Polyethylene glycol conjugation for solubility enhancement of Cefadroxil, a poorly soluble antibiotic

ABSTRACT:

Introduction:

Cefadroxil is the most widely used antibiotic for many bacterial infections but has the drawback of poorly solubility. In an attempt to provide an easier technique which can be scaled up on large scale to provide a simple method to enhance its aqueous solubility, this present work has exploited polyethylene glycol conjugation to enhance its aqueous solubility of cefadroxil.

Objective:

The main aim of the work is preparation of Polyethylene glycol conjugates of cefadroxil by solvent evaporation technique and to evaluate its solubility enhancement by solubility analysis and to assess drug content uniformity, drug - excipient interaction studies by FTIR spectroscopy.

Methodology:

Polyethylene glycol conjugates of cefadroxil are prepared by solvent evaporation technique using PEG 6000. Five conjugates of Cefadroxil to PEG6000 taken in weight proportions of (1:0.5), (1:1), (1:2) (1:3) and (1:4) were prepared.

Results:

Reasonable enhancement of solubility of cefadroxil was evidenced from all the prepared polyethylene glycol conjugates of cefadroxil. Among all CFDL: PEG 6000 (1:4) evidenced high percentage solubility of 81±0.61. IR spectrum of CFDL: PEG6000 (1:4) evidenced disappearance of amide group of cefadroxil indicating conjugate formation which is reversible to release cefadroxil to exhibit its therapeutic effect

Conclusion:

Polyethylene glycol conjugates of cefadroxil can be prepared easily by solvent evaporation and the conjugate made by weight proportion of CFDL: PEG 6000 (1:4) enhances solubility of cefadroxil by 88% and is promising to be used in formulations cefadroxil with enhanced dissolution and bioavailability.

KEY WORDS:

Cefadroxil, Polyethylene glycol conjugates, PEG6000, Solvent evaporation technique, Enhanced solubility.

1.Introduction:

Cefadroxil is a first generation cephalosporin bearing **methyl and (2R)-2-amino-2-(4-hydroxyphenyl) acetamido groups at positions 3 and 7, respectively, of the cephem skeleton**. Its IUPAC name is 4-[3-(4,5-dihydro-1,2-oxazol-3-yl)-2-methyl-4-methylsulfonylbenzoyl]-2-methyl-1H-pyrazol-3-one . The molecular formula is $C_{16}H_{17}N_3O_5S$. It is an antibiotic that inhibits the third and final stage of bacterial cell wall synthesis by binding to specific penicillin binding proteins found inside the bacterial cell wall. It is highly effective against gramme +ve bacteria and moderately effective against gramme -ve bacteria.

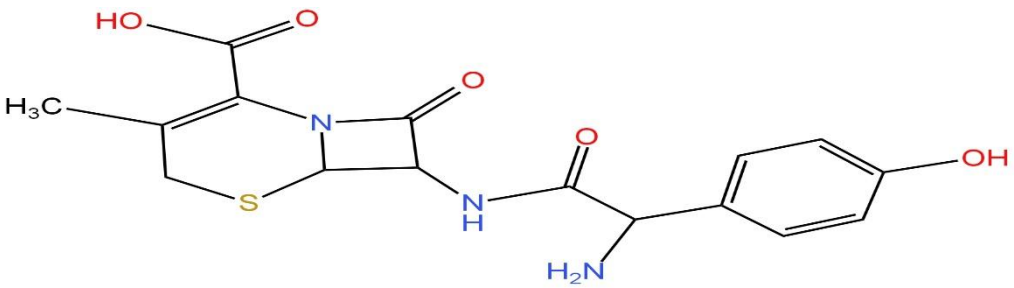

Image 1: Chemical structure

Cefadroxil is an antibiotic that inhibits the third and final stage of bacterial cell wall formation by attaching to certain penicillin-binding proteins inside the bacterial cell wall. It is completely absorbed from gastrointestinal tract and generally prescribed at 1-2 gm per day in single divided doses for ailments such as UTI for pharyngitis, transalites and skin infections.

Challenging task associated with this drug for its formulation development is its water insolubility.

Even though number of techniques have been reported in literature[2,], PEGylation i.e conjugation of high molecular weight polyethylene glycols with poorly soluble small molecules through covalent bonding which are generally physiologically labile and reversible may be a simple method to enhance their solubility, dissolution and thereby bioavailability [3,4,5]. PEG conjugates formed through covalent bonding are generally physiologically labile and release parent drug without affecting therapeutic effect[5]. PEG conjugates with enhanced solubility are promising for further design of cefadroxil dosage forms in the form of tablets or capsules.

Hence the present work is aimed at preparation of poly ethylene glycol conjugates of cefadroxil by solvent evaporation technique and to assess the conjugates for solubility enhancement of cefadroxil and drug PEG conjugation study by FTIR analysis.

2.MATERIALS

Cefadroxil was obtained as a gift sample from Karnataka Antibiotics and Pharmaceuticals **Ltd**., Bangalore INDIA. PEG6000 was procured from S D. fine chemicals, INDIA. Methanol was purchased from Loba Chem. Pvt. **Ltd**., INDIA. All other chemicals used in the study were of analytical grade.

3.METHODS:

3.1. Preparation of drug-PEG conjugates by solvent evaporation technique:

PEG conjugates of cefadroxil with PEG 6000 were prepared by taking various ratios of drug and PEG in weight proportions. Seven no.of trial compositions were made and are shown in **Table 1.** Drug and PEG6000 were dissolved separately in possible minimum volume of acetone (H30ml) and these solutions were mixed and stirred well in cyclone mixer for 45 min. After mixing, the solvent was removed by evaporation in a water bath at 35^0 C under vacuum. This dried mass was scrapped, sieved through # 100, collected and stored in 30 ml screw capped glass vials for further use. In each case 2 gm of mixture was prepared.

Table 1: Weight proportion of PEG conjugates of cefadroxil

S.No	Weight proportion of CFDL:PEG6000
1	1:0.5
2	1:1
3	1:2
4	1:3
5	1:4
6	1:5
7	1:6

3.2. Evaluation of drug-PEG conjugates:

The PEG conjugates of cefadroxil were evaluated by solubility studies, drug content uniformity studies, Drug excipient interaction study by FTIR spectroscopy..

3.2.1. Solubility analysis of cefadroxil-PEG conjugates:

Studies on the solubility of both the produced CFDL-PEG6000 conjugates and pure cefadroxil were conducted. In each instance, extra samples were added to sealed glass tubes containing 10 ml of distilled water. In order for equilibrium to be reached, the tubes were left aside for 24 hours at room temperature and sometimes combined in a vortex mixer. Then the supernatant liquid was filtered through 0.45µm Millipore filter and aliquot samples were estimated for cefadroxil using UV-Visible spectrophotometer (Shimadzu, JAPAN) at λ_{max} of 264nm.

3.2.2. Uniformity of drug content

"From each CFDL-PEG conjugate, three samples of 50 mg were analyzed for drug content. The sample was transferred into a stoppered conical flask, and dissolved in a minimum amount of methanol.. Then the volume was made up to 50 ml with Methanol" [7]. The contents were thoroughly mixed and kept aside for 24 hrs with occasional shaking to facilitate the extraction of drug from the solid mixture into solvent. The clear supernatant solution was collected by filtering through a 0.45 µm Millipore filter. The solutions were suitably diluted and assayed for their drug content by using UV-Visible spectrophotometer (Shimadzu, JAPAN) at λ_{max} of 264 nm.

3.2.3. FTIR analysis:

"IR spectra of pure cefadroxil and the promising dug-PEG conjugate, CFDL: PEG6000 (1:4) conjugates were obtained on a FTIR Spectrophotometer, (Bruker Labs, INDIA) equipped with a DTSG detector were prepared by KBr pressed pellet technique" [8]. The scanning range was maintained at 4000-400 cm^{-1} and the resolution was 1 cm^{-1}. The spectra are shown in Figure 1 to 2.

4. RESULTS AND DISCUSSION:

It was observed that, all the conjugates, CFDL: PEG6000 prepared in weight proportions of 1:0.5), (1:1), 1:2, 1:3, 1:4, 1:5 and (1:6) were free flowing and the results of various evaluation parameter such as are discussed as follows.

4.1. Solubility studies :

The results of solubility studies are shown in **Table 2.** As indicated pure cefadroxil possessing percentage solubility of 0.14% indicating that this drug is practically insoluble drug[7]. At the same time the values in the table indicate there is reasonable enhancement of solubility of cefadroxil from its polyethylene glycol conjugates. CFDL: PEG6000(1:0.5) exhibited 31±0.03% and all other CFDL: PEG6000 conjugates of ratios (1:0.5), (1:1), (1:2) (1:3), (1:4), (1:5) and (1:6) also evidenced same values with slight variation. These results indicated free solubility of cefadroxil when it is converted as conjugates with high molecular weight polyethylene glycol conjugate such as PEG 6000. But when we observe the results the ratio 1:4 was considered as optimum as beyond the addition of 4 parts of PEG6000 there is decrease in solubility values.This may be due to high value of polymer above 4 parts must be impeding the release of drug from conjugate into bulk

Table 2: Solubility of cefadroxil **in water at 25°C (n=3±s.d)**

Mixture	% Drug dissolved
Pure Cefadroxil	0.14%±0.1
CFDL:PEG6000(1:0.5)	31±0.03
CFDL:PEG6000(1:1)	64±0.7

CFDL:PEG6000(1:2)	68±0.52
CFDL:PEG6000(1:3)	73±0.55
CFDL:PEG6000(1:4)	81±0.61
CFDL:PEG6000(1:5)	46±0.72
CFDL:PEG6000(1:6)	34±0.22

4.2. Drug content uniformity:

The percent drug content values of all the prepared conjugates are given in Table 3. Values for the percentage of drugs in the samples ranged from 98.08 to 99.87 percent. All of the techniques used to prepare PEG conjugates did not result in a measurable loss of the drug content. However, conjugates showed a 2-3% loss, which might be the result of the medication being lost during the procedure. The low c.v. values in percent drug content values ensured the uniformity of drug in each batch. All the values were in agreement with the theoretical values.

Table 3: Percent cefadroxil in CFDL -PEG conjugates

Type of mixture	Percent CFDL content, [n=3(c.v)]
CFDL:PEG6000(1:0.5)	99.26(1.02)
CFDL:PEG6000(1:1)	99.29(0.88)
CFDL:PEG6000(1:2)	99.33 (0.92)
CFDL:PEG6000(1:3)	99.89 (1.09)
CFDL:PEG6000(1:4)	99.46(1.22)
CFDL:PEG6000(1:5)	99.46(1.10)
CFDL:PEG6000(1:6)	99.46(0.97)

4.3. FTIR analysis:

FTIR spectra of pure cefadroxil and promising dug-PEG conjugate are shown in **Fig. 1 and 2.** Relevant absorption peaks of functional groups of cefadroxil are shown in **Table 1**. Cefadroxil produced the absorption peak of C-S at 1118.52 cm^{-1}, SNH at 1561.66 cm^{-1}, COOH at 1757.12 cm^{-1}, OH Stretch at 3201.32 cm^{-1}, C-O-C at 1234.06 cm^{-1}. IR absorption peaks of all functional groups of Cefadroxil are also present in the IR spectrum of case CFDL:PEG 6000 conjugate (Fig. 2) exept SN-H vibrational stretch at 1561.66 cm^{-1} . This is expected due to conjugation of the end hydroxyl group of PEG with the amide group of cefadroxil. At this juncture it is expected that PEG conjugates which is reversible upon dissolution of polyethylene glycol moieties in aqueous solvents leading to release of parent drug cefadroxil in body fluids without affecting required therapeutic effect.

Fig 1: IR spectrum of Cefadroxil

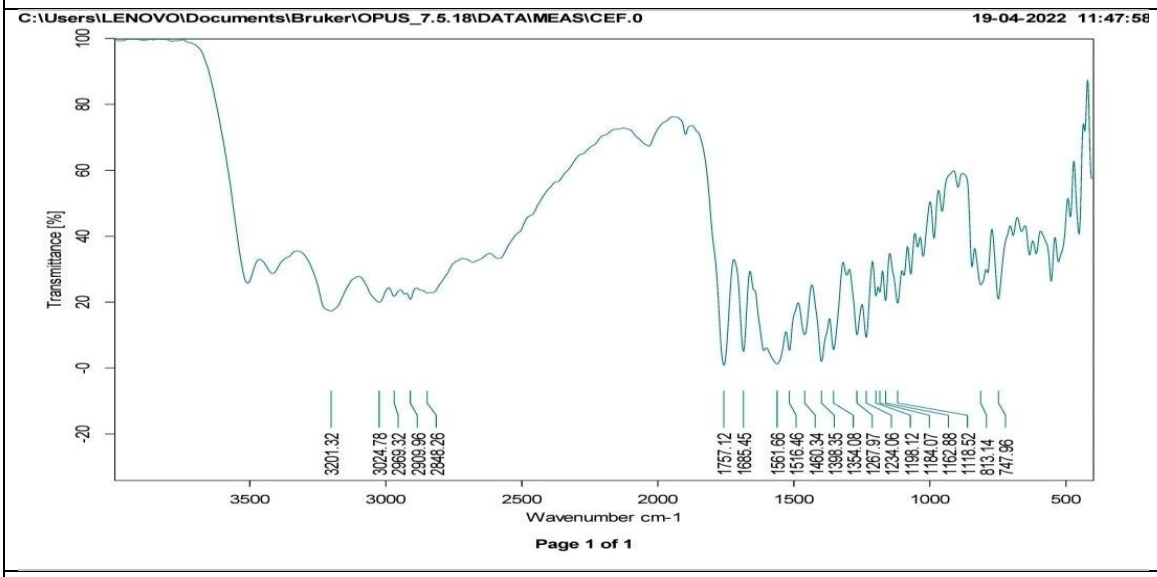

Fig 2: IR spectrum of CFDL:PEG 6000 (1:4) conjugate

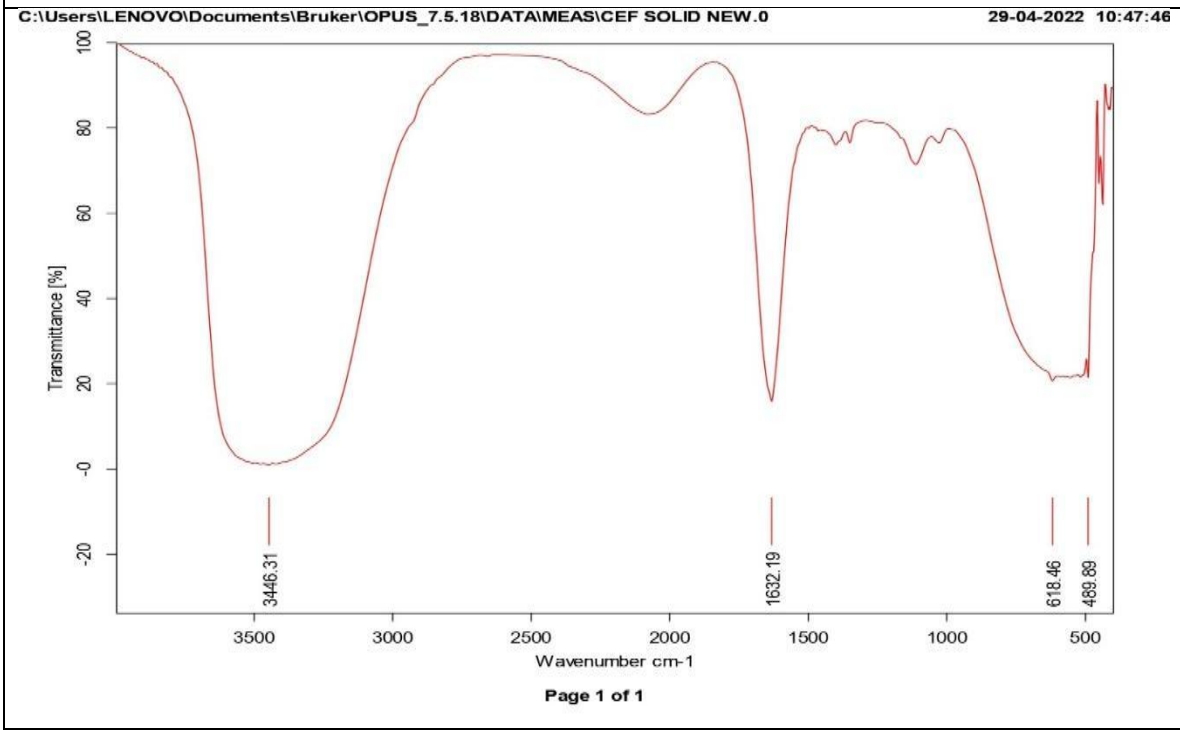

Table 4: IR absorption peaks of cefadroxil and CFDL:PEG6000(1:4)conjugate

Interpretation	Wave number of	
	Cefadroxil	CFDL:PEG 6000 conjugate

C-S	1118.52	1118.52
SNH	1561.66	-
COOH	1757.12	1632.19
OH Stretch	3201.32	3446.31
C-O-C	1234.06	1234.06

5.Conclusion:

Polyethylene glycol conjugates of cefadroxil can be prepared easily by solvent evaporation and the PEG conjugate made by weight proportion of cefadroxil: PEG6000 (1:4) enhances solubility of cefadroxil by 88% and is promising to be used in the design of formulations of cefadroxil with enhanced dissolution and bioavailability.

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