

# Formulation and Optimization of Varenicline Tartrate Dispersible Tablets: A Central Composite Design Approach

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Boddeda *et al.*: To Formulate and Characterize Varenicline Tartrate Dispersible Tablets

Varenicline tartrate is a smoking cessation aid that works by blocking nicotine receptors in the brain. It helps reduce cravings and withdrawal symptoms and helps you quit smoking. The study aimed to formulate and characterize varenicline tartrate orodispersible tablets using the synthetic disintegrants crospovidone and croscarmellose sodium in different ratios and directly compressible microcrystalline cellulose as diluent, and mannitol to improve mouthfeel using the direct compression method. A total of 13 varenicline orodispersible tablets are formulated and subsequently evaluated for pre-compression and post-compression physicochemical parameters such as angle of repose, Carr index, Hausner ratio, hardness, thickness, mass variation, drug content, friability, wetting time, disintegration time, dispersion time and water absorption ratio. Optimization was performed with percentage of crospovidone ( $X_1$  or A) and croscarmellose sodium ( $X_2$  or B) as independent variables, while disintegration time ( $Y_1$ ) and wetting time ( $Y_2$ ) were selected as dependent variables using the central composite design of Design-Expert® DX 12. Optimized formulations showed 99.68 % drug release in 60 min while the cumulative percentage drug release of pure drug was only 56.84 %. Finally, it was concluded that dissolution rate and bioavailability are improved with varenicline tartrate orodispersible tablets.

**Key words:** Varenicline tartrate, orodispersible tablets, super disintegrants, croscarmellose sodium, crospovidone

For every death caused by cigarette smoking, 30 people are left living with serious tobacco-related illnesses. Globally, the burden of disease will increase, with approximately 6 million deaths per year rising to a forecast of 8 million by 2030<sup>[1]</sup>. Nicotine provides rapid relief from cravings and withdrawal symptoms, contributing to high rates of failure and the need for repeated quit attempts. Therefore, there is a great need for more effective smoking cessation aids than nicotine replacement therapy and extended-release bupropion, which are moderately effective, with an odds ratio of  $\leq 2$  compared to placebo<sup>[2]</sup>. Varenicline tartrate acts on the Alpha-4 Beta-2 ( $\alpha 4\beta 2$ ) nicotinic receptor, which is the same receptor targeted by nicotine inhaled from smoke<sup>[3]</sup>. Unlike nicotine replacement therapy, varenicline has a dual effect by simultaneously reducing cravings and blunting the reward and pleasure associated with smoking through partial nicotinic acetylcholine receptor agonist activity<sup>[4]</sup>. It has a longer half-life compared to nicotine replacement therapy, which may be important in the hospital setting. Biopharmaceutics Classification System (BCS) class I indicate that varenicline tartrate is likely to have good bioavailability and predictable pharmacokinetics when

administered orally<sup>[5]</sup>. This classification also implies that varenicline tartrate is suitable for formulation into a variety of oral dosage forms, including tablets, capsules, and solutions, which contributes to its effectiveness as a smoking cessation aid. To facilitate rapid dissolution and absorption, it is necessary to develop fast-dissolving tablets of varenicline tartrate. This can lead to a faster onset of action and provide relief from cravings and withdrawal symptoms soon after administration<sup>[6]</sup>. Such tablets have the potential to improve the efficacy of varenicline by ensuring rapid absorption and distribution of the drug in the body. In addition, the ease and convenience of using fast-dissolving tablets may improve patient compliance with the prescribed treatment regimen. When patients find medication easy, they are more likely to adhere to the prescribed dosing schedule, increasing the likelihood of successful smoking cessation outcomes<sup>[7]</sup>.

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The rapid dissolution of the tablet is due to the rapid penetration of water into the matrix of the tablet, which results in its rapid disintegration. Thus, approaches to Orodispersible Tablets (ODT) development include maximizing the porous structure of the tablet matrix, incorporating a suitable disintegrating agent, and using highly water-soluble excipients in the formulation<sup>[8]</sup>. Hence, the present study aimed to formulate ODTs of varenicline tartrate using the direct compression method using various super disintegrants.

## MATERIALS AND METHODS:

The following ingredients were used in the production of the tablets; varenicline tartrate, Crospovidone (CP), Microcrystalline Cellulose (MCC), aspartame (all procured from Sigma Aldrich), magnesium stearate, talc, potassium dihydrogen phosphate, and sodium hydroxide (all procured from SD Fine Chem, Ltd., Mumbai). The equipment used in the production process included a tablet punching machine (16 punch), ultraviolet/visible spectrophotometer double beam (Elico), dissolution test apparatus-United States Pharmacopeia (USP) standards (Electro lab TDT 08L), single pan digital balance (Citizen), hardness tester (Monsanto, Electronics India), friability apparatus and disintegration test apparatus (Electronics India/2901).

### Experimental design:

A face-centered Central Composite Design (CCD) was utilized to develop varenicline-loaded ODTs through the optimization of formulation parameters. The design involved the evaluation of three factors at three different levels (+1, 0, -1), and 13 combinations of experimental trials were conducted. The percentage (%) of CP ( $X_1$  or A) and Croscarmellose Sodium (CCS) ( $X_2$  or B) were selected as the independent variables, while disintegration time ( $Y_1$ ) and wetting time ( $Y_2$ ) were chosen as the dependent variables for optimizing the response data.

The polynomial equation given below was used to

study the effect of variables on different evaluation responses ( $Y$ ), where the coefficients in the equation ( $\beta_0, \beta_1, \beta_2, \beta_{12}, \beta_{23}, \beta_{31}, \beta_{11}, \beta_{22},$  and  $\beta_{33}$ ) were related to the effects and interactions of the factors.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2$$

Where the pendent variable is a statistical term used to describe the variable being studied. In this case,  $\beta_0$  represents the arithmetic mean response of the 13 runs. Meanwhile,  $\beta_1$  and  $\beta_2$  are the estimated coefficients for the factors  $X_1$  and  $X_2$ , respectively. The main effect refers to the average result of changing one factor at a time from its low to high value. This is represented by  $X_1$  and  $X_2$ . On the other hand, the interaction term ( $X_1 X_2$ ) shows how the response changes when two factors are changed simultaneously. To investigate nonlinearity, the polynomial terms ( $X_1 X_1$  and  $X_2 X_2$ ) are included.

### Preparation of varenicline tartrate ODTs:

Fast-dissolving tablets of varenicline tartrate were prepared by direct compression method, using synthetic disintegrants CP and CCS in different ratios and directly compressible MCC as diluent and mannitol to enhance the mouth feel. Tablets of varenicline tartrate were prepared using the direct compression method. The tablets were made with synthetic disintegrants CP and CCS in different proportions. Directly compressible MCC was used as a diluent, and mannitol was added to improve the mouth feel. All the ingredients were passed through a #60 mesh separately, and then mixed to obtain a uniform mixture and set aside. The ingredients were weighed and mixed in a specific order. Finally, the mixed blend of excipients was compressed into a tablet. The formulae used in the preparation were given in Table 1. According to the formulae given in Table 2, all the ingredients were passed through #60 mesh separately. The drug and MCC were mixed by a small portion of both each time and blended to get a uniform mixture and kept aside. Then the ingredients were weighed and mixed in geometrical order. The mixed blend of excipients was compressed into a tablet.

**TABLE 1: CODED AND ACTUAL VALUES OF INDEPENDENT VARIABLES**

Name	Coded (%)	Actual (%)
CP	-1	5
	0	7.5
	+1	10
CCS	-1	5
	0	7.5
	+1	10

TABLE 2: FORMULAE OF DIFFERENT FORMULATIONS

Formulation code	A-CP (%)	B-CCS (%)	CP	CCS	MCC	Starch	Aspartame	Talc	Magnesium stearate
F1	10	5	10	5	61	5	2	1	1
F2	7.5	5	7.5	5	66	5	2	1	1
F3	7.5	7.5	7.5	7.5	61	5	2	1	1
F4	7.5	7.5	7.5	7.5	61	5	2	1	1
F5	7.5	10	7.5	10	56	5	2	1	1
F6	7.5	7.5	7.5	7.5	61	5	2	1	1
F7	5	5	5	5	71	5	2	1	1
F8	10	10	10	10	51	5	2	1	1
F9	10	7.5	10	7.5	56	5	2	1	1
F10	7.5	7.5	7.5	7.5	61	5	2	1	1
F11	5	10	5	10	61	5	2	1	1
F12	7.5	7.5	7.5	7.5	61	5	2	1	1
F13	5	7.5	5	7.5	66	5	2	1	1

### Methods:

Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were estimated; post compression parameters such as hardness<sup>[9]</sup>, friability<sup>[10]</sup>, drug content, wetting time<sup>[11]</sup>, water absorption ratio<sup>[12]</sup>, disintegration time<sup>[13]</sup> and *in vitro* dissolution studies were conducted.

### Statistical analysis:

The data obtained from the factorial design study was subjected to multiple regression analysis using Design-Expert<sup>®</sup> 12 software and were fitted in the equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2$$

The effect of the variables was interpreted by considering the magnitude of the correlation and the mathematical sign it carried (positive or negative). The adequacy of the fitted model was checked by Analysis of Variance (ANOVA). To study the main and interaction effects of the independent variables, response surface plots were constructed using the software Design-Expert<sup>®</sup> DX 12. Response surface plots were constructed using software to study the main and interaction effects of the independent variables. From the above statistical analysis, two formulations were optimized with specified constraints and the formula for the optimized formulation is presented in Table 3. The optimized formulation which was one of the initial 13 formulations was prepared based on the given formulae, and the evaluation tests were repeated and the % relative error of the predicted and the experimental values were

calculated. The formula for calculating the relative error: % Relative error =  $\frac{\text{Predicted value} - \text{experimental value}}{\text{predicted value}} \times 100$

### Kinetic model fitting:

Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. To compare dissolution profiles between two drug products model-dependent (curve fitting), statistical analysis, and model-independent methods can be used. The kind of drug, its polymorphic form, crystallinity, particle size, solubility, and amount in the pharmaceutical dosage form can influence the release kinetics using zero-order kinetics and first order kinetics (Higuchi model and Korsmeyer-Peppas model)<sup>[14]</sup>.

### Regression equation of the fitted model:

The final regression equation in terms of coded factors and the actual terms were as follows

**Disintegration time (coded values):** Disintegration time =  $65.369 + 2.37 \times A + (-12.9317) \times B + 2.6225 \times AB + (-14.7414) \times A^2 + (-0.636379) \times B^2$

**Disintegration time (actual values):** Disintegration time =  $(-17.7434) + 33.1803 \times CP + (-6.79236) \times CCS + 0.4196 \times CP \times CCS + (-2.35862) \times (CP)^2 + (-0.101821) \times (CCS)^2$

**Wetting time (coded values):** Wetting time =  $29.4869 + (-0.728333) \times A + (-7.39333) \times B + 5.1775 \times AB$

**Wetting time (actual values):** Wetting time =  $100.449 + (-6.50433) \times CP + (-9.17033) \times CCS + 0.8284 \times CP \times CCS$

**TABLE 3: CONSTRAINTS OF DEPENDENT VARIABLES IN OPTIMIZATION AND FORMULAE OF OPTIMIZED FORMULATIONS**

S. No.	Dependent variable	Constraints (minimize)
1	$Y_1$	30-50
2	$Y_2$	20-30
Code	% CP	% CCS
Optimized formulations	5	10

## RESULTS AND DISCUSSION

The oral route is the most important route of drug administration compared to other routes and is considered to be self-medication, ease of administration, and avoidance of pain compared to the parenteral route<sup>[15]</sup>. The researcher's activity was focused on the development of ODT, which quickly disintegrate in the oral cavity within 1 min. According to European Pharmacopeia 7.0, ODTs should disintegrate in <3 min, which is easy for patients who are mentally ill, disabled, uncooperative, pediatric, and geriatric population. Some of the techniques such as lyophilization, sublimation, cotton candy, melt granulation, molding, phase transition, hot melt extrusion, solvent casting, spray drying, and effervescent technology are some of the widely accepted techniques for the preparation of ODT<sup>[16]</sup>. Orally dispersible tablets are dosage forms that can be prepared by various techniques. Direct compression using super disintegrants is a technique used in preparation where the percentage of cross-linked povidone and CCS, the super disintegrants used, are critical in determining the quality and efficacy of the product. Super disintegrants are substances commonly contained in tablet formulations that aid in the breakdown of the compacted mass into primary particles to facilitate the dissolution or release of the active ingredients when placed in a liquid medium. Super disintegrants are generally used in low amounts in a solid dosage form, typically 1 % to 10 % by weight relative to the total weight of the dosage unit<sup>[17]</sup>. Their particles are generally small and porous, allowing the tablet to disintegrate rapidly in the mouth without the undesirable mouth feel of large particles or gelation. CCS is an internally cross-linked polymer of sodium carboxymethylcellulose. It has a high swelling capacity with minimal gelation, resulting in rapid disintegration<sup>[18]</sup>.

All the selected excipients were mixed according to the ratio and analyzed for pre-compression analysis. Thus, the current work was started to optimize these parameters using the model drug varenicline tartrate. It

is a highly soluble and highly permeable drug and is an ideal candidate for formulating as a dispersible tablet. The design of the formulation started with the CCD to optimize the independent variables like concentration of the super disintegrants, and the key ingredients in the formulation of varenicline tartrate. Formulation batches of varenicline tartrate ODTs were prepared by CCD.

The calibration curve was represented in fig. 1. From the slope and intercept values it is observed that the curve has a positive slope. The coefficient of correlation value of 0.9964 is good. From the data, it is evident that the concentration range from 2 µg/ml to 10 µg/ml is within the linearity range as per Beer's Lambert's law.

Thirteen formulations were prepared according to the different ratios of CP, cross carmellose sodium, MCC, aspartame, talc, and magnesium stearate. Pre-compression and post-compression analysis was done on all the prepared formulations.

The pre-compression parameters and the post-compression parameters were evaluated and listed in Table 4. The angle of repose was found to be in the range of (14.85±0.35) to (23.36±0.58). The prepared mixture formulations showed good flow properties with an angle of pour value from 20 to 30. It was known that a pour angle of <30° indicated excellent flow properties and values >56° indicated very poor flow properties<sup>[19]</sup>.

The Carr index was found to be in the range of (6.54±0.55) to (14.32±0.53), indicating that the flow is excellent to good. The Hausner ratio was found to be in the range of (1.02±0.09) to (1.1±0.04), indicating that the flow rate is excellent. Lower Carr indices indicated better powder flow ability and a high Hausner ratio reflected less free-flowing ability. The values obtained for the Carr index were in the range (5 %-15 %) and for the Hausner ratio <1.25, which indicates good compressibility of the granules<sup>[20]</sup>.

The hardness and friability were found to be within the limits as per official compendia. The drug content was found to be in the range of (96.54±0.2) to (99.54±0.37), which indicates that the values are within the Indian Pharmacopeia (IP) limits of 95 %-105 %. The wetting

time was found to be in the range of (18.15±2.79) to (42.49±2.18) s, while the water absorption ratio was found to be in the range of (96.45±3.71) to (118.46±2.72). Wetting time is used as an indicator of easy disintegration of the tablet in the buccal cavity. The reduction in wetting time and dispersion in all formulations can be attributed to the presence of a super-disintegrating agent that absorbs water and swells, causing the tablets to burst<sup>[21]</sup>. It has been shown that as the concentration of disintegrants increases,

the time required for wetting decreases. The wetting time of ODT was found to be directly related to the water absorption ratio. The water absorption ratio was performed to determine the moisture absorption and water absorption properties of the polymers. The water absorption ratio increased and the disintegration time and wetting time decreased with increasing polymer concentration<sup>[22]</sup>. The disintegration time was found to be in the range of (31.15±1.17) s to (69.35±1.43) s (fig. 2).

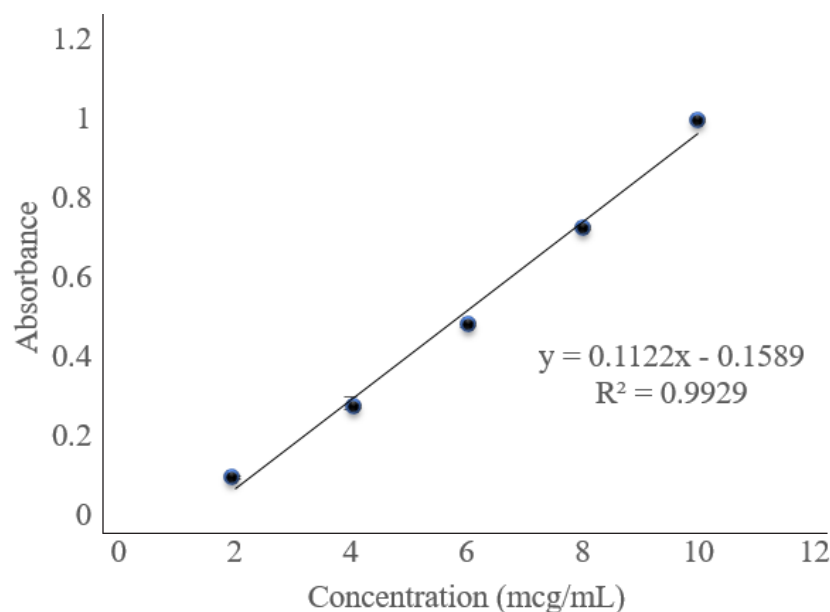
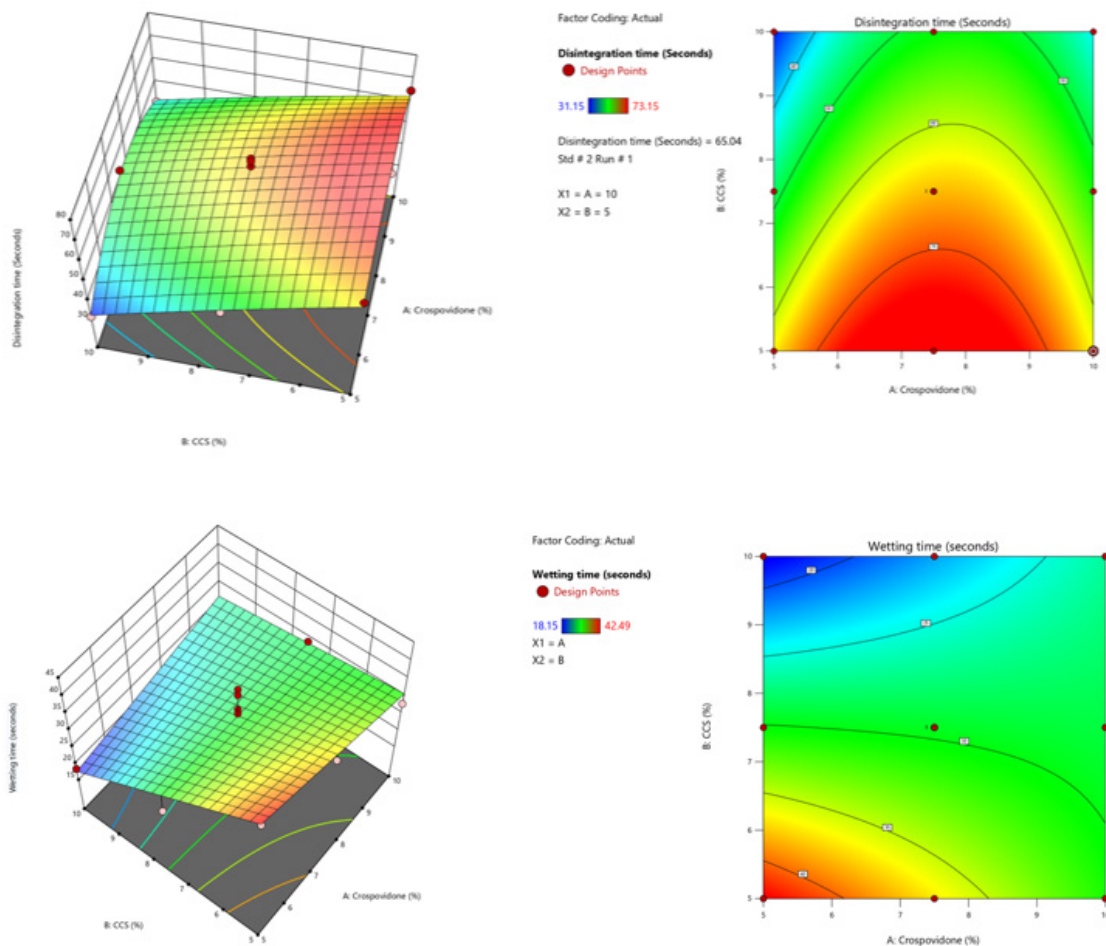


Fig. 1: Standard calibration curve of varenicline tartrate in phosphate buffer pH 6.8

TABLE 4: PRE-COMPRESSION AND POST-COMPRESSION EVALUATION PARAMETERS OF FORMULATIONS

Formulation code	Angle of repose	Carr's index	Hausner's ratio	Drug content	Wetting time	Water absorption ratio	Disintegration time
F1	23.32±0.25	8.32±0.49	1.06±0.02	98.22±0.66	28.05±2.67	96.45±3.71	65.04±2.87
F2	20.01±0.77	9.36±0.16	1.03±0.07	96.54±0.49	35.14±1.93	97.87±0.49	73.15±2.65
F3	19.86±0.84	11.34±0.26	1.05±0.03	97.56±0.44	30.15±2.22	99.04±2.61	69.35±1.43
F4	23.36±0.58	9.95±0.47	1.07±0.04	97.99±0.64	28.06±1.09	98.74±1.86	68.12±1.41
F5	20.55±0.71	7.42±0.38	1.1±0.04	97.54±0.35	18.15±2.79	112.35±1.31	53.41±1.39
F6	23.22±0.40	10.35±0.29	1.05±0.04	99.54±0.37	35.36±2.56	98.32±1.99	62.29±0.92
F7	19.54±0.29	11.11±0.57	1.04±0.03	97.32±0.79	42.49±2.18	99.85±3.63	65.32±1.21
F8	20.05±0.98	9.42±0.39	1.03±0.03	96.54±0.2	24.72±1.24	106.25±4.12	41.36±2.42
F9	14.85±0.35	6.54±0.55	1.04±0.05	98.11±0.79	29.12±1.01	100.14±4.25	51.32±1.29
F10	23.06±0.53	9.35±0.63	1.06±0.02	99.22±0.88	31.35±2.22	101.86±3.72	65.85±1.03
F11	15.05±0.55	10.22±0.19	1.07±0.05	97.73±0.44	18.45±0.98	118.46±2.72	31.15±1.17
F12	20.01±0.45	12.55±0.40	1.05±0.03	99.02±0.74	36.97±2.81	99.85±0.86	64.14±1.13
F13	20.22±0.99	14.32±0.53	1.02±0.09	99.21±0.92	25.32±1.09	104.87±1.16	47.03±2.16





**Fig. 2: Three-dimensional surface plot and contour plot of AB term for disintegration time and wetting time**

Statistical analysis was performed after inputting the results obtained in the characterization process into the Design of Experiments (DoE) software the designed models and the fitted model. DoE provides a better understanding of the relationship between independent and dependent variables in formulation development. Preliminary data obtained from previous experiments play an important role in DoE because they provide important information about process variability that can affect product quality<sup>[23]</sup>. Response Surface Design (RSD) is most commonly used in the pharmaceutical industry. RSDs are a set of statistical and mathematical techniques based on the collection of experimental data from an experimental design (Table 5).

In this CCD, two numeric factors were evaluated at 3 levels (+1, 0, -1), and % of CP and % CCS ( $X_2$  or B) were selected as independent variables. The dependent variables were subjected to statistical optimization and fitted to linear, interactive, and quadratic models. The summary of statistics was presented in Table 6. The comparative  $R^2$ , adjusted  $R^2$ , predicted  $R^2$ , Standard

Deviation (SD), F values, and p values were determined using the Design-Expert<sup>®</sup> software. A suitable polynomial model for describing the data was selected based on the coefficient of determination  $R^2$ . The responses followed the quadratic model. These models show higher  $R^2$  and F values and lower p values. The F value of the model for response and disintegration time was observed to be 34.13 for the varenicline tartrate ODTs, which indicates that the model is significant. The values of  $p < 0.05$  for all the responses except A, AB, and  $B^2$  indicated the significance of parameters except A, AB, and  $B^2$  on disintegration time.

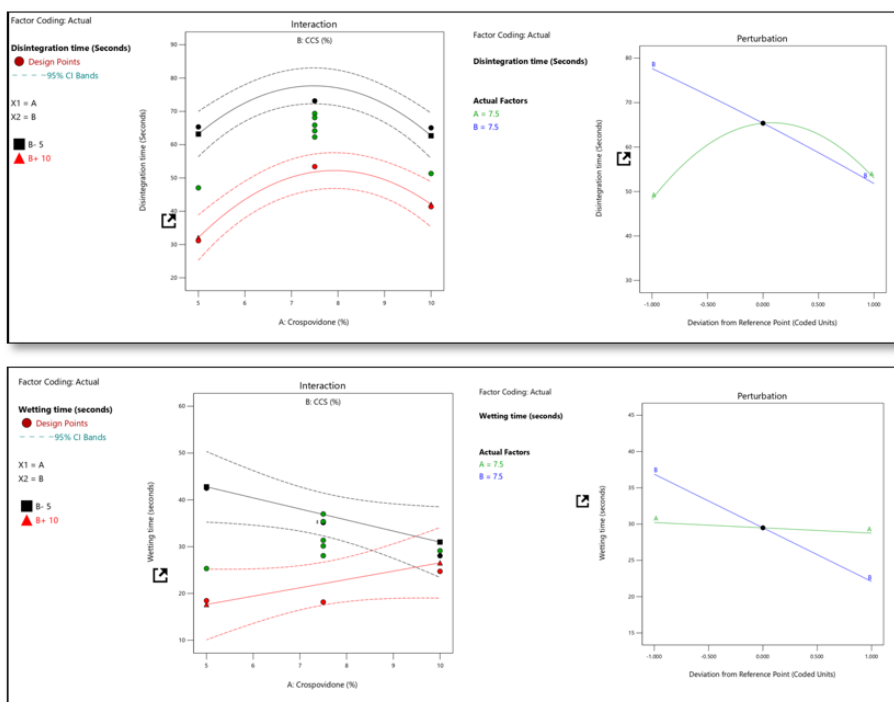
The F value of the model for response, wetting time, was observed to be 8.67 for the varenicline tartrate ODTs, which indicates that the model is significant. The values of  $p < 0.05$  for all the responses except A indicated the significance of the model and the insignificance of variable A in defining wetting time. All the terms except A and AB harm disintegration time, while the term AB hurt wetting time (fig. 3).

**TABLE 5: SUMMARY OF RESULTS OF REGRESSION ANALYSIS FOR RESPONSES**

Model	R <sup>2</sup>	Adjusted R <sup>2</sup>	Predicted R <sup>2</sup>	SD	% CV	Remarks
Disintegration time	124.501	124.501	124.501	124.501		
Linear model	0.5562	0.4675	0.1649	9.1		
Second order	0.571	0.428	-0.5305	9.43		
Quadratic model	0.9606	0.9325	0.7751	3.24	5.56	Suggested
Wetting time						
Linear model	0.5162	0.4374	0.00979	509		
Second order	0.7429	0.6572	0.4967	4.11	13.92	Suggested

**TABLE 6: ANOVA FOR THE RESPONSE AND DISINTEGRATION TIME**

Source	SS	Df	F	p	Remark
Disintegration Time					
Model	1791.05	5	34.13	<0.0001	Significant
A	33.7	1	3.21	0.1162	Not significant
B	1003.37	1	95.61	<0.0001	Significant
AB	27.51	1	2.62	0.1495	Not significant
A <sup>2</sup>	600.18	1	57.19	0.0001	Significant
B <sup>2</sup>	1.12	1	0.1066	0.7536	Not significant
Lack of fit	40.51	3	1.64	0.315	Not significant
Wetting time					
Model	438.38	3	8.67	0.0051	Significant
A	3.18	1	0.1888	0.6741	Not significant
B	327.97	1	19.45	0.0017	Significant
AB	107.23	1	6.36	0.0327	Significant
Lack of fit	97.08	5	1.42	0.3777	Not significant

**Fig. 3: Perturbation plot and interaction plot of disintegration time and wetting time**

With the increase in the % CP, the disintegration time increased initially and further increase decreased disintegration time. The % CCS caused a decrease in disintegration time with an increase in its percent. With the increase in the % CCS, the wetting time decreased initially and further increase wetting time. The % CP caused a decrease in wetting time with an increase in its percent (Table 7).

In this experimental design, optimization is done both numerically and graphically. In numerical optimization, the desired character for the response was selected, and automatically software will choose the solutions with desired characters and limits. Among different solutions, it also suggests the solution with desirability near to 1. Graphical optimization was done by desirability plot and overlay plot, which contains optimal values of independent variables. The higher the desirability, the more suitable the formulation. The overlay plot with the optimized formula was given in fig. 4.

Model validation and final formulation identification was done as follows, the relative error was calculated to validate the model. The relative error was calculated and the values were presented in Table 8. The desirability ramp graph of all the terms of the optimized formulation was given in fig. 5.

In *in vitro* drug release study of optimized formulation, the results of the study were presented in Table 9 and fig. 6. The results conclude that the optimized formulation released 99.68 % drug in 60 min while the cumulative % drug release of pure drug was just 56.84 %. It can be concluded that the dissolution is improved by varenicline tartrate ODTs.

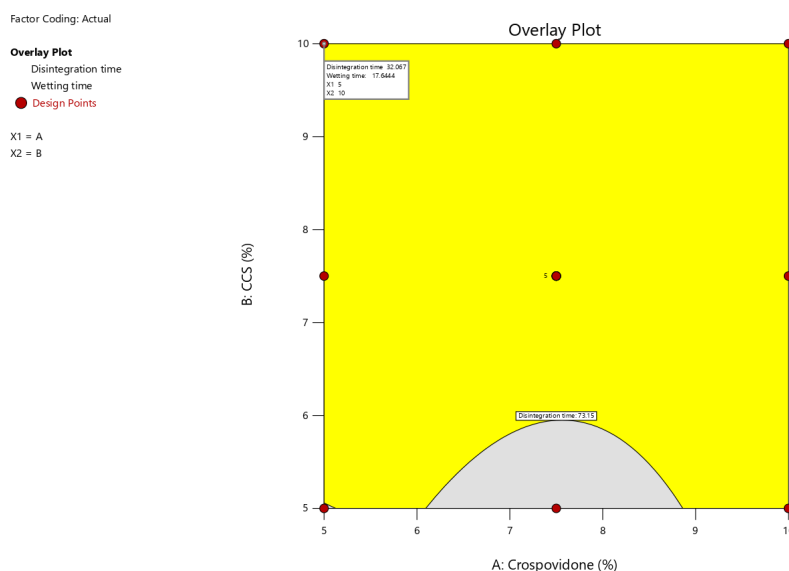
The results were tabulated in fig. 7. It can be concluded from the results that, the release followed zero order kinetics, and from the slope of the Korsmeyer-Peppas model, it can be concluded that the release is by super case II transport.

Varenicline tartrate ODT is made by the direct compression method. This method involves forming a solid dispersion that contains a super-disintegrant. The super-disintegrant increases the dissolution rate of the tablets when they are in the oral cavity. This results in an enhanced drug release profile that begins with an initial burst release from the matrix. The polymer in the matrix swells in the presence of liquid, causing the ODT to disintegrate within seconds with the help of super disintegrants. The optimized formulation created by DoE (CCD) revealed that the best formulation was the one with rapid drug release and increased bioavailability.

**TABLE 7: THE VALUES OF RESPONSES OF THE OPTIMIZED FORMULATION**

Parameter	Optimized formulation
Disintegration time	31.85±0.43
Wetting time	17.96±0.52

Note: All the values are presented as mean±SD (n=3)

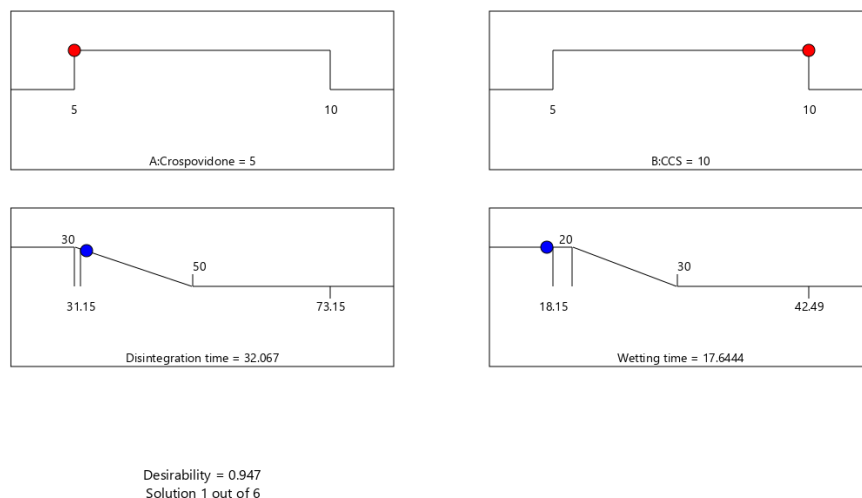


**Fig. 4: Overlay plot of optimized formulation**



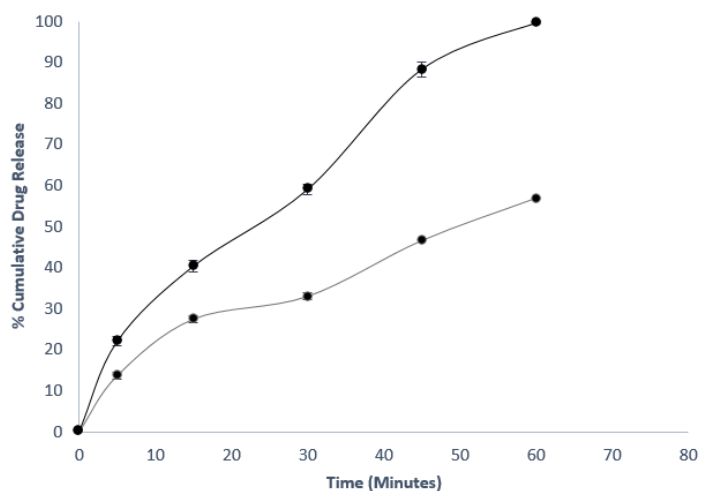
**TABLE 8: RELATIVE ERROR FOR OPTIMIZED FORMULATIONS**

Code	Response	Predicted values	Experimental values	Relative error (%)
Optimized formulation	Disintegration time	32.07	31.85	0.69
	Wetting time	17.64	17.96	-1.81

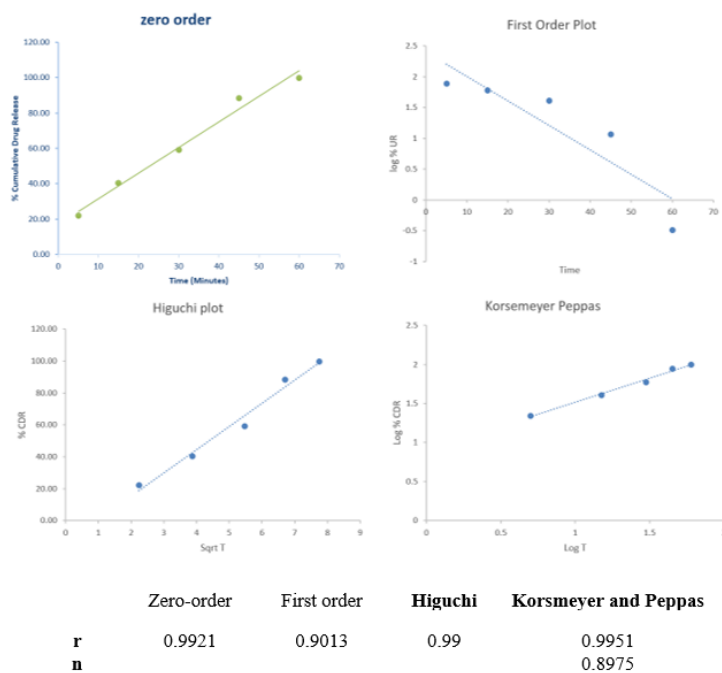
**Fig. 5: The ramp graph of all the terms of optimized formulation****TABLE 9: *IN VITRO* DRUG RELEASE PROFILES OF PURE DRUG AND OPTIMIZED FORMULATION**

Time (min)	% Cumulative drug release	
	Pure drug	Optimized formulation
0	0	0
5	13.65±0.91	22.04±1.14
15	27.44±0.77	40.40±1.36
30	32.96±0.90	59.08±1.20
45	46.52±1.43	88.34±1.79
60	56.84±1.36	99.68±0.31

Note: All the values are presented as mean±SD (n=3)

**Fig. 6: Dissolution profile of pure drug and optimized formulation**

Note: (—●—): Pure drug and (—○—): Optimized formulation



**Fig. 7: Kinetic model graphs of optimized formulation and correlation coefficient and kinetic model fitting of *in vitro* drug release studies**

### Conflict of interests:

The authors declared no conflict of interests.

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