Research Article

Formulation and Evaluation of Immediate Release Tablets of Eprosartan Mesylate

K. Satyavathi*, K.V.S.S. Annapurna, P. Gayathri, P. Bhojaraju, L.K. Kanthal, T. Veerraju
Department of pharmaceutics, Koringa College of pharmacy, Korangi, Tallarevu (M), E.G.Dist., A.P., India.
***Corresponding author's E-mail:** ksatyacharan@yahoo.com

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ABSTRACT

The aim of present work is to formulate and evaluate the immediate release tablets of Eprosartan mesylate by using solid dispersion (PEG) and kneading method. Polyethylene glycol 6000 was used as a carrier in solid dispersion (fusion method). The drug and carrier were taken in different ratios 2:1, 1:1, 2:3 and the corresponding physical mixtures were prepared. In inclusion complexation technique, β - cyclodextrin was used as a carrier in which the drug and carrier were taken in (1:1) ratio and corresponding physical mixture was prepared. The prepared formulations with the pure drug were subjected to post compression and pre compression parameters. The FTIR studies showed no interaction between drug and carrier. Formulation containing β –cyclodextrin in which Kneading technique used (F9) showed the best release (a cumulative release of 97%). All formulations were compared with marketed product (Teveten). Among all, F9 was similar to Teveten with f1 2.24 and f2 63.3.

Keywords: Eprosartan mesylate, Immediate release, Kneading method, Solid dispersion technique, β – cyclodextrin and Macrogol.

INTRODUCTION

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen.[1] Immediate release tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.[2, 3]

The formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in industry.[4,5] Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature, humidity, compatibility with solvents and excipients etc. Of these, solubility is the most important factor for developing formulations.[6] There are drug candidates that have poor solubility in water but can be dissolved by suitable conventional strategies which include co-solvents [7], milling techniques [8], super critical processing [9] and solid dispersions [10, 11] including complexation and precipitation techniques. Solid dispersion technique has often proved to be most commonly used in improving dissolution and bioavailability of poorly soluble active pharmaceutical ingredient because it is simple, economic and advantageous.[12] In solid dispersions water soluble carriers are used to improve dissolution characteristics of poorly water soluble drugs.[13] Eprosartan mesylate is a nonpeptide angiotensin II antagonist approved in more than 20 countries for treatment of patients with hypertension.[14] The oral bioavailability of eprosartan is limited by the solubility rather than the metabolism.

Therefore, there is a need for a formulation that enhances the bioavailability of Eprosartan. Eprosartan mesylate is monomethane sulfonate of (E)-2-butyl-1-(p-carboxybenzyl)-α-2thienylmethylimid-azole-5-acrylic acid. It is white fine powder having poor aqueous solubility (BCS class II drug). The present work is to formulate and evaluate the immediate release tablets of Eprosartan mesylate by using techniques like solid dispersion (PEG) and kneading method.

MATERIALS AND METHODS

Chemicals and reagents

Eprosartan mesylate, PEG6000, β –Cyclodextrin was obtained from Yarrow Chem. Products, Mumbai. Microcrystalline cellulose, Magnesium stearate obtained from Molychem, Mumbai. All other solvents and reagents used were of analytical grade.

Pre-formulation study

Preformulation can be defined as the investigation of physical and chemical properties of drug substance alone and when combined with excipients. The parameters like Bulk density, Tapped density, Angle of repose, Carr's compressibility Index, Hausner's ratio and solubility were found during pre-formulation studies. The IR spectrum of the drug was compared with that of the physical mixture to check any possible drug-excipients interaction.

Procedure for the preparation of calibration curve by UV

A stock solution of Eprosartan mesylate was prepared by dissolving 100mg of drug in little amount of pH 7.5 phosphate buffer and made up to 100ml with the same. From this stock solution different concentrations of Eprosartan mesylate like 2, 4, 6, 8, and 10µg/ml were prepared by diluting with pH 7.5 phosphate buffer and their absorbance's were measured at 233nm using UV-VIS spectrophotometer. A graph was plotted by taking concentration of Eprosartan mesylate (µg/ml) on x-axis and absorbance on y-axis.

Formulation of immediate release tablets

All together nine formulations were designed (Table 1).

Preparation of physical mixture (F 1, F2, F3, F7, F8)

The drug and carrier were weighed accordingly to the specified ratio and physical mixture was prepared by mixing of drug and carrier in a mortar .The powdered mixture was pulverized and passed through sieve no 80 to get uniform sized particles.

Preparation of solid dispersion (F4, F5, F6)

Three formulations of solid dispersions containing Eprosartan with PEG-6000 as a carrier in different ratios were prepared by fusion method .The carrier was weighed and taken in a china dish which was melted on Bunsen Burner. To that melt the drug was added and triturated. The melted mixture was solidified rapidly in an ice bath under vigorous stirring. The final solid mass was crushed, pulverized and sieved. The other excipients were added to the above mixture.

Preparation of F9 by kneading technique

F9 was prepared by using kneading method in which cyclodextrin was used as a carrier. In this technique the required quantity of cyclodextrin and distilled water were mixed together in a mortar so as to obtain a homogeneous paste. Drug was added slowly, while grinding with a small quantity of methanol which was added to assist the dissolution. The kneading mixture or paste was then dried in an oven at 45 – 50 ^{0}C for 24 hrs. The dried complexes were pulverized and then sieved through no. 120. To the above powdered mixture, the weighed quantities of excipients were added.

All the above blends were compressed as tablets using direct compression method.

Table 1: Formulae or composition of the different formulations of Eprosartan Mesylate

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Direct compression			Solid dispersion by fusion method			Plain	Direct compression	Kneading method
Eprosartan mesylate	300	300	300	300	300	300	300	300	300
PEG 6000	150	300	450	150	300	450	-	-	-
β -cyclodextrin	-	-	-	-	-	-	-	300	300
Cross carmellose sodium	40	40	40	40	40	40	40	40	40
HPMC 3cps	19	19	19	19	19	19	19	19	19
Micro crystalline cellulose	431.5	281.5	131.5	431.5	281.5	131.5	581.5	281.5	281.5
Magnesium Stearate	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5

Table 2: Preformulation studies of powder blend

FC	Loose Bulk Density (gm/ml)	Tapped Bulk Density (gm/ml)	Angle of Repose (°C)	Carr's Index	Hausner's Ratio
F1	0.3217	0.3911	37.6	17.74	1.2157
F2	0.3439	0.4244	36.7	18.96	1.2340
F3	0.3911	0.4639	35.5	15.6	1.1860
F4	0.3117	0.3836	36.6	18.7	1.2307
F5	0.5937	0.6785	32.5	12.5	1.1428
F6	0.5588	0.6064	28.5	7.84	1.08
F7	0.2977	0.3562	37.8	16.41	1.19
F8	0.4830	0.5937	36.5	18.64	1.22
F9	0.5699	0.6125	27.7	6.95	1.07

Post compression parameters

Post compression parameters like hardness, thickness, weight variation and friability were found for all the formulations.

Estimation of drug content

For drug content, the tablets were crushed and 950 mg of powder equivalent to one tablet weight was taken in a 100ml volumetric flask into which 10ml of methanol was added and kept for 20 minutes sonication and made up to 100ml with water. The absorbance of the solutions were determined at 233nm.From the absorbance total drug content was calculated.

***In vitro* dissolution studies**

The in vitro dissolution study was performed in USP Dissolution rate test apparatus type –II using 900ml of 0.2 M Phosphate buffer with pH 7.5. The tablets of each formulation were kept in dissolution flasks. Samples were

withdrawn at pre determined time interval and the same volume was replaced immediately to maintain sink condition. The withdrawn samples were suitably diluted and the absorbance of the solution was determined at specified wave length of 233nm.

Release kinetics

To analyze the *in vitro* release data, various kinetic models were used. The drug release profile obtained in dissolution test was plotted in Zero order kinetics, First order kinetics.

Comparison of dissolution profiles

The similarity in the drug release pattern of the marketed product and the formulation developed was determined by calculating the difference factor (f_1) and similarity factor (f_2). The two products are said to be similar if the value of f1 lies between 0 and 15 and if the value of f_2 lies between 50 and 100. f_1 and f_2 are obtained by the formulae given below:

$$f_1 = \{[S_{t=1}^{n} |R_t - T_t|] / [S_{t=1}^{n} R_t]\} x100...$$

$$f_2 = 50 x \log \{[1 + (1/n) S_{t=1}^{n} (R_t - T_t)^2]^{-0.5} x100\}....$$

Table 3: Evaluation of Eprosartan Mesylate tablet formulations

FC	Weight of the Tablet (mg)	%Weight Variation	Uniformity of thickness (mm)	Hardness (kg /cm^2)	Friability %
F1	950	±3.2	3.1	5.2	0.5
F2	948	±0.62	3.1	5.5	0.21
F3	954	±1.52	3.2	5.4	0.42
F4	949	±1.45	3.2	5.6	0.21
F5	950	±3.2	3.4	5.5	0.21
F6	952	±2.5	3.5	5.1	0.31
F7	949	±1.45	3.2	5.4	0.63
F8	952	±2.5	3.3	5.3	0.10
F9	948	±0.62	3.5	5.1	0.10

Table 4: Results of Dissolution study

% Drug Release in 1 hour										
Time(mints)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10 Teveten
5	8	9	10	12	15	18	7	16	19	21
10	15	16	36	37	39	42	13	40	45	48
15	24	28	45	49	50	72	20	68	75	76
20	48	53	56	57	65	87	40	83	89	92
30	60	62	72	73	80	89	58	87	97	98
45	63	71	76	81	85	90	64	88	98	99
60	68	74	78	84	87	91	68	89	99	99

Table 5: Pharmacokinetic Parameters and Statistical Evaluations

Formulation	R values Zero order	R values First order	K values	T 50	DE 30	PD10	Difference factor (f1)	Similarity factor (f2)	Inference
F1	0.9203	0.949	0.020	21.5	29.83	15	46.54	0.99	Indicates dissimilar
F2	0.9261	0.962	0.023	21	32.4	16	41.4	1.41	Indicates dissimilar
F3	0.889	0.947	0.025	17	41.16	36	30.2	7.99	Indicates dissimilar
F4	0.906	0.975	0.029	16	42.7	37	26.5	10.44	Indicates dissimilar
F5	0.890	0.963	0.034	15	46.9	39	21.30	14.96	Indicates dissimilar
F6	0.7979	0.873	0.041	11.4	58.58	42	8.59	35.17	Indicates dissimilar
F7	0.943	0.966	0.020	26	26.3	13	49.5	2.4	Indicates dissimilar
F8	0.810	0.885	0.036	12	55.91	40	11.9	28.91	Indicates dissimilar
F9	0.8210	0.961	0.087	11	61.58	45	2.24	63.3	Indicates similar
F10 **(Teveten)**	0.813	0.9447	0.087	11	63.16	48	---	---	---

Table 6: Stability studies of F9 formulation

FC	Time	Parameters					
		Hardness (kg/cm^2)	Friability	Drug content	DT (min-sec)	Dissolution	Appearance
F9	15 days	5.1	0.009	99.2	2.5	98	White
F9	45 days	5.1	0.009	99.1	2.5	97.5	White
F9	90 days	5.1	0.009	98.5	2.5	96.2	White

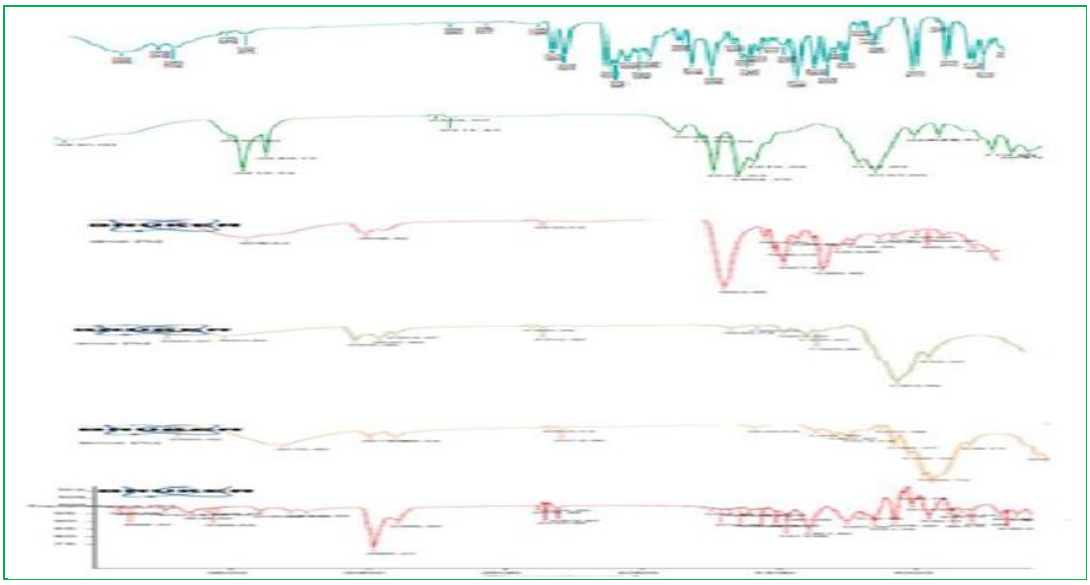

Figure 1: FTIR spectral data of Eprosartan Mesylate and other excipients

Accelerated stability studies

Short-term accelerated stability studies for a period of three months according to International Conference on Harmonization guidelines were performed on the optimized formulation. They were subjected to stability studies at 40°C/75%RH in a stability chamber for a period of three months. Initial evaluation of the tablets was done and at the end of 15days, 45 days and 90 days the tablets were again analyzed for physical appearance and *in vitro* drug release profile.

RESULTS AND DISCUSSION

Pre-formulation Studies

Evaluation of powder blend prepared

In the pre-formulation studies, the results (Table 2) indicated that among all formulations F6 and F9 had shown excellent flow property than other formulations.

Drug-compatibility studies

The compatibility between the drug and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug- excipients mixture, which confirmed the absence of any chemical interaction. The spectra were shown in figure 1. The following bands were observed in the spectra: N–H stretching (3301), COOH (2929), C=C aromatic stretching (1645), C-N vibration (1074).

Post compression studies

The post compression parameters were given in Table 3.

For all formulations the above all parameters are within the limit.

Drug Content Uniformity

For all the formulations drug content was estimated by UV absorbance and the percentage of drug content for all formulations was found to be between 97and 100 which lie in the USP limit.

Disintegration time

This is the most important test with respect to IRT formulations. All the formulations passed disintegration test. Among all formulations; F9 was selected as the best formulation as it gave the least in vitro disintegration time (2 minutes).

***In vitro* dissolution studies**

The dissolution rates of all formulations were given in Table 4 in which F5 (80 %), F6 (89%), F8 (87 %), F9 (97 %) were within 30min. Among these, F9 was selected as optimized formulation. F9 formulation released the maximum amount of drug 97% within 30minutes. These results were in tune with those obtained for the disintegration time for the respective formulation.

Release kinetics

For all formulations zero order, first order graphs were drawn and pharmacokinetic parameters were determined

depending upon the correlation coefficient values. All the formulations followed first order release. The pharmacokinetic parameters were given in Table 5 and from all these results F9 was optimized.

Comparison of dissolution profiles

First order plot of comparative dissolution profiles of F9 and F10 (Teveten) and Similarity factor (f2) and dissimilarity factor (f1) were calculated for all the formulations (given in Table 5). For formulations from F1 to F8, the similarity factor (f2) and dissimilarity factor (f1) were not within limits. For the formulation F9, similarity factor (f2) =63.3 and dissimilarity factor (f1) = 2.24 which indicates F9 was similar to the marketed product TEVETEN (F10).

Stability studies

The selected formulation F9 was subjected to stability studies (Table 6) and the formulation was evaluated for appearance, hardness, friability, drug content, disintegration time and in vitro dissolution test. The formulation was stored at 40 ± 1°C and RH 75 ±5% conditions and analyzed after every 15, 45, and 90 days. The formulation showed very little change in the above parameters.

CONCLUSION

The designed and tested F9 Eprosartan mesylate tablet with β – cyclodextrin prepared by Kneading technique is showing 97% drug release in 30 minutes in in vitro dissolution studies which is parallel to the marketed product Teveten. The next best formulation is F6 i.e Eprosartan mesylate with PEG prepared by fusion method which is giving 89% drug release in the same 30 minutes. Eprosartan mesylate untreated tablets showed only 58% of drug release in the same 30 minutes. Therefore F9 formulation has definitely improved drug availability and is very close to the marketed product Teveten. F9 formulation may be subjected to further investigation to meet the mandatory requirements.

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