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Research Article

OPTIMIZATION OF MELT-IN-MOUTH TABLETS OF LEVOCETIRIZINE DIHYDROCHLORIDE USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

The present research work was to design and develop an optimized melt-in-mouth tablet dosage form of an anti-allergic drug, Levocetirizine dihydrochloride by using sublimation technology.

A total number of thirteen formulations were prepared as per the standard experimental design protocol using Design Expert Software (Version 7.1.6, Stat- Ease Inc, Minneapolis, MN). Independent variables such as the amount of subliming agent –Camphor (X_1) and the amount of superdisintegrant- Crospovidone (X_2) were optimized by application of 2-factor, 3-level Central Composite Design. The dependent variables selected were the disintegration time, wetting time, cumulative % drug release in 10 min. and water absorption ratio of the tablet. All the physical parameters of the melt-in-mouth tablets were practically within control. The mathematical relationships were generated using multiple linear regression analysis and all the polynomial equations were found to be statistically significant ($P < 0.0002$), as determined using ANOVA.

The sublimation method used to prepare the melt-in-mouth tablets in this study is relatively simple and safe. A stable, effective and pleasant tasting mouth dissolving tablet, which has a good balance over disintegration time and mechanical strength, was formulated.

Keywords: Melt-in-mouth Tablets, Levocetirizine Dihydrochloride, Superdisintegrant, Subliming Agent and Central composite Design.

INTRODUCTION

Recent developments in technology have presented viable dosage alternatives for paediatric, geriatric, bedridden, nauseous or non compliant patients. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such patients. Hence, melt-in-mouth tablets/ mouth dissolving/disintegrating tablets (MDDTs) are a perfect dosage alternative for them. MDTs dissolve or more commonly disintegrate rapidly, in the saliva usually within a minute, without the aid of water. Also, this dosage form offers an advantage of convenience of administration while traveling, where there may not be an access to water. Moreover, this dosage form combines the advantages of both liquid and tablet formulation [1, 2, 3, 4] and also like liquid dosage forms, such as syrups, suspensions, emulsions, solutions, and elixirs, they do not suffer from the drawbacks of inaccuracy of dosage and inconvenience of transportation and handling. In addition, drugs are dissolved/disintegrate in oral cavity route which offers high permeability to drugs and good reproducibility. Drugs absorbed via the buccal mucosa enter the systemic circulation directly through the jugular vein. This ensures a rapid onset of action and avoids first- pass liver metabolism, gastric acid hydrolysis, and intestinal enzymatic degradation [5.]

Many technologies have come up for mouth dissolving tablets like Zydis, OraSolv, DuraSolv and Flash Tab. Technologies like Zydis, Flash Tab have resulted in tablets with a very low disintegration time, but poor mechanical strength. On the other hand, techniques like OraSolv, DuraSolv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time [6, 7, 8]. Therefore, Sublimation technique/ Vacuum drying method was selected to prepare tablets with low disintegration time and with sufficient mechanical strength.

Various drugs are effective in the treatment of allergies like first generation antihistamines but they possess the major disadvantage of causing sedation. The initial second generation antihistamines, Terfenadine and Astemizole, were effective non-sedating medications but had drug interactions associated with cardiac problems. Later second generation antihistamines, such as Loratadine and Cetirizine, have been found to be effective in the treatment of allergic rhinitis and the latter to be effective in the treatment of chronic idiopathic urticaria. Levocetirizine dihydrochloride is the R-enantiomer of Cetirizine and is believed to have a two fold higher affinity for human H-1 receptors than Cetirizine. Levocetirizine is also believed to be rapidly and extensively absorbed and is free from side effects on the central nervous system.

Considering all these points, melt-in-mouth tablets of Levocetirizine dihydrochloride were prepared, and optimization was done by the use of response surface methodology. Central composite design (CCD) is a response surface design which provides information on direct effects, pair wise interaction effects and curvilinear variable effects and is widely used for formulation and process optimization in the field of pharmaceutics [9, 10]. Melt-in-mouth tablets of Levocetirizine dihydrochloride prepared using vacuum drying approach have been optimized successfully using a face-centered Central Composite Design. It is very efficient and flexible, providing much information on experiment variable effects and overall percentage error in a minimal number of experimental runs. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation [11, 12]. Therefore, face-centered Central Composite Design was found to be a very suitable tool for process optimization of melt-in-mouth tablets in this study.

MATERIALS AND METHODS

Materials

Levocetirizine dihydrochloride obtained from Vardhman Pharmaceuticals (Paonta Sahib), Crospovidone from Macleod Pharmaceuticals (Baddi), Camphor, Sodium Saccharin, Microcrystalline Cellulose, Mannitol, Magnesium stearate, Talc were of analytical reagent grade.

Methods

Formulation of Mouth dissolving tablets

Levocetirizine dihydrochloride melt-in-mouth tablets were prepared by sublimation method according to the formula given in Table 1. A total number of thirteen formulations were prepared as per the standard experimental design protocol. All ingredients were weighed accurately and sifted through sieve no. # 40 and were mixed well to get a uniform mixture except magnesium stearate and talc. They were sifted through sieve no. # 60, and then mixed with

other ingredients. The lubricated directly compressible blend was compressed by using Fluid Pack 8 station Mini Rotary tablet punching machine (7 mm punch diameter). The tablets were sublimed at 60-65ºC in a vacuum oven for 24 hours to sublime camphor. The removal of camphor after sublimation was confirmed by weighing the tablets before and after sublimation.

Table 1: Composition of Melt-in-mouth tablet of Levocetirizine Dihydrochloride

Ingredients (mg)	Formulation Code												
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
Levocetirizine dihydrochloride	5	5	5	5	5	5	5	5	5	5	5	5	5
Camphor	5	5	5	10	10	10	15	15	15	10	10	10	10
Crospovidone	4	6	8	4	6	8	4	6	8	6	6	6	6
Sodium Saccharin	2	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	10	10	10	10	10	10	10	10	10	10	10	10	10
Micro crystalline Cellulose	121	119	117	116	114	112	106	104	102	114	114	114	114
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150	150

Evaluation of Tablet Properties

Thickness

Thickness of tablets was determined using Vernier caliper. Three tablets from each batch were used, and an average value was calculated. The mean ± standard deviation values of thickness were calculated.

Tablet Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted.

Friability

Friability is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for 4 minutes for 100 revolutions [13]. At the end of test, tablets were dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as;

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Disintegration Time

The test was carried out on 6 tablets using the disintegration apparatus. Phosphate buffer (pH 6.8) maintained at 37ºC ± 2ºC was used as a disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting Time

A piece of tissue paper folded twice was placed in a small petridish containing 6ml. of distilled water. A tablet was carefully placed on the surface of the paper and the time required for water to reach the upper surface of the tablet was noted as the wetting time. Less is the wetting time, indicates more porous the tablet [14].

Water Absorption Ratio

Water absorption ratio 'R' was determined using the equation,

$R = 100 (Wb - Wa) / Wa$

Where,

Wa is weight of tablet before water absorption and

Wb is weight of tablet after water absorption.

Drug Content

The drug content was determined by triturating 10 tablets, the powder equivalent to 5 mg of drug was accurately weighed and dissolved in 100 ml of phosphate buffer pH 6.8. The solution was filtered, suitably diluted and assayed for drug content, using UV Spectrophotometer at λ_{max} 231 nm.

In vitro Dissolution test

The in-vitro release studies of the prepared tablets were carried out using the USP II, paddle type apparatus at 37 ± 0.5 °C rotating at 50 rpm using the Electrolab dissolution tester (TDT 06P) and phosphate buffer, pH 6.8 (900 ml.) was used as dissolution medium. Sink conditions were maintained and 10 ml volume was withdrawn at various time intervals i.e. 2, 4, 6, 8, 10, 15, 20, 25, 30 min., filtered and analyzed using Systronics (2202) UV–Visible spectrophotometer at λ_{max} 231 nm. Absorbance for the sample withdrawn was recorded and % drug release at different time intervals were plotted as cumulative percent drug release versus time (min) curve.

Optimization Data Analysis and Numerical Optimization

Various RSM computations for the current optimization study were performed employing Design Expert Software (Version 7.1.6, Stat-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach.

The general form of the MLRA model is represented below:

$$Y = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1X_2^2 + \beta_7 X_1{}^2X_2$$

Where, β_o is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; β_1 to β_7 are the coefficients computed from the observed experimental values of Y; and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and X_i^2 (i = 1 to 2) represent the interaction and quadratic terms, respectively. Statistical validation of the polynomial equation was established on the basis of ANOVA provision in the Design Expert Software. Various feasibility and grid searches were conducted to find the composition of optimum formulations. Also, the 3-D response surface graphs and 2-D contour plots were constructed using the output files generated.

Numerical optimization using the desirability approach was employed to locate the optimal settings of the formulation variables to obtain the desired response. An optimized formulation was developed by setting constraints on the dependent and independent

variables and the formulation developed was than evaluated for the various response properties. The resultant experimental values obtained were compared with those predicted by the mathematical models generated.

Experimental design

A Central Composite Design using Design Expert Software (Version 7.1.6, Stat- Ease Inc, Minneapolis, MN) was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the disintegration time, wetting time, water absorption ratio and in vitro release of Levocetirizine dihydrochloride. A 2-factor, 3-level design was observed to be most suitable for exploring quadratic response surfaces and constructing second-order polynomial models. The amount of Camphor (X_1) and Crospovidone (X_2) were selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations and the translation of the coded levels to the experimental units employed during the study. The dependent and independent variables selected are also shown along with their low, medium and high levels, which were selected based on the results from preliminary experimentation.

Table 2: Factor Combination as per the Chosen Experimental Design

Formulation Code	Coded Factor Levels	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1
F10	0	0
F11	0	0
F12	0	0
F13	0	0

Translation of coded levels in actual units			
Coded level	-1 (low)	0 (middle)	+1(high)
X_1 : Camphor	5	10	15
X_2 : Crospovidone	4	6	8

Table 3: Response Parameters of various Melt-in-mouth Formulations Prepared as per the Experimental Design

Formulation Code	Camphor (X1)	CP (X2)	DT (sec)	WT (sec)	WAR (%)	% CDR
F1	5	4	213	93	65.85	86.78
F2	5	6	205	89	70.22	88.41
F3	5	8	196	82	73.00	89.36
F4	10	4	172	65	76.76	90.41
F5	10	6	164	59	85.92	91.76
F6	10	8	142	53	87.19	92.88
F7	15	4	64	32	89.68	93.42
F8	15	6	52	26	92.33	94.24
F9	15	8	45	20	94.54	96.48
F10	10	6	164	58	85.35	92.52
F11	10	6	163	57	86.22	91.38
F12	10	6	164	59	86.00	91.17
F13	10	6	165	58	85.49	92.36

CP- Crospovidone, DT- Disintegration Time, WT- Wetting Time

WAR-Water Absorption Ratio, % CDR- Cumulative % Drug Release

RESULTS AND DISCUSSION

Evaluation of Tablets

All the 13 formulations were evaluated for the disintegration time, wetting time, water absorption ratio and *in vitro* drug release. The results are shown in Table 3.

Drug Content and Physical Evaluation

The drug content in various formulations varied between 97.6% and 101.3% (mean 98.7%). Tablet weights varied between 148.0 and 150.2 mg (mean 149.3 mg), thickness between 3.7 and 3.9 mm (mean 3.83 mm), hardness between 2. 8 and 3.5 kg cm^{-2} (mean 3.3 Kg cm^{-2}), and friability ranged between 0.156 % and 0.323 % (mean 0.216 %). Thus, all the physical parameters of the mouth dissolving tablets were practically within control. Comparative dissolution profiles of various mouth dissolving tablet formulations (F1 to F13) of Levocetirizine dihydrochloride prepared by sublimation technology as per the experimental design are shown in Fig. 1 and Fig. 2.

ANOVA- Analysis of variance

Analysis of variance of the responses indicated that response surface models developed for disintegration time, wetting time, water absorption ratio and cumulative % drug release (10 min) were significant and adequate, without significant lack of fit. Influence of formulation variables on the response factors are shown in Table 4.

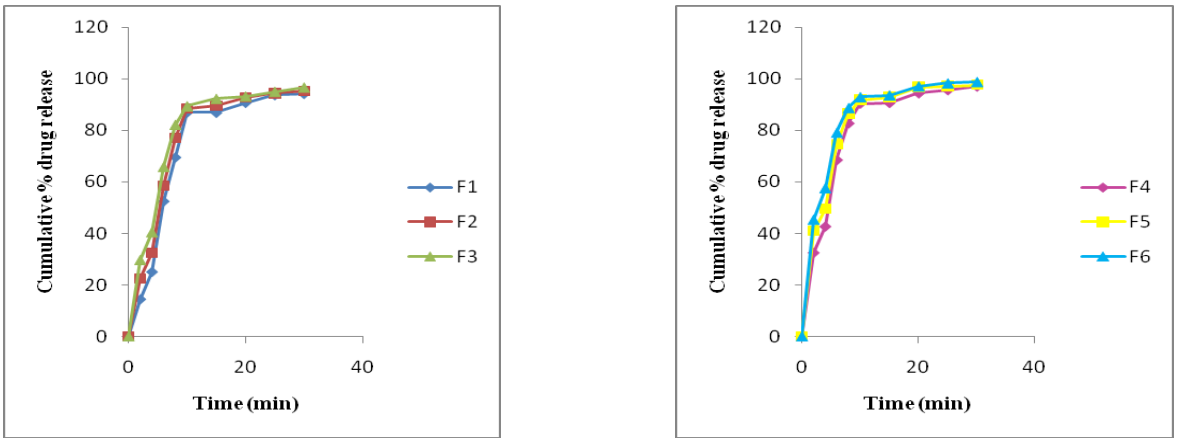

Fig. 1: Comparative dissolution profile of melt-in-mouth tablets prepared by sublimation method from formulation batches F1 to F6.

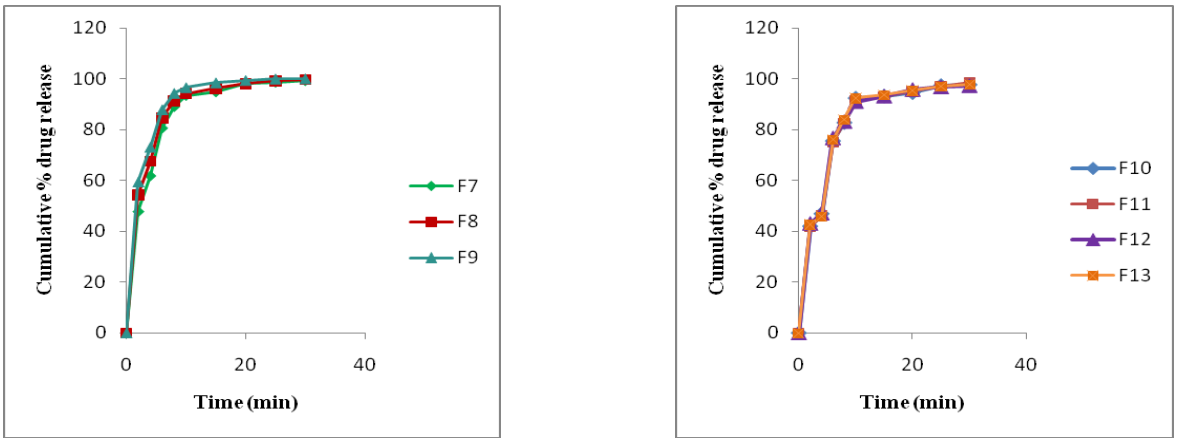

Fig. 2: Comparative dissolution profile of melt-in-mouth tablets prepared by sublimation method from formulation batches F7 to F13

Table 4: ANOVA –Influence of formulation variables on the response factors

Response factor	Model F-value	Prob > F	Lack of fit F-value	Prob > F
Disintegration Time	595.88	0.0001	3.21	0.1478
Wetting Time	958.04	0.0001	2.37	0.1988
Water Absorption Ratio	164.59	0.0001	2.12	0.2190
Cumulative % Drug Release	36.11	0.0005	0.28	0.6237

Model summary statistics for the selected significant models are shown in Table 5. It can be observed that R^2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2 value is in good agreement with the adjusted R^2 value, resulting in reliable models.

Table 5: Model Summary Statistics- Influence of formulation variables on the response factors

Response Factor	Std. Dev.	R^2	Adjusted R^2	Predicted R^2
Disintegration Time	3.04	0.9988	0.9971	0.8668
Wetting Time	0.94	0.9993	0.9982	0.9671
Water Absorption Ratio	0.84	0.9957	0.9896	0.8219
Cumulative % Drug Release	0.55	0.9806	0.9535	0.8253

Mathematical Modeling

Mathematical relationships generated using multiple linear regression analysis for the studied response variables are expressed as equations 1 to 4.

$$DT = 162.90 - 76.50\ X_1 - 15.00\ X_2 - 0.50\ X_1 X_2 - 31.64\ X_1^2 - 3.14\ X_2^2 + 1.50\ X_1 X_2^2 + 6.00\ X_1^2 X_2 \quad (1)$$

$$WT = 58.41 - 31.50\ X_1 - 6.00\ X_2 - 0.25\ X_1 X_2 - 1.45\ X_1^2 + 0.052\ X_2^2 + 0.75\ X_1 X_2^2 + 0.25\ X_1^2 X_2 \quad (2)$$

$$WAR = 85.04 + 10.25\ X_1 + 2.71\ X_2 - 0.18\ X_1 X_2 - 2.50\ X_1^2 - 1.11\ X_2^2 + 1.20\ X_1 X_2^2 - 0.11\ X_1^2 X_2 \quad (3)$$

$$\%\ CDR = 91.79 + 2.91\ X_1 + 1.23\ X_2 + 0.12\ X_1 X_2 - 0.33\ X_1^2 - 0.011\ X_2^2 + 0.52\ X_1 X_2^2 + 0.17\ X_1^2 X_2 \quad (4)$$

All the polynomial equations were found to be statistically significant (P < 0.0002), as determined using ANOVA, as per the provision of Design Expert Software.

The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor in Equations 1 to 4 reveal that Camphor individually, has rather more pronounced effect on the values of disintegration time, wetting time, water absorption ratio and % CDR (10min) respectively. At a given set of factor levels, however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

Response Surface Analysis

The 3-dimensional response surface plots are shown in Fig. 3(a) to 6(a) and the corresponding contour plots for the studied response properties viz., disintegration time, wetting time, water absorption ratio and cumulative % drug release (10 min) are shown in Fig. 3(b) to 6(b) respectively.

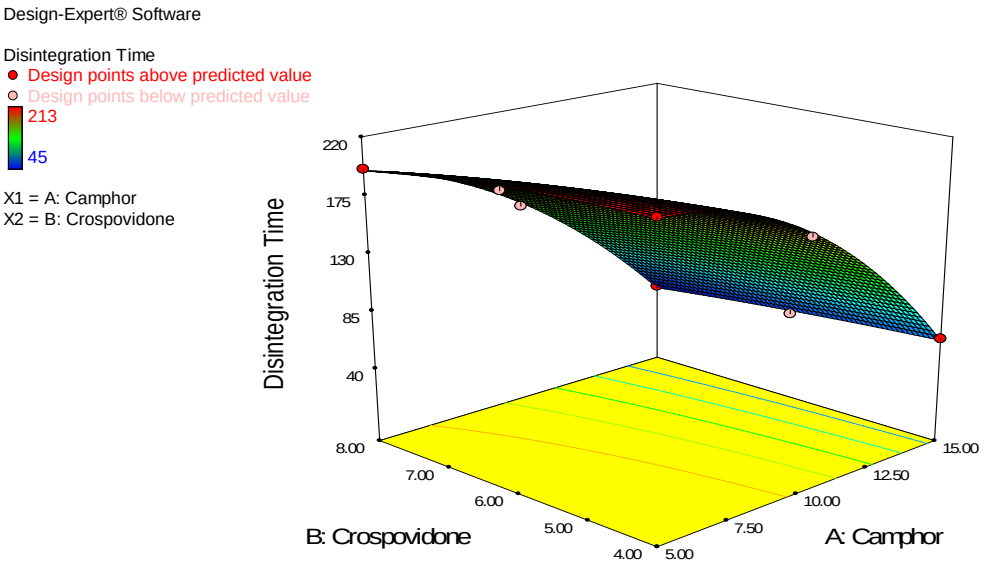

Fig. 3(a): Response surface plot showing the influence of two different superdisintegrants on disintegration time

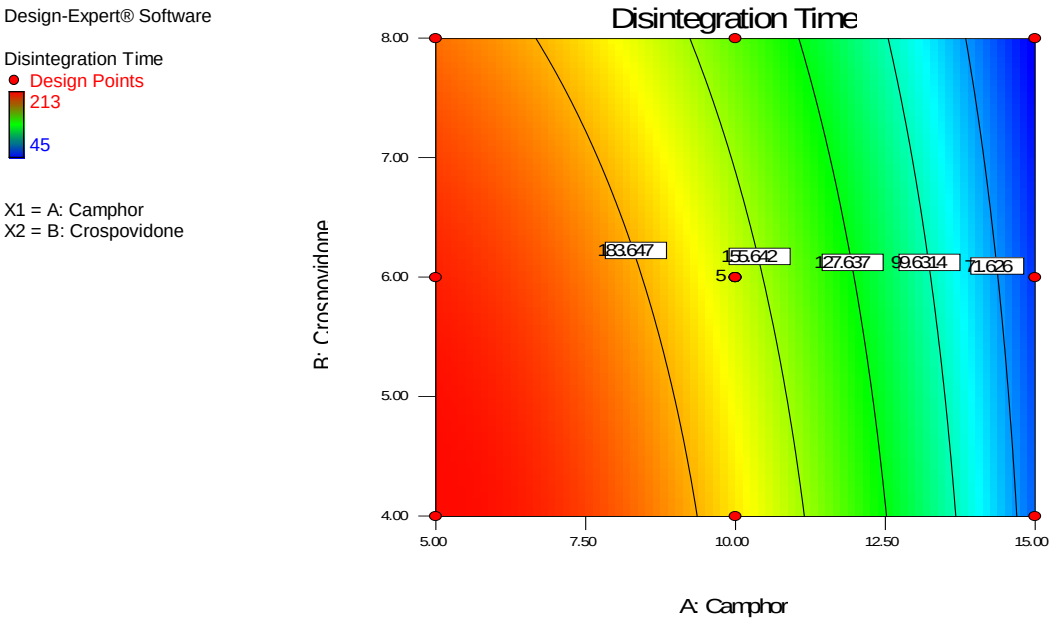

Fig. 3(b): Contour plot showing the relationship between various levels of two factors on disintegration time

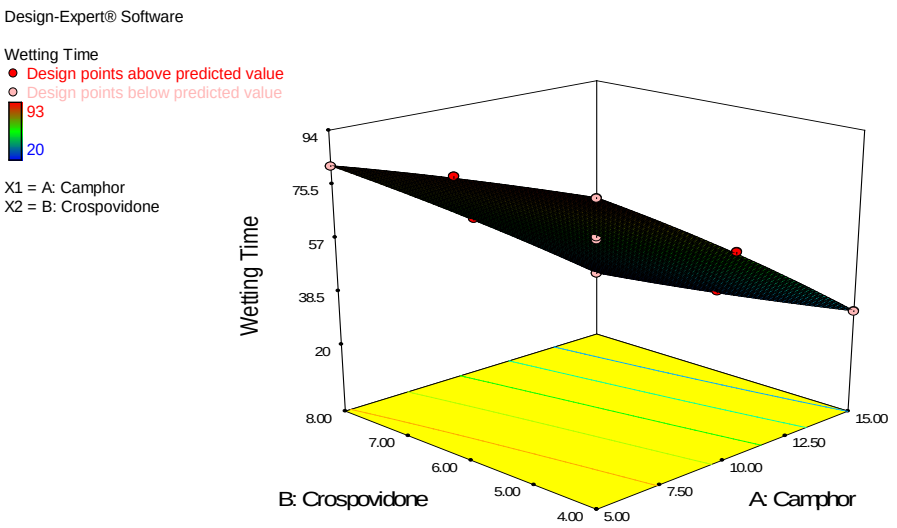

Fig. 4(a): Response surface plot showing the influence of two different superdisintegrants on wetting time

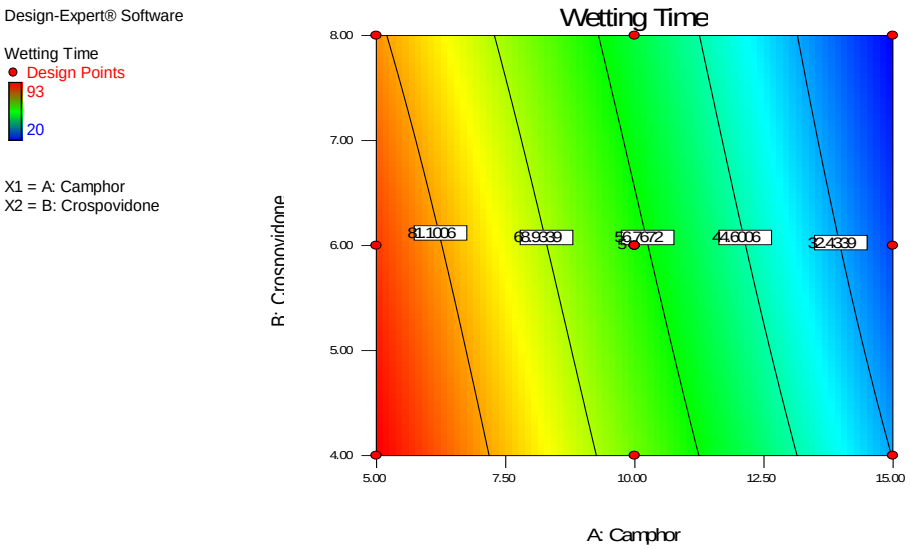

Fig. 4(b): Contour plot showing the relationship between various levels of two factors on wetting time

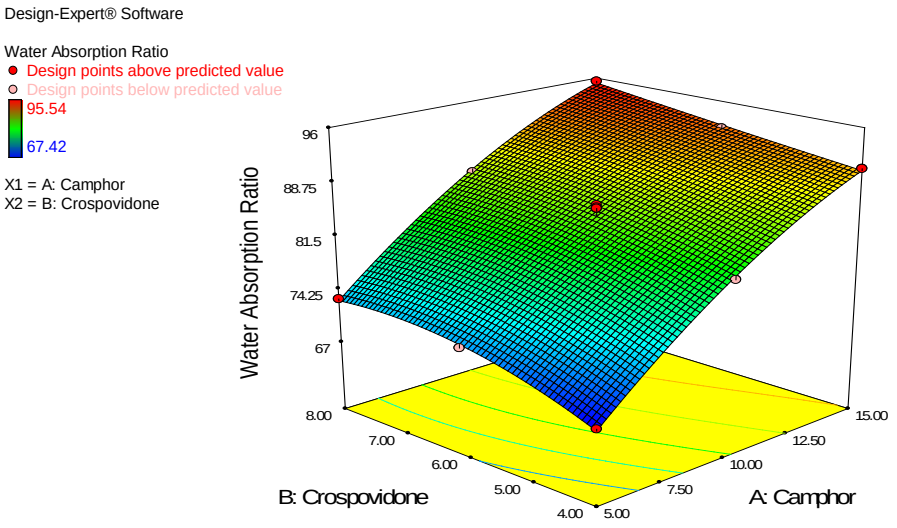

Fig. 5(a): Response surface plot showing the influence of two different superdisintegrants on water absorption ratio

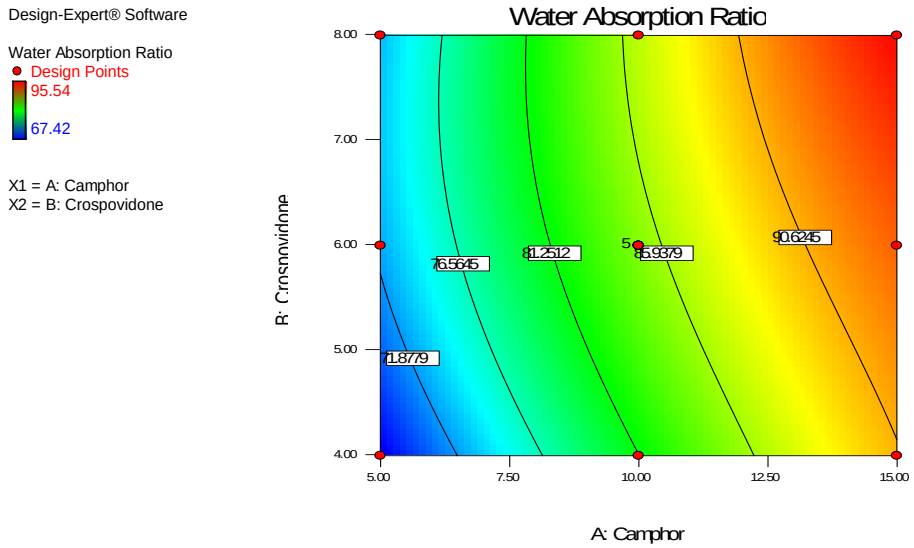

Fig. 5(b): Contour plot showing the relationship between various levels of two factors on water absorption ratio

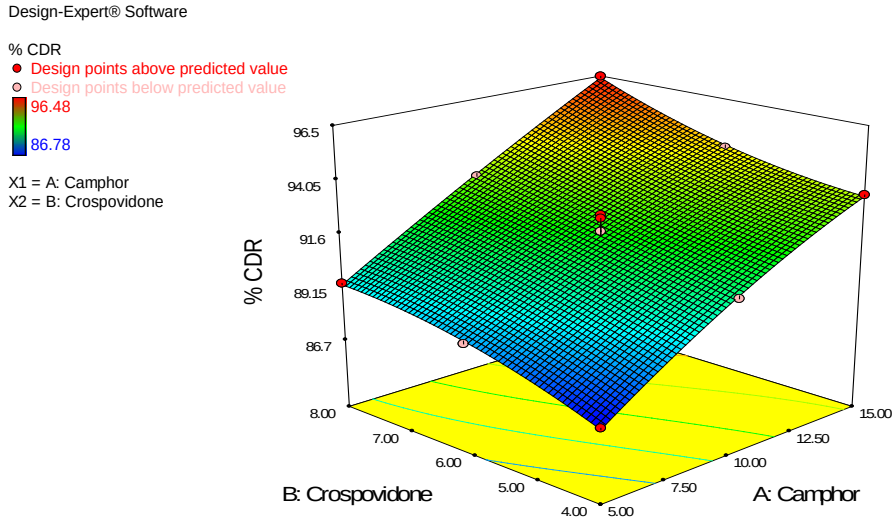

Fig. 6 (a): Response surface plot showing the influence of two different superdisintegrants on cumulative % drug release (10 min)

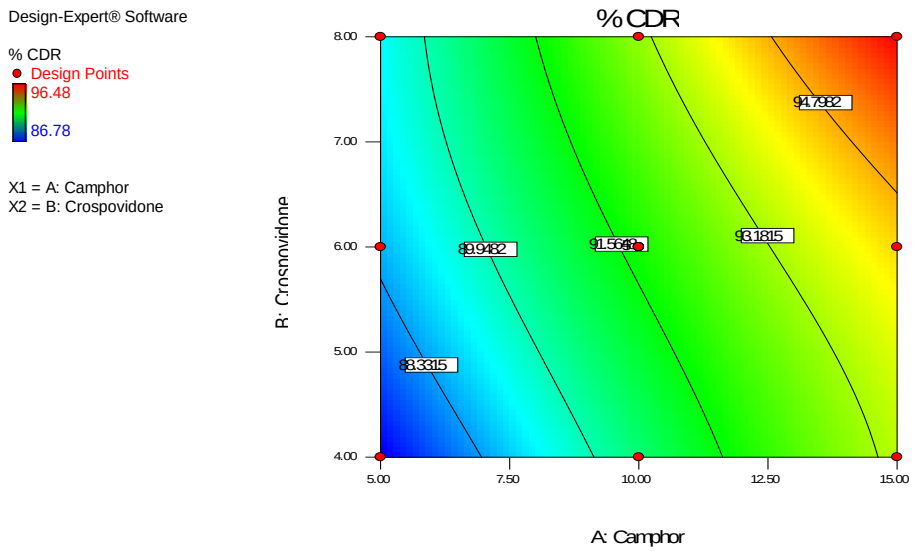

Fig. 6(b): Contour plot showing the relationship between various levels of two factors on cumulative % drug release (10 min)

Disintegration Time and Wetting Time

It could be seen that increasing the percentage incorporated of the subliming agent had a negative effect on the disintegration time and wetting time. On the other hand, increasing the amount of Crospovidone from 4 mg to 8 mg led to a decline in the disintegration time and wetting time. The results of multiple linear regression analysis showed that both the coefficients X_1 and X_2 bear a negative sign. Therefore, increasing the concentration of either Camphor or Crospovidone is expected to decrease the disintegration time and wetting time. However, the effect of Camphor seems to be more pronounced as compared with that of Crospovidone in both cases, disintegration time and wetting time, as revealed by the response surface and the mathematical model. This is because when higher percentage of Camphor is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated.

Water Absorption Ratio and Cumulative % Drug Release

Eqn. 3 and 4 revealed that both main factors independently exerted a significant positive influence on the Water absorption ratio and Cumulative % drug release respectively. However the effect of X_1 is more pronounced than X_2, in both cases as revealed by the response surface and the mathematical model. Fig. 5(a), Fig. 5(b) and Fig. 6(a), Fig. 6(b) shows that the Water absorption ratio and Cumulative % drug release varies in somewhat linear fashion with increase in the amount of Camphor as well as Crospovidone. The effect of increase in X_1 seems to be more pronounced as compared with that of X_2.

Numerical Optimization

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimum formulation was selected based on the criteria of attaining minimum disintegration time and wetting time with high water absorption ratio and cumulative % drug release. Upon "trading off" various response variables, constraints like minimizing the disintegration time and wetting time and maximizing the water absorption ratio and cumulative % drug release (10 min) were set at appropriate limits and importance. Upon comprehensive evaluation of feasibility search and subsequently exhaustive grid searches, the formulation composition with superdisintegrants levels of Camphor, 15mg, and Cp, 8mg, fulfilled maximum requisites of an optimum formulation because of better regulation of release rate and water absorption ratio and less disintegration and wetting time.

Validation of Results

In order to evaluate the optimization capability of the models generated according to the results of the central composite design, tablets including the optimized formulation were prepared using the optimal process variable settings. All results of the physical evaluation were found to be within limits. Table 6 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error.

Table 6: Composition of the Optimized Formulation, the Predicted and Experimental values of Response Variables, and Percentage Prediction Error

Composition Camphor : CP (mg)	Response Variable	Experimental Value	Predicted Value	Percentage Error
15:8	DT	44	43.62	0.871
	WT	20.31	20.26	0.246
	WAR	96.11	93.96	2.288
	% CDR	94.47	96.41	-2.012

Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between -2.012% and 2.288%. The closeness of the predicted and observed values indicates validity of derived equations for the dependent variables.

CONCLUSIONS

The response surface methodology (RSM) using Central Composite Design (Design Expert Software ,Version 7.1.6, Stat- Ease Inc, Minneapolis, MN) for 2 factors offers an advantage of fewer experimental runs (13 runs) as compared to that of central composite circumscribed (CCC) or central composite inscribed (CCI) models, which require 20 runs. A 2-factor, 3-level Central Composite design with different ratio of superdisintegrant (Crospovidone) and subliming agent (Camphor) was employed for optimization of mouth dissolving tablets of Levocetirizine dihydrochloride. The quantitative effects of the factors at different levels on the responses could be predicted by using polynomial equations. The observed responses were found to be in close agreement with the predicted values for optimized formulations. The sublimation method used to prepare the melt-in-mouth tablets in this study is relatively simple and safe and a stable, effective and pleasant tasting melt-in-mouth tablet, which has a good balance over disintegration time and mechanical strength, was formulated.

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