10.1 SUMMARY

Oral route is the most accepted drug administration route because of its advantages: painlessness, easy self-administration, high patient compliance, and feasibility for outpatients. Nevertheless, chemical and enzymatic barriers in the gastrointestinal (GI) tract hinder the effectiveness of oral drug delivery. The epithelial cell monolayer in the GI membrane also contributes to poor permeability for numerous drugs. Some poorly soluble drug molecules are difficult to dissolve in the GI tract, resulting in low bioavailability.

The improvement in oral delivery using nanocarrier systems has gained more attention recently. Nanoparticles are defined as particles ranging in size from 1 nm to several hundred nanometers that can load drugs for efficient delivery. With respect to pharmacokinetics, the drugs in nanocarriers generally revealed increased half-life, reduced clearance, and increased mean residence time (MRT). By optimizing the formulations, the delivery efficiency and bioavailability can be ameliorated to promote the therapeutic potency with reduced side effects.

Lipid-based drug delivery systems (LBDDS) are promising, since lipids are known oral drug absorption enhancers, can be prepared with low particle size and may be a promising strategy to improve the rate and extent of oral absorption. The availability of lipid excipients with acceptable regulatory and safety profiles with their bioactive property (ability to enhance oral bioavailability) has aided in the development of lipid based formulations as a means for drug delivery. The affinity of excipients with which lipophilic drugs bind to, and interchange between, these carrier systems can have a significant impact on the free drug fraction available for absorption, distribution, metabolism, and excretion and can therefore play a major role in defining both drug pharmacokinetics and therapy. Among the different types of lipid based nanocarriers, Solid Lipid Nanoparticles (SLNs) and Self Microemulsifying Drug Delivery System (SMEDDS) are at the forefront of the potential application in oral drug delivery systems. Because the co-administration of lipids with drugs also impact their absorption pathway because some lipophilic drugs are directly transported via intestinal lymphatic to the systemic circulation which improves its oral bioavailability. SLNs and SMEDDS can effectively overcome the challenges associated with oral delivery of drugs which are poor water soluble, instable in the GIT, having poor permeability, P-gp efflux and presystemic drug metabolism.

Schizophrenia is a complex neuropsychiatric disorder related to cognitive impairment, stereotype, locomotion, ataxia etc. Treatment approaches for schizophrenia include "typical" and "atypical" antipsychotics. "Typical" antipsychotics are characterized by undesirable side effects such as extrapyramidal symptoms (EPS), hyperprolactinemia, tardive dyskinesia and possible neuroleptic malignant syndrome. The "atypical" antipsychotic drugs can be differentiated from traditional antipsychotics by their low or negligible levels of these unwanted side effects.

The main hurdle in the treatment of CNS disorder is the complexity of the blood–brain barrier (BBB) hampers the entry of the chemical entities into the brain, causing an insufficient CNS exposure for the compound to be pharmacologically effective. The nanoparticles can improve brain uptake by augmenting brain-blood capillaries retention which results in a high concentration gradient across Blood Brain Barrier, opening of tight junctions and transcytosis of nanoparticle through endothelium.

Asenapine maleate (AM) is an atypical antipsychotic which shows strong $5HT_2A$ (serotonin) and D_2 (dopamine) receptor antagonism. Asenapine maleate is a BCS class II having log p of 4.9. The oral bioavailability of AM is <2% due to its extensive first pass metabolism. It is mainly metabolized by CYP450 isozymes such as CYP3A4, CYP1A2, CYP2D6, CYP2B6 and CYP2C19. It shows dose and time dependent hepatotoxicity with oral administration, metabolite concentration dependent cardiac arrhythmias, as well as significant drug-drug-interactions.

Lurasidone Hydrochloride (LH) is an atypical antipsychotic that is a D_2 and 5-HT_2A receptor blocker**.** Lurasidone HCl is a poorly water soluble having log P value of 5.6. The oral bioavailability of LH is 9-19% because it is metabolized mainly via CYP3A4. It is recommended that Lurasidone HCl should be administered with food. The adverse effects associated with LH is somnolence, akathisia, nausea, parkinsonism, and agitation.

Pharmaceutical formulation development involves complex procedure which includes various process and formulation variables that can affect quality of final product. The effect of these individual parameters and their interaction can affect the quality of critical quality attribute (CQA). Thus, Quality by Design (QbD) aids in understanding effect of these critical processing parameters (CPPs) by identifying risk identification (fishbone diagram), risk analysis (Screening design) and optimization using Design of Experiment (DOE).

The present investigation was aimed to develop, optimize by QbD and evaluate lipid based nanoformulations (SLNs and SMEDDS) of AM and LH to improve their oral bioavailability by reducing first pass metabolism via intestinal lymphatic system.

Asenapine maleate loaded Solid Lipid Nanoparticles (AM-SLNs) were prepared using high speed homogenization followed by ultrasonication method. The formulation was optimized by applying Quality by Design (QbD) concept. Initial risk assessment was carried out using Ishikawa diagram. Preliminary optimization of various process and formulation parameters were carried out to select range for screening design. The formulation and process parameters were screened using Plackett Burman Design (PBD) and critical factors were further optimized by applying Central Composite Design (CCD), a type of RSM. The particle size (PS) and entrapment efficiency (EE) were taken as response variables. Pareto chart, Normal plot and half normal plots identified Lipid concentration, Surfactant concentration and sonication time as critical factors affecting PS and EE. The optimized batch of CCD showed PS, EE and zeta potential of 114.3±3.5 nm, 84.10±2.90% and -12.9±3.8 mV respectively. Contour and response surface plots showed utility in explaining effects of independent variables on response. Check point batch was prepared and the observed value of PS and EE were found to be in good agreement with predicted values. Desirability plot showed value of 0.969 which is near to 1 which indicated accuracy and suitability of predicted desirability for responses. Overlay plot was generated to prove robustness of generated design space. AM-SLNs were lyophilized using different cryoprotectants and minimum enhancement ratio (1.16) was observed with trehalose in the ratio of 1:3 with respect to solid content.

The FTIR spectra of lyophilized AM-SLNs showed absence of characteristic peaks corresponding to AM but peak corresponding to GMS was present confirming the encapsulation of drug in GMS. DSC study of lyophilized AM-SLNs showed absence of AM peak in thermogram indicating conversion of crystalline state of AM to amorphous state. XRD study supported the results of DSC study and showed crystallinity was decreased by incorporating AM into SLNs. The TEM image of the AM-SLNs exhibited a spherical shape, and a dense lipid matrix without aggregation having particle size <200 nm.

In vitro release study from AM-SLNs showed only 9.23±2.72% in acidic medium indicating inclusion of AM into lipid nanoparticles significantly reduced the AM release in acidic pH. A slow and sustained release of AM (92.09±3.40%) from AM-

SLN was observed in phosphate buffer pH 6.8 at the end the 24 h. Of the various release models, AM SLN fitted well to Korsmeyer Peppas model and AM release was found to be classical fickian mechanism.

Ex vivo release study of AM-SLNs showed only 7.23±5.54% AM was diffused from SLNs in the stomach. Subsequent diffusion of the AM through intestine was relatively slower and total 99.45±3.70% of drug was diffused at the end of 24 h from AM-SLNs indicating significant amount of AM will be carried to the intestine by incorporating into SLNs. Moreover, small particle size and presence of permeation enhancer excipient (TPGS) in the SLNs might lead to an enhanced and effective absorption of AM.

Cell viability study showed 100% viability with blank and AM loaded SLNs upto 100 µg/ml concentration. Qualitative uptake study using confocal microscopy showed significant increase in the intracellular uptake of AM-SLNs, both in the cell cytoplasm as well as in the nucleus as compared to dye solution. Quantitative uptake study using flow cytometry showed that Mean Fluorescence Intensity (MFI) with Coumarin-6 loaded SLN was increased 99.24 times with respect to plain dye solution. The uptake mechanism across Caco-2 cell line followed energy dependent transport. The experimental results suggested that intracellular uptake of AM-SLNs was significantly reduced to 22% and 47% in presence of chlorpromazine and nystatin respectively. Thus, it can be said that uptake of AM-SLNs involved clathrin- and lipid raft/caveolae-mediated endocytosis. The apparent permeability coefficient (Papp) of the AM-SLNs and AM suspension was found to be 6.25×10^{-6} cm/s and 0.89×10^{-6} cm/s, respectively. The transport of SLNs exhibited 7.02 times higher drug permeation than that of AM suspension at the end of 4 h.

The in vivo pharmacokinetic, lymphatic transport, pharmacodynamic and acute toxicity study was carried out using female Sprague–Dawley (SD) rats. The peak plasma concentration (C_{max}) after oral administration of AM-SLNs and AM suspension was found to be 66.32±10.34 and 1396.44±116.81 ng/ml respectively which was 21.05 times of that from AM suspension. The relative bioavailability ($F_{relative}$) of AM-SLNs was 48.35 fold increased as compared to AM suspension. T_{max} and Mean Residence Time (MRT) was prolonged with AM-SLNs as compared to AM suspension. The enhanced intestinal permeation can be due to presence of TPGS having lymphotropic and strong CYP3A4 inhibitory activity. Thus, the intestinal absorption of AM was enhanced significantly by incorporating into SLN formulation compared with a AM suspension.

Lymphatic transport study using cycloheximide showed 31.06% reduction in AUC_{total} compared with that without the treatment of cycloheximide in rats. This study proved lymphatic transport of AM-SLNs. Thus, it can be said that both lymphatic transport and endocytosis involved in the transport of AM-SLNs.

The pharmacodynamic study showed significant improvement in cataleptic response, motor coordination, cognitive function and behavioral parameters such as locomotion, stereotypy and ataxia as compared to AM suspension. Thus, AM SLNs proved their efficacy in the treatment of schizophrenia with reduction in extrapyramidal symptoms (EPS).

Stability study showed no significant change in particle size, zeta potential and drug content when they were stored at refrigerated condition as compared to storage at room temperature. Hence, recommended storage condition for better stability of AM-SLNs is under refrigeration.

Asenapine maleate loaded SMEDDS (AM-SMEDDS) were prepared and optimized using D-optimal mixture design by taking oil concentration, surfactant concentration and cosurfactant concentration as independent variables. The globule size, % transmittance and self-emulsification time were taken as response variables. Capryol 90, Cremophor EL and Transcutol HP were selected as oil, surfactant and co-surfactant for formulation development. Pseudoternary diagram showed maximum microemulsion region at 1:1 ratio of Cremophor EL and Transcutol HP as compared to other ratios. The optimized batch showed globule size, zeta potential and drug content of 21.12±1.2 nm, -19.3±1.8 mV and 99.8±1.69% respectively. Two component mixture plot, contour plot and response surface plot showed utility in explaining effect of independent variables on response variables. The desirability of 0.950 indicating model was accurate and reliable. The optimized batch was found to be robust to dilution at different extent with different media. The self-emulsification time, viscosity and % transmittance was found to be 28±4 sec, 48.6±1.1 cP and 99.2±0.4% respectively. The developed SMEDDS showed cloud point at 87 °C, indicating stability at physiological temperature. The optimized SMEDDS was found to be stable at heating cooling cycle and centrifugation test.

FTIR spectra of AM-SMEDDS showed absence of characteristic peaks of AM indicating that drug was completely solubilized in oil phase of SMEDDS. The TEM image of optimized batch showed spherical globules with globule size in the range of

20-40 nm and each globule was surrounded by thick layer indicating presence of surfactant layer.

In vitro drug release study of AM suspension showed a fast release (89.44±3.03%) of drug was observed in 2 h in acidic condition. In contrast, AM-SMEDDS, only 20.23±4.02% of AM was released in acidic medium whereas more than 99.2±3.36% of AM was released at the end of 8 h in phosphate buffer pH 6.8 indicated significant amount of drug will be carried to intestine inside the small microemulsion globules and the small globule size provides high surface area, which permits fast drug release.

Ex vivo permeation study of AM suspension indicated most of the drug was permeated through stomach (~90%) and drug available for lymphatic uptake was very low whereas AM-SMEDDS showed only 15% diffusion through stomach and ~85% drug was diffused through intestinal membrane. Hence, it can be said that significant amount of AM will be carried to the intestine.

The cell viability did not decrease significantly with AM (>80%) indicating AM was non-toxic. Blank SMEDDS showed 100% cell viability upto 100 µg/ml concentration. No significant difference was observed in cell viabilities between blank and AM loaded SMEDDS which inturn confirmed non-toxic effect of AM. Qualitative uptake study using confocal microscopy showed significant increase in the intracellular uptake of AM-SMEDDS, both in the cell cytoplasm as well as in the nucleus as compared to dye solution. Quantitative uptake study using flow cytometry showed that MFI with Coumarin-6 loaded SMEDDS was increased 38.90 times with respect to plain dye solution. The permeability coefficient of the AM-SMEDDS was significantly higher than that of AM suspension. P_{app} of the AM-SMEDDS and AM suspension was found to be 4.46×10^{-6} cm/s and 0.89×10^{-6} cm/s, respectively, indicating that AM-SMEDDS showed significantly higher intestinal permeability than AM suspension. The SMEDDS exhibited 5.01 times higher AM permeation than that of AM suspension at the end of 4 h. The enhanced permeation of AM-SMEDDS might be due to the nano-size of droplets, solubilization improvement and CYP3A inhibitory activity of Cremophor EL which increased drug transport across Caco-2 cells as compared to drug suspension.

The pharmacokinetic study showed that the C_{max} and AUC_{total} of AM after oral administration of AM-SMEDDS (1031.34±39.60 ng/ml, 13361.42±189.34 ng.h/ml) were significantly higher than those obtained from AM suspension (66.32±10.34 ng/ml, 567.90±34.01 ng.h/ml). The relative bioavailability was found 23.53 times higher than that of drug suspension implying SMEDDS were effective in increasing oral

bioavailability of AM. T_{max} and Mean Residence Time (MRT) was prolonged with AM-SMEDDS as compared to AM suspension. This enhanced permeation could be due to nano sized globules, absorption enhancing property of Cremophor EL and Transcutol HP and CYP3A inhibitory activity of Cremophor EL.

Lymphatic transport study using CHX showed 35.67% reduction in AUC_{total} compared with that without the treatment of CHX in rats. This study proved lymphatic transport of AM SMEDDS.

The pharmacodynamic study showed significant improvement in cataleptic response, motor coordination, cognitive function and behavioral parameters such as locomotion, stereotypy and ataxia as compared to AM suspension. Thus, AM-SMEDDS proved their efficacy in the treatment of schizophrenia with reduction in EPS.

No significant change in the globule size, drug content, zeta potential and self-emulsification time was observed in AM-SMEDDS during 3 months of storage at room temperature.

Lurasidone Hydrochloride loaded solid lipid nanoparticles (LH-SLNs) were developed and optimized by applying QbD concept using two statistical approaches: Plackett Burman Design (Screening design) and Box Behnken Design, a type of RSM. Initial risk assessment was carried out using Ishikawa diagram. Seven high risk factors were identified in a risk analysis study to have potential impact on SLN particle size and EE. Pareto chart, normal plot and half normal plot indicated that lipid concentration, homogenization pressure and homogenization cycle were critical factors affecting PS and EE.

The optimized batch of LH-SLNs showed PS, EE and zeta potential of 139.8 ±5.5 nm, 79.10± 2.50% and -30.8±3.5 mV respectively. Contour and response surface plots showed utility in explaining effects of independent variables on response. Check point batch was prepared and the observed value of PS and EE were found to be in good agreement with predicted values. Desirability plot showed value of 0.916 which is near to 1 which indicated accuracy and suitability of predicted desirability for responses. Overlay plot proved the robustness of generated design space. LH-SLNs were lyophilized using different cryoprotectants and enhancement ratio was found to be lowest (1.16) for sucrose in 1:3 ratio of total solid content.

The FTIR spectra of lyophilized LH-SLNs showed absence of characteristic peaks corresponding to LH but peak corresponding to GMS was present confirming the encapsulation of drug in GMS. Thermogram of lyophilized LH-SLNs showed

endothermic peak at 56.58°C representing the melting point of GMS but the absence of endothermic peak of LH indicates conversion of LH from crystalline to amorphous form in the lipid matrix. The absence of typical peaks of LH in XRD of lyophilized SLN confirmed the amorphization of LH in lipid matrix. The change in crystallinity may have impact on drug release. The TEM image of LH-SLNs showed uniform size distribution of lipid nanoparticles (100–150 nm) having dense lipid matrix with spherical shape.

In vitro drug release profile of LH suspension indicated most of the LH (91.44±3.93%) was released in acidic medium and subsequent release 96.1±2.86% in phosphate buffer. In contrast, release profile of LH-SLNs showed slow release of LH in acidic medium (<10%) in 2 h. The inclusion of LH into lipid nanoparticles significantly reduced the LH release at acidic pH 1.2. Subsequently, it showed slow and sustained LH release (92.09±4.23%) up to 24 h in phosphate buffer. Drug release kinetics followed Higuchi model. The diffusional release was found to follow anomalous transport.

Ex vivo drug release from LH suspension showed that 94.30±2.97% of LH was diffused through stomach whereas only 1% LH was diffused through intestine. In contrast, LH-SLNs showed only 10.77±1.74% LH was diffused from LH-SLNs in the stomach. Subsequent diffusion of the LH through intestine was relatively slower and total 94.15±4.70% of drug was diffused at the end of 24 h indicating slow and sustained release of LH from LH-SLNs. The small particle size will provide high surface area for diffusion and more drug will be available for intestinal uptake.

The cell viabilities did not significantly decrease after incubation upto 100 µg/ml of blank SLNs for 4 h indicating the carrier used for SLNs itself was non-toxic. Qualitative uptake study using confocal microscopy for LH-SLN showed enhanced, time dependent intracellular uptake with strong fluorescence intensity, both in the cell cytoplasm as well as in the nucleus at the end of 4 h incubation period implicating nanoparticles was easily internalized into Caco-2 cells as compared to plain dye solution. Quantitative uptake study showed that MFI with Coumarin-6 loaded SLN was increased 71.71 with respect to plain dye solution. The enhanced uptake of SLNs might be due to penetration enhancing effect of sodium deoxycholate present in SLNs. The uptake mechanism across Caco-2 cell line followed energy dependent transport. The experimental results suggest that intracellular uptake of LH-SLNs was significantly reduced to 43% and 56% in presence of chlorpromazine and nystatin respectively. Thus, it can be said that uptake of LH-SLNs involved clathrin- and lipid raft/caveolae-

mediated endocytosis. The result of permeation study showed that P_{app} of the LH loaded SLN and drug suspension was found to be 4.46×10^{-6} cm/s and 1.79×10^{-6} cm/s, respectively. The transport of SLNs exhibited 2.50 times higher drug permeation than that of drug suspension at the end of 4 h. LH loaded SLNs showed significantly higher intestinal permeation as compared to drug suspension. This could be due to presence of penetration enhancer, sodium deoxycholate in SLNs.

In vivo pharmacokinetic study showed that C_{max} of LH from the LH SLNs (578.23±49.03 ng/ml) was significantly higher than LH suspension (209.23±27.41 ng/ml) which was 2.76 times of that from LH suspension ($p>0.05$). The area under curve (AUC_{total}) from LH-SLNs and LH suspension was 5871.84±139.30 ng.h/ml and 1139.02±90.17 ng.h/ml which was 5.16 fold compared with that of LH suspension. This could be due to presence of sodium deoxycholate which acts as penetration enhancer due to the membrane destabilizing activity which may have increased intestinal absorption of LH.

Lymphatic transport study showed that the AUC_{total} of LH-SLNs was reduced about 35.67% as compared to without the treatment of cycloheximide in rats. Thus, it can be said that both lymphatic transport and endocytosis involved in the transport of LH-SLNs.

The pharmacodynamic study showed significant improvement in cataleptic response, motor coordination, cognitive function and behavioral parameters such as locomotion, stereotypy and ataxia as compared to LH suspension. Thus, LH-SLNs proved their efficacy in the treatment of schizophrenia with reduction in EPS.

Stability study showed no significant change in particle size, zeta potential and drug content when they were stored at refrigerated condition as compared to storage at room temperature. Hence, recommended storage condition for better stability of LH-SLNs is under refrigeration.

Lurasidone hydrochloride loaded SMEDDS (LH-SMEDDS) were prepared and optimized using 3^2 factorial design by taking oil concentration and K_m (surfactant to cosurfactant ratio) as independent variables. The globule size, % transmittance and self-emulsification time were taken as response variables. Capmul MCM C8, Cremophor EL and Transcutol HP were selected as oil, surfactant and co-surfactant for formulation development. Pseudoternary diagram showed maximum microemulsion region at 3:1 ratio of Cremophor EL and Transcutol HP as compared to other ratios. The optimized batch showed globule size, zeta potential and drug content of 49.2±1.60 nm, -10.3±2.30

mV and 99.5±2.00% respectively. The desirability of 0.987 indicated that the model was accurate and reliable. The effect of independent variables on response variables were elucidated using contour and response surface plots. The optimized batch was found to be robust to dilution at different extent with different media. The self-emulsification time, viscosity and % transmittance was found to be 35.0±2.0 sec, 44.23±2.30 cP and 99.7±1.30 % respectively. The developed SMEDDS showed cloud point at 74.5 °C, indicating stability of LH-SMEDDS in vivo. The optimized SMEDDS was found to be stable at heating cooling cycle and centrifugation test.

FTIR spectra of LH-SMEDDS showed absence of characteristic peaks of LH indicating that drug was completely solubilized in oil phase of SMEDDS. TEM image of the optimized SMEDDS after dilution appeared as dark, spherical globules. The size was found to be in the range of 30-50 nm.

In vitro drug release profile LH suspension showed a fast release (91.67±3.78%) in 2 h during acidic condition. In the case of LH-SMEDDS, only 18.44±3.12% of drug was released in acidic medium whereas more than 98.2±4.19% of LH was released at the end of 8 h in phosphate buffer. More amount of drug would be reaching to intestine inside the small microemulsion globules. This small globule size will provide higher surface area, which will permit faster rate of drug release.

Ex vivo drug release profile of drug suspension indicated most of the drug was permeated through stomach (~83%) and drug available for lymphatic uptake was very low. In case of LH-SMEDDS, it showed only 15% diffusion through stomach and ~85% drug was diffused through intestinal membrane. The permeation of LH from the intestine was enhanced with SMEDDS as compared to drug suspension.

Blank and LH-SMEDDS showed 100% cell viability upto 100 µg/ml concentration. No significant difference was observed in cell viabilities between blank and LH-SMEDDS. Qualitative uptake study using confocal microscopy showed time dependent and enhanced intracellular uptake of LH-SMEDDS as compared to plain dye solution at the end of 4 h which could be due to presence of Cremophor EL and Transcutol HP. Flow cytometry study showed that MFI of Coumarin-6 loaded SMEDDS was increased 25.57 times with respect to plain dye solution. P_{app} of the LH loaded SMEDDS and drug suspension was found to be 3.57×10^{-6} cm/s and 1.79×10^{-6} cm/s, respectively, indicating that SMEDDS exhibited 2.5 times higher drug permeation than that of drug suspension at the end of 4 hours.

The C_{max} and AUC_{total} of LH after oral administration of SMEDDS (332.31±21.32 ng/ml, 3323.55±133.40 ng.h/ml) were significantly higher than those obtained from drug suspension (209.23±27.41 ng/ml, 1139.02±90.17 ng.h/ml) suggesting improvement in rate and extent of drug absorption from SMEDDS. The relative bioavailability was found 2.92 times higher than that of drug suspension.

The lymphatic uptake study showed that the AUC_{total} values of LH-SMEDDS reduced about 40.52 % compared with that without the treatment of cycloheximide in rats indicating its lymphatic transport.

The pharmacodynamic study showed significant improvement in cataleptic response, motor coordination, cognitive function and behavioral parameters such as locomotion, stereotypy and ataxia as compared to LH suspension. Thus, LH SMEDDS proved its efficacy in the treatment of schizophrenia with reduction in EPS.

No significant change in the globule size, drug content, zeta potential and self-emulsification time was observed in LH-SMEDDS during 3 months of storage at room temperature.

10.2 CONCLUSIONS

The lipid based nanoformulations, SLNs and SMEDDS of AM and LH were successfully developed, optimized and evaluated. The physicochemical characterization of both SLNs and SMEDDS showed the particle size of less than 200 nm which can provide augmented lymphatic uptake of SLNs and SMEDDS. The in vitro and ex vivo drug release study proved enhanced intestinal permeability of AM and LH by encapsulating into SLNs and SMEDDS. Transport mechanism study across Caco-2 cell line exhibited improved permeability of lipid based formulations of AM and LH. In vivo animal study proved their potential in enhancing bioavailability with respect to drug suspension via lymphatic uptake. Pharmacodynamic study showed efficacy of developed formulations in the treatment of schizophrenia. Hence, the present investigation suggested that lipid based nanoformulations with functional excipients were capable of enhancing oral bioavailability and mean residence time (MRT) of AM and LH with concomitant enhancement of their therapeutic efficacy. These findings provide a potential in developing lipid based nanoformulations for the delivery of poorly water-soluble drugs by the oral route.

However, we need to conduct toxicological studies, preclinical studies and further investigations in human beings under clinical conditions before they can be commercially exploited.