ABSTRACT OF DISSERTATION

The aim of the present investigation was to enhance the solubility and dissolution rate of poorly water soluble drugs by different solubility enhancement techniques. The hypothesis stating that improved solubility of drugs with poor solubility and good permeability may lead to increased bioavailability was the basis of the current investigation. For this purpose, different drugs having poor or unpredictable bioavailability due to poor dissolution rate were considered as drug candidates. The solubility enhancement techniques were employed to formulate suitable formulations with higher drug dissolution and evaluated for their in vitro and in vivo performance.

In the present study, Gliclazide (GLZ), Ketoconazole (KTZ) and Glipizide (GPZ) were selected as drug candidates and attempts were made to improve their solubility by solid dispersion, salt formation and liquisolid technique respectively.

In the first part, solid dispersion of gliclazide; an anti-diabetic drug, was prepared with poloxamer which is a hydrophilic carrier. Solid dispersions were prepared by melt fusion and solvent evaporation methods. Corresponding physical mixtures were also prepared for comparative evaluation. Interaction between drug and carrier in the formulated solid dispersions and physical mixtures was studied by thin layer chromatography (TLC), Fourier Transform Infra-Red (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC). TLC was used to identify any possibility of degradation during preparation and to optimize melting temperature for melt dispersion batches, which was supported by FTIR and DSC, showing absence of chemical interaction between the drug and carrier. Degree of crystallinity of drug in untreated form and in the formulation was characterized by X-Ray Diffractometry (XRD) which showed that GLZ was converted to amorphous form. From the in vitro dissolution study, it was evident that both the techniques in comparison with physical
mixture were successful to enhance the dissolution of GLZ but dissolution enhancement was found more prominent with melt dispersions. *In vivo* pharmacodynamic bioavailability study was performed on normal as well as diabetic wistar rats. Blood glucose levels were evidently lowered by solid dispersion compared to GLZ alone. Stability study of solid dispersion indicates that the prepared formulation is chemically stable. But the dissolution after stability period was reduced. This might be due to the tendency of amorphous form to get recrystallized.

In the second work, synthetic approach of salt formation was employed for improvement of solubility and dissolution rate of Ketoconazole, a water insoluble antifungal drug. Ketoconazole dihydrochloride was synthesized by gas bubbling method in which, anhydrous hydrogen chloride gas was passed into the acetonic suspension of KTZ to obtain its crystalline salt. The product was collected with a good yield. The preliminary assessment for the completion of reaction was done by determining melting points. Melting points were confirmed by thermal study by Differential Scanning Calorimetry. The elemental analysis, based on theoretical to calculated contributions of elements, elaborated the molecular formula of C_{26}H_{28}Cl_{2}N_{4}O_{4}·2HCl. Its structure was confirmed by Gas Chromatography-Mass Spectroscopy (GC-MS), FTIR- spectroscopy, UV-spectroscopic characterization and DSC. FTIR spectra showed that the fingerprint region of KTZ was not differed in salt form, suggesting intactness of basic skeleton required for the pharmacological activity. The morphological study by Scanning Electron Microscopy (SEM) showed that salt particles were in form of clusters of aggregated nanoparticles. Solubility study showed that aqueous solubility of the salt was extremely greater than its base. The percent dissolution of KTZ out of the salt after 15 min was also found more than 90%. Antifungal activities of KTZ and its dihydrochloride salt were compared using
two fungal strains 
Candida albicans and Aspergillus niger. It was observed that the salt formation did not affect the antifungal activity of KTZ moiety. The stability study indicated that the salt remained physically and chemically stable. The salt was crystalline, showed no hygroscopicity and significantly improved solubility and dissolution rate of KTZ without hampering its pharmacological activity. Hence, the method would be an easy, economical and practical alternative to the commercially available KTZ formulations.

In another investigation, formulation of liquisolid compacts of Glipizide, an anti-diabetic drug, was done for better dissolution rate as well as acceptable flowability and compressibility. The technique brings out conversion of liquid medications such as drug solution or suspension in a suitable non-volatile liquid vehicle into the powder with acceptable flow properties and compressibility. For the formulation of liquisolid system, polyethylene glycol 200 (PEG 200) was used as non-volatile vehicle. It was found that GPZ shows good solubility in PEG 200. Two grades of microcrystalline cellulose 

viz. Avicel PH102 and Avicel PH200 were employed as carrier, while colloidal silica was used as coating material. Sodium starch glycolate was included in the formulation as super-disintegrant. The mathematical model by Spireas and statistical approach of \(3^2\)-full factorial design was employed to formulate liquisolid systems using percentage of drug (\%D) in liquid medication and carrier to coat ratio (R) as two independent factors. FTIR spectroscopy and DSC study were employed to evaluate compatibility of GPZ in liquisolid tablets. The evaluation consisted of the precompression analysis including determination of flow properties and tablet evaluation for different tablet properties like hardness, friability and dissolution study. The dissolution study of all liquisolid formulations exhibited higher dissolution rates than conventional marketed tablets as well as drug alone. This can be attributed to
increased wetting properties and surface of drug available for dissolution. *In vivo* pharmacodynamic assessment in normal as well as diabetic wistar rats showed better reduction in blood glucose level with liquisolid formulation. Stability study of optimized liquisolid formulation showed that the dosage form was physically and chemically stable under stress stability condition. Thus it could be concluded that liquisolid technique can be an industrially feasible alternative for improving dissolution rate and oral bioavailability of glipizide.