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Formulation and evaluation of bi-layered tablet of divalproex sodium

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ABSTRACT

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. Six formulations (IF1-IF6) of immediate release tablets were prepared by using sodium starch glycolate and cross carmellose sodium. Nine formulations (SF1-SF9) of sustained release were prepared by using HPMC K4M and HPMC K100M in different ration and combination. 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 release pattern 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 40ºC/75% RH for 3 months. Stability studies at 40ºC/ 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: Divalproex sodium, starch glycolate and cross carmellose sodium, Bilayered tablets, HPMC

INTRODUCTION

There are different types of tablets are available in market conventional tablet, immediate tablet, fast dissolving tablet, controlled release tablet, sustained release tablet, delayed release tablet[9]. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments[10]. For immediate release formulation, super disintegrants play key component. Super disintegrants are used to 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[11]. Sustained release systems include any drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled release system. If it is unsuccessful of this day nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged released system[13].

MATERIALS

Table 1: List of materials

Sl No.	Ingredients	Company Name
1		Gift sample from ROAQ Chemicals
2.	Sodium Starch Glycolate	S.D. Fine Chem. Ltd, Mumbai
3.	Croscarmellose	S.D. Fine Chem. Ltd, Mumbai

4.	HPMC K4M	Yarrow Chem Products, Mumbai
5.	HPMC K100M	Yarrow Chem Products, Mumbai
6.	Lactose	S.D. Fine Chem. Ltd, Mumbai
	Micro Crystalline	
8.	PVP K 30	S.D. Fine Chem. Ltd, Mumbai
9.	Ponceau 4R	Indian fine chemicals, Mumbai-20
10.	Magnesium Stearate	S.D. Fine Chem. Ltd, Mumbai
11.	Talc	S.D. Fine Chem. Ltd, Mumbai

Table 2: 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

Table 3: 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.

Preparation of SRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortarand 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.

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-compression parameters

Table 4: Pre-compression parameters for IRL and SRL

Formulation	Bulk Density	Tapped Density	Car"s Index	Haunsers	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

Post-compression evaluation parameters

Table 5: Post-compression parameters for IRL and SRL

Batch	Weight	Hardness	Friability	Thickness	Drug	*In vitro*
IF1	249.9±1.57	5.95±0.05	0.74±0.09	2.87±0.04	98.12±1.19	120.33±1.5
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	-

Table6 : Post-compression parameters for bi- layered tablet

Formulation	Weight variation	Hardness	Friability	Thickness	Drug content
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 7: *in vitro* dissolution study of IRL

Time in min	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

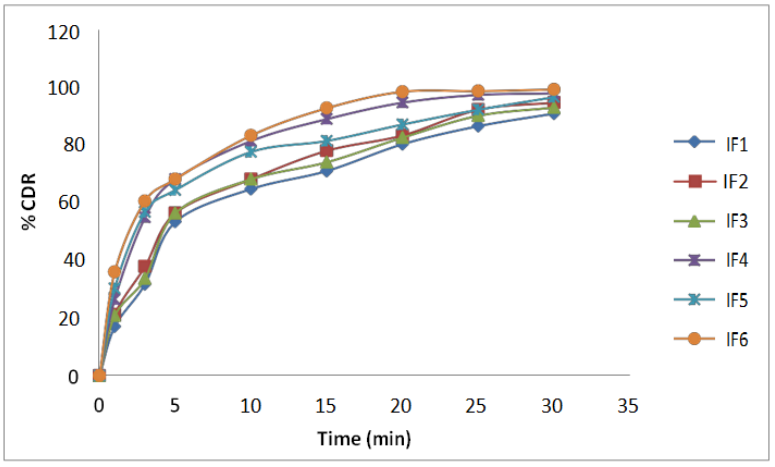

Fig 1: Release profile of immediate release layer

Table 8: *In vitro* dissolution study of SRL

Time in	% 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
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
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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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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
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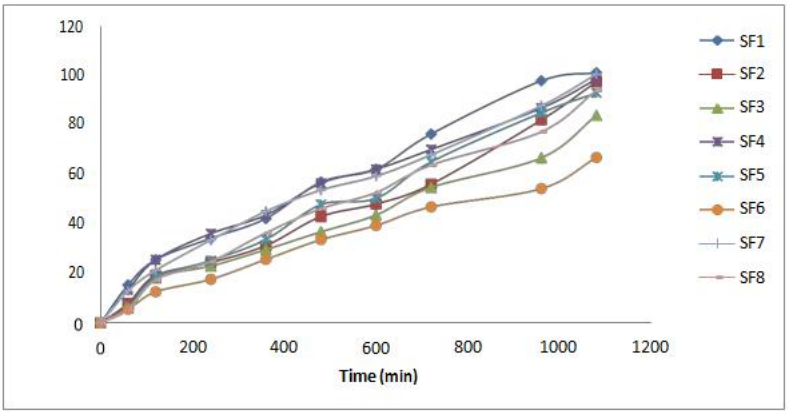

Fig 2: Release profile of sustained release layer

Table 9: 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

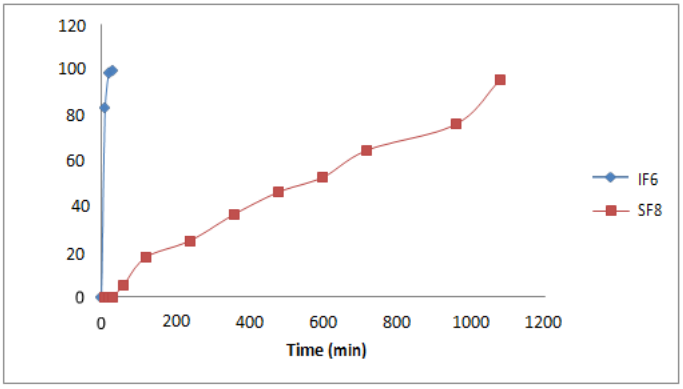

Fig 3: Release profile of Bi-layered Tablet

Kinetic Release

For immediate release tablets

Table 10: Kinetic release for IRL

FORMULATION	KINETIC MODELS				
	Zero Order	First Order	Higuchi	Korsmeyer	
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

For sustained release layer

Table 11: Kinetic release for SRL

FORMULATION	KINETIC MODELS				
	Zero order	First order	Higuchi	Korsmeyer	
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

Stability Studies

Table 12: Stability data

Stability period	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content	Drug release IRL	SRL
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

DISCUSSION

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

In the present work, formulation and evaluation of bi-layered tablet of Divalproex sodium was carried out. In the project, different formulations of immediate release and sustained release layer have been prepared separately. From above formulations best formulation of each immediate and sustained release layers were selected according to the dissolution profile and bi- layered tablet were prepared. Divalproex sodium a broad spectrum antiepileptic drug was chosen as a model drug as it is a right candidate for immediate as well as sustained release formulations. Divalproex sodium is soluble in 0.1 N NaOH, phosphate buffer pH 6.8, chloroform, methanol, ethanol (95%), and sparingly soluble in water. The result shown that the Divalproex sodium is more soluble in chloroform in compare to other solvents. The absorbance maximum of the Divalproex sodium was found to be at 210 nm when scanned in between 200-400 nm using methanol as well as phosphate buffer pH 6.8 solutions. Calibration curve of Divalproex sodium in methanol measured at 210 nm showed the slope of 0.0094 and regression coefficient of 0.9995.

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-SF9) of sustained release layer were developed by altering the excipients ratio as given in table number 13 and 14 respectively. Immediate release tablet were prepared by using super disintegrants such as sodium starch glycolate and cross carmellose sodium and Sustained release tablet were prepared by using polymer like HPMC K4M and HPMC K100M. The tablets were evaluated for weigh variation, friability, thickness, drug content and *in vitro* dissolution parameters using standard procedure. 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 compressibilityof 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 22.54º respectively suggested excellent flow property of powder blend.

Though the batch size of formulations were limited to 50-80, weight variation was reasonably satisfy the IP Limits 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 in table no 26 and 27 respectively. 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 20min as they consist of 5% SSG, 6% SSG, 5% CD and 6% CD respectively. 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 super disintegrants 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 uniformdistribution of drug in both layer. The release pattern of the drug from bi-layered tablet showed same as the individual layer tablets of immediate and sustained release.

The release kinetics of immediate release layer formulations (IF1-IF6) was found to following clearly first order kinetics as the values for „r‟ is (0.985 to 0.960) and values of „n‟ is more than 0.89 shown that Super case II transport. The release kinetics of sustained release layer (SF1-SF8) was found to following zero order kinetics as the value for „r‟ is (0.9918 to 0.9736) found to be high in comparison to first order (0.8986 to 0.7303) and Higuchi‟s square root oftime (0.9794 to 0.9074). „n‟ values in between 0.6634 to 0.6064 shown non- fickian release.

Stability studies at 40ºC / 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.

CONCLUSION

In the present work bi-layered tablet of Divalproex sodium were prepared by wet granulation method, using super disintegrants 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 super disintegrants, 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.

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