Abstract

Oral route is most preferred route for administration of the dosage forms but this route is frequently dependent upon the bioavailability of the active form of the drug which is affected by the drug’s physical-chemical properties. Together with permeability, the solubility of a drug is a key determinant of its oral bioavailability. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is associated with implications of low bioavailability, high intra and inter subject variability and lack of dose proportionality. In recent years, much attention has been focused on lipid-based formulations with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to enhance the solubility of poorly water soluble drugs and improving bioavailability to administer them through oral route resulting in increasing their clinical efficacy, cost effectiveness and ease of preparation. Self-emulsifying drug delivery systems are isotropic mixture of oils, surfactant and co-solvents/ surfactant, which forms fine stable o/w emulsions, when introduced in the aqueous phase under condition of gentle agitation. The natural digestive motility of the stomach and intestine provides the agitation required for self-emulsification in vivo.

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. Although there is an increase in the prevalence of type 1 diabetes also, the major driver of the epidemic is the more common form of diabetes, namely type 2 diabetes, which accounts for 80-90% of all cases of diabetes. Sulfonylureas (like gliclazide and glibenclamide etc.) are drug of choice for long term therapy for NIDDM. But sulfonylureas (like gliclazide and glibenclamide) possess solubility problem in aqueous fluids besides having low dissolution rate and variable low bioavailability. Hence, in the present study it was attempted to prepare self-emulsifying drug delivery systems of Gliclazide and Glibenclamide in order to improve the solubility, dissolution rate and to evaluate the SEDDS w.r.t. various in vitro and in vivo parameter.

The results of UV spectrophotometer, solubility, infrared spectroscopy and LOD complies with the pharmacopoeial specifications for the identification of gliclazide and glibenclamide. Retention time of gliclazide and glibenclamide with the optimized chromatographic method was found to be 6.4 min and 7.5 min. The bioanalytical method
was found to be accurate, precise and selective and linear over the wide range of concentration.

In case of gliclazide, Palm oil (17.65±2.34 mg/100 mg) exhibited higher solubility among the various oils tested. Tween 20 (18.13±2.67 mg/100 mg) and PEG 600 (12.22±2.24 mg/100 mg) showed the highest solubilizing potential for gliclazide among the various surfactants, cosurfactants screened. Based on the solubility data, Palm oil was selected as oil phase, Tween 20 as surfactant, PEG 600 as cosurfactant for formulating sedds of gliclazide. For Glibenclamide, sunflower oil (3.46±0.32 mg/100 mg) showed higher solubility for glibenclamide and Tween 80 (3.75±0.37 mg/100 mg) and PEG 600 (2.98±0.44 mg/100 mg) exhibited the higher solubility among the various surfactant and cosurfactant tested. So, Sunflower oil was selected as oil phase, Tween 80 as surfactant, PEG 600 as co-surfactant for formulating SEDDS of glibenclamide. In addition, vegetable oils like Palm oil and sunflower oil have been reported to possess nutritional and health properties, including antioxidant activities, cholesterol lowering, anti-cancer effects and protection against atherosclerosis. Also, non ionic surfactants with high HLB values are preferred for the design of sedds as they form o/w droplets faster and also leads to rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) (Gursoy et al., 2004).

Phase diagrams were constructed to determine optimum concentration of oil, surfactant, and cosurfactant. Larger the size of nanoemulsion region in ternary phase diagram, greater is the self-emulsification efficiency. For gliclazide, Smix (Surfactant:Cosurfactant) ratio of 4:1 (Ca) and 3:1 (Cb) showed greater nanoemulsification region with infinite dilutions. In addition, both these Smix ratio exhibited a greater range for oil incorporation (approx. 9% to 45%). Also, nanoemulsification regions were observed for Oil:Smix ratio of 1:1, 1:2, 1:3, 1:4, 1:5 (Ca1-Ca5 and Cb1-Cb5). For glibenclamide, Smix of 3:1 (Ba), 2:1 (Bb), 1:1 (Bc) showed a larger nanoemulsification region and exhibited greater range capacity for oil incorporation with Oil:Smix ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 (Ba1-Ba6, Bb1-Bb6, Bc1-Bc6). No significant differences in the area of self-emulsification were observed in the phase diagrams for SEDDS (containing gliclazide) with Smix ratio of 4:1, 3:1 and SEDDS (containing glibenclamide) with Smix ratio of 3:1, 2:1, 1:1 when compared with the corresponding phase diagrams for SEDDS without drug.
Thermodynamic stability tests were performed to eliminate the metastable systems. Gliclazide SEDDS Ca1 to Ca4 (Smix ratio 4:1), Cb1 to Cb4 (Smix ratio 3:1) did not show any signs of phase separation. This may be due to the presence of relatively high percentage of oil in the formulation and high solvent capacity of the cosurfactant. Glibenclamide formulations Ba1 to Ba6 (Smix ratio 3:1), Bb1 to Bb6 (Smix ratio 2:1), Bc1 (Smix ratio 1:1) were found to be stable during the thermodynamic stability studies and did not show any signs of phase separation during the stress test.

Self-emulsification ability of surfactants and cosurfactants were assessed to select the best ratio of Smix. Gliclazide SEDDS Ca1 to Ca4, Cb1 to Cb4 and Glibenclamide SEDDS Ba1 to Ba5, Bb1 to Bb5 and Bc1 formed clear dispersions and did not show any drug precipitation and thus were considered as stable. Factors such as HLB value, structure and relative length of hydrophobic chains of surfactants had been reported to influence the micro-emulsification (Borhade et al., 2008).

All gliclazide SEDDS Ca1 to Ca4, Cb1 to Cb4 and glibenclamide formulations Ba1 to Ba5, Bb1 to Bb5, Bc1 exhibited dark field under cross polarized light suggesting that all the formulations were isotropic in nature.

Initial viscosity of SEDDS was found to be very high but on dilution with water, viscosity of the respective systems was decreased. This suggests possibility of rapid absorption of SEDDS as viscosity of SEDDS will decrease on being diluted with body fluids inside.

Formulation Ca1-Ca4, Cb1-Cb4 and Ba1-Ba5, Bb1-Bb5, Bc1 showed no signs of drug precipitation or phase separation on diluting 10, 100 times. This implies that all the developed formulations were robust to dilution in the aqueous medium.

Formulations Ca1-Ca4, Cb1-Cb4 and Ba1-Ba5, Bb1-Bb5, Bc1 were diluted 10, 100 times with various dilution media, viz. phosphate buffer pH 1.2, pH 4.5, and pH 6.8. No signs of drug precipitation or phase separation were observed on storage in various dilution media which suggests that the various in vivo media were suitable for the release of the drug from SEDDS.
SEDDS of gliclazide with Smix ratio of 4:1 exhibited a lower emulsion droplet size as compared to formulations with Smix ratio of 3:1. Among all the formulations Ca2 showed the minimum emulsion globule size of 133.3 nm with PDI of 0.588 followed by Cb2 with globule size of 159.1 nm with PDI of 0.504. In case of SEDDS of glibenclamide with Smix ratio of 2:1, the emulsion globule size was found to decrease with the decrease in oil concentration but was higher as compared to Smix ratio of 3:1 with respective oil concentration. Formulation with Smix ratio of 1:1 showed the highest emulsion droplet size. Among all the formulations Ba3 showed the minimum emulsion globule size of 122.9 nm with PDI of 0.549 followed by Bb4 with globule size of 139 nm with PDI of 0.623.

In case of gliclazide, both SEDDS (Ca2 and Cb2) showed a very high and immediate drug release as compared to pure gliclazide (8.9±1.1%) and marketed tablet (40.1±1.2%). At the end of 1 hr., Ca2 released (98.1±1.2%) and Cb2 (94.2±1.5%) as compared to pure gliclazide (36.7±2.2%) and marketed tablet (82.7±2.3%). Formulation Ca2 showed a higher drug release as compared to Cb2 and also exhibited a smaller emulsion droplet size. For glibenclamide, both the formulations Ba3 and Bb4 exhibited high drug release as compared to pure glibenclamide (12.2±0.67) and marketed tablet (77.2±1.4). Even at the end of 60 min both formulations Ba3 (97.6 ± 1.8) and Bb4 (95.2±2.6) showed a much higher cumulative drug release as compared to pure glibenclamide (31.2±2.2) and marketed tablet (90.3±2.1). Formulation Ba3 showed a higher drug release and smaller emulsion droplet size as compared to Bb4 at every time point up to 60 min.

T\textsubscript{max} of Glicalzide SEDDS Ca2 was (2.02±1.03) hr which suggests rapid absorption in comparison with pure gliclazide and marketed tablet composition. C\textsubscript{max} values of the prepared SEDDS and the marketed tablet were almost same. t\textsubscript{1/2} and MRT values of the drug from all the different forms were found to be almost same and was found to be high (approx. 6 hr). AUC of gliclazide from SEDDS was found to be little higher than the marketed formulation but was found to be significantly higher than the pure gliclazide indicating an improvement in the bioavailability of gliclazide from the SEDDS formulation as compared to the pure drug. In case of Glibenclamide C\textsubscript{max} of the prepared SEDDS Ba3 was slightly higher than the marketed tablet but was significantly higher than the pure drug. T\textsubscript{max} of pure glibenclamide, SEDDS and marketed tablet was found to be almost similar. t\textsubscript{1/2} and MRT values of glibenclamide from all the different forms were found to be almost same and was found to be high which suggests that glibenclamide stays in the body for a longer duration of time before being eliminated. AUC of glibenclamide from SEDDS was found to be significantly higher
than pure glibenclamide indicating an improvement in the bioavailability of glibenclamide from SEDDS formulation as compared to pure drug.

All the SEDDS were found to form clear dispersion and none of the formulation showed any drug precipitation, capsule leak suggesting that developed SEDDS were stable upto 6 months at 40 °C/75% RH.

SEDDS formulation for poorly water soluble drugs, gliclazide and glibenclamide were successfully developed with increased dissolution rate and bioavailability. The developed formulations exhibited better pharmacokinetic profile as compared to plain drugs. Also, the stability study results confirmed that the developed formulation were stable. Thus the present study demonstrated successful preparation of self-emulsifying drug delivery systems of gliclazide and glibenclamide.

Keywords: SEDDS, Nanoemulsions, phase diagram, gliclazide, glibenclamide