4. SCOPE AND PLAN OF WORK

Use of in vitro drug release data to predict in vivo bioavailability parameters are desirable for rational development and evaluation of modified release (MR) dosage forms. Development and applications of predictive mathematical relationships between in vitro drug release and in vivo drug absorption data, reduces the need for in vivo bioequivalence tests to document unchanged quality and performance of MR products that undergo certain pre and post-approval changes.

The development of a correlation is based on the scientific principles associated with mathematical modeling, statistical evaluation and numerical deconvolution. The development and validation of an IVIVC is based on the ability of fraction of the drug absorbed versus fraction of the drug-dissolved relationship of various formulations.

The aim of In Vitro - In Vivo Correlation (IVIVC) is thus to enable the dissolution testing of modified release formulations poses many challenges. These challenges include developing and validating the test method, ensuring that the method is appropriately discriminatory and addressing the potential of an IVIVC.

A suitable dissolution method is capable of distinguishing the performance of formulations with different release rates, in vitro and in vivo, is an important tool in product development. IVIVC facilitates the process of such method development. Depending on the nature of the correlation further changes to the dissolution method can be made. When the discriminatory in vitro method is validated, further formulation development can be relied on the in vitro dissolution only.

Bioavailability and bioequivalence studies involve mathematical analysis of plasma level versus time curves which permits the estimation of half life, absorption rate, excretion rate, extent of absorption and other constants that are useful in describing the fate of given drug in an organism. It should be noted,
however, that neither bioavailability nor bioequivalence data could be generated without analytical methodology to accurately measure drugs in biological fluids.

For the estimation of the drugs present in the biological fluid, HPLC method is considered to be more suitable since it is a powerful and rugged method and also extremely specific, linear, precise, accurate, sensitive and rapid.

The present study, therefore, aims to develop and validate IVIVC of selected modified release formulations containing zolmitriptan and rizatriptan. At present there are no IVIVC studies and no sustained release formulations for these drug candidates have been reported in India. The present IVIVC studies, however, focus on the development and validation of a level A correlation.

Plan of Work

The project was carried out in the following stages:

Stage I Preformulation studies

1. Determination of physical properties of the drugs such as physical nature (amorphous or crystalline), solubility, melting point, etc.

2. Drug compatibility studies were performed by infra red (IR) spectral matching and differential scanning calorimetry (DSC) approach.

Stage II Development of oral controlled/sustained drug delivery systems

1. Single unit development of matrix tablets by wet granulation formulation and characterization of granules for
   - Angle of repose,
   - Loose bulk density,
   - Tapped bulk density,
   - Compressibility index and
   - Drug content.

2. Compression of the formulated granules into tablets and evaluation of
the tablets as per the pharmacopeial specifications for

- Average weight and weight variation,
- Thickness,
- Diameter,
- Drug content and content uniformity,
- Hardness,
- Friability,
- *In vitro* drug release behavior and comparison of the release with the in house developed immediate release dosage forms and
- Optimization of certain process and formulation variables on the physicochemical properties and *in vitro* drug release profile of the formulated tablets.

**Stage III Stability studies as per the ICH guidelines**

Selected batches from the above studies were subjected to stability studies at the following different temperature and humidity conditions as prescribed by the International Conference on harmonization (ICH).

- 25°C with 60 % RH
- 40°C with 75 % RH

Samples were withdrawn at different time intervals and evaluated for their physicochemical parameters and *in vitro* drug release behavior.

**Stage IV Bioavailability study design and data handling**

A randomized single dose bioavailability study was conducted in rabbits for the developed modified release formulations containing zolmitriptan & rizatriptan and in house developed immediate release formulations containing zolmitriptan & rizatriptan.

**Stage V Development HPLC methods for the estimation of selected drugs in plasma samples**

Chromatographic conditions like
• Selection of wavelength,
• Selection of initial separation conditions,
• Nature of the stationary phase,
• Nature of the mobile phase (pH, peak modifier, ratio and flow rate) and
• Selection of internal standard were optimized.

Stage VI Validating the developed method

Validation parameters such as,
• Accuracy and Precision,
• Linearity and Range,
• Limit of detection (LOD) / Limit of quantitation (LOQ),
• Selectivity / Specificity,
• Robustness / Ruggedness,
• Stability and System suitability of the developed methods were validated.

Stage VII Pharmacokinetic parameters

After estimating the selected drugs in rabbit plasma, the following pharmacokinetic parameters were calculated;

• $C_{\text{max}}$ Maximum plasma concentration
• $T_{\text{max}}$ Time of maximum plasma concentration
• $\text{AUC}_{0-t}$ Area under plasma concentrations time curve 0 to 24 h
• $\text{AUC}_{0-\infty}$ Area under plasma concentrations time curve 0 to $\infty$ h
• $t_{1/2}$ Elimination half-life
• $k_{\text{el}}$ Elimination rate constant

Stage VIII Development of IVIVC correlations

After carrying out an in vivo and in vitro data analysis, IVIVC was checked for the developed MR formulations.