To improve the sustainability and oral bioavailability of a weak acidic (pKa = 5.9) anti-diabetic drug, glipizide (GPZ; biological half-life, 3.4 ± 0.7 hr) the controlled release floating formulations including non effervescent floating tablets (NEFT), effervescent floating tablets (EFT) and floating microspheres (FM) were developed and optimized. To reach at the objective of research, whole experimental work was carried out as preformulation study of drug including drug-excipient interaction testing; bioanalytical method development and validation of drug in rabbit plasma for in vivo pharmacokinetic study; design, development, optimization of both non effervescent and effervescent floating tablet and chitosan floating microspheres of drug through $3^2$ factorial design, and their pharmacokinetic study.

Preformulation study confirms that solubility of the drug is directly proportional to the pH of the medium, flow property of drug powder was poor, which needed to be improved during formulation development, drug was found compatible with proposed excipients selected for formulations and drug was stable in simulated gastric as well as in intestinal fluid up to 96 hours. A good resolution was obtained between GPZ and internal standard (gliclazide) with retention times 7.32 min and 9.02 min respectively in bioanalytical method development in RP-HPLC. The method was validated and found to be linear ($r^2=0.999$) within the analytical range of 25.38 - 2046.45 ng/mL. The $3^2$ factorial design-based optimization was employed to investigate the effect of two factors, amount of HPMC K4M (55, 60 and 65 % w/w) and Carbopol 934 (12.5, 15 and 17.5 % w/w) on responses like time required to release 50 % ($t_{50}$), 80 % ($t_{80}$) of drug and similarity factor ($f_2$) in non effervescent floating table; amount of HPMC K4M (70, 80 and 90 mg; $X_1$) and

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Abstract

NaHCO₃ (14, 24 and 34 mg; X₂) on responses like floating lag time (FLT), time required to release 50 % (t₅₀) and 80 % (t₈₀) of drug in effervescent floating tablet, and drug-polymer ratio (1:1, 1:2 and 1:3; X₁) and percentage of sodium TPP (3, 4 and 5 % w/w; X₂) on responses like drug entrapment efficiency (DEE), particle size (PS) and time require for 80 % of drug release (t₈₀) in floating chitosan microspheres. The statistical optimization technique was employed to predict the composition of optimized formulation for desired product parameters and the predicted responses of optimized formulations were good agreement with experimental results. The in vitro pharmacokinetic study of optimized formulation resulted long biological half-life of 12.24 ± 0.46 hr, 11.16 ± 0.44 hr and 13.55 ± 1.36 hr for NEFT, EFT and FM respectively with enhanced area under the curve value in compare with reported value of glipizide.

It can be concluded that the enhancement of bioavailability with long biological half life of glipizide through non-effervescent floating tablet, effervescent floating tablet and floating microsphere could be made through this research work. The goal of research work was achieved through well designed plan of experimentation using factorial design, well thought of dosage form design and pharmacokinetics concept with support from statistical software and modern analytical instrumentation.