Summary & Conclusion

The majority of pharmaceutical compounds are poorly water soluble and new bioactive compounds that result from high-throughput screening programs tend to exhibit low solubility in water. Such compounds may exhibit insufficient dissolution throughout the gastrointestinal tract and therefore fail to achieve superior systemic exposure after oral administration. Today, failing bioavailability is one of the main reasons for abandoning innovative oral drug candidates. Circumventing low solubility and unfavorable dissolution equilibrium kinetics are the key issues in the development of an appropriate formulation.

Gliclazide, a second-generation hypoglycemic sulfonylurea and a drug of choice in the treatment of Type 2 diabetes mellitus shows irregular bioavailability due to low aqueous solubility and decreased dissolution rate. Domperidone is an antiemetic and prokinetic with an excellent safety profile but exhibit poor bioavailability. The poor aqueous solubility may be one possible reason for its low bioavailability.

Enhancement of oral bioavailability of gliclazide and domperidone like drugs remains a daunting task. Solid dispersion is one of the many techniques available to enhance drug dissolution and bioavailability of poorly water-soluble drugs. Further, such formulations can be dispensed in the form of fast dissolving tablets which disintegrate and/or dissolve rapidly in saliva; thus may help in improving the bioavailability of such drugs.

Solid dispersion has been used successfully earlier too to increase the solubility of poorly water soluble drugs like prednisone, rofecoxib and diclofenac and the mouth dissolving tablets of classes like neuroleptics, cardiovascular drugs, analgesics and antihistamines have provided an opportunity for a line extension in the market place.

The present project was designed to overcome the solubility problems associated with gliclazide and domperidone. Solid dispersion based solubility enhancement technique employed in the present study was expected to improve the solubility and bioavailability of these drugs.

The development of such dosage form may help in creating new opportunities in academics and industry. The enhanced solubility shall not only improve bioavailability but may
also result in reduction of dose and side effects. Moreover, the method(s) employed, seem process friendly which is important criterion for manufacture of dosage forms at large scale.

The drugs gliclazide and domperidone, selected for present study were identified using different methods reported in the literature viz. melting point determination, partition coefficient determination, determination of absorption maxima ($\lambda_{\text{max}}$), FTIR spectroscopy, XRD studies and drug excipient interaction studies.

Organoleptic properties of drug(s) indicated that both were almost white in color and odourless. The DSC thermogram showed sharp endothermic peaks of gliclazide and domperidone at 172.55°C and 247.15°C respectively. The partition coefficient value $P$ for gliclazide and domperidone was found to be 1.586 ± 0.226 and 2.527 ± 0.245 respectively.

The solubility of both the drugs was determined in different media. The solubility of gliclazide in water, 0.1N HCl, and phosphate buffer pH 6.8 was found to be 0.78 ± 0.03 mg/ml, 0.38 ± 0.01 mg/ml, and 0.75 ± 0.02 mg/ml, respectively. The solubility of domperidone in water, 0.1N HCl, and phosphate buffer pH 6.8 was found to be 0.986 ± 0.12 μg/ml, 62.6± 0.15 μg/ml, and 1.23 ± 0.15 μg/ml, respectively.

Calibration curves of both the drugs were prepared in 0.1N HCl and phosphate buffer pH 6.8. Calibration curve data of both the drugs were subjected to linear regression analysis. $R^2$-values for gliclazide in 0.1N HCl and phosphate buffer pH 6.8 were found to be 0. 9998 and 0.9996 respectively and for domperidone, 0.9994 and 0.9996 indicating good linearity. The linearity of the calibration curves showed that Beer Lambert’s law was obeyed in the concentration range of 2-20 μg/ml at $\lambda_{\text{max}}$ 227 nm for gliclazide. The linearity of the calibration curves of domperidone showed that Beer Lambert’s law was obeyed in the concentration range of 5-40 μg/ml in 0.1N HCl and 10-80 μg/ml in phosphate buffer pH 6.8 at $\lambda_{\text{max}}$ 284 nm.

FTIR spectra of the gliclazide exhibited characteristic N-H, C=O, C-H, S=O stretching bands at 3373 cm$^{-1}$, 1709 cm$^{-1}$, 1349 cm$^{-1}$, 2943 cm$^{-1}$, respectively. FTIR spectra of domperidone showed characteristic N-H, C=O, C-H, C=C stretching bands at 3360 cm$^{-1}$, 1716 cm$^{-1}$, 2933 cm$^{-1}$, and 2165 cm$^{-1}$ respectively. The FTIR spectra of both the drugs confirmed their identity and purity.
The crystalline state of the drugs was evaluated on the basis of X-ray powder diffraction patterns. The diffraction spectrum of pure gliclazide showed that the drug is of crystalline nature as demonstrated by numerous peaks observed at 2θ of 10.37, 14.85, 17.87, 17.85, 18.07, 21.06, 22.01, and 25.89 etc. in finger print region and that of pure domperidone showed that the drug was of crystalline nature as demonstrated by numerous peaks observed at 2θ of 9.39, 11.96, 14.08, 15.09, 15.74, 25.47, 26.23, 27.70, 28.24, 29.24 etc. in finger print region. The different formulation excipients, drug, and their physical mixtures were found to be stable under selected storage conditions for one month, as there was no change in their physical characteristics. Hence, it was inferred that the selected excipients were compatible with gliclazide and domperidone.

The poor aqueous solubility of many drugs results in difficulties in dosages form design and lead to poor bioavailability. The main possibilities for improving dissolution are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Larger the surface area, higher will be the dissolution rate. Since the surface area increases with decreasing particle size, which can be accomplished by conventional methods like trituration, grinding, ball milling, fluid energy micronization, salt formation and controlled precipitation. Although these conventional methods have been used commonly to increase dissolution rate of drug, there are practical limitation with these techniques as the desired bioavailability enhancement may not always be achieved. Therefore, formulation approaches are being explored to enhance bioavailability of poorly soluble drugs. One such formulation approach that has been shown to enhance absorption of such drugs significantly is to formulate as solid dispersion.

The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently to improve the bioavailability of poorly soluble drugs. In present study the fusion method was used for preparation of solid dispersion because of its simplicity and reproducibility. Moreover, it has advantage of avoiding solvent toxicity.

In all forty solid dispersions, twenty each for gliclazide and domperidone were prepared and characterized for drug content, phase solubility studies, in vitro dissolution studies. The powder characterization were assessed by Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry and X-ray diffraction.
The drug content in case of gliclazide solid dispersions were noted to be between 97 to 99 % while for domperidone solid dispersion they were between 97.5 to 100 %.

The aqueous solubility of the drugs in presence of selected polymers taken in varying ratios increased linearly with polymer concentration. Phase solubility diagrams showed A_{L} type as they were straight line with a slope of unity which indicates successful formation of complexes. In case of gliclazide the inclusion of polymers at a concentration of 18% w/v could increase the solubility 4-5 folds while for domperidone 0.3%w/v concentration of polymers increased the solubility 9-11 folds.

Solid dispersion formulations of gliclazide were formed to enhance the dissolution of the drug both in 0.1N HCl and phosphate buffer. The enhancement was found to be dependent on the molecular weight of the polymers (PEG 4000, PEG 6000, PEG 8000) as well as their amount. Q_{60} in drug to polymer ratio 1:1 was noted to be in the range of 75.5-90% while in ratio 1:3, 1:5 and 1:7 it was found to be 82.5-95%, 90-97% and 89-96% respectively as compared to 40% in case of plain drug. No significant increase in the dissolution of gliclazide was noted when drug to polymer ratio was enhanced from 1:5 to 1:7.

In case of phosphate buffer the Q_{60} was noted to be 75.5-82% with the drug to polymer ratio 1:1, 82.5-90% with the drug to polymer ratio 1:3, 89 to 94.5% with the drug to polymer ratio 1:5 and 87 to 94.5% with the drug to polymer ratio 1:7 as compared to 28% in case of plain drug. Dissolution rate of solid dispersion formulations enhanced as the molecular weight and amount of PEG was increased. The increase in the dissolution was almost similar with drug to polymer ratios 1:5 and 1:7.

Use of polyvinylpyrrolidone (PVP) also increased the dissolution of the drug in 0.1N HCl and phosphate buffer which was found dependent on the molecular weight and amount of the polymer. Q_{60} with drug to polymer ratio 1:1 was noted to be 80-81 % while with drug to polymer ratios 1:3, 1:5 and 1:7 it was noted 86-95%, 93-97% and 92-97% respectively. PVP K30 and K90 based solid dispersion of gliclazide also enhanced its dissolution in phosphate buffer. The Q_{60} values were observed to be 81-80 % in polymer and drug ratio 1:1, 88-95% in polymer and drug ratio 1:3, 94-97 in polymer and drug ratio 1:5 and 92 to 97 % in polymer and drug ratio 1:7. The increase in the dissolution was almost similar with drug to polymer ratios 1:5 and 1:7.
Solid dispersion formulations of domperidone were found to enhance the dissolution of the drug both in 0.1N HCl and phosphate buffer. The enhancement was found to be dependent on the molecular weight of the polymers (PEG 4000, PEG 6000, PEG 8000) as well as their amount. In case of 0.1N HCl, $Q_{60}$ in drug to polymer ratio 1:1 was noted to be in the range of 44-51% while in ratio 1:3, 1:5 and 1:7 it was found to be 54-66%, 80-89% and 79-87% respectively as compared to 63% in case of plain domperidone. No significant increase in the dissolution of domperidone was noted when drug to polymer ratio was enhanced from 1:5 to 1:7.

In case of phosphate buffer the $Q_{60}$ was noted to be 44-51% with the drug to polymer ratio 1:1, 54-66% with the drug to polymer ratio 1:3, 80-89% with the drug to polymer ratio 1:5 and 79-87% with the drug to polymer ratio 1:7 as compared to 12.5% in case of plain drug. Dissolution rate of solid dispersion formulations enhanced as the molecular weight and amount of PEG was increased. The increase in the dissolution was almost similar with drug to polymer ratios 1:5 and 1:7.

Use of polyvinylpyrrolidone (PVP) also increased the dissolution of the drug in 0.1N HCl and phosphate buffer which was dependent upon the molecular weight and amount of the polymer. $Q_{60}$ with drug to polymer ratio 1:1 was noted to be 82-84% while with drug to polymer ratios 1:3, 1:5 and 1:7 was found to be 86 to 89%, 95-97% and 94-97% respectively. In case of phosphate buffer $Q_{60}$ was noted to be 45-55 % in polymer and drug ratio 1:1, 66-72% in polymer and drug ratio 1:3, 81-90% in polymer and drug ratio 1:5 and 81-88 % in polymer and drug ratio 1:7. The increase in the dissolution was almost similar with drug to polymer ratios 1:5 and 1:7.

The higher dissolution rates of the drug(s) in case of solid dispersions can be ascribed to a number of factors such as, the formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present, and formation of amorphous forms of drug and carriers. The presence of carrier might also have prevented aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties might have also increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, and hence in higher dissolution rates. Furthermore, intermolecular hydrogen bonds between drug and carrier and local solubilization effect of carrier at the diffusion layer might have further contributed for higher dissolution rate of solid dispersions as evident in the present study.
FTIR spectroscopy was used to identify and establish the possible interactions between drugs and carriers in the solid dispersion. The FTIR spectra of solid dispersions of gliclazide and domperidone were compared with the standard spectrum of drug(s) and PEG alone. It was noted that NH group which was located at 3188 cm\(^{-1}\) in the IR spectra of gliclazide shifted to 3191 cm\(^{-1}\) in SDs. While NH group which was located at 3360 cm\(^{-1}\) from the IR spectra of domperidone shifted to 3427 cm\(^{-1}\) in SDs. The shift in the peaks indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG. This may be attributed to the intermolecular hydrogen bonding between gliclazide and PEG in the solid state. The FTIR spectra of SDs were compared with the standard spectrums of gliclazide and PVP K30 and K90 alone. In case of the SDs, the asymmetric vibration peak of the S=O was shifted from 1349 cm\(^{-1}\) to 1343 cm\(^{-1}\) and 1348 cm\(^{-1}\) in case of PVP K 30 and 90 solid dispersion, respectively while the absorption peak of carbonyl (C=O) sulphonyl urea group at 1709 cm\(^{-1}\) in pure gliclazide shifted towards higher wave number 1711 cm\(^{-1}\) and 1717 cm\(^{-1}\) in PVP K 30 and 90 based solid dispersions, respectively. A very broad band was also visible at 3443 cm\(^{-1}\) and 3446 cm\(^{-1}\) in PVP K 30 and 90 solid dispersions, respectively which may be attributed to presence of water. In the SDs, the asymmetric vibration peak of the N=H was shifted with increased intensity from 3360 cm\(^{-1}\) to 3417 cm\(^{-1}\) and 3437 cm\(^{-1}\) in PVP K 30 and 90 solid dispersions, respectively while the absorption peak of carbonyl (C=O) at 1716 cm\(^{-1}\) in pure domperidone shifted towards higher wave number 1718 cm\(^{-1}\) and 1719 cm\(^{-1}\) in PVP K 30 and 90 solid dispersions respectively. Peak at C-H was visible at 2883 cm\(^{-1}\) and 2881 cm\(^{-1}\) in PVP K solid dispersions 30 and 90, respectively which may be attributed to presence of water.

The DSC curve of pure gliclazide exhibited a single endotherm corresponding to the melting of the drug. The onset of melting was observed at 172.6 °C, and the corresponding heat of fusion (H) was 173.8 J/g. The onset of melting of domperidone was observed at 247.15°C and corresponding heat of fusion (H) was 122.65 J/g whereas pure PEG 4000 showed a melting endotherm at 60.2 °C and a corresponding H at 235.0 J/g. Similarly PEG 6000 showed endotherm at 60.5 °C with a H of 242.5 J/g and PEG 8000 showed melting endotherm at 60.7 °C with a H of 254.5 J/g. Thermograms of SDs showed the absence of a gliclazide melting peak and one exothermic peak at 253.9 °C; the corresponding H was 741.6 J/g F, suggesting that gliclazide was completely soluble in the liquid phase of the polymer or that the crystalline nature of gliclazide was absent. The exothermic peak is possibly due to crystallization above the glass
transition temperature, Tg. Pure PVP K 30 and PVP K 90 showed a broad endotherm ranging from 60°C to 100°C. Thermograms of SDs showed the absence of a gliclazide melting peak and one exothermic peak at 272.9 °C. Hence gliclazide was completely soluble in the liquid phase of the polymer or that the crystalline nature of gliclazide was absent. The exothermic peak may possibly be due to crystallization above the glass transition temperature, Tg.

The diffraction spectrum of pure gliclazide showed that the drug was of crystalline nature as demonstrated by numerous peaks observed at 2θ of 10.37, 14.85, 17.87, 17.85, 18.07, 21.06, 22.01, and 25.89 etc. in fingerprint region. Pure PEG 4000 showed two peaks with the highest intensity at 2θ and d-spacings of 19.04 and 4.65 Å; 23.18 and 3.83 Å. Similarly PEG 6000 showed peaks with the highest intensity at 2θ and d-spacings of 19.41 and 4.65 Å; 23.34 and 3.78 Å and PEG 8000 showed peaks with the highest intensity at 2θ and d-spacings of 19.10; 22.89 and 3.98 Å. Some changes in gliclazide peak position were observed in SDs. The diffraction spectrum of pure domperidone showed that the drug was of crystalline nature as demonstrated by numerous peaks observed at 2θ of 9.39, 11.96, 14.08, 15.09, 15.74, 25.47, 26.23, 27.70, 28.24, 29.24 etc. in fingerprint region. Similarly, some changes in domperidone peak position were observed in SDs. The prominent peaks in case of pure domperidone were clearly seen at the same positions in the SDs, but with decreased intensities. As the amount of PEG increased in the solid dispersion, relative reduction in diffraction intensity of gliclazide in PEG preparations at these angles was observed which suggested that the size of the crystals was reduced to a microcrystalline form. The PEG 4000, 6000 and 8000 peak patterns in the SDs were the same and superimposable, which, again, ruled out the possibility of a well-defined chemical interaction and new compound formation between these two components. Pure PVP showed absence of peaks in diffraction spectrum. As the amount of PVP increased in the solid dispersion, relative reduction in diffraction intensity of gliclazide in PVP preparations at these angles was observed which suggested that the size of the crystals was reduced to a microcrystalline form.

The solubility and dissolution rate of gliclazide and domperidone were enhanced by the use of drug-PEG 8000 solid dispersions and drug- PVP K 90 solid dispersions. The solubilisation effect of PEG 8000 resulted in the reduction of aggregation of the drug particles, elimination of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles, and this is probably responsible for the enhanced solubility and dissolution.
rate of drug in the SDs. DSC of SDs did not indicate the presence of crystalline drugs because the drug dissolved completely below its melting point. However, XRD studies indicated the presence of crystalline drug in SDs. No well defined chemical interaction between drug, PEG 8000 and PVPK 90 was observed.

Solid dispersions SD G815, SD GK915, SD D815 and SD DK915 were selected for formulation of fast dissolving tablets because they showed best dissolution both in 0.1N HCl pH 1.2 and phosphate buffer pH 6.8 dissolution media.

Several technologies are available to manufacture orally disintegrating tablets. The most common preparation methods include molding, lyophilization or freeze drying, direct compression, spray drying and sublimation. In the present investigation fast dissolving tablets of gliclazide and domperidone solid dispersions were prepared by direct compression method. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tableting.

The solid dispersion of gliclazide and domperidone were mixed with appropriate quantities of excipients to make the blends for fast dissolving tablets. The blends were evaluated for bulk density, tapped density, angle of repose, compressibility index and Hausner ratio.

Values for angle of repose for gliclazide blends were found in the range of 24.54°- 32.45° and that of domperidone blends were found to be 24.04°-29.47°. Compressibility index of the blends fell in the range of 10-19 for gliclazide and in the range of 11-21 for domperidone which complied with the Hausner ratio values which were in the range of 1.14-1.23 for gliclazide and 1.13-1.26 for domperidone. The prepared blends were found to possess good flow and compressibility properties and thus were suitable for tablet manufacture.

The tablets were prepared using direct compression method on single punch Cadmach tablet press using 8mm punches. The fast dissolving tablets were evaluated for various parameters including thickness, weight uniformity, hardness, wetting time, in vitro disintegration time, drug content and in vitro dissolution.

Uniformity of weight of the FDTs was assessed and the average weight for all formulations was found to be between 214-228 mg which was within in the prescribed limits i.e. ±7.5% (203.5 to 236.5mg).
Hardness and friability of all formulations were within acceptable limits. Hardness of tablets was in the range of 2.3-3.5 kg/cm for gliclazide tablets and 2.3-3.8 kg/cm for domperidone tablets. The friability of all formulations was found to be less than 1.0 % and hence the tablets exhibited sufficient strength against bear and tear during handling and shipping. Friability was found to be in the range of 0.207- 0.402% for gliclazide tablets and as well as for domperidone tablets.

Disintegration time is very important for FDTs which is desired to be less than 60 seconds. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared FDTs was in the range of 25-47 seconds for gliclazide tablets and 26-48 sec for domperidone tablets. The disintegration time was found to follow in the following order; Kyron<Crosscarmellose< SSG. This finding is in agreement with results obtained from wetting time, since SSG swells with more gelling than Crosscarmellose and Kyron, which extend disintegration time as a result. As the concentration of superdisintegrants in the formulations was increased the disintegration time was found to decrease.

Wetting time is used as an indicator for the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 23-48 seconds for all the tablets. It was observed that type of the disintegrant affected the wetting of the tablets. It was noted that the formulation containing SSG took more time to wet than the tablet containing Crosscarmellose and Kyron. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time while Crosscarmellose and Kyron perform their disintegrating action by wicking through capillary action and fibrous structure, with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing SSG swelled and the outer edge appeared gel-like. Tablets containing Kyron quickly wicked water and were hydrated, but were soft as compared to the tablets prepared with Crosscarmellose and SSG. It was further noted that the centers of the tablets with Crosscarmellose and SSG remained dry and hard.

The drug content of the gliclazide tablets was in the range of 98-100% while for domperidone tablets it was in the range of 98-99%. On the basis of better dissolution and other favourable parameters the formulation F10 i.e., tablet containing solid dispersion of gliclazide...
and PEG 8000 with 8 mg Kyron, formulation F19 i.e., tablet containing solid dispersion of gliclazide and PVP K90 with 8 mg Kyron, formulation F29 i.e., tablet containing solid dispersion of domperidone and PEG 8000 with 8 mg Kyron and formulation F38 i.e., tablet containing solid dispersion of domperidone and PVP K90 with 8 mg Kyron were selected for the stability studies.

Stability studies were performed as per ICH guidelines at 40°C and 75% RH for three months. All the formulations exhibited satisfactory stability as no significant change in hardness, wetting time, disintegration time, drug content and drug release was observed.

In the present study solubility of the selected drugs i.e. gliclazide and domperidone was successfully enhanced by preparing PEG and PVP based solid dispersions. The developed solid dispersions were further formulated in form of fast dissolving tablets. The tablets exhibited satisfactory disintegration and dissolution properties. The tablets containing Kyron as superdisintegrants were noted to be most acceptable in term of dissolution behaviour.