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Preformulation Profiling of Capecitabine: Foundation for Novel Oral Anticancer Drug Delivery Systems

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ABSTRACT

A crucial stage in creating a stable and efficient pharmaceutical formulation is preformulation studies. The preformulation study on capecitabine, a parenteral antineoplastic medication used to treat colorectal cancers, is the main subject of this work.The physicochemical characterization included solubility, partition coefficient, melting point, ultraviolet-visible spectroscopy, infrared/fourier transform infrared, X-ray diffraction, and high performance liquid chromatography.The findings give critical information for developing a strong and bioavailable formulation that ensures therapeutic efficacy while retaining stability and compatibility. This study serves as a platform for future formulation development and optimization of capecitabine-based medicines.

Keywords: *Preformulation, Capecitabine, Anticancer, Antineoplastic Agent, Solubility Studies. APH, Maternal outcomes, Fetal outcomes*

1. INTRODUCTION

The phase of medication and dosage form development that comes before the ideal formulation is called preformulation. Optimizing the process of turning a drug candidate into a drug product is the goal of preformulation. Drug candidates' physicochemical characteristics are ascertained during preformulation. Usually, the first characteristic to be identified is solubility [1]. Preformulation is an important stage in drug development that aims to create stable, bioavailable, and mass-producible dosage forms. Data on pharmacological properties, potency, stability, routes of administration, formulation techniques, and pharmacokinetics are gathered by synthetic chemists, frequently working in conjunction with preformulation specialists. This fundamental understanding guarantees scalable and successful medication development [2]. Preformulation studies evaluate characteristics such as toxicity, pharmacokinetics, bioavailability, and degradation. They serve as guidelines for analytical techniques, container systems, production procedures, formulation, and drug selection [3].

Antineoplastic Agent

Over the past two decades, the use of antineoplastic drugs in treating malignancies has significantly increased. These medications can be used alone or in combination with other treatments. Antineoplastic agents work by disrupting tumor cell growth through interference with various biochemical pathways. However, despite their effectiveness, all antitumor drugs carry potential side effects when used therapeutically [4].

Understanding how these medications work is the first step to using them wisely. The majority of anticancer medications either prevent DNA synthesis or directly damage DNA integrity by causing enzyme-mediated breaks or DNA adducts [5].

Capecitabine

A prodrug of 5-fluorouracil (5-FU), capecitabine has become an essential component in the management of several malignancies, especially stomach, colon and mammary cancer malignancies [6]. Compared to conventional 5-FU, capecitabine has some benefits. Three consecutive enzymatic reactions transform it into 5-FU once it has been absorbed throughout the digestive tract [7]. For the therapy of bowel cancer it is now authorized as a single drug for preventative therapy for bowel cancer of stage three [8].

Preformulation:

- Organoleptic test
- Solubility
- Melting point
- Ultraviolet Spectroscopy
- Standard graph
- Partition Coefficient
- IR/FTIR
- X-Ray Diffraction

2. MATERIALS AND METHODS

Capecitabine was obtained from Yarrow Chem Products (Batch No.- DT1274), Ghatkopar (West), Mumbai, India.

Organoleptic test:

Material:- Chemicals: Capecitabine, Distilled water.

Apparatus: White background surface, Sterile spatula, Magnifying lens.

Method:- Place a small quantity (approximately 100 mg) of the drug powder on a white background. Examine the odor, texture, taste and color under normal lighting conditions.

Solubility:

Material:- Chemicals: Capecitabine, Ethanol, Acetone, Toluene, Acetic acid, Benzene, Chloroform, Water.

Apparatus: Beaker, Glass rod,Magnetic stirrer, Analytical balance, Filter paper.

Method:- Place the weighed drug in a test tube or vial and add a fixed volume of the solvent (e.g. 10 ml) to maintain consistency across tests, mix it by using magnetic stirrer, observe the solution visually to check for complete dissolution or precipitation, filter the solution using a filter paper to remove any undissolved drug particles, then use UV-Visible spectrophotometry to determine the concentration of the drug in the filtered solution, prepare a calibration curve using standard drug solutions to calculate the solubility.

Melting point:

Material:- Chemicals: Castor oil, Capecitabine.

Apparatus: Thiele tube, Measuring cylinder, Heat source, Capillary tube, Thermometer, Thread.

Method:- At the first, arrangement of apparatus for melting point determination and sealing of capillary, then fill the larger side of the Thiele tube (the U-shaped section) with **castor oil.** Place a small amount of the drug sample into a **capillary tube.** Place the capillary tube containing the sample into the **Thiele tube,** ensuring that the capillary tube is submerged in the **castor oil** but not touching the bottom directly. Insert the thermometer into the side arm of the Thiele tube, gently heat the castor oil using a **heating source and record (at least three) melting point.**

Ultraviolet Spectroscopy:

Material:-

Chemicals:Capecitabine, Distilled water.

Apparatus: Ultraviolet spectrophotometer, Cuvette.

Method:- Turn on the spectrophotometer and allow it to warm up and select the wavelength range for the measurement (usually in the 200–400 nm region for UV or 200–800 nm for UV-Visible spectroscopy). Dilute the sample in the solvent (distilled water) of 2µg/ml,4µg/ml,6µg/ml,8µg/ml and 10µg/ml. Then perform the baseline correction of spectrophotometer, Place the sample solution in a clean, dry quartz cuvette and insert the cuvette into the sample holder of the spectrophotometer.

Scan the sample and record the graph of each dilutions. At the last identify the **λmax** (wavelength of maximum absorption).

Standard graph:

Material:- Apparatus: UV Spectrophotometer, Quartz cuvettes.

Method:- Preparation of Standard Solutions is the first step, then fill a cuvette with the solvent used for the standard solutions to serve as the blank. Perform a wavelength scan of the stock solution to determine the wavelength of maximum absorbance. Measure the absorbance of solution and record it. Use software like Microsoft Excel, Origin, or GraphPad Prism to plot the absorbance (y-axis) against the concentration (x-axis) of the standards.

Partition coefficient:

Material:- Chemicals:Organic solvent (Chloroform), Aqueous phase (Distilled water).

Apparatus: Separatory funnel, Stirrer or shaker, Analytical balance, Pipettes and burettes, Spectrophotometer.

Method:- A known amount of solute is added to a mixture of two immiscible liquids (water and chloroform). After shaking and reaching equilibrium, the solute concentration in each phase is measured by the help of spectrophotometer.

Fourier Transform Infrared Spectroscopy:

Material:- Chemicals: Capecitabine, Potassium Bromide, **Chloroform, Carbon Tetrachloride.**

Apparatus: FTIR Spectrophotometer, Sample Holders, Desiccator, Oven or Heater.

Method:- In the IR, the first step is sample preparation, two methods are there, (I) KBr Pellet Method: The solid is ground with potassium bromide (KBr) and pressed into a transparent pellet. (II) Mull Method: The solid is mixed with a mulling agent (like Nujol oil) to form a paste.The IR radiation is passed through the sample.Some frequencies are absorbed, corresponding to the vibrational energy levels of the bonds in the molecule.The remaining radiation is transmitted to the detector, generating an IR spectrum**.**

X-Ray Diffraction:

Material:- Chemicals: Crystalline solids.

Apparatus: XRD Instrument, Sample Holder, Cooling System, Database Software.

Method:- Sample preparation is the first step in the X-RD, finely ground powder is used to ensure uniform orientation of crystals. Put the sample in the X-RD, The sample is irradiated with X-rays, and the instrument records the intensity of diffracted X-rays as a function of angle (2θ). A **diffraction pattern**is generated, showing peaks corresponding to specific lattice planes in the crystal.

3. RESULT AND DISCUSSION

Organoleptic test:

The organoleptic properties of the capecitabine sample were evaluated as follows (Table-1)

Table 1: Organoleptic Properties of Capecitabine

S.No.	Physical Property	Observation	Standard
1.	Appearance	Off-white / light colored powder	White to off-white crystalline powder
2.	Odor	No significant odor (slightly chemical smell is present)	Odorless or faint characteristic odor
3.	Taste	-	Slightly bitter
4.	Texture	Fine and smooth	Smooth and fine crystalline powder

Fig. 1: physical form of capecitabine sample

Solubility:

Solubility studies of Capecitabine are done in various Solvents, and Distilled water (Figure-2). The solvents used are Ethanol, Acetone, Toluene, Acetic acid, Benzene and Chloroform. The result of Solubility studies is shown (Table-2).

Table 2: Solubility result of capecitabine with different solvent

S.No.	Solvents	Observation	Remark
1.	Water	Sparingly soluble	Not ideal due to poor solubility
2.	Ethanol	Soluble	Best solvent for IV route
3.	Acetone	Insoluble	Not compatible
4.	Toluene	Insoluble	Not compatible
5.	Acetic acid	Soluble	Best solvent for IV route
6.	Benzene	Very slightly soluble	Not ideal due to poor solubility
7.	Chloroform	Soluble	Best solvent for IV route

Fig. 2: Solubility of capecitabine

Melting point:

The melting point of the capecitabine powder sample was determined.

Table 3: Melting point result of Capecitabine

Trial No.	Observed Melting Point (°C)
1	121
2	115
3	118
Average Melting Point (°C)	118

Fig.3 (A) - 121°C

Fig.3(B) - 115°C

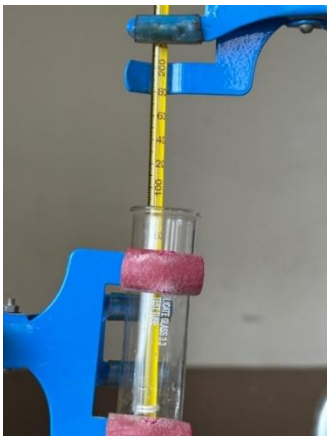

Fig.3 (C) - 118°C

Fig. 3(A)(B)(C): Melting point of Capecitabine

Ultraviolet Spectroscopy:

The UV-Vis spectroscopy analysis of the sample was conducted using a Shimadzu UV-1900i spectrophotometer.

Table 4: Ultraviolet Spectroscopy Absorption of Capecitabine

S.No.	Concentration (µg/ml)	Absorption
1.	100	3.920

Fig. 4: Ultraviolet spectroscopy Absorption spectrum of capecitabine

Standard graph:

The standard graph was prepared, and the absorption spectra of the samples were obtained using a Shimadzu UV-1900i spectrophotometer.The drug's maximum wavelength as measured by UV spectroscopy is 305 nm.A perfect correlation was found when the drug's calibration curve was generated. It was observed that the concentration and absorbance were completely linear.

Table 5: Ultraviolet Spectroscopy Absorption of dilutions of Capecitabine

S.No.	Concentration (µg/ml)	Absorption
1.	2	3.352
2.	4	3.434
3.	6	3.518
4.	8	3.599
5.	10	3.704

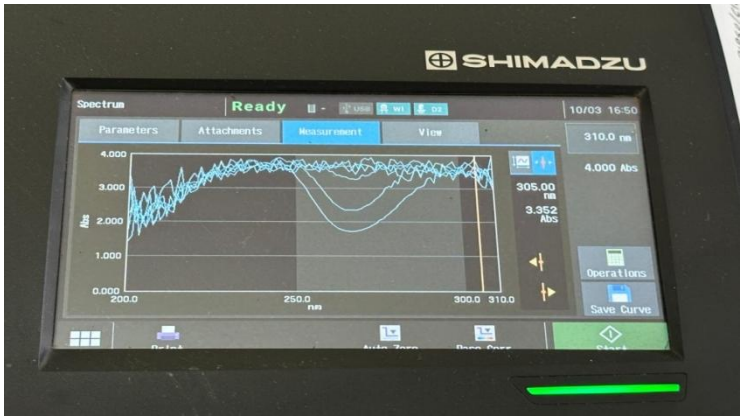

Fig. 5: Ultraviolet spectroscopy Absorption spectrum

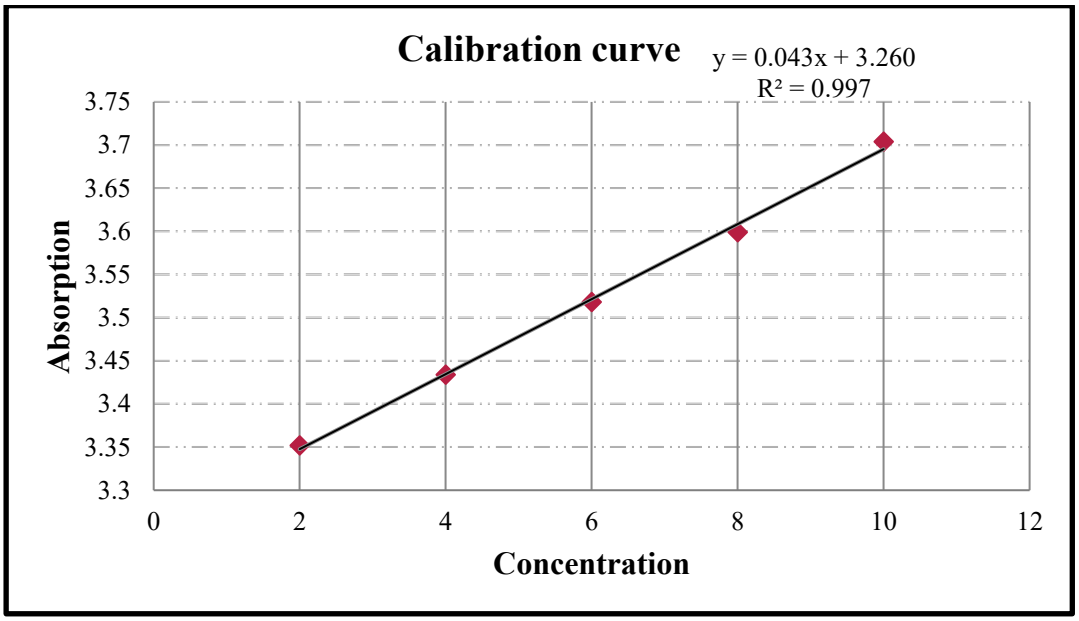

Fig. 6: Standard calibration curve

Partition coefficient :

SHIMADZU, (model: UV-1900i) was used.According to the partition coefficient (P=2.07), capecitabine has a moderate level of lipophilicity.

Table 6: Absorption of capecitabine in aqueous and organic phase

S.No.	Separated phase	UV Absorption
1.	Aqueous Phase	1.769
2.	Organic Phase	3.656

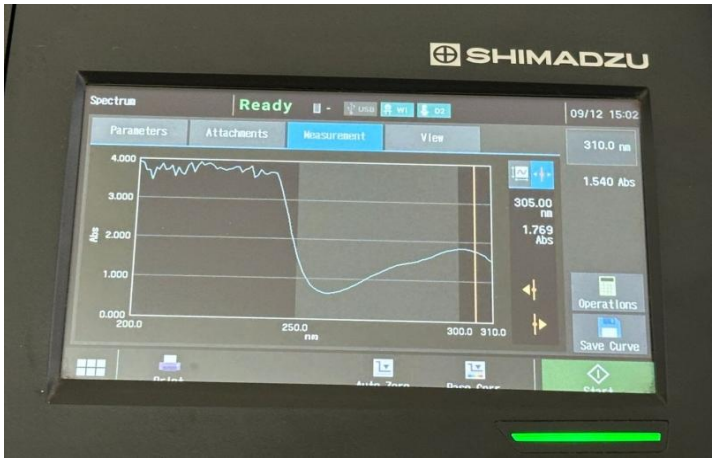

Fig. 7 (A) Uv absorption spectrum of aqueous phase

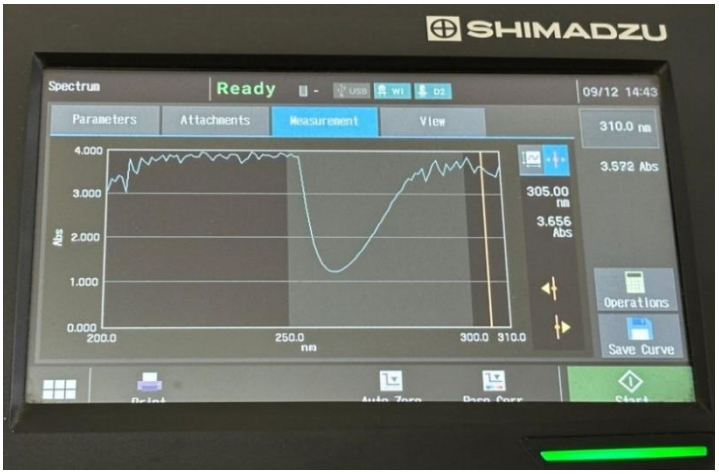

Fig. 7(B) Uv absorption spectrum of organic phase

Fourier Transform Infrared Spectroscopy (FT-IR):

That was used to conduct the FT-IR analysis. (Model: [IRSpirit,SHIMADZU]), serial number- A224060, available at Rungta College of Pharmaceutical Sciences and Research, Bhilai. The IR spectrum of the sample showed characteristic absorption peaks at 3454.32 cm^{-1} O-H stretching, 3389.71 cm^{-1} N-H stretching, 2959.00 cm^{-1} C-H stretching, 1760.18 cm^{-1} C=O stretching, 1632.40 cm^{-1} C=C stretching, 1392.64 cm^{-1} C-H bending, and 1210.03 cm^{-1} C-N stretching, among others. These peaks correspond to the functional groups present in capecitabine and are in agreement with standard literature values.

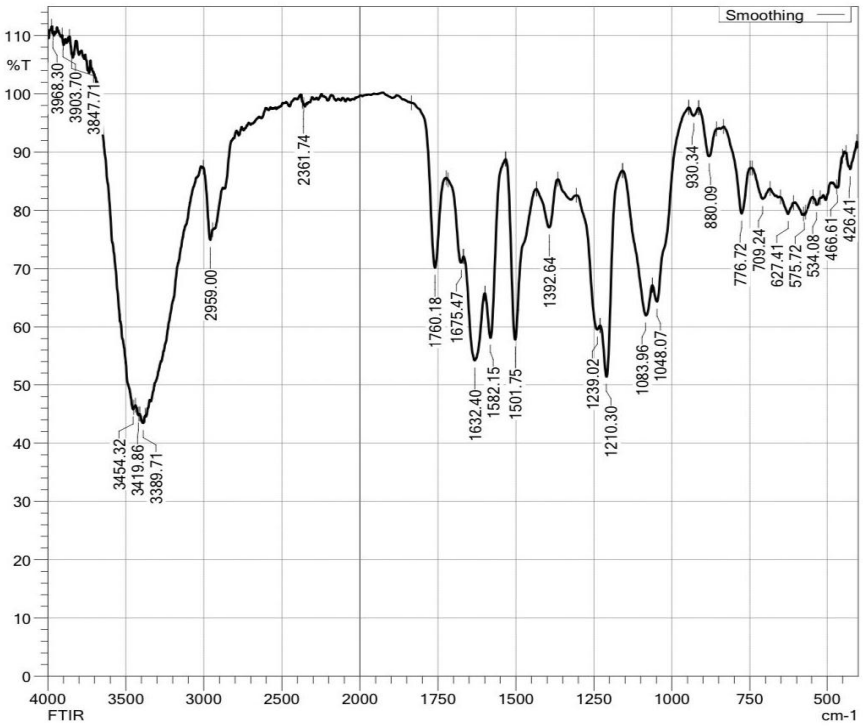

Fig. 8: The FTIR spectra of capecitabine

X-Ray Diffraction:

The X-ray diffraction (X-RD) analysis of the sample was performed using a Bruker D8 Advance A25 X-RD instrument at Indian Institute of Technology,Bhilai.Capecitabine's distinctive diffraction planes are shown by sharp, intense peaks in the sample's XRD pattern at 2θ values. These peaks(figure - 9) existence attests to the compound's crystalline nature. The sample's purity and structural identity are demonstrated by the diffraction pattern.

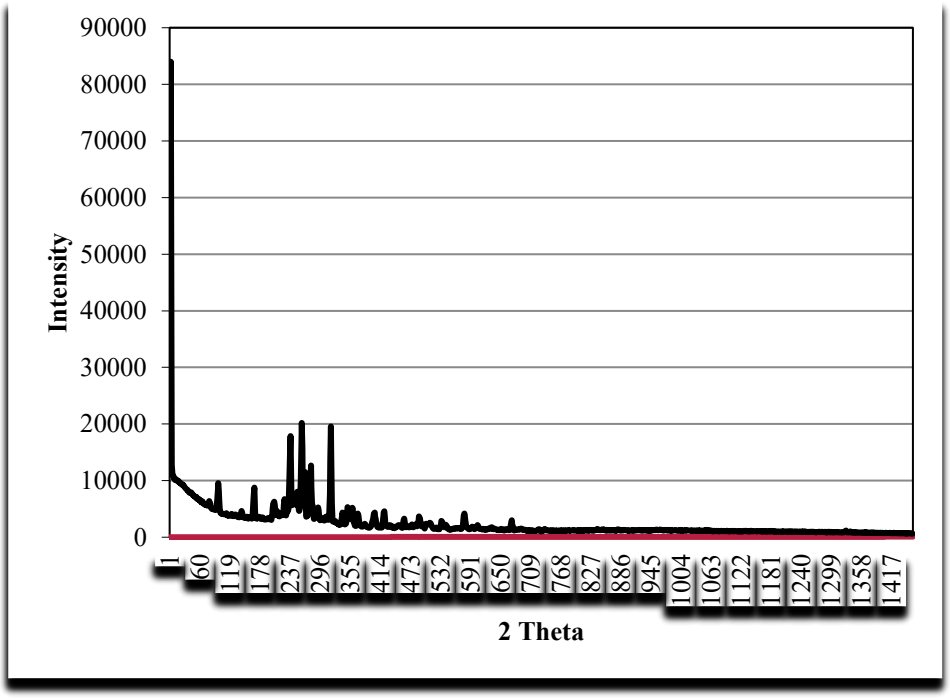

Fig. 9: X-RD of capecitabine

4. CONCLUSION

The overall outcomes of this preformulation study indicate that capecitabine has a stable profile and advantageous physicochemical characteristics that make it suitable for formulation development. Solubility and partition coefficient data highlight the need for enhancement strategies, while spectroscopic analyses confirm purity. The creation of an effective anticancer drug and additional formulation improvement are made possible by these findings.

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