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FORMULATION AND EVALUATION OF EPROSARTAN TABLETS USING β - CYCLODEXTRIN, POLOXAMER AND PVP K 30

K.V. Rama Rao[1] and G. Devala Rao*[2]

[1]Research Scholar, School of Sciences, Career Point University, Kota, Rajasthan
[2]KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada. Andhra Pradesh

*Corresponding Author E-mail id: drgdr1964@gmail.com

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ABSTRACT

Eprosartan, a widely prescribed anti hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Rate limiting step for eprosartan oral absorption is dissolution and it requires improvement in the solubility and dissolution rate for increasing oral bioavailability. The objective of the study is to formulate eprosartan tablets by using cyclodextrin complexation, Poloxamer 407 and PVP K30. Eprosartan tablet were formulated employing βCD, Poloxamer 407 and PVP K30 by direct compression method. All the eprosartan tablets prepared fulfilled the official requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Eprosartan tablets formulated employing βCD, Poloxamer 407 and PVP K30 gave much higher dissolution release when compared to tablets formulated using eprosartan alone (EF1). Eprosartan tablet formulation (EF4 and EF6) gave very rapid dissolution of eprosartan than other tablet formulations. Eprosartan tablets formulated with βCD and Poloxamer 407 (EF4) and βCD with PVP K30 (BF6) gave 100% dissolution in 50 min. Hence tablets formulated with βCD with Poloxamer 407 (EF4) or βCD with PVP K30 (EF6) is recommended for formulation of eprosartan tablets with fast dissolution characteristics.

INTRODUCTION

Eprosartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility[1]. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[2] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[3,4]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[5, 6]. Poloxamer 407 is a polymeric solubiliser with an amphiphilic chemical nature, which was

particularly developed for solid solutions . Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (PEG). The approximate length of the two PEG blocks is 101 repeat units, while the approximate length of the propylene glycol block is 56 repeat units [7]. Poloxamer 407 increased the solubility and enhanced the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Poloxamer 407[8]. The solubility and dissolution rate of etoricoxib was effectively enhanced by using Poloxamer 407 in the form of solid dispersions[9]. Poly vinyl pyrrolidone (PVP K 30) is also reported[10] to enhance the solubility and dissolution rate of poorly soluble drugs. Though cyclodextrin complexation and use of surfactants and PVP for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, very few reports are available on their combined use in enhancing the solubility and dissolution rate. The objective of the present investigation is to formulate eprosartan tablets using β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 (both alone and in combination). The prepared tablets were also evaluated for hardness, friability, drug content, disintegration and dissolution rate study.

EXPERIMENTAL

Materials

Eprosartan was a gift sample from M/s. Aurobindo Manufacturing Pvt. Ltd., Hyderabad. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Poloxamer 407 was a gift sample from BASF, the chemical company, Hyderabad. Methanol (Qualigens) and poly vinyl pyrrolidone (PVP K30) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Eprosartan: An UV Spectrophotometric method based on the measurement of absorbance at 234 nm in 0.2 M Phosphate Buffer, pH 7.5 was used for the estimation of eprosartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml.

Preparation of Eprosartan- βCD Complexes: Solid inclusion complexes of eprosartan in βCD with and without Poloxamer 407 - PVP K30 were prepared by kneading method. Eprosartan, βCD, Poloxamer 407 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of dichloromethane: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55ºC until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Eprosartan Tablets: Eprosartan (300 mg) tablets were prepared by direct compression method as per the formula given in Table1.The required quantities of eprosartan / inclusion complexes, Acacia, Crospovidone, Talc and magnesium stearate were mixed in a closed polyethene bag. The blend of ingredients was then compressed directly into tablets using an 8- station Cadmach tablet punching machine.

Evaluation of Tablets: All the eprosartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows:

Hardness: The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability: The friability of the tablets was measured in a Roche friabilator using the formula Friability (%) = [(Initial weight-Final weight) / (Initial weight)] x 100

Drug Content: Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of eprosartan was taken into 100 ml volumetric flask, dissolved in 0.2 M Phosphate Buffer, pH 7.5 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with 0.2 M Phosphate Buffer, pH 7.5 and assayed for eprosartan at 234 nm.

Disintegration time: Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study: The dissolution rate of eprosartan tablets prepared was studied in 900 ml 0.2 M Phosphate Buffer, pH 7.5 using

Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable diluted and assayed for eprosartan at 234 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of Data: The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan[11].

RESULTS AND DISCUSSION: The objective of the present study is to formulate the eprosartan tablet formulation employing βCD, Poloxamer 407 and PVP K30. Eight eprosartan tablet formulations were prepared by direct compression method employing selected combinations of βCD, Poloxamer 407 and PVP K30. βCD was used at a ratio of 1:2, Poloxamer 407 and PVPK 30 were used respectively at 2% concentration. Tablets were formulated as per the formula given in Table 1. All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The physical parameters of the eprosartan tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.0-5.5 kg/cm^2. Weight loss in the friability test was less than 0.82 % in all the cases. Eprosartan content of the tablets prepared was within 100±3 %. Many variations were observed in the disintegration and dissolution characteristics of the eprosartan tablets prepared. The disintegration times were in the range 1min to 6 min 40 sec. All the eprosartan tablets prepared fulfilled the official requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Dissolution rate of eprosartan tablets prepared was studied in 900 ml 0.2 M Phosphate Buffer, pH 7.5. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3. Dissolution of eprosartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.988. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Many variations were observed in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) values of the tablets prepared due to formulation variables. Eprosartan tablets formulated employing βCD, Poloxamer 407 and PVP K30 gave much higher dissolution release when compared to tablets formulated using eprosartan alone (EF1). Eprosartan tablet formulation (EF4 and EF6) gave very rapid dissolution of eprosartan than others. Eprosartan tablets formulated with βCD and Poloxamer 407 (EF4) and βCD with PVP K30 (BF6) gave 100% dissolution in 50 min. Hence tablets formulated with βCD with Poloxamer 407 (EF4) or βCD with PVP K30 (EF6) is recommended for formulation of eprosartan tablets with fast dissolution characteristics.

Table1: Formulae of Eprosartan Tablets Prepared Employing βCD, Poloxamer 407 and PVP K 30

Ingredient (mg/tab)	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8
Eprosartan	300	300	300	300	300	300	300	300
βCD	-	600	-	600	-	600	-	600
Poloxamer 407	-	-	20	20	-	-	20	20
PVP K 30	-	-	-	-	20	20	20	20
Acacia	20	20	20	-	20	-	-	-
Crospovidone	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	5
Magnesium stearate	10	10	10	10	10	10	10	5
Avicel	610	10	590	-	590	10	590	-
Total weight (mg)	1000	1000	1000	1000	1000	1000	1000	1000

Table 2 : Physical Parameters of Eprosartan Tablets Prepared Employing βCD, Poloxamer 407 and PVP K30

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time(min-sec)	Drug Content (%)
EF1	4.0	0.82	1-50	98.5
EF2	4.5	0.65	4-55	99.4
EF3	5.0	0.75	3-00	98.4
EF4	5.0	0.55	4-50	99.2
EF5	4.0	0.80	2-05	99.4
EF6	4.5	0.64	4-10	99.5
EF7	4.0	0.75	1-15	98.3
EF8	5.5	0.50	8-50	99.5

Table 3: Dissolution Parameters of Eprosartan Tablets Prepared Employing βCD, Poloxamer 407 and PVP K30

Formulation	PD_{15}(%)	DE_{30}(%)	K_1 (min^{-1})
EF1	32.28	34.18	0.0227
EF2	52.63	48.79	0.0331
EF3	75.54	68.56	0.0812
EF4	77.33	70.52	0.0862
EF5	69.23	64.28	0.0802
EF6	74.33	67.85	0.0869
EF7	69.35	63.95	0.0770
EF8	69.33	65.35	0.0841

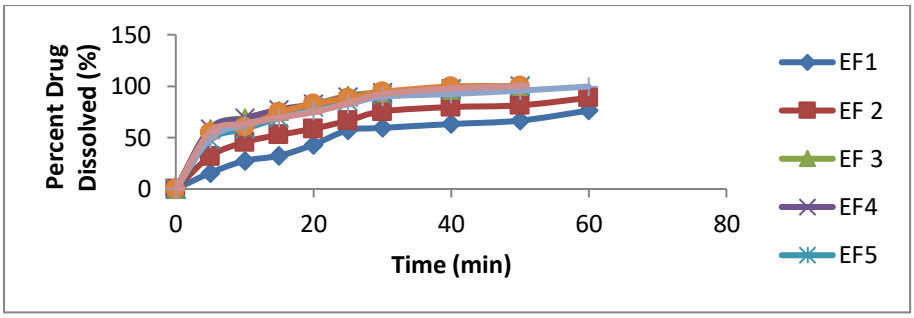

Fig.1: Dissolution Profiles of Eprosartan Tablets Prepared Employing βCD, Poloxamer 407 and PVP K30

CONCLUSION

Eprosartan tablet formulation employing βCD, Poloxamer 407 and PVP K30 by direct compression method. All the eprosartan tablets prepared fulfilled the official requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Eprosartan tablets formulated employing βCD, Poloxamer 407 and PVP K30 gave much higher dissolution release when compared to tablets formulated using eprosartan alone (EF1). Eprosartan tablet formulation (EF4 and EF6) gave very rapid dissolution of eprosartan than other tablet formulations. Tablets formulated with βCD with Poloxamer 407 (EF4) or βCD with PVP K30 (EF6) is recommended for formulation of eprosartan tablets with fast dissolution characteristics.

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