ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

INDIVIDUAL AND COMBINED EFFECTS OF CYCLODEXTRIN, POLOXAMER AND PVP ON THE SOLUBILITY AND DISSOLUTION RATE OF EPROSARTAN- A BCS CLASS II DRUG

K.V. Rama Rao[1] and Garikapati 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:** drgdr1964@gmail.com

ARTICLE INFO

Key words:
Eprosartan, β Cyclodextrin, Poloxamer 407, PVP K30, Solubility, Dissolution rate, Factorial Study

Access this article online
Website: https://www.jgtps.com
Quick Response Code:

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 enhance the solubility and dissolution rate of eprosartan by cyclodextrin complexation together with Poloxamer 407 and PVP K30. The solubility of eprosartan was determined in βCD, individually and along with Poloxamer 407 and PVP K30. Solid inclusion complexes of eprosartan-βCD were prepared with and without Poloxamer 407 and PVP K30 by kneading method and were evaluated. The individual and combined effects of βCD, Poloxamer 407 and PVP K30 in enhancing the solubility, dissolution rate and dissolution efficiency of eprosartan were highly significant ($P < 0.01$). βCD, Poloxamer 407 and PVP K30 significantly enhanced the solubility, dissolution rate and dissolution efficiency of eprosartan . βCD alone gave a 2.21 fold increase in the solubility of eprosartan. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of eprosartan. Combination of βCD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{20}) when compared to βCD alone. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 recommended enhancing the solubility, dissolution rate and dissolution efficiency of eprosartan, a BCS class II drug.

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 lengths 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. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of eprosartan, a BCS class II drug were evaluated.

EXPERIMENTAL

Materials

Eprosartan was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. 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.

Solubility Determination: Excess drug (50 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28±1^{o}C) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably and assayed for eprosartan by measuring absorbance at 234 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for three times each (n=3).

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 55^{o}C until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution Rate Study: The dissolution rate of eprosartan as such and from βCD complexes 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^{o}C was maintained throughout the study. Eprosartan or eprosartan- βCD complex equivalent to 400 mg of eprosartan was used in each test. 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).

RESULTS AND DISCUSSION

The objective of the study is to enhance the solubility and dissolution rate of eprosartan by cyclodextrin complexation along with Poloxamer 407 and PVP K30. The individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 on the solubility and dissolution rate of eprosartan was also tested. The individual main effects and combined (interaction) effects of βCD, Poloxamer 407 and PVP K30 on the aqueous solubility of eprosartan were evaluated in alone and in combination with Poloxamer 407 and PVP K30. For this purpose, two levels of βCD (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP K30 (0, 2%) were selected in each case and the corresponding eight treatments involved were purified water (1); water containing 5 mM βCD (ii); water containing 2% Poloxamer 407 (iii); water containing 5 mM βCD and 2% Poloxamer 407 (iv); water containing 2% PVP K30 (v); water containing 5 mM βCD and 2% PVP K30 (vi); water containing 2% Poloxamer 407 and 2% PVP K30 (vii) and water containing 5 mM βCD and 2% of each of Poloxamer 407 and PVP K30 (viii). The solubility of eprosartan in the above mentioned fluids was determined (n=3) and the results are given in Table-1. The results indicated that βCD alone gave a 2.21 fold increase in the solubility of eprosartan. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of eprosartan, To evaluate the individual and combined effects of βCD, Poloxamer 407 and PVP K30 on the dissolution rate of eprosartan, solid inclusion complexes of eprosartan- βCD were prepared with and without Poloxamer 407 and PVP K30. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of each of Poloxamer 407 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved were eprosartan pure drug (F1); eprosartan- βCD (1:2) inclusion binary complex (F2); eprosartan- Poloxamer 407 (2%) binary complex (F3); eprosartan- βCD (1:2) - Poloxamer 407 (2%) ternary complex (F4); eprosartan– PVP K30 (2%) binary complex (F5); eprosartan- βCD (1:2) - PVP K30 (2%) ternary complex (F6); eprosartan- Poloxamer 407 (2%) - PVP K30 (2%) ternary complex (F7) and eprosartan- βCD (1:2) - Poloxamer 407 (2%) - PVP K30 (2%) complex (F8). The CD complexes were prepared by kneading method. All the solid inclusion complexes of eprosartan- βCD - Poloxamer 407 /PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of eprosartan alone and from βCD complexes was studied in 900 ml 0.2 M Phosphate Buffer, pH 7.5. The dissolution of eprosartan followed first order kinetics with r (correlation coefficient) above 0.9750. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[11]. The dissolution parameters are given in Table-2. The dissolution of eprosartan was rapid and higher in the case of eprosartan- βCD binary and ternary complex systems prepared when compared to eprosartan pure drug as such. The dissolution profiles are given in Fig-1. βCD alone gave a 2.2 fold increase in the dissolution rate of (K_1) of eprosartan. When βCD is combined with Poloxamer 407 and PVP K30 the dissolution rate (K_1) was significantly enhanced. A 5.9 and 5.75 fold increase in the dissolution rate (K_1) was observed respectively with eprosartan- βCD – Poloxamer 407 and eprosartan- βCD – PVP K30 solid inclusion complexes. Poloxamer 407 (F_3) and PVP K30 (F_5) alone and in combination (F_7) also gave higher dissolution rates. DE_{30} values were also much higher in the case of βCD – Poloxamer 407 – PVP K 30 solid complexes when compared to eprosartan pure drug. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 recommended for enhancing the solubility, dissolution rate and dissolution efficiency of eprosartan, a BCS class II drug.

Table1. Solubility of Eprosartan in Various Fluids

Fluid (code as per 2^3-factorial experiment)	Solubility (mg/ml)	Increase in solubility (number of folds)
Distilled water(1)	0.019	----
Water containing 5mM βCD (ii)	0.042	2.21
Water containing 2 % Poloxamer 407 (iii)	1.31	68.94
Water containing 5mM βCD and 2% Poloxamer 407 (iv)	0.96	50.52
Water containing 2 % PVP K30 (v)	0.50	26.31
Water containing Water containing 5mM βCD and 2 % PVP K30 (vi)	0.75	39.47
Water containing 2 % Poloxamer 407 and 2 % PVP K30 (vii)	1.29	67.89
Water containing 5mM βCD ,2% Poloxamer 407 and 2% PVP K30 (viii)	1.57	82.63

Table 2: Dissolution Parameters of Eprosartan- βCD- Poloxamer 407-PVP K30 Inclusion Complexes

EF- β CD Complex	Composition	PD_{10} (10%)	K_1 (min^{-1})	DE_{30} (%)
F_1	EP	47.38	0.020	46.93
F_2	EP- βCD (1:2)	55.53	0.044	57.46
F_3	EP-Poloxamer 407 (2%)	74.23	0.180	77.22
F_4	EP- βCD (1:2) –Poloxamer 407(2%)	76.63	0.118	76.52
F_5	EP-PVP K30 (2%)	62.23	0.124	69.08
F_6	EP- βCD (1:2)- PVP K30(2%)	65.32	0.115	68.18
F_7	EP-Poloxamer 407 (2%) -PVP K30 (2%)	62.33	0.088	66.67
F8	EP- βCD (1:2)- Poloxamer 407 (2%)- PVP K30(2%)	63.32	0.084	65.35

EP - Eprosartan; βCD - Cyclodextrin; PVP - Poly vinyl pyrrolidone K 30

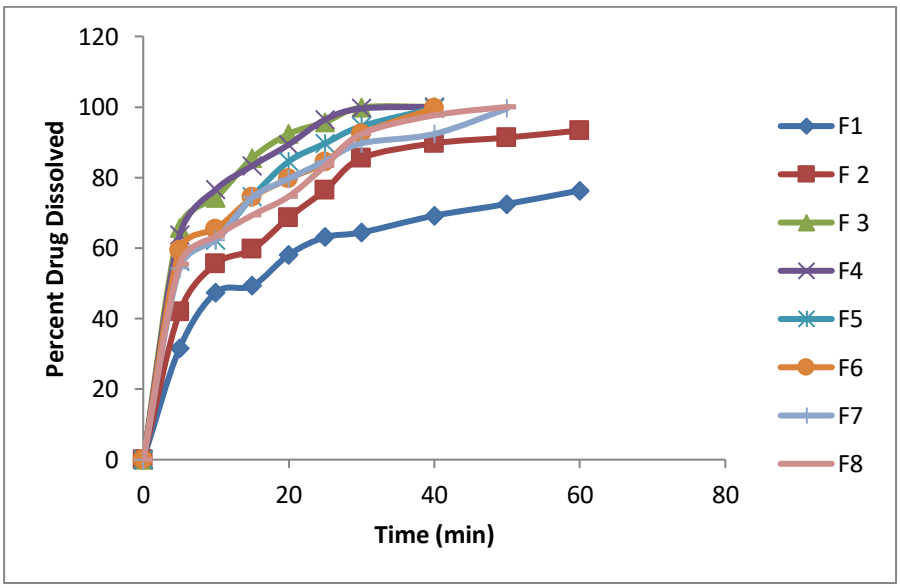

Fig.1: **Dissolution Profiles of Eprosartan– βCD Complexes Prepared by Employing βCD, Poloxamer 407 and PVP K30**

CONCLUSION

βCD, Poloxamer 407 and PVP K30 significantly enhanced the solubility, dissolution rate and dissolution efficiency of eprosartan . βCD alone gave a 2.21 fold increase in the solubility of eprosartan. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of eprosartan. Combination of βCD with Poloxamer 407 and PVP K30 also gave significantly higher dissolution rates (K_1) and dissolution efficiency (DE_{20}) when compared to βCD alone. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 recommended enhancing the solubility, dissolution rate and dissolution efficiency of eprosartan, a BCS class II drug.

REFERENCES

1. Muthadi Radhika Reddy, International Journal of Pharmaceutical Sciences and Research, 2019; 10(6): 2823-2837.
2. Chowdary, K. P. R and Madhavi, BLR, Novel Drug Delivery Technologies for Insoluble Drugs, Indian Drugs, 2005 42 (9), 557 – 562.
3. Fromming, K.H. and Szejtli, J. Cyclodextrins in Pharmacy. Kluwer Academic Publications, Dordrecghi, 1994, p 20.
4. Duchene, D., Woussidjewe, D. and Dumitriu, S. Polysaccharides in Medical Applications. Marcel Dekker, New York, 1996, 575-602.
5. Thompson, D.O. Crit Rev Therapeutic Drug Carrier System. 1997, 14 (1), 1-104.
6. Hedges, A.R. Chemical Review. 1998, 98, 2035-2044.
7. Dumortier, G., Grossiord, J.L., Agnely, F. et al., Pharm Res 2006; 23, 2709–2728
8. Giri, T. K., Badwaik, H., Alexander, A., and Tripathi, D. K., Int. J. Applied Biology and Pharmaceutical Tech., 2010, 1 (2), 793- 800.
9. Chowdary, K. P., & Prakasarao, K. S., *Asian J Pharm Clin Res*, 2012; *5*, 161-4.
10. Aejaz, A., Jafar, M. Dehghan, M. H. G., and Adil Shareef, S., . Int. J. Pharm. and Pharmaceutical Sci., 2010, 2 (1), 182- 190.
11. Khan, K.A., Journal of Pharmacy and Pharmacology. 1975, 27, 48-49.