3. AIM AND OBJECTIVES

Oral controlled drug delivery system has drawn increasing interest in the pharmaceutical field over the last few decades. Indeed, they have proven to be suitable for substantial increase in sophisticated therapeutic needs, which have been highlighted by impressive advances in the medical and pharmacological areas. One of the encouraging sites for the delivery of drugs is colon, recognized with several important therapeutic advantages.

Localized delivery of the drug to the specific site is recognized to bear several therapeutic advantages. The site-specific delivery declines the adverse effects as well as the dose of the drug by enhancing its therapeutic efficacy. The various routes include parenteral, nasal, pulmonary, transdermal, buccal, rectal, vaginal and oral can deliver the drug at the target site. Among all these oral route is the most organized conventionally for drug distribution due to ease of administration, avoidance of pain and discomfort leading to higher patient compliance, elimination of infections, and the ability to formulate more than one dosage form. Delivery of drugs through oral route can aid in maintaining plasma blood concentrations of drug inside the therapeutic range for a designed period thus reducing the dosing frequency.

The site specific delivery of drug refers to the release of drug in the designed regions. The administration of the drugs for the medication of local pathologies at large intestine such as IBS, IBD (ulcerative colitis and crohn’s disease), colon cancer, and infectious diseases could avoid unnecessary body exposure to active agent and provide the required therapeutic concentrations of the drug at reduced dose. Hence, while treating these pathologies higher concentrations of active agent may be efficiently localized at the target site using colon targeted drug release systems, not possible with conventional drug delivery system fails for such achievement. Drug of choice for colon specific delivery are those that are susceptible to upper GIT environment and those that are desirable to be targeted to colonic site in treating localized pathological conditions.
Since last fifteen years profound research has been carried out in this field utilizing inherent characteristics of the target site and/or polymers opted. The pH, transit time, microflora, and increased luminal pressure were the inherent characteristics that have been exploited for the successful release of the drug. The assorted approaches that were used for the colon specific drug delivery include: pH sensitive systems, microbial triggered systems, timed released systems, osmotically controlled drug release systems, and pressure dependent release systems.

Nanoparticles (NP’s) are exemplified as size under 100 nm particles however under feasible condition, particles up to 1000 nm in size have been reported as NPs. They serve as an efficient means of release by generosity of their small size thus offering various advantages; (i) Passage through smallest capillary vessels (ii) Avoidance of rapid clearance by phagocytes (iii) Control released properties due to biodegradability (iv) pH/temperature sensitivity (v) reduced cytotoxicity (vi) improved aqueous solubility (vii) Better adherence and site specificity.

Among nanoparticulate systems, Solid Lipid Nanoparticles (SLNPs) are solid lipid matrices that entrap drugs in their crystal structure. SLNPs are lipoidoial drug nanocarriers enclosing spherical particles in the nanometer range, diffused in water or in surfactant solution. SLNPs have been reported as suitable systems for enhancing the bioavailability of drugs in various systems. The advantages speculated with SLNPs are given as below:

- Biodegradable
- Provides exceptional physical stability
- Conservation of included drugs from debase
- Controlled drug release
- Substantial adequacy and low cytotoxicity due to absence of organic solvents
- The size of such particles range from 50 nm to 1000 nm for colloidal drug delivery.
• Controlled and targeted drug delivery
• Potential great drug payload
• Probability of importing both hydrophilic and lipophilic drug
• Water based formulation avoids organic solvents
• Physiological lipids decrease the prevalence of acute or chronic toxicity; no noted biotoxicity of the carrier system
• Enhanced drug stability
• Less expensive than polymeric or surfactant based carriers

Such a technology motivated us to explore its potential of SLNPs in achieving localized drug concentration of the entrapped drug(s) and advancement of SLNPs. In the present study utilization of stearic acid and tryglycerol monostearate combination can provide the rationale approach and in such drug delivery.

The inclusion of naturally ensued polysaccharides is captivating a portion of considerations for drugs targeting the colon because these polymers of monosaccharides are in affluence, great scope, are economical and are showed in a variety of design with diverse properties. The human colon has accomplished 400 apparent species of bacteria as native flora, an attainable population of up to 1010 bacteria per gram of colonic contents. Polysaccharides, the polymer of mono-saccharides maintain their probity by virtue they are antagonistic to the digestive activity of GI enzymes. The origin of sodium alginate, a polysaccharides are pretended to endure intact in the anatomical surroundings of stomach and small intestine. Formerly they extent the colon, they are stimulated by the bacterial polysaccharidases and consequently in debase of the matrices and acting as a substrate for the microbiota exist in the colon. Amidst the reactions accomplished by these gut flora are azo-reduction and enzymatic schism i.e. glycosides. Therefore, they introduced the class of "generally regarded as safe" (GRAS). Sodium alginate bear substantial anionic charge. The present study includes sodium alginate as a polysaccharide for targeting colon in an inflamed condition (IBD), as it’s known from literature that inflamed mucous is having a cationic charge (Jubeh et
al., 2004). This electrostatic gradient makes sodium alginate as an excellent carrier for opting colon targeted drug delivery system.

Inflammatory bowel syndrome is also an extensive principle of morbidity and mortality worldwide and becoming increasingly common in western as well as Asian countries. It is fifth prevalent gastro intestinal disorder burdens in worldwide. Each year in the United States, IBD details for more than 700,000 physician appointment, 100,000 hospitalizations, and disability in 119,000 patients. In the Indian subcontinent it is about 66,000 patients were reported every year. The disease may develop from inflammatory reasons of the undigested food particles, microbial organisms, and therefore, it is logical to assume that anti-inflammatory measure could be effective in prevention of inflammatory bowel disease.

A non-steroidal anti-inflammatory drugs (NSAIDs) is among a diversified group of active, which are highly effective in relieving pain and inflammation in a large number of diseases such as Arthritis, Spondylitis, Osteoarthritis, etc (Leslie 2013). These agents act through the inhibition in the action of the cyclooxygenase (COX) enzymes and due to this impact, the synthesis of Prostaglandins. Prostaglandins were local mediators, which are engaged in a broad extent of physiological approach further inflammation particularly the pro-inflammatory molecule PGE-2. It is noticed that a greater concentration of PGE-2 is present in ulcerative conditions than in the surrounding normal mucosa. Further studies confirmed that certain inflammatory bowel syndrome produces over PGE-2. These findings encouraged subsequent experiments to study the inhibitory potential of NSAIDs in chemically induced intestinal diseases.

Mesalamine is a dynamic anti-inflammatory agent with a minimal adverse effects and it carry an extensive value to both patient and physician in the execution of ulcerative colitis. It is an orally distributed amino salicylate descendants which effects on a diversity of inflammatory mediators and emerges to be specifically well indulged between the NSAIDs, with a minimal prevalence of gastrointestinal adverse effects. This exceptional profile outcomes as a declined retraction rate and still better consent
with the medication. Also mesalamine have better tolerability and safety as compared with other class of NSAIDs particularly amino salicylates and corticosteroids. Mesalamine has all the desirable features of a desk-designed multipurpose drug with pluriparmacological properties. Formulating mesalamine for clinical efficacy presents profuse objections assigned to its poor physicochemical properties. Inspite numerous formulation challenges, several strategies such as nanoparticles, liposomes, complexation with phospholipids and cyclodextrins and solid dispersions have been undertaken by scientific groups to enhance the bioavailability of mesalamine (Badhana et al., 2013).

Mesalamine plays a major protective role against ulcerative colitis. In light of anti-inflammatory effects of mesalamine, it has become a candidate compound for the prevention of ulcerative colitis. In the current study, we propose effective solid lipid nanoparticles of mesalamine to achieve high localized concentration in targeted site colon. Also it is well documented that the delivery of the drug to the affected site improves therapeutic efficacy, and patient compliance with the reduced incidence of side effects.

It will be worthwhile to suitably optimize the value of existing tradition based knowledge bank of traditional medicines rather than trying to synthesize new drug entities. Making renewed presentation of these molecules, by giving them a pharmaceutical design, represents a strategy proposed in present research work.

Microorganisms such as bacteria, cyanobacteria, actinomycetes, yeast, fungi and blue-green algae are acknowledged to incorporate nanoparticles in nature either inside or outside cells. At present investigations, microbial methods in the incorporation of nanomaterial of variant arrangements were intensely defined and enclosed. Blue-algae spirulina have potential ability to produce nanoparticles (Govindaraju et al. 2009). It is substantial to research the spirulina for biosynthesis of nanoparticles and pathways leads to increase advancement of nanoparticles of different classes of microbes. The
biosynthesis of nanoparticles with the use of microorganisms relies on various conditions (Mahdieh et al. 2012).

Combination therapies were acquired instant prominent superior of pursuits for the execution of colon targeted diseases. These pursuits may target multiple sites, multiple subpopulations or multiple diseases concurrently. The combinations with assorted approaches or modes of action may also explicit the outcome across single target or a disease and cure it more adequately. Combination pursuits have desperately altered the medication spectrum of diseases, such as inflammatory bowel disease by decreasing inflammation and have exhibited that reasonably described drug combinations offer current potentiality to cure chronic IBD. Thus, improvement in the combination medication could be exploited for reducing the reliance on the search for novel molecules which implicate economy and time. No appreciable research work is recorded on the advancement of combinational medication formulation development, exceptionally in case of colon targeted diseases. The formulation approaches pertinent to combination medication pursuits are being undertaken for advancements in drug delivery systems to exceptionally enhance the conventional colon targeted execution and distribution of active agents.

The current work explore the probiotic, spirulina the site targeted drug delivery of amino salicylate, mesalamine as monotherapy as well as combination therapy for the medication of IBD. Additionally, polysaccharide sodium alginate with mesalamine is considered and engaged in the designing of colonic formulations. The intention of the current work is to formulate, optimize and characterize Polysaccharide based novel drug delivery system to address drug related and formulation and treatment related issues by developing controlled drug delivery systems.

Following objectives are encompassed in present work to overcome

- The solubility issues
- Controlled drug release and the dosing frequency
- Localized delivery of drug by developing Polysaccharide based SLNPs
Issues pertaining to therapeutic potential

Plan of Work

➢ Literature studies

➢ Selection of drug and Polymer

➢ Procurement of

 ✓ Drug

 ✓ Excipients including Polymers

➢ Preformulation studies

Preformulation studies of mesalamine is performed to assess physicochemical parameters.

• Identification of drug

 ✓ By UV spectrophotometry

 o $\lambda_{\text{max}}$ determination

 o Preparation of calibration curve

 ✓ By RP-HPLC method

 o Preparation of calibration curve

• Physicochemical evaluation

 ✓ Melting point

 ✓ Solubility

 ✓ Partition coefficient
- Fourier transform Infrared spectroscopy (FTIR)
- Differential Scanning Calorimetry (DSC)
- X-ray Diffraction Studies (XRD)

- **Compatibility studies by**
  - Fourier transform infrared spectroscopy (FTIR)
  - Differential Scanning Calorimetry (DSC)
  - Powdered X-ray Diffraction studies

- **Formulation Development of Solid Lipid Nanoparticles**
  - At various ratio of Lipids and Fatty acids

- **Characterization of developed SLNPs**
  - Particle size by Malvern Zetasizer
  - Shape and surface morphology by
    - Scanning Electron Microscopy (SEM)
    - Transmission Electron Microscopy (TEM)
  - Zeta potential
    - by Malvern Zetasizer
  - Encapsulation efficiency
  - Loading efficiency
  - Polydispersity index
  - *In vitro* drug release study
Development of Polysaccharide based Colon Targeted Formulations.

Mesalamine loaded sodium alginate SLNPs by hot homogenization technique at assorted concentrations of sodium alginate.

Characterization of Developed formulation

- Particle size by Malvern Zetasizer
- Shape and surface morphology by
  - Transmission Electron Microscopy (TEM)
  - Scanning Electron Microscopy (SEM)
- Zeta potential
  - by Malvern Zetasizer
- Encapsulation efficiency
- Loading efficiency
- Polydispersity index
- In vitro drug release study

Selection of optimized formulation

In vitro Release kinetics

Stability studies

In vivo studies

- Diarrhoea assessment
- Change in body weight measurement
- Caecal bleeding assessment testing
✓ pH Assessment of caecal content
✓ Colon length measurement
✓ Histopathological studies

➢ Compilation, analysis and interpretation of data