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FORMULATION AND EVALUATION OF BI-LAYERED TABLET OF DIVALPROEX SODIUM

[*1]Neha Yadav, [2]Dr. Navjot Singh and [3]Dr. Anwar IQBAL Khan

[1,2,3]NRI Institute of Pharmacy, Bhopal, M.P.

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***Corresponding Author**
Neha Yadav
NRI Institute of Pharmacy,
Bhopal, M.P.

ABSTRACT

The aim of present work is a formulation and evaluation of bi-layer tablet of Divalproex sodium, which is used in treatment of epilepsy, bipolar disorders and used in prophylaxis of migraine, was carried out. The formulation known as bi-layered tablet was developed with the aim to deliver the Divalproex sodium as immediate release and extent the drug release for 18 hours for the better and extended clinical effect. Compatibility studies by FTIR indicate that no significant interactions between excipients. Both layer were prepared by wet granulation and punched separately. Six formulations (IF1-IF6) of immediate release tablets were prepared by using sodium starch glycolate and croscarmellose sodium. Eight formulations (SF1-SF8) of sustained release were prepared by using HPMC K4M and HPMC K100M in different ration and combination. All formulations were evaluated for pre-compression and post-compression parameters. Bi-layered tablets were prepared by using selected best formulations of each layer. IF6 from immediate release layer as they showed 98.62 % drug release within 20 minutes. SF8 from sustained release layer as they showed 94.29 % drug release at 18 hours and also the releasepattern was within the limit of sustained release tablet. Prepared bi-layered tablet were evaluated for post-compression paramaters. Drug excipient interaction was determined by FTIR. Short term stability studies of formulated bi-layered tablet were carried out at 40^0C / 75% RH for 3 months. Stability studies at 40 ^{0}C / 75 % RH for 3 months for bi-layered tablet batches indicated that there are no significant loss in drug content, release profile and physical appearance.

KEYWORDS: Sustained release, dosing frequency, Evaluation, drug content, bioavailability.

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 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.

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.

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. 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. 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 inthe form of tablet.

Advantage of the tablet dosage form

- They are unit dosage form and great dose precision and the lease content variability.
- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallow.
- Objectionable odour and bitter taste cab be masked by coating technique.
- Suitable for large scale production.

Advantages of Immediate Release Drug Delivery System

- Improved compliance
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives
- Allow high drug loading

- Ability to provide advantages of liquid medication in the form of solid preparation
- Adaptable and amenable to existing processing and packaging machinery
- Cost-effective
- Improved solubility of the pharmaceutical composition.

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The basic goal of therapy is toachieve a steady state drug in blood level for an extent period of time.

Advantage of Bi-layered tablets

- Bi-layered execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odor and bitter taste can be masked by coating technique.
- Flexible concept.
- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Easy to swallowing with least tendency for hang-up. Suitable for large scale production.

MATERIALS AND METHODS

MARETIALS: Divalproex sodium was purchased from jk chemical. Other chemicals such as Lactose, HPMCK4M, HPMCK100M, Microcrystalline cellulose, Magnesium stearate, and talc obtained from institute. All the chemicals should be analytical grade.

METHODS

A) Formulation of Immediate release layer

Table 1: Formulation of immediate release layer.

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	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

b. Formulation of sustained layer

Table 2: Formulation of sustained layer.

S. 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
8	Total	300	300	300	300	300	300	300	300	300

RESULT AND DISCUSSION

MELTING POINT: Melting point of drug was determined by capillary method. The result is found to be **219- 223^{0}C.**

EVALUATION OF PRE-COMPRESSION PARAMETERS

Table 3: Pre-compression parameters for IRL and SRL.

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
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

POST-COMPRESSION EVALUATION PARAMETERS

Table 4: 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) Mean ± SD
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	-

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	550.75±0.46	7.05±0.15	0.38±0.01	6.28±0.14	99.23±0.53

In-vitro Dissolution study

Table 6: In-vitro dissolution study of IRL.

Time in 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±0.612	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
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
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
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
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
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

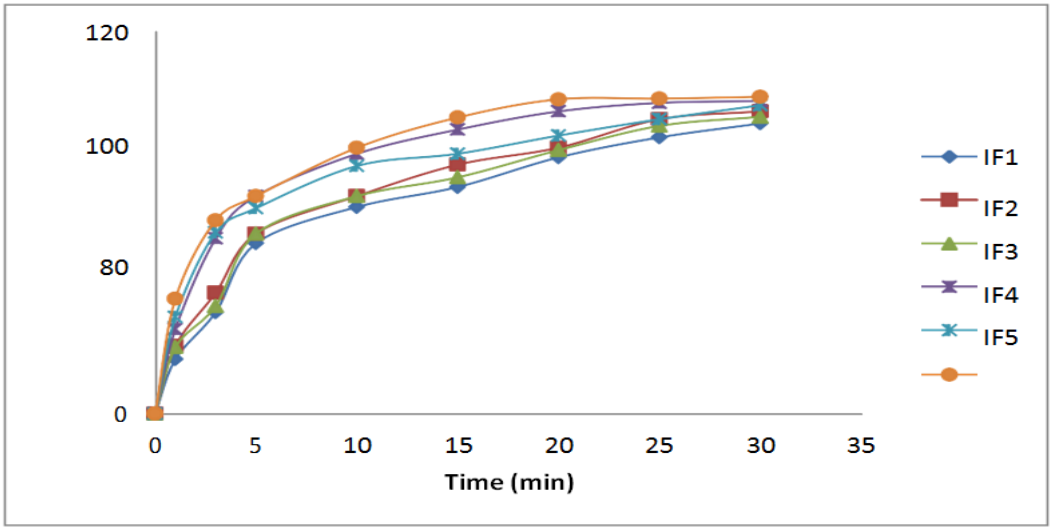

Figure 1: Release profile of immediate release layer.

Table 7: In-vitro dissolution study of SRL.

Time in min	% CUMULATIVE DRUG RELEASE						
	SF1	SF2	SF3	SF4	SF5	SF6	SF7
0	0.000±0.000	0.000±0.00	0.000±0.00	0.000±0.00	0.000±0.000	0.000±0.00	0.000±0.00
60	15.408±1.22	7.905±1.23	6.017±1.50	13.469±1.22	6.741±1.281	5.558±1.59	13.006±1.99
120	25.634±1.76	19.263±1.53	18.231±1.28	25.637±0.73	18.521±1.421	12.635±0.75	21.351±1.31
240	34.323±2.71	24.502±1.08	23.091±1.54	33.235±1.16	25.279±1.003	17.697±1.15	33.589±1.50
360	42.342±0.63	31.362±1.32	29.735±0.94	38.852±1.52	33.852±1.835	25.742±1.42	45.247±0.94
480	57.151±1.19	43.141±1.97	36.936±1.25	56.674±2.06	47.993±0.539	33.733±2.37	53.869±1.51
600	62.342±0.41	48.234±0.82	43.752±1.42	62.316±1.83	50.491±0.694	39.513±1.11	59.523±1.16
720	76.620±1.64	56.263±2.22	54.964±2.13	70.315±2.00	65.327±1.779	47.031±1.48	68.215±0.90
960	98.183±0.35	82.430±1.26	66.957±1.40	87.123±0.64	86.182±0.467	54.439±2.56	88.053±0.67
1080	101.512±1.09	97.816±0.63	84.113±1.31	98.822±1.32	97.692±0.844	67.057±1.19	100.859±2.16

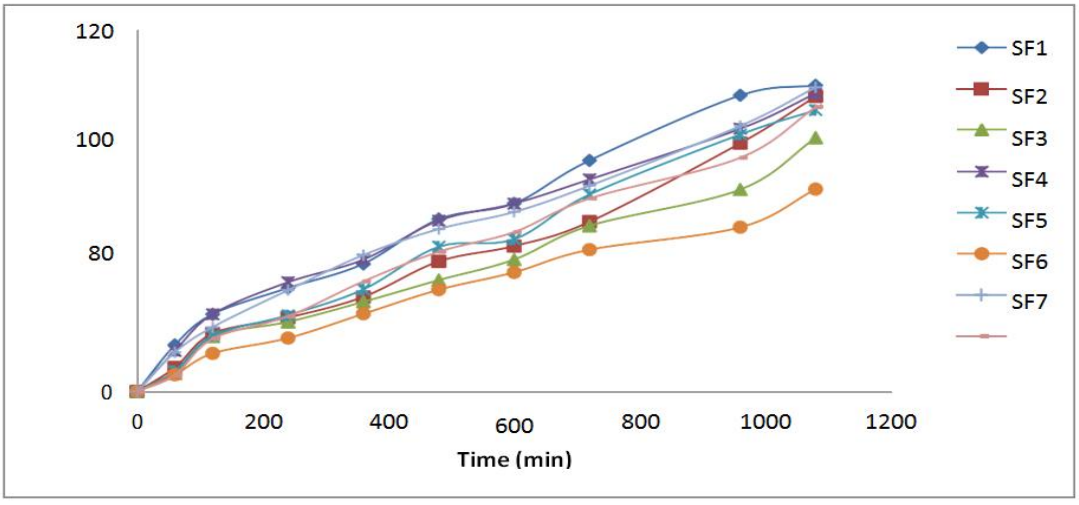

Figure 2: Release profile of sustained release layer.

Table 8: Dissolution study of bilayered tablets.

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	-
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

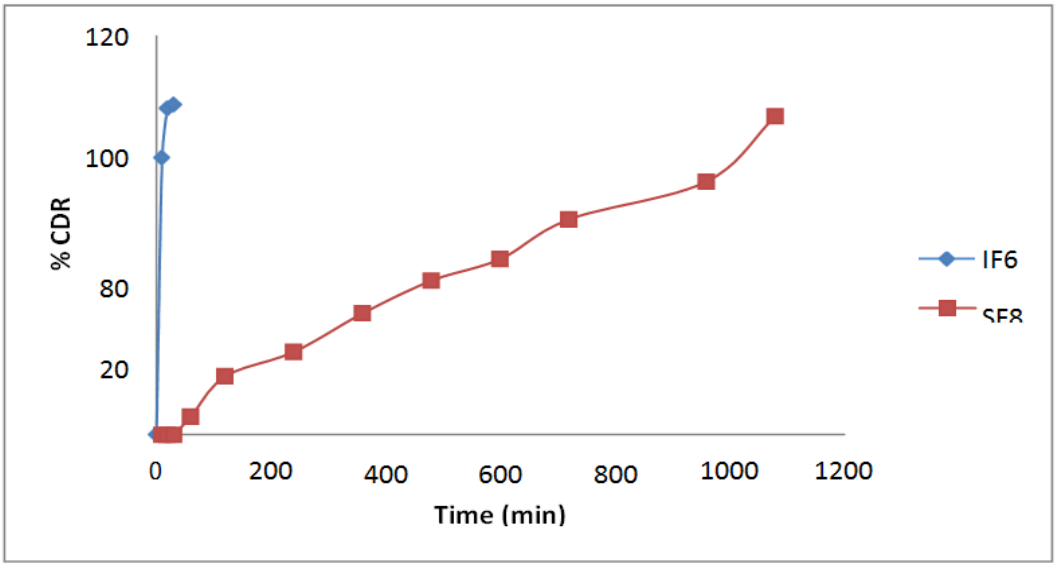

Figure 3: Release profile of Bi-layered Tablet.

STABILITY STUDIES

Table 9: Stability data.

Stabilityperiod	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.05±0.67	0.36±0.01	99.23±0.532	99.413	95.823
1 month	7.08±0.49	0.43±0.03	99.35±0.751	99.581	95.421
2 month	6.41±0.49	0.56±0.06	98.96±0.792	99.142	94.736
3 month	5.33±0.60	0.73±0.03	96.94±0.921	98.728	94.381

SUMMARY AND CONCLUSION

In the present work, formulation and evaluation of bi-layered tablet of Divalproex sodiumwas carried out. For this different formulations of immediate release and sustained release layer have been prepared separately.

Divalproex sodium is mainly antiepileptic drug and it is a right candidate for immediate as well as sustained release formulations.

Both immediate and sustained release formulations were prepared by wet granulation method using PVP K30 solution as binding agent. Six batches (IF1-IF6) of immediate release layer and nine batches (SF1-SF8) of sustained release layer were developed by altering the excipients ratio. Immediate release tablet were prepared by using superdisintegrants such as sodium starch glycolate and croscarmellose sodium and Sustained release tablet were prepared by using polymer like HPMC K4M and HPMC K100M. The tablets were evaluated for weight variation, friability, thickness, drug content and in vitro dissolution parameters. Best formulations for preparation of bi-layered tablet were selected depending upon the dissolution profile as all the formulation showed good content uniformity, friability, hardness and other physical parameters.

Pre-formulation studies were carried out for all the formulation. Powder properties suchas angle of repose, carr's inderx, hausner's ratio, bulk density, tapped density were determined. 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.

Though the batch size of formulations were limited to 50-80, weight variation wasreasonably satisfy the IP Limits as given in table no 18 and the drug content uniformity of all formulations was found to be 97.43-99.61 which indicated uniform distribution of drug in all batches of the formulations. Further hardness and friability was also between 4-6 kg/cm^2 and less1% respectively indicating stability of tablets against physical shocks.

In vitro drug release profile of the immediate release and sustained release formulations were given. Among all formulations of immediate release layer, formulation IF1, IF2, IF3 and

IF4 showed the least drug release 80.40, 83.44, 82.68 and 94.82 respectively in 20 min as they consist of 5% SSG, 6% SSG, 5% CD and 6% CDrespectively. Formulation IF6 releases 98.62% drug in 20 min. The release profile of the formulation IF6 was believed be due to combination of SSG and CD. The result indicated that increase in the concentration of superdisintegrants and combination of super disintegrants increases the release profile of drug. In sustained release formulation, the formulation SF1 (15% HPMC K4M) showed highest release in 16 hours compare to the formulations SF2 and SF3 (17.5 and 20% HPMC K4M) which showed the drug release of 97.81 and 84.11% in 18 hours. The formulations SF4 and SF5 containing 15% and 17.5% of HPMC K100M showed 98.82 and 97.69% drug release in 18 hours. SF8 was selected as best sustained release formulation based on dissolution profile as they showed more than 90% after 18 hours. The formulations found to contain combination of HPMC K4M and HPMC K100M in ratio 1:1 of the concentration 17.5% of total weight. The formulation SF9 showed floating behavior which consists of polymers in 20% of total weight so withdrawn the batches from the dissolution studies The selected formulation of immediate and sustained release layer was prepared as bi- layered tablet and the post-compression parameters tabulated in 25. Hardness and friability showed 7.05±0.15 and less than 1% respectively indicating the stability against physical stokes. Thickness was found to be 5.75±1.83 mm and content of uniformity 99.23±0.53 indicate uniform distribution of drug in both layer. In vitro drug release showed in table no 28. The release patternof the drug from bi-layered tablet showed same as the individual layer tablets of immediate and sustained release.

Stability studies at 40^0C / 75% RH for 3 month for bi-layered tablet tabulated in table no 32 showed that there are no significant loss in drug content, hardness and also no any changes in physical appearance within 2 month of the stability period. But there was slightly change in the hardness and drug content of uniformity in 3 month period stability data which indicates that special care during the storage condition. In in vitro drug release pattern no significant change than the initial period.

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