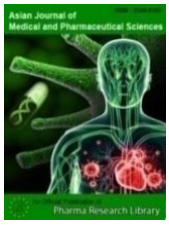

Asian Journal of Medical and Pharmaceutical Sciences
Journal Home Page: www.pharmaresearchlibrary.com/ajmps
ISSN (Online): 2348-0165 | Publisher: Pharma Research Library
A. J. Med. Pharm, Sci., 2024, 12(1): 34-40
DOI: https://doi.org/10.30904/j.ajmps.2024.4657

Formulation and Evaluation of Bi-Layered Tablet of Divalproex Sodium

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A B S T R A C T

Objective: To Formulate and Evaluate bi-layered tablet of Divalproex Sodium. **Method:** Divalproex sodium is broad-spectrum anticonvulsant. It increases the availability of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter, The bilayer tablet of Divalproex sodium were prepared by using sodium starch glycolate, croscarmellose sodium, lactose, microcrystalline cellulose, polyvinyl pyrrolidone, magnesium stearate, talc, hydroxyl propyl methyl cellulose, as Excipents using wet granulation by using different Super disintegrants. **Result:** 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. **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.

Keywords: Patient acceptance, Bi-layer tablets, flexibility

A R T I C L E I N F O

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Article History:
Received : 10 Feb 2024
Revised : 25 Feb 2024
Accepted : 20 Mar 2024
Published : 10 May 2024

Citation: *Shaik Mabuchan, et al. Formulation and Evaluation of Bi-Layered Tablet of Divalproex Sodium. A. J. Med. Pharm, Sci*., 2024, 12(1): 34-40.

C o n t e n t s

1. Introduction

Oral route is most commonly employed route of drug administration. Although different route of administration is used for the delivery of drugs, due to flexibility in dosage form design and patient compliance oral route is preferred1. 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 product2.There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation does not require sterile conditions and are therefore, less expensive to manufacture3.The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing4. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents5. According to Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents6. They are varying in size and weight, depending on number of medicinal substances and the intended mode of administration. It is most popular dosage

form and 70% of the total medicines are dispensed in the form of tablet7.

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 in compatible 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[20].

Advantages of Bi-layered tablets[21]:

- Bi-layered execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability overall oral dosage form.
- Objectionable odour 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.

Disadvantages of Bi-layered tablets:

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
- Difficult to swallow in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability.

Divalproex sodium:

Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy and bi-polar disorders, prophylaxis of migraine. Anticonvulsants (also known as antiepileptic drugs or antiseizure drugs) are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants suppress the rapid and excessive firing of neurons during seizure. It also prevents the spread of the seizure with in the brain. It also used in the treatment of bipolar disorder.

2. Materials and Methods

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.

Determination of λmax[49]

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 from190 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 other shaker at 250C ± 10C followed by filtration through Whatman filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

Melting point[50]

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

Standard Curve for Divalproex sodium[51]

100 mg of Divalproex sodium was accugrately 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, 25and 30of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 210nm against methanol blank.

Compatibility studies

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

FT-IR Spectroscopy[52]

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 1:1ratio) 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[53]

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 thematically sealed aluminium pan. Heat runs for each sample were set from 25 to 3500C at a heating rate of 100C/min, using nitrogen as blanket gas.

Preparation of IRL

IRL of Divalproex sodium (DS) was prepared by wet granulation by using different Super disintegrants 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 Super disintegrants and mix for 10 to15 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 500C for15 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 1.

Preparation of SRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder was 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 500C 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 2.

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:

Weight Variation Test:[59]

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

Hardness:[60]

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/cm2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:[61]

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.

Percentage friability was calculated by using the formula.

$$\% \text{ Friability} \quad \frac{Weight\ initial - Weight\ final}{Weight\ initial}$$

Tablet thickness:[62]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then read "hundredths of mm" of imperial scale (count the number of divisions until the lines concedes with the main metric scale. The imperial scale number is multiplied with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement.

In-vitro dissolution studies of immediate release layer:[63]

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at100rpm. Phosphate buffer PH6.8 dissolution media is maintained at37±0.500 C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with PH6.8, 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:[64]

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±0.50C 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:[65]

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 PH6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Table 1: Formulation of immediate release layer (IRL)

Sl. No.	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6	IF7
1	Divalproex sodium	125	125	125	125	125	125	125
2	Lactose	82	79.5	82	79.5	82	79.5	82
3	Croscarmellose sodium	10	12.5	-	-	5	6.25	10
4	Sodium starch glycolate	-	-	10	12.5	5	6.25	-
5	Microcrystalline cellulose	25	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	3
8	Talc	5	5	5	5	5	5	5

Table 2: Formulation of sustained release layer (SRL)

Sl. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25
2	Lactose	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMCK4M	60	-	-	-	22.5	26.25	30
4	HPMCK100M	-	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6
8	Total	300	300	300	300	300	300	300

3. Results and Discussion

Table 3: Pre-compression parameters for IRL and SRL

Formulation	Bulk Density Mean± SD	Tapped Density Mean±SD	Car's Index Mean ±SD	Haunser's 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
IF7	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SF1	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SF2	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SF3	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SF4	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
SF5	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF6	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
SF7	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
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
IF7	250.6±1.41	5.38±0.10	0.52±0.06	2.92±0.09	98.38±1.19	45.33±2.15
SF1	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
SF2	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57±0.85	-
SF3	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43±1.27	-
SF4	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63±0.61	-
SF5	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47±1.04	-
SF6	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51±1.20	-
SF7	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 variatio n Mean ±SD	Hardness Mean ±SD	Friability Mean ±SD	Thicknes s 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**	**IF7**
0	0.000±0.0	0.000±0.00	0.000±0.00	0.000±0.00	0.000±0.00	0.000±0.00	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	25.408±1.222
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	40.634±1.764
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	54.323±2.715
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	72.342±0.632
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	77.151±1.196
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	82.342±0.412
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	93.620±1.642
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	95.183±0.352

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±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
60	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591	13.006±1.994	5.391±0.882	7.905±1.234
120	18.231±1.281	25.637±0.732	18.521±1.421	12.635±0.751	21.351±1.317	17.527±1.114	19.263±1.532
240	23.091±1.547	33.235±1.164	25.279±1.003	17.697±1.151	33.589±1.503	24.917±1.426	24.502±1.083
360	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427	45.247±0.941	36.518±0.831	31.362±1.321
480	36.936±1.251	56.674±2.061	47.993±0.539	33.733±2.378	53.869±1.510	46.331±0.891	43.141±1.974
600	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114	59.523±1.163	52.852±0.792	48.234±0.826
720	54.964±2.137	70.315±2.001	65.327±1.779	47.031±1.480	68.215±0.906	64.017±0.710	56.263±2.227
960	66.957±1.402	87.123±0.645	86.182±0.467	54.439±2.565	88.053±0.676	77.498±0.918	82.430±1.267
1080	84.113±1.317	98.822±1.325	97.692±0.844	67.057±1.191	100.859±2.16	94.298±0.560	97.816±0.630

Table 8: 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

Table 9: Compatibility study of drug and excipients using FTIR

Functional Group	Standard peaks	Pure drug	SSG	Croscar mellose	HPMC K4M	HPMC K100M	lactose	MCC
Aliphatic C-Hstretch	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
C-H stretch	1300-1000	1211	1213.15	1210.95	1210.28	1211.01	1210.39	1212.95
Carboxy licacid	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

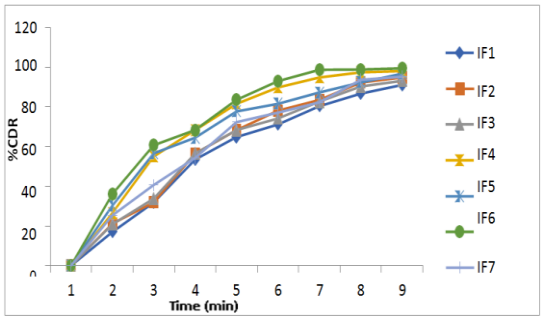

Figure.1

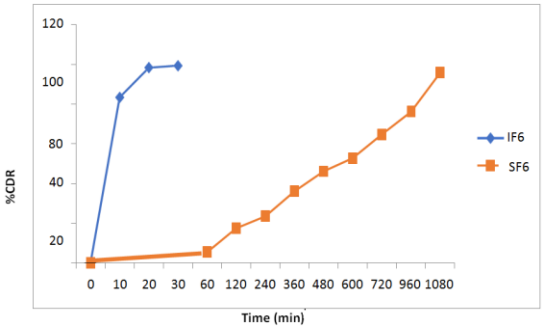

Figure.2

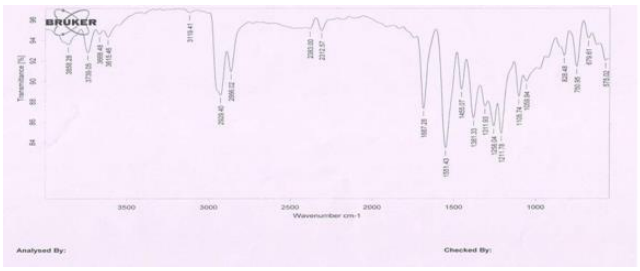

Figure.3. FTIR of Drug Divalproex sodium

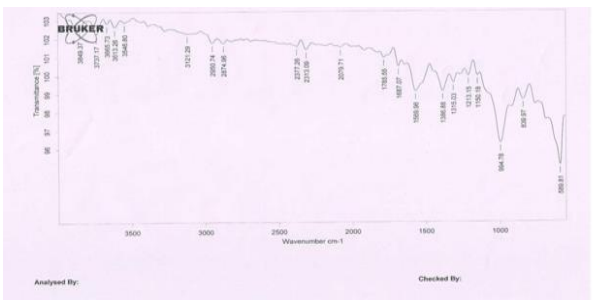

Figure.4. FTIR of Divalproex sodium + Sodium Starch Glycolate (SSG)

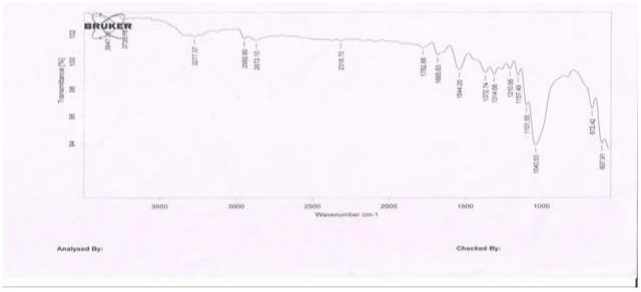

Figure.5. FTIR of Divalproex sodium + Croscarmellose sodium

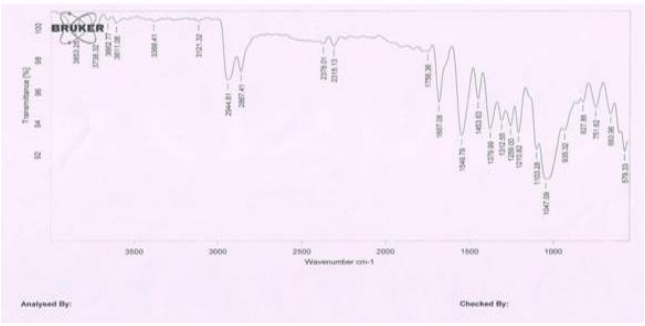

Figure.6. FTIR of Divalproex sodium + HPMC K4M

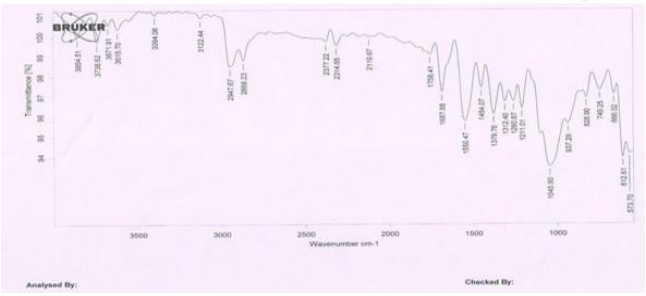

Figure.7. FTIR of Divalproex sodium+ HPMCK100M

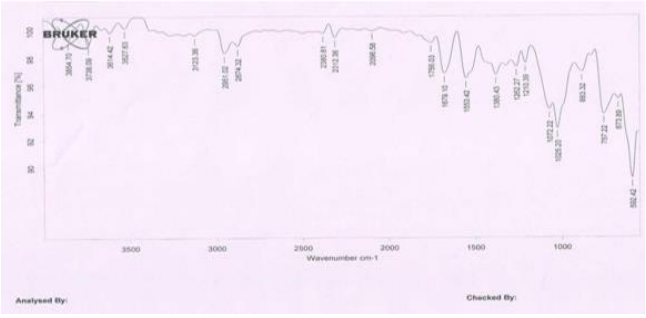

Figure.8. FTIR of Divalproex sodium+ Lactose

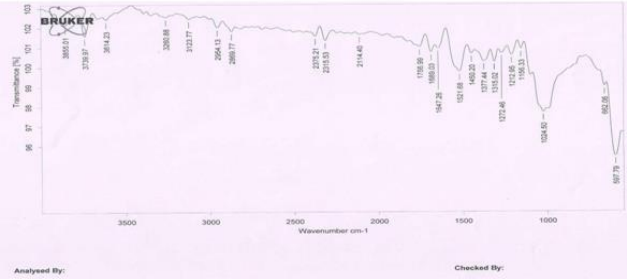

Figure.9. FTIR of Divalproex sodium + Microcrystalline Cellulose (MCC)

4. 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. 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.

5. References

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