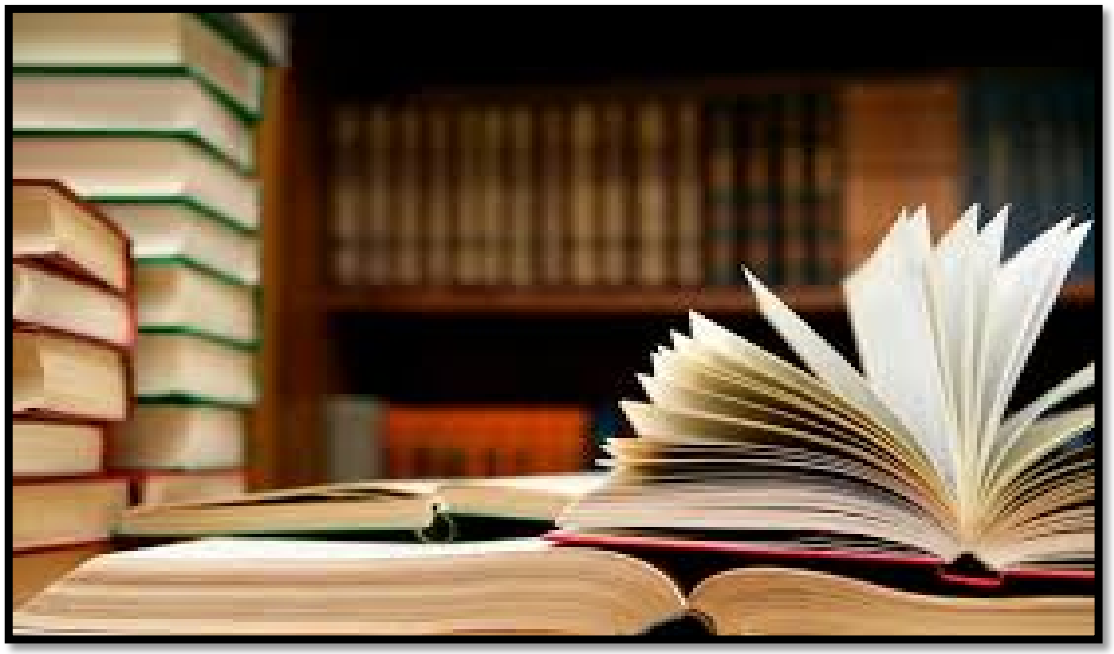
CHAPTER 2

"REVIEW OF LITERATURE"



CHAPTER 2: LITERATURE REVIEW

Jin *et al.*, 2021 formulated the new pH–enzyme double-dependent mesalamine colon-specific delivery system. From the pharmacokinetic study data, it has been confirmed that Eudragit S-100 coated mesalamine microparticles are considered to maintain the drug concentration within target ranges for an extended period. *In vivo* results from mesalamine-coated microparticles are thought to have the potential to maintain the concentration of mesalamine in the target range for a long time, ensure the efficiency of treatment and reduce the frequency of administration.

Sardou *et al.*, 2021 have developed the 5-ASA pellets using a coating composed of inulin/Eudragit RS. The coated pellets offered a superior therapeutic outcome compared to uncoated pellets in terms of colitis activity index (CAI) and the colon's tissue enzymes of glutathione and malondialdehyd*e*. The optimum coating composed of inulin and RS could offer a sustained release of 5-ASA throughout the small and large intestines with the sensitivity of drug release to microbial degradation.

Patel *et al.*, 2021 have prepared mesalamine microspheres for the treatment and management of UC. Tripolyphosphate (TPP) was used as a cross-linking agent during the preparation of the microspheres using the ionic gelation emulsification technique. Eudragit S-100 was applied to the microspheres to stop drug release in the stomach using the solvent evaporation method. Surface morphology, entrapment effectiveness, drug loading, micrometric properties, and in-vitro drug release were all assessed for the prepared microspheres. Scanning electron microscopy revealed that the surfaces of the microspheres formed were rough. The study's findings suggested that the prepared formulation might be the best approach for colitis management.

Hu *et al.*, 2020 determined the effect of *L. acidophilus* on dextran sodium-induced colitis. Compared to the DSS-induced group, the mice in the *L. acidophilus* XY27 group fared better in weight, DAI score, colon length, length-to-weight ratio, and colonic pathological sections. TNF-, Interleukin-6 (IL-6), Interleukin-12 (IL-12), and

Interleukin-1 (IL-1), malondialdehyde (MDA) content, and myeloperoxidase activity were all significantly reduced in the serum of UC mice treated with L. acidophilus XY27, whereas Interferon- (IFN-), Interleukin-10 (IL-10), Catalase (CAT), and total superoxide dismutase.

Remya *et al.*, 2020 have suggested that bovine serum albumin and pectin microspheres will be employed as carriers for a mesalamine medication that will treat UC in the colon. Coacervation-phase separation technology was used to make BSA/pectin mixture microspheres containing mesalamine medication. The findings of this study demonstrated that microsphere carriers created for delivering the mesalamine drug enhanced the mesalamine drug's adherence time, resulting in the effective treatment of UC.

Deshmukh *et al.*, 2020 prepared the sulfasalazine loaded amidated pectin microparticles by ionic gelation technique. The microparticles were filled in Eudragit S-100 coated hard gelatin capsules for pH and time-dependent drug delivery to the colon. They concluded that the coating of the capsule with enteric coating polymer could prevent the premature release of the drug from the stomach region. *In vivo* study in rabbits confirmed that the enteric polymer-coated capsule dissolves at colonic pH 7.4 to release the drug from microparticles.

Ehsan *et al.*, 2019 aimed to investigate effect of 5-ASA pellets. The *In vitro* data showed that uncoated formulations failed to control the 5-ASA release and burst release was observed. Meanwhile, incorporating Eudragit S-100 as a pH-dependent coating layer improved the controlled release of pellets. *In vivo* experiments revealed the therapeutic efficacy of Eudragit S-100 coated pellets of 5-ASA in alleviating the conditions of the induced colitis model, as reflected by weight gain and histological improvement. All these results confirmed the ability of this formulation for targeted drug delivery of 5-ASA to the colon.

Thakur *et al*., 2019 this study investigated the effect of mesalamine-loaded Eudragit S-100 with probiotic microparticles. The concentration of IL-8 was used to assess the impact of spray-dried microparticles on inflamed Caco-2 cells. Pretreatment of Mesalamine with probiotics reduces DNBS (Dinitrobenzenesulfonic acid) caused colitis in rats, according to an *in vivo* investigation. The findings lay the groundwork for a tailored strategy combined with the probiotic's anti-inflammatory capability, which could assist in reducing the issues associated with traditional UC treatment and care.

Dong *et al*., 2019 investigated the impact of *S. boulardii* on intestinal mucosal barrier and intestinal flora in a colitis mouse model. *S. boulardii* has an anti-inflammatory action and protects the mechanical barrier of the gut mucosa. S. *boulardii* may specifically upregulate the abundance of the S24-7 family, and this could be a mechanism underpinning its function.

Wang *et al*., 2019 developed a carcinogenesis model; C57BL/6 mice were given azoxymethane and dextran sulphate sodium (AOM/DSS). S. *boulardii* was lavaged for 12 weeks in the treatment group. Treatment with *S. boulardii* reduced AOM/DSS-induced UC carcinogenesis in mice, as evidenced by lower tumor load and TNF- and IL-6 levels *in vivo* and effects on TNF- and IL-6 activities *in vitro*. The control, AOM/DSS treated, and AOM/DSS plus *S. boulardii* treated groups significantly changed their fecal and mucosal microbiota.

Patole *et al*., 2018 have used an emulsion cross-linking approach to create mesalamine-loaded alginate microspheres for the local treatment of UC. Microspheres were encapsulated in alginate microspheres and placed in HPMC capsules that had been enteric coated with Eudragit FS-30D. An *in vitro* drug release analysis revealed a burst drug release pattern in the first hour, necessitating the use of alginate microspheres. In rat research with colonic inflammatory lesions, microsphere treatment resulted in a significant reduction in ulcer index. A histopathological

examination revealed no evidence of ulcers or bleeding.

Nidhi *et al.*, 2018 have exploited embelin-loaded guar gum microparticles through the emulsification technique. The *in vitro* release of the optimized formulation exhibit remarkably sustains and delays the release of embelin at a specific site. Embelin-loaded microparticles showed an average particle size of 12.9± 0.75 µm. The drug release was site-specific and sustained. From these observations, it has been concluded that the microparticulate system helps enhance stability and controlled release at specific colonic sites.

Kaur *et al.*, 2017 formulated microspheres of mesalamine and prebiotics using guar gum and xanthan. These were mixed with *Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum* and *Saccharomyces boulardii.* Comparative evaluation of fecal contents, weight gain trend, and histological studies in rats demonstrated the therapeutic advantage of simultaneous synbiotic administration with mesalamine. The findings show that combining synbiotics with mesalamine could be a handy way to achieve efficient and cost-effective therapeutic targeting in the colon

Lopez *et al.*, 2017 formulated pellets of triamcinolone acetonide by using pectin: and ethyl cellulose as film-coating material. Triamcinolone acetonide (TA), a valuable drug in intestinal inflammatory disorders, was loaded into cyclodextrin-based pellets. These results suggest that the delivery system based on pectin: ethylcellulose coating for pellets has an excellent colon release performance for triamcinolone acetonide-protecting drugs that are unstable at acidic pH.

Rashmi *et al.*, 2016 studied the pH-triggered delivery of curcumin to the colon, which was successfully achieved by using Eudragit S-100 coated microspheres. The colon-specific delivery of curcumin from microspheres exhibited a distinct increase in the pharmacological effect compared to free curcumin. From the observed data, it has been concluded that the developed formulation of curcumin utilizing pH-triggered delivery may seem promising for UC.

Rashid *et al.*, 2016 have suggested that polymeric microparticles have proven to be a potential technique for treating ulcerative colitis as a targeted drug delivery system. Microparticle systems are one out in terms of particle size, as the ideal carrier particle size for drug localization should be in the range of 5–15 mμ to extend drug residence duration in the colonic region. Particles in this size range can stick to the active site and collect in the targeted area.

Xiao *et al.*, 2015 prepared microparticles (MPs) with pH-sensitive Eudragit S-100 (ERS 100) and (polylactide-co-glycolide) (PLGA) using an emulsion-solvent evaporation process and the MPs were loaded with curcumin (an efficient anti-inflammatory agent). *In vivo* tests demonstrated that orally given MPs-4 had a higher therapeutic efficacy than curcumin in relieving colitis in a UC animal model. Our one-step fabricated curcumin-loaded MPs feature pH sensitivity, controlled drug release, and colon targeting capabilities, which may hold promise as a scalable drug carrier for the effective clinical therapy of UC.

Chen *et al.*, 2015 have exploited that *L. acidophilus* affects the IL-23/Th17 immunological axis in experimental colitis. Saline, hormones, and varying amounts of *L. acidophilus* intervention were to be used in DSS-induced UC mice models. The results demonstrated that *L. acidophilus* administration reduced Th17 cell-mediated release of the pro-inflammatory cytokine IL-17 by downregulating IL-23 and TGF1 expression and phosphorylating p-STAT3 downstream.

Vishwakarma *et al.*, 2015 aimed to investigate the mesalazine effect and probiotics when encapsulated in pectin beads to shield the medicine from the gastric environment and direct it to the colon. *In vivo* investigations have shown that mesalazine and Probiotic-loaded pectin beads may be employed for efficient medication and probiotic administration to the colonic region and that they aid in cell regeneration and protect the colon against ulcer development.

Neelam *et al.*, 2015 have prepared mesalamine and probiotic-loaded beads. A

sustained drug release was observed for 5 hrs; nearly 60% of the drug was released at the end of 10 hrs. Microbiological studies of probiotics showed the best cell viability. In the acetic acid-induced UC model, the mesalazine–probiotic beads-treated group showed a significant ulcer protection index. Mesalazine–probiotic-loaded beads may serve as a useful colon-specific drug delivery system for the treatment of colitis.

Xu *et al.*, 2014 have developed 5-aminosalicylic acid (5-ASA) colon adhesive pellets to treat ulcerative colitis. By combining bioadhesive agents Carbomer 940 and hydroxypropyl cellulose (HPC), the pellet's core was produced. Extrusion/spheronization process, Surelease as an inner layer for waterproofing, and Surelease as an outer layer for pH regulation, Eudragit S-100 is used as an exterior layer. The 5-ASA-loaded colon adhesive pellets had the most significant therapeutic effect in animal testing.

Badhana *et al.*, 2013 formulated the microspheres by the ionic-gelation emulsification method using tripolyphosphate (TPP) as cross-linking agent. The microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach. It was observed that Eudragit S-100 coated chitosan microspheres gave a full release of the drug in the colonic environment. Eudragit-coated chitosan microspheres were promising carriers for colon-targeted delivery of mesalamine.

Abbas *et al.*, 2013 studied the 5-ASA using pectin, Eudragit RS, and Eudragit RL. Eudragit in buffer media also controlled drug release, but in the simulated colonic fluid, pectin degraded to its monomers due to degradation by pectinolytic enzyme followed by pore creation and relatively fast drug release. Therefore, pellets with suitable characteristics for colonic delivery of 5-ASA could be achieved by extrusion-spheronization of an optimized mixture of pectin, Eudragit RS, and Eudragit RL.

Veerappan *et al.*, 2012 have suggested that probiotics are microbes that have been shown to impact human health positively. Probiotics can benefit our pouchitis patients

and possibly our mild-to-moderate UC patients, and when more research is published, we will know more. As time goes on, it may become a realistic and natural treatment option.

Soyturk *et al.*, 2012 explored the effects of *S. boulardii* in an experimental rat model of trinitrobenzene sulfonic acid (TNBS)-induced colitis. In an AOM/DSS-induced mouse model, *S. boulardii* substantially reduced UC carcinogenesis. The reduction or blockages of TNF- and IL-6 levels and changes in the gut microbiota are likely responsible for this favorable outcome.

Ham *et al.*, 2012 reviewed that mesalamine is a 5-aminosalicylic acid drug used to treat mild-to-moderate UC. It has anti-inflammatory and anti-oxidant activity. It reduces pro-inflammatory cytokines and inhibition of COX-2 receptor and the anti-oxidant property of the drug reduces the reactive oxygen species (ROS), ultimately reducing inflammation.

Ganguly K *et al.*, 2011 have formulated polyethylene glycol cross-linked chitosan microspheres loaded with 5-fluorouracil (5-FU) prepared by emulsion cross-linking and enteric-coated with cellulose acetate phthalate to facilitate direct targeting of 5-FU to the colon. Coated microspheres were found to be more suitable for colon targeting than uncoated microspheres, as the former extended 5-FU release from 6 to 12 hrs by protecting 5-FU in the stomach's acidic environment.

Jagdale *et al.*, 2011 developed a colon-targeted drug delivery system combining polymer chitosan and cellulose acetate phthalate was attempted to be optimized. *In vitro* and *in vivo* results confirmed a potential colon-targeted drug therapy for treating IBD.

Sriamornsak *et al.*, 2011 have reviewed that pectin is a naturally occurring heteropolysaccharide comprising 1, 4 linked a-D-galactosyluronic acid residues and neutral sugars such as galactose, rhamnose and arabinose. According to recent

research, pectin positively affects colitis, has mucoadhesive properties, and is generally utilized as a colon-specific drug delivery carrier for colon disease. It is degraded by colon enzymes named pectate lyases and polygalacturonases.

Shah *et al.*, 2011 have suggested that when the physiological circumstances of the colon precisely activate polysaccharide-based colon-targeted drug delivery systems, they are successful. The absence of enzymes during colonic diseases may prevent the delivery system from being activated. Polysaccharides should be combined with enteric or cellulose polymers to ensure drug distribution to the colon.

Kawadkar *et al.*, 2010 have prepared pectinate microparticles using the ionotropic gelation process for colonic administration of mesalazine. Scintigram revealed that ZPG-MPs (filled in enteric-coated capsule) stayed in the colon for more than 9 hrs and delivered almost the entire drug loading dosage. The findings of this study show that the ZPG-MP formulation could be used as a colonic medication delivery method.

Atyabi *et al.*, 2010 developed gelatin microspheres containing 5-aminosalicylic acid using the solvent evaporation method. It was observed that this technology might provide an appropriate drug release pattern for colonic distribution of active drugs, as 30% of the medication was released from ethylcellulose-coated microcapsules within 6 hrs, compared to 90% of the loaded drug for gelatin microspheres under the same conditions.

Wei *et al.*, 2010 prepared the Chitosan/Kollicoat SR 30D film-coated pellets for colonic drug delivery. The coated pellets had a considerable moderating impact on experimental colitis in rats, according to an in vivo therapeutic experiment. For the treatment of IBD, the coated pellets provided an effective and long-lasting local therapeutic concentration with the potential to reduce the side-effect.

Dashora *et al.*, 2009 have developed the pectin-prednisolone microspheres (PPMS) and pectin prednisolone eudragit microspheres (PPEMS) were made using an

emulsion-dehydration approach and an o/o solvent evaporation method, with certain modifications. pH-dependent release profiles were achieved by coating the microspheres with Eudragit- S 100. After 4 hrs, the cumulative percent drug release of prednisolone from pectin microspheres in SGF and SIF ranged from 30-45%, while the cumulative percent drug release from Eudragit coated microspheres ranged from 6.25 to 8.95%. Drug release was shown to be increased in the presence of rat caecal contents, demonstrating that pectin is susceptible to colonic enzymes released by rat caecal contents.

Jain *et al.*, 2009 aimed to investigate an oil-in-oil solvent evaporation process. These microspheres were coated with Eudragit S-100. *In vitro* drug release experiments revealed no drug release at gastric pH; however, continuous drug release from the formulation was seen at colonic pH. *In vivo* tests were also carried out, with drug concentrations measured in various sections of the GIT at different time intervals, demonstrating the formulation's potential for colon targeting. As a result, it may be inferred that Eudragit-coated pectin microspheres can be employed for drug administration to the colon.

Abdin et al., 2008 in this research work, *L. acidophilus* was chosen as a probiotic therapy to evaluate its effects in a rat model of oxazolone-induced colitis that matches the human situation. A significant reduction in serum levels of CRP, TNF-α, IL-6, and disease activity index (DAI) (treated with olsalazine). As a result, it was concluded that the *L. acidophilus* probiotic could be used as adjuvant therapy in conjunction with olsalazine to improve the efficacy of UC treatment.

Paharia *et al.*, 2007 have prepared and evaluated Eudragit-coated pectin microspheres for colon targeting 5-fluorouracil (FU). Pectin microspheres were prepared by emulsion dehydration method using different ratios of FU and pectin (1:3 to 1:6), stirring speeds (500–2000 rpm) and emulsifier concentrations (0.75%–1.5% w/v). In addition, an in vitro drug release analysis of the improved formulation was

carried out in simulated colonic fluid containing 2% rat fecal content. An albino rat organ distribution study was conducted to determine the targeting potential of the improved formulation in the colon. Eudragit-coated pectin microspheres are potential controlled release carriers for colon-targeted delivery of FU.

Guslandi *et al.*, 2003 reviewed that *S. boulardii* could help people with ulcerative colitis. The preliminary findings indicate that *S. boulardii* may help to treat UC.

Tozaki *et al.*, 1999 formulated the azopolymer-coated pellets budesonide using azopolymer-coated pellets to accelerate the healing of 2, 4, 6-trinitrobenzene sulphonic acid sodium salt (TNBS)-induced colitis in rats. Such findings suggested that azopolymer-coated pellets could be a helpful dosage form for delivering budesonide as an anti-inflammatory steroid drug to rats suffering from TNBS-induced colitis.