PUBLICATIONS


5. Sankar, R. and Jain, S. A new method to evaluate the GI retention property of gastroretentive dosage form.
Determination of Target In-Vitro Drug Release Profile for Extended Release Formulation of Acyclovir through Pharmacokinetic Simulations

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Abstract: Acyclovir, a widely used anti-viral drug, is the treatment of choice for initial episodes and management of recurrent episodes of genital herpes. Oral immediate release (IR) formulations of acyclovir have limitations of poor and variable bioavailability (15-30%), and dosing frequency up to five times a day. Such limitations lead to poor patient compliance and development of drug resistance. An oral extended release (ER) formulation of acyclovir can overcome these limitations. In the present study, a simple simulation technique for determination of the dose and in-vitro drug release profile required for an ER formulation of acyclovir to achieve steady state maximum and minimum plasma concentrations (Cmax and Cmin) similar to or better than those of an IR formulation, has been reported. First order drug release and absorption models were used. The dose and in-vitro drug release rate required for the ER formulation were found to be 725 mg and 0.259 h⁻¹, respectively. Cmax and Cmin values of the ER formulation were 90% and 218%, respectively, compared to those of the IR formulation. The fluctuation index of the ER formulation (FIER) was 69% of that of the IR formulation (FIIR), indicating that the ER formulation can maintain more constant plasma concentrations than the IR formulation. Results of the simulation study indicated the feasibility of an ER formulation of acyclovir for twice daily administration. If the target in-vitro drug release and dose required for an ER formulation are known prior to initiation of formulation development, the number of experiments, cost and development time can be significantly reduced.

Keywords: Acyclovir, Conventional delivery limitations, Extended release, Simulation model, Target in-vitro drug release, Oral delivery.

INTRODUCTION

For many years, oral route has been the most acceptable route of drug administration. This is due to many advantages such as convenience of administration, non-invasive nature and ability to accommodate numerous drugs. Different technologies and strategies have been developed to achieve desired in-vivo performance of drugs that widely vary in their physico-chemical and pharmacokinetic properties. An Extended Release (ER) / Controlled Release (CR) oral formulation is one such strategy that helps to achieve predetermined rate of drug release, leading to controlled plasma drug concentrations and subsequently to controlled therapeutic effect.

Acyclovir is a purine nucleoside analog with in-vitro activity against Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Epstein - Barr virus (EBV) and Cytomegalovirus (CMV) [1]. This drug has been shown to be of clinical benefit when administered topically, orally, or parenterally for the prophylaxis and treatment of certain herpes virus infections. It is recommended clinically for treatment of herpes zoster infections, genital herpes and chickenpox. Currently, acyclovir is one of the treatments of choice for initial episodes and management of recurrent episodes of genital herpes [2, 3].

In spite of its effective antiviral activity, acyclovir still has a number of biopharmaceutics and pharmacokinetic limitations like poor oral bioavailability of 15 to 30% with high variability and short elimination half-life of 2.3 h [4, 5]. These limitations necessitate frequent administration of acyclovir up to five times a day. This leads to poor patient compliance, which in turn leads to reduction in therapeutic efficacy and development of drug resistance. Acyclovir has a better solubility in low pH of the stomach and is predominantly absorbed from upper parts of the gastrointestinal tract (GIT). There are indications of its active absorption from the duodenum and jejunum regions of the GIT [6]. The fraction of dose absorbed from commercially available dosage forms is very low due to short residence time at the absorption site. As a result, most of the drug is excreted in faeces (50–60%), in an unabsorbed form [7]. Hence, it can be envisaged that absorption and bioavailability of acyclovir can be increased by increasing residence time of the dosage form at the absorption site. A twice-a-day oral ER formulation of acyclovir will improve patient compliance and control fluctuations in plasma concentrations. The overall effect will be enhancement of therapeutic efficacy of this drug.

The first step towards successful development of an ER formulation of a drug is the determination of the required dose and release characteristics with due considerations to its biopharmaceutics and pharmacokinetic properties. In this work, an attempt has been made to determine the target dose and in-vitro drug release profile required for an ER formulation of acyclovir to achieve a pharmacokinetic profile similar to
APPROACHES FOR ENHANCING THE BIOAVAILABILITY OF ACYCLOVIR: A CRITICAL REVIEW

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ABSTRACT

Acyclovir, a purine nucleoside analogue, is a promising antiviral compound effective against Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Epstein-Barr virus (EBV), and Cytomegalovirus (CMV). From the past 3 decades, it has been extensively exploited by the scientists for the diseases caused by these infective viruses. Upto a certain extent they are able to make dosage forms which can treat the infections caused by these viruses but, cannot perfectly/completely cure the ailments. In spite of its effective antiviral activity, oral bioavailability of Acyclovir is low (15 to 30%) and highly variable. This review discusses various possible reasons for the poor oral bioavailability of Acyclovir. In addition, it also focuses on various formulation approaches investigated by formulation scientists for the improvement of its oral bioavailability such as self microemulsifying drug delivery system, gastroretentive mucoadhesive microspheres, microemulsions, niosomes etc. Though the reasons for the poor oral bioavailability of Acyclovir are conflicting and inconclusive, many authors have reported widely varying formulation approaches to circumvent this problem and results suggested that these dosage forms can take place in the market. However detailed clinical studies are still needed to reconfirm these findings. The present review critically analyzes the pharmacokinetic and clinical limitations of conventional therapy of Acyclovir and different formulation strategies taken by the research scientists to overcome its formulation and clinical limitations.

KEYWORDS: Acyclovir, Bioavailability, Clinical limitations, Formulation strategies, Clinical studies.

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Development and characterization of gastroretentive sustained-release formulation by combination of swelling and mucoadhesive approach: a mechanistic study

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Background: Ayclovir has pharmacokinetic limitations, including poor oral bioavailability of 15%–30%, high variability, and short elimination half-life of 2.3 hours. These limitations necessitate frequent administration of ayclovir, up to five times daily, leading to poor patient compliance, which in turn leads to a reduction in therapeutic efficacy and development of resistance.

Methods: A gastroretentive sustained-release (GR) formulation of ayclovir, based on a combination of swelling and mucoadhesive mechanisms, has been developed. Composition has been optimized after evaluation of different polymers, carbomer, polyethylene oxide, and sodium alginate alone and/or in combination. GR formulations were characterized for in-process quality-control tests, drug release and release rate kinetics, similarity factor analysis, swelling index, and matrix erosion.

Results: A formulation containing a combination of carbomer and polyethylene oxide had the highest similarity of drug release compared with a target drug-release profile obtained by pharmacokinetic simulations. The measurement of mucoadhesive strength, carried out with a texture analyzer, showed that the mucoadhesive strength of the GR formulation was significantly higher than that of the immediate-release (IR) tablet. The optimized GR formulation was found to be retained in the upper part of the gastrointestinal tract for 480 minutes; the IR tablet was retained for only 90 minutes as measured using a gastrointestinal retention study in albino rabbits. The GR formulation was also found to maintain more sustained plasma concentrations than the IR tablet. Mean residence time of the GR formulation was 7 hours versus 3.3 hours for the IR formulation. The relative bioavailability of the GR formulation was 261% of the IR formulation.

Conclusion: The GR formulation of ayclovir, based on swelling and mucoadhesive mechanisms, has prolonged retention in the upper gastrointestinal tract, sustained in vitro drug release, prolonged in vivo absorption, and better bioavailability than the IR formulation. Such a formulation would improve patient compliance and increase the efficacy of therapy.

Keywords: gastroretentive, swelling and mucoadhesive mechanism, mucoadhesive measurement, GI retention study, pharmacokinetic study

Introduction
Oral sustained-release (SR) dosage forms have retained prominence for the past 3 decades due to their clinical advantages in comparison with their immediate-release (IR) forms. However, the conventional SR formulations are not suitable for drugs possessing a narrow absorption window in the upper part of the gastrointestinal tract (GIT).