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Research Article

Designing fabrication and evaluation of Oral fast Disintegrating tablet of Ranitidine HCL

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ABSTRACT

The aim of this research work was to design develop & evaluate oral fast disintegrating tablets of Ranitidine HCL. The Orodispersible tablets of Ranitidine HCL were prepared by using direct Compression technique with a Synthetic Superdisintegrant such as Croscopovidone and a natural Superdisintegrant Fenugreek gum in different concentration. 3^2 factorial designs was applied to study the effect of independent variables, concentration of Croscopovidone & Fenugreek gum on dependent variables like Cumulative % Drug release and Disintegration time by using design expert software. Prepared oral fast disintegrating tablets evaluated for Pre and Post-compression parameters. The prepared tablets exhibited satisfactory physico-chemical characterise especially fast disintegration & dissolution property. Full factorial design and optimization technique successfully used in the development oral fast disintegrating tablets. Comparing the all the formulations, formulation F9 was considered as optimized formulation which shows excellent fast disintegration, in vitro dissolution, and faster drug release within 6 min in comparison to other batches also stable in stability study.

Keywords: Fast disintegrating, Ranitidine, Croscopovidone, Gum, Optimizations, Water absorption ratio**Article Info:** Received 10 Nov 2018; Review Completed 20 Dec 2018; Accepted 02 Jan 2019; Available online 15 Jan 2019

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INTRODUCTION

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing. The difficulty is experienced in particular conventional tablet dosage form by pediatric and geriatric patients, bedridden patient and to those active working patients who are busy or traveling, especially those who have no access to water¹.

For the past three decades, there has been an enhanced demand for more patient compliant dosage form. As a result, the demand for their technologies increasing two to three folds annually¹.

Recent developments in technologies have come out with mouth dissolving tablets that can be ingested simply by placing them on the tongue. An orally fast disintegrating tablet is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste^{3,4}.

Orally fast disintegrating tablets is also known as orally mouth dissolving tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet. Fast disintegrating dosage form has been successfully commercialized and the growing importance was highlighted recently when the European Pharmacopoeia

adapted the term 'Orodispersible Tablets' as a tablet to be placed in the mouth where it disperses rapidly before swallowing⁴. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute^{5,6,7}.

USFDA defined OD tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term "Oro Dispersible tablet" as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing. These dosage forms dissolve or disintegrate in the patient's mouth within 15 seconds to 3 minutes without the need of water or chewing. Despite various terminologies used, Oro-Dispersible tablets are here to offer unique form of drug delivery with many advantages over the conventional oral solid dosage forms^{8,9,10}.

Ranitidine HCL is a used for the maintenance treatment of acidity. It is usually administered orally. With oral administration, the mean half-life of Ranitidine HCL is 2.7-5.5 hours. It is rapidly absorbed following oral administration (bioavailability is 64%), metabolize in liver, and its

metabolites are excreted by urine. The drug undergoes hepatic metabolism, so the attempt has been made to administer it as mouth dissolving tablet to increase its oral bioavailability. Oral fast Disintegrating tablets are the oral solid dosage forms which when placed on tongue, disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and swallowed without the need of drinking water. Thus, they are beneficial to patients who find it difficult to swallow tablets particularly the geriatric and pediatric patients. Hence, an attempt was made to develop and evaluate FDT of Ranitidine HCL using direct Compression technique^{11,12,13}.

MATERIALS AND METHODS

Ranitidine HCl was gift sample from Gift sample from J.B. Chemicals. Ltd. Anklaeshwar, Fenugreek gum powder was purchased from Agro food industry Ahemadabad, Crosspovidone, Aspartame Mg. stearate, Talc and Lactose were purchased from Research Lab Fine Chem. Ltd. Mumbai

I) Drug-Excipients Compatibility Studies:

FTIR STUDIES:

IR spectra for pure drug Ranitidine HCl and Combination of drug with Superdisintegrants were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Perkin Elmer Instruments, USA) with KBr pellets.

II) Method of preparation of Oral Fast Disintegrating Tablets:

Tablets of Ranitidine HCl were prepared by Direct Compression method. Specified quantity of drug, Fenugreek gum, crosspovidone, Aspartame, Talc, Magnesium stearate, Lactose were weighed accurately and passed through 60# screen prior to mixing. All the excipients without Magnesium stearate were mixed uniformly followed by addition of

magnesium stearate. All the materials were transferred to mortar and triturated till it mixed uniformly and compressed into single punch tablet machine of 9 mm sizes flat round punch to get tablet using Rimek Compression Machine Karnavati Minipress II model.

Factorial Design

In the present research work 3^2 factorial designs was applied to study the effect of independent variables, i.e. concentration of crosspovidone & Fenugreek gum on dependent variables like Cumulative % Drug release and Disintegration time by using design expert software.

Table 1: Layout of coating material by 3^2 full factorial designs

| Batch no | X1 | X2 |
|----------|----|----|
| F1 | -1 | -1 |
| F2 | +0 | -1 |
| F3 | +1 | -1 |
| F4 | -1 | 0 |
| F5 | 0 | 0 |
| F6 | +1 | 0 |
| F7 | -1 | +1 |
| F8 | 0 | +1 |
| F9 | +1 | +1 |

Table 2: Value codes of factorial design

| Coded value | Crosspovidone(mg) (X1) | Fenugreek gum(mg) (X2) |
|-------------|------------------------|------------------------|
| -1 | 10 | 12 |
| 0 | 13 | 15 |
| +1 | 16 | 18 |

Table 3: Formulation of 3^2 Factorial Design Batches

| Formulation | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ingredients(mg) | | | | | | | | | |
| Ranitidine HCl | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Crosspovidone | 10 | 13 | 16 | 10 | 13 | 16 | 10 | 13 | 16 |
| Fenugreek gum | 12 | 12 | 12 | 15 | 15 | 15 | 18 | 18 | 18 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Lactose | 58 | 55 | 52 | 55 | 52 | 49 | 52 | 49 | 46 |
| Total wt. of Tablet | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

III) Evaluation of Oral Fast Disintegrating Tablets:

14,19,20,21,22,23,24

a) General Appearance and Physical Properties

i) Color, Odor

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance.

b) Uniformity of thickness^{5,6}

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using screw gauge on randomly selected samples.

c) Hardness/crushing/tensile strength:

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the

hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for Crushing (T) is calculated using equation:

$$= 2F / \pi dt$$

d) Friability test:

It is the phenomenon where by tablet surfaces are damaged and show evidence of lamination or breakage when subjected to mechanical shock of attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (W_{initial}) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minute surround up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

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

% Friability of tablets less than 1% is considered acceptable.

e) Uniformity of Weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on an electronic weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

f) In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

g) Wetting time:

The following method for calculating the wetting time of the tablet. A piece of filter paper (circularly cut) was placed in a small Petri- plate containing water soluble dye solution. Tablet was placed on the paper and the time required for complete wetting of the tablet was determined used a tissue paper folded twice and was placed in a small culture dish (id = 6.5 cm) containing 6 ml of water.

h) Water absorption ratio:

Similar to the procedure followed in determination of wetting time. However, here the initial weight and the final weight (after complete wetting) of tablet were calculated and the water absorption ratio was calculated by given formula:

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

Where, R is water absorption ratio, W_a and W_b are the weights of tablet before and after wetting respectively.

i) Drug content uniformity:

Ten tablets were powdered and blend equivalent to 150 mg of Ranitidine hydrochloride was weighed and dissolved in suitable quantity of phosphate buffer pH 6.8. The solution was filtered through 0.45 mm membrane filter and the amount of Ranitidine was estimated by using standard calibration curve of the drug. UV absorbance was measured at 315 nm.

j) In-vitro dissolution studies:

The release of drug from different batches of prepared tablets was studied by using USP dissolution apparatus type II. The dissolution medium consisted of 900ml of 6.8 phosphate buffer, speed of 50rpm & the temperature was maintained at $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Samples of 1ml were withdrawn at through a filter of 0.45 mm at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 315nm for sustained release layer against a blank.

k) Stability Studies:

The stability study of optimized formulation was carried out as per ICH guidelines at $40^\circ\text{C} \pm 2^\circ\text{C}$ and 75% RH using stability chamber for three months.

RESULT AND DISCUSSION

Drug polymers compatibility studies

The IR spectrum of pure drug was found to be similar to their reference standard IR spectrum of Ranitidine HCL given in pharmacopoeia.

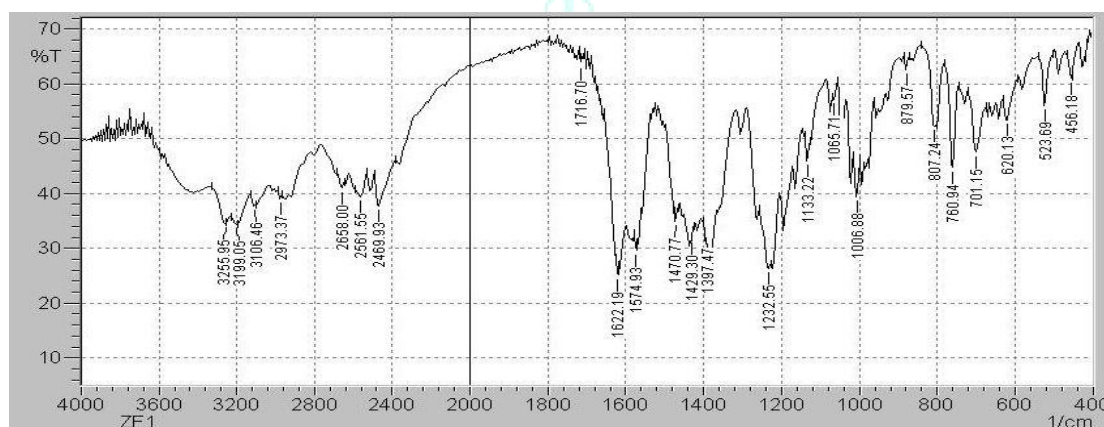


Figure 1: FTIR Spectrum of Pure drug (Ranitidine HCL)

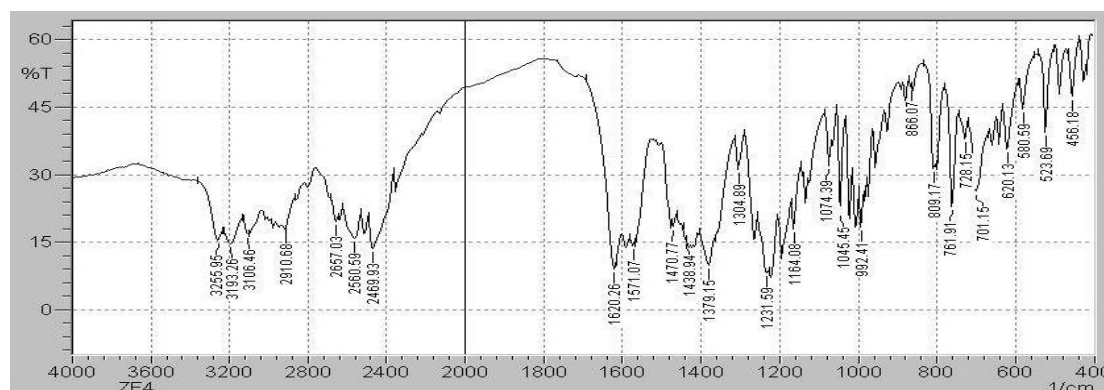


Figure 2: FTIR spectrum of Drug in Formulation blend

From FTIR study it can be concluded that the drug Ranitidine HCL have maintained its identity without losing its characteristic properties in formulation blend.

Evaluation parameter of Oral fast disintegrating Tablets:

a) General Appearance and Physical Parameter:

Color: off White

Odor: odorless

b) Thickness: The thickness of all formulations was found to be in the range between 3.96 ± 0.24 to 4.03 ± 0.06 mm.

c) Hardness: The hardness of all the entire formulations was found to be in the range between 3.10 ± 0.09 to 3.56 ± 0.22 kg/cm².

d) Percentage Friability: The Friability of all formulations was found to be in the range between 0.21 ± 0.02 to $0.27 \pm 1.06\%$.

e) Uniformity of weight: The Weight variation of all formulations was found to be in the range between 246.64 ± 0.9 to 249.21 ± 1.24 mg.

f) Disintegration time: The Disintegration time all batches were found between the ranges 22-34 seconds.

Table 4: Evaluation parameter for FDT of Ranitidine HCL

| Formulations | Thickness mm \pm SD, n=3 | Hardness Kg/cm ² \pm SD, n=3 | Friability % \pm SD, n=3 | Average wt. (mg) \pm SD, n=3 | Disintegration time sec. \pm SD, n=3 |
|--------------|-------------------------------|--|-------------------------------|-----------------------------------|---|
| F1 | 3.96 ± 0.24 | 3.21 ± 0.22 | 0.21 ± 0.02 | 249.21 ± 1.24 | 29 ± 0.7 |
| F2 | 4.01 ± 0.02 | 3.10 ± 0.09 | 0.22 ± 0.14 | 247.94 ± 1.02 | 28 ± 0.4 |
| F3 | 4.02 ± 0.09 | 3.28 ± 0.64 | 0.24 ± 1.04 | 246.64 ± 0.9 | 28 ± 0.8 |
| F4 | 4.00 ± 0.75 | 3.25 ± 0.39 | 0.25 ± 0.27 | 248.32 ± 1.41 | 31 ± 0.7 |
| F5 | 4.01 ± 0.66 | 3.11 ± 0.22 | 0.22 ± 0.26 | 247.96 ± 1.23 | 33 ± 0.8 |
| F6 | 4.00 ± 0.76 | 3.13 ± 0.12 | 0.27 ± 1.06 | 249.02 ± 0.32 | 34 ± 0.2 |
| F7 | 3.98 ± 0.84 | 3.31 ± 0.19 | 0.25 ± 0.46 | 248.66 ± 1.41 | 27 ± 0.5 |
| F8 | 4.03 ± 0.06 | 3.56 ± 0.22 | 0.23 ± 0.27 | 247.06 ± 0.23 | 25 ± 0.9 |
| F9 | 4.00 ± 0.16 | 3.12 ± 0.02 | 0.27 ± 0.18 | 248.98 ± 0.64 | 22 ± 0.2 |

\pm SD= Standard deviation

Table 5: Wetting time, Water absorption ratio, % Drug content

| Batches | Wetting time (Sec) \pm SD, n=3 | Water absorption ratio \pm SD, n=3 | % Drug content \pm SD, n=3 |
|---------|-------------------------------------|---|---------------------------------|
| F1 | 26 ± 0.56 | 60 ± 0.60 | 99.10 ± 1.08 |
| F2 | 23 ± 1.20 | 52 ± 1.63 | 98.44 ± 1.22 |
| F3 | 28 ± 0.06 | 66 ± 0.38 | 97.98 ± 1.16 |
| F4 | 22 ± 1.40 | 67 ± 1.04 | 96.90 ± 1.44 |
| F5 | 24 ± 1.08 | 62 ± 1.16 | 95.46 ± 1.21 |
| F6 | 25 ± 0.41 | 56 ± 0.72 | 98.14 ± 1.28 |
| F7 | 22 ± 1.14 | 61 ± 0.44 | 97.80 ± 1.44 |
| F8 | 23 ± 1.28 | 68 ± 1.06 | 98.46 ± 1.20 |
| F9 | 19 ± 0.82 | 68 ± 0.72 | 99.20 ± 1.08 |

g) Wetting time: Wetting time of all formulations was found to be in the range between 19 ± 0.82 to 26 ± 0.56 .

h) Water absorption ratio: Water absorption ratio of all formulations was found to be in the range between 52 ± 1.63 to 68 ± 1.06 .

i) Drug content: Drug content of all formulations was found to be in the range between 97.98 ± 1.16 to 99.20 ± 1.08 .

j) In vitro dissolution profile of formulation batches

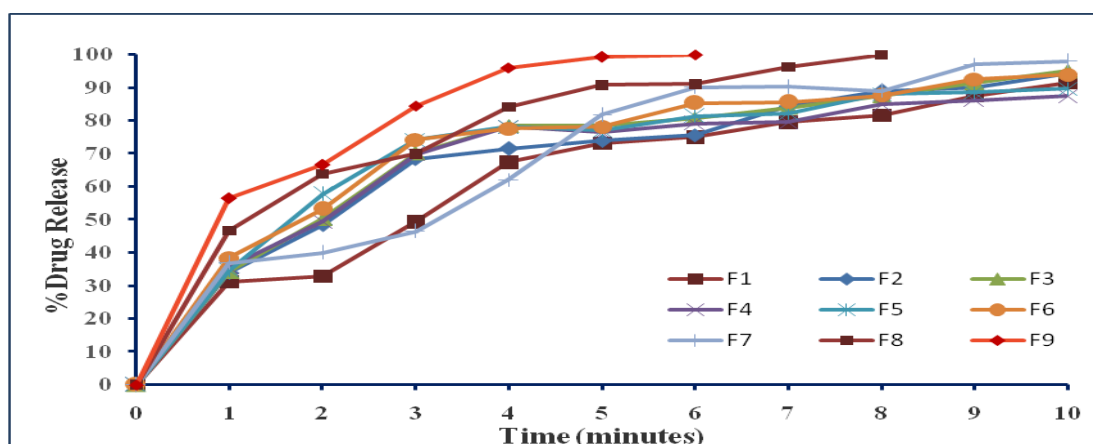


Figure 3: In-vitro drug dissolution studies of Formulations F1 to F9

All the nine formulations were subjected for the in vitro dissolution studies using tablet dissolution tester. The sample were withdrawn at different time intervals and analyzed at 315 nm. Cumulative drug release was calculated on the basis of mean amount of Ranitidine HCl present in respective tablet. The results obtained in the in vitro drug release for the formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 are tabulated in Table 6.8 the dissolution rate was found to increase linearly with increasing Concentration of superdisintegrants.

From the outcome of above results, it was clear that the formulation F9 was the best formulation having comparable disintegration time and in vitro drug release.

The drug release of the best F9 formulation was found to be 99.56% with in 6 minute. The tablet prepared using Crosspovidone and fenugreek powder (F9) were found to be best formulations that showed the dissolution rate in 6 minutes.

Optimization study outcome:

The targeted response parameter were statistically analyzed by applying one way ANOVA at significant level and the significance of the model was calculated by Design & Expert software. The individual parameter evaluated by using F test and mathematical relationship was generated between the factor dependent variables and independent variables for determining the level of factor which give optimum Disintegration time and drug release.

The response surface diagram gives knowledge to understand contribution of the variables and their

interaction. The response curve map is shown for all response in figure.

Figure 4 & 5 shows both variables have effect on the Disintegration time (R1) and Cumulative % drug release (R2). The model F-value for disintegration time was found to be 37.92 and for Cumulative % drug release 11.90 which imply model is significant. The result of ANOVA study shows model is significant.

Final Equation for D.T. in Terms of Coded Factors:

$$\begin{aligned} \text{DT} = & +33.03 \\ & -1.33 * A \\ & -3.17 * B \\ & +0.25 * AB \\ & -0.62 * A^2 \\ & -9.12 * B^2 \end{aligned}$$

Final Equation in Terms of Coded Factors:

$$\begin{aligned} \text{DR in 5 minutes} = & +76.91 \\ & +4.11 * A \\ & +7.73 * B \\ & +3.09 * AB \\ & +0.58 * A^2 \\ & +5.64 * B^2 \end{aligned}$$

Table 6: The result of ANOVA

| Response model | Sum of square | Degree of freedom | Mean square | F value | P value | R square | Ade. Precision |
|--|---------------|-------------------|-------------|---------|---------|----------|----------------|
| Disintegration Time | 283.94 | 2 | 141.97 | 37.92 | 0.0002 | 0.9312 | 11.185 |
| Cumulative % drug release in 5 Minutes | 11.95 | 2 | 55.97 | 11.90 | 0.0056 | 0.9488 | 16.75 |

Design-Expert® Software
Factor Coding: Actual
D.T. (Sec)
● Design points above predicted value
● Design points below predicted value
34
18
X1 = A: crosspovidone
X2 = B: Fenugreek gum

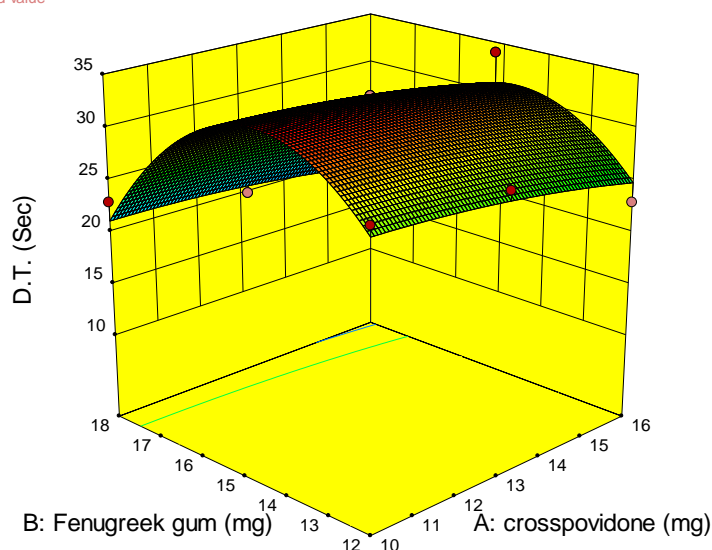


Figure 4: A response surface plot showing effect of concentration of independent variables on the Disintegration time

Design-Expert® Software
Factor Coding: Actual
D.T. (Sec)
● Design Points
34
18
X1 = A: crosspovidone
X2 = B: Fenugreek gum

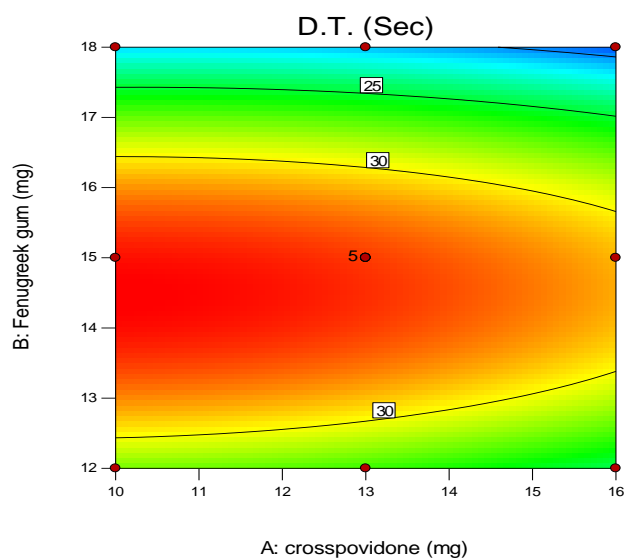


Figure 5: A counter plot showing relationship between various levels of independent variables to gain fixed value of Disintegration time

Design-Expert® Software
Factor Coding: Actual
DR in 5 minutes (%)
● Design points above predicted value
● Design points below predicted value
99.42
73.21
X1 = A: crosspovidone
X2 = B: Fenugreek gum

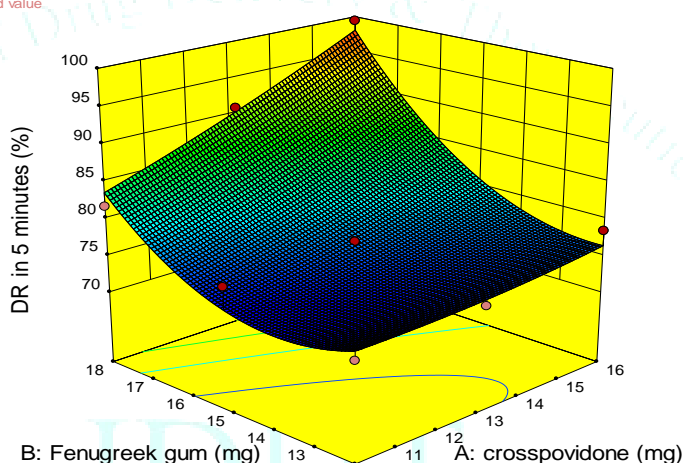


Figure 6: A response surface plot showing effect of concentration of independent variables on the % Drug release

Design-Expert® Software
Factor Coding: Actual
DR in 5 minutes (%)
● Design Points
99.42
73.21
X1 = A: crosspovidone
X2 = B: Fenugreek gum

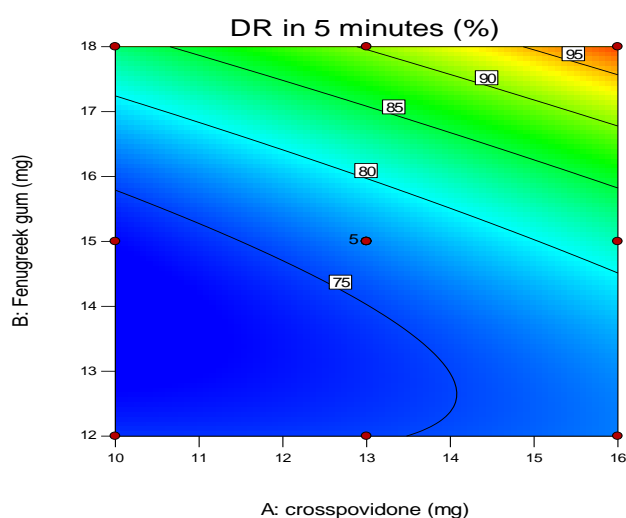


Figure 7: A counter plot showing relationship between various levels of independent variables to gain fixed value of % Drug release

Full factorial design and optimization technique successfully used in the development oral fast disintegrating.

k) Stability study

Table 7: Stability study of optimized batch F9

| Condition | Time (months) | Wetting time (sec) \pm SD, n=3 | Friability (%) | Disintegration time (sec) \pm SD, n=3 | % Drug release |
|---|---------------|----------------------------------|-----------------|---|----------------|
| Accelerated temperature 40°C and 75% RH | 3 | 19 \pm 0.72 | 0.20 \pm 0.12 | 22 \pm 0.2 | 99.39 |

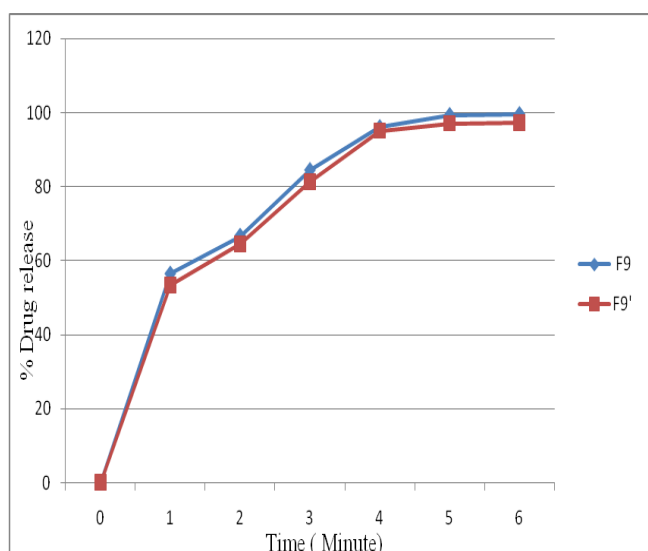


Figure 8: In-vitro drug dissolution Stability study of f9 optimized Formulation

F9= Before stability study

F9= After stability study

Stability Studies are done according to the ICH Guidelines to assure that the product retains its full activity up to the end of its shelf-life at 40°C \pm 2°C at 75% RH during 3 months. The results were found to be satisfactory with no significant variable changes.

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CONCLUSION

Oral fast Disintegrating tablet of Ranitidine HCl were prepared by using direct Compression technique with a Synthetic Superdisintegrant such as Crosspovidone and a Natural Superdisintegrant Fenugreek powder in different concentration. 3² factorial designs was applied by using design expert software. IR spectroscopic study indicates no drug-excipient interaction in the prepared formulations. The prepared Orodispersible tablets exhibited satisfactory physic-chemical characteristic. 3² full factorial design and optimization technique successfully used in the development of orodispersible tablets. The drug release of the best F9 formulation was found to be 99.56% within 6 min. The tablet prepared using Crosspovidone and fenugreek powder F9 were found to be best formulations that showed the dissolution rate in 6 minutes. This is a Novel combination of fenugreek gum with Crosspovidone. Comparing the all the fabricated formulations, batch F9 was considered as optimized formulation since it shows excellent fast disintegration, in vitro dissolution, and faster drug release within 6 mins in comparison to other batches also stable in stability.

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