Abstract

In the present study an attempt was made to develop gastroretentive sustained formulations of acyclovir for improving its bioavailability and reducing the frequency of administration. Acyclovir, chemically known as 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one, is a purine nucleoside analogue, known for its potent and selective anti-viral activity against viruses of the herpes group. In spite of its effective anti-viral activity, the use of acyclovir still has biopharmaceutics and pharmacokinetic limitations. Oral bioavailability of acyclovir is low (15 to 30%) and highly variable. It also has a short elimination half-life of 2.3 h. Absorption of acyclovir from the GIT is slow, variable and incomplete. Acyclovir is soluble in acidic pH and predominantly absorbed from the upper GIT. In commercially available IR dosage forms, the fraction of dose absorbed is very low due to short residence time of the dosage form at the absorption site. As a result, most of the administered drug is excreted in the feces (50–60%), in an unabsorbed form. These limitations necessitate frequent administration of acyclovir up to five times a day, leading to poor patient compliance, which in turn leads to reduced therapeutic efficacy and development of resistance. Formulation development studies were carried out with aforementioned targets of dose and in-vitro drug release profiles. Extensive preformulation studies were carried out before formulation development. Acyclovir was characterized for polymorphic form and solubility. Compatibility of acyclovir with different excipients was determined by storing mixture of the drug with individual excipients packed in glass vials and low density polyethylene (LDPE) bags to 40°C/75% RH and 60°C for 15 and 30 days. SR formulations that are based on swelling and mucoadhesion approach contained polyethylene oxide (Polyox WSR 303), carbomer (Carbopol 974P) and sodium alginate (Keltone HVCR). Carbomer, polyethylene oxide and sodium alginate were used as mucoadhesive–release controlling polymers either individually and/or in combination. Drug release profile of the batch containing 7.5% carbomer and 2.5% polyethylene oxide was closest to the target and the f2 value of this batch was 85. To avoid the gastric emptying, size of the dosage form should be greater than about 13 mm. The optimized SR formulation maintained the size greater than 13 mm up to 8 h. Drug release of optimized SR formulation AGR-6 followed first order kinetic model and its drug release mechanism was anomalous transport (non-fickian). Mucoadhesive strength was measured using texture analyzer. Mucoadhesive strength of the optimized formulation was much higher than the marketed IR tablet formulation, Zovirax (19.3 ± 4.7 g vs. 9.3 ± 0.8 g). In-vivo radiographic study was conducted on healthy albino rabbits to determine gastric retention time of the SR formulations in comparison with IR
tablets. For this study, tablets of 6.0 mm diameter and 110 mg weight were prepared for optimized batches of SR formulations based on swelling and mucoadhesion, and floating. It is clear that the conventional IR tablet was quickly emptied from stomach, but the retention of GR formulation was prolonged up to 8 h. The increased gastric retention time of GR formulation was due to the synergistic mechanism of swelling and mucoadhesion or floating. These results were in accordance with the results of in-vitro studies. At the end of 8 h, rabbits were sacrificed and fluorescence intensity at different parts of the GIT was determined using fluorescence assay. 6-CF was not detected from the stomach, duodenum and jejunum regions of the rabbits administered with IR formulation. About 32% of 6-CF was recovered from intestine below ileum. In contrast, fraction of 6-CF recovered from stomach, duodenum and jejunum regions of rabbits administered with optimized mucoadhesive and floating SR formulations were 65% and 58%, respectively. Results of this single dose study were also simulated to steady state using superposition method. Both the SR formulations were able to achieve more than 80% of $C_{\text{ssmax}}$ and more than 170% of $C_{\text{ssmin}}$ of the IR formulation. Developed GR formulation might represent a better alternative for sustained and more efficacious delivery of acyclovir, improve patient compliance and reduce development of resistance.

**Keywords:** Acyclovir, gastroretention, mucoadhesion, floatation, swelling, pharmacokinetic simulation, extended release