Poor solubility in biological fluids is one of the major obstacles in drug discovery and formulation development. Such drugs exhibit poor oral bioavailability. Owing to this many promising new chemical entities fail to reach the market. A plethora of technologies are available to overcome this hurdle and which have been successfully applied to many drug candidates. Of course, these technologies have their limitations which do not make them universally applicable/viable.

Nanotechnology based and lipid based approaches are being widely investigated to improve the solubility profile of BCS class II/IV drugs. Nanosizing is a classical approach based on Noyes-Whitney equation wherein the dissolution rate and saturation solubility of drugs could be increased by reducing size at the micro- or nano-scale to increase the surface area of drug particles. The conventional approaches to produce ultrafine drug particles can be divided into top-down and bottom-up technologies. The use of natural and synthetic lipids has generated much academic and commercial interest as a potential formulation strategy for improving the oral bioavailability of poorly water soluble drugs. These formulations can also enhance drug absorption by a number of ancillary mechanisms, including inhibition of P-glycoprotein-mediated drug efflux and preabsorptive metabolism by gut membrane-bound cytochrome enzymes, promotion of lymphatic transport, which delivers the drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and by increasing GI membrane permeability. These formulations comprise simple solutions of drug in dietary oil and multi-excipient, self-emulsifying drug delivery systems. Self-emulsifying formulations are physically stable, isotropic mixtures of oil, surfactant, co-surfactant and solubilized drug that are suitable for oral delivery in soft or hard gelatin or HPMC capsules. Nanosponges are nanoporous colloidal systems which can be used as carriers for drug delivery. They can be used to solubilize poorly water-soluble drugs and provide prolonged release as well as improve a drug’s bioavailability. Nanosponges may be prepared cross-linking β-cyclodextrins with carbonate bonds. They are used as carriers for active ingredients. Their unique features include possibility of fabrication of particles with a range of dimensions (1µ or more), tunable polarity of the cavities and ability to be linked with different functional groups.
The objective of the present work was comparative evaluation of technologies for solubility and dissolution rate enhancement of some BCS class II/IV drugs and to study the effect on bioavailability of the drug. Telmisartan and cefpodoxime proxetil were the two drugs belonging to BCS class II and IV, respectively which were selected for the study. TEL is an orally active nonpeptide angiotensin II receptor antagonist that acts on the AT$_1$ receptor subtype and is used in the management of hypertension. It is a BCS Class II drug having aqueous solubility of 9.9 µg/ml. Its log P is 7.7 and melting point is 261-263º C. Cefpodoxime Proxetil is an orally administered, extended spectrum, semi synthetic, β-lactam antibiotic of the cephalosporin class. It is a prodrug that is de-esterifed in vivo to Cefpodoxime, its active metabolite, by gastrointestinal wall esterase. Absolute bioavailability of administered dose as a 130 mg tablet (equivalent to 100 mg of Cefpodoxime) in humans is only about 50%. The low bioavailability of CP is mainly attributed to the degradation of its ester side chain by cholinesterase present in the intestinal lumen. Its poor water solubility (approx.400 µg/ml), may also be responsible for its poor bioavailability, as dissolution is a rate-limiting factor in intestinal absorption of poorly water soluble drugs. It is a BCS Class IV drug having log P of 0.99 and melting point 84º.

**Chapter 3: Section 3.4** describes the formulation of nanospores of β-CD cross linked with diphenyl carbonate. The nanospores thus prepared were used as carriers for TEL with the aim to study their effect on solubility of TEL. A linear increase in the solubility of the TEL was observed with increasing concentration of nanospore. The phase solubility plot showed an A$_p$ curve. Solution state interaction studies confirmed entrapment of the drug within the nanochannels as evident from the shift in wavelength ($\lambda$ max) at increasing concentration of NS. The solubility of binary systems (NS and drug) and ternary complex (NS, alkalizer and drug) was found to be increased in D. W., pH 6.8 buffer and 0.1 N HCl. The binary complex with NS showed a 1.91 fold increase in FaSSIF whereas the ternary complex showed 3.35 fold increase. Binary complex with NS showed a release of 30 %, 95% and 36 % in DW., 0.1NHCl and pH 6.8 buffer, respectively in 2h whereas the binary β-CD complex released 52%, 90% and 44% in 2h in DW,0.1N HCl and pH 6.8 buffer. Drug release was higher in case of ternary complex with NS i.e. 67.68% in DW, 75.05% in pH 6.8 buffer and 97.65% in 0.1N HCl after 2h. Ternary complex with β-CD exhibited a
release of 99% in all three media in 2h. We can thus conclude that the release was much faster in the binary and ternary β-CD complexes whereas the nanosponge complexes exhibited a controlled release profile. This property can be exploited to enhance the saturation solubility and dissolution rate as well provide a controlled release of the drug as discussed in Chapter 4: Section 4.4. 

Chapter 3: Section 3.5 describes the preparation of TEL nanocrystals by evaporative antisolvent precipitation technique. Nanosuspensions were first prepared by dissolving TEL in DCM followed by addition of this solution to the antisolvent (water) under high speed stirring. Various solvents were initially screened for preparing the nanosuspensions. Different stabilizers that were used included PVP K30, PEG 6000, poloxamer 188 and TPGS, singly and in combinations. The particle size ranged from 85.63-127.2 nm and zeta potential was between 6.54 and 10.8 mV. An increase of 116.45 % in surface area was evident and contact angle was found to be 27° as against 50.8° for pure drug. Saturation solubility studies in various media revealed an exponential increase in comparison with plain drug. The solubility of nanoparticles in 0.1N HCl was found to be 156.55µg/ml, an almost 4.5 fold increase. In distilled water the increase was 16 fold and in phosphate buffer pH 6.8 the increase was to the tune of 6 times. An increase of 3.74x in solubility in FaSSIF and 5.02x in FeSSIF was observed. The in vitro dissolution studies of nanoparticles revealed 99% drug being released within 30 min whereas in case of Espheres coated with the nanosuspension, almost 95% drug was released in 30 min in 0.1 N HCl as described in Chapter 4:Section 4.5. 

TEL nanosuspension was subjected to in vivo evaluation as the magnitude of increase in saturation solubility and dissolution rate of TEL was greater as compared to that in nanosponges. A 12.59 fold increase in AUC\textsubscript{0-∞} is indicative of significant enhancement in bioavailability of TEL in the form of nanosuspension. The AUMC\textsubscript{0-∞} was found to be 49.085 and 1801.944 for plain TEL and the TEL-nanosuspension respectively. The mean residence time was calculated as 13.706 h for TEL and 39.95 h for TEL-nanosuspension. Thus an increase of 2.91 times was evident in the MRT for the nanosuspension. The apparent elimination rate constant computed from the reciprocal of MRT was found to be 0.072 h\textsuperscript{-1} for TEL and 0.025 h\textsuperscript{-1} for the nanosuspension. This corroborates the MRT values of the formulations. The t\textsubscript{1/2} was found to be 10.12 h and 29.5 h , respectively for TEL and TEL nanosuspension. A
15.6 fold increase in Cmax was observed from 0.364 μg/ml for TEL to 5.7 μg/ml for the nanosuspension. A significant improvement in pharmacodynamic parameters were also observed. Toxicological screening revealed no abnormalities in the cellular structure of the vital organs i.e., heart, liver and kidneys.

Three strategies were evaluated for enhancing the solubility of CP which included self nano emulsifying drug delivery systems (SNEDDS), complexation with nanosponges and nanosizing by bottom up technique. The phase solubility plots of nanosponges with CP were of Bs type indicating formation of complexes of limited solubility. A marginal increase or significant decrease in solubility in various media was evident. In DW an increase of 1.08x was seen whereas in 0.1N HCl and pH 6.8 buffer a decrease of 2.08x and 1.09x respectively, was observed. Interestingly, in FaSSIF and FeSSIF an increase of 1.39x and 2.35x was seen as compared to plain drug in the same media. Binary complexes with β-CD revealed a decrease in saturation solubility in DW and buffers but an increase of 1.14 fold and 1.17 fold in FaSSIF and FeSSIF. The increase in solubility in biorelevant media could be due to presence of surfactants which formed mixed micellar systems causing solubilization of CP. These results with both β-CD and NS indicated that inclusion complexation was not be suitable approach for enhancing bioavailability of CP (Discussed in Chapter 4: Section 4.7).

Nanosuspensions of CP were prepared using combination approach of bottom-up and top-down technology. Different steric stabilizers (non ionic surfactants/hydrophilic polymers) were used to prepare the nanosuspensions. The nanosuspensions were characterized in terms of particle size and zeta potential by Malvern zeta sizer. The free flowing freeze dried nanoparticles were further evaluated by FTIR, DSC, PXRD, saturation solubility studies in different media, surface area, contact angle and in vitro dissolution kinetics. CP nanosuspensions prepared using PEG 6000 and Poloxamer 188 with or without TPGS were found to have minimum particle size and reasonably favourable polydispersity index. The average particle size ranged from 408 nm to 925 nm. Both P 188 and PEG 6000 individually, proved to be better stabilizers in comparison with combinations with TPGS. CP is a soft amorphous powder and hence not amenable to particle size reduction unlike TEL which is a ‘brick-dust’ powder. Hence the extent of particle size reduction was lesser for CP. The specific surface area of nanoparticles containing P188 in a ratio of 1:1 was found to be 2.785 m²/g whereas
for CP it was 1.131 m$^2$/g, an increase of 146.24%. Contact angle of the pure drug was 53.25° and for the nanoparticles it was decreased to 35.5°. The saturation solubility studies in various media indicated a nominal increase of 1.35x in DW, 1.16x in phosphate buffer, 3.14x in FaSSIF and 3.08x in FeSSIF. *In vitro* dissolution studies of CP nanosuspension coated Espheres in DW revealed 49% release in 30 min whereas plain drug was released to the extent of 1.66% during the same period. Thus a significant improvement in dissolution rate was evident. **Chapter 4: Section 4.8.**

SNEDDS were prepared by combining various surfactants, co surfactants and oils. Since CP was found to have maximum solubility in Capmul MCM, Capmul MCM C8, propylene glycol, PEG 400 and TPGS, further studies were conducted using different ratios of these oils and surfactants to identify the microemulsion area. For this ternary phase diagrams were constructed by diluting mixtures of oil and surfactant/co surfactant at certain weight ratios and adding water. After identifying the appropriate combination of surfactant-co surfactant and oil, drug was loaded and the formulations evaluated for % transmission in various media. Five formulations showing maximum % transmission were further characterized on the basis of globule size, zeta potential, self emulsification time, cloud point and *in vitro* dissolution profiles as discussed in **Chapter 3: Section 3.9.** The formulation showing higher & drug release was adsorbed on various adsorbents to convert into solid dosage form. The micromeritic properties as well as retention of self emulsifying properties of solid SNEDDS were determined. The phase solubility study revealed that the microemulsion region was found to be the maximum with a surfactant to co surfactant ratio of 1:0.75 in case of surfactant mix of tween 80: TPGS (1:0.75) and Capmul MCM but at this ratio the mixture was solid at room temperature so the ratio of surfactant mix of tween 80: TPGS (1:0.5) was selected for further studies. Seven formulations (C$_1$-C$_7$) containing varying combinations of oil and surfactant mix and 160 mg CP were prepared and evaluated for % transmittance in different media to assess the retention of solvent properties on dilution. It ranged from 98-99% for C$_1$-C$_6$ except for the formulation containing least concentration of surfactant (C$_7$) which showed % transmittance of 75.26 indicating precipitation of CP on dilution. The globule size for the formulations ranged from 52-63 nm and zeta potential from -13.9 to -4 mV. The formulations released 31-99% drug in a span of 120 min in 0.1N HCl. The self emulsification time ranged from 221-370 sec. All the formulations had a cloud point
above 37°C. For ease of handling, liquid SNEDDS was converted into solid state by adsorption on various adsorbents such as aerosil, blank nanosponge and magnesium trisilicate. In case of aerosil, a ratio of 1:3 (drug: aerosil) was required and with magnesium trisilicate a ratio of 1:1.5 was required. Discoloration was evident in presence of nanosponge which may be attributed to incompatibility between nanosponge components and the oil-surfactant mixture. The micromeritic properties of the solid SNEDDS were evaluated and were found to be satisfactory. SNEDDS mixture was also dissolved in mixture of Isopropyl alcohol and DCM (8:2 v/v) and sprayed onto MCC pellets (Espheres) as a novel method for preparing solid SNEDDS. 

*In vitro* dissolution studies in 0.1 N HCl revealed 90.34% release in 60 min whereas for the liquid SNEDDS it was 93% release in 60 min. Plain CP showed a release of 59% in 60 min. In pH 6.8 buffer the pellets released 98.45% CP in 60 min as against 15% for CP thus indicating enhanced dissolution rate in the form of both liquid and solid SNEDDS. *In vivo* studies of the liquid SNEDDS revealed a significant improvement in oral bioavailability of CP. Microbiological studies revealed lower MIC value for the SNEDDS as compared to plain drug. A 5.36 fold increase in AUC$_{0-\infty}$ was observed in case of CP-SNEDDS as compared to plain CP. The MRT was found to be 2.74 h for CP-SNEDDS while for CP the MRT was 35.63 h. The Cmax and Tmax were found to be 16.768 μg/ml in 3h for CP-SNEDDS whereas for plain CP, Cmax was 3.152 μg/ml in a similar span of time. An increase of 5.31 fold was evident in the Cmax for CP-SNEDDS as compared to plain CP. The apparent elimination rate constant computed from the reciprocal of MRT was found to be 0.0280 h$^{-1}$ and 0.364 h$^{-1}$ for CP-SNEDDS and plain CP, respectively. The plasma half-life as computed by the software was 0.989 and 38.978 h respectively for plain CP and CP-SNEDDS as discussed in Chapter 4: Section 4.9.

Different approaches are available for increasing the solubility, dissolution rate and thereby bioavailability of BCS class II and IV drugs. No approach is universally applicable to all drugs and hence a judicious selection of method is necessitated for every drug candidate. Some, not all, criteria for selection of suitable method can be deduced based on physicochemical attributes of drug molecules. For TEL, nanosizing by bottom-up technology proved to be most effective in achieving the desired increase in solubility and bioavailability. It can also be considered the simplest and most cost-effective methods among all approaches. SNEDDS proved to
be a suitable system for CP as compared to complexation with β-CD nanosponges and nanosizing. It is a relatively simple method and scale-up is easy as the SNEDDS can be directly filled into capsules or converted into solid form by adsorption onto adsorbents or coating onto pellets.

Thus we may conclude that improvement in solubility, dissolution rate and thereby oral bioavailability was achieved by preparing nanoparticles and self nano-emulsifying drug delivery systems for telmisartan and cefpodoxime proxetil, respectively.

**LIMITATIONS:**

Solubility is one of the most fundamental properties of drugs governing its biological effects. Number of approaches are available to enhance the solubility and hence the bioavailability of poorly water soluble drugs. However there is no approach that is universally applicable to all drug moieties. Each method has its inherent drawbacks. Nanosizing using bottom up technology, though well documented and a simple technique, involves use of organic solvents which raises environmental concerns. The top down technology is the preferred option for preparing nanoparticles. However it is an energy intensive process which may have undesirable repercussions on the physical properties of the drugs such as changes in crystalline structure, polymorphism and contamination due to erosion of metallic parts during processing. In both top down and bottom up techniques the percent yield of the nanoparticles is a major issue which needs to be addressed by identifying and controlling key process parameters.

Development of self nano/microemulsifying drug delivery systems is an attractive methodology to improve the aqueous solubility of drugs. However major drawbacks of this technique are that the drug should be lipophilic so that it can solubilize in the oil-surfactant mixture and the use of large amount of surfactants-co surfactants to impart self emulsification properties. Non ionic surfactants are primarily used in SEDDS, SMEDDS and SNEDDS formulations due to their relatively low toxicity. However at high concentrations they cause brittleness of hard and soft gelatin capsules due to their dehydrating effect on the capsule gelatin. Surfactant-free formulations do not have the self emulsifying properties and require *in vivo* digestion.
of the oil to enable the drug to be released. Prolonged use of surfactants may also cause undesirable alterations in the membrane permeability.

**FUTURE SCOPE:**

The prevalence of drugs with poor aqueous solubility has led to the development of multitude approaches to overcome this basic problem affecting pharmacological effect of the drugs. Across the world number of scientists are working on existing methodologies and exploring newer techniques for improving the solubility problems of many drugs. However the focus is drug-centric which means that solubility problems related to individual drugs are being tackled. This involves a lot of scrupulous and time consuming trial and error efforts to suit individual requirements. The reasons for poor drug solubility are variable ranging from lipophilicity, large molecular size to strong crystal lattice bonds, to name a few. There is a need to develop resources in such a way that methods can be selected which are tailor-made for drugs with certain key physicochemical properties affecting drug solubility. This will reduce the time and effort required in such studies. The onus is on the formulators and scientists to develop such resources which will improve the clinical efficacy of poorly water soluble drugs and optimize therapy with respect to pharmacoeconomics.