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Research Article

Preformulation study of Levofloxacin

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Abstract

Levofloxacin is the L-isomer of the racemate ofloxacin, a quinolone antimicrobial agent. Chemically levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (S)-enantiomer of the racemic drug substance Ofloxacin.Preformulation studies are needed to ensure the development of a stable as well as therapeutically effective and safe dosage form. The Preformulation studies, performed in this research include identification of drug, solubility analysis, partition coefficient and drug compatibility.

In present work complete preformulation study was carried out, which include identification of drug, quantitative estimation of drug, solubility determination, melting point determination,partition coefficient determination etc.

Keywords:

Levofloxacin ,
ofloxacin ,
preeclampsia,
antibiotic ,
preformulation

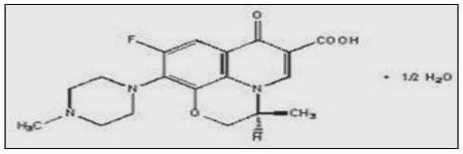
1. Introduction

Levofloxacin is the L-isomer of the racemate ofloxacin, a quinolone antimicrobial agent. Chemically levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (S)-enantiomer of the racemic drug substance Ofloxacin.

1.1 Chemical Name: 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, hemihydrate.

1.2 Chemical Formula: $C_{18}H_{20}FN_3O_4 \cdot H_2O$ [1]

1.3 Chemical Structure:



1.4 Molecular weight: 361.3675 [2]

1.5 Melting point: 225-227°C

1.6 Availability: 99%

1.7 Protein binding: 24 to 38%

1.8 Half-life: 6 to 8 hours

1.9 Appearance: Pale yellow solid crystalline powder.

1.10 Solubility: Freely soluble in glacial acetic acid, chloroform; sparingly soluble in water.

1.11 Derivatives: Levlevofloxacin is a quinolone/fluoroquinolone antibiotic related to ciprlevofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, grepafloxacin, lomefloxacin, moxifloxacin, norfloxacin, levofloxacin, pefloxacin, prulifloxacin, rufloxacin, sparfloxacin, temafloxacin, trovafloxacin, sitafloxacin**.**

1.12 Specification::

Table 5 . Specification of Levofloxacin

Characteristics	**Light yellowish crystalline powder**
Identification	Positive
Solubility	Positive
Loss on drying	≤4.0%
Heavy metals	≤20ppm
Residue on ignition	≤0.2%
Specific rotation	-95° To -103°
Other impurities	≤0.32%
Assay	98.5%-99.5%

1.13 Overdose: n the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levlevofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.[3]

1.14 Pharmacology: Levlevofloxacin is the L-isomer of the racemate levofloxacin, a quinolone antimicrobial agent. In chemical terms, levlevofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance levofloxacin. The chemical name is (-)-(S)-9fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.

The empirical formula is $C_{18}H_{20}FN_3O_4$ • ½ H2O, and the molecular weight is 370.38. Levlevofloxacin is a light-yellowish-white to yellow-white crystal or crystalline powder.[3]

Some of the endogenous compounds that are affected by the levlevofloxacin include GABA receptors (inhibitor), OCTN2 (inhibitor),[4] blood glucose (alteration) potassium channels (in myocardial cells - inhibitor),[5] pancreatic β-cell potassium channels (inhibitor)[115] and glutathione (depletor).

1.15 Pharmacokinetics: Levlevofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Levlevofloxacin is rapidly and, in essence, completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The plasma concentration profile of levlevofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for LEVAQUIN Tablets when equal doses (mg/mg) are administered. Levlevofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levlevofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levlevofloxacin given orally or intravenously.[3] Glucuronidation and hydroxylation have been cited as one of the major metabolic pathways for levlevofloxacin hydrochloride.[6] However the drug card for levlevofloxacin states that the biotransformation information is not available.[7] Specific information regarding biotransformation does not appear to be readily available within the package inserts. Half-life is 6–8 hours.[7]

1.16 Mechanism of action: Levlevofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase iv,[8] which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division.

The fluoroquinolones interfere with DNA replication by inhibiting an enzyme complex called DNA gyrase. This can also affect mammalian cell replication. In particular, some congeners of this drug family display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases, and are toxic to cultured mammalian cells and in vivo tumor models. Although the quinolone is highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is

not known. Quinolone-induced DNA damage was first reported in 1986.[9]

Recent studies have demonstrated a correlation between mammalian cell cytotoxicity of the quinolones and the induction of micronuclei.[10-13] As such some fluoroquinolones may cause injury to the chromosome of eukaryotic cells.[14-19]

There continues to be debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe and non-abating adverse reactions experienced by some patients following fluoroquinolone therapy.[20-22]

1.17 Interactions: The toxicity of drugs that are metabolised by the cytochrome P450 system is enhanced by concomitant use of some quinolones. Coadministration may dangerously increase warfarin (Coumadin) activity; INR should be monitored closely. They may also interact with the GABA A receptor and cause neurological symptoms; this effect is augmented by certain non-steroidal anti-inflammatory drugs.[23] Quercetin, a flavonol, a kind of flavonoid, occasionally used as a dietary supplement, may interact with fluoroquinolones, as quercetin competitively binds to bacterial DNA gyrase. Some foods such as garlic and apples contain high levels of quercetin; whether this inhibits or enhances the effect of fluoroquinolones is not entirely clear.[24]

Specific drug interaction studies have not been conducted with levlevofloxacin. However, the systemic administration of some quinolones has been shown to interfere with the metabolism of caffeine, elevate plasma concentrations of theophylline, and enhance the effects of the warfarin and its derivatives. In patients receiving systemic cyclosporine concomitantly, transient elevations in serum creatinine has been noted.[25]

1.18 Indications: apply to sensitive strains caused by :

- Genitourinary infections, including simple and complicated urinary tract infections, bacterial prostatitis, urethritis Neisseria gonorrhoeae or cervicitis (including producing strains caused).
- Respiratory infections, including sensitive Gram-negative bacilli induced bronchial infection and acute lung infection.
- Gastrointestinal tract infections, Shigella, Salmonella spp, Enterotoxigenic E. coli endotoxin, hydrophilic Aeromonas, such as Vibrio parahaemolyticus caused.
- Typhoid. Donor. Bone and joint infections.
- Skin and soft tissue infections.
- Septicemia systemic infection.

1.19 Significant drug interactions: Levlevofloxacin has been reported to interact with a significant number of other drugs, as well as a number of herbal and natural supplements. Such interactions increased the risk of cardiotoxicity and arrhythmias, anticoagulant effects, the formation of non-absorbable complexes, as well as increasing the risk of toxicity.

Some drug interactions are associated with molecular structural modifications of the quinolone ring, specifically interactions involving NSAIDS and theophylline. The fluoroquinolones have also been shown to interfere with the metabolism of caffeine [172] and the absorption of levothyroxine. The interference with the metabolism of caffeine may lead to the reduced clearance of caffeine and a prolongation of its serum half-life, resulting in a caffeine overdose. Ciprlevofloxacin has been shown to interact with thyroid medications (levothyroxine) resulting in unexplained hypothyroidism.[26] As such it is possible that levlevofloxacin may interact with thyroid medications as well.

1.20 Adverse effects: The serious adverse effects that may occur as a result of levlevofloxacin therapy include irreversible peripheral neuropathy,[27] spontaneous tendon rupture and tendonitis, QTc prolongation/torsades de pointes, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome, erythema multiforme, severe central nervous system disorders (CNS), including seizures[28] and clostridium difficile associated disease (CDAD: Pseudomembranous colitis)[29-32] photosensitivity/phototoxicity reactions,[33] fatal hypoglycemia, kidney damage, rhabdomyolysis (muscle wasting),[34,35] as well as anaphylactoid reactions[36] and myasthenia crisis.[37]

1.20.1 Paediatrics: Safety not established.
1.20.2 Pregnancy & Lactation: Safety not established.
1.20.3 Elderly: Safe.
2.21 Side-Effects: Mild transient smarting sensation and itching. Temporary blurred vision, eye discomfort, itching, redness, dryness, tearing, feeling as if something is in your eye, or sensitivity to light may occur.

1.22 Purity : Not less than 99%.

1.23 Contraindication: The use of eye drop Levofloxacin is contraindicated in patients with hypersensitivity to Levofloxacin or to other quinolones or to any of the components of the medication.

1.24 Uses: This medication is used to treat eye infections. Levofloxacin belongs to a class of drugs called quinolone antibiotics. It works by stopping the growth of bacteria. This medication treats only bacterial eye infections. It will not work for other types of eye infections. Unnecessary use or overuse of any antibiotic can lead to its decreased effectiveness.

1.25 Storage: Preserve in well-closed containers, protected from light. Store at 25 excursions permitted between 15 and 30 .

2. Preformulation Study

2.1 Method: Identification of Drug: [38]

2.1.1 UV Spectrophotometric analysis of drug: Ultraviolet absorption in the range 200 to 400 nm of a 25 mg/ml solution in methanol was determined.

2.1.2 Fourier Transform Infra Red analysis of drugs: The FTIR analysis of the sample was carried out for qualitative compound identification. The KBr pellet of approximately 1 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of KBr in pressure compression machine. The infrared spectrum of levofloxacin in a KBr pellet for wave number range of 4000– 500 cm-1

Preparation Of Buffers And Reagents: [39]

- Sodium hydroxide solution 0.2 M – 8.0 gm of sodium hydroxide was dissolved in distilled water and diluted to 1000 ml with distilled water.
- Potassium dihydrogen phosphate solution 0.2 M – 27.218 gm of potassium dihydrogen phosphate was dissolved in distilled water and diluted to 1000 ml..
- Phosphate buffer solution PH 7.4 – 250 ml of 0.2 M potassium dihydrogen phosphate was placed in 1000 ml volumetric flask. 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. PH was adjusted to 7.4 with dilute sodium hydroxide.

Quantitative Estimation Of Drug:

- **Determination of absorption maxima (λmax)/wavelength maxima –** The standard sock solution of levofloxacin was prepared by dissolving 50 mg of drug in methanol in 100 ml volumetric flask. Stock solution of Levofloxacin was further diluted in methanol to get standard solution concentration of 100 mcg/ml. The resulting solution was then scanned between 200 -400 nm. UV visible spectrophotometer (shimadzu 1601 UV Japan). [38]
- **Standard curve of levofloxacin in phosphate buffer solution (PH 7.4)** Accurately weighed 100 mg of levofloxacin was dissolved in 100 ml of pH 7.4 phosphate buffer to give a solution of 1 mg/ml (1000 µg/ml) concentration and thi served as the first standard stock solution. From this stock solution 1 ml was taken and diluted to 100 ml using pH 7.4 phosphate buffers to get a solution of 10 µg/m concentration and this solution served as the second standard solution. Into a series of 10 ml volumetric flasks, aliquots of second standard solution (i.e.) 2 ml, 4 ml, 6 ml, 8ml, 10ml and 12 ml was added and the volume made up to 10 ml using pH 7.4 phosphate buffer. The absorbance of these solutions was measured against reagent blank at 292 nm using Shimadzu (UV-1601) UV spectrophotometer. Standard curve was plotted with concentration on x-axis and absorbance on y-axis

2.2 Preformulation Study Of Drug: Preformulation studies are needed to ensure the development of a stable as well as therapeutically effective and safe dosage form.[40,41] The Preformulation studies, performed in this research include identification of drug, solubility analysis, partition coefficient and drug compatibility. [42,43]

- **Solubility determination**:- For quantitative solubility studies, known amount of drug (10mg) was suspended in a series of different solvents and shaken for 24 hrs. Using wrist action shaker (York India). Solubility of levofloxacin in different solvents is recorded.[44-47]
- **Melting point determination**:- Melting point determination of levofloxacin is done by using Melting Point Apparatus. In that method the presealed capillary is filled by the small amount of drug. Then capillary and thermometer were placed in Melting Point Apparatus. Then see capillary for melting the drug. The temperature were noted when the drug start to melt and the drug till complete melt.

- **Partition coefficient determination**:- The partition coefficient of Levofloxacin was determined by shaking flask method in n-octanol: water system. 10 mg of drug Levofloxacin was added into 50 ml each of n-octanol and water. The mixture was shaken for 24 hours until equilibrium was reached. Phases were separated in a separating funnel and the aqueous phase was filtered through 0.2µ filter, suitably diluted and amount of Levofloxacin in aqueous phase was determined by measuring the absorbance at 258nm using UV spectrophotometer. The partition coefficient ($P_{o/w}$) of Levofloxacin was calculated from the ratio between the concentration of Levofloxacin in organic (C_{oil}) and aqueous phase ($C_{aq.}$) using following equation.

$$P_{o/w} = (C_{oil}/C_{aq.})\ \text{equilibrium}$$

3. Results And Discussion

3.1 Organoleptic Properties

3.1.1 Colour: Yellowish white.

3.1.2 Crystalinity: crystalline powder**.**

3.1.3 Hygroscopicity: No Hygroscopicity

3.1.4 Taste: Bitter

3.1.5 Odour: odorless

3.2 Identification of Drug

3.2.1 Determination of λmax: The λmax was found to be at 293 nm .

4. Discussion:

λmax is 293. The obtained peak was found to be identical to the reported absorbance maxima. This λmax is matches with the λmax given in I.P.

4.1 FT-IR Study for identification of drug: An FT infrared (FT-IR) spectroscopy study was carried out to check the compatibility between the drug levofloxacin. The spectra obtained from FT infrared spectroscopy studies at wavelength from 4000 cm to 400-1 cm are shown Figures characteristic peaks obtained.

This study was carried out to find out the possible drug levofloxacin . FT-IR of levofloxacin showed the following characteristic peaks peak at 3265^{-1} cm due to carboxylic group 2931^{-1} cm due to alkanes group stretching 1724^{-1} cm due to stretching of carbonyl group, 1294^{-1} cm due to stretching of amines, in between 1100 to 1400^{-1} cm due to the presence of halogen group. thus revealing compatibility of the selected drug

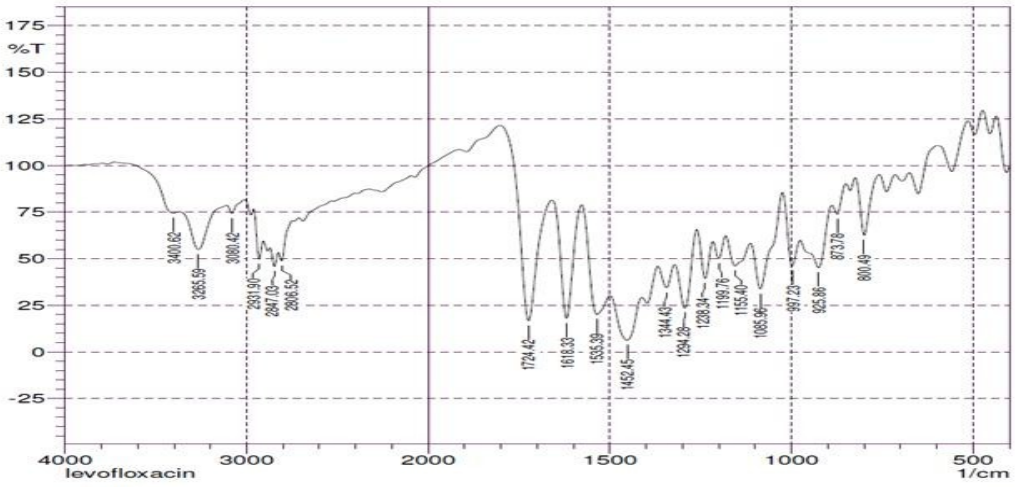


Fig no 1. FTIR interpretation of levofloxacin

Table 1: IR interpretation of drug:

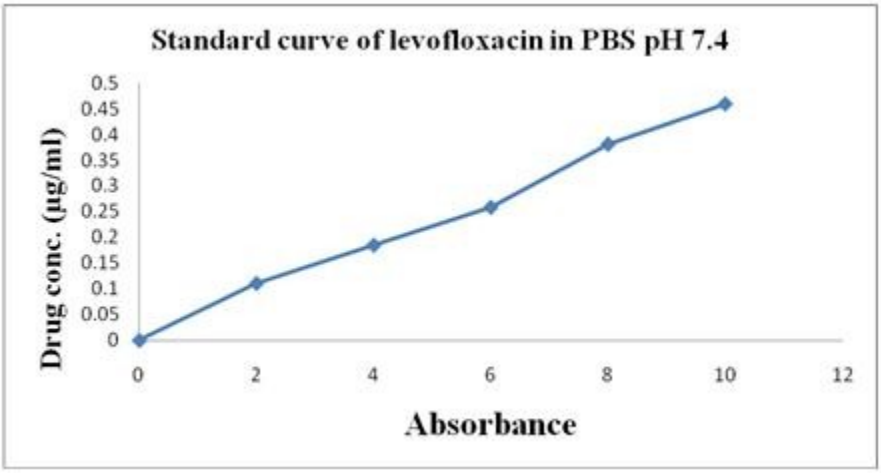
Name of the compound	Interpretation				
	-COOH	-CH3	C=O	C-N	F (halogen group
Levofloxacin (standard)	3265	2931	1724	1294	1085
Levofloxacin drug	3265.59	2931.90	1724.42	1294.26	1085.96

4.2 **Calibration Curve:** Standard curve of levofloxacin in phosphate buffer solution (PH 7.4)

Table 2: Absorbance value of levofloxacin in PBS pH 7.4 (λmax 292 nm).

S. No.	Drug Conc. (µg/ml)	Absorbance
1	2	0.1106
2	4	0.1848
3	6	0.2583
4	8	0.3809
5	10	0.4590

Fig 2: Standard curve of levofloxacin in PBS pH 7.4 (λmax 292 nm).



4.3 Solubility properties: Solubility of levofloxacin in different solvents is recorded.

Table 3 : Solubility of levofloxacin in different solvent.

Solvent	Solubility
Water	Slightly soluble
Glacial acetic acid	Freely soluble
PBS (pH 7.4)	practically soluble
Ethanol	Slightly soluble
Methanol	sparingly soluble
Chloroform	Freely soluble

4.4 Partition Coefficient: The partition coefficient of Levofloxacin was determined in n-octanol: water system at pH 7.4 buffers.

Test	Specification	Observation
Partition coeff.	n-octanol:pbs (7.4)	4.3

.**4.5 Melting Point:** Melting Point of Levofloxacin is 224^{o}**C**

5. Discussion:

Melting point of the drug Levofloxacin is found 224 ^{o}C, which is approx. same as reported in I.P 2007 so it shows the purity of the drug. The melting point of the drug is found in 225-227°C range this shows that, the drug is amorphous in nature.

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