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**Original Research Article**

# Preformulation Studies of Famciclovir: Vital Part of Formulation Design

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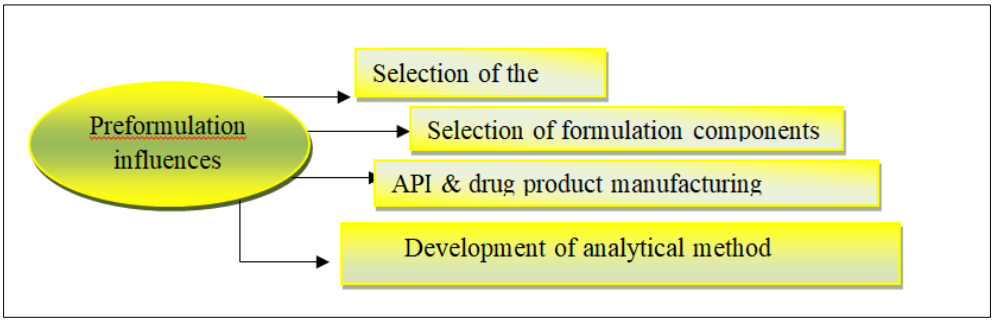
**Abstract:** The preformulation investigation commences upon the introduction of a new molecule. It encompasses the examination of physical, chemical, analytical, and medicinal aspects associated with molecules and offers insights into appropriate modifications to enhance molecular performance. The study of preformulation parameters is associated with the development of effective, safe, stable, and dependable pharmaceutical formulations. Famciclovir is a diacetyl-6-deoxy derivative of penciclovir. All of this is absorbed upon oral administration and is rapidly converted to penciclovir through deacetylation in the digestive tract, blood, and liver; subsequently, it is oxidized by the liver at position 6 of the purine cycle. The half-life of the dynamic intracellular medication, penciclovir triphosphate, is significantly prolonged, allowing for a once-daily dosage. Famciclovir is effective against genital herpes and the varicella-zoster virus. The primary aim of the preformulation studies of Famciclovir is to produce knowledge that aids in the development of stable and bioavailable dosage forms.

**Keywords:** Preformulation Study, Famciclovir, Solubility & Analytical Methods.



## INTRODUCTION

The preformulation research is the fundamental phase in the systematic creation of pharmacological dosage forms. The study encompasses an examination of the physical and chemical properties of a pharmacological substance both in isolation and in conjunction with excipients. The primary objective of preformulation testing is to produce information that assists the formulator in creating stable and bioavailable dosage forms suitable for mass production. Preformulation research are conducted to provide essential data, particularly on the physicochemical, physico-mechanical, and biopharmaceutical properties of medicinal ingredients, excipients, and packaging materials [1]. These investigations should focus on the physicochemical features of the new molecule that may influence medication performance and the development of an effective dosage form. A comprehensive understanding of these features may ultimately justify formulation design or need molecular alteration. This study aimed to ascertain many physicochemical parameters, including solubility, melting point, pKa, dissolution, assay development, and solution stability [2-3].

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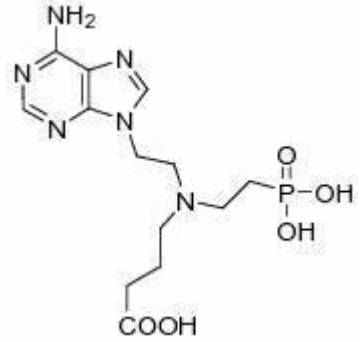
The synthetic acyclic guanine derivative famciclovir is a prodrug that rapidly converts to the readily available antiviral agent penciclovir upon oral administration. Penciclovir demonstrates in vitro efficacy against varicella zoster virus (VZV), herpes simplex virus (HSV)-1, and herpes simplex virus (HSV)-2 [4].

**Famciclovir [5-7]**

| | |
|---|---|
| **Molecular Formula** | $C_{14}H_{19}N_5O_4$ |
| **Synonyms** | famciclovir<br>Famvir<br>Famciclovirum |
| **Molecular Weight** | 321.33 g/mol |
| **Structure** |  |
| **IUPAC Name** | [2-(acetyloxymethyl)-4-(2-aminopurin-9-yl)butyl] acetate |
| **Pharmacodynamics** | Famciclovir is a prodrug that swiftly converts into the active antiviral agent penciclovir. Penciclovir is an antiviral agent that exhibits inhibitory effects against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), as well as varicella zoster virus (VZV). Consequently, the synthesis and replication of herpes viral DNA are specifically impeded. |
| **Mechanism of action** | Famciclovir is swiftly metabolized into the active antiviral agent penciclovir, which exhibits inhibitory effects against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), as well as varicella zoster virus (VZV). In cells infected with HSV-1, HSV-2, or VZV, viral thymidine kinase phosphorylates penciclovir to its monophosphate form, which is subsequently transformed to penciclovir triphosphate by cellular kinases. In vitro investigations indicate that penciclovir triphosphate competitively inhibits HSV-2 DNA polymerase in relation to deoxyguanosine triphosphate. As a result, the synthesis of herpes virus DNA and, consequently, replication are specifically impeded. |
| **Absorption** | 77 % |
| **Volume of distribution** | 1.08±0.17 L/kg [healthy male subjects following a single intravenous dose of penciclovir at 400 mg administered as a 1-hour intravenous infusion]. Famciclovir is an antiviral medication utilized for the treatment of illnesses induced by herpes viruses, encompassing genital herpes, cold sores, and shingles. |
| **Protein binding** | 20-25% |
| **Metabolism** | Hepatic |
| **Uses** | Famciclovir is an antiviral medicine that is used to treat infections caused by herpes viruses, including genital herpes, cold sores, and shingles. |

## MATERIAL AND METHODOLOGY

**Procurement of Drug:** Drug (Famciclovir) was obtained as a gift sample from Sini Pharma, Gujarat.

**Organoleptic Properties:** Organoleptic properties of the drug sample were studied by visual inspection.

**Preformulation Studies [8-10]**

**Identification of Drug**

**Melting Point Determination**

To determine the M.P. of drug powder, it was filled in a capillary tube with one end open and the other end closed and then the capillary was placed in a digital melting point apparatus.

**Solubility**

The solubility of Famciclovir was assessed in various solvent systems and buffers. An excess quantity of the medication was combined with 10 ml of each solvent in screw-capped glass tubes and agitated on a continual water bath shaker for 24 hours at 25 ℃. The solutions were physically analyzed for the presence or absence of the medication.

**Partition Coefficient**

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating

funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 234nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous}}$$

**Hygroscopicity**

Hygroscopic substance absorbs water because of hydrate formation. These type of change in moisture content may greatly influence the parameters like chemical stability, flowability and compatibility. Hygroscopic analysis is done by placing 2mg of drug at two petri dish with a thin powder bed for assure maximum atmospheric exposure. These samples are then exposed to the atmosphere and kept for 48 hrs and then again, the powder.

**Bulk Density**

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring perceived blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by.

Bulk density = weight of the blend /bulk volume of the blend

**Tapped Density**

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density =weight of blends/ tapped volume of blends

**Carr's Index**

Carr's index is measured using the values of the bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(TD - BD)}{TD} x100$$

Where,
TD – Tapped density
BD – Bulk density

**Angle of Repose**

The manner in which stresses are transmitted through a bed and the beds response to applied stress are reflected in the various angles of friction and repose. The most commonly used of these is angle of repose, which may be determined experimentally by a number of methods. The method used to find the angle of repose is to pour the powder in a conical heap on a level, flat surface and measure the inclined angle with the horizontal pile.

$\tan\theta = h/r$

$\theta = \tan^{-1} h/r$

Where, h- Height of the heap
r- Radius of the heap.

**FTIR Spectroscopy Studies**

FTIR (ATR Bruker, Germany) was used. The IR spectrum was obtained by scanning it in the range 4000-500nm and compared with the reference pharmacopoeia (IP-2014).

**Analytical Method:** UV spectroscopy was selected as the suitable analytical method for estimation of the drug.

**Standard Stock Solution**

The standard stock solutions of famciclovir was prepared by dissolving accurately weighed 100 mg of drug in 100 ml of distilled water in two 100 ml volumetric flasks to get a concentration of 1000 µg/mL. The Solution was diluted with distilled water, to get a concentration of 100 µg/mL, and was kept as the stock solutions.

**Determination of λmax**

1 ml of standard stock solution of famciclovir was taken in 10 ml standard volumetric flask diluted to 10 ml with distilled water to get the concentration of 10 µg/ml. The absorbance of resulting solution was measured against respective blank solution (distilled water) in the UV region of 200-400 nm, which shows maximum absorbance at 310 nm.

**Preparation of Calibration Curve**

100mg of famciclovir was dissolved in phosphate buffer 7.4 in a 100ml standard flask and filled up to the mark using phosphate buffer 7.4. Serial dilutions were made in phosphate buffer pH 7.4 in order to obtain 10µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml. Absorbance of these solutions were measured at 310 nm using UV-Visible Spectrophotometer [Schimadzu 159] and standard graph was plotted.

## RESULT AND DISCUSSION

The preformulation study of famciclovir was carried out. The organoleptic characterization showed in

table1.The solubility of Famciclovir was performed by using various solvents such as ethanol, DMSO, methanol, 0.1N HCl, Phosphate buffer saline (pH 7.4) and water. The observations suggest that Famciclovir has good solubility in Phosphate buffer saline (pH 7.4)[table 2].The identification of drug was carried out by A-IR which indicated characteristics peaks belonging to measure functional groups such as principal peaks at wave numbers 1210.83 $cm^{-1}$(C-O stretching), 1727.48 $cm^{-1}$ (C=O stretching), 2308.15 $cm^{-1}$ (O=C=O stretching), 961.28 $cm^{-1}$ (C=C bending) and 3227.54 $cm^{-1}$ (O-H Stretching)[table 3 & fig 1 -2]. The percentage loss on drying was found to be 0.0286%w/w. This is good and similar to reference data. The pH of Famciclovir was performed by using the digital pH meter and was found to be 6.45.This matches the reference data. The melting point of Famciclovir was found out to be 102ºC. This complies with the reference data [table 4]. The partition coefficient of the Famciclovir was found to be 1.49. This shows that the drug is hydrophilic in nature and has poor lipophilicity[table 5]. The result shows that the untapped density of Famciclovir was 0.82 g/cc and that of tapped density after 50 tapping was found to be 2.3 g/cc. The Compressibility Index of Famciclovir was determined to be 47.2% which is good and matches with the reference data of drug. The Hausner ratio of the Famciclovir was determined and found to be 1.9. The result shows the data obtained complies with the reference data. The Angle of repose of Famciclovir is 34.6 $^{0}$ .The Moisture content by Karl-Fischer for Famciclovir was found to be 2.10%. Particle size pass through #40 is 100 (%w/w). The Comparative data of preformulation showed in table 6 The λmax was determined by UV spectroscopy which showed λmax at 310 nm. The calibration curve was plotted between concentration and absorbance. It gives the straight line in the concentration range between 5- 25µg/ml. The correlation coefficient was found to be 0.979. This shows that it follows Beer's law [fig 4].

**Table No. 1: Organoleptic property of Famciclovir**

| | |
|---|---|
| **Colour** | White crystalline powder |
| **Odour** | Odourless |
| **Taste** | Bitter |

**Table No. 2: Solubility of Famciclovir in different solvents**

| S.No. | Solvent | Solubility |
|---|---|---|
| 1 | Ethanol | Sparing |
| 2 | DMSO | Sparing |
| 3 | Methanol | Soluble |
| 4 | 0.1 N HCl | Soluble |
| 5 | PBS (pH 7.4) | Soluble |
| 6 | Water | Soluble |

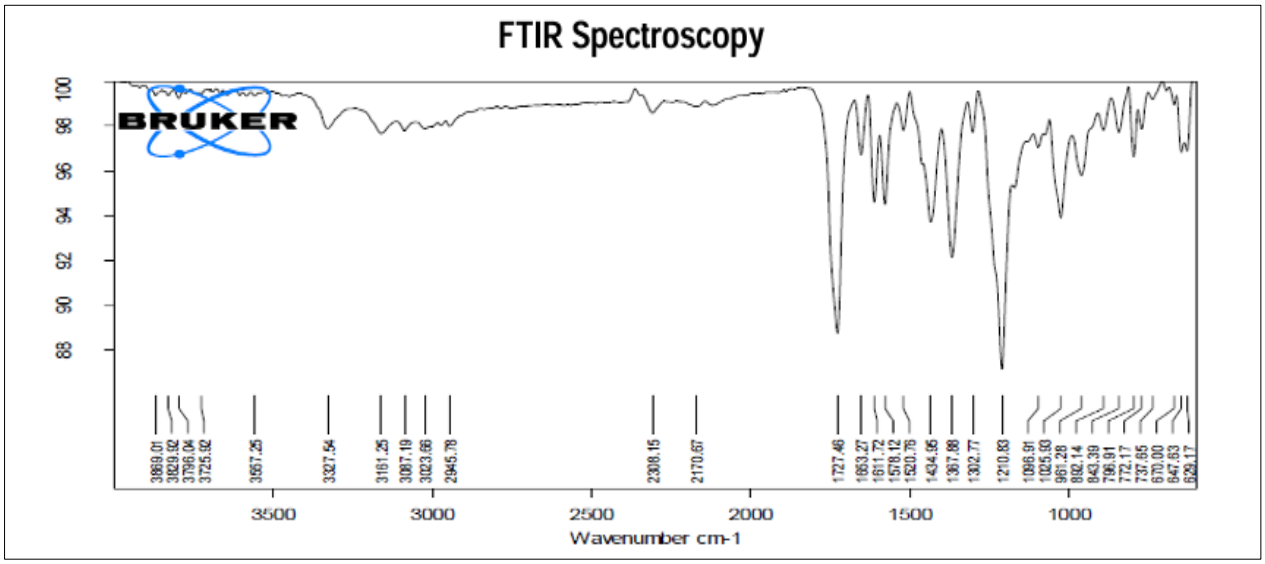



**Fig. No 1: FT-IR Spectrum of Drug sample (Famciclovir)**

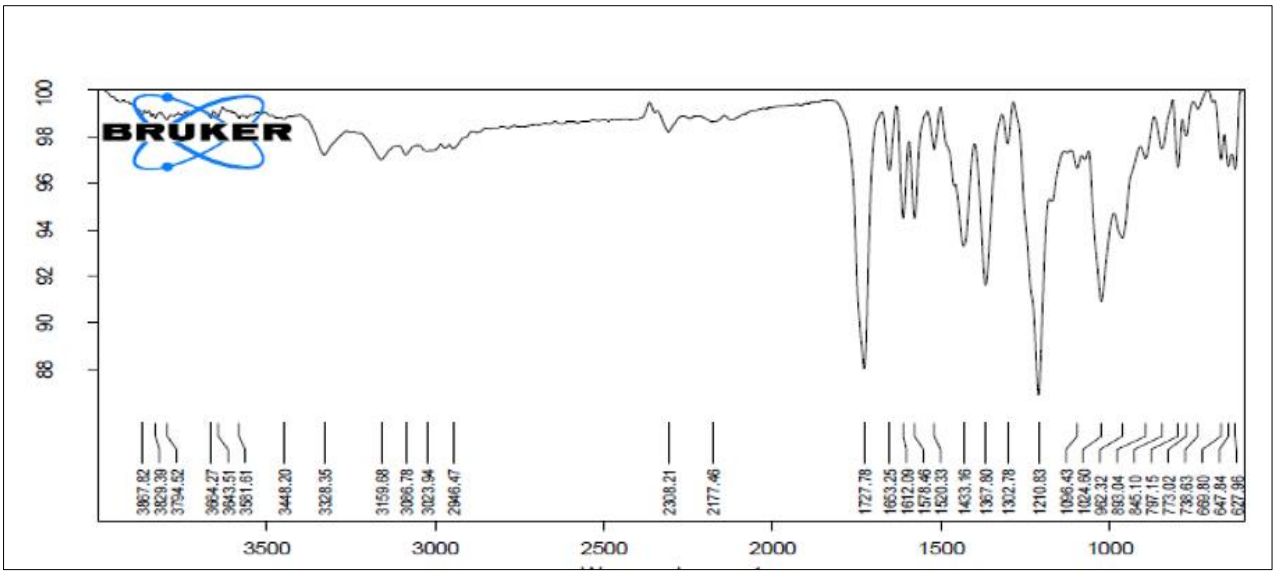



**Fig. No 2: FT-IR Spectrum of Reference (Famciclovir)**

**Table No. 3: IR interpretation for Famciclovir**

| S.No. | Frequency, $cm^{-1}$ | Band |
|---|---|---|
| **1)** | 1210.83 $cm^{-1}$. | (C-O stretching) |
| **2)** | 1727.48 $cm^{-1}$ | (C=O stretching) |
| **3)** | 2308.15 $cm^{-1}$ | (O=C=O stretching) |
| **4)** | 961.28 $cm^{-1}$ | (C=C bending) |
| **5)** | 3227.54 $cm^{-1}$ | (O-H Stretching) |

**Table No. 4: Result for Melting point**

| | |
|---|---|
| **Melting Point** | **100ºC** |
| | **102ºC** |
| | **102ºC** |

**Table No. 5: Result for partition coefficient**

| | | |
|---|---|---|
| **Partition coefficient** | **Water/ chloroform** | **1.49** |

**Table No. 6: Comparative data of preformulation**

| S.No. | Parameter | Observation |
|---|---|---|
| **1.** | **Solubility** | Sparing soluble in Ethanol& DMSO.<br>Soluble in Methanol water and soluble in buffer pH 7.4 |
| **2.** | **Loss on drying** | 0.0286% |
| **3.** | **pH ( 1% w/v solution in water)** | 6.45 |
| **4** | **Moisture content with KF** | 2.10 mg |
| **5** | **Melting point determination** | $100^0$C |
| **6** | **Untapped Density** | 0.82 g/cc |
| **7** | **Tapped Density** | 2.3 g/cc |
| **8** | **Compressibility index** | 47.2%. |
| **9** | **Hausner ration** | 1.9 |
| **10** | **Angle of repose** | $34.6^0$ |

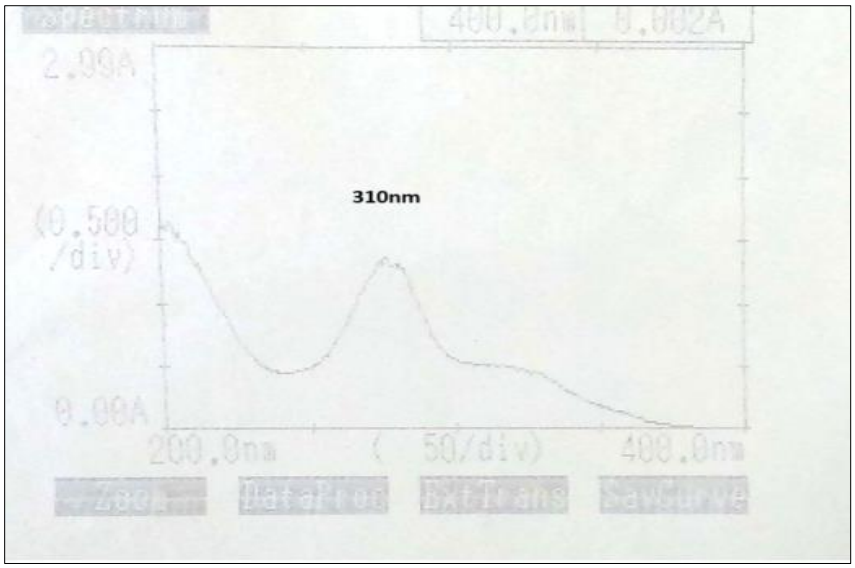



**Figure No: 3: Determination of λmax of Famciclovir**

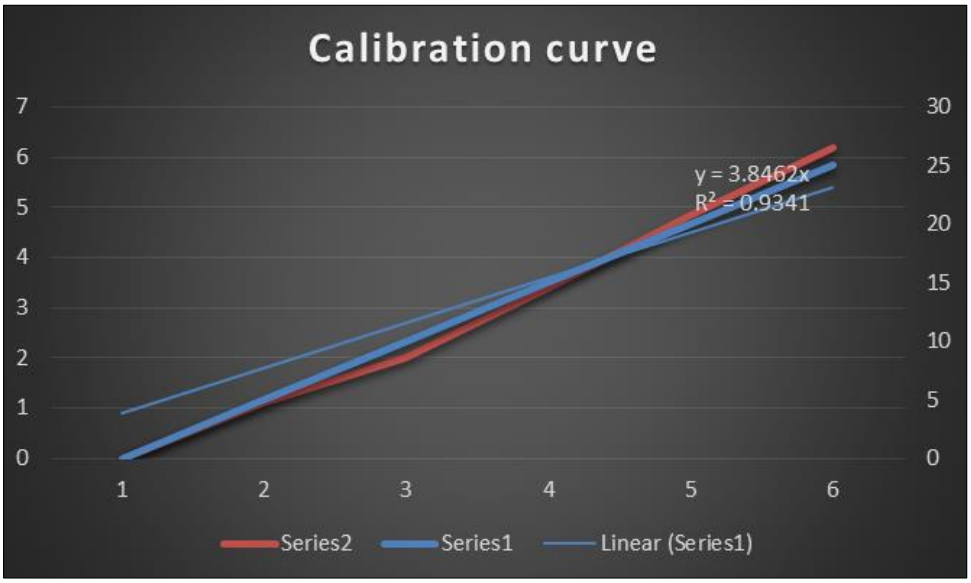



**Figure No. 4: Calibration curve of Famciclovir**

## CONCLUSION

The preformulation stage is crucial for determining the features of a medicine, facilitating appropriate risk assessment for development. Typically, it commences during the lead optimization phase, persists through predominance, and extends into the initial stages of development. Therefore, it is imperative that preformulation is conducted with utmost precision to enable informed decision-making. The preformulation research of famciclovir aims to produce information beneficial for the development of stable and bioavailable dosage forms.

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