3. RESEARCH ENVISAGED, AIM AND OBJECTIVES

3.1. Research Envisaged

DM is a chronic disorder characterized by increased blood glucose level which is caused either due to failure of insulin production by the body or, absence of response from cells to the produced insulin. Due to the increased blood glucose level, symptoms like polyuria, polydipsia and polyphagia are observed in patients suffering from DM. With the progression of disease, pathological changes like nephropathy, retinopathy and cardio-vascular complications occur leading to multiple organ failure eventually (Melmed et al., 2011). According to the IDF’s report of 2017, about 425 million people were reported to be suffering from DM and among them 90% cases were of T2DM. By 2045, this number is expected to reach 628.6 million (IDF, 2017). The prevalence of DM is higher in India than in any other country in the world. The global economic burden reported for the treatment of DM was U.S. $1.3 trillion in 2015 and is expected to rise to about U.S. $ 2.5 trillion by 2030 (Bommer et al., 2018). Despite being such a threat, no treatment is available till date that is free from debilitating side effects. Though a number of synthetic drugs have been in use, none of them has been able to achieve complete success due to the associated side effects. Emphasis is now being given to nutraceuticals for the management of DM due to their less side effects, multiple pharmacological effects and ease of availability. Among the plant-based nutraceuticals, formulations of PPK and CRM are well reported for their antidiabetic properties. However, both the drugs on their conventional oral delivery exhibit low oral bioavailability and stability owing to low solubility and rapid GI degradation (Kaur et al., 2016a).

Various strategies have been utilized to improve the poor oral bioavailability of these drugs such as particle size reduction to micron or submicron level, complexation with hydrophilic carriers, solid dispersions, polymorphism, solid lipid nanoparticles, nano emulsions, SEDDS (SMEDDS/SNEDDS) and liquisolid technology. Among them, outstanding results have been reported through SNEDDS due to their obvious benefits like improved drug release control, enhanced solubility, enhanced bioavailability, conducive pharmacokinetic profile. The formulation of SNEDDS requires a plethora of excipients like lipids, surfactants and co-solvents which regulate the bioavailability of the incorporated drugs (Garg et al., 2016a).
Also, for subsequent commercialization of these formulations, these excipients are required to give robust formulations with high reproducibility and cost-effectiveness. Preference, therefore, needs to be given to the excipients such as Labrafil, Lauroglycol, Transcutol, Labrafac, Tween-80 and Cremophor etc. that have given reproducible results in earlier reports. Use of QbD based formulation development leads to precise prognosis of optimized formulations in less time with less number of excipients. The BBD was, therefore, adopted for development of SNEDDS. Optimized formulation was further solidified by using various hydrophilic and hydrophobic carriers followed by their spray drying. These were characterized for various pre and post compression and physical parameters. Furthermore, in order to prove the success of oral administration of PPK and CRM through SNEDDS, the antidiabetic effect of formulation was evaluated through STZ induced rat model (Garg et al., 2016a; Rao and Shao, 2008a and 2008b).

3.2. Aim

Design and optimization of SNEDDS for PPK: alone and in combination with CRM for effective management of DM.

3.3. Objectives

The objectives of the present study are summarized below:

- Analytical method development and validation by UV spectroscopy for qualitative and quantitative analysis of PPK and CRM for accomplishing simple, fast, robust, sensitive and cost-effective spectrophotometric method of analysis.
- Selection of excipients as per the laid down paradigms of QbD using BBD for optimization of L-SNEDDS.
- Characterization of optimized L-SNEDDS for parameters like droplet size, zeta potential and % drug loading.
- Conversion of optimized L-SNEDDS to S-SNEDDS through spray drying using various porous carriers.
- Characterization of optimized S-SNEDDS for micromeritic behaviour, % drug loading, in vitro dissolution and ex vivo permeation studies.
- Characterization of optimized S-SNEDDS for parameters like droplet size, zeta potential, PXRD and DSC.
• Stability studies of optimized S-SNEDDS by varying temperature, pH and dilution.

• Evaluation of *in vivo* effect of optimized S-SNEDDS vis-a-vis naive drugs in rat model of diabetes induced with STZ to assess parameters like serum glucose, body weight, lipid profile, liver parameters, serum creatinine, urea, total proteins and antioxidant levels.

• Statistical analysis of all the *in vitro* and *in vivo* results using suitable tests like model independent analysis, ANOVA and paired t test using suitable softwares like Graph Pad Prism and MS Excel worksheet.