hossam maghraby

شبكة المعلومات الجامعية

بسم اللّه الرحمن الرحيم

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التوثيق الالكتروني والميكروفيلم

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التوثيق الإلكتروني والميكروفيلم

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بالرسالة صفحات
لم ترد بالأصل

Formulation and Availability of Timolol in Certain Ocular Drug Delivery Systems.

Thesis Presented

By

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Presented for the master degree in pharmaceutical sciences (pharmaceutics)

Under the supervision of

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2003

﴿قالوا سبحانك لا علم
لنا إلا ما علمتنا إنك أنت
العليم الحكيم﴾

صدق الله العظيم

سورة البقرة "آية ٣١"

Acknowledgment

First of all, prayful thanks to our merciful god, who supported me throughout this whole work.

It is with great honor that I take this opportunity to record my deep gratitude and appreciation to Prof. Dr. Mohammed Aly Kassem, professor and head of the department of pharmaceutics and industrial pharmacy, faculty of pharmacy, Cairo University. His continuous advice, valuable suggestions, precious instructions, indispensable help, and great encouragement have been of great value throughout this work.

I would like also to express my reflective appreciation to Dr. Abla Abdelmaaboud, Ass. Prof. of pharmaceutics and industrial pharmacy, faculty of pharmacy, Cairo University.

I would like to extend my deep cordial thanks to all the teaching staff members and to all my colleagues in the department of pharmaceutics and industrial pharmacy, faculty of pharmacy, Cairo University, for their sincere help and kind support.

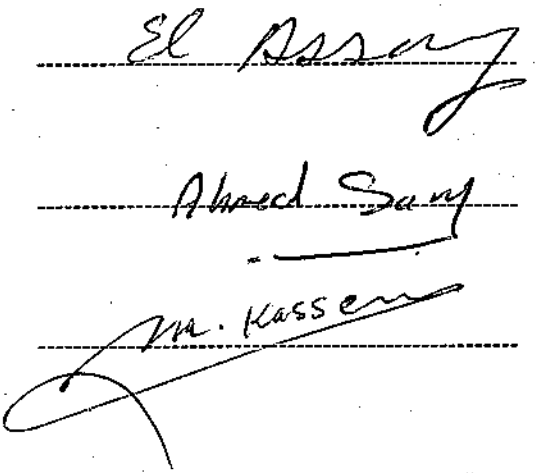
Finally, no words could ever express my profound appreciation and sincere thanks and gratefulness to my dear mother, father, sister and brother and my whole family and friends for their endless help, support and encouragement.

To all of you, thank you.

Rania Hassan Fahmy

Approval Sheet

Approved By:



(Committee in charge)

Date: / / 2003

Part II

Preparation and evaluation of timolol maleate ophthalmic gels.

Part III

In-vivo pharmacodynamic evaluation of timolol maleate ophthalmic formulations

Abstract

Abstract

Traditionally, topical drug delivery is preferred in the eye to avoid under and over medication and undesired side effects of systemic administration. Nevertheless, conventional eye drops deliver drugs in a pulsatile fashion that is called "pulse entry effect". Additionally, ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations such as, the poor corneal penetration due to the hydrophobic nature of the upper epithelial layers of the cornea, rapid nasolacrimal drainage, nonproductive absorption through the conjunctiva, and complex tear fluid dynamics.

To achieve effective ophthalmic therapy, an adequate amount of the active ingredient must be delivered and maintained at its site of action within the eye. Therefore, here arises the value of formulating controlled drug delivery systems to the eye.

Nanoparticles as drug carriers have attracted more and more interest in the last decade. The major goal in employing nanoparticles was the controlled and sustained-release of the pharmacologically active agent to the specific site of action are the therapeutically optimal rate and dose regimen and therefore provide increased drug efficacy, reduced toxicity and prolonged therapeutic activity.

Studies that have investigated the potential of nanoparticles for ocular drug delivery have shown several promising results compared to conventional ocular dosage forms.

Glaucoma is one of the most serious ocular diseases; it is frequently asymptomatic at the time of diagnosis, but it can result in progressive visual field loss and eventual blindness.

Timolol maleate, a non- selective beta- adrenergic blocking agent, represents one of the most significant advances in the topical treatment of glaucoma. Timolol maleate administered directly to the eye as ophthalmic drops appears to be rapidly absorbed, producing a decrease in the intra-ocular pressure through the reduction of the aqueous humour formation rate.

It is evident that the possibility of introducing an efficient anti-glaucoma agent such as timolol maleate in a sustained release formulation will help a lot in the effective treatment of glaucoma with minimum side effects and the prophylaxis against long term complications associated with glaucoma and ocular hypertension.

Therefore, the work in this thesis aimed to formulate timolol maleate in prolonged action dosage forms such as, timolol maleate-loaded nanoparticles and gels.

The work in this thesis is divided into three main parts:

Part I: Preparation and evaluation of timolol maleate loaded ocular nanoparticles.

This part is divided into two chapters:

Chapter 1: preparation and *in-vitro* evaluation of timolol maleate ocular nanoparticles using fixed Eudragit S-100 concentration and different polyvinyl alcohol (PVA) concentrations.

Chapter 2: preparation and *in-vitro* evaluation of timolol maleate ocular nanoparticles using various Eudragit S-100 concentrations and fixed polyvinyl alcohol (PVA) concentration.

Part II: preparation and evaluation of timolol maleate ocular gel.

Part III: *In-vivo* pharmacodynamic evaluation of timolol maleate ophthalmic formulations.

Part I

Preparation and evaluation of timolol maleate loaded ocular nanoparticles.

In this part of the thesis, our aim was to utilize the salting out procedure for the preparation of timolol maleate-loaded nanoparticles using **either** various concentrations of *Polyvinyl alcohol* as the water-soluble stabilizer and protective polymer added to the aqueous phase (chapter one) **or** different concentrations of *Eudragit S-100* as the polymer used in the organic phase to form the nanoparticles (chapter two). Then, the produced nanoparticles were evaluated for drug loading capacity, particle size, morphological characters of the prepared nanoparticles, and drug release profile in order to select the best formulae.

Chapter 1: *Preparation and in-vitro evaluation of timolol maleate ocular nanoparticles using fixed Eudragit S-100 concentration and different polyvinyl alcohol concentrations.*

The work in this chapter include the formulation of timolol mlaeate-loaded nanoparticles, using constant concentration of *Eudragit S-100* (17%) as the nanoparticle-forming polymer and various concentrations of *polyvinyl alcohol* as the water-soluble protective stabilizing polymer; namely, 1, 2, 3, 4, and 6%, and utilizing the salting- out procedure.

First, the prepared nanoparticles were analysed using differential scanning calorimetry (DSC) in order to characterize the physical state of timolol maleate in the nanoparticle colloidal system. However, in the thermograms obtained for the loaded nanoparticles, the endothermic peak of timolol maleate was not detected, a fact that establishes the formation of a molecular dispersion of timolol maleate inside the nanoparticles.

The viscosity measurements of the nanoparticle suspensions prepared at different pH values revealed that the dispersion, buffered to pH 7.4, has the highest viscosity over all

other pH ranges. Consequently, the pH 7.4 was selected as the most suitable pH at which the suspension can be prepared.

The nanoparticles were studied for their drug loading capacity, morphological characters of the prepared nanoparticles, particle size analysis, and drug release pattern in order to select the best prepared formula.

The actual drug loading into the nanoparticles was determined by two methods, the crushing method and the extraction method. The loading efficiencies observed with the crushing method were higher than that of the extraction method; they were 12.38, 13.66, 18.41, 23.76, and 36.29% for 1, 2, 3, 4, and 6% PVA, respectively. Hence, the results indicated an increase in both the amount of drug loaded and the loading efficiency of the nanoparticles with the increase in the PVA concentration.

The inspected morphological characters of the prepared nanoparticles revealed that all the nanoparticles prepared were spherical in shape and non- aggregated.

The mean particle size of the nanoparticles prepared using different polyvinyl alcohol concentrations were measured using laser diffraction particle size analyzer. The results clearly demonstrated that increasing the concentration of the hydrocolloid (PVA) in the external aqueous phase leads to a consequent decrease in the particle size of the produced nanoparticles, this increase in PVA concentration with the consequent decrease in particle size was also associated with an expected increase in the specific surface area of the nanoparticles which could explain the increased drug loading efficiency associated with the increase in PVA concentration.

From the *In-vitro* release studies of timolol maleate from the commercial eye drops and the nanoparticles prepared using 1, 2, 3, 4, and 6% PVA concentrations, a slower release rate was observed for the timolol maleate-loaded nanoparticles than that observed for the commercial eye drops examined.

The release of timolol from its nanoparticles were slightly biphasic with an initial fast rate, which was probably due to the externally adsorbed drug onto the nanoparticles surfaces, then, another release phase which was attributed to the drug encapsulated inside the nanoparticles. Additionally, the *in-vitro* release of timolol from its nanoparticles was