RESEARCH ARTICLE

Formulation Development and Evaluation of Divalproex Sodium Extended-release Tablets

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ABSTRACT

There are two important parameters for a control release formulation. Primarily, it should be available in the form of a single-dose formulation. It should be given to the patient per day or few days a week during the treatment of patients suffering from diseases like arthritis, angina and diabetes. The second important characteristic of such formulation is that they release the active molecule at the site of action. This will reduce the chances and the level of the side effects of the drug.

Among the available such type of dosage form, sustained-release formulations (SR) give the most promising and desirable results.

In the SR dosage form, the drug release profile is controlled by the pharmaceutical engineering in the core matrix of tablet. In this study, SR oral tablet of divalproex sodium was manufactured by varying the quantity of drug release-controlling polymers like metolose 65 SH and metolose 90 SH. In the formulations, these polymers were used in different proportions and evaluated their impact on the physical and chemical characteristics of the finished drug product. The results of all formulations were as per the requirement of standard pharmacopoeial monograph. However, drug dissolution results of two formulations *viz.* DF9 and DF16 were observed to be optimum and excellent among all batches.

Keywords: Divalproex sodium, Controlled release, Modified release.

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INTRODUCTION

In the present scenario, the demand for normal release dosage form is diminishing quickly. This is all happening due to their drawbacks and the inconvenience felt by the patients. Each drug molecule is unique in character because they have distinctive physicochemical properties like solubility, permeability, and their biological half-life. Due to these variations, the availability of the drug at the site of action also varies. Therefore, when the drug is presented in the form of a conventional dosage form, the plasma level of the active molecule fluctuates very fast. This fluctuation may go beyond the level of minimum therapeutic concentration and the toxic level concentration.[1]

For that reason, now a day's demand of dosage form which can control the drug plasma level under the safe limit is increasing very fast. Hence, manufacturing the dosage form known as the controlled release dosage form or modified release dosage form comes out to cover these shortcomings. Control release dosage forms have multiple benefits over normal-release products. These dosage forms control the drug plasma level by limiting its fluctuation and keep it under the safe therapeutic window. Additionally, *in-vitro* drug release is controlled and per the requirement of therapeutic needs. Reduction in the dose frequency and the limited exposure of the drug to the blood, observed side effects are also less in these dosage forms. Therefore, these type of dosage forms shows better acceptability among patients.

Controlled-release dosage forms are being manufactured in multiple ways among them, engineering on the tablet core matrix is most popular and acceptable in the formulators. In this technology, work is done on the drug entrapped inside the tablet core matrix. To control the release of drugs from the tablet matrix, one has to choose type and concentration of polymers very wisely.[2,3]

In the pharmaceuticals, polymers are basically two types hydrophilic and hydrophobic. For control release manufacturing, both types of polymers are being used. For controlling the drug release in the dosage form a broad range

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of hydrophilic and hydrophobic polymers are available in the pharmaceutical system. In this study, work is performed on the two hydrophilic polymers *viz.* metolose 65 SH and metolose 90 SH. Basic difference between these polymers are of viscosity. Viscosity of metolose 90 SH is higher as compared to metolose 65 SH. To modify the release of drug from a dosage form, work on the hydrophilic polymers is more advantageous due to their flexibility in controlling the release of drug.[4] Hydrophilic polymers get swelled in the aqueous media and form a gel-like structure in which drug molecules get entrapped. Release of the drug molecules from this gel type structure happens only through diffusion. Hydrophobic polymer ethyl cellulose was selected for its better acceptability and compatibility in formulation development.[5,6]

Over the past several years, many people have suffered from neurological disorders like epilepsy. Epilepsy is spreading worldwide very fast and is very common in people who belong to poor or undeveloped countries.[7] In this disease patient start to behave abnormally, convulsions started and may loss his memory. Brain functioning becomes abnormal due to that neurological disorder happens. Nerves functioning become irregular and as results, seizures start to generate in the body. These seizures may be of multiple types based on their origin and severity. Severity of seizures may affect a person's lifestyle and may cause a permanent loss of sensation.[8,9]

One of the most common drugs used to treat epilepsy is divalproex sodium.[10,11] Major cause behind epilepsy is the gamma-aminobutyric acid (GABA) transaminase enzyme. Divalproex sodium act by inhibiting this enzyme. Divalproex sodium works on neurological functioning, therefore, the chance of occurrence of side effects becomes very common. Hence, to reduce the level of side effects, it was tried to

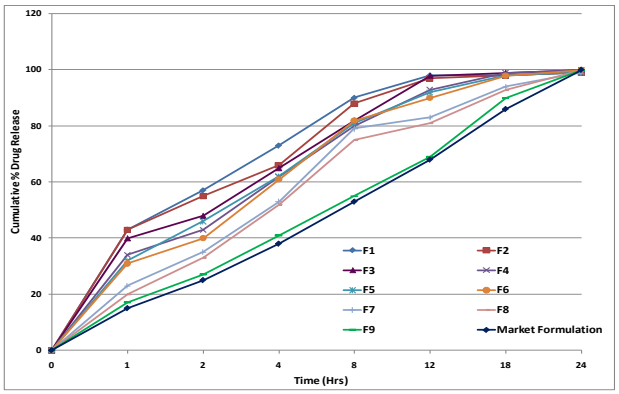

Figure 1: Drug dissolution of formulations having Metolose 60 SH.

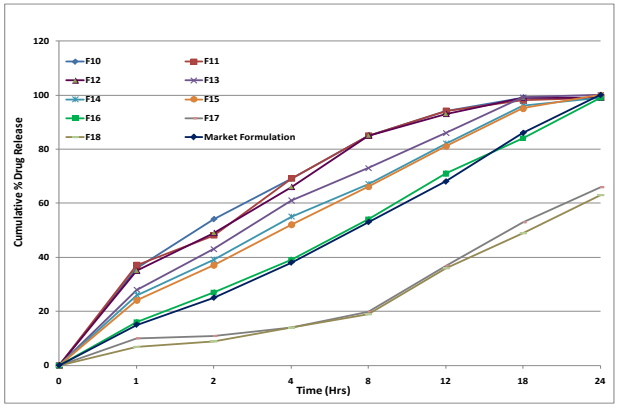

Figure 2: Drug dissolution of formulations having Metolose 90 SH.

Table 1: Formulations of tablets employing Metolose 90 SH

Constituents	*Batch No.*								
	F01	*F02*	*F03*	*F04*	*F05*	*F06*	*F07*	*F08*	*F09*
Drug	250	250	250	250	250	250	250	250	250
Metolose 90 SH	20	40	60	20	40	60	20	40	60
EC 10 cps	10	10	10	20	20	20	30	30	30
Floccel 200	163	143	123	153	133	113	143	123	103
Calcium stearate	4	4	4	4	4	4	4	4	4
Talcum Powder	3	3	3	3	3	3	3	3	3
Total wt.	450	450	450	450	450	450	450	450	450

Table 2: Formulations of tablets employing Metolose 60 SH

Constituents	*Batch No.*								
	F10	*F11*	*F12*	*F13*	*F14*	*F15*	*F16*	*F17*	*F18*
Drug	250	250	250	250	250	250	250	250	250
Metolose 60 SH	20	40	60	20	40	60	20	40	60
EC 10 cps	10	10	10	20	20	20	30	30	30
Floccel 200	163	143	123	153	133	113	143	123	103
Calcium stearate	4	4	4	4	4	4	4	4	4
Talcum Powder	3	3	3	3	3	3	3	3	3
Total wt.	450	450	450	450	450	450	450	450	450

Table 3: Physical parameters of formulations having Metolose 60 SH

Batch No.	*Avg. weight (mg)*	*Tablet Strength (Kp)*	*Thickness (mm)*	*Friability (%)*	*Assay (%)*
F01	452	5.6	3.42	0.28	99.8
F02	448	5.8	3.30	0.17	99.7
F03	455	5.0	3.45	0.43	99.4
F04	453	5.7	3.46	0.40	99.0
F05	455	5.7	3.43	0.31	98.8
F06	453	5.1	3.48	0.24	99.8
F07	448	5.8	3.50	0.31	99.6
F08	452	5.7	3.43	0.22	99.8
F09	446	5.1	3.41	0.26	99.7

Table 4: Physical parameters of formulations having Metolose 90 SH

Batch No.	*Avg. weight (mg)*	*Tablet strength (Kp)*	*Thickness (mm)*	*Friability (%)*	*Assay (%)*
F10	455	5.7	3.43	0.31	99.8
F11	451	5.9	3.48	0.24	99.6
F12	453	5.2	3.50	0.31	99.8
F13	455	5.7	3.43	0.22	99.9
F14	453	5.9	3.5	0.28	98.8
F15	455	5.2	3.43	0.26	99.6
F16	446	5.9	3.41	0.28	99.7
F17	453	5.9	3.43	0.18	99.9
F18	447	5.3	3.48	0.21	99.8

Table 5: % Drug dissolution of formulations having Metolose 60 SH

Batch No.	*Percent release*						
	1 hour	*2 hour*	*4 hour*	*8 hour*	*12 hour*	*18 hour*	*24 hour*
F01	43	57	73	90	98	98	99
F02	43	55	66	88	97	98	99
F03	40	48	65	82	98	99	100
F04	34	43	62	80	93	99	100
F05	32	46	62	81	92	98	99
F06	31	40	61	82	90	98	100
F07	23	35	53	79	83	94	99
F08	20	33	52	75	81	93	100
F09	17	27	41	55	69	89	100
Marketed Product	15	25	38	53	68	86	100

formulate a controlled-release dosage form of divalproex sodium. As per the pharmacokinetic behavior of the drug, it is better to give this formulation with the food to enhance absorption. In this study, modified drug release formulation of divalproex sod. was tried to form using the hydrophilic polymers metolose 65 SH and metolose 90 SH.

MATERIALS AND METHODS

Materials

A free drug sample quantity received from Aarti Drugs. Sample of metolose 65 SH and metolose 90 SH were received from Shin etsu. All other ingredients are received from different vendors.

Compatibility Study of Drug and Excipients

This study is practiced understanding the behavior between drug and different excipients. For these two methods are generally used i.e., IR and DSC scanning.[12] A mixture of drug excipients is prepared in the proportion of 1:1 and scanned under these instruments. In DSC sample is scanned at the heating range of 50 to 300°C at 5°C/min. For IR sample is scanned under the spectrum range of 400 to 4000 cm^{-1}.

Manufacturing of Tablets

As per the literature usual dose of drug is 250 mg. Therefore, the dosage form was manufactured using the 250 mg quantity per tablet of API (Tables 1-2). Drug and hydrophilic polymers i.e., metolose 65 SH or metolose 90 SH (as per formulation)

Table 6: % Drug dissolution of formulations having Metolose 90 SH

Batch No.	*Percent Release*						
	1 hour	*2 hour*	*4 hour*	*8 hour*	*12 hour*	*18 hour*	*24 hour*
F10	36	54	69	85	94	99	99
F11	37	48	69	85	94	98	99
F12	35	49	66	85	93	99	99
F13	28	43	61	73	86	99	100
F14	26	39	55	67	82	96	99
F15	24	37	52	66	81	95	100
F16	16	27	39	54	71	84	99
F17	10	11	14	20	37	53	66
F18	7	9	14	19	36	49	63
Marketed Product	15	25	38	53	68	86	100

were mixed together and passed through a sieve of #30. This blend was mixed with the floccel 200 and passed through the sieve of #30. Again, this blend was mixed for 10 minutes with ethyl cellulose (EC 10 cps) and other lubricants and passed through the sieve of #30. This blend was compressed at the avg. wt of 450 mg at the Rimek compression machine using suitable punch.

Evaluation of Tablets

The finished product was characterized for multiple parameters, e.g. variation in tablet weight, thickness, tablet strength, drug content and drug release.

Drug dissolution parameter was determined in dissolution apparatus IP type I (Paddle) at 75 rpm in 900 mL purified water. Test was conducted for 24 hours. At different time intervals aliquots was withdrawn and replaced with fresh media. The amount of the drug in solution was determined after proper dilution and then analyzed under the high-pressure liquid chromatography (HPLC) method.

RESULTS AND DISCUSSION

As per the analytical results of differential scanning method drug shows an endothermic peak at 102.0°C, denoting its melting point. This endothermic peak also observed in the mixture of drug and excipients which indicate that the properties of excipients are not affecting the physicochemical behavior of the drug.

When the IR spectrum of pure drug was compared with the spectra of the mixture of drug and excipients, it was observed that the characteristic peaks of drug were present in the mixture's spectra. This only happens when there is no chemical interaction between drug and excipients.

Tablets were manufactured after compressing the powder blend of different formulations. Finished tablets were evaluated for different parameters (Tables 3-4). Weight variation in the tablet was observed within the range of pharmacopoeial requirements. Tablet thickness and hardness was observed between 3.20–3.45 mm and 5.0 to 7.1 Kp, respectively. Tablet friability and drug content was within the limit for all formulations. These parameters indicate that the physical parameters of tablets of all formulations were satisfactory.

Development trials (F01 – F06) processed using the release controlling agent metolose 60 SH released the drug from the dosage form around 90% in the 12 hours time period while the development trials (F07 – F08) release the more than 90% drug within 18 hours. Trial F09 confirms a control release dosage form by releasing the drug up to final time point (Tables 5 and Figure 1).

Development trials (F10–F18) were processed using the release controlling agent metolose 90 SH. In these trials F10–F12 possess the drug dissolution around 90% in the 12 hours. Time period while the development trials F13–F15 possess more than 90% of drug dissolution within 18 hours. Development trials no. F17–F18 have incomplete drug release in dissolution media even after 24 hours time period (Figure 2). Trial F16 confirms a control release dosage form by release the drug up to final time point.

Therefore, the development trials F09 and F16 have the ideal characteristics of the controlled release dosage form, and this is also evident when the release is compared with the marketed formulation.

CONCLUSION

As per the study a controlled-release dosage form of divalproex sodium can be manufactured using the optimum quantity of metolose 60 SH and metolose 90 SH. In this development, finished formulations were evaluated for all the parameters required in the pharmacopoeial monograph of tablets. All physical parameters were found satisfactory and within the limit for these formulations.

The study shows that the drug release forms a formulation is directly affected by the type and quantity of polymer. Both hydrophilic and hydrophobic polymer shows an impact on drug release.

Development trials F09 and F16 show promising results in contrast to the market product.

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