8. SUMMARY AND CONCLUSION

Compounds with poor solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughput screening have a very poor solubility. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence comprising oral bioavailability.

The Biopharmaceutical Classification system divides drugs into four classes depending on *in vitro* and *in vivo* permeability data. For class II drugs dissolution/solubility and for Class III drug permeability limits the oral drug absorption. It is obvious that class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs.

Among all technique solid dispersion (SD), is the most efficient technique from the dispersion in carrier more especially poloxamer have been recently widely used as wetting and solubilizing agents as well as surface adsorption excipients. They have been employed to enhance the solubility, dissolution and bioavailability of many hydrophobic drugs using various techniques, for some drugs, the improvement in solubility using poloxamer was higher compared to the other meltable polymers such as PEGs and complex forming agents such as cyclodextrin. In the present study, poloxamer was thus empirically selected as a hydrophilic carrier for its excellent surfactant properties and oral safety.

As solubility and permeability is the deciding factor for the in-vivo absorption of the drug, these can altered or modified by enhancement technique like the novel approach for particle size reduction on basis of crystallization by using ultrasound is
sonocrystallization this utilizes ultrasound power characterized by a frequency range of 20-100KHz for inducing crystallization it’s not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API) There are reports on application of ultrasonic (US) energy during crystallization i.e. sonocrystallization.US energy has been used to achieve nucleation at moderate super saturation during crystallization process or terminal treatment to achieve deagglomeration and to obtain crystal habit

Melt sono crystallization (MSC) is particle engineering technique are developing to modify the physicochemical and biopharmaceutical properties of drug, hence for above mentioned techniques BCS Class II drugs are selected low solubility and high permeability like pioglitazone androsiglitazone. Antidiabetic drugs to be absorbed must be present in the form of an aqueous solution at the site of absorption for their hypoglycemic activity, the available literature on the suggests solubility enhancement techniques are more essential for drugs like Pioglitazone,(-)-(P-(2-(5-Ethyl-2Pyridyl)ethoxy [benzyl 1]-2-thiazolinedione monohydrochloride, is thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action decreases insulin resistance in the periphery and in the liver resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output, unlike sulphonyl urea .Pioglitazone is highly selective agonist for peroxisome proliferators activated receptor – gamma (PPARγ) pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance, androsiglitazone-(RS)-5-{4-(2[methyl (pyridine-2-yl)amino]ethoxy benzyl]thiazolidione-2-4-dione is oral hypoglycemic agent in the thiazolidinedione class of drug. It works as an insulin sensitizer, by binding to the PPARγ receptor in fat cell and making the cells more responsive to insulin, however, the drawback of this potentially useful hypoglycemic agent is that it is highly hydrophobic and practically insoluble in water.

The selected antidiabetic agents were subjected for preformulation drug characterization like solubility, UV spectroscopy, IR-spectroscopy, Thin layer chromatography, melting point and drug excipients compatibility for quantitative estimating calibration curves of Pioglitazone was prepared in the conc. range of 0-20µg/ml in 0.1N HCl and pH 7.4 phosphate buffer and Rosiglitazone 5.10,15 up to 40 µg/ml in 0.1N HCl and Phosphate
buffer. The suitability of method was confirmed by correlation coefficient values of 0.99 to 1.0.

The solid dispersion was prepared by using poloxamer grades i.e. Poloxamer 188 and Poloxamer 407. Poloxamer was polymer of choice because it gives surface active activity with hydrophilic linkage and melt sono-crystallization of drugs give different crystal habit which gives solubility enhancement. All the prepared formulations of solid dispersion as well as melt sono crystallization give high degree of dissolution and solubility enhancement. The formulation was optimized on the basis of characteristics like DSC X-ray diffraction studies, DCS shows drug completely dissolved in the polymer below melting temp. The solid dispersion with poloxamer namely amorphous precipitation of the drug result in better solubilization in carrier and for melt sono crystallization confirmation of changes in thermal properties of drugs which gives broadening and asymmetry describe different crystals.

The XRPD study indicates amorphous nature of drug after entrapment in to the Poloxamer carrier on XRPD solid dispersion and melts sonocrystallization. Scanning electron microscopy examination showed the individual surface properties of poloxamer and drugs during kneading and formation of effective solid dispersion system. In case of melt sono crystallization pure drugs in the form plate and needle shape resulted agglomeration of crystalline drug with number of shallow circular pits on the surface reduction in particle size surface roughness with porous nature.

According to observations, drug dissolution was increased gradually with increasing the concentration of both the grades of poloxamer (i.e., PXM 188 and PXM 407) up to a certain limit, and after that then it almost becomes constant. The dissolution of drug from solid dispersion was found to be faster than that from physical mixtures and drug this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of poloxamer. And by melt sonocrystallization drugs agglomeration of crystalline drug and surface roughness with porous nature so it gives increase dissolution.

The optimized product from different analytical test subjected to a short term stability study for three months at accelerated condition temperature 40° C and 75% relative humidity changes in physical properties and drug content were noticed.
The stability study data demonstrate marked stability of formation after short term stability study. The optimized formulation PG5 was also subjected for in-vivo studies using rabbits. The result obtained from in vivo test were plotted as plasma concentration vs. time. Non compartmental pharmacokinetic parameter including $T_{\text{max}}$, $C_{\text{max}}$ and AUC were estimated by kinetic 5.0 computer program the AUC values from curves were used to calculate the relative bioavailability.

In summation it can be said that the dissolution rate of pioglitazone and rosiglitazone can be enhanced to a great extent by solid dispersion technique using an individually feasible kneading method without any physical and chemical interaction. Drugs agglomerates comprising of irregular in shapes having rough surface area with pores obtained by melt sonocrystallization technique agglomerates has shown some number of shallow circular pits on surface cracks in the crystal of the drug and has significantly higher specific surface area and thereby increase in solubility and dissolution profile.

The result of present study clearly indicated promising potential of solid dispersion of pioglitazone and rosiglitazone with poloxamer 188 and 407 and particle engineering technique melt sono crystallization to enhancing the solubility and from these methods could be viewed as alternative to conventional method of solubility enhancement of poorly soluble drugs.