Current Research in Pharmaceutical Sciences
Available online at www.crpsonline.com

ISSN: 2250 – 2688

Received: 11/08/2022
Revised: 12/09/2022
Accepted: 26/09/2022
Published: 08/10/2022

Rajveer Singh Rajput, Bala Kumar Chandrasekaran
ITM University, Gwalior (M.P), India 474001

Correspondence

Rajveer Singh Rajput
ITM University, Gwalior (M.P), India 474001

Email: rs5388935@gmail.com

DOI: 10.24092/CRPS.2022.120303

Website: www.crpsonline.com

Quick Response Code:

Formulation and *In vitro* Evaluation of Divalproex Sodium Bi-Layered Tablet

Rajveer Singh Rajput, Bala Kumar Chandrasekaran

ABSTRACT

Divalproex sodium is the anticonvulsant agents that used in the treatment certain types of seizures. The aim of the present study is to formulate and evaluate divalproex sodium bilayer tablet. Divalproex Sodium Bi-layer tablets (BLT) were prepared by simple blending and punching with HPMC, Xanthan Gum, Sodium starch glycolate, MCC, PVP, and Magnesium stearate. Optimized formulation was designed on the basis of best formulation of the immediate release layer and sustained release layer. The pre and post compression parameters were evaluated and stability studies of the optimized formulation was also performed. FTIR studies was checked and no interaction found between the drug and polymers. Optimized tablet batch had shown excellent range in weight variation (553.2±1.42) mg, thickness (4.9±0.52) mm, Diameter (1.4±0.13) cm, hardness (5.2±0.31) Kg/cm2, friability (0.35±0.10) % and % drug content (99.34±1.6) %. IRL-5 and SRL-3 showed excellent drug release of 98.13 and 95.74% from all formulation's layers. Divalproex Sodium Bi-layer tablet (BLT) was formulated by combining both layers IRL- 5 and SRL-3. The stability study was shown that optimized formulation stable at 45 ±2 0C for 45 days. So that, the optimized formulation might be suitable for the treatment of seizures.

Keywords: Divalprox Sodium, Bi-layered Tablet, Formulation, Anticonvulsant.

1. INTRODUCTION

The most preferable route of drug delivery is the oral route. Although, various route of administration is used to deliver the drugs through the oral route because this route gives many benefits, such as flexibility in the formulation of patient compliance. The oral route is gaining huge popularity for ease of administration, patient acceptance, accurate dosing, cost-effective manufacturing technique, and generally enhanced shelf-life of the pharmaceutical formulation[1,2].

Bilayer tablet tablets are formulated with one drug layer for immediate release, while the second layer is designed for a later release of the drug, either as a second dose or in a prolonged-release manner. Bilayer tablets are acceptable for sequential release of two combination drugs, separating two incompatible components, and extended-release tablets where one layer is the immediate release as the initial dose and the second layer is the maintenance dose. The primary goal of therapy is to achieve stable blood levels of the drug over a more extended period of time[3,4].

Epilepsy is an abnormal, high-frequency electrical discharges in the brain that cause seizures with or without loss of consciousness and characteristic body movements (convulsions).

Worldwide, epilepsy is the third most prevalent neurological disorder after cerebrovascular disease and Alzheimer's disease. About 10% of the population will have a seizure at least once in their lifetime[5,6].

Anti-convulsion drugs that are effectively work in the reduction of seizure accomplish this by a variety of mechanisms including blockade of voltage- gated channels (Na+ or Ca2+), 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[7,8].

2. MATERIALS AND METHODS

Divalproex Sodium was procured from Ranbaxy, Devas (M.P). HPMC was taken from Meditab Pharmaceuticals Pvt. Ltd., Satara. Talc was purchased from Ozone, New Delhi. Sodium Bicarbonate, Citric Acid, Magnesium stearate, and PVP were all purchased from Rankem, Mumbai.

2.1 Methods of Preparation of Bilayer Tablets

Table 1: Formulation of Immediate Release Layer of Divalproex Sodium

Formulation Code	IRL-F1	IRL-F2	IRL-F3	IRL-F4	IRL-F5
Xanthan Gum (mg)	50	50	50	50	50
Divalproex Sodium (mg)	100	100	100	100	100
Sodium starch glycolate (mg)	10	20	30	40	50
MCC (mg)	25	25	25	25	25
Colorant	qs	qs	qs	qs	qs

The immediate-release layer was prepared using super disintegrants-sodium starch glycolate, xantham gum as a binder, Dicalcium phosphate, and microcrystalline cellulose. All ingredients were bland together and subjected to precompression evaluation[9].

Hydrophilic polymers such as HPMC, xanthan gum, MCC, and PVP were used to design the sustained release layer. The ratios of the ingredients were used and seen in the formulation table. Before the preparation of the tablets all the pre-formulation parameters were examined. For direct compression into tablets, a premix was developed by combining the drug and excipients.

Table 2: Formulation of Sustained Release Layer of Divalproex Sodium

Formulation Code	SRL-F1	SRL-F2	SRL-F3	SRL-F4	SRL-F5
HPMC (mg)	10	20	30	40	50
Xanthan gum (mg)	100	100	100	100	100
Magnesium stearate (%)	10	10	10	10	10
PVP (mg)	20	20	20	20	20
MCC (mg)	50	50	50	50	50
Divalproex Sodium (mg)	100	100	100	100	100
Talc (%)	5	5	5	5	5

2.2 Evaluation of Bilayer Tablet

2.2.1 Pre-Compression Studies

The powder blends were evaluated suitably for their characteristic parameters such as the angle of repose, Hausner's ratio, bulk density, tapped density and Carr's index[10].

2.2.2 Post Compression Parameter

2.2.2.1 Weight Uniformity Test

Twenty tablets were randomly chosen for the weight uniformity test, and average weights were calculated. The weight of

each tablet was then measured, and the results were compared to the average[10].

$$\textbf{Calculate the average weight of tablets} = \frac{\textbf{Total weight of tablet}}{\textbf{Numbers of tablets}}$$

2.2.2.2 Thickness and Diameter

The packaging of tablets must take into account the thickness of the tablets; very thick tablets have an impact on packaging in plastic or blister packaging. The thickness of the tablet, the amount of fill allowed to enter the die, and the force or pressure used during compression are determined by the die's diameter. The tablet's thickness can be measured automatically or manually. Tablets' diameter and thickness were measured using Vernier's Calipers[11].

2.2.2.3 Friability (F)

Roche Friabilator was used to check the tablet friability. Firstly 20 tablets were accurately weight and these tablets were picked and transferred into the apparatus. The friabilator was run for four minutes at a speed of 25 rpm (100 revolutions). The tablets were once more weighed (w final). The friability test was determined using formula[11].

$$F = W_{initial} - W_{final}/W_{initial}$$

2.2.2.4 Hardness Uniformity Studies

The prepared formulation's hardness was determined using a Pfizer hardness tester. Five bilayer tablets were used to check the hardness of the prepared tablet. The mean and standard deviation were computed using the hardness data[11].

2.2.2.5 % Drug Content

The amount of drug present in each of the twenty tablets was measured. The tablets have been crushed in mortar with the help of pestle, and the powder containing 100 mg of the drug was then added to a standard flask with a capacity of 100 ml. The powder was dissolved in an appropriate solvent, and a suitable buffer solution was used to make up the remaining volume. The sample was thoroughly blended before being passed through a 0.45µ membrane filter. Using buffer solution as a blank, the filtrate was appropriately diluted before being subjected to a UV spectrophotometer analysis to determine its drug content[11].

2.2.3 In vitro Dissolution Studies

2.2.3.1 In vitro Dissolution Studies of Immediate-Release Layer (IRL)

A USP-II (paddle) dissolution apparatus is used for the in-vitro dissolution studies at 100 RPM. The dissolution medium for phosphate buffers 6.8 is used as dissolution medium and kept at 37±0.50^{O}C. At predetermined intervals, 5 ml were removed and replaced with an equal volume of fresh medium. The withdrawn samples were diluted with phosphate buffer pH 6.8, filtered, and then tested at 210 nm. Calculated was the cumulative drug release percentage[12,13].

2.2.3.2 In vitro Dissolution Studies of Sustained Release Layer (SRL)

Using a USP type-II apparatus (DT-1200) and 900 ml of 0.1N HCL maintained at 37 ±0.5^{O}C for the first 45 minutes and 900 ml of phosphate buffer pH 6.8 for the following 18 hours. The sustained release layer was released in *In-vitro* for 18 hours. At various times, 5 ml were taken out and replaced with an equal amount of brand-new medium. The samples were diluted with a dissolution medium, filtered, and examined at 210nm using a UV spectrophotometer[12,14].

2.2.4 Drug Release Kinetics

The information gathered from in vitro release studies was subjected to Higuchi's, Zero order, and First-order models to analyze the drug release mechanism from the prepared formulation[15].

2.2.5 Stability Studies

Stability studies sought to ascertain how the formulated bilayer release tablet would fare about aging and storage under various circumstances. Divalproex Sodium in formulated tablets was tested for stability after 45 days of storage at different temperatures. For 45 days, the tables were kept at a temperature of 45±2°C and relative humidity of 75±5%. Utilizing a double beam UV visible spectrophotometer, the amount of divalproex sodium and in-vitro drug release studies were determined[16].

3. RESULT AND DISCUSSION

3.1 Pre-Compression Evaluation of Divalproex Sodium Tablet

The Angle of repose of all the formulations was within 30.25^{O}. The bulk density was found to be in the range of 0.31-0.35gm/ml. It is within the acceptable limit. The tapped density was found to be in the range of 0.41-0.48gm/ml. The result of the Hausner ratio of all the formulations is 1.31-1.52. Carr's index was found between 23.91-34.04. The result indicates good flow properties. These results showed that the granules of all formulations have good flow properties.

Table 3: Pre-compression Evaluation of Divalproex Sodium Tablet

Formulation	Angle of repose (Ɵ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Compressibility Index (%)
IRL-1	30.25	0.33±0.14	0.47±0.029	1.42 ± 0.04	29.78 ± 0.14
IRL-2	26.33	0.30±0.15	0.45±0.031	1.50 ± 0.05	33.34 ± 0.15
IRL-3	28.34	0.32±0.34	0.42±0.159	1.31± 0.02	23.81 ± 0.32
IRL-4	29.84	0.31±0.12	0.47±0.037	1.52 ± 0.05	34.04 ± 0.28
IRL-5	28.97	0.31±0.27	0.41±0.053	1.32 ± 0.65	24.39 ± 0.31
SRL-1	26.54	0.33±0.12	0.45±0.018	1.36 ± 0.05	26.66 ± 0.18
SRL-2	27.63	0.35±0.25	0.46±0.028	1.31 ± 0.01	23.91 ± 0.82
SRL-3	26.25	0.33±0.15	0.46±0.028	1.39 ± 0.01	28.26 ± 1.33
SRL-4	29.47	0.32±0.11	0.44±0.024	1.37 ± 0.02	27.27 ± 1.60
SRL-5	28.36	0.35±0.16	0.48±0.026	1.37 ± 0.01	27.08 ± 0.84

3.2 Post-compression Evaluation of Divalproex Sodium Bi-layer Tablet

IRL and SRL layers were subjected to many in-process tests separately and optimized tablets. The hardness value was found between 4.7-6.2Kg/cm2. The friability values were approximately 0.35-0.48%. All the formulations showed the thickness in the range of IRL 2.5-2.8 mm and for SRL 3.2-3.8mm, diameter between 1.4-1.6cm and Weight variation between 185.1-349.3 and Drug content (%) found 95.32 - 99.71. Optimized tablet batch has weight variation (553.2±1.42) mg, thickness (4.9±0.52) mm, Diameter (1.4±0.13) cm, hardness (5.2±0.31) Kg/cm2, friability (0.35±0.10) % and drug content (99.34±1.6) %.

Table 4: Post Compression Evaluation of Divalproex Sodium Tablet

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (cm)	Hardness Kg/cm^2	Friability (%)	Drug content (%)
IRL-1	185.1±0.53	2.5±0.24	1.5±0.64	5.2±0.63	0.48±0.03	95.32±0.52
IRL-2	195.2±0.74	2.5±1.52	1.4±0.23	5.7±0.34	0.42±0.12	97.32±0.35
IRL-3	206.5±0.53	2.6±0.36	1.5±0.74	5.1±0.34	0.39±0.53	98.62±0.72
IRL-4	214.6±0.68	2.7±0.74	1.4±0.63	6.2±0.52	0.46±0.85	98.91±0.23
IRL-5	224.7±0.51	2.8±0.43	1.5±0.84	4.7±0.76	0.41±0.33	99.71±0.31
SRL-1	306.5±0.34	3.5±0.12	1.4±0.59	5.1±0.02	0.35±0.07	98.51±0.64
SRL-2	315.2±0.24	3.2±0.07	1.4±0.05	5.3±0.11	0.46±0.05	98.44±3.36
SRL-3	328.3±0.45	3.6±0.08	1.6±0.02	4.8±0.19	0.41±0.07	98.32±2.36
SRL-4	336.2±0.48	3.8±0.20	1.3±0.09	5.2±0.15	0.38±0.02	99.23±2.36
SRL-5	349.3±0.55	3.6±0.10	1.4±0.08	5.3±0.20	0.39±0.09	98.83±3.09
BLT	553.2±1.42	4.9±0.52	1.4±0.13	5.2±0.31	0.35±0.10	99.34±1.6

3.3 *In vitro* Dissolution Studies

The *In -vitro* dissolution studies were performed to evaluate the dissolution character of both layers of Divalproex Sodium Bi-layer tablet. The dissolution study of all immediate-release layer (IRL) formulations found as the percentage drug release were IRL-1(70.39), IRL-2(78.77), IRL-3(83.57), IRL-4(82.57), and IRL-5(98.13) after 20 min study. The dissolution study of all sustained release layer (SRL) formulations found as the percentage drug release were SRL-1(88.53), SRL-2(81.09), SRL-3(95.74), SRL-4(83.12), and SRL-5(82.12) %, in 720 min. IRL-5 and SRL-3 showed excellent drug release of 98.13 and 95.74% from all formulations' layers. Divalproex Sodium Bi-layer tablet (BLT) was formulated by combining both layers IRL- 5 and SRL-3. BLT was therefore deemed to be an optimized formulation and put through stability and kinetic modelling tests.

Table 5: *In -vitro* Dissolution Studies Data of IRL Formulation

Time (min)	% Drug Release				
	IRL-1	IRL-2	IRL-3	IRL-4	IRL-5
0	0	0	0	0	0
1	3.45	4.27	5.36	5.72	6.79
5	13.13	19.23	18.41	24.50	25.51
10	28.32	39.05	45.76	41.95	52.59
15	48.57	57.20	69.18	68.03	76.11
20	70.39	78.77	83.57	82.57	98.13

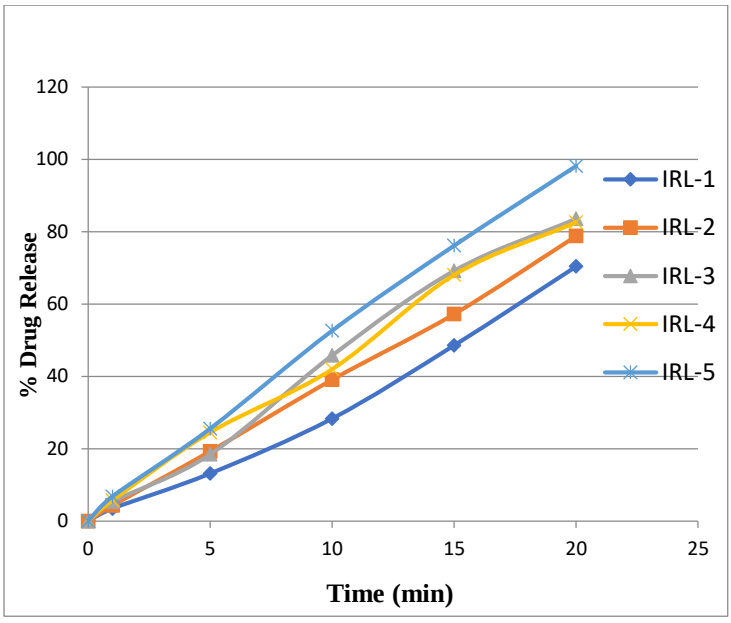

Figure 1: *In vitro* Dissolution Studies Data of IRL Formulation

Table 6: *In -vitro* Dissolution Studies Data of SRL Formulation

Time (min)	% Drug Release				
	SRL-1	SRL-2	SRL-3	SRL-4	SRL-5
0	0	0	0	0	0
60	5.45	4.27	8.36	6.72	3.79
120	12.13	7.23	16.41	12.50	9.51
180	19.32	17.05	24.76	19.95	21.59
240	25.57	24.20	33.18	27.03	28.11
360	41.39	35.77	51.57	44.57	38.13
480	58.57	48.15	65.95	56.64	49.66
600	69.85	65.82	83.63	67.21	66.32
720	88.53	81.09	95.74	83.12	82.42

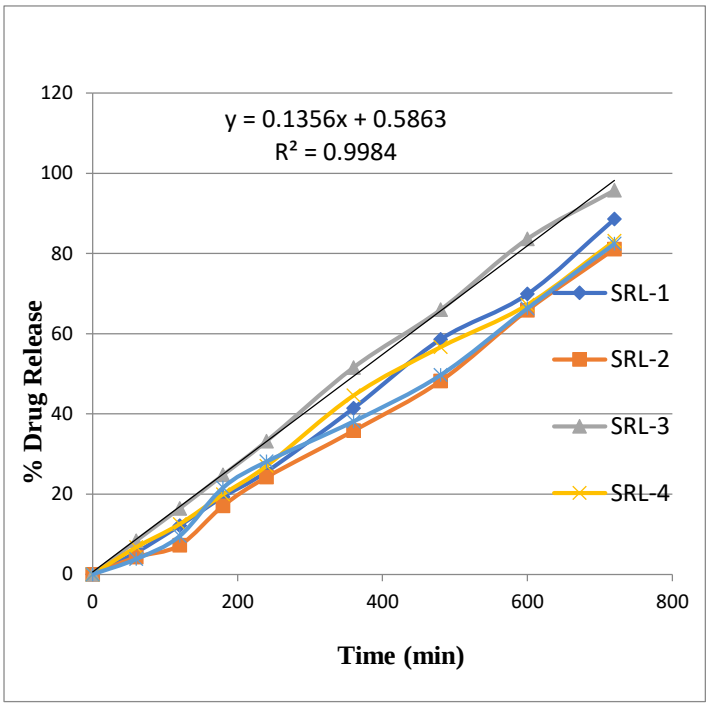

Figure 2: *In -vitro* Dissolution Studies Data of SRL Formulation

3.4 Drug Release Kinetic

Divalproex Sodium Bi-layer tablet (BLT) kinetic modeling was obtained using the data of drug release of IRL-5 and SRL-3 batch. It was found that BLT follows Zero Order release with a greater R2- the value of 0.998 for both layers, which means a diffusion mechanism with continuous drug release.

Table 7: Kinetic Release for Optimized Bi-layer Tablet (BLT)

Formulation Code	Kinetic model		
	Zero order (R^2)	First order (R^2)	Higuchi (R^2)
IRL-5	0.998	0.821	0.941
SRL-3	0.998	0.880	0.921

Table 8: *In -vitro* Dissolution Studies Data of Optimized Bi-layer Tablet (BLT)

Time (min)	SRT	LogT	% CR	Log % CR	% Drug remaining	Log % drug remaining
IRL-5						
0	0	-	00.00	-	100	2
1	1	0	06.79	0.832	93.21	1.969
5	2.236	0.699	25.51	1.407	74.49	1.872
10	3.162	1	52.59	1.721	47.41	1.676
15	3.873	1.176	76.11	1.881	23.89	1.378
20	4.472	1.301	98.13	1.992	01.87	0.272
SRL-3						
0	0	-	00.00	-	100	2
60	7.746	1.778	08.36	0.922	91.64	1.962
120	10.954	2.079	16.41	1.215	83.59	1.922
180	13.416	2.255	24.76	1.394	75.24	1.876
240	15.492	2.380	33.18	1.521	66.82	1.824
360	18.974	2.556	51.57	1.712	48.43	1.685
480	21.909	2.681	65.95	1.819	34.05	1.532
600	24.495	2.778	83.63	1.922	16.37	1.214
720	26.833	2.857	95.74	1.981	04.26	0.629

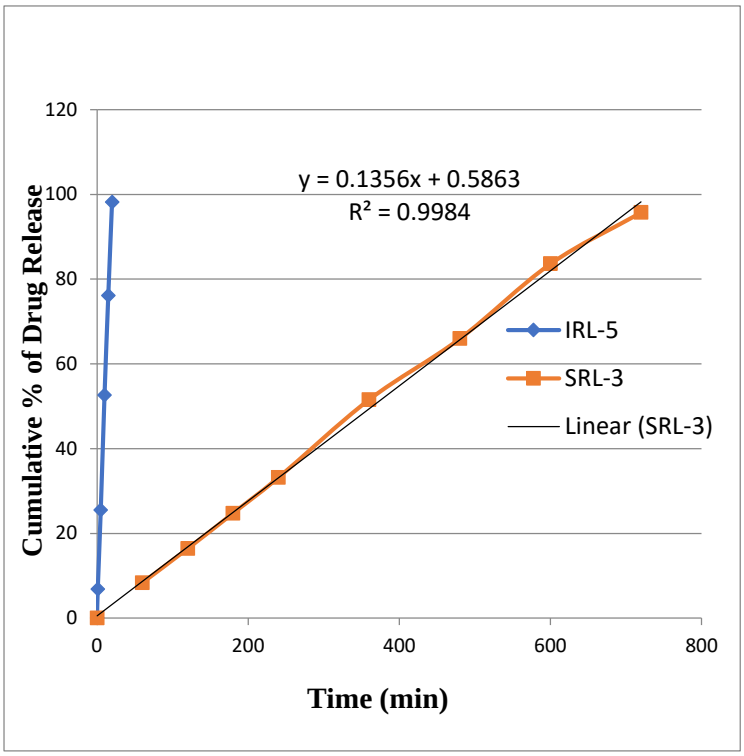

Figure 3: Zero Order Kinetics of Optimized Bi-layer Tablet (BLT)

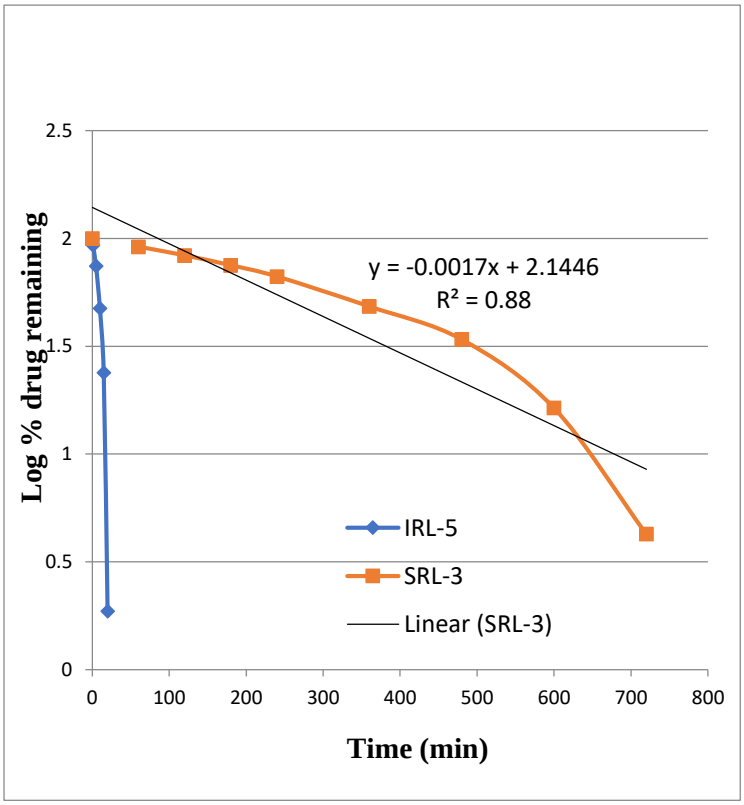

Figure 4: First Order Kinetics of Optimized Bi-layer Tablet (BLT)

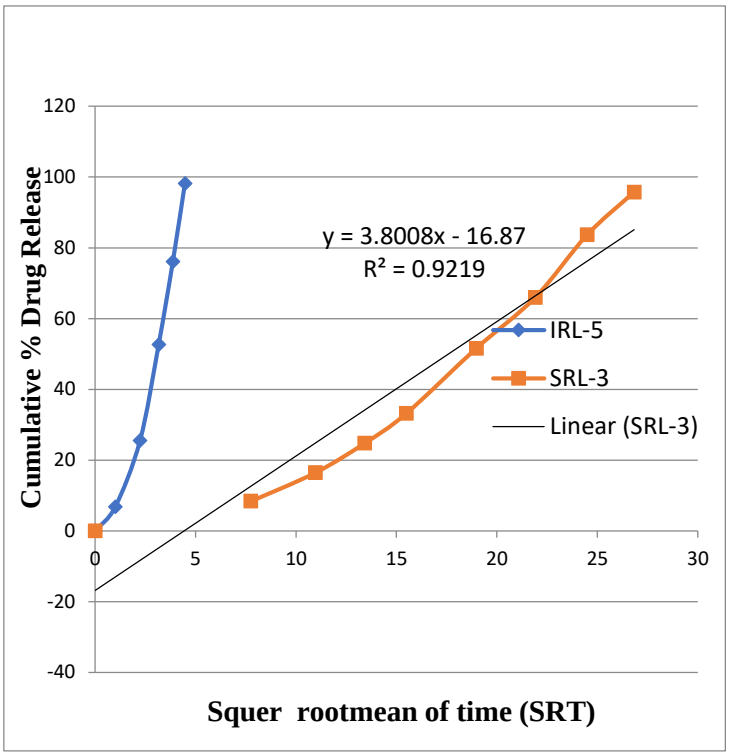

Figure 5: Higuchi Kinetics Model of Optimized Bi-layer Tablet

3.5 Stability Studies

The data for stability studies were carried out for Divalproex Sodium Bi-layer tablet (BLT) at 45 ±2 0C for 45 days, and it revealed no considerable difference in drug content.

Table 9: Stability Data of Optimized Bi-layer Tablet (BLT)

Stability period (days)	45±2^{0}C, RH 75±5%				
	Hardness	% Friability	% Drug Content	% Drug release	
				IRL (20 min)	SRL (720 min)
Initial	5.2±0.31	0.35±0.10	99.34±1.6	98.13	95.74
15 days	5.1±0.21	0.36±0.12	99.12±1.5	98.01	95.21
30 days	5.0±0.10	0.37±0.42	98.42±1.2	98.31	94.52
45 days	5.0±0.23	0.37±0.21	98.17±0.9	97.64	93.81

4. CONCLUSION

Divalproex Sodium Bi-layer tablets (BLT) were prepared by simple blending and punching with HPMC, Xanthan Gum, Sodium starch glycolate, MCC, PVP, and Magnesium stearate. Talk for oral application in two steps immediate and sustained release layer formulation. Divalproex Sodium is a drug with anticonvulsant and antiepileptic action having high metabolism by the liver, low oral bioavailability, and low half-life. Drug delivery systems that address these issues enhance the bioavailability and reduce administration frequency are necessary for the drug. The best formulations for each layer were chosen to create bi-layered tablets, which were then made. Drug-polymer interaction, drug content uniformity, weight variation, friability, and hardness were all tested on bi-layered Divalproex sodium tablets. Pre-compression and post-compression testing, % drug content, and in-vitro drug release were all used to characterize the prepared Divalproex Sodium Bi-layer Tablets (BLT) batch.

This drug delivery system demonstrated good sustained release and continuously supplies the body with divalproex sodium for 12 hours, thanks to the choice of an appropriate polymer ratio. The system has many benefits, including simplicity of preparation, high drug release, and an extended duration of over 12 hours. According to the results of this study, Divalproex Sodium Bi-layer Tablets (BLT) provide the best immediate release in the first few minutes to reach therapeutic levels. A better-sustained release also follows it in a continuous manner that helps to maintain bioavailability for a long time and lower dose and dose frequency.

ACKNOWLEDGEMENT

Authors are thankful to the ITM University, Gwalior (M.P.) for providing the necessary facilities in my research work.

REFERENCES

1. Jaimini M, Kothari AH. Sustained release matrix type drug deliery system: A review. Journal of drug delivery and therapeutics. 2012;2(6):15.
2. Vikas K, Arvind S, Ashish S, Gourav J, Vipasha D. Recent advances in Ndds (Nov el Drug Delivery System) for delivery of anti-hypertensive drugs. International Journal of Drug Development and Research. 2011;3(1):0-.
3. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. International journal of pharmaceutics. 2014;461(1-2):549-58.
4. Jamunadhevi V, Sahoo PK, Kailasam P. Formulation and in vitro evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR-A novel fixed dose combination. Int J Res Pharm Sci. 2011;2(2):170-8.
5. Mendhi SM, Suralkar A, Chitlange S, Mane PB, Gairola N, Sharma, AN. Epilepsy: Current perspective. International Journal of Pharmaceutical Sciences Review and Research 2014;25:23-35.
6. Moshé SL, Perucca E, Ryvlin P, Tomson T, Epilepsy: new advances. Lancet (London, England) 2015, 385 (9971), 884-98.
7. Acharya A, Ahmed MG, Chaudhari R, Chitti R. Formulation and Development of Divalproex Sodium Bi-Layered Tablets using Superdisintegrants and Release Retardant Polymers. International Journal of Pharmaceutical Sciences and Nanotechnology 2017; 10: 3669-3675.
8. Kumar V, Gautam GK, Dasgupta S. Design development and evaluation of bi-layered tablet of Divalproex sodium. 2019;10:6280-6288.
9. Chaudhari R, Ahmed M. Design and evaluation of immediate release tablets of divalproex sodium. Pharm Lett. 2015;7(5):87-92.
10. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, Foudah AI, Alrobaian MM, Shukla R, Singh S, Kesharwani P. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. Heliyon. 2020;6(11):e05459.
11. Hashem FM, Nasr M, Fathy G, Ismail A. Formulation and in vitro and in vivo evaluation of lipid-based terbutaline sulphate bi-layer tablets for once-daily administration. AAPS PharmSciTech. 2016;17(3):727-34.
12. Chanda R, Bahadur S, Saha S, Das S, Choudhury A. Formulation of terbutaline sulphate mucoadhesive sustained release oral tablets from natural materials and in vitro-in vivo evaluation. Asian Journal of Pharmaceutical Sciences 2010; 5: 168-174.
13. Prajapati M, Shende S, Jain V, Gupta A, Goyal MK. Technology, Formulation and In vitro Percutaneous Permeation and Skin accumulation of Voriconazole Microemulsified Hydrogel. 2021; 11(4): 267-272.
14. Bahadur S, Bhuyan NR, Chanda R, Roy A, Das S, Choudhury A, Saha S. Physicochemical characterization and evaluation of mucoadhesive tablets of omeprazole for local action. Journal of Pharmaceutical Sciences and Research. 2009;1(4):116.
15. Momin S, Khan S, Ghadage DM, Yadav AV, Wagh A. Formulation and evaluation of bilayer tablets of propranolol hydrochloride. Journal of Drug Delivery and Therapeutics. 2017;7(2):50-7.
16. Nazim S, Abdul RD, Patel S. Formulation and Evaluation of Bilayer tablets of Metoprolol Succinate. Research Journal of Pharmacy and Technology. 2015; 8: 292.