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DEVELOPMENT OF ONDANSETRON HCL FAST DISINTEGRATING TABLETS USING 3^2 FULL FACTORIAL DESIGN

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Keywords:

Ondansetron HCl, Fast Disintegrating Tablets, *Plantago ovata* mucilage, *Ocimum basilicum* mucilage, 3^2 Full Factorial Design

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ABSTRACT: The present investigation was carried out to study the disintegrant property of *Plantago ovata* and *Ocimum basilicum* mucilages. The objective of the work was to develop Fast disintegrating tablets of Ondansetron HCl with a view to enhance patient compliances and dissolution rate by direct compression method using 3^2 full factorial design. *Plantago ovata* (2-10% w/w), *Ocimum basilicum* (4-8%w/w) mucilages were used as natural superdisintegrant and microcrystalline cellulose was used as diluent, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity, in vitro dispersion time, wetting time and water absorption ratio. Based on in vitro dispersion time (approximately 11 s); the formulation containing 10% w/w *Plantago ovata* and 8% *Ocimum basilicum* mucilages were found to be promising and tested for in vitro drug release pattern (in 0.1 N HCl), short-term stability (at 40°/75 % RH for 6 mo) and drug-excipient interaction. Surface response plots are presented to graphically represent the effect of independent variables (concentrations of *Plantago ovata* and *Ocimum basilicum* mucilages) on the *in vitro* dispersion time. The validity of the generated mathematical model was tested by preparing two extra-design check point formulations. The optimized tablet formulation was compared with conventional commercial tablet formulation for drug release profiles. This formulation showed two-fold faster drug release ($t_{50\%}$ 3.6 min) compared to the conventional commercial tablet formulation ($t_{50\%}$ 7 min). Short-term stability studies on the formulation indicated that there are no significant changes in drug content and in vitro dispersion time ($p < 0.05$).

INTRODUCTION: Mucilage is most commonly used as excipients in the manufacturing of different pharmaceutical dosage forms. They have a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportion in different pharmaceutical dosage forms [1-4].

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Natural mucilages are preferred over semi-synthetic and synthetic materials due to their non-toxic, low cost, free availability, emollient and non-irritating nature [5-6].

Fast disintegrating tablet system can be defined as a tablet that disintegrates and dissolves rapidly in saliva without need of drinking water [7]. In spite of tremendous development in drug delivery technology, oral route remains perfect route for administration of because of low cost of therapy, ease of administration, accurate dose, self medication, pain avoidance, leading to high level of patient compliance. Tablets and capsules are the most popular dosage forms [8] but main drawback of such dosage forms is dysphasia or difficulty in

swallowing. This problem led to development of novel solid dosage forms such as Fast disintegrating tablets that disintegrate and dissolve rapidly in saliva without need of water. Fast disintegrating tablets avoid first pass metabolism and enhance bioavailability of active ingredient [9].

Ondansetron HCl is a potent highly selective antagonist at the 5 HT_3. It is a carbazole which causes anti nauseant and anti emetic effects by selective and comperative blockade of the 5 HT_3 receptors [10]. The aim was to develop Ondansetron HCl fast disintegrating tablets using 3^2 full factorial design with enhanced bioavailability.

MATERIALS AND METHODS: Ondansetron HCl was obtained as gift sample from Arabindo Pharmaceuticals Pvt Ltd, Hyderabad. The seeds of *Plantago ovata* and *Ocimum basilicum* were purchased from the local market of Ongole, Andhra Pradesh. Directly compressible mannitol (Pearlitol SD200), sodium stearyl fumarate and microcrystalline cellulose (Avicel PH-102) were generous gifts from Strides Arco Labs, Bangalore, Glenmark Ltd., Nashik and Alkem Labs Pvt Ltd, Mumbai, India. All other chemicals used were of analytical reagent grade.

Isolation of mucilage: For the isolation of mucilage [11], seeds of *Plantago ovata* were used. They were soaked in distilled water for 48 hours and then boiled for 1 hr for complete release of mucilage into water. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 60^0 C), powdered, sieved (#60) and stored in a desiccator until further use.

Isolation of *Ocimum basilicum* Mucilage: Basil seeds were rinsed with water to remove foreign particles. Seeds were soaked in water (seed: water= 1:10) for 20 minutes. The swollen seeds subjected to high agitation using homogenizer at 1500 rpm to separate gel layer from seeds [12]. The separated gel layer was passed through muslin cloth to remove unwanted particles and then precipitated using acetone. The precipitate was washed with ethanol and dried in hot air oven at 40^0C. The dried mucilage was powdered and stored in airtight container.

Preparation of Fast disintegrating tablets of Ondansetron HCl by direct compression method: Fast disintegrating tablets of Ondansetron HCl were prepared by direct compression method [13]. According to the formulae given in **Table 1**. All the ingredients were passed through #60 mesh separately. The drug and MCC were mixed by taking small portion of both each time and blending it to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using 6 mm round flat punches to get tablets of 100 mg weight on a 10-station rotary tablet machine (Clit, Ahmedabad).

TABLE 1: FACTORIAL DESIGN FORMULATIONS OF ONDANSETRON HCl PREPARED BY DIRECT COMPRESSION METHOD

Ingredients (mg/tablet)	Formulation code											
	OD F_0	OD F_1	OD F_2	OD F_3	OD F_4	OD F_5	OD F_6	OD F_7	OD F_8	OD F_9	C_1	C_2
Ondansetron HCl	4	4	4	4	4	4	4	4	4	4	4	4
Plantago ovate mucilage	---	2	2	2	6	6	6	10	10	10	4	8
Ocimum basilicum mucilage	---	4	6	8	4	6	8	4	6	8	5	7
MCC	10	0	15	30	0	15	30	0	15	30	7.5	22.5
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Sodium stearyl fumarate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Banana flavour	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol SD-200	78	82	65	48	78	61	44	74	57	40	71.5	50.5
Total	100	100	100	100	100	100	100	100	100	100	100	100

Formulation ODF_9 was selected as the best and used in further studies;
ODF_0 control formulation, C_1 and C_2 are extra design check-point formulation

Evaluation of Fast Disintegrating Tablets: The prepared Fast disintegrating tablets were evaluated for different parameters like hardness, thickness, friability, weight variation test, drug content, wetting time and water absorption ratio, *in vitro* dispersion time and *in vitro* dissolution test.

Hardness: The crushing strength of tablets was measured by using Monsanto hardness tester [14].

Thickness: Tablet thickness was measured by using Screw gauge. Three tablets were randomly taken, and measured by placing between two arms of Screw gauge.

Weight variation test: Twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu BL-220H). Tablets were weighed individually and compared with average weight [15].

Friability test: The friability of tablets was measured in Roche friabilator [16]. Twenty tablets were dedusted at 25 rpm for 4 min and weighed again. Percentage friability was calculated from loss in weight as given in equation below. The weight loss should not be more than 1% (**Table 2**).

% Friability = [(Initial weight _ Final weight)/Initial weight]×100.

TABLE 2: EVALUATION OF FACTORIAL FORMULATIONS

Formulation	Hardness* (kg/cm^2)± SD	Thickness (mm)	Friability (%)	*In vitro* dispersion time* (sec) ±SD	Drug content* (%)±SD	Wetting time* (seconds) ±SD	Water absorption ratio (%)
ODF_0	4.2±0.109	3.11	0.54	170±1.22	99.1±0.5	172.1±1.5	48.1
ODF_1	4.1±0.189	3.03	0.66	47.94±0.73	96.72±0.48	51.89±0.67	63.75
ODF_2	4.07±0.131	3.1	0.59	40.77±0.65	95.17±0.92	42.27±0.37	67.96
ODF_3	4.04±0.06	3.05	0.72	26.38±0.54	99.52±0.45	27.91±0.11	73.05
ODF_4	4.12±0.104	2.87	0.83	40.08±0.18	100.16±1.0	41.24±0.26	69.47
ODF_5	4.03±0.068	3.15	0.51	33.99±0.176	97.02±0.12	36.32±0.39	74.25
ODF_6	4.25±0.05	3.29	0.48	20.05±0.1	104.78±0.48	19.97±0.11	77.1
ODF_7	4.14±0.1	3.26	0.61	31.98±0.18	97.16±0.42	34.19±0.22	76.3
ODF_8	4.37±0.064	2.94	0.79	21.06±1.63	104.74±0.51	22.81±0.25	80.14
ODF_9	4.15±0.06	3.03	0.85	11.07±0.13	100.1±0.11	13.05±0.14	84.19
C_1	4.30±0.10	2.9	0.48	34.17±0.86	100.10±0.10	35.27±0.31	73.8
C_2	4.46±0.057	3.06	0.52	20.81±0.52	99.73±0.73	22.01±0.59	79.94

*Average of three determinations. Weight variation (95-105 mg) within the IP limits of ±10%

TABLE 3: *IN VITRO* DISSOLUTION PARAMETERS IN 0.1 N HCl

Formulation code	D_5 (%)	D_{10} (%)	DE_{10min} (%)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
ODF_0	29.0	48.5	26.89	4.3	10.5	>12
ODF_9	60.0	85.7	54.23	1.5	3.6	11.6
CCF	35.00	66.5	34.54	3.5	7.0	>12

ODF_0 is control formulation, ODF_9 is promising fast disintegrating tablet formulation, CCF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, DE_{10min} is dissolution efficiency at 10 min, $t_{25\%}$ is time for 25% drug dissolution, $t_{50\%}$ is time for 50% drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

Drug content: A tablet was crushed and dissolved 1 ml of dilute HCl and 30 ml of distilled water [17]. This solution was shaken for 15 min, the volume of this solution was made up to 50 ml with distilled water and centrifuged. 5 ml of the clear supernatant was mixed with 10 ml of 0.1 N HCl, and made up to 100 ml with distilled water. The absorption of the solution was determined spectrophotometrically at 249 nm. The same procedure was followed for another nine tablets.

Wetting time and water absorption ratio: For determination of wetting time and water absorption ratio [18], a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio 'R' was calculated using the equation: R=100×(Wa–Wb)/Wa, where Wa is weight of tablet after water absorption and Wb is weight of tablet before water absorption.

***In vitro* dispersion time:** *In vitro* dispersion time was determined by placing one tablet in a Petri dish containing 10 ml of water and the time required for complete dispersion was determined [19-20].

***In vitro* dissolution test:** *In vitro* dissolution studies of the optimized fast disintegrating tablets of Ondansetron HCl and commercial conventional tablet was performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of 0.1 N HCl at 37±0.5ºC as dissolution medium [21]. One tablet was used in each basket. Aliquotes of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10 and 12 min) and replaced with the equal volume of fresh medium. The samples were analyzed for drug content by measuring the absorbance at 249 nm. Drug concentration was calculated from the standard calibration curve and states cumulative percent drug dissolved.

Drug-excipient interaction study: IR spectra of Ondansetron HCl and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to ruled out drug-excipients interactions.

Stability testing: Accelerated stability studies on formulation ODF_9 were carried out by storing 15 tablets in an amber coloured rubber stoppered vials at 40o/75% RH over a period of 6 months.

Experimental design: The 3^2 full factorial design was used for the optimization of Fast disintegrating tablets of Ondansetron HCl (Design Expert 8.0.7.1).The two independent factors, concentration of *Plantago ovata* mucilage (X_1) and concentration of *Ocimum basilicum* mucilage (X_2), were set to three different levels and experimental trials were performed for all nine possible combinations [22]. The dependent response, *in-vitro* dispersion time (Y_1) was evaluated.

Validation of the experimental design: To validate the experimental design using a polynomial equation, the dependent response, *in-vitro* dispersion time was selected. The following second order polynomial equation was applied as a tool of mathematical modeling [23].

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 (b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for corresponding factor X_1 (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) describes the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

RESULTS AND DISCUSSION: Fast disintegrating tablets of Ondansetron HCl were prepared by direct compression method using *Plantago ovata* and *Ocimum basilicum* mucilages were natural superdisintigrants and MCC as diluent along with directly compressible mannitol (Pearlitol SD 200), which was used to enhance the mouth feel. A total of nine formulations, a control formulation (ODF_0, without superdisintegrant) and two extra-design check point formulations (C_1 and C_2 to check validity of the developed polynomial equation), were designed.

Powder blends were evaluated for the flow parameters such as angle of repose, tapped density, bulk density and Carr's index. As the material was free flowing (angle of repose values were found to be <30º and Carr's index <15%).

The tablets were evaluated for weight variation, uniformity of drug content, hardness, friability, *in vitro* dispersion time, *in vitro* dissolution studies, tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications (±10%). Drug content was found to be in the range of 95-105%, which is within acceptable limits. Hardness of the tablets was found to be 4.0 to 4.5 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Formulation ODF_9 was found to be promising and shown an *in vitro* dispersion time of 11 s, which facilitates faster dispersion in the mouth.

In order to investigate the factors systematically, a factorial design was employed in the present investigation. Formulation has been done by using 3^2 full factorial design, preparing nine batches of formulations (ODF_1 to ODF_9).

A polynomial equation was derived for *in vitro* dispersion time, by Design Expert 8.0.7.1 software. Formulation ODF_9 containing 10% w/w *Plantago ovata*, 8% w/w *Ocimum basilicum* mucilages were found to be promising with an *in vitro* dispersion time of 11 s against the 170s displayed by control formulation (DF_0), which does not contain the superdisintegrants.

In vitro dissolution studies on the promising formulation (ODF_9), the control (ODF_0) and conventional commercial tablet formulation (CCF) were carried out in 0.1 N HCl and the various dissolution parameter values, viz., percent drug dissolved in 5 min (D_5), 10 min (D_{10}), dissolution efficiency at 10 min (DE_{10}min), $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ are shown in Table 3 and the dissolution profile shown in **Fig. 1**. This data reveals that overall, the formulation ODF_9 has shown two-fold faster drug release ($t_{50\%}$ 3.6 min) when compared to CCF ($t_{50\%}$ 7min).

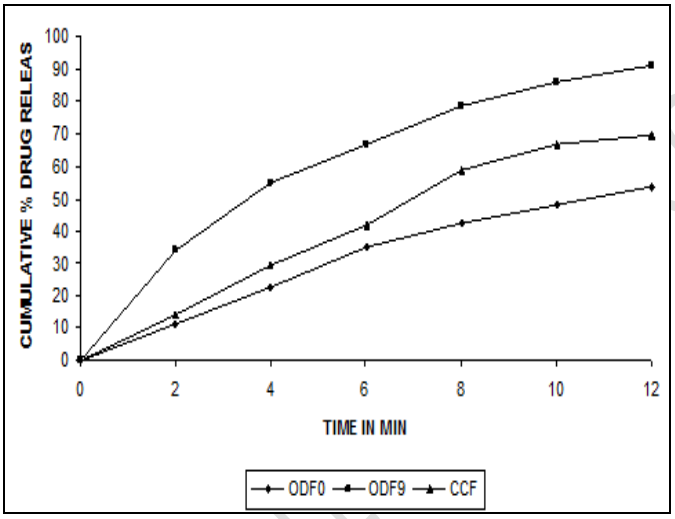

FIG. 1: *IN VITRO* CUMULATIVE PERCENT DRUG RELEASE VERSUS TIME PROFILE OF PROMISING ONDANSETRON HCL FORMULATIONS Plot showing cumulative percent drug release in 0.1 N HCl from control formulations (-♦-); promising ODF_9 formulation (-▪-); conventional commercial tablet formulation CCF (-▲-).

IR studies indicated that the drug is compatible with all the excipients. The IR spectrum of ODF_9 shown all the characteristic peaks of Ondansetron HCl, thus confirming that no interaction of drug with the components of the formulation. Short-term stability studies of the above formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 6 months period (P<0.05).

The equation derived for *in vitro* dispersion time of the factorial formulations is, Y_1= 30.36- 10.41 X_1- 8.49X_2. The negative sign for coefficients of X_1 and X_2 indicate that as the concentration of disintegrants increases, *in vitro* dispersion time decreases. Validity of this equation was verified by designing two extra design check point formulations (C_1 and C_2) and determining the *in vitro* dispersion time. The *in vitro* dispersion time values predicted from the equation for these formulations are 37.21 and 16.5 sec, where as those observed from experimental results are 39.76 and 20.96 sec, respectively. The closeness of the predicted and observed values for C_1 and C_2 in the method indicates validity of derived equation for the dependent variable (*in vitro* dispersion time). The computer generated response surface and contour plots for the dependent variable are shown in **Fig. 2** and **3**, respectively.

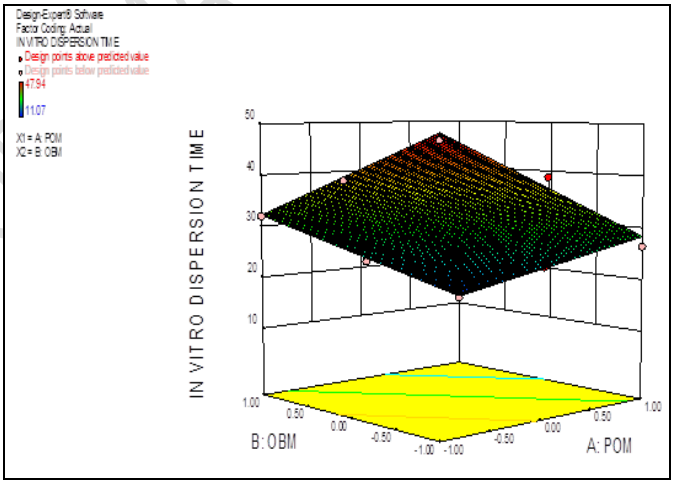

FIG. 2: RESPONSE SURFACE PLOT OF FACTORIAL VARIABLES ON *IN VITRO* DISPERSION TIME

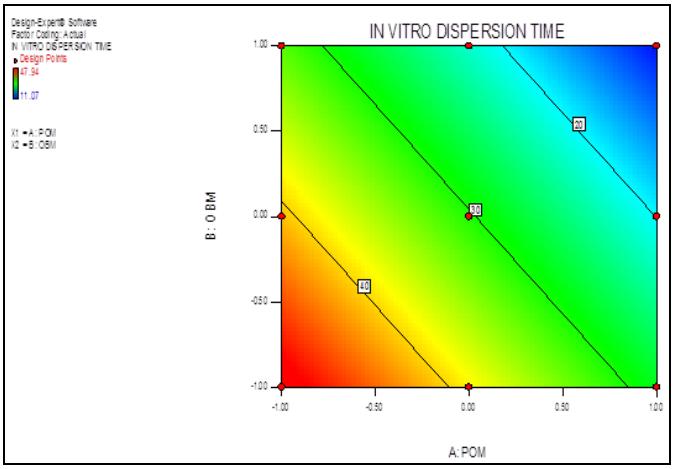

FIG. 3: CONTOUR PLOT OF FACTORIAL VARIABLES ON *IN VITRO* DISPERSION TIME

CONCLUSION: A 3^2 full factorial design revealed that the amounts of *Plantago ovata* mucilage (X_1) and *Ocimum basilicum* mucilage (X_2) significantly affect the dependent variable (Y_1), the *in vitro* dispersion time. It is thus concluded that, by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Direct compression method by using natural superdisintegrants would be an effective approach compared with the use of more expensive excipients in the formulation of fast disintegrating tablets with smaller disintegration time, improved drug dissolution, patient compliance, convenience and acceptability.

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