International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

A novel sustained release matrix tablets of olopatadine HCl: Formulation optimization by using 3^2 full factorial design

Annamdevara Balaji, Kolapalli Venkata Ramana Murthy*

A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India

Abstract

The main aim of this study is to develop a robust, reproducible, bioavailable and cost-effective once a day olopatadine HCl sustained release matrix tablets containing hydroxy propyl methyl cellulose, binder, diluent and lubricant. Conventional wet granulation technology was used for the manufacture of sustained release tablets. The theoretical dissolution profile was predicted based on pharmacokinetic profile of the drug. Full factorial design is adopted to select the optimized formulation with specific dissolution release rate coinciding with theoretical profile at different time intervals. The design was composed of two formulation variables: binder concentration (X_1) and hydrophilic polymer concentration (X_2). The drug release percent at 1, 2, 4, 6 and 8 hours are predicted theoretical dissolution profile (response) and limits are restricted to 30%, 40%, 60%, 80% and not less than 100% respectively. The statistically optimized formulation showed dissolution pattern equivalent to the predicted target dissolution profile, which indicated that the optimized formulation could be obtained using response surface methodology.

Keywords: Olopatadine hydrochloride, Hydroxypropyl methylcellulose, Polyvinyl pyrrolidone, Design of experiments (DoE).

Full length article **Corresponding Author*, e-mail: annamdevarabalaji@yahoo.co.in

1. Introduction

In recent years, the prevalence of the symptomatic allergic conditions are increasing due to the change in environment and change in the lifestyle. Allergic conditions, also called as allergic diseases, are resultant of hypersensitivity response of immune system. Most commonly seen allergic diseases are allergic rhinitis and conjunctivitis, eczema, choric urticaria and bronchial asthma [1]. The most common symptoms observed in the allergic rhinitis and conjunctivitis are red eyes, itchy rash, sneezing, runny nose, nasal obstruction and itching of nose and eyes [1]. As per current statistics, common allergic diseases like allergic rhinitis and conjunctivitis are affecting approximately 10 to 30% of the adult population and up to 40% of children population in the world [2-3]. As a part of discovery, Kyowa Hakko Kogyo Co., Ltd. developed and evaluated a new anti-allergic agent olopatadine HCl, an orally active antihistamine agent with low incidence of side effects of the central nerve system. The blood brain barrier is relatively impermeable to olopatadine and marketed under the brand name of Allelock in Japan for the treatment of common allergic diseases. It is considered as a potent histamine H1 receptor antagonist and administered twice a day to adults. It is soluble in water. The pharmacokinetic profile of olopatadine HCl is linear at doses from 5 to 80 mg [4-5]. The main site of absorption is the duodenum to the jejunum. The favorable pharmacokinetic parameters and twice a day dosage regimen give an undoubted opportunity of developing controlled release formulations over conventional dosage forms for improved patient compliance for this drug [6-9]. Now a days, sustained release dosage form, which is intended for once daily dosage regimen against twice a day dosage regimen has been extensively used, because of their significantly improved patient compliance [10-12]. Hydrophilic matrix tablets are the most frequently manufactured and used as sustained release dosage forms for oral administration. Hydrophilic sustained release matrices do not disintegrate and are formulated in such a way that the drug is released over a defined period following exposure to water or after oral administration. An oral sustained release matrix tablet dosage form allows a reduction in dosing frequency compared to a conventional dosage form [13-15]. Hydrophilic polymer matrix systems are widely used in oral sustained drug delivery because of their most cost-effective method of fabrication, flexibility to obtain a desirable drug release profile and broad regulatory acceptance [13-19]. Among all hydrophilic retarding materials, hydroxypropyl methylcellulose is most popular and widely used as rate controlling polymer. The varying ratios of hydroxypropyl and methoxyl groups affect viscosity, degree of hydration and barrier properties of the formed gel. They are inert due to nonionic nature and water-soluble polymers. HPMC exhibit pH independent drug release profile and stable over a pH range of 3-11 [20-26]. For the development of sustained

release formulation olopatadine HCl, statistical experimental designs were used for reducing the number of experimental runs as well as to study the interaction of the variables for obtaining the optimized formulation on an economical way [27-29]. These designs will investigate the empirical relationship between one or more measured responses and a number of independent variables in the form of polynomial equations, mapping of the response over the experimental domain, with the ultimate goal of obtaining an optimal olopatadine sustained release formulation.

2. Materials & methods

2.1. Materials

Olopatadine hydrochloride (MSN Labs, Hyderabad), hydroxypropyl methylcellulose (HPMC K4MCR & HPMC K100 LVCR), viscosity 100 (Colorcon, India), povidone K30 (ISP, USA), lactose monohydrate (DMV International, Netherlands), microcrystalline cellulose (FMC Biopolymer, USA), colloidal silicon dioxide (Evonik, Germany) and magnesium stearate (Peter Greven, Nederland). All other chemicals and solvents were of analytical reagent grades and used without further purification.

2.2. Calculation of initial and maintenance dose for the design of sustained release matrix tablets of olopatadine

There are no sustained release formulations for olopatadine HCl in the market. Hence, it is proposed to design the sustained release matrix tablets of olopatadine HCl. The total dose (D_T) consisting of initial (D_I) and maintenance doses (D_M) for formulating the olopatadine HCl sustained release matrix tablets was calculated as per Robinson and Eriksen equation with a zero-order release principle [30,31]. The pharmacokinetic data of olopatadine HCl reported in the literature is shown in **Table 1 [**32]. The initial dose required for achieving the minimum therapeutic concentration immediately after dosing (D_I) is calculated by using the below **Eq. 1**.

$$\text{Initial dose } (D_I) = \left[\frac{C_{ssavg} \times V_d}{F}\right] \qquad \textbf{Eq. 1}$$

where, C_{ssavg} is the average steady state plasma level, V_d is the volume of distribution and F is the fraction of dose absorbed.

$$k_0 = D_I k_{el} \qquad \textbf{Eq. 2}$$

where, k_{el} is overall first order drug elimination rate constant (per hour). Hence k_0 should be equal to the elimination rate constant so as to maintain the steady state condition. In the ideal condition it is assumed that the maintenance dose (D_M) is released after D_I has produced a minimum therapeutic concentration of the drug. However, due to the solubility of the drug substance and hydrophilic nature of polymer used in the formulations, drug release even starts from D_M also from the beginning of ingestion of dosage form along with D_I thus increasing the initial drug level in the blood. Hence, it is necessary to reduce the initial dose of the drug to account for the excess release for drug from D_M by using a correction factor, k_0t_p. This correction factor is the amount of drug provided by D_M during the period from t=0 to the time of the peak drug level, t_p. The corrected initial dose (D_I*) becomes D_I-(k_0t_p). Then the total dose is

$$D_T = D_I^* + k_0H = (D_I - k_0t_p) + k_0H \qquad \textbf{Eq. 3}$$

Using the above equations the initial and maintenance doses were calculated.

2.3. Preparation of model formulations

Initial formulation trials executed with different proportions of hydrophilic release retardant polymers HPMC K4MCR and HPMC K100 LVCR. Though both grades of HPMC extended the drug release over a period of 8 hours, higher s.d. values were observed for HPMC K4MCR compared to HPMC K100 LVCR. This may be due to higher viscosity of HPMC K4MCR (i.e., 4000 mPa.s) which forms a thicker gel layer and causes dissolution variation. Hence, by considering the consistent drug release as indicated by low s.d. values and besides meeting the predicted theoretical dissolution profile, HPMC K100 LVCR was selected for the further development. Lactose and microcrystalline cellulose (MCC) were used as diluents, to improve compressibility. Polyvinyl pyrrolidone in purified water was used as granulating agent. Colloidal silicon dioxide was used as glidant to enhance the flow property of the granules and magnesium stearate was used as a lubricant in the formulation. From the initial formulation screening studies, it was confirmed that quantity of hydrophilic polymer and binder played critical role in the finished product integrity and performance. Hence, optimization of the amounts of binder and hydroxypropyl methylcellulose for the preparation of olopatadine HCl matrix tablets for drug release over 8 hours was done by using 3^2 factorial designs [33,34]. Design Expert 11, Stat-Ease, Minneapolis, USA (Version: 11.0.3.0) was used to define the design space. This design is a type of response surface methodology which utilizes two factors at three levels (-1, 0 and +1) to develop the experimental design to optimize the responses chosen. In the present study, the two independent variables (factors) selected were amount of binder (polyvinyl pyrrolidone) (X_1) and hydrophilic polymer (HPMC) (X_2) for the preparation olopatadine HCl sustained release matrix tablets. The levels of factors and target responses for 3^2 factorial designs are listed in Table 2. A total of nine experimental runs were predicted by the software and performed as per the factor combinations shown in Table 3. Cumulative % drug released at 1, 2, 4, 6 and 8 hours were selected as five responses i.e., dependent variables. All the ingredients were passed through the sieve no. 30 (ASTM, 300 µm) the ingredients sufficient for a batch of 500 tablets according to the formulae shown in Table 4 were geometrically mixed until a homogenous blend was achieved. Wet granulation technique was used, and granules were prepared using purified water as a granulating agent. The wet granulated mass was dried at 60ºC until the moisture content of the granules reached to 2-3% and then sieved through sieve no. 25 (ASTM, 710µm). Lubricant concentrations of magnesium stearate were added as required. Final blend was

then compressed into tablets on a 16-station rotary tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) using 7 mm round standard concave punches appropriately at the hardness of around 40 to 60 N.

2.3. Evaluation of olopatadine HCl matrix tablets

The prepared olopatadine HCl matrix tablets were evaluated for general appearance, thickness, hardness. They were also evaluated for the official requirements of friability, uniformity of weight, uniformity of content as per Indian Pharmacopoeia [35] and *in vitro* dissolution studies [36].

2.4. Uniformity of content

From each batch, 10 intact tablets were randomly collected, and each tablet was placed in a 10 mL dry volumetric flask. 5 mL of methanol was added, and the mixture was sonicated for 45 minutes (till complete dispersion of tablets). The volume was made up to 10 mL with methanol and mixed. Above solution was filtered using #1 Whatman filter paper. It was further diluted appropriately, and drug content was estimated by using below mentioned HPLC method.

2.5. *In vitro* studies

In vitro dissolution studies were carried out by using USP XXIV type-II (Paddle) dissolution test apparatus (Model DISSO 2000, M/s. Lab India). In these studies, stirring rate was 50 rpm and 0.1N HCl was used as dissolution medium (900 mL) and temperature of dissolution medium was maintained at 37±0.5°C. Dissolution samples of 10 mL were collected at predetermined time intervals with syringe fitted with a filter and replaced with fresh quantity of 10 mL of same dissolution medium maintained at the same temperature[36]. The collected samples were analyzed for the percentage olopatadine release by using reported HPLC method[37]. Each dissolution study was performed with 6 units and mean values taken.

2.5.1. HPLC conditions

Waters, e2695 model HPLC (gradient) with 100 µL loop capacity, which is qualified from 5 µL to 100 µL injection volume and, photo diode array detector 2998 was used in the study for the estimation of olopatadine HCl. A C18 analytical column (Inertsil C18, 5 µm, 150 X 4.6 mm) was used. The mobile phase consists of pH 3 phosphate buffer and methanol in the ratio of volume 65:35. The effluent was monitored at UV absorption wavelength of 299 nm, at a flow rate of 2.0mL/min. The analytical method was validated according to ICH recommendations [37].

2.5.2. Similarity factor (f_1) and difference factor (f_2) [38]

In general, similarity (f_2) and difference factors (f_1) measure the closeness between the two dissolution profiles. The $f_1$and $f_2$were calculated according to the following equations:

$$f_1 = \left| \sum_{j=1}^{j=n} (R_j - T_j) / \sum_{j=1}^{j=n} R_j \right| x100$$

$$f_2 = 50x\log\left\{ \left| 1 + (1/n)\sum_{j=1}^{j=n} (R_j - T_j)^2 \right|^{-0.5} x100 \right\}$$

Where, n is sampling number, Rj and Tj are respectively % drug dissolved from reference and experimental formulations at time j. In general, f_1 value lower than 15 (i.e. 0 to 15) and f_1 value higher than 50 (i.e. 50 to 100) show the similarity of the dissolution profiles. In the present investigation, f_1 and f_2 were calculated for optimized formulation against theoretical dissolution profile [39].

2.4. Analysis of statistical data

According to established theoretical predicted dissolution profile 30% of drug release to be achieved with in 1 hour, 40% of drug release in 2 hours, 60% of drug release in 4 hours, 80% of drug release in 6 hours and near complete drug release at 8 hours. Hence, five responses i.e., D_1 (% drug release in 1 hour), D_2 (% drug release in 2 hours), D_4 (% drug release in 4 hours), D_6 (% drug release in 6 hours) and D_8 (% drug release in 8 hours) were selected for the statistical optimization and fitted to linear, 2 factor interactive and quadratic models. The comparative R^2, adjusted R^2, predicted R^2, PRESS, s.d., F-values and p-values were determined using the Design Expert 11, Stat-Ease, Minneapolis, USA. A suitable polynomial model for describing the data was selected based on R^2, PRESS and p-values. The polynomial equation was generated using the Design Expert software as shown in Equation [40].

$$D = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2 + \beta_{11}X_1X_1 + \beta_{22}X_2X_2 \quad \textbf{Eq. 5}$$

2.5. Desirability and cross validation of model

The higher desirability value indicates the more suitability of the formulation, and the optimized formula can be directly obtained from the desirability function response plots. The desirability function was found to be higher (near to 1) for the optimized formula indicating the suitability of the formulations. The predicted optimized concentrations of binder and hydrophilic polymer per tablet besides other ingredients, the dependent variables D_1, D_2, D_4, D_6 and D_8 were predicted (i.e. target dissolution profile).

3. Results & Discussion

3.1. Calculation of D_I and D_M

The initial dose (D_I) corrected initial dose (D_I*), maintenance dose (D_M) and total dose (D_T) were calculated according to calculations described above.

Initial dose (D_I) = 0.0196 ×133/0.7 = 3.724 mg

Desired input rate from maintenance dose (k_0) = 3.724 ×0.27= 1.005 mghr^{-1}

Olopatadine HCl is having more absorption from duodenum to jejunum[3] and hence it is proposed to have sustained action of drug release over a period of 7 hours after the release of initial dose i.e. 8-1 hours.

D_M = 1.005 × 7 = 7.038 mg

3.1.1. Calculation of corrected initial dose Di*

$D_I^* = 3.724 – (1.005 \times 1) = 2.719$ mg

3.1.2. Calculation of total dose

$D_T = 2.719 + 7.038 = 9.757$ mg

From the above calculations the total dose obtained for sustained release of olopatadine HCl for 8 hours is 9.757 mg. The total dose was rounded off to 10 mg for the convenience. Initially the dosage form should release the total initial dose (i.e. 2.7 mg ~ 3.0 mg means 30% of total dose) in the first 1 hour followed by maintenance dose (i.e. 10-2.0=7.0mg of drug) for up to 7 hours thereafter at a release rate of 1.0 mg/hour (i.e. 10% of the dose administered/hour). Based on these assumptions the theoretical release profile was predicted and shown in **Table 5.** Based on the pharmacokinetic properties of the olopatadine HCl, total dose obtained for the once daily sustained release formulation was 10 mg and the sustained release formulation designed to provide constant and consistent release of drug for 8 hours. Here loading dose around 30% releases in 1 hour to attain drug therapeutic concentration in blood and remaining 70% of drug release rate at 10% per hour to maintain drug therapeutic concentration in blood for 7 hours. After achieving 100% drug release in 8 hours, plasma drug concentration is maintained in blood due to its inherent elimination half-life of olopatadine HCl 7-9 hours over a period of 16 to 17 hours. Hence, it was decided to develop olopatadine HCl sustained release formulation 10 mg with 8 hours target theoretical release profile. The results of the evaluation of tests of olopatadine HCl matrix tablets prepared according to the predicted runs are shown in **Table 6**. Appearance of the tablets prepared in each batch were found to be white to off white standard biconvex round tablets, which are free from tablet defects such as sticking, picking, and capping. The tablets of all batches were found to have uniformity of weight and the percent deviation was found to comply with compendial standard for uniformity of weight of IP. The hardness for all the formulations was found to be in the range of 50–60 N and was satisfactory. The friability values were found to be less than 0.33% for all the batches, which indicated that the test was complied with the official compendial test for friability for tablets as per IP. All the batches of tablets passed the uniformity of content test as per IP as the drug content values were around 100% (within the limits of 85-115%). The results of the drug release from the matrix tablets are mentioned in **Table 7** and the dissolution profiles are shown in **Figure 1**. The drug release from the matrix tablets was slow and sustained. Dissolution data indicated that the drug release from matrix tablets was inversely proportional to the polymer concentration used. An increase in binder and polymer concentration lead to increase in viscosity, thicker gel layer with longer diffusion path and it retarded the drug release. The formulations F2-F8 followed the target theoretical release profile and the results of f_1, f_2 values were found to be <15 and >50. The formulations F1 and F9 failed to match with target theoretical release profile as the difference (f_1) and similarity (f_2) factors for these batches were found to be close to 15 and 50. F1 was prepared with low level of binder and polymer and released more than 90 percent of drug in 6 hours and failed to sustain the drug release for 8 hours. In case of F9, dissolution profile was found to be slower than the theoretical dissolution profile and drug release was extended beyond 8 hours, which may be due to higher binder and polymer concentrations extending the drug release beyond 8 hours.

3.2. Statistical data evaluation

The five responses i.e., D_1 (% drug release in 1 hour), D_2 (% drug release in 2 hours), D_4 (% drug release in 4 hours), D_6 (% drug release in 6 hours) and D_8 (% drug release in 8 hours) were selected for the statistical optimization and fitted to linear, 2 factor interactive and quadratic models. The summary of the statistics is presented in **Table 8.** Responses D_1, D_2, D_4, D_6 and D_8 followed quadratic model for the matrix tablets prepared with different combinations of binder and hydrophilic polymer levels by using 3^2 factorial designs. P values (less than 0.05) and the lower values of PRESS for the responses D_1, D_2, D_4, D_6 and D_8 were found to be 20.28, 12.02, 15.33, 0.83 and 33.82 respectively indicating the significance of the model. The goodness of the fit of the model was checked by the coefficient of determination (R^2). The R^2 values of D_1, D_2, D_4, D_6 and D_8 were 0.9890, 0.99966, 0.9930, 0.9997 and 0.9748 respectively and formulation indicated a good correlation between the independent and dependent variables. The models were found significant with respect to Adjusted R^2 (0.9707, 0.9909, 0.9813, 0.9992 & 0.9328) for responses. The predicted R^2 values were in reasonable agreement with Adjusted R^2 values i.e., the difference is less than 0.2. The application of response surface methodology yielded the polynomial equations which are an empirical relationship between the logarithm value D_1, D_2, D_4, D_6 and D_8. In the equation, the term D is the response, X_1X_2 are independent variables, β is the coefficient of the term X. To analyze the response, interactive multiple regression analysis was used along with the F-statistics. The multiple regression analysis data is used to obtain the best fitting model, linear effects (X_1, X_2) interactive effects (X_1X_2) or quadratic effects ($X_1^2X_2^2$). The regression equations obtained for all the responses are given below.

$D_1 = 32.78-3.67X_1-4.00X_2+1.25X_1X_2-2.67X_1X_1+0.33X_2X_2$	**Eq. 5.2**
$D_2=39.67-6.17X_1-3.50X_2-0.25X_1X_2+2.50X_1X_1+0.50X_2X_2$	**Eq. 5.3**
$D_4=60.56-3.67X_1-4.50X_2+0.25X_1X_2-2.33X_1X_1+1.17X_2X_2$	**Eq. 5.4**
$D_6=82.22-7.50X_1-2.50X_2+0.50X_1X_2-0.83X_1X_1+0.17X_2X_2$	**Eq. 5.5**
$D_8=100.67-3.33X_1-1.50X_2-0.50X_1X_2-1.00X_1X_1-6.50X_2X_2$	**Eq. 5.6**

Where, X_1 and X_2 are coded values of the test variables of the binder (Povidone K30) and hydrophilic polymer (HPMC K100 LVCR) concentration respectively. In the present study, full model having both significant and no significant terms were used for obtaining dependent variables. Coefficients with one factor indicate the effect of the factor, while two coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively.

Table 1: Pharmacokinetics of olopatadine HCl

C_{max}/C_{ssavg}	0.0196 mg/L
T_{max} or t_p	1 hour
V_d	133 L
k_{el}	0.27 $hour^{-1}$
Biological half life ($t_{½}$)	6.0±4.0 hours
Bioavailability (F)	0.7
Elimination	63-72% eliminated unchanged

Table 2: Levels of factors and responses for 3^2 factorial design

Factors : Formulation variables		**Level**		
		-1	0	+1
X_1	Binder amount per tablet (%)	6.6	10.0	13.3
X_2	Hydrophilic polymer amount per tablet (%)	13.3	20.0	26.6
Responses		**Target**		
D_1	Cumulative % drug released at 1 hour	30		
D_2	Cumulative % drug released at 2 hours	40		
D_4	Cumulative % drug released at 4 hours	60		
D_6	Cumulative % drug released at 6 hours	80		
D_8	Cumulative % drug released at 8 hours	100		

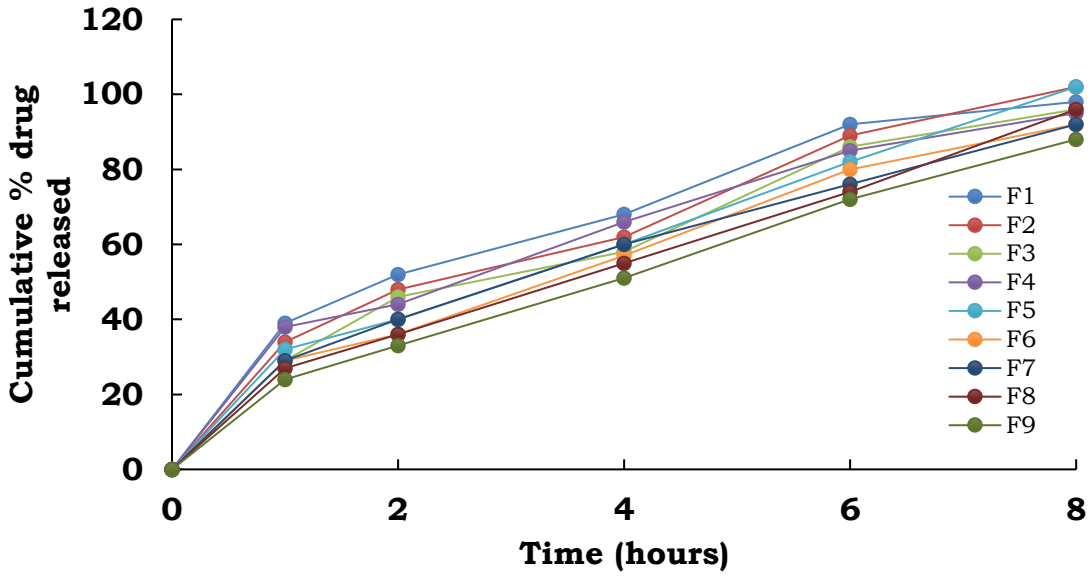


Figure 1: Comparative dissolution profile of olopatadine matrix tablets prepared using 3^2 factorial design runs

Table 3: Notation of coded levels of independent variables

Run	Transformed values of Factors (%)		Coded values with 3 levels -1 (minimum), 0 (middle), +1 (maximum)				
Formula code	**Binder concentration (X_1)**	**Polymer concentration (X_2)**	**X_1**	**X_2**	**X_1^2**	**X_2^2**	**X_1X_2**
F1	6.6	13.3	-1	-1	1	1	1
F2	6.6	20.0	-1	0	1	0	0
F3	6.6	26.6	-1	1	1	1	-1
F4	10.0	13.3	0	-1	0	1	0
F5	10.0	20.0	0	0	0	0	0
F6	10.0	26.6	0	1	0	1	0
F7	13.3	13.3	1	-1	1	1	-1
F8	13.3	20.0	1	0	1	0	0
F9	13.3	26.6	1	1	1	1	1

Table 4: Formulae of sustained release matrix tablets using 3^2 factorial design runs

Ingredients	Formula code (% w/w)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Olopatadine HCl	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7
Lactose monohydrate	47.4	40.7	34.0	44.0	37.3	30.7	40.7	34.0	27.3
MCC	23.3	23.3	23.3	23.3	23.3	23.3	23.3	23.3	23.3
Hydroxypropyl methylcellulose	13.3	20.0	26.7	13.3	20.0	26.7	13.3	20.0	26.7
Polyvinyl pyrrolidone	6.7	6.7	6.7	10.0	10.0	10.0	13.3	13.3	13.3
Colloidal silicon dioxide	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Magnesium stearate	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Total weight	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 5: Predicted theoretical release profile

Time (hours)	Cumulative % drug to be released
1	30
2	40
3	50
4	60
5	70
6	80
7	90
8	100

Table 6: Tablet properties of olopatadine HCl matrix tablets prepared according to 3^2 factorial design runs

Formula code	Thickness (mm)[a]	Hardness (N)	Friability (%)[b]	Uniformity of weight (mg)[c]	Uniformity of content (%)[d]
F1	3.66±0.07	50-60	0.28	150.3±1.2	100.6±2.2
F2	3.70±0.04	50-60	0.26	148.8±2.1	99.8±2.0
F3	3.74±0.09	50-60	0.33	150.2±1.7	99.5±1.3
F4	3.75±0.05	50-60	0.33	149.5±1.8	99.4±1.2
F5	3.65±0.07	50-60	0.28	151.2±1.2	100.6±2.1
F6	3.72±0.08	50-60	0.26	150.4±2.1	98.8±2.0
F7	3.76±0.04	50-60	0.33	149.6±1.7	99.5±1.5
F8	3.78±0.06	50-60	0.33	150.5±1.7	99.6±1.3
F9	3.65±0.12	50-60	0.28	152.4±1.2	100.6±2.6

a:Mean±s.d., n=5 tablets; b: Tablets equivalent to 6.5 g (43 tablets; c:Mean ±% deviation, n=20 tablets; d: Mean±s.d., n=10

Table 7: Cumulative percent of olopatadine HCl released vs. time from olopatadine matrix tablets (F1 to F9) (mean±s.d. n=6)

Time (hours)	Cumulative percent (mean± s.d. n=6) olopatadine released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	39±2.3	34±2.8	29±3.6	38±3.6	32±4.1	29±3.9	29±4.0	27±4.4	24±5.2
2	52±2.6	48±2.6	46±2.8	44±2.8	40±3.6	36±3.8	40±3.8	36±3.6	33±3.8
4	68±1.8	62±2.2	58±3.0	66±2.5	60±3.0	57±2.7	60±2.5	55±3.4	51±3.6
6	92±1.0	89±1.8	86±2.4	85±1.8	82±2.6	80±2.8	76±2.2	74±2.8	72±3.0
8	98±1.0	102±1.2	96±2.0	95±2.0	102±2.0	92±2.5	92±2.0	96±2.4	88±2.5
f_1	14	8	6	9	2	5	4	7	14
f_2	51	61	68	62	87	68	69	67	53

Table 8: Summary of model statistics for responses D_1 D_2 D_4 D_6 and D_8

Model	R^2	Adjusted R^2	Predicted R^2	PRESS	s.d.	F-Value	p-Value	Remarks
Influence of binder and hydrophilic polymer concentration on dissolution profile								
Response D_1 (% drug release at 1hour)								
Linear	0.8853	0.8471	0.7137	57.12	1.9	23.16	0.0015	
2Factor Interactive	0.9166	0.8666	0.6633	67.20	1.8	1.88	0.2289	
Quadratic	0.9890	0.9707	0.8984	20.28	0.9	9.87	0.0479	Suggested
Response D_2 (% drug release at 2hours)								
Linear	0.9546	0.9395	0.8969	32.58	1.5	63.14	<0.0001	
2Factor Interactive	0.9554	0.9287	0.7819	68.91	1.7	0.09	0.7778	
Quadratic	0.9966	0.9909	0.9620	12.02	0.7	18.00	0.0213	Suggested
Response D_4 (% drug release at 4hours)								
Linear	0.9293	0.9057	0.8546	31.64	1.6	39.41	0.0004	
2Factor Interactive	0.9304	0.8887	0.8105	41.23	1.7	0.08	0.7854	
Quadratic	0.9930	0.9813	0.9296	15.33	0.8	13.36	0.0321	Suggested
Response D_6 (% drug release at 6 hours)								
Linear	0.9932	0.9910	0.9825	6.60	0.7	440.22	<0.0001	
2Factor Interactive	0.9959	0.9934	0.9850	5.66	0.6	3.21	0.1330	
Quadratic	0.9997	0.9992	0.9978	0.83	0.2	19.50	0.0191	Suggested
Response D_8 (% drug release at 8 hours)								
Linear	0.4661	0.2881	-0.0246	176.24	3.9	2.62	0.1522	
2Factor Interactive	0.4719	0.1550	-0.8262	314.11	4.3	0.05	0.8238	
Quadratic	0.9748	0.9328	0.8034	33.82	1.2	29.94	0.0104	Suggested

Table 9: Formula of sustained release matrix tablets for cross validation of model (statistical optimization batch)

Name of the ingredients	Formula code
	F10 (% w/w)
Olopatadine	6.7
Lactose monohydrate	36.8
Microcrystalline cellulose	23.3
Hydroxy propyl methyl cellulose	19.6
Polyvinyl pyrrolidone	11.0
Colloidal silicon dioxide	1.3
Magnesium stearate	1.3
Total weight	**100**

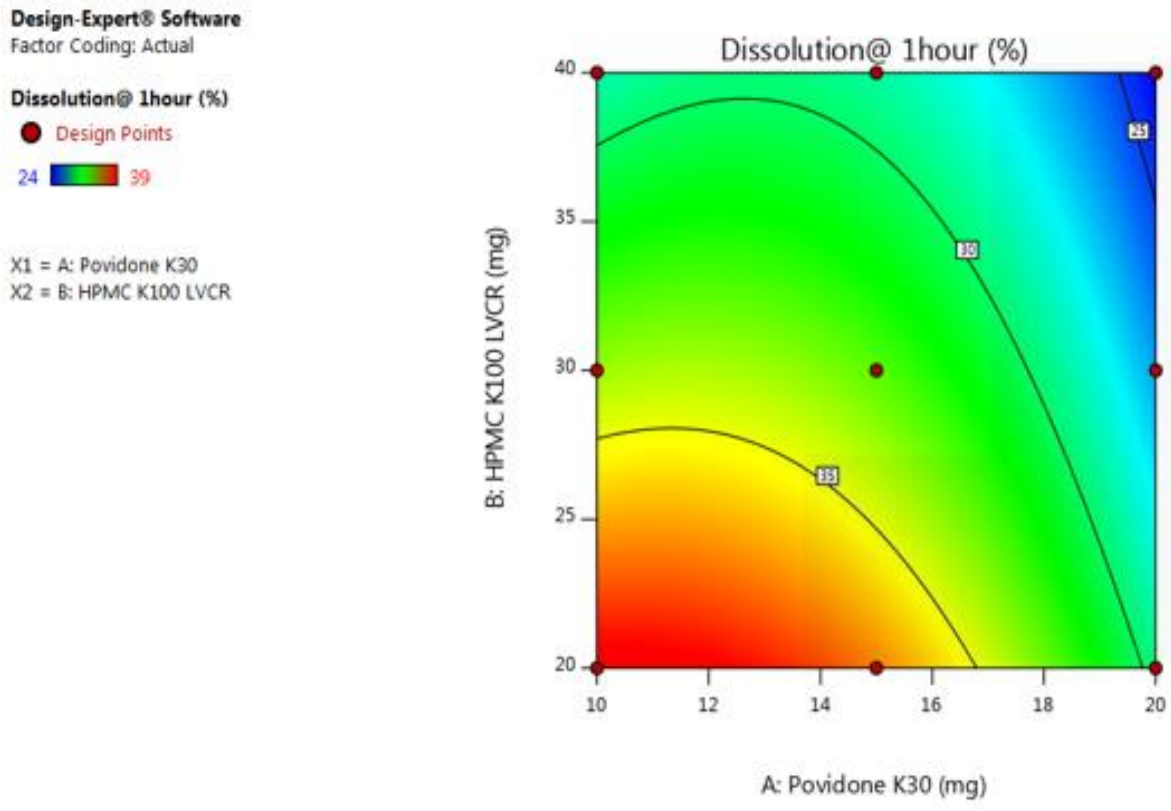
Table 10: Tablet properties of optimized olopatadine HCl matrix tablets (F10)

Thickness (mm)[a]	3.71±0.08
Hardness (N)	50-60
Friability (%)[b]	0.55
Uniformity of weight (mg)[c]	150.4±1.2
Uniformity of content (%)[d]	98.6±1.6

a: Mean ± s.d., n=5 tablets; b: Tablets equivalent to 6.5 g (43 tablets; c: Mean ± % deviation, n=20 tablets; d: Mean ± s.d., n=10

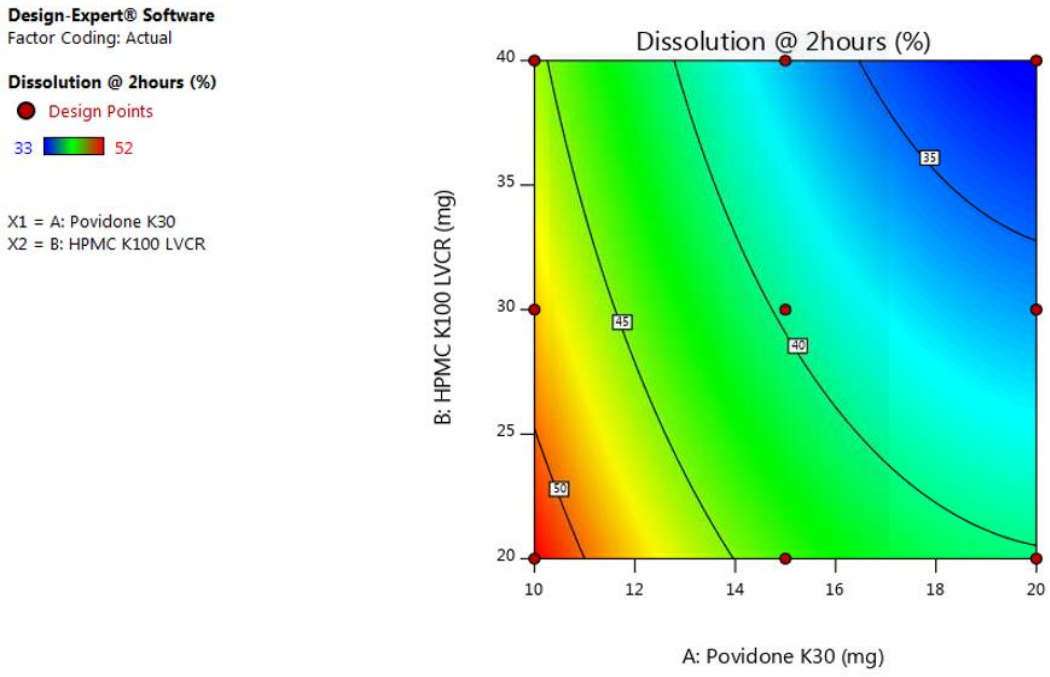
Table 11: Dissolution data of cross validation of model (mean± s.d. n=6)

Time (hours)	Cumulative percent olopatadine released		f_1	f_2
	F10	Predicted target values		
1	31±3.1	32	2	88
2	39±3.0	38		
4	61±2.8	60		
6	82±1.5	80		
8	99±0.8	100		



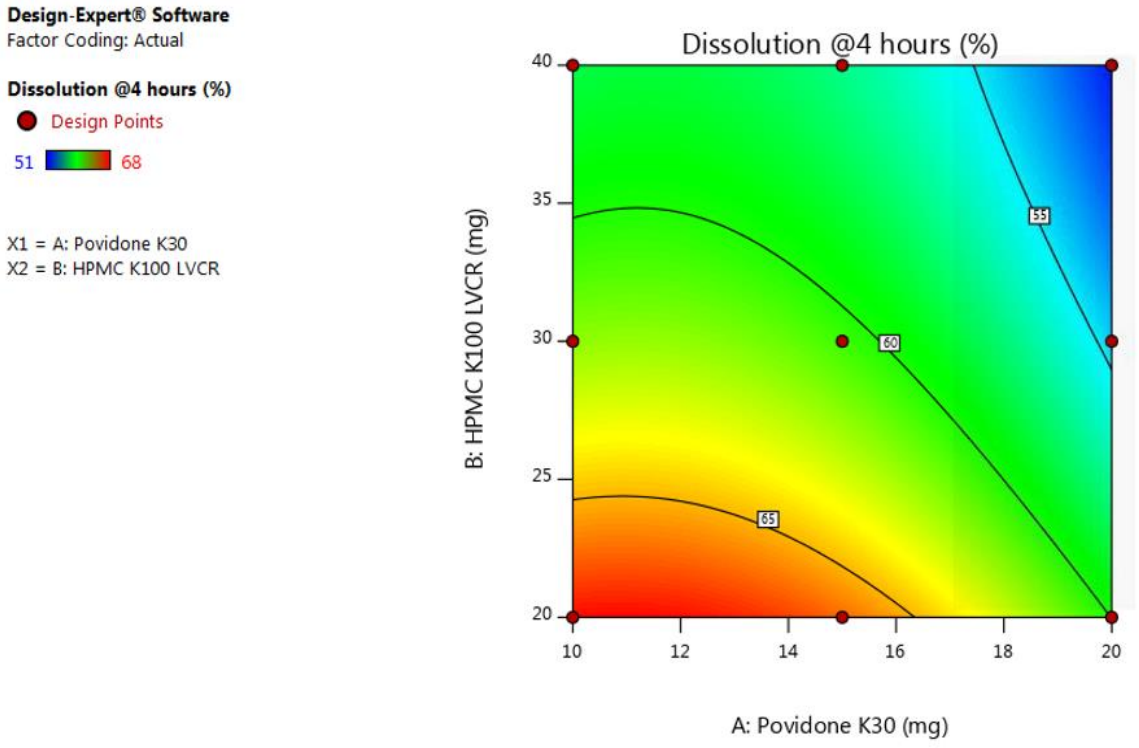
X_1 = Binder concentration X_2 = Hydrophilic polymer concentration

Figure 2: Contour plot showing the influence of binder and hydrophilic polymer on D_1 (% drug release at 1 hour)



X_1 = Binder concentration X_2 = Hydrophilic polymer concentration

Figure 3: Contour plot showing the influence of binder and hydrophilic polymer on D_2 (% drug release at 2 hours)



X_1 = Binder concentration X_2 = Hydrophilic polymer concentration

Figure 4: Contour plot showing the influence of binder and hydrophilic polymer on D_4 (% drug release at 4 hours)

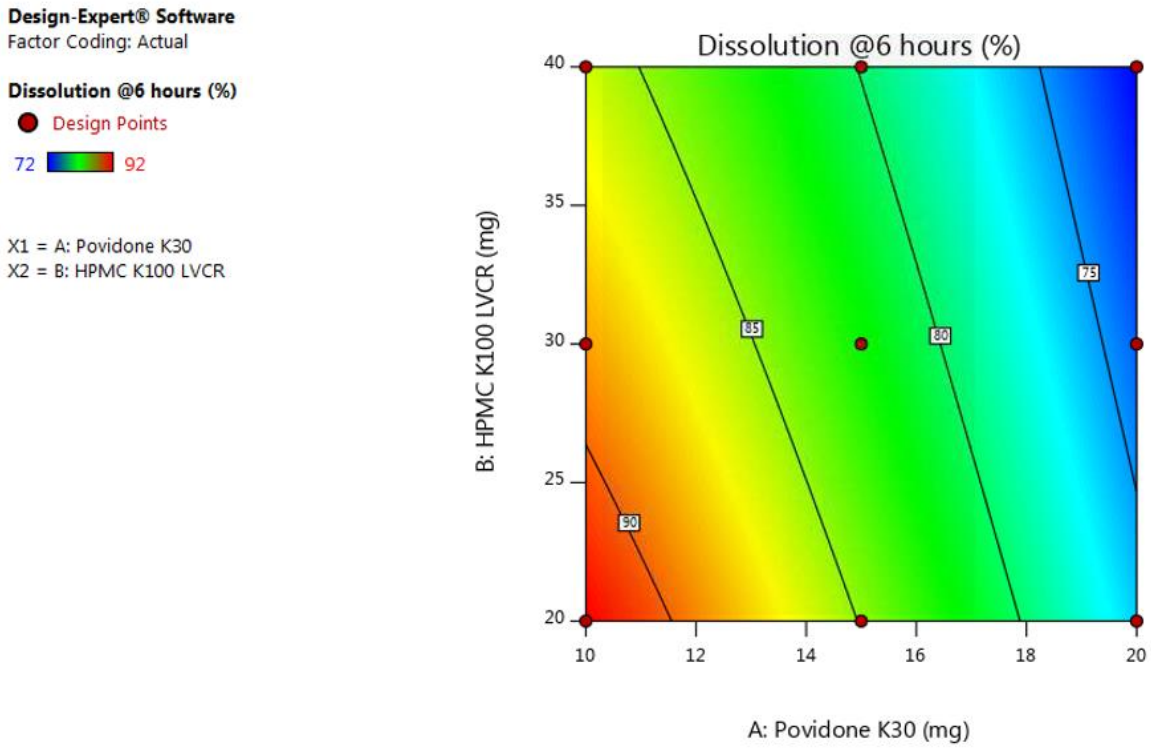


Figure 5: Contour plot showing the influence of binder and hydrophilic polymer on D_6 (% drug release at 6 hours)

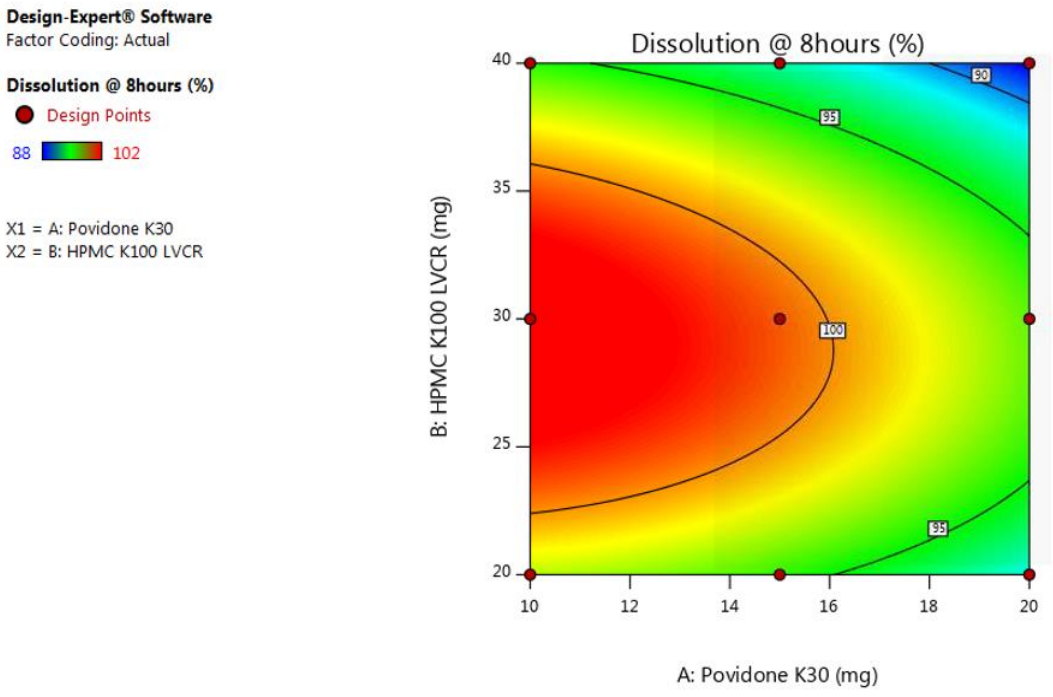
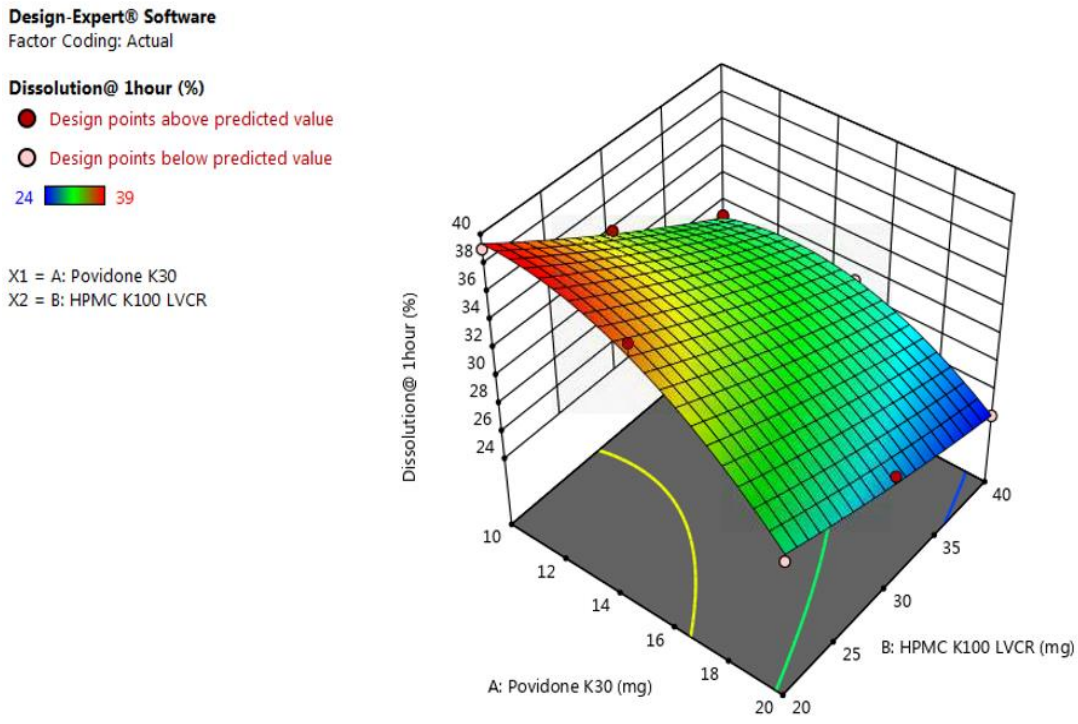
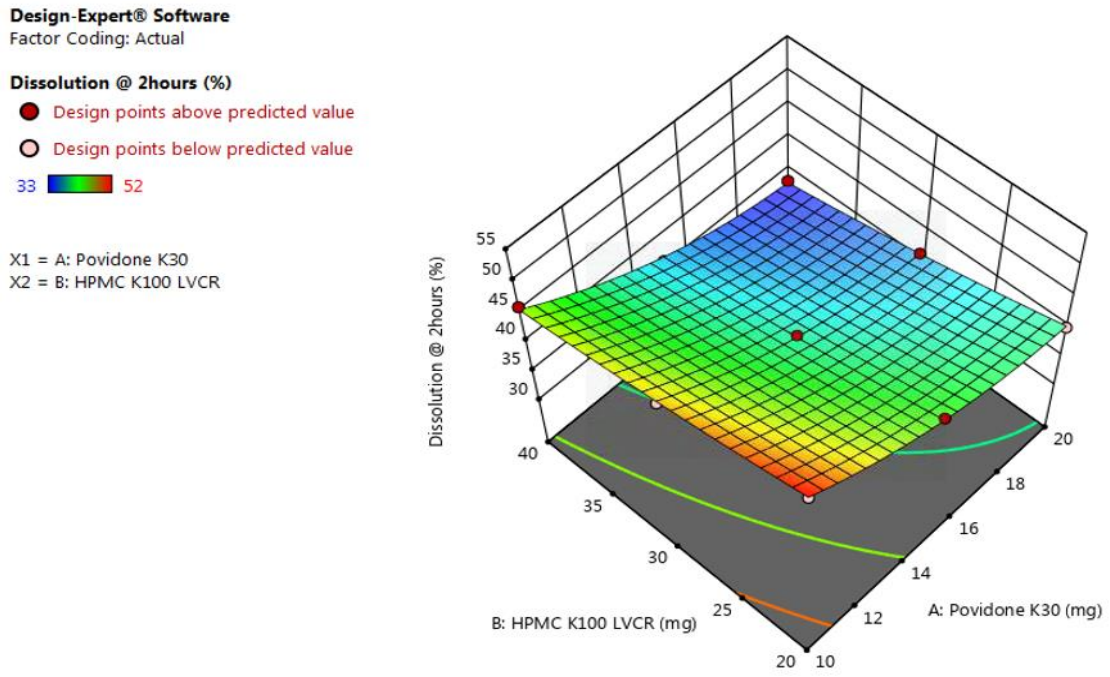


Figure 6: Contour plot showing the influence of binder and hydrophilic polymer on D_8 (% drug release at 8hours)



X_1 = Binder concentration X_2 = Hydrophilic polymer concentration

Figure 7: Response surface plot showing the influence of binder and hydrophilic polymer on D_1 (% drug release at 1 hour)



X_1 = Binder concentration X_2 = Hydrophilic polymer concentration

Figure 8: Response surface showing the influence of binder and hydrophilic polymer on D_2 (% drug release at 2 hours)

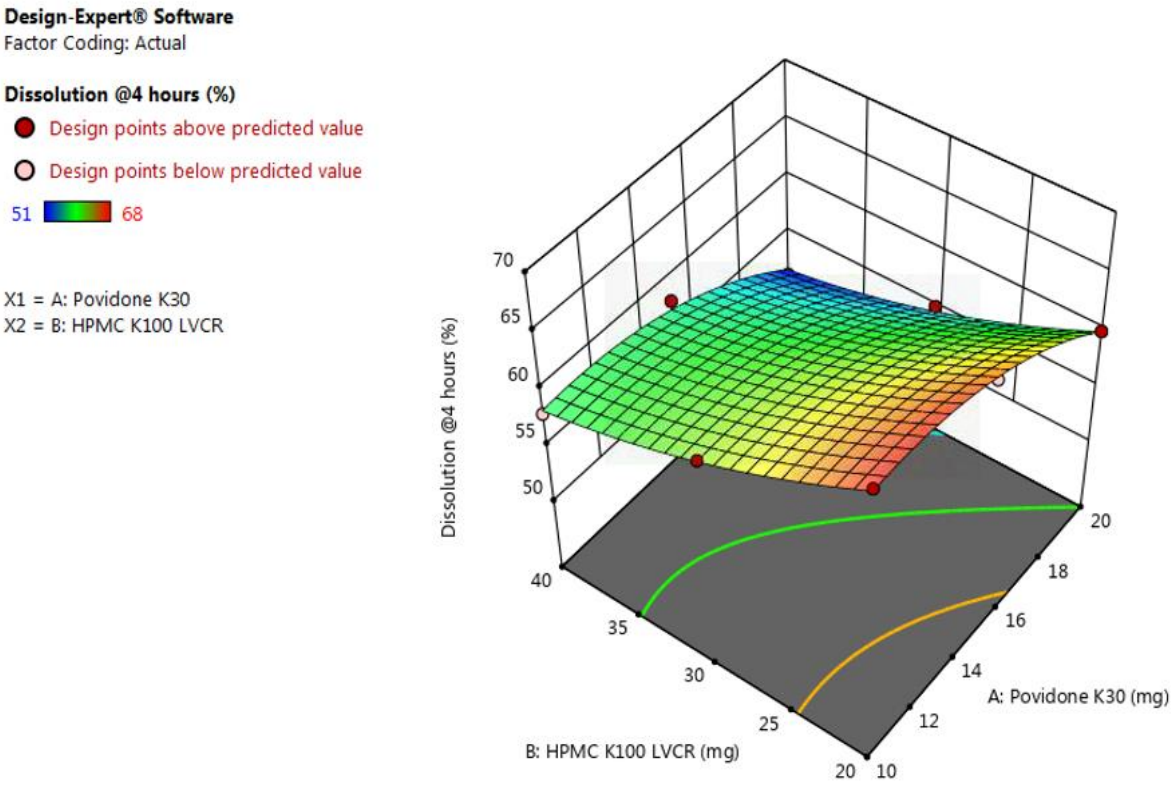


Figure 9: Response surface showing the influence of binder and hydrophilic polymer on D_4 (% drug release at 4 hours)

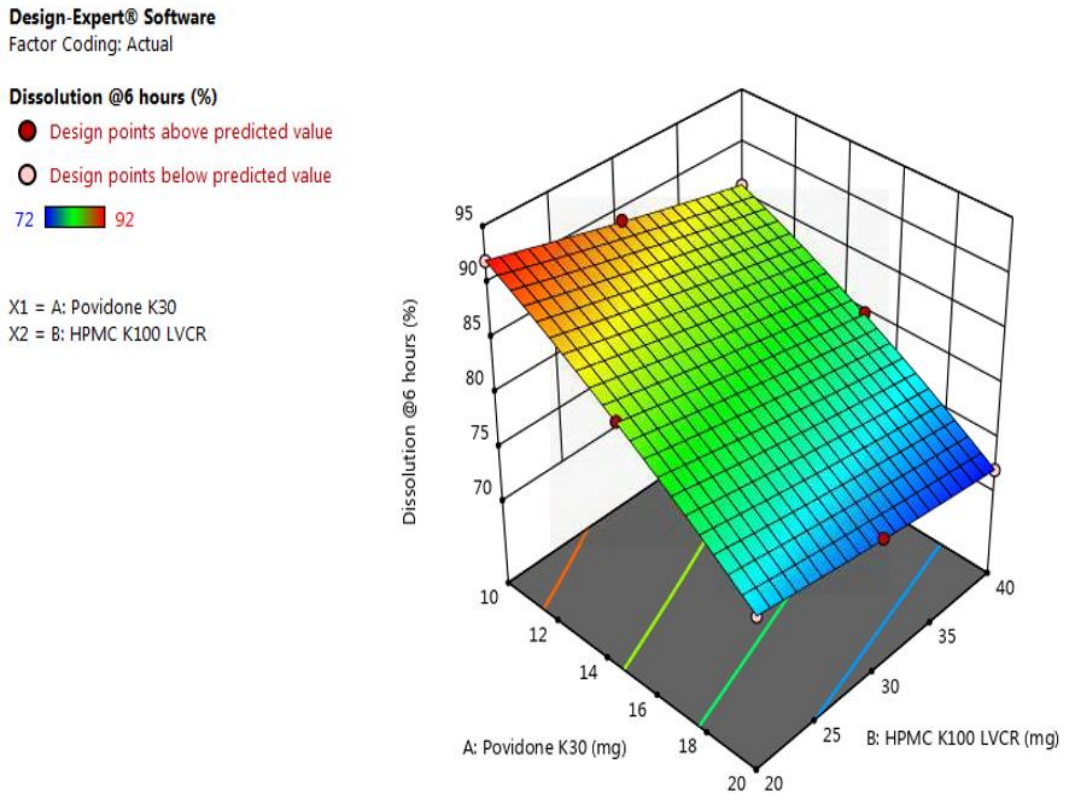


Figure 10: Response surface showing the influence of binder and hydrophilic polymer on D_6 (% drug release at 6 hours)

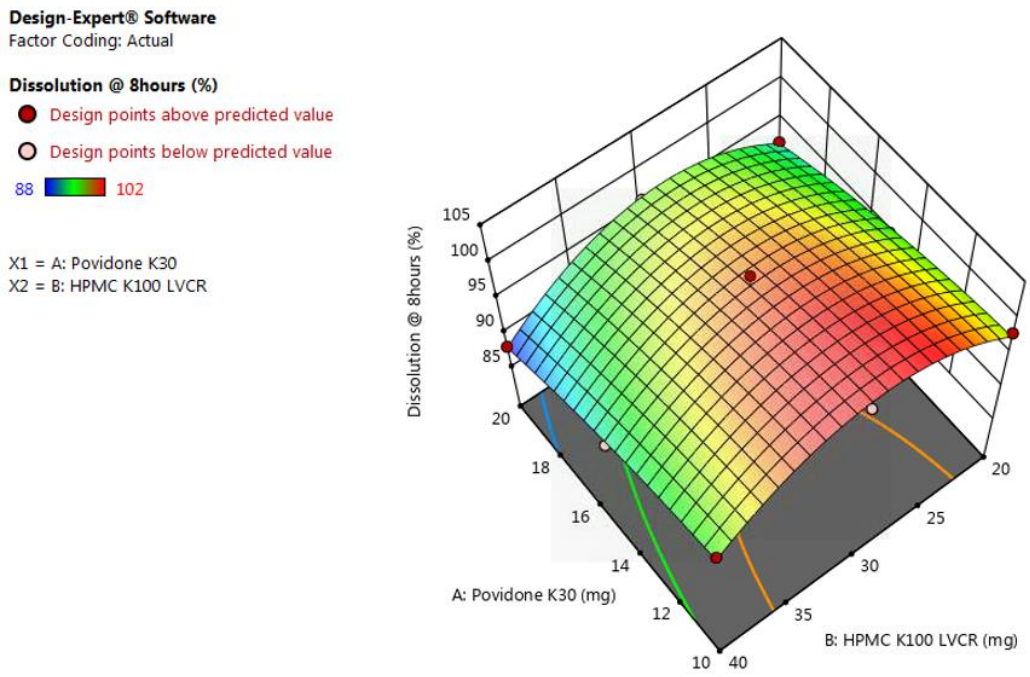


Figure 11: Response surface showing the influence of binder and hydrophilic polymer on D_8 (% drug release at 8 hours)

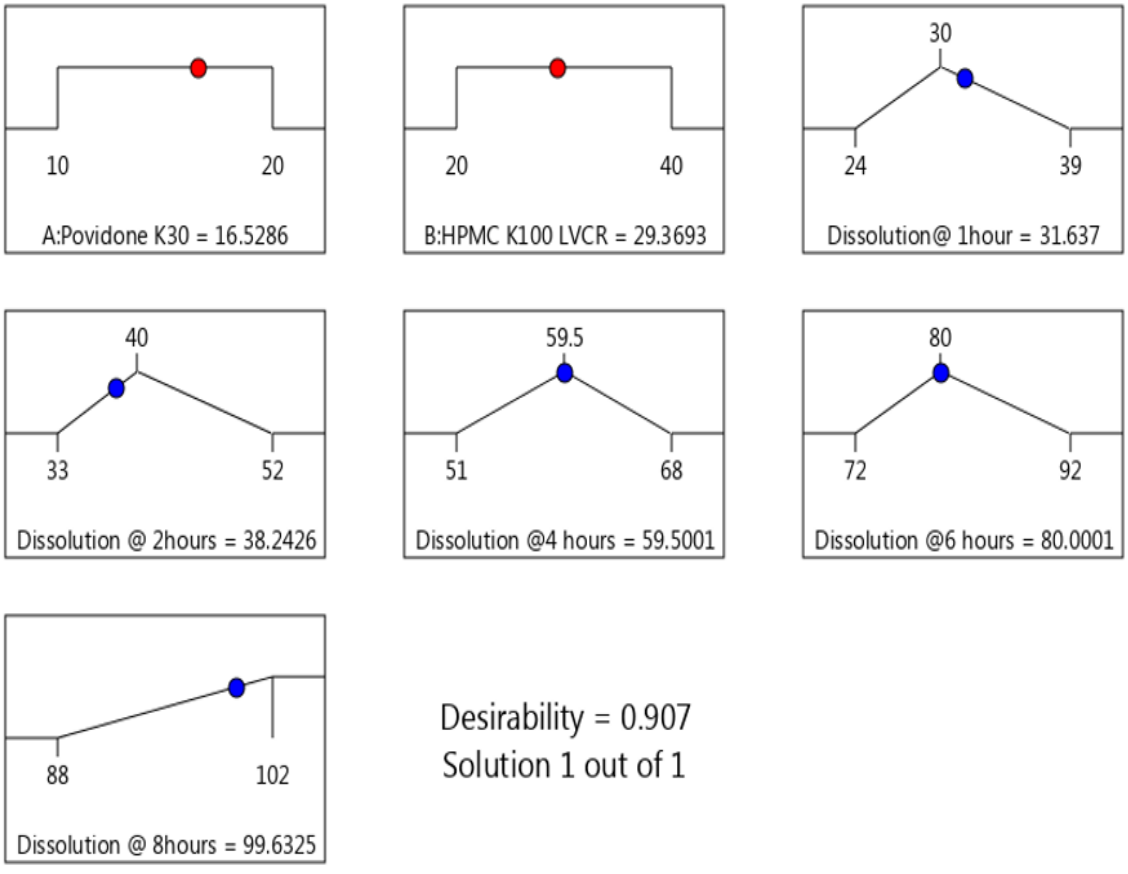


Figure 12: Desirability plot with D_1,D_2 ,D_4, D_6 & D_8

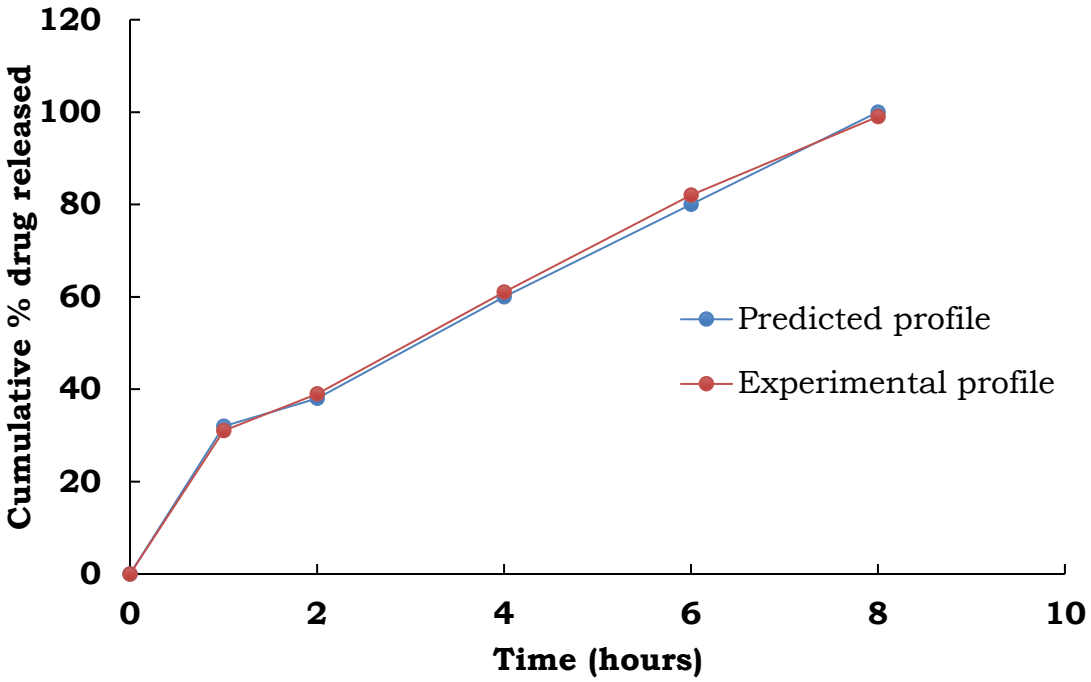


Figure 13: Comparative dissolution profile

Positive sign of the term indicates positive (additive) effect, while negative sign indicates negative (antagonistic) effect of the factor on the response. The contour plots (Figure 2-6) and response surface plots (Figure 7-11) were built to evaluate the relationship between binder content and hydrophilic polymer and their effect on the formulation parameter, particularly dissolution profiles at 1, 2, 4, 6 and 8 hours for formulations prepared with different combinations of factors. Increase in the binder concentration from 6.6 to 10 percent and later to 13.3 percent; polymer concentration from 13.3 to 20 percent and later to 26.6 percent decreased drug release at 1, 2, 4, 6 and 8 hours respectively. This could be due to the increase in resistance of the gel layer to drug dissolution and gel erosion at higher binder and polymer levels.

3.3. Desirability and cross validation of model

The predicted optimized formulation contains 11.0 percent of povidone K30 as binder and 19.60 percent of hydroxypropyl methylcellulose as hydrophilic polymer per tablet which was obtained from the statistical desirability function (as shown in **Figure 12**). With these concentrations of binder and hydrophilic polymer per tablet besides other ingredients as mentioned in **Table 9**, the dependent variables D_1, D_2, D_4, D_6 and D_8 were predicted as 32%, 38%, 60%, 80% and 100% respectively (i.e. predicted target dissolution profile) prepared and hardness of the tablets were found to be in the range of 50-60 N and complies with compendial standards of friability, uniformity of weight and uniformity of content as per IP and shown in Table 10. Similarity factor f_1 value of the optimized formulation was very close to '0' (<5) and f_2 value was more than '50' (>85) indicating the similarity between the optimized formulation and predicted target dissolution profile as shown in Table 11 and Figure 13. This proved the desirability and validity of the model and assessment of the effects of binder and amount of polymer on the drug release.

4. Conclusions

The conclusion of these studies indicating that, optimized formulation of sustained release matrix formulation of olopatadine developed by using factorial design. A three level and two factor factorial design with different concentrations of binder & hydrophilic polymer were evaluated. The quantitative effect of these factors on the release rates could be predicted by using polynomial equation. The levels of studied factors were predicted to the maximized responses. Observed responses were close to the predicted values for the optimized formulation.

References

[1] K. Ohmori, K.-i. Hayashi, T. Kaise, E. Ohshima, S. Kobayashi, T. Yamazaki, A. Mukouyama. (2002). Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. The Japanese Journal of Pharmacology. 88(4): 379-397.

[2] D.V. Wallace, M.S. Dykewicz, D.I. Bernstein, J. Blessing-Moore, L. Cox, D.A. Khan, D.M. Lang, R.A. Nicklas, J. Oppenheimer, J.M. Portnoy. (2008). The diagnosis and management of rhinitis: an updated practice parameter. Journal of Allergy and Clinical Immunology. 122(2): S1-S84.

[3] G.W. Canonica. (2006). Treating asthma as an inflammatory disease. Chest. 130(1): 21S-28S.

[4] Monograph on ALLELOCK®. (2014). Tablets 2.5 and

5mg,http://www.esearch.ne.jp/jpr/PDF/KYOWA08.PDF.Date of accession.

[5] M.A. Kaliner, J. Oppenheimer, J.R. Farrar. (2010). Comprehensive review of Olopatadine: The molecule and its clinical entities. Allergy & Asthma proceedings. 31:112-119.

[6] S.A. Eisen, D.K. Miller, R.S. Woodward, E. Spitznagel, T.R. Przybeck. (1990). The effect of prescribed daily dose frequency on patient medication compliance. Archives of internal medicine. 150(9): 1881-1884.

[7] T. Pullar, A. Birtwell, P. Wiles, A. Hay, M. Feely. (1988). Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily. Clinical Pharmacology & Therapeutics. 44(5): 540-545.

[8] S.A. Eisen, D.K. Miller, R.S. Woodward, E. Spitznagel, T.R. Przybeck. (1990). The effect of prescribed daily dose frequency on patient medication compliance. Archives of internal medicine. 150(9): 1881-1884.

[9] J. Brun. (1994). Patient compliance with once-daily and twice-daily oral formulations of 5-isosorbide mononitrate: a comparative study. Journal of International Medical Research. 22(5): 266-272.

[10] A.J. Claxton, J. Cramer, C. Pierce. (2001). A systematic review of the associations between dose regimens and medication compliance. Clinical therapeutics. 23(8): 1296-1310.

[11] A.D. Beaulieu, P.M. Peloso, B. Haraoui, W. Bensen, G. Thomson, J. Wade, P. Quigley, J. Eisenhoffer, Z. Harsanyi, A.C. Darke. (2008). Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain due to osteoarthritis: a randomized controlled trial. Pain Research and Management. 13: 103-110.

[12] J. Duchier, F. Iannascoli, M. Safar. (1987). Antihypertensive effect of sustained-release isosorbide dinitrate for isolated systolic systemic hypertension in the elderly. The American Journal of Cardiology. 60(1): 99-102.

[13] M.V. Varma, A.M. Kaushal, A. Garg, S. Garg. (2004). Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. American Journal of drug delivery. 2: 43-57.

[14] P. Colombo, R. Bettini, P. Santi, N.A. Peppas. (2000). Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical science & technology today. 3(6): 198-204.

[15] S.-F. Nie, H. Liu, Y.-L. Liu, W.-S. Pan. (2011). Comparison of the characteristics of several polymer materials used in hydrophilic matrix tablets. Yao Xue Xue Bao= Acta Pharmaceutica Sinica. 46(3): 338-343.

[16] J.W. Skoug, M.V. Mikelsons, C.N. Vigneron, N.L. Stemm. (1993). Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. Journal of Controlled Release. 27(3): 227-245.

[17] N. Shah, G. Zhang, V. Apelian, F. Zeng, M.H. Infeld, A.W. Malick. (1993). Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration. Pharmaceutical research. 10: 1693-1695.

[18] T.D. Reynolds, S.H. Gehrke, A.S. Hussain, L.S. Shenouda. (1998). Polymer erosion and drug release characterization of hydroxypropyl hethylcellulose matrices. Journal of Pharmaceutical Sciences. 87(9): 1115-1123.

[19] H. Omidian, K. Park. (2008). Swelling agents and devices in oral drug delivery. Journal of Drug Delivery Science and Technology. 18(2):83-93.

[20] A.R. Rajabi-Siahboomi, R.W. Bowtell, P. Mansfield, M.C. Davies, C.D. Melia. (1996). Structure and behavior in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. Pharmaceutical research. 13: 376-380.

[21] Dow excipients. ((2014). Methocel TM products. http://www.dow.com/dowexcipients/products/Methocel.htm.

[22] C.B. McCrystal, J.L. Ford, A.R. Rajabi-Siahboomi. (1999). Water distribution studies within cellulose ethers using differential scanning calorimetry. 2. Effect of polymer substitution type and drug addition. Journal of Pharmaceutical Sciences. 88(8): 797-801.

[23] Metolose®.(2014).http://metolose.jp/e/pharmaceutical/metolose.shtml. Date of accession: 25-06-2014.

[24] Aqualon pharmaceutical excipients. (2014). http://www.herc.com/aqualon/pharma/index.html. Date of accession.

[25] M.A. Dabbagh, J.L. Ford, M.H. Rubinstein, J.E. Hogan, A.R. Rajabi-Siahboomi. (1999). Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropyl methylcellulose. Pharmaceutical development and technology. 4(3): 313-324.

[26] E. Mašková, K. Kubová, B.T. Raimi-Abraham, D. Vllasaliu, E. Vohlídalová, J. Turánek, J. Mašek. (2020). Hypromellose–A traditional pharmaceutical excipient with modern applications in oral and oromucosal drug delivery. Journal of Controlled Release. 324: 695-727.

[27] R.H. Myers, D.C. Montgomery, C.M. Anderson-Cook. (2016). Response surface methodology: process and product optimization using designed experiments. John Wiley & Sons: pp.

[28] G.E. Box, N.R. Draper. (1987). Empirical model-building and response surfaces. John Wiley & Sons: pp.

[29] R.H. Myers, A.I. Khuri, W.H. Carter. (1989). Response surface methodology: 1966–l988. Technometrics. 31(2): 137-157.

[30] J. Robinson, S. Eriksen. (1966). Theoretical formulation of sustained-release dosage forms. Journal of Pharmaceutical Sciences. 55(11): 1254-1263.

[31] L. Lachman, H.A. Lieberman, J.L. Kanig. (1976). The theory and practice of industrial pharmacy. Lea & Febiger Philadelphia: pp.

[32] N.-N. Chu, W.-L. Chen, H.-R. Xu, X.-N. Li. (2009). Pharmacokinetics of orally administered single-and

multiple-dose olopatadine in healthy Chinese subjects: an open-label study. Clinical Drug Investigation. 29: 451-457.

[33] A. Bodea, S.E. Leucuta. (1997). Optimization of propranolol hydrochloride sustained release pellets using a factorial design. International journal of pharmaceutics. 154(1): 49-57.

[34] P. Roy, A. Shahiwala. (2009). Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Journal of Controlled Release. 134(2): 74-80.

[35] I. Pharmacopoeia. (2007). The Indian pharmacopoeia commission. Central Indian Pharmacopoeia Laboratory, Ministry of Health and Family Welfare, Govt of India, Sector. 23.

[36] D. Akiladevi, M. Nappinnai, T. Sudha. (2017). A Study on the Effect of disintegrants and Processing Methods on the Physicochemical and In Vitro Release Characteristics of Immediate Release Tablets of Bosentan Monohydrate. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 7(4): 222-226.

[37] P.D. Bhatt PD, J. Akhtar. (2011). Development and validation of stability indicating RP-HPLC method for estimation of olopatadine hydrochloride in bulk drug and its formulations. International Journal of Pharmaceutical Science Review and Research. 9:153-158.

[38] V.P. Shah, Y. Tsong, P. Sathe, J.-P. Liu. (1998). In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f2. Pharmaceutical research. 15: 889-896.

[39] P. Costa, J.S. Lobo. (2001). Influence of dissolution medium agitation on release profiles of sustained-release tablets. Drug Development and Industrial Pharmacy. 27(8): 811-817.

[40] Y.-B. Huang, Y.-H. Tsai, W.-C. Yang, J.-S. Chang, P.-C. Wu, K. Takayama. (2004). Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. European journal of pharmaceutics and biopharmaceutics. 58(3): 607-614.