# Development and Characterization of a Controlled-Release Ciprofloxacin Hydrochloride Drug Delivery System

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## Abstract

Ciprofloxacin Hydrochloride (CFX-HCl) is an antibiotic used to treat bacterial infections in many different parts of the body.

The study was able to outline development and characterization of a controlled-release CFX-HCl drug delivery system. The study has utilized propylene glycol (PG), carbopol 934P (C-934), xanthan gum (XG) and micro-encapsulated them by making use of spray drying method.

According to British Pharmacopoeia, the drug delivery systems were sterilized with the assistance of gamma radiation. Investigation of spray dried powder has been carried out by scanning electron microscopy (SEM), and assessed for microbial effectiveness. Similarly, stability studies were also performed.

These systems displayed drug's sustained and controlled release of CFX-HCl in the in-vitro studies over a prolonged period. Product's shelf life having PG was analyzed to be above two years.

These systems that are physically and chemically stable, display assurance of huge therapeutic benefits in the management of conjunctivitis and corneal ulceration.

## Methodology

### Preparing Spray Dried Powder (Drug Loading Technique)

The formulation was prepared by soaking Carbopol 934 (C-934) in de-ionized water. Stirring water at low velocity, adding gradually Xanthan Gum (XG) powder to water with continuous stirring. Then adding the C-934 suspension gradually to the XG suspension. Adding Propylene Glycol (PG), adding CFX-HCl solution and finally adding water q.s. to produce a solution containing XG 0.5 % w/w: C-934 0.5 % w/w: CFX-HCl 0.5 % w/w (SD1), or to produce another solution containing XG 0.5 % w/w: C-934 0.5 % w/w: CFX-HCl 0.5% w/w: PG 0.5 % w/w (SD2).

The solution was spray dried with BUCHI 190 mini-spray dryer,

### Fabrication of Powders for Drug Delivery Systems Uncoated Ocular Inserts and Coated Ocular Inserts

The spray dried powder SD2 was mixed with suitable amounts of the free drug CFX-HCl to produce different ratios of drug to matrix (spray dried product) powders and to produce different tablet formulas, as shown in **Table I**. Then compressing the powder mixtures with the help of hydraulic press in flat-faced tablets.

Tablets were then film coated (to prepare coated Ocular Inserts) with Eudragit RL 100 (RL) polymer solution.

### Physicochemical Characterization of the Drug Powder and Formulations

Techniques that were utilized in characterization of the original drug alone as well as the prepared spray dried powders, were X-ray diffractometry (XRD), Scanning electron microscope (SEM), Differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA), Fourier transform infrared spectroscopy (FTIR) and others.

| Formula No. | Amount of free drug (mg) | Amount of complexed drug (mg) | Amount of SD2 (mg) | Total tablet weight (mg) |
|---|---|---|---|---|
| F1 | 0 | 6.25 | 25 | 25 |
| F2 | 1 | 5.25 | 21 | 22 |
| F3 | 2 | 4.25 | 17 | 19 |
| F4 | 3 | 3.25 | 13 | 16 |
| F5 | 4 | 2.25 | 9 | 13 |
| F6 | 5 | 1.25 | 5 | 10 |
| F7 | 6.25 | 0 | 0 | 25 (Lactose 18.75 mg) |

**Table I:** Composition of ocular tablets formulas

### Microbiological Susceptibility Test Studies

The release of CFX-HCl from the drug delivery systems was investigated bacteriologically in agar plates seeded with *Staphylococcus aureus* 25925 (*S. aureus*), and *Pseudomonas aeruginosa* 27853 (*P. aeruginosa*) as the test microorganisms.
Using Mueller Hinton Agar plates.

### Sterilization

Spray dried powders (SD1 and SD2) and film coated ocular inserts (of F1 formula) were sterilized with the help of gamma radiation.

### Stability Studies

Accelerated stability studies were performed on spray dried powders (SD1 and SD2). Samples were withdrawn at different time breaks (at 0, 1, 2, three months) and analyzed for crystalline, thermal, and dissolution changes with time for around three months. Samples were even assessed for the content of the drug.

### In Vitro Release of CFX-HCl from Spray Dried Powders

Tablets of CFX-HCl or the spray dried products SD1 and SD2 were prepared by pressing 100 mg weight, in an intrinsic dissolution disks. Dissolution experiments were done in 900 ml of 0.9 % NaCl solution in deionized water at 37 $^{o}$C stirred under controlled hydrodynamics using intrinsic dissolution apparatus of surface area = 1 cm$^2$ operated at 50 rpm. Samples were analyzed using HPLC method of analysis.

### In Vitro Release of CFX-HCl From Uncoated and Coated Ocular Inserts

The inserts were placed into opened dissolution baskets using Erweka-Dissolution apparatus in 500 ml of normal saline thermo stated at 37 ± 0.5 $^{o}$C, stirred under controlled hydrodynamics by a paddle operated at 50 rpm. Samples were withdrawn at separate time intervals for 24 hours and analyzed using HPLC method.

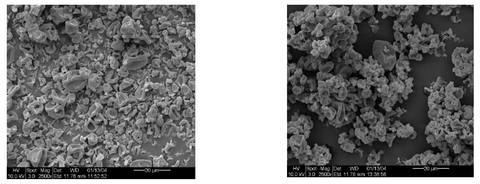
## Results and Discussion

### Physical Properties

FTIR revealed an interaction between XG and CFX-HCl. This interaction is due to chelation between the C=O of the 4-oxo-quinoline moiety and COOH of the CFX-HCl with the ½ $Ca^{++}$ and 0.1% $Mg^{++}$ of the hydrophilic polymer XG.

The XRD pattern of the crystal form of CFX-HCl is characteristic of the crystal form with distinctly different peak positions. While, the XRD patterns of CFX-HCl SD and SD1 and SD2 spray dried matrix systems indicate the amorphous character of all compounds upon spray drying.

SEM photomicrographs of SD1 and SD2 matrix systems are mentioned in **Figure I**. The particles possess spherical amorphous rather than crystalline shape, smooth surface and a size below 6 µm.



(a) (b)

**Figure I:** SEM photomicrographs for SD1 (a) and SD2 spray dried matrix systems (b).

### Antimicrobial Activity Studies

Formulations were considered useful against *P. aeruginosa* and *S. aureus*.

### Sterility Tests

The ocular inserts tested met the USP requirements of the test for sterility.

### Physical and Chemical Stability of the Spray Dried Powders

Accelerated stability studies at raised humidity and temperature levels showed no important alterations in the physical characteristics of the SD2 system. The spray-dried powder could be safely stored at study storage circumstances. But, the temperature of storage below 40 $^{o}$C and moisture proof packing are suggested to guarantee formulation's stability.

The degradation rate constant for formulations with PG (SD2) and without PG (SD1) were found to be 1.4994 X $10^{-4}$ and 2.9041 X $10^{-4}$ day$^{-1}$, respectively. As total degradation is below 5%, a tentative shelf life of two years (666.927 day) can be given to the SD2 formulation according to ICH guidelines (International Conference on Harmonization (ICH).

### In-Vitro Release Characterization of the Spray Dried Systems

The results of intrinsic dissolution testing showed that the release of CFX-HCl form SD1 and SD2 spray dried systems is very slow during the first 4-5 hours, while it increases rapidly later until reaching a plateau, dissolution profiles of SD1 and SD2 systems are suggesting sustained release behavior, **Figure II**. Spray dried matrix systems without PG (SD1) and with PG (SD2) released 90.01% and 98.04% of drug, respectively, over 26 hour time period during the dissolution studies.

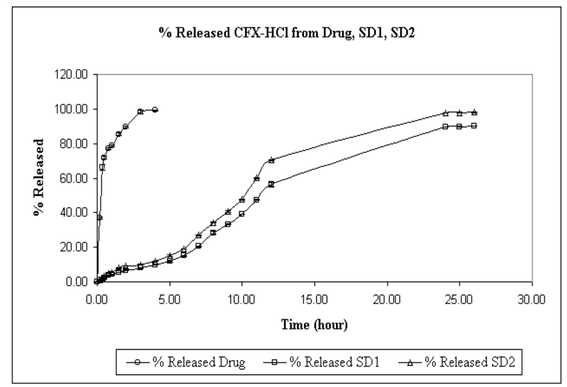



**Figure II:** Average percent released of CFX-HCl from SD1, and SD2 spray dried matrix system in 900 ml of 0.9% NaCl at 37 $^{o}$C and 50 rpm. compared to the release from a disk containing CFX-HCl alone.

## Conclusion

The present study displayed drug's sustained release in the in-vitro researches over a lengthy period. Product's shelf life having PG was analyzed to be above two years. These systems that are physically and chemically stable, display assurance of huge therapeutic benefits in the management of conjunctivitis and corneal ulceration.

In particular, the device based on F1 formula (composed of free CFX-HCl 0 mg: spray dried matrix system (SD2) 25 mg) (SD2 composed of XG 1: C-934 1: PG 1: CFX-HCl 1) exhibited a profile typical of a controlled delivery system. This device could give a helpful concentration of the drug over days, with a decreased application numbers.

## References

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