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A NOVEL APPROACH FOR FORMULATION AND EVALUATION OF ANTICONVULSANT BI LAYERED TABLETS

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Abstract:
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. The present work has been done to formulate bi-layered tablet of Divalproex sodium containing immediate release layer and sustained release layer. The FTIR study revealed that there was no interaction between drug and polymer and combination can be safely prepared. Both layers were prepared by wet granulation technique as poor flow property exhibited by pure drug. The immediate release layer was formulated by using sodium starch glycolate, croscarmellose sodium as superdisintegrants and evaluated for physical parameters, disintegration time and in vitro drug release. The optimized immediate release layer (IF6) with highest in vitro release of 98.11 was selected for bi-layered tablet formulation. HPMC K4M and HPMC K100M polymer used to retard the drug release from sustained release layer in different proportion and combination and evaluated for physical parameter along with in vitro drug release studies.. The optimized sustained release layer (SF8) which extends the Divalproex sodium release more than 18 hrs was selected. 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. Finally Bi-layered tablets were prepared by double compression of selected sustained release layer and immediate release layer of Divalproex sodium. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content uniformity and in vitro drug release. All the physical parameters were in acceptable limit of pharmacopeial specification. The stability studies, shown the bi-layer tablet was stable at 40°C/ 75% RH for a period of 3 months.

Keywords: *Bi-layered tablet, epilepsy, wet granulation, Divalproex sodium, immediate release, sustained release.*

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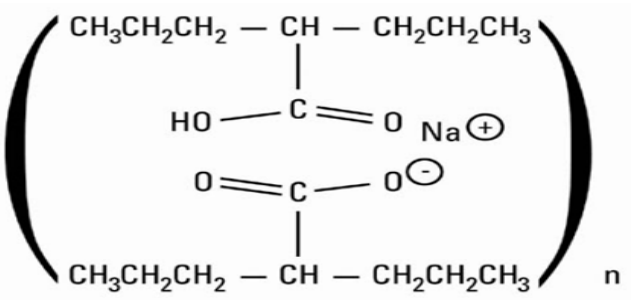
INTRODUCTION:

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms [30]. Bi-layered tablet concept has long been utilized to develop sustained released formulation. 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 [32]. The aim of the present research work was to develop the different immediate and sustained release formulation of Divalproex sodium and compare their release profile, from above formulation select a best formulation for manufacturing bi-layered tablet.

DRUG PROFILE:

DIVALPROEX SODIUM

Chemical structure:



Structure of Divalproex sodium

MECHANISM OF ACTION:

Divalproex sodium is broad-spectrum anticonvulsant. 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.

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 = 173.25 mg.

Hence, the formulation should release 125 mg drug within 1 hour and 173.25 mg drug in 18 hours.

Formulation of immediate release layer (IRL)

Sl. 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 released layer.

Formulation of sustained release layer (SRL)

Sl. 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

Preparation of IRL:
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 coloring 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 color.
- Pass the cohesive mass through sieve # 16 to get uniform granules.
- Dry the granules at 50°C 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 no 13.

Preparation of SRL:
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°C 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. The formulations were shown on table no 14.

Preparation of bi-layered tablet
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: 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 greely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

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

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

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
- *In-vitro* Dissolution Studies
- Stability Studies

Weight Variation Test:
To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

IP standards of Uniformity of weight

S.N.	Avg. Wt of Tablet (mg)	% of Deviation
1	≤80 mg	10
2	> 80 mg – 250 mg	7.5
3	≥250 mg	5

Hardness:
The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm^2 . 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:
Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.

Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{Weight\ initial - Weight\ final}{Weight\ initial} \text{ X } 100$$

Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

Sl. No	'n' value	Drug release
1	0.45	Fickian release
2	0.45 < n> 0.89	Non-Fickian release
3	0.89	Case II transport
4	Higher than 0.89	Super case II transport

RESULTS:

Evaluation of pre-compression parameters:

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
SF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

POST-COMPRESSION EVALUATION PARAMETERS:

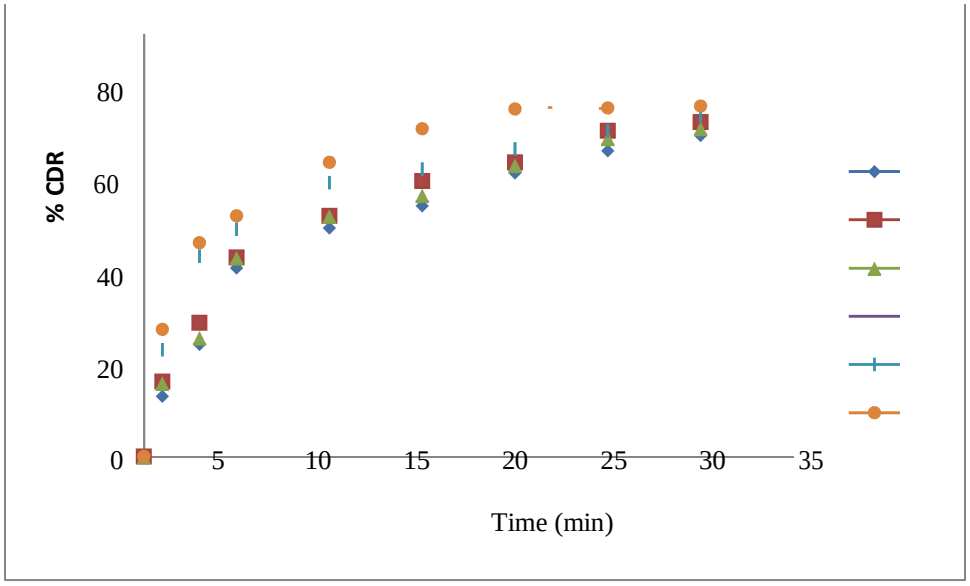
Post-compression parameters for IRL and SRL

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	-
SF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49±0.93	-

***In-vitro* dissolution study**

***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



Release profile of immediate release layer

***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
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±2.165	94.298±0.560

Kinetic Release

Kinetic release for IRL

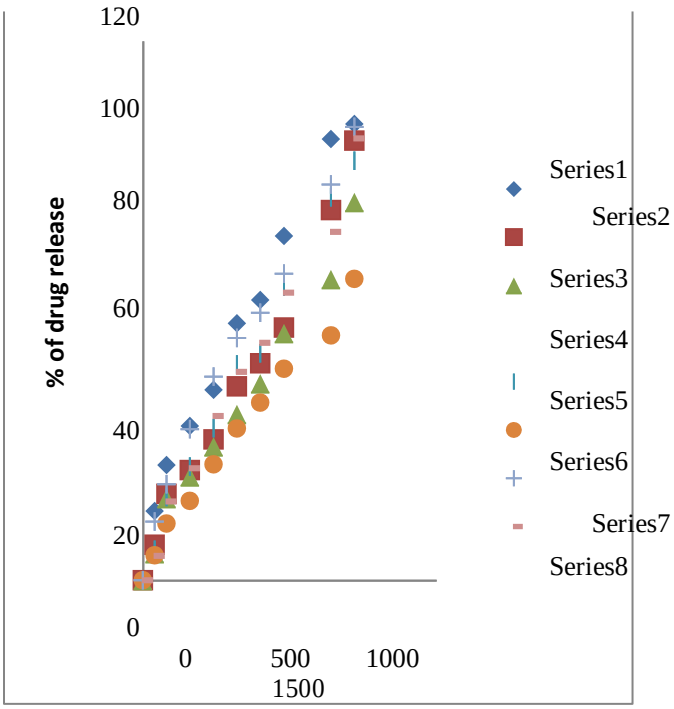
FORMULATION CODE	KINETIC MODELS				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
IF1	0.8362	0.9816	0.9689	0.8915	0.6657
IF2	0.8228	0.9844	0.9677	0.8694	0.6263
IF3	0.8231	0.9819	0.9643	0.8711	0.6336
IF4	0.7068	0.9850	0.9059	0.8424	0.5642
IF5	0.7101	0.9606	0.9055	0.804	0.5134
IF6	0.6835	0.9792	0.8945	0.8034	0.5129

Korsemeyer-peppas release Kinetics for IRL II) For sustained release layer:

Kinetic release for SRL

FORMULATION CODE	KINETIC MODELS				
	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
SF1	0.9821	0.8296	0.9653	0.6549	0.9975
SF2	0.9838	0.7303	0.9074	0.6426	0.9794
SF3	0.9838	0.8986	0.9297	0.6296	0.9699
SF4	0.9736	0.7718	0.9794	0.6510	0.9983
SF5	0.9918	0.8975	0.9404	0.6571	0.9736
SF6	0.9847	0.8975	0.9518	0.6064	0.9692
SF7	0.9827	0.7693	0.9685	0.6528	0.9987
SF8	0.9873	0.7926	0.9427	0.6634	0.9602

Zero order kinetics for SRL



zero order kinetics for SRL

Bi-layered tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

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

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	-
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

Stability Studies:

Stability data

Stability period	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

The bi-layered tablets were subjected to short term stability study, storing the formulation at 40°C / 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 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.

The above studies lids to following conclusions:

- FTIR and DSC studies indicated that the drug is compatible with all the excipients.
- 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.
- 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 bi-layered tablets of Divalproex sodium using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

REFERENCE:

1. Notari, R., Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980,152-54.
2. Vinay K, Prajapati SK, Girish CS, Mahendra S, Neeraj k. Sustained release matrix type drug delivery system. IRJP 2012;1(3):934-60.
3. Kumar V, Sharma A, Sharma A, Joshi G, Dhillon V. Recent Advances In Novel Drug Delivery System for Delivery Of Anti-Hypertensive Drugs. Int J D D Res.2011;3(1):252-59.
4. Basu B, Bagadiya A, Makwana S, Vipul V, Batt D,Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. J Adv Pharm Technol Res. 2011;2(4):266-73.
5. http//www.pharmacopeia.cn/v29240/USP29nf24s0-c115/587.htm/
6. The Indian Pharmacopoeia, Government of India Ministry of health and family welfare, the indian pharmacopoeia commission Ghaziabad, 2014;vol.II:959.
7. Pahade AA, Jadhav VM, Kadam VJ. Formulation and Development of a Bilayer Sustained Released Tablets of Isosorbide Mononitrate. Int J Pharma Bio Sci. 2010;1(4):305-14.
8. Sahoo PK. Phamaceutical Technology,Tablets. New Delhi,2007, P 2-3
9. The Indian Pharmacopoeia, Government of India Ministry of health and family welfare, the indian Pharmacopoeia commission Ghaziabad, 2014; vol II:960-61.
10. Sandeep N. & Gupta M.M, Immediate Drug Release Dosage Form: A review. Journal of Drug Delivery & therapeutics. 2013;3(2):155-61.
11. Pahwa R, Gupta N. A Review: Superdisintegrants in the development of orally disintegrating tablets. Int J Pharm Sci Res. 2011;2(11):2767-2780.
12. Patel U, patel K, Shah D, Shah R. A review

on immediate release drug delivery system. Int. j.pharm. Res. Bio-Science. 2012;1(5):37-66.
13. Chugh I, Seth N, Rana A.C. Oral sustained release drug delivery system. International Research Journal of Pharmacy 2012;3(5):57-62.