

PREPARATION AND EVALUATION OF IBUPROFEN ORO-DISPERSIBLE TABLETS FOR PEDIATRIC USE

Md Mustakim Mallick*¹, Kunal Mondal*², Amlan Bishal*³, Subrata Hazra*⁴,
Bratati Bandyopadhyay*⁵

*^{1,2,4}B. Pharm, 4th-year student, Bharat Technology, Uluberia, West Bengal, India.

*^{3,5}Asst. Professor, Department of Pharmaceutics, Bharat Technology, Uluberia, West Bengal, India.

Abstract: ODTs are solid dosage forms containing medicinal substances which is easily disintegrate in the mouth within few seconds. The products of ODT technologies are taking place in the market in the 1980s, as the development of the drug delivery system in the pharmaceutical industry the popularity of ODTs products is continuously increased. ODTs products demand is increased in the market because of a preferred alternative to conventional tablets and capsules and great impact on patient willingness especially for the pediatrics, geriatric, and psychiatric patients with dyspepsia. Ibuprofen is a non-steroidal anti-inflammatory drug. It is widely used in children to defeated pain, fever, and inflammation. Due to its quick onset of analgesic effects and optimum serum concentration, it is the most preferred drug of choice for pediatric formulations. In our research work, the wet granulation technique is chosen for the preparation of granules and super-disintegrant like crospovidone and sodium starch glycolate has been added in the intragranular portion to get faster disintegration of tablets. All the physical evaluation parameters of tablets are checked and found within the limit in every formulation except the disintegration time which is achieved in the final formula. It has been found from the experiment that with the increase in the concentration of super disintegrant, the time of disintegration of tablet decreases, and the percentage drug release profile increases. In the final formulation, the desired target of disintegration time is achieved and also good release profile in the dissolution studies is found. Since Ibuprofen is a bitter drug so it is required to optimize the concentration of sweetening agent in the formulation and also further investigation will be carried out to optimize the effect of formulation processing variables on the preparation of tablets.

Keyword: - Ibuprofen, Oral Disintegrating Tablet, Super Disintegrant, Tablets, Pediatric, Granules, Geriatric.

I. INTRODUCTION

Ibuprofen namely 2-(4-isobutylphenyl) propionic acid is known as a medicament with antipyretic, analgesic & anti-inflammatory properties. It is usually available in the form of racemic Ibuprofen. It is used for the treatment of pain & anti-inflammatory including osteoarthritis, rheumatoid arthritis, postorder operative pain, ankylosing agent, postpartum pain & soft tissue injuries, generally at doses up to 3200mg/day. It is used for the treatment of pain & fever including rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea, headache, migraine, dental pain & colds & flu, generally at doses up to 1200mg/day. It is marketed available is generally equivalent to 200mg, 400mg, 600mg, or 800mg racemic Ibuprofen. The disintegration time of the tablet by the present invention is less than 10 minutes as measured by the method described in the European Pharmacopeia 1986, Ref V.5.1.1 (Updated 1995). A disintegration test for tablet and capsule preferred disintegration times are less than 6 minutes (eg. 1-6min), more preferably less than 5 minutes (eg. 1-5min) and most preferably 3 minutes or less (eg. 1-3min).

II. MATERIALS AND METHODS

List of Chemical's

Ibuprofen purchased from Cipla, Mumbai, Crospovidone, Sodium starch glycolate, Magnesium stearate, Talc, Starch, Lactose purchased from Loba Chemie Pvt. Ltd. Microcrystalline cellulose and Lactose purchased from DFE pharma.

List of Equipment's and Instrument's

SL. NO	INSTRUMENT	SUPPLIER
1	Digital weighing balance	Labpro
2	Sieve	Elysian
3	Hot air oven	La Machinotech
4	8 station Single Rotary Compression Machine	Digicon Pharma Machinery



5	Monsanto hardness tester	Vinsyst technologies
6	Friability test apparatus	Electrolab
7	Tablet disintegration tester	Lab India
8	Vernier caliper	India Tools & Instruments co.
9	Dissolution apparatus	Labindia
10	UV Visible spectroscopy	Shimadzu
11	Fourier Transform Infra-Red Radiation	Brooker

Ingredients(mg/tab)	F1	F2	F3	F4	F5	F6
Ibuprofen	100	100	100	100	100	100
Crospovidone	4	6	-	-	-	-
Mannitol	31	31	31	30	27	25
MCC	50	50	50	50	50	50
Sodium starch glycolate	-	-	4	4	6	6
Starch	8	6	6	6	6	6
Sucralose	6	6	8	8	8	10
Talc	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3
Peppermint flavor	2	2	2	3	4	4
Purified water	QS	QS	QS	QS	QS	QS
Total	210	210	210	210	210	210

METHODS

Method Of Preparation of granules

Ibuprofen oro-dispersible tablets were prepared by wet granulation method using starch paste as binder. Different formulas were designed using crospovidone and sodium starch glycolate as a super-disintegrant. The concentration of sucralose and peppermint flavor has been optimized to get a robust formula. The composition of the orodispersible tablet is given in Table 1. Following steps were followed for the preparation of granules:

Step 1 Sifting: Ibuprofen was weighed accurately as per composition and sifted through 20#, Microcrystalline cellulose, Crospovidone, Mannitol, Sodium starch glycolate, and Sucralose sifted through 40#.

Step 2 Dry Mixing: Above sifted materials were collected in a polybag and mixed for 30 minutes to get a perfect homogenous mixture of drugs and excipients. Here powder samples were collected after mixing to check the LOD of dry mix blend and also for blend uniformity.

Step 3 Preparation of Binder solution: As per composition required quantity of purified water is taken in a beaker and heated up to 80°C in a water bath. Previously prepared starch slurry is added slowly to this purified water under stirring from a clear translucent paste. Cool the paste up to 45°C before addition.

Step 4 Wet mixing: The binder solution is next added slowly in a dry mix blend and mixes continuously until the coherent wet mass is obtained. The granulation endpoint was determined by continuous visible observation on the formation of granules.

Step 5 Wet sifting: Wet mass sifted through 10# to get uniform size particles.

Step 6 Drying: After wet sifting granules were kept for air drying for 10 minutes and then kept inside a tray dryer at 50°C until target LOD is achieved.

Step 7 Dry screening: Dried granules sifted through 30# and collected in a double polythene lined container.

Step 8 Lubrication: Peppermint flavor is sifted through 60# and added to the sifted dried granules. Talc and Magnesium Stearate was weighed and sifted through 60# and added to the above granules and mixed in a blender to get a lubricated blend.

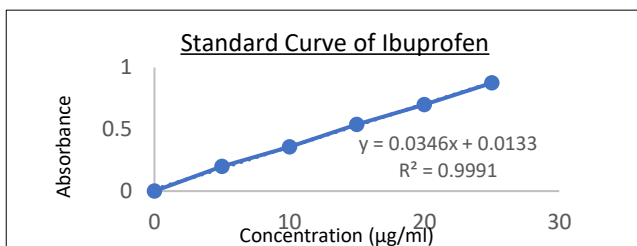
Step 9 Compression: Tablets were compressed in an 8-station single rotary tablet press (Digicon Pharma Machinery, Ahmedabad, India) equipped with 10 mm, circular convex punches, plain on both sides. A constant compression force is required to produce hardness of tablets about 4-6 kg/cm². All physical parameters were checked and tablets were stored in airtight containers for further use.

III. RESULTS AND DISCUSSION

Standard Calibration Curve of Ibuprofen

The standard curve of Ibuprofen was prepared in Buffer pH 6.8; correlation coefficient R and calibration curve equation are as given below. Using absorbance and concentration data, Beer lamberts plots were prepared which are shown in Figure 1. In all the standard curves, the calibration curve equation has shown a linear relationship and a high degree of correlation in the range of 5-25 µg/ml. These curves were utilized in drug estimation as and when required.

Sr No	Concentration(µg/ml)	Absorbance
1	0	0
2	5	0.201
3	10	0.359
4	15	0.538
5	20	0.7
6	25	0.875



Evaluation

Pre-compression parameter:

A. Angle of repose:

The angle of repose was determined by fixed funnel method. The powder was poured from a funnel that can be raised vertically until a maximum cone height; H was obtained. The diameter of the heap, D, was measured.

B. Bulk density:

Bulk density is of great importance when considers the size of the high-dose product or the homogeneity of low dose formulation in which there are large differences in drug and excipients densities. It is defined as the weight of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume, and internal pore volume. It is the ratio of the bulk mass of powder to the bulk volume. It is denoted by ρ_b . Bulk density is used to find out homogeneity

$$\text{Bulk density } (\rho_b) = M/V_b, \text{ Where } M \text{ is the mass of the sample, } V_b \text{ bulk volume}$$

C. Tapped density:

It is determined by placing a graduated cylinder containing a known mass of drug or formulation on mechanical tapping apparatus, which is operated for a fixed number of taps (1st 10 taps, 2nd 500 taps and finally 1250 taps) until the powder bed volume has reached a minimum. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

$$\text{Tapped density } (\rho_t) = \text{weight of powder blend/Minimum volume occupied by cylinder}$$

D. Powder flow properties:

One of the ways of measurement of the free-flowing ability of powder is compressibility.

$$\% \text{ Compressibility} = (\rho_t - \rho_b) / \rho_t \times 100$$

Where ρ_t = tapped density,

ρ_b = initial bulk density

Table 2-Results of Pre -Compressional Parameters

Formulation	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's Index (%)	Hausner's Ratio	The angle of Repose (°)
F1	0.46	0.57	19.298	1.239130435	29.29
F2	0.48	0.56	14.286	1.166666667	29.34
F3	0.49	0.58	15.517	1.183673469	28.96
F4	0.52	0.62	16.129	1.192307692	28.62
F5	0.51	0.6	15.000	1.176470588	28.87
F6	0.49	0.58	15.517	1.183673469	28.84

Post-Compression Parameter:**A. Thickness of tablets**

Thickness is measured by using an instrument called digital "vernier calipers" (Index). Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

B. Weight variation

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. The first weight of 20 tablets was determined.

From that average weight was calculated. Then, individual tablets were weighed and the individual weight was compared with an average weight as per I.P.

C. Hardness

The strength of the tablet is expressed as tensile strength (Kg/cm²). The tablet crushing load, which is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Monsanto Hardness Tester).

D. Friability

Ten tablets were accurately weighed and placed in the friability apparatus and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated.

E. Content uniformity

Twenty tablets were powdered, and powder equivalent to 100 mg of Ibuprofen was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution was filtered, diluted suitably, and analyzed by a spectrophotometer at 221 nm.

F. Fineness of dispersion

This test is performed by placing two tablets in 100 ml of water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μ m without leaving a residue on the mesh.

G. In vitro dissolution studies

In vitro dissolution studies are performed by using USP dissolution test apparatus using 6.8 phosphate buffer as dissolution medium. The paddles are allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37 \pm 0.5 OC and samples are withdrawn at an interval of every 5 min. The volume of the withdrawn samples is replaced by a fresh dissolution medium to keep the volume of the dissolution medium constant. The withdrawn samples were filtered and absorbance was measured at absorption maxima of 221nm using a UV-visible spectrophotometer.

H. In-Vitro Dispersion time

In vitro dispersion time was measured by dropping a tablet in a spoonful of water or 20ml of water in a beaker. The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and in vitro dispersion time was performed.

I. Water absorption ratio

Formulation	Average Weight of Tablet (mg) \pmSD	Hardness (kg/cm²) \pm SD	Thickness(mm) \pm SD	Friability (%)	Disintegration Time(sec)
F1	205 \pm 4.87	6.3 \pm 1.35	2.99 \pm 0.0156	0.58	1min 15sec
F2	210.7 \pm 3.88	5.35 \pm 0.70	2.99 \pm 0.0147	0.51	1min 02sec
F3	210.6 \pm 3.94	5 \pm 0.74	2.98 \pm 0.0150	0.42	50sec
F4	209.1 \pm 4.12	5.15 \pm 0.78	2.99 \pm 0.0165	0.41	42sec
F5	205.2 \pm 4.13	5.05 \pm 0.79	2.87 \pm 0.0171	0.39	31sec
F6	206.2 \pm 4.02	5.3 \pm 0.75	2.97 \pm 0.0174	0.37	28sec

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed.

Observation of post compression evaluation parameters

The percentage weight variation was found to be within the limit of \pm 7.5% as per Indian pharmacopeia. Hence all the tablet formulations were within the pharmacopeia limits. Hardness was maintained to be within 4.5kg/cm² to 6 kg/cm².

Orally disintegrating tablets are less hard than conventional ones, due to lower compression force. These tablets can, therefore, be fragile and need individual packaging. Thickness was found in the range from 2.99 mm to 3.02mm. Formulation F-1 to F-6 possess good mechanical strength (0.39% to 0.58% friability). The most important parameter that needs to be optimized in the development of an orally disintegrating tablet is the disintegration time of the tablet. In the present study, all the formulations except (F1 and F2) disintegrated within 1 minute. By using Croscopovidone in formula F1 and F2 the disintegration time is not coming within 1 minute but Sodium starch glycolate when used in formula F3, F4 and F5 gives the satisfactory result, and with an increase in the concentration of super-disintegrant the disintegration time decreased. The drug content of tablets was found between 98.25% to 99.23%. The results indicated that in all the formulations drug content was uniform. The dispersion time for the formulation prepared with Croscopovidone in the range of 1.29 mins to 1.32 mins but for the formulation prepared with Sodium starch glycolate the dispersion time range is within 1 minute. All batches pass through a sieve screen with a nominal mesh aperture of 710 μm without leaving a residue on the mesh.

Table 4: Post Compressional evaluation of tablets

Formulation	In vitro dispersion time (min) ± SD	Wetting time (sec)	Water absorption ratio	Drug content (%)	Fineness of Dispersion
F1	1.32 ± 0.05	62 ± 1.42	75.08	98.25	Pass
F2	1.29 ± 0.04	60 ± 1.63	78.00	98.39	Pass
F3	0.56 ± 0.02	45 ± 2.02	88.06	97.56	Pass
F4	0.49 ± 0.06	42 ± 1.58	89.12	99.23	Pass
F5	0.30 ± 0.02	32 ± 1.28	97.25	99.21	Pass
F6	0.28 ± 0.04	29 ± 1.38	98.24	98.76	Pass

In vitro dissolution study

It was observed from the trial that the disintegration time of formulation F1, F2, F3, and F4 is coming much more than 30 secs, so the dissolution of these tablets was not performed. The only dissolution of formulation F5 and F6 were performed and percentage drug release was calculated and the release was found satisfactory in both the formulation F5 and F6.

SR NO	TIME (mins)	F5 (%CDR)	F6 (%CDR)
0	0	0.00	0.00
1	5	78.06	79.56
2	10	85.28	86.02
3	15	94.23	94.08
4	20	96.21	96.16
5	30	98.86	98.02

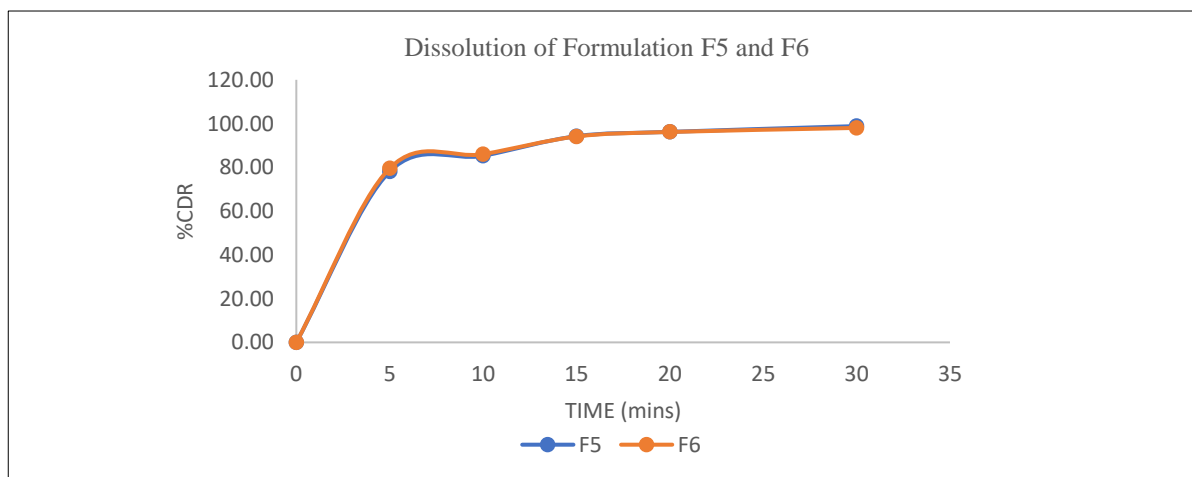


Fig 1: Dissolution profile of Formulation- F5 AND F6

Discussion of evaluation parameters

The pre compressional parameters for all the formulations from F1 to F6 were found satisfactory. During the evaluation of post compressional parameters, it has been found that for formulation F1 and F2 where crospovidone has been used as super disintegrant here the disintegration time not get reduced after using sufficient quantity of the same. But from formulation F3 to F6 it has been observed that with an increase in the number of super disintegrants the disintegration time of tablets decreases gradually. So, in formulation F5 and F6, the quantity of super disintegrant works best to get an optimized drug release. But the taste of formulation F5 found slightly bitter. Hence in the final formula, the quantity of sucralose and flavor has been adjusted to mask the bitterness of the drug and to get a smooth cooling effect inside the mouth after consuming the tablets. Also, the dissolution profile shows that within 15mins more than 90% of the drug gets released.

IV.CONCLUSION

Orally, disintegrating tablet of Ibuprofen IP for pediatric use was successfully prepared with sodium starch glycolate as super disintegrants by wet granulation method. No chemical interaction between drug and excipients were found from the FTIR analysis. The present studies helped in understanding the effect of formulation process variables especially the concentration of super disintegrants on the dispersion time and drug release profile. An overall result indicates that formulation F6 containing 2.86% of sodium starch glycolate with Peppermint flavor exhibited the least disintegration time and faster drug dissolution will lead to enhance patient compliance. Optimized F6 formulation has a good physical appearance, in vitro dispersion time, and drug release. All pre-formulation parameters were within range indicates that powder has good flow properties. All the pharmacopeial and non-pharmacopeial tests were performed and the results were observed within a limit. Only the in vivo studies were left to conduct in the animal body to find the in-vivo in-vitro co-relationship of the optimized formula.

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