# PREFACE

With respect to field of oncology, extensive research is undergoing in developing oral chemotherapeutics in order to eliminate the trauma and serious side effects caused to the patients by long exposure and profusion of anticancer drugs through intravenous administration. From the past few years to present, numerous anticancer drugs Dasatinib, Erlotinib, Lapatinib, Sorafenib, Imatinib etc. have been switched from intravenous to oral delivery. From this it could be expected that in the near future there would be chances of development of numerous oral anticancer drugs that can reduce the toxicity due to rotational chemotherapy schedule that lasts from week to months with enhanced patient compliance and clinical safety. Capecitabine (CAP, prodrug of 5-fluorouracil (5-FU), a model drug for the present study and also an example of oral chemotherapeutics, has successfully translated into an oral chemotherapeutic. Earlier 5-FU bolus injection was widely preferred against colon cancer. Its poor oral absorption and rapid elimination within 20-30 min. provided a rationale to the pharmaceutical scientist to focus towards continuous infusion of 5-FU and that resulted in an excellent response rate and limited toxic profile in comparison to bolus injection of 5-FU. Further, to avoid the complications caused due to the intravenous route of administration of continuous infusion of 5-FU provided a strong reason for the development of oral delivery of CAP and through clinical trials it has proved its efficiency also. However, beside these merits it suffers from disadvantages also. CAP, is a high dose drug (1250 mg/m$^2$ twice daily) with severe side effects, is commercially available under the brand name Xeloda®. Once inside the systemic circulation and following its trienzymatic bioconversion pathway it converts into 5-FU. This 5-FU, after 4 half-lives (1-2 h) i.e. approximately 6 h is undetectable in plasma. Thus, its recommended twice daily dosing of morning and evening creates an irregular, intermittent two exposure gaps of 6 h out of 24 h. To overcome the above problem

of capecitabine there is a need to develop an extended oral dosage form that can reduce the dose as well as the dosing frequency. Multiparticulate based delivery systems composed of natural polymers are gaining interest due to their extended drug release behaviour and biocompatible nature. Unfortunately, these polymers exhibit low mechanical strength that directly influence its functional property thus, to enhance and improve the mechanical and physical property, interpenetrating polymeric network (IPN) a new group of polymers have been introduced that by involving two or more polymers where at least one polymer network is either synthesized or cross-linked independently in the immediate presence of each other is establishing its place in extending the release of drug. The idea to develop an IPN drug delivery system could be advantageous in reducing both dose and dosing frequency of capecitabine resulting enhanced elimination half-life and bioavailability. The present research work involves three formulation preparations. The first two are locust bean gum and sodium alginate based IPN microbeads of capecitabine cross-linked with divalent and trivalent ion calcium and aluminum chloride (F-1 and F-2 respectively) and a third formulation of aluminum ion cross linked IPN microbeads (F-3) with a concept of dual mechanism of buoyancy and mucoadhesiveness in order to prolong the release of drug and surmounting the in and between dosing gap.

Optimization and development of the multiparticulate IPN microbeads were performed by employing Quality by design (QbD) method that involved assessment of risk by different methods such as risk ranking and filtering; failure mode and effective analysis and risk estimation matrix followed by screening of the important independent factors (obtained through various risk assessment study) by Fractional Factorial Design and finally optimization of the formulations by Box-Behnken Design based on screened characteristics. The optimized batches of all the three different formulations were evaluated for several

physiscochemical properties, in vitro and in vivo activity to ensure their feasibility, safety and utility.

The entire thesis is divided into six chapters. **Chapter one** includes introduction to colon cancer, brief introduction related to the drug delivery vehicle, drug, polymers and the basis of the study present undertaken work. **Chapter two** deals with an overview of colon cancer, anatomy, stages, and its current treatment. Alongwith an emphasis on the drug delivery vehicles, drug, polymers and their application in different research works. **Chapter three** illustrates the objective and plan of the study involved for the preparation of the formulation. **Chapter four** deals with optimization and development of three types of formulations i.e. (Part I) Preparation of IPN microbeads and its cross-linking using divalent cation calcium ion and its optimization by employing QbD approach; (Part II) Preparation of IPN microbeads and its cross-linking using trivalent cation aluminum ion and its optimization by employing QbD approach; Part III involving preparation and optimization of aluminum ion cross-linked gastroretentive buoyant IPN microbeads. **Chapter five** illustrates the result and discussion of the outcomes of the studies performed in the previous chapter four. **Chapter six** includes the summary and the findings of research work that depicts that formed newly developed interpenetrating polymeric network microbeads formulations could be a promising drug delivery vehicle in enhancing the elimination half-life of a water soluble drug by prolonging the drug release as well as therapeutically more effective in treatment of colon cancer.