

DESIGN, DEVELOPMENT AND OPTIMIZATION OF FAST DISSOLVING TABLET OF ONDANSETRON HCl USING MANNITOL WITH CAMPHOR, A SUBLIMING MATERIAL

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ABSTRACT

Objective: The crucial aspect of present work was to develop fast dissolving tablet of Ondansetron HCl with rapid disintegration, adequate hardness and pleasant mouth feel.

Method: In the present work response surface approach was applied to investigate main and interaction effects of formulation parameters in optimizing fast dissolving tablet (FDT) formulation using subliming material (camphor) and mannitol. The variables studied were mannitol (X_1) and camphor (X_2). Tablets were prepared using sublimation technique.

Results: It was observed that the responses (disintegration time and hardness) were strongly affected by both the factors studied. The statistical models were validated and can be successfully used to prepare and optimized fast dissolving tablets of Ondansetron HCl with rapid disintegration (31 seconds) and excellent hardness (4.0 kg/cm²).

Conclusion: It was concluded that fast dissolving tablets with high mechanical strength and rapid disintegration without the use of superdisintegrant could be prepared, which provide better patient compliance.

Keywords: Ondansetron HCl, Fast dissolving tablet, Optimization, Factorial design, Sublimation technique.

INTRODUCTION

Tablets and capsules constitute a major portion of currently available drug delivery systems. However, many patient groups such as the elderly, children, the mentally retarded, or uncooperative, nauseated, or patients with dysphagia, have difficulty in swallowing these dosage forms. Fast dissolving tablets (FDT) are very beneficial for the patient with difficulties in swallowing and in condition where excess of water is difficult. These dosage forms when placed in the mouth disintegrate in the oral cavity within 60 s or less without the need for water, thus providing optimal convenience to the patient [1-2]. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients, they are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water and also the bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [3].

Innovators and inventor companies have given these tablets various names such as rapidly disintegrating, mouth dissolve, quick dissolving, fast melting, or Oro-disperse tablets [4-5].

This dosage form combines the advantages of dry and liquid formulations. The technologies should allow high drug loading, have an acceptable taste, offer a pleasant mouth feeling and leave minimal residue in the mouth after oral administration. The advantages of fast dissolving tablets are recognized by industry and patients, since there are several products available on the market. These products have a number of drawbacks, including the manufacturing methods used and the mechanical strength. Three techniques are mainly applied to formulate these tablets, namely freeze-drying, moulding and direct compression. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in the oral cavity [6-7]. The main disadvantages of this dosage form are, in addition to the cost intensive production process, the lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Moulded tablets reveal rapid disintegration and weak mechanical strength as well, yet their costs of manufacture are even higher. Therefore direct compression is a convenient and cheap way to produce tablets with sufficient structural integrity. The tablet's fast disintegrating property is attributable to the quick ingress of water into the tablet matrix, which depends on the tablet's porous structure, resulting in rapid disintegration. Ondansetron HCl is a

potent selective serotonin 5HT₃ receptor antagonist which has a role in prophylaxis of postoperative chemotherapy/ radiotherapy induced emesis. The adult dose is 8 mg and its metabolites are excreted in urine with about 10% of unchanged drug and having 67% of bioavailability through oral route.

In the present investigation FDT of Ondansetron HCl was developed by maximizing the porous structure of the tablet matrix, incorporating the porosity inducing agent and using highly water-soluble excipients. Further For systematic development of the formulation, an

Optimization technique based on response surface methodology was utilized. Response surface methodology can be defined as a statistical method that uses quantitative data from appropriate experiments to determine and simultaneously solve multivariate equations. It is generally used to determine the optimum combination of factors that yield a desired response and describes the response near the optimum. This methodology was used in the present study to optimize the variables affecting the formulation.

MATERIAL AND METHOD

Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Camphor was obtained from a local ayurvedic pharmacy. Mannitol, lactose and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. All other chemicals used in the study were of analytical reagent grade.

Methods

Preparation of drug polymer complex

The drug polymer complex (DPC) was prepared and characterized as per previously published method [8].

Formulation development

DPC was used to prepare FDT by direct compression technique. Composition of tablet is mentioned in (Table 1). All the raw materials were passed through a # 60 sieve prior to mixing. Drug polymer complex (1:5), containing amount equivalent to 10 mg of Ondansetron HCl, was mixed with the other excipients. The powder blend was lubricated with magnesium stearate and compressed on a 10 station mini press tablet machine (CPMD 3-10, ChamundaPharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm

concave punch. The tablets were dried in a vacuum oven for 4 h at a temperature of 60 °C and at a pressure of 300 mm Hg.

Table 1: It shows typical formula for fast dissolving tablet of Ondansetron HCl

Ingredients	Quantity (%) ^a
DPC	24
Camphor	0-40
Mannitol	10-50
Mag stearate	1.5
Lactose	q.s. to 250

^a Tablet weight = 250 mg

Experimental design of Ondansetron HCl fast dissolving tablets

A randomized 3 level full factorial design using two factors was adopted to systematically study the formulation of FDT of Ondansetron HCl. A total of 12 experimental run with 3 centre points were performed at all possible combination (Table 3). The amount of Mannitol (X_1) and concentration subliming agent, camphor (X_2) were selected as independent variable (Table 2). The disintegration time and hardness were selected as dependent

variable. The responses were analysed for analysis of variance (ANOVA) using Design Expert version 8.0 software. Statistical models were generated for each response parameter. The models were tested for significance.

Table 2: It shows variables in 3 level full factorial design

Independent variables-Factor	Levels (%)		
	Low (-1)	Middle (0)	High (+1)
X_1 = Mannitol	30	40	50
X_2 = Camphor	10	20	30

Dependent variable- Response
 Y_1 = Disintegration time (seconds)
 Y_2 = Hardness (kg/cm²)

Validation of statistical model

Levels of both the factors were selected at two different points and responses predicted by the statistical models were calculated. Fast dissolving tablets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

Table 3: It shows matrix of full factorial design and responses for each experimental run

Run	X_1 : Mannitol (%)	X_2 : Camphor (%)	Response ^a	
			Y_1 (sec.)	Y_2 (kg/cm ²)
1	-1	-1	35±0.89	4.2±1.51
2	0	0	23±0.57	3±1.32
3	0	0	23±0.73	3±1.57
4	0	-1	33±0.59	4.6±1.28
5	1	0	28±0.96	3.3±1.34
6	1	1	8±0.62	1.5±1.52
7	0	0	23±0.71	3.1±1.24
8	0	1	11±0.67	1.3±1.29
9	-1	1	12±0.91	1.2±1.47
10	0	0	22±0.85	3±1.19
11	-1	0	15±0.89	2.7±1.28
12	1	-1	32±0.90	4.9±1.30

^aData are expressed as mean±SD (standard deviation), n=3.

Response surface plots

Response surface plots were generated for each response to study the effect of both factors on each response.

Evaluation of prepared tablets

Uniformity of Mass

The test was performed as per specification given in I.P.1996 on 20 tablets. The maximum acceptable limit is ± 5% deviation of an individual mass from average mass.

Friability

Twenty tablets were weighed and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4min. The tablets were taken out, de dusted, and reweighed. The percentage friability of the tablets was calculated using the following equation [9]

$$F \% \left(1 - \frac{W}{W_0} \right) \times 100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Hardness

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Wetting time

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on

the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time [10].

Disintegration time

Disintegration of fast dissolving tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the centre of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time [11].

Dissolution studies

Tablet test condition for the dissolution rate studies were used according USP specification [12] using USP 24, type II apparatus. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2). The temperature of the dissolution medium and the rate of agitation were maintained at 37± 0.5° C and 50 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37± 0.5°C. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimadzu S 1700, Japan).

Scanning electron microscopy (SEM)

The optimized tablet was also observed by scanning electron microscope (ESEM TMP with EDAX, Philips, Holland). Pictures were taken at an excitation voltage of 30 kv and a magnification of 120 X.

RESULT AND DISCUSSION

Evaluation of tablet

The outcomes of various evaluation parameters are shown in (Table 4). In-vitro drug release profile of all factorial batches and optimized batch showed in (Fig. 1) and it was found to be more than 95% in 4 minutes than compare to 90 % in 10 minutes for marketed product (ONDEM MD8). The disintegration time of FDTs should be less than 60 s and ideally between 20 and 40 s. Thus, it was observed that the simple addition of a superdisintegrant could not obtain the most

desirable feature of an FDT, and that another suitable technique would have to be used. The vacuum- drying technique was then adopted to create a porous structure in the tablets. In this technique, subliming agent (camphor) was used to increase the tablets' porosity. The porous structure induced in the tablet matrix due to the sublimation of camphor was responsible for faster water uptake, thus facilitating rapid disintegration. On the other hand higher concentration of camphor formed fragile tablet, thus there was a need to optimize the concentration of camphor. Mannitol was used to increase the mechanical strength and provide pleasant mouth feel.

Table 4: It shows characterization of fast dissolving tablets

Parameters ^a Formulations	Weight (mg)	Friability (%)	Wetting time (Seconds)
OV1	249.5±1.25	0.32±0.54	25±1.48
OV2	250.2±1.47	0.64±0.47	14±1.59
OV3	251±1.59	0.67±0.53	13±1.28
OV4	248.5±1.25		24±1.39
OV5	250±1.39	0.58±0.27	19±1.25
OV6	249.5±1.28	1.2±0.39	4±1.29
OV7	250±1.45	0.56±0.58	14±1.44
OV8	250±1.28	1.8±0.37	5±1.57
OV9	250.5±1.39	1.6±0.48	5.5±1.04
OV10	249.8±1.40	6.2±0.47	12±1.43
OV11	250.5±1.25	7.2±0.53	7±1.41
OV12	251±1.32	0.24±0.63	22±1.29

^a Data are expressed as mean±SD (standard deviation), n=3.

Statistical design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_1^2 X_1^2 + b_2^2 X_2^2 + b_1 b_2^2 X_1 X_2^2$$

Y is the measured response associated with each factor-level combination, b_0 is the arithmetic mean response of the total 12 runs, X_1 and X_2 are the factors studied, b_1 is the regression coefficient for factor X_1 computed from the observed response Y. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1 X_2$) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. Two conclusions could be drawn from the equation: (1) a coefficient with a negative sign increases the response when the factor level is decreased from a higher level to a

lower level, and (2) the factor with a higher absolute value of the coefficient and a lower significance value "P" has a major effect on the response variables.

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The dependent variables, Disintegration time and Hardness showed a wide variation (11 s to 35 s and 1.2 to 4.9 kg/cm² respectively). The data clearly indicates that the response variables are strongly dependent on the selected independent variables. The high values of the correlation coefficient for disintegration time and the hardness indicate a close fit.

The fitted equations (full and reduced) relating the responses to the transformed factor are shown in (Table 7). Analysis of variance (ANOVA) was carried out to identify the insignificant factors, which were then removed from the full model to generate the reduced model (Table 5) and (Table 6).

Table 5: It shows ANOVA for response surface reduced cubic model for disintegration time

Response model	Sum of square	df	Mean square	F value	P value	R ²	Adequate precision
DT	892.75	6	148.79	343.37	<0.0001	9976	52.708

The Model F-value of 343.37 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. "Adeq Precision" measures the signal to noise ratio. A

ratio greater than 4 is desirable. The ratio of 52.708 indicates an adequate signal. This model can be used to navigate the design space.

Table 6: It shows ANOVA for response surface reduced quadratic model for hardness

Response model	Sum of square	df	Mean square	F value	P value	R ²	Adequate precision
Hardness	16.16	4	4.04	1885.53	<0.0001	0.9991	126.057

The Model F-value of 1885.53 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are

significant. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 126.057 indicates an adequate signal. This model can be used to navigate the design space.

Table 7: It shows summary of result of regression analysis:

Model*	b_0	b_1	b_2	b_{12}	b_1^2	b_2^2	$b_1 b_2^2$
FM	22.58	-6.50	-11.50	-0.25	-0.75	-0.25	-8.25
RM	22.58	-6.50	-11.50	-	-	-	-8.25
Model*	b_0	b_1	b_2	b_{12}	b_1^2	b_2^2	$b_1 b_2^2$
FM	3.02	0.27	-1.62	-0.10	-	-0.067	-

For disintegration time, the coefficients of X_1 and X_2 that is, b_1 , and b_2 respectively, bear a negative sign, thus on increasing the concentration of Mannitol and concentration of camphor, a decrease in disintegration time is observed. For hardness, the coefficients of X_1 and X_2 that is, b_1 , and b_2 respectively, bear a positive sign and negative sign respectively, thus on increasing the concentration of mannitol and concentration of camphor, an increase and decrease in hardness is observed. When a higher percentage of camphor is used, porosity in the tablet matrix is greater and thus assists in water uptake and subsequent disintegration. Further result showed that mannitol concentration had significant effect on tablet hardness, thus by using combination of mannitol and camphor provide tablets with high mechanical strength with low disintegration time.

Validation of statistical model

To validate the statistical model checkpoint batches, CP1 and CP2 were prepared according to the formula (Table 8). From the response surface plot (Fig. 2 and Fig. 3) and the calculations from the statistical equation obtained by regression, the results revealed the close match of the experimental results. Thus, we can conclude that the statistical model is mathematically valid. The best batch was selected after considering the requirements of an FDT. To full fill these requirements, concentration of mannitol was set maximum and concentration of camphor 15%. Disintegration time and hardness were kept in range. The batches' dissolution rates were also considered and batches with higher dissolution rates were given priority. Different constraints were applied; solution with desirability 1 was selected (Table 9).

Table 8: It shows comparison of predicted values and experimental values for check point batches

Formulation code	Predicted Values (DT)	Experimental Values (DT) ^a	Residual	Predicted Values (Hardness)	Experimental Values (Hardness) ^a	Residual
CP1 $X_1 = +1$ $X_2 = +0.75$	15.81	17±1.24	1.1	1.96	2±0.89	0.04
CP2 $X_1 = +0.75$ $X_2 = +1$	9.76	11±1.17	1.24	1.4	1.6±0.95	0.02

^a Data are expressed as mean±SD (standard deviation), n=3.

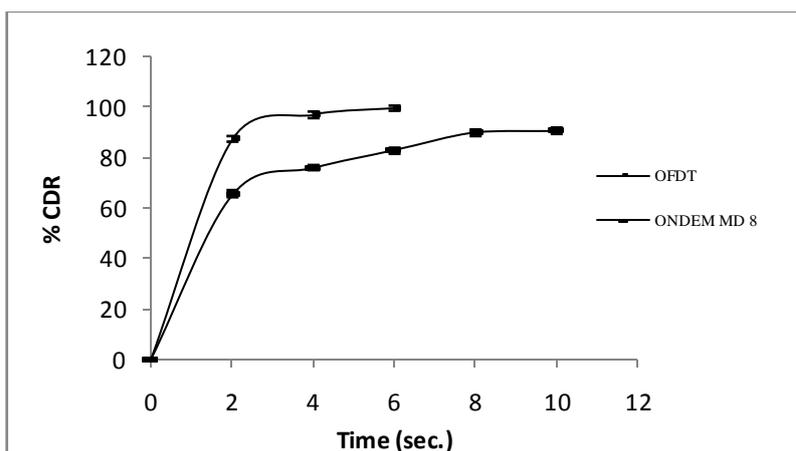


Fig. 1: It shows in-vitro release profile of optimized formulation (OFDT) and marketed product (ONDEM MD 8)

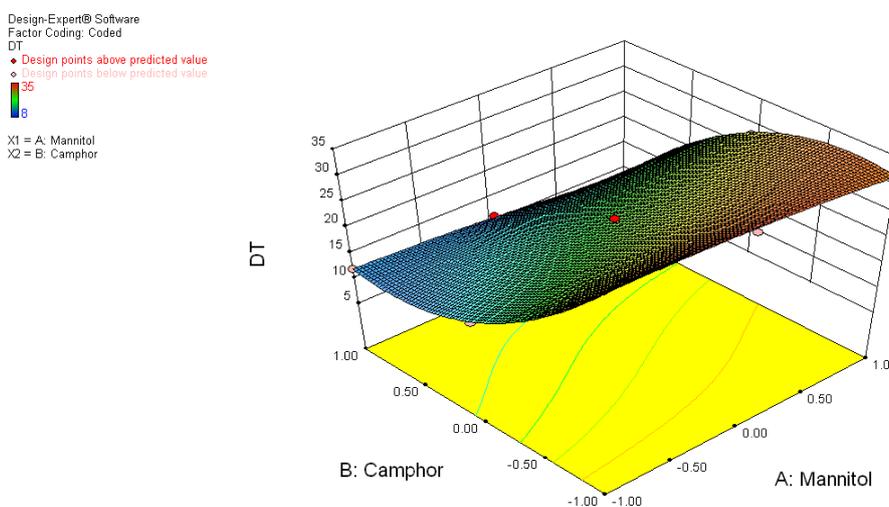


Fig. 2: It shows response surface plot eliciting the effect of X_1 (mannitol concentration) and X_2 (camphor concentration) on Y_1 (DT)

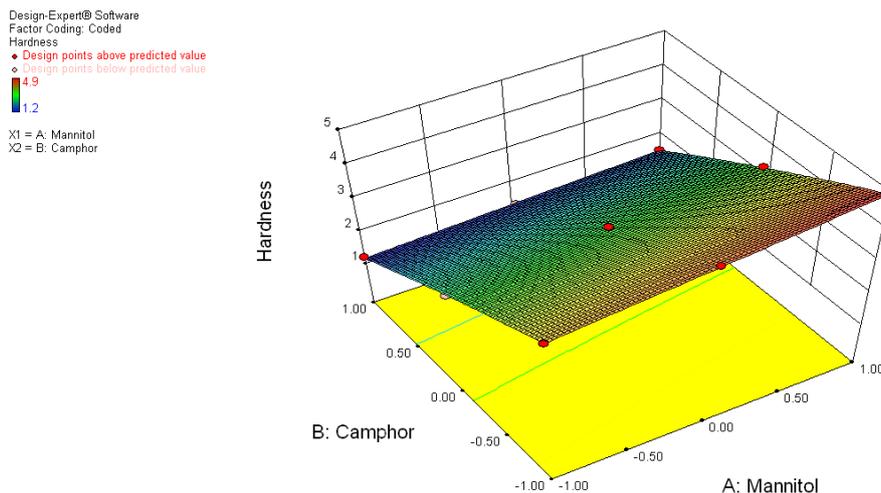


Fig. 3: It shows response surface plot eliciting the effect of X_1 (mannitol concentration) and X_2 (camphor concentration) on Y_2 (hardness)

Table 9: It shows predicted desirability:

Number	Mannitol	Camphor	Hardness	DT	Desirability	
1	50	15	4.125	32.0833	1.000	Selected
Predicted response at 95% confidence (n=1)						
Response	Prediction	Std Dev	SE (n=1)	95% PI low	95% PI high	Response
Hardness	4.125	0.046291	0.054281	3.9964	4.25335	Hardness
DT	32.0833	0.658281	0.841161	29.9211	34.2456	DT

Friability of optimized tablet was below 1% which showed good mechanical resistance. All the parameters i.e. thickness, diameter, weight, friability, drug content and wetting time were under acceptable limits.

Table 10: It shows characterization of optimized tablet (OFDT)

Parameters ^a	Thickness (mm)	Diameter (mm)	Weight (mg)	Friability (%)	Drug Content (%)	Wetting time (Seconds)
Formulations	3.9±0.72	9.0±0.24	250±1.38	0.36±0.89	99.57±1.18	23±0.68

^aData are expressed as mean±SD (standard deviation), n=3.

(Fig. 4) shows a micrograph of the cross section of a high porosity fast dissolving tablet. It was found that many porous cavities in the tablet were formed due to the sublimation of camphor.

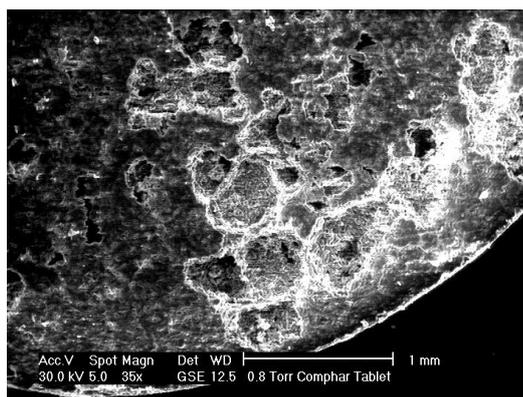


Fig. 4: It shows SEM Micrograph of the cross sectional view of optimized tablet after sublimation

Comparison of predicted responses and observed values for the disintegration time and hardness were in close agreement (Table 11), and the models were found to be valid. Thus, full factorial design with two factors can be successfully used to optimize the formulations.

Table 11: It shows comparison between predicted and observed response

Predicted Values ^a (Disintegration time)	Experimental Values ^a (Disintegration time)	Predicted Values ^a (Hardness)	Experimental Values ^a (Hardness)
32.0833±0.65	31±0.81	4.125±0.046	4.0±1.025

^aData are expressed as mean±SD (standard deviation), n=3.

CONCLUSION

Response surface methodology was used to generate a highly significant mathematical model. A statistical experimental design allowed collecting maximum information with minimum number of experiments. In the present investigation Fastdissolving tablets of Ondansetron HCl having rapid disintegration and good mechanical strength was prepared using sublimation technique. Result of the study showed that disintegration time and hardness was strongly dependent on concentration of mannitol and camphor. Comparison of predicted responses and observed values for the same showed close agreement, and the models were found to be valid. Hence, 3 level full factorial design and statistical models can be successfully used to optimize the formulations.

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