

Available online on 15.07.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Open  Access

Research Article

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

Kusum, Avinash Kumar Gupta, Manish Kumar Gupta, Vijay Sharma

Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Raj, India

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.

Article Info: Received 14 May 2019; Review Completed 24 June 2019; Accepted 28 June 2019; Available online 15 July 2019



Cite this article as:

Kusum, Gupta AK, Gupta MK, Sharma V, Design, Formulation and evaluation of sustained release tablet of divalproex sodium, Journal of Drug Delivery and Therapeutics. 2019; 9(4):382-388 <http://dx.doi.org/10.22270/jddt.v9i4.3063>

*Address for Correspondence:

Kusum, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Raj, India

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 brain. Divalproex 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 dose⁵. Additionally, it may be incorrect to assume that an even serum concentration profile

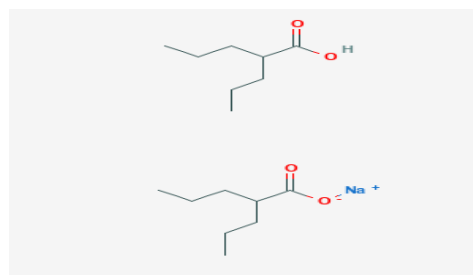
is more beneficial than a profile consisting of peaks and troughs. Only well-controlled studies can determine which frequency of administration is optimal and whether any benefit can be expected from an extended-release formulation⁶⁻⁹.

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 made up to 100 ml in 100 ml volumetric flask. The stock solution concentration was 100 mcg/ml obtained. It was diluted with 0.1 N NaOH to obtain solution of concentration range 10 to 60 µg/ml. Absorbance of µg/ml solution was measured at 200-400 nm by using 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 method¹².

2.5 FTIR Spectra of pure drug

Infrared spectroscopy analysis of Divalproex Sodium pure drug was performed by Fourier transform infrared spectroscopy¹³.

2.6 Differential scanning calorimetry

The DSC of Tablet was recorded by differential scanning calorimeter equipped with a computerized data station¹⁴.

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 method¹³.

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 Bulk 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 bulk density was calculated using following formula:

$$\text{Bulk density} = \text{Weight of granules} / \text{Volume of granules}$$

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:

$$\text{Tapped density} = \text{Weight of granules} / \text{Volume of granules after 100 tapping}$$

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:

$$\text{Tapped density} = \text{Weight of granules} / \text{Volume of granules after 100 tapping}$$

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:

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

4. FORMULATION DESIGN:

4.1 Preparation of sustained release formulation²⁰⁻²³:

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 through sieve # 16 and the granules were dried in a hot air oven at 50°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 weighed 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.

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

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 $37 \pm 0.5^\circ\text{C}$ and 75 rpm.²⁸

4.4 Accelerated stability study of the optimized batch²⁹

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

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) = 0.0159xconc - 0.0399

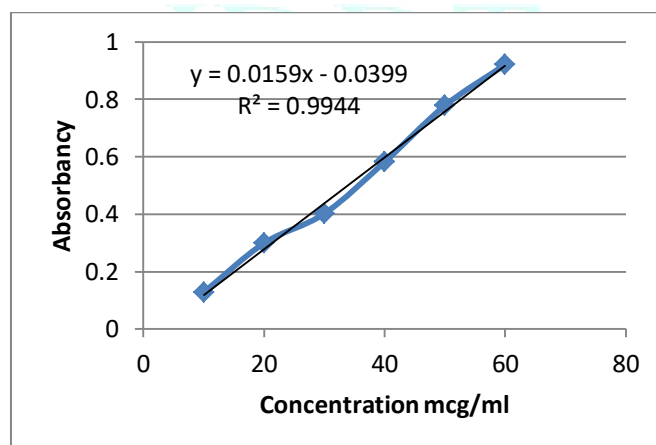


Fig 5.1 Drug calibration curve in NaOH 0.1 N.

5.2 Melting point

The average melting point of pure drug is 222°C which is complies with Stander melting point of drug.

5.3 Drug Excipient Compatibility Studies

5.3.1 FTIR Study:

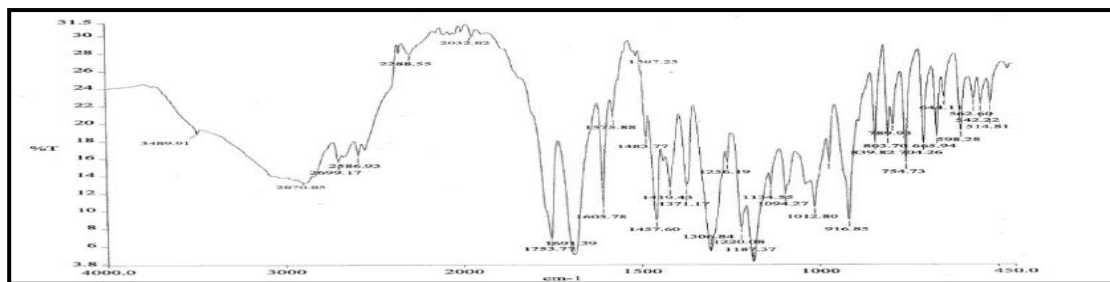


Fig 5.2 FTIR of Drug (Divalproex Sodium)

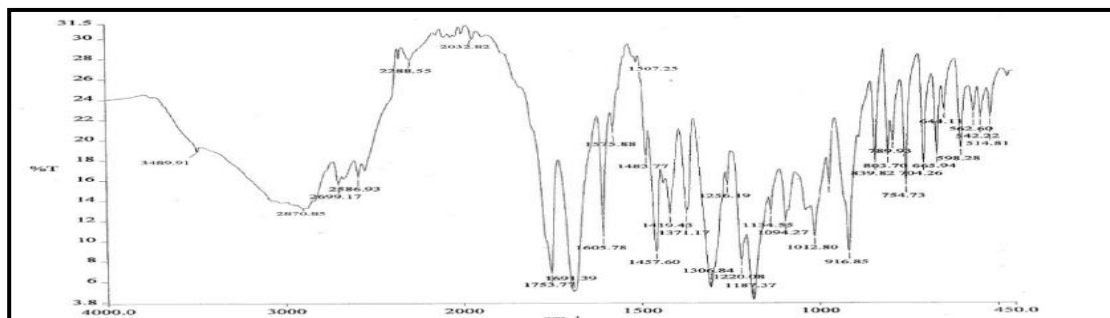


Fig 5.3 FTIR of Drug + HPMC

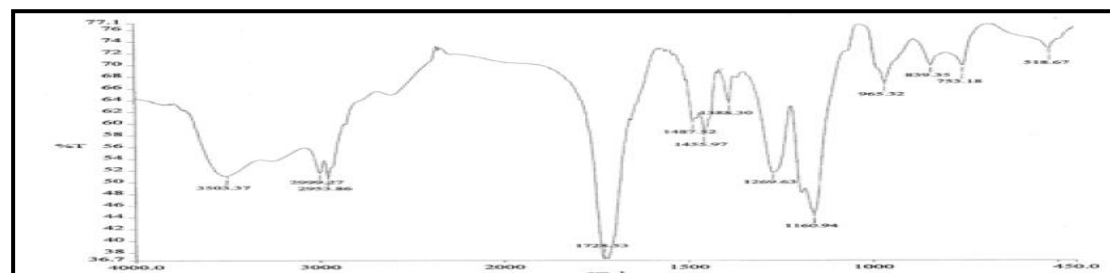


Fig 5.4 FTIR of Drug + Lactose Anhydrous

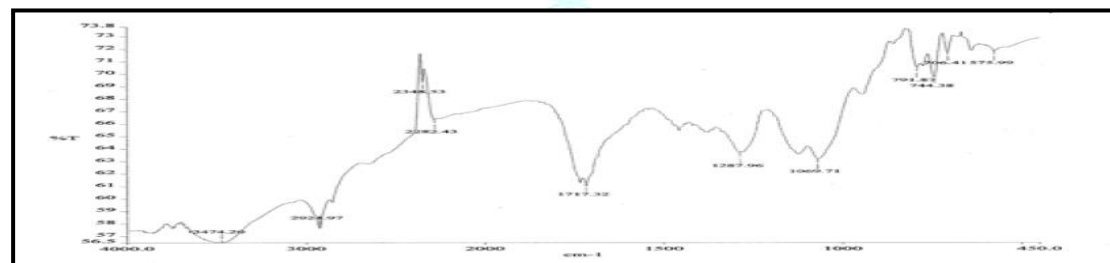


Fig 5.5 FTIR of Drug + Microcrystalline cellulose

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)	28°50'±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

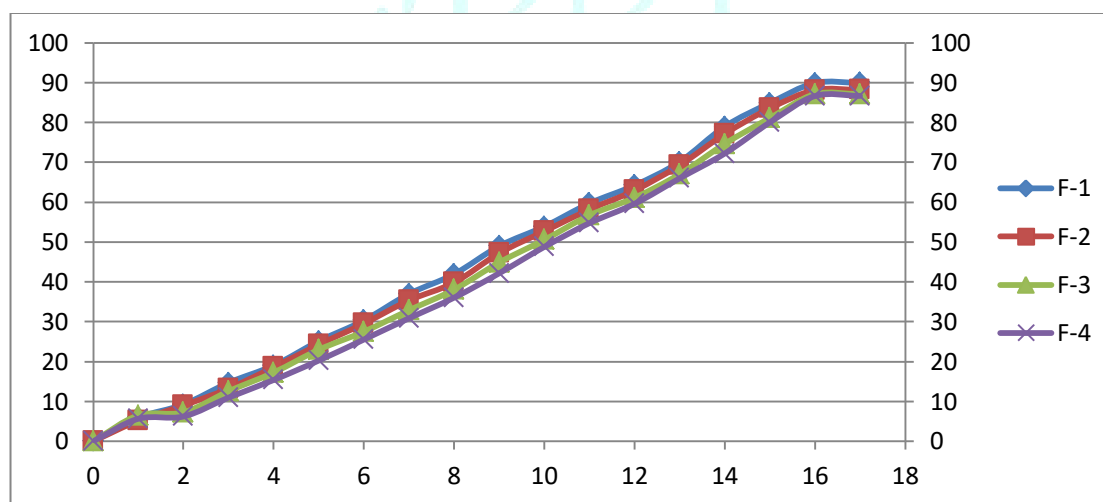


Fig 5.6 Cumulative Release of Formulation F-1 to F-4

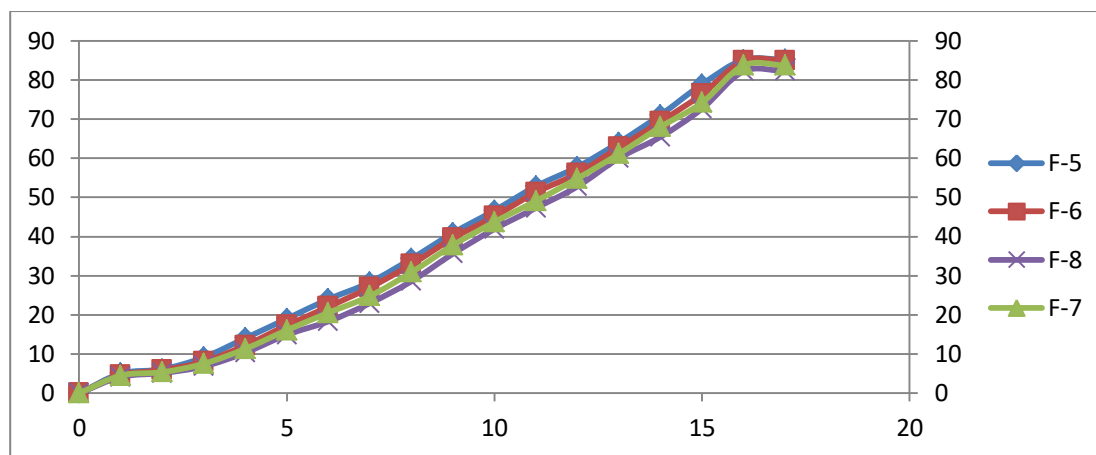


Fig 5.7 Cumulative Release of Formulation F-5 to F-8

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°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.

7. REFERENCES:

- Chow SC. Encyclopedia of biopharmaceutical statistics. New York: Marcel Dekker; 2003.
- Chopra S, Patil GV, Motwani SK. Release modulating hydrophilic matrix systems of losartan potassium: optimization of formulation using statistical experimental design. *Eur J Pharm Biopharm.* 2007;66:73-82.
- Ren S, Mu H, Alchaer F, Chtatou A, Müllertz A. Optimization of self nanoemulsifying drug delivery system for poorly water-soluble drug using response surface methodology. *Drug Dev Ind Pharm* 2012; 1-8. (doi:10.3109/03639045.2012.710634)
- Singh G, Pai RS, Devi VK. Response surface methodology and process optimization of sustained release pellets using Taguchi orthogonal array design and central composite design. *J Adv Pharmaceut Tech Res.* 2012;3:30.
- Minitab. Minitab online Help, Copyright © 2003-2005 Minitab Inc. Available from: <http://www.scribd.com/doc/17451466/15/ResponseOptimizer>. Accessed 2012 September.
- Qiu Y, Cheskin HS, Engh KR, Poska RP. Once a day controlled release dosage form of divalproex sodium I: formulation design and in vitro/in vivo investigations. *J Pharm Sci.* 2003;92:1166-73.
- rxlist. The Internet Drug Index-Sodium Valproate. Available from: <http://www.rxlist.com/depacon-drug.htm>. Accessed 2012 September.
- rxlist. The Internet Drug Index. Available from: <http://www.rxlist.com/depakote-er-drug.htm>. Accessed 2012 September.
- Bialer M. Extended-release formulations for the treatment of epilepsy. *CNS Drugs.* 2007;21:765-74.
- <https://pubchem.ncbi.nlm.nih.gov/compound/Divalproex-sodium>.
- Centorrino F, Kelleher JP, Berry JM, Salvatore P, Eakin M, Fogarty KV, Fellman V, Baldessarini RJ. Pilot comparison of extended-release and standard preparations of divalproex sodium in patients with bipolar and schizoaffective disorders. *Am J Psychiatry.* 2003;160:1348-50.
- Phaechamud T, Mueannoom W, Tuntarawongsa S, Chitrattha S. Preparation of coated valproic acid and sodium valproate sustained-release matrix tablets. *Indian J Pharmaceut Sci.* 2010;72:173.
- Dutta S, Zhang Y, Selness DS, Lee LL, Williams LA, Sommerville KW. Comparison of the bioavailability of unequal doses of divalproex sodium extended-release formulation relative to the delayed-release formulation in healthy volunteers. *Epilepsy Res.* 2002;49:1-10.
- Zeng XM, Martin GP, Marriott C, Pritchard J. The effects of carrier size and morphology on the dispersion of salbutamol Monajjemzadeh et al. Author's personal copy sulphate after aerosolization at different flow rates. *J Pharm Pharmacol.* 2000;52:1211-21.
- Rowe RC, Sheskey PJ, Owen SC, American Pharmacists A, Library R. Handbook of pharmaceutical excipients, vol. 4. London: Pharmaceutical Press; 2006.
- Parrott EL, Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger; 1986. p. 317-56.
- Qiu Y, Garren J, Samara E, Cao G, Abraham C, Cheskin HS, Engh KR. Once a day controlled release dosage form of divalproex sodium II: development of a predictive in vitro drug release method. *J Pharm Sci.* 2003;92:2317-25.
- United States Pharmacopoeial C., USP 32: United States Pharmacopoeia 32 and National Formulary No 27. 2010, Mack Printing Rockville.
- Emery E, Oliver J, Pugsley T, Sharma J, Zhou J. Flowability of moist pharmaceutical powders. *Powder Technol.* 2009;189:409-15.
- Dutta, Sandeep, Ronald C. Reed, and John H. Cavanaugh. "Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy volunteers." *The Journal of Clinical Pharmacology* 44, no. 7 (2004): 737-742.
- Hayashida, Tomohiro, Kadoya Kikumar, and Omura Tomoyuki. "Sustained release tablet." U.S. Patent 5,593,694, issued January 14, 1997.
- Dutta, Sandeep, Ronald C. Reed, and John H. Cavanaugh. "Absolute bioavailability and absorption characteristics of divalproex sodium extended-release tablets in healthy

- volunteers." *The Journal of Clinical Pharmacology* 44, no. 7 (2004): 737-742.
23. Dutta, Sandeep, Yiming Zhang, Daniel S. Selness, Lillian L. Lee, Laura A. Williams, and Kenneth W. Sommerville. "Comparison of the bioavailability of unequal doses of divalproex sodium extended-release formulation relative to the delayed-release formulation in healthy volunteers." *Epilepsy research* 49, no. 1 (2002): 1-10.
24. Bialer, Meir. "Extended-release formulations for the treatment of epilepsy." *CNS drugs* 21, no. 9 (2007): 765-774.
25. Dulac, Olivier, and Jean-Claude Alvarez. "Bioequivalence of a new sustained-release formulation of sodium valproate, valproate modified-release granules, compared with existing sustained-release formulations after once-or twice-daily administration." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 25, no. 1 (2005): 35-41.
26. Chen, Chih-Ming, and Boyong Li. "Divalproex sodium tablets." U.S. Patent 6,610,326, issued August 26, 2003.
27. Smith, Michael C., Franca Centorrino, Jeffrey A. Welge, and Michelle A. Collins. "Clinical comparison of extended-release divalproex versus delayed-release divalproex: pooled data analyses from nine trials." *Epilepsy & Behavior* 5, no. 5 (2004): 746-751.
28. Friedman, Michael, Meir Bialer, Avraham Rubinstein, and Upd Dufrovsky. "Novel controlled release dosage form of valproic acid." U.S. Patent 4,913,906, issued April 3, 1990.
29. Daste, Georges. "Pharmaceutical composition providing the sustained-release of valproic acid." U.S. Patent 5,019,398, issued May 28, 1991.

