7. SUMMARY AND CONCLUSION

This thesis deals with the studies carried out by the writer for the past three years on the “Development and validation of In Vitro – In Vivo correlations for the developed modified release formulations of selected drug candidates”.

Thesis begins with a brief account of the in vitro - in vivo correlations, biopharmaceutical classification systems, IVIVC models, in vitro dissolutions and estimation of drugs in biological medium. The methods used for the IVIVC model development, validation, the steps involved in bio analytical method development, in vitro dissolution methods and their importance have also been discussed. A review of literature on IVIVC model development available for the drugs in biological fluids is presented.

Thesis deals with the scope and objective of the present investigation. The merits of IVIVC in the development of dosage forms and how IVIVC model development necessitates development of in vitro dissolution methods, bio analytical method development and validation are discussed. The objectives of the present study, namely, to optimize the chromatographic conditions, to develop and validate the methods to estimate the selected drugs in the biological fluids by HPLC, development of in vitro dissolution methods and IVIVC model development and validation have been described.

Thesis also deals with the experimental procedures adopted. It describes in detail the procedures adopted for the bio availability study design & data handling, optimization and validation of the chromatographic conditions for the estimation of the drugs in plasma and selected modified release (MR) formulations, IVIVC model development and validation.

The results obtained are presented, supported by tables and figures and discussed in detail. The discussions include,

- Bioavailability study design and data handling,
- Optimization and validation of the chromatographic conditions for the
estimation of the drugs in plasma and selected MR formulations are discussed such as,

- chromatograms obtained,
- accuracy,
- reproducibility (intraday and interday variations),
- specificity,
- linearity and range,
- LOD and LOQ,
- ruggedness and robustness,
- stability and
- system suitability studies.

➤ *In vivo – in vitro* data analysis

- *In vitro – in vivo* correlation model development

The following are some of the salient features of the present study;

i) A single dose study was conducted in healthy rabbits and plasma concentrations were estimated by a sensitive and validated methods.

ii) The selected drug candidates zolmitriptan and rizatriptan that are predominantly ionized at gastrointestinal pH ranges and are well absorbed after oral administration.

iii) The selected drugs can be categorized as high solubility/low permeability drugs under the proposed Class III of Biopharmaceutical Classification System (BCS) and hence it should be possible to determine the *in vitro–in vivo* correlation for these drugs.

iv) The target to find out a predictive *in vitro* dissolution method was reached gradually. The first step was taken by observing the *in vitro* dissolution method predicted best similarities and differences in bioavailability.
Apparatus I, pH 6.8 at 50 rpm was found to yield acceptable IVIVC for zolmitriptan and Apparatus I, pH 7.4 at 75 rpm was found to yield acceptable IVIVC for rizatriptan.

v) From a comparison of the differences in the *in vivo* pharmacokinetic parameters and the differences in the *in vitro* dissolution curves, it may be concluded that the developed dissolution method will discriminate bio in equivalent batches.

vi) Level A correlation was observed for the selected formulations at the *in vitro* dissolution conditions developed. These dissolution methods predicted also the best absorption rate for the selected MR formulations.

In conclusion, it may be pointed out that the developed *in vitro* dissolution methods can replace absorption studies during the pre-approval process to develop a desirable formulation and to ensure batch-to-batch bioequivalence. It will also be very useful in performing possible post-approval changes in the formulation scale-up or changes in the drug substance or excipients supplier.

**Recommendations**

This *In Vitro- In Vivo* correlations (IVIVC) have been applied for setting bio-relevant dissolution specifications, guiding new product development, supporting Scale-Up and Post Approval Changes (SUPAC), waiving bioequivalence study and more importantly, ensuring commercial product quality over the years. However, further investigations in human are required to prove the clinical usability of the experimental extended-release formulation.