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Complexation Approach for Dissolution Rate Improvement and Kinetics Investigation of Eprosartan, an Antihypertensive BCS Class Ii Drug

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ABSTRACT
Eprosartan (EP), chemically 4-[[2-butyl-5-[(E)-2-carboxy-3-thiophen-2-ylprop-1-enyl]imidazol-1-yl]methyl]benzoic acid. EP's melting point is 248-250 °C. EP is a commonly prescribed antihypertensive medication. It is BCS class II drug with low &variable oral bioavailability[1]. Dissolution is the rate limiting step for eprosartan oral absorption. It is necessary to improve solubility and dissolution rate in order to increase bioavailability.The purpose of the study is to increase Eprosartan solubility, dissolution profile rate, and dissolution kinetics using cyclodextrin complexation.The dissolution rate of eprosartan in cyclodextrins (CD) alone and in binary or trinary mixtures with Povidone K30 and/or Poloxamer 407 is investigated. Eprosartan dissolution rate and kinetics were very significantly enhanced. CD, PVP K30 &Poloxamer 407prominently increased eprosartan dissolution rate and drug release kinetics. CD alone resulted in a 1.7 times increase in eprosartan dissolution rate. The combination of CD with PVP K30 &Poloxamer 407 resulted in a much greater increase in eprosartan dissolution rate and significantly reduced the time required to release 90% of drug (T90%). When compared to CD alone, combining CD with Poloxamer 407 and PVP K30 resulted in substantially higher dissolution rates (kKP). As a result, combining CD with PVP K30&/Poloxamer 407 was suggested to improve the solubility, dissolution rate of eprosartan.
Keywords: Eprosartan (EP), Solubility, Complexation, Dissolution rate

I. INTRODUCTION

Eprosartan, a frequently prescribed antihypertensive medication. EP is classified as BCS II drug, because of its poor water solubility. It has a low and variable oral bioavailability. EP is essentially insoluble in water and other aqueous fluids. As a result, its oral absorption is dissolution rate constrained and its dissolution rate requires improvement to be improved oral bioavailability. Several techniques[2], including micronization, cyclodextrin complexation, the use of surfactants,solubilizers, solid dispersion in water soluble & dispersible media, have been explored. Poorly soluble medications' solubility, dissolution rate, and bioavailability have been improved by using carriers, prodrugs, salts, and polymorphs that display high solubility, micro emulsions, complexation and hot melt extrusion. Among the different techniques, complexation with cyclodextrins has acquired widespread adoption in industry in recent years for improving the solubility and dissolution rate of poorly soluble drugs. Many types of lipophilic drugs can fit into the inner cavity of cyclodextrins (CDs), which are cyclic torus-shaped molecules with a lipophilic outer surface.The inclusion complex process can improve a variety of physicochemical properties such as solubility, dissolution rate,bioavailabilityand stability.[3,4] Cyclodextrins have seen increased use in pharmaceutical formulation in recent years as a result of their acceptance by various regulatory agencies.[5,6] Poloxamer 407 is an amphiphilic polymeric solubiliser that was created specifically for solid solutions. Poloxamer 407 is a triblock copolymer composed of a hydrophobic polypropylene glycol block in the centre and two hydrophilic polyethylene glycol (PEG) blocks on each side. The two PEG blocks are around 101 repeat units long, whereas the propylene glycol block is approximately 56 repeat units long[7]. Poloxamer 407 improved the solubility and bioavailability of actives in solid solutions. Poloxamer 407[8] significantly increased the bioavailability of itraconazole and fenofibrate. Poloxamer 407 in the form of solid dispersions

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successfully increased the solubility and dissolution rate of etoricoxib[9]. It has also been reported that polyvinyl pyrrolidone (PVP K 30) can increase the solubility and dissolution rate of poorly soluble pharmaceuticals.[10]The current study investigated the individual effects as well as combined effects of cyclodextrin (CD) with PVP K30 &/ Poloxamer 407) on dissolution rate & kinetics of eprosartan.

II. EXPERIMENTAL

Materials

M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam, provided a free sample of eprosartan. M/s. Cerestar Inc., USA provided a free sample of cyclodextrin. Poloxamer 407 was a free sample provided by BASF, a chemical business based in Hyderabad. Commercially available methanol (Qualigens) and poly vinyl pyrrolidone (PVP K30) were used. All other materials utilised were of the highest quality.

Methods

EstimationofEprosartan: For the determination of Eprosartan, a UV Spectrophotometric approach was used. Test solution absorbance measurement done at 234 nm in pH 7.5 Phosphate buffer. For linearity, accuracy, precision, and interference, the procedure was validated. The procedure followed Beer's rule at concentrations between 0 and 20 µg/ml

Preparation of Eprosartan- βCD Complexes

Solid inclusion complexes of eprosartan in CD with and without PVP K30-Poloxamer 407 have been developed employing the kneading technique.Formulations composition presented in Table 1. In a mortar, Eprosartan, CD, PVP K30, and/or Poloxamer 407 were triturated with a tiny amount of dichloromethane: methanol (1:1) solution. After 45 minutes of kneading, the resulting thick slurry was dried at 55 degrees Celsius and dried till dry.The dry substance was pulverised and sieved through mesh No. 120.

Phosphate buffer, pH 7.5

Dissolved 14.4 g of Sodium hydrogen phosphate (Na_2HPO_4) anhydrous and 80 gm of Sodium Chloride & 2 gm of potassium chloride in 10000 mL of water. Adjusted pH to 7.50±0.05 either with 0.2N NaOH or phosphoric acid.

Dissolution Rate Study:

The tests were conducted using either eprosartan or an eprosartan-CD complex equivalent to 400 mg of eprosartan. At varied time intervals, samples of dissolution medium (5 ml) were taken out via a filter (0.45), appropriately diluted, and tested for eprosartan at 234 nm. The dissolution fluid sample collected each time was replaced with a fresh fluid.A total of three replicates (n=3) were conducted for each dissolution experiment. The dissolution test carried out as per the specifications mentions in table 2.

Table 1: Formulation of various Eprosartan complexes

Code	Composition	Ratio/ %
CF1	EP	1
CF2	EP- βCD	1;2
CF3	EP-Poloxamer 407	1:2%
CF4	EP- βCD (1:2) –Poloxamer 407	1:2:2%
CF5	EP-PVP K30	1:2%
CF6	EP- β CD - PVP K30	1:2:2%
CF7	EP-Poloxamer 407 -PVP K30	1:2%:2%
CF8	EP- βCD - Poloxamer 407 - PVP K30	1:2:2%:2%

EP stands for Eprosartan; βCD is for Cyclodextrin; and PVP stands for Poly vinyl pyrrolidone K 30.

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Table 2: Dissolution test conditions

Sr. No	Parameter	Conditions
1	Medium	Phosphate Buffer, pH 7.5
2	Molarity	0.2 M
3	Volume	900 ml
4	Speed	50 rpm
5	Apparatus	8-station dissolution test apparatus, Disso 2000 (Labindia).
6	n	3
7	Temperature	37±1^{o}C

Table 4: Release kinetics R^2 values of EP– βCD complex

Code/ Order	Zero	First	Higuchi model	Korsmeyer-Peppas model
CF1	-4.37	-2.32	-0.668	0.363
CF2	-1.17	0.563	0.657	0.854
CF3	-17.5	0.424	-3.909	0.909
CF4	-3.35	0.949	0.132	0.826
CF5	-6.56	0.772	-0.759	0.799
CF6	-4.00	0.915	0.066	0.920
CF7	-3.14	0.617	0.322	0.965
CF8	-2.31	0.799	0.540	0.988

Table 5: Drug release rate kinetics as per Korsmeyer Peppas model

Parameter	kKP	R^2	R^2 adjusted
CF_1	25.477	0.443	0.363
CF_2	22.695	0.873	0.854
CF_3	58.509	0.92	0.909
CF_4	40.034	0.847	0.826
CF_5	46.761	0.824	0.799
CF_6	40.648	0.93	0.92
CF_7	35.687	0.969	0.965
CF_8	32.544	0.989	0.988

kKP: Korsmeyer rate constant, n= diffusional release exponent.

III. RESULTS AND DISCUSSION

The study's goal is to improve eprosartan dissolution rate by cyclodextrin complexation with PVP K30&/Poloxamer 407. The effects of CD alone and in combination with PVP K30 &/ Poloxamer 407on eprosartan dissolution rate and kinetics were also investigated.According to the dissolution profile shown in Table 3, EP release is only 48% at 60 minutes. EP release was more than 1.7 times greater in EP-CD complexes as compared to EP. The dissolution rate of the CD complex developed with Poloxamer 407 and PVP K30 was far faster. DDSolver[11] was used to fit the results of the in-vitro drug dissolution (DD) study using various kinetic models, including zero order, first order, Higuchi's, and Korsemeyer Peppa's. Table 4 shows the adjusted R^2 of dissolution kinetics.

Adjusted R^2 values suggest that the formulations are using either the first order (CF4) or the Korsmeyer-Peppas model (CF7 & CF8) for drug release from inclusion complexes. Considering the results of this study, it was decided to compute dissolution kinetics using the Korsmeyer-Peppas model and the data shown in table 5.The adjusted R2 values of the Zero order and Higuchi models show that the none formulation does not follow these drug release models. Since the R2 values of all formulations are less than 0.95.

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The kKP of drug and inclusion complexes ranges between 25.477 to 58.509. Variations in the rate constant were found.This variance is attributable to the formulation ingredients present in each formulation and their impact on eprosartan dissolution rate enhancement.A significant increase in thekKPwas observed, when P407, PVP, and β--CD were combined. Dissolution rate kKPincreased 1.57 and 1,59 fold with EP- β -CD - P407 and EPR- β -CD - K30 solid ICs, respectively. Additionally, CF3 formulation exhibited highest kKP value (58.509). T25%, T50%, T75%, and T90%, which reflect the time needed in minutes to release 25%, 50%, 75%, and 90%, were determined using the Korsmeyer Peppas model, for better understanding of drug release kinetics. Table 6 shows the data

Table 3: Dissolution profile data

Time (min)	**CF1**	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**	**CF7**	**CF8**
5	18.59	24.83	73.64	45.64	61	55.33	58.23	50.33
10	47.38	55.53	74.23	76.63	62.23	65.32	62.33	63.32
15	47.48	57.63	85.54	78.54	83	78.33	70.32	68.33
20	47.62	60.63	90.34	83.34	90	86.63	73.67	74.63
25	47.08	63.45	93	93.69	92	91.32	79.63	79.32
30	47.22	68.45	96	97.87	94	95.35	85.68	86.35
40	47.36	73.69	97	99.5	96	99.63	95.35	94.63
50	47.68	76.32	98	100	96	100	100	98
60	47.96	80.33	100	100	96	100.58	100	100

Table 6: Drug release kinetics T25%, T50%, T75%, and T90%

Parameter	**CF1**	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**	**CF7**	**CF8**
T25	0.898	1.356	0.002	0.143	0.038	0.128	0.250	0.391
T50	46.461	12.058	0.315	2.505	1.418	2.404	3.723	4.619
T75	467.325	43.283	6.190	13.375	11.767	13.386	18.086	19.586
T80	674.828	53.048	9.942	17.462	16.479	17.594	23.260	24.650
T90	1319.523	76.895	23.604	28.406	30.469	28.973	36.814	37.504

The time required to release 90% of the drug ranges from 23.604 minutes to 1319.523 minutes.βCD inclusion complexes significantly enhanced dissolution rate (CF2 to CF8) compared to EP. Combining CD with P407, PVP 30 considerably increased dissolution rate, and these formulations required significantly less time to release 90% of the medication (23.604 minutes to 37.504 minutes).

IV. CONCLUSION

CD, PVP K30 &/ Poloxamer 407 significantly enhanced eprosartan dissolution rate and kinetics. CD alone increased the dissolution rate of eprosartan by 1.7 times.When CD was combined with Poloxamer 407 and PVP K30, the dissolution rate of eprosartan was significantly increased.When compared to CD alone or EP, the combination of CD with PVP K30&Poloxamer 407 resulted in considerably greater dissolution rates (kKP) and less time to release 90% drug (T90%).As a result, a combination of CD with PVP K30 and/or Poloxamer 407 was proposed to improve the dissolution rate and T90% of eprosartan, a BCS class II medication, employing a complexation strategy with kneading technique.

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