CHAPTER-3

Plan of the Study

The aim of this research was to develop, optimize and characterize natural polymer based interpenetrating polymeric network of an antineoplastic drug Capecitabine for achieving, prolonged release and improved treatment of colon cancer. Following were developed as a part of this research work, characterized and evaluated.

- Preparation of LBG and NaAlg based divalent calcium ion (Ca^{2+}) cross-linked IPN microbeads loaded with CAP
- Preparation of LBG and NaAlg based trivalent aluminium ion (Al^{3+}) cross-linked IPN microbeads loaded with CAP
- Preparation of LBG and NaAlg based trivalent aluminium ion (Al^{3+}) cross-linked IPN microbeads loaded with CAP exhibiting dual mechanism of floating and mucoadhesion.

Objective of study

Capecitabine (CAP) is an oral chemotherapeutic prodrug of 5-Fluorouracil (5-FU) used in the first line treatment of the colorectal cancer. Although, 5-FU is widely used in treatment of colon cancer. Due to its poor oral absorption and intra patient variability, it is administered intravenously in the form of rapid bolus injection that distributes and eliminates rapidly approximately within 20-30 min. Thus, with respect to the problems associated with bolus injection, when continuous infusion of 5-FU is administered the response rate increased not only in terms of anticancer effect but also exhibited low and acceptable toxic profile in comparison to intravenous bolus injection. This successful and better extended exposure of 5-FU through intravenous infusion provided a rationale to prepare an oral delivery of CAP in order for continuous and prolonged drug release to avoid the complications related to

intravenous route of administration. Currently, CAP is widely in demand for treatment of advanced colorectal and breast cancer and is commercially available under brand name Xeloda® with recommended twice daily dosing of 1250 mg /m^2. So far Xeloda® has lessen the side effects, pain, and number of rotational schedule during chemotherapy but still its short elimination half-life of 1- 2 h and complete elimination of 5-FU (i.e. conversion of CAP into active agent 5-FU by following trienzymatic bioconversion pathway) within 6 h exhibits a dosing exposure gap of 6 h in between the two subsequent doses. For getting continuous treatment, thus a prolonged release formulation of CAP is required to overcome this exposure gap. Therefore, present study is an effort towards the preparation of a sustained/controlled release formulation for once /twice a day medication with continuous maintenance of drug concentration in therapeutic range.

Study plan:

A) Preformulation study

- Physical appearance
- Melting point
- FTIR
- Analytical method development of CAP (UV/HPLC)
- Standard curves of CAP in different media

B) Preparation of Interpenetrating Polymeric Network (IPN)

- *Name of the method:* Ionotropic gelation method
- *Types of formulation*
    - Ca^{2+} cross-linked CAP loaded IPN microbeads of locust bean gum and sodium alginate.

- Al^{3+} cross-linked CAP loaded IPN microbeads of locust bean gum and sodium alginate.
- Al^{3+} cross-linked CAP loaded buoyant and mucoadhesive IPN microbeads of locust bean gum and sodium alginate.

C) Optimization of the formulation

- Identification and selection of Critical Quality Attributes (CQAs) or responses.
- *Screening Design:* Fractional Factorial Design (FFD)
- *Response Surface Based Design (optimization process):* Box Behnken Design (BBD)

D) Characterization and Evaluation

- Particle size
- Morphology (Optical microscopy, SEM)
- Elemental Analysis (EDX)
- Swelling study
- Drug- excipient compatibility study (FTIR/DSC)
- Crystallinity analysis (XRD)
- Differential Scanning Calorimetry (DSC)
- *In vitro* drug release study
- *In vitro* buoyancy study
- *Ex vivo* mucoadhesion study
- Cytotoxicity study (Against HT-29 colon cancer cell line)
- Histocompatibility study (Swiss albino female mice)
- *In vivo* pharmacokinetic study

- *In vivo* antitumor activity
- *γ-scintigraphy study*
- *S*tatistical analysis