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Formulation and Evaluation of Extended Release Tablet of Divalproex Sodium

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ABSTRACT

In the present work, an attempt was made to design an oral Extended release matrix tablet of Divalproex sodium and to optimize the drug release profile using 3^2 full factorial design. Tablets were prepared by direct compression method using HPMC K100M and Eudragit L100 as matrix forming polymers. Tablets were evaluated for various physicochemical parameters like Hardness, Thickness, Friability, Weight variation test, Content Uniformity and *In vitro* drug release. All the formulations complied with pharmacopoeial standards. A 3^2 full factorial design for 2 factors at 3 levels each was employed to systematically optimize drug release profile. HPMC K100M and Eudragit L100 were taken as the independent variables. The dependent variables selected were % of drug released in 3 hrs, % of drug released in 12 hrs. *In vitro* drug release study showed that batch F8 (HPMC K100M-15%, Eudragit L100-10%) was found to be optimized as it had almost identical dissolution profile with marketed product. The formulated tablets exhibited Non–fickian drug release kinetics approaching Zero–order as the value of release rate exponent (n) varied between 0.6024 and 0.7354, resulting in regulated and complete release until 24 hrs. The polymer HPMC K100M and Eudragit L100 had significant effect on the drug release from the tablets ($P<0.05$). Validation of optimization study performed using confirmatory run indicated very high degree of prognostic ability to 3^2 full factorial design. Stability study of optimized batch F8 was conducted at accelerated conditions for one month and it was found to be stable.

KEYWORDS

Extended release tablet, Divalproex sodium, HPMC K100M, Eudragit L100.

INTRODUCTION

Conventional oral drug delivery systems are slowly fading away in the market due to its disadvantages. These delivery systems produce fluctuation of drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level. This effect is usually totally dependent on the particular agent's biological half life, frequency of administration and release rate[1]. Extended or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half – life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Matrix type Extended delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pelletization during manufacturing and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation[2].

Hydrophilic polymer matrix[3] system are widely used for designing oral extendned release delivery systems because of their flexibility to provide a desirable drug release profile, cost

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effectiveness, and broad regulatory acceptance. The hydrophilic polymer selected for the present study was HPMC K100M. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix. For such drugs, it becomes essential to include hydrophobic polymers in the matrix system such as Eudragit L100. Among the several polymers available as possible matrix forming materials, methacrylic resins (Eudragit) appear particularly attractive, due to their high chemical stability, good compatibility properties and large variety of products with different physicochemical characteristics present on the market.

Divalproex sodium[4,5,6] is a GABA transaminase enzyme inhibitor used in the treatment of Epilepsy and migraine disorder. Divalproex sodium can be given twice a day or thrice a day. Because of its use in neurological disorder and its adverse effect, by preparing extended release formulation of this drug reduce dosage frequency; obtain optimized and controlled therapy, better patient compliance. So, Divalproex sodium is best candidate for extended release formulation. The prepared formulation is given after a meal for better absorption through GI tract.

The aim of the current study was to develop an extended release matrix tablet of Divalproex sodium using HPMC K100M and Eudragit L 100 by direct compression method and to optimize the formulation using Full factorial design. Use of the full factorial design has been proved to be a useful tool in the development and optimization. Different steps involved in full factorial design include experimental design, regression analysis, optimization and validation.

MATERIALS AND METHODS

Divalproex sodium was received as a gift samples from Mirambika Pigment Ltd., Ahmedabad, India. HPMC K100M was gifted by colorcon Asia Pvt. Ltd., India. Eudragit L100 was procured from MG Pharma Ltd., India. Lactose, Microcrystalline Cellulose, Povidone K30 were gifted by Supato Ingredients Ltd., India. Talc, Magnesium Stearate, Colloidal Silicon Dioxide were received by Gangotri Inorganic Chemical, India.

DRUG – EXCIPIENTS COMPATIBILITY STUDY

DSC studies[11] were carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

FULL FACTORIAL DESIGN

A 3^2 randomized full factorial design[7] was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amounts of Eudragit L100 (A) and HPMC K100M (B) were selected as independent variables. Percentage release of drug for 3rd hour (Q_3) and 12th hour (Q_{12}) were selected as dependent variables.

PREPARATION OF CORE TABLETS BY DIRECT COMPRESSION METHOD[8]

Step 1: Divalproex sodium was sifted through 20≠ sieve.

Step 2: Polymer HPMC K100M, Povidone K30, MCC (Avicel pH-102), Lactose DCL-21 was sifted through 40≠ sieve.

Step 3: The step 1 & 2 ingredients were loaded into planetary mixer and mixed for 30 minutes.

Step 4: Talc, Aerosil and Magnesium Stearate was sifted through 40≠ sieve.

Step 5: Then the above sieved materials were transferred to planetary mixer and mixed for 5 minutes with step 3 material.

Step 6: Finally this dry mixed powder was compressed into tablets and evaluated for all physical and chemical parameters.

3^2 FULL FACTORIAL DESIGN

Table 1: Variable Level in Coded Form

Batch No.	Concentration of Eudragit L100 % (A)	Concentration of HPMC K100M % (B)
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

Table 2: Translation of Coded Levels in Actual Units

Variables level	Low (-1)	Medium (0)	High (+1)
Concentration of Eudragit L100 % (A)	10	12.5	15
Concentration of HPMC K100M % (B)	10	12.5	15

COATING OF TABLETS[9]

The Divalproex sodium extended release core tablets were coated with film coater using HPMC 15 cps based coating solution for 1hr. The coating solution was prepared by adding 1.4% HPMC, 0.18 % PVP K30 and 1 % titanium dioxide into a mixture of 1:1 Isopropyl alcohol and Methylene dichloride. The conditions for coating were as follows: inlet air temperature, 60°C; atomizing air pressure, 300,000 Pa; pan speed, 8 rpm and coating time, 1 hr.

Table 3: Composition of Batches According to Full Factorial Design

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Divalproex sodium	538.1	538.1	538.1	538.1	538.1	538.1	538.1	538.1	538.1	538.1
Lactose	152.1	127.1	102.1	127.1	102.1	77.1	102.1	77.1	52.1	84.1
Micro-crystalline cellulose	34.6	34.6	34.6	34.6	34.6	34.6	34.6	34.6	34.6	34.6
Eudragit L100	100	100	100	125	125	125	150	150	150	135
HPMC K100M	100	125	150	100	125	150	100	125	150	133
Povidone K30	37.6	37.6	37.6	37.6	37.6	37.6	37.6	37.6	37.6	37.6
Aerosil	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4
Talc	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1
Magnesium stearate	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1
Total weight	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**

Table 4: Coating Composition of Divalproex Sodium Exetended Release Tablet

Sr No.	Ingredients	Quantity (%)
1	HPMC	1.4
2	Isopropyl alcohol	25
3	Titanium dioxide	1
4	PVP K30	0.18
5	Methylene dichloride	25

EVALUATION OF TABLET BLENDS[10]

Angle of repose

Angle of repose was determined by using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained Diameter D was measured to calculate the angle of repose Φ by formula

$\Phi = \tan^{-1} h/r$

Where,

h = height of tip of funnel from horizontal ground surface

r = the radius of base of conical pile

Bulk density

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is. That is calculated by formula

$D_b = W/V_b$

Where,

W = Weight of powder taken

V_b= bulk volume

Tapped Density:

Tapped density was determined by USP method II. Tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum. That was calculated by formula

$$D_t = W/V_t$$

Where, W = Weight of powder taken, V_t= tapped volume

Compressibility index and Hausner ratio

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions. Compressibility index was calculated by following equation

Compressibility index = (Dt –Db) x 100

Hausner ratio was calculated by following equation

Hausner ratio = Dt/ Db

Where, Dt= tapped density, Db= bulk density

EVALUATION OF TABLETS[11]

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study etc.

Uniformity of weight

Uniformity of weight test as described in the USP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded.

Hardness

Hardness of the tablet was determined by Monsanto Hardness Tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Thickness

The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

Friability

Friability of tablets was performed in a Roche Friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed.

$$\% \text{ Friability} = \frac{Wo - W}{W} * 100$$

Where, Wo = Initial weight, W= Final weight

Content uniformity[12]

Transfer an amount of powder (from NLT 20 Tablets) to a suitable volumetric flask to obtain a nominal concentration of 1 mg/ml of valproic acid. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, and pass through a suitable filter. Sample was analyzed by HPLC method and the chromatographic conditions are column – 3.9mm*15cm packed with phenyl group bonded to porous silica (4 µm), detector: UV 210nm, Flow rate: 1ml/min, injection volume: 20 µl, run time: 6min and the mobile phase composition is methanol and buffer (11:9), Adjust with phosphoric acid to a pH of 5.0. Buffer: 0.5 gm of citric acid monohydrate and 0.4 gm of dibasic sodium phosphate in 1 L of water. The actual content in sample was read by comparison with standard Divalproex sodium.

***In-vitro* dissolution study**[12]

Dissolution studies were performed for all the formulation combinations, in triplicate, determined using USP type II dissolution apparatus (Electro lab , TDT- 08 L) where 500 ml of 0.1 N HCl and 900 ml of phosphate buffer of pH 5.5 were used as dissolution media maintained at 37^{o}C (±0.5^{o}C) at 100 rpm . The release rates from the tablets were conducted in the dissolution medium of 0.1 N HCl for 45 min and thereafter in phosphate buffer of pH 5.5. 5 ml of aliquot were withdrawn at 3, 9, 12, 14, 16, 18, 20, 22 and 24 hours with replacement of fresh media. Solution samples were analyzed after suitable dilution by above HPLC method. The actual content in samples was read by comparison with standard Divalproex sodium. Drug release profiles were drawn using MS-Excel Software and the values were obtained by interpolation from Excel Graph.

DISSIMILARITY FACTOR (F1) AND SIMILARITY FACTOR (F2)[13]

FDA recommends the use of f1 and f2 value to compare the dissolution data when the coefficient of variation is not more than 20% at the earlier time point and not more than 10% at other dissolution time points.

Dissimilarity factor were calculated using following equation.

$$F1 = (R-T/ R) *100$$

Where,

f1 = Dissimilarity factor

R = mean percent drug dissolved of reference product

T = mean percent drug dissolved of test product

For curves to be considered similar, f1 values should be close to 0. Generally, f1 values up to 15 ensure sameness or equivalence of the two curves.

The similarity may be compared by model independent or model dependent method e.g.by linear regression of the percentage dissolved at specific time points, by statistical comparison of the parameters of the weibull function or by calculating similarity factor as f_2:

$$F_2 = LOG\ (\{\{[(\sum(R-T)^2)/n] +1\}^{-1/2})*1OO)*50$$

Where,

f_2 = similarity factor

n = number of observations

R = mean percent drug dissolved of reference product

T = mean percent drug dissolved of test product

APPLICATION OF PHARMACOKINETIC MODEL[14]

In order to investigate the model of release from tablets, the drug release data of the formulation was analyzed with the following models, Qt = Qo – Ko t (Zero Order kinetics), Log C = Log C_0 - kt / 2.303 (first order kinetics) , $Q_0^{1/3}$ – $Qt^{1/3}$ = K_{HC} t (Hixon crowell model), Qt = k_H $(t)^{0.5}$ (Higuchi Model) and Koresmeyer-peppas equation(Log (Mt/ M∞) = log K + nlog t. where Mt is the amount of the drug release at time t, M∞ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indications of the drug release mechanism.

ACCELERATED STABILITY STUDIES[15, 16]

Tablets from optimized formulated batch F3 was packed in an air tight high density polythene bottles and kept at 45°C with 75±5% RH for 3 months as per International Congress on Harmonization states (ICH) guidelines. Samples were withdrawn at 0, 30, 60 and 90 days of storage and evaluated for appearance, hardness, friability, drug content and *In-vitro* drug release study.

RESULT AND DISCUSSION

Differential scanning calorimetry (DSC) analysis

The DSC thermograms for drug and polymer mixture are represented in figure 1. DSC analysis of Divalproex sodium shows the endothermic peak at its melting point i.e. at 98.8ºC. The peak of Mixture of excipients with Divalpreox sodium showed the little change in melting point of drug from 98.8ºC to 98.5ºC. It indicates that it may not affect the stability of formulation, so it is confirmed that drug is compatible with all excipients.

EVALUATION OF POWDER BLENDS OF BATCH F1 TO F9

The prepared powder blend was evaluated for Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose. The observations are listed in table 5. The observation has shown that the bulk density of above batches was in the range of 0.2416 – 0.3726gm/ml and tapped density were in the range of 0.3918 – 0.3984gm/ml.

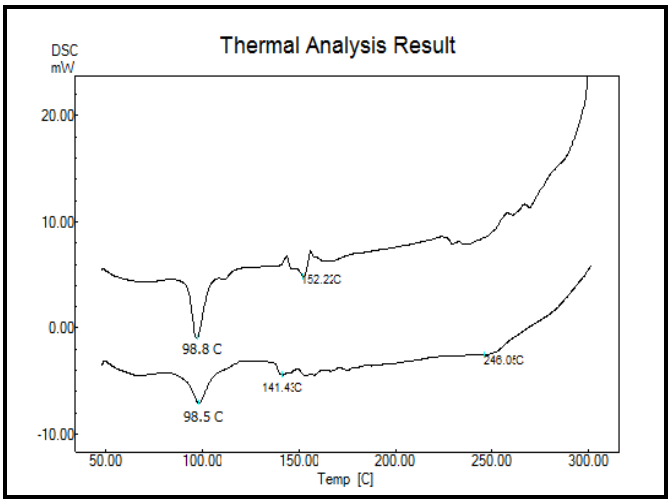

Figure 1: DSC Graph of (A) Divalproex Sodium and (B) Divalproex Sodium with other Excipients

Table 5: Flow Properties of Powder Blend of Batch F1 to F9

B. No.	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner Ratio
F1	0.3726	0.3984	14.64	6.46	1.0692
F2	0.3672	0.3834	15.12	4.23	1.0441
F3	0.3208	0.3456	15.78	7.18	1.0773
F4	0.3518	0.3726	16.44	5.59	1.0591
F5	0.3491	0.3694	16.96	6.50	1.0587
F6	0.2831	0.3112	17.25	9.03	1.0993
F7	0.2729	0.3008	18.28	9.28	1.1022
F8	0.2594	0.3027	20.86	14.30	1.1669
F9	0.2416	0.3918	31.93	19.95	1.2492

In batch F1 to F7, the Carr's index and angle of repose were in the range of 4.23 – 9.28 % and 14.64 – 18.28º, respectively. The result of Carr's index and angle of repose indicates that the

above batch blend having excellent flow property. In batch F8 and F9, the Carr's index and angle of repose were in the range of 14.30 – 19.95 % and 20.86 – 31.93º, respectively. The result of Carr's index and angle of repose indicates that the above two batch blend having passable flow property. The results of Hausner ratio were in the range of 1.0441 - 1.2492.

EVALUATION OF ER TABLETS

All prepared batches were evaluated for various physical characteristic like Hardness, Thickness, Friability, Weight variation test and Drug content.

Thickness of all batches was in the range of 5.92 – 6.1mm. Hardness of all batches was in the range of 4 – 5.1kg/cm^2 that ensures good handling characteristics of all batches. Friability of all batches was in the range of 0.34 – 0.46 % that ensuring tablets were mechanically stable.

The percentage weight variations for all formulations were tabulated in table 6. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

The percentage of drug content for F1 to F9 was found to 98.11% to 99.92% of Divalproex sodium, it complies with official specifications (90% – 110%). The results were shown in table 6.

In-vitro Drug Release Study

Dissolution studies were performed for all the formulation combinations using USP type II dissolution apparatus at 100 rpm and analyzed by HPLC.

Table 6: Physical and Chemical Characteristic Evaluation of Tablet

Batch No.	Hardness* (kg/cm^2)	Thickness* (mm)	Friability (%)	Weight Variation# (mg)	Drug Content* (%)
F1	5±0.13	5.98±0.02	0.37	1070±4.24	99.34±0.28
F2	5±0.10	5.99±0.02	0.36	1071±5.34	99.86±0.21
F3	5±0.11	6±0.01	0.37	1070±4.16	99.54±0.44
F4	5.1±0.05	6.1±0.01	0.35	1070.5±3.12	99.22±0.40
F5	5±0.12	5.98±0.04	0.37	1070±4.18	99.43±0.32
F6	5±0.11	5.95±0.06	0.36	1071±6.24	99.47±0.21
F7	4.8±0.16	6±0.07	0.39	1070±2.12	99.62±0.13
F8	4.5±0.14	5.93±0.09	0.43	1069±4.56	98.48±0.52
F9	4±0.04	5.92±0.07	0.46	1066±8.24	98.11±0.68
Marketed product	5±0.02	6	0.35	1000±1.12	99.89±0.12

Where, *n = 5, #n = 20

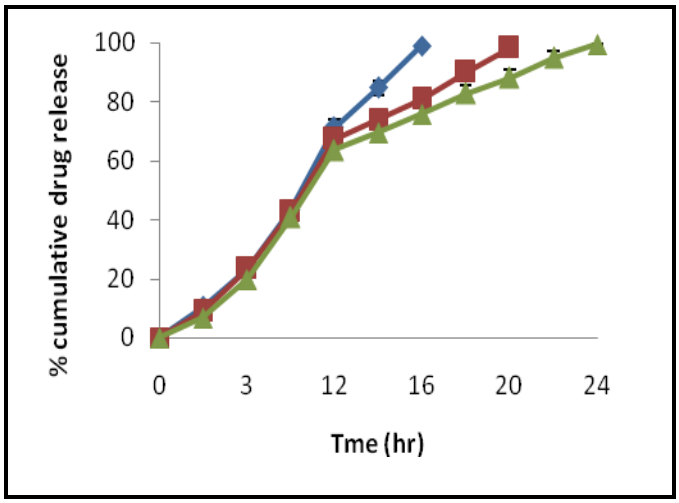

Figure 2: *In vitro* Drug Release Profile of Batch F1 to F3

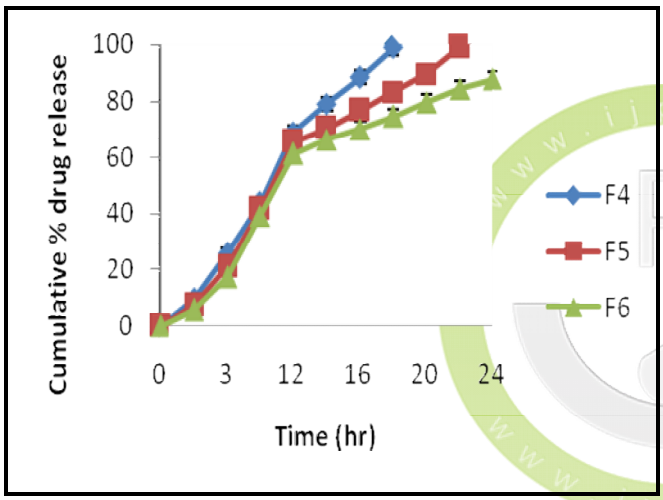

Figure 3: In vitro Drug Release Profile of Batch F4 to F6

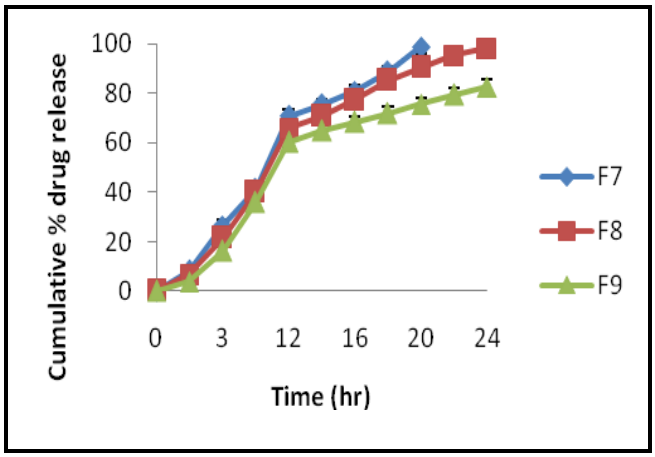

Figure 4: In vitro Drug Release Profile of Batch F7 to F9

Total amount of Divalproex sodium released from all the formulations up to 12 hrs ranged between 60.13% and 71.21% indicating in complete drug release at different concentration of Eudragit L100 as well as HPMC K100M. Rate of drug release tended to decrease with increase in the content of either Eudragit L100 or HPMC K100M. Thereby the viscosity of the gel layer around the tablet increases with increase in the hydro gel concentration, thus limiting the release of active ingredient. With further increase in polymer amount, thicker gel forms inhibiting dissolution media penetration more strongly, resulting in significant reduction in the values of release at 12 hr indicates slower drug release. The values of release at 3 hr enhanced markedly from 28.34% and release at 12 hr enhanced markedly from 60.13%, observed at low level of Eudragit L100 and high level of HPMC K100M. This indicated considerable release retarding potential of the Eudragit L100 and HPMC K100M. Figure 2, 3, 4 exhibits that release at 45 min vary in linear fashion, in ascending pattern with an increase in the amount of Eudragit L100 and HPMC K100M. From the result of above study, it was concluded that as the concentration of Eudragit increases, amount of drug release during the initial hours was controlled.

From the in-vitro drug release study of batches F1 to F9, it was observed that batch F3 and F8 has shown better and controlled drug release for 24 hr. Thus, optimization of formulation was carried out by performing similarity and dissimilarity study between batches F3, F8 and Marketed product (Dicorate ER).

Comparison of Dissolution Profiles of Batch F3 and F8 with Marketed Product by Dissimilarity Factor f1 and Similarity Factor f2 Study:

Dissolution profile of marketed product and optimized batch F3, F8 were compared for dissimilarity factor (f1).

For curves to be considered similar, f1 values should be close to 0. Generally, f1 values up to 15 ensure sameness or equivalence of the two curves.

Dissimilarity factor was found to be 0.39, -4.07 for batch F3, F8 respectively. It shows that batch F3 has dissimilarity value near to 0 than F8. It indicates F3 batch is similar to marketed product.

Dissolution profile of marketed product and optimized batch F3, F8 were compared for similarity factor (f2). f2 values close to 100 suggests that the two dissolution profiles are similar. Generally, f2 values between 50 to 100 ensure sameness or equivalence of the two curves.

Similarity factor was found to be 88.63, 74.89 for batch F3, F8 respectively. It shows that batch F3 have similarity value near to 100 than F8. It indicates F3 batch is similar to marketed product.

STATISTICAL ANALYSIS

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The % drug release at 3 hr and 12 hr were selected as dependent variables. The values of % drug release at 3 hr and 12 hr for the 9 batches (F6 to F14) showed a wide variation; the results were shown in Table 6.14. The data clearly indicate that the values of dependent variables were strongly dependent on the independent variables.

Table 7: Value of Dependent Variables

Batch No.	%Cumulative Drug Release at 3 hr	%Cumulative Drug Release at 12 hr
F1	27.34	71.21
F2	23.21	67.41
F3	19.77	63.64
F4	25.02	69.77
F5	21.93	65.83
F6	17.15	61.11
F7	26.54	70.02
F8	21.43	65.92
F9	16.75	60.13
Marketed Product	20.88	62.51

Table 8: Summary of results of regression analysis for extended release matrix tablet of divalproex sodium

Coefficient	B0	B1	B2	B11	B22	B12	R^2
Q_3	59.37	-0.19	-3.82	-0.015	0.18	-0.088	0.9932
Q_{12}	88.56	1.045	-2.526	-0.065	0.13	-0.09	0.9980

FACTORIAL EQUATION FOR DEPENDENT VARIABLES

Factorial Equation for % Cumulative Drug Release at 3 hr

$$Y= 59.37 – 0.19X1 – 3.82X2 – 0.088X1X2 – 0.015X_1^2 + 0.18X_2^2, R^2= 0.9932$$

The % cumulative drug release is an important parameter for extended release tablets. The % cumulative drug release at 3 hr of extended release tablets varied from 16.75 % to 27.34% and showed good correlation coefficient as 0.9932. Results of the regression analysis indicate that both variables A (Concentration of Eudragit L100) (p = 0.0003) and B (Concentration of HPMC K100M) (p = 0.0209) were significant.

Factorial Equation for % Cumulative Drug Release at 12 hr

Y= 88.56 + 1.045X1 – 2.526X2 – 0.09X1X2 – 0.065X12 + 0.13 X22, R2= 0.9980

The % cumulative drug release at 12 hr of extended release tablets varied from 60.13 % to 71.21 % and showed good correlation coefficient as 0.9980. Results of the regression analysis indicate that both variables A (Concentration of Eudragit L100) (p = 0.0001) and B (Concentration of HPMC K100M) (p = 0.0031) were significant.

CONTOUR PLOT AND RESPONSE SURFACE PLOT

Contour plot and Response surface plot were drawn using design expert software. Following are Contour plot and Response surface plot.

Contour Plot and Response Surface Plot for % Cumulative Drug Release at 3 hr

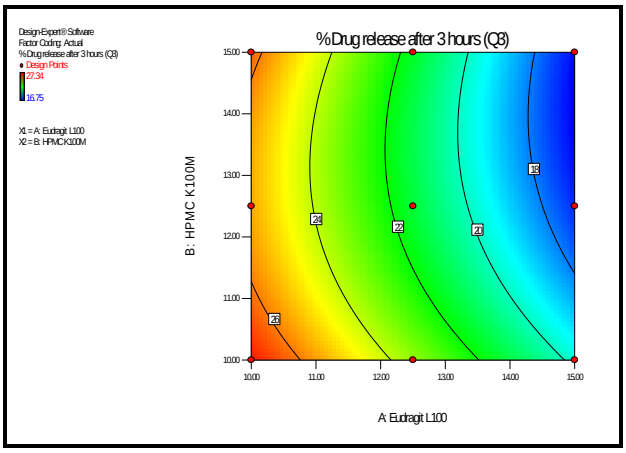

Figure 5: Contour Plot for % Cumulative Drug Release at 3 hr

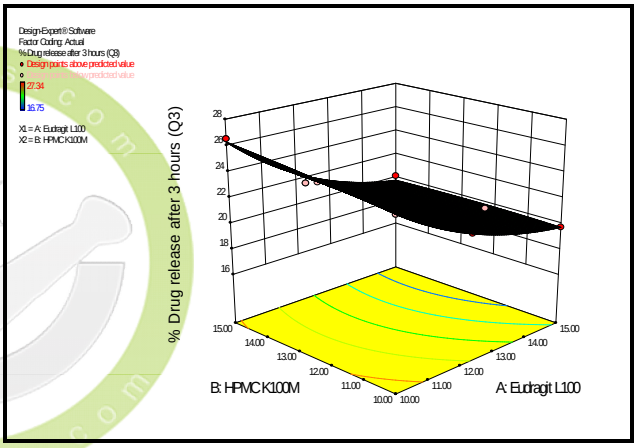

Figure 6: Response Surface Plot for % Cumulative Drug Release at 3 hr

ANOVA for % Cumulative Drug Release at 3 hr

Table 9: ANOVA Data of Dependent Variable at 3 hr

	SS	Df	MS	F value	p value
Regression	115.17	5	23.03	87.82	0.0019
Eudragit L100	106.09	1	106.09	404.50	0.0003
HPMC K100M	5.23	1	5.23	19.93	0.0209
Residual	0.79	3	0.26	-	-
Total	115.96	8	-	-	-

From results of ANOVA, **v**alues of p less than 0.0500 indicate model terms are significant. Response surface plot indicate that augmentation of line is toward the A factor (Eudragit L100). So Factor A is more significant than factor B (HPMC K100M).

Contour Plot and Response Surface Plot for % Cumulative Drug Release at 12 hr

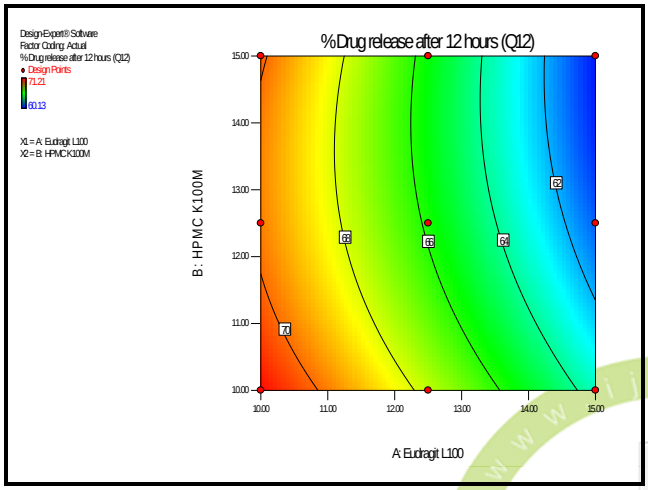

Figure 7: Contour Plot for % Cumulative Drug Release at 12 hr

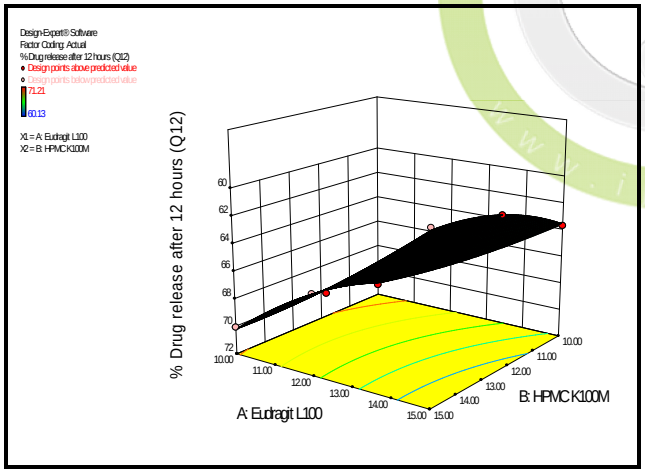

Figure 8: Response Surface Plot for % Cumulative Drug Release at 12 hr

ANOVA for % Cumulative Drug Release at 12 hr

From results of ANOVA, values of p less than 0.0500 indicate model terms are significant. Response surface plot indicate that augmentation of line is toward the A factor (Eudragit L100). So Factor A (Eudragit L100) is more significant than factor B (HPMC K100M).

Table 10: ANOVA Data of Dependent Variable at 12 hr

	SS	Df	MS	F value	p value
Regression	123.11	5	24.62	297.32	0.0003
Eudragit L100	113.71	1	113.71	1373.05	0.0001
HPMC K100M	6.39	1	6.39	77.11	0.0031
Residual	0.25	3	0.083	-	-
Total	123.36	8	-	-	-

VALIDATION OF 3^2 FULL FACTORIAL DESIGN

Validation of 3^2 Full Factorial Design is necessary for confirmation of applied model. Check point batch F10 contains 13.5 % of Eudragit L100 and 13.3 % of HPMC K100M was formulated and evaluated for different physico chemical parameter to validate the design.

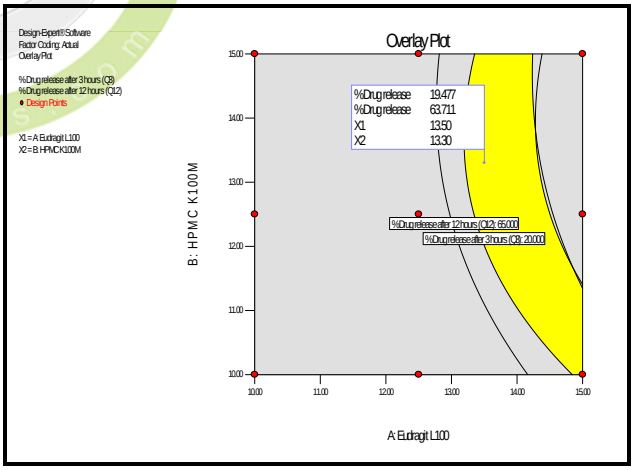

Figure 9: Overlay Plot

From the full factorial model, it is expected that the % drug release value of the check point batch at 3 hr and 12 should be 19.47 and 63.71 %. Table 11 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid.

Table 11: Evaluation Parameters of Check Point Batch

Pre-compression Evaluation Parameters	
Bulk density (gm/ml)	0.3190 ± 0.01
Tapped density (gm/ml)	0.3429 ± 0.01
Angle of repose (°)	15.64 ± 0.03
Compressibility index (%)	6.97 ± 0.02
Hausner ratio	1.0749 ± 0.01
Evaluation Parameters of Tablets	
Weight variation	1070 ± 5.21
Hardness (kg/cm^2)	5 ± 0.19
Thickness (mm)	6 ± 0.02
Friability (%)	0.37 ± 0.03
% Drug content	99.12 ± 1.15

***In vitro* Drug release Study of Check Point Batch (F10) and Comparison with Batch F3 and Marketed Product:**

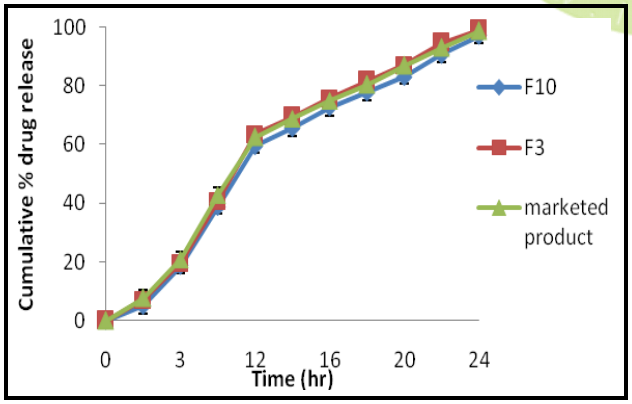

Figure 10: *In Vitro* Drug Release study of Batch F10 and F3 and Marketed Product

Drug release profile of batch F3, Batch F10 and Marketed product are as shown in figure 10. From the graph, it was concluded that batch F3 has same release profile as release profile of marketed product. So, Batch F3 was selected as optimized formulation.

APPLICATION OF PHARMACOKINETIC STUDY

The regression parameters obtained after fitting dissolution release profile to various kinetics models are tabulated in table 12. The *in vitro* release data were kinetically analyzed for establishing kinetics of drug release. Zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixon Crowell models were tested.

Table 12: Model Fitting for Optimized Batch (F3)

Model	R^2	Slope	Intercept	Equation
Zero Order Kinetic	0.984	4.165	5.907	Y = 4.165x + 5.907
First order Kinetic	0.756	-0.067	2.201	Y = -0.067x + 2.201
Higuchi	0.97	21.21	-8.992	Y = 21.21x - 8.992
Korsmeyer-Peppas	0.988	0.697	1.027	Y = 0.697x + 1.027
Hixon-Crowell	0.937	0.234	-0.321	Y = 0.234x - 0.321

The best fit model was selected on the basis of R^2 value. It is evident from the data the Zero Order Kinetic and Korsmeyer-Peppas model were the best fit model for batch F3. The value of n is indicative of release mechanism. Here $0.5 < n < 1$ so, anamolous (non-fickian) diffusion was seen. The values of diffusional exponent (n) of all batches are between 0.5-1.0, so all batches showed diffusion and erosion control release mechanism.

STABILITY STUDY OF OPTIMIZED BATCH

Stability study was done to see the effect of temperature and humidity on tablets. Tablets were evaluated periodically (initial, and after 1 month) for appearance, hardness, friability, drug

content and i*n vitro* drug release. The results of the stability study for the optimized batch F3 is given in table 13.

Table 13: Stability Study of Optimized Batch (F3) at Accelerated (40 ± 2ºC & 75 ± 5% RH) Condition

Test	**Initial**	**After 1 month**
Appearance	White colour, Capsule shaped biconvex tablet	No change in appearance
Hardness (Kg/cm^2)	5.0 ± 0.44	4.9 ± 0.22
Friability	0.3816 %	0.3894 %
Drug content (%)	99.75 ± 0.915	99.56± 0.96
In vitro drug release (%)	98.87 ± 0.854	98.24 ± 0.745

No significant changes were observed in any of the studied parameters during the study period, thus it can be concluded that formulation was stable.

CONCLUSION

Divalproex sodium is a GABA transaminase enzyme inhibitor used in the treatment of Epilepsy and migraine disorder. In the present study, an attempt was made to prepare matrix tablets of Divalproex sodium by direct compression method using HPMC K100M and Eudragit L100 as matrix forming material. Prepared matrix tablets were evaluated for hardness, friability, weight variation, drug content uniformity, *In vitro* drug release and short-term stability studies. All the formulations complied with pharmacopoeial standards. From the *in vitro* drug release study, it was concluded that as we increased the amount of HPMC K100M and Eudragit L100 from 10 % to 15 %, reduction in the drug release rate and linearization of the drug release curve was observed.

From the result of 3^2 full factorial design and regression analysis, it was concluded that factorial batch F3 prepared with combination of 10 % Eudragit L100 and 15 % HPMC K100M has shown highest % drug release and comparable to the marketed product with f1 value 0.39 and f_2 value 88.63. Based on the f_2 value and targeted release profile, batch F3 was considered as optimized batch.

By applying different model for Batch F3, the Korsemeyer model was good fit with linearity value 0.988. The drug release followed Korsemeyer model and which indicates a coupling of diffusion and erosion mechanisms so called anomalous diffusion. The results of stability indicatd that there was no change in the formulation after 1 month accelerated stability study. The prepared formulation of Divalproex sodium extended release matrix tablet was stable.

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