CHAPTER I

INTRODUCTION

1.1 Introduction

The twentieth century can well be called the golden age of science. A virtual explosion in the body of knowledge of almost every field of science was ushered in drastic changes in the lifestyle of humans. Perhaps, in no other field is this change more striking than in healthcare where far-reaching innovation have ensured a healthcare. More disease free & longer life for man than ever before. However, the struggle for improving human life is not yet over. Effective therapies for many disease states are still elusive. A striking example is that of malaria. Globally malaria is a major public health problem & continues to be a predominant cause of morbidity & mortality in the tropical & subtropical areas of the world, where approximately 300 -500 million clinical cases & nearly 3 million deaths each year. Malaria kills more people than any other communicable disease except tuberculoses. Malaria is a preventable & curable disease if promptly & adequately treated (Peter & Anatoli, 1998, Chauhan, 1997, Krongthony & Willium 1996). Combined with preventive measures for mosquito (the malarial vector) control like spraying of insecticides, antimalarial drugs performed spectacularly only in the initial few years to bring about a rapid decline in cases of malaria the world over. The story of mosquito resistance to insecticides & parasite resistance to drugs impeding malaria control is familiar one. Therapy with malaria has, no doubt, come a long way from bleeding & blisters in the Middle Ages (which probably killed more patients than they saved) through decoctions of cinchona in the eighteenth & nineteenth centuries to modern day drugs and while there are renewed efforts to combat malaria both through conventional & novel drugs & through vector control activities an effective vaccine would constitute a powerful addition to these tools (Howard & Nina 1998) Drug resistance to *P. falciparum* is an alarming situation through out the tropical & subtropical countries.

These reemergence of malaria has resulted in global efforts to discover more effective antimalarial drugs to investigate the potential of other tools for malaria control such as malarial vaccines & new forms of drug delivery.

One such promising tool for the therapy of malaria, falling under the category of new drug delivery systems is microsphere.

Chloroquine (CQ) still remains an important antimalarial drug. It is one of the most effective & widely used drugs. All the alternative antimalarial are considerably more expensive than CQ & the other quinolines are less well tolerated. Fortunately CQ still retains its efficacy against *P.Vivax, P. Malaria & P.Ovale* (White N.J. 1992). Chloroquine is a very potent blood schizonticidal drug effective against the erythrocytic forms of all four *Plasmodium* species (Rang et. al. 1995) CQ is well absorbed from the gastrointestinal tract & rapidly form intramuscular (i.m.) & subcutaneous (s.c.) sites. The initial distribution volume is one thousand times smaller than the total apparent volume of distribution. These may cause potentially fatal hypotension. Because of extensive tissue binding a loading dose is required to achieve effective concentration in plasma. There after together with slow exit of chloroquine from small central compartment it can attain potentially lethal concentration of the drug in plasma.

Hence, CQ is given either slowly by constant intravenous (i.v.) infusion or in small divided doses by the subcutaneous (s.c.) or intramuscular (i.m.) route.

CQ is usually administered orally, except in cases of severe or complicated malaria where in it can be administered parentrally in small divided doses. However, fast parentral administration of aqueous solutions of CQ may cause life-threatening toxicity, which may limit its clinical use. Since serum CQ concentration related side effects is well established, the treatment regimen with this drug has become of great importance.

Sustained release drug carrier system continuously releasing the drug from the site of administration into the circulation, may help to overcome these problems. Encapsulation of chloroquine in liposomes has proven to reduce toxicity & to improve therapeutic efficacy against malaria parasite in mice. Chloroquine containing liposome act as local depot, which provide prolonged release (Titulaer et al 1990, Kadir et al. 1992).

Mefloquine (MQ) is effective against multidrug resistant strains of *P. falciparum*. Mefloquine was used first to treat chloroquine resistant falciparum malaria in Thailand with pyrimethamine & sulfadoxine. Mefloquine is now recommended for use alone exclusively for the prophylaxis & chemotherapy of CQ resistant & multi drug resistant falciparum malaria (Tracy & Webster 1996).

Mefloquine so far, has been considered relatively safe although in therapeutic doses, cardiac effect mainly bradycardia have been reported. The other side effects are prolongation of QTC interval & electrocardiograph (ECG) abnormalities (Joachin et al. 1996) Mefloquine is given orally because parentral preparations cause severe local reaction (Tracy & Webster 1996). These reactions can be overcome by coating mefloquine with suitable polymer, which gives slow release from the microsphere depot.

Mefloquine has become the drug for first line treatment due to multi drug resistant against falciparum malaria (kondrachine & trigg 1997).

Chitin is one of the most abundantly available natural materials. Deacetylated chitin (chitosan) is used for making surgical sutures. Synthetic skin, artificial biomembrane, for separation procedure and support to different immobilization processes. It is suitable as a biodegradable matrix for the production of microparticulate systems owing to its biocompatibility, biodegradability, bioadhesive & low toxicity properties. The possibility of being covalently cross linked through its amino groups allowing its

stabilization as a matrix for controlled release system (Wang et al 1996, Chandy & Das 2000 Singla & Chawla 2001).

The importance of cellulose ethers has increased in recent years because of easily available & cheap in comparison with other synthetic polymer, kato et. al. have reported that intravascular Mitomycin C (MMC) micro capsules reduces the toxicity by 50 % of nonencapsulated MMC ethyl cellulose forms a stable semipermeable capsular membrane. Intraperitoneal injection of one g/kg ethyl cellulose in rats was shown to cause no toxic reaction for the observed period up to 400 days. It was also used as a carrier for cisplatin & nonreleagnine hydrochloride parentral preparation (Mala et al 2000 Gohel & Avani 1999, Kato 1983).

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate & for a predetermined time. Recently such devices have been introduced for parentral administration. The most important objective for the development of these systems is to furnish an extended duration of action & thus assure greater patient compliance (Parmar & Shivprakash 1997).

Implant is one of the oldest & most highly developed forms of drug delivery to implant a drug bearing polymeric device subcutaneous or in various body cavities (Marks & Joseph 1990).

To avoid surgical problems associated with large implants, suspension of nanoparticles & microparticles are recommended for implantation in a suitable vehicle. The colloidal particles of submicron size like nanoparticles nanocapsules, nanopellets & microparticulates because of their ultra fine size, act as drug carrier for parentral purpose (Venkatesan et al 1995).

Injectable implants for controlled drug delivery made up of biodegradable – drug carrier offer several advantages to overcome the

problems of classical implants. It eliminates the necessity for surgical removal of implanted devices following depletion of drug. So has higher level of patient & physician compliance.

1.2 Proposed plan of work

The proposed plan of work is as under :

(1) Preparation of Chloroquine Phosphate(CQP) microspheres using

1.1 Ethyl Cellulose

1.2 Chitosan

(2) Characterization of microspheres of Chloroquine Phosphate for

2.1 Percentage yield

2.2 Particle size analysis

2.3 Percentage drug content

2.4 In-vitro drug release study

(3) Application of factorial design for various variables and parameters for the preparation of Chloroquine phosphate microspheres.

(4) Preparation of mefloquine hydrochloride(MQH) microspheres using Ethyl Cellulose

(5) Characterization of microspheres of mefloquine Hydrochloride

5.1 Percentage yield

5.2 Particle size analysis

5.3 Percentage drug content

5.4 In-vitro drug release study

(6) Application of factorial design for various variables & parameters for the preparation of mefloquine hydrochloride microspheres.

(7) In-vivo study for optimized formulation of Chloroquine phosphate microspheres.

(8) In-vivo study for optimized formulation of mefloquine hydrochloride microspheres.

1.3 References

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