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STATISTICAL OPTIMIZATION OF ORALLY DISINTEGRATING TABLETS OF MEMANTINE HYDROCHLORIDE

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Keywords:

Memantine hydrochloride, Statistical optimization, Orally-disintegrating, Tablets, Alzheimer's disease

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ABSTRACT: Objective: The present work deals with the statistical optimization of memantine hydrochloride orally disintegrating tablets by the design of experimentation. The study was aimed at the development of a stable and robust formulation for the well-being of society for the treatment of Alzheimer's disease, which is the most common form of dementia. **Methods:** Binder (X_1), disintegrant (X_2), and diluent (X_3) concentrations were selected as independent variables, and their levels were optimized by employing a Central composite design, whereas dissolution (Y_1) and disintegration time (Y_2) were selected as the dependent variables. **Results:** All formulations were evaluated for physical parameters of lubricated blend and compressed tablets. Mathematical equations and response surface plots were used to relate the dependent and independent variables. The regression equation generated for dissolution was $Y_1 = 93.51 - 7.00B + 5.20C - 4.28B^2 - 2.28C^2$ and for disintegration time (DT) was $Y_2 = 4.80 + 0.0148A + 0.3690B - 0.3181C$. **Conclusion:** The statistical significance of each variable with respect to the model was established, and optimized formulation factors were selected by feasibility and grid search. The factorial batches were evaluated by contour plots and response surface methodology.

INTRODUCTION: Dementia is one of the brain disorders which lead to Alzheimer's disease (AD) as a result of neurofibrillary degeneration affecting neurons of the central nervous system. The process includes a decrease in cholinergic transmission, higher sensitivity to oxidative stress, alterations in the cytoskeleton, and neuronal death [1, 2]. The elderly patients are affected by the formation of two main protein aggregates; senile plaques and neuro-fibrillary tangles.

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Recently, the demand for the development of orally disintegrating tablets (ODTs) has enormously increased as it has a significant impact on patient compliance. The bitterness of various drugs can be masked by formulating ODTs with good taste and flavor and thereby increasing the acceptability.

The conventional dosage forms are associated with a high prevalence of noncompliance and unsuccessful therapy with respect to swallowing, especially in the case of geriatric, pediatric, or in mentally retarded persons. Drugs present in orodispersible tablets are also not affected by first-pass metabolism [3]. Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is associated with excessive loss of memory [4-6]. It has been shown that AD afflicts about 8-10% of the population over 65 years of age, and its prevalence

doubles every 5 years thereafter [7]. In this disease, the change in forgetfulness is more dramatic than normal, which commonly gets increased with age. More importantly, this difficulty is persistent, progressive, and severe, and there is usually a noticeable, rapid decline in cognitive skills [8].

There are two types of Alzheimer's diseases, one is a familial type that is passed from one generation to another through a dominant gene, is very rare and is seen in only 5-10% of cases. About 90% of cases are the sporadic type, which can be developed even if nobody in the family has had the disease [9, 10]. It is the fourth leading cause of death and the most common cause of dementia in the United States. The total number of people with dementia worldwide is anticipated to nearly double every 20 y, 65.7 million in 2030, and 115.4 million in 2050 [11-13]. The total number of new cases each year worldwide is nearly 7.7 million, implying one new case every 4 seconds. The fastest growth is taking place in China, India, and their south Asian and western Pacific neighbors. As per projection, by 2050, people aged 60 and over will account for 22% of the world's population, with 80% living in Asia, Latin America, or Africa [14].

Memantine hydrochloride belongs to a low-moderate affinity, uncompetitive n-methyl-d-aspartate (NMDA) receptor antagonist with sturdy voltage dependency and quick blocking/unblocking kinetics [15, 16]. These pharmacological features appear to allow memantine to block the sustained activation of the receptor by glutamate that may occur under pathological conditions, and to rapidly leave the NMDA receptor channel during normal physiological activation.

Response surface methodology (RSM) is a widely exploited tool for the development and optimization of drug delivery systems. In this investigation, we explored the utility of RSM for the optimization of ODTs. Based on the principle of design of experiments, the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to optimize the tablets. The technique selected based on its benefits as minimum experimentation and time, more effective and cost-effective as compared to the conventional methods of formulating dosage forms. The current approach is intended to apply central composite design for optimization of an orally disintegrating drug delivery system of memantine hydrochloride to avoid complexities in the optimization of various dependent and independent variables. as these systems are beneficial for many patients, particularly from paediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules and also in patients travelling with little or no access to water, leading to non-compliance and ineffective therapy [17-20].

MATERIALS AND METHODS:

Chemicals and Reagents: Cadila Healthcare Ltd, India has provided the memantine hydrochloride as gift sample. Microcrystalline cellulose, mannitol, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate procured from Signet chemicals ltd, Eudragit EPO as a gift sample from Evonik GmbH, India. All these suppliers were based in Mumbai, India.

Methods:

Preparation of Orally Disintegrating Tablets of Memantine Hydrochloride: Initial developmental trials by wet granulation to formulate the orally disintegrating tablets of memantine hydrochloride was taken to select excipients and their primary levels. The taste and flavor enhancers were used to mask the bitterness of the drug.

Memantine hydrochloride, microcrystalline cellulose, mannitol were sifted through # 40 sieve and transferred to a bowl of top spray granulator. Eudragit EPO ready mix clear was dispersed in purified water and sprayed on the blend by top spray granulation method and subsequently dried. The dried granules were milled using a suitable screen and blended with sifted extra granular materials *viz.* croscarmellose sodium, silica colloidal anhydrous, tartaric acid, neotame, acesulfame potassium, and tutti-frutti flavor. The blend was lubricated with magnesium stearate in the blender. The lubricated blend was transferred to the hopper of the compression machine, and tablets were compressed at the hardness of 2-4 kg/cm^2 using 8 mm circular, flat-faced beveled edge, plain punches using Cadmach single rotary compression machine.

Experimental Design: The Central composite design was utilized to study the effect of independent variables on dependent variables, as shown in **Table 1**. The prepared tablets were evaluated for physicochemical characterization. The experimental design with statistical screening was used to optimize the formulation factors and evaluate main effects, interaction effects, and quadratic effects on the disintegration time and dissolution with the help of RSM and possible curvature in the response function. A three-factor, the three-level design was used to explore linear and quadratic response surfaces and to construct second-order polynomial models with Design Expert (Version 11.1.2.0, Stat-Ease Inc. Minneapolis, MN, USA). A design matrix comprising of 17 experimental runs was constructed. The non-linear computer-generated quadratic model is given as $Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_{12} + b_{22}X_{22} + b_{33}X_{32}$ where Y1 and Y_2 is the measured response associated with each factor level combination: b_0 is constant; b_1, b_2, b_3 are linear coefficients, b_{11}, b_{22}, b_{33} are quadratic coefficients computed from experimental runs and X_1, X_2 and X_3 are coded levels of independent variables. The independent variables selected were the concentrations of binder (X_1), disintegrant (X_2), and diluent (X_3). The dependent variables were dissolution (Y_1) and disintegration time (Y_2) with constraints applied to the formulation of tablets. The concentration range of independent variables was selected based on the observations from preliminary experimentation. The selected concentration range of independent variables under study with their low, medium, and high levels are shown in **Table 1**.

TABLE 1: VARIABLES AND OBSERVED RESPONSES IN CENTRAL COMPOSITE DESIGN FOR TABLET

Trials	Independent variables			Dependent variable	
	EPO Concentration (%) (X_1)	CCS Concentration (%) (X_2)	Diluent Concentration (%) (X_3)	Dissolution (%) (Y_1)	Disintegration time (seconds) (Y_2)
F1	2.00	4.00	40.00	99	93
F2	4.00	4.00	20.00	94	118
F3	4.00	4.00	40.00	91	104
F4	6.00	6.00	60.00	84	140
F5	2.00	6.00	20.00	97	64
F6	4.00	4.00	60.00	96	118
F7	2.00	2.00	60.00	87	118
F8	6.00	2.00	20.00	78	228
F9	6.00	4.00	40.00	80	205
F10	2.00	6.00	60.00	100	61
F11	4.00	6.00	40.00	98	84
F12	6.00	6.00	20.00	86	125
F13	2.00	2.00	20.00	89	112
F14	6.00	2.00	60.00	74	235
F15	4.00	2.00	40.00	85	195
F16	4.00	4.00	40.00	93	113
F17	4.00	4.00	40.00	91	104

Evaluation of Blend: The lubricated blend was evaluated for flow characteristics: bulk density (BD), tapped density (TD), compressibility index (CI), Hausner's ratio (HR), and angle of repose. The flow characteristics were determined by using approximately 25 g weighed amount of blend in 100 ml measuring cylinder.

Evaluation of Tablets: The formulations were characterized for physical aspects like hardness, weight variation, thickness, friability, disintegration time, disintegration time in the oral cavity, *in-vitro* dispersion time, wetting time and water absorption ratio as well as for chemical tests like assay, content uniformity and in vitro dissolution study.

Tablet Hardness: The crushing strength of the tablet was measured in terms of hardness, which determines the ease of handling and the rigors of transportation. 10 tablets per formulation were used for the study.

Weight Variation Test: The weight variation test was done by individually weighing 20 tablets, calculating the average weight, and comparing the individual tablet weight to the average. The table given below shows the weight variation tolerance for uncoated tablets.

Thickness: The digital vernier caliper was used to measure the thickness of the tablets.

Friability: To assess the effect of friction along with shocks, which may often cause the tablet to chip, cap or break, friability test was performed using Roche friabilator. This device subjects the tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed tablet samples were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted prior to re-weighing.

Disintegration Time: One tablet was placed in each of six tubes of disintegration test apparatus. The disintegration test was carried out at 37 ± 2 °C with respect to United States Pharmacopoeia (USP) 22nd edition. The time required for the complete passage of tablet fragments through the sieve (#10) was measured as a disintegration time of the tablet.

Disintegration Time in Oral Cavity: The disintegration time in the oral cavity of 6 human volunteers was calculated by placing the tablet on the tongue until no lumps remain. It is expressed in seconds [17].

***In-vitro* Dispersion Time:** The measurement of *in-vitro* dispersion time was done by dropping tablets in 100 ml of water and stirring until completely dispersed. A smooth dispersion is produced which passes through a screen with a nominal mesh aperture of 710 μm.

Wetting Time and Water Absorption Test: The inner structure of tablets and the hydrophilicity of the excipients are important factors to determine the wetting time. According to the equation proposed by Washburn E. W., the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powder. It is apparent that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus, wetting time is an important step for the disintegration process. A piece of tissue paper folded twice was placed in a small petri dish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37 °C [17].

The same procedure was repeated for determining the water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to the following equation:

$$R = \{(W_a - W_b) / W_a\} \times 100$$

Where, W_a = Weight of tablet before the study, W_b = Weight of tablet after study.

Assay: 30 tablets were randomly selected from each batch. Out of 30 tablets, 10 tablets were crushed into a fine powder. Powder equivalent to label claim was weighed accurately, dissolved in the media, and analyzed for assay.

Uniformity of Dosage Units (By Content Uniformity): One tablet was taken in a 100 ml volumetric flask, which was shaken with 15 ml of methanol and sonicated for 10 min. 15 ml of 0.2 N sodium hydroxide solution was added and sonicated for 15 min with vigorous shaking. 10 ml of internal standard solution was added and shaken for 15 min and then allowed to separate 2 layers for about 15 min. The top toluene layer was separated by using pasture pipette and dried over anhydrous sodium sulphate. The initial 2-3 ml was discarded, and the remaining solution was used for analysis.

***In-vitro* Dissolution Studies:** The *in-vitro* dissolution study was carried out using 900 ml of 0.01 NHCl at 37 ± 0.5 °C temperature at 50 rpm using USP Type 2 (paddle) dissolution test apparatus. Samples were withdrawn at 1, 2, 4, 6, 8, and 10 min time intervals.

RESULTS AND DISCUSSION:

Formulation Development:

Evaluation of Tablets: The tablet parameters observed are depicted in **Tables 2**, **3,** and **4**. The tablets were compressed at the acceptable weight

variation range of target weight ± 5% as per USP. The hardness ranging from 2.5 to 4.0 kg/cm^2 for all formulations, was observed. The hardness is not an absolute indicator of the strength, and hence, all formulations complied with the weight variation and hardness test indicated the minimal impact of formulation compositions. The friability value of all the formulations was found less than 0.517%. The results of friability indicated the mechanical strength of the tablets to withstand the rigors of transportation and handling. The thickness of all the formulations was observed between 2.60 – 2.88 mm, indicating fairly acceptable tableting. Disintegration time is a very vital parameter of fast disintegrating tablets. The inner structure of a tablet, pore size distribution, water penetration into tablet, and swelling of disintegrant are key aspects to establish the mechanism of disintegration.

The disintegration time of formulation was gratifying because it disintegrated in the range of 1 to 4 min. The trial, F10, demonstrated the best disintegrating time, *i.e.,* **Table 3,** which depicts the impact of high concentration of mannitol and croscarmellose sodium.

***In-vitro* Dissolution Study:** The dissolution study on formulation F1 – F17 showed the dissolution ranging from 74 ± 2.27% to 100 ± 1.09% in 10 min **Table 2-4**. High dissolution resulted due to faster breakdown and rapid dispersion of the tablet. It may be due to rapid diffusion or the porous nature of the tablet. Based on the data, it can be concluded that the addition of super disintegrant improved the dissolution profile of the water-soluble drug besides expediting the disintegration time.

TABLE 2: PHYSICO-CHEMICAL CHARACTERISTICS OF FORMULATION F1-F5

Parameters	F1	F2	F3	F4	F5
Bulk density (g/ml)	0.467	0.498	0.477	0.389	0.396
Tapped density (g/ml)	0.556	0.612	0.538	0.497	0.492
Compressibility Index (%)	16.007	18.627	11.338	21.730	19.512
Hausner's ratio	1.191	1.229	1.128	1.278	1.242
Angle of repose	27.9	31.2	26.8	29.5	31.2
Weight variation (mg)	150 ± 4	150 ± 3	150 ± 1	150 ± 2	150 ± 2
Thickness (mm)	2.75 ± 0.06	2.75 ± 0.08	2.70 ± 0.08	2.75 ± 0.04	2.80 ± 0.08
Friability (%)	0.419	0.208	0.234	0.312	0.419
Hardness (kg/cm^2)	2.8 ± 0.4	3.4 ± 0.2	3.6 ± 0.4	2.7 ± 0.3	3.5 ± 0.4
Disintegration time (s)	93 ± 3.05	118 ± 2.32	104 ± 1.04	140 ± 3.21	64 ± 2.13
Dispersion time (s)	113 ± 2.17	138 ± 1.01	126 ± 2.95	157 ± 1.89	99 ± 1.29
Content uniformity (%)	97.2 ± 1.2	91.4 ± 2.9	98.8 ± 2.1	95.0 ± 1.37	92.6 ± 3.20
Water absorption ratio	58 ± 0.8	69.6 ± 1.2	63.5 ± 1.1	79.2 ± 1.2	53.1 ± 1.9
Assay (% w/w)	97.3 ± 1.12	95.4 ± 2.87	98.9 ± 0.93	97.1 ± 1.27	93.2 ± 2.23
Wetting time (s)	127.1 ± 1.12	152.6 ± 1.55	139.6 ± 1.18	180.0 ± 1.09	110.0 ± 3.1
Dissolution (%)	99 ± 1.03	94 ± 2.23	91 ± 1.51	84 ± 2.05	97 ± 0.98

Values are represented as Mean ± standard deviation, n=3 for assay, n=6 for dissolution and n =10 for all physical parameters

TABLE 3: PHYSICO-CHEMICAL CHARACTERISTICS OF FORMULATION F6-F11

Parameters	F6	F7	F8	F9	F10	F11
Bulk density (g/ml)	0.315	0.322	0.378	0.477	0.398	0.481
Tapped density (g/ml)	0.466	0.451	0.488	0.543	0.478	0.539
Compressibility Index (%)	32.403	28.603	22.541	12.155	16.736	10.761
Hausner's ratio	1.479	1.401	1.291	1.138	1.201	1.121
Angle of repose	26.3	28.4	34.3	28.5	26.6	26.1
Weight variation (mg)	150 ± 2	150 ± 1	150 ± 5	150 ± 3	150 ± 4	150 ± 1
Thickness (mm)	2.65 ± 0.04	2.68 ± 0.04	2.80 ± 0.05	2.70 ± 0.06	2.68 ± 0.07	2.70 ± 0.06
Friability (%)	0.277	0.293	0.437	0.119	0.258	0.311
Hardness (kg/cm^2)	2.7 ± 0.2	2.8 ± 0.3	3.0 ± 0.5	3.3 ± 0.4	3.0 ± 0.3	3.4 ± 0.3
Disintegration time (s)	118 ± 1.48	118 ± 3.65	228 ± 2.11	205 ± 1.10	61 ± 2.08	84 ± 1.27
Dispersion time (s)	138 ± 2.15	152 ± 0.95	252 ± 2.17	238 ± 2.11	98 ± 1.10	108 ± 1.46
Content uniformity (%)	98.3 ± 1.70	91.1 ± 1.90	96.2 ± 3.20	99.5 ± 2.10	98.7 ± 1.50	98.3 ± 1.70
Water absorption ratio	64.3 ± 1.4	70.1 ± 1.0	132.3 ± 1.8	132.0 ± 1.4	51.1 ± 0.9	54.3 ± 1.1
Assay (% w/w)	97.6 ± 1.08	92.0 ± 2.59	95.5 ± 1.99	99.8 ± 0.23	98.9 ± 0.67	97.6 ± 1.12
Wetting time (s)	148.1 ± 1.15	162.5 ± 2.10	263.1 ± 1.12	258.1 ± 1.75	109.1 ± 0.85	119.3 ± 1.37
Dissolution (%)	96 ± 1.12	87 ± 1.23	78 ± 1.17	80 ± 2.21	100 ± 1.09	98 ± 3.01

Values are represented as Mean ± standard deviation, n=3 for assay, n=6 for dissolution and n =10 for all physical parameters

TABLE 4: PHYSICO-CHEMICAL CHARACTERISTICS OF FORMULATION F12-F17

Parameters	F12	F13	F14	F15	F16	F17
Bulk density (g/ml)	0.337	0.331	0.357	0.469	0.480	0.477
Tapped density (g/ml)	0.499	0.517	0.504	0.537	0.541	0.538
Compressibility Index (%)	32.465	35.977	29.167	12.663	11.275	11.338
Hausner's ratio	1.481	1.562	1.412	1.145	1.127	1.128
Angle of repose	29.1	32.8	30.7	26.9	26.3	26.8
Weight variation (mg)	150 ± 2	150 ± 5	150 ± 2	150 ± 3	150 ± 3	150 ± 1
Thickness (mm)	2.65 ± 0.05	2.78 ± 0.05	2.68 ± 0.06	2.70 ± 0.06	2.70 ± 0.04	2.70 ± 0.08
Friability (%)	0.517	0.473	0.336	0.112	0.276	0.234
Hardness (kg/cm^2)	3.2 ± 0.3	3.5 ± 0.5	2.8 ± 0.3	3.4 ± 0.3	3.3 ± 0.2	3.6 ± 0.4
Disintegration time (s)	125 ± 0.31	112 ± 1.12	235 ± 2.36	195 ± 1.47	113 ± 1.23	104 ± 1.04
Dispersion time (s)	145 ± 2.05	139 ± 3.17	267 ± 3.19	218 ± 2.15	142 ± 1.19	126 ± 2.95
Content uniformity (%)	94.5 ± 4.20	93.6 ± 1.90	98.3 ± 1.70	98.3 ± 1.70	98.5 ± 0.9	98.8 ± 2.1
Water absorption ratio	72.1 ± 1.9	70.0 ± 1.5	136.2 ± 1.2	109.1 ± 1.8	72.4 ± 1.7	63.5 ± 1.1
Assay (% w/w)	96.1 ± 2.10	94.3 ± 3.12	98.8 ± 0.78	99.0 ± 0.44	99.1	98.9
Wetting time (s)	161.3 ± 1.07	148.9 ± 1.01	289.1 ± 1.15	228.6 ± 1.30	157.3 ± 0.99	139.6 ± 1.18
Dissolution (%)	86 ± 1.09	89 ± 1.61	74 ± 2.27	85 ± 1.17	93 ± 1.18	91 ± 1.51

Values are represented as Mean ± standard deviation, n=3 for assay, n=6 for dissolution and n=10 for all physical parameters

Experimental Design: The independent variables and the responses for all 17 experimental runs are given in **Table 1**. The 17 experimental formulations of tablets were prepared using different concentrations of binder, disintegration, and diluent. The responses, dissolution (Y_1), and disintegration time (Y_2) were found to be 100 ± 1.09 and 61 ± 2.08 s respectively for F10 trial in which mannitol and croscarmellose sodium were used at high concentration levels as diluent and disintegrant respectively. The response, Y_1, and Y_2 vary from 74% to 100% and 61 sec to 235 sec, respectively. For estimation of the quantitative effects of the different combinations of factors and their levels on disintegration time and dissolution profile, the response models were calculated with Design-Expert software by applying coded values of factor levels. The model described could be represented as: Coded level: Dissolution (Y_1) = 93.51 - 7.00B + 5.20C - 4.28 B^2 - 2.28 $C^2$and for disintegration time (Y_2) = 4.80 + 0.0148A + 0.3690B - 0.3181C.

Fitting of Data to the Model: A three-factor, a three-level central composite statistical experimental design was used, which involved the preparation of 17 trials. Formulation F1 showed a significantly better disintegration time and dissolution among the experimental runs. All the responses observed for 17 formulations prepared were simultaneously fit first order, second-order, and quadratic models using Design Expert 11.1.2.0. It was observed that the best fit model was the quadratic model with sum of squares is type III - partial for response Y_1 (dissolution) and linear for response Y_2 (disintegration time). A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and response. It is evident that out of three independent variables, the binder (X_1) have a negative relationship for response Y_1 (dissolution) and positive for response Y_1 (dissolution), whereas, disintegrant (X_2) and diluent (X_3) have a positive relationship for response Y_1 (dissolution) and negative for response Y_2 (disintegration time). The quantitative effects of the different combinations of factors and factor levels on the disintegration time were calculated using response surface models. The significant p-value ($p<0.05$), R^2, adjusted $R^{2,}$ and coefficient of variation values of this model indicated that the assumed regression model was significant and valid for each considered response. The values of the coefficients in the model are related to the effect of these variables on the response. The 3-D response surface **Fig. 1** was drawn to estimate the effects of the independent variables on response and to select the optimal formulation.

Data Analysis: The dissolution and disintegration time (dependent variable) obtained at various levels of the three independent variables (X_1, X_2, and X_3) were subjected to multiple regression to yield a polynomial equation. The value of the correlation coefficient (r^2) of the equation was found to be 0.9462 and 0.9458 for response Y_1 and Y_2, respectively, indicating a good fit. VIF value found to be 1, indicating the model is significant.

According to **Table 5**, the result calculated using equation 1 was statistically significant with $p<0.005$, indicating that the developed model exhibited good agreement between the response Y_1 and the significant variables. The value for lack of fit for the equation (more than 0.05) indicated that the proposed statistical model fits well. The F values from ANOVA results suggested that the derived models have a significant influence on the responses. R^2 and adjusted R^2 value for both the responses, as depicted in **Table 6** demonstrate the accuracy of the test and the fitness of the results with the prepared model. The disintegration time measured for the different formulations showed wide variation (*i.e.*, values ranged from 61 to 235 sec). The results indicate that the disintegration time is strongly affected by the variables selected for the study. The main effects of X_1, X_2, and X_3 represent the average result of changing one variable at a time from its low level to its high level. The interaction terms (X_1X_2, X_1X_3, X_2X_3, X_{12}, X_{22}, and X_{32}) shows how the disintegration time and dissolution changes when two variables are simultaneously changed.

The negative coefficient for all three independent variables has an unfavorable effect on the disintegration time, while positive coefficients for the interactions between two variables indicate a favorable effect on disintegration time.

TABLE 5A: SUMMARY OF ANOVA FOR RESPONSE Y1 (DISSOLUTION) FOR FITTING TO QUADRATIC MODEL

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	898.81	4	224.70	52.80	< 0.0001	significant
B-EPO	490.00	1	490.00	115.13	< 0.0001	
C-CCS	270.40	1	270.40	63.53	< 0.0001	
B^2	55.56	1	55.56	13.05	0.0036	
C^2	15.79	1	15.79	3.71	0.0781	
Residual	51.07	12	4.26			
Lack of Fit	48.41	10	4.84	3.63	0.2352	not significant
Pure Error	2.67	2	1.33			
Core Total	949.88	16				

TABLE 5B: SUMMARY OF ANOVA FOR RESPONSE Y2 (DT) FOR FITTING TO QUADRATIC MODEL

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.38	3	0.7919	75.56	< 0.0001	significant
A-Diluent	0.0022	1	0.0022	0.2083	0.6556	
B-EPO	1.36	1	1.36	129.95	< 0.0001	
C-CCS	1.01	1	1.01	96.53	< 0.0001	
Residual	0.1362	13	0.0105			
Lack of Fit	0.1303	11	0.0118	4.00	0.2167	not significant
Pure Error	0.0059	2	0.0030			
Core Total	2.51	16				

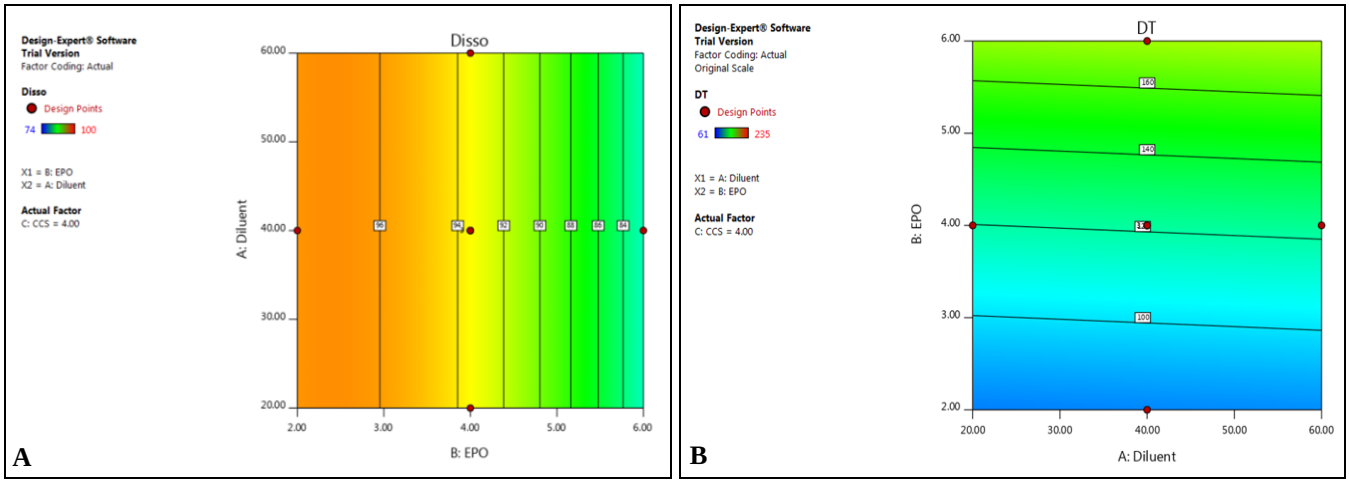

FIG. 1: (A) COUNTERPLOT SHOWING EFFECT INDEPENDENT VARIABLES ON RESPONSE Y1 (B) COUNTER PLOT SHOWING EFFECT INDEPENDENT VARIABLES ON RESPONSE Y2

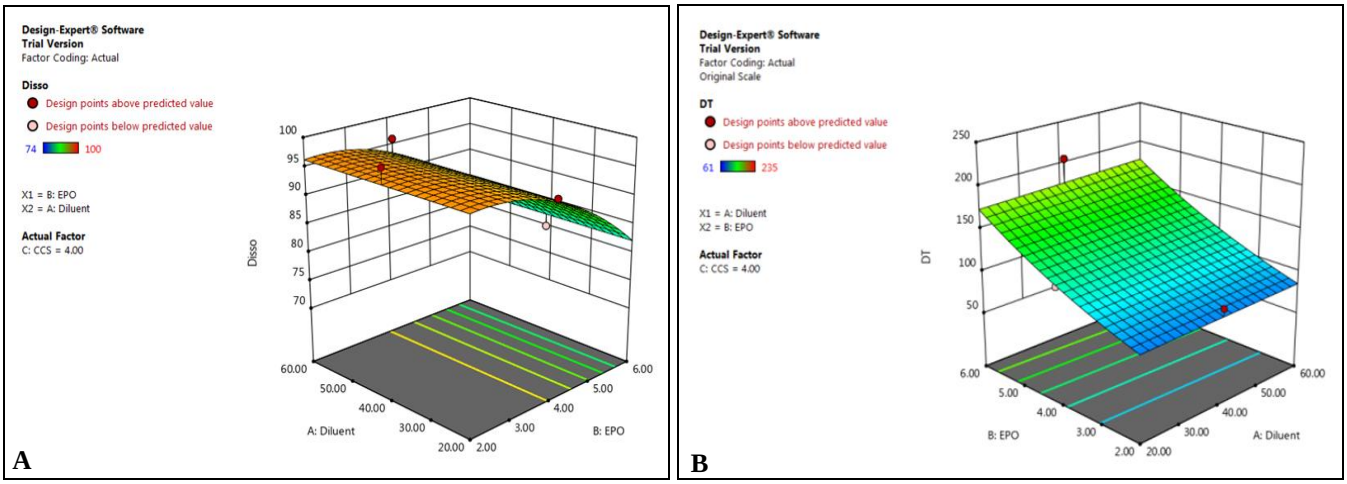

FIG. 2: (A) RESPONSE SURFACE PLOT SHOWING EFFECT INDEPENDENT VARIABLES ON RESPONSE Y1 (B) RESPONSE SURFACE PLOT SHOWING EFFECT INDEPENDENT VARIABLES ON RESPONSE Y2

Counterplots and Response Surface Analysis: Two-dimensional counterplots and 3-D response plots are shown in **Fig. 1A**, **1B,** and **Fig. 2A**, **2B,** which are very useful to study the interaction effects of the factors on the responses. These types of plots are useful in the study of the effects of two factors on the response at one time.

In all the presented figures, the third factor was kept at a constant level. All the relationships among the three variables are non-linear, although they exhibit a nearly linear relationship of factors.

Optimization: The optimum formulation was selected based on the criteria of attaining a maximum value of dissolution and minimum value of disintegration time by applying constraints on Y_1 andY_2. Upon trading of various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation F_1 was found to fulfill the maximum requisite of an optimum formulation because of the desired dissolution, disintegration time values along with other parameters **Table 6**.

TABLE 6: SIMULTANEOUS OPTIMAL SOLUTION BY RSM

Response	Predicted Mean	Predicted Median*	Std Dev	n	SE Pred	95% PI low	95% PI high
Disso	93.5094	93.5094	2.063	1	2.2313	88.6479	98.371
DT	121.541	120.907	12.4098	1	N/A	96.2983	151.805

Validation of Response Surface Methodology: 17 formulations were obtained from RSM, the composition, and predicted response of which are listed in **Table 6**.

To confirm the validity of the optimal calculated parameters and predicted responses, the optimum formulations were prepared according to the above value of the factors. From the results presented in **Table 5**, the predicted error is below 15%, indicating that the observed responses were very close to the predicted values, shown in **Table 6**.

The linear correlation plots were drawn between the predicted and experimental values. Thus, the low magnitudes of error, as well as the R^2 values in the present investigation, prove the high prognostic ability of the RSM.

CONCLUSION: The data obtained from the central composite study revealed that independent variables at used concentration levels have significant impacts on selected responses. After the determination of significant parameters by using experimental design methodology, levels of variables were optimized to formulate the stable and robust formulation of memantine hydrochloride orally disintegrating tablets.

The chosen responses were dissolution and disintegration time. The levels of these factors were predicted to obtain an optimal response concerning set constraints. It is essential that experimental design methodology is a very economical way for extracting the maximum complex information, a significant experimental time-saving factor, and it

saves the material used for analyses and personal cost as well. It is concluded that by adopting a systematic formulation approach, an optimum can be reached in the shortest time with minimum efforts.

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