

Comparative Study on the Effect of Various Superdisintegrants in the Formulation of Ibuprofen Fast Dissolving Tablets

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ABSTRACT

In the present study, an attempt has been made to formulate fast dissolving tablets of Ibuprofen. Tablets were prepared using a direct compression method employing superdisintegrants such as Kyron T-314, sodium starch glycolate (Explotab), croscarmellose sodium (Ac-Di-Sol), and crospovidone. The prepared tablets were evaluated for their physicochemical properties like wetting time, water absorption ratio, dispersion time, disintegration time and *in vitro* drug release studies. It was observed that the results obtained from formulations containing the Kyron T-314 and CP as superdisintegrants showed a better profile in comparison to CCS and SSG. The hardness of the tablets was in the range of 3.0 - 4.0 Kg/cm². The percent weight variation of the tablets was below the range. Weight variation test results showed that the tablets were deviating from the average weight within the permissible limits of $\pm 7.5\%$. Drug content uniformity study results showed the uniform dispersion of the drug throughout the formulation, i.e. 97.24% to 99.98%. Tablets of ibuprofen prepared using cross povidone (CP) exhibited the least friability and disintegration time 54 seconds along with the rapid release (99.81% drug within 15 min) CP was found to be better suited for the formulation of the fast dissolving tablet of ibuprofen compared to other superdisintegrants used in the study. Stability studies indicated that there are no significant changes in hardness, percentage friability, drug content and *in-vitro* disintegration time and cumulative percentage drug release (%CDR).

Keywords: Fast-dissolving tablets, ibuprofen, percentage drug release, superdisintegrants

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INTRODUCTION

Solid dosage forms and capsules are most popular and preferred drug delivery system because they have a high patient compliance [1]. The concept of fast dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallows able dosage forms [2]. Most

commonly used methods to prepare FDT are freeze-drying/ lyophilization, tablet molding and direct compression. Superdisintegrants added in the formulation increase the drug release, thus increasing the bioavailability of drugs. Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency [3]. As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements.

Ibuprofen is a commonly used NSAID. Low-dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over-the-counter (OTC)

medication. Ibuprofen is used as an analgesic, anti-inflammatory agent and anti-pyretic agent [4].

It used for pain relief, fever reduction, and against swelling. Ibuprofen has an antiplatelet effect, though relatively mild and somewhat short-lived compared with aspirin or prescription antiplatelet drugs. In general, ibuprofen also has a vasodilation effect. Ibuprofen is a 'core' medicine in the WHO's medicines necessary to meet the minimum medical needs of a basic health care system. Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H₂ (PGH₂).

MATERIAL AND METHOD

Materials

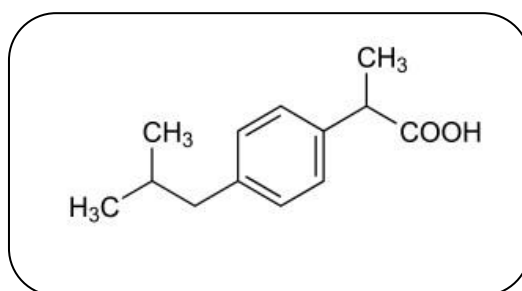
Ibuprofen was purchased from National Chemicals, Vadodara, Gujarat, India. Sodium

starch glycolate, croscarmellose sodium, and crosspovidone were obtained as gift samples from Alembic Ltd. Vadodara, India. Kyron T - 314 was obtained as gift samples from Corel pharma chem. (Ahmadabad, India), Strawberry flavor (Gogia Chemical Industries Pvt. Ltd., Greater Noida) were used and all other chemicals/solvents used were analytical grade.

Method

Excipient compatibility study:

The study was carried out for any interference of drug and excipients used for the formulation of fast dissolving tablet of ibuprofen. The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm⁻¹ to 400 cm⁻¹.



Chemical structure of ibuprofen

Standard calibration curve of ibuprofen

For standard curve of ibuprofen, first of all stock solution was prepared by taking 100 mg of ibuprofen in 100 ml solvent (6.8 pH phosphate buffer) in a volumetric flask. The drug was dissolved in the solvent with ultra

sonicator. Different dilutions were prepared of the stock solution (0.1 mg/ml) having concentrations, 5-30 µg/ml, these prepared dilutions were then analyzed by UV-spectrophotometer (Lab India) at λ_{max} 224nm. The values of absorbance were plotted against concentrations and a slope was developed as given in (Figure 1) [5].

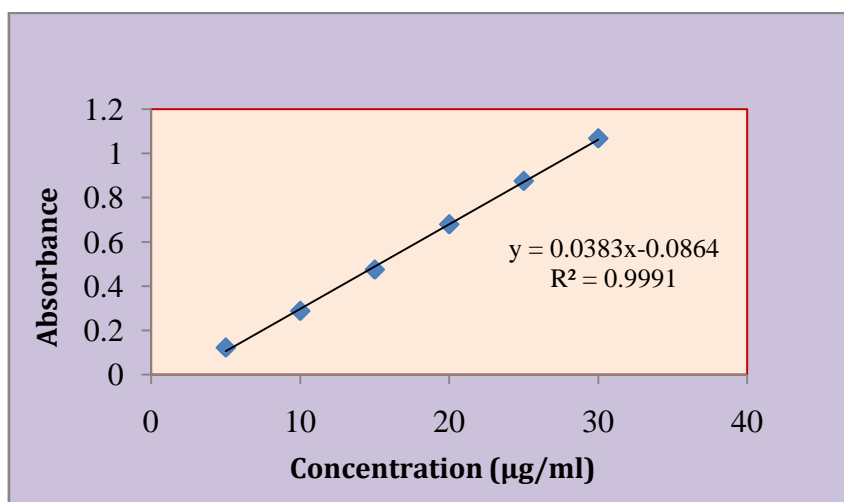


Figure 1: Calibration curve of ibuprofen

PREPARATION OF TABLETS

Method formulation of fast dissolving tablets of ibuprofen tablet each containing 200 mg Ibuprofen was prepared as per composition given in (Table 1). The drug and excipients were passed through sieve #60 to ensure the better mixing. Ibuprofen and the superdisintegrants (Kyron T-314/Sodium starch glycolate/ Croscarmellose sodium/Crosspovidone) in different concentration were blended. The powder

blend was lubricated with 8.0% talc and 0.5% aerosil. The powder blend was compressed using a single stroke punching machine with concave shape 10 mm die and punch (Cadmach, Ahmadabad, India) to produce tablets weighing about 500 mg (± 5 mg) each with a diameter of 10 mm, a minimum of 50 tablets was prepared for each batch, and results are given in (Table 4).

Table 1: Composition of different batches of fast dissolving tablets

Ingredients	Formulation (mg)				
	F ₁	F ₂	F ₃	F ₄	F ₅
Ibuprofen	200	200	200	200	200
Kyron T-314	...	4%
Primogel (SSG)	4%
Croscarmallos sodium	4%	...
Primellose (CP)	4%
Mannitol	249.5	229.5	229.5	229.5	229.5
Aerosil	2.5	2.5	2.5	2.5	2.5
Talc	40	40	40	40	40
Sucralose	5	5	5	5	5
Strawberry flavor	3	3	3	3	3
Total	500	500	500	500	500

EVALUATION OF TABLETS

The mechanical strength of the tablets is often defined as the force required fracturing a tablet across its diameter. Mechanical strength is directly related to porosity and disintegration time. The packaging process and transportation of the final product requires appropriate tablet strength. To ensure tablet strength the formulations were evaluated for hardness, weight variation, thickness, friability,

disintegration time and *in-vitro* dissolution study.

Pre-compressional evaluation [6]**Bulk density**

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_p) and weight of the powder (M) was determined. The bulk density was calculated by using the formula mentioned below,

$$\rho_b = \frac{M}{V_p}$$

Where; ρ_b = Bulk Density

M = Weight of sample in gm

V_p = Volume of sample in ml

Tapped density

The measuring cylinder containing a known mass of the blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend

was measured using tap density tester (Electro lab, ETD: 1020). The tapped density was calculated using the following formula,

$$\rho_t = \frac{M}{V_t}$$

Where ρ_t = Tap Density

M = Weight of sample in gm

V_t = Tap volume of sample in ml

Percent compressibility

The simplest way for the measurement of free flow of powder is compressible, an indication of the ease with which a material

can be induced to flow is given by compressibility index (C) which is calculated as by using the following formula,

$$C = \left[\frac{\rho_t - \rho_b}{\rho_t} \right] \times 100$$

Table 2: Relationship between Percent compressibility and flow ability

Percent Compressibility	Flow ability
5 - 12	Excellent
12 - 16	Good
18 - 21	Fair Passable
23 - 35	Poor
33 - 38	Very Poor
< 40	Very Very Poor

Angle of repose

Angle of repose was determined using the fixed funnel method. The blend was poured through a funnel that can be raised

vertically to a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula.

$$\tan \theta = \frac{h}{r}$$

$$\theta = \tan^{-1} \frac{h}{r}$$

Where θ = Angle of repose

h = height of the cone

r = Radius of the cone base

Hausner's Ratio:

It is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\text{Hausner's Ratio} = \frac{\rho_t}{\rho_b}$$

Whereas, ρ_t is the tapped density; ρ_b is the bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

The data for Hausner's ratio is shown in (Table 3).

Post-compressional evaluation [7]**Uniformity of weight**

20 units selected at random were weighed individually in electronic balance (Essae, DS-852G), the average weight and

maximum percentage deviation were calculated.

Tablet hardness

The crushing tolerance of tablets was measured using a Harrison's hardness tester. The test was performed in triplicate.

Table 3: Pre-compressional Evaluation of Tablets

Parameters	Formulation				
	F ₁	F ₂	F ₃	F ₄	F ₅
Bulk density (gm/ml)	0.444±1.24	0.398±0.73	0.434±0.91	0.421±1.36	0.415±0.38
Tapped density (gm/ml)	0.705±0.46	0.714±0.33	0.726±1.32	0.701±1.18	0.694±2.17
Carr's index	37.021±1.02	43.14±0.17	40.771±0.46	39.948±0.75	40.245±1.18
Hausner's ratio	0.630±0.52	0.564±1.42	0.592±0.11	0.601±0.47	0.598±0.89
Angle of repose (°)	35.412±0.08	33.703±1.03	32.005±0.88	30.963±0.91	35.107±0.06

The data are expressed as mean ± S.D. (n=3).

Tablet friability

The friability of sample of tablets were measured using a Roche friabilator (Veego, VFT-2D). This device consists of a plastic chamber that is set to revolve around 25 RPM for 4 minutes dropping the tablets at a

distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted and reweighed. The friability (F %) was calculated by following formula,

$$\text{Percent Friability} = \left[\frac{\text{Loss in Weight}}{\text{Initial Weight}} \right] \times 100$$

Conventional compressed tablets that lose less than 1.0% of their weight are generally considered acceptable

In vitro disintegration time [8]

The test was carried out on 6 tablets using tablet disintegration tester ED-20, (Electro lab), distilled water at 37°C ± 2°C was used

as a disintegration medium and the time in second taken to complete. Disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. The data for all post-compression parameters is shown in (Table 4).

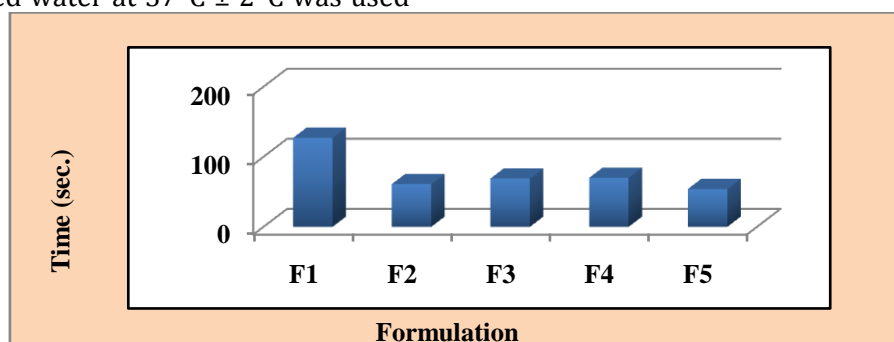


Figure 2: Disintegration time of different formulation batches

Percent drug Content [9]

Randomly twenty tablets were weighed and taken in a mortar and crushed to make powder. A quantity of powder weighing equivalent to 200 mg of ibuprofen was taken in 100 ml volumetric flask containing

6.8 pH phosphate buffers. An aliquot of 2 ml sample was withdrawn and diluted to 10ml and analyzed by a UV spectrophotometer at λ_{\max} 224nm against the blank. Then the amount of drug present was calculated using standard graph.

$$\text{Percent drug content} = \left[\frac{(\text{Theoretical wt of drug} - \text{Observed wt of drug})}{\text{Theoretical wt of drug}} \right] \times 100$$

Wetting time [10]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10cm diameter. 10 ml of water-containing

amaranth a water soluble dye was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet is noted as a wetting time.

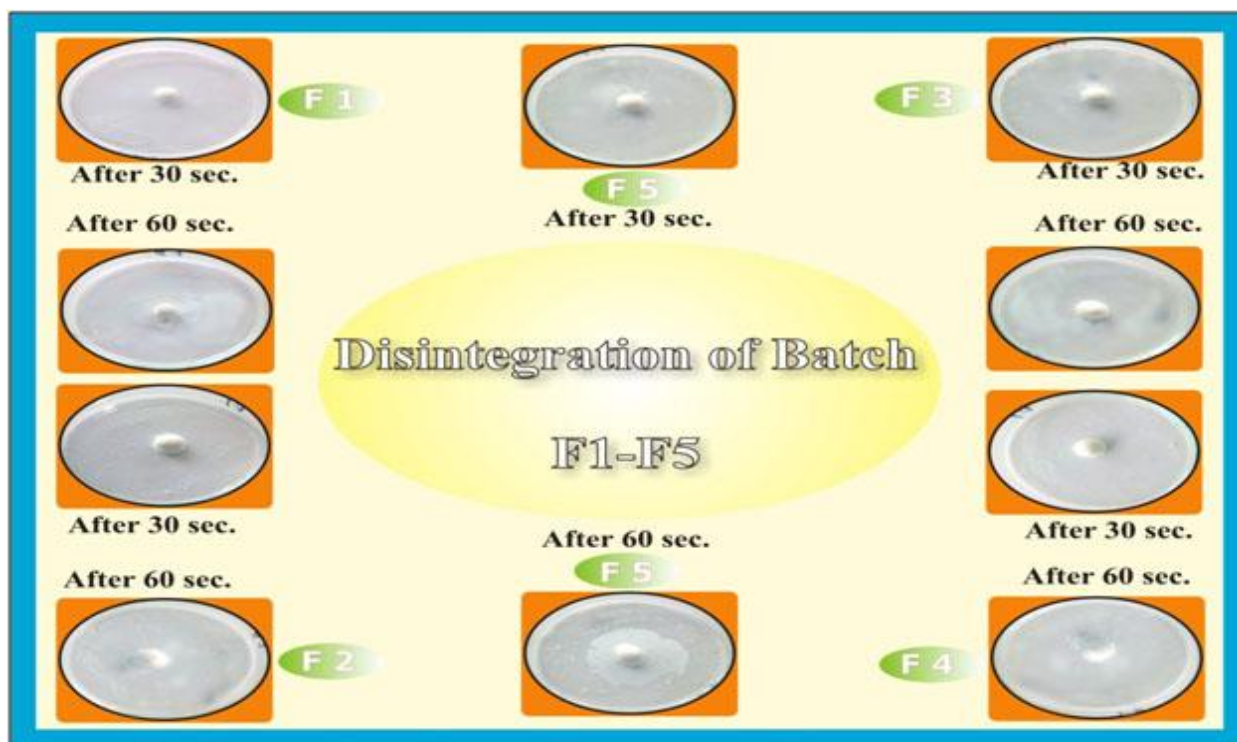


Figure 3: Disintegration time of different formulation batches

Water absorption ratio [11]

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the tissue

paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = \frac{W_a - W_b}{W_a} \times 100$$

Where, W_a = weight of tablet after water absorption

W_b = weight of tablet before water absorption.

Table 4: Post-compressional Evaluation of Tablets

Formulation code	Thickness (mm)	Weight variation (mg)	Hardness (kg)	Friability (%)	% Drug content	Wetting time (Sec.)	Disintegration Time (Sec.)
F_1	4.893±0.12	0.502±0.51	3.783±1.05	0.353±0.34	99.64	108±2.38	127±0.29
F_2	4.813±0.11	0.501±1.73	3.600±0.78	0.256±0.19	98.95	67±1.24	69±1.06
F_3	4.963±0.08	0.498±0.85	3.567±1.56	0.453±0.27	99.42	64±2.02	70±1.17
F_4	4.920±0.47	0.502±0.67	3.667±0.72	0.330±1.02	97.24	59±0.81	61±0.58
F_5	4.923±1.31	0.498±0.97	3.557±0.48	0.226±1.48	99.98	51±1.06	54±1.21

The data are expressed as mean ± S.D. (n=3).

Table 5: Accelerated stability studies of formulation F_5

Parameters	Initial	After 30 Days
Percent friability	0.226±1.48	0.231±1.02
Hardness (kg)	3.557±0.48	3.428±0.27
Disintegration time (Sec.)	54±1.21	49±0.62
% Drug content	99.98	99.91

The data are expressed as mean ± S.D. (n=3).

Dissolution studies [12]

In-vitro dissolution studies for all the preparations tablets was carried out using the USP paddle method at 50 RPM in 900 ml of phosphate buffer solution (pH 6.8, saliva pH) as dissolution media, maintained at $37 \pm 0.5^\circ\text{C}$ of sample was withdrawn from

the dissolution medium at the specified regular intervals, filtered through Whatsmann filter grade 1 paper and assayed spectrophotometrically at $\lambda_{\text{max}} 224\text{nm}$ and the drug content was determined by from the Standard calibration curve.

Table 6: Percentage cumulative drug release of different formulation batches

Time in (min)	Formulation (%w/v)				
	F ₁	F ₂	F ₃	F ₄	F ₅
0	0	0	0	0	0
5	21.66±0.87	54.42±1.08	25.86±0.59	58.41±1.62	66.31±2.36
10	34.33±2.53	74.85±0.66	60.32±1.21	69.86±1.88	81.34±1.90
15	48.82±1.49	86.63±0.41	69.09±2.74	80.36±0.77	99.65±0.24
20	56.23±0.41	99.48±2.11	76.94±0.78	92.91±0.57	
25	67.41±1.71		81.25±1.35	95.41±2.31	
30	77.15±0.85		87.89±0.86	99.28±1.05	

The data are expressed as mean \pm S.D. (n=3).

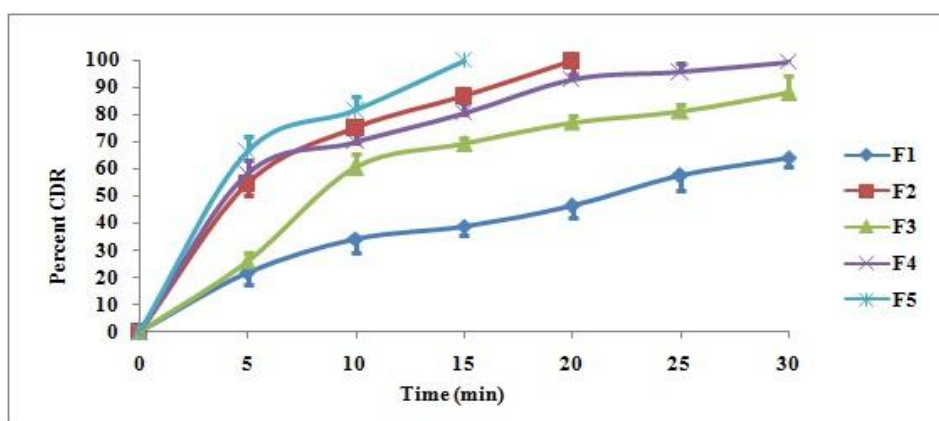


Figure 4: *In-vitro* drug release versus time profiles of different formulation batch in pH 6.8 phosphate buffer solution

RESULT AND DISCUSSION

Five formulations of ibuprofen were prepared by concentration of four superdisintegrants: Kyron T-413, sodium starch glycolate, croscarmellose sodium, crospovidone and were used as a direct compressible vehicle (Table 1).

Pre-compressional evaluation of powders: Pre-compression and post compressional evaluation was done. Prior to compression of the tablets, the powder blends were subjected to various physical tests and the result was calculated. Bulk density was found in the range of 0.398-0.444gm/ml and the tapped density between 0.694-0.726gm/ml. After compression tablets were evaluated for various parameters. Wetting process was

very rapid in almost all formulations. This may be due to ability of swelling and also capacity of water absorption and causes swelling. Rapid dispersion within a few minutes was observed in all the formulations. The results showed that tablet containing crospovidone having low dispersion time as compare to other superdisintegrants.

Disintegration and dissolution profiles:

The *in-vitro* disintegration time (DT) of the tablets was found to be less than 2.5min. Tablets containing 4% Kyron-T 314 (F₂), 4% sodium starch glycolate (F₃), 4% croscarmalose sodium (F₄) and 4% cross povidone (F₅), showed lowest disintegration time compared to control batch (F₁). The order of enhancement of

dissolution rate with various superdisintegrants found to be crospovidone>Kyron T 314 >cross carmellose>sodium starch glycolate. Stability study shows no significant changes in best formulation values during one-month study.

CONCLUSION

The *in-vitro* drug release profile of all formulations was evaluated and the release studies demonstrated that the release of ibuprofen from all formulations was generally immediate. The release characteristics were significantly influenced by the type of superdisintegrants used. Disintegration time was also governed by the type and amount of superdisintegrants. The various mechanical and physical parameters of granules and tablets, such as the flow properties, hardness, friability etc. were seen to comply with the standards set by different international organizations e.g. pharmacopoeias. Thus, the granules and tablets were found satisfactory in terms of physical parameters, disintegration time as well as the drug release profiles from the immediate release tablets.

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