Chapter 9

Summary and conclusions

9.1. Introduction:

By many estimates up to 40 per cent of new chemical entities (NCEs) discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry. Relative to highly soluble compounds, low drug solubility often manifests itself in a host of *in vivo* consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher inter-patient variability. Poorly soluble compounds also present many *in vitro* formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the *in vivo* absorption. These *in vivo* and *in vitro* characteristics and the difficulties in achieving predictable and reproducible *in vivo/in vitro* correlations are often sufficiently formidable to halt development on many newly synthesized compounds due to solubility issues. A fundamental step in the solubilization of drug compounds is the selection of an appropriate salt form, or for liquid drugs, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilization techniques such as nanosuspensions and microemulsions utilize co-solvents when applied to a polar compound. Due to the regulatory implications, the selection of an appropriate salt form is essentially a preformulation goal undertaken prior to particle engineering.

Poorly soluble drugs have motivated the development of drug delivery technologies to overcome the obstacles to their solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule, or physically altering the macromolecular characteristics of aggregated drug particles. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution and spray drying, addition of surfactants and inclusion in cyclodextrin-drug

complexes, and the use of more novel mechanisms such as self-emulsifying systems like microemulsion, micronisation via nanoparticles, pH adjustment and salting-in processes.

Microemulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long- and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self-emulsifying systems. The growth of self-emulsifying drug delivery systems in recent years has resulted in the optimization of several methods of solubilising active compounds using novel, synthetic MCTs and co-solvents in addition to non-ionic surfactants. Non-ionic surfactants, such as Tweens (polysorbates) and Labrasol (caprylocapryl macrogol glycerides), with low hyrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production. Ampiphillic, non-ionic surfactants allow higher degrees of drug solubilization to occur and may prevent the precipitation of drug out of the microemulsion *in vivo*.
Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30 per cent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co-solvents increases processing complexity while improving the potential drug load of the emulsion.

Besides the microemulsion technology, Solid lipid nanoparticles (SLN) show great promise for enhancing the oral bioavailability of some of the most poorly absorbed components and the simultaneous digestion. SLN are an alternative carrier system to polymeric nanoparticles with increasing attention from different research groups SLN combine advantages of polymeric nanoparticles (solid matrix for controlled release), emulsions and liposomes (physiological material of high toxicological acceptance,

facility of industrial scale production by high pressure homogenization). The areas of application are very broad. The SLN can be incorporated in topical or ophthalmic formulations or administered perorally for controlled release inside the gastrointestinal tract (GIT). Their matrix can protect drugs against chemical degradation, the general adhesive properties of small particles to the gut wall opens the perspectives of less variable and/or enhanced bioavailability of drugs. Intravenous administration of SLN can be used for the delivery of poorly water-soluble drugs avoiding toxicologically less acceptable solubilize excipients (e.g. Cremophor EL) or in general for drug targeting similar to polymeric nanoparticles.

9.1.1. Acyclovir

Acyclovir is a synthetic purine nucleoside analog of guanine, is clinically used in the treatment of herpes simplex virus infections because of its affinity for the viral thymidine kinase. However, the treatment of these infections has become problematic because of the inability of the active drug to achieve desirable concentrations in blood requiring frequent administrations of an oral dose. The oral absorption of acyclovir is dose dependent and highly variable with bioavailability ranging from 15 to 30%. The possibility of microemulsion and SLN formulations was explored for the improvement of bioavailability.

9.1.2. Efavirenz

Efavirenz is an antiviral drug that slows the growth of HIV, the virus associated with AIDS. Efavirenz does not cure AIDS, but it helps by decreasing the amount of virus in the body (decreases the viral load). It is a non-nucleoside reverse transcriptase inhibitor. This antiviral drug exhibits the ability to prohibit HIV from replicating, which is accomplished by preventing the reverse transcriptase enzyme from properly functioning. It is practically insoluble in water (<10 mg/mL). Its inherent lipophilicity makes the drug suitable for lipid based delivery like o/w microemulsion and SLN. The advantage of this new drug delivery technology was adopted for the controlled drug delivery, reduction of intra- and inter-subject variability and subsequent increase of bioavailability.

9.2. Preparation of microemulsion:

Solubility of the drug was evaluated in different oil and surfactant. The particular oil and surfactant showing the maximum solubility for the drug was taken for evaluation. After selecting the suitable oil and surfactant, the appropriate surfactant and cosurfactant and their ratio was found out by estimating the interfacial tension using spinning drop tensiometer and by pseudoternary phase diagram study

For the preparation of microemulsions, ratio of surfactant to cosurfactant (Km) was kept constant. The required quantity of oil phase was taken in screw-capped test tube. Then known quantity of drug was mixed and dissolved into it by vortexing. Then required quantity of surfactant and cosurfactant at a fixed ratio was added into the above mixture, which was followed by through mixing. The resulted mixture was titrated against distilled water to check the transparency of the system. The mixture was shaken after each addition of water for a short time (about 1 min) by hand or by using a Vortex mixer. The experiment was carried out at room temperature (25 ±2 °C).

Different surfactant to cosurfactant ratio (km) like 4:1, 3:1, 2:1, 1:1, 1:2, 1:0 (no surfactant) was tried to evaluate the phase diagram.

9.2.1. Acyclovir:

Surfactant and cosurfactant mixture of different ratio (Km= 4:1, 3:1 and 2:1 for labrasol, plurol olique, labrafac and water system and Km=3:1, 2:1 and 1:1 for Tween 80, propylene glycol, labrafac and water system) was prepared. Labrafac was added into the preformed surfactant mixture (STmix) at different ratios. The known quantity of acyclovir was added into the mixture of labrafac and STmix with a constant stirring until the mixture become clear. The resultant microemulsion pre-concentrate was diluted by 100% with water. The mixture was gently shaken and kept at ambient temperature (25°C) to obtain a clear or translucent microemulsion.

To check any un-dissolved or precipitated drug in the microemulsion system, the concentration of was acyclovir was checked after 2 hours and after 3days. Briefly acyclovir loaded microemulsion was filtered through 0.45m membrane filter to separate any undissolved or precipitated drug. The amount of acyclovir in the resulting clear

filtrate was estimated by UV spectrophotometer at 252nm after appropriate dilution with ethanol.

9.2.1. Efavirenz:

It was observed that, microemulsion formation takes place when 4:1= Km > 1:2 in Labrasol transcutol, labrafil M 1944 CS and water system and Cremophor RH 40, propylene glycol, labrafil M 1944CS and water system. The undissolved drug was estimated by UV-VIS spectrophotometer at 247nm after appropriate dilution with methanol.

9.3. Characterizations of microemulsion

The entrapment efficiency of the prepared microemulsion was estimated. The particle size distribution was estimated by Zetasizer. Electro-conductivity, percolation threshold, viscosity, pH, refractive index, % transmittance, effect of dilution on particle size, zeta potential of the prepared microemulsion system was evaluated.

9.3.1. Acyclovir:

All the prepared microemulsions are in nanometer range and showing drug entrapment >97%. Upon dilution also it retains the nanometric property. The percolation behavior observed for labrasol, plurol olique, labrafac and water system. Upon dilution with water, viscosity of the labrasol, plurol olique, labrafac and water system increases and then decrease whereas for Tween 80, propylene glycol, labrafac and water system it gradually decreases. All the prepared system showing transparent and % transmittance was greater than 96%. After 5hr of diffusion study only 22.1% and 66.5% of drugs get diffused from pure drug suspension and tablet suspension respectively but at similar time, 98.2%, 97.8% and 86.2% of acyclovir get diffused form different formulation of microemulsions when surfactant to cosurfactant ratio (Km) was 3:1, 2:1 and 1:1 respectively for Tween 80, propylene glycol, labrafac and water system. Similar observation was made for labrasol, plurol olique, labrafac and water system also. It was also observed that maximum absorption takes place from labrasol, plurol olique, labrafac and water system when Km was 4:1 as compared to when Km=2:1 or 3:1 for system A. After 5 hr of

diffusion study only 22.1% of drugs got diffused from pure drug suspension. At similar time 66.5% 96.0, 84.6%, and 80.2% of acyclovir got diffused from tablet, Km=4:1, Km=3:1 and Km=2:1 respectively. On stability, it observed that the prepared microemulsions system was quite stable which retains its transparency and particle size below 100nm.

9.3.2. Efavirenz:

Like acyclovir microemulsion, similar observation was made for the efavirenz microemulsion formulations. Here also all the formulations are having particle size less than 100nm and upon dilution also it retains the nanometric property. The percolation behavior was not observed in these formulations. The viscosity of the Labrasol transcutol, labrafil M 1944 CS and water system and Cremophor RH 40, propylene glycol, labrafil M 1944CS and water system was increased and then decreased upon dilution with water. All the formulations studied were composed of constituents of positive surface charge. The microemulsion formulation although consist of non-ionic component, showed high positive surface charge which suggest the possibility of better adherence to the intestinal mucosa which is negatively charged. All the formulations showed a pH in the range of 6-8, which is most suitable for oral formulation. After 5 hr of diffusion study only 8.2% of drugs get diffused from pure drug suspension. At similar time, 54.2% 95.6%, 89.8% and 83.4% of efavirenz get diffused from capsule, form the Labrasol transcutol, labrafil M 1944 CS and water system when Km was 4:1, 3:1 and 2:1 respectively and 85.2%, 96.4% and 87.4% of efavirenz get diffused from Cremophor RH 40, propylene glycol, labrafil M 1944CS and water system when Km was 3:1, 2:1 and 1:1 respectively. Stability of the prepared microemulsions was reveled that the formulations are stable.

9.4. Preparation and characterization of SLN

Taguchi orthogonal experimental design was applied for the preparation of SLN using High Pressure Homogenization (HPH) technique. Taguchi orthogonal experimental design [$L_9(3^4)$] varying four independent variables, type of lipid, concentration of lipid molar ratio, Type of surfactant and concentration of surfactant at three levels. Taguchi's signal to noise ratio was used for finding the optimum levels. Since further optimization

of the factors could not be possible by making use of Taguchi's signal to noise ratio values as there was no degree of freedom available for estimation of effect of factors. The concept ANOVA was further used to find the optimum levels of the factors.

Briefly the preparation of SLN as follows: the drug, lipid and surfactant were separately weighed in different ratios in a beaker. Hydrophilic surfactants (Sodium deoxycholate, Polaxomer 188 or their combinations) were separately weighed in another beaker and dissolved in distilled water. The drug and lipid mixture was heated till complete melting of all lipid ingredients. Simultaneously, the aqueous surfactant containing phase was also heated to the same temperature as the melt. The drug containing lipid melt was then added to the hot aqueous phase under high speed stirring to form an initial pre-emulsion. This pre-emulsion was subsequently homogenized in a heated High Pressure Homogenizer maintained at 70-80°C in a water bath. The homogenization was carried out at high pressures of about 10000 psi for three cycles, wherein the pre-emulsion is pushed through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to a very high velocity (over1000 Km/h). Very high shear stress and cavitations forces disrupt the particles down to the submicron range, giving a hot nano-emulsion which contains liquid lipid droplets. This nano-emulsion was allowed to cool down to room temperature which resulted in the re-crystallization of the lipid back to the solid state giving an SLN dispersion containing drug entrapped solid lipid nanoparticles suspended in an aqueous medium.

The process validation of the SLN formulations was carried by changing homogenization pressure, number of homogenization cycle. Optimization of drug loading was checked by changing the drug load on the lipidic core. Reproducibility of the formulation was also carried out by taking similar formula at six different days.

The prepared SLN was evaluated for particle size distribution by Malvern particle size analyzer, drug entrapment efficiency, lyophilization of nanoparticle dispersion with cryoprotectant. The surface morphology was evaluated by SEM. Differential Scanning Calorimetry (DSC) studies were conducted for optimum batches having minimum particle size and maximum entrapment efficiency. The surface charge for the prepared formulations was recorded by Zetasizer.

9.4.1. Acyclovir:

Stearic acid (SA), glyceryl mono-stearate (GMS) and glyceryl di-stearate (GDS) was taken as lipid. Polaxomer 188 and sodium deoxycholate (SDC) and 1:1 ratio of Polaxomer 188 and SDC was taken as surfactant. The concentration of lipids was varied from 3-5% and concentration of surfactant was varied from 1-3% with respect to the total aqueous phase. All the batches were prepared under similar conditions keeping the all process parameters constant. 25ml distilled water taken as aqueous phase. Homogenization pressure was fixed at 10,000psi and process continued for 3 cycles.

The type and concentration of lipid, concentration of surfactants had a statistically significant ($P<0.001$) influence on the particle size of Acyclovir SLNs. The mean particle size was decrease in case of GDS which was followed by GMS and SA. When concentration of lipid was 4%, the mean diameter of Acyclovir SLN was smallest. The type of different surfactant showed only a slight influence on the size of resultant SLNs but concentrations of surfactant have significant impact on particle size.

From ANOVA it can be concluded that, optimum batch should consist of GDS as lipid at 4% concentration and SDC as surfactant at 2% concentration. The average particle size and entrapment was found 201nm and 70.7% respectively.

The effect of drug load very slightly increases the particle size but drastically decreases the drug entrapment after 20mg of drug loading. Particle size slightly increases to 264nm as compared to 238 when drug load was increased to 30mg from 20mg. But drug entrapment was drastically decreases and it comes to 56.67% from 65.55% when drug load was increased from 20 to 30mg. From SEM, it was found that the SLN had a smooth surface and were spherical in shape. Also, there was a complete absence of any other colloidal species like liposome or micelles. The zeta potential of SLN was found -45.5mV, when dispersion was made in water. In vitro diffusion study revels that, all the SLN formulation having some initial burst release followed by sustained release. Percentage cumulative drug released vs vt curve shows a straight line with regression coefficient (R^2) greater than 0.94, suggesting that SLN formulation follows Higuchi kinetics. Optimum SLN formulation shows higher flux rate 15.381 ($\mu g\ cm^{-2}\ min^{-1}$) and higher permeation constant 0.015381 ($cm\ min^{-1}$) as compare to the other SLN formulation. On stability, the particle size of SLN was increased from208 nm to 259 nm

and 302 nm when stored at 4^0C and 25^0C (dark, amber color bottle), respectively for 6 months. But when stored at clear bottle the particle size increase very fast and it goes upto 2.462μm after 1 month storage.

9.4.2. Efavirenz:

Glyceryl monostearate (GMS), glyceryl di-stearate (GDS) and glyceryl tri-stearate (GTS) was taken as lipid. Polaxomer 188 and sodium deoxycholate (SDC) and 1:1 ratio of Polaxomer 188 and SDC was taken as surfactant. Like acyclovir SLN, the concentration of lipids was varied from 3-5% and concentration of surfactant was varied from 1-3%with respect to the total aqueous phase.

The different type and concentration of lipid as well as surfactants had a statistically significant ($P<0.001$) influence on the particle size. The mean particle size was decreased in case of GTS which was followed by GDS and GMS. With an increasing concentration of lipid, the mean diameter of SLNs decreased significantly. The different type and concentrations of surfactant have significant impact on particle size. When combination of surfactants (Polaxomer 188: SDC, 1:1) was used in the SLN preparation, best results obtained. It was also observed that, the greater the concentration of surfactant, lesser particle size. From ANOVA, it can be concluded that optimum batch should consist of GTS at 5%) and Polaxomer 188: SDC (1:1) at 3%. The average particle size and entrapment was found 217nm and 97.4% respectively. The drug loading into SLN was neither altered the particle size nor drug entrapment significantly. It was also observed that upto 40mg of efavirenz loading entrapment was found satisfactory (98.23%) but further increase of drug load (50mg) decreased entrapment to 90.84%. The SEM of spray-dried nanoparticles shows spherical nature. The zeta potential value of efavirenz SLN was found -20.5mV in aqueous dispersion. Form in vitro drug diffusion study it was found that, % diffusion of drug hindered by increasing the lipid concentration irrespective of the type and concentration of surfactant and follow Higuchi kinetics. Optimum SLN formulation shows higher flux rate 13.317 ($\mu g\ cm^{-2}\ min^{-1}$) and higher permeation constant 0.013317 ($cm\ min^{-1}$) as compare to the other SLN formulation. The SLN formulations of efavirenz show stable for 6 months when stored at 4^0C.

9.5. *In-Vivo* bioavailability evaluation:

Absorption studies were performed in male albino rats. The animals were divided were separate groups each consist of four animals. Different formulations (microemulsion and SLN and commercially available dosage form) were given orally to different groups of rat. The solution of drug was injected intravenously to separate group of rat, to estimate the absolute bioavailability. After suitable time intervals, blood samples were collected and plasma was separated out from the blood. The amount of drug was quantified by HPLC analysis.

9.5.1. Acyclovir

It was observed that Cmax of tablet formulation was 0.813mcg/ml achieved after 30miniute where as 1.64 mcg/ml achieved for microemulsion formulation (ME04) after 2hours. In case SLN formulation release rate is slower as compared to the tablet or microemulsion formulation. Cmax of the SLN was achieved 1.25mcg/ml after 4 hours. Although Cmax of SLN formulations was not so high as compared to the microemulsion formulation, but total AUC is much higher than the microemulsion formulation. For Acyclovir it was found as 2047.54(µg. hr/ml) as compared to 1067.78 (µg. hr/ml) (for ME04) and 1647.12(µg. hr/ml) (for ME11).The relative bioavailability of the microemulsion (ME11) and SLN were 27.34 and 33.98, respectively, as compare to the commercially available tablet dosage form.

9.5.2. Efavirenz

In case SLN formulation release rate is slower as compared to the capsule or microemulsion formulation. It was also observed that Cmax of capsule formulation was 3.212mcg/ml achieved after 60miniute where as 2.64 mcg/ml achieved for microemulsion formulation (ME13) after 2hours. The total AUC of the SLN formulations was much higher as compare to microemulsion or commercially available capsule dosage form. AUC (µg. hr/ml) of efavirenz was found as 1304.13 (from SLN) as compared to 1094.05 and 1161.90 for ME13 and ME23 respectively. The relative bioavailability of the SLN formulation was 3.49 times as compare to the commercially available capsule

dosage form. Similarly, for microemulsion the relative bioavailability was 3.11 times and 2.93 times for ME13 and ME23 formulations.

9.6. Toxicity study of the formulations

9.6.1. Acyclovir

Nephrotoxicity study was carried out for different microemulsion and SLN formulations. Blood urea, creatinin and BUN value was estimated for control rat and rat treated with different formulations for 15 days. DAM method was used for the estimation of urea and BUN whereas alkaline picrate method was used for the estimation of creatinin. The animals were then sacrificed and the kidney was examined macroscopically and cross sections of kidney were collected in 5% formalin in saline for histopathological evaluation.

The administration of microemulsion or SLN formulations does not elevate the levels of creatinin, urea or BUN. Also from histopathology evaluation it was observed that necrosis occurred in the tubular epithelial cells located in the outer stripe of the outer medulla. Necrosis was also accompanied by scattered apoptosis, as evidenced by diminished cells when compared to the control rat kidney. Microemulsion and SLN treatment for 15 days had shown not an increase of necrosis on kidney.

9.6.2. Efavirenz

To check the safety of the different formulations (microemulsion as well as SLN) hepatoxicity tests was carried by estimating SGPT and SGOT on control rat and rat treated with different formulations for 15days. From the histopathology studies, it was clear that the microemulsion or SLN formulation does not show any significant damage irrespective to the formulation and SLN formulation are even less toxic than microemulsion formulations. The hepatic globules with accessories structure such as bile caneli-culi, peripheral and pericentral region clearly visible in SLN formulations. Active drug and microemulsions formulation shows a similar toxic effect.

9.7. Conclusion

The present study demonstrates some new findings which may be helped to improving the therapeutic efficacy of anti-viral drugs using microemulsion and SLN based drug delivery systems. It was found from the study that the reversed phase high-performance liquid chromatography (HPLC) methods for estimation of drugs involved less time consuming in the sample preparation steps. The methods were shown to be highly reproducible and it seems to be adequate for routine therapeutic drug monitoring. It could be used without any interference from surfactants, tablet or capsule excipients and endogenous substances from the plasma samples. Simple stirring method was adopted for microemulsion formulation whereas for High Pressure Homogenization (HPH) technique utilized for SLN preparation. Pseudoternary phase diagram study and interfacial tension measurement was utilized for the optimization of microemulsion formulation whereas for SLN, Taguchi orthogonal experimental design [$L_9(3^4)$] varying four independent variables, type of lipid, concentration of lipid molar ratio, type of surfactant and concentration of surfactant at three levels were utilized for optimization.

Two different microemulsion formulations of acyclovir were prepared using two different strategies. One utilized the labrasol as surfactant and plurol olique as cosurfactant. In another tween 80 was utilized as surfactant and propylene glycol as cosurfactant. Similarly for efavirenz two different formulations were prepared. One utilizes Labrasol and another cremophor as surfactant. All the systems were characterized by various methods mentioned in regular quality control tests used for ensuring batch to batch reproducibility in the preparation of theses novel drug delivery systems. It includes viscosity, water uptake, electro conductivity, refractive index, % transmittance, particle size, pH, TEM, effect of dilution on particle size, in vitro diffusion study, stability of the formulations etc. Finally in vivo absorption study and toxicity study of the developed formulations was carried out. Oral bioavailability of the developed formulations was much higher than the pure drug or commercially available dosage form. The stability data of microemulsion showed that there was no increase in particle size after storage for 6 months.

Similarly, optimum SLN formulation of acyclovir was made with GDS as lipid at 4% concentration and SDC as surfactant at 2% concentration. The efavirenz SLN was made

with GTS as lipid at 5% concentration and Polaxomer 188 and SDC (1:1) at 3% concentration. All the prepared SLN was evaluated for particle size distribution, drug entrapment, SEM, DSC, zeta potential, in vitro diffusion, stability, toxicity and finally in vivo absorption study. The prepared SLN formulation shows major improvement in bioavailability as compare to the commercially available dosage form.

Thus the study presents some new findings which may be exploited in therapeutic efficacy of acyclovir and efavirenz using microemulsion and SLN as delivery systems. However, extensive clinical trials have to be performed to establish the efficacy and safety of the formulated microemulsion or SLN in clinical practice.

List of papers:

1. P. K. Ghosh, RSR Murthy., "Micro-emulsion: a potential drug delivery system" In press. *Current drug delivery journal*
2. P. K. Ghosh, Rita Majithia , Manish Umrethia, , RSR Murthy, "Design and development of microemulsion drug delivery system of Acyclovir for improvement of oral bio-availability" Communicated to *AAPS PharmSciTech journal.*
3. P. K. Ghosh, Manish Umrethia, Rita Majithia, RSR Murthy., "Preparation and physico-chemical characterization of Caprylo-capryl macrogol -8 glyceride micro-emulsion for oral drug delivery, *ARS Pharmaceutica*, 45(3), 353-372, 2004
4. P. K. Ghosh, Manish Umrethia, Rita Majithia, RSR Murthy.A highly sensitive High Performance Liquid Chromatography (HPLC) method for the determination of acyclovir in rat blood plasma as well as in pharmaceutical dosage form. Communicated to *ARS Pharmaceutica*
5. P. K. Ghosh, Rita Majithia , Manish Umrethia, , RSR Murthy, "Design and development of solid lipid nanoparticles of Acyclovir for improvement of oral bio-availability". In communication.

Paper presented:

1. P. K. Ghosh, Rita Majithia , Manish Umrethia, , RSR Murthy , "Preparation and physico-chemical characterization of microemulsion using polyoxyethylene Sorbitan mono-oleate: Influence of oil having different chain length." 56th IPC, 2004, Scientific Abstracts, A (12), Pg No: - 4. (Oral)
2. P. K. Ghosh, Rita Majithia , Manish Umrethia, , RSR Murthy, "Preparation and physicochemical Characterization of Acyclovir Microemulsion using Caprylocapryl Macrogolglycerides". 56th IPC, 2004, Scientific Abstracts, A (41), Pg No: - 15. (Oral)