INTRODUCTION
1. INTRODUCTION

Malaria, an infectious disease caused by protozoan parasites from the *Plasmodium* family, continues to be one of the greatest health challenges worldwide. The World Health Organization (WHO) estimates that more than 250 million people are infected with acute and chronic malaria annually and 1.5 million individuals die annually. The prevention and treatment of malaria today constitutes an acute challenge for modern and public health management because of many of the traditional drugs like chloroquine, amodiaquine, quinine, mefloquine, halofantrine are becoming ineffective in certain parts of the world.\(^1\) The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the non specific targeting to intracellular parasites resulting in high dose requirements and subsequent intolerable toxicity.\(^2,3\) Artemisinin derivatives are the few antimalarial drugs that remain effective against multidrug resistant strains of *Plasmodium falciparum* malaria.\(^4,5\) However, even artemisinin therapy suffers from recrudescence after monotherapy\(^6\) and most probably due to the pharmacological factor such as host metabolism. Moreover, there is no convincing evidence yet that the failure of Artemisinin derivatives in humans is due to parasite resistance. This has led to the advocacy for new chemical combination therapies.

Combination therapy probably attacks the organism through different mechanisms of action producing at least additive or perhaps synergic effect. Artemisinin derivatives are administered in combination with another effective antimalarial drug (with a blood schizonticide) to reduce the recrudescence as well as to prevent or slow the

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**Figure 1.1: life cycle of Plasmodium parasite in human**
development of resistance.\textsuperscript{7,8} Pyrimethamine and sulphadoxine combination formally used as prophylactic and suppressive agent against chloroquine resistance strains of \textit{P. falciparum} is no more successful and is prescribed in combination with artemisinin derivative.

Now, with the advent of combination therapy, the compatibility of drugs in a combined preparation is a critical factor for the development of pharmaceutical formulations. The existence of incompatibility between active ingredients and excipients result in toxic or no clinical effects.\textsuperscript{9} These are sometimes manifested by precipitation or color changes. Interactions in the solid state between the active ingredients in pharmaceutical dosage forms can give rise to changes in the stability, solubility, dissolution rate and bioavailability of drugs.\textsuperscript{10,11} Thus, it is essential for the development of new pharmaceutical formulation to have readily available knowledge about potential physical and chemical interactions between the drugs in combined formulation. Occasionally \textit{in vitro} interactions occur without any observable change and can be determined quantitatively by determining their excess thermodynamic properties in solution. The present work predicts any specific and non-specific interaction in solid state and solution phase between the drugs prescribed in double and triple regimen therapy. The drugs used in study are given below:

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{drug_structures.png}
\caption{Drug structures used in the study: Artemether, Artesunate, and Arteether.}
\end{figure}
Unfortunately, many of the drugs used in combination therapy exhibit poor water solubility and belong to the Class II of Biopharmaceutical Classification System showing decreased systemic bioavailability and a number of negative clinical effects. This can cause formulation problems and limit their therapeutic applications.

The great challenge in the pharmaceutical development is to create new formulation approaches and efficient drug-delivery systems to overcome solubility and dissolution problems of the drug candidates which are also often associated with poor oral bioavailability.

Although, numerous strategies exist for enhancing the bioavailability of drugs with low aqueous solubility, the success of these approaches is yet to be guaranteed and is greatly dependent on the physical and chemical nature of the molecules being developed.

One of the recent approaches to such an adjuvant problem is to explore the crystal modifications with improved physico-chemical parameters. One crystalline modification may show five to ten times absolute solubility and bioavailability as to another crystal modification of the same drug. One crystal habit of a drug may lead to formation of tablet while another may cause trouble, but both have the same melting point and apparently the same X-ray pattern. A significant solubility difference between two crystals forms is likely to result in a difference in oral absorption rate, reflected in a difference in $C_{max}$. Therefore, the present work reports an attempt to prepare the alternate crystal forms of these drugs with improved solubility and dissolution. However, none of the new prepared form could lead to desired results;
therefore, inclusion complexes of these drugs were prepared with the aim to improve solubility, dissolution and bioavailability.

Cyclodextrins (CDs) were widely used because of their ability to enhance solubility, chemical stability and bioavailability of poorly soluble drugs, control the rate of release and reduce toxicity. Complexation with cyclodextrins is particularly attractive owing to the relative easiness of the procedure, the avoidance of organic solvents, stability and the high biological tolerance of the complexes. The inclusion complexes were prepared by various methods and have been evaluated both in solid state and solution phase. The stability constant, enthalpy of binding as well as entropy of binding accompanying the encapsulation has been determined. In vivo studies were performed using balb/c mice to evaluate their therapeutic effectiveness.

The inclusion complexes of two of the drugs (arteether and artesunate) were incorporated in the chitosan/lecithin nanoparticles. The rational was to implement simultaneously the CD drug complexation power as well as the inherent properties of nanoparticle formulation. These nanoparticles exhibited promising results.