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Formulation Development and *in vitro* Release Kinetics of Divalproex Sodium Sustained Release Matrix Tablet

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Divalproex sodium sustained release (SR) matrix tablet has been prepared with different polymers like HPMC K15M, ethyl cellulose, sodium CMC. When the polymer content in the formulation increases, the rate of release becomes more controlled and achieves the desirable limit. The same pattern has been observed incase of all three polymers. No significant difference has been observed between HPMC K15M and sodium CMC towards it's dissolution pattern. The weights, hardness, thickness, percentage friability of the matrix tablets have been found to be identical. It is further observed that inter and intra granulation does not make much variation in release profiles of matrix tablets. The different kinetic models like zero order, first order, Higuchi have been computed with experimental results and the release kinetics largely corroborate the good fitting obtained with Higuichi's model.

Key Words: Divalproex sodium, Sustained release, Matrix tablet, HPMC, Ethyl cellulose, Sodium CMC.

INTRODUCTION

Divalproex sodium[1] is a stable coordination compound comprising of sodium valproate and valproic acid in a 1:1 molar relationship. Divalproex sodium is carboxylic acid derivative, anticonvulsant that also is used to treat acute manic episodes or for prophylaxis of migraine, headache as well as certain other psychiatric disorders.

Chemically, it is designated as sodium hydrogen *bis*(2-propylpentanoate) (Fig. 1)[1,2]. Divalproex sodium exists as crystalline aggregates that appear as waxy white flakes with melting point of approximately 100 ºC. It is stable in the solid state and dissociates to the valproate ion in the gastrointestinal tract before being absorbed. A controlled release dosage

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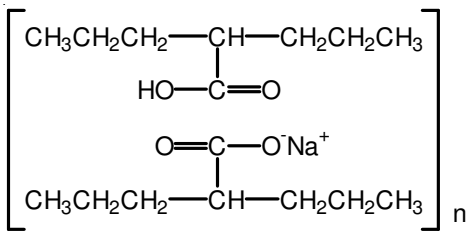

Fig. 1. Chemical structure of divalproex sodium

form may provide increased clinical value over conventional formulations as a result of improved patient compliance, a decreased incidence and/or intensity of the side effects and a more constant or prolonged therapeutic effect. It is one of the most widely used bipolar and anti-epileptic agents[3]. Due to short biological half life, the conventional formulation of divalproex sodium must be taken orally twice or three times daily to maintain the effective blood concentration of 40 to 120 μgm/mL. Patients usually take antiepileptic drug for years with a high level of compliance in order to control clinical seizures. Less frequent dosing, *e.g.*, once a day, is desirable for both therapeutic and psychological reasons[1].

The objectives of the present study were to design a sustained-release tablet formulation of divalproex sodium intended for once-daily administration and to study the role of cost-effective polymer like sodium CMC in comparison with HPMC and ethyl cellulose on modified pharmaceutical solid dosage formulations. Various kinetic models like zero-order, first-order and Higuchi were computed with the experimental data to evaluate release kinetics of matrix tablet of divalproex sodium.

EXPERIMENTAL

Valproic acid and sodium valproate were gifted from A.N. Pharmacia. HPMC K15M, lactose, ethyl cellulose, colloidal SiO_2, magnesium stearate were obtained from Dey's Medical Stores (Mfg.) Ltd. KH_2PO_4, acetonitrile and orthophosphoric acid were of analytical grade and purchased from Merck, India.

Preparations of sustained release matrix tablets: Sodium valproate and valproic acid were mixed in molar ratio and settled for two to 3 h. Then the product (divalproex sodium) was grinded. The matrix tablets each containing 500 mg of valproic acid were prepared by wet granulation as per the schedule given in Table-1. The polymer was dry mixed with drug and other excepients in the high shear mixer for 20 min. Wet granules were prepared by adding 80 mL/Kg of granulation fluid and screening through 10 mesh sieve followed by drying at 55 ºC up to the moisture content of not more

than 1 %. The dried granules were screened through a 20-mesh sieve and blended with lubricating materials for 10 min for formulation F1 to F12 and for formulation F13, which is of same composition as formulation F5, dried granules were mixed with inter-granulating materials and lubricating materials for 10 min. 1.152 g of tablets were compressed using rotary tablet machine with an oval punch of hardness 6.5-7.5 kg/cm^2. The prepared matrix tablets were subjected to drug release testing[1].

TABLE-1
COMPOSITION OF VARIOUS FORMULATIONS OF
DIVALPROEX SODIUM SR MATRIX TABLET

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Divalproex sodium (%)	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7	46.7
HPMC K15M (%)	30.0	25	22.5	20.0	15.0	10.0	30.0	35.0	40.0	-	-	-	15.0
Ethyl cellulose (%)	-	5.0	7.50	10.0	15.0	20.0	-	-	-	-	-	-	15.0
Sodium CMC (%)	-	-	-	-	-	-	-	-	-	30.0	35.0	40.0	-
Lactose (%)	21.3	21.3	21.3	21.3	21.3	21.3	5.0	5.0	5.0	21.3	16.3	11.3	21.3
MCC (%)	-	-	-	-	-	-	16.3	11.3	6.3	-	-	-	-
Magnesium stearate (%)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talcum (%)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Total weight (mg)	1152	1152	1152	1152	1152	1152	1152	1152	1152	1152	1152	1152	1152

Tablet characterization: The tablets were characterized immediately after preparation. The weight variation of the tablets was evaluated on 20 tablets according to official method[4] using an electronic balance (Sartorius GC 103). Friability was determined using 10 tablets in a Roche friabilator for 4 min at a speed of 25 rpm. For each formulation the hardness of 10 tablets was also evaluated using a Monsanto hardness tester (Campbell Electronics, India). The thickness of the tablets was measured on 10 tablets with a vernier caliper (Mitutoyo, Japan).

***in vitro* Drug release study:** The *in vitro* release rates of valproic acid from matrix tablets were determined using the USP apparatus I at 100 rpm and a temperature of 37 ± 0.5 °C. Release testing was carried out in 900 mL of 0.1 M HCl for the first 2 h followed by 900 mL of pH 6.8 phosphate buffer for next 10 h. Samples of 2 mL were withdrawn at 1 h interval up to 12 h and replaced with an equal volume of the fresh medium. Valproic acid calibrators consisting of 6 standard concentrations (range 15-250 mgm/mL) were used to perform an assay specific calibration prior to sample analysis. The samples were filtered through 0.45 μm filter paper and were analyzed

by HPLC with UV detector at 220 nm. The mobile phase consisting of mixture of acetonitrile and phosphate buffer at pH 3 at the ratio of 45:55 (v/v) at flow rate of 1.2 mL/min. Quantification of the compounds was carried out by measuring the peak areas in relation to those of standard chromatograph under the same conditions[5-7].

Drug content studies: 20 Tablets were taken and crushed to powder with mortar and pestle. Exact amount of powder equivalent to 100 mg valproic acid was taken and diluted with water up to 100 mL of volumetric flask. After sonication for 15 min, solution was filtered through 0.45 μm filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of test solution by using the HPLC method as described above against the reference solution of pure valproic acid prepared in the same procedure.

Release kinetics: Several mathematical models can be used to describe the kinetic behaviour of the drug release mechanism from matrix tablets, the most suitable being the one that best fits the experimental results. The choice of a specific model for a particular data set depends on the shape of the plot obtained, as well as on the underlying mechanism.

The kinetics of valproic acid release from matrix tablets was determined by finding the best fitting of the dissolution data (amount of drug released *vs.* time) to the following kinetic equations:

$$\text{Zero-order equation: } Q_t = Q_0 + k_0 t \quad (1)$$

where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero order release rate.

$$\text{First-order equation: } \ln Q_t = \ln Q_0 + k_1 t \quad (2)$$

where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

$$\text{Higuchi's equation}[8]\text{: } Q = k_H t^{1/2} \quad (3)$$

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

RESULTS AND DISCUSSION

Tablet characteristics and drug content: The tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, friability and drug content test. The results of these parameters are given in Table-2. All the formulations showed uniform thickness. Average weight was around 1.152 g with maximum standard deviation (SD) of 0.98. Good uniformity in drug content was found among different batches of tablets. Tablet hardness is not an absolute indicator of strength[8]. Another measure of a tablet's strength is friability. Conventional compressed tablet

TABLE-2
PHYSICAL CHARACTERIZATION OF MATRIX TABLETS

Formulation	Weight† (g)	Hardness‡ (Kg/cm^2)	Thickness‡ (mm)	Friability‡ (%)	Drug† content (mg)
F1	1.1502 (0.98)	7.45 (0.78)	7.64 (0.08)	0.85	502.23 (0.23)
F2	1.1478 (0.85)	7.15 (0.96)	7.61 (0.06)	0.65	498.56 (1.05)
F3	1.1512 (0.75)	6.95 (0.42)	7.59 (0.11)	0.74	503.35 (0.85)
F4	1.1520 (0.68)	7.35 (0.58)	7.62 (0.02)	0.95	497.13 (0.78)
F5	1.1495 (0.78)	7.45 (0.85)	7.65 (0.06)	0.78	500.55 (0.92)
F6	1.1489 (0.96)	7.25 (0.78)	7.60 (0.05)	0.84	502.26 (1.56)
F7	1.1515 (0.64)	6.95 (1.05)	7.62 (0.07)	0.58	501.85 (1.04)
F8	1.1506 (0.76)	6.95 (0.96)	7.64 (0.10)	0.85	497.54 (0.85)
F9	1.1497 (0.89)	6.85 (0.84)	7.63 (0.08)	0.94	497.56 (1.64)
F10	1.1488 (0.55)	7.10 (0.79)	7.59 (0.04)	0.76	498.25 (1.25)
F11	1.1509 (0.75)	7.45 (0.79)	7.63 (0.09)	0.79	500.20 (0.95)
F12	1.1523 (0.96)	7.25 (0.92)	7.64 (0.12)	0.84	499.56 (1.25)
F13	1.1543 (0.73)	7.25 (1.06)	7.63 (0.06)	0.69	496.23 (0.93)

†All values are expressed as mean ± SD (Standard deviation), n = 20.
‡All values are expressed as mean ± SD (Standard deviation), n = 10.

that lose < 1 % of their weight are generally considered acceptable. In present study, the percentage friability was below 1 %, indicating it to be within the prescribed limits[9].

Dissolution samples were analyzed by HPLC method. The calibration curve of valproic acid was linear within the range of 15 to 250 mcg/mL (Fig. 2). *in vitro* drug release from matrices (F1 to F6) containing polymers are shown in Fig. 3. The mechanism of drug release from matrix system involves polymer swelling/erosion and Fickian diffusion of the drug. Release kinetics of hydrophilic and hydrophobic systems has been studied extensively and is dependent upon the solubility, dose and diffusivity of drug, as well as different characteristics of the rate controlling polymers. The proportions of other excepients added[10-12] also affect the release kinetics to some extent.

By reviewing the *in vitro* drug release profile of various formulations, it is evident that tablets of formulations F1, F2, F3 show releases of drug more than 80 % within 3-4 h which does not conform with the guidelines of sustained release drug delivery system as per USP. The drug release profile depicted by formulations F4 and F5 gives a comparatively satisfactory result. The formulation F6 also shows very slow release profile having 75 % release in 12 h. But compared between the two F4 and F5, the release profile of F5 is more acceptable than F4 where the polymers-ethyl cellulose and HPMC K15M in equal ratio have been used. It is further evident that

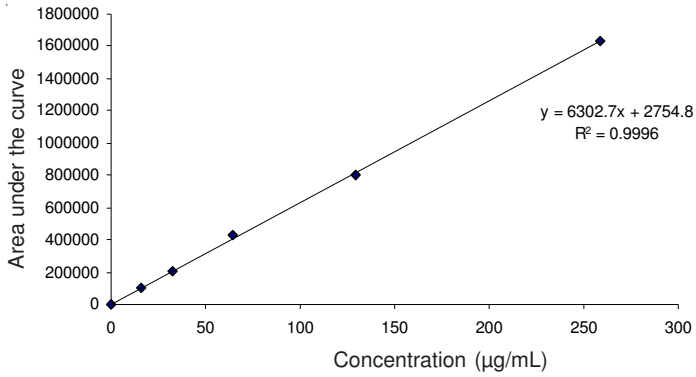

Fig. 2. Calibration curve of raw valproic acid

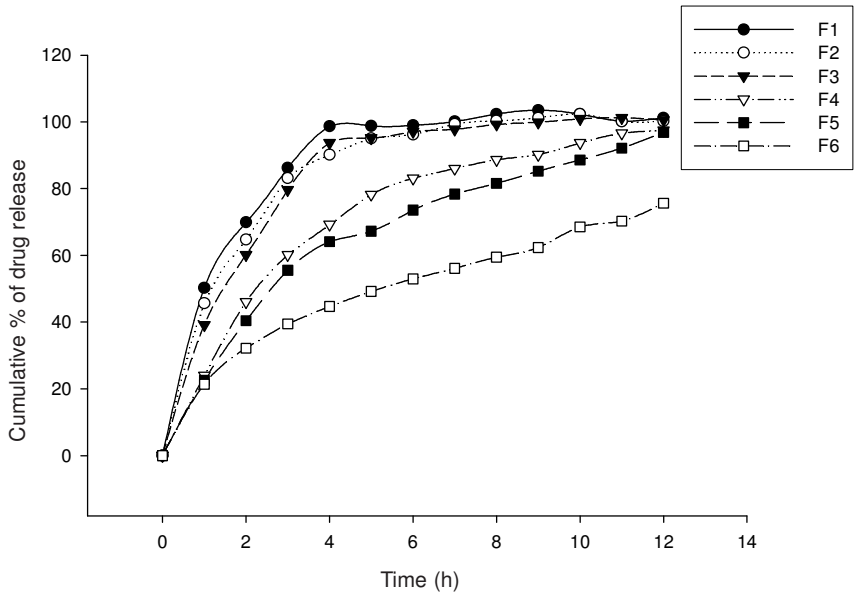

Fig. 3. Cumulative percentage of drug release *vs.* time for SR matrix tablet (F1 to F6)

as the content of ethyl cellulose in the matrix increases the release of drug decrease. Since ethyl cellulose is more expensive, the other cheaper polymers like HPMC K15M and sodium CMC have been tried to prepare matrix tablets, the release profiles of which are illustrated in Fig. 4 and 5. As usual due to the variation of polymer content the release also varies. Moreover almost identical release characteristics have been obtained in both cases of HPMC K15M and CMC matrix tablets. But preference has been given to CMC tablets due to its low cost.

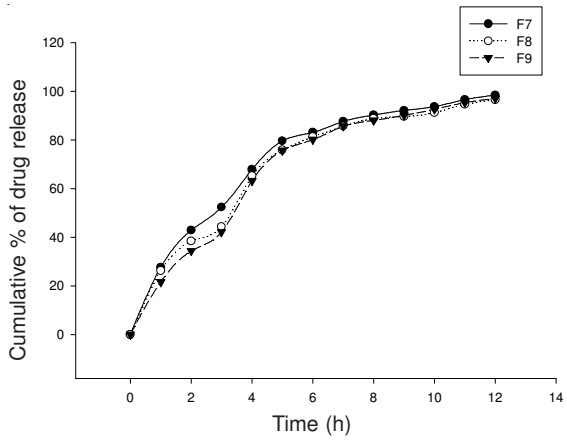

Fig. 4. Cumulative percentage of drug release *vs.* time for SR matrix tablet (F7 to F9)

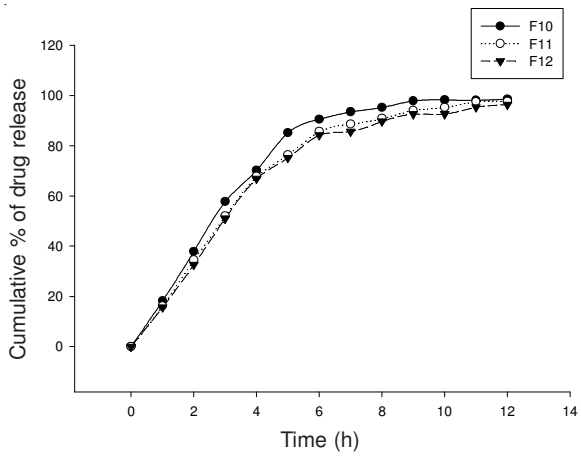

Fig. 5. Cumulative percentage of drug release *vs.* time for SR matrix tablet (F10 to F12)

It is further evident that as the content of polymer in the matrix increases, the release of drug decreases. By comparing the release profile of formulations it is evident that 35 % polymer has given optimum release of drug.

By reviewing the *in vitro* release profiles it is found that formulation F5, F8 and F11 showed (Fig. 6) most satisfactory release profiles. As the variation among them is not significant, the CMC matrix tablet may be commercialized due to its cost-effectiveness.

Release kinetics: The kinetic study was carried out for all formulations except F1, F2 and F3 due to their extremely fast drug release kinetics. Different types of rate constants and regression values were shown in Table-3. Both diffusion and erosion could contribute to the drug release process from

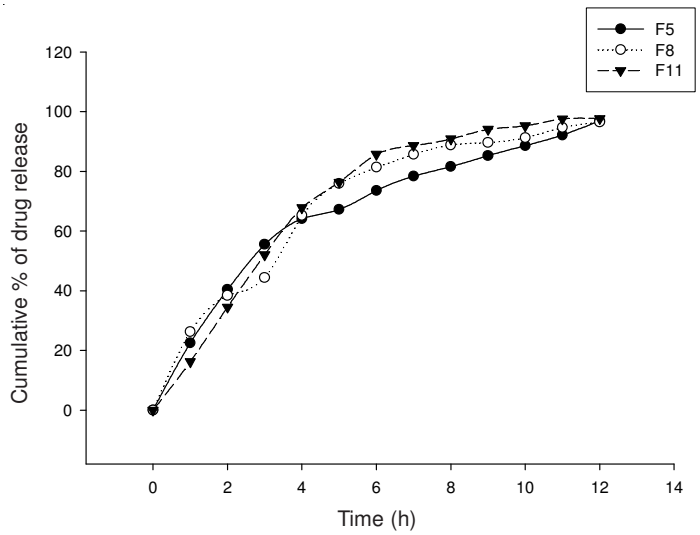

Fig. 6. Cumulative percentage of drug release *vs.* time for SR matrix tablet (F5, F8 and F11)

TABLE-3
in vitro RELEASE KINETICS (ANALYZED BY REGRESSION COEFFICIENT METHOD) OF DIFFERENT TRIAL FORMULATIONS

Polymer used	Formulation	Zero order		First-order		Higuchi	
		k_0 (% h^{-1})	R^2	k_1 (h^{-1})	R^2	k_H (% $h^{-½}$)	R^2
Ethyl cellulose & HPMC K15M	F4	7.0061	0.8150	0.0941	0.6881	19.398	0.9613
	F5	6.9057	0.8706	0.1000	0.7540	28.366	0.9840
	F6	5.2106	0.9070	0.0946	0.8743	21.101	0.9964
	F13	7.2834	0.8929	0.1164	0.7484	29.531	0.9833
HPMC K15M	F7	7.2001	0.8355	0.0954	0.7565	29.936	0.9676
	F8	7.2807	0.8520	0.1035	0.7736	29.930	0.9646
	F9	7.6223	0.8684	0.1172	0.7611	31.003	0.9625
Sodium CMC	F10	7.7505	0.7977	0.1148	0.6382	32.350	0.9309
	F11	7.8047	0.8411	0.1243	0.6714	32.058	0.9506
	F12	7.6777	0.8405	0.1260	0.6695	31.515	0.9407

R^2 = Regression coefficient.

matrix tablets. In fact, it is well known that water-soluble drugs are released mainly by diffusion across the gel layer, while barely water-soluble drugs are predominately released by attrition mechanism[13]. The mechanism of drug release from swellable matrix system is complex and is not completely understood. Some process could be characterized as either purely diffusional or purely erosion controlled, several others could only be rationalized as being due to coupling of both. Results of *in vitro* drug release are largely

corroborated by the good fitting obtained with Higuichi's model. All the tested kinetic models were well fitted ($R^2 > 0.9$), in particular the Higuchi one.

Conclusion

It may be concluded that sustained release characteristics of matrix tablets are achieved when the hydrophobic and hydrophilic polymers such as ethyl cellulose and HPMC are used in equal proportion keeping the compressional pressure constant. It is further evident that as the content of ethyl cellulose in the matrix increases, the release of drug decrease. Since ethyl cellulose is more expensive, the other cheaper polymers like HPMC K15M and sodium CMC have been tried to prepare matrix tablets. Moreover, almost identical release characteristics have been obtained both in case of HPMC K15M and CMC matrix tablets. But preference has been given to CMC tablets due to its low cost.

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