STATISTICAL OPTIMIZATION AND ASSESSMENT OF DIVALPROEX SODIUM EXTENDED RELEASE TABLET

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ABSTRACT

The purpose of the current experimental research was to optimize the quantities of macromolecules such as Eudragit L/100-55 and HPMC-K-100M for the development of extended release tablets of divalproex sodium, an anti-convulsant or epileptic agent used in the effective management of bipolar disorders, mania, seizures, convulsions, tremors/epilepsy. Divalproex sodium ER tablets were formulated with the help of Eudragit L/100-55 and HPMC-K-100M in variable compositions and variable amounts as per 3^2 factorial design technique. Tablets were prepared by direct compression technique. Quantities of polymers required for exhibiting extended release of active agent from the tablet were chosen as independent variables, in similar manner time required for drug release was chosen as dependent variable ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$). Nine formulations were created in accordance with the plan, formulated, and tested for quality control criteria. It is obvious from the data that all formulations exceed the compendial restrictions. Kinetic parameters were established, and the data from the dissolution investigation suited kinetic models very well. For the responses, polynomial equations were created and validated. The optimum formulation of SOD5, which contains 31.25 mg of Eudragit L/100-55 & 31.25 mg of HPMC-K-100M, exhibits resemblance to the commercial product of f_2=85.91 and f_1=2.25 (DIVALEX). SOD5 is made in a zero-order fashion, and the mechanism of drug release was found to be non - Fickian in nature (n = 0.645).

Keywords: Divalproex sodium, HPMC-K-100M, Eudragit® L/100-55, 3^2 factorial design, Non-Fickian diffusion

INTRODUCTION

Extended release (ER) formulations prolong effective plasma concentration for longer periods of time while simultaneously reducing the frequency of dosage in a two-fold decline pattern. They raise patient adherence. Moreover, they give enhanced *in vivo* clinical results[1-2]. Extended release dosage forms were commonly referred to by the symbols XL, LA (long acting), and XR[3]. Many problems were experienced by formulation scientists while developing novel formulations for obtaining good absorption and enhanced bioavailability with sustained or prolonged release medications.

Divalproex is popularly used as an anticonvulsant agent for the effective management of bipolar disorders and epilepsy. It is also used as a prophylactic measure in case of migrane. It acts by the prolongation of sodium channel blockade or inactivation. It also shows a significant effect on GABA levels in the brain. It inhibits GABA degradation by increasing its levels in brain and exerts anticonvulsant property. Due to its lower elimination half-life (5±1 h), to achieve good clinical outcome there is the need to administer it 3-4 times a day. The drug is a difficult task. The drug exhibits a first pass effect. By considering all these issues, we made an attempt to design and develop an extended release tablet formulation for divalproex for the effective management of epilepsy[4-15].

Several tools are available to the formulation scientist for optimising the developed formulations with the help

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of statistical significance. Among all available statistical tools, response surface methodology is a widely used technique in industry as well as academia. Popular methods in the above-mentioned category include factorial approach, central composite approach, Box-behnken approach and others[16-17].

Direct compression method is the most widely used method of manufacture to produce tablets, as seen in many cases[18].

The present investigation focuses on the development of extended release tablet formulations for divalproex sodium to reduce the dosing frequency and thereby enhance the patient compliance. ER formulations for divalproex were prepared with the help of polymers Eudragit® L/100-55 (partially neutralized pH dependent polymer) along with HPMC-K-100M (pH independent polymer)[19].

Table I: Experimental design layout

Formulation code	X_1	X_2
SOD_1	1	1
SOD_2	1	0
SOD_3	1	-1
SOD_4	0	1
SOD_5	0	0
SOD_6	0	-1
SOD_7	-1	1
SOD_8	-1	0
SOD_9	-1	-1
CD_1	-0.5	-0.5
CD_2	+0.5	+0.5

MATERIALS AND METHODS

Materials

Divalproex sodium was procured from Gulan Pharma, India as a complementary sample. Eudragit® L/100-55 and, HPMC-K-100M were purchased from commercial sources. All other excipients were obtained from Aman Scientifics, Vijayawada, India.

Design and development of gastro retentive floating tablets for divalproex sodium

Quantities required of the Eudragit® L/100-55 and HPMC-K-100M for the development of divalproex sodium extended release tablets were labeled as independent variables (X_1, X_2). Time required for drug release were labeled as dependent variables ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$,) Polynomial equations were developed for dependent variables using PCPDisso software, Pune, India[20].

The three X_1 values (Eudragit®, L/100-55) were 3.75, 6.25, and 8.75 percent. The X_2 (HPMC-K-100M) values were 3.75, 6.25, and 8.75 percent. (% based on the active ingredient's weight). As part of a 3^2 factorial design, nine different divalproex sodium extended release tablet formulations were developed. The design layout is presented in Table I.

Preparation of divalproex sodium extended release formulations

523 mg of divalproex sodium, equivalent to 500 mg of divalproex, was taken as dose and tablets were prepared by direct compression technique. Table II represents

Table II: Formulae for divalproex sodium extended release tablets

Name of ingredient	Quantity of ingredient per tablet (mg)								
	SOD_1	SOD_2	SOD_3	SOD_4	SOD_5	SOD_6	SOD_7	SOD_8	SOD_9
Divalproex sodium	523	523	523	523	523	523	523	523	523
Dicalcium phosphate	18.5	25	31	25	31	37	31	37	43.5
Starch	18	24	30.5	24	30.5	37	30.5	37	43
Eudragit® L 100-55	43.75	43.75	43.75	31.25	31.25	31.25	18.75	18.75	18.75
HPMCK100M	43.75	31.25	18.75	43.75	31.25	18.75	43.75	31.25	18.75
Magnesium stearate	7	7	7	7	7	7	7	7	7
Talc	6	6	6	6	6	6	6	6	6
Total Weight	660	660	660	660	660	660	660	660	660

Table III: Post-compression parameters

Batch code	Hardness (kg cm^{-2})	Thickness (mm)	Friability (%)	Average weight (mg)	Drug content (%)
SOD_1	8.46±0.26	4.05±0.08	0.10±0.001	661.09±0.01	99.94±0.49
SOD_2	8.19±0.29	3.99±0.085	0.11±0.001	661.11±0.01	99.45±0.50
SOD_3	7.92±0.27	3.91±0.08	0.09±0.001	661.10±0.01	99.11±0.51
SOD_4	8.51±0.41	4.12±0.06	0.06±0.001	661.14±0.02	99.74±0.32
SOD_5	8.12±0.42	4.06±0.06	0.07±0.001	661.2±0.02	99.95±0.33
SOD_6	7.69±0.40	3.98±0.05	0.07±0.001	661.31±0.02	99.11±0.34
SOD_7	8.34±0.43	4.19±0.05	0.05±0.001	660.66±0.02	99.70±0.43
SOD_8	7.90±0.41	4.06±0.06	0.04±0.001	661.2±0.01	99.23±0.47
SOD_9	7.5±0.40	4.01±0.06	0.05±0.001	660.65±0.01	98.77±0.35

the formulation table for the preparation of tablets. All ingredients were weighed accurately and subjected to sieving to ensure uniform size and to prevent segregation. Mixing operation was carried out in polybag for 10 min to obtain uniform blend. Powder mix was compressed to obtain tablets by using tablet punching machine. Obtained tablets were subjected to various quality control tests[19-20].

Divalproex sodium ER tablets- evaluation tests

Crushing strength

The hardness of tablets was measured as per the diametric breakdown when operated with Pfizer tablet hardness tester.

Friability

This test is carried out with the help of friabilator. 20 tablets were selected randomly and their weight was recorded as W_0. The tablets were placed in the drum of apparatus and subjected to 100 freefalls and weight of tablets again taken and recorded as W_1. Percentage weight loss was measured as follows,

$$\text{Friability} = \frac{(W_0 - W_1)}{(W_0)} \times 100$$

Estimation of drug content

20 tablets were selected randomly and pulverized them to fine powder. A powder equivalent to 100 mg of divalproex was taken into volumetric flask and then added 100 mL of pH 1.2 buffer and get dissolved. The resultant solution was subjected to estimation of drug content by measuring the absorbance using spectrophotometer at 210 nm.

Thickness

It was obtained using vernier calipers on the principal of longitudinal measurement of object.

Dissolution test

This test was carried out with the help of tablet dissolution test apparatus (USP-23) containing paddle as rotating mechanism. It simulated the physiological conditions such as 900 mL of pH 1.2 buffer as SGF and was maintained for first 2 h and phosphate buffer for subsequent time intervals upto end of the current study. Temperature maintained throughout the study period was constant (37±0.5 °C) and paddle was operated at a rate of 50 revolutions per min. Samples were collected as per predetermined intervals (In accordance with USP-NF). The samples were analyzed for the estimation of drug content using spectrophotometer at 210 nm. The same was repeated to get results in triplicate[5-7].

Dissolution data was fitted to kinetic modeling, in order to find out the mechanism of release of drug from tablet[20-22].

RESULTS AND DISCUSSION

Extended release tablets of divalproex sodium were formulated according to 3^2 factorial approach. In Table I, the formulation design is displayed. Time needed for drug release was designated as the dependent variable ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$), while the quantity of Eudragit® L/100-55 and HPMC-K-100M was designated as independent variables (X_1 and X_2, respectively). In accordance with the formulae listed in Table II, 9 trials were developed.

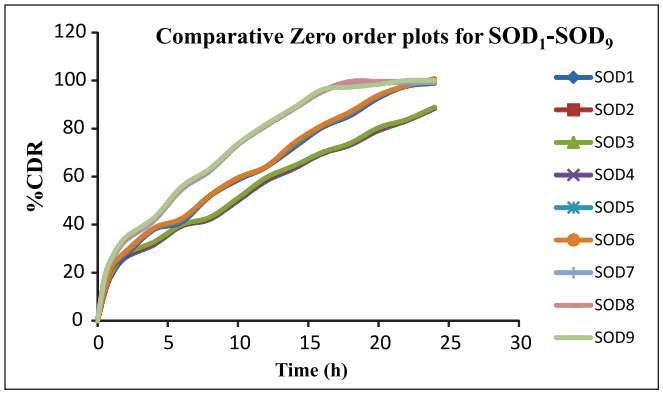

Fig. 1: Comparative zero order plots

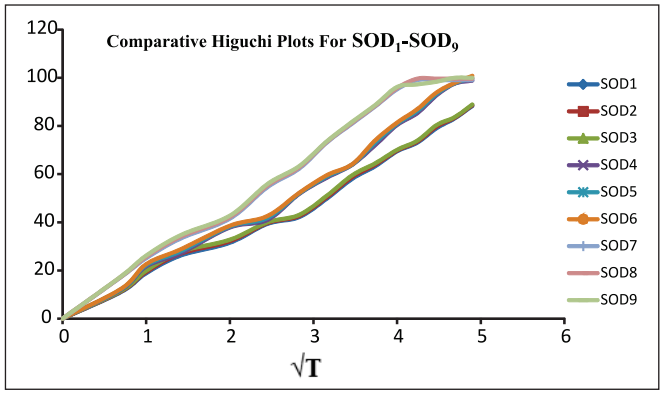

Fig. 3: Comparative higuchi plots

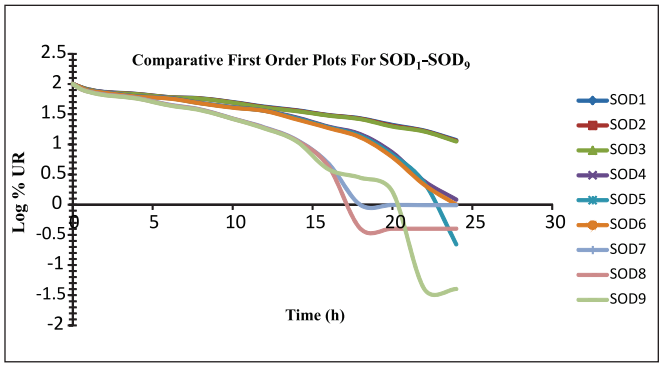

Fig. 2: Comparative first order plots

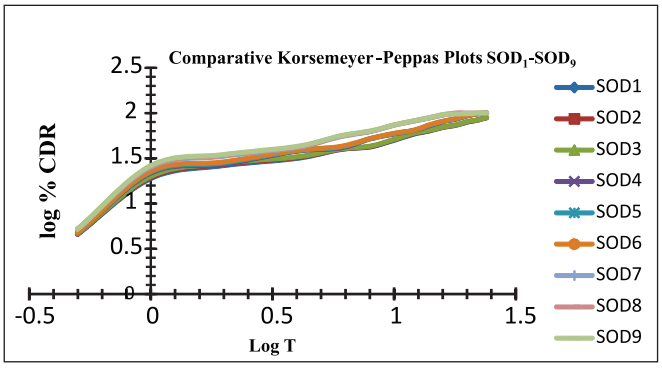

Fig. 4: Comparative Korsemeyer-Peppas plots

Table IV: Regression analysis for factorial trials

Formulation code	Kinetic parameter											
	Zero order			First order			Higuchi			Korsemeyer-Peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
SOD_1	14.42	3.285	0.982	1.988	0.034	0.986	1.685	17.614	0.995	1.089	0.629	0.962
SOD_2	14.86	3.286	0.981	1.986	0.034	0.986	1.308	17.641	0.995	1.098	0.625	0.959
SOD_3	15.31	3.287	0.979	1.985	0.034	0.986	0.930	17.667	0.995	1.107	0.621	0.957
SOD_4	15.95	3.820	0.982	2.110	0.065	0.931	2.738	20.473	0.995	1.125	0.651	0.960
SOD_5	16.31	3.834	0.982	2.171	0.077	0.877	2.481	20.560	0.995	1.132	0.645	0.958
SOD_6	16.66	3.85	0.981	2.117	0.068	0.931	2.224	20.646	0.995	1.138	0.647	0.956
SOD_7	23.41	3.92	0.948	2.112	0.093	0.964	2.240	21.685	0.992	1.199	0.641	0.950
SOD_8	23.78	3.924	0.948	2.185	0.110	0.949	2.539	21.742	0.993	1.204	0.638	0.948
SOD_9	24.31	3.890	0.946	2.286	0.124	0.915	3.157	21.565	0.993	1.210	0.634	0.945

All trials have divalproex sodium 523 mg equivalent to 500 mg divalproex as an extended release tablet dosage form prepared using direct compression method.

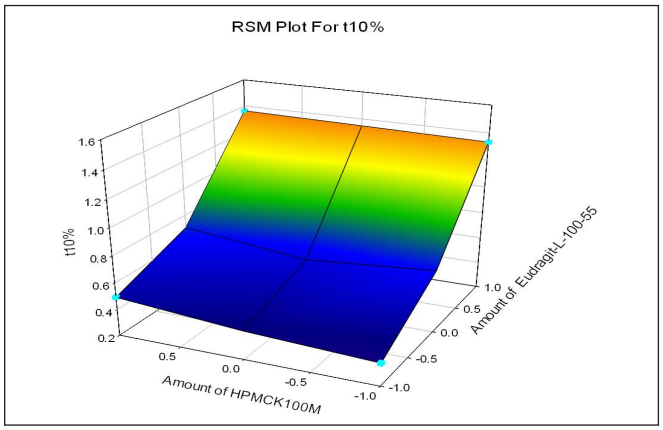

Fig. 5: Response surface morphology plot for $t_{10\%}$

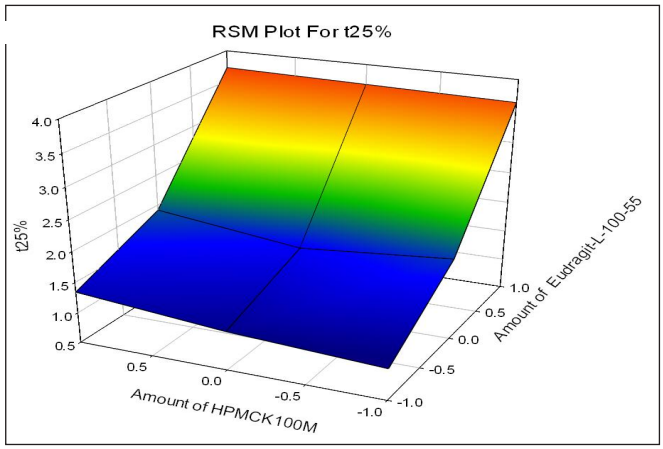

Fig. 6: Response surface morphology plot for $t_{25\%}$

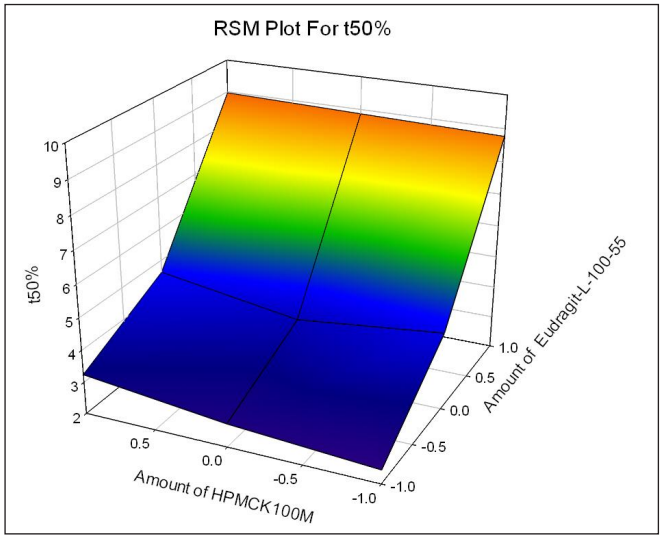

Fig. 7: Response surface morphology plot for $t_{50\%}$

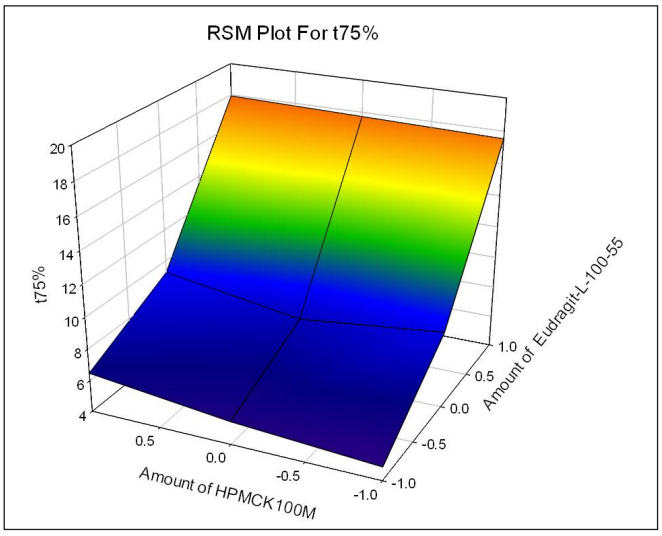

Fig. 8: Response surface morphology plot for $t_{75\%}$

Table V: Dissolution parameter

Formulation code	Dissolution parameters				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
SOD_1	1.362	3.719	8.962	17.923	29.779
SOD_2	1.348	3.679	8.865	17.731	29.460
SOD_3	1.333	3.639	8.769	17.537	29.139
SOD_4	0.701	1.913	4.611	9.221	15.321
SOD_5	0.596	1.627	3.921	7.843	13.030
SOD_6	0.669	1.827	4.401	8.803	14.626
SOD_7	0.493	1.345	3.242	6.484	10.773
SOD_8	0.415	1.132	2.728	5.456	9.065
SOD_9	0.369	1.007	2.426	4.852	8.061
MP	1.362	1.447	3.487	17.923	11.589

Prepared tablets were subjected to evaluation tests. Results are summarized in Table III. All formulations have sufficient hardness and were found to be less brittle. The weight variation test and drug content were both passed by all formulations. According to Indian Pharmacopoeia, a drug release rate study was conducted. To identify the drug release mechanism, kinetic analysis was applied to the data from the drug release investigation. Findings are shown in Figs. 1-4 and Table IV. After analyzing, it was evident that there was a direct correlation between the amounts of polymers combined and the rate of drug release (both were inversely proportional to each other). Divalproex sodium predicted extended release

Table VI: Dissolution parameters for check point formulations

Formulation code	Predicted value					Actual observed value				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
CD_1	0.625	1.71	4.11	8.22	13.65	0.63	1.75	4.25	8.25	13.72
CD_2	1.117	3.05	7.35	14.69	24.401	1.119	3.07	7.45	14.75	24.64

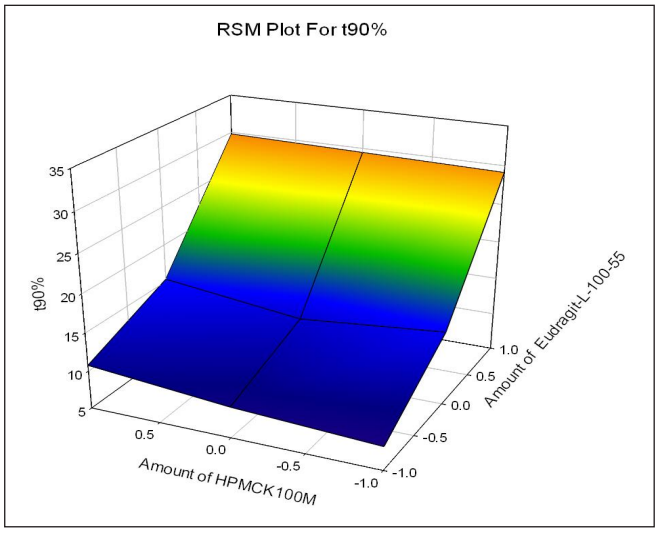

Fig. 9: Response surface morphology plot for $t_{90\%}$

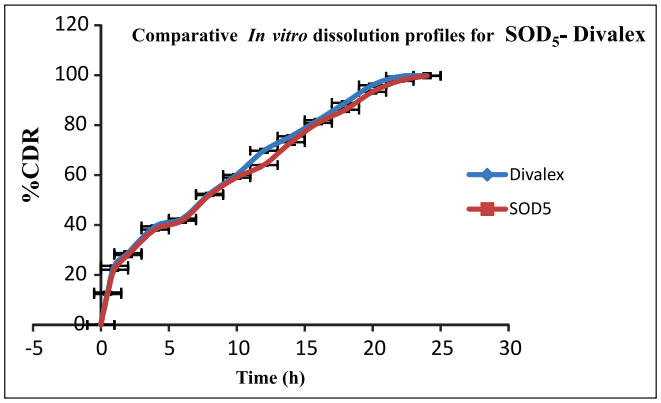

Fig. 10: Comparative dissolution profiles for SOD_5-Divalex

was accomplished using the right quantities of Eudragit® L/100-55 and HPMC-K-100M. Table V provides a summary of the dissolution parameters. Response surface morphology (RSM) plots, shown in Figs. 5-9, were used to examine the combined impact of various polymer ratios on the drug delivery of divalproex sodium. Sigmaplot V13 was used to construct RSM graphs.

SOD_5 is regarded as the ideal formulation out of all batches (based on desirability factor). SOD_5, which include equal amounts of both Eudragit® L/100-55 and HPMC-K-100M, i.e 31.25 mg each, provided promising dissolving properties that helped the study's goal by extending the time during which the drug was released (allowing for the best possible drug delivery from the dosage form).

Polynomial equations were developed to determine the predicted drug release parameter and they are as follows;

$$Y_1 = 0.811 + 0.462X_1 + 0.037X_2 - 0.023X_1X_2 + 0.23X_1^2 + 0.04X_2^2 \ (t_{10\%})$$

$$Y_2 = 2.215 + 1.24X_1 + 0.085X_2 - 0.07X_1X_2 + 0.64X_1^2 + 0.11X_2^2 \ (t_{25\%})$$

$$Y_3 = 5.29 + 3.03X_1 + 0.22X_2 - 0.16X_1X_2 + 1.53X_1^2 + 0.24X_2^2 \ (t_{50\%})$$

$$Y_4 = 10.66 + 6.14X_1 + 0.42X_2 - 0.33X_1X_2 + 3.05X_1^2 + 0.501X_2^2 \ (t_{75\%})$$

$$Y_5 = 17.702 + 10.09X_1 + 0.68X_2 - 0.518X_1X_2 + 5.05X_1^2 + 0.77X_2^2 \ (t_{90\%})$$

X_1, X_2, $X_1X_2X_1^2$, X^2 were tested for their effects on $t_{10\%}$, $t_{25\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ using the factor tool. The results of the study indicated that two variable factor X_1, X_2 and X_1^2, X_2^2 indicated show the curve in a additive fashion and parallel to one another. In addition to that, the coded factor suggests that a synergistic effect is observed in binate amount of constrained independent variables such as X_1^2 and X_2^2. X_1 and X_2 alone could not effectively prolong the drug release. It was confirmed by respective p-value and coded equation. Furthermore, the coded factor claims that a negative effect (antagonistic effect) was observed in amounts of constrained independent variables X_1X_2 (-0.023, -0.07, 0.16, -0.33 and -0.518). The combination of X_1 and X_2 in a equal ratio at 31.5mg (mid level) provides appropriate release of drug compared to the other level of formulations. The interaction between the anionic polymer and HPMC in the dissolution medium most likely has the retarding effect. According to the theory, erosion could take place at a raté equal to the movement of the front between the glassy and rubbery polymers because of the synergistic increase in viscosity that is seen in the polymers. Later, it was observed that complex formation between the nonionic and anionic polymer with ionized form of drug also played a significant role in modulating the drug release profile and that viscosity enhancement

was not the only factor. The same has been witnessed in RSM Figs. 5-9.

Comparative results for both original dissolution parameters as well as predicted parameters are shown in Table VI. Closeness was observed between the original and theoretical responses. It confirms that the developed equation was valid. SOD_5 has shown greater similarity with marketed product DIVALEX {f_2=85.91, f_1=2.25}. Comparative dissolution plots SOD_5 and DIVALEX are presented as shown in Fig. 10.

CONCLUSION

Based on the results of the current investigation, combining large molecules (polymers) offered advantages for maintaining the formulation's integrity and extending drug release. The suitable proportional mix of partially neutralised pH dependent polymer and pH independent polymer will yield the desired extended drug release, which ultimately leads to a 2-fold decrease in the dose frequency of divalproex sodium. To obtain this, the divalproex sodium was prepared utilising a combination of polymers (Eudragit® L/100-55, HPMC-K-100M), additional excipients and a 3^2 factorial design technique. The formulation SOD_5 was regarded as the best formulation among the several ER formulations examined since it achieved the best results across all objective metrics. SOD_5 uses non-Fickian diffusion and zero order drug release mechanism. By lowering the dose frequency by two or more times, it may increase patient compliance and, as a result, enhance therapeutic response.

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