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In this study we have developed drug delivery devices for transport of active pharmaceutical ingredients specifically to the diseased mucosa of the colon. The main objective was efficient amelioration of Inflammatory Bowel Disease and control the side effects associated with the drugs used for treatment. We have used both traditional and modern drugs for the development of these delivery devices. We attempted for the development of a drug loaded matrix tablet, a microparticle and a nanoparticle. We optimized the drug–polymer ratio and the polymer composition of each of these delivery devices and evaluated their specific advantages for localized delivery of drug for the treatment of inflammatory bowel disease (IBD) in 2,4,6-Trinitrobenzene sulfonic acid induced animal model of colitis.

We studied the efficacy of these delivery systems using three model drugs. One of these is a glucocorticoid, Prednisolone (PD), the second one is amine salt of Glycyrrhizic acid, a triterpene saponin obtained from the root extract of Glycyrrhiza glabra (GA) and the third one is a bile acid derivative – Ursodeoxycholic acid (UDCA). PD is a drug established for its efficacy in the treatment of moderate to severe conditions of IBD and is associated with a number of side effects. In order to minimize these associated side effects keeping its efficacy unaltered, we designed a matrix drug delivery system using PD as model drug. The second one is mono ammonium salt of Glycyrrhizic acid. This molecule is found to have anti-inflammatory properties and effective in the treatment of gastric ulcer disease. In this dissertation the efficacy of this molecule loaded in cross linked microparticles has been evaluated in amelioration of IBD. The third one is a bile acid derivative - Ursodeoxycholic acid. This molecule shows dose dependant efficacy and suffers from poor oral bioavailability. In this study we prepared UDCA loaded matrix nanoparticles in
order to improve its oral bioavailability through enhancement of its aqueous solubility and to achieve localized drug delivery at the sites of inflammation in the colon.

The matrix tablet based colonic drug delivery system was formulated using a natural polymer Guar Gum obtained from the ground endosperm of seeds of *Cyamopsis tetragonoloba* and a synthetic polymer Eudragit RS100, a aminoalkylmethacrylate copolymer. Guar gum is a polymer established for its potential in colon targeted delivery. However, on swelling the large swelled structure fails to prevent the first hour burst release. To control the drug release a synthetic water insoluble polymer having low porosity was used along with guar gum in order to attain an optimal colonic drug delivery of PD.

On observing the potential of guar gum as a matrix forming polymer for development of colon targeted drug delivery devices several derivatives of guar gum were synthesised in our laboratory which includes amine, amide and ester derivatives. Among these the amine derivative of Guar gum was chosen for the preparation of glycyrrhizic acid loaded microparticles. This derivative is found to have similar chemical properties like guar gum with an additional amine functionalization and is found to be compatible with the drug used.

The third formulation is a matrix nanoparticle synthesised using two aminoalkylmethacrylates – Eudragit RL100 and Eudragit RS100. These are water insoluble polymers having different porosity and similar chemical properties. In this study we first reported the application of these two polymers in the colonic delivery of Ursodeoxycholic acid. Previously the application of these two polymers as coating material for sustained drug delivery and as nanoparticle matrix for controlled ophthalmic drug delivery was reported.
Physically each of the formulations were characterized using powder X-ray diffraction study, Fourier Transform Infrared Spectroscopy, Atomic Force Microscopy, Scanning Electron Microscopy, Photon Correlation Spectroscopy, Differential Scanning Calorimetry, Liquid Chromatography, Mass spectroscopy etc. Each of the formulations were studied for their individual drug content and cumulative drug release in simulated gastric, intestinal and colonic fluid containing rat caecal contents. The analysis was carried out using validated liquid chromatographic techniques specific for each drug substance used in formulation. The high performance liquid chromatographic method for the estimation of glycyrrhizin from root extract and the prepared microparticle formulation was developed and validated as per ICH guidelines. The accuracy of the estimation was further ascertained using LC-MS/MS analysis. The PXRD studies presented the entrapment of PD within the matrix formulation in crystalline form with relative degree of crystallinity 0.263. However, in the micro and nanoparticle formulation a sharp decrease in crystallinity of the drug within the formulation was observed and both of them were entrapped in amorphous form with the polymer matrix. The FT-IR studies showed no possible drug polymer interaction for the matrix tablet formulation. Interaction between drug and polymers in the microparticle formulation and nanoparticle formulation was observed and this might be the reason of successful entrapment of drug within the formulations. The decrease in the sharp endothermic peak of UDCA in the DSC study data of Ursodeoxycholic acid loaded nanoparticles further confirmed the entrapment of drug in amorphous form within the nanoparticle. The Atomic Force Photomicrographs of PD loaded matrix tablets presented uniform distribution of drug within the biopolymer matrix. The AFM photomicrographs of UDCA nanoparticles presented an almost spherical shape with very few signs of aggregations and the PCS experiments presented an uniform size distribution of these nanoparticles with average particle size around 100nm. The scanning electron microscope photomicrographs presented uniform and spherical glycyrrhizic acid
loaded microparticles with average particle size 4.9 to 6.9µm. The drug entrapment of these microparticles varied from 75.36% to 98.36%.

The in vitro drug release in simulated gastric, intestinal and colonic fluids predicted the in vitro efficacy in successful delivery of the drug to the diseased mucosa of the colon. The drug-polymer ratio and the polymer ratio in each formulation were optimized using a $3^2$ factorial design model with an objective to achieve the optimized formulation with a minimum number of experiments. The response surface plots were drawn using the cumulative drug release profile data. The optimization was done on the basis of closeness between the observed and predicted values. A combination of guar gum 64.44% and Eudragit RS100 23.70% was found to be optimal for targeted release of PD in the large bowel and the colon. The optimized drug polymer ratio in case of microparticle formulation was 1:5 and for nanoparticle formulation the optimized composition was Eudragit RS100 35.56 %, Eudragit RL100 8.89%, PVA 11.11% and UDCA 44.44%.

The efficacy of each optimized formulation was further studied in 2,4,6-Trinitrobenzene sulfonic acid induced animal model of Inflammatory Bowel Disease. A comparatively significant amelioration was observed in animals treated with the optimized formulation containing PD in comparison to free drug treated groups. The colon to body weight ratio, colon length, stool consistency and rectal bleeding parameters studied presented the efficacy of the device. The longitudinal sectional view of the colon of all representative groups of animals and the biochemical analysis of those sections presented least accumulation of inflammatory cells and signs of inflammation in optimized formulation treated group of animals. The histological analysis of the tissue sections supported these findings. The thymus to body weight ratio presented the reduced toxic side effects of PD on treatment with drug loaded in optimized delivery device compared to free drug treatment. Therefore the application of an enzyme and time dependant approach for the
colonic delivery presented successful delivery of PD as predicted from in vitro experiments. The treatment with prednisolone loaded-optimized bi-polymer combination markedly ameliorates the inflammation in rat model of colitis. The delivery device allowed the localized delivery and prevented the early release of PD. The tissue macroscopic and microscopic studies and the observed biochemical parameters predict the efficacy and potential of the colonic delivery device for prednisolone along with a reduction of toxic side effects.

The in vivo efficacy studied with the optimized microparticle formulation in TNBS induced animal model of IBD presented reduction in accumulation of inflammatory cells in drug loaded microparticle treated group with subsequent reduction of tissue myeloperoxidase activity and tissue nitric oxide content. The tissue sections stained using haematoxylin and eosin presented lesser accumulation of inflammatory cells mainly the neutrophil in colon tissues of animals treated with drug loaded microparticles compared to treatment with free drug. Therefore it may be predicted that there was effective accumulation of drug loaded microparticles at the sites of inflammation in the colon and those particles have been able to release their drug load as observed from in vitro drug release study. This study therefore presented successful application of this newer biopolymer in preparation of colonic delivery devices.

The in vivo studies revealed a greater efficacy of the drug loaded nanoparticles compared to drug in the free form, in prompt healing of inflammation in the colon. The visual severity score for drug loaded nanoparticles treated groups of animals was much impressive compared to free drug treated group and the same was further supported by the histological analysis of the colon tissue sections of animals. Therefore, the encapsulation of ursodeoxycholic acid within the nanoparticles may have increased its colonic residence time thereby facilitating the complete release of the drug at the desired site of action.