RESEARCH PAPER

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Betacyclodextrin for improved Stability and Delivery of Anti- Infective Drugs

D.B. MARTIN and N. UDUPA*
College of Pharmaceutical Sciences, Kasturba Medical College, Manipal

Betacyclodextrin inclusion complexes of ciprofloxacin, norfloxacin and tinidazole are prepared and incorporated in ocular implants to try as sustained release ocular preparations of anti-infectiove drugs for prolonged use. It is found that the stability of drugs improved after complexation. The release characteristics are also better. The ocular preparations may be very useful for treating ophthalmic ailments due to infection requiring chronic treatment with anti-infective drugs.

NOVEL drug delivery systems are designed in order to overcome various drawbacks of conventional formulations and having improved patient compliance and better therapeutic efficacy. The conventional eye medications suffer from problems like frequent medication, dilution and drainage of meciation by tears and nasolacrimal secretions, rapid reduction in the drug level, reduced bioavailability, massive and unpredictable dosage etc. Prolonged ocular contact and controlled drug release in tear fluid were shown to increase ocular bioavailability of certain drugs. Opthalmic inserts manufactured with alginate salts, polyvinyl pyrolidone (1), modified collagen (2,3) and hydroxypropyl cellulose (4,5) allow the prolonged drug release of drugs.

Improved stability of antiinfectives was reported after forming inclusion complexes. The stability aspect of these antiinfectives will be discussed elsewere. The present study was attempted with an aim to determine the release characteristics and therapeutic efficacy of the implants containing antiinfectives such as ciprofloxacin hydrochloride, norfloxacin and tinidazole complexed with β cyclodextrin (BCD). The BCD complex of these antiinfectives were used in order to improve the stability of drugs in the implants.

*For Correspondence

MATERIALS AND METHODS

Drug Betacyclodextrin Complex Preparations were tried using

a) Neutralization method for CIP/NOR BCD complex and

b) Kneading method for tinidazole BCD complex.

Equimolar concentrations of NOR/CIP and BCD (1:1 M-106.45 mg of NOR and 378.35mg BCD:122.60mg of CIP and 378.35mg of BCD) were separately dissolved in 0.1N NaOH, mixed and stirred for about half an hour. pH was recorded and 0.1N HCl was added dropwise while stirring until the pH reached 7.5, where in the complex precipitates. The residue was filtered and washed until it was free from chloride ions. It was dried at 25°C for 24 hrs and stored in a desicator.

Equimolar concentration of Tinidazole and BCD (1:1M; 62.43mg of Tinidazole and 378.35 mg of BCD) were taken in a mortar and mixed thoroughly. Small quantities of water was added while triturating to get a slurry like consistency. The trituration was continued for 1 hr. The slurry was later dried at 25°C for 2 days in dark and stored in the desicator.

Sustained release film sheets were prepared using ethyl cellulose and HPMC (50 cps) along with PVP, drug and solvent. The matrix was weighed accurately and dissolved in sufficient quantity of ethyl alcohol to obtain a viscous solution. The drug was then dispersed uniformly in the viscous solution by continuous, thorough mixing. The resulting mass was poured in a glass mould lined with aluminium foil. Ethyl alcohol was allowed to evaporate. The dried film was then cut into pieces of required size (0.4 x 0.3 cm) containing 2mg of drug per strip.

In all these formulations, the drug to polymer ratio was kept constant (1:3)

Compositon of Implants:

Drug/BCD Complex (equivalent to drug)	120 mg
Ethyl cellulose	250 mg
HPMC (50 cps)	110 mg
PVP K-30	7.2 mg

For **In vitro** drug release from Implants sets of 5 strips were placed in vials containing 5 ml of Phosphate buffered Saline (pH 7.4). The stoppered vials were closed and incubated at 37°C for a period of 14 days. The samples (1ml of solution) were withdrawn on 1st, 3rd .... 14th day, which were replaced by 1 ml of fresh buffer each time.

Samples were analysed for drug content, spectrophotometrically after appropriate dilution. A blank solution was used for which the same proporation of polymer without drug was taken. **Table 1.**

The films was tested for drug release pattern in the ophthalmic cavity of rabbit. Six Albino rabbits were chosen. One film each was placed below the upper eye lid into both the eyes. The films were then taken out at specified time intervals upto 8 hours. The drug content in films was determined spectrophotometrically. **(Table-2).**

RESULTS AND DISCUSSION

The release rate of the drug from the implants containing drug alone and drug-BCD complex were almost identical in case of tinidazole. However, in the case of norfloxacin and ciprofloxacin implants, the release of the drug from its BCD complex was much greater compared to that from drug-only implants. The drug released from the implants containing plain norfloxacin was about 23.5%, where as 75% of norfloxacin was released from the implants containing the norfloxacin BCD complex at the end of 14 days.

Similarly 15.4% of drug was rleased from the plain ciprofloxacin implants, whereas about 51.7% of ciprofloxacin was released from the implants containing the ciprofloxacin BCD complex at the end of 14 days (Table 1,2.)

In case of tinidazole as the relase from the implants containing plain drug and complex are almost identical, it indicates that the complexation of tinidaxzole with BCD had least effect on the release of drug from the implants.

In case of ciprofloxacin and norfloxacin BCD complexation, increases the release of the drug from the implants. From the earlier studies on the same drugs, it was reported that the dissolution of norfloxacin and ciprofloxacin from the complex (1:1 M) was higher than that obtained with the plain drugs. This was due to enhanced aqueous solubility of the complex compared to the plain drug. This increased solubility contributed by the BCD has increased the release of drug from the complex at pH 7.4.

The **in vivo** release studies in rabbits also showed an increased relase of these drugs from their BCD complex compared to the plain drugs. On the other hand, there seemed to be no effect of complexation of tinidiazole with BCD, as is evident from the **in vitro** release profile of the ocular implantable dosage forms.

Table-1 In Vitro Release Pattern of Drugs from Implants

Time	Cumulative amount of drug released (mcg)					
	Trnidazole		Ciprofloxacin		Norfloxacin	
days	Plain	Complex	Plain	Complex	Plain	Complex
01	0840.0	0691.9	0109.0	1021.5	0230.0	0800.4
03	3757.5	3975.0	1302.8	4494.7	1715.0	5145.9
06	4032.5	4119.7	1272.8	4167.8	2075.0	6471.6
10	4432.5	4338.6	1182.8	4249.5	2305.0	7089.0
14	3937.5	4250.4	1537.8	5168.9	2345.0	7500.7

Table-2 In Vivo Release Pattern of Drugs from Implants into Rabbit Ophthalmic Cavity

Time	Amount of drug remaining to be released (mcg)					
	Trnidazole		Ciprofloxacin		Norfloxacin	
hours	Plain	Complex	Plain	Complex	Plain	Complex
0	1780.0	1780.0	1816.0	1816.0	1855.0	1855.0
2	1760.0	1616.0	1800.0	1830.0	1848.4	1809.6
4	1764.0	1452.0	1788.0	1602.0	1848.4	1765.2
8	1750.0	1490.0	1780.0	1730.0	1824.4	1684.0

The improved stability of drug BCD complexes under sunlight and at 45°C was noticed for above antiinfective drugs (**Table- 3**). Any symptom of eye irritation was not observed in rabbits during the studies.

Table-3 Degradation Rate Constant (K x 10^{-4} days $^{-1}$) for Antiinfective drugs

Drugs	Plain	Complex
Under 45°C	3.838	1.790
Under sunlight	20.471	2.712
Ciprofloxacin at 45°C	3.838	1.535
Under Sunlight	17.912	2.584
Tinidazole at 45°C	7.677	5.370
Under sunlight	102.355	8.960

CONCLUSION

As per the **in vitro** studies an effective opthalmic thereapy may be possible by a single ocular implant of anti-infective drugs like cirpofloxacin and norfloxacin after incorporating the inclusion complexes of these drugs. The betacyclodextrin inclusion complex may help to improve stability of antibiotics and the improve the release characteristics. Clinical investigations evaluating the feasibility of the prep-

aration for ophthalmic anti-infective therapy are in progress.

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