



FORMULATION DEVELOPMENT AND EVALUATION OF DIVSODIUM EXTENDED RELEASE TABLET

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ABSTRACT

The objective of present work was to develop a stable solid dosage form of extended release tablets of Divalproex 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 controlling 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. All the formulations were evaluated for physical characteristics, *in vitro* dissolution and stability.

Keywords: Epilepsy, Divalproex Sodium, Extended release, HPMC and Korsemyer Peppas

INTRODUCTION

Controlled release technology is relatively a new field and as a consequence research in this field has been extremely fertile and has produced many discoveries. New and more sophisticated sustained release drug delivery systems are constantly being developed and tested. Successful fabrication of sustained release products is usually difficult and involves consideration of the physicochemical properties of the drug, pharmacokinetic behaviour of the drug, and route of administration, diseased state to be treated and most importantly placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug¹.

There are literally dozens of names associated with sustained release products such as continuous release, controlled release, delayed release, delayed action, depot, extended action, gradual release, long acting, long lasting, long-term release, prolonged release, repository retard, slow acting, slow release, time coat, sustained release, sustained action, timed disintegration, timed release etc².

Spatial placement relates to the targeting of the drug to a specific organ or tissue while temporal delivery refers to controlling the rate of the drug delivery to the target tissue. An appropriately designed drug delivery system can be a major step towards solving these two problems. This technique for the drug administration is termed as 'sustained release' or 'controlled release³. Drugs with dosage not exceeding 125mg - 325mg are more suited as extended release products in order to limit the size of the delivery system⁴.

In the case of soluble matrix the matrix swells or dissolves. These matrices then undergo surface erosion with little or no bulk erosion. The surface area of the matrix decreases with time, with a concomitant decrease in drug release. The diffusion depends on the solubility of the drug in the polymer⁵. The drug release mechanism across the membrane involves diffusion of water through the membrane to the inside of the core, dissolution of the drug and then diffusion of the drug into the surrounding fluid⁶.

In reservoir dissolution control system the drug particles are coated or encapsulated by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose derivatives, poly ethylene glycols, waxes etc., the resulting reservoirs may be filled as such in hard gelatin capsules or compressed into tablet⁷. Oral osmotic pump, popularly called as OROS works with the principle of osmotic pressure to release the drug at a constant rate. The rate of release of drug in these products is determined by the constant inflow of water across a semi-permeable membrane into a

reservoir, which contains an osmotic agent. The hydrophilic gel-forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping⁸.

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 brain⁹.

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. 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. 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.

MATERIALS

The Divalproex sodium was obtained as a gift sample from Sun Pharma. Ltd, Mumbai. HPMC K-100M (Dow international. Ltd, Mumbai.), HPMC K4M (Colorcon Ltd., Asia.) Microcrystalline cellulose pH- 102 (Reliance Ltd., Mumbai.). All other ingredients used are of analytical grade.

METHODS

Pre-formulation studies

The compatibility studies were carried out to study the possible interactions between Divalproex sodium and inactive ingredients, physical mixture of Divalproex sodium and excipients were prepared in the following ratio and kept for stability condition at 25°C/ 60%RH for one month. All ingredients individually with KBr were compressed under 10 tones pressure in a hydraulic press to form a transparent pellet, the pellet was scanned from 4000 to 400cm⁻¹ in IR spectrophotometer¹⁰.

Manufacturing process

The Manufacturing procedure for the formulation of Divalproex sodium extended release tablets 500mg consists of the following steps¹¹.

1. Sifting: Divalproex sodium through 20 mesh sieves, Sift HPMC K-100M, HPMC K4M, PVP-K30, Avicel pH102, Starch, Lactose DCL-21 Through 40 mesh sieve.

2. Dry mixing: Divalproex sodium HPMC K100M, HPMC K4M, PVP-K30, Avicel pH102, Starch, Lactose DCL-21 in a planetary mixer for 30 minutes.

3. Lubrication: Sift Talc, Aerosil, and Magnesium stearate through 60 mesh sieve and add to step 2 and mix it for 3 minutes.

4. Compression: Compress the lubricated blend using (D-Tooling) 19.2 x 8.9 mm oblong shaped punches.

5. 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. Add Polyethylene glycol to step ii 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, under the following condition. (Table-1)

Evaluation of granules

Flow Property Measurements

It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from various parameters like Angle of repose, Bulk & Tapped density, compressibility index and Hausner Ratio.

Evaluation of tablets

All the prepared film coated tablets were evaluated for the following official and unofficial parameters. (Following quality control tests) like Thickness, Hardness, Friability, Weight variation and Assay¹².

Dissolution test

The in-vitro drug release was estimated by using USP Type-2 apparatus using pH -1.2 & pH-7.2 for 2 & up to 24 hrs respectively at 37 ± 0.2°C¹³.

Drug release kinetics

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released Vs time, first order (Equation 2) as log cumulative percentage of drug remaining Vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released Vs square root of time¹⁴.

Stability studies

These are in line with the ICH guidelines The optimized formulations of T₇, T₈ and was chosen for stability studies, Tablets were kept for 90 days at 40° C /75% RH and 30° C /65% RH in a stability chamber. The tablets were evaluated interval of 1, 2, 3 months analysis as per in-house specification limit¹⁵.

RESULTS AND DISCUSSION

Drug and drug-excipients compatibility test was conducted at the temperature of 25°C ± 2°C and Relative Humidity 40 ± 2%RH the results indicated that there are no physical changes like colour, odour, etc., during storage period. IR Spectral analysis for drug alone and in combination with other excipients was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interaction.

The results of bulk density ranged from 0.363 to 0.408g/cc and Tapped density 0.454 to 0.526g/cc respectively. The bulk density depends on particle size, shape and cohesiveness of the particles. Hausner's ratio was found to be between 1.25 – 1.30, Which is well within the specified limits between 1.5 and the granules is possible so addition of glidant normally improves the flow during compression. The results of compressibility index, ranged from 20.00 % to 21.45% as it indicates pair to possible flow properties. The results of angle of repose ranged from 33.10° to 35.53° as it indicates possible flow properties of the granules and maybe flow improved by addition of glidant. The results of moisture content of granules ranged from 1.02% to 1.97%. According to the results obtained from in-vitro dissolution studies it was found that formulation T₄ complied as per In-house specification and similar to marketed sample for their release rate. (Fig 1).

Table 1: Composition of different Trials

Ingredients	Quantity used in mg			
	Trial 1 per 1000 tablets	Trial 2 per 1000 tablets	Trial 3 per 1000 tablets	Trial 4 per 1000 tablets
Divalproex sodium	808.62	808.62	808.62	808.62
HPMC K100M	-	60.00 (4%)	60.00 (4%)	60.00 (4%)
Maltose 90SH ₄₀₀₀ SR	120.00	-	-	-
HPMC K4M	-	45.00 (3%)	45.00 (3%)	45.00 (3%)
Povidone (K30)	20.00	37.50	37.50	37.50
Avicel pH 102	79.38	133.58	133.58	133.58
Starch	-	150.00	150.00	150.00
Lactose DCL 21	145.00	120.00	120.00	120.00
Talc	30.00	45.00	45.00	45.00
Magnesium stearate	15.00	22.50	22.50	22.50
Aerosil	12.00	17.80	17.80	17.80
Target weight	1200.00 ±1%	1440.00 ±1%	1440.00 ±1%	1440.00 ±1%

The results of dissolution studies indicated that T₁, T₂, T₃, T₄ released from acid medium end of first hour found satisfactory as per in our specification but release profile not achieved in buffer medium within the limit as per in our specification with marketed sample. Because HPMCK100M, HPMCK4M having high viscosity grade using in the formulation and so that release rate is very slow. Gradually decreasing the polymer concentration from Trial No. 1 to 5. Finally release profile was achieved in the Trial No.5. In addition to decreasing the polymer concentration Trial No-6 release profile was more than the specification limits. This formulation not achieved the extended release. Based on Trial No.5.

Drug release kinetics profiles were determined for formulation of Trial No.5. The zero-order rate (Equation 1) describes the systems where the drug release rate is independent of its concentration. Figure- 14 shows the cumulative amount of drug release Vs time for zero-order kinetics. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined. It was found that the in vitro drug release of Divalproex Sodium was best explained by Higuchi's equation, as the plots showed the highest linearity ($r^2 = 0.992$), followed by zero order ($r^2 = 0.990$), first order ($r^2 = 0.826$). The mechanism of release for the matrix tablets were elucidated as per korsmeyer-pappas indicated a good linearity ($r^2 = 0.933$) The release exponent n was 0.99, which

appears to indicate case II and super case transport where the drug release does not change over time and the release is characterized

by zero order release. Also the drug release can be predicted to be dominated by erosion and swelling of the polymer.

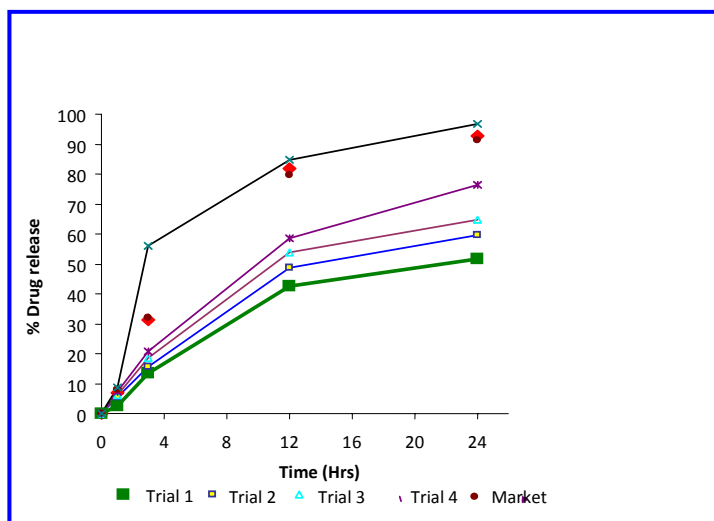


Fig. 1: Comparative drug release profile of divalproex sodium ER tablet of trial 1-4 with market sample

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 conditions as shown in Table No.15 and Table No.16. So T₄ formulations were found to be stable.

CONCLUSION

It is concluded that Divalproex sodium ER tablet was formulated by using the rate controlling polymer like HPMC K100M and HPMC K4M with direct compression technique was found to be stable.

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