ABSTRACT

Objective: Formulation, Evaluation and Characterization of Metformin Hydrochloride and Repaglinide in Sustain Release Bilayer Dosage Form

Experimental Work: A combination therapy of Repaglinide (RG) and Metformin HCL (MH) attains a perfect control of glycemia; although, the immediate release/conventional form of them must be taken several times in a day, negotiating the healing aids and also not convenient to the patients. The sustain release of both drug in single tablet using bilayer formulation technique was selected as target formulation. For that studies were initiated with simultaneous estimation of MH and RG, analytical technique was developed and validated using Shimadzu-1800 double beam UV - Visible spectrophotometer. Three different techniques wet granulation, dry granulation and melt granulation were used along with suitable release retarding polymers in these studies. In dry granulation technique, MH layer was prepared with Guar gum (GG); HPMC K100 M; Eudragit RSPO (E-RSPO) in 10-30% and RG layer was prepared with Carbopol-971, HPMCK 100M and Gum Acacia (AG), in 20-40% concentration. In another technique wet granulation, for MH layer 20% Polymer (Xanthan gum, Guar gum, HPMC K100 M, Eudragit RSPO and for RG layer 40% Gum Acacia (GA), Carbopol-971 and HPMC K 100 M were used. In melt granulation, Hydrogenated castor oil (HCO), stearic acid (SA) and bees wax (BW) as binder that retard drug release in 10-30% concentration for MH and Polyethyleneglycol 6000 and poloxamer 188 for RG in 10 & 20% concentration as binder were used. In melt granulation, for RG layer, HPMCK100M was used for additional release retarding polymer. To select finest amount and to check mixing effect of binder & polymer on release of drug in SR formulation, $3^2$ factorial design was used. Characterization and comparison of designed batches, using different evaluation parameter was carried out viz. drug-excipient compatibility, flow properties, dimension, physical strength, variation of weight, assay, invitro dissolution study. For selected formulation, the kinetic of drug release as well as accelerated stability study was carried out. The invivo pharmacokinetic testing was carried out and compared for marketed formulation and optimised formulation.

Result and Discussion: For the estimation of MH and RG simultaneously, absorbance correction method by UV spectrophotometric was developed, validated...
and compared with existing method; current method was found to be simple, accurate and robust. Based on preformulation study results, the low soluble drug RG was complexed with β-Cyclodextrin in molar ratio. The prepared complexion was confirmed by calorimetric (DSC) & solubility study. The results of evaluation for dry granulation technique batches showed %friability at higher side 0.80-0.96%, all other tests were in control. The best batch in this group, F20 showed fickian diffusion of MH layer and non fickian drug release mechanism for RG layer. The evaluation after accelerated stability study revealed almost unacceptable % friability of formulation. The evaluations of formulations prepared with wet granulation showed all parameter good with better invitro drug release for 12h. In formulation F38, MH layer gave anomalous drug release and RG layer gave dissolution controlled drug release. The accelerated stability studies for them showed similarity index before and after stability for invitro release, with MH layer was 94.27% and with RG layer was 93.53%. The melt granulation technique showed highest hardness with same mechanical force as in all granulation technique. For RG layer, factorial design followed by full models were generated and based on p value of regression analysis, reduced models were developed (if p<0.05). The equations were validated by preparing check point and optimized batches. In MH layer HCO (F67) & SA (F66) both provided good drug release, anomalous release mechanism. Based on stability study with higher % similarity index, F66 was selected. The comparison of selected formulations with market preparation was carried out. The results showed with similar AUC, increased $T_{\text{max}}$ in optimised formulation compared to conventional market formulation conformed sustain drug release. The relative bioavailability, $F_r$ (%) for F38, 98.11 & 102.05 and for F66 it is 101.97 & 102.96 respectively for MH and RG compare to market formulation. The FTIR for final formulation was carried out, that confirmed no drug-excipient incompatibility present. Raman spectroscopy of finalised batch revealed distribution of melt-able binder throughout formulation.

**Conclusion:** In formulated three techniques, melt granulation showed cost effective, eco-friendly, robust formulation that provided drug release for 12 h with zero order drug release kinetics, with better bioavailability, at overall low cost.

**KEYWORDS:** Diabetes; Simultaneous estimation; Metformin Hydrochloride; Melt granulation; Repaglinide; Experimental design; *InVivo* pharmacokinetics