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Design, Development And Evaluation of Matrix Tablet of Divalproex

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A B S T R A C T :

The bi-layered tablet formulation was designed to deliver Divalproex sodium as an instant release and extend the medication release for 18 hours in order to offer a better and longer therapeutic impact. There are no observable interactions between the excipients according to FTIR compatibility testing. The two layers were prepared by wet granulation and punched separately. Six distinct formulations of immediate release tablets (IF1–IF6) were made using sodium starch glycolate and croscarmellose sodium. Nine sustained release formulations (SF1–SF9) were created using different ratios and combinations of HPMC K4M and HPMC K100M. For every formulation, pre-compression and post-compression parameters were evaluated. Bi-layered tablets were made using the best formulations from each layer.

IF6 from the immediate release layer showed 98.62% drug release in 20 minutes. The sustained release layer's SF8 showed 94.29 percent drug release at 18 hours, and the release pattern was within the parameters of the sustained release tablet. The produced bi-layered tablets were evaluated for post-compression characteristics. To determine the drug-excipient interaction, FTIR was employed. The produced bi-layered tablet was subjected to short-term stability testing for three months at 400C and 75% relative humidity. The instant release layer formulations (IF1-IF6) were found to have satisfactory results.

Keywords: Matrix Tablet, Divalproex Sodium, Sustain release tablet, delayed release tablet, Anti-Epileptic drug.

Introduction

The tablet is the most widely used dosage form due to its ease of self-administration, small size, and ease of manufacture. Tablets are solid dosage forms that may or may not include medicinal drugs and the proper diluents5. The Indian Pharmacopoeia defines pharmaceutical tablets as solid, flat, or biconvex dishes used as unit dose forms. Compressing a drug or mixture of drugs, with or without diluents, is how they are created. They differ in size and weight according to the amount of drug and the preferred mode of administration. Tablets are the most often used dose form, accounting for 70% of all pharmaceuticals.

Introduction of Epilepsy

A transitory episode (seizure) with or without loss of consciousness and a distinctive movement of the body (convulsion) are hallmarks of epilepsy, which is defined as an abnormal, high frequency electrical discharge in the brain. After Alzheimer's disease and cerebrovascular disease, epilepsy is the third most prevalent neurological condition worldwide. Approximately 10% of people will experience at least one seizure over their lifetime.
Manic-depressive disease, another name for bipolar disorder, is a brain ailment that results in abnormal changes in mood, energy, activity levels, and the capacity to do daily tasks. Bipolar illness patients go through "mood episodes," which are times of very high emotional states. A manic episode is characterised by excessive delight or excitement, while a depressive episode is characterised by overwhelming sadness or hopelessness.
Anticonvulsants, sometimes referred to as antiepileptic or antiseizure medications, are a broad class of pharmaceuticals used to treat epileptic seizures. Anticonvulsants prevent excessive and fast neuronal activity during seizures. Additionally, it stops the seizure from spreading across the brain. Bipolar disorder is also treated with it.

Mechanism of action of antiepileptic drugs

Various methods, such as blocking voltage-gated channels (Na+ or Ca2+), enhancing inhibitory GABAergic impulses, or interfering with excitatory glutamate transmission, are used by drugs that effectively reduce seizures. While the mechanism of action for some antiepileptic medications is unclear, others seem to have several targets within the central nervous system.

Material and Methods

Apparatus and chemicals: Divalprex sodium by M/s Drug India Hydrabad., Sodium starch glycolate by Dr. Reddy's Laboratories, Hyderabad, Twin 20, Span 20, Isopropyl Alcohol by Ranchem Ltd.., India, Mineral oil by Loba Chemie, Mumbai.

Methods: Preparation of Matrix Tablet

In a mortar and pestle, precisely weighed Divalproex sodium, polymer, and additional materials were combined. The powder was combined with enough PVP K30 solution to create a moist mass. After passing the cohesive mass via sieve #16, the granules were dried for 20 minutes at 500C in a hot air oven. To break up the big lumps, the dried granules went through sieve #22 once more. After that, granules were combined with magnesiumstearate and talc, and their hardness was adjusted to compress them into 300 mg tablets. Table No. 14 displayed the formulae. Making a two-layered tablet

The optimal formulas for each layer were selected based on an analysis of the drug release and disintegration profiles of IRL and SRL. A single rotating tableting machine was used to twice compress the resulting bi-layered tablet.

Table 1: Preparation of Matrix Tablet

S.N.	Ingreditent	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25
2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMC K4M	45	52.5	60	-	-	-	22.5	26.25	30
4	HPMC K100M	-	-	-	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6
8	Total	300	300	300	300	300	300	300	300	300

Experimental work

3.1 Preformulation Studies

The study of a medical ingredient's physical and chemical properties, both alone and in conjunction with excipients, is known as preformulation. Preformulation studies aim to identify the physicochemical properties and excipients that may affect the manufacturing process, formulation design, and pharmacokinetic-biopharmaceutical aspects of the final product.

3.2 Determination of Solubility

Solubility was tested in various media including ethanol, methanol, absolute ethanol, acetone, chloroform, ether, water, 10% v/v HCl and 10% w/v sodium hydroxide.

3.3 Melting Point

The melting point of Divalproex sodium was measured in triplicate using the capillary method.

3.4 UV and FTIR Spectroscopy

To determine if the medicine and excipients were compatible, FT-IR spectroscopy was used. Using a S thermo Nicolet FTIR, infrared spectroscopy was performed, and the spectra was acquired between 4000 and 400 cm-1.

Result and discussion

4.1 Preformulation Study

4.1.1 Description

Divalproex sodium is observed odour less, white or off white crystalline powder.

4.1.2 Result of Solubility

The drug's solubility experiments were conducted using a range of media, such as phosphate buffer pH 6.8, methanol, chloroform, and pure water. The results of the solubility research in various media are shown in Table 5. The outcome shows maximum solubility in chloroform.

4.2 Result of Melting Point

The medicine's melting point was determined to be comparable to the stated value, confirming that the drug samples that were received met the stated specifications. The melting point of a particular pharmacological ingredient will vary depending on any impurities that may be present The capillary technique was used to determine the drug's melting point. It turns out to be between 219 and 2230C.

4.3 UV Spectroscopy

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

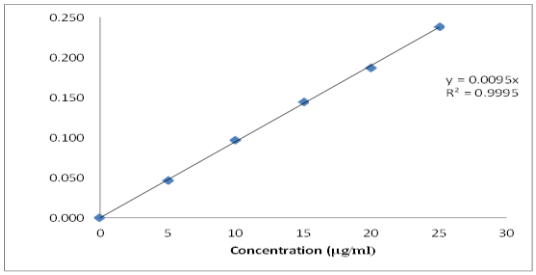

Fig 1. Lambda max of Divalproex Sodium

4.3.1 FT-IR Spectroscopy

Figures display the FT-IR spectra of the medicine Divalproex sodium in its pure form as well as the drug in combination with polymers. Drug and polymer compatibility was demonstrated by the presence of all of Divalproex sodium's distinctive peaks in the spectra of the drug and polymer combination. Table 22 is a tabulation of the whole FT-IR spectrum.

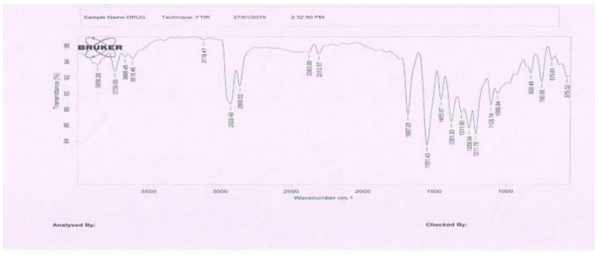

Fig 2. FT-IR of Divalproex sodium

4.3.2 Drug - Excipients Compatibility Study

FT-IR Spectroscopy

The drug and excipients were found to be compatible after FTIR analysis of the physical mixes of the drug and excipients in a 1:1 ratio that had. Drug and polymer compatibility was demonstrated by the presence of all of Divalproex sodium's distinctive peaks in the spectra of the drug and polymer combination. Table 22 is a tabulation of the whole FT-IR spectrum.

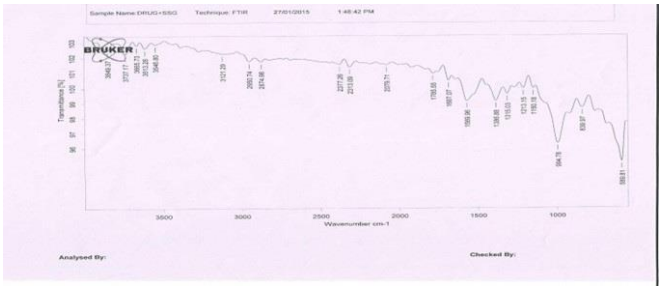

Figure 3 FT-IR Spectra of Divalproex sodium + Sodium Starch Glycolate

4.4 DSC Study DSC Analysis

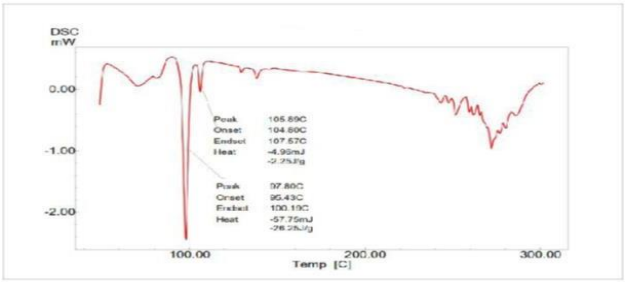

Figure 4: DSC spectrum of Divalproex sodium

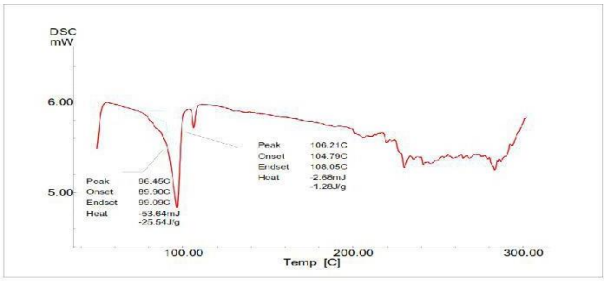

Figure 5: DSC spectrum of Formulation

4.5 Evaluation of Matrix Tablet

4.5.1 Precompression evaluation parameter of formulation

Table 2: Precompression parameters of matrix tablet.

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
MF1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
MF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
MF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
MF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
MF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
MF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
MF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
MF8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
MF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

4.5.2 Post compression evaluation parameter of formulated matrix tablet

Table 3: Post compression parameters of matrix tablet.

Batch Code	Weight variation Mean ± SD	Hardness (kg/cm2) Mean ± SD	Friability (%)Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	In vitro disintegration time (sec)
MF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09	99.38±1.19	-
MF2	302.9±2.29	4.33±0.02	0.35±0.02	3.30±0.14	98.61±1.03	-
MF3	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
MF4	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57±0.85	-
MF5	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43±1.27	-
MF6	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63±0.61	-
MF7	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47±1.04	-
MF8	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51±1.20	-
MF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49±0.93	-

4.5.2 Kinetic of drug formulation

Table 4: Kinetic drug Release

FORMULATION CODE	KINETIC MODEL				
	Zero order R^2	First Order R^2	Higuchi R^2	Korsmeyer	
				n	R^2
MF1	0.9821	0.8296	0.9653	0.6549	0.9975
MF2	0.9838	0.7303	0.9074	0.6426	0.9794
MF3	0.9838	0.8986	0.9297	0.6296	0.9699
MF4	0.9736	0.7718	0.9794	0.6510	0.9983
MF5	0.9918	0.8975	0.9404	0.6571	0.9736
MF6	0.9847	0.8975	0.9518	0.6064	0.9692
MF7	0.9827	0.7693	0.9685	0.6528	0.9987
MF8	0.9873	0.7926	0.9427	0.6634	0.9602

4.5.3 In vitro Drug Release

Table 5: Invitro drug release of matrix tablet.

TIME IN MIN	% CUMULATIVE DRUG RELEASE							
	MF1	MF2	MF3	MF2	MF2	MF2	MF2	MF2
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

4.5.4 Stability Studies

Table 2: Stability studies of formulation

Stability Period	**40^0C/75% RH**			
	Hardness Mean ± SD	**% Friability Mean ± SD**	**% Drug content Mean ± SD**	**Drug release In Min.**
Initial	7.05±0.67	0.36±0.01	99.23±0.532	95.823
1 month	7.08±0.49	0.43±0.03	99.35±0.751	95.421
2 month	6.41±0.49	0.56±0.06	98.96±0.792	94.736
3 month	5.33±0.60	0.73±0.03	96.94±0.921	94.381

Conclusion

The Matrix tablet formulation was designed to deliver Divalproex sodium as an instant release and extend the medication release for 18 hours in order to offer a better and longer therapeutic impact. There are no observable interactions between the excipients according to FTIR compatibility testing. The two layers were prepared by wet granulation and punched separately. Six distinct formulations of immediate release tablets swere made using sodium starch glycolate and croscarmellose sodium. Nine sustained release formulations were created using different ratios and combinations of HPMC K4M and HPMC K100M. For every formulation, pre-compression and post-compression parameters were evaluated. Matrix tablets were made using the best formulations from each layer.

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