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Design and evaluation of immediate release tablets of divalproex sodium

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ABSTRACT

Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy, bi-polar disorders and prophylaxis of migraine. The present work has been done to formulate immediate release tablets of divalproex sodium containing sodium starch glycolate (SSG) and croscarmellose as super disintegrating agents. 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 as poor flow property exhibited by pure drug. 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. In vitro drug release studies were performed using USP type II apparatus (paddle method) in 900 ml of phosphate buffer pH 6.8 at 100 rpm. The optimized formulation (F6) was found to exhibit the highest in- vitrodrug release of 98.11percent at the end of 20 minutes. Further the drug release of immediate release tablets was compared with the drug release profile of 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, immediate release, wet granulation.

INTRODUCTION

Oral route is most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs,due to flexibility in dosage form design and patient compliance oral route is preferred. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing [1].

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. For the drugs which required to be released faster for the better therapeutic effect, the designing of the immediate release tablets dosage form plays a significant role in the therapy. For immediate release formulation, superdisintegrants play key componentto improve the efficacy of solid dosage form. This achieved by various mechanisms, swelling, porosity and capillary action, heat of wetting, particle repulsion forces, deformation recovery, enzymatic reaction by which the tablets are broken into small particles[2].

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[3].

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)[4]. 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[5].

The aim of present study is to develop immediate release tablets of divalproex sodium and to evaluate with respect to various *in-vitro*evaluation studies. Presently no scientific reports are available on the development immediate release tablets of divalproex sodium. Hence an attempt has been made for its development.

METERIALS AND METHODS

Materials:

Divalproex sodium was a kind gift from ROAQ Chemicals Pvt. Ltd. Vadodara. Sodium starch glycolate and Croscarmellose sodium were purchased from S.D. Fine Chem. Ltd,Mumbai. All other chemicals used were of analytical grade.

Methods:

Preparation of immediate release tablet:

Immediate release tablets were prepared by wet granulation process using PVP K30 solution as binding agent. All the materials were passed through the sieve #100 separately to ensure the uniformity in particle size. The binding agent is prepared by dissolving PVP K30 in specified quantity of IPA.Drug and micro crystalline cellulose was mixed geometrically and then added lactose and superdisintegrants (sodium starch glycolate&croscarmellose) in mortar and pestle.Added the binding agent which is previously prepared and pass the damp mass through sieve # 16 and dry in hot air oven for 20 minutes at 45^0C. Then passed the dried granules through sieve #22 and mixed the above granules with lubricants (magnesium stearate and talc) for 5 min. Then the tablets were compressed by using single rotatory tableting machine with desired hardness [6].

Similarly the conventional tablets of divalproex sodium were also prepared by omitting super disintegrants and changing the concentrations of micro crystalline cellulose. The formulation design of both immediate release and conventional tablets were given in table1.

Table 1: Formulation of divalproex sodium tablets

Sl. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
1	Divalproex sodium	125	125	125	125	125	125	125
2	Lactose	81	78.5	81	79.5	81	78.5	101
3	Croscarmellose sodium	10	12.5	-	-	5	6.25	-
4	Sodium starch glycolate	-	-	10	12.5	5	6.25	-
5	Microcrystalline cellulose	25	25	25	25	25	25	15
7	Magnesium stearate	3	3	3	3	3	3	3
8	Talc	6	6	6	6	6	6	6
9	Total	250	250	250	250	250	250	250

Evaluation parameters:

I. 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]

$\text{Tan } \theta = h/r$

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.

C.I =(Dt – Db)100/Dt

Where, Dt – Tapped density of the powder
Db – Bulk density of the powder

II. 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. Friabilitywas 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.Fromthat 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.Disintegrationtime for tablets was performed using disintegration testing apparatus by using water maintained at 37 ± 0.5^0C[8].

***In vitro* dissolution of tablets:**
Dissolution rate of tablets was studied by using USP type-II apparatus at 100 rpm using 900ml of phosphate buffer pH6.8 as dissolution medium maintained at 37 ± 0.5^0C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 210 nm using phosphate buffer pH 6.8 as a blank and percentage cumulative drug release was calculated[9,2].

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].

RESULTS AND DISCUSSION

Pre-formulation studies were carried out for all the formulation. Various pre compression powder properties such as angle of repose, carr'sinderx, hausner's ratio, bulk density, tapped density were determinedand the results were shown in table 2. Pre-formulation studies for the formulations depicted bulk density 0.512 to 0.66 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 1.13 to 1.25 and 16.59 to 22.54^{o} respectively suggested excellent flow property of powder blend.

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	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	16.596±0.356
F2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
F3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
F4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
F5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
F6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077
F7	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077

The tablets were evaluated for various 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 4.14 to 5.74 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. Content uniformity was in range of 97.12 to 98.96% indicated uniform dispersion of Divalproex sodium. The disintegration time of immediate release tabletswas found to be 57.91 to 112.63 seconds for the formulations(F1 & F2) containing sodium starch glycolate and the formulation containing croscarmellose sodium (F3 & F4) showed 39.75 to 53.83 seconds. The disintegration time of the tablets containing combination of both superdisintegrants (F5 & F6) showed 22.53 to 47.31seconds. As the concentration of superdisintegrants increased and combination of super disintegrants made, there was a drastic decrease in the disintegration time was noted. This shows the relationship between the concentration and disintegration time of super disintegrants. Whereas for the conventional tablets (F7) the significant delay in disintegration i.e287 sec was observed.

Table 3: Post-compression parameters

Formulation	Weight variation Mean ±SD	Hardness (kg/cm^2) Mean ±SD	Friability (%) Mean ± SD	Thickness Mean ±SD	Drug content(%) Mean ±SD	Disintegration time (sec) Mean ±SD
F1	249.9±1.57	5.45±0.05	0.74±0.09	2.36±0.04	98.12±1.19	120.33±1.52
F2	250.3±1.60	4.18±0.10	0.58±0.04	2.27±0.10	97.65±1.82	91.66±2.08
F3	250.9±1.60	4.35±0.03	0.56±0.06	2.29±0.07	98.65±1.28	73.33±2.51
F4	251.55±1.99	5.17±0.07	0.65±0.05	2.35±0.03	99.61±0.94	48.33±3.05
F5	251.45±2.52	4.14±0.04	0.63±0.03	2.27±0.06	99.43±1.32	59.33±2.08
F6	250.05±1.81	5.13±0.11	0.69±0.04	2.31±0.09	99.51±1.81	37.33±1.52
F7	249.58±1.59	4.64±0.04	0.43±0.03	2.93±0.03	97.43±1.28	287.64±1.26

In vitro drug release performed on all formulations and the data is given in table 4 and release profile is shown in figure 1. Among all the immediate release formulations (F1 to F6), formulations F1, F2, F3 and F4 showed the least drug release of 80.40 %, 83.44 %, 82.68 % and 94.82 % respectively at the end in 20 minutes, as they contain one super disintegrant. Formulation F6 releases 98.62% drug in 20 minutes as it contains the combination of two super disintegrants i.e., sodium starch glycolate and Croscarmellose. The result indicated that increase in the concentration of superdisintegrants and combination of superdisintegrants increases the release profile of drug. Whereas the *In vitro* dissolution results of conventional tablets (F7) showed 65 % at 20 minutes and 99.31% at the end of 45 minutes, indicated that the release of the drug from immediate release tablets is faster when compared to the conventional tablet. From the kinetic data of release profile it is clearly indicated that all the immediate release formulations (F1 to F6) follows first order kinetics as the values for 'r' is (0.985 to 0.961) and values of 'n' is more than 0.89 shown that Super case II transport. The release kinetics of conventional tablet(F7) was also found to following first order kinetics as the value for 'r' is (0.928) and 'n' was found to 1.1212 shown Super case II transport.

Table 4: *in vitro* dissolution

Time (min)	% CUMULATIVE DRUG RELEASE						
	F1	F2	F3	F4	F5	F6	F7
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.056±0.612	21.226±0.872	20.847±0.450	26.532±1.306	30.323±1.125	36.008±1.174	-
3	31.805±1.075	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255	-
5	53.454±2.280	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723	5.367±0.713
10	64.837±2.481	68.251±3.001	68.250±1.176	81.525±0.896	77.735±1.791	83.424±2.060	11.725±0.864
15	71.106±1.634	78.121±1.913	74.141±1.523	89.829±1.107	81.543±0.873	92.918±1.314	25.832±1.471
20	80.408±1.038	83.445±1.088	82.685±0.582	94.829±0.788	87.246±1.865	98.624±0.722	36.531±0.647
25	86.676±1.427	92.366±1.472	90.280±1.281	97.497±0.931	92.376±1.325	98.827±1.427	51.413±0.1.952
30	91.047±2.031	94.842±1.632	93.135±0.852	98.075±1.265	96.743±1.731	99.404±1.162	65.538±0.621
45	-	-	-	-	-	-	87.371±0.362
60	-	-	-	-	-	-	98.852±1.372
90	-	-	-	-	-	-	99.272±1.035

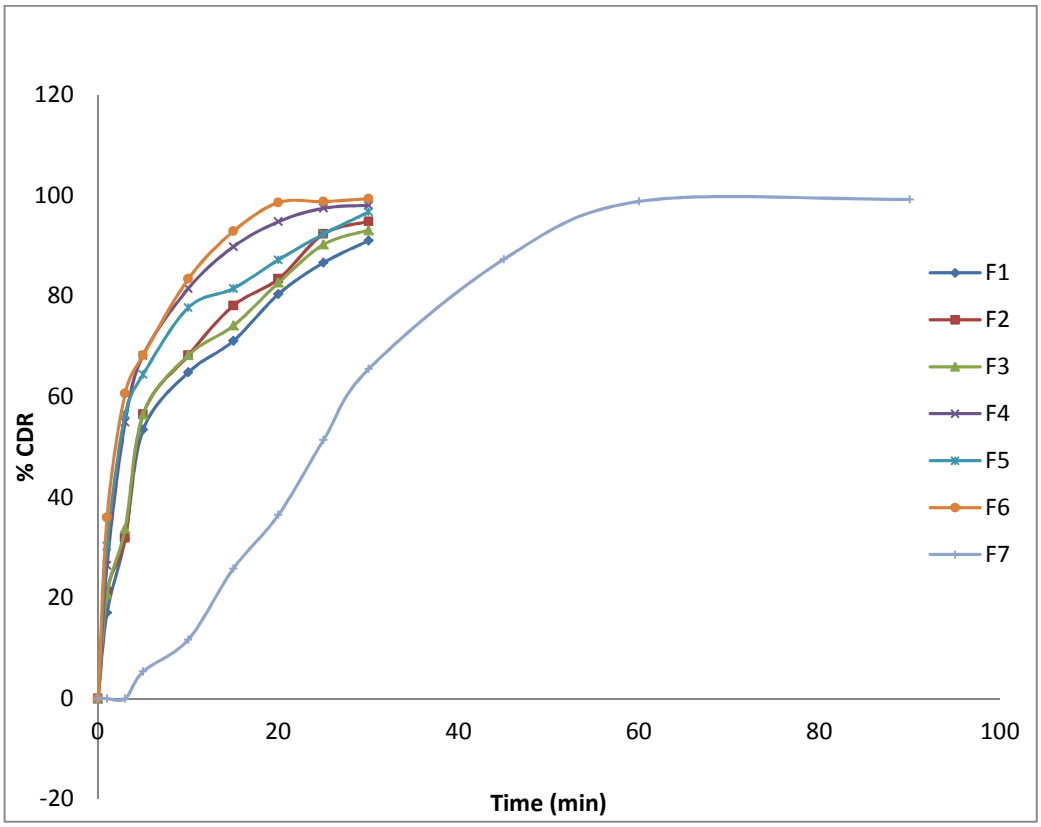

Figure 1: Comparative dissolution profile

The formulations subjected to short term stability study, storing the formulation at 40^0C / 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

In the present work immediate release tablets of divalproex sodium were prepared by wet granulation method, using super disintegrants such as sodium starch glycolate and Croscarmellose. The developed tablets were subjected to hardness, weight variation, friability, drug content uniformity, disintegration time and *in vitro* drug release studies.

FTIR studies indicated that the drug is compatible with all the excipients. The prepared tablets were found to be good and free from chipping and capping. The stability study showed that no significant changes in tablets after 3 months study. Based on the observations, it can be concluded that the formulated immediate release tablets of divalproex sodium using super disintegrants capable of exhibiting all the properties of immediate release tablets. They are thus reducing the time of disintegration and dissolution leading to faster onset of action, and ultimately improve the patient compliance and drug efficiency.

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