CHAPTER 1:
INTRODUCTION
1.0 INTRODUCTION

Oral drug delivery is the preferred route for drug administration because of its non-invasive nature. The oral route presents the advantage of avoiding pain and discomfort associated with injections as well as eliminating contaminations [Payne, 1992; Liu et al., 1997]. In contrast, in oncology most anticancer agents are delivered by intravenous injection. This is probably due to the narrow therapeutic index of many antineoplastic drugs and the pharmacologic observation that oral administration often results in a large intra- and inter-subject variability in drug exposure. However, the burden of intravenous administration is evident: every intravenous injection carries, although small, a risk of bleeding, extravasation, infection and thrombosis and requires medically qualified personnel at a hospital setting. Moreover, especially in cancer patients, repeated intravenous injections are hampered by the fact that a patient’s accessible vein may disappear during chemotherapy due to flebitis or thrombosis.

Oral delivery is also especially appropriate where prolonged drug exposure is desirable as with schedule dependent agents such as taxanes, topoisomerase I inhibitors or the fluoropyrimidines. The same argument applies to novel agents such as signal transduction inhibitors and anti-angiogenic drugs that may need to be taken daily for months or years in contrast to the intermittent, short term use of conventional antiproliferative cytotoxics that are often well suited to i.v. administration. For reasons of patient convenience, oral chemotherapy seems a valuable addition to standard iv use. Besides, the outpatient administration of oral agents may potentially reduce total healthcare system costs. In addition, oral formulations are of benefit in therapies that require prolonged exposure by means of a protracted treatment course. This also fits in the concept of ‘metronomic scheduling’ of frequent administration of chemotherapy at low dose to increase anti-angiogenic activity.

1.1. Origin of Proposal

Taxanes (Paclitaxel and Docetaxel) are potent anticancer drugs with proven activity against a broad range of human malignancies, including ovarian and breast cancer and non-small cell lung carcinoma [Rowinsky and Donehower, 1995; Huizing et al., 1995]. Currently marketed formulation of Paclitaxel (Taxol®) and Docetaxel (Taxotere®) are administered intravenously at different dosages and infusion schedules. Currently global sales of taxanes (Taxol® and Taxotere®) are approximately $3.0 billion.
Oral treatment has not appeared feasible because of the low oral bioavailability of taxanes [Malingré et al., 2001a]. Taxane delivery by the oral route would be very valuable with respect to improving patient compliance and ease of administration, as well as the development of chronic treatment schedules, which would in addition decrease the costs of therapy. However, oral treatment with taxanes is not possible until now because of their low oral bioavailability (approximately 1% for Paclitaxel and 8% for Docetaxel) owing to several factors. Taxanes show limited aqueous solubility and dissolution, affinity to the cell membrane-bound drug efflux pump P-glycoprotein (P-gp) [Malingré et al., 2001b; Sparreboom et al. 1997a], and metabolism by cytochrome P450 3A4 (CYP3A4) [Walle, 1996], as they belong to the BCS Class IV group.

The choice of suitable pharmaceutical formulation with an acceptable level of bioavailability is an essential step in chemotherapy. Numerous strategies have been developed so far to enhance the aqueous solubility and dissolution of taxanes. Nano-sized carriers such as polymeric micelles [Tsallas et al., 2009; Bromberg, 2008], self-micro-emulsifying drug delivery systems (SMEDDS) [Yang et al., 2004], solid self-emulsifying drug delivery systems (S-SEDDS) [Gao et al., 2003], microemulsions [Nornoo et al., 2009; Yin et al., 2009], lipid nanocapsules [Roger et al., 2009; 2010; Peltier et al., 2006], and nanoparticles [Saremi et al., 2011; Agüeros et al., 2009; Feng et al., 2009; Chavanpatil et al., 2006; Zhang and Feng, 2006] have been prepared to enhance oral bioavailability of taxanes. In recent years, much attention has focused on lipid-based formulations to improve the oral bioavailability of poorly water-soluble drug compounds [Humberstone and Charman, 1997]. In fact, the most popular approach is the incorporation of the drug compound into inert vehicles such as oils, surfactant dispersions [Chiou et al., 1976], self-emulsifying formulations [Pouton 1985; 1997; 2000], emulsions [Kararli et al. 1992] and liposomes [Schwendener & Schott, 1996] with particular emphasis on self-microemulsifying drug delivery systems (SMEDDS) [Shen & Zhong, 2006; Wang et al., 2006]. Among the various nanoscale drug delivery systems, self-microemulsifying drug delivery systems (SMEDDS) were proven to be a promising technology to improve the rate and extent of absorption of poorly water-soluble drugs [Pouton, 2000, 1997]. SMEDDS formulations are a pre-concentrate mixture of oil, surfactants and co-surfactants, which on oral ingestion creates fine droplets of emulsion (5–100 nm), when diluted with water or the body fluids in the aqueous lumen of the gut [Constantinides, 1995]. Apart from this, some excipients, such as polyethylene glycols
(PEGs) and Cremophor, which may be part of SMEDDS, can inhibit both pre-systemic drug metabolism and intestinal efflux mediated by P-gp, resulting in an increased oral absorption of cytotoxic drugs [Chervinsky et al., 1993].

Self-microemulsifying drug delivery systems (SMEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions [Hong et al. 2006]. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification [Pouton 2000; Shah et al. 1994]. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm.

Because of their unique solubilization properties this system offers various advantages over the current marketed formulations [Constantinides 1995; Ghosh and Murthy 2006]:

1. Bio-availability enhancement of poorly aqueous soluble drugs: SMEDDS offer the opportunity to present lipophilic drugs to the gastrointestinal tract in a dissolved state, avoiding the dissolution step (which can limit absorption rate of BCS Class 2 and 4 drugs).

2. Reduction in Inter-Subject and Intra-Subject Variability.

3. Reduction of Food Effect

4. Ease of Manufacturing and Scale Up.

5. Ability to Deliver Peptides that are Prone to Enzymatic Hydrolysis in GIT.


Self-microemulsifying drug delivery systems have widely been available in the market for quite a long time. The clinical usefulness of SMEDDS is evident from commercially available formulations like Neoral® (cyclosporin A), Norvir® (ritonavir) and Fortovase® (saquinavir). These formulations are globally acclaimed for their safety and efficacy, better stability and in-vivo acceptability.

P-glycoprotein (Pgp) efflux mechanism also plays an important role in decreasing the oral bioavailability of various anticancer drugs including taxanes. P-gp is a member of the
ATP-binding cassette superfamily of transport proteins and is expressed in numerous tissues such as the luminal membrane of the small intestine and blood-brain barrier, and the apical membranes of excretory organs such as liver and kidney [Ayrton and Morgan, 2001]. Pgp has broad substrate recognition, which can affect the pharmacokinetics, efficacy, safety, and target organ specificity of drugs. Co-administration of a potent inhibitor of p-glycoprotein, results in enhancement of the oral bioavailability for taxanes. Various 1st and 2nd generation P-gp inhibitors, such as cyclosporine A [Terwogt et al., 1999; Terwogt et al., 1997; Woo et al., 2003] or its analogues [Malingre et al., 2001c; Britten et al., 2000; Asperen et al., 1997], or KR30031, a verapamil analogue [Woo et al., 2003] were used for this purpose. Studies clearly demonstrated that oral bioavailability of taxanes was greatly improved when the drug was administered in the presence of P-gp inhibitors. This therapeutic approach, however, is fraught with various drawbacks, such as toxicity, non-specificity, low potency and unpredictable pharmacokinetic interactions of inhibitors with the drug [Terwogt et al., 1999].

To overcome this problem, 3rd generation P-gp inhibitors came into existence, which had no pharmacological response, high specificity and minimal pharmacokinetic interactions [Thomas and Coley, 2003]. The third-generation P-gp inhibitors currently in clinical development include the anthranilamide derivative, tariquidar (XR9576) [Roe et al., 1999], the cyclopropyl dibenzosuberane zosuquidar (LY335979) [Dantzig et al., 1999; Starling et al., 1997], laniquidar (R101933) [Zuylen et al., 2000], the substituted diarylimidazole ONT-093 [Newman et al., 2000], and the acridone carboxamide derivative GF120918 (Elacridar) [Maliepaard et al., 2001]. GF120918 is one of the most promising third-generation P-gp inhibitors, which binds with high affinity to the P-gp transporter while potently inhibiting its activity [Malingre et al., 2001a; Hyafil et al., 1993].

GF120918 (Elacridar) is an acridonecarboxamide derivative and has been shown to be a potent blocker of P-gp in tumor cells in vitro and in vivo. It is a potent and selective inhibitor of the drug pumps P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP; A3CG2). Expression of P-gp or BCRP in cancer cell lines is associated with efflux-out of drug from the cells and is held responsible for chemotherapeutic treatment failure in cancer patients [Juliano and Ling 1976]. Furthermore, the native presence of these proteins in the apical membrane of the epithelial cells in the intestine limits the entry of substrates, e.g., several anticancer drugs, into the bloodstream by actively
pumping the drug back into the intestinal lumen. Elacridar was discovered in the search for potent and selective P-gp inhibitors. Many of these agents were appeared to be weak competitive P-gp inhibitors, or potent inhibitors of cytochrome P4503A4 (CYP3A4), causing undesirable pharmacokinetic interactions. Elacridar, on the other hand, is about 100-fold more potent than the widely used P-gp inhibitor cyclosporin A and has very low affinity for CYP3A47 and is therefore less likely to cause undesirable pharmacokinetic interactions [Hyafil et al. 1993].

The objective of present work was development of self-microemulsifying lipid formulations containing highly lipophilic cytotoxic drugs like taxanes derivatives (i.e. Paclitaxel, Docetaxel, etc) [Malingr´e, 2001b], which thereby on oral ingestion increases the absorption of these bio-actives and hence enhances their oral bioavailability. Because of their unique solubility characteristics, the proposed system is expected to absorb completely in the aqueous lumen of GIT and hence, will ensure maximum bioavailability of the drug leading to the reduction in dose and adverse effects.

The present study aimed at “Nanometric carrier system for the effective delivery of anticancer bioactives” with special emphasis on:

- Design, Development and Optimization of taxanes loaded SMEDDS formulation for oral delivery.
- Determining the effect of novel P-gp inhibitors on the permeability and uptake of taxanes SMEDDS by Ex-vivo cell line study.
- Determination of absolute bioavailability of SMEDDS formulation (with and without co-administration of novel P-gp inhibitors) in suitable animal model.
1.2. PLAN OF WORK

- Review of Literature
- Procurement of drug sample and their characterization
- Analytical method development and validation of Paclitaxel & Docetaxel
- Screening of various excipients for the formulation development of Paclitaxel and Docetaxel
- Solubility studies of Paclitaxel & Docetaxel in various excipients
- Formulation development and characterization of Paclitaxel & Docetaxel SMEDDS formulation
- Permeability study of SMEDDS formulation of Paclitaxel & Docetaxel along with or without P-gp inhibitor in Caco-2 cells
- Cell Uptake Study using A549 cells
- In vivo Pharmacokinetic study of Paclitaxel & Docetaxel (with and without co-administration of P-gp inhibitors)
- Compilation of results, statistical assessments, and thesis compilation