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TECHNOLOGICAL DEVELOPMENT AND STABILITY STUDY OF DIVALPROEX SODIUM EXTENDED RELEASE TABLETS

S. Jeganath[1*], K. Senthil kumaran[1], V. Ashlin viji[2], K. Sheeja devi[3]

[*,1]Department of Pharmaceutics, K.K. College of pharmacy, Chennai, Tamilnadu, India.
[2]Department of Pharmaceutics, Periyar College of Pharmaceutical sciences, Trichy, Tamilnadu, India.
[3]Department of Pharmaceutical chemistry, KMCH college of Pharmacy, Coimbatore, Tamilnadu, India.

ABSTRACT

The behavior of different technological variants of extended release tablets of divalproex Sodium (960mg) obtained by direct compression technique. The extended time and the percentage of the dissolved drug showed a significant dependence of the polymers ratios present in formulae. The physical and chemical properties of tablets were assessed during Three months (accelerated stability), respectively. From the formulae selected it was possible to obtain granulates and tablets with organoleptic, physiochemical and technological properties, demonstrating the feasibility of the process of fabrication of this product. Results showed the good stability in the extended release divalproex Sodium tablets selected. The in vitro dissolution hasn't significant differences, thus, neither the time elapsed nor the composition of formula influenced on the percentages of dissolved drug. The assessment demonstrated significant differences, however, assessed formulae fulfilled with official pharmaceutical specifications during 3 months.

Keywords:-Divalproex sodium, Hydroxyl Propyl Methyl Cellulose, Extended release, Direct compression technique, Stability studies.

INTRODUCTION

The terms of "sustained or extended release", "prolonged release, and controlled release", as applied to drug formulations, have the meanings ascribed to them in Remington's pharmaceutical Sciences, Sustained or extended release (Remington's., 1996) drugs systems include any drug delivery system which achieves the slow release of drug over an extended period of time, and include both prolonged and controlled release system (Theodore JR *et al.*, 1983; Donald LW *et al.*, 1984). If such a sustained release system is effective in maintaining substantially constant drug level in the blood or target. It is considered a prolonged released system. The sustained or extended release is explained below a figure.

Careful selection of the excipients, components of all pharmaceutical products, is essential for the development of stable and effective dosage forms (Garnet EP *et al.*, 1989; Serajuddin ATM *et al.*, 1999). For an efficient development of stable formulations a two-step procedure should be recommended. First, design and optimization of pharmaceutical formulation with appropriate technological properties and minimum trials. For that purpose statistical methods have been widely used (Furlanetto S *et al.*, 2006). Then, further studies on complete model formulation with selected excipients

Corresponding Author

S.Jeganath
Email: jeganaths@gmail.com

should be conducted to verify the actual stability of the drug in the final dosage form and identify the most suitable composition in order to maximize drug stability (Fernandez EG *et al.,* 2008; Mura P *et al.,* 2004). Stability parameters are useful for drug formulation and storage conditions, good practical decisions have to be made on the basis of the most important parameters like drug dissolution to solid dosage forms.

MATERIALS AND METHODS

MATERIALS

Divalproex sodium was obtained as a gift sample from (Sun pharma.Ltd, Mumbai.). HPMC K-100M and HPMC K_4M was obtained as a gift sample from Dow international. Ltd, Mumbai, and Colorcon Ltd, Asia. Micro crystalline cellulose and Magnesium Stearate from LobaChem (Mumbai, India). All other chemicals and ingredients were used for study are of Analytical grade.

METHODS

Preparation of divalproex Sodium extended release tablets

Sift Divalproex sodium through 20mesh sieves, Sift HPMC K-100M, HPMC K4M, PVP-K30, Avicel pH102, Starch, Lactose DCL-21 Through 40mesh sieve, dry Mix Divalproex sodium HPMC K4M, HPMC K4M, PVP-K30, Avicel pH102, Starch, Lactose DCL-21 in a planetary mixer for 30 minutes. Sift Talc, Aerosil, and Magnesium stearate through 60 mesh sieve and add to step 2and mix it for 3 minutes. Compress the lubricated blend Using (D-Tooling) 19.2 x 8.9 mm oblong shaped punches. For film Coating, Dissolve required amount of HPMC 15cps in IPA & Methylene chloride solution. Add Talc, Titanium dioxide, Iron oxide yellow to step 1 and mix it in a colloidal mill for 10 minutes. Polyethylene glycol to step 2 and mix it for 5 minutes. Filter the solution through 200 mesh nylon cloth. Use this coating solution to coat the core tablets in a Neo-cota coating pan. Spray gun pressure should be held at an angle of approximately 60°C to the surface of the tablet bed and 30cms away from bed (Huang BY *et al.,* 2005; Manon Thibault *et al.,* 2002).

EVALUATION PAPRAMETERS

STABILITY STUDIES

Stability conditions

Once the final formula is arrived at, and then the stability batches are prepared where three batches of the same formula are prepared and packed in Alu strip, Alu Blister, amber PVDC 60, and HDPE. These packed samples are stored in three conditions.

- 25°C and 60%RH
- 30°C and 65% RH
- 40°C and 75% RH

For periods of 1, 2,3,6,9,12,18,24 and 36 months as may be the case applicable. These are in line with the ICH guidelines The optimized formulations of T_7,T_8 and was chosen for stability studies, Tablets were packed in Alu-Alu Blister and kept for 90 days at 40^0 C /75% RH and 30^0 C /65% RH in a stability chamber (New tronic walk in humidity chamber, India). The tablets were evaluated interval of 1, 2, 3 months analysis as per in-house specification.

RESULTS AND DISCUSSION

The Aim of the present study was to formulate the Extended Release Tablet of Divalproex Sodium using different viscosity concentration of hydrophilic polymer like Hydroxyl Propyl Methyl Cellulose K4M and Hydroxyl Propyl Methyl Cellulose K100M with diluents like microcrystalline cellulose, Maize starch by direct compression method.

The prepared formulation (ER tablets) was evaluated precompression and invitro studies. The results are showed good with in IP specification limits. The in vitro dissolution studies were performed for the T_1, T_2, T_3, T_4, T_5, and T_6 formulations. In this formulation T_5 complies as per in-house specification with marketed sample.

STABILITY STUDIES

The In-vitro release of formulation T_5 complies with the in-house specification release profile hence was chosen T_5 batch taken for their stability studies. The stability studies were performed on selected formulations i.e. T_5 at $30^0C \pm 2^0C$ / 60% ± 5% RH (Real time stability), and $40^0C \pm 2^0C$ / 75% ± 5% RH (accelerated stability), for 3months. At the interval of 1 month the formulations were checked for physical appearance, drug content, hardness and dissolution profile etc. There was no physical change has been observed in the formulations at stability conditions and also there was no significant change has been observed in drug content, Hardness and friability dissolution profile of the selected formulations at stability conditions as shown in Table.no.3. So T_5 formulations were found to be stable.

Table no. 1: Formulation of divalproex sodium extended release tablets

S.No	Ingredients	$T_{1\ (mg)}$	$T_{2(\ mg)}$	$T_{3\ (mg)}$	$T_{4\ (mg)}$	$T_{5\ (mg)}$	$T_{6\ (mg)}$	$T_{7\ (mg)}$
1	Divalproex sodium	549.00	549.00	549.00	549.00	549.00	549.00	549.00
2	HPMC K100M	75.00(8%)	56.00(6%)	56.00 (6%)	47.00 (5%)	40.00 (4%)	18.50 (2%)	40.00 (4%)
3	HPMC K4M	47.00(5%)	37.00(4%)	28.20(3%)	18.80(2%)	25.00(2.5%)	14.0(1.5%)	25.00(2.5%)
4	Povidone (K30)	25.00	25.00	25.00	25.00	25.00	25.00	25.00
5	Avicel pH 102	14.00	43.00	51.80	70.2	71.00	103.50	71.00
6	Starch	100.00	100.00	100.00	100.00	100.00	100.00	100.00
7	Lactose DCL 21	80.00	80.00	80.00	80.00	80.00	80.00	80.00
8	Talc	30.00	30.00	30.00	30.00	30.00	30.00	30.00
9	Magnesium stearate	15.00	15.00	15.00	15.00	15.00	15.00	15.00
10	Aerosil	5.00	5.00	5.00	5.00	5.00	5.00	5.00
11	Target Weight	940.00±1%	940.00±1%	940.00±1%	940.00 ±1%	940.00±1%	940.00±1%	940.00±1%

Core tablets are film coated with following ingredients listed in Table no.2

Table no. 2: Coating formula

Ingredients	Quantity
HPMC 15CPs	12.00
Titanium dioxide	3.90
Talc	2.40
Iron oxide yellow	0.10
Propylene glycol	1.6
Isopropyl alcohol	Quantity sufficient
Methylene chloride	Quantity sufficient
Target weight of a coated tablet	960.00±1%

Table no. 3: Comparative drug release profile of trial no.5 with market sample (DIVALPRID-OD Tablet)

S.No	Medium	Time (in hours)	Cumulative % drug release	
			Trial no-5	Marketed Sample
1	Acid(1.1N Hcl)	1	8.1	6.8
2	Phosphate Buffer (pH 6.8)	3	31.9	31.4
3		12	79.5	81.9
4		24	91.3	92.7

Table no. 4: Stability data for divalproex sodium ER tablets T_5

Accelerated Stability- 40^0C/70%RH Real Time Stability-30^0C/65%RH

S.No	Parameter	Limits	Initial	40^0c/70%RH			30^0C/65%RH
				1Month	2Month	3Month	3Month
1	Appearance	Light yellow colored, oblong shaped film coated tablets	√	√	√	√	√
2	Average weight	950-970mg(Taget weight-960mg)	960.2mg	960.4mg	960.0mg	957.0mg	951.0mg
3	Hardness of tablets	4.00 to 8.00 kg/cm^2	6.0	5.8	5.0	5.2	5.2

4	Dissolution 1st Hour 3rd Hour 12th Hour 24th Hour	NMT15% Between20%to45% NLT 60% Not less than 80%	6.9% 24.3% 69.8% 89.9%	8.2% 32.1% 75.5% 85.6%	12.3% 30.6% 70.95% 86.6%	9.2% 22.1% 73.8% 88.5%	9.9% 23.7% 74.9% 86.3%
5.	Assay Each film coated ER tablet contain divalproex sodium	90.0% to 110.0% (490-550.0mg)	98.6%	99.40%	99.75%	99.21%	99.8%

√ - indicate complies as per in-house specification

Fig 1. Hypothetical plasma concentration-time profile from single doses of sustained or extended delivery formulations

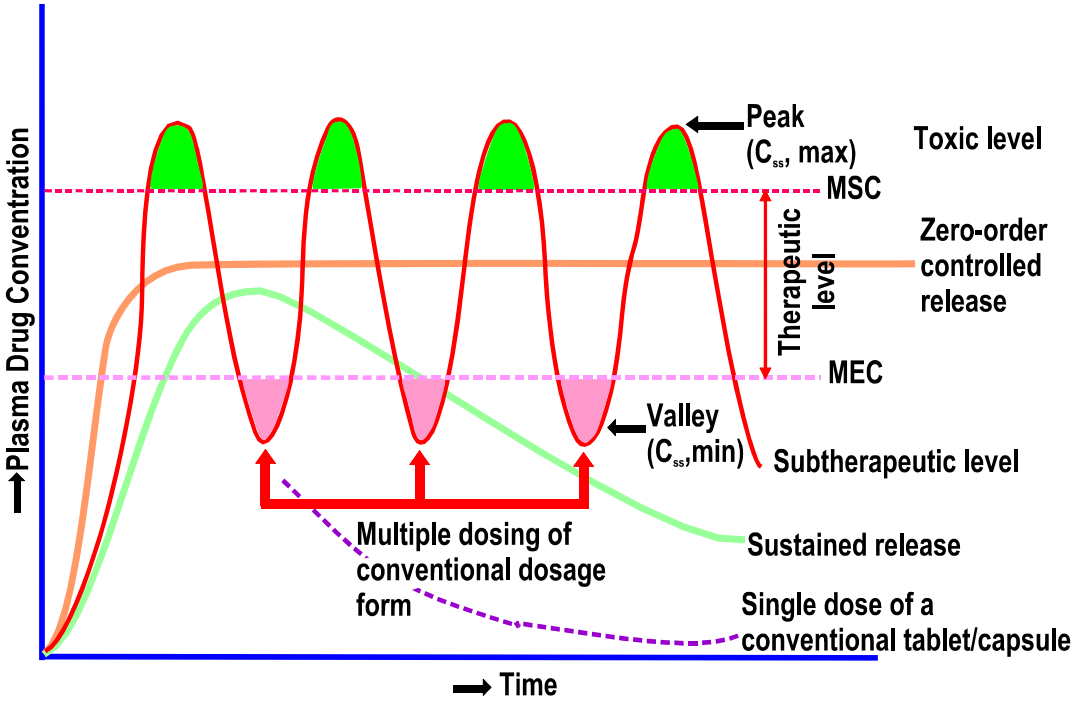
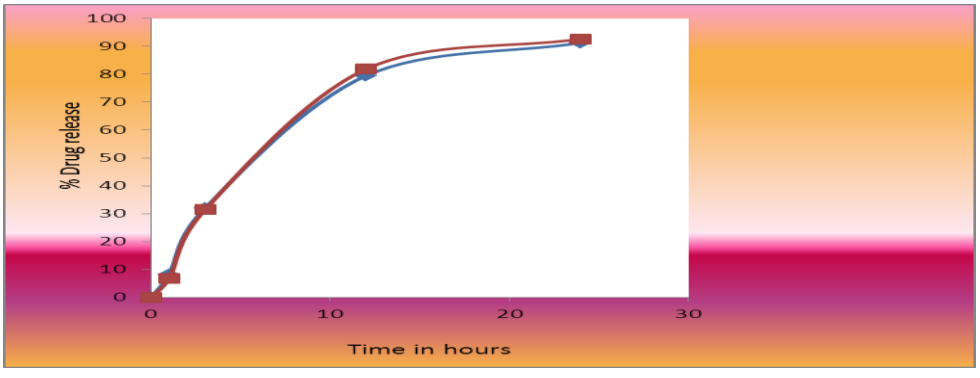


Fig 2. Comparative release profile of fabricated divalproex sodium ER trial no.5 with market sample



CONCLUSION

The conclusion of this work was to develop a stable solid dosage form of extended release tablets of divalprex sodium for the treatment of epilepsy bipolar disorder, and migraine headache. In the present study extended release of divalproex sodium tablet was prepared by using direct compression technique. Different formulations were made by using two rate retaining polymer like HPMCK 100M and HPMC K4M combined with directly compressible grade diluents like Microcrystalline cellulose pH102, Starch, Lactose DCL21 and finally tablet was made film coated. From the above study the formula used for T_5 formulation was concluded as an optimized formula due to its good in vitro release characteristics and stability studies.

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