Ellagic Acid loaded pH Sensitive nanoparticles for the treatment of inflammatory bowel disease

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ABSTRACT SUMMARY
Ellagic Acid loaded pH sensitive nanoparticles were developed using solvent evaporation technology with Eudragit®S100 as pH sensitive polymer for treatment of inflammatory bowel disease. The results demonstrated the superior anti ulcerative colitis activity of 2.5 mg/kg Ellagic Acid loaded pH sensitive nanoparticles as compared to Celecoxib suspension and Ellagic Acid suspension.

INTRODUCTION
Inflammatory Bowel Disease (IBD) is broadly classified into Ulcerative colitis and Crohn’s diseases. These are recurrent, idiopathic inflammatory disorders involving the mucosa and sub-mucosa of the colon. Since, intestinal inflammation is confined to specific mucosal or transmural locations, it is possible to deliver drugs specifically to the site(s) of inflammation. Ellagic acid (EA) (4, 4, 5, 5, 6, 6-hexahydroxydiphenic acid, 2, 6, 2, 6-dilactone) is a potent dietary antioxidant found in variety of fruits, nuts and many other food sources. It possesses a broad range of pharmacological actions like prevention and treatment of cancer, diabetic complications, atherosclerosis, hypertension, antibacterial and blood coagulating properties etc. EA is a BCS IV drug (solubility in phosphate buffer pH 7.4 was <10 mg/ml). Apart from poor solubility and permeability, EA has poor stability at physiological pH. Additionally, it is metabolized by intestinal microorganism upon oral administration and rapidly eliminated from the body due to short plasma half life.

Eudragit® S100, the pH sensitive enteric polymer, was used for this selective delivery to colon. This co-polymer of methacrylic acid and methyl methacrylate dissolves at the pH 7.0 by ionization of its carboxylic functional group. This pH dependant release is particularly important, for the treatment of IBD which is primarily confined to the colon.

The agents currently used are of varying efficacy, show side effects and expensive. Consequently, there is a need for alternative agents that may be equally or more effective, besides being less expensive.

Hence, the objective of this study was to investigate the potential of the Ellagic Acid loaded pH sensitive nanoparticles for ameliorating IBD.

EXPERIMENTAL METHODS
To ensure selective delivery to colon, pH sensitive Eudragit® S100 was chosen as the polymer to formulate the polymeric nanoparticles. Solvent evaporation technique was employed for the formation of nanoparticles. Various process parameters were optimized to aid selection of optimized formula with lower particle size, narrow size distribution and optimized encapsulation efficiency (EE). The optimized formulation was then freeze dried and the product was characterized for particle size, drug content, FTIR, DSC, XRD and in vitro drug release.

In vivo anti-ulcerative colitis efficacy of the developed formulation was evaluated by using murine ulcerative colitis model in male SD rats (n=6). For this study, TNBS was used as an inducing agent. Visual assessment of parameters like erythema, edema, bleeding, erosion, ulcer, and tissue necrosis was undertaken and histopathological analysis was carried out. Furthermore, assay was performed for estimation of the enzymes myeloperoxidase, superoxide dismutase and lipid peroxidase. The developed formulation was subjected for stability studies as per ICH guidelines.
RESULTS AND DISCUSSION
Nanometric range (250 ± 1.0 nm), homogenous, spherical shape were obtained with EE of around 72 %. The particle size and distribution was not significantly affected by freeze drying. The resulting product exhibited a drug content of 101 % and presence of drug in amorphous form. The developed nanoparticulate formulation when given orally reduced the degree of hemorrhagic diarrhoea and the weight loss in animals caused by TNBS. However, in comparison to EA suspension and celecoxib suspension showed a significant reduction in the degree of colonic injury, decline in lipid peroxidation and myeloperoxidation and rise in superoxide dismutase levels with 2.5 mg/kg of EA loaded pH sensitive nanoparticles (Figure 1). A stability study indicates the formulations were stable over the period of six months.

![Figure 1. Results of MPO activity. Data are presented as mean ± SD (n=6)](image)

CONCLUSION
EA loaded pH sensitive nanoparticles were successfully developed using simple, industrially feasible technology. 2.5 mg/kg of EA loaded pH sensitive nanoparticulate formulation exhibited superior anti ulcerative colitis efficacy as compared to celecoxib as standard drug and EA suspension.

REFERENCES

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