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RESEARCH ARTICLE

Formulation and Evaluation of Extended Release tablets of Valacyclovir by DoE Implementation

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ABSTRACT

Recent scientific and patent literature shows increased interest in academics & industrial research groups regarding novel dosage forms that can be retained in the stomach for prolonged & predictable period of time and the most feasible approach for this is to control the gastric residence time using gastro-retentive dosage forms which will provide new & important therapeutic option but the problem can arise if there is a narrow window for drug absorption in the GIT or drug is unstable in the intestinal fluid. So the development of oral controlled dosage form is not just to prolong the drug release but also to ensure the presence of dosage form in the stomach or upper GIT so that drug is released and absorbed for the desired period of time. Valacyclovir was used with various ingredients like HPMC K15, HPMC K4M, Eudragit, MCC 102 and Aerosil. The tablets were prepared by wet granulation method. Fourier-transform infrared (FTIR) studies of the prepared tablets and the drug and the excipients showed compatibility. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. Results of in-vitro release profile indicated that formulation (F7) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. DoE is implemented by applying 2 level 3 factor full factorial design by using Design Expert software version 7. From DoE studies it were showed that as increase in concentration of Eudragit, MCC 102 and HPMC the drug release also increased and by maintaining the concentrations in required range the extended release is shown.

Keywords: Valacyclovir, Extended Release tablets, Evaluation, DoE implementation

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CONTENTS

1. Introduction

Herpes and Shingles:

In their lifetimes, most human beings will be exposed to a herpes virus. This family of viruses (Herpes viridae) has been implicated in a wide range of diseases and conditions, including chickenpox, oral or facial herpes, genital herpes, mononucleosis, and corneal blindness. It is also likely that we have not yet discovered all herpes viruses. One variety was discovered as recently as 1990, and researchers still are not sure which diseases, if any, it causes in humans. Herpes viruses are distinguished by their ability to lay dormant, or "hide" in the human body after primary infection. They then reappear during periods of reactivation. The mechanism of reactivation is not really understood. Although there is no effective cure for herpes, many studies have shown that herpes reactivation is more common among patients with compromised immune systems, suggesting that a strong immune system is a good defence against herpes reactivation. To manage herpes, physicians try to reduce the number and severity of outbreaks.

Extended Release Tablets:

In recent years in association with progress and innovation in the field of pharmaceutical technology there has been an increasing effort to develop prolonged release dosage forms. The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet from which the drug is slowly released. This formulation helps to avoid the side effects associated with low concentration and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

Objective of the Study:

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral Extended release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence, in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate extended release system for in order to achieve even plasma concentration profile up to 24 hrs.

Reason for the selection of API as a model drug:

- API is a potent antihypertensive.
- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to extend the drug release. Bioavailability after oral administration is 20% Silent features to design formulation in extended release tablets are,
- Less risk of dose dumping.
- Less inter and intra subject variability.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
- Transport of drug is independent of gastric emptying.

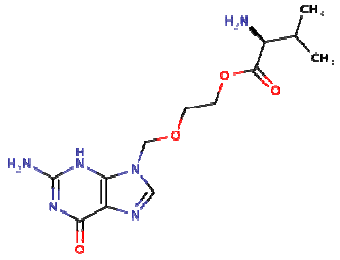

Fig 1: Chemical Structure of Valacyclovir

Mechanism of Action: Valaciclovir is phosphorylated by viral thymidine kinase to acyclovir triphosphate (the active metabolite) which then inhibits herpes viral DNA replication by competitive inhibition of viral DNA polymerase, and by incorporation into and termination of the growing viral DNA chain. When used as a substrate for viral DNA polymerase, acyclovir triphosphate competitively inhibits dATP leading to the formation of 'faulty' DNA. This is where acyclovir triphosphate is incorporated into the DNA strand replacing many of the adenosine bases. These results in the prevention of DNA synthesis, as phosphodiester bridges can longer to be built, destabilizing the strand.

Excipients used:

- Hydroxy propyl methyl cellulose
- Microcrystalline cellulose
- Mannitol
- Polymethacrylates
- Colloidal silicon dioxide

2. Materials and methods

Table 1: List of Materials

S.No	Material	Supplier
1.	Valacyclovir	Dr.Reddy's laboratoriesPvt. ltd, Hyderabad.
2.	HPMC (k4m, k15m)	Cadila Pharma, Ahmedabad,India.
3.	Eudragit L100	S.D. Fine chemical Pvt. Ltd, Mumbai,India.
4.	Mannitol	Loba Chemie Pvt. Ltd, Mumbai.
5.	MCC 101	Vilin Biomed, New Delhi
6.	Aerosil	Qualikems Fine Chemicals Pvt. Ltd, New Delhi
7.	Sodium Hydroxide	Finar Chemicals

	Pellets	Limited, Ahmedabad.
8.	Hydrochloric acid	Merck specialties Pvt. Ltd, Mumbai

Methodology

DoE Implementation:

2 level 3 factor design is chosen for present study by using Design Expert software version 7.0. HPMC K4M, Eudragit , and MCC102 are taken as factors (independent factors). The drug release at 12 hours are considered as response (dependent factor) and experiment is run with these factors and total 9 formulations were obtained.

Evaluation of granules:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Evaluation of matrix tablets:

The prepared tablets were evaluated for General appearance, thickness, hardness, weight variation, friability and uniformity of weight.

In-vitro dissolution studies:

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900ml of pH 7 buffers as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c ±0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 24 hrs in pH 7 buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn and filtered (0.45µm) .The volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 255nm using UV-spectrophotometer.

Kinetic Data Analysis:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero, first-order, diffusion and exponential equations .The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation and Peppas-Korsemeyer's equation.

Stability Studies: The optimized matrix tablets were subjected to stability studies(as per ICH guide lines) at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their physical characteristics, drug content, and In-vitro drug release profiles over a period of 3 months.

3. Results and Discussion

Ultraviolet Visible (UV-visible) spectroscopy:

Drug sample showed wavelength of maximum absorption (λ-max) 255 nm.

Calibration curve of Valacyclovir HCl in phosphate buffer pH 7:

Wavelength of maximum absorption: 255 nm.

Release Kinetic Studies:

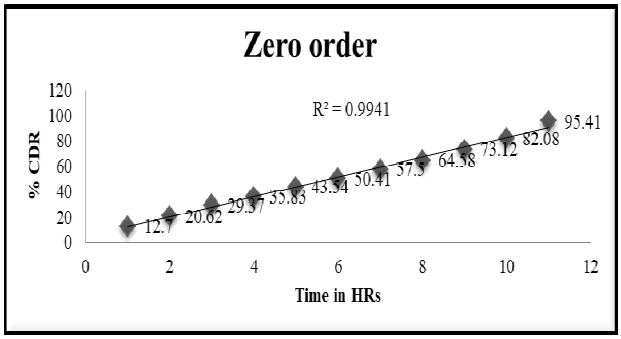

Fig 2: Zero order kinetic studies of F7

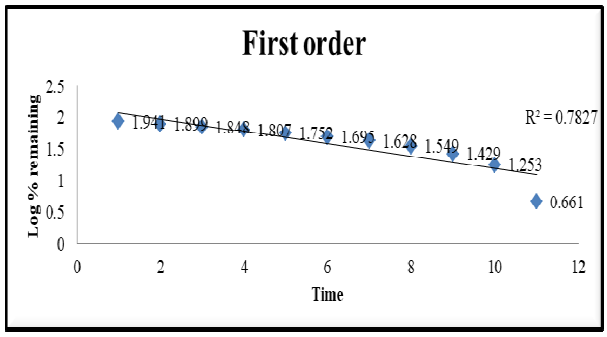

Fig 3: First order kinetic studies of F7

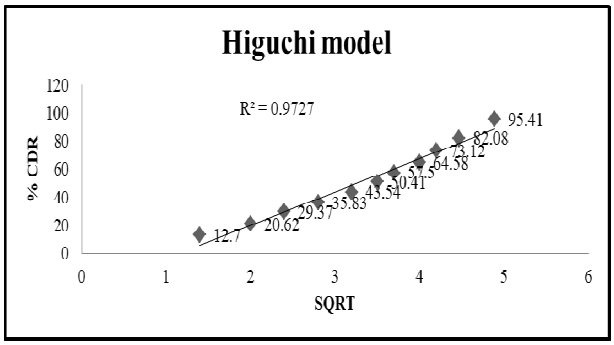

Fig 4: Higuchi Equation of F7

Table 2: Evaluation of Tablets

Formulation	Avg. Wt (g)	Diameter(mm)	Hardness (Kg\cm^2)	Friability	Thickness
F1	3.678	12.5	7.1	0.11	6.1
F2	3.12	12.5	7.3	0.06	6.5
F3	3.698	12.5	7.6	0.14	5.8
F4	3.641	12.5	7.5	0.04	6.9
F5	3.681	12.5	7.1	0.14	6.8
F6	3.698	12.5	7.2	0.06	6.7

F7	3.689	12.5	6.9	0.16	6.8
F8	3.682	12.5	6.8	0.41	6.8
F9	3.702	12.5	7.2	0.02	6.9

Table 3: Representation of Zero order kinetics

Time (hrs)	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr	18hr	20hr	24hr
F7 (% CDR)	12.7	20.62	29.37	35.83	43.54	50.41	57.5	64.58	73.12	82.08	95.41

Table 4: Representation of First order kinetics

Time	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr	18hr	20hr	24hr
First order (Log % remaining)	1.941	1.899	1.848	1.807	1.752	1.695	1.628	1.549	1.429	1.253	0.661

Table 5: Representation of Higuchi model

SQRT	1.4	2	2.4	2.8	3.2	3.5	3.7	4	4.2	4.47	4.89
Higuchi model (%CDR)	12.7	20.62	29.37	35.83	43.54	50.41	57.5	64.58	73.12	82.08	95.41

4. Conclusion

Valacyclovir HCl is antiviral drug. It slows the growth and spread of the herpes virus so that the body can fight off the infection. It will not cure herpes, but it can lessen the symptoms of the infection. Extended release tablets of Valacyclovir HCl were prepared using HPMC and Eudragit as retardant polymers. Various evaluation parameters like thickness, hardness, friability weight variation and drug content of the formulations were found to be satisfactory. Among all formulations prepared and evaluated F7 appeared to have desired release pattern than others. The viscosity of the polymer was found to affect the drug release and inverse relationship appeared to exit between polymer viscosity and drug release thus, higher the viscosity of the polymer, lower the drug release. The polymer used Eudragit is powder in nature and hence improves the flow properties of the blend. Also it is concluded that it improves the drug release up to 24hr.

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