

Formulation and *in-vitro* Evaluation of Oro-dispersible tablets of Indomethacin

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ABSTRACT

Introduction: Oro-dispersible tablets are rapidly dissolved in saliva without the need of water and beneficial for renal impaired, bedridden and psychiatric patients.

Objective: The study aimed to formulate oro-dispersible tablets of indomethacin with reduced adverse effects, better patient compliance, faster action and convenient for patients.

Methods: Oro-dispersible tablets of indomethacin were prepared using three different superdisintegrants; croscopovidone, croscarmellose sodium and sodium starch glycolate with three different concentrations (2.5%, 5.2%, and 7.7%) by direct compression method. The prepared tablets were evaluated for pre and post compression parameter including bulk density, tapped density, compressibility index, angle of repose, hausner's ratio, hardness, friability, wetting time, in vitro disintegration time, and in vitro drug release.

Results: The percentage of drug released in 5 minutes of all formulations of Oro-dispersible tablets of Indomethacin was found to be 74.36% to 80.16% and percentage of drug released in 10 minutes was 96.18% to 100%. All formulations showed disintegration time in the range of 19-78 second. The tablets prepared with 7.7% croscopovidone (F6) shows faster disintegration (19 second) as compared to tablet prepared with sodium starch glycolate and croscarmellose sodium. The in-vitro dissolution studies showed that tablets of formulations batch containing 7.7% croscopovidone releases 100% of drug after 10 minutes which was fast released as compared to sodium starch glycolate and croscarmellose sodium.

Conclusions: Oro-dispersible tablets of indomethacin prepared with croscopovidone showed better disintegration time and dissolution profile as compared to other superdisintegrants.

Keywords: Direct compression; indomethacin; oro-dispersible; superdisintegrants.

INTRODUCTION

Oro-dispersible tablet also known as mouth dissolving tablet or fast dissolving tablet has been developed as it can be dissolve rapidly in saliva without the need of drinking water, when placed in mouth disintegrate rapidly in contact with saliva with release of active drug, providing

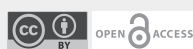
maximum drug bioavailability as compared to the conventional dosage.¹⁻³ It is beneficial for geriatric, unconscious, bedridden patients, patients affected by renal failure, psychiatric patients.⁴ Oro-dispersible tablets are developed by the addition of super disintegrants like cross linked cellulose derivative; carboxymethyl cellulose, sodium starch glycolate, polyvinylpyrrolidone, which gives burst disintegration when gets in contact with salivary secretions.

Superdisintegrants are generally used at a low concentration typically 1 - 10 % by weight relative to the total weight of the dosage unit. Their particles are generally small and porous, which allow for rapid

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tablet disintegration in the mouth. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity.^{5,6}

Indomethacin is non-steroidal anti-inflammatory drug (NSAID) that belongs to as class II drug according to the Biopharmaceutics classification systems.⁷ Indomethacin is a potent non selective Cyclooxygenase (COX) Inhibitor used in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, chronic low back pain, arthritis acute pain and gout.⁸

Hence, this study aimed to formulate oro-dispersible tablets of indomethacin with reduced adverse effects, better patient compliance, faster action and convenient for geriatric, unconscious and bedridden patients in management of mild to severe pain.

METHODS

The solubility of Indomethacin was performed in solvents water, methanol, chloroform, ethanol. Accurately weighed 25 mg of pure drug was transfer into 100 ml volumetric flask containing Methanol. 10ml from this solution was withdrawn and diluted to 100 ml methanol which made it 25µg/ml (stock solution) then concentration was made by withdrawing 0.5, 1, 1.5, 2, 2.5, 3 ml from stock solution and diluted to 10ml it makes solutions of concentration 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml,

25µg/ml, 30µg/ml and sample were scanned between 300-350nm regions using UV spectrophotometer (ELICO®/SL210) to determine the peak wavelength (λ_{max}) of indomethacin in methanol.⁹

Indomethacin oro-dispersible tablets were manufactured in nine formulations F1 to F9 using the ingredients mentioned in the table (Table 1) keeping the total weight (350 mg) of the tablet constant in all the formulations. An excipient (diluents, superdisintegrants, sweetener, flavouring agent, binder) were passed through sieve #0 and active drug was passed through the sieve #100 and finally all the ingredients were passed through the sieve #40 and mixed the above blend for 15 minutes time (in an air tight plastic bag). After that magnesium stearate and talc were mixed thoroughly for 5 minutes and above mixtures were compressed by direct compression method.

Evaluation of Oro-dissolving tablet^{10,11}

Bulk Density: It was determined by pouring the blend into a graduated cylinder. A quantity of 6 gm of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. The bulk volume and mass of the powder was determined.

$$\text{Bulk density} = \frac{\text{mass of powder (g)}}{\text{bulk volume (ml)}}$$

Table 1: Formulations chart of indomethacin mouth dissolving tablets. (F1-F9).

Formulations	Ingredients (mg)			
	Indomethacin	Sodium starch glycolate	Crospovidone	Croscarmellose sodium
F1	25	9	-	-
F2	25	18	-	-
F3	25	27	-	-
F4	25	-	9	-
F5	25	-	18	-
F6	25	-	27	-
F7	25	-	-	9
F8	25	-	-	18
F9	25	-	-	27

Tapped Density

The measuring cylinder containing known mass of blend was tapped for fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured.

$$\text{Tapped density} = \frac{\text{mass of powder (g)}}{\text{bulk volume (ml)}}$$

Carr's Index

The simplest way for measurement of free flow of powder is compressibility, an indication of ease with which a material can be induced to flow is given by Carr's index which is calculated as follow.

$$\text{Carr's index (\%)} = \frac{[(TD-BD)/TD]*100}$$

Hausner's ratio: It is an indirect index of ease of powder flow. It is calculated by the following formula. Hausner's ratio value is less than 1.5 indicates good flow and greater than 1.5 indicates poor flow property.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

Angle of Repose: The powder mixture was taken in a funnel. The height of the funnel was adjusted at definite height in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug blend was allowed to flow through the funnel freely on to the surface. The diameter of the powdered cone was measured and the angle of repose was calculated using the following equation;

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

Where, θ = Angle of repose

h = height of the cone
 r = Radius of the cone

Post- compression parameters^{10, 12}

Physical Characterization of tablets: Twenty tablets were randomly selected from the prepared formulation and examined for shape, thickness and diameter.

Weight Variation: As per IP specifications to perform test for uniformity of weight twenty tablets from each formulation were selected randomly and their average weights were calculated. Percentage weight differences were calculated and checked with Indian Pharmacopeia 1996 (IP) specifications.

The thickness of tablet was measured by placing the tablet between two arms of the digital Vernier caliper. Five tablets were taken and their thickness was measured.

The tablet hardness, which is the force required to break a tablet in diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) or a sample of 6 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W_1) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\text{Friability(\%)} = \frac{\text{Initial weight}(W_0) - \text{Final weight}(W_1)}{\text{Initial weight}(W_0)} \times 100\%$$

A piece of tissue paper folded twice was placed in a petridish (internal diameter= 8cm). 15ml of phosphate buffer pH 6.8 containing a drop of

Table 2: Table showing range of weight variation as their tablet weight in mg.

Average weight of tablet (%)	% Deviation
80mg or less	±10
80mg to 250mg	±7.5
250mg or more	±5

methylene blue was added to petridish. A tablet was placed carefully on the surface of tissue paper. The time required for phosphate buffer to each upper surface of the tablet was noted as a wetting time.

Tablet was added to 100ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was performed.

The test was carried out on 3 tablets using Tablets disintegration tester, phosphate buffer pH 6.8 at $37^{\circ}\text{C}\pm 2^{\circ}\text{C}$ was used as a disintegration media and the time taken for complete disintegration of the tablet with no passable mass remaining in the apparatus was measured in seconds.

In-vitro Drug release¹³

Preparation of standard

Accurately 25mg of indomethacin was weight and transfer to 100ml volumetric flask (VF). Drug was dissolve in phosphate buffer pH 6.8 and volume was made up to mark by phosphate buffer pH 6.8.

Preparation of sample

In-vitro release of sample was carried out using USP-Type II dissolution apparatus (paddle type). In this method phosphate buffer pH 6.8 was used as a dissolution medium. The dosage form were placed in 900ml of phosphate buffer and maintained at temperature $37\pm 0.1^{\circ}\text{C}$ and rotational speed was maintained at 50rpm. 10ml of the sample were withdrawn at 5, 10 minutes and purified through membrane filter (pore size $1\mu\text{m}$). The dissolution medium was then replaced by 10ml of fresh dissolution fluid to maintain a constant volume. The sample was then analyzed at 320nm by using UV-visible spectrophotometer.

Assay⁹

Preparation of standard:

Accurately 25 mg standard Indomethacin was weighed with electronic balance(Kern & sohn GmbH/D- 72335) and transferred to 100 ml

volumetric flask (VF). Drug was dissolved in methanol and volume was made up to the 100ml and from that 1ml was taken out and volume was made up to 10ml by methanol.

Preparation of Sample:

Six tablets from each formulation were weighted and crushed in a motor. Powder equivalent to 25mg Indomethacin was weighed and transferred in 100ml of volumetric flask. Powder was dissolved in methanol with the aid of ultrasound. The solution was filtered then 1ml of filtrate was further diluted to 10ml with methanol and analyzed spectrophotometrically at 320 nm.

Procedure:

The absorbance was measured at 320nm to find out the content of indomethacin. Content of Indomethacin in tablet in percentage was calculated by using following formula.

$$(\%) = \frac{\text{absorbance of sample}}{\text{absorbance of standard}} \times \frac{\text{weight of standard}}{\text{weight of sample}} \times \text{dilution} \times \frac{\text{average weight}}{\text{label claim}} \times 100\%$$

RESULTS

Solubility studies of API was carried out in different solvents and observations are presented in Table 3 where it was found to be soluble in methanol and chloroform, insoluble in water and sparingly soluble in ethanol.

Table 3: Solubility Profile of Indomethacin.

Solvent	Solubility
Methanol	Soluble
Chloroform	Soluble
Water	Insoluble
Ethanol	Sparingly soluble

λ_{max} of Indomethacin was found to be 320 nm as shown in figure 1. A Standard Calibration Curve for Indomethacin was obtained by measuring absorbance at 320 nm and by plotting graph of absorbance vs concentration as shown in figure 2.

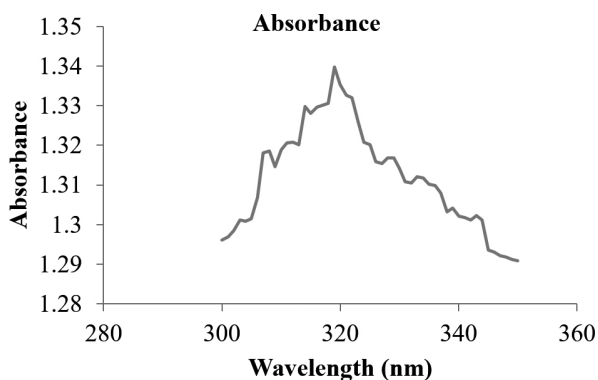


Figure 1: λ_{max} of indomethacin in Methanol

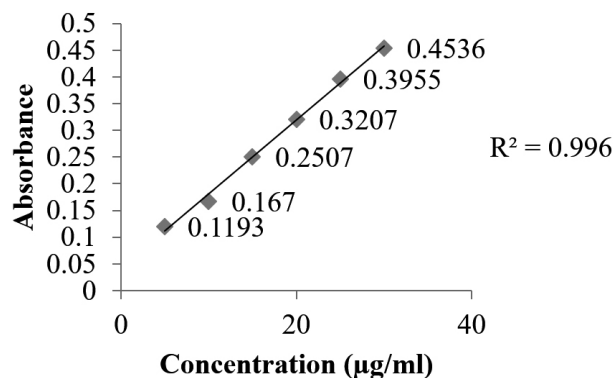


Figure 2: Standard Calibration Curve of Indomethacin

Table 4: Pre-Compression Parameters.

Formulation code	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Compressibility index (%)	Hausner's Ratio	Angle of repose(θ)
F1	0.55	0.66	16.66	1.2	26.56
F2	0.5	0.65	23.07	1.3	27.02
F3	0.5	0.65	23.07	1.3	34.12
F4	0.54	0.73	26.02	1.35	33.02
F5	0.6	0.75	20	1.25	37.23
F6	0.5	0.65	23	1.3	34.21
F7	0.5	0.65	23	1.3	32.61
F8	0.42	0.58	27.6	1.38	37.23
F9	0.6	0.74	18.9	1.23	36.5

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density,

tapped density, Hausners ratio and Carr’s index. Bulk density of all formulation prepared fall within the range of 0.42-0.6 g/cm³, tapped density of all formulation range from 0.58-0.75g/cm³.

The weight of the developed formulations F1 to F9 varied from 346 to 350 mg, being F5 and F6 exactly 350 mg. The weight of the formulated oro-dispersible tablets were uniform with standard deviation values were less than 5 for all formulations (Table 5).The thickness of the developed formulations F1 to F9 varied from 3.85 to 4 mm which was found to be

uniform. The thickness of the optimised formula F6 was found to be 4 mm. The thickness of the oro-dispersible tablet increases with increase in crospovidone concentration. The standard deviation values were less than 1 for all formulations indicating uniformity of the oro-dispersible tablets.

The hardness of the developed formulations F1 to F9 varied from 2.94 to 3.3 Kg/cm². The hardness of the optimised formula F6 was found to be 3.26Kg/cm². F3 showed maximum hardness (3.3 Kg/cm²) due to higher concentration of sodium starch glycolate. This showed that the hardness of the oro-dispersible tablet increases with increase in sodium starch glycolate concentration. The friability of the developed formulations F1 to F9 varied from 0.42 to 0.62%. According to Indian Pharmacopoeia

Table 5: Table Showing Post Compression Parameters.

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm ²)	Friability %	Disintegration time (sec)	Dispersion time (sec)
F1	349±1.52	3.9±0.032	2.94±0.023	0.37	58±1.14	65±0.76
F2	348±1.11	3.85±0.028	3.2±0.012	0.48	35±0.83	36±0.99
F3	349±1.34	3.87±0.031	3.8±0.018	0.51	48±0.52	31±0.86
F4	348±1.91	3.87±0.038	3.20±0.021	0.47	23±0.62	25±0.52
F5	350±1.32	3.89±0.014	3.28±0.012	0.48	21±0.95	21±0.32
F6	350±0.99	4.0±0.023	3.26±0.011	0.47	19±0.36	20±0.14
F7	346±2.31	3.88±0.018	3.22±0.014	0.42	51±0.32	78±0.52
F8	347±2.18	3.86±0.011	3.3±0.041	0.53	43±0.52	54±0.92
F9	349±2.36	3.90±0.031	3.0±0.042	0.62	38±0.39	49±0.54

(IP 2010), total weight loss during the friability should be less than or equal to 1% (<1%). Since, all formulation was within the range. The friability of F9 was most which indicated that the friability of the oro-dispersible tablet increases with increase in croscarmellose sodium concentration.

The disintegration time of the developed formulations F1 to F9 varied from 19 to 58 sec. i.e. less than 1 minute. Disintegration time of all formulations was within a range within 3 min. (as per IP 2010). The disintegration time of the optimised formula F6 was found to be 19 sec. in which high concentration (27 mg) crospovidone was used (Table 1). The disintegration time of the

oro-dispersible tablet decreases with increase in crospovidone concentration. The dispersion time of the developed formulations F1 to F9 varied from 20 to 78 sec. The formulations containing croscarmellose sodium showed least dispersion time in comparison to formulations containing sodium starch glycolate and croscarmellose sodium. The dispersion time of the optimised formula F6 was found to be 20sec. in which high concentration (27 mg) crospovidone was used (Table 1). This suggested that disintegration time of the oro-dispersible tablet can be decreased with increase in crospovidone concentration.

As per IP 2010, the content of Indomethacin in prepared Oro-dispersible tablet should be in range

Table 6: Assay and In-Vitro Drug Release.

Formulation	Assay (%)	%Drug Release in 5min	% Drug Release in 10min
F1	100.22±0.25	74.36±0.83	96.18±0.99
F2	97.96±0.36	78.62±0.92	99.12±0.88
F3	102.30±0.52	79.35±0.56	98.42±0.89
F4	101.23±1.21	75.51±0.34	97.41±0.51
F5	98.28±0.23	78.32±0.59	99.38±0.41
F6	100.24±0.18	80.16±0.42	100.00±0.21
F7	98.53±1.51	80.02±0.97	99.34±0.72
F8	96.01±0.36	79.84±0.39	98.40±0.91
F9	99.25±0.52	80.01±0.97	99.6±0.58

of not less than 90% and not more than 110%. All developed formulations F1 to F9 varied from 96.01 to 101.23 %. The percentage drug release in 5 min. of the developed formulations F1 to F9 varied from 74.36 to 80.02 %. The percentage drug release of the optimised formula F6 was found to be 80.02%. Similarly, the percentage drug release in 10min. of the developed formulations F1 to F9 varied from 96.18 to 100 %. The percentage drug release of the optimised formula F6 was found to be 100%. This indicates that the drug release can be enhanced with increase in the concentration of crospovidone.

DISCUSSIONS

In this study, Oro-dispersible tablets of indomethacin were prepared using three different superdisintegrants; crospovidone, croscarmellose sodium and sodium starch glycolate with three different concentration (2.5%, 5.2%, 7.7%) by direct compression method and drug release in 10 minutes was 96.18% to 100% whereas Siddiqui MN et.al⁵ have formulated and optimized the mouth dissolving tablet containing indomethacin using Polyvinylpyrrolidone (PVP-K30, Polyethylene glycol (PEG)-4000 and PEG-6000 and mouth dissolving tablet by direct compression and sublimation method and drug release was found to be 99.83% within 8 minutes.⁵

Dhiman et al.,¹⁴ have formulated and evaluated fast dissolving tablet of telmisartan by direct compression method using superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate.¹⁴ It was found that the tablet containing higher concentration of crospovidone showed the fastest disintegration within 23 second which similar to our study which also showed Oro-dispersible tablets of indomethacin prepared with crospovidone showed better disintegration time and dissolution profile as compared to sodium starch glycolate and croscarmellose sodium.

In our study, all formulations showed disintegration time in the range of 19-78 second. The tablets

prepared with 7.7% crospovidone shows faster disintegration (19 second) as compared to tablet prepared with sodium starch glycolate and croscarmellose sodium. Tablet prepared with 5.2% of sodium starch glycolate showed disintegration within 35 sec. In contrast, Kiran NR, et.al¹⁵ have formulated oro-dispersible tablet of piroxicam by direct compression method using superdisintegrants like crospovidone and sodium starch glycolate in two different concentration i.e 3% and 5% and found tablet prepared with 5% of sodium starch glycolate showed better disintegration within 33 sec.¹⁵

CONCLUSIONS

The oro-dispersible tablet of indomethacin were successfully prepared by using different superdisintegrants; crospovidone, sodium starch glycolate and croscarmellose sodium varying different concentration along with sweetener saccharin to impart good taste. All formulations showed disintegration time in the range of 19 -78 second. The tablets prepared with 7.7% crospovidone (F6) shows faster disintegration (19 second) as compared to tablet prepared with sodium starch glycolate and croscarmellose sodium

The *in-vitro* dissolution studies for tablets were carried out and tablets of formulations batch containing 7.7% crospovidone release 100.22% of drug after 10 minutes which is fast released as compared to sodium starch glycolate and croscarmellose sodium.

From this study, it can be concluded that the oro-dispersible tablet of indomethacin prepared with crospovidone showed better disintegration time and dissolution profile as compared to other superdisintegrants.

Conflict of Interest: None.

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