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RESEARCH PAPER

COMBINED EFFECT OF HPMC K100M AND EUDRAGIT L/100-55 ON RELEASE RATE OF ANTICONVULSANT DRUG

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The present study aims to check the influence of HPMC K100M and Eudragit L/100-55 on the Divalproex sodium release from modified release tablet dosage form. Divalproex sodium, an anti-convulsant/epileptic agent, is used in the effective management of bipolar disorders, mania, seizures, convulsions and tremors/epilepsy. The current research objective was to achieve 90% of drug release at 8-12 hrs. Extended-release tablets of Divalproex sodium were prepared using various proportions of Eudragit L/100-55, HPMC K100M by direct compression technique. Nine formulations were developed and characterized for pharmacopoeial limits. Results for all evaluation tests were found satisfactory. Drug release profiles were subjected to kinetic modeling to determine the kinetic parameters. Formulation (DEH_5) containing equal quantities i.e. 31.25 mg of Eudragit L/100-55 and HPMC K100M, was found to be the best formulation showing similarity factor f_2=85.75 and difference factor f_1=2.29 with the reference marketed product (DIVALEX). Formulation DEH_5 followed zero order, whereas release mechanism was non-Fickian type transport.

Key words: Divalproex sodium, Extended-release, Anticonvulsant, Eudragit L/100-55, HPMC K100M.

INTRODUCTION

Extended-release drugs are beneficial for long-term care because they help maintain a consistent level of medication in the body. XL (Extra Long/Extra Large); LA (Long acting); XR (Extended Release) are popularly used symbols for modified or extended formulations. They show much reduction in the repeated administration of formulation approximately to two-folds, thereby, improve patient compliance and also maintain good clinical response [1-2].

Divalproex sodium, antiepileptic; a stable moiety contains 1:1 ratio of valproic acid and sodium valproate formed by the partial neutralization of valproic acid when treated with sodium hydroxide. Its chemical name is sodium; 2-propylpentanoate; 2-propylpentanoic acid (**Figure 1**). It is ionized in GI fluids and dissociated into valproate ion [3-5].

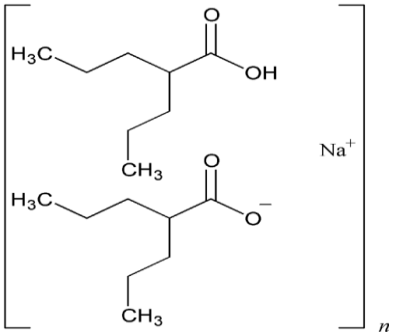


Fig. 1. Structure of Divalproex sodium

From the literature, it was found that valproate shows anticonvulsant property by improving the γ-amino butyric acid levels in CNS (brain) and produces significant decline in convulsions/ seizures. Due to this, divalproex was used in the effective management of bipolar disorders, seizures, convulsions, tremors/epilepsy. It is also used in managing migraines.

Divalproex sodium has a very less biological half-life (4-6 hours). For chronic management of epilepsy, there is need to administer oral doses multiple times to maintain steady state concentration level [6-9].

In the present study, an attempt is made to reduce the dosing frequency and to enhance patient compliance by formulating an extended-release dosage form for Divalproex sodium using combination polymers (pH dependent and pH independent) [10]. Direct Compression method considered to be widest method of tablet manufacturing, as seen in many cases [11-14].

MATERIALS & METHODS

Divalproex sodium was procured form Krishna Pharmaceuticals, Hyderabad, Telangana, India as a complementary sample. Eudragit L/100-55 and HPMC K100M were purchased from commercial sources. Marketed samples were obtained from Manchineni Pharmacy, Guntur, Andhra Pradesh, India.

Preparation of Divalproex modified release tablets

500 milligrams of Divalproex was considered as dose for each tablet, an equivalent of 523 milligrams of Divalproex sodium was taken instead of Divalproex. Tablets were prepared by direct compression technique. Various ingredients were taken as per the formula for the preparation of tablets (**Table 1**).

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 evaluated for quality control tests [13].

Table 1. Formulae for the preparation of Divalproex sodium modified release tablets

Name of Ingredients	Quantity per tablet (mg)								
	DEH_1	**DEH_2**	**DEH_3**	**DEH_4**	**DEH_5**	**DEH_6**	**DEH_7**	**DEH_8**	**DEH_9**
Divalproex sodium	523	523	523	523	523	523	523	523	523
Starch	18.5	25	31	25	31	37	31	37	43.5
Emcompress	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
HPMC K100M	43.75	31.25	18.75	43.75	31.25	18.75	43.75	31.25	18.75
Talc	7	7	7	7	7	7	7	7	7
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	660	660	660	660	660	660	660	660	660

Evaluation of Divalproex sodium extended-release formulations

Crushing strength

The hardness of tablets was measured as per diametric break down when operated with Monsanto apparatus.

Friability test

The friability test was carried out with the help of friabilator. Twenty 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 free-falls. The weight of tablets was taken again and recorded as W_1. Percentage weight loss was measured as per following equation:

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

Estimation of drug content

Twenty tablets were selected randomly and pulverized to obtain fine orientation. An amount which is equivalent to 100 mg of drug, was taken into volumetric flask and then, 100 ml of pH 1.2 buffer was added to get the drug dissolved. The resultant solution was subjected to estimate the amount of Divalproex by means of spectro-photometry at 210 nm.

Drug release rate study

Release rate study was determined as per the drug dissolution, which was carried out with the help of Tablet dissolution test apparatus (USP-23) containing Paddle as rotating mechanism. It simulates the physiological environment by maintaining the volume of dissolution media 900 ml (pH 1.2 buffer as SGF for first 2 hours;

phosphate buffer for subsequent time intervals up to end of the current study). Temperature maintained throughout the study period is constant (37±0.5°C). The apparatus was run as per the standard guidelines i.e. 50 rpm as agitation rate. Various samples were collected by virtue of time as per the standard methods specified in monograph. Obtained samples were estimated for drug release using spectro-photometer at 210 nm. This was repeated to get triplicate result [3, 15]. Results of drug release rate were subjected to kinetic modeling to know drug release pattern from formulation [12-13].

RESULTS AND DISCUSSION

Modified release formulations of Divalproex were prepared using combination of Eudragit L/100-55 and HPMC K100M and to find out the combined effect on the release rate of Divalproex from the tablet. Totally nine formulations were designed and prepared (**Table 1**). All trials have Divalproex sodium 523 mg equivalent to 500 mg Divalproex, as an extended-release tablet dosage form prepared using direct compression method. Prepared tablets were subjected to evaluation tests. All tablets were found to be of adequate hardness. All batches were found to be less friable. All formulations passed the weight variation test as well as drug content. Drug release rate study was performed as per IP (**Table 2**). Results of dissolution study were subjected to kinetic evaluation to know the drug release pattern (**Table 3**, **Figure 2**).

After observing the results, majority of the formulations followed zero order kinetics, based on comparative regression analysis. It was observed that the existence of relation between HPMC K100M and Eudragit L/100-55 showed significant effect on the drug release of Divalproex. Modified release was obtained from suitable composition of combined agents (**Table 4**). The combined effect of various compositions of HPMC K100M and Eudragit L/100-55 on the Divalproex sodium release were studied using Contour plots that were constructed using Sigmaplot V13 (**Figure 3**).

DEH_5 was concluded as ideal formulation when compared to other formulations. Equal amounts of HPMC K100M, Eudragit L/100-55 (31.25 mg each) showed good dissolution characteristics, which helps in meeting the purpose of research by modified/optimum delivery of drug from dosage form. DEH_5 has 85.75 % similarity and 2.29 % difference (t_{cal}<0.05) with respect to DIVALEX. Comparative zero order graphs for DEH_5 and DIVALEX are shown in **Figure 4**.

Table 2. Post-compression parameters for the formulations (n= 3)

Batch code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
DEH_1	8.49±0.31	4.01±0.1	0.10±0.001	99.95±0.5
DEH_2	8.22±0.32	3.96±0.09	0.11±0.001	99.44±0.51
DEH_3	7.99±0.21	3.92±0.08	0.09±0.001	99.12±0.50
DEH_4	8.52±0.46	4.06±0.05	0.06±0.001	99.75±0.33
DEH_5	8.11±0.40	4.07±0.05	0.07±0.001	99.99±0.35
DEH_6	7.7±0.42	3.99±0.04	0.07±0.001	99.12±0.32
DEH_7	8.4±0.4	4.21±0.04	0.05±0.001	99.71±0.42
DEH_8	7.93±0.42	4.09±0.07	0.04±0.001	99.24±0.46
DEH_9	7.5±0.40	4.04±0.05	0.05±0.001	98.71±0.38

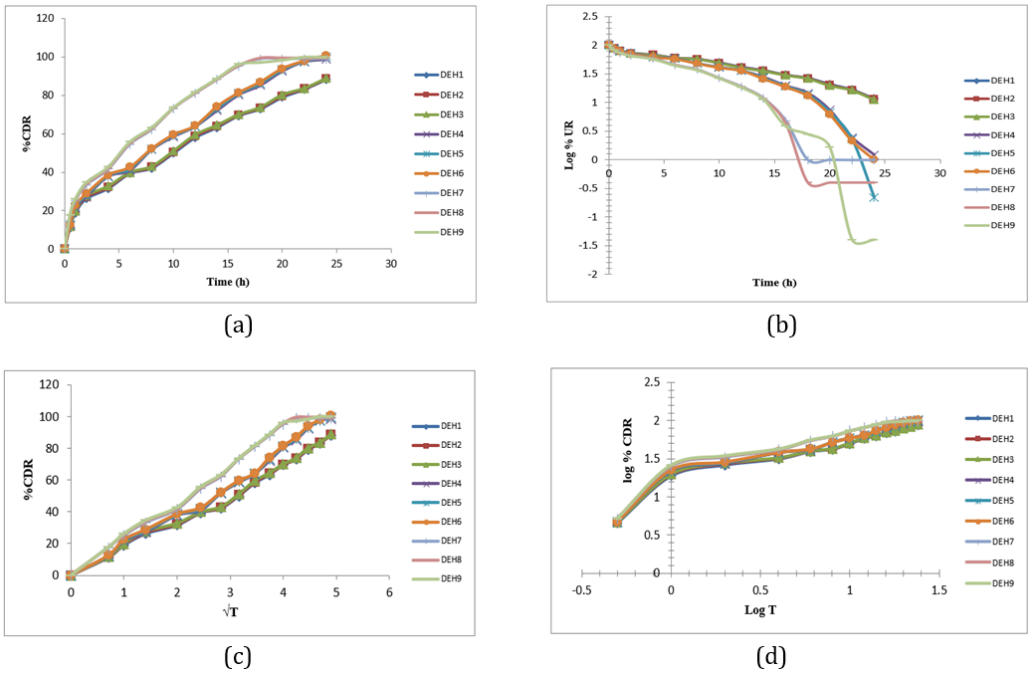
Table 3. Regression analysis data

Formulation code	Kinetic Parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
DEH_1	14.42	3.27	0.983	1.990	0.034	0.986	1.685	17.614	0.995	1.089	0.629	0.962
DEH_2	14.87	3.28	0.982	1.987	0.034	0.986	1.308	17.641	0.995	1.098	0.625	0.959
DEH_3	15.30	3.29	0.980	1.984	0.034	0.986	0.930	17.667	0.995	1.107	0.621	0.957
DEH_4	15.96	3.81	0.983	2.111	0.065	0.931	2.738	20.473	0.995	1.125	0.651	0.960
DEH_5	16.32	3.83	0.985	2.172	0.077	0.877	2.481	20.560	0.995	1.132	0.655	0.958
DEH_6	16.67	3.84	0.980	2.118	0.068	0.931	2.224	20.646	0.995	1.138	0.647	0.956
DEH_7	23.40	3.96	0.951	2.111	0.093	0.964	2.240	21.685	0.992	1.199	0.641	0.950
DEH_8	23.79	3.94	0.950	2.186	0.110	0.949	2.539	21.742	0.993	1.204	0.638	0.948
DEH_9	24.30	3.91	0.947	2.287	0.124	0.915	3.157	21.565	0.993	1.210	0.634	0.945

a - Intercept; b - Slope; r - Correlation coefficient

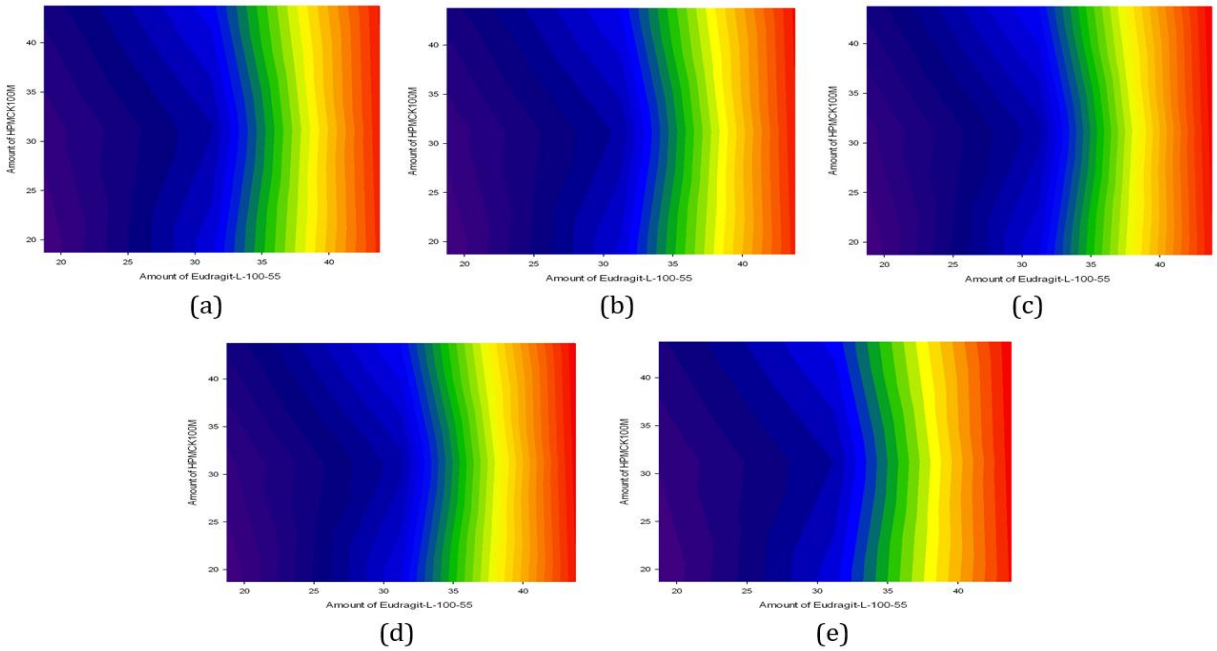
Table 4. Dissolution parameters for formulations

Formulation code	Dissolution Parameters				
	$t_{10\%}$ (h)	$t_{25\%}$ (h)	$t_{50\%}$(h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
DEH_1	1.360	3.71	8.98	17.94	29.79
DEH_2	1.351	3.667	8.86	17.73	29.46
DEH_3	1.339	3.636	8.79	17.52	29.12
DEH_4	0.719	1.919	4.61	9.21	15.31
DEH_5	0.605	1.627	3.92	7.84	13.03
DEH_6	0.669	1.82	4.40	8.80	14.62
DEH_7	0.51	1.349	3.249	6.45	10.75
DEH_8	0.419	1.15	2.726	5.43	9.04
DEH_9	0.368	1.02	2.425	4.82	8.02



(a) (b) (c) (d)

Fig. 2. (a) Comparative zero order plots (b) Comparative first order plots (c) Comparative Higuchi plots (d) Comparative Korsmeyer-Peppas plots



(a) (b) (c) (d) (e)

Fig. 3. Contour plots for (a) $t_{10\%}$, (b) $t_{25\%}$, (c) $t_{50\%}$, (d) $t_{75\%}$ and (e) $t_{90\%}$

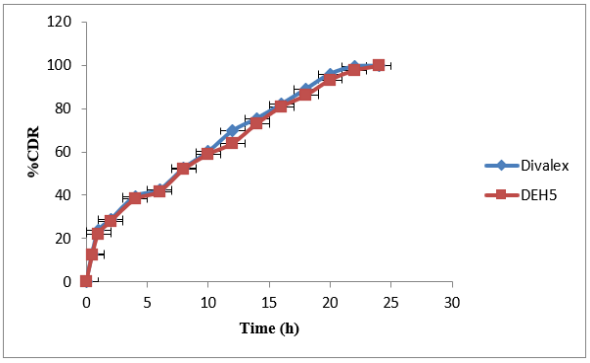


Fig. 4. Dissolution profiles for DEH_5-DIVALEX

CONCLUSION

The formulation (DEH_5) composed of combination of HPMC K100M, Eudragit L/100-55 in equal ratio (31.25 mg each) at 6.25 % provided almost similar drug release from the formulation as compared to DIVALEX. DEH_5 showed non-Fickian zero order release for Divalproex. Due to its prolonged pattern of drug release, it may reduce the frequency of administration to two-folds. It may also promote patient compliance and clinical outcome.

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