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EVALUATION OF FEW CIPROFLOXACIN (CIP) AND NORFLOXACIN (NOR) FORMULATIONS

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ABSTRACT

Formulations containing ciprofloxacin hydrochloride and norfloxacin for the treatment of ophthalmic and skin infections were made. The stability, bioavailability and therapeutic efficacy of the preparations were evaluated. These antibiotics were not systematically absorbed, when applied locally. Preparations were found more effective for the treatment of skin and eye infections. Betacyclodextrin improved the bioavailability of antibiotics.

INTRODUCTION

Ciprofloxacin (CIP) was the most potent quinolone antibacterial against Enterobacteriacea and Pseudomonas and was effectively used in the treatment of many infectious diseases.[1,2] Norfloxacin was used in the treatment of urinary tract infections, gonorrhoea, gastrointestinal and other infections.[2,3] So far only tablets, capsules and injections of CIP and NOR were used in therapy. An attempt was made to formulate preparations of CIP and NOR as ophthalmic and ointment preparations in suitable gel type of bases. Efforts were also made to improve the efficacy of drugs using suitable carriers. Albumin microsphere was also used as a drug carrier for administration of many drugs with better efficacy. Various methods of preparing microspheres were explained by many investigators.[4-6] Bioavailability of many drugs improved using cyclodextrin in formulations. Solubility of drugs was increased by complexation with it.[7] The bioavailability, therapeutic efficacy and stability aspects of preparations were investigated in this study.

METHODS AND MATERIALS

0.5% CIP and 0.5% NOR were incorporated in gel bases of following having suitable consistency separately.

Sodium Alginate (SA - 12.2% w/w), Methyl Cellulose (MC - 3.8% w/w) Carboxy Methyl Cellulose (CMC - 4.3% w/w), Guar Gum (GG- 1.96% w/w), Hydroxy Propyl Methyl Cellulose (HPMC - 56% w/w).

0.5% CIP was also incorporated in ophthalmic preparations of suitable consistency as follows : Sodium Alginate (SA - 4.2% w/w), Methyl Cellulose (MC - 1.5% w/w), Carboxy Methyl Cellulose (CMC - 1.5% w/w), Guar Gum (GG - 0.74% w/w), HPMC (16.6% w/w).

Preparation of albumin microspheres (Alb micro)

1. Mixture of 2 ml of 20% albumin solution and 100 mg of drug was prepared. 2. Mixture of 8.5 ml of Arachis Oil and 0.1 ml of 0.5% Sodium Lauryl Sulfate in n-heptane was prepared. Mixture (1) was added to mixture (2) with stirring and kept in a water bath, temperature was gradually raised to 80°C, it was mixed thoroughly for 10 minutes, cooled to room temperature with stirring. To this mixture 0.02 ml of formaldehyde and 0.4 ml of n-hexane was added, filtered using whatman No. 1 filter paper, then residue was washed with 1 ml each of n-hexane and dried in vacuum desicator for 24 hours. 40% of CIP and 20% of NOR were entrapped in albumin microspheres.

Preparation of Beta-cyclodextrin - Drug Complex

Equal quantity of drug (0.5 gm) and betacyclodextrin (0.5 gm with sufficient quantity of water were mixed using magnetic stirrer for 2 hours. It was then incorporated with sufficient quantity of HPMC. The final preparation contains 0.5% of drug and 56% of HPMC.

Stability study

Stability study of preparations were conducted under two different temperatures for 8 weeks at room temperature (RT) and 37^{o}C.

Bioavailability study of CIP and NOR

For oral administration vehicle containing 5% drug was used. The rats were divided into 3 groups. One group received orally 1 ml of 5% of CIP/NOR in 4% HPMC solution. The second group received 1 ml of alb. micro preparation containing 5% CIP/NOR dispersed in 4% HPMC solution. The third group received 5% drug incorporated along with 5% betacyclodextrin in 4% HPMC vehicle. Blood samples were collected from eye using capillaries, at different time intervals. Blood was centrifuged and plasma sample was collected and analysed by microbiological method (disc

diffusion method). In transdermal preparation, gel was applied to the 1 cm^2 area on the back of the rat which is already shaved prior to the application of gel.

Study of local action on skin and eye

The ointment containing drug (CIP/NOR) was applied to the wound made on rat for 1 week, to study the effect of drug on local infection. The eye preparation containing CIP was applied to eye infected with nonpathogen and swab was collected from treated eye and untreated eye, inoculated in nutrient broth and incubated for 24 hrs.

RESULTS AND DISCUSSION

CIP and NOR were more stable in HPMC base (Table 1) compared to other bases. Bioavailability of CIP and NOR was improved when administered orally with betacyclodextrin ($p < 0.05$) and lowered when drug was entrapped in albumin microspheres, compared to free drug ($p < 0.05$). Drug was not detected in measurable quantity in the plasma by microbiological method when applied locally on the skin (Table 2). The healing of local infection of wounded rat was better in treated group. There was no growth in media inoculated with swab collected from rat eye infected with nonpathogen and treated with drug

TABLE 1 : STABILITY STUDY DATA FOR CIP AND NOR (RATE CONSTANT AND % DEGRADED IN GEL BASES AND OPHTHALMIC PREPARATIONS AT 37°C

Bases	For CIP		For NOR		Ophthalmic Solutions for CIP	
	K days^{-1}	% degraded	K days^{-1}	% degraded	K days^{-1}	% degraded
HPMC	1.15	61.86	0.93	62.76	0.95	69.54
MC	1.14	81.28	1.38	85.72	0.97	75.11
CMC	2.23	84.93	2.27	86.98	2.13	83.22
SA	1.25	64.12	1.11	67.50	1.22	79.90
GG	2.24	88.49	1.98	76.28	1.12	75.59
TP	1.96	82.27	1.21	81.33	-	-

TABLE 2 : PHARMACOKINETIC DATA FOR CIP AND NOR ADMINISTERED ORALLY IN HEALTHY RATS

Preparations	K_{eL} hr^{-1}		Elimination half life hr		AUC^{0-} ug/ml/hr		Cp ug/ml±S.D. plasma peak concn.	
	CIP	NOR	CIP	NOR	CIP	NOR	CIP	NOR
Drug in HPMC	11.89	0.42	0.06	1.64	20.66	19.79	4.89 ±0.18	4.07 ±0.09
Drug in alb. micro incorporated	14.63	19.62	0.05	0.04	10.97	12.04	1.99 ±0.27	2.29 ±0.30
Drug with betacyclodextrin in HPMC	0.23	14.23	2.96	0.05	28.14	24.22	5.89 ±0.16	4.46 ±0.09

All the cases the peak concentration reached at 3rd hour.

preparation. Growth was observed in media inoculated with swab collected from untreated group. Thus the preparation was effective for treatment of ophthalmic infections.

CONCLUSION

CIP and NOR were most stable in HPMC base compared to other gel preparations. Bioavailability of CIP and NOR was better when they were incorporated with betacyclodextrin. Bioavailability decreased when drugs were entrapped with albumin microsphere, which may be due to binding. They were not systemically absorbed when applied locally. The preparations were found to be more effective locally for the treatment of skin and eye infections.

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