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PH TRIGGERED IN-SITU OPHTHALMIC GEL CONTAINING NEPAFENAC: FORMULATION, CHARACTERIZATION AND IN VITRO DRUG RELEASE

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non – academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and my research.

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ABSTRACT

Amongst the different delivery methods to the eye, an *in-situ* forming hydrogel is considered as one of the most effective delivery methods. An *in-situ* forming hydrogel is a formulation that can undergo gelation in response to the variations in its external environment. The pH triggered *in-situ* ophthalmic gel systems have been widely investigated in regard to their spontaneity of gelation, gel system characterization, *in-vitro* drug release and ophthalmic compatibility. However the involved energetics and thermodynamics related to the phenomenon of sol-gel transition have been investigated sporadically. Hence the present study aimed to examine and elucidate the involved energetics and thermodynamics during the sol-gel transitions of carbopol in the presence of viscosity-enhancing agents such as Hydroxypropyl Methylcellulose (HPMC) and surfactant such as Benzalkonium chloride (BKCL). Using viscometric and conductometric titration, various concentrations of carbopol and carbopol-based solution systems in the presence of HPMC and BKCL were analyzed to determine the thermophysical parameters such as molar conductivity (λ), activation energy (E_s), enthalpy (ΔH), entropy (ΔS), Gibb's free energy (ΔH) and heat capacity (ΔC_p) of the systems. These parameters were discussed in terms of the phenomena of sol-gel transitions, emphasizing the effect of polymer concentration and the presence of co-excipients such as HPMC and BKCL. Based on the thermophysical experimentations, the suitable concentrations of carbopol, HPMC and BKCL was selected for use in the optimized formulation. The optimized formulation was achieved by incorporating buffering agents such as citric acid and sodium dihidrogen phosphate, and various concentrations of chitosan for added anti-microbial and mucoadhesive activity. The formulation optimization was carried out on the basis of parameters such as viscosity, surface tension and spontaneity of gelation. The pH adjustment was done by varying the concentration of sodium hydroxide and accordingly the suitable formulations were selected. The drug nepafenac was investigated as a model drug .The optimized formulations were further characterized for the *in-vitro* drug release study. The data related to drug release studies were treated using the release kinetic models and the optimized *in-situ* gel resulted in a controlled release (with a release index of 0.538 for F_{14}) of the candidate drug nepafenac.

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CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND OF STUDY

Ophthalmic drug delivery is one of the most interesting and challenging efforts for the pharmaceutical formulators. The eye possesses a special anatomic structure and very efficient protective mechanisms, as a result of which many challenges are presented during the formulation development stage. The tear flow and the blinking reflex remove foreign materials from the eye and maintain a good environment of the eye. However these protective properties also lead to an effective drainage of the drugs, when instilled into the eye. This causes low ocular bioavailability that is commonly less than 10% [1, 2, 3], owing to short ocular residence time resulting in a reduced therapeutic effect of the drug. The nasolacrimal drainage is another route for the drug to enter the circulatory system during topical administration. If the drug is potent, then the systemic exposure through nasolacrimal drainage after topical administration can cause systemic toxicity [4].

By increasing the viscosity of the vehicle, the drainage rate can be decreased and the residence time of the ophthalmic eye drop can be increased. This method only moderately affects the contact time of the drug. Though ointment provides long residence time, it is associated with a low patient compliance and only can be used at bed time. The ocusert i.e. ocular insert can also provide a long residence time that can deliver the drug at a desired rate for a prolonged period of time. In case of ocuserts, the patient compliance is low.

Gel systems are better retained in the eye than conventional eye drops and are better tolerated by patients than inserts and ointments. The use of preformed hydrogels has drawbacks that can limit their interest. They do not allow accurate and reproducible administration of drugs, and after administration, they often produce blurred vision, crusting of eye lids and lacrimation [5].

A new approach is to combine the advantage of both solutions and gels such as accuracy and facility of administration of the former and prolonged residence time of the latter. The *in-situ* gels can be instilled as eye drops and undergo an immediate transition in to gel as it contacts the eye. These *in-situ* gels are liquid upon instillation