World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers © All Rights Reserved
Available online at: http://www.wjpsonline.org/
Original Article

Design and evaluation of sustained release tablets of divalproex sodium

Ravi Chaudhari and Mohammed Gulzar Ahmed*

Department Of Pharmaceutics, Sri Adichunchanagiri College Of Pharmacy, Karnataka -571448

Received: 20-04-2015 / Revised: 25-05-2015 / Accepted: 31-05-2015

ABSTRACT

Epilepsy is abnormal, high frequency electrical discharge in brain characterized by transient episode (seizure) with or without loss of consciousness and characteristic body movement (convulsion). Among many drug of antiepileptic drug, Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy. The present work has been done to formulate sustained release tablets of divalproex sodium containing HPMC K4M and HPMC K100M as release retarding agent. The FTIR study revealed that there was no interaction between drug and polymer and combination can be safely prepared. The tablets were prepared by wet granulation technique using PVP K30 solution as binding agent. Tablets were evaluated for hardness, thickness, weight variation, disintegration time, drug content and *in vitro* drug release. All the physical parameters were in acceptable limit of pharmacopeial specification. The *in vitro* release of sustained release tablet was carried out for 18 hours using USP type-II apparatus (DS-1800) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ± 0.5^0C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. The optimized formulation (F8) was found to exhibit more than 90% after 18 hours. Further the drug release of sustained release tablets was compared with the conventional tablet which was prepared by using 5% micro crystalline cellulose (MCC) as disintegrating agent. The stability studies, shown the optimized tablets of immediate release formulation were stable at 40^0C / 75% RH for a period of 3 months.

Key Words: Divalproex sodium, Epilepsy, sustained release, wet granulation.

INTRODUCTION

Sustained release systems include maintaining drug concentration in a body over an extended period of time. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design[1]. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance, such as the type of delivery system, the disease being treated, the patient, the duration of therapy and the properties of the drug[2]. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled release system. If it is unsuccessful of maintaining constant drug levels but able to maintain for long time, it is considered as a prolonged released system[3].

Epilepsy is abnormal, high frequency electrical discharge in brain characterized by transient episode (seizure) with or without loss of consciousness and characteristic body movement (convulsion). Globally epilepsy is the third most common neurological disorder after cerebrovascular and Alzheimer's disease. About 10 percent of the population will have at lease one seizer in their life time[4].

Divalproex sodium is a unique preparation consisting of sodium valporate and valporic acid in 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically, it is designated as sodium hydrogen bis (2-propylpentanoate)[5]. Besides its role as a broad spectrum antiepileptic, used for the treatment of bipolar disorder, it is prescribed as antimigraine prophylactic agent for migraine. Divalproex sodium appears to act by multiple mechanisms: Prolongation of Na^+ channel inactivation, augmentation of release of inhibitory transmitter GABA by inhibiting its degradation[6].

The aim of present study is to develop sustained release tablet of divalproex sodium using HPMC K4M and HPMC K100M as release retarding agent and to evaluate with respect to various *in-vitro* evaluation studies.

***Corresponding Author Address:** Mohammed Gulzar Ahmed, Department Of Pharmaceutics, Sri Adichunchanagiri College Of Pharmacy, Karnataka -571448*

METERIALS AND METHODS

Materials: Divalproex sodium was a kind gift from ROAQ Chemicals Pvt. Ltd. Vadodara. HPMC K4M and HPMC K100M were purchased from Yarrow chemical Pvt. Ltd, Mumbai. All other chemicals used were of analytical grade.

Methods:

Preparation of sustained release tablet: All the materials were passed through the sieve #100 separately to ensure the uniformity in particle size. Accurately weighed Divalproex sodium, 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 50^0C 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 400 mg each tablet by adjusting hardness[3]. Further the conventional tablets were also prepared in similar manner without using HPMC i.e., release retarding agent and the formulations design were shown on table no 1.

Evaluation parameters:

Pre compression Parameters: Angle of Repose: The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel and the height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [7]

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

Db= Mass powder/Volume

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is given by

Dt =M/Vt

Where, M - Mass of the powder

V t – Tapped volume of the powder.

Compressibility index (I) and Hausner's ratio: Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula[5].

C.I =(Dt – Db)100/Dt

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

Post compression Parameters: The various post compression evaluation parameters like hardness, friability, thickness, weight variation, drug content and disintegration time were performed on the developed formulations as per the standard procedure. Hardness for each formulation was done by taking 6 tablets and determined using the Monsanto hardness tester. Friability was done for 6 tablets by using Roche friabilator. The thickness of the tablets was done by using vernier caliperse for the 6 tablets and average was taken. Weight Variation was done by taking 20 tablets of each formulation was weighed using an electronic balance and the test was performed according to the official method. Drug Content was determined by taking 6 tablets and triturated. From that transferred an accurately weighed portion of the powder equivalent to about 100mg of drug in a 100ml volumetric flask containing methanol as the extracting solvent and then concentration was determined spectrophotometrically by measuring the absorbance at 210 nm. Disintegration time for tablets was performed using disintegration testing apparatus by using water maintained at 37 ± 0.5^0C [8].

***In vitro* dissolution of tablets:** The in vitro release of sustained release tablet was carried out for 18 hours using USP type-II apparatus (DS-8000) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 $\pm0.5^0$C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 210nm[9]. Further the release data obtained were fitted into various mathematical models like Zero order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell. Regressional analysis was performed by using axel Software on the *in vitro* release data to best fit into various kinetic models according to the regression coefficient 'r'[10].

Stability: The optimized formulation was subjected for three month stability study according to standard guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were stored at 40^0C / 75% RH for 3 months and evaluated periodically[11].

RESULT AND DISCUSSION

Pre-formulation studies were carried out for all the formulation. Various pre compression powder properties such as angle of repose, carr's inderx, hausner's ratio, bulk density, tapped density were determined and the results were shown in table 2. Pre-formulation studies for the formulations depicted bulk density 0.512 to 0.623 gm/cm^3 which indicated packing characteristics in dies. The carr's compressibility index was found to be below 18% which suggested good compressibility of blend. The values of hausner ratio and angle of repose were found in the range of 1.12 to 1.25 and 17.39 to 22.54^o respectively suggested excellent flow property of powder blend. The tablets were evaluated for post compression parameters like hardness, thickness, friability, weight variation, drug uniformity and disintegration time and the results were shown in in table 3. The hardness was in the range of 4.33 to 6.74 kg/cm^2 which was the acceptable range. The friability was less than 1% indicated good handling and weight variation results suggested uniformity in weight of both types of tablet. The thickness of all the sustained release formulations was in between 5.35 to 5.42mm shows the good uniformity and the conventional tablet was 2.92mm little less as it contains 50% less dose when compared to Sustained release tablets. Weight variation results were also satisfactory as all the tablets were in the range of 448 mg to 451 mg. Content uniformity was in range of 97.43 to 99.51% indicated uniform dispersion of Divalproex sodium. As the disintegration time for sustained release tablets will not equal to the conventional tablets, though the disintegration test performed for a period of 10 minutes but the tablets were found intact. Whereas the disintegration time for the conventional tablets was found to be 5 to 6 minutes. *In vitro* drug dissolution study performed on all formulations and the profile of drug release is shown in figure 1. Among all the sustained release formulations (F1 to F9), higher concentration of single polymer will significantly retard the drug release for long time. In case of F1, F2 and F3 a single polymer HPMC K4M in an increasing concentration gives drug release of 99.52%, 97.81% and 84.11% respectively. Similarly in case of F3, F4 and F5 a single polymer HPMC K100M in an increasing concentration gives drug release of 98.82%, 97.69% and 67.05% respectively at the end of 18 hours. The combination of polymers (F7, F8 & F9) will release the drug quite faster when compared to alone. In case of conventional tablets F10 the 98.85% of drug release was observed within 1 hour. From the kinetic data of release profile it is clearly indicated that all the sustained release formulations (F1 to F9) follows Zero order kinetics as the values for 'r' is (0.9918 to 0.9736) and values of 'n' values in between 0.6634 to 0.6064 shown non-fickian release. The release kinetics of conventional tablet (F10) was found to follow first order kinetics as the value for 'r' is (0.928) and 'n' was found to 1.1212 shown Super case II transport. The formulations subjected to short term stability study, storing the formulation at 40^{0}C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and *in vitro* drug release rate were observed.

CONCLUSION

From the above results and discussion it is concluded that formulation of sustained release tablets of proper composition of release retarding agents can successfully release the drug for a desired sustained period. As in this it is appreciate to know the release time of drug can be altered by changing the concentration of single polymer or proportionately combining the polymers if using more than one polymer.

ACKNOWLEDGEMENTS

The authors are sincerely thankful to principal Sri Adichunchanagiri College of Pharmacy, B.G.Nagara for provided us infrastructure facilities and moral support to carry out this research work.

Table 1: Formulation of divalproex sodium tablets

Sl. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Divalproex sodium	250	250	250	250	250	250	250	250	250	125
2	Lactose	85.5	74.25	63	85.5	74.25	63	85.5	74.25	63	101
3	HPMC K4M	67.5	78.75	90	-	-	-	33.75	39.37	45	-
4	HPMC K100M	-	-	-	67.5	78.75	90	33.75	39.37	45	-
5	Microcrystalline cellulose	35	35	35	35	35	35	35	35	35	15
6	Magnesium stearate	4	4	4	4	4	4	4	4	4	3
7	Talc	8	8	8	8	8	8	8	8	8	6
8	Total	450	450	450	450	450	450	450	450	450	250

Table 2: Pre-compression parameters

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
F1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
F2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
F3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
F4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
F5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
F6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
F7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
F8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
F9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021
F10	0.586±0.004	0.674±0.004	13.056±0.249	1.150±0.028	18.055±0.077

Table 3: Post-compression parameters

Batch code	Weight variation Mean ± SD	Hardness (kg/cm^2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	*In vitro* disintegration time (sec) Mean ± SD
F1	450.21±1.41	5.38±0.10	0.32±0.06	5.42±0.09	99.38±1.19	-
F2	450.72±2.29	4.33±0.02	0.35±0.02	5.35±0.14	98.61±1.03	-
F3	448.94±1.59	6.14±0.04	0.43±0.03	5.37±0.03	97.43±1.28	-
F4	451.01±1.14	6.23±0.06	0.36±0.02	5.41±0.05	98.57±0.85	-
F5	450.93±1.37	5.14±0.03	0.41±0.06	5.39±0.06	98.43±1.27	-
F6	450.51±1.31	4.52±0.02	0.48±0.03	5.42±0.03	97.63±0.61	-
F7	450.25±1.46	6.74±0.04	0.42±0.06	5.42±0.08	99.47±1.04	-
F8	449.52±1.55	6.16±0.02	0.37±0.04	5.39±0.04	99.51±1.20	-
F9	450.02±1.04	6.56±0.03	0.31±0.03	5.40±0.07	98.49±0.93	-
F10	220.58±1.59	4.64±0.04	0.43±0.03	2.92±0.03	97.43±1.28	387.64±1.26

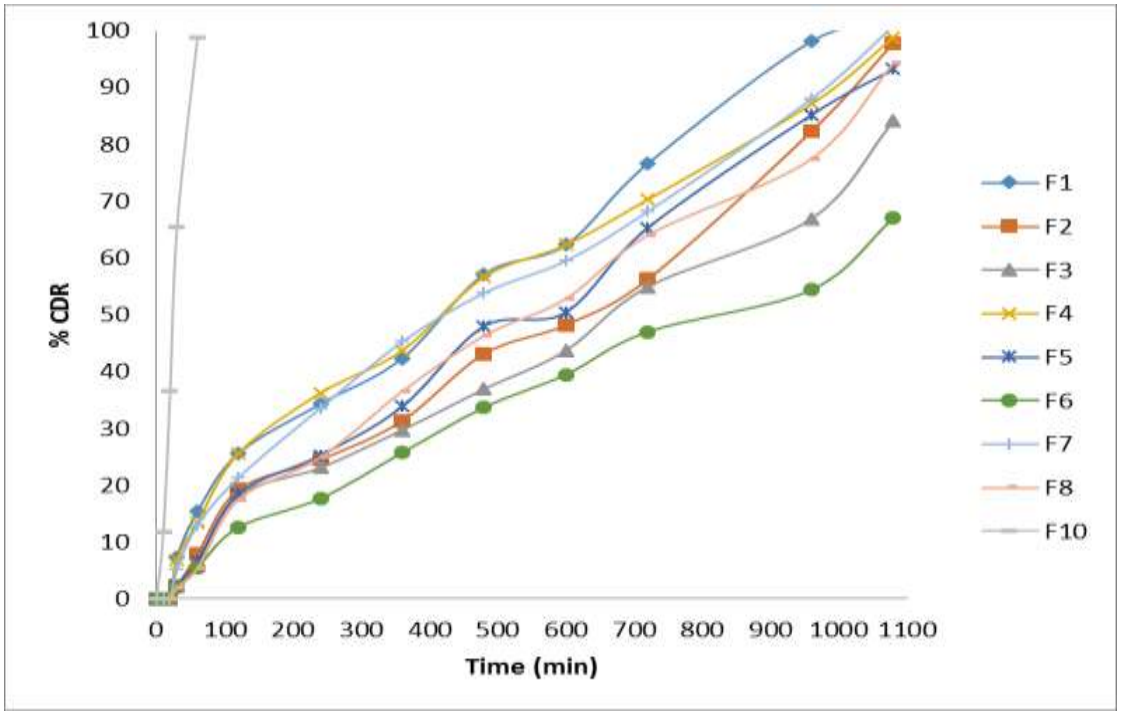

Figure 1: Comparative dissolution profile

REFERENCES

1. Lakshmi Parvathi A, Senthil Kumar K, Mohammed Gulzar Ahmed, Abdul Nasir K and Ramesh B. Formulation and Evaluation of oral controlled release dosage forms of Anti-hypertensive agents. Journal of Pharmaceutical and Scientific Innovations. Sci. 2012;1(6). 31-34.
2. Pahade AA, Jadhav VM, Kadam VJ. Formulation and Development of a Bilayer Sustained Released Tablets of Isosorbide Mononitrate. Int J Pharma Bio Sci. 2010;1(4):305-14.
3. Prabhakara Prabhu, Harish N.M, Gulzar Ahmed, R. Narayana Charyulu, Santhosh P, D. Satyanarayana. Formulation and *in vitro* evaluation of sustained release tablets of domperidone. Research J Pharm and Tech 2009, 2(2); 358-362.
4. Sridharan R. Epidemiology of epilepsy. Current Sciences. 2002;82 (6):664-70.
5. Lakhani KM, Shah SV, Patel KN, Patel BA, Patel PA. Formulation and evaluation of Extended Release Tablet of Divalproex Sodium. Int J Pharma Res Sch. 2012;1 (2):122-35.
6. Vamsy KA, Srinath KR, Chowdary CP, Planisamy P, VIjayasanker GR. Formulation Development and Evaluation of Divalproex Sodium Extended Release Tablets. Int J Res Pharma Bio Sci. 2011;2(2):809-32.
7. Puroshattam Timilsina, Vedamurthy Joshi, Pramod Dhakal, Sachin AB and Mohammed Gulzar Ahmed. Formulation and Evaluation of Diclofenac Sodium Dual Type Mini Tablets for Extended Action. American Journal of Pharmatech Research. , 2014, 4(5); 722-735.
8. Patel HP, Karwa P, Patel NJ. A Noval Approch to Sustained Zolpidem Tartrate Release: Compressed Mini-Tabets. Int J Pharma Sci Rev Res. 2011;7(2):53-8.
9. Shibu B.S, Suresh S, Saravanan C. Formulation and Evaluation of Extended Release Tablet of Divalproex Sodium using Different Polymers as Release Retarding Agent. Int J Pharma Devel Tech. 2014;4(3):145-50.
10. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic Modeling on drug Release From Controlled Drug Delivery Systems. Acta Poloniae Pharma-drug Res. 2010;67(3):217-23.
11. Prabhakar Prabhu, Harish Nayari M, Md Gulzar Ahmed, Brijesh Yadav, Narayana Charyulu R, Sathyanarayana D and Subrahmanyam EVS., Formulation and *in vitro* Evaluation of Gastric oral Floating Tablets of Glipizide. Indian J. Pharm. Educ. Res,2008, 42(2);174-183.