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DESIGN AND OPTIMIZATION OF OLANZAPINE IMMEDIATE RELEASE TABLETS USING NATURAL SUPER DISINTEGRANTS BY RESPONSE SURFACE METHODOLOGY

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Keywords:

Olanzapine, Immediate release, Fenugreek, Isapghul, Response Surface Methodology

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ABSTRACT: Purpose: To formulate and evaluate Olanzapine immediate-release tablets using direct compression. Immediate release of drug from the dosage form is required for rapid onset of action and produce an immediate therapeutic effect. **Method:** Tablets were formulated using two different natural super disintegrants like Fenugreek and Isabghul and in combination by using Response Surface Methodology. The selected independent variables (Y1) Fenugreek and (Y2) Isabghul showed a significant effect on dependent *variables, i.e.,* disintegration time (X1) and percentage drug release (X2). Drug and excipients compatibility studies were done by FTIR studies. **Results:** No significant drug-polymer interactions were observed in FTIR studies. The prepared tablets were evaluated for weight variation, friability, hardness, disintegration, and dissolution. A formulation containing 2% fenugreek and 5% isabghul was offered the relatively rapid release of Olanzapine when compared with other concentrations employed in this investigation. The formulation with 4.2% Fenugreek and 5% Isabghul was optimized, and the tablets were evaluated. **Conclusion:** The optimized formulation AOF14 showed the desired level of % CDR 98.43 at the end of 30 minutes, and their similarity factor (f2) was calculated with innovator whose value was found to be 97.52% at the end of 30 min.

INTRODUCTION: Immediate-release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. The immediate-release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption [1].

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Olanzapine is a benzodiazepine belonging to Antipsychotics agents, and it is used in the treatment of schizophrenia, depressive episodes associated with acute manic episodes, and maintenance treatment in bipolar disorder. It is a relatively new drug in the market [2].

The pharmacokinetics of Olanzapine is linear and dose-proportional within the approved dosage range from 1 mg up to 20 mg. Olanzapine is well absorbed following oral administration in both fed and fasted states. Food does not affect the rate or the extent of Olanzapine absorption [3]. The absolute bioavailability is only approximately 31.5% due to extensive hepatic metabolism.

Olanzapine chemically is 2-methyl-4-(4-methyl-piperazin-1-yl)-5H-thieno [3,2-c][1,5] benzodia-zepine [4]. The proper choice of superdisintegrants and its consistency of performance are of impor-tance to the formulation of a rapidly disintegrating dosage form or immediate releasing dosage forms.

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family [5]. Fenugreek seed mucilage is also known as Billy-goat Clover, Camel Grass and Common Fenugrec and is widely used as a natural disintegrant in conventional formulations [6].

Ispaghula mucilage consists of the epidermis of the dried seeds of Plantago ovate was carried out to study the disintegrant property of mucilage in comparison with crospovidone [7].

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous fami.

The main aim of the work was to formulate Olanzapine immediate-release tablets using natural super disintegrants at different concentrations by Response Surface Methodology.

MATERIALS AND METHODS:

Materials: Olanzapine obtained as a gift sample from Aurobindo Pharma Pvt, Ltd. Hyderabad. Mannitol, Microcrystalline Cellulose, Guargum, magnesium stearate, and talc were procured from S.D. Fine chemicals, Mumbai. Fenigreek and Isabghul were purchased from Sirigiri venkappa ayurvedic stores, Kurnool, Andhra Pradesh.

Methods:

Study Type: Response Surface methodology, Design expert: 8.0.7.1, Design type: 3-level factorial design (Miscellaneous), Design mode: Quardratic.

Response surface methodology (RSM) was used in the development and optimization of formulations Based on the principles design of experiments (DOE). The methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships, and mapping of the response over the experimental domain to select the optimum formulation [8, 9, 10]. Box-Behnken statistical design is one type of RSM design that is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at the midpoints of the edges of the process space and at the center [11, 12]. Independent variables used such as Fenugreek (X1), Ishabgul (X2), and dependent variables are disintegration time (Y1), and percentage drug release in 0.1N HCL for 1 h (Y2) was studied.

Computer-Aided Optimization Design: A computer-aided response surface methodology using design with 2 factors, 2 levels were employed for optimization study. This design is suitable for exploration of quadratic response surfaces, thus helping in optimizing a process using a small number of experimental runs (13 runs) with Design expert (version 8.0.1), RSM to study the effect of the amounts of various super disintegrants used as two independent variables (factors), on the property of Olanzapine immediate-release tablets. The disintegration time and % cumulative drug release were selected as dependent variables [13].

Experimental Design of Olanzapine IR Tablets: In the present investigation, two independent formulation variables evaluated were X1: natural superdisintegrants and dependent variables investigated were (Y1) disintegration time in 0.1N HCl, (Y2) % drug release in 0.1N HCl. 13 different formulation batches of Olanzapine IR tablets were evaluated to determine the potential effect of those independent variables on the dependent variable.

TABLE 1: DESIGN SUMMARY TYPE - NUMERIC & SUBTYPE – CONTINUOUS

Factor	Name	Unit	Minimum	Maximum	Mean	Std. Dev
A	Fenugreek	%	2	8	5	2.04
B	Isabghul	%	2	8	5	2.04

Preformulation Studies:

FTIR (Fourier Transform Infrared Spectro-scopy) Studies: The infrared (IR) spectra were recorded using an FTIR spectrophotometer (Bruker Alpha) by KBr pellet method in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for Olanzapine and the physical mixture of drug with polymers were compared to check the compatibility of drug with polymers.

Preparation of Olanzipine Immediate Tablets: The drug and the excipients used were all passed through 80-mesh sieve. The active ingredient Olanzapine and each single diluent mannitol, polymer (MCC) and binder (guargum), lubricant (Magnesium stearate), glidant (Talc) were blended together by dry mixing in a laboratory mixer for 10minutes, and superdisintegrants were added. The mixture was compressed by using an eight-station tablet punching machine (Elite scientific and equipment) with an 8mm standard flat round punch and die set at compression force 4-6 ton. The hardness of all tablets was adjusted to 4.5 to 5.0 Kg/cm^2. The total weight of the tablet was found to be 150 mg [14].

Physical Properties of Olanzipine Immediate Release Tablets: The tablets were characterized immediately after the formulation. The weight variation of the 20 tablets was accomplished according to guidelines mentioned in IP 2010 using an electronic balance. Friability of 10 tablets was evaluated by Electrolab friability test apparatus for 4 min at the rate of 25 rpm. For each formulation, the hardness of 10 tablets was evaluated using Monsanto hardness tester (chambell electronics, India). The thickness of the 10 tablets was measured by Vernier calipers. A disintegration test of 6 tablets was performed by Lab India disintegration test apparatus.

Content Uniformity: The tablets are tested for their drug content uniformity. At random 10 tablets are weighed and powdered. The powder equivalent to 100 mg of the drug was weighed accurately and dissolved in 100 ml of 0.1N HCl. The solution is shaken thoroughly. The undissolved matter is removed by filtration through Whatman no.1 filter paper (0.45µm). The absorbance of the diluted solutions is measured at 260 nm. The concentration of the drug is computed from the standard curve of Olanzapine in the 0.1N HCl.

***In-vitro* Dissolution Studies:** *In-vitro* dissolution study of Olanzapine is carried using the USP dissolution test apparatus, type II (Paddle method) (Lab India 8 basket dissolution apparatus) at 37 ºC ± 0.5 ºC. The paddle rotates at a speed of 50 rpm. The tablets are placed in the dissolution apparatus containing 900ml of 0.1N HCl buffer as a medium. Samples are withdrawn (5ml) and are replaced with an equal amount of fresh dissolution medium at particular time intervals; samples are immediately filtered through Whatmann filter paper and diluted with the dissolution media. The absorbance's of these diluted samples is noted at λ_{max} 260 nm using UV-Visible Spectrophotometer. The amount of the drug present in the samples is calculated by using the calibration curve constructed from the reference standards. Cumulative % drug release is plotted against time is calculated [15].

TABLE 2: FORMULATION TABLE OF OLANZAPINE IR TABLETS

S. no.	Ingredients (mg)	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9	OF10	OF11	OF12	OF13
1	Olanzapine	10	10	10	10	10	10	10	10	10	10	10	10	10
2	Mannitol	64	64	61.5	64	68.5	66.5	64	61.5	64	68	54.5	64	64
3	Microcrystalline cellulose	52	52	50	52	52	54	52	50	52	57	52.5	52	52
4	Fenugreek	3	7.5	12	7.5	7.5	3	7.5	7.5	7.5	3	12	12	7.5
5	Isabghul	12	7.5	7.5	7.5	3	7.5	7.5	12	7.5	3	12	3	7.5
6	Guargum	6	6	6	6	6	6	6	6	6	6	6	6	6
7	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
8	Mag. stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
9	Total wt (mg)	150	150	150	150	150	150	150	150	150	150	150	150	150

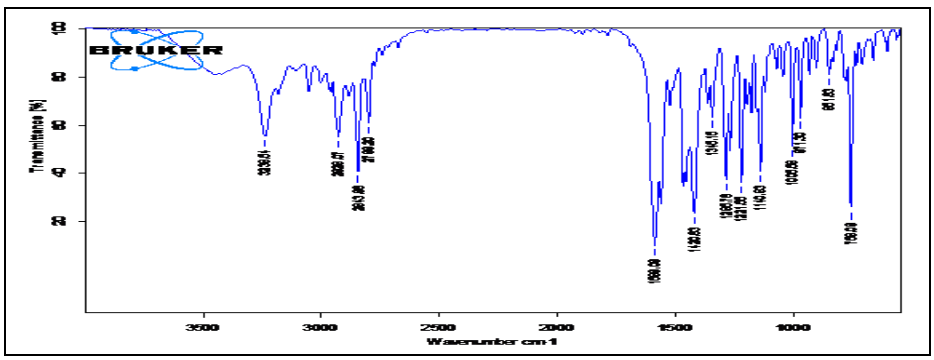

FIG. 1: FTIR SPECTRA OF PURE OLANZAPINE

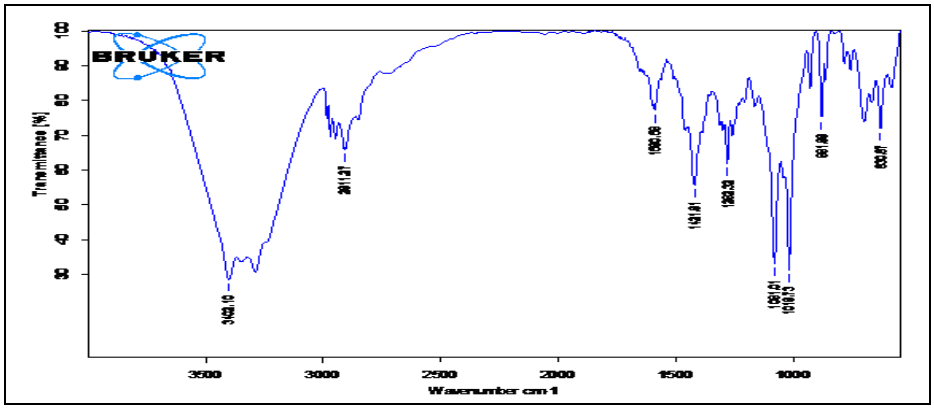

FIG. 2: FTIR SPECTRA OF OLANZAPINE, FENUGREEK, AND ISABGHUL

TABLE 3: RESULTS OF PRECOMPRESSION PARAMETERS FROM OF1-OF13 FORMULATIONS

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Car's index (%)	Hausner's ratio	Angle of Repose (°)
OF1	0.264±0.028	0.319±0.037	17.24±0.100	1.32±0.030	33.24±0.025
OF2	0.268±0.034	0.315±0.006	14.92±0.55	1.40±0.010	32.13±0.021
OF3	0.255±0.024	0.294±0.044	13.265±0.25	1.34±0.032	32.12±0.053
OF4	0.268±0.034	0.315±0.006	14.92±0.55	1.40±0.010	32.13±0.021
OF5	0.248±0.016	0.322±0.032	22.98±0.20	1.40±0.040	34.22±0.054
OF6	0.255±0.012	0.287±0.022	11.14±0.25	1.35±0.010	30.18±0.012
OF7	0.268±0.034	0.315±0.006	14.92±0.55	1.40±0.010	32.13±0.021
OF8	0.255±0.012	0.287±0.022	11.14±0.25	1.35±0.010	30.18±0.012
OF9	0.268±0.034	0.315±0.006	14.92±0.55	1.40±0.010	32.13±0.021
OF10	0.248±0.016	0.322±0.032	22.98±0.20	1.40±0.040	34.22±0.054
OF11	0.255±0.012	0.287±0.022	11.14±0.25	1.35±0.010	30.18±0.012
OF12	0.248±0.016	0.322±0.032	22.98±0.20	1.40±0.040	34.22±0.054
OF13	0.268±0.034	0.315±0.006	14.92±0.55	1.40±0.010	32.13±0.021

TABLE 4: RESULTS OF POST COMPRESSION PARAMETERS OF OPTIMIZED FORMULATIONS

Formulation code	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration time (in secs)	Assay (%)
OF1	150.66±0.288	0.88±0.363	4.9±0.1	3.698±0.0308	21±1	94.25±1.15
OF2	150.33±0.763	1.09±0.263	4.9±0.0577	3.691±0.0242	14.66±0.577	93.1±1.15
OF3	150.5±0	0.88±0.363	5.133±0.0567	3.666±0.0217	15.66±0.577	92.4±1.15
OF4	150.33±0.763	1.09±0.263	4.9±0.0577	3.691±0.0242	14.66±0.577	93.1±1.15
OF5	153.5±0.288	1.12±0.392	5.133±0.0577	3.672±0.0214	14.66±1.15	90.1±1.15
OF6	150.16±0.767	1.35±0.362	4.966±0.0577	3.661±0.0347	16.66±0.577	95.23±1.15
OF7	150.33±0.763	1.09±0.263	4.9±0.0577	3.691±0.0242	14.66±0.577	93.1±1.15
OF8	148.16±0.288	0.900±0.392	4.933±0.01154	3.674±0.0356	15±0.11	91.31±1.32
OF9	150.33±0.763	1.09±0.263	4.9±0.0577	3.691±0.0242	14.66±0.577	93.1±1.15
OF10	147.8±0.288	1.35±0.389	5.1±0.1	3.647±0.0188	18.33±0.577	82.75±1.15
OF11	149.5±0	1.35±0.005	5.2±0.01	3.712±0.0256	16.66±1.52	91.95±1.15
OF12	150.66±0.288	0.68±0.011	5.033±0.0577	3.659±0.0196	18±0.211	86.96±3.51
OF13	150.33±0.763	1.09±0.263	4.9±0.0577	3.671±0.0242	14.66±0.577	93.1±1.15

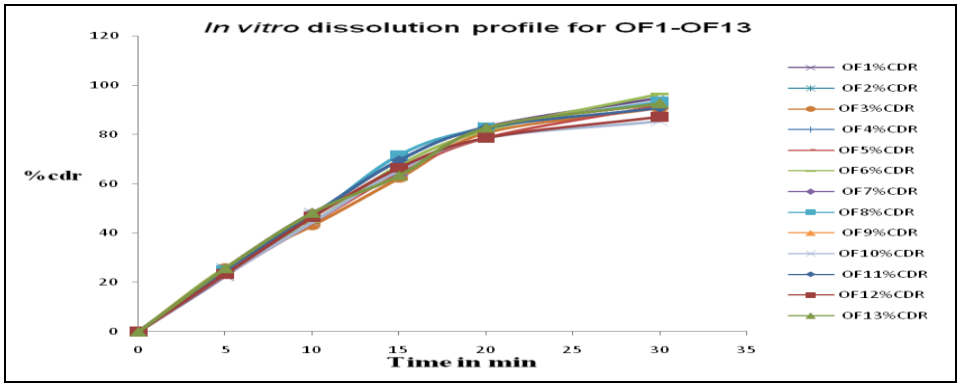

FIG. 3: *IN-VITRO* DISSOLUTION PROFILES OF OLANZAPINE

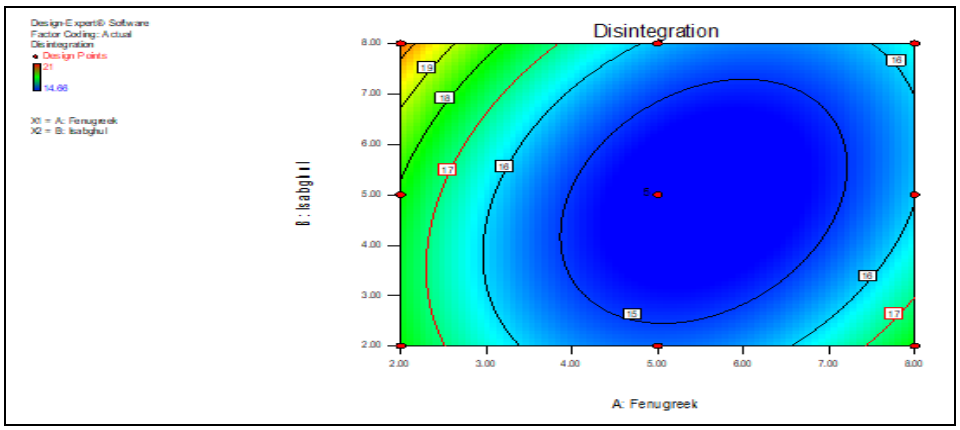

FIG. 4: CONTOUR PLOT OF DISINTEGRATION TIME

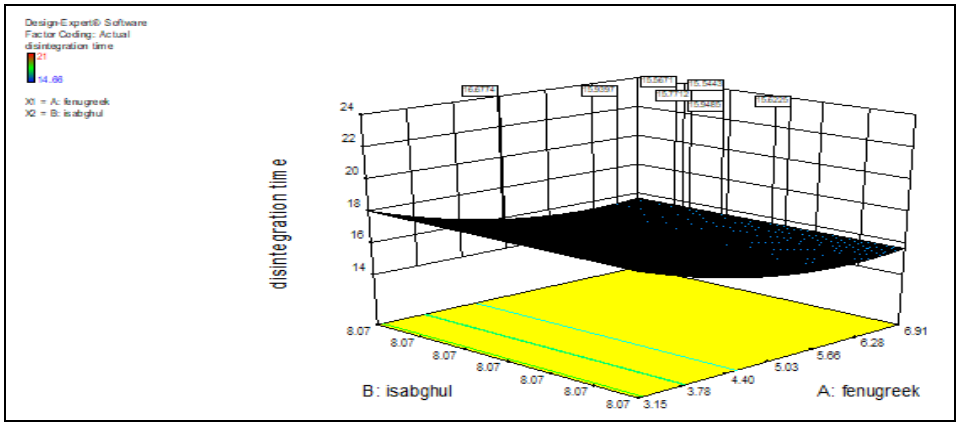

FIG 5: 3D GRAPH OF DISINTEGRATION TIME

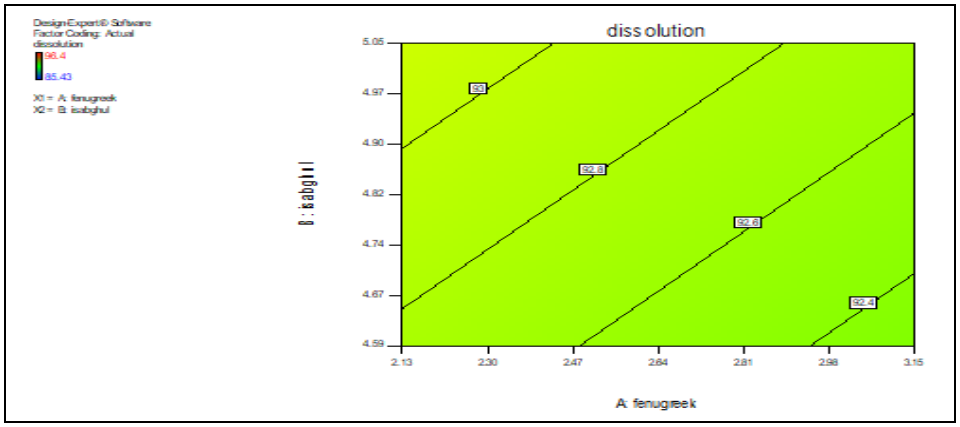

FIG. 6: CONTOUR PLOT OF DISSOLUTION

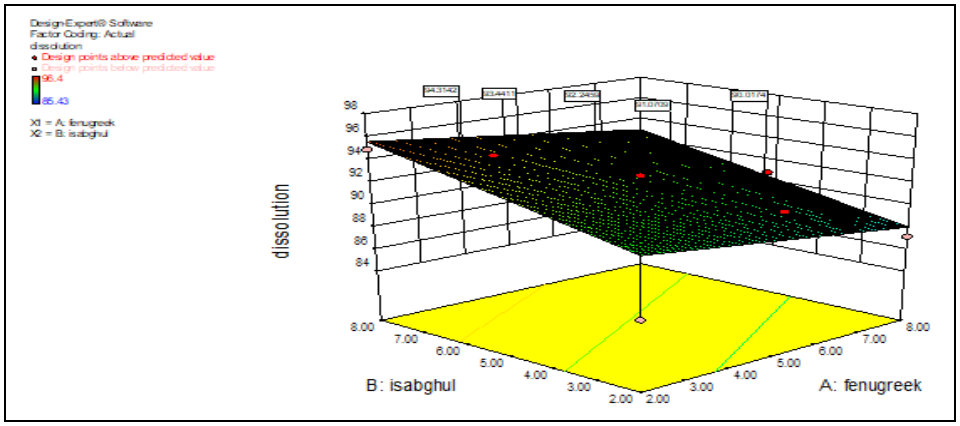

FIG. 7: 3D GRAPH OF DISSOLUTION

TABLE 5: PRECOMPRESSION AND POST COMPRESSION PARAMETERS OF OPTIMIZED FORMULATION AOF14

S. no.	Precompression Parameters		Post compression Parameters	
1	Bulk density (gm/cc)	0.508±0.002	Tablet wt (mg)	150.16±0.767
2	Tapped density (gm/cc)	0.585±0.003	Hardness (kg/cm^2)	4.966±0.0577
3	Carr's index (I)	13.688±1.051	Thickness (mm)	1.35±0.362
4	Hausner's ratio	1.150±0.001	Friability (%)	0.658±0.100
5	Angle of repose (º)	29.323±0.360	Drug content	96±0.767
6			% Drug released	98.43

All the values are calculated as (Mean ±SD, n=3

TABLE 6: PERCENTAGE PREDICTION ERROR OF THE OPTIMIZED FORMULATION

Response	Predicted Value	Experimental Value	Percentage Prediction Error
Disintegration Time	15.96 Sec	15.41 Sec	-3.44
Dissolution in 0.1N HCl	99.6199 %	98.43%	-1.19

Percentage prediction error can be calculated by using below formula.

Percentage prediction error = (Experimental Value – Predicted Value) × 100 / Experimental Value

RESULTS AND DISCUSSION: The immediate release tablets of Olanzapine were successfully prepared by direct compression method using natural superdisintegrants fenugreek and isabghul at varying concentrations and an optimized formula was selected.

Compatibility Studies: FTIR spectrum of pure drug and physical mixture of drug and excipients were studied. In the present study, it was observed that, there were no shifts in individual main peaks of the pure drug substance. So this indicates that there were no incompatibility issues of drug with formulation excipients used. From **Fig. 1** and **2**, it is evident that the absorption bands at 3237.2 1 cm^{-1}, 2927.57 cm^{-1}, 1588.73 cm$^{-1,}$ and 1419.84 cm^{-1} indicate the presence of Amine (N-H Stretch), Alkane (Aliphatic C-H stretch), Nitrile (C-N stretch), and Thiole (C-S stretch) correspond to the Olanzapine pure drug.

Pre-compression Parameters: The Compressibility Index (%), Hausner's ratio and angle of repose of all the formulations [OF1-OF12] developed in the formulation development phase were found to be very poor, *i.e.,* 11.14±0.25 to 22.98±0.20, HR values were excellent to good, *i.e.,* 1.32±0.030 to 1.40±0.040 and angle of repose was good to passable *i.e.,* 30.18±0.012′ to 34.22±0.054′. Results are shown in **Table 3**.

Post-compression Parameters: All the formulated tablets containing the active drugs were evaluated to find the physical properties like Hardness, thickness, friability, and drug content **Table 5**. In the weight variation test, the pharmacopeial limits of percentage deviation for tablets whose weight is less than 230 mg are ±7.5%. The average percentage deviation of all the tablets friability was found within the limit, which was less than 1%. The hardness of the tablets was found to be acceptable and uniform from batch to batch. The drug content was also found uniform and within the prescribed limits.

The disintegration test revealed that all the formulations OF1- OF12, was within the range, *i.e.*, 14.66±0.577 to 18±1 Sec. Shown in **Table 4.**

From the release profiles, it was concluded that the variation in concentrations of disintegrants had a variable effect on drug release. The effect of fenugreek and isabghul could be observed at a constant level. Among all formulations (OF1-OF13), OF6 has the drug release of 96.4% Formulation containing fenugreek and isabghul showed the early release in dissolution medium, but as the concentration of isabghul enhances, the drug release enhances due to its more disintegrant property.

Optimization Results:

Data Analysis: All responses were fitted to Quadratic and linear models, as suggested by Design expert software 8.0.7.1. A quadratic model is suggested for disintegration time and the % cumulative drug release. All dependent and independent variables are shown in **Table 6**.

The F value for disintegration, %CDR were found to be 15.63, 4.33, respectively, indicating that the models are significant. The values of F were found to be < 0.0001 for all responses indicating that the models are significant.

The contour and response surface plots for all responses of all formulation factors are shown in **Fig. 4, 5, 6,** and **7,** respectively. The contour and response surface plots of the response surface as a function of two factors at a time, with all other factors fixed, are more helpful in understanding both the main and interaction effects of the two factors.

To optimize all the responses with different targets, a multi-criteria decision approach (a numerical optimization technique by the desirability function and a graphical optimization technique by the overlay plot) was used. The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. Constrains were: disintegration time in 0.1N HCl; % CDR at 30 min. These constraints are common for all the formulations. The recommended concentrations of the independent variables were calculated by the Design expert software from the above plots, which has the highest desirability near 1.0.

The critical formulation factors that affect the desired response of the formulation were found to be different concentrations of the fenugreek was 4.2 %, and isabghul is 5%.

The statistically optimized formulation fulfilled all the physicochemical criteria. *In-vitro* drug release studies were carried out on the prepared optimized formulation. The *in-vitro* drug release study showed that the %CDR was and is in close agreement with the model predictions. The relative error (%) between the predicted and experimental values confirms the predictability and validity of the model.

The optimized formulation gave disintegration, % CDR values of 15.41 sec and 98.43% in 30 min respectively.

CONCLUSION: The central composite design was used to optimize Olanzapine immediate-release tablets using Natural Super disintegrants by which can be used as pharmaceutical excipients. Based on the results, suitable disintegrants were selected for formulation development by response surface methodology. So natural superdisintegrant like fenugreek, isabghul exhibited faster drug dissolution, which lead to improving effective therapy, patient compliance, and satisfies all the criteria as an immediate-release tablet. The Immediate release tablets of Olanzapine with the super-disintegrant fenugreek 4.2% and isabghul 5% matched with the *in-vitro* dissolution profile of the innovator drug (zyperexia) at each and every time interval as well as the overall drug release within 30 min. So, the olanzapine immediate-release formulations of AOF14 of 150 mg & ZYPEREXIA of 100mg had met the desired *in-vitro* drug release.

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CONFLICTS OF INTEREST: All authors declare that they have no conflict of interest.

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