2. RESEARCH ENVISAGED

Poorly water-soluble BCS class II drugs are associated with poor rates of drug absorption leading to inadequate and variable bioavailability (Dressman & Reppas, 2000). Oral absorption for this class of drugs is known to be dissolution/solubility limited. As a consequence, improvement in these two properties tends to improve the rate of drug absorption (Serajuddin et al., 1990). The formulation approaches, these days, are targeted to achieve higher dissolution rates in vivo. As per the BCS, rational prediction of the in vivo performance based on the in vitro dissolution data should be possible in case of Class II drugs. The in vitro dissolution conditions in such studies, however, should mimic those of the in vivo environment. Lately, the physiological dissolution media have been investigated as promising in vitro tools for predicting the in vivo performance of class II drugs (US FDA, 1997; Wyatt, 1999). From the standpoint of a formulation scientist, the enhancement of drug dissolution rate and eventually, its absorption rate can be accomplished using varied formulation approaches including solid/semisolid supersaturated systems formulated using different types of carriers, inclusion complexes and self-emulsifying systems. The above-mentioned systems can result in manifold enhancement of solubility/dissolution and thus provide the drug in solution form for rapid absorption across the g. i. lumen.

The drugs, RFX and NMS, are poorly soluble drugs, (Singla et al., 2000, Ahuja et al., 2003; Ahuja & Singh, 2004; Ahuja et al., 2006). They are almost completely absorbed (permeated) through g.i. tract. Thus, both of these drugs can be safely regarded as BCS Class II drugs. These drugs are known to exhibit poor and erratic bioavailability, as reflected from their poor and inconsistent rates of drug absorption. Also, both of these drugs are known to demonstrate dissolution or solubility limited absorption. Accordingly, their bioavailability may be improved by enhancing their dissolution rate through various solubility enhancement techniques. The following study protocols, therefore, were envisaged on these drugs:

**Phase-solubility studies at varied temperatures:** Experiments would be carried out to study the nature of drug-carrier interactions in solution state, and their thermodynamics would be explored in an attempt to understand the mechanisms of solubilization.
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**Formulation of binary systems:** In solid state, it was planned to formulate various binary supersaturated systems employing water-soluble, amphiphilic and lipid-soluble carriers, and formulation of adsorbent dispersion and inclusion complexes by various methods like fusion, solvent evaporation, cogrinding, kneading and physical mixing. Amongst the diverse carrier types, hydrotropes, polyols, sugars, polyhydroxy organic acids, polymers, blockcopolymers, polyglycolized fatty acid esters, adsorbents, lipids, natural cyclodextrins, and cyclodextrin derivatives would be studied. All these carriers would be investigated for carrier concentration effect too in both solution and solid state. Dissolution profile comparison studies would be conducted extensively by analyses of various drug release parameters like DE, $t_{90\%}$, $t_{10\%}$, $t_{90\%}$, $R_{90\%}$, and MDT to discriminate between the solubilizing efficiencies of these carriers.

**Mathematical modeling of drug release data:** Drug release kinetics would be thoroughly investigated employing various release kinetic models like Higuchi, Hixson Crowell cube root law, Weibull, Korsmeyer-Peppas, first-order, zero-order, etc. to look into the most apt model and potential drug release mechanism.

**Formulation of multicomponent systems:** It was also planned to formulate ternary or quaternary systems to explore the synergism between the promising carriers, if any, for solubility and/or dissolution enhancement.

**Optimization studies:** Systematic optimization employing RSM techniques were planned to be conducted to develop the best possible formulation under the given set of conditions to save considerable time, effort and developmental cost. Earlier studies carried out in our laboratories at the Institute have been found to be highly successful in the performance prognosis of varied drug delivery systems *viz.* hydrophilic matrices of diclofenac sodium, diltiazem hydrochloride and verapamil hydrochloride (Singh & Gupta, 1997, Singh et al., 2002a, Singh et al., 2004a), lipid matrices of captopril (Singh et al., 1998), microcapsules of diltiazem hydrochloride (Singh & Agarwal, 2002), buccoadhesive dosage forms of diltiazem hydrochloride (Singh & Ahuja, 2002), mucoadhesive tablets of atenolol (Singh et al., 2006b), vesicular drug delivery systems of nimesulide (Singh et al., 2005b), transdermal hydrogels of tenoxicam (Singh et al., 2004b), oral fast drug delivery system of flurbiprofen, meloxicam and etodolac (Singh et al., 2003a, Singh & Goel, 2004; Singh et al., 2005d;
Singh & Dahiya, 2005), and hydrodynamically balanced bioadhesives of tramadol hydrochloride, verapamil hydrochloride, lamivudine and stavudine (Singh et al., 2005c; Singh & Saharan, 2005; Mandsaurwale et al., 2006; Singh et al., 2006c). Hence, the current study also aimed at extending the remarkable benefits of systematic optimization techniques on the formulation of solid dispersions and inclusion complexes of both the drugs. An appropriate experimental design like central composite, Box-behenken or D-Optimal design would be employed to ascertain the effect of various formulation factors on the response variables like DE, l_{50}, MDT, etc. Response surface analysis and generation of mathematical model would be carried out using FACTOP and/or Design-Expert® software. Quadratic or cubic polynomials would be generated using MLRA. Numerical and graphical optimization would be employed using techniques like grid search, desirability functions, overlay plots, etc. to search for an optimum formulation. The generated mathematical model would be validated by formulating the checkpoints (confirmatory runs) and the results would be critically compared with those predicted using RSM. The linear correlations between predicted and observed would be explored, and their statistical significance discerned.

**Solid state characterization:** The drugs, carriers, most promising binary system, their physical mixture, and selected optimum formulation(s) would be thoroughly characterized using scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction, Fourier transform infra-red spectroscopy, etc. to investigate the drug-carrier interactions responsible for solubility enhancement of the BCS class II drugs.

**Formulation of tablets and stability studies:** The optimized formulation would be finally compressed as tablet dosage form and its dissolution performance compared with various commercial brand(s) employing factors like f1, f2, etc. The optimized formulation will be investigated for stability studies too to explore any change in dissolution performance upon storage.

**In vivo pharmacokinetic and pharmacodynamic studies:** The current studies also aim at investigating the in vivo pharmacokinetic performance of the optimized drug formulation vis-à-vis marketed formulation, corresponding physical mixture and pure drug in experimental animals like rabbit or rats, after obtaining requisite
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approval from the appropriate ethical committee of Panjab University or otherwise. Comprehensive pharmacokinetic analysis and modeling would be carried out on the serum concentration data using the in-house pharmacokinetics software and PC-NONLIN. Also, attempts would be made to study the onset and duration of pharmacological action of the drug(s) using in vivo carrageenan induced rat paw oedema model. Comprehensive statistical analysis using ANOVA-based factorial analysis and parametric significance tests on the pharmacokinetic/pharmacodynamic data would be conducted to draw rational conclusions from the in-vivo studies in animals.

IVIVC: Attempts would be made to develop mathematical relationship between in vitro release data and in vivo pharmacokinetic parameters and establish various levels of IVIVC. Level A correlation would be constructed between percent drug release and percent absorbed data at the corresponding time points using deconvolution or Wagner Nelson method. Level B correlation would be investigated between noncompartmental absorption and dissolution parameters. Level C would be explored between single point parameter like t50%, DP30min, DE and the pharmacokinetic parameters depicting absorption rate like K_a, MAT and C_max.