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Development and Characterization of Bilayer tablet of Divalproex sodium

Bhushan Ramesh Borse*, Saurabh Jain and Karunakar Shukla

College of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore (M.P.) - India

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Abstract

In the present work bi-layered tablet of Divalproex sodium were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellosefor immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Divalproex sodium were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction

Keywords: Bilayer Tablet, Divalproex, Formulation

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[1]. The popularity of the oral route is attributed ease of administration, patient acceptance, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product[1-2].

There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation do not require sterile conditions and are therefore, less expensive to manufacture[3].

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing[4]. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents[5]. According to Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents[6]. They are varying in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is most popular dosage form and 70% of the total medicines are dispensed in the form of tablet[7].

The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustained layer. Particularly bilayer tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profile[31]. After stoke and dementias, epileptic seizures constitute the 3rd most frequent neurologic disorders encountered in elderly in developed countries[8].

***Corresponding Author**

The aim of the present research work was to develop the different immediate and sustained release formulation of Divalproex sodium and compare theirrelease profile, from above formulation select a best formulation for manufacturing bi-layered tablet.

Hence, in the present research investigation attempt was made to formulate and evaluate bi-layered tablet of Divalproex sodium.

Materials and Methods

Pre-formulation studies

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the excipients that could affect drug performance and development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

Formulation design

Formulation of Immediate release layer

Table 1: Formulation of immediate release layer (IRL)

Sr. No.	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6
1	Divalproex sodium	125	125	125	125	125	125
2	Lactose	82	79.5	82	79.5	82	79.5
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
6	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5
9	Total	250	250	250	250	250	250

Formulation of sustained released layer

Table 2: Formulation of sustained release layer (SRL)

Sr. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25
2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMC K4M	45	52.5	60	-	-	-	22.5	26.25	30
4	HPMC K100M	-	-	-	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6

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8	Total	300	300	300	300	300	300	300	300	300

Preparation of IRL [9-10]

IRL of Divalproex sodium (DS) was prepared by wet granulation by using different Superdisintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing colouring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-

- Pass all the ingredients though sieve #80.
- Mix Divalproex sodium with MCC geometrically and then mix with lactose.
- Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle.
- Make wet mass using binding agent PVP K 30 solution containing colour.
- Pass the cohesive mass through sieve # 16 to get uniform granules.
- Dry the granules at 50^0C for 15 min in hot air oven.
- Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness. The formulations are shown on table.

Preparation of SRL[9-10]

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder 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 300 mg each tablet by adjusting hardness.

Preparation of bi-layered tablet[9-10]

By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.

Evaluation of Pre-formulation Parameters: [9-10]

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. 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 granules. The granules were allowed to flow through the funnel onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$\theta = \tan^{-1}(h/r)$

Where,

θ = the angle of repose, h = height of the heap of the powder, r = radius of the heap of the powder.

Table 15: ANGLE OF REPOSE

Sr. No.	Angle of Repose(θ)	Type of flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	> 40	Very poor

Determination of bulk density and tapped density:[80]

A quantity of 2 g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using following formulas.

$$Db = \frac{mass\ of\ the\ powder}{bulk\ volume\ of\ the\ powder}$$

$$Dt = \frac{mass\ of\ the\ powder}{tapped\ volume\ of\ the\ powder}$$

Carr's index:[81]

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

$$\text{Carr's index}\ \% = \frac{tapped\ density - bulk\ density}{tapped\ density} X\ 100$$

Hausner's ratio:[82]

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{tapped\ density}{bulk\ density}$$

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Evaluation of prepared formulations

Evaluation of Divalproex sodium IRL, SRL and bi-layered tablet

The tablets prepared were evaluated for the following parameters Weight variation, Hardness, Friability, Drug content and In-vitro Dissolution Studies.

Results and Discussion

Table 2: Pre-compression parameters for IRL and SRL

Formulation	Bulk Density Mean ± SD	Tapped Density	Car's Index Mean ± SD	Haunsers Index	Angle of Repose
IF1	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	16.596±0.356
IF2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
IF3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
IF4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
IF5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
IF6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077
SF1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
SF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
SF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
SF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

Table 3: Post-compression parameters for IRL and SRL

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)
IF1	249.9±1.57	5.95±0.05	0.74±0.09	2.87±0.04	98.12±1.19	120.33±1.52
IF2	250.3±1.60	4.18±0.10	0.58±0.04	2.91±0.10	97.65±1.82	91.66±2.08
IF3	250.9±1.60	6.35±0.03	0.56±0.06	2.90±0.07	98.65±1.28	73.33±2.51

IF4	251.55±1.99	6.17±0.07	0.65±0.05	2.87±0.03	99.61±0.94	48.33±3.05
IF5	251.45±2.52	4.14±0.04	0.63±0.03	2.92±0.06	99.43±1.32	59.33±2.08
IF6	250.05±1.81	4.53±0.11	0.69±0.04	2.89±0.09	99.51±1.81	37.33±1.52
SF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09	99.38±1.19	-
SF2	302.9±2.29	4.33±0.02	0.35±0.02	3.30±0.14	98.61±1.03	-
SF3	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
SF4	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57±0.85	-
SF5	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43±1.27	-
SF6	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63±0.61	-
SF7	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47±1.04	-
SF8	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51±1.20	-
SF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49±0.93	-

Table 4: Post-compression parameters for bi-layered tablet

Formulation	Weight variation	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%)
BTF	550.75±0.46	7.05±0.15	0.38±0.01	6.28±0.14	99.23±0.53

Table 5: in vitro dissolution study of IRL

Timein min	% CUMULATIVE DRUG RELEASE					
	IF1	IF2	IF3	IF4	IF5	IF6
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
1	17.056±0.61	21.226±0.872	20.847±0.450	26.532±1.306	30.323±1.125	36.008±1.174
3	31.805±1.07	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255
5	53.454±2.28	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723
10	64.837±2.48	68.251±3.001	68.250±1.176	81.525±0.896	77.735±1.791	83.424±2.060
15	71.106±1.63	78.121±1.913	74.141±1.523	89.829±1.107	81.543±0.873	92.918±1.314
20	80.408±1.03	83.445±1.088	82.685±0.582	94.829±0.788	87.246±1.865	98.624±0.722
25	86.676±1.42	92.366±1.472	90.280±1.281	97.497±0.931	92.376±1.325	98.827±1.427
30	91.047±2.03	94.842±1.632	93.135±0.852	98.075±1.265	96.743±1.731	99.404±1.162

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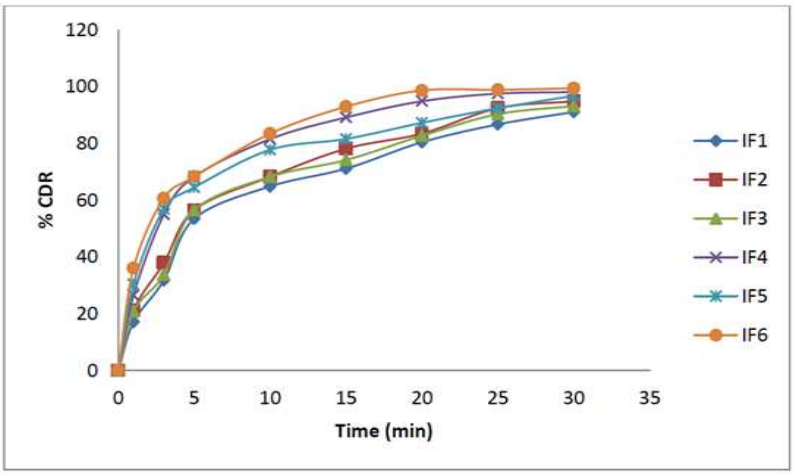

Fig. 1: Release profile of immediate release layer

Table 6: In vitro dissolution study of SRL

Time in min	% CUMULATIVE DRUG RELEASE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
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	0.000±0.000
60	15.408±1.222	7.905±1.234	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591	13.006±1.994	5.391±0.882
120	25.634±1.764	19.263±1.532	18.231±1.281	25.637±0.732	18.521±1.421	12.635±0.751	21.351±1.317	17.527±1.114
240	34.323±2.715	24.502±1.083	23.091±1.547	33.235±1.164	25.279±1.003	17.697±1.151	33.589±1.503	24.917±1.426
360	42.342±0.632	31.362±1.321	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427	45.247±0.941	36.518±0.831
480	57.151±1.196	43.141±1.974	36.936±1.251	56.674±2.061	47.993±0.539	33.733±2.378	53.869±1.510	46.331±0.891

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600	62.342±0.412	48.234±0.826	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114	59.523±1.163	52.852±0.792
720	76.620±1.642	56.263±2.227	54.964±2.137	70.315±2.001	65.327±1.779	47.031±1.480	68.215±0.906	64.017±0.710
960	98.183±0.352	82.430±1.267	66.957±1.402	87.123±0.645	86.182±0.467	54.439±2.565	88.053±0.676	77.498±0.918
1080	101.512±1.093	97.816±0.630	84.113±1.317	98.822±1.325	97.692±0.844	67.057±1.191	100.859±2.1865	94.298±0.560

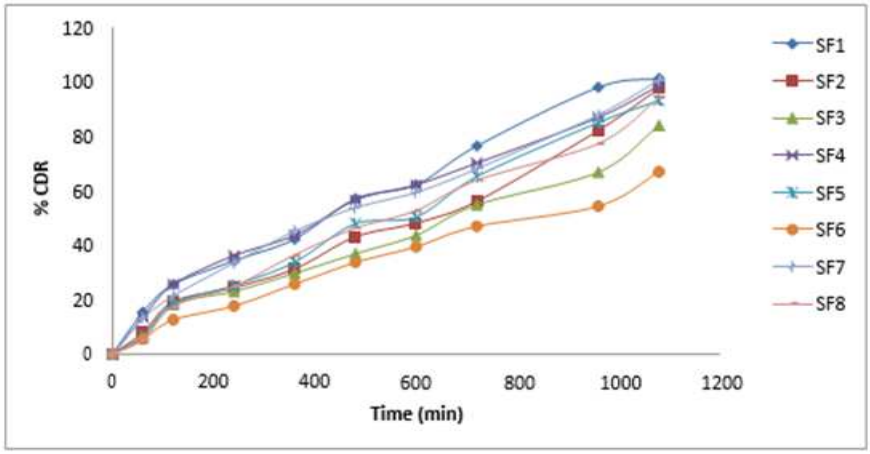

Fig. 2: Release profile of sustained release layer

Table 7: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	BTF	
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	83.424±1.063	-
20	98.351±1.147	-
30	99.413±0.731	-

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60	-	5.384±1.032
120		17.512±0.853
240	-	23.483±1.520
360		36.164±0.638
480	-	46.054±0.825
600		52.854±0.841
720	-	64.781±0.527
960	-	76.149±0.952
1080	-	95.823±0.614

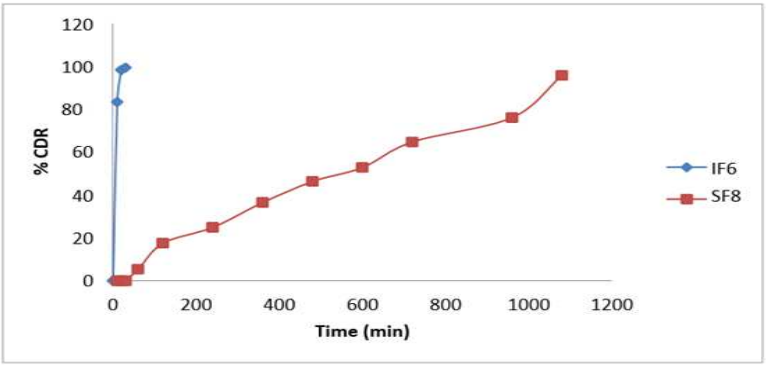

Fig. 3: Release profile of Bi-layered Tablet

Conclusion

Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters. According to the in vitro dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed 98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours. The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping. The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^2.. The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared. The friability of the prepared tablet was found to be less than 1%. The percentage drug content was uniform in all the formulations of prepared bi-layered tablets. In vitro drug release pattern of the bi-layered tablets were same as individual layer tablets.

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