4. RATIONALE FOR THE STUDY

4.1 SELECTION OF DRUG DELIVERY SYSTEM

Liquisolid compacts (LSC)

LSC is a new and promising technique based on powder solution technology for the improvement of dissolution rate. Water-insoluble drugs dissolved/dispersed in non-volatile solvent are converted to a free-flowing, non-adherent, dry looking and readily compressible powders with the use of hydrophilic polymers like Avicel PH 102 as carrier and highly porous silica as coating material.

The suggested mechanism of enhanced drug release is due to following reasons:

**Increased drug surface area:** The drug is completely dissolved in non-volatile solvents and adsorbed on to the carrier. The solvent used was non-volatile; hence, the drug will be present in solubilized and molecularly dispersed state in the final dosage form. This will greatly enhance the surface area available for release in the dissolution media *in vitro* compared to directly compressed tablet. Increased surface area of drug will enhance the dissolution, absorption and there by bioavailability of the poorly soluble drugs. The increase in dissolution is directly proportional to fraction molecularly dispersed drug ($F_M$) in the solvent that depends on the solubility of drug in the given non-volatile solvents.

**Improved wetting:** The non-volatile vehicle in which drug is dissolved can act as surfactant and lowers the surface tension resulting in increased wetting of the drug particles. This increase in wetting also improves the effective surface area available for dissolution medium.

**Increased solubility:** The non-volatile solvent used in the formulation may act as co-solvent contributing to the solubility improvement of the poorly soluble drug along with improved wetting and surface area. The improved solubility will increase concentration gradient and there by dissolution rate according to Noyes – Whitney equation.

LSC technology not only enhances the drug dissolution but can be commercially viable which has industrial scale-up feasibility due to low cost and ease of handling.
Melt dispersion granules

Solid dispersions have been used traditionally as an effective method to improve the dissolution rate and bioavailability of poorly water-soluble drugs. In spite of these advantages, solid dispersions are not used in the commercial products due to poor flow properties and poor stability. Hence the present investigation combines the two techniques, surface adsorption and solid dispersion. The use of surface adsorbents in the solid dispersion melt will convert sticky mass in to free flowing granules with improved handling and flow properties. The use of polymers as carriers further prevents the crystallization of drug and can improve the stability of the final formulation.

The improvement in dissolution of drug can be achieved by,

**Reduction in particle size and increased surface area:** The drug is homogeneously dispersed in polymeric carriers. As carrier dissolves in dissolution media the drug will be presented in a molecularly dispersed state that may lead to particle size reduction and enhanced surface area and improved dissolution rate.

**Improved wetting of the particles:** The wettability of hydrophobic drugs can be improved due to surrounding hydrophilic carriers. The use of surfactants as carriers further reduces the surface tension and thus increases the wetting of particles. The improvement in wetting results in improved dissolution of poorly soluble drugs. Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution.

**Particles with high porosity:** The use of polymers as carriers will produce particles with high porosity. The increased porosity of solid dispersion particles also hastens the drug release profile. The increase in porosity also depends on the carrier properties. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers.

**Change in solid state of the drug:** During the formation of solid dispersion the drug may be precipitated in amorphous form in the crystalline carrier. Amorphous forms produce more dissolution compared to crystalline forms because no energy is required to break up the crystal lattice of a drug during the dissolution process.
4.2 SELECTION OF DRUGS

Valsartan and telmisartan are potent and highly selective antagonist of angiotensin II AT1 receptor used to treat hypertension, concomitant renal diseases and congestive heart failure.

**Rationale for selection of valsartan**

Valsartan belongs to BCS class II in biopharmaceutics classification system with low solubility (<100 mg/mL). Valsartan also exhibits pH dependant solubility with low solubility at lower pH conditions. The drug is rapidly absorbed from the upper part of GIT and shows oral bioavailability of about 23%. Furthermore, the presence of food decreases its absorption by 40%. In addition weakly acidic nature hinders the solubility of drug in upper part of GIT where the absorption window exists for the drug. As a result, valsartan exhibits inter- and intrasubject variability in absorption resulting in poor oral bioavailability and pharmacokinetics. Rapid onset of action is also desirable to provide fast relief in the treatment of heart failure.

Literature reports indicate development of solid dispersions with pH modifiers and surfactants, self nano emulsifying drug delivery system (SNEDDS), mucoadhessive pellets, spherical agglomerates for improving the bioavailability of valsartan. However, to our knowledge these delivery systems did not show significant improvement in the dissolution specifically at lower pH conditions where the absorption window exists for valsartan. Hence, valsartan was selected as a model drug to develop different formulations that specifically improves the dissolution of drug in lower pH conditions to obtain faster onset of action, minimize the variability in absorption and improve its oral bioavailability.

**Rationale for selection of telmisartan**

Telmisartan is a BCS class II drug (aqueous solubility is 0.09 μg/mL) with pH-dependent solubility (practically insoluble in the range of pH 3–9) and is highly hydrophobic in nature. Preclinical studies on telmisartan pharmacokinetics also report significant variation in the pharmacokinetic parameters under fed and fasted conditions. The poor aqueous solubility of drug is associated with slow drug
dissolution and slow/erratic absorption leading eventually to inadequate and low oral bioavailability (43%).

Similarly, to date, all the drug delivery approaches reported in the literature were aimed at improving the dissolution rate by using alkalizers to modulate the microenvironmental pH\textsuperscript{116}. However, few limitations associated with the present technology include the stability of drug with the use of pH modifiers and formulation stability in case of solid dispersions, toxicity due to high amounts of surfactants used in the formulation of SEDDS\textsuperscript{115}, toxicity associated with the use of cyclodextrins\textsuperscript{117}. Hence, telmisartan was selected as model drug to develop a suitable formulation that produces improvement in dissolution independent of pH without any toxicity or stability issues.