Formulation and Evaluation of Bi-layered Tablet of Divalproex Sodium

[1]Aditya Gupta, [2]Dr. Nidhi Bais

Oriental College of Pharmacy and Research
Oriental University, Indore, (M.P.) - India

Abstract- **The objective of the current study was to develop bi-layered tablets of Divalproex Sodium containing immediate release layer and sustained release layer. Divalproex Sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy and bi-polar disorders and prophylaxis of migraine. Both layer of divalproex sodium were prepared by wet granulation method. The immediate release layer was formulated by using sodium starch glycolate, croscarmellose sodium as super disintegrants. HPMC K4M and HPMC K100M polymer used to retard the drug release from sustained release layer in different proportion and combination. The optimized Immediate release layer (IF6) & sustained release layer (SF6) were selected to prepare Bi-layered tablet of Divalproex Sodium. *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. All the formulations were evaluated for post-compression parameters like hardness, weight variation, friability, thickness, disintegration time, drug content and *in-vitro* % drug release. The formulations were selected based on their disintegration time and *in-vitro* % drug release. The final results obtained showed that the disintegration time is 35.33 seconds and *in-vitro* % drug release of IRL 99.50 % & *in-vitro* % drug release of SRL 99.56%.**

Keywords: **Divalproex Sodium, Bi-layered Tablet, Antiepileptic, Patient acceptance, Immediate Release, Sustained Release.**

INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of Dosage form[1].The popularity of the oral route is attributed to ease of administration, patient compliance, accurate dosing, cost effective manufacturing method and generally improves shelf-life of the product[2].

Bilayer tablet is convenient for sequential release of two drugs in combination it is also capable of separating the two types of incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and the second layer is maintenance dose[3].Bilayer tablet is a great example of avoiding chemical incompatibilities between the APIs and providing different drug release profiles (Immediate release with extended-release)[4].

Divalproex sodium is considered as the most important antiepileptic drug and broadly used for treatment of epilepsy and bi-polar disorders and prophylaxis of migraine[4]. It increases the availability of gamma amino butyric acid (GABA), an inhibitory neurotransmitter. It has inhibitory action against GABA transaminase which breakdown GABA, it leads to increased concentration of GABA in the synapses. Other propose mechanisms of action that account for their anticonvulsant properties is it either enhance the action of GABA or mimic its action at postsynaptic receptor sites. It also block voltage gated sodium channels and T-type calcium channels, and cause inhibitory activity in the brain[5].

MATERIAL AND METHODS

Materials

Divalproex sodium was a gift sample obtained from ROAQ Chemicals Pvt. Ltd. Varodara. Sodium Starch Glycolate, Microcrystalline cellulose, Croscarmellose sodium, HPMC K 4M, HPMC K 100M, Magnesium stearate, Talc, from Kasliwal Brothers, Indore. All chemicals were used of analytical grade.

Methods

Melting Point determination

Capillary tube was taken and its one end was sealed by heating. Capillary tube was filled upto 2-3 mm high with drug powder. The capillary tube kept inside melting point apparatus and temperature was increased slowly. The temperature was noted when the drugs gets starts melting and again noted when drug completely melted.

UV Spectroscopy

50 mg of Divalproex sodium was weighed and dissolved in 50 ml of Methanol to prepare a 1000µg/ml stock solution from which a 10µg/ml dilution was prepared. Baseline correction was performed using Methanol and sample was run between the range 190-380 nm wavelengths in spectrum mode by using schimadzu 1800 UV visible spectrophotometer.

Calibration curve

The calibration curve of Divalproex sodium was prepared in Methanol and phosphate buffer pH 6.8 by using schimadzu 1800 UV spectrophotometer.

Accurately weighed 50 mg of Divalproex sodium was transferred into a 50 ml volumetric flask and the volume was made up with Methanol to obtain a 1000µg/ml stock solution of Divalproex sodium.

From the above stock solution 1ml was taken and transferred into 10ml volumetric flask and the volume was made up with Methanol to obtain 100 µg/ml of solution from which 2, 4, 6, 8 & 10µg/ml dilutions were prepared. Same procedure was followed for phosphate buffer pH 6.8 to prepare a calibration curve respectively.

Solubility studies

The solubility of Divalproex sodium in various medium was determined by using shake flask method. In this method 2ml of each solvent was taken into vials and an excess amount of Divalproex sodium was added. The vials was sealed properly and stirred for 10 min. They were the kept on orbital shaker at 37°C for 24 h. After solubilization of Divalproex sodium, An extra amount of Divalproex sodium was added to the vials containing drug-solvent mixture. The process was repeated until saturation solubility of Divalproex sodium was indicated by presence of un dissolved drug. The mixture was then kept at room temperature for 24 h and centrifuged using Remi 12C micro-centrifuge at 3000 rpm for 15 min. The supernatant were separated and diluted with respective solvents. The drug concentration was analyzed spectrophotometrically at 210 nm using UV-visible spectrophotometer (schimadzu 1800).

Formulation design

Calculation of dose

The total dose of Divalproex sodium for once daily formulation was calculated by the following equation, using available pharmacological data.

Dt = Dose (1+0.693xt/t1/2)

Where, Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hr during which the sustained release is desired (18 hrs)

t1/2 = half life of the drug (9 hrs)

Therefore, Dt = 125(1+0.693x18/9), Dt ≈ 298.25 Therefore maintenance dose = 298.25-125

A) Formulation of Immediate Release Layer.

Table 1: Formulation of Immediate Release Layer (IRL)

S. 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	Ponceau4R	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

Total	250	250	250	250	250	250

B) Formulation of Sustained Released Layer.

Table 2: Formulation of Sustained Release Layer (SRL)

S. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6
1	Divalproex sodium	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
3	HPMCK4M	45	52.5	60	-	-	-
4	HPMCK100M	-	-	-	45	52.5	60
5	Microcrystalline cellulose	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6
Total		300	300	300	300	300	300

Precompression Parameters[6]

a) Bulk density:

Bulk density was determined by pouring a 10 gm of powder into a 100 ml measuring cylinder through funnel and measure the volume of powder.

Bulk density = Mass of powder / Poured volume of powder

b) Tapped density:

10 gm of powder was weigh and transferred into the measuring cylinder. The measuring cylinder was then kept on a mechanical tapper apparatus and tapping of 100 times was done. The volume was occupied by the powdered bed was noted.

Tapped density = Mass of powder / Tapped volume of powder

c) Angle of repose

The powder flow property was determined by using the angle of repose. The height of the funnel was adjusted to 4 cm above the working slab. The accurately weighed powdered blends were poured through the funnel until pile of powder touches the pipe of the funnel and the height of the powder and the diameter of the powder was noted and calculated. The powder flow property was determined by using angle of repose.

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

Where, θ = angle of repose

h = height

r = radius

d) Carr's index:

The Carr's index was an indication of compressibility of a powder and calculated using the formula given below.

Carr's = bulk volume – tapped volume / bulk volume x 100

e) Hausner's ratio:

It is found that the ratio of tapped density and bulk density. A value greater than 1.5 indicates poor flow, between 1.25 and 1.5 added glidant to improve flow and value less than 1.25 indicated good flow.

Hausner's ratio = Tapped density / bulk density

Preparation of Immediate Release Layer

Divalproex sodium (DS) Immediate release layer was prepared by wet granulation method by using different Superdisintegrants such as SSG and Croscarmellose sodium. PVP K30 solution which contain coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used asadsorbent. Manufacturing steps-

- All the weigh ingredients were passed though sieve #80.
- Mix Divalproex sodium with MCC geometrically and then add lactose.
- Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle.
- Make wet mass by using binding agent PVP K 30 solution containing color.
- To get uniform granules cohesive mass were passed through sieve # 16.
- Dry the granules at 50^0C for 15 min in hot air oven.
- Granules was lubricated with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness. The formulations are shown on table no 1.

Preparation of Sustained Release Layer

- Accurately weighed Divalproex sodium, polymer and other ingredients were taken in mortar and pestle and mixed well.
- The powder were mixed with sufficient quantity of PVP K30 solution until wet mass prepared.
- The cohesive mass 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 lumps.
- Then Talc and Magnesium stearate were added in the granules and compressed into 300 mg each tablet by adjusting hardness. The formulations are shown on table no 2.

Preparation of Bi-layered tablet

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

Evaluation of Tablet[7,8]

a) Weight variation:

20 tablets were selected randomly and weighed. The average weight was calculated and compares individual tablet weight with average weight. In case of 20 tablets not more than 2 tablets show % weight variation. If more than 2 tablets were deviate from the range, re-tests 20 tablets were done and not more than two tablets should deviate from 40 tablets.

b) Hardness:

The tablet was placed on the holder and the scale was set at "0" on Monsento tester. The range of Monsento hardness tester was "0 to 20" kg. The pressure was applied on tablet till they break. The reading was noted.

c) Thickness:

Thickness of the tablet was measured by Vernier caliper. The tablet was placed laterally between the jaws of Vernier caliper. Jaws were adjusted to just touch object to be measured. The reading was noted.

d) Friability:

The friability was used to define the % weight loss due to mechanical action. The tablets were weight and placed in a Friabilator after 100 revolutions the tablets were again weight and their % weight loss was calculated using formula.

% friability = (Initial weight- final weight) / Initial weight X 100

e) Disintegration Time:

In the 6 glass tube 1 tablet was placed and added a disc to each tube. The assembly was suspended in the beaker containing purified water. The apparatus was operated until the tablets completely disintegrate. The time taken was noted for the complete disintegration of the tablet.

f) Drug Content:

The drug content was determined by using calibration curve method. Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 210 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

g) *In-vitro* dissolution studies of immediate release layer:

The *in-vitro* drug release studies were performed by using USP-II (paddle type) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 is used as a dissolution media and temperature is maintained at 37 ± 0.50^0C. A 5 ml sample was withdrawn and replaced with same volume of fresh media at specific time intervals. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 210 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

h) *In- vitro* dissolution studies of sustained release layer:

The *in-vitro* drug release of sustained release layer was carried out for 18 hours using USP type-II apparatus (DT-

1200) at 100 rpm for the first 45 minute in 900 ml of 0.1N HCL and temperature is maintained at 37 ±0.5^{0}C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml sample 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.

i) Stability studies:

Formulation was exposed to different conditions of temperature as well as relative humidity ICH guidelines (37°C±2°C and 75±5% RH Q1C) for a period of 3 month. Samples were withdrawn at 1 month time intervals and evaluated for weight variation, hardness, disintegration time, *in-vitro* % drug release and the drug content.

RESULT & DISCUSSION:

Table 7.3: Pre-compression Parameters for IRL and SRL

Formulation	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Car's Index	Hausner's Index	Angle of Repose (Degree)
IF1	0.55	0.63	12.61	1.14	16.59
IF2	0.56	0.65	15.08	1.17	18.36
IF3	0.52	0.62	15.7	1.16	19.42
IF4	0.58	0.68	13.89	1.16	20.14
IF5	0.61	0.68	11.76	1.18	17.81
IF6	0.65	0.75	11.14	1.14	17.05
SF1	0.59	0.69	13.77	1.15	19.60
SF2	0.58	0.69	14.49	1.16	18.48
SF3	0.60	0.68	11.22	1.13	18.20
SF4	0.62	0.70	11.53	1.13	22.54
SF5	0.59	0.71	16.14	1.20	18.34
SF6	0.59	0.72	18.71	1.25	18.17

Table 4: Post-compression Parameters for IRL and SRL

Batch Code	Weight Variation 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
IF1	247.9±1.57	5.93±0.05	0.74±0.09	2.89±0.04	99.12±1.19	118.33±1.52
IF2	251.3±1.60	4.16±0.10	0.58±0.04	2.93±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	96.65±1.28	75.33±2.51
IF4	252.55±1.99	6.10±0.07	0.65±0.05	2.87±0.03	95.61±0.94	46.33±3.05
IF5	251.45±2.52	4.30±0.04	0.63±0.03	2.92±0.06	96.43±1.32	60.33±2.08
IF6	249.05±1.81	4.53±0.11	0.69±0.04	2.89±0.09	99.51±1.81	35.33±1.52
					98.38±1.19	-

SF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09		
SF2	300.9±2.29	5.33±0.02	0.35±0.02	3.33±0.14	98.61±1.03	-
SF3	303.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
SF4	302.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	96.57±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	6.12±0.02	0.48±0.03	3.33±0.03	99.63±0.61	-

Table 5: Post-compression Parameters for Bi-layered Tablet

Formulation	**Weight variation Mean±SD**	**Hardness Mean±SD**	**Friability Mean±SD**	**Thickness Mean±SD**	**Drug content (%) Mean±SD**
BTF	549.75±0.46	7.02±0.15	0.43±0.01	6.31±0.14	99.34±0.53

Table 6: *In-vitro* % drug release of IRL

Time (min)	**IF1**	**IF2**	**IF3**	**IF4**	**IF5**	**IF6**
0	0	0	0	0	0	0
1	17.06	21.22	20.84	26.53	30.32	36.08
3	32.80	33.90	33.73	54.96	56.56	62.65
5	55.45	56.48	56.48	68.24	63.45	69.24
10	66.83	68.25	69.20	79.52	75.73	83.42
15	70.10	78.12	74.14	89.82	81.54	92.91
20	82.40	83.44	83.68	94.82	87.24	96.42
25	86.67	92.36	89.28	96.49	92.37	98.72
30	91.04	94.84	93.13	97.70	95.74	99.50

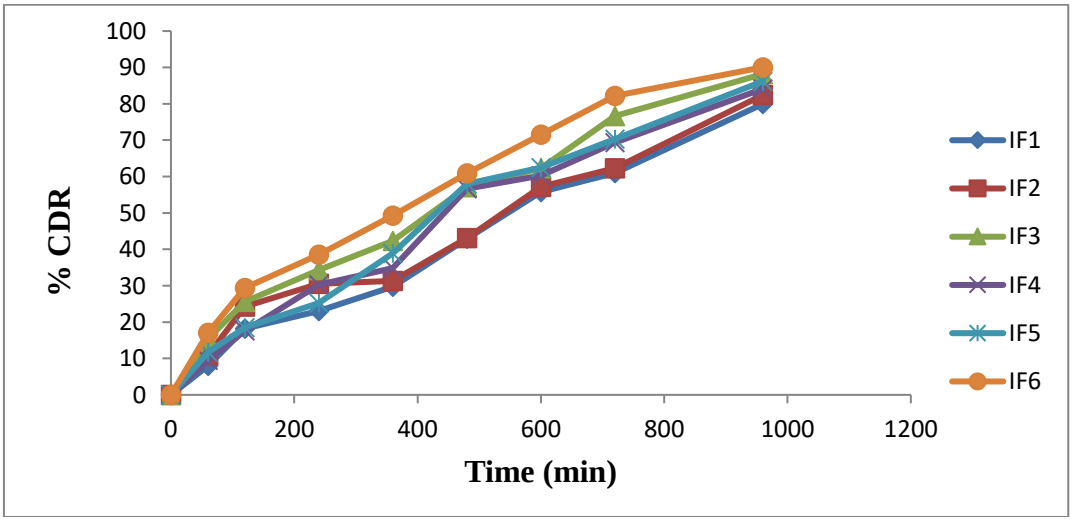

Figure 1: *In-vitro* % drug release of IF1 to IF6 formulations.

Table 7: *In-vitro* % drug release of SRL

Time (min)	SF1	SF2	SF3	SF4	SF5	SF6
0	0	0	0	0	0	0
60	08.01	10.90	15.40	09.46	11.74	17.05
120	18.23	24.26	25.63	17.63	18.52	29.35
240	23.09	30.50	34.32	30.23	25.27	38.58
360	29.73	31.36	42.34	34.85	38.85	49.24
480	42.90	43.14	57.15	56.67	57.99	60.86
600	55.75	57.23	62.34	60.31	62.49	71.52
720	60.96	62.26	76.62	69.31	70.32	82..23
960	79.95	82.43	88.18	84.12	86.18	90.05
1080	95.11	96.81	97.51	97.82	98.69	99.56

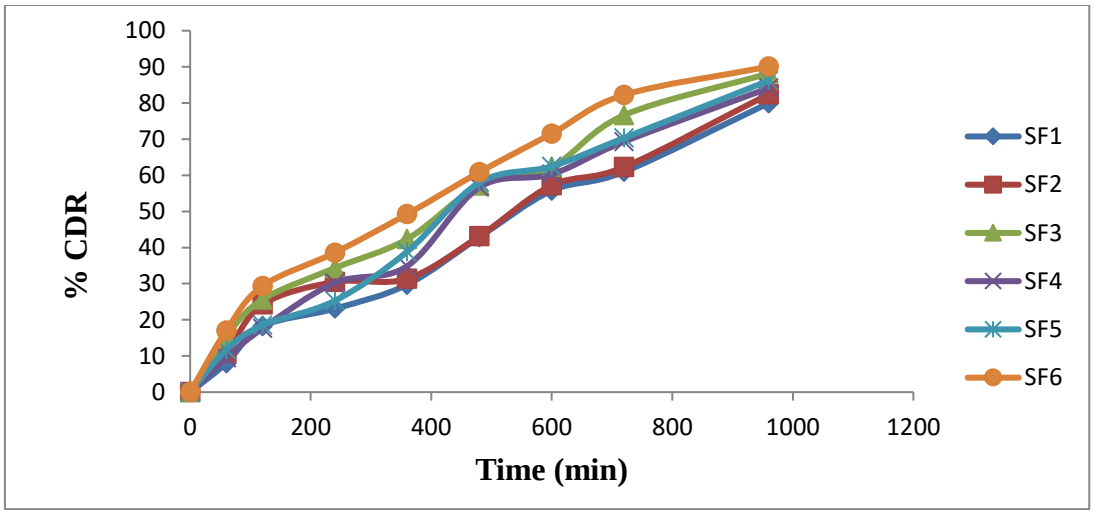

Figure 2: *In-vitro* % drug release of SF1 to SF6 formulations

Table 8: Dissolution study of Bi-layered Tablet

Time (min)	% Drug release of IRL	% Drug release of SRL
0	0	0
10	83.42±1.063	-
20	96.42±1.147	-
30	99.50±0.731	-
60	-	17.05±0.731
120	-	29.35±1.147
240	-	38.58±1.20
360	-	49.24±1.145
480	-	60.86±0.731
600	-	71.52±1.240

720	-	82..23±1.31
960	-	90.05±1.25
1080	-	99.56±0.731

Table 9: Stability data

Stability period	40^0C/ 75%RH				
	Hardness Mean±SD	Weight Variation	%Drug content Mean±SD	Drug release	
				IRL (30min)	SRL (1080 min)
Initial	7.02±0.67	549.75±0.46	99.63±0.61	99.50	99.56
1 month	7.02±0.49	549.75±0.46	99.63±0.751	99.50	99.56
2 month	7.02±0.49	549.75±0.46	99.63±0.792	99.50	99.56
3 month	6.90±0.60	551.60±0.32	97.88±0.921	98.80	98.52

CONCLUSION:

In the present work bi-layered tablet of Divalproex sodium were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for 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.

ACKNOWLEDGEMENT:

The authors are thankful to Oriental College of Pharmacy and Research, Indore for providing necessary facilities in the institute. Sincerely thanks to ROAQ Chemicals Pvt. Ltd, Vadodora for providing drug as a gift sample.

REFERENCES:

1. Momin et al; Formulation and evaluation of Bilayer tablets of propranolol hydrochloride Journal of Drug Delivery and Therapeutics 2017; 7(2). 50.
2. Sreya and Suja studies on formulation and evaluation of bilayered tablets of curcumin IJPSR, 2020; Vol. 11(3) 1190
3. Bhosale M D and Kulkarni K S: Bilayer tablet-A comprehensive review. EJPMR 2017; 4(9): 241-251.
4. Costa LLO, et al. Update on epilepsy: literature review. Rev Med (São Paulo). 2020; 99(2):171
5. Ajaz A., Satkar P. and Gaurav D. Formulation and evaluation of bi-layered tablet of divalproex sodium. Journal of Pharmacognosy and Phytochemistry. 2023; 12(2): 16-17.
6. Hadi M A, Rao N G, Firangi S. Mini-Tablets Technology: An Overview. Am J Pharma Tech Res. 2012; 2(2):128-49.
7. Kumari L P, et. al., Formulation and Evaluation of Bi-layer Floating of Tablets Quinapril HCL. Int J Pharma P. 2013;4(1):34-40
8. Patel H P, Karwa P, Patel N J. A Noval Approch to Sustained Zolpidem Tartrate Release: Compressed Mini-Tablets. Int J Pharma Sci Rev Res. 2011;7(2):53-8.