SUMMARY AND CONCLUSION
Summary
The ever-increasing number of drugs in the market is remarkable evidence to medical progress whereby more effective treatments are available for a variety of diseases. With increasing drug usage there are unavoidable problems pertaining to adverse effects. These may manifest in many ways, but the small and large intestine is one of the most frequent sites of drug induced side effects accounting for 20–40% of all adverse reactions. Major classes include antibiotics, non-steroidal anti-inflammatory drugs, laxatives, anticancer drugs and immunosuppressive agents that affects intestine. The pathogenesis of the lesions caused by drugs is highly variable and needs treatment. Amongst various pathologies, one of intestinal pathological state such as “Melanosis coli” develops due to prolonged intake of anthraquinone laxatives. Therefore, present study was aimed to assess the potential of curcumin (CUR) for the prophylactic action / treatment of Melanosis coli via optimization of colon targeted drug delivery systems. Owing to poor solubility and extensive presystemic clearance of CUR parallel to the reported advantages of lipoidal formulation, the present work includes the development and optimization of nanoemulsifying preconcentrate formulation with good emulsification ability and optimal globule size, using the design of experiment methodology. Various levels of excipients such as Peceol® (oil), Cremophor® EL (surfactant) and Transcutol® HP (co-surfactant) were selected for formulation optimization. Results suggested that globule size was appreciably influenced by concentration of oil (Peceol®). On the contrary, higher levels of Peceol® and lower levels of Cremophor® EL led to lower emulsification time required to attain the therapeutic effect at targeting site. Plasma drug profile suggested limited systemic absorption with enhanced opportunity of localised delivery of drug at colonic sites. The results indicate the suitability of developed formulation in the treatment of inflammed colonic region.
Work also includes design and optimization of polymeric Self-emulsifying nanocapsule (PSN) formulation using a pH-sensitive polymer bearing self-emulsification ability and high loading efficiency. It was hypothesized that use of polymer (HPMCAS-HF) having emulsifying properties could obviate the issues related to use of high concentration of surfactant (30–70%) in conventional self-emulsifying formulations. Self-emulsification property of formulation was considered as an important parameter while designing the formulation in order to prevent precipitation and recrystallization of the drug from formulation. The high viscosity of HPMCAS-HF may contribute to the rate of emulsification. In vitro studies revealed that polymeric self-emulsifying formulation, released the drug after 5 h lag time corresponding to the time to reach the colonic region. Pronounced localized action was inferred from the insignificant plasma concentration profile that depicts limited systemic absorption. Results signified either degradation of drug or localized delivery of formulation to colonic site. Roentgenographic studies are in close agreement with in vitro dissolution studies and indicated the presence of carrier in lower gastrointestinal region up to 24 h. Optimized formulation, showed significantly
higher cytotoxicity (IC₅₀ value 20.32 μM) in HT 29 colonic cancer cell lines. The present work confirms the suitability of polymeric self-emulsifying nanocapsule for localized delivery in colonic region.

Further, work includes the development and optimization of CUR loaded dual sensitive nanosphere formulation by considering the fact that nanoparticle based drug delivery systems recently emerged as a new strategy with distinctive ability to taken up by inflamed tissues in the colon than macro particles. Study includes the estimation of impact of excipients CUR:hydroxy propyl methyl cellulose acetate succinate ratio, concentration of polyvinyl alcohol and internal phase volume particle size and encapsulation efficiency of formulation. Results suggest that mean particle size significantly influenced by an increasing concentration of drug to polymer ratio, whereas, concentration of polyvinyl alcohol and internal phase volume significantly impacts entrapment efficiency of formulation. CUR loaded nanospheres displayed improved dissolution profile that was reflected in the form of enhanced bioavailability compared to reference formulation. The results showed increased soluble form of CUR in the said nanosphere formulation.

While comparing the performance of various formulations it has been observed that self-emulsifying nanocapsule formulation favors the conditions such as limited systemic absorption (plasma drug profile), intact drug until reaching the large intestine (roentgenographic study) and effective delivery of drug to target site (cell line study); required for localized delivery. Therefore, it can be concluded that the developed PSN formulation could be considered as a promising delivery strategy towards localized targeting of CUR to colonic region for the effective treatment of colorectal pathologies.

Study was preceded with in vivo localization of optimal PSN formulation using guinea pig model to mimic “Melanosis coli” environment (induced by sennosides administration). Performance of the developed polymeric Self-emulsifying nanocapsule formulation was compared with reference formulation (modified marketed formulation). Efficacy of formulation(s) was characterized by change in body weight, stool consistency, level of tumour necrosis factor in tissues and histopathological changes (as a marker of pathology) of animals kept under test conditions. Animals used during the study were found to have prominent laxative action, whereas, no such (laxative) effects were seen in control group. A continuous decrease in body weight was observed in animals of positive control and standard prevention group, in contrast, insignificant weight loss was observed in the animals kept under prevention group (treated with CUR loaded polymeric Self-emulsifying nanocapsule formulation). Autopsy studies indicated the dark brown pigmentation in mucosal membrane infers the induction of melanosis coli. Further, induction of disease was confirmed by raised level of TNF-α in tissues removed from control group. Results showed that animals kept under prevention group (administered PSN formulation and sennosides simultaneously) were maintained their normal physiology in
Comparison to standard prevention group (administered reference formulation and sennosides simultaneously). Reference formulation failed to maintain the normal physiology of animals. Therefore, it was concluded that polymeric Self-emulsifying nanocapsule formulation presents as a favorable delivery system for colonic pathologies such as Melanosis coli, in comparison to reference formulation.

**Conclusion**

Following conclusions were drawn from the present work:

- "Lipid based drug delivery system" can be one of the most reliable approaches for localized delivery of curcumin to inflammed colonic sites.
- The developed formulations overcome issues associated with curcumin by presenting the drug in solubilized form.
- Developed formulations were observed to exhibit *in vitro* drug released after desired lag time corresponding to the time to reach colonic region and thereafter exhibited controlled release pattern.
- Roentgenographic studies are in close agreement with *in vitro* dissolution studies and indicating colonic localization.
- Pronounced localized delivery and action was inferred from limited systemic absorption. Histopathological analysis and levels of TNF-α in the tissues removed from the diseased animals ensures the localized delivery of selected drug to the inflammed colonic region.

It can be concluded that the present work paved way to coin a methodology for the systematic development of lipid based drug delivery system for localized action in colonic region.