ABSTRACT

5-Fluorouracil (5-FU) is one of the most commonly used chemotherapy agents in clinical oncology. The use of high doses not only affects the tumor cells, but also cells of the gastrointestinal mucosa and the hematopoietic system. Therefore, colon specific release of 5-FU could minimise the side effects and enhance the efficacy during the treatment of colon cancer.

A large number of polysaccharides such as pectin, chitosan, cyclodextrin, dextrans have been investigated as promising drug carriers in a biomimetic approach, for colon-specific drug delivery. As these polymers are usually soluble in water, they must be made water insoluble by cross-linking or hydrophobic derivatization. Physical or chemical cross-linking of the polymers can reduce the water/acid solubility of natural polysaccharides to form swellable hydrogels.

Tablets were prepared using spray dried lactose as diluents. The *in vitro* release of 5-FU from different selected uncoated tablet batches (B3, B6 or B9) was investigated for identifying the best combination of binder and coating system, that could successfully deliver 5-FU to large intestine by crossing the upper GIT environment. 5-FU released from batch EU-B9 was found to be high in pH6.8 with rat caecal content as compared to batch EU-B3 and EU-B6 (Fig-B). This was due to inherent ability of CCG-CH as binder to retard the release of 5-FU in pH 1.2 and pH 7.4 conditions. The release of 5-FU in pH 6.8 containing rat caecal content was due to activity of enzymes present in the rat caecal that had broken the CCG-CH conjugate thereby releasing the drug. This effect was found to be more pronounced when Eudragit L-100 (2 %w/v) coating was replaced with CCG-CH coating to form CCG-CH B3, CCG-CH-B6 and CCH-CH-B9 batches Hence, the results indicated CCG-CH conjugate to be an effective carrier for delivering 5-FU to colon. Further, The results indicated that coating the tablets with adhesive system [CCG-CH (70:30)] was not suitable for delivering 5-FU in the colon, probably due to its hydrophilic nature. The coating of cohesive force strength reduction system over these tablets significantly reduced the release of 5-FU from these tablets to 6% in acidic pH, thus complying with the requirement of enteric release tablets. FTIR, SEM and DSC analysis strongly indicated the role of hydrogen bonding between primary alcoholic (-CH_2OH) groups of carboxy methylated *cassia fistula* gum and Si-O-Si or Mg-O moieties of magnesium silicate in reducing the release of 5-FU from coated tablets in acidic pH. The results of pharmacokinetic investigations showed greater MRT of 5.93-fold of coated tablets as compared to uncoated tablets further supported CCG-CH coated tablets to enhance the residence time of 5-FU. The disintegration of these tablets in the colon was also ascertained by X-ray imaging studies.

The results of the present investigation revealed that CCG-CH (70:30) containing magnesium silicate (0.2% w/w) as coating film composition possessed the desired attributes of high adhesive force strength and low cohesive force strength. This film composition was observed to release 5-FU in the alkaline pH of colon while preventing its release in acidic pH as required for an enteric coated tablet. Further investigations involving the use of calcium salts of either CEG (CaCEG) or CCG (CaCCG) revealed their potential as superdisintegrants in FDTs because both these derivatives produced disintegration of FDTs within 10 seconds as required by USP standards.