solutions were noted at 221 λ max against appropriate blanks on UV spectrophotometer.

Determination of Particle size of drug

Preparation of ibuprofen tablets

The composition of different formulations of ibuprofen tablets is shown in table 6.6. Ibuprofen along with hydroxyl propyl cellulose and micro crystalline cellulose were weighed accurately and pass throughball mill at the constant speed of 50 rpm which ball mill consisting of different size of balls for 8-16 hrs to form the agglomerate of fine cohensive particles. These milled powder are weighed according to formulation. These agglomerate are mixed with magnesium stearate to improve its flow properties, then compressed on a 10 punch tablet machine (CMD4, Rimek 10 station compression machine). The tablets were round and flat with an average diameter of 10.0 ± 0.1mm and a thickness of 4.1 ± 0.2mm.

Evaluation parameters of tablets

Appearance

Tablet from each formulation were randomly selected and organoleptic properties such ascolor, taste, and shape were evaluated.

Hardness test

The hardness of tablets for fast dissolving tablets is usually kept low for easy disintegration in the mouth. The hardness was measured using monsento hardness tester.

Thickness

The thickness of tablets was determined using a Digimatic vernier caliper (Mitutoya, Japan). Three tablets from each batch were used, and average values were calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. It is express in percentage (%). Ten tablets were initially weighed and revolved at 25 rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated. The % friability was then calculated by,

F = Winitial – Wfinal x 100 / Winitial

Acceptance criteria for % friability % weight loss should be less than 1%.

Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The individual weighed is then compared with average weight for the weight variations. The following percentage deviation in weight variation is allowed. The results are shown in Table no 6.

Disintegration time testing

It was determine using USP tablet disintegration test apparatus, using 900 ml of distilled water without disk at room temperature. Test was performed on 6 tablets.

Content Uniformity Test

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.5 g of Ibuprofen, extract with 60 ml of chloroform for 15 minutes and filter. Wash the residue with three quantities, each of 10 ml, of chloroform and gently evaporate the filtrate just to dryness in a current of air. Dissolve the residue in 100 ml of ethanol (95%), previously neutralized to phenolphthalein solution, and titrate with 0.1Msodium hydroxide using

phenolphthalein solution as indicator. Each ml of 0.1M sodium hydroxide is equivalent to 0.02063 g of $C_{13}H_{18}O_2$.

In vitro drug release study

The release rate of ibuprofen from tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method;Electrolab). The dissolution test was performed using 900ml of 7.2 pH phosphate buffer, at 37 ± 0.5 0C and 50 rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 7.2 pH phosphate buffer. Absorbance of these solutions was measured at 221 nm using a Thermospectronic-1 UV/V is double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability studies

Stability of a drug can be define as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. In any design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection.

Objective of the stability study

The purpose of stability testing is to predict the quality of drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage condition, re-test periods and shelf-lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The international Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements.

In the present work stability study was carried out for the optimized formulation at 40^0C/75%RH for 3 month. After time period of every month sample was collected and analysis is carried out for,

1. In vitro Drug release study
2. % Assay
3. Physical parameters

APOC is a novel means of producing a pharmaceutical granulation. Agglomeration of the fine cohesive particles produced during grinding particularly with ball mills. Reduction of particle size during prolonged grinding by a ball mill. Increase surface area may enhance the rate of dissolution. This method produced mechanically stronger tablets with a higher dissolution rate than those compacted from granules made by a conventional wet granulation method.

An APOC granulation method is one of the recent technique used in powder granulation technology in the production of pharmaceutical products, particularly in modern pharmaceutical manufacturing. The chief reasons to apply this method in granulation technology for the manufacture of pharmaceutical dosage forms are described:

- To improve the aqueous Solubility of BCS class II drug.
- To increase dissolution rate of drug.
- To improve bioavailability of drug.
- To prevent active product ingredient from segregating.
- To reduce bulk volume, thereby minimizing storage and enhancing transport.
- To reduce potential environmental and safety hazards.

The purpose of the study is to investigate the effect of ball mill on the properties of drug powder and tablets. This study is carried out by using ball mill at constant speed with various sizes of balls in ball mill resulting in agglomeration and its impact on tablet hardness, thickness and friability. For this study ibuprofen is the model drug selected. The tablets are also evaluated for disintegration time and in vitro drug release study.

Solubility Studies

The solubility of drug was studied in different solvent media at 37^0 C ± 0.5^0 C.

Analysis of drug

Spectrophotometric Analysis

λ max of drug in 7.2 pH buffer was found to be 221 nm.

Linearity

The standard curve of drug was prepared in 7.2 pH buffer as shown in fig.5 the standard values are given in the table 8.

Weight of drug: 10 mg

Concentration of stock solution: 100 µg/ml.

Conclusion

The standard curve prepared shown very linearity hence it was used for further analysis.

Dissolution profiles of marketed product

The dissolution profile of reference product was studied using earlier maintained parameters at specific time intervals, samples were withdrawn and drug concentrations were determined by UV. This was taken into a account in

the calculation of the % drug release. Release profile was determined over a period of 60 minutes. Drug concentration in each withdrawn aliquot was determined by measuring the absorbance of the solution at 221 nm against blank on UV spectrophotometer. The drug amount was extrapolated from standard curve of the curve in 7.2 pH buffer.

Stability study of optimized formulation batch F2

It is very essential that any product developed in the formulation department should be stable. The regulatory agencies in different countries try to ensure that the stability studies are carried out on the product. The formulation is subjected to accelerated stability conditions (40ºC ± 2ºC / 75% RH ± 5%).The effects of temperature and time on the physical and chemical characteristics of the tablet were evaluated for assessing the stability of the formulated tablets. The results indicate that there wasn't any significant change in hardness & % drug content. Disintegration and *in vitro* drug release was found to be increased a little more at 40^0C temperature. No significant change was observed in drug content.

Accelerated stability studies as per ICH guidelines

The optimized formulation (Batch F2) was wrapped in aluminum foils and kept in petri -dish at 40 ºC ± 2ºC / 75% RH ± 5% in humidity chamber. The stability studies were conducted after 30 and 60 days.

Before the medicines effect actually begins and patients get released quickly .The present work was aimed to formulate the oral tablets ibuprofen by using ball mill to form an agglomeration which results in higher dissolution and decrease in Disintegration time. The absorption maximum (λ max) of ibuprofen was measured in phosphate buffer pH 7.2 and was found to be 221 nm. The drug and polymer were subjected to compatibility studies by IR and were found to be compatible to each other. Five batches (Batch F1– Batch F5) were prepared by ball mill method in the present study. The batches are prepared at different sizes of balls and at constant speed. The tablets of all the batches were carried out weight variation, hardness, thickness, friability, disintegration time, assay and in vitro drug release and found to comply with the pharmacopoeial specification. The Batch F2 was selected as an optimized batch based on the results indicated.

The tablets of batch F2 were subjected to accelerated stability studies at (40ºC ±2ºC/ 75% RH ±5%) for 60 days. Analysis of the stability sample for all parameters (weight variation, hardness, disintegration time, thickness assay and in vitro dissolution study) at the end of 3 month complied with the standard specification limits. For the present study, it was concluded that the oral tablets of ibuprofen can be prepared successfully. From the result obtained in the present work, it was observed all the prepared batches fulfilled the official requirements. It was observed that the ball mil agglomeration affect the properties of granules and the tablets. The Batch F2 was considered as the best formulation and compared with the marketed preparation.

Table 1. Comparative table of Standards for Carr's index/Angle of repose/ Hausner's ratio

Carr's Index	H.R	Angle of Repose	Flow
5-15	1.2-1.3	25-30	Excellent
12-16	1.3-1.4	30-35	Good
18-21	1.4-1.5	35-40	Fair
23-35	1.5-1.6	40-45	Poor
35-38		45-50	Very poor
More than 40			Extremely poor

Table 2. Particle size of Ibuprofen

Sr.no	Samples of Ibuprofen	Particles size in (nm)
1)	Unmilled Ibuprofen	268 nm
2)	Milled Ibuprofen + MCC	6700 nm P.d.i=<0.5

Table 3. Formulation of ibuprofen tablets

Ingredients (mg)	F1 (Without Ball mill)+ NoDisintegrant	F2 (Ball mill) APOC	F3 (Without Ball mill)+ Disintegrant	F4 (Without ball mill) +Superdisintegrant
Ibuprofen (Drug)	200	200	200	200
Hydroxypropyl cellulose (Disintegrant)	32	-	36	32
Crossmellose sodium (Superdisintegrant)	-	-	-	8
Microcrystalline	166	198	162	158

Cellulose (Diluent)				
Magnesium stearate (Lubricant)	2	2	2	2
Total weight (mg)	400 mg	400 mg	400 mg	400 mg

Table 4. Percentage weight deviations

Average weight	% difference
130 mg or less	10
130 – 324 mg	7.5
324 mg and greater	5

Table 5. ICH guidelines for stability study

Long term	25^0 C±2^0 C/60% RH±5% RH	12 month
Intermediate	30^0 C±2^0 C/65% RH±5%RH	6 month
Accelerated	40^0 C±2^0 C/75% RH±5%RH	6 month

Table 6. Test of drugs

Tests	Results of Analysis
Colour	White powder
Odour	No characteristic odour
Taste	Bitter taste
Solubility	Slightly soluble in water
Bulk density	0.384
Tapped density	0.588
Angle of repose	42^0 70’
Carr’s Index	Index 34.69
Hausner’s ratio	1.53
Assay	99.02%

Table 7. Concentration of stock solution

Sr.no.	Volume of stocksolution(ml)	Diluted to (ml)	Theoretical Conc.(mg/ml)	Theoretical concentration(ppm)
1	0.1	10	0.001	1
2	0.2	10	0.002	2
3	0.3	10	0.003	3
4	0.4	10	0.004	4
5	0.5	10	0.005	5
6	0.6	10	0.006	6
7	0.7	10	0.007	7
8	0.8	10	0.008	8
9	0.9	10	0.009	9
10	1	10	0.10	10

Table 8. Absorbance of drug in 7.2 pH buffer

S.No	Conc. Inppm	Conc.(µg/ml)	UVabsorbance
1	1	1	0.057
2	2	2	0.109
3	3	3	0.159
4	4	4	0.198
5	5	5	0.235
6	6	6	0.236
7	7	7	0.326
8	8	8	0.371
9	9	9	0.407
10	10	10	0.464

Table 9. Evaluation parameters of premix blend

Parameters	Results
Bulk density (gm/cm^3)	0.357
Tapped density (gm/cm^3)	0.526
Carr's index (%)	32.13
Hausner's ratio	1.47
Angle of repose (θ)	42^0 93'

Table 10. Evaluation parameters of blend Batches F1, F2, F3&F4

Formulations	Batch F1	Batch F2	Batch F3	Batch F4
Bulk density (gm/cm^3)	0.365 ± 0.067	0.390 ± 0.062	0.440 ± 0.060	0.480 ± 0.059
Tapped density (gm/cm^3)	0.549 ± 0.032	0.588 ± 0.029	0.631± 0.031	0.631± 0.027
Carr's index (%)	33.5 ± 1.24	33.67 ± 1.18	30.26 ± 1.13	32.64 ± 1.16
Hausner's Ratio	1.5 ± 0.023	1.50 ± 0.020	1.43 ± 0.019	1.52 ± 0.021
Angle of repose (θ)	$41^0$32' ± 1.38	$38^0$41' ± 1.35	$35^0$55' ± 1.29	$36^0$40' ± 1.32

Table 11. Evaluation parameters of Batches F1, F2, F3, F4 and F5 (n=3 All values are mean ± S.D)

Parameters	Without ball mill+Nodisintegrant Batch F1	Ball mill (drug+MCC) Batch F2	Without ball mill+ Disintegrant Batch F3	Without Ball mill Superdisintegrant Batch F4	Marketed Formulation Batch F5
Appearance	Round shaped	Round shaped	Round shaped	Round shaped	Round shaped
Average weight(mg)	402.98±2.198	399.17±1.220	402.1±1.490	398.2±0.643	401.17±2.140
Hardness (Kg/cm^2)	12.31±0.23	4.9±0.80	9.34±0.63	7.65±0.75	6.98±0.80
Thickness (mm)	4.57 ± 0.02	4.57±0.06	4.56±0.013	4.56±0.011	4.57±0.10
Fraibility (% (w/w)	0.36	0.16	1.2	0.96	0.10
Disintegration time	1min 11sec	48 sec	1 min 2 sec	57 sec	5 min 10 sec
Assay (%)	95.3 ± 0.75	99. 20± 0.16	98.7± 0.18	97.2± 0.47	98.97± 0.19

Comparative study of density of blend of the formulation

Table 12. Comparative study of density of blends of the formulation

Ball speed (rpm)	Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)
50	Batch F1	0.365	0.549
50	Batch F2	0.390	0.588
50	Batch F3	0.440	0.631
50	Batch F4	0.480	0.631

Table 13. Comparative study of Hardness of Formulations

Ball mill speed (rpm)	Formulation	Hardness of tablets (kp)
50	Batch F1	6.98
50	Batch F2	9.34
50	Batch F3	7.65
50	Batch F4	10.11
50	Batch F5	11.09

Table 14. Physical characterization of marketed product

Parameters	Reference product: ibuprofen oral tablets Trade Name-Brufen 200
Appearance	Round dark pink tablets
Label claim(mg)	200 mg

Friability	0.357
Disintegration time	5min10sec
Assay (%)	98.97%

Table 15. Dissolution profile of marketed product

Time (min)	% Drug Release
0	0
5	15.74
15	34.13
20	45.13
25	58.33
30	72.16
45	86.51
60	98.97

Comparative study of in vitro dissolution profile of marketed product and optimized formulation batch F-2.

Table 16. Dissolution profile of marketed product and Batch F2

Time (min)	Marketed product	Batch F2
0	0	0
5	15.74	21.99
10	34.13	41.93
15	45.13	53.18
20	58.33	67.81
30	72.16	83.97
45	86.51	99.20
60	98.97	

Table 17. Physical Characteristics of ibuprofen tablet Batch F2 at Temperature (40ºC±2ºC/ 75% RH ±5%)

Physical Parameters	0 DAYS	30 DAYS	60 DAYS
Weight Gain(mg)	399.17 ± 1.220	399.15± 0.42	399.12± 0.17
Percent drug content(%)	100.8± 0.30	100.1± 0.19	100± 0.18
Hardness(kp)	9.34± 0.80	9.31± 0.1	9.42± 0.1
Disintegration Time(SEC)	48 ± 0.09	45 ± 0.11	47 ± 0.07

Table 18. Percent Drug release at 40^0 C / 75% RH 5% of Optimized Batch F2

Time (min)	% Drug release in 0 days	% Drug release in 30 days	% Drug release in 60 days
5	21.99	20.64	19.79
10	41.93	41.11	40.25
15	53.18	52.29	51.76
20	67.81	66.56	65.78
30	83.97	82.12	81.46
45	99.20	98.13	97.34

Fig 1. Theoretical diagram of grinding process (Ho T *et al*., 1979)

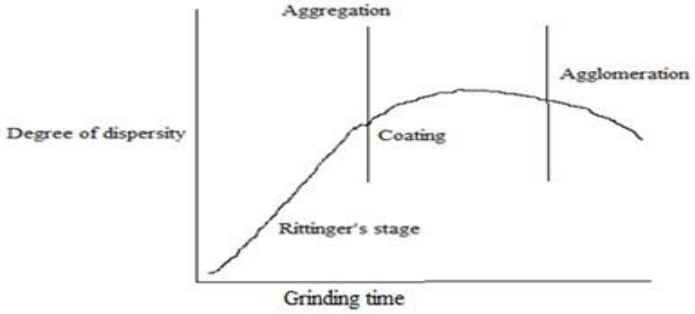


Fig 2.Particle size of UnmilledIbuprofen drug

		Size (d.nm):	% Intensity	Width (d.nm):
Z-Average (d.nm): 268.6	Peak 1:	368.9	44.0	140.3
PdI: 0.651	Peak 2:	122.1	41.2	35.25
Intercept: 0.674	Peak 3:	5010	14.8	604.8
Result quality : Refer to quality report				

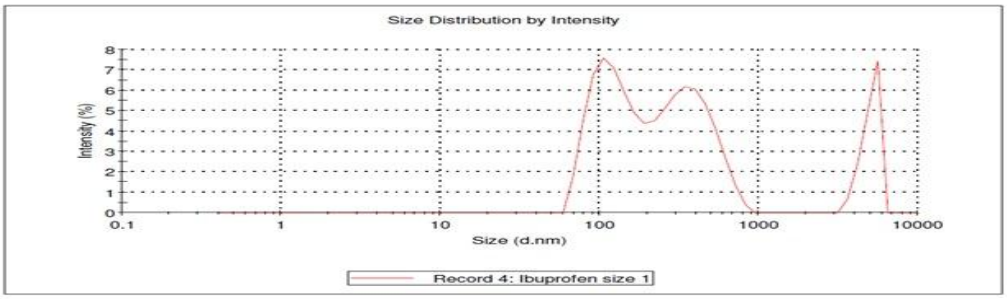


Fig 3. Particle size of milled Ibuprofen drug

		Size (d.nm):	% Intensity	Width (d.nm):
Z-Average (d.nm): 3728	Peak 1:	179.1	100.0	12.82
PdI: 1.000	Peak 2:	0.000	0.0	0.000
Intercept: 1.38	Peak 3:	0.000	0.0	0.000
Result quality : Refer to quality report				

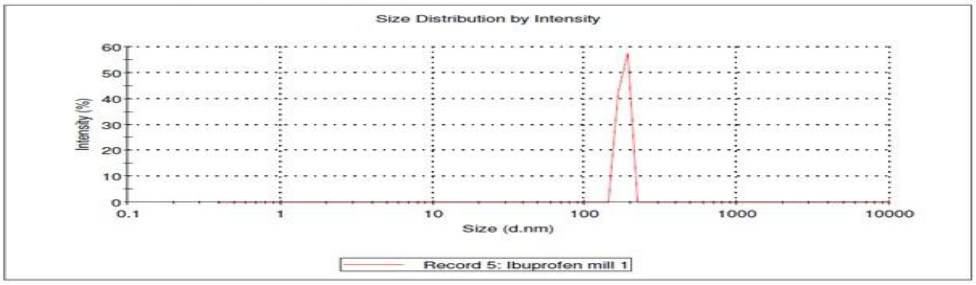


Fig 4. Solubility of ibuprofen drug in various solutions

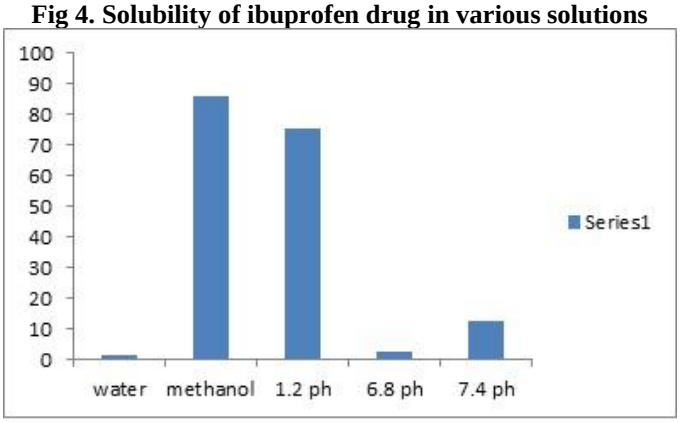


Fig 5. UV Standard curve of drug in pH 7.2

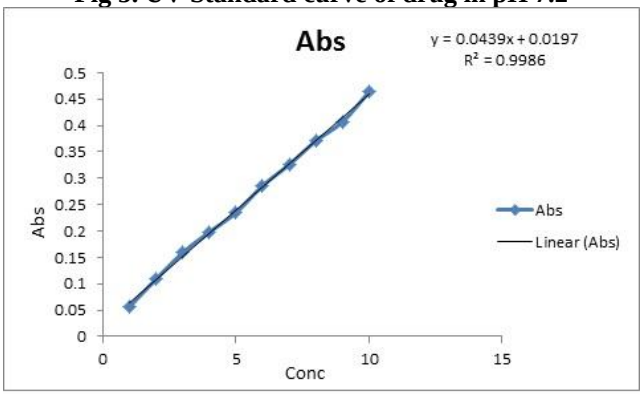


Fig 6. Dissolution of Marketed batch and milled Batch F-2

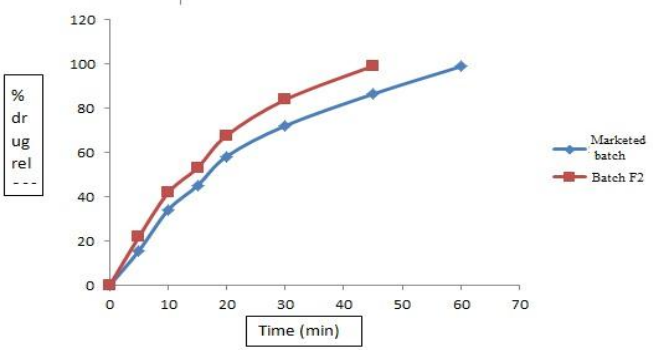
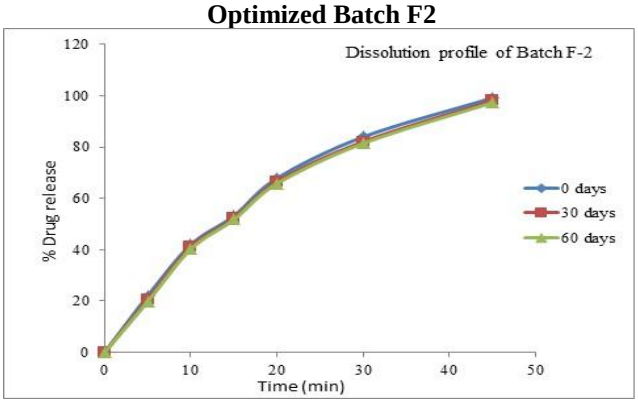


Fig 7. Dissolution profile at 40^0 C 2^0 C/ 75% RH 5% of Optimized Batch F2



CONCLUSION

The in vitro dissolution profile indicated faster and maximum drug release from formulation Batch F2. Formulation Batch F2 is formulated by using ball mill with the constant 50 rpm and formed the agglomerates of Ibuprofen blend within 8-16 hrs. Stability studies shown that there was no significant change when compared with zero day of formulation (Batch F2). Inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leucocytes from the blood into the injured tissues. NSAID'S are used in the treatment of pain. In condition of pain, the rapid disintegration also impose a placebo effect.

ACKNOWLEDGEMENT

The authors pay their sincere thanks to R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur for providing facilities to carry out this research work.

REFERENCES

Allen LV, Popovich NG, Ansel HC. Pharmaceutical dosage form and drug delivery systems, Lippincott Williams. 2005; 6: 184.
Ball DF, Dartnell J, Davison J, Grieve A and Wild R. Agglomeration of Iron Ores, Heinemann, London. 1973.
Basanta Kumar Reddy B, Karunakar A. Biopharmaceutics classification system: A Regulatory Approach. 2011; 1-7.
Bergman R, Johansson ME, Lundstedt T, Seifert E, Aberg J. Optimization of a granulation and tableting process by sequential design and multivariate analysis. *Chemometr.Intell.Lab. Syst.* 1998; 44: 2711- 286.
Bhaskar R, Monika O.Patil PH. Dispersion process: Role in the formulation of particulate disperse system or poorly soluble drugs. *Journal of drug Delivery & Therapeutics.* 2013; 3(1): 93-94.
Buckley S, Frank K, Fricker G, Brandl M. Biopharmaceutical classification of poorly soluble drugs with respect to "enabling formulation. *EJPS.* 2013; 50: 8-16.
Capes CE. Particle size enlargement. 1980; 73-78.
Carter GC and Wright F. Analysis of sintering and pelletizing including laboratory investigation. *Inst. Mining Met. Soc. Proc. Adv. in Extractive Metallurgy.* 1967; 89-113.
Cross M. Mathematical model of balling- drum circuit of a pelletizing plant. *Ironmaking Seelmaking.* 1980; 3: 159-169.
De Villiers M. Influence of agglomeration of cohesive particle on the dissolution behavior of the furosemide powder. *IJPER.* 1996; 122: 175-179.
Fisher ES. Milling of active Pharmaceutical ingredients.In encyclopedia of pharmaceutical technology. 3rd ed, Swarbrick J. Ed; Informa healthcare: New York, USA. 2006; 4: 2339-2351.
Gunns C, Carter SJ, Cooper and Gunns. Tutorial pharmacy, 6th ed., CBS publication. 2005;16: 188-189.
Hilfiker R, Blatter F, VonRaumer M. Relevance of solid State properties for pharmaceutical Industry; R. Hilfiker Ed; Wiley-VchVerlag GmbH & Co. KGaA: Weinheim, Germany. 2006; 1- 9.
Ho T, Hersey JA. Granulation using the Agglomeration phase of comminution. *Elsevier Sequoia S.A, Lausanne, powder technology.* 1979; 23: 191-195.
Kaerger JS, Edge S, Price R. Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose. *EJPS.* 2004; 22: 173-179.
Krycer I and Hersey JA. Fine powder mixing in Vibratory mill. *IJPER.* 1980; 6: 119-129.
Krycer I and Hersey JA.Grinding and Granulation in a vibratory Ball mill. *Elsevier Sequoia, Lausanne, Powder Technology.* 1981; 28: 91-95.
Krycer I, Hersey JA. A Comparative Study of comminution in Rotary and Ball mills. *Powder technology, Elsevier Sequoia, SA, Laussane, Netherlands.* 1979; 27: 137- 141.
Kumar GS, SubbaRao V. Batch grinding of dolomite using Box- Behnken design. *Chemical engineering & process technology.* 2013; 4: 171.
Lundstedt T, Seifert E, Abramo L, Thelin B, Nystrom A, Pettersen J, Bergman R. Experiment design and optimization. *Chemometr. Intell. Lab. Sust.* 1998; 42: 3- 40.
Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly water soluble compounds. *Eur. J. Pharm. Sci.* 2003; 18: 113- 120.
Moothedath SK, Ahluwalia SC. Mechanism of action of grinding aids in comminution. *Powder technology.* 1992; 71: 229-237.
Mosharaff M, Nystrom C. The particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. *IJPER.* 1995; 122: 35-47.
Nomura S, Hasoda K, Tanaka T. An analysis of the selection function for mills using balls as grinding media. *Powder technology.* 1991; 68: 1-12.
Richard H, Snow, Peter T, Luckie. Annual Review of size reduction. *Elsevier Sequoia, Lausanne, Powder technology.* 1974; 13: 33-48.
Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio. *Pharm. Res.* 2003; 20(21): 1917-1925.
Rumpf H, in Knepper WA.(Ed.). Agglomeration.Wiley, New York. 1962; 379- 414.

Schwedes J, Bunge F. Comminution and transport behavior in agitated ball mills. *Advanced powder technology.* 1992; 3: 55-70

Singh B, Gupta RK and Ahuja. N. Computer assisted optimization of pharmaceutical formulation and processes. 301.

Stewart PJ, Zhao FY. Understanding agglomeration of indomethacin during the dissolution of micronized indomethacin mixtures through dissolution and de- agglomeration modeling approaches. *European Journal of pharmaceutics and Biopharmaceutics.* 2005; 59: 315-323.

Tousey MD. The Granulation Process 101 Basic Technologies for tablet making. *Elsevier publication, Pharmaceutical Technology Granulation.* 2002; 7: 8-13.

Zimper U, Aaltonen J, Kranuel- Goellner K, Gordon KC, Strahan CJ, Rades T. The influence of milling on the dissolution performance of simvastatin. *Open access pharmaceutics.* 2010; 2: 419- 431.