RESEARCH ARTICLE

Development and *In-vitro* Assessment of Divalproex Sodium Bilayered Tablets

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Abstract

Objective: The aim of the current research work is to develop a bi-layered divalproex sodium tablet with an immediate release layer and a sustained release layer. Divalproex sodium is regarded as the most significant antiepileptic medication and is frequently used to treat bipolar illness, epilepsy, and migraine prevention.

Methods: Wet granulation was used to prepare both (Immediate release, Sustained release) layers since divalproex had poor flow properties. Superdisintegrants were used to produce the immediate release layer, which was then assessed for physical characteristics, disintegration time, and in-vitro drug release.

Results: For the bi-layered tablet formulation, the optimal immediate release layer (IF6) with the maximum in-vitro release of 98.11 was chosen. Along with in-vitro drug release tests, HPMC-K4M and HPMCK100M polymers were utilized in varying amounts and combinations to delay the release of the drug from the sustained release layer. The polymers were also assessed for physical parameters. The divalproex sodium release is prolonged for more than 18 hours by the optimized sustained release layer (SF8). Ultimately, divalproex sodium's chosen sustained release layer and immediate release layer were twice compressed to create bi-layered tablets. The tablets were assessed for their in-vitro drug release, consistent drug content, friability, thickness, hardness, and weight variation. Every physical parameter fell within the pharmacopeial specification's permitted range.

Conclusion: The best formulation (SF8) contained 26.25 mg of HPMC-K4M and 26.25 mg of HPMC-K100M and showed promising results for obtaining desired drug release (>90%) after 18 hours and may produce patient compliance by means of reducing dosing frequency and provide chronotherapy for effective management of epilepsy.

Keywords: Divalproex sodium, Superdisintegrants, HPMC K 4M, HPMC-K100M, Immediate release layer, Sustained release layer.

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INTRODUCTION

Owing to patient compliance and dosage form design flexibility, the oral route is the most widely utilized method of medication delivery. The oral route's widespread use is ascribed to its simplicity in administration, patient acceptance, precise dosage, economical production process, and generally longer product shelf life.[1]

Drug carriers for the oral route include tablets, liquids, capsules, and pills. Among these, solid dosage forms are less expensive to produce as they don't need to be kept under sterile conditions. Because of their simplicity of self-administration, small size, and ease of production, tablets are the most often used dosage form; over 70% of all medications are delivered in this manner.

There are numerous varieties of tablets on the market. There are several types of tablets available: conventional, instantaneous, fast dissolving, controlled release, sustained release, delayed release, and bi-layered.[2]

The pharmaceutical industry has been more interested in creating single dosage forms that combine two or more active pharmaceutical ingredients (API) in order to improve patient convenience and compliance over the past ten years. In order to prevent chemical incompatibilities between API through physical separation and to facilitate the creation of distinct drug release patterns, bi-layered tablets may be the principal choice.[3-4]

There are many advantages of Bilayer Dosageforms, which includes-

- Drug blood levels can be maintained at a constant therapeutic level to increase drug delivery precision safety, and minimize side effects.
- By directing the Drug release to the absorption site and regulating its rate of release, it is possible to lessen the deleterious effect while also lowering the overall drug concentration.
- Compared to traditional methods, fewer daily dosages

are needed, improving patient convenience. Increased patient compliance results in more effective medication regimens.

- Repeat action products are easily made with bi-layered tablets, where the maintenance dose is provided by the second layer and the initial dose is provided by the first.
- Divide components that are incompatible chemically or physically is possible.

Bi-layer tablets consist of a first layer of medication intended for quick release and a second layer intended for drug release at a later time, either as a second dosage or in an extended-release fashion.

A bi-layered tablet can be used to segregate two chemicals that are incompatible, release two medications sequentially in combination, or create a sustained-release tablet with an initial dose that is released immediately and a maintenance dose that is released gradually over time.

Superdisintegrants are crucial for the rapid release of drugs in the immediate release layer, while release retardant polymers maintain the release of the drug in a subsequent layer. This allowed for the long-term achievement of the therapy's primary objective, which was to maintain a steady state level of medication in the blood.

An irregular, high-frequency electrical discharge in the brain that is typified by brief episodes (seizures) with or without unconsciousness and distinctive bodily movements (convulsions) is known as epilepsy. After Alzheimer's disease and cerebrovascular accidents, epilepsy is the third most frequent neurological illness worldwide. Ten percent of people will use a seizer at least once in their lifetime.

A broad class of pharmaceutical drugs known as anticonvulsants is used to treat epileptic seizures. These medications inhibit the rapid and excessive firing of neurons during a seizure, as well as halt the seizure from spreading throughout the brain.

Divalproex sodium was selected as the model medication in this study in order to develop a bi-layer tablet. Divalproex sodium is a special preparation made by partially neutralizing valproic acid with 0.5 equivalent sodium hydroxide. It contains sodium valproate and valproic acid in a 1:1 molar ratio.

Divalproex sodium has an oral bioavailability 84% and a plasma half-life of 9–16 hours. It is used to treat bipolar illness in addition to its function as a broad-spectrum antiepileptic.[5-7]

It is recommended as a preventative antimigraine medication. Divalproex sodium seems to work through a number of methods, including extending the inactivation of the Na+ channel and increasing the release of the inhibitory transmitter GABA by preventing its breakdown.

The current study's objective was to prepare several immediate and sustained-release formulations of divalproex sodium, compare their release profiles, and then choose the most effective formulation from the list of formulations to use in the production of bi-layered tablets. Therefore, an effort has been made to develop divalproex sodium tablets with two layers: an immediate release layer made of superdisintegrants and a sustain release layer built of release retardant polymers.

Materials and Methods

Materials

A free sample of divalproex sodium (CAS No: 76584-70-8) was acquired from MP Pharmaceutical Pvt. Ltd, Hyderabad. We bought Primojel and sodium Ac-Di-Sol from S.D. Fine Chem. Ltd, Mumbai. HPMC-K4M and HPMC-K100M were procured from Gulshan Pharmaceutical Ltd, Salipur. Analytical-grade chemicals were employed for the remaining ingredients.

Formulation of Immediate Release Layer

Wet granulation was used to manufacture the IRL of Divalproex sodium utilizing various superdisintegrants, including SSG and Ac-Di-Sol. The binding solution was PVP K30 solution, which contained a coloring agent. Since the medication had oily properties, microcrystalline cellulose (MCC) was employed as an adsorbent. The formula for the immediate release layer is presented in Table 1.

Wet granulation was used to prepare the immediate release layer. Separately pass each substance through sieve number 100. The binding agent is made by dissolving PVP K30 in an amount of IPA that is specified. Lactose and superdisintegrants were added to the drug and MCC mixture in a geometric manner using a mortar and pestle. After adding the previously made binding agent, strain the wet material through sieve number 16, and let it dry for 20 minutes at 45°C in a hot air oven. Next, after the granules have dried, strain them through sieve number 22 and combine them with talc and magnesium stearate as lubricants for 5 minutes. Next, an 8-station rotatory tableting machine was used to compress the tablets to the appropriate hardness.

Preparation of Sustained Release Layer

The formula for the sustained release layer is presented in Table 2. Divalproex sodium, polymer, and other chemicals were weighed precisely and thoroughly mixed with a mortar and pestle. Until a moist mass formed, the powder was combined with enough PVP K30 solution. After passing the cohesive mass through sieve number 16, the granules were dried in a hot air oven for 20 minutes at 500 degrees Celsius. To break up the big lumps, the dried granules went through sieve # 22 once more. Granules were then combined with talc and magnesium stearate, and their hardness was adjusted to compress them into 300 mg tablets.

Preparation of Sustained Release Layer

The optimal formulations for each layer were selected through observation on the drug release profiles and disintegration of IRL and SRL. Double compression in a single rotatory tableting machine was then used to create the bi-layered tablet.

Evaluation Tests for Prepared Formulations

Hardness

It was carried out with the help of Monsanto Tablet Hardness Tester.[8]

Friability/ durability

Twenty tablets were weighed and noted as W_0 cumulatively (Initial weight). The pills were then dedusted with a Roche Friabilator, Mumbai for 4 minutes at a speed of 25 rpm, and weighed again recorded as (W). The following equation was used to obtain the percentage of friability (%Friability ≤1).

$$\text{Friability (\%)} = (W_0 - W) / W_0 \times 100$$

Assay

20 tablets were chosen and ground in an impartial manner. The powder corresponding to 100 mg of Divalproex sodium was weighed, added to a volumetric flask with 50 mL of phosphate buffer pH 6.8 (PBS), made into the solution using a sonicator and the final volume was made upto 100 mL with phosphate buffer. From this, 1-mL of solution was withdrawn and diluted to 10 mL with PBS. The resulting solution absorbance was measured at 210 nm using a UV-visible spectrophotometer (Analytical UV Double beam -2800, Baroda).[7]

Thickness

It was measured with the help of vernier calipers.[7]

In-vitro Dissolution Study

In-vitro dissolution study for immediate release layer

IRL was analyzed for drug release study utilizing a Lab-India USP type-II tablet dissolution test apparatus (Labindia Tablet dissolution Apparatus DS 8000, Navi Mumbai) and 900 mL of phosphate buffer pH 6.8 (PBS) in accordance with the official method (i.e, apparatus rotated at a speed of 100 rpm at 37 ± 0.5°C). Using a UV-visible spectrophotometer, samples' absorbance was measured at 210 nm and the data was subjected to kinetic modeling.[7,9]

In-vitro dissolution study for sustained release layer

This test was carried out for 18 hours. SRL was analyzed for drug release study utilizing a Lab-India USP type-II tablet dissolution test apparatus (Labindia Tablet dissolution Apparatus DS 8000, Navi Mumbai) and 900 ml of 0.1 N HCl for initial 45 minutes and Phosphate buffer pH 6.8 (PBS) for next 18 hours in accordance with the official method (i.e apparatus rotated at a speed of 100 rpm at 37 ± 0.5°C). Using a UV-visible spectrophotometer, samples' absorbance was measured at 210 nm and the data was subjected to kinetic modeling.[7,9]

Table 1.1: Formulae for the preparation of divalproex sodium immediate release layer

Name of Ingredients	*Quantity of Ingredients per each tablet (mg)*					
	IRF_1	IRF_2	IRF_3	IRF_4	IRF_5	IRF_6
Divalproex sodium	125	125	125	125	125	125
Lactose	39	37	39	37	39	37
Ac-di-sol	8	10	-	-	4	4
Primojel	-	-	8	10	5	5
Microcrystalline cellulose (MCC)	20	20	20	20	20	20
Talc	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4
Total Weight	200	200	200	200	200	200

Table 1.2: Formulae for the preparation of divalproex sodium sustained release layer

Name of Ingredients	*Quantity of Ingredients per each tablet (mg)*								
	SRF_1	SRF_2	SRF_3	SRF_4	SRF_5	SRF_6	SRF_7	SRF_8	SRF_9
Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25
Lactose	58.75	48.75	38.75	58.75	48.75	38.75	58.75	48.75	38.75
HPMC-K-4M	40	50	60	-	-	-	20	25	30
HPMC-K-100M	-	-	-	40	50	60	20	25	30
Microcrystalline cellulose (MCC)	20	20	20	20	20	20	20	20	20
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total Weight	300	300	300	300	300	300	300	300	300

Table 2: Post-Compression parameters for IRL

Formulation-Code	*Hardness (kg/cm²)*	*Thickness (mm)*	*Friability (%)*	*Average Weight (mg)*	*Drug Content (%)*	*Disintegration Time (sec)*
IRF_1	5.95 ± 0.05	2.87 ± 0.04	0.74 ± 0.09	199.9 ± 1.57	98.12 ± 1.19	120.32 ± 1.53
IRF_2	4.18 ± 0.10	2.91 ± 0.10	0.58 ± 0.04	200.3 ± 1.60	97.65 ± 1.82	91.66 ± 2.08
IRF_3	6.35 ± 0.03	2.90 ± 0.07	0.56 ± 0.06	200.9 ± 1.60	98.65 ± 1.28	73.33 ± 2.51
IRF_4	6.17 ± 0.07	2.87 ± 0.03	0.65 ± 0.05	201.55 ± 1.99	99.61 ± 0.94	48.33 ± 3.05
IRF_5	4.14 ± 0.04	2.92 ± 0.06	0.63 ± 0.03	201.45 ± 2.52	99.43 ± 1.32	59.33 ± 2.08
IRF_6	4.53 ± 0.11	2.89 ± 0.09	0.69 ± 0.04	200.05 ± 1.81	99.51 ± 1.81	37.34 ± 1.51

Table 3: Kinetic parameters for IRL

S.NO	*Formulation Code*	*KINETIC PARAMETERS*											
		ZERO ORDER			*FIRST ORDER*			*HIGUCHI*			*KORSMEYER-PEPPAS*		
		a	*b*	*r*	*a*	*b*	*r*	*a*	*b*	*r*	*a*	*b*	*r*
1	IRF_1	22.662	2.683	0.914	1.927	0.033	0.991	4.631	16.873	0.984	1.287	0.483	0.979
2	IRF_2	24.648	2.797	0.911	1.939	0.041	0.992	5.733	17.629	0.983	1.347	0.452	0.981
3	IRF_3	24.954	2.706	0.907	1.923	0.036	0.991	6.493	17.110	0.982	1.353	0.441	0.981
4	IRF_4	35.752	2.658	0.840	1.872	0.056	0.992	15.28	17.584	0.951	1.511	0.363	0.959
5	IRF_5	35.466	2.457	0.843	1.859	0.042	0.980	16.71	16.198	0.952	1.548	0.313	0.970
6	IRF_6	39.718	2.575	0.827	1.895	0.074	0.990	19.44	17.186	0.945	1.605	0.293	0.978

Table 4: Dissolution parameters for divalproex IRL formulations

S.NO	*Formulation Code*	*Dissolution Parameters*				
		$t_{1/2}$ *(Min)*	$t_{10\%}$ *(Min)*	$t_{90\%}$ *(Min)*	$t_{75\%}$ *(Min)*	$t_{25\%}$ *(Min)*
1	IRF_1	9.236	1.404	30.691	18.472	3.833
2	IRF_2	7.402	1.125	24.595	14.803	3.072
3	IRF_3	8.250	1.254	27.416	16.501	3.424
4	IRF_4	5.341	0.812	17.749	10.682	2.217
5	IRF_5	7.157	1.088	23.782	14.313	2.970
6	IRF_6	4.046	0.615	13.445	8.092	1.679

Table 5: Post-Compression parameters for SRL

FormulationCode	*Hardness (kg/cm²)*	*Thickness (mm)*	*Friability (%)*	*Average Weight (mg)*	*Drug Content (%)*
SRF_1	5.38 ± 0.10	3.34 ± 0.09	0.32 ± 0.06	302.6 ± 1.41	99.38 ± 1.19
SRF_2	4.33 ± 0.02	3.30 ± 0.14	0.35 ± 0.02	302.9 ± 2.29	98.61 ± 1.03
SRF_3	6.14 ± 0.04	3.31 ± 0.03	0.43 ± 0.03	302.5 ± 1.59	97.43 ± 1.28
SRF_4	6.23 ± 0.06	3.28 ± 0.05	0.36 ± 0.02	301.75 ± 1.14	98.57 ± 0.85
SRF_5	5.14 ± 0.03	3.30 ± 0.06	0.41 ± 0.06	300.65 ± 1.37	98.43 ± 1.27
SRF_6	4.52 ± 0.02	3.33 ± 0.03	0.48 ± 0.03	302.30 ± 1.31	97.63 ± 0.61
SRF_7	6.74 ± 0.04	3.28 ± 0.08	0.42 ± 0.06	303.20 ± 1.46	99.47 ± 1.04
SRF_8	6.16 ± 0.02	3.30 ± 0.04	0.37 ± 0.04	301.25 ± 1.55	99.51 ± 1.20
SRF_9	6.56 ± 0.03	3.32 ± 0.07	0.31 ± 0.03	302.42 ± 1.04	98.49 ± 0.93
DBLT	7.04 ± 0.16	6.29 ± 0.11	0.38 ± 0.02	500.75 ± 0.45	99.24 ± 0.52

Table 6: Kinetic parameters for SRL

S.NO	Formulation Code	KINETIC PARAMETERS											
		ZERO ORDER			FIRST ORDER			HIGUCHI			KORSMEYER-PEPPAS		
		a	*b*	*r*	*a*	*b*	*r*	*a*	*b*	*r*	*a*	*b*	*r*
1	SRF_1	9.947	5.358	0.990	2.471	0.162	0.820	8.85	24.448	0.983	1.178	0.644	0.994
2	SRF_2	8.233	4.657	0.939	2.116	0.066	0.838	7.784	21.121	0.927	1.010	0.744	0.934
3	SRF_3	3.795	4.232	0.992	2.038	0.037	0.948	10.05	18.904	0.964	0.870	0.807	0.982
4	SRF_4	9.757	5.051	0.989	2.151	0.081	0.878	8.107	23.107	0.984	1.147	0.654	0.992
5	SRF_5	3.846	5.177	0.995	2.151	0.072	0.892	13.16	23.154	0.969	0.901	0.857	0.990
6	SRF_6	3.507	3.485	0.994	2.007	0.024	0.987	8.276	15.724	0.976	0.784	0.815	0.995
7	SRF_7	9.006	5.099	0.991	2.272	0.108	0.797	8.929	23.288	0.985	1.115	0.684	0.999
8	SRF_8	3.993	4.928	0.995	2.090	0.055	0.920	12.49	22.160	0.973	0.841	0.901	0.987
9	SRF_9	3.654	3.858	0.994	2.019	0.030	0.973	9.161	17.314	0.970	0.830	0.810	0.989
10	DBLT-IRL	46.436	1.240	0.662	1.574	0.046	0.929	21.58	13.097	0.872	1.843	0.097	0.835
11	DBLT-SRL	3.572	4.966	0.994	2.107	0.059	0.894	12.90	22.277	0.970	0.834	0.906	0.987

Table 7: Dissolution parameters for divalproex SRL formulations

S.NO	Formulation Code	Dissolution Parameters				
		$t_{1/2}$ (h)	$t_{10\%}$ (h)	$t_{90\%}$ (h)	$t_{75\%}$ (h)	$t_{25\%}$ (h)
1	SRF_1	1.854	0.282	6.160	3.707	0.769
2	SRF_2	4.539	0.690	15.082	9.077	1.883
3	SRF_3	8.160	1.240	27.116	16.320	3.386
4	SRF_4	3.721	0.566	12.366	7.443	1.544
5	SRF_5	4.196	0.638	13.943	8.392	1.741
6	SRF_6	12.452	1.893	41.376	24.903	5.167
7	SRF_7	2.782	0.423	9.245	5.564	1.155
8	SRF_8	5.432	0.826	18.050	10.864	2.254
9	SRF_9	10.182	1.548	33.835	20.364	4.225
10	DBLT-IR	6.575	0.999	21.849	13.150	2.729
11	DBLT-SR	5.106	0.776	16.967	10.212	2.119

Results and Discussion

Using polymers like HPMC-K4M and HPMC-K100M for the sustained release layer and superdisintegrants such Primojel and Ac-Di-Sol for the immediate release layer, the bi-layered Divalproex sodium tablets in this study were made using the wet granulation process.

Results for hardness, friability, drug content, and *in-vitro* disintegration for IRL are shown in Table 2. In all of the formulations, the hardness test indicated good mechanical strength, whereas the friability was less than 0.8%, which indicated that the tablets had good mechanical resistance. The *in-vitro* disintegration times for the formulations IRF_1 to IRF_6 varied from 37.34 ± 1.51 to 120.32 ± 1.53 seconds. It was observed that when primojel was used as a disintegrant, the tablets were disintegrated within a short time due to the easy and high swelling abilities wicking action of primojel as compared to Ac-Di-Sol. For the development of the Bilayer formulation, disintegration time had to be short to obtain the burst effect for the immediate release layer. The drug content was found to be high (99.61 ± 0.94) and uniform in all of the tablet formulations. It ranged from 97.43 ± 1.28 to 99.61 ± 0.94 and was uniform in all tablet formulations.

The rapid increase in the dissolution of divalproex with an increase in Ac-Di-Sol may be attributed to the rapid swelling and disintegration of the tablet. Primojel exhibited capillary activity (wicking) and pronounced hydration with little tendency of gel formation and disintegrated the tablet rapidly. Formulation IRF_6 showed satisfactory hardness, % drug content, the lowest disintegration time, and high drug release. So IRF_6 was considered as the optimized formulation

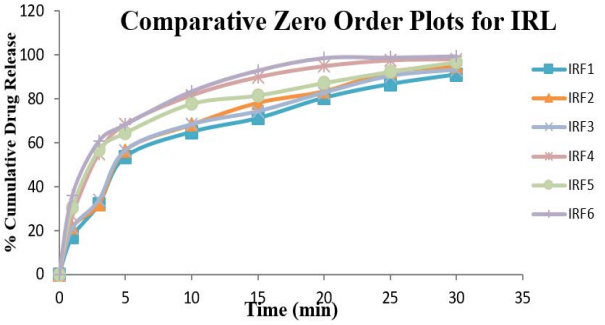

Figure 1: Comparative Zero order plots for IRL formulations of Divalproex sodium

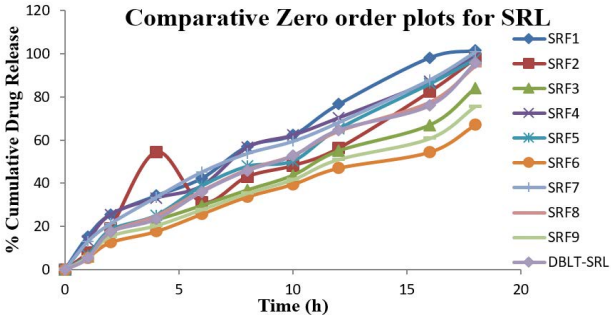

Figure 5: Comparative Zero order plots for SRL formulations of Divalproex sodium

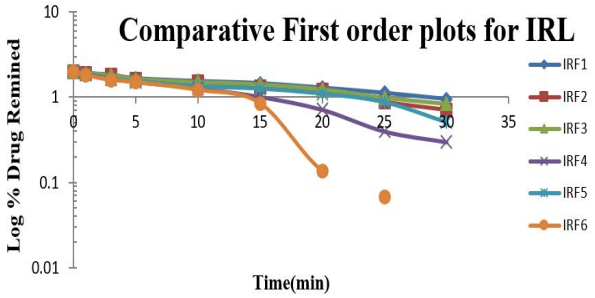

Figure 2: Comparative First order plots for IRL formulations of Divalproex sodium

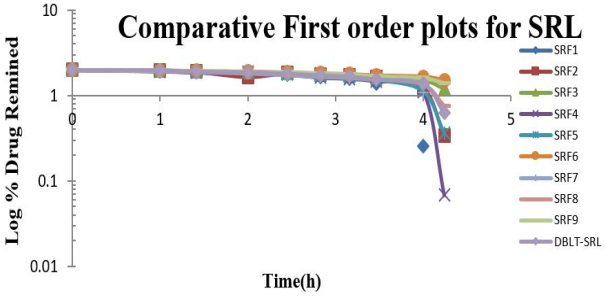

Figure 6: Comparative First order plots for SRL formulations of Divalproex sodium

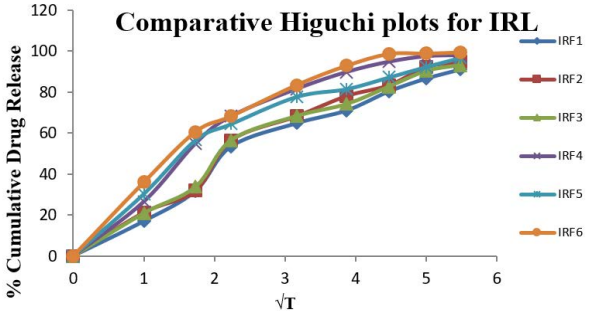

Figure 3: Comparative Higuchi plots for IRL formulations of Divalproex sodium

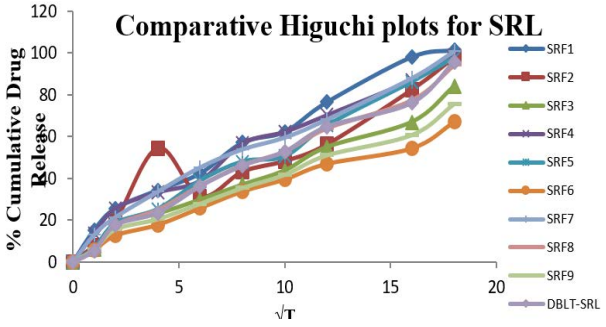

Figure 7: Comparative Higuchi plots for SRL formulations of Divalproex sodium

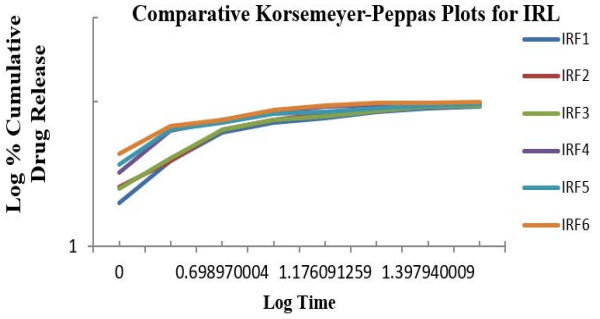

Figure 4: Comparative Korsemeyer-Peppas plots for Divalproex sodium IRL formulations

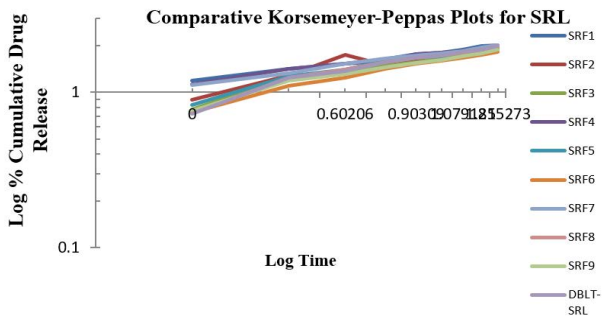

Figure 8: Comparative Korsemeyer-Peppas plots for Divalproex sodium SRL formulations

and it was taken for further studies. The dissolution data for the IRL are fitted to kinetic modeling and the results were presented in Table 3-4 and the same shown in Figure 1-4.

Results for hardness, thickness, friability, uniformity of weight, and drug content for SRL are given in Table 5. It is observed that the various quantities of release retardants show an impact on drug release from the sustained release layer. The low concentration of HPMC-K-4M showed the highest drug release compared to all other formulations. From this quantitative relationship clearly understood that, the amount of polymer is inversely proportional to drug release from the polymer matrix. The combination of polymers also proved the synergistic retardation effect on the drug release profile. Formulation SRF_8 showed satisfactory or promising results in all aspects of current study. So SRF_8 was considered as the optimized formulation and it was taken for further studies. The dissolution data for the IRL are fitted to kinetic modeling and the results were presented in Tables 6 and 7 and the same shown in Figure 5-8.

The selected formulation of the immediate and sustained release layer was prepared as a bilayer tablet. Hardness and friability showed 7.04 ± 0.16 $Kg.cm^{-2}$ and less than 1%, respectively, indicating the stability against physical stokes. Thickness was found to be 6.29 ± 0.11 mm and content of uniformity 99.24 ± 0.52%, indicating uniform distribution of a drug in both layer. The release pattern of the drug from a bi-layered tablet showed the same as the individual layer tablets of immediate and sustained release.

Conclusion

The drug release from the bilayer divalproex tablet formulation can be readily modulated by varying the concentration of superdisintegrants and release retardants composition. From the experimental findings, it can be concluded that bilayer tablets of divalproex sodium can give efficient therapy by reducing the dose and dosing frequency and minimizing the dose-related adverse effects cost for effective management of epilepsy. Finally, it may be concluded that the bilayer tablet formulation of divalproex offers a valuable dosage form treatment of hypertension with improved patient compliance drug efficiency.

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References

1. Notari R. An Introduction to drug delivery in Bio pharmaceutics and clinical pharmacokinetics, 3rd Ed., Marcel Dekker Inc. New York, 1980:152-154.
2. Vinay K, Prajapati SK, Girish CS, Mahendra S and Neeraj K. Sustained release matrix type drug delivery system: A Review. World journal of Pharmacy and Pharmaceutical Sciences. 2012;1(3): 934-960.
3. Rohan DD, Gowda DV, Nawaz Mahammed, Deepak NM. Bi-Layer Tablets- An Emerging Trend: A Review. International Journal of Pharmaceutical Sciences and Research. 2011;2(10):2534-2544. doi.org/ 10.13040/IJPSR.0975-8232.2(10).2534-44
4. Kumar AH, Kavitha K, Kumar SAK, Kumar MR and Singh SDJ. Novel approach of bilayer tablet technology-A review. International Journal of Pharmaceutical, Chemical, Biological Sciences. 2013;3(3): 887-893.
5. Sridharan R. Epidemiology of epilepsy. Current Science. 2002;82(6): 664-670.
6. Ravi C, Mohammed GA Design and evaluation of immediate release tablets of divalproex sodium, Der Pharmacia Lettre.2015;7(5):87-92.
7. Raghavendra K. Gunda, Naga Suresh K. Jujjuru , Vijayalakshmi A., Prathap M. and Koteswararao GSN. Statistical Optimization and assessment of Divalproex sodium Extended Release tablets. Indian Drugs.2023; 60(8):31-37. doi.org/ 10.53879/id.60.08.13485
8. Patil SS, Hiremath D, Basha KM, Udupi RH. Design and *in-vitro* evaluation of gastroretentive bilayer floating tablets of Rosiglitazone Maleate. International Journal of Pharmaceutical & Biological Archive. 2012; 3: 204-212.
9. Shibu BS, Suresh S and Saravanan C. Formulation and evaluation of extended release tablet of Divalproex sodium using different polymers as release retarding agent. International Journal of Pharmaceutical Development and Technology. 2014; 4(3): 145-150.

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