Drugs are rarely administered in their pure forms and usually they have to be admixed with various kinds of adjuncts resulting into their transformation into 'dosage forms' (Micheal et al., 1990). For the administration of the dosage forms, oral route is most preferred route but this route is frequently dependent upon the bioavailability of the active form of the drug. Bioavailability is affected by the drug's physical-chemical properties, such as water solubility, oil solubility, its dissolution, pKa, stability, as well as its absorption, distribution, metabolism and excretion.

Together with the permeability, the solubility of a drug is a key determinant of its oral bioavailability. There have been certain drugs for which solubility has presented a challenge to the development of a suitable oral dosage form e.g. griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol (Leuner et al., 2000).

Approximately 40% of new drug candidates have poor water solubility and the oral deliveries of such drugs is associated with implications of low bioavailability, high intra and inter subject variability and lack of dose proportionality (Robinson., 1996; Gursoy et al., 2004). With the recent advent of high throughput screening of potential therapeutic agents, the numbers of poorly soluble drug candidates are increasing and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

1.1. Factors affecting systemic absorption (Loebenberg et al., 2000)

The therapeutic effect of orally administered drugs depends on the drug concentration at the site of action which in turn depends on systemic absorption of the drug. Since only dissolved drug can pass the gastrointestinal membrane, dissolution is one of the main factors to determine drug absorption.

The bile fluids secreted by liver aid in the solubilization of lipophilic drugs by forming micelles in which poorly drug molecules are solubilized (Dahan et al., 2008).

The unstirred layer of water adjacent to the absorption membrane of enterocyte is hydrophilic and thick (500 micron in human jejunum). This unstirred layer may be a major permeability barrier for absorption of lipophilic drugs as diffusion across the unstirred layer is the rate limiting step in the permeation process of BSC class II drugs (Loebenberg et al., 2000; Read et al., 1977; Westergaard et al., 1974).
The short transit time of the drugs in small intestine may limit the absorption of a lipophilic compound and if the compound reaches the colon prior to solubilization its bioavailability is expected to be low. The first pass hepatic metabolism is another barrier to the absorption of certain lipophilic drugs (Yu et al., 1996; Yu et al., 1999).

Enterocyte cytochrome P-450 3A4 (CYP3A4) enzymes are responsible for the metabolism of most of the drugs in intestine and many studies have revealed its role as a major barrier to the absorption of lipophilic drugs (Wacher et al., 1998).

P-glycoprotein (P-gp) and the multidrug resistance associated protein pumps reduces fraction of drug absorbed by transporting drug from enterocyte back to the intestinal lumen (Gottesman et al., 1996; Seelig et al., 2000).

1.2. Strategies to improve drug absorption (Aungst., 1993; Patel et al., 2006; Burcham et al., 1997; Serajuddin et al., 1988; Aungst et al., 1994).

To increase the amount of dissolved drug at the absorption site several strategies have been tried. The most straight forward method is to use a dosage form in which drug molecules are already dissolved in an aqueous solution. However, this may require large volumes of the liquid to dissolve the complete drug dose, which is highly unwanted. To increase the solubility, buffers, surfactants or complex forming excipients (e.g. cyclodextrins) have been used (Loftsson et al., 2004). Another strategy is to increase their dissolution rate. Often the absorption of lipophilic drugs is reduced by the slow rate of dissolution from the solid drug particles. Dispersion of the drug as very fine particles will increase the surface area available for dissolution (Wadke et al., 1989). Also solid dispersions can be used to increase the dissolution rate of poorly soluble drugs (Serajuddin et al., 1999), and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability (Aungst et al., 1993; Amidon et al., 1995; Robinson et al., 1996).

In recent years much attention has been focused on lipid-based formulations (Humberstone et al., 1997) with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to enhance the solubility of poorly water soluble drugs and improving bioavailability to administer them through oral route resulting in increasing their clinical efficacy, cost effectiveness and ease of preparation. Self-emulsifying drug delivery systems are isotropic mixture of oils, surfactant and co-solvents/ surfactant, which forms fine stable o/w emulsions,
when introduced in the aqueous phase under condition of gentle agitation. The natural digestive motility of the stomach and intestine provides the agitation required for self-emulsification in vivo (Gursoy et al., 2004; Pouton et al., 2000). The spontaneous formation of an emulsion upon release in the GI tract advantageously presents the drug in a dissolved form and the small droplets size provides a large interfacial surface area for drug absorption (Shah et al., 1994). Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability of the drug by permeating through the biological membrane (Pouton et al., 2000).

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance (Davis et al., 1996). With an increasing incidence worldwide, diabetes mellitus likely continues to be a leading cause of morbidity and mortality for the foreseeable future (Davis et al., 1996). Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 20002. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025 (Sicree et al., 2006). India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. Type 1 diabetes (Insulin Dependent Diabetes Mellitus; IDDM) and Type 2 (Non Insulin Dependent Diabetes Mellitus; NIDDM) diabetes are the two major types of diabetes mellitus. Although there is an increase in the prevalence of type 1 diabetes also, the major driver of the epidemic is the more common form of diabetes, namely type 2 diabetes, which account for 80-90% of all cases of diabetes (Davis et al., 1996). There are many drugs to treat NIDDM. Insulin is the mainstay for treatment of virtually all IDDM and many NIDDM patients. However, most patients with NIDDM can be treated with oral antidiabetic agents sulfonylureas, meglitinides, biguanides, glitazones, etc (Satoskar et al., 2001). Sulfonylureas (like gliclazide and glibenclamide etc.) are drug of choice for long term therapy for NIDDM. But sulfonylureas (like gliclazide and glibenclamide) possess solubility problem in aqueous fluids besides having low dissolution rate and variable low bioavailability. At present hardly any scientific literature is available on the formulation of self-emulsifying drug delivery system of gliclazide, glibenclamide, etc. which possess solubility problem in aqueous fluids besides having variable low bioavailability.
Hence, in the present study it was attempted to prepare self-emulsifying drug delivery systems of Gliclazide and Glibenclamide in order to improve the solubility, dissolution rate and to evaluate the SEDDS with respect to various in vitro and in vivo parameters.

OBJECTIVES

The present research work was planned with following objectives.

1. To develop and validate analytical and bioanalytical method for the estimation of gliclazide and glibenclamide.
2. To carry out the solubility studies and construct the phase diagrams.
3. To formulate and evaluate self-emulsifying drug delivery systems of Gliclazide & Glibenclamide.
4. To evaluate the in vitro release studies of developed formulations.
5. To carry out pharmacokinetic evaluation of the developed formulations.
6. To assess the stability of the optimized formulations as per ICH guidelines.