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Research Article

IMPROVEMENT OF DISSOLUTION RATE OF INDOMETHACIN FROM FAST DISSOLVING TABLETS

Rabinarayan Parhi*, Nishant Reddy

GITAM Institute of Pharmacy, GITAM University, Gandhi Nagar Campus, Rushikunda, Visakhapatnam-530045, Andhra Pradesh, India

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*Corresponding author
Rabinarayan Parhi

Email :
bhu_rabi@rediffmail.com

ABSTRACT

In the current study Indomethacin (IM) fast dissolving tablets (FDTs) were prepared by direct compression technique in order to enhance its dissolution rate. The tablets were formulated using two different approaches; super-disintegration and efferves-cence. A combination formulation of above approaches was also developed to further improve its properties. The super-disintegrants used in the formulae were sodium starch glycolate (Primogel), cross-povidone (Kollidon) and cross-carmellose (Ac-di-sol). Sodium bicarbonate and citric acid combination was employed as effervescent ingredients. The prepared powder mixtures of IM were subjected to evaluation of various pre-compression parameters and tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration, wetting time, uniformity of dispersion, *in vitro* drug release and stability studies. The FT-IR spectra shown there are no interaction between of IM with excipient. The results of pre-compression studies indicate acceptable flow property for all the powder mixtures. The data of weight variation, dimension, hardness, friability, uniformity of dispersion and drug content studies were within the official limits. The wetting time and disintegration time decreases considerably with the increase in super-disintegrants amount. By using the combination approach, the disintegration and wetting time further decreased. *In vitro* dissolution studies were carried out using phosphate buffer pH 6.8 as dissolution medium for 60min and observed that formulation IF9, among super-disintegration approach, released highest percentage (97.13±2.09) of IM. *In vitro* drug release was highest (98.54±2.89) at 60 min for formulation IF11, when all the formulations were taken into consideration. The stability study was performed on the promised formulation IF11 at 40±2^{o}C/ 75±5% RH for 3 months and the results indicated that there were no significant changes in aforesaid tablet properties.

Key words: Fast dissolving tablet, Indomethacin, Super-disintegration, Effervescence.

INTRODUCTION

Oral drug delivery is the most widely used route of drug administration among all the routes that have been explored for the systemic delivery via various pharmaceutical products of different dosage forms (Ghosh *et al*., 2005) because of its distinct advantages of ease of administration, improved patient compliance, flexibility in designing the dosage form, least sterility requirements and avoidance of pain compared to parenteral route (Krishnaiah *et al*., 2002, Saurabh *et al*., 2011, Prabhu *et al*., 2011, Bhalla *et al*., 2012). Tablets and capsules are the most popular solid dosage forms administered orally. It is estimated that 50 % of the population is affected by dysphasia (difficulty in swallowing), which is the major limitation associated with solid dosage forms such as tablet (Barnhart *et al*., 2007). In addition, it may pose problem for pediatric and geriatric patients who find swallowing difficult and for the treatment of some patients when water is not available in the case of motion sickness (kinetosis) and sudden attack of coughing during the common cold and bronchitis (Gryczke *et al*., 2011, Tritthart *et al*., 2001). This can be resolved by the preparation of rapidly dispersing or dissolving oral forms that combines both the properties of liquid and tablet dosage forms (Habibh *et al*., 2000).

The orally disintegrating tablets are also called as orodispersible tablets (ODTs), quick disintegrating tablets, fast disintegrating tablets, fast dissolving tablets. United States Food and Drug Administration (US FDA) defined ODTs as "a solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". US FDA further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity with an in-vitro disintegration time of approximately 30 s or less (Guidance for industry, 2008). In addition, ODTs should have an acceptable taste and very short disintegration time, generally from few seconds to about a minutes, in the mouth. It is always a challenge to prepare ODTs having short oral disintegration time as it is with positive correlation with the mechanical strength of the tablets (Szakonyi *et al*., 2013).

Indomethacin belongs to non-steroidal anti-inflammatory drug class, which is used to reduce fever, pain and inflammation associated with musculo-skeletal and joint disorders including ankylosing spondolysis, rheumatoid arthritis, osteoarthitis and acute gout (Shen, 1982, Kulmacz, 1989, Nunchanit *et al*., 2013). It is described as Class II (poorly aqueous solubility and high permeability) drug in BCS. So, it is proposed to develop ODT dosage form of indomethacin to increase its solubility and subsequently bioavailability.

In the present investigation FDTs of IM were prepared by direct compression method using two approaches namely; super-disintegration and effervescence. The physico-chemical properties of the particular disintegrants determine the disintegration mechanism followed by the disintegration time (Douroumis, 2007). The super-disintegrants used were Primogel, Kollidon and Ac-di-sol. In case of effervescence approach, sodium bicarbonate and citric acid were incorporated in tablet formulation as effervescent ingredients. Various powder mixtures underwent various pre-compression tests such as FT-IR studies, bulk and tapped density, angle of repose, Carr's index and Hausner ratio. The prepared tablets were evaluated for various physical parameters and in-vitro disintegration and dissolution tests.

MATERIAL AND METHODS

Indomethacin, Cross-carmellose sodium (Ac-di-sol), Cross-povidone (Kollidon) and Aerosil were suppied by Yarrow Chem Products, Mumbai. Lactose monohydrate, mannitol, menthol, magnesium stearate and sodium saccharin obtained from LOBA Chemie PVt. Ltd., Mumbai. Sodium starch glycolate (Primogel) and microcrystalline cellulose (Avicel PH101) were purchased from CDH, New Delhi. All other chemicals used throughout the research were of analytical grades.

Preparation of tablets

Fast dissolving tablets of IM were prepared by direct compression technique using two different approaches such as super-disintegration and effervescence and also a formulation containing their combination. The formulae for all batches are represented in table I. Indomethacin dose was 150mg and the total weight of tablet was fixed at 350mg. Avicel PH102 and mannitol were used as directly compressible material and diluent, respectively. Mentioned quantities of drug and other ingredients were weighed accurately and passed through mesh no # 60 before mixing. All the above ingredients were transferred to mortar and mixed thoroughly for 15 minutes except magnesium stearate, which was added and mixed for 5min before compression by spatulation method. The above powder mixture were compressed into tablets using ten station minipress punching machine (Rimek Compression Machine) equipped with flatefaced 9.0mm punch. For tablets prepared by effervescent technique, sodium bicarbonate and citric acid were accurately weighed and preheated to 80ºC to obtain a constant weight before mixing with other ingredients (Kadria *et al*., 2013).

Drug–Excipient Interaction Study

Drug-excipient interaction study was carried out by FT-IR technique (FTIR-1700, Shimadzu, Kyoto, Japan) in order to determine the interaction of IM with the excipient used in the formulations. The pure drug and the physical mixture (1:1) of drug with MCC, Primogel, Kollidon and Ac-di-sol were scanned in KBr discs in the range of 4000–400 cm^{-1}.

Table I. Formulation of fast dissolving tablets of Indomethacin

Formulation/ Ingredients	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9	IF10	IF11
Indomethacin	150	150	150	150	150	150	150	150	150	150	150
MCC	120	120	120	120	120	120	120	120	120	120	120
Mannitol	53	59	45	53	59	45	53	59	45	12	---
Primogel	4	8	12	----	----	----	----	----	----	---	---
Kollidon	----	----	----	4	8	12	----	----	----	---	---
Ac-di-sol	----	----	----	----	----	----	4	8	12	---	12
Sodium bicarbonate	---	---	----	---	---	---	---	---	---	25	25
Citric acid	---	---	---	---	---	---	---	---	---	20	20
Aerosil	4	4	4	4	4	4	4	4	4	4	4
Sod. saccharin	10	10	10	10	10	10	10	10	10	10	10
Mag. stearate	4	4	4	4	4	4	4	4	4	4	4
Menthol	5	5	5	5	5	5	5	5	5	5	5

* Total weight of tablet = 350 mg

Micromeritics study

Bulk density and Tapped density

Bulk density determined by filling fixed amount (10gm) of powder blends into a volumetric flask (50mL) followed by recording its volume. Tapped density was determined in a graduated measuring cylinder after subjecting to 100 taps fixed over a digital tapped density apparatus (Electrolab-ETP-1020) (Peppas *et al.*, 1985).

Angle of repose

Angle of repose of powder blends were measured by fixed height cone method or funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the tip of the heap of the powder blends (4cm). Accurately weight amount of powder mixtures were taken in the above funnel and allowed to flow through the funnel freely. The height and radius were measured and the angle of repose were calculated (Cooper *et al.*, 1986)

Carr's index and Hausner ratio

Compressibility index and Hausner ratio for all powder blends were determined by following equations (Wells, 2002)

$$\text{Carr's index (\%)} = \frac{\mathbf{TBD\text{-}LBD}}{\mathbf{TBD}} 100\%$$

$$\text{Hausner ratio (\%)} = \frac{\mathbf{TBD}}{\mathbf{LBD}} 100\%$$

Post-compression parameters (Goto *et al.*, 2004, Wu *et al.*, 2009)

Dimension

Thickness and diameter were measured for five tablets by using Vernier calipers and the average was expressed in mm.

Weight uniformity

Twenty tablets were weighed individually using electronic balance (Shimadzu Corporation-BL-220H) and then the average tablet weight was calculated. The percentage variation of each tablet from the average tablet weight was determined.

Hardness

Hardness was determined by randomly taking 10 tablets from each batch, using Monsanto hardness tester (Electrolab Pvt. Ltd., India) and the average diametric compression force (Kg/cm^2) to crush the tablets were determined.

Friability

The friability of a sample of 10 tablets was measured using Roche friabilator (Electro lab, EF-2, Mumbai, India). The weight of 10 tablets was recorded and was placed in drum of a Roche Friabilator, which was run at 25rpm

for 4min. Tablets were reweighed after dedusting and the percentage of friability was determined.

Disintegration

Disintegration test was carried out by using disintegration apparatus (ED-2L Electrolab). One tablet was placed in each of the six tubes of the basket assembly and was dipped in phosphate buffer pH 6.8 maintained at 37±1°C. The time in seconds taken for complete disintegration of tablets were recorded.

Drug content

Five tablets were taken and crushed in mortar. From this the amount of powder equivalent to 25mg of IM was transferred in to a conical flask containing 25ml of methanol. The absorbance was measured at 320nm after suitable dilution.

Wetting time and Water absorption ratio

The method used a piece of tissue paper folded twice was placed in a petri dish with a 10cm diameter containing 10 ml of phosphate buffer pH 6.8. A tablet was placed on the tissue paper and the time required for complete wetting was recorded (Tejvir *et al*., 2011). Three trials for each batch were performed. Water absorption ratio was calculated employing following equation;

$$WA = \frac{(Wa - Wb)}{Wb} \times 100$$

Where, Wa and Wb are the weight after and before water absorption, respectively

Dispersion

Uniformity of dispersion was performed to determine the dispersion of the drug in the water uniformly. Two tablets were placed in 100mL of water in a 250mL beaker and were stirred uniformly for a minute and then the solution was passes through the 710µm mesh or sieve no 22 # see that whether all the contents of the mixture pass through the sieve without leaving a residue on the mesh (Indian Pharmacopeia, 2010).

In-vitro dissolution studies

Dissolution test for prepared FDTs of IM were performed using USP type II apparatus (Electrolab TDT-08L, Mumbai). Phosphate buffer pH 6.8 (900ml) maintain at 37±0.5°C was used as dissolution medium and the rotational speed of paddle was kept at 50 rpm. Five milliliter of aliquots were withdrawn at 5, 10, 15, 30 and 60min and replaced with fresh dissolution media maintained at same temperature. The samples were passed through membrane filter (pore size, 0.45µm) and assayed immediately for IM content by UV spectrophotometer at 320nm (UV-1800, Shimadzu, Japan). This test was performed on 6 tablets and mean ± SD calculated.

Statistical analysis

One way analysis of variance (One-way ANOVA) with student Newman Keuls multiple comparison tests was used to perform statistical significant differences between various *in vitro* drug release data at 95% confidential level (5% significance level). It was carried out employing 30 days trial version of GraphPad Instat software.

Stability studies

Short-term stability study was performed on the promising formulation (IF11) for a period of 3 months at accelerated condition (40°± 2° C/ 75±5% RH). Fixed number of tablets (25) were packed in amber colored rubber stoppered vials and placed in stability chamber (JRIC 11, Osworld, Mumbai) maintained at above condition. At intervals of 1 month, the tablets were visually examined for any physical changes; changes in drug content and at the end of three months, tablets were withdrawn and evaluated for *in vitro* drug release (Swamy *et al*., 2011).

RESULT AND DISCUSSIONS

Fast dissolving tablets of IM were prepared by direct compression technique, which is said to be most simple, less time consuming and economical. Two approaches such as super-disintegration and effervescence were employed for fast dissolving of tablets. Mannitol was incorporated into tablet formulation for multiple purposes such as cooling effect due to negative heat of solution, non-hygroscopic, good aqueous solubility and pleasant feeling in the mouth (Banker *et al*., 1987).

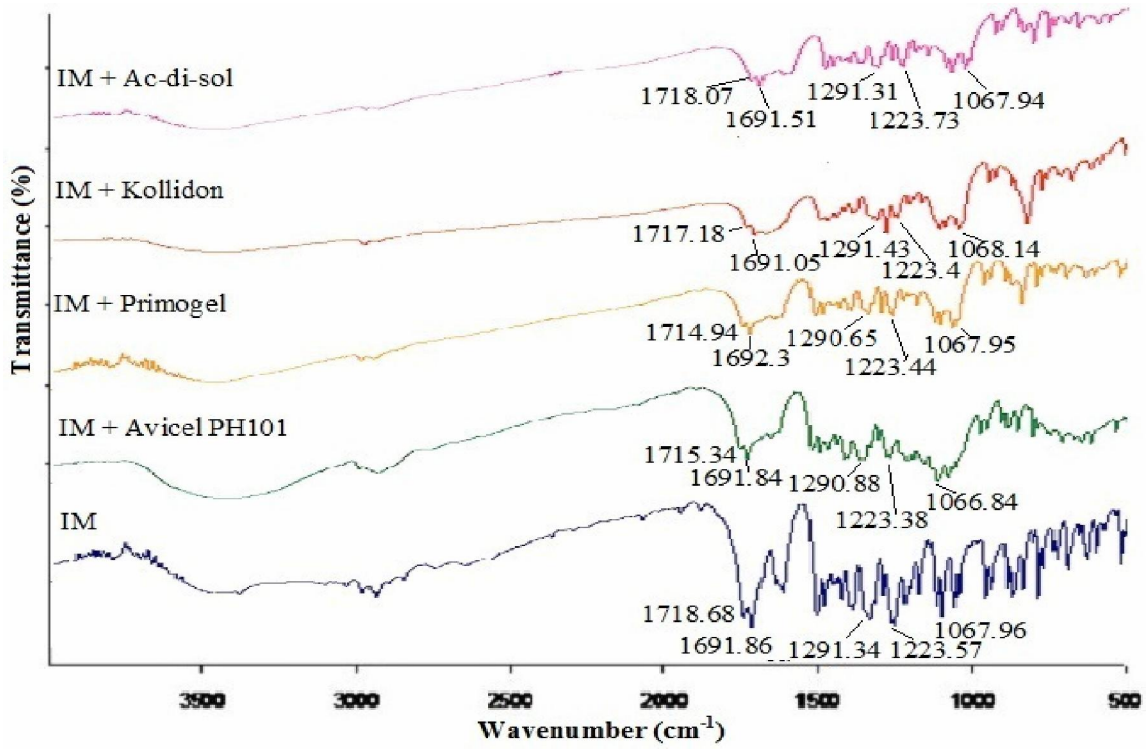

Figure 1. FT-IR spectra of pure drug and drug with Avicel, Primogel, Kollidon and Ac-di-sol.

Table II Physical Characteristics of powders of all the formulations of IM

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Carrs index	Angle of repose (θ)	Hausner ratio
IF1	0.57±0.90	0.84±0.78	14.65±0.43	28.94±0.74	1.48±0.67
IF2	0.55±0.67	0.85±0.65	17.53±0.70	27.94±0.36	1.48±0.87
IF3	0.54±0.67	0.84±0.89	15.92±0.13	26.14±0.65	1.45±0.25
IF4	0.57±0.21	0.85±0.56	16.46±0.31	29.94±0.73	1.46±0.19
IF5	0.52±0.26	0.85±0.16	12.67±0.54	27.94±0.37	1.48±0.11
IF6	0.57±0.29	0.84±0.76	15.09±0.78	26.14±0.62	1.45±0.04
IF7	0.54±0.22	0.84±0.55	12.50±0.66	25.14±0.40	1.47±0.94
IF8	0.51±0.35	0.84±0.52	15.56±0.52	26.19±0.56	1.48±0.33
IF9	0.53±0.54	0.85±0.68	14.24±0.66	24.94±0.24	1.47±0.78
IF10	0.51±0.35	0.81±0.52	15.56±0.52	27.39±0.56	1.41±0.53
IF11	0.51±0.54	0.88±0.68	13.73±0.36	25.54±0.27	1.37±0.73

Drug-excipient interaction study

FT-IR spectra of pure IM, IM with Avicel, Primogel, Kollidon and Ac-di-sol were determined by KBr disc method and are presented in figure 1. The characteristic peaks of IM were at 1067.96cm^{-1}, 1223.57cm^{-1}, 1291.34cm^{-1}, 1691.86cm^{-1} and 1718.68cm^{-1}. There was no such significant shift in the position of major peaks in the above physical mixtures indicating that no chemical reaction or interaction between the drug and excipient took place.

Table III. Comparison of physical parameters of all the of tablet formulations

No	A	B	C	D	E	F	G	H	I	J
IF1	348±0.45	3.2±0.67	5.84±0.77	9.0	0.40	92	98.63±0.99	58	16.9	passes
IF2	348±0.56	3.1±0.86	5.85±1.76	9.0	0.54	69	97.53±0.59	46	31.5	Passes
IF3	347±0.76	3.1±0.65	5.85±1.00	9.0	0.66	56	97.33±0.78	25	59.5	Passes
IF4	348±1.20	3.2±0.34	5.84±0.76	9.0	0.40	83	98.44±0.43	42	34.1	Passes
IF5	348±0.65	3.0±0.56	5.84±0.87	9.0	0.17	68	98.16±1.07	31	47.2	Passes
IF6	347±0.67	3.1±0.73	5.86±0.99	9.0	0.55	51	99.72±0.98	18	53.6	Passes
IF7	349±0.98	3.0±1.10	5.85±0.34	9.0	0.20	78	96.47±0.65	35	30.2	Passes
IF8	348±0.52	3.1±0.23	5.85±0.55	9.0	0.18	58	97.65±0.32	27	39.8	Passes
IF9	348±0.56	3.0±0.41	5.84±0.36	9.0	0.22	44	98.21±0.61	19	52.8	Passes
IF10	349±0.46	3.2±0.45	5.84±0.34	9.0	0.24	56	99.43±0.78	23	23.8	Passes
IF11	347±0.88	3.3±1.0	5.85±0.29	9.0	0.28	38	98.87±0.65	17	61.5	Passes

A=Weight (mean±SD, mg) n=20; **B**=Hardness (mean±SD, kg/cm^2) n=10; **C**=Thickness (mean±SD, mm) n=20; **D**=Diameter (mean±SD, mm) n=20; **E**=Diameter (mean±SD, mm) n=20; **F**=Diameter (mean±SD, mm) (n=6); **G**= Drug Content (%)(n=10). ; **H**=Wetting time (sec) (n=6); **I**=Water absorption ratio (n=6); **J**=Uniformity of dispersion (n=2).

Table IV. Comparison of physical parameters for optimized formulation IF11 before, during and after 3 months of stability study

Parameters	IF11 Initial	40^o± 2^{o}C/ 75±5% RH		
		At the end of 1st month	At the end of 2nd month	At the end of 3rd month
Thickness (mm)	5.85±0.29	5.87±0.23	5.88±0.31	5.91±0.04
Diameter (mm)	9.0	9.0	9.07	9.1
Hardness (kg/cm^2)	3.3±1.0	3.2±1.0	3.3±1.0	3.1±1.0
Friability (%)	0.28	0.28	0.29	0.30
Weight Variation (mg)	347±0.88	348±0.27	348±0.09	349±0.7
Content Uniformity	98.87±0.65	98.27±0.12	98.07±0.64	97.77±0.75
Disintegration time	38 sec	35 sec	34 sec	34 sec
In-Vitro release after 60 minutes	99.54 ±2.89	---	---	99.04±1.79

*Mean ± SD, n = 10 (hardness, friability and drug content studies), n = 20 (thickness, diameter and weight variation), n = 6 (disintegration and in-vitro drug release)

Micromeretrics studies

Powder mixtures of all the formulation were evaluated for various physical characteristics and the values were presented in table II. The values of bulk and tapped density are indicative of good packing character. Angle of repose gives qualitative and quantitative assessment of internal cohesive and frictional force. Values for angle of repose for all the formulations were ranged between 24.94±0.24 and 29.94±0.73º, which indicated good flow properties (Martin *et al.,* 2002). Further, Carr's index for all the formulation was found to be below 18 %. This indicates acceptable flow properties (Wells, 2002). Hausner ratio values for all the formulations were ranging from 1.37±0.73 to 1.48±0.87, indicating desirable flow properties. Hence, the prepared blends possessed good flow properties and these can be used to manufacture tablets by direct compression method.

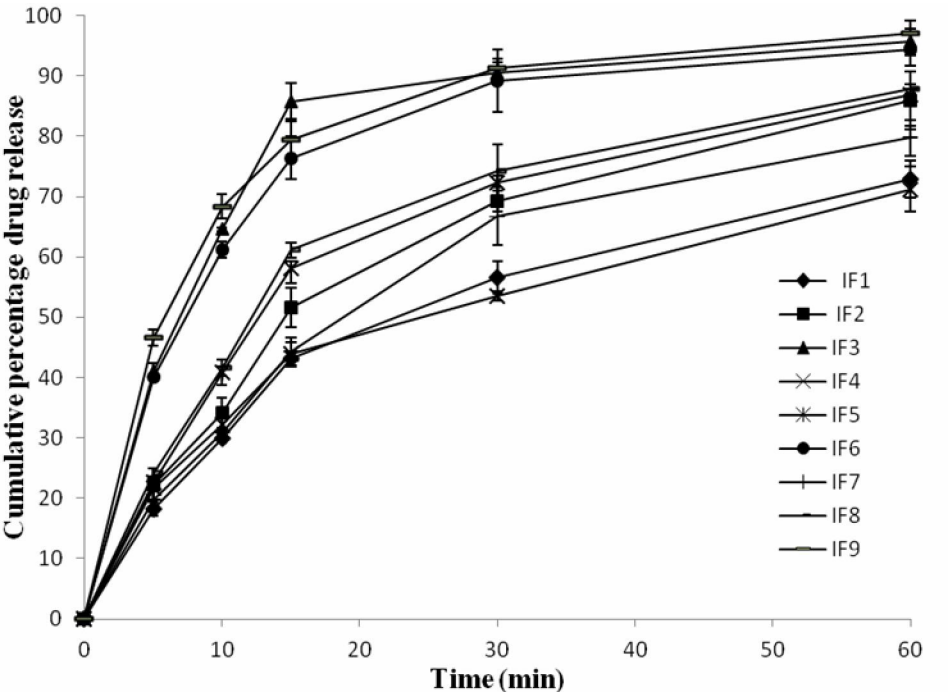

Figure 2. Dissolution profile of formulations from IF1 to IF9 (mean ± SD, n = 6)

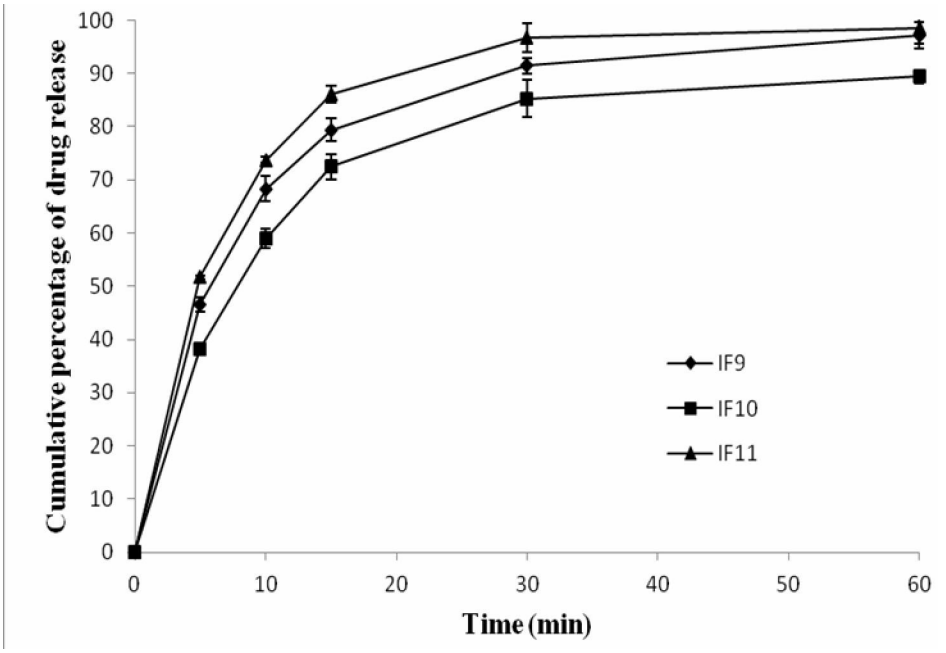

Figure 3. Dissolution profile of formulations from IF9 to IF11 (mean ± SD, n = 6)

Physical parameters of tablets

All the tablet formulations were processed under similar condition to avoid any type of variation in physical tests and the results are given in the table III. The average percentages of weight variation for all the tablet formulations were within the acceptable limit. All the formulation shows uniform diameter and the percentage of thickness deviations were within the limit. Hardness of all the batches of tablets was above 3kg/cm2. Hardness is not an absolute indicator of tablet strength. So, friability was measured by taking 10 tablets in Roche friabilator from each batch and the values demonstrates that the friability of all the batches were within the official limit (≤1%) (Swamy *et al.*, 2011, United States Pharmacopeia, 2009). The hardness and friability values indicate good mechanical strength to withstand handling and transportation. The drug content uniformity of FDTs was between 96.4±0.65 and 99.43±0.78.

The wetting and disintegration time, for formulations contaning Primogel as super-disintegrants, decreases with increase in super-disintegrant amount per tablet from 4mg in IF1 to 12mg in IF3. Same trend was also observed in case of formulations containg Kollidon and Ac-di-sol as super-disintegrants. This was attributed to the fact that more the amount of super-disintegrant higher is the water absorption and swelling, resulting in rapid wetting and disintegration of tablets. The disintegration time for all the batches of tablets were well below the accepted official limit of 3min. The least values for wetting time (17s) and disintegration time (38s) were shown by formulation IF11. This may be due to the combination of super-disintegration and efferevescence approaches. Uniformity of dispersion is performrd to predict how well the tablet is going to disintegrats in mouth without any particulate matter above size 710 nm. All the dveloped tablet batches passed the test.

***In vitro* dissolution studies**

In-vitro dissolution studies of all the FDT formulations were carried out for 60min in USP dissolution apparatus II containing phosphate buffer pH 6.8 and data were represented in Figure 2 & 3. In addition to two approaches namely super-disintegration and effervescence, a combination approach containing both the ingredients was used. The order of increased drug dissolution using above approaches was as follows; combination > super-disintegration > effervescence.

In case of super-disintegration, the cumulative percentage of drug release for formulation IF1-IF9 increases with the increase in super-disintegrants amount from 4mg to 12 mg per tablet. It is based on the fact that higher the concentration of super-disintegrants more rapid is the disintegration followed by drug release. Among different super-disintegrants used Ac-di-sol shown highest percentage of drug release after 60min of dissolution at same concentration followed by Primogel and Kollidon, which is in accordance with Gryczke *et al.*, 2011. This result was attributed to different disintegration mechanisms of selected super-disintegrants. Primogel and Kollidon act by swelling by absorbing water leading to separation of tablet into particles. In case of Ac-di-sol the mechanism of action is wicking via capillary action followed by disruption of the inter-particular matrix bonds resulting in the tablet disintegration (Kottke *et al.*, Be *et al.*, 1999). Formulation IF9 containing 12mg of Ac-di-sol released highest cumulative percentage of drug (97.13±2.09%) at 60min.

For formulation based on effervescence principle, provides a cumulative percentage of drug release of 89.41±1.21% after 1 hr, which was in between the formulations (IF2, IF5 and IF8) containing 8 mg per tablet and formulation (IF3, IF6 and IF9) having 12mg per tablet of different super-disintegrants. Combination of two approaches resulted in increase in dissolution rate. Among all the ODT formulations, IF11 released highest amount of drug release (98.54±2.9%) after 60 min. This could be due to the synergistic effect of Ac-di-sol and CO_2 released as soon as the tablet came in contact with water. This released CO_2 accelerated the disintegration, which was in accordance with wetting and disintegration time (Table 3).

Statistical analysis

One-way ANOVA data showed that there were significant differences of *in vitro* drug release ($P<0.05$ level), when IF9 compared with batches from IF1 to IF8, between the batches

except IF9-IF3 and IF9-IF6. Among IF9-IF11, the significant differences observed between IF9 with IF10 and IF10 with IF11. The former results could be due to different types of super-disintegration and their concentrations and the different approaches may be reason in the later case.

Stability studies

The evaluated physical parameters of formulation IF11 before and at the end of each months and *in vitro* drug release for optimized formulation IF11 before and after 3 months of stability study were presented in Table 4. From the mentioned data it was evident that there was no significant change in thickness, diameter, weight variation, hardness, content uniformity and in-vitro dissolution profile of optimized formulation.

CONCLUSIONS

Fast dissolving tablets of IM were prepared in the present research work to increase its solubility and followed by the bioavailability. Super-disintegration (IF1-IF9), effervescence (IF10) and combination of the both approaches (IF11) were used to develop FDT. It was observed that, among all the super-disintegrants used, formulations having Ac-di-sol showed highest amount of drug release at same concentration as compared to Primogel and Kollidon. The formulation IF10 released less amount of drug when compared to formulation containing super-disintegrants at higher concentration at 60min. Out of all the eleven formulations, IF11 showed highest amount (98.54±2.89) of drug release at the end of 1 hr. There were no significant changes in physical and *in vitro* data obtained after 3 months of stability studies at accelerated condition. *In vivo* studies required to further ascertain its commercial viability.

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