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Research Paper

DEVELOPMENT OF SUSTAINED RELEASE DIVALPROEX SODIUM TABLETS AND THEIR EVALUATION

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If one were to imagine the ideal DDS, two prerequisites would be required. First, it would be a single-dose for the duration of treatment, whether it is for days of weeks, as with infection, or for a lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the drug directly to the site of action, thereby minimizing or eliminating side effects. SR has received most of the attention because of the fact that there is more feasibility in dosage form. The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. The present study was aim to formulate and evaluate the Sustained release oral matrix tablet by using Divalproex Sodium as a model drug and see the effects of different polymers to prolong the release of drug for extended period of time. Various formulations of extended release tablets of Divalproex Sodium were developed using the polymers like Benecil K4M and Benecil K100M in different proportion by direct compression technique. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. Results of in vitro release profile indicated that formulation SF9 & SF16 were the most promising formulation as the extent of drug release from this formulation was optimum when compared to other formulations.

Key words: Divalproex Sodium, direct compression, Sustained Release.

INTRODUCTION

Conventional oral drug delivery systems are slowly fading away in the market due to its disadvantages. These delivery systems produce fluctuation of drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level. This effect is usually totally dependent on the particular agent's biological half life, frequency of administration and release rate[1]. Extended or Sustained release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half – lifedrugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Matrix type Sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pelletization during manufacturing and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation[2,3].

Hydrophilic polymer matrix system are widely used for designing oral Sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[4]The hydrophilic polymer selected

for the present study was Benecil K4M and Benecil K100M. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix. For such drugs, it becomes essential to include hydrophobic polymers in the matrix system such as Ethyl Cellulose. Among the several polymers available as possible matrix forming materials, Ethyl Cellulose appear particularly attractive, due to their high chemical stability and good compatibility properties.[5,6]

Epilepsy affects up to 1% of the population, making it second to stroke as one of the most common serious neurologic disorders. About 50 million people worldwide have epilepsy and 90% of them are from developing countries.[7] In the past several years, our understanding of epilepsy has increased in several respects. It is a common chronic neurological disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability and characterized by recurrent unprovoked seizures. There is now clear evidence that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence and management. The seizures are associated with characteristic signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain.[8,9]

Divalproex sodium[10,11]is a GABA transaminase enzyme inhibitor used in the treatment of Epilepsy and migraine disorder. Divalproexsodium can be given twice a day or thrice a day.[12]Because of its use in neurological disorder and its adverse effect, by preparing extended release formulation of this drug reduce dosage frequency; obtain optimized and controlled therapy, better patient compliance. So, Divalproex sodium is best candidate for extended release formulation. The prepared formulation is given after a meal for better absorption through GI tract. The aim of the current study was to develop an Sustained release matrix tablet of Divalproexsodium using Benecil K4M and Benecil K100Mby direct compression method and to optimize the formulation.

MATERIALS AND METHODS

Materials

Divalproexsodium was obtained as a gift sample from Sun Pharma Pvt. Ltd. Baroda, India. Benecil K4M/K100M, Ethyl cellulose, were received from Signet., Mumbai. All other excipient (Avicel pH 102, Magnesium Stearate and Talc,) obtained as gift samples from BASF.

Preformulation studies

The compatibility studies were carried out to study the possible interactions between

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Divalproex sodium and inactive ingredients. Physical mixture of Divalproex sodium and excipients were prepared in the (1:1) ratio and analyzed by DSC & FTIR method. For DSC Heat runs for each sample were set from 25 to 350^{0}C at a heating rate of 10^{0}C/min, using nitrogen as blanket gas. For FTIR the spectrum was recorded in the region of 4000 to 400 cm^{-1}.

Formulation design of ODTs tablets

Tablets containing 250 mg Divalproex Sodium were prepared by direct compression. The respective powders, namely Divalproex Sodium, release retarding polymer viz. (BenecilK4M / Benecil K100M), a Hydrophobic Agent (Ethyl cellulose) were passed through sieveno.40 separately. Mixing of powders was carried out using a mortar & pestle for 10 min, then other ingredient viz. microcrystalline cellulose (Avicel pH 102) was added in geometric proportions, and all these were

Table 1.0: Formulations of Divalproex Sodium tablets employing Benecil –K4M

Ingredients	Quantity (mg)								
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
Drug	250	250	250	250	250	250	250	250	250
Benecil K4M	30	60	90	30	60	90	30	60	90
Ethyl Cellulose	20	20	20	30	30	30	40	40	40
Avicel pH 102	194	164	134	184	154	124	174	144	114
Mg stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Table 2.0: Formulations of Divalproex Sodium tablets employing Benecil –K100M

Ingredients	Quantity (mg)								
	SF10	SF11	SF12	SF13	SF14	SF15	SF16	SF17	SF18
Drug	250	250	250	250	250	250	250	250	250
Benecil K100M	30	60	90	30	60	90	30	60	90
EthylCellulose	20	20	20	30	30	30	40	40	40
AvicelpH102	194	164	134	184	154	124	174	144	114
MgStearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

mixed homogenously and then lubricated with the previously weighed and sieved (sieve no.60) magnesium stearate, talc in a polybag for about 5-10 min, to obtain the blend for compression. Finally, 500 mg of each mixture was compressed on sixteen station rotary tablet punching machine having 10 mm punches to produce the desired tablets.

Evaluation of tablets

All the prepared tablets were evaluated for the following parameters. like Thickness, Hardness, Friability, Weight variation and Assay and Dissolution. Drug release studies of the prepared tablets were performed, in a USP Dissolution Apparatus, type II (Paddle method) at 37°C ± 0.5°C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 ml phosphate buffer pH 6.8 for up to 24 hour. Aliquots of 5 ml were withdrawn from the dissolution apparatus at different time intervals & filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined by HPLC method. At each time of withdrawal, 5ml of fresh medium was replaced into dissolution flask.

RESULTS AND DISCUSSION

The DSC Thermogram of Divalproex sodium exhibits a sharp endothermic peak at 101.54^{0}C within the range 2.0^{0}C indicating the sample is in the pure form. The of Drug Excipient samples showed a wide range of similar peak which has started at around 95^{0}C and completed at around 105^{0}C suggesting that drug in the formulation had remained in a unreacted form.

The Infra-red spectrum of drug and excipients were recorded over KBr disc method. All the characteristic peaks of Divalproex sodium were present in the spectrum of drug and excipient mixture, indicating compatibility between drug and excipients.

The results of Post compression Parameter for the tablets are shown in table No. 3&4. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. Tablet hardness was maintained constant in all the formulations and was in the range of 5.1 to 6.2 kg/cm^2. Tablets mean thickness were almost uniform in all the formulations and were found to be in the range of 3.22 mm to 3.43 mm. The % friability was NMT 1% in all the formulations ensuring that the tablets were mechanically stable. The percentage of drug content was found to be between 98.34 to 101.71 %, which was within acceptable limits.

Among the formulations Manufactured with the Polymer Benecil K4 M (SF1 to SF9), for the formulation SF1, SF2, SF3, SF4, SF5 and SF6, approx 90% drug release within 12 Hours. For the formulation SF7 & SF8 approx 90% drug gets release in dissolution media within 18 Hours. Formulation SF9 shows the sustained effect by releasing the drug upto

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24hrs.

Among the formulations Manufactured with the Polymer Benecil K100 M (SF10 to SF18), for the formulation SF10, SF11 & SF12 drug release more than 90% within 12 Hours and for the formulation SF13, SF14 & SF15 drug release more than 90% within 18 Hours. Formulation SF17 & SF18 shows the

Table 3.0 Results of physical parameters of tablets containing Benecil K4M

Formulations	Tablet weight(mg)	Hardnes (kg/cm2)	Thickness (mm)	Friability (%)	Drug Content (%)
SF1	503	5.6	3.30	0.30	99.21
SF2	500	5.5	3.26	0.20	101.11
SF3	502	6.2	3.29	0.50	99.12
SF4	499	5.8	3.41	0.35	98.76
SF5	503	6.1	3.31	0.29	101.71
SF6	504	5.7	3.22	0.10	99.54
SF7	505	5.8	3.28	0.27	98.34
SF8	503	6.0	3.40	0.12	98.41
SF9	500	5.7	3.43	0.20	101.34

Table 4.0 Results of physical parameters of tablets containing Benecil K100 M

Formulations	Tablet weight (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Drug Content (%)
SF10	500	5.2	3.28	0.21	101.50
SF11	502	5.1	3.25	0.24	99.40
SF12	501	5.8	3.25	0.41	98.52
SF13	500	5.6	3.37	0.25	98.87
SF14	500	6.2	3.29	0.34	101.23
SF15	501	5.7	3.28	0.21	98.75
SF16	504	5.9	3.25	0.18	99.91
SF17	503	5.9	3.29	0.22	99.23
SF18	501	5.3	3.35	0.29	99.71

Table 5.0 Percentage Drug Release of tablets containing Benecil K-4M

Formu-lations	% Drug Release						
	1hr	2hr	4hr	8hr	12hr	18hr	24hr
SF1	44	56	72	91	99	99	100
SF2	42	54	67	89	98	99	99
SF3	41	49	66	83	99	100	100
SF4	33	44	61	79	92	100	100
SF5	33	45	60	80	91	99	100
SF6	30	39	60	81	89	99	99
SF7	22	34	52	78	82	93	100
SF8	19	32	51	74	80	92	99
SF9	16	26	40	54	70	89	99

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Table 6.0 Percentage Drug Release of tablets containing Benecil K-100M

Formu-lations	% Drug Release						
	1hr	2hr	4hr	8hr	12hr	18hr	24hr
SF10	37	53	68	86	95	100	100
SF11	36	47	68	84	93	99	100
SF12	34	48	65	84	92	99	100
SF13	27	42	60	72	85	99	99
SF14	25	38	54	68	81	95	100
SF15	23	36	51	65	80	94	99
SF16	15	26	38	55	70	85	100
SF17	9	11	15	19	38	52	65
SF18	8	10	13	18	35	48	62

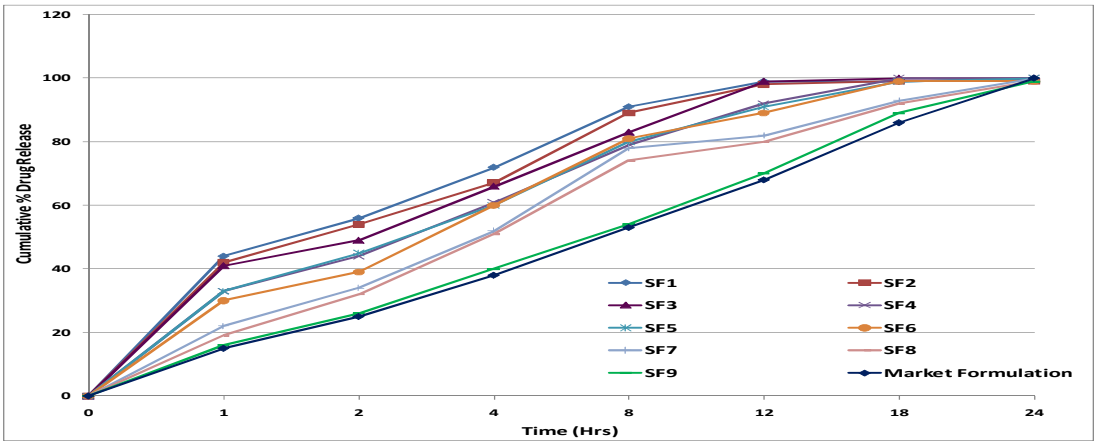

Fig. 1: Drug Release profiles of tablets containing Benecil K- 4M

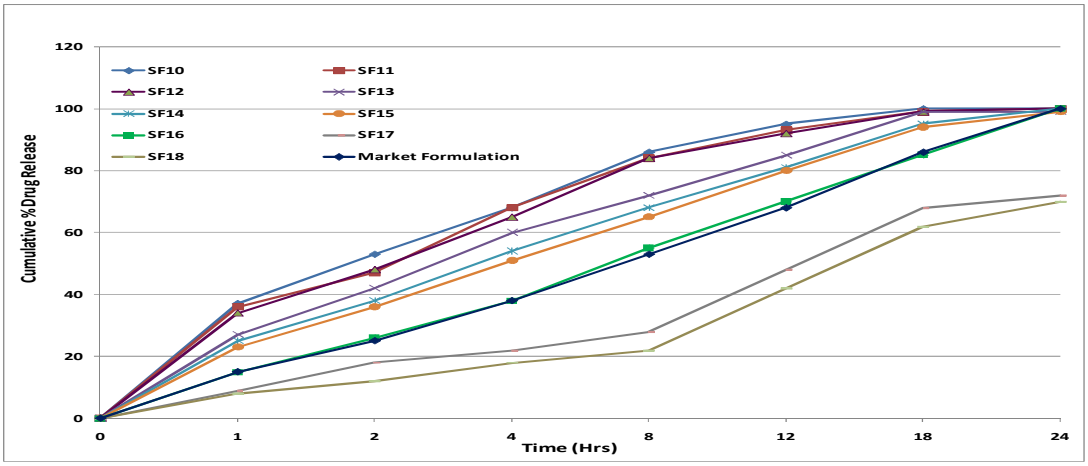

Fig. 2: Drug Release profiles of tablets containing Benecil K- 100M

sustained effect but the drug not releases completely even after 24 Hours. Formulation SF16 shows the sustained effect and drug get release completely within 24 Hours. From the Graphical representation of drug release of different formulations it is evident that the drug release of formulation SF9 & SF16 are more similar to the drug release of marketed product.

CONCLUSION

The aim of development of Sustained Release tablets of Divalproex sodium by direct compression technique was achieved. Various parameters have been evaluated for the prepared tablets like thickness, hardness, friability, weight variation, Drug content (assay) and the results of all the formulations are in accordance with the Pharmacopoeial limits. Drug release profile of all the formulations of Divalproex sodium in the current study was dependent on the type and concentration of the polymer alongwith the concentration of Ethylcellulose.

Among the formulations SF9 and SF16 was the optimized formulation based on the drug release behavior and similarity with the Marketed Product. These formulations were successful in maintain the sustained effect upto 24 hrs.

REFERENCE

1. Lippincott Williams, Wilkins. Remington The science and practice of pharmacy. 20th edition Vol II;2022.

2. James MA, Sung Wankim. Advances in drug delivery systems. Controlled release series, New York: Elsevier, 2011, 22, 181-196.

3. Remington's pharmaceutical Sciences,27nd edition, 2022

4. Theodore JR, Mansdorf SY. Controlled release drug delivery system. New York: Marcel Dekker; 15th edition 2021.

5. Donald LW. Bioploymeric controlled release system. Vol I USA: CRS Press Inc; 2018

6. Fuiz RC. Rapidly Dissoluble Medicinal Dosage Unit and Method of Manufacture, US Patent No, 4, 855, 326:1989.

7. Gregory LH, Yehezkiel Ben-A. The Neurobiology and Consequences of Epilepsy in the Developing Brain. Pediatric Research 2001; 49(3):320-25.

8. Rang HP, Dale MM, Ritter JM, Moore PK Pharmacology. New Delhi: Churchill Livingstone Reed Elsevier India (P) Ltd, 15th ed. 2016:550-60.

9. Bechgaard H, Nielson GH. Controlled release multiple units and single unit dosage. Drug Dev Ind Pharm 2018;4(1):53-67.

10. The United State Pharmacopoeia Convention, Twinbrook Parkway, Rockville, USP40/NF35, 2017; Vol. 2: 3832 - 3839.

11. The Indian Pharmacopoeia, Government of India Ministry of Health & family welfare, the Indian Pharmacopoeia Commission,

Ghaziabad, 2018; Vol. 1:308.

12. Qiu Y, Cheskin HS, Engh KR, Poska RP. Once a day controlled release dosage form of divalproex sodium I: formulation designand in vitro/in vivo investigations. J Pharm Sci. 2003;92:1166–73.

Conflict of Interest

The authors declare that they have no conflict of interest