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Formulation and Evaluation of bi-layered tablets of Divalproex sodium

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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 super disintegrantsand 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 40^0C / 75% RH for a period of 3 months.

Keywords: Bi-Layered Tablets, Epilepsy, Wet Granulation, Divalproex Sodium, Immediate Release, Sustained Release

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[2].

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 to achieve a steady state drug in blood level for an extent period of time[3].

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Epilepsy is abnormal, high frequency electrical discharge in brain characterized by transient episode (seizure) with or without loss of consciousness and characteristic body movement (convulsion). Globally epilepsy is the third most common neurological disorder after cerebrovascular and Alzheimer's disease. About 10 percent of the population will have at least one seizer in their life time.

Drugs that are effective in seizure reduction accomplish this by a variety of mechanisms, including blockade of voltage- gated channels (Na^+ or Ca^{2+}), enhancement of inhibitory GABAergic impulses, or interference with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

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.[4-6]

Determination of λ_{max}[23]

Divalproex sodium was dissolved in methanol further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 190 to 380 nm.

Solubility

The solubility of Divalproex sodium was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount of Divalproex sodium is added to each vial containing 10 ml of selected solvent till the saturation of the solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at $25^0C \pm 1^0C$ followed by filtration through watmann's filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

Melting point

Melting point of the Divalproex sodium was determined by capillary method in triplicate.

Standard Curve for Divalproex sodium

100 mg of Divalproex sodium was accurately weighted and dissolved in 100 ml of methanol to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further diluted to get 5, 10, 15, 20, 25 and 30 g of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 210 nm against methanol blank.

Compatibility studies

The compatibility studies of the drug with polymers are studies using FT-IR spectroscopy.

FT-IR Spectroscopy

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted using thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR-spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug-excipients.

DSC Analysis for formulation

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter -60, Shimadzu limited Japan. The samples were heated in a thermetically sealed aluminium pans. Heat runs for each sample were set from 25 to 350^0C at a heating rate of 10^0C/min, using nitrogen as blanket gas.

Formulation of Immediate release layer

Formulation of sustained released layer

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 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 Super disintegrants 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 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 50^0C 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. 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 Parameters

The prepared formulations were evaluated for hardness, friability, weight variation, drug content, dissolution studies and stability as per standard procedures.

In-vitro dissolution studies of immediate release layer[7]

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37 ± 0.50^0C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. 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.

In vitro dissolution studies of sustained release layer[7]

The in vitro 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 0.1N HCL maintaining at 37 $\pm0.5^0$C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml 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.

Drug Content for IRF, SRF and Bi-layered tablet[7]

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 pH6.8 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 210 nm against pH6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Mathematical modelling of drug release profile[7]

The cumulative amount of Divalproex sodium release from the formulated tablets at different time intervals were fitted to Zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release.

Stability Studies[8-9]

The optimized formulation was subjected for two month stability study according to standard guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were stored at 40^0C / 75% RH for 3 months and evaluated periodically.

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Determination of λ_{max}

The λ_{max} of Divalproex sodium was found to be 210 nm in methanol and phosphate buffer pH 6.8.

Standard curve of Divalproex sodium

The absorbance was measured in a UV spectrophotometer at 210 nm against methanol.

Table 1: Spectrophotometric data of Divalproex Sodium

Sr. No.	Conc. (µg/ml)	Absorbance			Mean ±SD
		Trial 1	Trial 2	Trial 3	
1	0	0.000	0.000	0.000	0.000±0.000
2	5	0.050	0.043	0.046	0.046±0.004
3	10	0.097	0.095	0.098	0.097±0.002
4	15	0.143	0.144	0.146	0.144±0.002
5	20	0.185	0.188	0.187	0.187±0.002
6	25	0.240	0.237	0.237	0.238±0.002

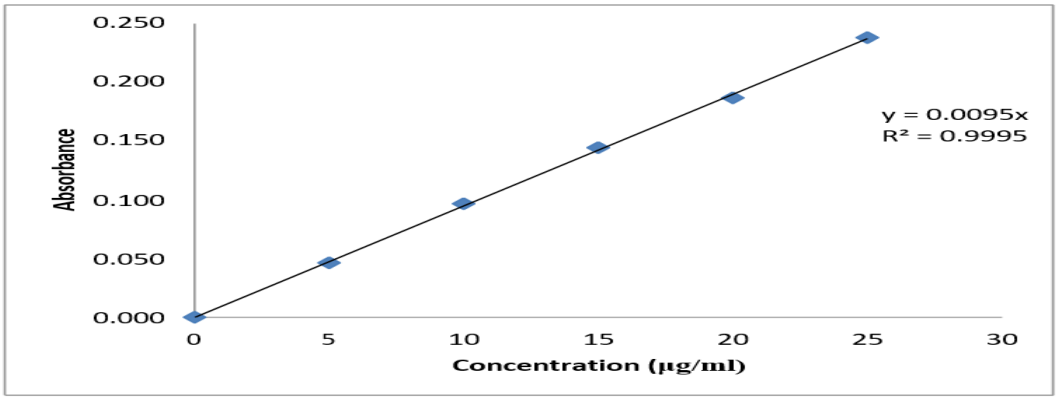

Fig. 1: Standard graph of Divalproex sodium

Drug solubility studies

The solubility studies of drug were done by using various media like distilled water, methanol, chloroform and phosphate buffer pH 6.8. Result showed that Divalproex sodium is more soluble in chloroform in compare to other solvents.

Table 8: Solubility of Divalproex sodium

Solvents	Solubility (mg/ml)
Distilled water	7.35
Methanol	48.45
Chloroform	55.24
Phosphate buffer pH 6.8	29.73

Melting Point

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

FT-IR spectrum

FT-IR spectrum of pure drug Divalproex sodium and combination of drug with polymers were obtained. All the characteristic peaks of Divalproex sodium were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The entire FT-IR spectrum and was tabulated in Table 2.

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Table 2: Compatibility study of drug and excipients using FTIR

Functional group	Wave number (cm-1)							
	Standard Peaks	Pure drug	SSG	Croscar mellose	HPMC K4M	HPMC K100M	Lactose	MCC
Aliphatic C-H Stretch	3300-2500	2919.4	2950.74	2950.80	2944.81	2947.67	2951.02	2954.13
C-H bend	1470-1450	1455	1386.88	1372.74	1453.63	1454.07	1380.43	1450.20

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C-H stretch	1300-1000	1211	1213.15	1210.95	1210.28	1211.01	1210.39	1212.95
Carboxylic Acid	3100-3300	3119.41	3121.29	3277.37	3121.32	3122.44	3123.36	3123.77
O-H bend	-	1059.94	994.78	1040.53	1047.09	1045.80	1025.20	1024.50

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

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

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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 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

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

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Table 7: 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

Table 8: Dissolution study of Bi-layered Tablet

Timein 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

Table 9: 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

Table 10: 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

Table 11: 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 40^0C / 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 was shown in figure number 2.

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 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 weigh variation, friability, thickness, drug content and in vitro dissolution parameters using standard procedure as shown in tablet number 24. 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 such as angle of repose, Carr's index, hausner's ratio, bulk density, tapped density were determined which shown on tablet number 23. Pre-formulation studies for the formulations depicted bulk density 0.512 to0.66 gm/cm^3 which indicated packing characteristics in dies. The carr'scompressibility index was found to be below 18% which suggested good compressibility ofblend. 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.

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 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.

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 tabletsindicate 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.

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