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Design, Formulation and evaluation of sustained release tablet of divelproex sodium

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ABSTRACT

In the present work, formulation and evaluation of Sustained tablet of Divalproex sodium was carried out. In the project, different formulations of sustained release layer have been prepared. From above formulations best formulation of each sustained release was selected according to the dissolution profile. Divalproex sodium is soluble in 0.1 N NaOH, phosphate buffer pH 6.8, chloroform, methanol, ethanol (95%), and sparingly soluble in water. The absorbance maximum of the Divalproex sodium was found to be at 210 nm when scanned in between 200-400 nm using methanol as well as phosphate buffer pH 6.8 solutions. All the characteristic peaks of Divalproex sodium were present in the spectrum of drug and excipient mixture, indicating compatibility between drug and excipients. In the present work SR tablets of Divalproex sodium were prepared by wet granulation method, using polymer like HPMC K4M for sustained release. Best formulations of was selected for Divalproex sodium were subjected to hardness, weight variation, friability, drug content uniformity, *in vitro* drug release and drug polymer interaction.

Keywords: Divalproex sodium, Sustained Release, HPMC and Epilepsy.

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1. INTRODUCTION

Epilepsy is a common chronic neurological disorder that is characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain9Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established.[1-3] It has been suggested that its activity in epilepsy is related to increased brain concentrations of Gamma-Amino Butyric Acid (GABA). The absolute bioavailability of Divalproate ER tablets administered a single dose after a meal was approximately 90% relative to intravenous infusion. Formulation of Divalproex sodium ER tablets expected to reduce Divalproex sodium ER is used by patient for treatment of chronic epilepsy.[4] So reduces the frequent administration of dose (twice in a day), avoids first pass metabolism, improved patient compliance, maintain therapeutic action by administration of a single dose in a day

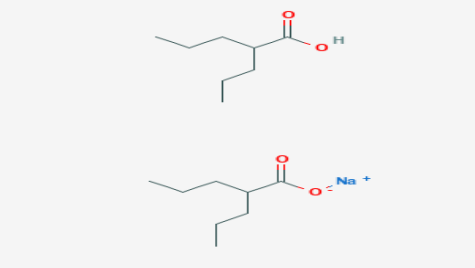
For reasons discussed, a short half-life (i.e., ≤8 hours) is not necessarily synonymous with a short duration of action. In fact, even with rapidly distributed and reversibly acting drugs, the duration of action is dependent not only on half-life but also on the size of the dose[5]. Additionally, it may be incorrect to assume that an even serum concentration profile is more beneficial than a profile consisting of peaks and troughs. Only well-controlled studies can determine which frequency of administration is optimal and whether any benefit can be expected from an extended-release formulation[6-9].

2. MATERIALS AND METHOD:

2.1 Drug profile:

Divalproex Sodium is a stable coordination compound comprised of sodium valproate and valproic acid with anticonvulsant and antiepileptic activities. Divalproex dissociates to the valproate ion in the gastrointestinal tract.[10]

2.2 Description of drug molecule (Divalproex Sodium):



(Fig 2.1: Chemical structure of Divalproex Sodium)[10]

2.3 Preparation of standard calibration curve of Divalproex Sodium[11,12]

10 mg of drug was dissolved in 0.1 N NaOH and final volume was make up to 100 ml in 100 ml volumetric flask. The staock solution concentration was 100 mcg/ml obtained. It was diluted with 0.1 N NaOH to obtain solution of Concentration range10 to 60 µg/ml. Absorbance of µg/ml solution was measured at 200-400 nm by using of Shimadzu UV-1601 UV/Vis double beam spectrophotometer and 0.1 N NaOH as reference standard.

2.4 Melting point determination

The Melting point of Divalproex Sodium was determined using open capillary method[12].

2.5 FTIR Spectra of pure drug

Infrared spectroscopy analysis of Divalproex Sodium pure drug was performed by Fourier transfer infrared spectroscopy[13].

2.6 Differential scanning calorimetry

The DSC of Tablet was recorded by differential scanning calorimeter equipped with a computerized data station[14].

2.7 Solubility Studies

The solubility of Divalproex sodium was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method[13].

3. EVALUATION OF DIVALPROEX SODIUM POWDER BLEND (PRE-COMPRESSION PARAMETERS)[14-19]

3.1 Angle of Repose

The angle of repose of powder was determined by the funnel method.

$$Tan\ \theta = h/r,$$

Where θ = angle of repose, h = height of the cone, r radius of the cone base.

3.2 Bilk Density

A quantity of 10 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulkdensity was calculated using following formula:

Bulk density= Weight of granules/ Volume of granules

3.3 Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula:

Tapped density= Weight of granules/ Volume of granules after 100 tapping

3.4 Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula:

Tapped density= Weight of granules/ Volume of granules after 100 tapping

3.5 Hausner's ratio

Hausner's ratio value is less than 1.25 indicates good flow and greater than 1.5 indicates poor flow property which was calculated by using following formula:

Hausner's ratio = Tapped density/ Bulk density

4. FORMULATION DESIGN:

4.1 Preparation of sustained release formulation[20-23]:

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortar and pestle and mixed well. The powders were mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 50^{0}C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 275 mg each tablet by adjusting hardness.

Table 1: Formulation of Sustained Release (SR) Tablet

S. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
1	Divalproex sodium	150	150	150	150	150	150	150	150
2	Lactose dehydrogenase	52	45	37	52	45	37	52	45
3	HPMC K4M	45	52	60	-	-	-	22	26
4	HPMC K100M	-	-	-	45	52	60	22.5	26
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20
6	Magnesium stearate	2	2	2	2	2	2	2	2
7	Talc	6	6	6	6	6	6	6	6
8	Total	275	275	275	275	275	275	275	275

4.2 Evaluation of prepared formulations (Divalproex sodium SR tablet) [24-27]

The tablets prepared were evaluated for the following parameters:

4.2.1 Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

4.2.2 Hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester.

4.2.3 Friability

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Percentage friability was calculated by using the formula.

$$\% \ Friability = \frac{Initital\ Weight - Final\ Weight}{Weight\ Initial} \times 100$$

4.2.4 Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation

4.3 *In Vitro* dissolution studies

The release rate Divalproex sodium SR tablet (n=3) was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 75 rpm.[28]

4.4 Accelerated stability study of the optimized batch[29]

The tablets of batch F5 were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 3 months in a humidity jar. Drug dissolution profile of exposed sample was carried out.

5. RESULT AND DISCUSSION:

5.1 Standard Calibration Curve (CC) of divalproex Sodium in 0.1 N NaOH

Table 2 Standard CC of Divalproex Sodium in 0.1 N NaOH

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	10	0.128	0.124	0.132	0.128
2	20	0.299	0.292	0.305	0.299
3	30	0.402	0.404	0.401	0.402
4	40	0.582	0.578	0.587	0.582
5	50	0.778	0.769	0.783	0.778
6	60	0.921	0.916	0.925	0.921
Correlation Co-efficient (R^2) = 0.9944 Absorbance(y) = 0.0159_xconc - 0.0399					

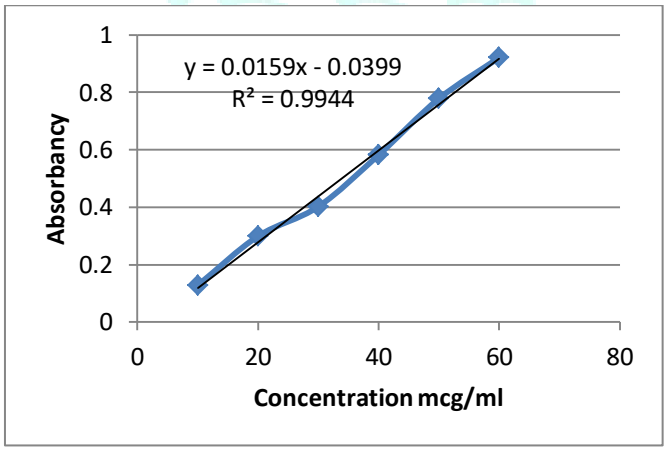


Fig 5.1 Drug calibration curve in NaOH 0.1 N.

5.2 Melting point

The average melting point of pure drug is 222^{0}C which is complies with Stander melting point of drug.

5.3 Drug Excipient Compatibility Studies

5.3.1 FTIR Study:

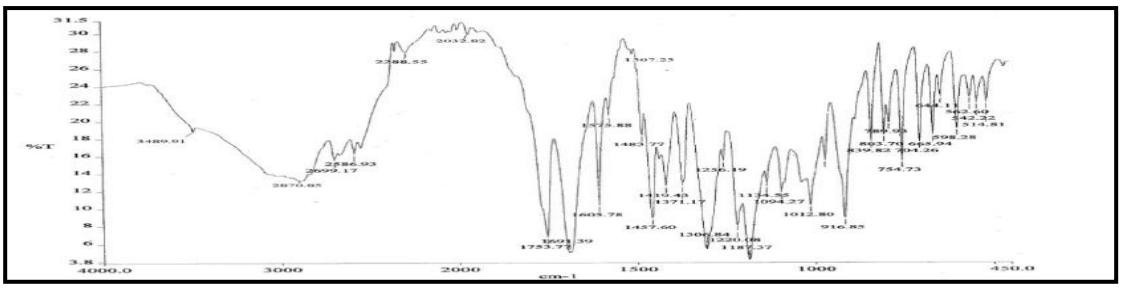


Fig 5.2 FTIR of Drug (Divalproex Sodium)

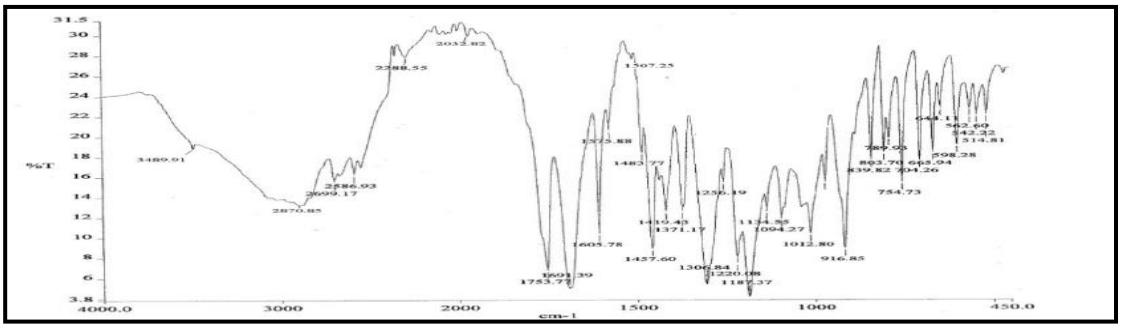


Fig 5.3FTIR of Drug + HPMC

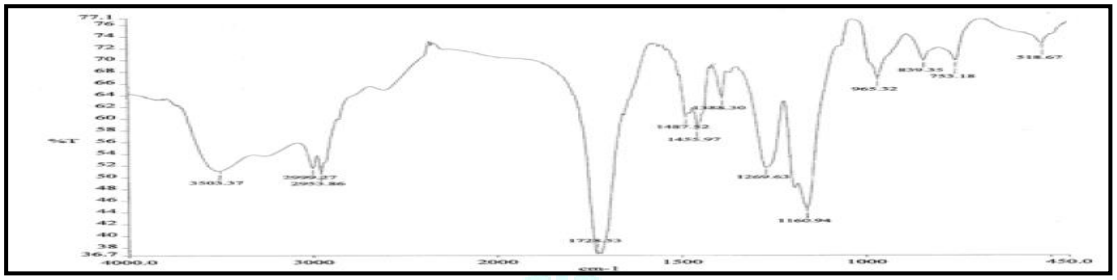


Fig 5.4 FTIR of Drug + Lactose Anhydrous

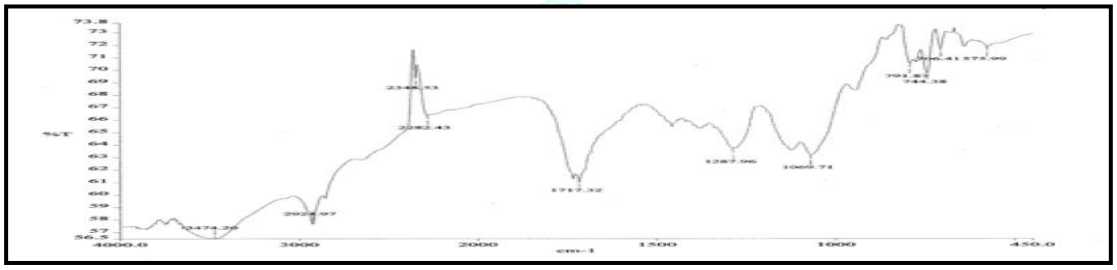


Fig 5.5 FTIR of Drug + Microcrystalline cellulose

5.3.2 Pre Compression Parameter of Formulation:

Table 3: Pre compress parameter

S. No	Parameters	Values obtained
1.	Bulk density (gm/ml)	0.448± 0.007
2.	Tap density (gm/ml)	0.520±0.009
3.	Angle of repose (θ)	28º50'±0.121
4.	Carr's index	13.84 ± 0.21
5.	Hausner's ratio	1.16 ± 0.003

5.3.3 Post Compression Parameter of Formulation:

Table: 3 Physical Characteristics of powder blend					
Formulation code	**Angle of Repose(°)**	**Bulk density**	**Tap density**	**Hausner ratio**	**Carr's Index**
F1	20 ° 28 ± 0.4568	0.374 ± 0.017	0.446± 0.002	1.16± 0.002	14.23± 0.532
F2	21 ° 22 ± 0.5449	0.352 ± 0.013	0.423± 0.003	1.17± 0.004	13.64± 0.368
F3	20 ° 17 ± 0.4225	0.380 ± 0.014	0.417± 0.001	1.18± 0.003	14.20± 0.398
F4	20 ° 14 ± 0.3326	0.360 ± 0.011	0.445± 0.004	1.17± 0.001	14.42± 0.215
F5	21 ° 09 ± 0.8547	0.358 ± 0.019	0.442± 0.004	1.16± 0.003	13.80± 0.309
F6	20 ° 18 ± 0.5226	0.353 ± 0.011	0.424± 0.002	1.15± 0.004	14.78± 0.408
F7	20 ° 54 ± 0.6548	0.364 ± 0.014	0.438± 0.006	1.15± 0.001	12.92± 0.554
F8	22 ° 16 ± 0.5547	0.376 ± 0.016	0.415± 0.002	1.16± 0.001	15.55± 0.612

5.3.4 Dissolution profiles of formulation:

Table 4 Cumulative Drug release (F-1 to F-8)								
Time (hr)	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	5.91	5.18	6.51	5.65	5.02	4.59	4.51	4.15
2	9.23	8.99	7.26	6.22	6.11	5.89	5.36	5.13
3	14.69	13.22	12.56	10.96	9.16	8.04	7.53	6.85
4	19.02	18.57	17.26	15.38	14.04	12.19	11.33	10.34
5	25.12	24.26	22.98	20.26	19.01	17.32	16.09	14.93
6	30.32	29.54	27.52	25.53	23.99	22.05	20.54	18.32
7	36.99	35.36	32.89	30.87	28.31	26.99	24.81	22.97
8	41.94	39.81	38.06	36.04	34.33	32.87	30.86	28.56
9	48.99	47.21	44.88	42.16	40.89	39.56	37.78	35.61
10	53.89	52.69	50.55	48.78	46.65	45.13	43.72	41.91
11	59.71	58.17	56.71	54.75	52.84	51.28	49.09	47.31
12	64.22	62.95	61.13	59.59	57.78	56.11	54.84	52.79
13	70.12	69.27	67.03	65.99	64.03	62.74	61.12	60.04
14	78.99	77.13	74.65	72.22	71.04	69.33	67.99	65.46
15	84.89	83.54	81.12	80.02	78.88	76.35	74.19	72.65
16	89.91	88.15	87.11	86.65	85.12	84.89	83.68	82.21
17	89.95	88.19	87.12	86.67	85.14	84.92	83.71	82.24

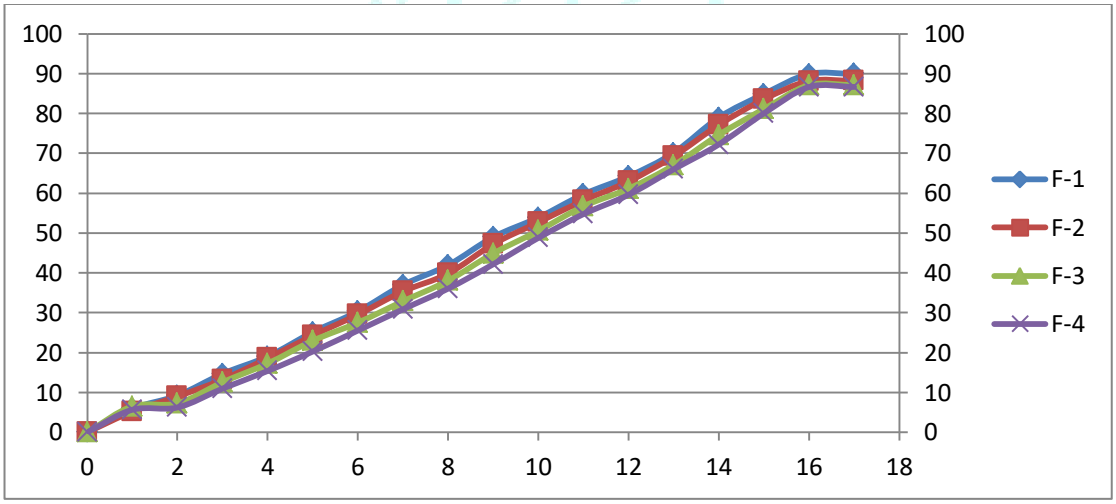


Fig 5.6 Cumulative Release of Formulation F-1 to F-4

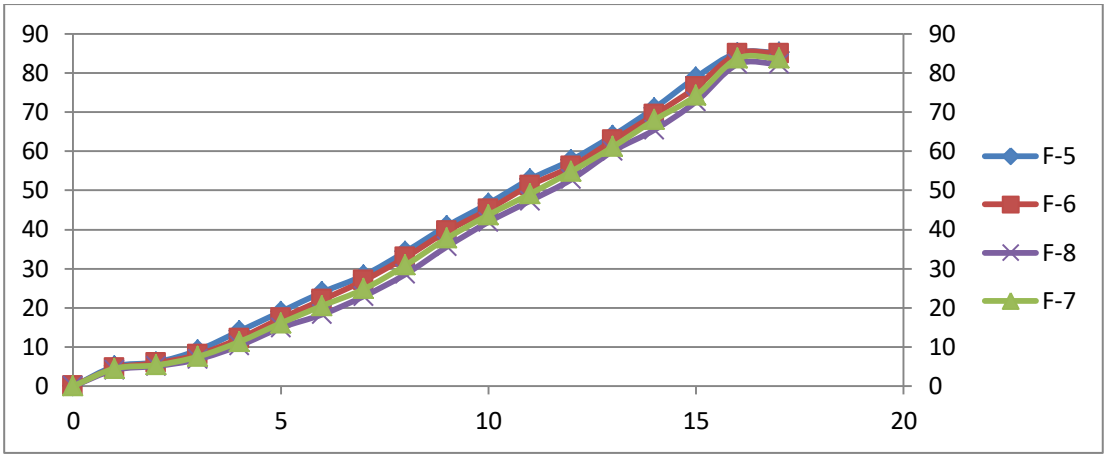


Fig 5.7 Cumulative Release of Formulation F-5 to F-8

5.3.5 Content uniformity of sustained release tablets of Divalproex sodium:

Formulation Code	Content uniformity (%)
F1	99±0.65
F2	98±0.14
F3	98±0.95
F4	98±0.09
F5	99±0.02
F6	99±0.19
F7	98±0.72
F8	99±0.45

6. CONCLUSION:

The FTIR spectra showed that drug and polymer used in formulation of SR tablet are compatible with each other. The average melting point of pure drug is 222^{0}C which is complies with Stander melting point of drug. The pre compress parameter result showed that powder blend of all formulations were good flow properties. The absorbance maximum of the Divalproex sodium was found to be at 210 nm when scanned in between 200-400 nm using methanol as well as phosphate buffer pH 6.8 solutions. Calibration curve of Divalproex sodium in methanol measured at 210 nm showed the slope of 0.0094 and regression coefficient of 0.9995 was recorded.

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