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OPTIMIZATION OF EFFECT OF SUPERDISINTEGRANTS AND SUBLIMING AGENT ON ORODISPERSIBLE TABLET OF ONDANSETRON RESINATE

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ABSTRACT

Ondansetron is a serotonin $5HT_3$ antagonist; anti emetic drug. Bitter taste of the ondansetron is a major problem in ensuring patient compliance. Resinates of ondansetron were prepared with Indion 234 and loading process was optimized. A 3^2 factorial design was used for formulation development of orodispersible tablet of these taste masked resinates. The amount of subliming agent (camphor) and superdisintegrants (sodium starch glycolate) were taken as formulation variables (factors) for optimizing disintegration time, drug release after 15 minutes and friability as dependent or response variables. A mathematical model was generated for each response parameter. The disintegration time was found to linearly increase with the increase in the amount of superdisintegrants. The percentage friability showed no definite relationship with either amount of subliming agent or superdisintegrants. The optimum formulations were chosen by grid search method and their predicted results were found to be in close agreement with experimental findings.

INTRODUCTION: Fast disintegrating /dissolving drug delivery system is a novel system which has advantages such as administration without water anytime and anywhere specially for geriatric and paediatric patients. It is also suitable for mentally ill, bedridden and patients who do not have easy access to water. The benefits in terms of patient compliance such as rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. In addition, several business benefits such as expanded product lines, improved life cycle management, extended patent life and marketing advantages [2, 3]. The basic approach is to bring about fast disintegration due to increased water uptake which causes explosion of tablet matrix [2]. Various superdisintegrants like crosscarmellose sodium, sodium starch glycolate and crosspovidone are used.

However; there are various other techniques are reported such as lyophillization [6] and vacuum drying [7, 8] these involve maximization of the pore structure of tablet matrix, thus leading to enhanced disintegration. But it yields tablets, which are fragile and hygroscopic. Sublimation, a useful technique that gives less fragile tablets by formation of a porous hydrophilic matrix which picks up disintegrating medium and disintegrates quickly [7]. Various other patented technologies like Zydis, Oraquick, Durasolv, Flash dose; Wowtab etc are also been used to prepare fast disintegrating tablets [8]. Systematic optimization technique can be successfully employed for the design and development of oral disintegrating tablets. These studies usually involve the use of response surface methodology (RSM), which has proven to be a useful tool in the development of solid dosage forms. Factorial design is one such optimization technique, where all the factors are studied in all possible combination. This technique is considered most efficient in estimating the influence of individual variables (main effects) and their interaction using minimum experimentation.

A Factorial Design for two factors at three levels each 3^2 is considered identical to a two factor composite design [10, 12]. The main aim of the current study was to develop and optimize the fast disintegrating tablets of taste-masked ondansetron resinates prepared by wet granulation for oral delivery. A computer aided optimization process using a 3^2 factorial design was employed to investigate the effect of two independent variable (factors) i.e.; amount of subliming agent: camphor and amount of superdisintegrants; Sodium starch glycolate (SSG). The disintegration time, release after 15 minutes and percentage friability were taken as the response variables.

Mouth dissolving tablets are also suitable for [7]:

- Patients suffering from nausea or vomiting;
- Patients with upper gastrointestinal tract disease e.g., injury in food pipe;
- Patients who have undergone upper GI surgery;
- Elderly patients e.g. Suffering from parkinson's disease;
- Children;

MATERIALS AND METHODS:

Method of Analysis [4]: The drug was estimated spectrophotometrically at 272.6 nm using JASCO-V520 UV VIS spectrophotometer over concentration range of 2-12 µg/ml.

Drug Loading: For drug loading batch method [1] was used. Drug solution of concentration 1mg/ml was prepared in deionised water; the required quantity of resin was placed in drug solution and was stirred till attainment of equilibrium. Time for attainment of equilibrium was decided to be 6 h. from preliminary experimentation. The slurry was filtered and amount of drug remaining in the filtrate was determined spectrophotometrically. The amount of drug adsorbed was determined by the difference between amount of drug present in stock solution and amount remaining in filtrate at the end of equilibrium.

Optimization of Drug Loading Process: The resin that showed highest loading efficiency was optimized for the drug: resin ratio. The loading efficiency of optimized ratio was further checked to find optimum pH conditions for drug loading.

Determination of Drug Content of Resinate: - Resinate (100mg) was placed in 1M HCl and stirred at 100 rpm for one hour. The solution was filtered and analyzed for content of ondansetron. Stability of complexes was determined by placing weighed quantity of complex in deionized water for 24 hours and analyzed for drug content.

Taste Evaluation: [5, 6] Evaluation of taste was done in two parts;

- Determination of threshold bitterness concentration**:** Various concentrations (1-30 mcg /ml) of drug were prepared in phosphate buffer pH 6.7. Mouth was rinsed with phosphate buffer and then, l0 ml of the most dilute solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 seconds. If the bitter sensation was no longer felt in the mouth after 30 seconds, the solution was spat out and wait for 1 minute to ascertain whether this is due to delayed sensitivity. Then rinse with safe drinking water. The next highest concentration should not be tasted until at least 10 minutes have passed. The threshold bitter concentration is the lowest concentration at which a material continues to provoke a bitter sensation after 30 seconds. After the first series of tests, rinse the mouth thoroughly with safe drinking water until no bitter sensation remained. Wait for at least 10 minutes before carrying out the second test.
- ***In-vitro*** **Evaluation of Bitter Taste of Resinates:** An accurately weighed (8 mg drug equivalent) resinate and 10 ml of pH 6.7 phosphate buffer (0.1 M) was taken in series of volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0,10, 30,60 and 120 sec., dispersion was filtered, and the concentration of ondansetron in filtered resinate was determined. Time for resinate to achieve drug concentration corresponding to threshold bitterness in 10 ml phosphate buffer is recorded.

Formulation of Orodispersible Tablets of Resinate: The tablets were formulated using resinate equivalent to 8 mg of drug, superdisintegrants, camphor, talc and lactose. Nine formulations were prepared as per table 1.

TABLE 1: DOE PARAMETER SETTINGS IN THE 3^2 FACTORIAL DESIGN LAYOUTS

Coded Levels	Actual Levels	
	X_1	X_2
-1	0	6
0	15	12
1	30	18

TRIAL		1	2	3	4	5	6	7	8	9
CODED FACTOR LEVELS	X_1	-1	-1	-1	0	0	0	1	1	1
	X_2	-1	0	1	-1	0	1	-1	0	1

Translation of coded levels in actual units; X_1 indicates amount of camphor (mg), X_2 amount of sodium starch glycolate (mg)

Evaluation of Tablet Properties: 10 tablets of each batch were evaluated for tablet weight, content uniformity and hardness. The hardness of the tablets was measured using a Monsanto hardness tester (Campbell, Mumbai, India). The wetting time of tablets war measured using a simple procedure. A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of distilled water. A tablet having amaranth powder on the upper surface is placed in folded tissue paper.

Time required to develop red color on the upper surface of tablet is recorded as wetting time [11]. The friability of a sample of 10 tablets from each batch was measured using a Roche Friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India). The weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines (using no. 85 mesh screen) and the % weight loss was calculated. The disintegration time was measured using a modified disintegration method (n=3). For this purpose, a petri dish 10cm (in diameter) was filled with 10ml of water. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine packets was noted [10].

***In vitro* Release:** Drug release studies (n=6) were conducted for all the formulation combinations using dissolution rate test apparatus (DA-6D USP Standard). 0.1 M HCl (900ml) was taken as release medium at 50rpm and 37±1 ^{0}C employing USP XXIII paddle method (apparatus 2). Aliquots of 10ml samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically (Jasco V-530 UV/VIS Spectrophotometer) at 272.6 nm.

Data Analysis: Various computations for the current optimization study using RSM were carried out, employing software Design Expert Version 7 [12] and MS EXCEL. Statistical second order models including interaction and polynomial terms were generated for all the response variables. The general form of the model is represented as in equation given below.

$$Y = \beta o + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X1^2 + \beta 5X2^2 + \beta 6X1X2^2 + \beta 7X1^2X2 + \beta 8X1^2X2^2 \quad (1)$$

Where Y is the dependent variable, βo is the arithmetic mean response of the nine runs, β1

to β8 are the coefficient computed from the observed experimental values of Y, and X1 and X2 are coded levels of independent variables. The interaction term X1X2 show how response changes when the two factors are simultaneously changed and the polynomial terms Xi^2 (i = 1, 2) are included to investigate nonlinearity. Subsequently, feasibility as well as grid search method was performed to locate the composition of optimum formulation. Also, three dimensional response surface graphs and contour plots were drawn in MS- Excel using the output files generated by the Design Expert Version 7 software [10].

Validation of Optimization Model: Nine optimum formulations were selected by intensive search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of formulation was primarily based on the highest possible values of disintegration time, drug release after 15 minutes and friability. The formulation corresponding to these formulations were prepared and evaluated for various responses.

The resultant experimental data of responses were subsequently quantitatively compared with the predicted values. Also, linear regression plots between observed and predicted values of the responses were attempted using MS- Excel, forcing the line through the origin.

RESULTS AND DISCUSSION: The % drug content in drug resin ratio of 1:1 is more and drug loading is also more with low concentration of resin hence ondansetron: indion-234 (1:1) selected for further study (Table 2). The threshold bitterness concentration was found to be 20 µg/ml as indicated by volunteers, such concentrations was not achieved even after 2 min in *in vitro* dissolution of drug equivalent resinate in simulated salivary buffer (table 3).

TABLE 2: EFFECT OF DRUG: RESIN RATIO ON LOADING

RESIN	DRUG: RESIN RATIO	% DRUG CONTENT OF RESINATE
Indion 234	1:0.5	41.20± 0.4083
	1:1	44.77± 0.3885
	1:1.5	45.85 ± 0.1836
	1:2	47.73 ± 0.2405

The % drug content in drug resin ratio of 1:1 was not improved in higher resin content; the pH had no effect on drug loading

TABLE 3: TIME FOR ATTAINMENT OF THRESHOLD BITTERNESS & *IN VITRO* CONCENTRATION (N =5)

STIRRING TIME (S)	CONCENTRATION (µG/ML)
0	1.25± 0.124
5	1.45± 0.2587
10	1.57± 0.2478
30	1.91± 0.1569
60	3.75± 0.1782
120	6.62± 0.2247

The orodispersible tablets of ondansetron are beneficial in case of vomiting and nausea. The fast disintegration was brought about by use of superdisintegrants and also due to high porosity tablets. Preliminary studies carried out prior to experimental design involved the use of various superdisintegrants and subliming agents and accordingly, a suitable range for each was selected as depicted in table 1.

OPTIMIZATION RESULTS: Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on response variable [14]. In the current study, a 3^2 full factorial design was used. The mathematical relationship constructed for the studied response variables are expressed in equation (2) – (4). All the polynomial equations were found to be highly statistical significant (P< 0.001) as determined by ANOVA.

% FRIABILITY = 1.02 + 0.26*A[1] + 0.025*A[2] - 0.24B[1] + 0.024*B[2] - 0.075*A[1] B[1] - 0.04* A[2]B[1] + 4.583*10^{-3}* A[1] B[2] + 9.306* 10^{-3}A[2] B[2] ---------- (2)

REL in 15 mins = 73.15 + 12.13* A[1] - 1.74A[2] + 3.65* B[1] + 0.72* B[2] - 3.78 A[1] B[1] + 1.97A[2] B[1] + 0.87A[1] B[2] + 0.18A[2] B[2]---------- (3)

DT = 58.56 – 37.67*A[1] + 8.44*A[2] - 21.50* B[1] - 0.72*B[2] + 12.75A[1] B[1] - 3.75A[2] B[1] - 0.083A[1] B[2] - 1.03A[2] B[2] ----------(4)

The response surface plotted (fig. 1) for all the three response variables shows that with the increasing amount of camphor and sodium starch glycolate, the disintegration time and percent drug release also increased linearly (Figure 1 (a), (b) and (c). Application of two-way ANOVA based factorial analysis indicates that high amount of camphor and sodium starch glycolate has a significant influence on disintegration time and percent drug release (P<0.001).

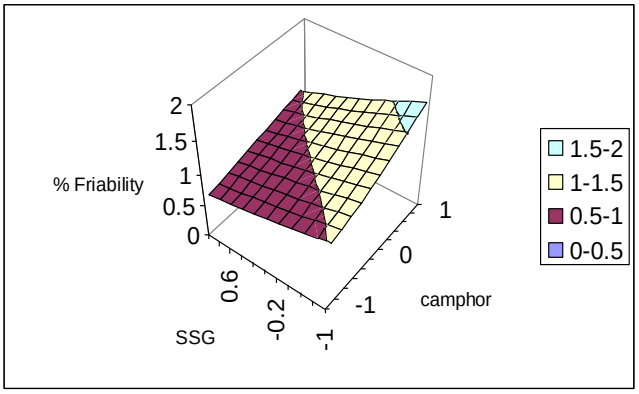

FIG. 1 (A): RESPONSE SURFACE PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON % FRIABILITY

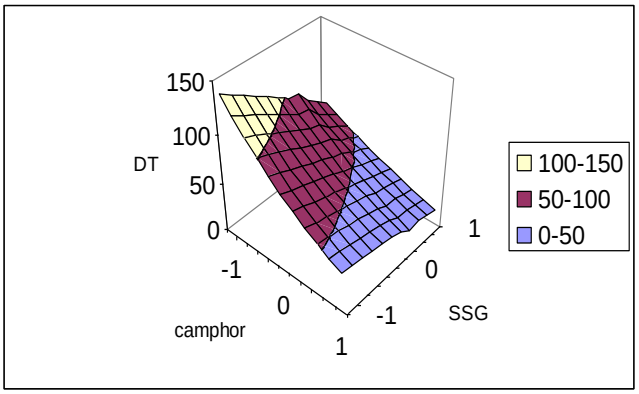

FIG. 1 (B): RESPONSE SURFACE PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON DISINTEGRATION TIME (DT)

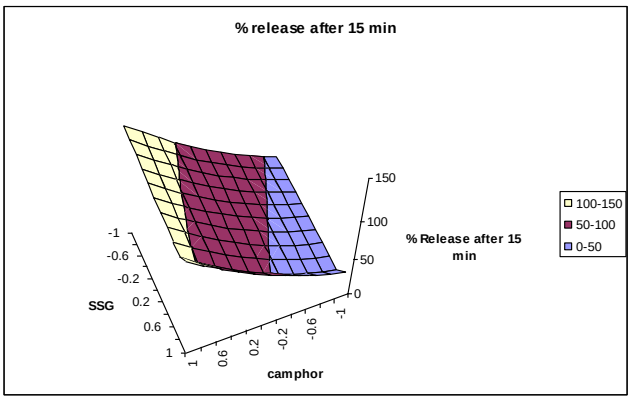

FIG. 1 (C): RESPONSE SURFACE PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON % RELEASE FOR ORODISPERSIBLE TABLETS OF ONDANSETRON

Subsequent application of one-way ANOVA showed a statistically significant difference amongst the observed data for disintegration time and percent release (P<0.001), ratifying the significant positive influence of each factor on both disintegration time and percent release in 15 minutes. It is seen when higher percentage of camphor is used, higher porosity is expected in tablets. Due to increased porosity the water uptake is also increased which further facilitates disintegration. It is obvious that in presence of high concentration of superdisintegrants, sodium starch glycolate faster disintegration is facilitated [13]. However percentage friability of all the formulation gave nonlinear results but it was observed that with highest level of camphor, the % friability was found to be more than 1% due to increased porosity. The amount of superdisintegrants didn't show any significant effect on percentage friability, disintegration time and % release. (Fig: 2, 3, 4 respectively). Application of one-way ANOVA based analysis showed that camphor alone had significant effect on friability.

Table 4 gives records of the value of observed and predicted responses using factorial design along with percentage prediction error for these nine optimum formulations (Table 5). The prediction error for the response variable ranged between -2.983 to 2.011 with the mean ± SD of the percentage error -0.45±1.351%. Also high values of r^2 (ranging between 0.9936-0.9974) between the predicted and observed responses indicate excellent fit .thus low magnitude of error as well as the significant value of r^2 designate a high prognostic ability of RSM.

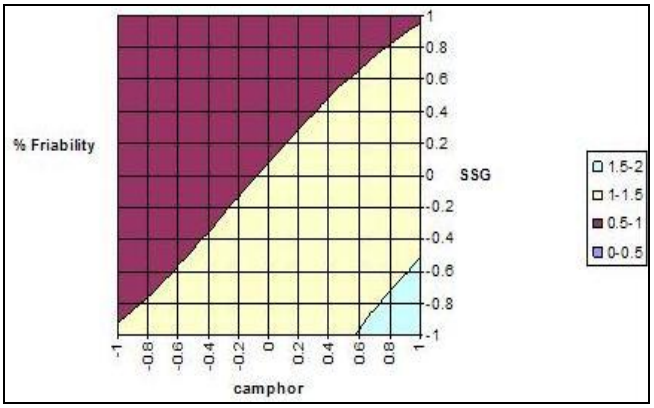

FIG. 2: CONTOUR PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON % FRIABILITY

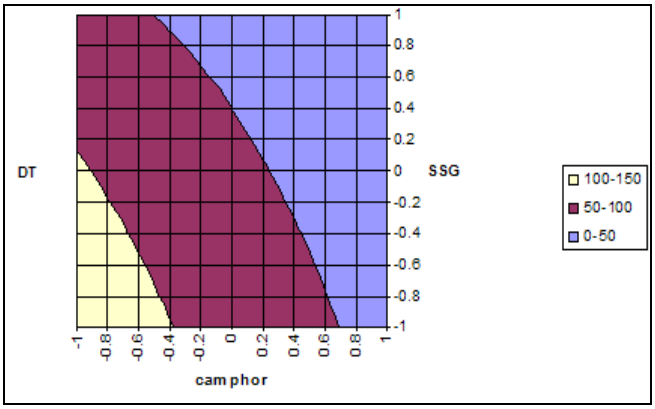

FIG. 3: CONTOUR PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON DISINTEGRATION TIME (DT)

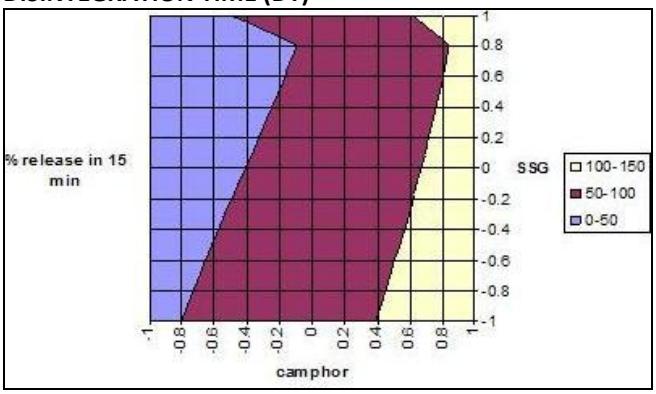

FIG. 4: CONTOUR PLOTS SHOWING INFLUENCE OF CAMPHOR AND SODIUM STARCH GLYCOLATE ON % RELEASE FOR ORODISPERSIBLE TABLETS OF ONDANSETRON

TABLE 4: PROPERTIES OF ONDANSETRON TABLETS PREPARED AS PER FACTORIAL DESIGN

TRIAL	FORMULATION COMPOSITION		DT (S) ± SD min ± SD	RELEASE IN 15 ± SD	% FRIABILITY
	X_1	X_2			
1	0	12	140±2.588	49.23±0.046	1.012 ± 0.029
2	0	6	108±2.236	59.14±0.0280	0.730 ± 0.046
3	0	18	64±3.536	68.70±0.095	0.612 ± 0.044
4	15	6	55±2.302	79.27±0.092	1.139 ± 0.023
5	15	12	39±1.673	75.91±0.086	0.962 ± 0.031
6	15	18	29±2.881	76.77±0.082	0.818 ± 0.058
7	30	6	39±2.775	83.47±0.093	1.700.± 086
8	30	12	33±2.387	87.61±0.081	1.23 ± 0.047
9	30	18	15±3.209	87.14±0.041	0.99 ± 0.019

TABLE 5: EXPERIMENTALLY OBSERVED RESPONSE PARAMETER OF NINE OPTIMUM FORMULATION AND COMPARISON WITH PREDICTED VALUES FOR VALIDATION OF RSM

FORMULATION	RESPONSES	PREDICTED RESULTS	EXPERIMENTAL RESULTS	PERCENT ERROR
F1	DT (sec)	25.41	26.15	2.91
	% Rel 15 min.	89.73	88.36	- 01.64
	% Friability	1.003	1.042	3..55
F2	DT (sec)	22.49	22.32	- 07.68
	% Rel 15 min.	89.74	87.98	- 12.02
	% Friability	1.069	1.035	4.42
F3	DT (sec)	25.31	25.01	-4.99
	% Rel 15 min.	89.59	86.15	-3.85
	% Friability	0.9467	0.991	4.47
F4	DT (sec)	28.34	27.61	-0.0988
	% Rel 15 min.	88.56	88.09	0.410
	% Friability	0.932	0.998	0.503
F5	DT (sec)	14.91	15.83	-1.199
	% Rel 15 min.	94.99	94.90	-0.020
	% Friability	0.973	0.961	0.822

F6	DT (sec) % Rel 15 min. % Friability	31.13 83.22 0.762	32.80 85.02 0.845	0.217 0.950 1.972
F7	DT (sec) % Rel 15 min. % Friability	47.61 86.31 1.480	44.99 82.82 1.398	-1.416 -0.603 -2.727
F8	DT (sec) % Rel 15 min. % Friability	46.76 88.78 1.228	44.81 85.10 1.640	-1.989 -0.792 0.0737
F9	DT (sec) % Rel 15 min. % Friability	36.63 86.61 1.013	37.64 84.51 0.988	0.823 -0.071 -1.480
Mean % Error ± SD				-0.49 ±1.249

Physical Evaluation of Optimum Formulations Prepared by Intensive Search: The tablet weights varied from 148.5 to 152.8 mg and hardness was kept between 4-5 kg/cm². The assay content of ondansetron varied between 98.6% and 99.5%, the wetting time ranged between 30- 160 seconds and water absorption ratio was in the range 18.14 to 35.71.

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