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Research Article

DESIGN AND FORMULATION DEVELOPMENT OF FAST-DISSOLVING TABLETS OF IBUPROFEN USING NOVEL NATURAL SUPERDISINTEGRANT

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ABSTRACT

Objective: The objective of the study was to evaluate *Ocimum gratissimum* mucilage as a novel superdisintegrant in the formulation of fast-dissolving tablets (FDT) of Biopharmaceutical Classification System-II drug (Ibuprofen) employing a 2^3 factorial design.

Methods: *O. gratissimum* mucilage was extracted by seeds and it was subjected to physical, chemical, and micrometric studies were evaluated. To establish FDT of ibuprofen with *O. gratissimum* mucilage as a superdisintegrants in different ratios using direct compression method employing 2^3 factorial design. All the formulation tablets were evaluated pre-compression and post-compression parameters like dissolution efficiency (DE%) percent of drug dissolved at 5 min.

Results: The mucilage was to be found fine, free-flowing crystalline powder, and excellent swelling nature in all suitable solvents and buffers. The Fourier transform infrared and differential scanning calorimetry studies were indicated to no interactions between ibuprofen and *O. gratissimum* mucilage. All the FDT formulated employing novel mucilage shows good quality with regard drug content (98.05±0.31–99.39±0.54), hardness (3.6–4 kg/sq. cm), and friability (0.12–0.15%). The optimized formulation batch shows less disintegrant time (30±0.06). I*n vitro* wetting time was less (i.e., 90 s) in optimized formulation F2. The water absorption ratio of the formulated tablets was found to be in the range of 99±0.56. The cumulative drug dissolved in the optimized formulation F2 was found to be 99% in 10 min.

Conclusion: *O. gratissimum* mucilage was found to be a novel superdisintegrant which enhanced the DE when combined with crospovidone and croscarmellose sodium; hence, it could be used in the formulation of FDT to provide immediate release of the contained drug within 5 min.

Keywords: Optimization, Fast dissolving, Superdisintegrant.

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INTRODUCTION

Oral routes of drug administration have a wide acceptance of up to 50–60% of the total dosage form. Fast-dissolving tablets (FDTs) are solid dosage form containing indicated substances that disintegrate rapidly, usually within few seconds when placed on tongue requiring additional water to facilitate swallowing. FDTs offer great advantages for the patients having difficulty in swallowing. The elderly constitute a major portion of today's population mainly because of the increased life span of individuals. Physiological and neurological conditions, such as dysphasia, a risk of choking, and hand tremors are leading causes of patient non-compliance in the self-administration of conventional solid oral dosage forms [1-3].

FDT formulation provides sufficient strength, quick disintegration/dissolution in the mouth without water, rapid dissolution, and absorption of the drug, which will produce the quick onset of action. Pre-gastric absorption of FDTs can result in improved bioavailability and as a consequence of reduced dose. Various techniques can be used to formulate FDT. Direct compression one of the techniques which need for a particular purpose the inclusion of super disintegrate or highly water-soluble excipients into the formulation to reach fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-liable medication.

The present investigation deals with an attempt of a systematic formulation approach for optimization of ibuprofen FDT employing *Ocimum gratissimum* mucilage, croscarmellose sodium, and crospovidone as superdisintegrants. A 2^3 factorial design was applied to investigation the main and interaction effects of the three formulation variables, i.e., *O gratissimum* mucilage (A), croscarmellose sodium (B), and crospovidone (C) in each case to find the formula with less disintegration time and more dissolution efficiency (DE) 5 min and to permit arbitrary selection of tablets with immediate release of drug within 5 min [4].

MATERIALS AND METHODS

Materials

Ibuprofen pure drug obtained from Yarrow chemicals Mumbai. Mannitol, sodium and croscarmellose sodium were obtained from Yarrow chem. products, Mumbai. Microcrystalline cellulose was bought from Qualigens Fine Chemicals, Mumbai. Talc and magnesium stearate was obtained from Molychem, Mumbai.

Isolation of *O. gratissimum* mucilage (a novel disintegrate)

The seeds of *O. gratissimum* were soaked for 12 h in distilled water and then added to a blender to separate mucilage from seeds. After blending for 15 min, the mass was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding three parts of acetone (75%) to the mucilage. The powder was weighed to calculate the yield after drying at 45°C for 6 h [5].

Characterization of *O. gratissimum* mucilage (a novel disintegrate)

The *O. gratissimum* mucilage prepared was evaluated for the following [6,7].

Solubility

O. gratissimum mucilage solubility was tested in various solvents such as distilled water, aqueous buffers of pH 1, 2, 3, 4, and 6 mentioned in

IP and organic solvents such as alcohol, dichloromethane, chloroform, acetone, and petroleum ether.

pH

The pH of 1% w/v slurry was measured by pH meter.

Melting point

The melting point was determined using melting point apparatus.

Viscosity

The viscosity of 1% dispersion in water was measured using Ostwald viscometer.

Swelling index

Mucilage powder (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index (%) of the material was calculated as follows.

$$SI = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffine}}{\text{Volume of sediment in light liquid paraffine}} \times 100$$

SI = Swelling index

Test for gelling property

Mucilage prepared was evaluated for their gelling property by heating a 7% w/v dispersion of each in the water at 100°C for 30 min.

Particle size

Particle size analysis was done by sieving using standard sieves.

Density

Density (g/cc) was determined by the liquid displacement method using benzene as liquid.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by transferring the accurately weighed amount of sample in 50 ml measuring cylinder, measured the volume of packing and tapped 50 times on a plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula [8].

$$LED = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$TBD = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

LBD = Loose bulk density
TBD = Tapped bulk density

Percentage compressibility index

The percentage compressibility of the powder mixed was determined by Carr's compressibility index calculated by the following formula [9].

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

TBD = Tapped bulk density

Angle of repose

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a mass of powder or granules and the horizontal plane. The angle of repose is calculated [8,9].

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

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

θ = angle of repose; h = height of pile; r = radius of pile.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of mucilage were recorded on samples prepared in potassium bromide (KBr) disks using a FTIR (Tokyo, Japan). The scanning range was 500–4000 cm^{-1}. Samples were mixed with (KBr) to form disks by means of a hydrostatic press at 6–8 tons pressure.

Differential scanning calorimetry (DSC)

DSC therm *O. gratissimum* rams of ibuprofen and their mixtures (1:1) with *O. gratissimum* were recorded on PerkinElmer Thermal Analyzer samples (2–5 mg) were sealed into aluminum pans and scanned at a heating rate of 10°C min^{-1} over a temperature range 30–350°C.

Preparation of ibuprofen FDT

The tablets were prepared by direct compression method employing 2^3 factorial design in which three independent variables

Table 1: Formulae of ibuprofen fast-dissolving tablets employing *Ocimum gratissimum* mucilage

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Ibuprofen	200	200	200	200	200	200	200	200
Ocimum gratissimum	-	25	-	25	-	25	-	25
Croscarmellose sodium	-	-	25	25	-	-	25	25
Crospovidone	-	-	-	-	25	25	25	25
Mannitol	30	55	55	30	55	30	30	5
MCC	250	200	200	200	200	200	200	200
Talc	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10
Total	500	500	500	500	500	500	500	500

MCC: Microcrystalline cellulose

Table 2: Evaluation of physicochemical proprieties for *Ocimum gratissimum* mucilage

Parameters	*Ocimum gratissimum*
Solubility studies Water and all aqueous and organic solvents	Slightly soluble in cold water and hot water, form in viscous colloidal solution and insoluble in all aqueous and organic solvents
pH studies	7.6
Phytochemical tests	Pass
Molisch test	
Ruthenium test	Pass
Iodine test	Fail
Melting point	203°C
Swelling index	100%
Test for gelling property	Particle swelling
Density	0.30 g/cc
Tapped density	0.48 g/cc
Compressibility index	0.309
Hausner's ratios	1.60
Particle size	152 µm
Angle of repose	25°

*SD standard deviation from mean, n=3

(superdisintegrants, i.e., *O. gratissimum* [A], croscarmellose sodium [B], and crospovidone [C]) and one dependent variable (DE in 5 min) were selected. The composition of formulation is shown in Table 1 for *O. gratissimum* (A), the lower level, i.e., 0% concentration and upper level, i.e., 5% concentration. For croscarmellose sodium (B) and crospovidone (C), the lower level is zero concentration and higher level, i.e., 5% concentration. For uniformity in particle size, each ingredient was passed through # 100 mesh sized screen before mixing. *O. gratissimum*, croscarmellose sodium, crospovidone, mannitol, and microcrystalline cellulose were accurately weighed and mixed using mortar and pestle, and the added to ibuprofen. Finally, talc and magnesium stearate was added to the powder mixture [10,11].

Evaluation of ibuprofen FDT

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto Hardness Tester and expressed in kg/cm^2 [12,13].

Uniformity of weight

Weight variation test was done with 20 tablets. It is the individual variation of the tablet weighed from the average weight of 20 tablets.

Friability

The friability of tablets was measured using a Roche friabilator. Tablets were rotated at 25 rpm for 4 min or up to 100 revolutions. The tablets were then reweighed after removal of fines, and the percentage of weight loss was calculated [14].

$$F = \frac{100 \times W(\text{initial}) - W(\text{final})}{W(\text{initial})}$$

Drug content uniformity

For content uniformity, ten tablets were weighed and powdered a quantity of powder equivalent to 10 mg of ibuprofen was extracted into pH 1.2 HCL buffer and filtered. The ibuprofen content was determined by measuring the absorbance spectrophotometrically at 205 nm after appropriate dilution with pH 1.2 HCL buffer. The drug content was calculated as an average of three determinations [15].

Wetting time

The wetting time of tablets was measured by placing five circular tissue papers in a Petri dish of 0.10 m in diameter. 10 ml of water containing a water-soluble dye (amaranth) was added to the Petri dish. A tablet was carefully placed on the tissue paper. The time required for water to reach the upper surface of the tablet was noted as wetting time [16].

Water absorption ratio

A piece of tissue paper folded was kept in a small Petri dish to which 6 ml of water was added. A tablet was kept on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ration R was determined using the following equation [17-19].

$$R = \frac{100\ (Wd - We)}{We}$$

Where,
Wd = Tablet weight after water absorption
We = Tablet weight before water absorption

***In vitro* disintegration time**

Disintegration time for FDTs was determined using United States Pharmacopeia (USP) disintegration apparatus 0.1 N HCl buffer. The volume of medium was 900 ml and the temperature was 37±0.2°C. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured [19].

***In vitro* dissolution studies**

In vitro dissolution rate study of ibuprofen FDT was performed using eight-stage dissolution test apparatus (lab India) fitted with paddles (50 rpm) at 37±0.5°C, using pH 7.2 phosphate buffer (900 ml) as a dissolution media. At the predetermined time intervals, 5 ml samples were withdrawn, filtered through a 0.45 µ membrane filter, diluted, and assayed at 221 nm using an analytical technology *O. gratissimum* Eli co SL 218 Ultraviolet/visible double beam spectrophotometer. The cumulative percentage release was calculated using standard absorbance from the calibration curve. All the dissolution experiments were conducted in triplicate (n=3) [20,21].

RESULTS AND DISCUSSION

The isolation of *O. gratissimum* mucilage was found to be fine, free-flowing good swallowing powder. The physical and micrometric properties of the *O. gratissimum* mucilage are summarized in Table 2. It was insoluble in aqueous solvents and insoluble in organic solvents tested (methanol, petroleum ether, dichloromethane, and chloroform). The pH of 0.1% aqueous dispersion was found to be 7.62±0.001.

O. gratissimum mucilage exhibited good swelling in water. The swelling index was found to be 100%±0.003%, indicating that it is suitable for superdisintegrant. All micrometric properties indicated good flow properties needed manufacturing tablets. The density of *O. gratissimum* mucilage was found to be 0.3012±0.0004 g/cc. The angle of repose and compressibility index showed good flow properties of *O. gratissimum* mucilage.

The FTIR spectrum of *O. gratissimum* mucilage is shown in Figs. 1-4. The presence of peaks absorption at 1434.10 cm^{-1} characteristic peak of ester, so from FTIR studies, it was concluded that *O. gratissimum* mucilage (ester) was formed when mucilage was allowed to react with formic acid. The DSC studies are shown in Fig. 4 of *O. gratissimum* mucilage showed characteristic peaks, which indicates that the structure is slightly crystalline. As the *O. gratissimum* mucilage was slightly fine powder and it had got all the characteristics of superdisintegrants, it was concluded that *O. gratissimum* mucilage can be used as novel superdisintegrant in the formulation of FDT.

Table 3: Physical properties: Hardness, friability drug content of ibuprofen fast-dissolving tablets prepared by direct compression method involving mannitol as a diluents

Formulation	Hardness (kg/cm^2) n±SD	Friability (%) n±SD	Drug Content (mg/tab) n±SD	Disintegration Time (s) n±SD	Water absorption ratio (%) n±SD (%)
F1	3.6±0.04	0.14±0.021	98.05±0.31	1648±0.02	20±0.01
F2	3.5±0.06	0.13±0.019	99.85±0.65	30±0.06	99±0.56
F3	3.7±0.07	0.14±0.016	99.23±0.58	37±0.08	71±0.37
F4	3.7±0.02	0.12±0.013	98.94±0.61	43±0.09	79±0.94
F5	3.9±0.06	0.12±0.015	99.46±0.89	41±0.08	68±0.61
F6	3.8±0.03	0.13±0.024	98.04±0.18	39±0.04	86±0.38
F7	3.9±0.07	0.13±0.028	98.61±0.35	36±0.26	79±0.96
F8	3.6±0.05	0.13±0.034	99.39±0.54	29±0.57	100±0.21

SD Standard Deviation from mean, n=3

Table 4: ANOVA of percentage dissolved in 5 min of ibuprofen fast-dissolving tablets formulated employing *Ocimum gratissimum*

Source of variation	d.f	S.S	M.S.S	Variance ratio	Result
Replicates	2	0.02	0.01	0.5	p>0.05
Treatments	7	3475.21	496.75	2408.5	p<0.05
O. gratissimum (A)	1	3325.20	3325.20	2408.5	p<0.05
Crospovidone (B)	1	178.25	178.25	2473.72	p<0.05
O. gratissimum+crospovidone (AB)	1	435.67	435.67	3378.99	p<0.05
Croscarmellose sodium (C)	1	1448.58	1448.58	2837.7	p<0.05
O. gratissimum+croscarmellose sodium (AC)	1	854.26	854.26	2924.1	p<0.05
Crospovidone+croscarmellose sodium (BC)	1	1.28	1.28	3474.56	p<0.05
O. gratissimum+crospovidone+croscarmellose sodium (ABC)	1	450.25	450.25	3353.7	p<0.05
Error	14		0.02	-	-
Total	23	-	-	-	-

*SD: Standard deviation from mean, n=3, p<0.05 indicates significance; p>0.05 indicates non-significance, d.f: Degree of freedom *S.S: Sum of square *M.S.S: Mean Sum of Squares, ANOVA: Analysis of variance. *O. gratissimum*: *Ocimum gratissimum*

Table 5: ANOVA of percentage of water absorption ibuprofen fast-dissolving tablets formulated employing *O. gratissimum*

Source of variation	d.f	S.S	M.S.S	Variance ratio	Result
Replicates	2	0.02	0.01	0.5	p>0.05
Treatments	7	4132.0	590.29	2408.5	p<0.05
O. gratissimum (A)	1	8.02	8.02	2408.5	p<0.05
Crospovidone (B)	1	72.56	72.56	2473.72	p<0.05
O. gratissimum+Crospovidone (AB)	1	338.25	338.25	3378.99	p<0.05
Croscarmellose sodium (C)	1	760.35	760.35	2837.7	p<0.05
O. gratissimum+Croscarmellose sodium (AC)	1	12.50	12.50	2924.1	p<0.05
Crospovidone+Croscarmellose sodium (BC)	1	1200.50	1200.50	3474.56	p<0.05
O. gratissimum+Crospovidone+Croscarmellose sodium (ABC)	1	1740.25	1740.25	3353.7	p<0.05
Error	14		0.02	-	-
Total	23	-	-	-	-

*SD: Standard deviation from mean, n=3, p<0.05 indicates significance; p>0.05 indicates non-significance, d.f: Degree of freedom *S.S: Sum of square *M.S.S: Mean Sum of Squares, ANOVA: Analysis of variance. *O. gratissimum*: *Ocimum gratissimum*

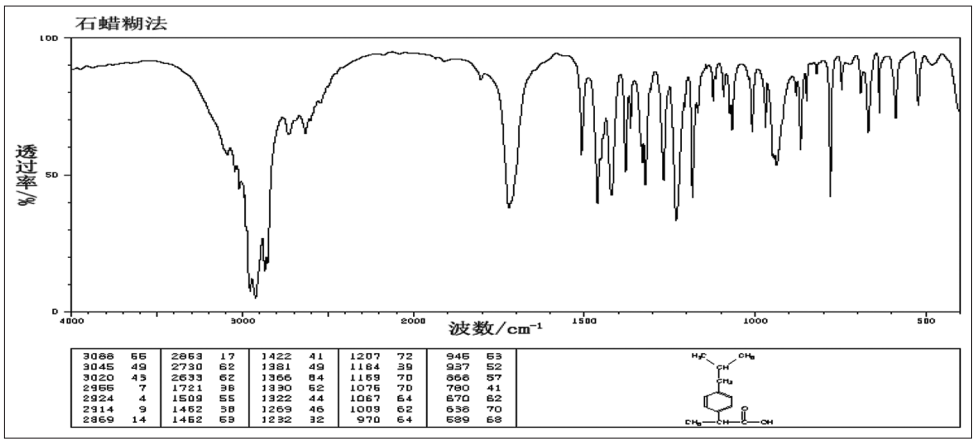

Fig. 1: Fourier transform infrared pure ibuprofen

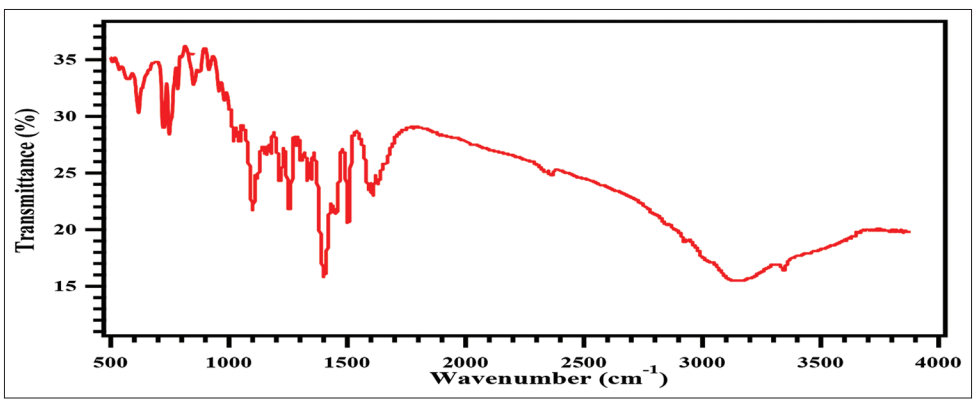

Fig. 2: Fourier transform infrared pure mucilage

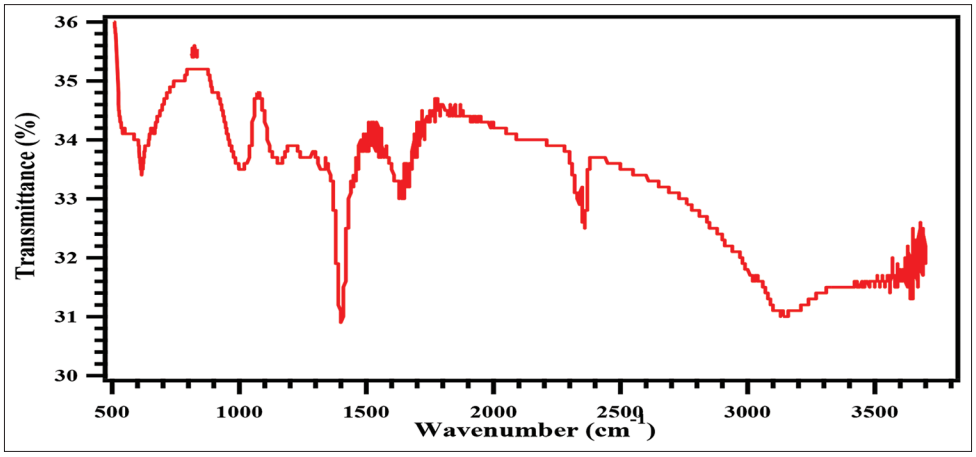

Fig. 3: Fourier transform infrared ibuprofen and mucilage

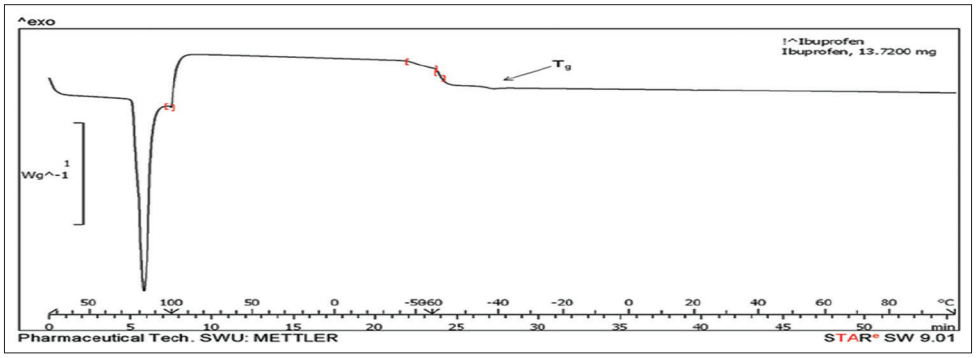

Fig. 4: Differential scanning calorimetry thermogram of mucilage and pure drug

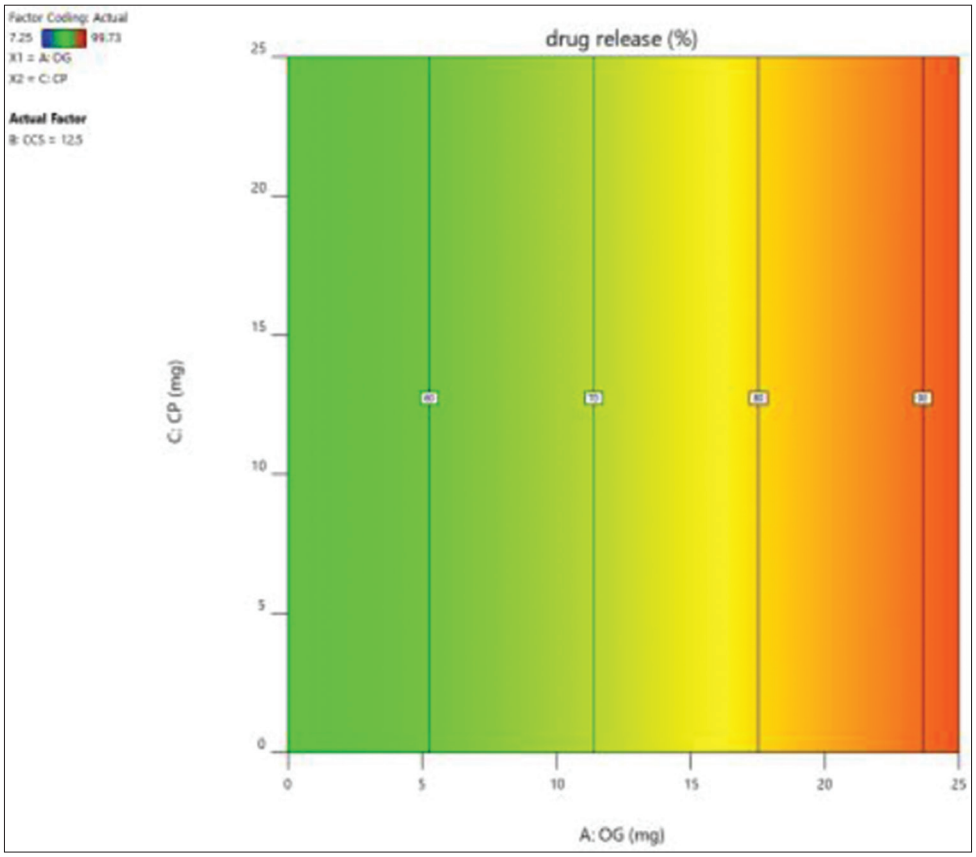

Fig. 5: Contour plot graph for with *Ocimum gratissimum*

Evaluation of tablets

Hardness

The hardness of tablets from all batches was found to be in the range of 3.5±0.06 kg/cm^2–3.9±0.07kg/cm^2. All tablets were found hard enough so that they could easily withstand the handling and storage conditions without getting broken.

Friability

All the tablets exhibited acceptable friability, as none of the tested batches showed percentage friability that exceeded 1%. The percent friability of all batches found in the range of 0.09%–0.19%, indicating good mechanical resistance of tablets. Thus, it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage, and manufacturing processes.

Drug content

The drug content of all the formulation batches was found to be between 98.05±0.31 and 99.39±0.54. Hence, it can be concluded that all the formulations are having an accurate amount of drug distributed uniformly in powder mass and followed acceptable limits as per IP [14], i.e., 85–115% of average content (Table 3).

Disintegration studies

In vitro disintegration time was done by the USP disintegration apparatus. The disintegration rate has a correlation with the water absorption capacity of disintegrate and the *in vitro* disintegration time was found between 1648±0.02 and 29±0.57 s. The outcomes were tabulated and data demonstrated in Table 3. All the formulation showed disintegration time of <240 s. It was found that the formulation F8 will show least disintegration time 30 s as compared to other formulation. The order for a disintegration time in the FDT was found to be F8<F2<F7<F6<F3<F5<F4<F1. The order of disintegration time may be due to the interaction and main effects of the super disintegrants used in the FDT.

Water absorption ratio and wetting time

The water absorption ratio founded from 20±0.01 to 100±0.21 s. This increased behavior due to the water taking the ability of superdisintegrants. The wetting time found was tabulated and data demonstrated in Table 3 and Figs. 5 and 6. It was found that the formulation F2 containing 5% mucilage and 5% croscarmellose sodium showed less wetting time, i.e., 30±0.39 s as compared to other formulations.

***In vitro* dissolution studies**

Dissolution rate depends on the wetting time of the disintegrant; among all the formulations, F8 has less wetting time and has greater dissolution rate, and then this is the other conformance test for correct selection of desirable. *In vitro* dissolution studies of all the formulation were done and depicted in Fig. 7. In all formulations, F8 formulation was selected as the promising formulation containing

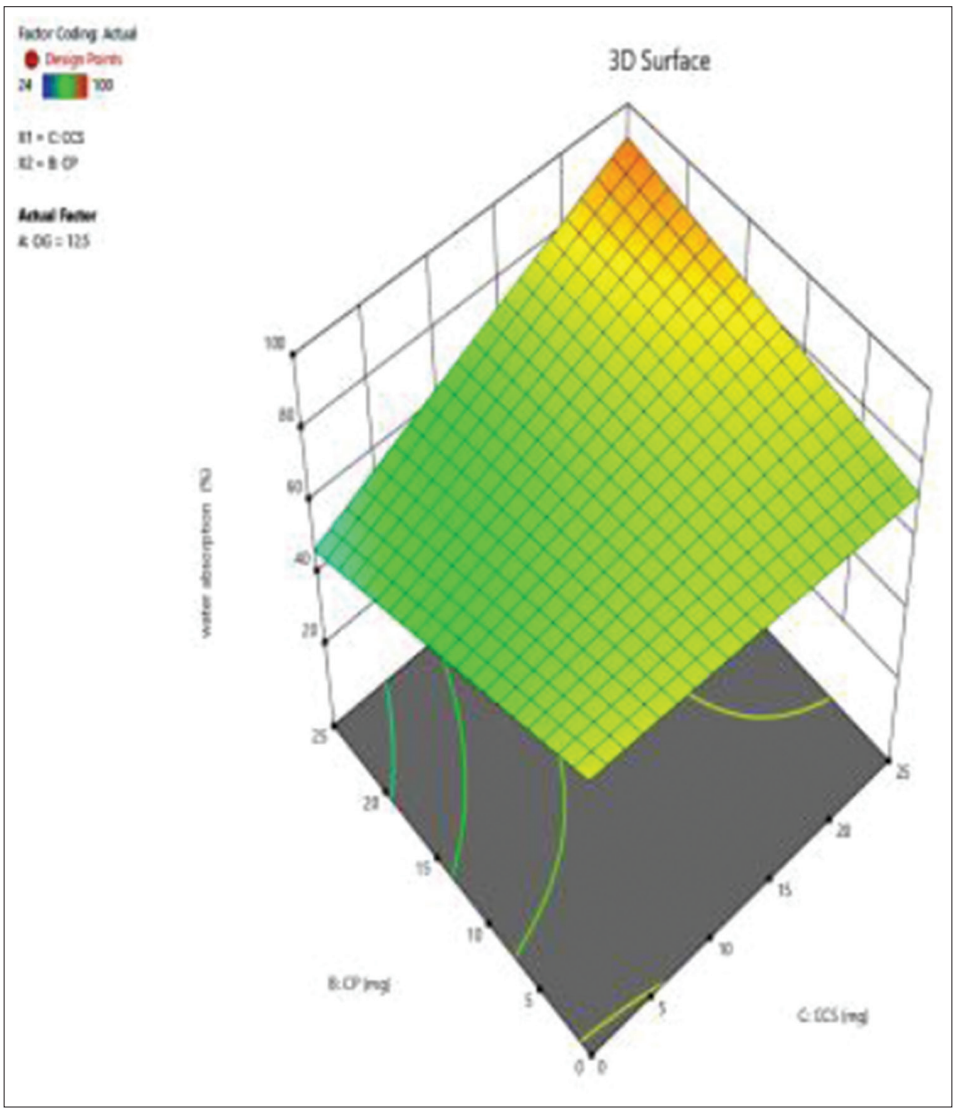

Fig. 6: Three dimensional graph for optimized formulation (F2)

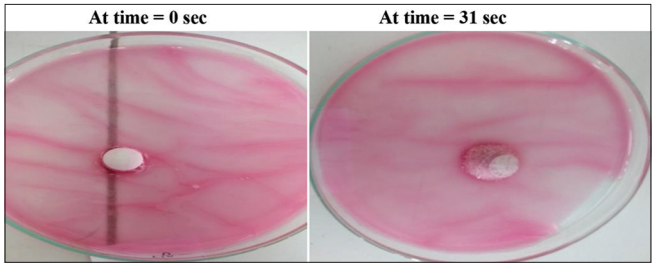

Fig. 7: Optimized formulation (F2) of ibuprofen fast-dissolving tablet

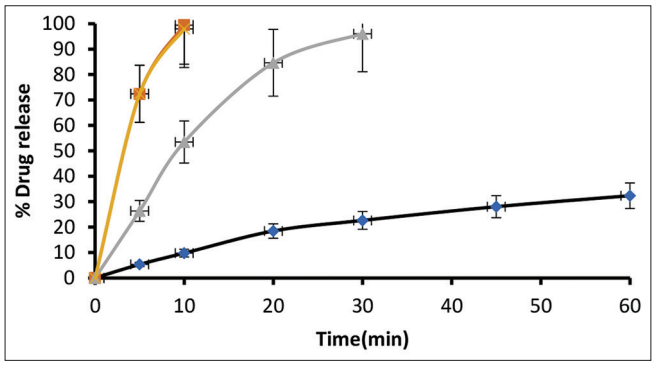

Fig. 8: Dissolution profiles of ibuprofen fast dissolving tablets prepared employing Ocimum gratissimum involving Mannitol as a diluents (F1-F4)

5% *O. gratissimum*, 5% crospovidone, and 5% croscarmellose sodium with 99.15% release in 10 min which may be due to the interaction effect between the two super disintegrates, i.e., *O. gratissimum*, crospovidone, and croscarmellose sodium at a concentration of 5% each. The dissolution parameters of the formulation from F1 to F8, which were made by direct compression method are shown in Table 1. In all these cases, the percent dissolved in 5 minute (PD5) was more in F8, which consists of 5% *O. gratissimum*, 5% crospovidone, and 5% croscarmellose sodium. The same was in the case of DE5 % (DE in 5 min). The PD5 and DE5 % revels that *O. gratissimum* was effective at 5%, crospovidone at 5% along with 5% croscarmellose sodium when the formulations were made by direct compression using these superdisintegrants. From the results, it was concluded that *O. gratissimum* (new super disintegrate) could be used as a superdisintegrant in the formulation of FDT of ibuprofen. To evaluate the individual and combined effects of the three factors involved, FDTs were formulated employing selected combinations of the factors as per 2^3 factorial design. The FDTs and release parameters (percent drug released in 5 min) of the fast-dissolving formulated were analyzed as per the analysis of variance (ANOVA) of 2^3 factorial design. ANOVA of percentage dissolved in 5 min (Table 4), ANOVA of water absorption (Table 5), indicated that the individual effects of *O. gratissimum* (A), crospovidone (B), and croscarmellose sodium (C) as well as the combined effects of AB, AC, BC, and ABC factors, were significant ($p<0.05$) on percentage dissolved in 5 min, wetting time, water absorption ratio, and DE in 5 min of ibuprofen FDT.

FDT formulated employing *O. gratissimum* (5%), crospovidone (5%), and croscarmellose sodium (5%) as superdisintegrants exhibited in percentage dissolved in 5 min, wetting time, water absorption ratio, and DE in 5 min. Formulation F2 gave release of 99.15% in 10 min fulfilling the official specification, based on percentage dissolved in 5 min, wetting time, water absorption ratio, and DE in 5 min. Formulation F2 is considered a good FDT formulations of ibuprofen, which was found to better than the ibuprofen FDT (Figs. 8 and 9).

Overall, natural novel mucilage was found to be a superdisintegrant which enhanced the DE when combined with crospovidone and

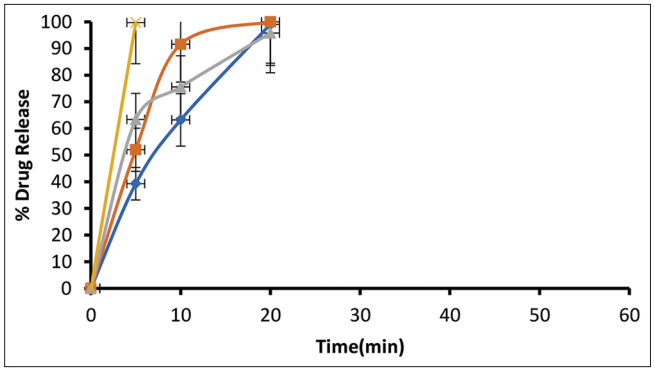

Fig. 9: Dissolution profiles of ibuprofen fast dissolving tablets prepared employing Ocimum gratissimum involving Mannitol as a diluents (F5-F8)

croscarmellose sodium, with the ibuprofen and hence it could be used in the formulation of FDT to provide immediate release of the contained drug within 1 min.

CONCLUSION

FDTs of ibuprofen were formulated and optimized using 2^3 factorial design. Three independent variables, that is, amount of X_1 – amount of *O. gratissimum*, X_2 – croscarmellose sodium, and X_3 – crospovidone at three levels were selected on the basis of preliminary studies. The addition of superdisintegrant *O. gratissimum* mucilage leads to significant effect on disintegration characteristics as well as drug release. However, higher concentrations of mucilage had negative impact on drug release and disintegration. Addition of croscarmellose sodium and crospovidone leads to improved dissolution characteristics, not much affecting 10 International Scholarly Research Notices (ISRN) pharmaceutics disintegration time but higher concentration of *O. gratissimum* drug disintegration and drug release. The porous nature of tablets with swelling and wicking characteristics of mucilage along with increased drug solubility by ocimum gratissimum in combination lead to maximum drug release from fast dissolving tablets. The Design-Expert Software was used to optimize, and response surface plots and contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. Polynomial mathematical models, generated for various response variables using multiple regression analysis, were found to be statistically significant ($p<0.05$). Formulation F2 was selected by the Design-Expert Software which exhibited water absorption (97%), and *in vitro* drug release (100%) within 10 min.

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AUTHOR'S CONTRIBUTIONS

Dr. A. Bharathi the guarantor of this study has designed and supervised the experimental process. Mr. D. Chandra Sekhar Naik has carried out the experiments and analyzed the results. Dr M. V. Basaveswara Raohas contributed to preparation and revision of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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