3.1 Research envisaged

Vitamin D is a lipophilic micronutrient and it is a necessary component in the human diet for the good health of the individual. The two main chemical versions of vitamin D are vitamin D2, known as ergocalciferol and D3, known as cholecalciferol. Cholecalciferol, which is generally formed in the skin following sunlight exposure, is more potent than ergocalciferol. The active form of cholecalciferol is calcitriol (chemically known as 1, 25-dihydroxyvitamin D3), which plays an important role in calcium and phosphorus homeostasis, bone metabolism, blood pressure, reabsorption of calcium in the kidney, and secretion of insulin. The insufficient exposure to sunlight and disease conditions (e.g., hyperparathyroidism, obesity, inflammatory bowel disease) can lead to cholecalciferol deficiency. Abnormalities in calcium and phosphorus absorption and bone metabolism can cause osteoporosis in adults and rickets in children. The sources of cholecalciferol are very much limited (e.g., dairy products, beef, liver, egg yolk, and fish), leading to the great demand for enrichment of food and beverages with cholecalciferol and demand for cholecalciferol-based formulation as a supplement to food. The enrichment of food products with cholecalciferol or the development of cholecalciferol-based formulations is challenging because it is highly susceptible to degradation under environmental conditions including light, temperature and oxygen that can cause loss of its functionality and physiological benefits. Moreover, it has been observed that the degradation rate of cholecalciferol is high in the low pH range, the rate decreases as pH rises, and the optimum pH for the stability was 6.5 to 8.0. Keeping these aspects into consideration, novel formulation strategies are required for the efficient delivery of cholecalciferol. To protect cholecalciferol from the susceptible acidic environment of the gastrointestinal tract, the development of enteric solid dispersion is proposed. Solid

dispersion is one of the most efficient strategies to tackle poorly soluble molecules. Cholecalciferol is hydrophobic nutraceutical with poor aqueous solubility and stability concern, therefore development of enteric solid dispersion is envisaged to address these issues. In another approach, cholecalciferol solid dispersion encapsulated in the HPMC based delayed release capsules is proposed which could offer protection of cholecalciferol from the low pH of the stomach because HPMC capsules could delay the release of cholecalciferol until the capsule is in the intestine (i.e. pH>5.5). In the third, approach, for efficient delivery of cholecalciferol, development of self-emulsifying delivery system is envisaged. The proposed delivery strategies possess potential and could be important for further development in this particular area of research.

3.2 Objectives

Keeping into the consideration, the physico-chemical and stability related issue of cholecalciferol some drug delivery strategies are proposed with the following objectives:

- Development and characterization of enteric polymer-based solid dispersion for cholecalciferol delivery
- Development and characterization of delayed release HPMC capsules for efficient delivery of cholecalciferol solid dispersion
- Development and characterization of self-emulsifying drug delivery systems for cholecalciferol

3.3 Plan of work

1. Literature survey

2. Preformulation studies of cholecalciferol

2.1 Determination of solubility

2.2 Determination of partition co-efficient

2.3 Determination of melting point

3. Development of the analytical method for the determination of cholecalciferol using UV spectroscopy and HPLC

4. Development and characterization of enteric polymer-based solid dispersion for cholecalciferol delivery

4.1 Preparation of HPMCAS-based solid dispersion

4.2 Characterization of HPMCAS-based solid dispersion

4.3 Fourier transform – infra red (FT-IR) spectroscopy of HPMCAS-based solid dispersion

4.4 Scanning electron microscopy (SEM) of HPMCAS-based solid dispersion

4.5 Differential scanning calorimetry (DSC) analysis of HPMCAS-based solid dispersion

4.6 X-ray diffraction analysis of HPMCAS-based solid dispersion

4.7 Evaluation of effect of formulation on viability of caco-2 cells

4.8 Evaluation of dissolution profile of cholecalciferol in HPMCAS-based solid dispersion

4.9 Evaluation of relative bioavailability of cholecalciferol in developed formulations

4.10 Determination of stability of cholecalciferol in developed formulations

5. Development and characterization of delayed release HPMC capsules (DRHCap-SD) for efficient delivery of cholecalciferol solid dispersion

5.1 Preparation of DRHCap-SD of cholecalciferol

5.2 FT-IR Spectroscopy study of cholecalciferol solid dispersion

5.3 Scanning electron microscopy study of cholecalciferol solid dispersion

5.4 Differential scanning calorimetry analysis of cholecalciferol solid dispersion

5.5 X-ray diffraction analysis of cholecalciferol solid dispersion

5.6 Effect of developed formulation on viability of Caco-2 cells

5.7 *In vitro* dissolution study of cholecalciferol in DRHCap-SD

5.8 Evaluation of flow properties of cholecalciferol solid dispersion

5.9 Determination of stability of cholecalciferol in DRHCap-SD

6. Development and characterization of self-emulsifying drug delivery systems for cholecalciferol

6.1 Solubility of cholecalciferol in various excipients

6.2 Preparation of pseudo-ternary phase diagram

6.3 Characterization of self-emulsifying drug delivery system (SEDDS)

6.4 Assessment of self-emulsification

6.5 Morphological examination of SEDDS by transmission electron microscopy

6.6 Determination of emulsion particle size and zeta potential

6.7 Cholecalciferol content in the SEDDS formulation

6.8 *In-vitro* stability assessment in SGF and SIF

6.9 *In vitro* dissolution study

6.10 *In-vitro* bio-accessibility of cholecalciferol in SEDDS

6.11 Effect of SEDDS formulation on viability of Caco-2 cells

6.12 Stability study of cholecalciferol in SEDDS

7. Compilation and analysis of data