بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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Optimization of an ocular formulation for treatment of Glaucoma

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والحمد لله رب العالمين.....

Ayman Ismail

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%	Percent
%RSD	Percent relative standard deviation
%v/v	Percent volume per volume
ºC	Celsius degree
ACG	Angle closure glaucoma
ANOVA	Analysis of Variance
AUC	Area under the curve
CAI	Carbonic anhydrase inhibitors
cm	Centimeter
C_{max}	Maximum concentration reached
COPD	Chronic obstructive pulmonary disease
EIP	emulsion inversion point
EMA	European Medicines Agency
FDA	Food and drug administration
g	Gram
h	Hour
HPLC	High performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
ICH	International conference on Harmonization
IOP	Intraocular pressure
Kg	Kilogram
LC	Liquid chromatography
LOD	Limit of detection
LOQ	Limit of Quantitation
M.wt	Molecular weight
mg	Milligram
µg	Microgram
min	Minute
ml	milliliter
µl	Microliter
µm	Micrometer
mm	Millimeter

mV	Millivolt
N	Normal
NDA	New drug application
nm	Nanometer
O/W	Oil in water
PDI	Polydispersity index
PIT	phase inversion temperature
PK/PD	Pharmacokinetic/Pharmacodynamic
r	Correlation coefficient
RGC	Retinal ganglion cells
RPE	Retinal pigmented epithelium
Rpm	Rotations per minute
SD	Standard deviation
STF	Simulated tear fluid
TEM	Transmission electron microscope
T_{max}	Time needed to reach maximum concentration
UK	United Kingdom
USA	United states of America
USP	United states pharmacopoeia
UV	Ultraviolet
W/O	Water in oil
w/v%	Weight per volume percent
WHO	World health organization
ZP	Zeta potential

Abstract

Optimization of an ocular formulation for treatment of Glaucoma

Glaucoma is a complex ocular disease that is mainly characterized by increased intraocular pressure (IOP) which may lead gradually to optic neuropathy and gradual loss of sight. Different types of glaucoma had been identified which are caused by multiple causes. Several treatment options have been widely used through the conventional ocular delivery routes such as topical instillation. The conventional delivery routes encounter some drawbacks such as reduced residence time and ocular bioavailability. Multiple attempts were made to overcome these drawbacks through utilization of novel ocular delivery systems such as nanoemulsions. Travoprost is one of the emerging synthetic prostaglandins that showed high efficacy in reducing IOP through increasing outflow of aqueous humor from the eye structure. Hence, it was chosen in the current thesis to be incorporated into oil-in-water (O/W) nanoemulsion for ocular delivery.

The aim of the first chapter was to formulate and characterize different nanoemulsion formulations using different types and concentrations of oils and a surfactant. The formulations were visually examined for their appearance, and the formulations which showed suitable nanoemulsion appearance proceeded for further characterization. The selected formulations were characterized for particle size, polydispersity index, zeta potential, pH, refractive index, and travoprost content. The *in vitro* cumulative release was assessed in comparison to the marketed drug product. The stability of the formulations was monitored through assessing the change in particle size, polydispersity index, zeta potential, and travoprost's content when stored at 25ºC for 3 months. The best formulation was selected for further characterization studies. The effect of sterilization on the best formulation was studied through assessing the difference in travoprost's content and formulation particle size after sterilization by filtration. The best formulation was also examined using transmission electron microscope (TEM). The trials resulted in successful preparation of five stable formulations using Labrafac

Lipophile® oil and Tween 80 as a surfactant. The characterization of these five formulations showed particle size ranging from 157 to 291 nm, polydispersity index ranging from 0.26 to 0.56, and zeta potential ranging from -8.12 to -16.6 mV. Refractive index and pH measurements showed acceptable values that indicated good ocular tolerability without visual blurring tendency. Travoprost's content values ranged from 98.47% to 100.42%. The *in vitro* cumulative release results showed sustained release over 8 hours, on the contrary to the marketed drug product which showed immediate release. Characterization of the selected formulation after 3 months stability storage showed acceptable results with no significant change in particle size, polydispersity index, zeta potential, and travoprost's content. The selected best formulation showed spherical morphology upon TEM examination with no change in travoprost's content or particle size after sterilization by filtration. The best formulation was selected for further *in vivo* studies.

In the second chapter, the selected formulation and the marketed drug product were tested for ocular irritation and histopathological changes of rabbits' eyes to assess their ocular tolerability. The extent of IOP reduction was studied for both groups. The *in vivo* pharmacokinetic behavior of travoprost was studied by quantification of travoprost in aqueous humor of rabbits' eyes after instillation of the best formulation in comparison to the marketed drug product. Results showed no ocular irritation from the best formulation and the marketed drug product. Histopathological examination demonstrated no changes in both groups. The pharmacokinetics results showed significant increase in C_{max} and AUC values after administration of the best formula compared to the marketed drug product.

The approach presented in this thesis showed very promising results in improving the ocular bioavailability of travoprost.

Keywords: Glaucoma, travoprost, nanoemulsion, pharmacokinetic, stability.