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Some of the drugs and macromolecules are not absorbed completely due to factors such as limited solubility, poor permeability across the GI mucosa or rapid removal from the region of their maximum absorption. Therefore, major portion of the administered dose remain unabsorbed and excreted in feces. One of the greatest challenges to the formulation scientists is developing an appropriate delivery system for such molecules, which show poor bioavailability, as limited amount of the dose reaches the plasma in a specified period. Low bioavailability leads to variation in the drug absorption amongst the patients and makes it very difficult to administer the effective dosage. Hence, it has been a long awaited requirement for the drug delivery scientists to enhance the bioavailability of such orally administered drugs.

Acyclovir is a commonly used anti-viral drug with *in-vitro* activity against Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Epstein - Barr virus (EBV), and Cytomegalovirus (CMV). It is widely used for the treatment of herpes infections and chicken pox. In spite of its effective antiviral activity, 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 gastrointestinal tract (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. Acyclovir is currently marketed in tablets, capsules, suspension, injectable and topical dosage forms. Oral formulations are most commonly used for the management of genital herpes. The recommended dosage regimen is 200 mg every four hours, five times daily. Administration of conventional dosage forms such as tablets and capsules for five times a day at four hours interval suffers from drawbacks of poor patient compliance. Depending on the administration of the first dose in the morning, the fourth and/or the fifth dose will have to be taken during the night at sleeping hours. Due to this reason, many patients skip the dose that results in drug-free period and in turn, results in propagation of virus and development of resistance.
Thus, there is a need for a dosage form, which will overcome the above said disadvantages of acyclovir therapy, increase success rate of the treatment and reduce development of resistance. Development of a controlled release (CR) formulation of acyclovir and similar pharmacokinetic performance of IR dosage form will not only reduce the frequency of administration, but also possess similar or better anti-viral activity due to constant maintenance of plasma concentration of drug.

The basic rationale for the development of CR dosage forms is to modulate the magnitude and duration of drug action(s), and to dissociate from the inherent properties of the drug molecule. Development of a CR formulation of acyclovir will dissociate them from its biopharmaceutic weaknesses. Release of the drug in a predetermined slow rate in the GIT will avoid the saturation of the absorption process thereby reducing the dose required for anti-viral activity. For the development of CR formulation of acyclovir the following two very important aspects are to be considered.

1. pH dependent solubility of acyclovir.
2. Absorption window of acyclovir.

Solubility of acyclovir is high in acidic pH and decreases as the pH increases, and is least at a pH of about 6.0. Hence, acidic environment of stomach is very conducive for the maintaining its solubility high. In a human trial Lewis et al. (1986) determined that the bioavailability of acyclovir following administration as an intraduodenal infusion or sipping solution was significantly higher than following administration of tablets, due to increased contact time with absorptive surfaces of gastrointestinal tract, i.e., duodenum. In another study based on in-situ perfusion in rats (Park et al., 1992), absorption of acyclovir was found to be high from duodenum, low from upper jejunum, but virtually nil from lower jejunum and colon. These two studies provided definitive evidence of presence of an absorption window for acyclovir in the upper GIT. Attempting to retain a dosage form of acyclovir in the stomach is advantageous for increasing it solubility as well as delivering it to absorbable areas, i.e., duodenum and upper jejunum. Hence CR formulation of acyclovir shall be developed in the form of a gastroretentive (GR) formulation to achieve following advantages:

- Increased patient compliance, as less number of doses to be administered per day.
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- Reduced adverse events, as no sudden peaks and troughs are observed in blood levels of the drug.
- Increased therapeutic efficacy, as the blood levels are maintained at therapeutic levels for significantly longer duration as compared to conventional dosage forms.

In the past few decades, significant advances have been made in the development and commercialization of CR formulations. Availability of polymers with a wide range of physico-chemical properties and technological improvements in the design of process equipment has resulted in the development of many CR formulations based on matrix, reservoir and osmotic technologies. Drying drug discovery pipelines have also developed a compulsive need to design CR formulations for existing drugs, as a part of product life-cycle management. However, development of CR formulations requires a large number of experiments, both in-vitro and in-vivo, to achieve optimal pharmacokinetic and pharmacodynamic properties. This is necessitated by the distinct physico-chemical and pharmacokinetic properties of the drug, and unique physiological aspects of different regions of the GIT. A considerable part of the development period is spent in achieving the required pharmacokinetic profile, which will drive the pharmacodynamic effect for most drugs. If the target in-vitro drug release profile of the CR formulation is known prior to initiation of formulation development, the number of experiments involved can be significantly reduced. Therefore in this study, pharmacokinetic simulations were carried out as a first step before initiation of formulation development to determine dose and/or in-vitro drug release profile required for the CR/GR formulation of acyclovir to match steady state plasma concentrations of IR formulation.

In the literature many approaches such as mucoadhesive microspheres (Dhaliwal et al., 2008), mucoadhesive tablets (Fuertes et al., 2006), floating tablets (Garg and Gupta, 2009; El-Gamal et al., 2011), swelling and expanding systems (Gromova et al., 2007), magnetic tablets (Groning et al., 1998), floating capsules (Ahmed et al., 2011), beads (Singhal et al., 2010), hollow microsphere (Junyaprasert and Pornswuwanapha, 2008) have been reported. In all these approaches, formulation development had been done with the aim of sustaining drug release and retaining the formulation in the stomach for a prolonged period of time. But, no systematic study has been reported for the development of acyclovir gastroretentive formulation after
determination of dose and \textit{in-vitro} drug release profile required to achieve pharmacokinetic performance similar to or better than that of IR formulation. In the present study, attempt has been made for development, optimization, \textit{in-vitro}, \textit{ex-vivo} and \textit{in-vivo} characterization of acyclovir gastroretentive formulations based on the dose and target \textit{in-vitro} drug release profile determined by pharmacokinetic simulations. Such simulations lead to scientific method of development of new formulations of existing drugs and reduce the number of formulation development trials and human pharmacokinetic studies.

Two different approaches have been used for the development of gastroretentive dosage forms in the present study. In the first approach, formulations have been developed with mucoadhesive and swelling mechanism, which will assist adhesion to gastric mucosa and delay clearance through pyloric sphincter, respectively. In the second approach, a floating delivery system has been developed.

### 3.1 Objectives of the Study

- To determine the dose and target \textit{in-vitro} drug release profile required for oral gastroretentive formulations of acyclovir through pharmacokinetic simulations using available pharmacokinetic data of conventional dosage forms.
- To develop gastroretentive formulations of acyclovir with \textit{in-vitro} drug release similar to the target profile obtained through pharmacokinetic simulations.
- To characterize the gastroretentive formulations for \textit{in-vitro} quality control tests including \textit{in-vitro} drug release
- To optimize the gastroretentive formulations with respect to formulation and process variables.
- To evaluate the \textit{in-vivo} performance of optimized gastroretentive formulations.

### 3.2 Plan of Work

- Identification and Characterization of acyclovir
  - Description
  - Solubility
  - Infrared (IR) spectrum
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- Preformulation Studies
  - UV absorption spectrum of acyclovir
  - Calibration curve of acyclovir by UV spectrophotometry
  - pH solubility profile of acyclovir
  - Powder X-ray diffraction (pXRD)
  - Differential scanning calorimetry (DSC)
  - Thermo gravimetric analysis (TGA)
  - Water content estimation
  - Drug-excipient compatibility study
  - Determination of bulk properties
    - Angle of repose
    - Bulk density and tapped density
    - Compressibility index
    - Hausner’s ratio
    - Particle size distribution of acyclovir

- Preparation of gastroretentive formulations based on mucoadhesion

- Characterization of gastroretentive formulations based on mucoadhesion
  - In-process characterization
  - *In-vitro* drug release and similarity factor determination
  - Drug release kinetics
  - Swelling index and erosion

- Preparation of gastroretentive formulations based on floating

- Characterization of gastroretentive formulations based on floating
  - In-process characterization
  - Floating lag time and duration of floating
  - *In-vitro* drug release and similarity factor determination
  - Drug release kinetics

- Stability study

- *Ex-vivo* studies
  - Measurement of mucoadhesive strength

- *In-vivo* studies
  - Gastroretention Study using X-ray radiography
  - Gastroretention Study using Fluorescence microscopy
  - Pharmacokinetic study

- Compilation, analysis of data and interpretation of results