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PRE-FORMULATION STUDIES FOR THE DEVELOPMENT OF LIPOSOME BASED SUSTAINED RELEASE DELIVERY SYSTEM AS ANTICANCER DRUG

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ABSTRACT

To address the disadvantages of traditional drug delivery methods, there are several approaches available for the design and production of formulations for extended- release drug delivery. Such drug delivery systems are mainly intended to enhance disease control by altering the pharmacokinetic profiles of therapeutic agents usually administered as traditional tablets or capsules. Preformulation is a study which deals with the structure for the combination of drug with pharmaceutical ingredients in dosage form manufacturing. The analysis of preformulation is to create the elegant dosage form by determining the kinetic rate profile, compatibility with the other ingredients, defining the new drug 's physicochemical parameter and polymorphism. The pre-formulation also provides details on the organoleptic property, solubility, melting point and drug-related partition coefficient, drug stability, drug absorbance, and analysis of FTIR among these properties. As the 6-mercaptopurine is a very powerful medication, this medication is used by many researchers in their work. This research paper helps those people who want to use 6-mercaptopurin for development of new formulation related to this drug.

KEYWORDS: 6-Mercaptopurine, Preformulation study, Sustain Release system, Liposome

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INTRODUCTION

Mercaptopurine anhydrous is the anhydrous form of mercaptopurine, a thiopurine-derivative antimetabolite with antineoplastic and immunosuppressive activities.

Mercaptopurine metabolism produced by hypoxanthine-guanine phosphoribosyl-transferase (HGPRT), mercaptopurine metabolites 6-thioguanosine-5'-phosphate (6-thioGMP), and 6-thioinosine monophosphate (T-IMP) inhibit nucleotide interconversion and de novo purine synthesis, thus blocking the formation of purine nucleotides and inhibiting DNA synthesis. This agent is also introduced into DNA in the form of deoxythioguanosine, resulting in a DNA replication disruption. However, by 6-thiopurine methyltransferase mercaptopurine is converted to 6-methylmercaptopurine ribonucleotide (MMPR); MMPRs are also active inhibitors of de novo purine synthesis [1]. This is used to treat everything, chronic myeloid leukemia (CML), Crohn's disease and ulcerative colitis [2, 3].

Liposomes provide an excellent opportunity for selective drug targeting, which is supposed to optimize the pharmacokinetic parameters, pharmacological effects, avoid local inflammation and the toxicity of encapsulated drugs [4, 5]. The tolerability and health of inhaled liposome aerosols was previously tested in animals and in volunteers [6, 7]. No adverse effects were recognised. Additionally, the closed vesicular structures consisting of one or more lipid bilayers

covering an inner aqueous compartment allow the successful encapsulation of both hydrophilic and lipophilic drugs. Water-soluble drugs can be encapsulated in the inner aqueous container, while lipid-soluble drugs can be integrated into the bilayers of liposomes [8].

Preformulation Studies

Studies of preformulation were initiated in 1950 & early 1960. Nearly all the drugs are sold as tablets, capsules or both. It is important to examine the physical and chemical properties of the drug product alone or in combination with excipients in the correct form before this production of the main dosage type [9]. The drug's first learning process is called preformulation. Preformulation is the intervention of the new drug entity and the creation of the formulations [10].

Need/Importance of Dosage Form

- ✓ To deliver accurate drugs in a safe, effective and convenient way.
- ✓ To protect against harmful conditions such as oxygen or humidity.
- ✓ To guard against gastric acid and the effect following oral administration. Example: Tablet with enteric coating.
- ✓ Suppress the drug's odour and taste.
- ✓ To provide unstable or insoluble solubility and stability for that liquid preparation. E.g., suspension.
- ✓ To provide drug action that is controlled by rate.

Objective of Preformulation

- ✓ Formulating or designing elegant dosage types.
- ✓ It provides the formulator with know-how to design an optimal drug delivery system.
- ✓ This is the first step before raw material is formulated or formed into dosage form [9].

MATERIALS AND METHODS

Organoleptic Property of Drug

A typical pre-formulation scheme should begin with definition of the drug product. The colour, odour and taste of the new product must be recorded using descriptive terminology [11].

Determination of Melting Point

Melting point of 6-Mercaptopurine was determined by capillary method.

Solubility

The solubility of 6-Mercaptopurine was tested in various solvents such as distilled water, ethanol 95%, NaOH, dimethyl formamide and dimethyl sulfoxide [12].

FT-IR Spectroscopy

The FT-IR spectrum of the sample drug was obtained using FTIR spectrophotometer (Pekin Elmer Spectrum II) and this was compared with the standard FT-IR spectra of the pure drug[13].

Determination of Partition Coefficient

In a 20 ml (1:1) mixture of n-octanol and 0.1 NaOH, 10 mg of 6-mercaptopurine was shook for 30 minutes in separating funnel. The aqueous layer and oil layer were separated, and the amount of drug dissolved in aqueous phase and oil phase was measured using UV-Vis Spectrophotometer [14]. The formula used to calculate the partition coefficient (Ko/w) for the drug:

Ko/w = Concentration of Drug in Oil phase (n-Octanol) /Concentration of Drug in aqueous phase (.1 N NaOH)

Determination of λ_{max}

λ_{max} for the given sample of drug was determined by using UV-Vis spectrophotometer.

Compatibility Studies

FT-IR spectroscopy was performed to check the drug-phospholipid compatibility. The FT-IR spectrum of 6-Mercaptopurine physical mixtures with phospholipid and cholesterol was contrasted with the pure drug's normal FT-IR spectrum to test for incompatibility [15].

Standard Calibration curve of 6-Mercaptopurine

Accurately weighed 10 mg 6-Mercaptopurine was dissolved in 100ml 0.1 N NaOH solution to get the 100 µg/ml solution. This solution has been used as the final solution on stock. Aliquots of 2 ml, 4 ml, 6 ml and 8 ml were removed from this stock solution and further diluted to 10 ml with a solution for concentrations between 2 and 8 µg/ml [16].

The absorbance of the solutions was measured at 307 nm by using UV-Vis spectrophotometer (UV-1700 Pharma Spec). A graph of Concentration vs. Absorbance was plotted.

RESULTS AND DISCUSSION

Organoleptic Property of 6-Mercaptopurine

- Colour: - White
- Odour: - Odourless
- Taste: - Bitter
- State: - Crystalline powder

Determination of Melting Point

Melting point of 6-Mercaptopurine was found to be 308- 313 ºC.

Solubility

6-Mercaptopurine was found to be freely soluble in 0.1 N NaOH, DMF, Slightly soluble in ethanol (95 per cent) and methanol and practically insoluble in water and in ether.

FT-IR Spectroscopy

The FT-IR spectrum of the 6-Mercaptopurine pure sample recorded by FTIR spectrometer is shown in **Figure 1**, which was compared with standard functional group frequencies of 6-Mercaptopurine as shown in **Table 1**. **Table 1** indicates that the major functional groups in accordance with the structure of 6-MP as shown below are present in the drug sample and thus it indicates the purity of the sample under study.

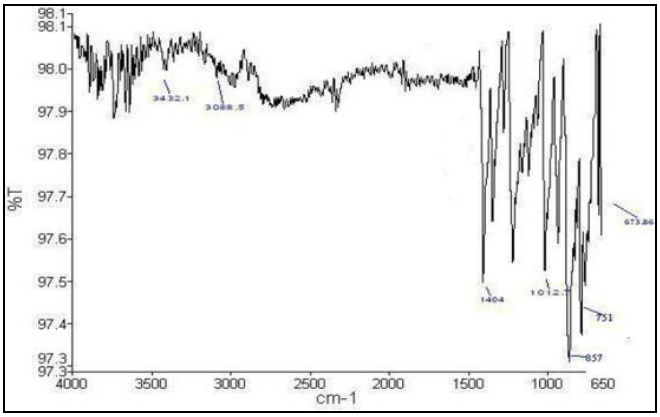

Figure 1: FTIR Spectra of 6-Mercaptopurine

Table 1: FTIR Frequencies of Various Functional Groups of 6-Mercaptopurine

S. No.	Functional group	Reported Frequency Range (cm^{-1})	Observed Frequency (cm^{-1})
1	N-H stretching	3400-3100	3433
2	C-N stretching	1450-1400	1410
3	S-H bending	800-700	751
4	C-H aromatic	3100-3000	3080

Determination of Partition Coefficient

Partition coefficient for the 6-Mercaptopurine monohydrate in octanol / phosphate buffer pH 7.4 was found to be 1.583 indicating that the drug is lipophilic in nature.

Determination of λ_{max}

λ_{max} for the given sample of drug was determined by using UV-Vis spectrophotometer. λ_{max} for 6-Mercaptopurine monohydrate was found to be 307 nm in 0.1 N NaOH.

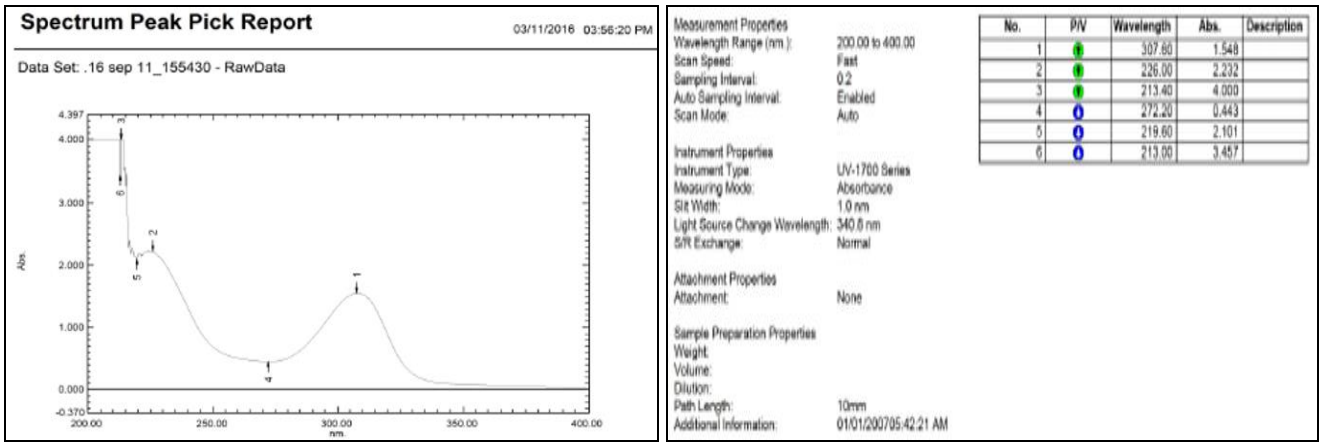

Figure 2: Peak Report of 6-Mercaptopurine in 0.1 N NaOH Solution

Compatibility Study (FTIR Studies)

The individual IR spectra of soya lecithin and cholesterol and Physical mixtures of 6-Mercaptopurine is shown in the **Figure 3, 4** & **5,** respectively. This indicates no interaction between 6-Mercaptopurine and cholesterol and soya lecithin when compared with infrared spectrum of pure drug.

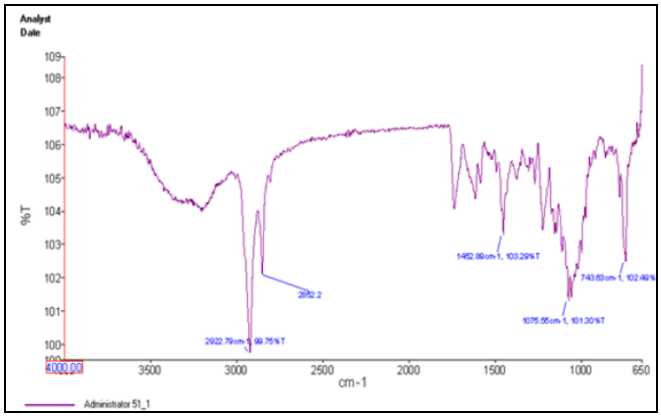

Figure 3: FT-IR of Soya Lecithin

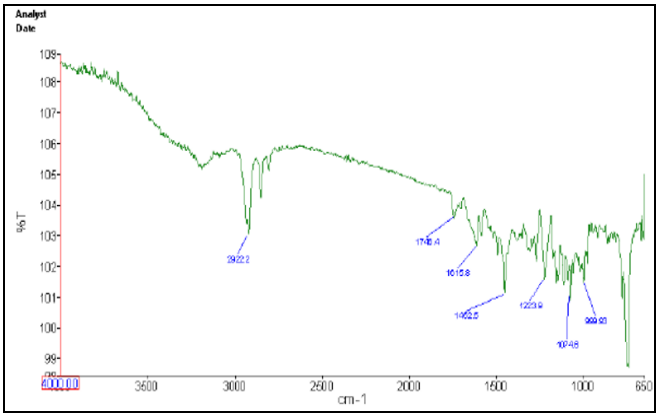

Figure 4: FT-IR of Cholesterol

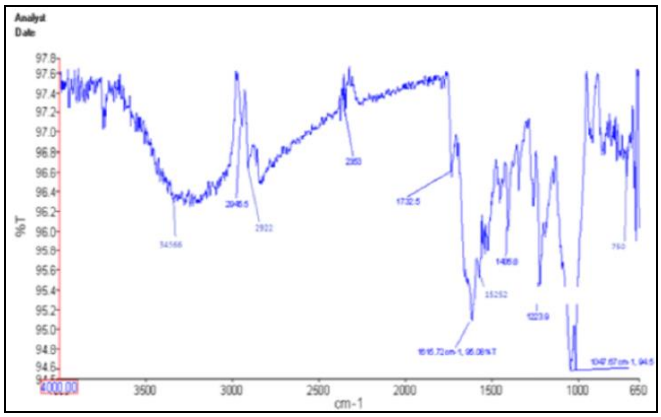

Figure 5: FTIR of Physical Mixture of Drug and Cholesterol

Table 2: IR Frequencies of Various Functional Groups of Drug and Cholesterol

Substance	Functional group	Reported frequency	Observed frequency
6-Mercaptopurine	N-H stretching	3400-3100	3456
	C-N stretching	1450-1400	1406
	S-H bending	800-700	750
	C-H aromatic	3100-3000	2946
Cholesterol	-OH	2500-3300	2922
	C=C	1400-1600	1525

Standard Calibration Curve of 6-Mercaptopurine

Accurately weighed 10 mg 6-Mercaptopurine was dissolved in 100ml of .1 N NaOH solution to get the solution of 100 µg/ml. This solution was used as the final stock solution.

From this stock solution aliquots of 2 ml, 4ml, 6 ml and 8 ml were withdrawn and further diluted to 10 ml with solution to obtain concentrations within the range of 2 to 8 µg/ml.

Table 3: Absorbance Value of 6-Mercaptopurine in 0.1N NaOH solution at 307 nm

S. No.	Concentration(µg/ml)	Abs.
1	2	0.161
2	4	0.318
3	6	0.505
4	8	0.682
5	10	0.854

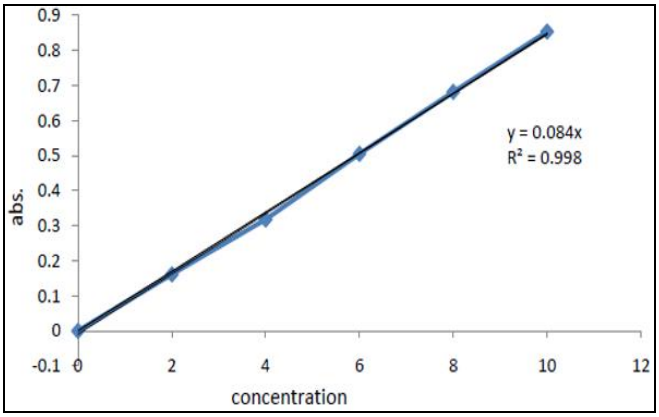

Figure 6: Standard Calibration Curve of 6-Mercaptopurine

The absorbance of the solutions was measured at 307 nm by using UV-Vis spectrophotometer (UV-1700 Pharma Spec). A graph of Concentration vs. Absorbance was plotted.

CONCLUSION

Preformulation experiments have a major role to play in predicting issues with the formulation and finding rational pathways in both liquid and solid technology dosages. It cannot be stressed that adequate drug solubility is required.

The most suitable salt for growth, solution stabilities studies should indicate the feasibility of parenteral or other type of liquid dosing. The pre-formulation experiments above indicated that the excipients were photo-stable, and pre-formulation tests were discarded. Excipients are best suited for formulating anticancer drug delivery dependent on liposome.

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CONFLICT OF INTEREST

None

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