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Design, development, and optimization of mouth dissolving tablets of levocetirizine dihydrochloride using central composite design

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Abstract

The aim of the present research work was to design and develop an optimized mouth dissolving tablet dosage form of an anti-allergic drug, Levocetirizine dihydrochloride. Independent variables such as the amount of subliming agent-camphor (X_1) and the amount of superdisintegrant-crospovidone (X_2) were optimized using a 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. 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.

Keywords: mouth dissolving tablets, levocetirizine dihydrochloride, superdisintegrant, subliming agent, 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, 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 (Indurwade et al. 2002, Wilkosz et al. 2003, Kaushik et al. 2004), 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 (Welling 2002).

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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 (Dobetti 2000 and 2011, Yunxia 1999). 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.

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 (Krogars et al. 2000 and Vaithiyalingam and Khan 2002). Mouth dissolving tablets of Levocetirizine dihydrochloride prepared using vacuum drying approach has 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 (Singh et al. 2005 and 2006). Therefore, face-centered Central Composite Design was found to be a very suitable tool for process optimization of mouth dissolving tablets in this study.

Materials and Methods

Materials

Levocetirizine dihydrochloride obtained from Vardhman Pharmaceuticals, India. Crospovidone from Macleod Pharmaceuticals, USA. Camphor, sodium saccharin, microcrystalline cellulose, mannitol, magnesium stearate, talc were of analytical reagent grade.

Formulation of mouth dissolving tablets

Levocetirizine dihydrochloride mouth dissolving 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 60-65°C in a vacuum oven for 24 h to sublime camphor. The removal of camphor after sublimation was confirmed by weighing the tablets before and after sublimation.

Table 1. 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

Experimental design

A Central Composite Design 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. Composition of mouth dissolving 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
Microcrystalline 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 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.

Table 3. Evaluation of tablets

Batch Code	Hardness (kg/cm^2)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio (%)
F1	3.26 ± 0.115	213 ± 1.000	93 ± 1.0	65.85 ± 0.010
F2	3.06 ± 0.208	205 ± 2.000	89 ± 1.0	70.22 ± 0.055
F3	3.23 ± 0.208	196 ± 1.000	82 ± 3.0	73.00 ± 1.000
F4	3.56 ± 0.057	172 ± 3.000	65 ± 1.0	76.76 ± 0.195
F5	3.13 ± 0.152	164 ± 1.000	59 ± 1.0	85.92 ± 0.020
F6	3.36 ± 0.115	142 ± 2.000	53 ± 3.0	87.19 ± 0.050
F7	3.16 ± 0.152	64 ± 2.000	32 ± 2.0	89.68 ± 0.020
F8	3.43 ± 0.208	52 ± 1.000	26 ± 1.0	92.33 ± 1.000
F9	3.5 ± 0.200	45 ± 1.000	20 ± 1.0	94.54 ± 0.055
F10	3.26 ± 0.251	164 ± 1.000	58 ± 2.0	85.35 ± 0.010
F11	3.06 ± 0.057	163 ± 3.000	57 ± 2.0	86.22 ± 0.055
F12	3.23 ± 0.057	164 ± 2.000	59 ± 1.0	86.00 ± 2.000
F13	3.16 ± 0.115	165 ± 1.000	58 ± 1.0	85.49 ± 0.195

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 (India) UV–visible spectrophotometer at λ_{max} 231 nm. Absorbance for the sample withdrawn was recorded and % drug release at different time intervals were plotted. All experiment was performed in triplicate and the results are shown in table-4 and 5.The drug release from different batchs of tablets was shown in Fig. 1 and 2.

Results and Discussion

The response surface methodology (RSM) using Central Composite Design 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.

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.

Table 4. Dissolution profile of tablets prepared by sublimation method from formulation batches F1 to F6

Time (min.)	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	14.37 ± 1.353	22.45 ± 2.230	29.64 ± 1.106	32.44 ± 2.235	40.84 ± 2.505	45.32 ± 1.340
4	24.99 ± 2.320	32.41 ± 0.826	40.45 ± 0.205	42.63 ± 0.273	49.54 ± 1.210	57.55 ± 0.330
6	52.38 ± 0.937	58.54 ± 0.430	65.80 ± 1.161	68.48 ± 1.105	74.46 ± 2.096	79.09 ± 1.230
8	69.40 ± 1.162	77.11 ± 1.148	82.15 ± 1.176	82.71 ± 0.265	86.4 ± 0.455	88.66 ± 1.220
10	86.78 ± 1.105	88.41 ± 2.011	89.36 ± 2.015	90.41 ± 2.011	91.76 ± 1.105	92.88 ± 2.020
15	86.74 ± 1.206	89.52 ± 1.040	92.23 ± 1.115	90.64 ± 0.268	92.78 ± 1.146	93.58 ± 1.200
20	90.56 ± 2.376	92.75 ± 1.096	93.15 ± 2.060	94.37 ± 1.281	96.69 ± 3.025	97.04 ± 0.270
25	93.56 ± 1.100	94.47 ± 2.090	94.97 ± 0.132	95.63 ± 1.102	97.05 ± 1.085	98.24 ± 1.184
30	94.03 ± 3.076	95.22 ± 1.105	96.63 ± 1.190	97.01 ± 1.100	97.53 ± 2.328	98.76 ± 1.201

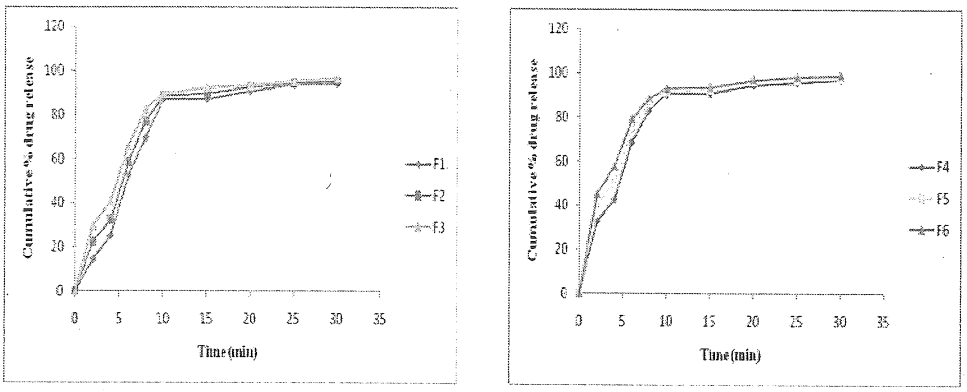

Figure 1. Comparative dissolution profile of formulation batches F1 to F6

Table 5. Dissolution profile of tablets prepared by sublimation method from formulations F 7 to F 13

Time (min.)	Cumulative % Drug Release						
	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
2	47.76 ±1.20	54.26 ± 0.31	59.39 ± 0.40	42.03 ± 0.22	41.88 ± 0.35	43.12 ± 1.16	42.67 ± 0.38
4	61.80 ± 1.21	67.58 ± 1.36	73.04 ± 2.18	46.98 ± 1.11	46.08 ± 0.20	47.22 ± 2.06	45.94 ± 1.14
6	80.61 ± 0.25	84.57 ± 2.37	87.78 ± 1.27	75.66 ± 0.24	75.22 ± 0.12	76.82 ± 1.17	76.18 ± 1.08
8	89.05 ± 1.19	91.39 ± 1.18	94.24 ± 1.14	82.84 ± 1.17	82.60 ± 0.31	83.29 ± 0.50	83.94 ± 0.22
10	93.42 ± 3.04	94.24 ± 2.11	96.48 ± 1.10	92.52 ± 3.05	91.38 ± 2.04	91.17 ± 1.02	92.36 ± 2.01
15	94.87 ± 2.05	96.26 ± 1.03	98.36 ± 1.28	93.32 ± 0.19	93.11 ± 1.02	93.26 ± 0.19	93.65 ± 1.16
20	97.96 ± 1.12	98.12 ± 2.10	99.29 ± 1.10	94.64 ± 2.11	95.12 ± 1.16	95.86 ± 2.10	95.32 ± 1.09
25	98.63 ± 1.17	99.17 ± 1.13	99.87 ± 3.09	97.48 ± 0.21	97.23 ± 2.02	96.89 ± 1.12	97.08 ± 1.15
30	99.23 ± 1.11	99.66 ± 1.13	99.94 ± 1.08	97.81 ± 1.07	98.66 ± 1.27	97.42 ± 0.12	97.65 ± 2.53

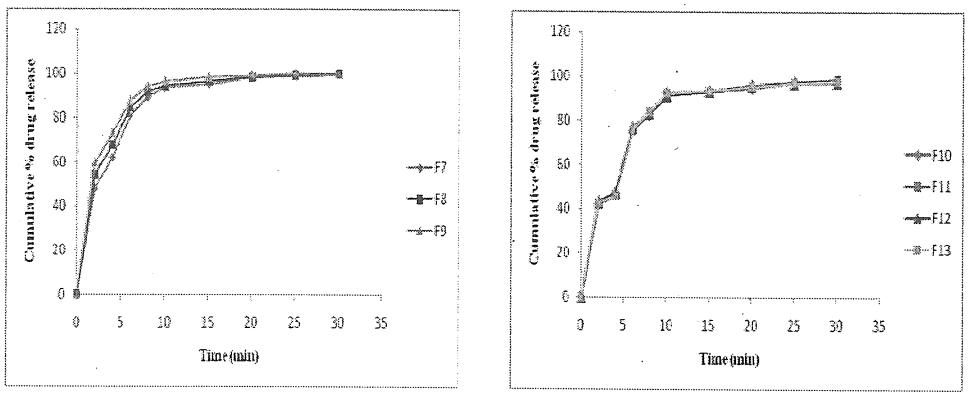

Figure 2. Comparative dissolution profile of formulation batches F7 to F13

Response surface methodology optimization

Response parameters of various mouth dissolving formulations prepared as per the experimental design is depicted in Table 6.

Table 6. Response parameters of various mouth dissolving 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

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 7.

Table 7. 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

Table 8. 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

Model summary statistics for the selected significant models are shown in Table 8. It can be observed that R2 is high for all responses, which indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R2 value is in good agreement with the adjusted R2 value, resulting in reliable models.

Mathematical modeling

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

$$DT = 162.90 - 76.50\ X1 - 15.00\ X2 - 0.50\ X1\ X2 - 31.64\ X12 - 3.14\ X22 + 1.50\ X1\ X22 + 6.00\ X12\ X2. \quad (1)$$

$$WT = 58.41 - 31.50\ X1 - 6.00\ X2 - 0.25\ X1\ X2 - 1.45\ X12 + 0.052\ X22 + 0.75\ X1\ X22 + 0.25\ X12\ X2. \quad (2)$$

$$WAR = 85.04 + 10.25\ X1 + 2.71\ X2 - 0.18\ X1\ X2 - 2.50\ X12 - 1.11\ X22 + 1.20\ X1\ X22 - 0.11\ X12\ X2. \quad (3)$$

$$\% \text{ CDR} = 91.79 + 2.91\ X1 + 1.23\ X2 + 0.12\ X1\ X2 - 0.33\ X12 - 0.011\ X22 + 0.52\ X1\ X22 + 0.17\ X12\ X2. \quad (4)$$

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. 3a to 6a 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. 3b to 6b respectively.

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 X1 and X2 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 X1 is more pronounced than X2, 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 X1 seems to be more pronounced as compared with that of X2.

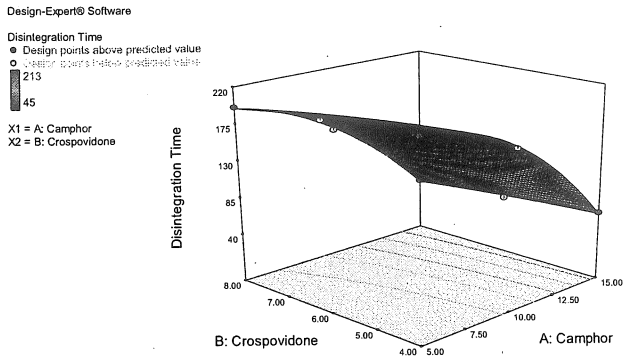

Figure 3a. Response surface plot showing the influence of two different superdisintegrants on disintegration time

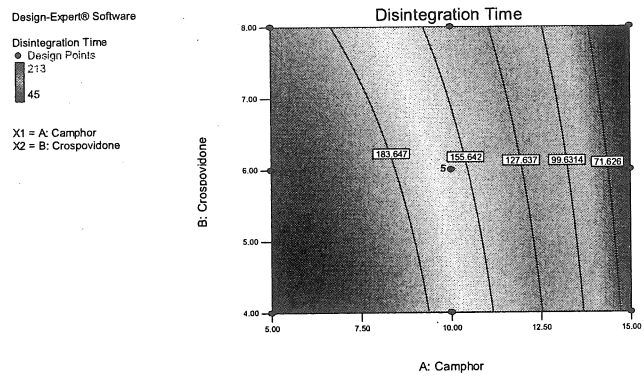

Figure 3b. Contour plot showing the relationship between various levels of two factors on disintegration time

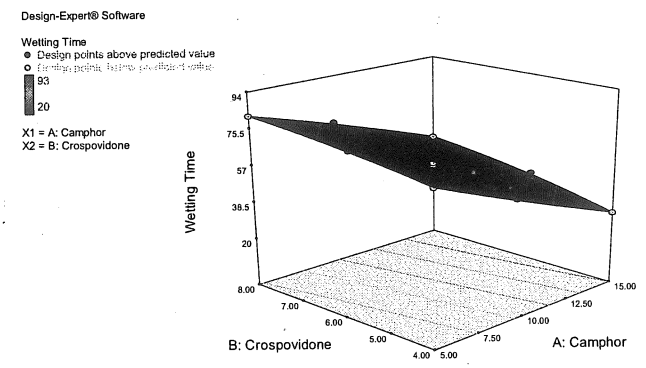

Figure 4a. Response surface plot showing the influence of two different superdisintegrants on wetting time

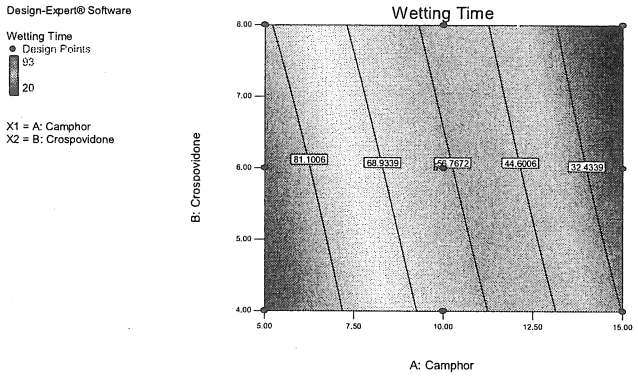

Figure 4b. Contour plot showing the relationship between various levels of two factors on wetting time

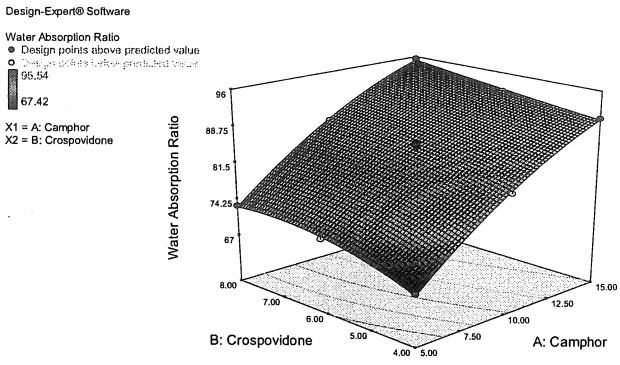

Figure 5a. Response surface plot showing the influence of two different superdisintegrants on water absorption ratio

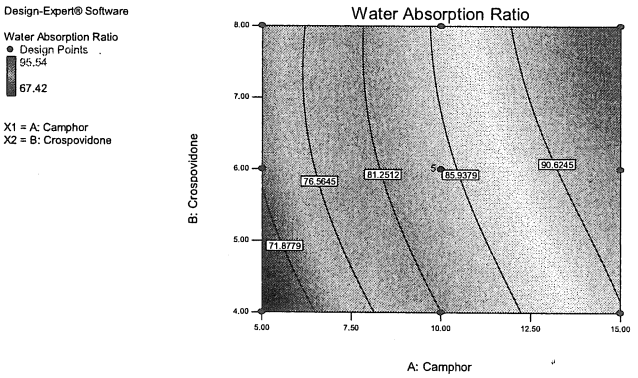

Figure 5b. Contour plot showing the relationship between various levels of two factors on water absorption ratio

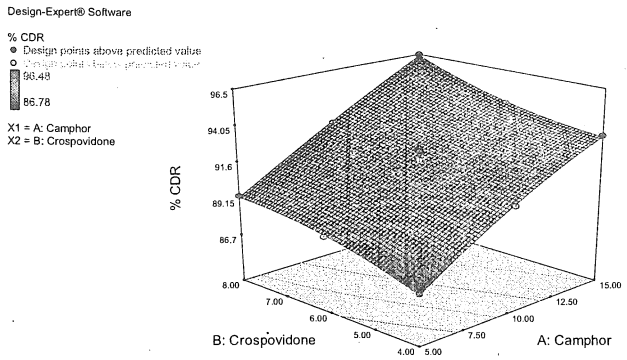

Figure 6a. Response surface plot showing the influence of two different superdisintegrants on cumulative % drug release (10 min)

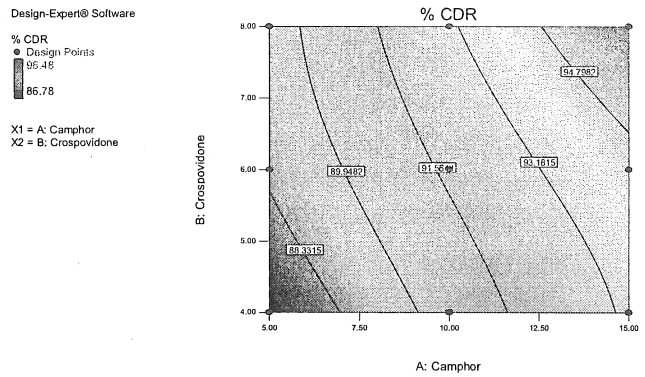

Figure 6b. Contour plot showing the relationship between various levels of two factors on cumulative % drug release (10 min)

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. Table 9 depicts the constraints set and the solution provided by the software.

A new formulation was prepared using 15mg of Camphor and 8mg of Crospovidone, all other excipients were same (as shown in Table 2), the method of manufacturing and all other factor were remain constant. For the optimized formulation, the results of the physical evaluation tests were found to be within limits.

Table 9. Solution provided by Central Composite Design (DOE)

Constraints							
Name	**Goal**	**Lower Limit**	**Upper Limit**	**Lower Weight**	**Upper Weight**		**Importance**
Camphor	is in range	5	15	1	1		3
Cp	is in range	4	8	1	1		3
DT	minimize	45	213	1	1		5
WT	minimize	20	93	1	1		5
WAR	maximize	65.85	94.54	1	1		5
% CDR	maximize	86.78	96.48	1	1		5
Solutions							
Number	**Camphor**	**Cp**	**DT**	**WT**	**WAR**	**% CDR**	**Desirability**	
1	15	8	43.62	20.26	93.96	96.41	0.99	**Selected**

Table 10. Evaluation parameters of tablet of optimized batch

Batch Code	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg)	Thickness of tablets (mm)	DT (sec)	WT (sec)	Drug Content (%)	WAR (%)
FO1	3.53±0.152	0.533	150.6±1.155	4 ± 0.10	44±1.0	20.3± 0.01	98.8±2.01	96.11±1.21

Dissolution in phosphate buffer pH 6.8

Dissolution study was done on three tablets and the result obtained is shown in Table 11.

Table 11. Dissolution profile of optimized batch

Optimized Formulation (FO1)										
Time (min)	**0**	**2**	**4**	**6**	**8**	**10**	**15**	**20**	**25**	**30**
% CDR	0	57.14 ± 1.030	71.28 ± 0.820	85.43 ± 1.120	92.66 ± 0.525	94.47 ± 1.011	96.35 ± 1.035	97.49 ± 1.015	98.08 ± 2.030	98.88 ± 0.735

In vitro release kinetics

In order to investigate the order of drug release, the data of optimized batch was fitted to models representing zero-order, first-order, Higuchi model and Koresmeyer-Peppas model .On the basis of value of R^2 it was concluded that the optimized batch followed first order release kinetics. Model providing the value nearest to 1 describes the order of drug release. The R^2 value for the first order model was found out to be 0.898. Results of data fitting to First order drug release model is shown in Table 12 and graph is shown in Fig. 7.

Table 12. *In vitro* release data of the optimized batch: First order kinetics

Time (min)	% Cumulative Drug released	% Cumulative Drug retained	Log % Cumulative Drug retained
2	57.14	42.86	1.632
4	71.28	28.72	1.458
6	85.43	14.57	1.163
8	92.66	7.34	0.865
10	94.47	5.53	0.742
15	96.35	3.65	0.562
20	97.49	2.51	0.399
25	98.08	1.92	0.283
30	98.88	1.12	0.049

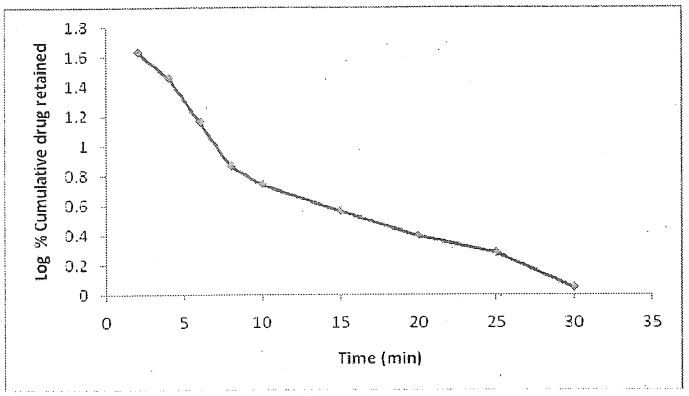

Figure 7. *In vitro* release data of the optimized batch: First order kinetics

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 13 lists the composition of the final batch, its predicted and experimental values of all the response variables, and the percentage error.

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.

Table 13. 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

Conclusion

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 mouth dissolving tablets in this study is relatively simple and safe and a stable, effective and pleasant tasting mouth dissolving tablet, which had a good balance over disintegration time and mechanical strength, was formulated.

References

Dobetti, L. (2000). Fast-melting tablets: Developments and technologies. *Pharm.Tech. Eur.* 12: 32-42.

Dobetti, L. (2001). Fast-melting tablets: Developments and Technologies. *Pharma Tech.* (Suppl.), 44-50.

Indurwade, N.H., Rajyaguru, T.H. and Nakhat, P.D. (2002). Novel approach: Fast dissolving tablets. *Indian Drugs* 39: 405-409.

Kaushik, D., Dureja, H. and Saini, T.R. (2004). Orally Disintegrating Tablets: An overview of melt in mouth tablet technology and techniques. *Tablets and Capsules.* 2: 30-36.

Krogars, K., Hein¨am¨aki, J., Vesalahti, J., Marvola, M., Antikainen, O. and Yliruusi, J. (2000). Extusion-spheronization of pH-sensitive polymeric matrix pellets for possible drug delivery. *Int. J. Pharm.* 199: 187–194.

Singh, B., Chakkal, S.K. and Ahuja, N. (2006). Formulation and Optimization of Controlled Release Mucoadhesive Tablets of Atenolol Using Response Surface Methodology. *AAPS Pharm. Sci. Tech.* 7(1): 19-28.

Singh, B., Mehta, G., Kumar, R., Bhatia, A., Ahuja, N. and Katare, O.P. (2005). Design, development and optimization of nimesulide-loaded liposomal systems for topical application. *Curr. Drug Deliv.* 2: 143-153.

Vaithiyalingam, S. and Khan, M.A. (2002). Optimization and characterization of controlled release multi-particulate beads formulated with customized cellulose acetate butyrate dispersion. *Int. J. Pharm.* 234: 179–193.

Welling, P.G. (2002). Absorption of Drugs. Encyclopedia of Pharmaceutical Technology. 2nd Ed. Marcel Dekker, New York, pp 10.

Wilkosz, F. and Robin, H. (2003). Fast Dissolving Tablets. *US Pharmacist.* 27.

Yunxia, B. and Yonezawa, Y. (1999). Rapidly disintegratingTablets prepared by wet Compression method: Mechanism and Optimization. *J. Pharm. Sci.* 88: 1004-1010.

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