

Chapter | 1

Introduction and aim of study focussing on the relevancy of the thesis. It gives a detailed problem statement with specific objective and aims. Reference style is a modified version of the North-West University Harvard style

1. Introduction

Drugs are compounds intended for use in the diagnosis, treatment or prevention of diseases in humans. Drugs can be described as one of the great scientific accomplishment with new drugs either derived from plants or animals, chemically synthesised or by molecular modification. Drugs are complex and diverse with different properties, mechanism of action, intended uses and disadvantages. It is therefore necessary to determine chemical and physical characteristics, conduct biological testing and determine pharmacological, properties including mechanism of action before formulation into products (Allen *et al.*, 2005; Allen, 2008). Poor solubility and permeability are some of the reasons for 40% of compounds fail to reach the market (Venkatesh *et al.*, 2000). Different strategies are followed to increase the amount of drugs to reach the market. This includes computer screening of potential compounds, formulation into dosage forms to improve certain properties, formulation of prodrugs and synthesis of derivatives.

Parasitic diseases affect 30% of the world's population but only 1% of drugs that reach the market is used to treat these diseases (Date *et al.*, 2007). Malaria, leishmaniasis and trypanosomiasis are some of well-known parasitic infections. Malaria cases reported in 2008 were an estimated 243 million with 85% in Africa. Deaths due to malaria showed to be the highest in Africa with a total of 863 000 cases recorded (WHO, 2010c). This parasitic disease is caused by the *Plasmodium spp.* with infections mostly caused by *Plasmodium falciparum*. Two distinct cycles during the life cycle of the parasite occur. The sexual cycle occurs in the Anopheles mosquito after which the human is infected when a blood meal is taken, injecting the parasite into the blood stream. The asexual cycle in the human has distinct liver and erythrocytic stages. After a 5 to 15 day incubation period in the liver the merozoites are released into the blood stream. Infection of the erythrocytes occurs and the clinical manifestations of malaria transpire. Maturation of the parasite occurs in 48 hours, after which rupturing of the erythrocytes releases the merozoites which reinfect the host erythrocytes. Clinical symptoms include headache, fever, body pain, fatigue and vomiting. Severe malaria characterised by organ failures includes cerebral malaria, anaemia and renal failure and is common when left untreated. Cerebral malaria is characterised by impaired consciousness, seizures, coma and death (WHO, 2010a; WHO, 2010b). Treatment of malaria is mostly achieved by drugs that are

active against the erythrocytic cycle of the parasite. Quinoline antimalarial drugs, including chloroquine, quinine, mefloquine and primaquine, were widely used but are currently limited due to resistance and unwanted adverse reactions. Artemisinins, extracts of sweet wormwood have been used for more than 2000 years with great value against resistant strains. Other drugs include antibiotics like doxycycline, erythromycin and azithromycin. Resistance to current drugs has become one of the most important problems in the disease control increasing the severity of the disease. Combination therapy and effective treatment are some of the strategies followed to alleviate this problem. Resistance to all current drugs is inevitable if nothing is done to decrease resistance. The economic burden of this disease is increased by the emergence of resistance. High financial burdens on individuals and government are observed with more than 60% of infections occurring in the poorest countries of the world (Bloland, 2010; Rosenthal, 2004; WHO, 2010a; WHO, 2010b). The limited amount of new drugs, the increase in resistance and unwanted adverse reaction and physicochemical properties of current antimalarial drugs increase the burden and need for research to be done on malaria.

Modulating the delivery of existing antimalarial compounds is one of the strategies to help decrease the demand for new drugs (Date *et al.*, 2007). Mefloquine, a highly effective compound classified by the WHO as treatment especially in combination with artemisinins, is mainly used against chloroquine resistant infections. Resistance has been reported but is limited to certain endemic areas including Tanzania (Mockenhaupt, 1995; Wichmann *et al.*, 2003). The low solubility and toxicity of mefloquine decrease the use of the drug. Low solubility leads to inadequate blood levels with ineffective treatment and possibility of resistance. The neurotoxicity of mefloquine is dose related and includes seizures, psychosis and depression (Barrett *et al.*, 1996; Tin *et al.*, 1982). Mefloquine has successfully been incorporated into submicron oil-in-water emulsions with high antimalarial activity (Mbela *et al.*, 1998; Mbela *et al.*, 1994).

Drug delivery systems are the combination of drugs with various excipients to improve drug delivery, bioavailability and efficacy. The most comprehensively researched carrier system, liposomes can entrap both hydrophilic and lipophilic drugs. Increase in solubility is seen with lipophilic drugs in combination with liposomes. Antimalarial drugs incorporated into liposomes include chloroquine, artemether and primaquine with increase efficacy and bioavailability (Joshi *et al.*, 2008a; Joshi *et al.*, 2008b; Qiu *et al.*, 2008;

Stensrud *et al.*, 2000). Incorporation of mefloquine into liposomes is a novel approach to possibly increase the solubility of the drug leading to higher efficacy. Pheroid™ technology is a novel lipid based colloidal drug delivery system similar in shape and size to liposomes (Grobler *et al.*, 2007). It can entrap both hydrophilic and lipophilic drugs but the exact entrapment efficacy has not yet been evaluated. Entrapment of mefloquine showed an increase in efficacy (Odendaal, 2009; Van Huyssteen, 2010) but further investigation is needed to assess the potential of Pheroid™ vesicles as drug delivery system.

Development of dosage forms consist of an active drug in combination with excipients that have their own unique physical and pharmacological properties (Allen, 2008). A well thought out research strategy should be followed to evaluate these formulations before expensive clinical trials can be done. This includes preformulation assessment, pharmacokinetic and pharmacodynamic properties, toxicology and efficacy studies (Devalapally *et al.*, 2007). Preformulation mostly consisting of literature search (Ramani *et al.*, 1992) during which the physiochemical properties are characterised (Wei-Qin, 2010) defining the nature of the active drug (Allen, 2008). This is followed by a development phase including dosage form selection and formulation, *in vitro* and *in vivo* evaluation of efficacy, toxicity and pharmacodynamic and kinetic properties. During the development phase, emphasis should be placed on the optimisation and development of assays to perform characterisation and biological evaluation to obtain accurate results. After a thorough assessment of the drug delivery systems, products can be considered for clinical trials and registration (Devalapally *et al.*, 2007). A complete and thorough profiling can be used as research tool to avert potential issues during trials (Di *et al.*, 2003).

High efficacy, toxicity and low solubility makes mefloquine a prime candidate for assessment in drug delivery systems. The ability of both liposomes and Pheroid™ vesicles to entrap highly lipophilic compounds makes these vehicles ideal to entrap mefloquine and evaluate the stability and physiochemical properties as well as efficacy and toxicity. The novelty of entrapment of a currently used antimalarial drug, mefloquine to improve certain key properties like solubility, efficacy and toxicity profile as well as optimization of assays for biocompatibility will aid in the war against malaria.

2. Objective and aim of study

Product intended for marketing, has a specific and goal orientated research strategy. This is used to avert potential problems before clinical trials are done. The objective of this study is the preformulation and development of two lipid drug carriers loaded with the effective but toxic drug, mefloquine. The strategy followed was preformulation evaluation of the highly lipid antimalarial drug, mefloquine hydrochloride by conducting a literature search. This is followed by the development phase including a literature study, dosage form selection and formulation. Characterisation of the dosage form, stability, *in vitro* efficacy and toxicity were evaluated to determine the viability of these formulation for possible marketing.

The objective of this study will be evaluated by the following aims:

- The formulation of Pheroid™ vesicles and liposomes.
- The incorporation of mefloquine hydrochloride into Pheroid™ vesicles and liposomes.
- Optimization of methods to determine physicochemical properties.
- Determination of size, pH, entrapment efficacy and stability of the formulations.
- Optimization of methods to determine the efficacy and toxicity of the formulations.
- *In vitro* efficacy evaluation of the formulations on a multidrug resistant *P. falciparum* strain.
- *In vitro* evaluation of cellular toxicity.

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