Formulation of Some Drugs to Improve their Bioavailability Using Different Ophthalmic Delivery Systems

Thesis presented by
Saeed Abdul Kareem Saeed AL- Zuhairy
B. Pharm. Baghdad University (2005)
Submitted in Partial Fulfillment for the Master Degree in Pharmaceutical Sciences (Pharmaceutics)

Under the Supervision of

Prof. Dr. Abd EL-Gawad H. Abd EL-Gawad
Professor of Pharmaceutics
Faculty of Pharmacy; Mansoura University

Prof. Dr. Osama Abd EL-Azeem Soliman
Professor of Pharmaceutics
Faculty Pharmacy; Mansoura University

2016
Abstract

Today, topical ophthalmic application is considered as the desired way to achieve the therapeutic level of the drug to treat the ocular diseases. The drugs administered topically to the eye are rapidly absorbed at the desired site of action to exert their therapeutic effect. Bioavailability of ocular drops ranges from 1 to 10% of the total administered dose due to the rapid clearance resulting from reflex tearing and blinking. The viscosity increasing agents are used to increase the viscosity of the ophthalmic preparations, leading to increase drug bioavailability by two ways; increase the drug ocular residence time and decreasing the drainage rate. Also, the polymers have a lubricating effect on the eye tissues.

Hence, the work in this thesis deal with the formulation of certain ophthalmic preparations including ophthalmic drops, microemulsions, gels, in-situ gels and ocuserts using different drug carriers. In-vitro release characteristics and in-vivo study has been carried out on some selected formulae to ensure the ocular availability of the drug in eye tissues. In this thesis, two drugs were selected; the first drug was econazole nitrate (antifungal agent) and the second one was moxifloxacin hydrochloride (antibacterial agent).

The thesis includes the following two parts:

PART I

Formulation and Evaluation of Ophthalmic Preparations Containing Econazole Nitrate

The work in this part was carried out to investigate the formulation, release characteristics and ocular bioavailability of econazole nitrate from ophthalmic drops, gels and ocuserts, this part includes the following two chapters:
Chapter 1

Preparation and In-vitro Evaluation of Econazole Nitrate Cyclodextrin Complexes from Different Ophthalmic Preparations

This chapter deals with the study of preparation of inclusion complexes of econazole nitrate (EC) with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin. Characterization of the complexes was performed using fourier transform infrared spectroscopy (FT-IR), differential scanning calometry (DSC) and powder x-ray diffraction (PXRD). Also, the formulation of different ophthalmic preparations as; drops, gels and ocuserts containing econazole nitrate-cyclodextrins complexes were investigated. The different polymers used in this study; methylcellulose (MC), carbopol 940 (CP 940) and hydroxylpropyl methylcellulose (HPMC). The characterizations of the prepared formulae were performed through the determination of drug content, pH, viscosity and in-vitro characteristics. Then, the release data were analyzed mathematically using variable kinetic orders and mathematical models. From the obtained results, it was evident that:

Econazole nitrate cyclodextrins complexes was successfully formulated as drops, gels and ocuserts using different polymers combinations. The solubility and the rate of drug release improved by complexation with β-CyD or HP- β-CyD. Furthermore, HP- β-CyD has a higher solubilizing effect for EC than β-CyD. The amount of drug released from different formulations, is varied according to complex types, polymer types and dosage forms. The amount of the drug released from eye drops and gels were higher than that released from ocuserts. Generally, the tested formulations were arranged in the following order; eye drops > eye gels >
Ocuserts. Mathematical analysis of the release data revealed that, the release of drug from the different ophthalmic formulations was a combination of two mechanisms, higuchi model followed by zero-order model or first-order model, in which one is more predominant than the other.

Chapter 2

Bioavailability of Ophthalmic Formulations Containing Econazole Nitrate Cyclodextrin Complexes

This chapter deals with the study of the effect of vehicle, dosage form and complexation of the drug with cyclodextrins on the uptake of econazole nitrate by eye tissues and aqueous humor of rabbits, at different time intervals after instillation of the selected ophthalmic preparations.

The obtained results showed that, the peak time for maximum concentration of the drug from tested formulations in eye tissues and aqueous humor after instillation in rabbit's eyes was 3 hrs for eye drops, eye gels and ocuserts. In all ophthalmic preparations, econazole nitrate was available in cornea in a higher concentration than in conjunctiva. While iris-ciliary body and aqueous humor at all time intervals showed low drug concentration. The entire bioavailability of econazole nitrate when prepared as complex with HP-β-CyD was improved more than that complexed with β-CyD. Regarding the ocular bioavailability of the drug from the tested formulations, it can be arranged in the following order; EC-HP-β-CyD > EC-β-CyD > EC alone, respectively.

PART II
Formulation and Evaluation of Ophthalmic Preparations Containing Moxifloxacin Hydrochloride

The work in this part deals with the formulation of moxifloxacin hydrochloride in different ophthalmic preparations; microemulsions, \textit{in-situ} gels, and ocuserts. Also, to investigate the release characteristics and ocular bioavailability of moxifloxacin hydrochloride from different ophthalmic formulations, this part includes two chapters:

Chapter 1

Preparation and In-vitro Evaluation of Moxifloxacin Hydrochloride from Different Ophthalmic Preparations

In this chapter three different ophthalmic forms were prepared; microemulsions, \textit{in-situ} gels and ocuserts, containing 0.5\% moxifloxacin hydrochloride. The different polymers were used as; sodium carboxymethylcellulose (sod. CMC), hydroxypropyl methylcellulose (HPMC), chitosan, polyvinylpyrrlidon (PVP) and sodium alginate polymers. The characterizations of the prepared formulae were performed through the determination of drug content, pH, viscosity and \textit{in-vitro} release behavior. Then, the release data were analyzed mathematically using variable kinetic orders and mathematical models.

From the obtained results, it was evident that: moxifloxacin hydrchloride 0.5 w/v \% was effectively formulated as microemulsions, \textit{in-situ} gels and ocuserts using different polymers combinations. The amount of drug released from different formulations, it was found that, the drug release is varied according to; polymer types and dosage forms. The amount of the drug released from eye microemulsions, \textit{in-situ} gels were higher than that released from ocuserts. Generally, the amount of the drug released from the tested formulations were arranged in the following order;
Abstract

Microemulsions > \textit{in-situ} gels > ocuserts. Analysis of the release data revealed that, the drug release mechanism of moxifloxacin hydrochloride from the different ophthalmic formulations was a combination of two mechanisms, higuchi model followed by zero-order model, in which, one is more predominant than the other.

Chapter 2

Bioavailability of Ophthalmic Formulations Containing Moxifloxacin Hydrochloride

This chapter deals with the study of the effect of polymers and dosage form of the drug on the uptake of moxifloxacin hydrochloride by eye tissues and aqueous humor of rabbits, at different time intervals after instillation of the selected ophthalmic preparations. The obtained results showed that, the peak time for maximum disposition of the drug from selected formulations in eye tissues and aqueous humor after instillation in rabbits eyes was 2 hrs for microemulsions, \textit{in-situ} gels and ocuserts. In all ophthalmic preparations, moxifloxacin hydrochloride was available in conjunctiva in a higher concentration than in cornea. Additionally, iris-ciliary body and aqueous humor showed low drug concentration. Regarding the relative bioavailabilities of ocuserts were higher than that of \textit{in-situ} gels and eye microemulsions, respectively.