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Process variable studies for preparation of optimized system for bupropion hydrochloride using CCD

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ABSTRACT

Aim of present work is to develop optimized sustained release dosage form of Bupropion hydrochloride using Formulation by Design (FbD) approach. Development and optimization of formulation batches was done by design experiment using Central Composite Design (CCD). Tablets were formulated by direct compression technique and evaluated. The impact of independent variables like concentration of Hydroxypropyl Methyl Cellulose (HPMC K4M) and Carbopol (CP 934P) were observed on dependent variable like hardness of tablet, drug release in 12 h (Q_{12h}) and the time for fifty percent release of drug ($T_{50\%}$). Polynomial equations were generated using multiple linear regression analysis (MLRA), response surface plots and contour plots were drawn, optimum formulations were selected by brute force method. The hardness and Q_{12h} was found in the range of 4.4- 4.7 Kg/cm^2 and 88.19- 96.7% respectively, while $T_{50\%}$ was found in the range of 3.5- 5.5h. Validation of optimization study performed using four confirmatory experimental runs which indicated very high degree of prognostic ability of FbD methodology with percentage error varied between -0.024% and 0.024 %. The overlaying of all these plots provided an overlay plot, which signified the region of optimization. Thus, central composite design (CCD) is a useful tool in the development of optimized dosage form along with the significance of independent variable as well as least investment of money, manpower and time.

Keywords: Formulation by Design, Central Composite Design, Bupropion Hydrochloride.

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Introduction

Bupropion Hydrochloride is an antidepressant of the amino-ketone class, which is chemically unrelated to tricyclic, tetracyclic, serotonin reuptake inhibitor, or other known antidepressants. It is somewhat related to phenylethylamines [1]. Bupropion is an atypical antidepressant, which is used for depression as well as for smoking cessation. This is the first-line treatment for tobacco cessation [2]. As per state by Maurizio Fava et al., Bupropion is having a lower incidence of weight gain, sexual dysfunction and somnolence as compared to all the newly discovered antidepressants so far. It is proved to be an effective antidepressant, in terms of efficacy as compared to Selective Serrotonin Reuptake Inhibitor (SSRI) and other antidepressants. This drug can also be used as an adjunctive therapy, for the reversal of other antidepressant induced sexual dysfunction and also to elevate their efficacy[3]. The depression has out broken on today's youth, and the reason might be their lifestyle. Several studies in elders revealed that, especially death in the family and financial problems are the most drastic events for depression and the same happens in the case of adolescents [4]. Since depression and smoking are the two most major problems of our society. So, such reasons necessitate formulating a Sustained Drug Delivery System (SDDS) of Bupropion Hydrochloride, which would become a good solution for such problems. Thus a floating-bioadhesive formulation of Bupropion Hydrochloride could be a most suited form, as the bioavailability of the drug will be more predictable and there will be a better control in the fluctuations in plasma drug concentration[5].

Optimization is a smarter way for substituting the trial and error method for formulating any drug delivery system. Trial and error method was a traditional method for preparation of any formulation and was having certain limitations like; time consuming, uneconomical, energy utilising and unpredictable[6].Thus optimization is the process for finding out the most suitable way to develop the best product with

the existing sources while taking into account all the factors that somehow influence decisions in any experiment [7]. The word optimize defines itself as perfect, effective and functional as possible. *"Variables"* and *"factors"* plays vital role in the process of optimization. There are two types of variables i.e. independent and dependent. Independent variables are those, which are not dependent on any other value, e.g. concentration of binder, drug to polymer ratio, etc, whereas dependent variables are those which depends on the concentration of independent variables used. Factors are basically assigned variables such as concentration, drug-to-polymer ratio, temperature etc[8].

Formulation by design (FbD), is one of the optimization technique, which specifically make use of design of experiment (DoE) in drug formulation development. It is a sort of statistical strategy which helps in organizing the experiments in such a manner, that the required information is obtained as efficiently and precisely as possible. FbD is useful in systematically optimizing almost all types of orally administered drug delivery systems. Besides screening, this method is also advantageous for systematically developing products as well as processes[9]. It acts as a beneficial tool for attaining scientific knowledge regarding establishment of multi- factorial relationship. Because of all above said reasons, this method is gaining popularity for the production process in industries[9].

Materials & methodology

Materials:

Bupropion Hydrochloride was obtained as gift sample from Lara Labs, India; HPMC K4M purchased from Colorcon Asia Pvt. Ltd., India; CP934P from Zydus Cadila, India; magnesium stearate, talc and microcrystalline cellulose from SD Fine, India; were also used in the study. All other chemicals used were of analytical grade and used as received. Double distilled water was used in the study.

Pre-optimization studies:

Selection of polymers & their range

The task of designing the sustained release tablet of Bupropion Hydrochloride with desired release characteristics began with the selection of potential polymer that allows the matrices to sustain the release of drug. During preliminary studies, three polymers CP934P, HPMC K4M & HPMC K100M were investigated for formulating oral sustained tablet of Bupropion Hydrochloride. After intensive investigation of various literatures, polymers and excepients (Table 1) were selected for pre-optimization studies.

Table 1: List of ingredients and their selected range

S.No.	Ingredient	Percentage (%w/w)
1	Bupropion Hydrochloride	24.7
2	HPMC K4M	24-55
3	HPMC K100M	10-61
4	CP 934P	3-9
5	Magnesium stearate	2
6	Talc	1
7	Microcrystalline Cellulose	q.s.

Preparation of sustained release tablets of Bupropion Hydrochloride

The pre-optimization batches (Batch A and B) were prepared, by using direct compression technique as per the formula stated in table 2.

Table 2: Selected Formula for tablet preparation for pre-optimization

S.No.	Ingredient	Batch A	Batch B
1	Bupropion Hydrochloride	24.7 %	24.7%
2	HPMC K100M	35.5%	-
3	HPMC K4M	-	39.5%
4	CP 934P	6%	6%
5	Magnesium stearate	2%	2%
6	Talc	1%	1%
7	Microcrystalline Cellulose	q.s.	q.s.

Initially, the drug and the polymers (HPMC K4M and HPMC K100M) were passed through mesh # 60 sieve. After that, glidant, lubricant and diluents were passed through mesh # 120 sieve. Then for preparing an appropriate powder blend all the ingredients were taken in a V- cone blender and were allowed to mix properly for 10 minutes. Finally the tablets were prepared by compressing the powder blend in tablet compression machine (Rimek Mini Press- I) having 12mm flat faced punch[10].

The prepared trial batches were subjected for two evaluation parameters i.e. swelling index and *in-vitro* dissolution study. Based on the results of preliminary evaluation parameters; the polymers and their ranges were selected for further preparation of batches (table 3).

Table 3: Formula for Experimental Design

S.No.	*Ingredients*	*Percentage (%w/w)*
1	Bupropion Hydrochloride	24.7
2	HPMC K4M	24-55
3	CP 934P	3-9
4	Magnesium stearate	2
5	Talc	1
6	Microcrystalline cellulose	q.s.

Therefore various batches (F1- F13) were prepared using Central Comopsite Design (CCD), as shown in table 4. CCD with α = 1(face centred) was employed as per the standard protocol and thirteen batches were prepared by using HPMCK4M and CP934P where centre point was taken in quintuplicate (all experimental runs, coded and actual levels of independent variables were summarized in table 4)[11]. In the study impact of varying concentration of HPMC K4M (A) and CP934P (B) on dependent variables like hardness, Q_{12h} and T_{50}.

Table 4: Various batches, with their coded values and actual values

Batch Code	Coded Value		Actual Value (%)	
	HPMC K4M (A)	CP 934P (B)	HPMC K4M (A)	CP 934P (B)
F1	-1	-1	24	3
F2	-1	0	24	6
F3	-1	+1	24	9
F4	0	-1	39.5	3
F5	0	0	39.5	6
F6	0	+1	39.5	9
F7	+1	-1	55	3
F8	+1	0	55	6
F9	+1	+1	55	9
F10	0	0	39.5	6
F11	0	0	39.5	6
F12	0	0	39.5	6
F13	0	0	39.5	6

Precompression evaluation

Drug-excipients compatibility

FT-IR Spectroscopy (Fourier Transform Infrared Spectroscopy)

The IR analysis of pure drug and physical mixture (drug-excepient) was conducted. Potassium Bromide disc method was utilised for IR analysis. The spectrum was taken by scanning the samples individually over a wave number range of 4000- 400 cm^{-1} using Fourier transform infrared spectrophotometer (FTIR)[12].

Evaluation of powder blend

The prepared powder blend was subjected to various evaluation parameters like angle of repose, bulk density (B_D), tapped density (T_D), Carr's index and Hausner's ratio.

Preparation of sustained Bupropion Hydrochloride tablets

Different tablet batches were prepared by utilising same technique as stated in pre optimization. The range of polymers selected for preparation of sustained Bupropion Hydrochloride tablet shown in table 3 and 4.

Confirmation of crystalline structure of drug by X- Ray Diffractometery

To analyse the Crystallinity of drug in formulated tablets X ray diffraction study was done. A voltage of 40 kV and current of 40 mA in the angular range of 10°<2θ<60°, was used. After that, step scan mode (step width=0.02°, counting time=1 s/step) was used[13].

Physicochemical characterization of tablet

General appearance and dimensions

Twenty tablets were randomly selected from the prepared batch, to check any discoloration or degradation of drug in the tablets by visual method[14].

Thickness of the tablets was measured using vernier caliper (Mitech Meterology Ltd., China). The values of thickness were used to adjust the initial stages of compression. The thickness of tablet was controlled within a limit of ±5% variation of a standard value[15].

Weight variation test and Hardness

The 20 tablets from the batch were selected randomly and were weighed individually. After that average weight was calculated[16]. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopoeia and none deviates by more than twice that percentage[17].

Mitutoyo digital hardness tester, Japan was utilised for determination of hardness[18].

In- vitro swelling study

Single tablet was weighed (W_1) and placed in a glass beaker containing 200 ml of 0.1N HCl, and maintained in a water bath at 37.0 ± 0.5 ^{0}C. At regular time intervals, the tablet was removed from beaker and the excess surface liquid was carefully removed with bloating paper. The swollen tablet was weighed again (W_2)[19]. The swelling index (SI) was calculated using eq.1:

$$SI = [(W_2-W_1)/W_1]*100 \quad \textit{(eq. 1)}$$

In- vitro Drug Release study

In-vitro drug release study for the prepared sustained release tablets was conducted in 0.1 N HCl for period of 12 hours using a six-station USP type II (paddle) apparatus (Electrolab Pvt. Ltd.) at 37°C± 0.5 °C and 50 rpm speed. Sampling was done after every one hour interval; samples of 10 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. Absorbance was measured in UV spectrophotometer (Shimadzu, Japan) at λ max 298nm (Pharmacopoeia).

Drug release statistics

Based on phenomenological analysis, the type of release was predicted, *i.e.*, whether Fickian, non Fickian or zero-order[21]. Drug release data were subjected to various release models, including Higuchi model (eq. 2), which indicates whether the drug release mechanism deviates from Fick's laws and shows anomalous behaviour.

$$Q = K_H t^{1/2} \quad \textit{(eq. 2)}$$

where, Q is the amount of drug release at time t, and KH is the Higuchi rate constant.

The dissolution data was also fitted to Koresmeyer model which is used to describe drug release behaviour from polymer systems (eqs. 3 and 4) [22].

$$Mt/M\alpha = k.t^n \quad \textit{(eq. 3)}$$

$$Log\ (Mt/M\alpha) = log\ K + n\ Log\ t \quad \textit{(eq. 4)}$$

where 'Mt' is the amount of the drug release at time 't', 'Mα' is the amount of drug release after infinite time and 'K' is a release rate constant incorporating structural and geometric characteristic of the tablet and 'n' is the diffusion exponent indications for release mechanism.

Optimisation Data Analysis

A statistical design was utilized in order to derive the relationship between the response variables and the independent variables. Design- Expert Version 10 (trial version) was utilised for unveiling the relationship between dependent and independent variable. In order to get the optimized formulation, concentration of both the polymers i.e. HPMC K4M (A) & CP 934P (B), were selected as independent variables, while the dependent variables hardness (Y_1), Q_{12h} (Y_2) and T_{50} (Y_3) were selected as independent variables[23].Each factor was set at low, medium and high factor. The actual values and coded values are given in table 4. [24]

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 as the following equation

$$y = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 AB + \beta_4 B_1 + \beta_5 B^2 + \beta_6 AB^2 + \beta_7 B_1 B \quad \textit{(eq. 5)}$$

Where, β_0 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 response values of y; and A and B are the coded levels of the independent variable(s). The terms AB and B_i (i=1 to 2) represent the interaction and quadratic terms, respectively.

Validation of optimization analysis

Four formulations were selected as the confirmatory check-points to validate by response surface methodology (RSM). The observed and predicted responses were critically compared. Linear correlation plots were constructed for the chosen four optimized formulations, and the percent bias (prediction error) was calculated with respect to the observed responses[25].

Results & discussion

Precompression evaluation

Drug-excepient compatibility

FT-IR Spectroscopy

The FTIR spectrum of Bupropion Hydrochloride and its physical mixture is shown in Figure 1 and Figure 2. The characteristic peaks of Bupropion Hydrochloride are clearly shown in both the spectrums. The most prominent peaks are obtained at 1690cm^{-1} & 1691cm^{-1} of Bupropion Hydrochloride and its physical mixture respectively, representing aromatic C=C bending, whereas due to asymmetric C-H bending, the peak for Bupropion Hydrochloride was observed at 1459 cm^{-1} while the peak for Bupropion Hydrochloride in physical mixture was observed at 1457 cm^{-1}. The C-OH stretching in the spectrum was observed at peaks 1240 cm^{-} & 1239 cm^{-1} respectively.

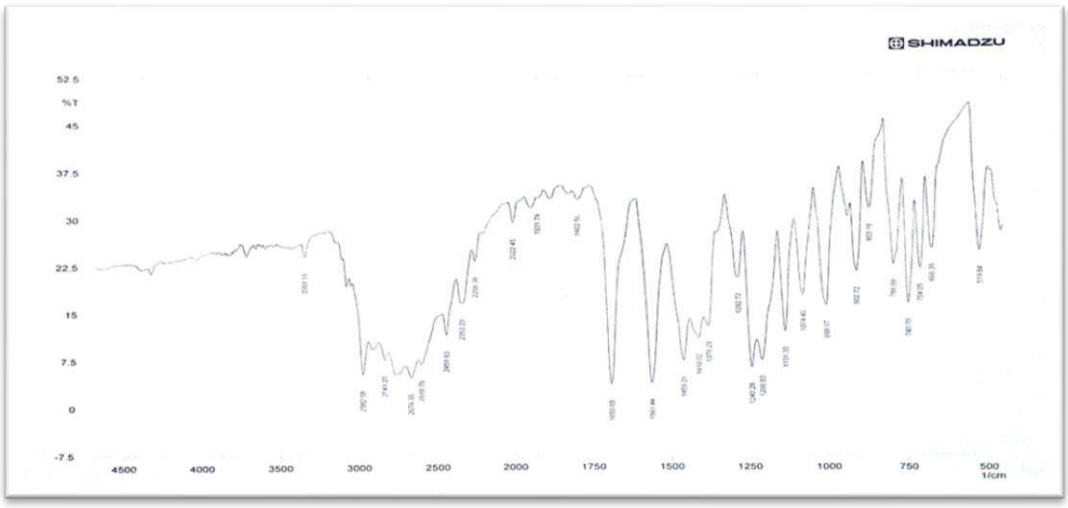

Figure 1.FTIR spectrum of Bupropion Hydrochloride

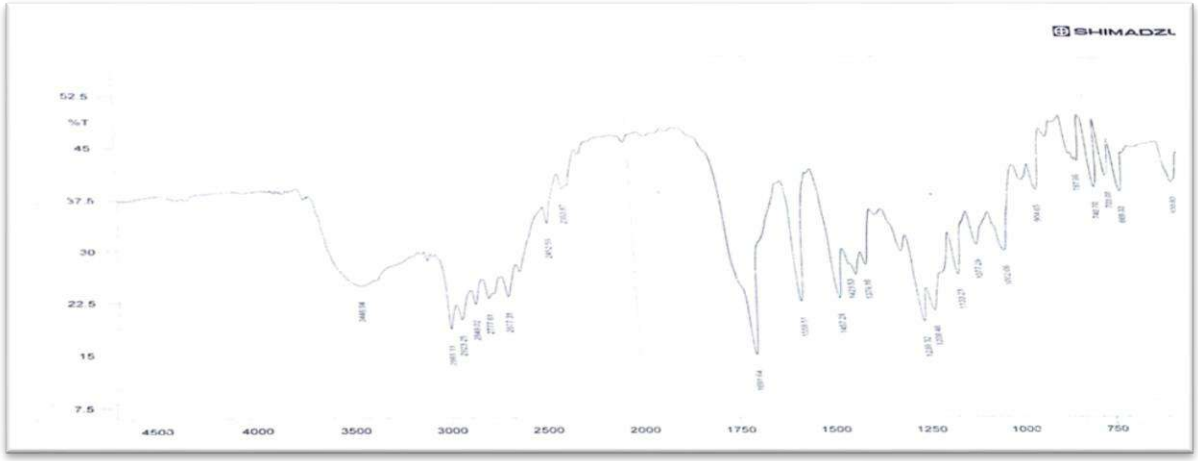

Figure 2: FTIR Spectrum of physical mixture

Confirmation of crystalline structure of drug by X- Ray Diffractometery

The X-RD spectrum as shown in Figure. 3 for pure drug (Bupropion Hydrochloride), reveals its crystalline nature, which is evident from its sharp peaks. On the other hand, the spectrum of X-RD (Figure. 4) for physical mixture also shows the sharp peaks, which confirms its crystalline nature as well as also signifies that there is no interaction between drug and the excepients.

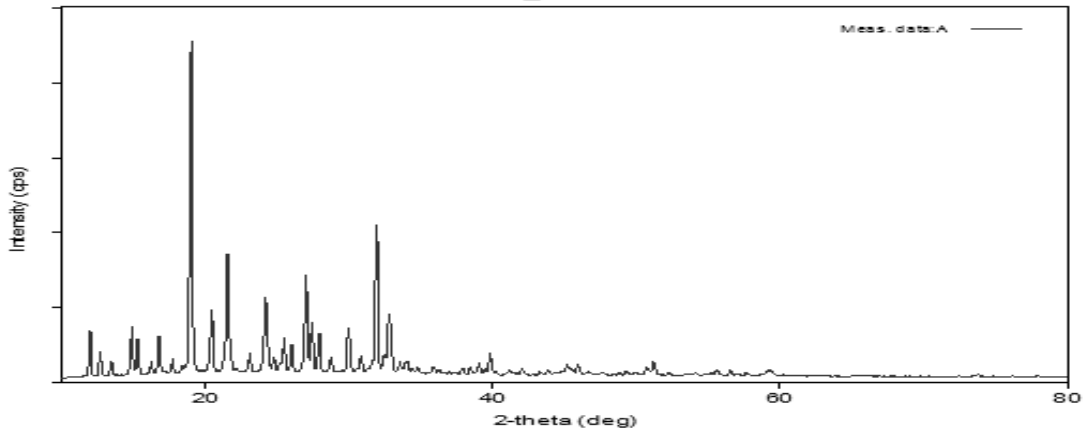

Figure 3: X-RD spectrum of pure drug (Bupropion Hydrochloride)

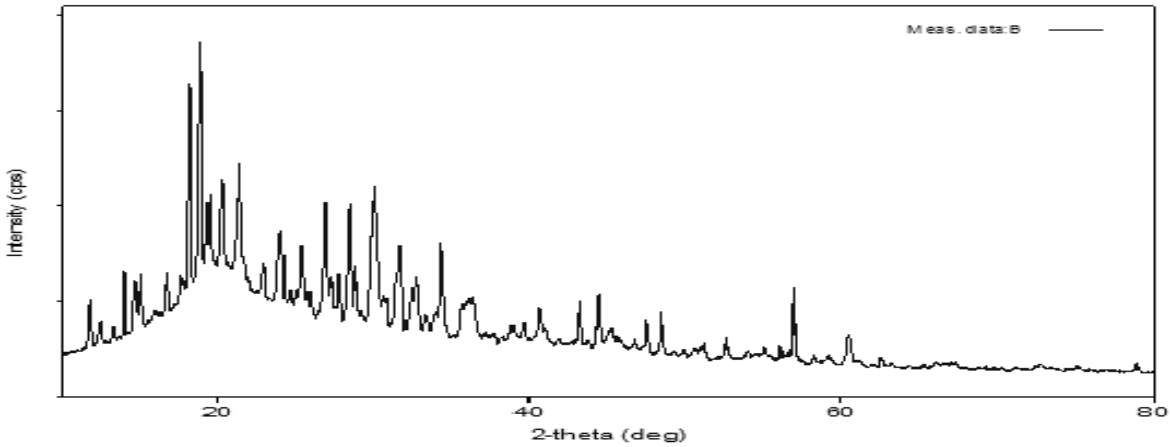

Figure 4: X-RD spectrum of physical mixture of Bupropion Hydrochloride

Evaluation of powder blend

The results of various evaluation parameters of powder blend is summarised in table 5. The results of powder blend evaluation revealed that the prepared blend exhibits excellent packaging properties as well as flowing property.

Table 5: Results for evaluation of powder blend

Batch no.	Angle of repose (°)	Bulk density	Tapped density (g/ml)	Carr's index	Hausner's ratio
F1	24± 1.08	0.435±1.10	0.535±1.02	0.539±1.02	1.146±1.09
F2	23± 1.05	0.434±1.12	0.533±1.08	0.535±1.07	1.220±1.12
F3	24± 1.18	0.437±1.03	0.601±1.09	0.600±1.12	1.159±0.09
F4	26± 1.05	0.500±1.09	0.549±1.01	0.602±1.10	1.162±1.03
F5	27±1.08	0.439±1.18	0.537±0.09	0.533±1.05	1.219±1.05
F6	24± 1.11	0.501±1.12	0.602±1.12	0.534±0.06	1.166±1.01
F7	25± 1.12	0.505±1.11	0.545±1.06	0.536±1.18	1.189±1.13
F8	27± 1.07	0.438±1.05	0.567±1.09	0.544±1.12	1.765±1.10
F9	26± 1.02	0.502±1.12	0.602±1.14	0.549±1.10	1.231±1.05
F10	25± 1.06	0.505±1.04	0.600±1.13	0.555±1.05	1.229±1.01
F11	23± 1.01	0.434±1.02	0.545±1.10	0.551±1.12	1.230±1.13
F12	27± 1.21	0.438±1.06	0.534±1.05	0.546±1.08	1.149±0.09
F13	26± 1.10	0.503±1.14	0.539±1.08	0.601±1.09	1.156±1.10

Physicochemical characterization of tablet

The prepared tablets were observed visually. Defects such as capping, chipping and lamination were absent. The thickness for the tablets of all the formulation (F1- F13) was found in the range of 4.29±0.05- 4.61±0.09.

Weight variation test and Hardness

The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits, all formulations complied with the test for weight variation (table 6) according to the pharmacopoeial specifications.

The hardness was found in the range of 4.4 to 4.7 kg-cm (table 6).

In- vitro swelling ability

The *in- vitro* swelling ability of the tablet was found in the range of 0.44-0.81%. The result (Figure5) signified that, the increase in the concentration of HPMC K4M was more impactful for the swelling of tablet, since HPMC K4M exhibits the property of swelling.

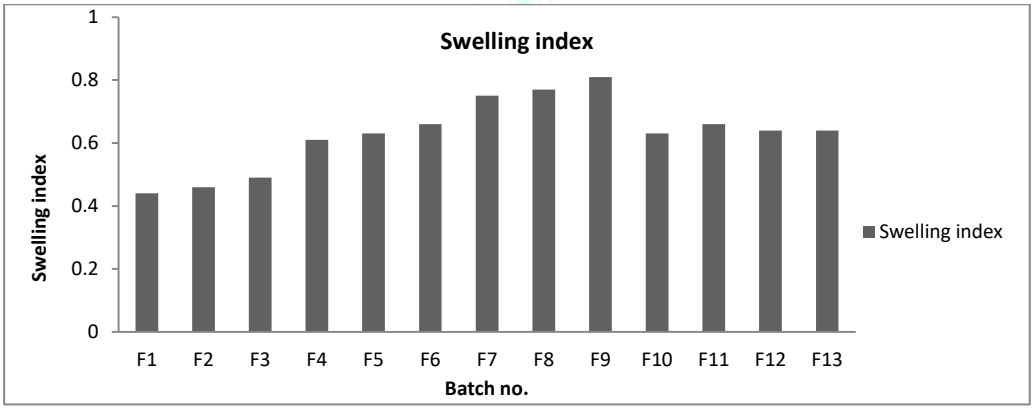

Figure 5: Swelling index of formulated batches

Table 6 Results of physicochemical characterization of tablet

S.No.	Dimensions * (mm)	Weight variation *(mg)	Hardness (kg/cm²)	Swelling ability
F1	4.44±0.02	607.25±2.39	4.5	0.44
F2	4.37±0.06	606.25±1.39	4.5	0.46
F3	4.45±0.10	607.05±1.75	4.6	0.49
F4	4.29±0.05	605.55±1.75	4.4	0.61
F5	4.61±0.09	605.05±1.94	4.6	0.63
F6	4.44±0.03	606.75±2.04	4.5	0.66
F7	4.40±0.10	604.09±1.94	4.6	0.75
F8	4.54±0.02	605.41±2.04	4.7	0.77
F9	4.30±0.06.	606.25±0.19	4.6	0.81
F10	4.32±0.06	605.15±2.94	4.6	0.63
F11	4.32±0.06	605.09±1.67	4.6	0.66
F12	4.32±0.06	605.05±1.90	4.6	0.64
F13	4.32±0.06	605.14±1.98	4.6	0.64

*All the values are expressed as mean± SD, n=3

In- vitro Drug Release

The drug release profile of all the batches was studied for 12 h. The drug release of all formulated batches lies between 88.2- 96.7%, within 12 h (Figure 6). Summary of the dissolution parameters, i.e. "n" and "k" is indicated in Table 7. The *in- vitro* release profile of all the formulations could be best expressed by 'Korsmeyer Peppas equation'.

As observed from the data of dissolution parameters so obtained, the correlation coefficient of all the formulations were high (R^2 value ranged from 0.9131- 0.9959), which was enough to evaluate the drug dissolution behaviour. The release exponent (n) was found to be the function of polymer used. The n value (ranged from 0.5033- 0.7141) indicated non- fickian diffusion mechanism, which is also called as *anomalous transport*. This indicated that dissolution was the dominant mechanism of drug release.

An increase in the amount of both polymers will decrease the drug release; hence lower value of drug release constant (k), at higher polymer content was obtained.

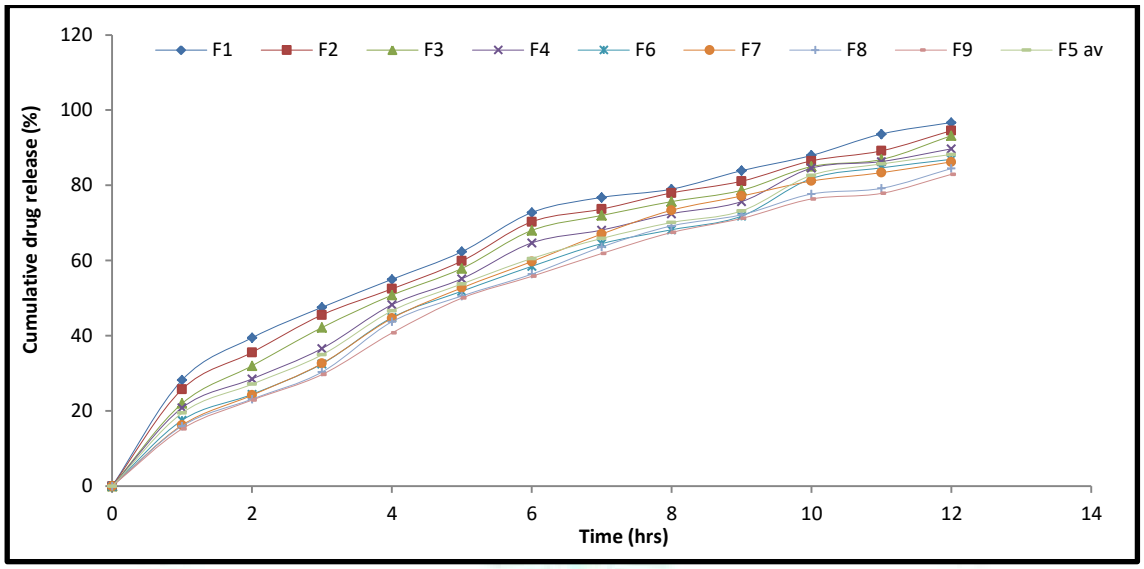

Figure 6: Release pattern of formulated batches

Table 7: Various dissolution parameters for different formulations

Batch Code	R^2					n	k
	Zero order	Ist order	Higuchi matrix	Korsmeyer-Peppas	Hixson-crowell		
F1	0.9174	0.9406	0.9131	0.9970	0.9852	0.5033	4.2308
F2	0.9243	0.9665	0.9137	0.9961	0.9896	0.5336	4.0765
F3	0.9345	0.9704	0.9154	0.9949	0.9800	0.5876	3.8387
F4	0.9490	0.9836	0.9146	0.9913	0.9935	0.6192	3.6651
F5	0.9598	0.9806	0.9148	0.9932	0.9936	0.6531	3.5039
F6	0.9646	0.9809	0.9158	0.9912	0.9734	0.6810	3.3881
F7	0.9541	0.9966	0.9203	0.9903	0.9954	0.7122	3.3251
F8	0.9859	0.9945	0.9191	0.9890	0.9954	0.7045	3.2785
F9	0.9618	0.9959	0.9191	0.9914	0.9859	0.7141	3.2211
F10	0.9569	0.9808	0.9138	0.9916	0.9929	0.6321	3.5771
F11	0.9594	0.9812	0.9144	0.9945	0.9940	0.6460	3.5263
F12	0.9572	0.9805	0.9138	0.9918	0.9929	0.6328	3.5781
F13	0.9563	0.9824	0.9138	0.9937	0.9939	0.6284	3.6017

Data analysis

The ANOVA equations obtained from the software was helpful in estimating the relationship between independent variable and dependent variable. Following equations were obtained, for the following three dependent variables:

Hardness = 4.58 A+ 0.050 B+ 0.025 AB+ 0.084 A^2- 0.066 B^2+ 0.025 A^2B- 0.025 AB^2 **(eq.10)**

Q_{12h} = 88.06- 3.84 A- 1.40 B- 0.15AB+ 0.61 A^2+ 0.61 B^2- 0.62A^2B- 1.55 AB^2 **(eq.11)**

T_{50}= 4.14 +1.25 A+ 0.24 B+ 0.18 AB+ 0.67 A^2+ 0.67 B^2- 0.16 A^2B- 0.16 AB^2 **(eq.12)**

From the results of multiple regression analysis, it was found that the dependent variables i.e. hardness, Q_{12h} and T_{50} are strongly dependent on independent variables.

Various response surfaces plotted for the studied response showed the effect of polymers in combination on the properties and they were known to facilitate an understanding of contribution of the variables and their interactions.

Figure 7 depicts hardness of tablets were increased as the concentration of HPMC K4M and CP 934P were increased.

Figure 7 is showing the effect of CP 934P & HPMC K4M on hardness. As per the figure, with increase in both the polymers, the strength of the tablet increases.

At minimum concentration of CP 934P, when HPMC K4M increases from lower to higher concentration, the increase in hardness is almost linear and the same is applicable for increase in the concentration of CP 934P from lower to higher concentration, at minimum concentration of HPMC K4M, while at higher concentration of HPMC K4M, when CP 934P increases from lower to higher concentration, the initial increase in the hardness is sudden, while it is almost static at the end. All these statements are much more, strength fully depicted in the contour plot of the same.

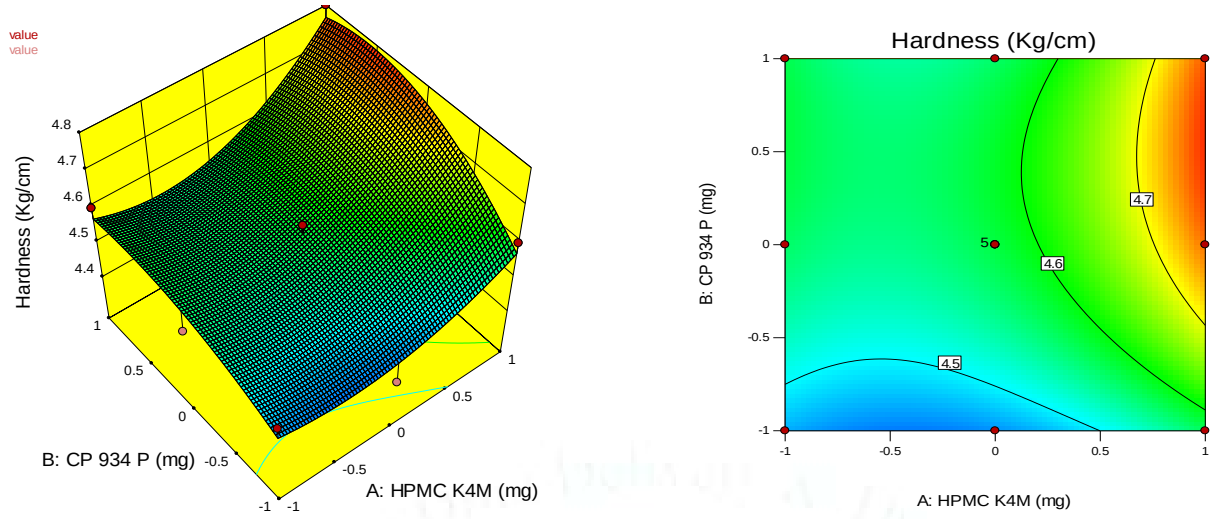

Figure.7. Response Surface plot & contour plot showing effect of HPMC K4M and CP 934P on Hardness

Figure 8 represented the response surface plot and the contour plot showing the effect of both the polymers on Q_{12h}. Both the plots are signifying that on increase in concentration of both the polymers, Q_{12h} is decreasing. At minimum concentration of CP 934P, when HPMC K4M in increasing from lower to higher concentration, the decrement in Q_{12} is more prominent as compared to CP 934P and the same can be observed through contour plot. This may be due to the fact; HPMC K4M forms a strong viscous gel on contact with aqueous media with the gel controlling delivery of the highly water- soluble drug.

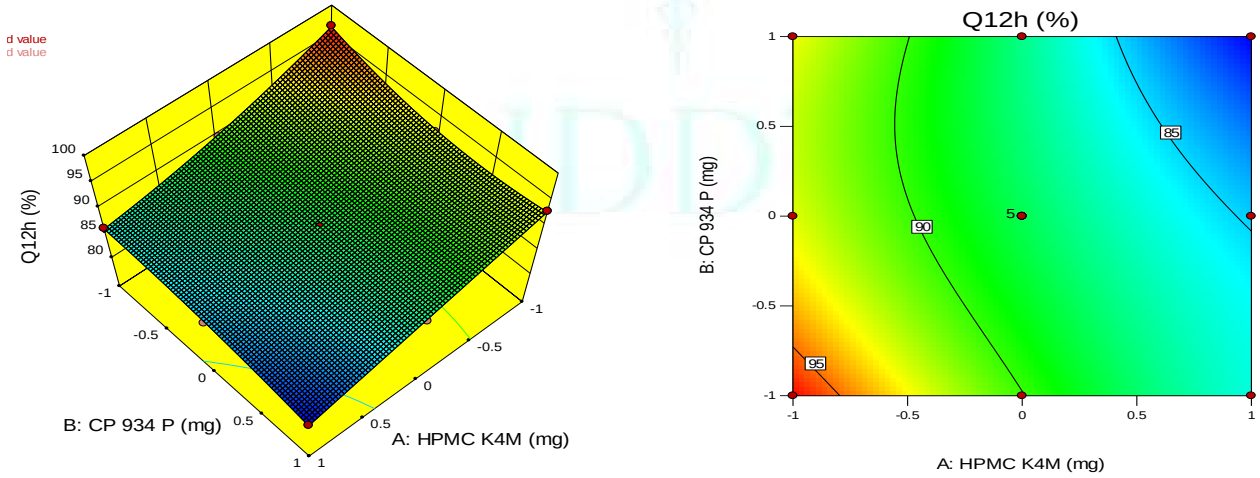

Figure. 8: Response Surface plot & contour plot showing effect of HPMC K4M and CP 934P on Drug Release

The response surface plot and contour plot as shown in Figure 9, signifies that on increasing the concentration of both the polymers the T_{50} is also increasing. The value of T_{50} is increasing with the increment in concentration of HPMC K4M, while with CP 934P the value of T_{50} tends to increase slowly but linearly. The same was observed through contour plot, which is showing almost inclining linear contour lines.

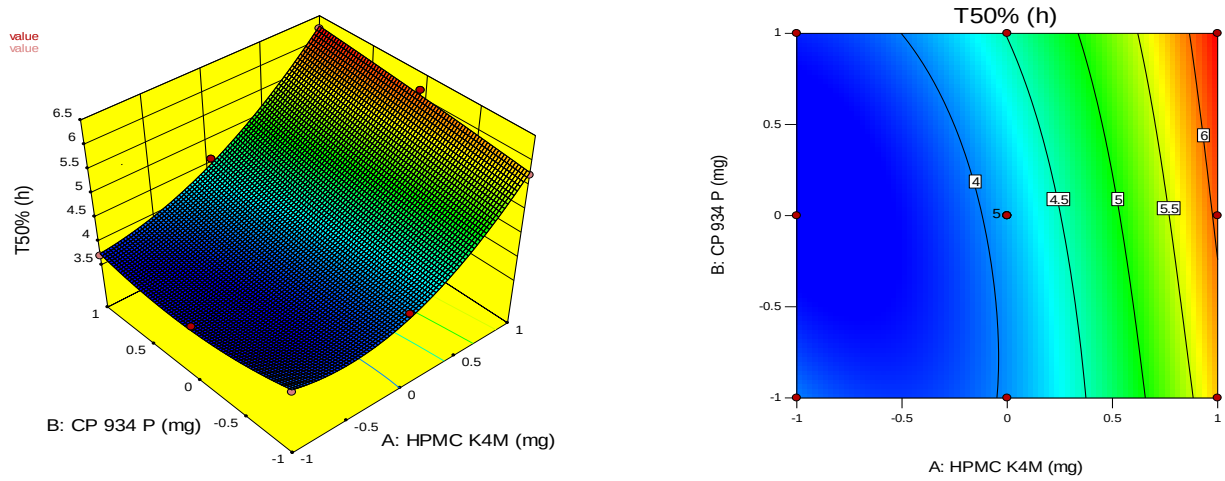

Figure. 9: Response Surface plot & contour plot showing effect of HPMC K4M and CP 934P on time for 50% release

3.5 Overlay plot

The overlay plot obtained by the software shows the area of optimization, which is signified by yellow colour, as shown in Figure10. The overlay plot so obtained was useful for the purpose of validation.

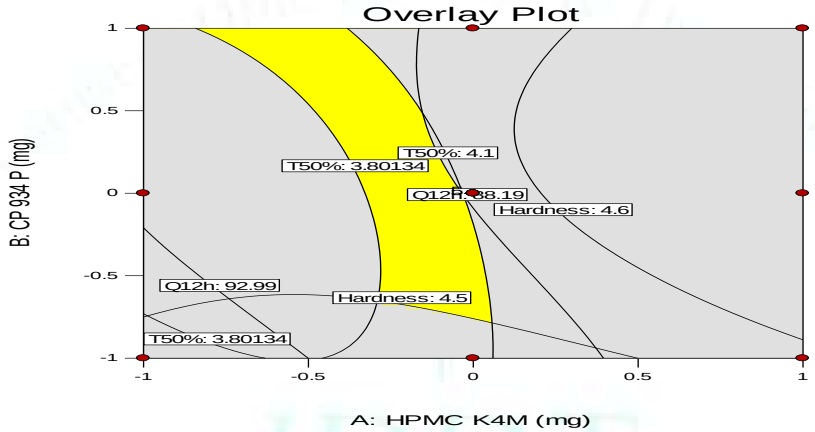

Figure 10: Overlay plot showing optimized region

Validation:

The validation checkpoints chosen from the overlay plot.. The checkpoints taken from the overlay plot showed the predicted values of both the independent and dependent variables. The percentage error was then calculated between the predicted values and observed values, to check the accuracy of software. The various validation batches along with their predicted values, observed values and percentage error is summarised in table 8. The regression coefficient between the anticipated and experimental values for hardness, Q_{12} & T_{50} is represented in Figure11A, Figure11B & Figure11C, respectively.

Table 8: Checkpoint Composition, their results and percentage error

Validation batch	A HPMC K4M mg	B CP 934P mg	Response variables	Predicted values	Experimental values	Percentage error (%)
VCT1	34.85	7.2	Hardness (kg/cm²)	4.55	4.8	-0.054
			Q_{12} (%)	89.11	87.42	0.021
			T_{50} (h.)	3.89	3.83	0.015
VCT2 (optimized)	31.75	8.7	Hardness (kg/cm²)	4.54	4.65	-0.024
			Q_{12} (%)	90.32	89.99	0.003
			T_{50} (h.)	3.91	3.87	0.010
VCT3	37.95	6.21	Hardness (kg/cm²)	4.56	5.00	-0.096
			Q_{12} (%)	88.44	86.23	0.024
			T_{50} (h.)	4.01	3.98	0.007
VCT4	36.4	31.75	Hardness (kg/cm²)	4.51	4	0.11
			Q_{12} (%)	90.22	89.55	0.007
			T_{50} (h.)	3.81	3.75	0.015

Conclusion

The relationship between various process variables chosen for the study was successfully determined with the help of response surface plots and overlay plot obtained by the software. The concentration of the polymers (HPMC K4M & CP 934P) were chosen as independent variables, while hardness, Q_{12} & T_{50}, were selected as dependent variables. It was observed that on increasing the concentration of both the polymers the hardness & T_{50} was increasing while Q_{12} was decreasing, this is because of specific drug release controlling power of HPMC K4M & CP 934P. Thus, the study was helpful in obtaining the optimized formulation of Bupropion.

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