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IVIVC from theory to application- Development of once daily extended release formulation of Trimetazidine di HCl using IVIVC

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In-vitro in-vivo correlation (IVIVC) models are developed to explore the relationships between in vitro dissolution/release and in vivo absorption profiles. This model relationship facilitates the rational development and evaluation of immediate/extended-release dosage forms as a tool for formulation and defining the critical variable depending on pharmacokinetic profile of the drug. IVIVC modeling involves three stages: (a) Assume IVIVC Development, (b) In- vitro and vivo profiling and (c) model application to develop retrospective IVIVC.

The purpose of this paper is to utilize IVIVC tools in the development of oral controlled formulation of Trimetazidine Di HCl (TDH). TDH is anti anginal drug. It increases cell tolerance to ischemia by maintaining cellular homeostasis. It is freely soluble in water and has a short half life (6hr); making it ideal candidate for controlled release dosage form. Commercially two dosage forms are available; 20mg immediate release tablet as twice or thrice a day and sustained release tablet 35mg as twice a day. This provides an opportunity of developing once daily (OD) extended release formulation thereby reducing dose frequency.

The development of OD formulation was initiated from development of "Assumed IVIVC". Assumed IVIVC was developed by obtaining in-vivo data from literature of single dose IR formulation and twice dosing sustained release formulation and generating in-vitro data in lab for same.

In-vivo absorption was calculated using Wagner-Nelson method and same was used as target to develop OD formulation. In-vitro dissolution profile as a surrogate to in-vivo absorption was studied by evaluating the pH and RPM dependency of OD formulation. In-vivo study of the selected formulation was carried out on healthy human volunteers as a single dose fasting study and retrospective IVIVC was developed using software WinNonlin and IVIVC toolkit ver 5.3.

A linear model with a time-scaling factor clarified the relationship between in vitro and in vivo data. The predictability of the final model was consistent based on internal validation. Average percent prediction errors for pharmacokinetic parameters were ± 10% and individual values for all formulations were ± 15%. Therefore, a Level A IVIVC was developed and validated providing robust predictions of in vivo profiles based on in vitro dissolution profiles.

Development of liquid oral sustained release formulation of Metformin Hydrochloride

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The purpose of this study was to evaluate the potential for oral liquid sustained release formulation of Metformin Hydrochloride with in situ gelling properties. The low bioavailability, short half life, high dose requirement and drug absorption being limited to the upper part of small intestine makes the development of gastro retentive forms of Metformin Hydrochloride desirable. It is a promising alternative for pediatric and geriatric patients who find difficulty in swallowing bulky oral tablets. Oral administration of aqueous solution of Gellan gum (0.6%w/v) containing sodium citrate (0.25%w/v) and calcium chloride (0.09%w/v) in complexed form resulted in the formation of gel in simulated gastric fluid as a consequence of release of calcium ions in the acidic condition leading to cross linking of polymer and hence gelation. Rheological study on sols revealed its Non Thixotropic, Psuedoplastic and Shear thinning behavior. Effect of polymer was found to be greater on viscosity as well as drug release than calcium chloride as depicted by the response surface and perturbation plots. Rheological study on gel showed the elastic nature of gel being able to remain intact for prolonged period of time. In Vitro drug release study demonstrated diffusion-erosion controlled release of drug from gel matrix over a period of 8 h. The drug release profile was similar to that of commercially available sustained release tablet, f2 value being obtained 69.64. Accelerated stability studies for 1 month at 40±2°C and Relative Humidity at 75±5% revealed that the formulation is stable at the ambient temperature and humidity.