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DEVELOPMENT OF POLYMER CONJUGATED CEFACLOR FORMULATION WITH ENHANCED HALF LIFE AND BIOLOGICAL EFFECT

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ABSTRACT

Purpose of the study is to develop polymer conjugated cefaclor formulation with enhanced half life and biological effect. Antimicrobial drugs are the greatest contribution of therapeutics. Their advent changed the outlook of the physicians about the power drugs can have on diseases. Their importance is magnified in the developing countries, where infective diseases predominate. Cefaclor is a second generation cephalosporin antibiotic. Cefaclor is active against most strains both *in vitro* and *in vivo* clinical infections. Cefaclor is a gram-positive and gram negative antibacterial drug, widely used for the treatment of certain human diseases. The drug acts as an inhibitor of cell wall synthesis of bacteria. The efficacy of cefaclor is hampered by its very short plasma half life. The objectives of present work were conjugation of cefaclor with mPEG and its characterization in order to increase the drug plasma half life. The PEG was taken for conjugation purpose because it is highly water soluble, practically non-toxic, non-immunogenic and approved by FDA. On the basis of above discussion it may be concluded that cefaclor conjugates with the PEG enhance its blood plasma half life. Our current investigation based on preliminary results focuses on the aspects that these conjugates of cefaclor with PEG could further be exploited as an efficient alternative to formulation of cefaclor.

KEYWORDS: Cefaclor, PEG, Polymer Conjugated, half life and biological effect.

INTRODUCTION

Antimicrobial drugs are the greatest contribution of therapeutics. Their advent changed the outlook of the physicians about the power drugs can have on diseases. Their importance is magnified in the developing countries, where infective diseases predominate. As a class they

are one of the most frequently used drugs. Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. In order to increase the circulation time of drug in blood, they are coated or coupled with polar molecules. The rationale of this approach is based on the assumption that properties of the macromolecular conjugate dominated by the properties of the polymeric carriers determine the above mentioned characteristics. The main objective of the present study was develop polymer conjugated cefaclor formulation with enhanced half life and biological effect.

MATERIALS AND METHODS

Materials

Cefaclor was gifted by Cipla Research and Development Mumbai. PEG was received from Evonic Degussa Private limited Mumbai India. Methoxy Poly Ethylene Glycol All the solvents and chemicals used during formulation were of analytical grade.

Methods

Preparation of cefaclor conjugates

Cefaclor is a β -lactum analogous containing free carboxylic acid group, which provide an ideal site for attachment with methoxy poly ethylene glycol. The cefaclor-PEG conjugates were synthesized by the reaction of hydroxyl group of mPEG with free carboxylic group present in the drug, which results in the formation of ester linkage.

Reagents and solvents

The chemicals used for the experimental work were commercially procured from various chemical units the HiMedia, Lobachem India Ltd. and CDH. These compounds were purified and dried before their use.

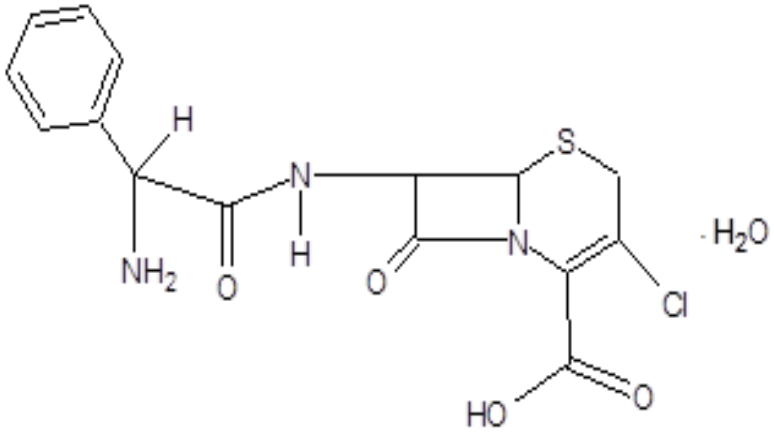
Conjugation of cefaclor with poly ethylene glycol (mol. wt 5000)

Accurately weigh the 368 mg (1.0 m mol) cefaclor drug and dissolved it in small quantity of dimethyl formamide in a round bottom flask. In another beaker solution of 500 mg (1.0 m mol) methoxy polyethylene glycol (molecular weight 5000) in dimethyl formamide was made. Added both the solutions in round bottom flask and added 2-3 drops of concentrated sulfuric acid (Conc. H_2SO_4). Refluxed the mixture for about 36h. After the completion of reaction pour the mixture into about 250 ml of distilled water. Dark brown coloured

precipitate was obtained which was filtered, washed with distilled water and dried at room temperature.

Conjugation of cefaclor with poly ethylene glycol (mol. wt. 750)

Conjugation of cefaclor with $mPEG_{750}$ is same as discussed above.



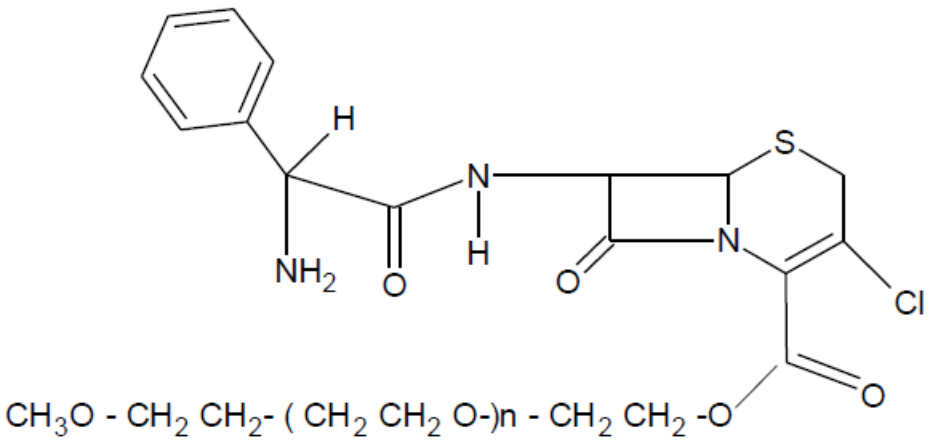
Cefaclor

+

$CH_3O - CH_2 CH_2 - (CH_2 CH_2 O-)n - CH_2 CH_2 -OH$

(mPEG $_{750}$)

Conc. H_2SO_4



Scheme 1.1 Reaction of cefaclor with methoxy poly ethylene glycol (mol. wt. 750).

RESULT AND DISCUSSION

From the identification studies performed on the drug, In all, the gift sample of cefaclor was authentic and results of this study were in accordance with the standards given in official monographs.

Table no. 1: Physical characterization of cefaclor.

Parameter(s)	Observation
Physical appearance	White to cream colored crystalline powder.
Melting point	326 ± 1^0C

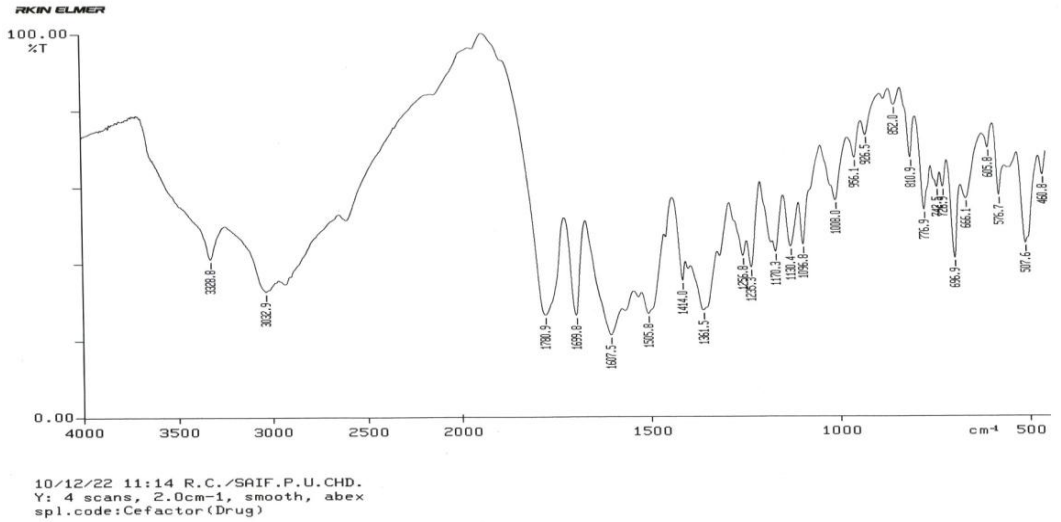


Fig. 1: IR Spectrum of cefaclor.

Table no. 2: Half life of test compounds in plasma samples.

S no.	Test compounds	Peak concentration (µg/ml)	Trough Concentration (µg/ml)	Time interval (hrs)	Plasma half life (min)
1	Cefaclor	8.32	5.05	3.34	42
2	CEF-PEG5	9.52	7.07	3.17	54
3	CEF-PEG7	8.55	6.24	3.17	57

Table no. 3: CEF-PEG5 samples.

S no.	Time (min)	Absorbance	Concentration (µg/ml)
1	10	0.1308	7.10
2	20	0.1419	7.95
3	30	0.1415	8.38
4	40	0.1555	8.99
5	50	0.1625	9.52

Table no. 4: Standard curve of cefaclor at λ_{max} 340 nm.

Concentration (µg/ml)	Absorbance	Regressed bsorbance	Statistical parameters
2	0.0504	0.0640	**Equation of line** y = 0.0131x + 0.0378 **Correlation coefficient** r^2 = 0.9973
4	0.0849	0.0902	
6	0.1296	0.1164	
8	0.1316	0.1426	
10	0.1563	0.1688	
12	0.1945	0.1950	
14	0.2153	0.2212	
16	0.2354	0.2474	
18	0.2756	0.2736	
20	0.2994	0.2998	

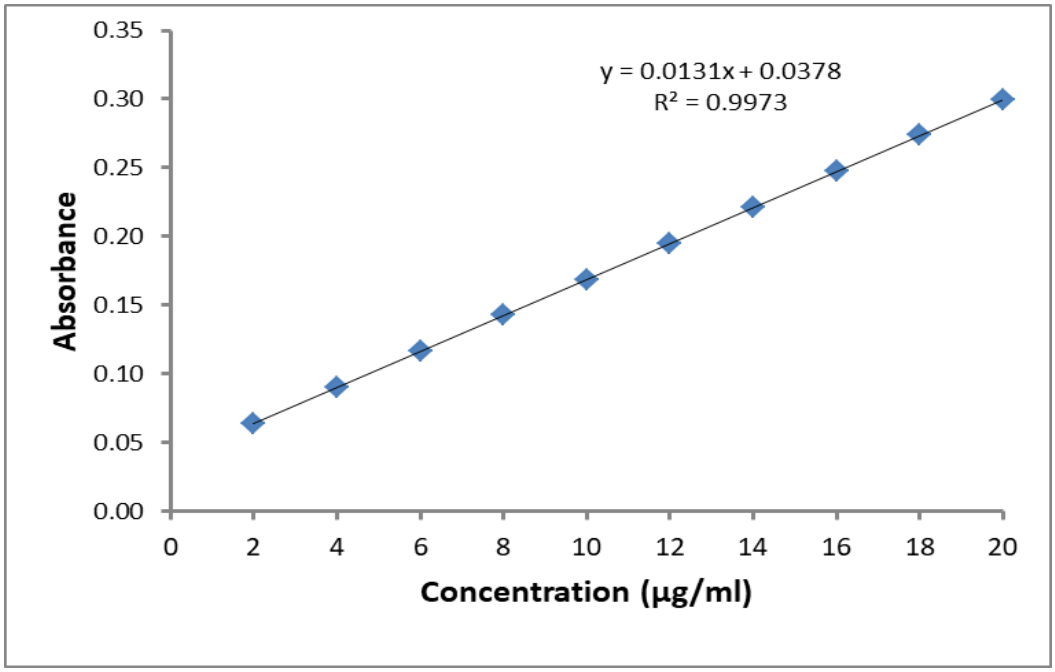


Fig. 7.1: Concentration v_s absorbance graph for cefaclor.

CONCLUSION

The drug sample was identified and found to be authentic. Various preformulatory parameters like solubility and quantitative estimation of cefaclor in various solvents was performed. All these successful explorations paved the way for further studies.

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