ScienceDirect

Journal of Drug Delivery Science and Technology

Volume 55, February 2020, 101495

Controlled release of sulfasalazine loaded amidated pectin microparticles through Eudragit S 100 coated capsule for management of inflammatory bowel disease

Rohitas Deshmukh [a], Ranjit K. Harwansh [a], Swarnali Das Paul [b], Rishikesh Shukla [c]

Show more

https://doi.org/10.1016/j.jddst.2019.101495

Get rights and content

Highlights

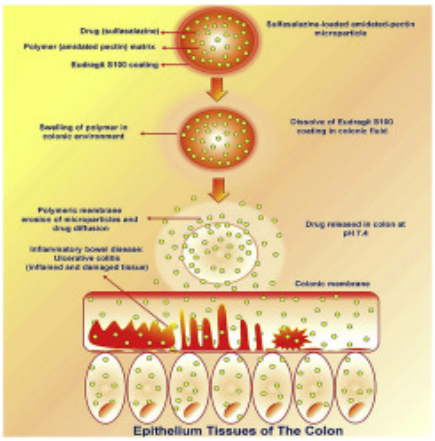
- Sulfasalazine loaded microparticles was prepared for treatment of IBD.
- Microparticles were filled in Eudragit s 100 coated capsules for colon targeting.
- Drug release from microparticles was 98% in presence of rat ceacal content.
- The pH dependent Eudragit S 100 dissolve only in the colonic pH.
- The developed microparticles can effectively deliver the drug in colon part.

Abstract

Inflammatory bowel disease (IBD) is a common colonic disorder affecting most of the world population. In order to overcome the IBD, present study was aimed to fabricate 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 especially for the treatment of IBD. The effects of variables such as concentration of crosslinking agent (calcium chloride) and amidated pectin-sulfasalazine ratio were optimized through the particle size, zeta potential, % yield, encapsulation efficiency (% EE), swelling index and *in vitro* drug release. The optimized formulation, F4 exhibited average particle size (463.33±6.72 μm), zeta potential (−32.10±0.80 mV), yield (91.62±1.97%) and EE (95.62±1.21%). The significant swelling index, 0.88±0.02 θ and 0.98±0.03 θ was achieved with F4 at pH 6.8 and pH 7.4 respectively. The F4 showed maximum drug release (91.12±5.11%) in simulated colonic fluid (SCF, pH 7.4) and 98.07±3.92% ($P<0.05$) in rat cecal content (RCC, pH 7.4) for 24 h in a sustained manner. It may be due to the drug released through polymer by diffusion-matrix erosion and bacterial degradation of the microparticles. The F4 formulation displayed *non-Fickian* pattern of drug release. *In vivo* study in rabbits confirmed that the enteric polymer coated capsule dissolve at colonic pH 7.4 to release the drug from microparticles. The F4 exhibited remarkable stability at room temperature and shelf-life was found to be 3.3 years. Thus, the sulfasalazine loaded amidated pectin microparticles filled in Eudragit S 100 coated hard gelatin capsule was found to be a potential delivery system for management of IBD.

Graphical abstract



Download: Download high-res image (359KB)

Download: Download full-size image

Introduction

IBD is a group of gastrointestinal tract (GIT) disorders, including Crohn's disease (CD) and ulcerative colitis (UC). They are chronic and relapsing in nature characterized by elevated levels of various inflammatory cytokines and disturbed immune response which results in inflammation and tissue damage [[1], [2], [3]]. In CD, inflammation occurs at any part of GIT but the region of the terminal ileum and colon is mostly affected. In contrast, UC is a chronic autoimmune disorder that results in ulcer and inflammation in the colon or large intestinal region. The occurrence of IBD is a very common in Western countries. The incidence of IBD was estimated about 1.4 million in the United States and 2.2 million in Europe and it is increasing rapidly [[4], [5], [6]]. Moreover, in last two decades epidemiological crossroads of many diseases of the Western world have been witnessed in

Asian countries. Presently, it is expected that India will have the highest (1.4 million) disease burden of IBD. Prevalence of IBD in developed and developing countries are increasing dramatically due to highest demand of modern life style expectancy [[7], [8], [9]].

Oral is the most convenient and preferred route of drug delivery because of significant patient compliance, ease of administration, flexibility of dosage form design and no or least sterility controls. But the conventional drug delivery system (CDDS) through oral route requires the frequent intake of drugs at higher doses. In addition, conventional dosage form is absorbed in the upper part of GIT rather than the colon to exhibit site specific activity [[10], [11], [12]].

Sulfasalazine is an approved anti-inflammatory prodrug, used for the management of IBD. It is an azo-conjugate of 5-amino salicylic acid (5-ASA) and sulfapyridine which is liberated by activity of colonic bacteria. 5-ASA has been found to inhibit cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing several mediators like cytokines, platelet activating factors (PAFs), prostaglandins (PGs) and leucotrienes (LTs) especially LTB4 in the gut. Migration of inflammatory cells into bowel wall is interfered and mucosal secretion reduced, which provides considerable relief from pain and inflammation [13].

Pectin is a natural polysaccharide. It has a relatively high degree (70–75%) of esterification which is a limiting factor for hydrogel formation. This limitation of pectin can be resolved by de-esterification and amidation in pectin [14] (see Fig. 1).

In the last two decades, an emergence of novel drug delivery systems (NDDSs) like microparticule carriers (microparticles) are pioneering for site specific drug delivery. These micro carriers can overcome the problems of CDDS by delivering drugs to the colon for the management of IBD. Therefore, colon specific targeted drug delivery system (CSTDDS) can directly deliver the drug to the site of action resulting in reduced drug dose and related side effects [15]. However, fabrication of CSTDDS through the oral route is a challenging job, as the incorporated drug needs to be delivered and released absolutely in the colon region without degradation in upper GIT. The most widely used approach for CSTDDS are pH sensitive polymer based carriers, timed release prodrugs and colonic microflora activated delivery systems [12,[16], [17], [18]]. Microcarriers like microsphere, microparticles, microbeads/granules, pellets, spheroids and nanoparticles are promising for drug delivery to the colon. These have certain advantages over CDDS like enhanced absorption, hence increased bioavailability. Thus, improved patient compliance [[19], [20], [21]].

The objective of the current work was to prepare amidated pectin as a polymer for fabricating sulfasalazine loaded microparticles for colon delivery specially to treat IBD. Eudragit S 100, a pH dependent enteric coating polymer was used to coat the hard gelatin capsules. The capsules were filled with drug loaded microparticles for a time and pH dependent release in the colon. After oral administration, the coated capsules remained intact in the stomach (pH 1.2) and small intestine (pH 6.8) environment but dissolved in colonic fluid at pH 7.4. This results in release of drug through microparticles for localized action, which is prerequisite for an effective treatment of IBD.

Section snippets

Materials

Sulfasalazine was supplied as a gift sample by Wallace Pharmaceuticals Pvt. Ltd., Goa, India. Pectin was purchased from HiMedia laboratories Pvt. Ltd. Mumbai, India. Eudragit S 100 was obtained as a gift sample from Degussa India Pvt. Ltd., Mumbai, India. Calcium chloride dihydrate was purchased from central drug house Pvt. Ltd., New Delhi, India. Analytical grade chemicals and reagents were used in the experiments. …

Preparation of amidated pectin

It was prepared by de-esterification and amidation as the procedure described by …

Statistical analysis

Release kinetic models like zero order, first order, Higuchi and Korsmeyer-Peppas were fitted for different formulations to predict their drug release mechanism. Student t-test was conducted by software (Graph Pad Prism Version 5.0, San Diego, CA, USA). The differences between means were considered to be significant at value ($P<0.05$). …

Physico-chemical characterization

SAMs were prepared by the ionic gelation method. Aqueous amidated pectin solution containing sulfasalazine was added drop wise into the crosslinking agent ($CaCl_2$ dihydrate). This intermolecular crosslinking between positively charged Ca++ of $CaCl_2$ and negatively charged COO- groups of amidated pectin results in formation of beads. These beads were separated by filtration, washed and dried. The various formulation variables viz, amidated pectin, sulfasalazine and $CaCl_2$ solution concentration …

Discussion

Targeted drug therapy is a novel approach where the drug is delivered to specific site without delivering in other parts of the body. This therapy helps to improve the absorption of the drug at target site and reduced the dose related side effects, thus enhanced bioavailability. Targeted drug delivery is a challenging task and need more research through novel techniques like microcarriers or nanocarriers [29]. IBD is a deadly disease and affecting human population worldwide. Number of new cases …

Conclusion

Microcarriers are intended to increase the bioavailability, drug stability, minimize dose and related side effects by site specific targeting. The objective of the current work was to fabricate microparticles which can ensure drug release in colonic pH for prolonged periods for the management of IBD. In order to achieve the above objective an amidated pectin based sulfasalazine-microparticles were prepared by the ionic gelation method using calcium chloride (5%, w/v) as a crosslinking agent. …

CRediT authorship contribution statement

Rohitas Deshmukh: Writing - original draft. **Ranjit K. Harwansh:** Data curation, Formal analysis. **Swarnali Das Paul:** Visualization, Resources. **Rishikesh Shukla:** Writing - review & editing. …

Declaration of competing interest

Authors have no conflict of interest. …

Acknowledgements

Authors are highly thankful to Prof. Anoop K. Gupta, Dean Academics, GLA University, Mathura for his kind support and motivation for research work. Authors are also thankful to IPR, GLA University, Mathura for providing necessary facility. …

Recommended articles

References (31)

S. Hua *et al.*
Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue
Nanomed. Nanotechnol. Biol. Med. (2015)

F. Li *et al.*
Synthesis, colon-targeted studies and pharmacological evaluation of an anti-ulcerative colitis drug 4-Aminosalicylic acid-beta-O-glucoside
Eur. J. Med. Chem. (2016)

C. Lautenschlager *et al.*
Drug delivery strategies in the therapy of inflammatory bowel disease
Adv. Drug Deliv. Rev. (2014)

E.V. Loftus
Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences
Gastroenterology (2004)

L. Yang *et al.*
Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation
Int. J. Pharm. (2002)

P. Roy *et al.*
Multiparticulate formulation approach to pulsatile drug delivery: current perspectives
J. Control. Release : Off. J. Control. Release Soc. (2009)

M. Ansari *et al.*

Colon targeted beads loaded with pterostilbene: formulation, optimization, characterization and in vivo evaluation
Saudi Pharm. J. (2019)

N.M. Anande *et al.*
Con-A conjugated mucoadhesive microspheres for the colonic delivery of diloxanide furoate
Int. J. Pharm. (2008)

R.K. Harwansh *et al.*
Nanoemulsion: promising nanocarrier system for delivery of herbal bioactives
J. Drug Deliv. Sci. Technol. (2019)

D.K. Podolsky
Inflammatory bowel disease
N. Engl. J. Med. (2002)

View more references

Cited by (52)

Mucoadhesive carriers for oral drug delivery
2022, Journal of Controlled Release

> *Citation Excerpt :*
> …This study indicated that mucoadhesive pectin-based nanoparticles are safe and promising carrier for controlled and targeted delivery of resveratrol to the colon. Deshmukh et al. formulated microparticles of amidated pectin for controlled delivery of sulfasalazine for inflammatory bowel disease [252]. They have used ionic gelation method to fabricate amidated pectin microparticles.…

Show abstract

Recent advances on biomedical applications of pectin-containing biomaterials
2022, International Journal of Biological Macromolecules

Show abstract

The potential roles of natural plant polysaccharides in inflammatory bowel disease: A review
2022, Carbohydrate Polymers

Show abstract

Pectin in biomedical and drug delivery applications: A review
2021, International Journal of Biological Macromolecules

Show abstract

Recent advances in utilization of pectins in biomedical applications: a review focusing on molecular structure-directing health-promoting properties ↗
2023, Critical Reviews in Food Science and Nutrition

Current strategies and potential prospects of nanomedicine-mediated therapy in inflammatory bowel disease ↗
2021, International Journal of Nanomedicine

View all citing articles on Scopus ↗

View full text