COLONIC DELIVERY SYSTEMS FOR METHYLPREDNISOLONE

A Thesis Submitted in Partial Fulfillment of the Requirements for the Master Degree of Pharmaceutical Sciences (Pharmaceutics)

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Abstract

"Colonic delivery systems for methylprednisolone"

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The use of methylprednisolone (MP) in the treatment of inflammatory bowel disease, a local colonic disease, is restricted by the serious side effects resulting from the unnecessary systemic absorption of the drug when it is administered in a conventional oral dosage form. Targeting MP to the colon would help in avoiding unwanted drug absorption from the G.I.T. Hence, serious side effects will be minimized as well as more concentration of drug at the target site is expected to occur, providing more efficient disease treatment. Thus, the work in this thesis aimed at formulating, either single or multiple unit dosage forms, that target MP to the colon and proving the efficiency of the prepared dosage forms.

Methylprednisolone press coated tablets (MPPCTs) consisted of a directly compressed drug core tablets which were compression coated by the enteric polymer hydroxypropylmethylcellulose actetate succinate (HPMCAS). Colon targeting was achieved via two strategies; first, the use of triethylcitrate (TEC) as a plasticizer with the enteric polymer in different ratios, in addition to stearic acid. The second strategy was to apply heat to the compression coated tablets consisting of HPMCAS and hydrophobic additives namely; magnesium stearate, calcium stearate and stearic acid. A factorial design experiment was build up on the heat treated tablets prepared

using HPMCAS and stearic acid to determine the effect of different factors, in the heat treatment process namely; heating time, temperature and HPMCAS:stearic acid ratio, on the characteristics of the prepared tablets. The lag time (T_L) elapsed before drug release was taken as response. The press coated tablets were evaluated for their physical appearance, thickness, diameter and *in-vitro* release studies. Further investigations were done through differential scanning calorimetry and scanning electron microscopy.

The results revealed that the use of HPMCAS alone wasn't effective in preventing drug release even in pH 1.2. Upon addition of TEC, a lag time of 3 hours was obtained which was not affected by the amount of TEC used. Addition of stearic acid to this combination increased the lag time and decreased the % of MP released at 5 hours. The heat treatment of tablets composed of HPMCAS and magnesium stearate or calcium stearate didn't affect the drug release profiles. However, in case of stearic acid a significant increase in lag time was noticed accompanied by a significant decrease in the % of MP released at 5 hours. Factorial design analysis revealed that heating time, temperature and HPMCAS:stearic acid ratio had a significant effect on lag time. Tablets coated with HPMCAS:stearic acid in 4:1 ratio and heated at 90^{o}C for 3 minutes with a lag time of 4.5 hours was used for the *in-vivo* study done through the X-ray imaging technique adopted on a healthy human volunteer, which proved that the tablets reached the colon intact and disintegrated in the proximal colon.

MP microspheres were prepared using the oil/oil solvent evaporation technique. For colon targeting, enteric polymers were combined with time dependent polymer either in a single microsphere coat or as a double coat.

The enteric polymers used were HPMCAS and Eudragit S and the time dependent polymer used was cellulose acetate butyrate (CAB). Evaluation of the prepared microspheres was done through the determination of drug loading capacity and encapsulation efficiency (EE%), photomicroscopic analysis, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), particle size analysis and *in-vitro* release studies. EE% increased upon increasing polymers concentration and the amount of drug used. All the prepared microspheres were discrete spherical and non-aggregated. Coating of MP-CAB microspheres with Eudragit S caused a significant change in surface morphology and significant increase in microspheres size. CAB:Eudragit S microspheres was found to have a very rough and wrinkled surface while that of CAB:HPMCAS microspheres were porous with smoother indentations and depressions. *In-vitro* release studies revealed that Eudragit S coated time dependent MP-CAB microspheres were more efficient in targeting MP to the colon than enteric/time dependent microspheres where the former released only 22.8% of MP before reaching the colon and exhibited controlled MP release at the target area due to CAB, hence, it would be useful in IBD cases with diffuse inflammation throughout the colon. The efficiency of this formula was further tested *in-vivo* by studying its effect on induced colonic inflammation in rabbits. Evaluation was done through macroscopic examination, determination of colon/ body weight and histopathological examination. All parameters proved these microspheres to be very effective in the treatment of colonic inflammation.

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List of Abbreviations

Capillary force promoter	CFP
Cellulose acetate butyrate	CAB
Colony forming unit/gram	CFU/g
Core	Cr
Differential Scanning Calorimetry	DSC
Encapsulation efficiency %	EE %
Figure	Fig
Gastrointestinal tract	G.I.T.
Glass transition temperature	Tg
Hydroxypropylmethylcellulose acetate succinate	HPMCAS
Hydrochloric acid	HCl
Inflammatory bowel disease	IBD
Lag time	T_L
Methylprednisolone	MP
Methylprednisolone press-coated tablets	MPPCTs
Polymer:stearic acid ratio	P:S ratio
Pressure controlled delivery capsules	PCDCs
Scanning electron microscope	SEM
Triethylcitrate	TEC
Standard deviation	S.D.
Ultraviolet	UV

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