SYNOPSIS

of the thesis titled

STUDIES ON ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY OF BCS CLASS II/IV DRUGS

To be submitted to
S.N.D.T.Women’s University, Mumbai

For the degree of
Doctor of Philosophy
(Faculty of Technology)

By
Mrs Monica R Rao
M Pharm

Research Guide
Dr. Amrita Bajaj
Professor of Pharmaceutics

C.U.Shah College of Pharmacy,
S.N.D.T. Women’s University,
Juhu Road, Santacruz (W), Mumbai 400 049
June 2011
INTRODUCTION

Drug solubility enhancement is one of the most important challenges in the field of pharmaceutics. Among the five key physicochemical parameters in early compound screening viz. dissociation constant, solubility, permeability, stability and lipophilicity, poor solubility tops the list of critical compound properties. Advances in combinatorial chemistry and high throughput screening have led to the development of large number of molecules with requisite pharmacological activity. However these immobilized receptor techniques lead to the selection of compounds with undesirable physicochemical attributes like high lipophilicity, poor aqueous solubility and high molecular weights. The biopharmaceutical classification system (BCS) is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral absorption of drugs. BCS class II and IV drugs which have low solubility provide a number of challenges for formulation scientists working on oral delivery of drugs. Numerous methodologies have been suggested and practically applied to improve the marketability of such drug candidates. These include the use of particle size manipulation via micronization and nanonization, use of complexing agents such as cyclodextrins, preparation of high energy drug states related to polymorphic or amorphous transformation, use of co-solvents, micellar solutions and lipid based systems for lipophilic drugs.

OBJECTIVES

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. 12-14

**PLAN OF WORK**

- Selection of BCS class II/IV drugs
- Selection of carrier systems/excipients
- Application of nanotechnology based approaches such as nanosizing and use of nanocarriers like nanosponges and lipid based approaches for enhancing solubility
- Evaluation of various systems developed in terms of enhancement of solubility, dissolution rate and permeability (for BCS class IV drugs) and other parameters such as spectral analysis, compatibility studies and stability studies.
- Comparison of approaches for degree of enhancement of above parameters
- Evaluation of suitable approach for increase in oral bioavailability
- *In vivo* studies including toxicological studies, pharmacokinetic and pharmacodynamic assessment

**DRUG PROFILES**

**Telmisartan**: It is an orally active nonpeptide angiotensin II receptor antagonist belonging to BCS class II with an aqueous solubility of 9.9 µg/ml and log P of 7.7. Its oral bioavailability is dose dependent with a 40 mg dose reportedly having an oral bioavailability of 42%. 15
Cefpodoxime proxetil: It is an oral third generation cephalosporin antibiotic of BCS class IV with an aqueous solubility of ~400 µg/ml and absolute bioavailability of 50%\(^6\).

PART I:

- Preformulation studies
- Literature search to identify and select BCS Class II and IV drugs

i) Standardization of drugs: The drugs were characterized as per appropriate monographs.

ii) Spectral characterization by IR, DSC, UV: This was performed to confirm the purity and identity of selected drugs and to identify \(\lambda_{max}\).

iii) Analytical method development: UV and HPLC methods were developed to facilitate quantification of the active.

iv) Drug-excipient compatibility studies: Drug and excipients were mixed in a ratio of 1:1, subjected to different environmental conditions for predetermined time periods and analysed by FTIR.

v) Bioanalytical method development: This was carried out for quantification of drugs in plasma for in vivo studies.

PART II: EXPERIMENTAL (Telmisartan-TEL)

IIA) Formulation development of TEL nanoparticles: TEL nanoparticles were prepared by evaporative antisolvent precipitation technique. Required amount of TEL was dissolved in sufficient volume of solvents. The polymers/surfactants were dissolved in water separately and resulting mixture stirred at 4000 rpm. After formation of a homogenous solution, drug solution was added using a micro pipette with continuous stirring. After complete addition of the drug solution, stirring was continued for 2 h at 10,000 rpm. Various solvents investigated included N-methyl pyrrolidone, acetone, acetonitrile, dichloromethane, chloroform and carbon tetra chloride. The polymers evaluated for their ability to stabilize the nanosuspensions included poloxamer 188, poloxamer 407, HPMC, polyvinyl pyrrolidone K30, tocopherol polyethylene glycol succinate (TPGS) and PEG 6000, singly and in combinations. The nanosuspensions were subjected to particle size analysis using Malvern zeta sizer. Statistical tools were used to identify effect of some
key independent variables on particle size of nanosuspension. The batch showing least particle size was further subjected to ultracentrifugation, freeze drying and characterization by FTIR, DSC, PXRD, saturation solubility studies in different media such as distilled water, 0.1 N HCl, pH6.8 buffer, fasting state intestinal media (FaSSIF) and fed state intestinal media (FeSSIF) and *in vitro* dissolution studies. Surface area, contact angle, solvent residue and metal content of the nanoparticles were also determined. Effect of pH and electrolytes (monovalent & bivalent) was investigated. The nanosuspension was spray coated on Espheres (18-20#MCC pellets) which were then subjected to *in vitro* dissolution studies and SEM.

**IIIB] Formulation development of nanosponge inclusion complex with TEL:** Three types of β-CD nanosponges were prepared using diphenyl carbonate (DPC) as cross-linker. β-CD and DPC in different ratios were mixed and allowed to react at 100°C for 5h under magnetic stirring. Phase solubility equilibrium plots were obtained for binary complexes at room temperature in distilled water. Studies on binary system of drug-NS were carried out by adding excess amount of drug to 20 ml of aqueous solution containing increasing concentrations of NS and stirred for 48 h. Samples were filtered and absorbance read at 296 nm (UV/Vis spectrophotometer). The apparent stability constant was calculated. Solution state interaction studies were carried out by adding increasing concentrations of NS solutions (1–80 ppm) to fixed concentrations of TEL (10 ppm). The samples were kept overnight and then scanned for λmax and absorbance was measured. Spectral shift was observed using UV spectrophotometer. Binary and ternary complexes of TEL with the nanosponge and β-CD separately were prepared by solvent evaporation method and evaluated for drug content ,% yield, saturation solubility, porosity, FTIR, DSC, PXRD, NMR, particle size analysis ,zeta potential, SEM and *in-vitro* dissolution studies.

**PART III: EXPERIMENTAL (Cefpodoxime proxetil-CP)**

**IIIA] Formulation development of CP-SMEDDS:** Self micro emulsifying drug delivery systems (SMEDDS) were prepared by combining various surfactants, co surfactants and oils. The solubility of CP in different oils, surfactants and co surfactants was investigated. The oils investigated included Capmul MCM C8, Capmul MCM, Sunflower oil, Labrafac lipophile WL 1349, and Labrafil M 1944 CS. Different surfactants and co surfactants/cosolvents like tween-20,
TPGS, tween-80, polyethylene glycol (PEG-400) & propylene glycol were incorporated in varying concentrations for preparing the self emulsifying formulations. 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. For each phase diagram, the ratio of the Smix to oil to was varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9(w/w). For the surfactant-co solvent mixture of tween 80 and propylene glycol, ratios of 1:1, 2:1, 3:1, 4:1 (w/w) were taken. Samples were visually checked and determined as being clear micro emulsions or emulsions. The surfactant-co surfactant ratios of 1:0.25, 1:0.5 and 1:0.75 of tween 80 and TPGS and Capmul MCM as the oil phase were investigated. 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. The formulation showing optimum characteristics was adsorbed on various adsorbents to convert into solid dosage form. The micromeritic properties as well as retention of self emulsifying properties of solid SMEDDS were determined.

**IIIB] Formulation development of CP-nanosponges:** CP was also incorporated into nanosponges as described previously for TEL. The complexes were evaluated in terms of phase solubility studies, solution state interaction studies, saturation solubility and *in vitro* dissolution. Compatibility between CP and excipients was evaluated by DSC and FTIR. The products were characterized by SEM and PXRD studies.

**IIIC] Formulation development of Nanosuspensions:** CP nanosuspensions 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 nanoparticles were collected by ultracentrifugation of nanosuspensions and freeze drying the residue. Prior to this, since a sticky mass was obtained on freeze drying the residue of
batch showing least particle size, 1 g of aerosil was dispersed in 100 ml of nanosuspension, frozen in liquid Nitrogen in a cryocan and subjected to freeze drying at -50°C and pressure of 0.04-0.05 mbar. The freeflowing nanoparticles thus obtained were further evaluated by FTIR, DSC, PXRD, saturation solubility studies in different media, surface area, contact angle and in vitro dissolution kinetics.

PART IV: IN VIVO STUDIES:

Pharmacokinetic studies (Cmax, tmax, AUC) for TEL and CP: Wistar/Sprague Dawley rats of either gender were divided into 04 groups as follows: Normal control (Untreated/vehicle), Positive control (drug), Test formulation (nanosuspension for TEL and SMEDDS for CP) Conventional formulation. The formulations were given orally and blood was withdrawn at different time intervals from the retro orbital vein of the animals into heparinized vials, centrifuged and diluted appropriately for analysis by developed HPLC bioanalytical method.

Pharmacodynamic studies (for TEL): Hypertension was induced in the animals by one-kidney-one-clip method and blood pressure was monitored for test and conventional formulation.

Microbiological studies (for CP): MIC of CP was determined by Broth tube dilution method using Nutrient broth for the following organisms: Staphylococcus aureus, Bacillus subtilis, Escherichia coli.

Ex vivo permeability studies (for CP): Permeation studies were performed using Franz diffusion cell with goat intestine as barrier membrane and phosphate buffer pH 6.8 as diffusion media. The sample (liquid SMEDDS) was placed in the donor compartment. Aliquots were withdrawn at time intervals of 30 min upto 8 h and flux was calculated using Fick’s first law eqn.

PART V: RESULTS AND DISCUSSION: (Telmisartan)

VA] Nanosuspension/Nanoparticles of TEL: Evaporative antisolvent precipitation technique combined with moderate shearing was found to be successful in preparing nano sized particles. Among various solvents that were screened DCM was selected as the solvent for TEL due to its higher solubilization potential and low boiling point.
Nanosuspensions containing TPGS in combination with P188/PVK30/PEG 6000 showed particle size range of 85.63-127.2 nm. Since non ionic surfactants were used the zeta potential of all the batches ranged between 6.54 and 10.8 mV due to steric stabilization. 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. The nanosuspensions were found to be stable in presence of monovalent (NaCl) and bivalent electrolyte (CaCl₂) and at pHs of 1.2, 4.6, 6.8 and 7.4. Percent transmittance of the dispersions was measured and found to be almost similar to plain nanosuspension.

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 156.55 μg/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 almost 95% drug was released in 30 min in 0.1 N HCl. No solvent residue was evident in the chromatogram of the freeze dried product. To confirm that the processing does not cause metal contamination, the nanosuspension was subjected to atomic absorption spectroscopy and the Fe content was found to be < 2 ppm and Cr content was < 0.1 ppm.

**VB] Nanosponges:** A linear increase in the solubility of the TEL was observed with increasing concentration of NS. The phase solubility plot showed an Aₚ curve for NS which indicated formation of inclusion complex of TEL with NS in 1:2 stoichiometric ratio. The stability constant for complex at 25°C was found to be 255.10² M⁻¹. Solution state interaction studies confirmed entrapment of the drug into the β-CD and the nanochannels as evident from the shift in wavelength (λ max) at increasing concentration of NS. Saturation solubility of TEL in the β-CD complex was found to be 57.22 μg/ml whereas in NS it was 45.92 μg/ml. However, solubility in NS was much better than TEL itself. 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. Binary and ternary complexes with β-CD exhibited greater increase in saturation solubility than NS complexes. Solubility was enhanced over 8.53-folds in case of ternary complex and 4.63-folds in case of binary complex with NS in D.W. Ternary complex with β-CD and NaHCO₃ showed an exponential 20 fold increase in solubility. Solubility was enhanced over 4.66-folds in case of
ternary complex and 3.72 folds in case of binary complex with NS in pH 6.8 buffer. The binary complex with NS showed a 1.91 fold increase in FaSSIF whereas the ternary complex showed 3.35 fold increase. Interestingly in FeSSIF all the complexes exhibited a marginal increase in saturation solubility in the range of 1.05-3.17 times that of TEL whereas ternary complex with β-CD showed an increase of 8 fold. A 68.12% increase in the porosity of NS as compared to β-CD was evident.

IR spectra of complex showed broadenings and disappearance of some peaks. The DSC spectra of TEL showed a sharp melting endothermic peak at 269°C. DSC thermograms of drug loaded NS did not contain sharp drug melting peak and that of NaHCO₃ added drug loaded NS showed broad endothermic peak at 260°C. Diffraction pattern of pure drug showed distinctive peaks at 2θ diffraction angle of 6.8°, 14.2° and 22.3°. PXRD spectra of β-CD and NS showed a significant reduction in the number and intensity of peaks whereas that of NS complex showed reduced peak intensity indicating drug entrapment as well as amorphization of the drug. The particle size of the plain NS was found to be 664 nm with a polydispersibility index of 0.451. Zeta potential and mobility was found to be -3.73 mV.

*In-vitro* dissolution studies revealed that the inclusion complexes released the drug to a greater extent as compared to TEL. Binary complex with NS showed a release of 30 %, 95% and 36 % in D.W., 0.1NHCl and pH 6.8 buffer, respectively in 2h whereas the binary β-CD complex released 52, 90 and 44% in 2h. Drug release was higher in case of ternary complex with NS i.e. 67.68% in D.W, 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.

**PART V] RESULTS AND DISCUSSION: (Cefpodoxime Proxetil)**

**VIA] SMEDDS:** CP was found to have maximum solubility in Capmul MCM, Capmul MCM C8, propylene glycol, PEG 400 and TPGS. For constructing ternary phase diagrams to identify the microemulsion region the surfactant-co surfactant ratio was taken as 1:0.25, 1:0.5 and 1:0.75 of Tween 80 and TPGS and Capmul MCM was selected as the oil phase. The phase solubility study revealed that the micro emulsion 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 (C1-C7) containing varying combinations of oil and surfactant mix and 160 mg CP were prepared and evaluated for % transmittance in different media. It ranged from 98-99% for C1-C6 except for the formulation containing least concentration of surfactant (C7) 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 -13.8 to -4 mV. Polydispersity index ranged from 0.19-0.26 indicating uniform particle size distribution except for formulation C3 which had a PDI of 0.605.

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. Self emulsification time is an important benchmark for the emulsification ability of the oil-surfactant mixture. A cloud point of above 37°C is desirable as such a formulation will not lose its emulsification potential at physiological temperature. All the formulations had a cloud point above 37°C. For ease of handling, liquid SMEDDS 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 SMEDDS were evaluated and were found to be satisfactory. SMEDDS mixture was also dissolved in mixture of isopropyl alcohol DCM (8:2) and sprayed onto MCC pellets as a novel method for preparing solid SMEDDS. In vitro dissolution studies in 0.1 N HCl revealed 90.34% release in 60 min whereas for the liquid SMEDDS 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 SMEDDS.

VIB] Nanosponge formulation: The phase solubility plots of nanosponge with CP were of Bs type indicating formation of complexes of limited solubility. The stability constant of the complexes is indicative of the strength of interaction between the host and guest. At the same time a high value also leads to slow release of the drug. The stability constant for NS-CP was found to be 1868.79 kg/mol, thus pointing to the likelihood of very slow release of CP from the complexes. This was further corroborated by the results of saturation solubility and dissolution rate of CP. 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 pH6.8 buffer 2.08x and 1.09x decrease was seen respectively. 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 1.71 fold in FaSSIF and FeSSIF. The increase in solubility in biorelevant media could be due to presence of surfactants which form mixed micellar systems causing solubilization of CP. These results with both β-CD and NS indicate that inclusion complexation may not be suitable approach for enhancing bioavailability of CP.

IR spectra of the CP loaded nanosponge did not show the characteristic peaks of the drug whereas the DSC thermograms of CP loaded NS showed a very broad and shallow endothermic peak with an onset at 80°C and endset at about 100°C which could be due to presence of CP in the from of non inclusion complex with NS. The PXRD spectra of plain NS and CP-NS also showed similarities with sharp peaks evident at 11, 14, 18 and 27°. The diffractogram for plain CP showed a halo pattern indicative of its amorphous nature. Thus we can infer from these results that nanosponge inclusion complexation did not result in increased solubility and dissolution rate of CP.

VIC] Nanosuspension/Nanoparticles: For CP, nanosuspensions prepared using PEG 6000 and Poloxamer 188 with or without TPGS were found to have least particle size and reasonably favourable polydispersity index. The average particle size ranged from 407 nm to 925 nm. Both P 188 and PEG 6000 singly, proved to be better stabilizers in comparison with combinations with TPGS. The average particle size for nanosuspension prepared with PEG 6000 (1:1 of CP & PEG 6000) was found to be 408 nm and with P188, it was 410 nm with a polydispersity index of 0.489 and 0.123 respectively. Combining TPGS resulted in flocculation and thereby destabilization of the nanosuspension in case of PEG 6000 (1:1:1).With TPGS and P188 (1:1:1) combination, the particle size was 465 nm and in ratio of 1:2:1 it was 724 nm with PDI of 0.385 and 0.267 respectively. The magnitude of particle size reduction was 39-65 %.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 zeta potential ranged from 0.979-
11

9.45 mV. 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 m²/g, an increase of 146.24%. Contact angle of the pure drug was found to be 53.25° and for the nanoparticles it was 35.5°. Lower contact angle is indicative of improved wettability of the nanoparticles.

The saturation solubility studies in various media indicated a nominal increase of 35.64% in DW, 16.38% in phosphate buffer, 214% in FeSSIF and 208.23% in FeSSIF. In 0.1N HCl a 9.17% decrease was observed. The higher % increase in saturation solubility in FaSSIF and FeSSIF could be attributed to presence of soya lecithin and sodium taurocholate in the media which could be causing micellar solubilization effect as well as reducing the solid-liquid interfacial tension thereby improving the wettability of the particles. In vitro dissolution studies of CP nanosuspension coated MCC pellets in DW revealed 49% release in 30 min whereas plain drug released 1.66% during the same period. Thus a significant improvement in dissolution rate was evident.

VII] Selection of formulations:
Based on the results of saturation solubility and percent drug released at various time points, nanoparticles of TEL exhibited greater enhancement and were therefore subjected to in vivo studies. In case of CP, the SMEDDS formulation showed a significant improvement in saturation solubility and dissolution rate and hence further studies were conducted on the SMEDDS of CP.

VIII] Statistical studies were conducted for nanosuspensions of TEL and SMEDDS of CP using factorial design. The effect of certain key independent variables on the selected response variable subjected to statistical studies using Design Expert software.

IX] Scale up studies: Based on the results of saturation solubility and in vitro dissolution studies in various dissolution media the nanocrystal/nanosuspension formulations were found to have the maximum enhancement in these two parameters for TEL. For CP, the SMEDDS was found to have a significant effect on saturation solubility and dissolution rate. Hence these formulations were subjected to scale up studies. For preparing the nanosuspension of TEL, a stainless steel jacketed vessel (Capacity: 1 L) equipped with an overhead stirrer was used. The time and speed of stirring was optimized at 4h and 10,000 rpm. A gradient increase and decrease in rpm was required to minimize formation of foam due to the surfactants which tends to interfere with evaporation of the solvent. Baffles were required to prevent localized shearing and to ensure uniform turbulence in
the dispersion. The nanosuspension was characterized in terms of particle size which was found to be slightly higher than that of lab-scale batch (nm). Scale-up of SMEDDS of CP was relatively simple as it involved only two steps i.e. mixing of the drug and oil-surfactant-co surfactant and spray coating onto preformed MCC pellets after dissolving the liquid SMEDDS in DCM. For scale-up, 10 g of liquid SMEDDS containing 1.6 g CP was dissolved in 100 ml of DCM and sprayed on 100 g of pellets at a pan speed of 40 rpm, atomizing air pressure of 2lb/inch² and pellet bed temperature of 60-70°C. The time required for applying the complete solution (dispersion) was 75 min. The pellets were evaluated in terms of weight gain, % drug content and in vitro dissolution studies which were found to be almost similar to the lab-scale batch with only marginal differences.

X] STABILITY STUDIES: The following samples were subjected to stability studies:
- TEL- Nanosuspension (T8) and pellets coated with nanosuspension
- CP- Liquid SMEDDS (C5) and pellets coated with liquid SMEDDS

Conditions: 1] 40°C & 75%RH  2] 4°C  3] Ambient conditions (all for 6 months)
Samples will be visually inspected for discoloration, flocculation, sedimentation, particle size (for nanosuspension), self emulsification and % transmittance (SMEDDS)

XI] IN VIVO STUDIES:
- Pharmacokinetic studies (Cmax, tmax, AUC) for TEL and CP: The developed formulation of TEL and CP showed a significant improvement in bioavailability as compared to plain drugs and conventional/marketed formulations.
- Pharmacodynamic studies (for TEL): The nanosuspension formulation showed a faster onset of action as compared to pure drug.
- Microbiological studies (for CP): MIC of CP-SNEDDS was found to have a lower value of MIC than the plain drug and marketed product
- Ex vivo permeability studies (for CP): The average flux for plain CP and CP-SMEDDS was found to be 0.104 and 0.985 µg/cm²-min, respectively; an increase of ~ 9.5 times. Permeability (P), determined from the slope of amount diffused vs time, was found to be 19.72 for CP and 206.0 for the SMEDDS formulation. It was found to be enhanced to the tune of 10.4 times.
➢ **Toxicological studies (for TEL and CP):** Sub acute oral toxicity studies were performed as per OECD guidelines using Fixed dose procedure and no gross physical and clinical changes were observed. Tissue distribution studies and histopathological screening of various organs were performed.

**XII] CONCLUSION:**
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 could also be considered the simplest and most cost-effective methods among all approaches. **SMEDDS** proved to be a suitable method 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 liquid SMEDDS 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 micro-emulsifying drug delivery system for telmisartan and cefpodoxime proxetil, respectively.

**KEY REFERENCES:**


4. Kim,C.,Park,J.,Solubility enhancement for oral drug delivery:can chemical structure modification be avoided’ *Am.J.Drug Deliv.*,2(2004),113-130


15. http://www.drugbank.ca/drugs/DB0096 Telmisartan accessed on 14.06.2.11


Research Guide
Dr. Amrita Bajaj
Professor (Pharmaceutics)

Research candidate
Mrs. Monica Rao

Date:

C.U. Shah College of Pharmacy
S.N.D.T. Women’s University,
Juhu Road, Mumbai 400 049