بسم الله الرحمن الرحيم

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POTENTIATION OF PRESERVATIVE EFFICIENCY IN OPHTHALMIC PREPARATIONS

A Thesis

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CONTENTS

List of Abbreviations

BZ	: Benzalkonium chloride
PMA	: Phenyl mercuric acetate
MP	: Methyl paraben
PEA	: Phenethyl alcohol
CHB	: Chlorbutol
PMN	: Phenyl mercuric nitrate
CP	: Carbopol
PG	: Propylene glycol
EDTA	: Ethylenediamine tetraacetate
CMC	: Carboxymethyl cellulose
PVP	: Polyvinyl pyrrolidone
DMS	: Dimethyl sulphoxide

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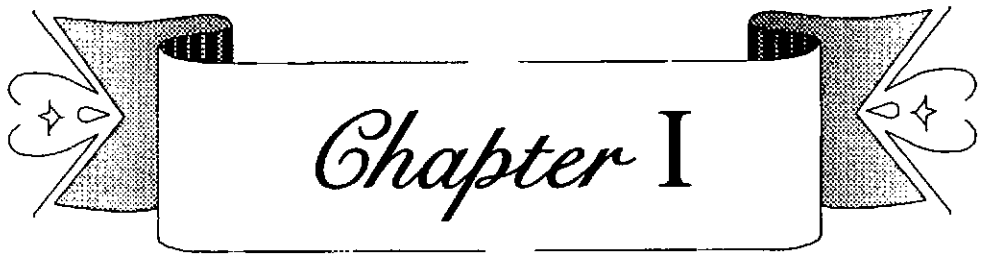

Chapter I

INTRODUCTION

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Over the course of the last decades, very few new antimicrobial preservatives have been introduced for use in parenteral and ophthalmic products. Toxicity considerations have restricted the application of those preservatives, which have been developed during this period, to the protection of topical products. It is therefore, becoming increasingly common for formulated medicines to be protected against microbial spoilage with a combination of preservatives rather than a single agent. Frequently, the reason for this change is because a single agent can not provide a sufficiently broad spectrum of antimicrobial activity. There is, however, also the need to achieve acceptable levels of product protection from the limited choice of available agents by capitalizing on potential synergistic interactions between preservatives, whilst at the same time minimizing the risk of adverse reactions by avoiding the use of unnecessarily high concentrations.

While the conditions of manufacture and microbiological quality of the active substances and excipients are responsible for the initial level of purity, the aim of preservation is to maintain this purity during the entire life of the preparation. This is particularly true in case of sterile preparations in multiple dose containers such as ophthalmic preparations and injections, where if any of them contains micro-organisms, they could be injurious to the health of the patient.[1,2]

The health hazard from contaminated pharmaceuticals which has attracted most notice is that arising from bacterial contamination of eye drops and ophthalmic solutions by Gram-negative bacteria, principally *Pseudomonas aeruginosa*.[3]

Several reports have established the widespread occurrence of this species in eye drops and have emphasized the danger of contamination by this organism which can cause eye damage and even loss of sight.[4,5] Upon entrance to the corneal epithelium, *Pseudomonas aeruginosa* can be totally destructive to the eye and will almost certainly cause rapid, severe and permanent damage. Even minute abrasion on the corneal surface can lead to corneal destruction when infected with this organism. This could happen because of the use of contaminated contact lenses or the application of contaminated mascara.[6] In addition, *Pseudomonas aeruginosa* may produce either necrosis of the sclera with thickening and marked inflammation of the underlying space, or multiple scleral abscesses containing organisms, or both.[7]

In 1963, Kohn *et al* investigated the antibacterial agents employed as preservatives in ophthalmic preparations. They concluded that there was a need for methods which would determine the effectiveness of :

a. Antibacterial agents used as preservatives in ophthalmic solutions against *Ps. aeurginosa*, and

b. Substances which are capable of inactivating or inhibiting the antibacterial action of the preservatives used.[8]

Addition of a properly selected preservative in ophthalmic preparation is of special importance, particularly, in dealing with the contamination during consumption. Among the prominent factors to be considered in the choice of the proper preservative are : the combination of active substances and excipients, the physical and chemical properties and, if need be, effective antimicrobial additives.[1]

According to the British Pharmaceutical Codex (1994), multidose eye drops have to contain chlorhexidine acetate 0.01% (w/v), benzalkonium chloride 0.01% (w/v),

phenyl mercuric nitrate or phenyl mercuric acetate 0.002% (w/v). Some proprietary preparations contain chlorbutol 0.5% or thiomersal 0.01% instead of one of the official preservatives.[2,9]

Richards and McBride in 1971, suggested that the selected preservative system for ophthalmic solutions should be capable of inactivating heavy contamination with *Ps. aeruginosa* as quickly as possible and that a sterilizing time of one hour or less is what should be expected of an antibacterial substance considered suitable for the preservation of ophthalmic solutions.[10]

In 1973, Coates explained that an acceptable preservative system must be effective against :

- Gram-positive and negative bacteria, moulds and yeasts including spore formers,
- Organisms likely to be introduced during production and by the consumer,
- Organisms previously found troublesome in similar products,
- *Ps. aeruginosa* - a commonly encountered resistant pathogen, and
- Combination of different organisms.[11]

The addition of antimicrobial preservative to a product may produce irritation or sensitization in a small portion of users. Hugbo in 1976, stated that concentration of the antimicrobial agent should be limited to the minimum necessary to prevent the growth of any microbial contaminants.[12]

An ideal preservative compound does not exist, and regarding the incidence and possible seriousness of infections which may result from the use of contaminated products, several workers have studied the use of multiple preservative systems with the aim of extending the spectrum of activity, increasing the overall concentration in

water, delaying the emergence of resistant mutants and finally, allowing the use of lower concentrations of individual preservatives.[13-15]

In 1985, Denyer *et al* concluded that a single antimicrobial agent, at a permissible concentration, was ineffective for the complete protection of many pharmaceutical and cosmetic formulations against microbial contamination. They emphasized the importance of the development of preservative combinations designed to give a more adequate protection. Occasionally, these antimicrobial combinations showed synergy, that is, their combined effects were greater than would be expected from simple additive effect. Such a situation was obviously advantageous providing enhanced activity at lower individual preservative concentrations. They explained that this situation was especially important in case of providing protection against contamination by *pseudomonads* where no single agent was entirely satisfactory in reducing sterilization time and protecting against multiple challenges of bacteria at high inoculum levels.[16]

Formulations containing two or more preservatives are increasing in number. Richards and McBride in 1973, stated that 50% of commercial ophthalmic preparations contained such combination. They explained that this was due to an increased necessity for a preservative system with bactericidal capability rather than bacteriostatic activity.[17]

In the same year, Garett discussed the justifications for using combinations of preservatives. These were listed as follows :

1. The spectrum of antimicrobial activity is increased;
2. The toxic effects of the concentration level of one preservative alone required to give the equivalent effect of the mixture may be averted;