



Preformulation Study of Mefenamic Acid

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KEYWORDS

Preformulation, efficacious, Mefenamic acid, inflammation, cosolvency.

ABSTRACT:

Introduction: The preformulation study is the process of maximizing the delivery of the drug through the determination and evaluation of physicochemical properties of the new compound that could affect drug performance and development of stable, efficacious and safe dosage form. The primary step within the rational development of dosage forms of a drug substance is the Preformulation testing

Objectives: The aim of our research work is to do preformulation study and solubility enhancement of a low water-soluble drug, that is Mefenamic drug.

Methods: We opted for the Cosolvent technique for the same, as it has high solubility in water-miscible organic solvent which works by decreasing the interfacial surface tension between the solution and hydrophobic matter (solvent blending).

Results: Various cosolvent hydrophilic hydrogen-bonding groups ensure water solubility, while the hydrophobic hydrocarbon regions interfere with water hydrogen bonding network, decreasing the altogether intermolecular attraction of water. By disrupting water self-association, cosolvents reduce water's ability to squeeze out non-ionic, hydrophobic compounds, thus increasing solubility. .

Conclusions: Mefenamic acid is NSAID drug. It acts by reducing hormones which cause pain and inflammation by inhibiting the body's production of a substance that causes fever, inflammation and pain. Due to its great effectiveness many researchers use Mefenamic acid in their research.

1. Introduction

The preformulation study is that the method of increasing the delivery of the drug through the determination and analysis of physicochemical properties of the new compound that might have an effect on drug performance and development of stable, efficacious and safe indefinite quantity type. Discovering and developing new medicines could be a long, valuable and sophisticated method and therefore the negligence rate is high throughout the method. To minimise abrasion it's essential, to grasp the physicochemical properties of compounds or biological entities that are candidates for

development into finished merchandise. Preformulation studies will thus be explained as; Laboratory studies to see the characteristics of excipients and active substances which will influence formulation, method style and performance. It's been referred as Learning before doing. Knowledge nonheritable from preformulation studies additionally forms a vital basis for understanding the potential pharmacology of a drug in humans and animals. Preformulation could be a many-sided development of a drug candidate.



Principal Areas of Preformulation:

Bulk Characterization:

- I. Crystallinity and polymorphism
- II. Hygroscopicity
- III. Fine particle characterization.
- IV. Powder flow.

Solubility Analysis:

- I. Ionization constant – pKa
- II. pH solubility profile.
- III. Common ion effect – KSP.
- IV. Thermal effects.
- V. Solubilization
- VI. Partition coefficient.

Dissolution

- I. Stability Analysis:
- II. Stability in toxicology formulation.
- III. Solution stability– pH stability profile.
- IV. Solid state stability - Bulk stability, Compatibility

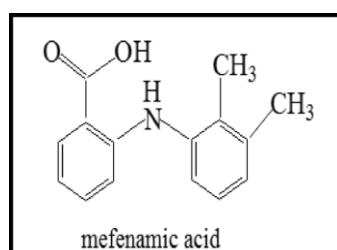


FIG. 1: MEFENAMIC ACID

2. Objectives

A Drug Mefenamic acid belongs to class of anthranilic acid derivatives (fenamate) nonsteroidal anti-inflammatory drugs (NSAIDs), which is moderately used to treat mild to moderate pain.^{1,2} It is also used to treat pain and inflammation in osteoarthritis, rheumatoid arthritis and postoperative pain, acute pain including toothache, backache, headache muscle pain and menstrual pain. It has also been prescribed for menorrhagia.^{3,4,5}

Mefenamic acid belongs to the Biopharmaceutical Classification System (BCS) class II drug which has lower water solubility but high

permeability.⁶ Mefenamic acid is administered by the oral route and should be taken with food to reduce GI side effects.⁷ It is metabolized by the liver enzyme CYP2C9 to the only weakly active 3'-hydroxymefenamic acid. 3'-carboxymefenamic acid has been identified as a metabolite, along with carboxyglucuronides of all three substances. Mefenamic acid and its metabolites are excreted through urine (52–67%) and faeces (20–25%, or less than 20% following another source). The parent substance has a half-life of two hours; the half-life of its metabolites can be longer.^{4,8,9} There is evidence that supports the use of mefenamic acid for premenstrual migraine headache prophylaxis, with treatment starting two days prior to the onset of flow or one day prior to the expected onset of the headache and continuing for the duration of menstruation.⁴ Mefenamic acid is recommended to be taken with food.¹⁰ A study has been conducted on transgenic mouse model of Alzheimer's disease to check if mefenamic acid can treat Alzheimer's. Mefenamic acid showed improvement in the behavior of transgenic mouse having Alzheimer's disease, this evidence proves that mefenamic acid or other NSAIDs can treat or prevent Alzheimer's in humans; clinical trials of NSAIDs other than mefenamic acid for treatment of Alzheimer's have found more harm than benefit.^{11,12,13} As the mefenamic acid is very effective drug many researchers use this drug, some of the research articles is listed below:

1. Use of Mefenamic Acid in COVID-19 as a Supportive Treatment¹⁴
2. Determination of Mefenamic acid in topical emulgel which is validated by HPLC method¹⁵
3. To Formulate and evaluate Mefenamic acid solid dispersions using PEG-4000¹⁶
4. An insight of mefenamic acid drug as a non-steroidal anti-inflammatory drug.¹⁷
5. Use of novel techniques to enhance solubility of mefenamic acid.¹⁸
6. Development of Mefenamic acid as prodrugs and CoDrugs¹⁹
7. Various Analytical Methods to determine Mefenamic Acid²⁰
8. Prepare and characterize spherical agglomerates of mefenamic acid by neutralization method.²¹



3. Material and Methods

1. Organoleptic Properties: The drug samples were studied for appearance, color, and odour. The results are manifest in **Table 1**.

2. Melting Point: The melting points of the drugs were determined by an open capillary method using the melting point apparatus. The melting point is shown in **Table 2**.

3. Solubility Study of Drug²²: Solubility studies of the drug were disbursed in numerous varieties of solvents which are used for further study. Saturated solutions were prepared by adding 10mg of drug in a different solvent and then this sample kept in ultrasonicator for 15-30 min. After this era the solutions were filtered, diluted and analyzed by UV spectrophotometer. Three determinations were administered for every sample to calculate the solubility of the drug. Mostly the solubility of drug observed in Methanol and PEG400. The results are manifest in **Table 3**.

4. Fourier Transform Infrared Spectroscopy of Drug: The infrared spectra of the pure drug were recorded by PerkinElmer FT-IR spectrometer. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined within the transmission mode. Each spectrum was a frequency range of 4000–400 cm^{-1} . The results are manifest in **Table 4** and **Fig. 1** and **Fig. 2**.

5. Ultraviolet Spectroscopy:^{23,24}

1. Determination of Maximum Wavelength (λ_{max}):

a. In Methanol: Drug (10 mg) was accurately weighed and transferred to 100 ml volumetric flask, volume was made up to the mark with methanol to get strength 100 $\mu\text{g/ml}$. It was used as a typical stock solution. This stock solution was further diluted suitably to offer a degree of 10 $\mu\text{g/ml}$. The UV spectrums were recorded within the range 200-400 nm by using UV-Visible double beam spectrophotometer (Shimadzu 1800). The wavelength of maximum absorption (λ_{max}) decided and is manifest in **Fig. 3** and **Table 5**.

b. In methanolic HCl²⁵: Drug (10 mg) was accurately weighed and transferred to 100 ml volumetric flask, volume was made up to the mark with 0.1 M methanolic HCl to obtain strength 100 $\mu\text{g/ml}$. It was used as a typical stock solution. This stock solution was further diluted suitably to offer a degree of 10 $\mu\text{g/ml}$. The UV spectrums were recorded within the range 200-400 nm by using UV-Visible double beam spectrophotometer (Shimadzu 1800). The wavelength of maximum absorption (λ_{max}) decided and is manifest in **Fig. 4** and **Table 6**.

c. In Phosphate Buffer (pH-7.4): 20 mg of drug was accurately weighed, transferred into a 100 ml volumetric flask and dissolved in 15 ml of methanol. The volume was made up to 100 ml using PBS pH 7.4 to urge a degree of 200 $\mu\text{g/ml}$. From the prepared stock solution, 10 ml solution was withdrawn and transferred to a different 100 ml volumetric flask and volume were make up to 100 ml to urge a degree of 20 $\mu\text{g/ml}$. The UV spectrums were recorded within the range 200-400 nm by using UV-Visible double beam spectrophotometer (Shimadzu 1800). The wavelength of maximum absorption (λ_{max}) decided and is shown in **Fig. 5** and **Table 7**.

4. Determination of Beer-Lambert's Plot:

a. In Methanol: 20 mg of drug was accurately weighed, transferred into 100 ml volumetric flask and dissolved in 15 ml of methanol. The volume was make up to 100 ml using methanol get a concentration of 200 $\mu\text{g/ml}$. From the prepared stock solution, 10 ml solution was withdrawn and transferred to a different 100 ml volumetric flask and volume was make up to 100 ml to urge a degree of 20 $\mu\text{g/ml}$. From the above solution 1, 2, 3, 4, and 5 ml of solutions were transferred into 10ml volumetric flasks respectively, and volume was made up to 10 ml to urge a concentration of 2, 4, 6, 8, 10 $\mu\text{g/ml}$ respectively. To scan the wavelength maxima 20 $\mu\text{g/ml}$ solution was taken during a quartz cuvette and scanned on UV-Visible double beam spectrophotometer in range of 200-400 nm. The above-prepared samples were analyzed at 285nm (λ_{max}). Calibration Curve is manifest in **Fig. 6**.

b. In methanolic HCl²⁵: 10 ml of 100 $\mu\text{g/ml}$ standard stock solution was diluted up to 50ml to get a typical working solution of 20 $\mu\text{g/ml}$ concentration which was used for further dilutions of the calibration curve.



Aliquots (2.5, 3.7, 5.0, 6.2, 7.5) ml of 20 µg/ml working standard solution like 2.5-7.5 µg/ml were taken during a series of 20 ml volumetric flask and volume made up with 0.1M methanolicHCl. The absorbance measurements of those solutions were administered against 0.1M methanolicHCl as blank at 280nm. A calibration curve was plotted in **Fig. 7**.

c. In Phosphate Buffer (pH-7.4): 20 mg of drug was accurately weighed, transferred into a 100 ml volumetric flask and dissolved in 15 ml of methanol. The volume was made up to 100 ml using PBS pH 7.4 to get a degree of 200 µg/ml. From the prepared stock solution, 10 ml solution was withdrawn and transferred to a different 100 ml volumetric flask and volume was make up to 100 ml to urge a degree of 20 µg/ml. From the above preparation 1, 2, 3, 4, and 5 ml of solutions were transferred separately into 10 ml volumetric flasks respectively, and volume was make up to 10 ml to urge concentration of 2, 4, 6, 8, 10 µg/ml respectively. To scan the wavelength maxima 20 µg/ml solution was taken in a quartz cuvette and scanned on a UV-Visible double beam spectrophotometer in range of 200-400 nm. The above prepared samples were analyzed at 286 nm (λ_{max}). Calibration Curve is shown in **Fig. 8**.

7. Differential Scanning Calorimetry (DSC) Study of Drug²⁶: DSC analysis was performed using Hitachi 7020 thermal analysis system on 2-5 mg samples. The sample was heated in an open nitrogen pan at a rate of 10 °C/min conducted over a temperature range of 30 to 240 °C for Mefanamic acid under a nitrogen flow of two bar pressure. Thermogram, as shown in **Fig. 9** and inference, showed in **Table 8**.

8. Partition Coefficient (Kp)²⁶: The partition coefficient of the drug decided by shaking equal volumes of oil and aqueous solution and therefore it was introduced into a separating funnel. A drug solution of 1 mg/ml was prepared in water and 50 ml of this solution was taken during a separating funnel and shaken with an equal volume of octanol for 10 min and allowed to face for twenty-four hours with intermittent shaking. Using a UV spectrophotometer get the partition coefficient values which is shown in **Table 9**.

4. Results

Organoleptic Properties: The Sample of Mefanamic acid obtained was studied for its organoleptic characters which includes color, odor, and appearance as these are one of the primary standards for identification of compound and it shows results/properties which comply with stated literature standards. The end result is presented within the following **Table 1**.

TABLE 1: COMPARISON OF THE RESULT OF ORGANOLEPTIC CHARACTERS OF DRUG SAMPLE WITH THE REPORTED STANDARDS

Sr. No.	Identification Test	Observed Result	Reported standard
1	Appearance	Powder	Crystalline Powder
2	Colour	White	White/ Off-white
3	Odour	Odourless	Odourless

It is complying with the description that is found in the literature.

Melting Point: According to the Indian Pharmacopoeia, the temperature /melting range of a substance is defined as the temperature points in which /the point at which the substance begins to coalesce and is completely melted, as defined differently for certain substances.⁶ The melting point of the drug is consistent with reported literature values. The melting point of drug was observed to be in the range of 230-231 °C with decomposition, that is, substance is characterized when it begins to melt, as shown in the **Table 2**.

TABLE 2: COMPARISON OF THE RESULT OF THE MELTING POINT OF DRUG SAMPLE WITH THE REPORTED STANDARDS

Sr. no.	Identification Test	Observed Result	Reported standard
1	Melting Point	230 °C	230-231 °C

Solubility Study of Drug: A solubility test becomes a purity test only when a special quantitative test is given in the individual monograph and is an official



requirement. Mefenamic acid has poor solubility in water and on the other hand it has high solubility in water-miscible organic solvent²⁶. The solubility study of the drug sample was studied in different kinds of solvents, and the data shows that the drug was slightly soluble in water, soluble in phosphate buffer (pH 7.4) and freely soluble in the rest of another solvent which is shown in **Table 3**.

TABLE 3: SOLUBILITY OF DRUG IN A DIFFERENT SOLVENT

Sr. no.	Solvent	Solubility (mg/ml)
1	Isopropyl Myristate	67.05
2	Oleic acid	0.285
3	PG	0.417
4	PEG 400	4.351
5	Tweens 80	0.285
6	Methanol	1.451
7	MethanolicHCl	0.548
8	Phosphate Buffer pH 7.4	2.32
9	Water	10

Fourier Transform Infrared Spectroscopy of Drug:

As we know, the infrared spectroscopy is mostly used for the identification of organic compound whose spectra are complex and as it provides numerous maxima and minima that are useful for comparison purpose. Infrared spectroscopy finds application in qualitative and quantitative analysis as no two compounds give similar absorption spectra in the IR region. The spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} using FTIR spectrophotometer. The FTIR spectra of Mefenamic acid were taken which is shown in **Fig. 2**. The IR peak should be compared with Literature (IP 2014 vol.1) **Fig. 3**. The principal peak for IR of drug sample matched with the standard spectrum for Mefenamic acid which is shown in **Table 4**.

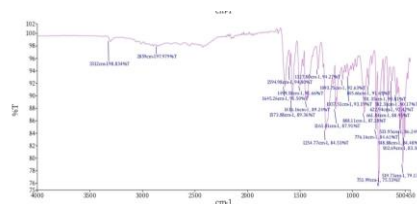


Figure 2: IR SPECTRA OF DRUG

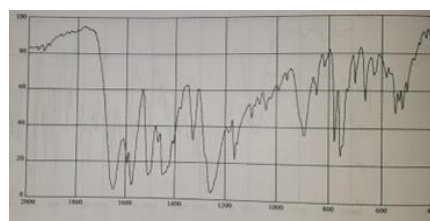


Figure 3: IR SPECTRA IN IP 2014

TABLE 4: INTERPRETATION OF IR OF DRUG

Sr. No	Functional Groups	Reported Values	Observed Peak Values
1	-OH Group Lending and Vibrations COOH	950-910	938 cm^{-1}
2	-NH Stretching	3500-3300	3312 cm^{-1}
3	C=O Stretching	1760-1690	1645.26 cm^{-1}
4	Aromatic C-H Plane deformation	3100-3000	3005 cm^{-1}
5	Aromatic C-C Vibration for Ortho	735-770	751.79 cm^{-1}
6	Aromatic -NH	1360-1259	1327.80 cm^{-1}

Ultraviolet Spectroscopy:

Determination of Maximum Wavelength (λ_{max}):

Maximum wavelength (λ_{max}) is different and specific for each drug substances, and it is also helps in identification criteria. The maximum absorbance for drug is taken in Methanol, MethanolicHCl and



Phosphate Buffer (pH- 7.4). Observed peak and reported standard peak are shown in **Table 5**.

TABLE 5: MAXIMUM WAVELENGTH (λ_{max}) OF THE DRUG IN METHANOL, METHANOLIC HCL AND PHOSPHATE BUFFER

Solvent	λ_{max} (nm) Observed Peak
Methanol	285
MethanolicHCl	280
Phosphate buffer (pH-7.4)	286

λ_{max} for the drug in methanol, methanolicHCl, and phosphate buffer (pH-7.4) was found, and it is shown in **Fig. 4**, **Fig. 5**, and **Fig. 6** respectively.

Spectra for the drug in methanol is observed in the range of 200 nm to 400 nm which it shows absorption maxima at about 285nm and minimum at about 257 nm which is shown in **Fig. 4**.

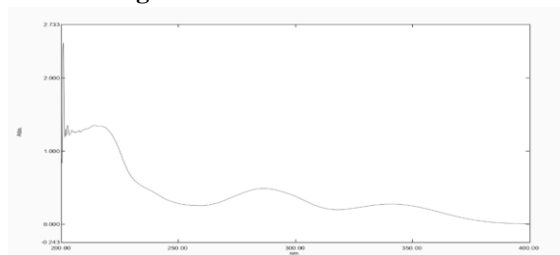


Figure 4: λ_{max} FOR THE DRUG IN METHANOL

Spectra for the drug in methanolicHCl observed in the range of 220 nm to 400 nm for 0.0007% w/v solution of 0.01M methanolicHCl - absorption maxima at about 220 nm and 280nm and minimum at about 248nm which is shown in **Fig. 4**.

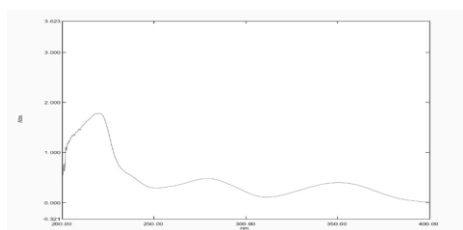


Figure 5: λ_{max} FOR THE DRUG IN METHANOLIC HCL

spectra for the drug in phosphate buffer (pH-7.4) obtained in the range of 200 nm to 400 nm for phosphate buffer (pH-7.4). This spectrum shows three peak absorption maxima at about 280nm, and 348 nm and minimum at about 249nm which is shown in **Fig. 5**.

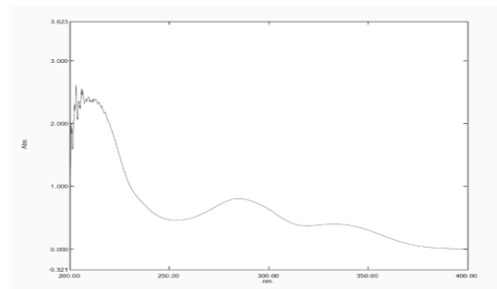


Figure 6: λ_{max} FOR THE DRUG IN PHOSPHATE BUFFER

Preparation of Beer Lambert's Plot:

In Methanol: Beer Lambert's plot of the drug sample that was prepared in Methanol. A linear relationship was obtained between concentration (2-10 $\mu\text{g/ml}$) and the absorbance of the drug in Methanol with an R2 value of 0.9994 at 285 nm is shown in calibration curve **Fig. 7**. line equation, $y=0.049 x-0.002$

TABLE 6: ABSORBANCE VALUE FOR DIFFERENT CONCENTRATION OF DRUG IN METHANOL

Sr. No.	Concentration($\mu\text{g/ml}$)	Absorbance (nm)
1	0	0.000
2	2	0.090
3	4	0.198
4	6	0.290
5	8	0.395
6	10	0.484

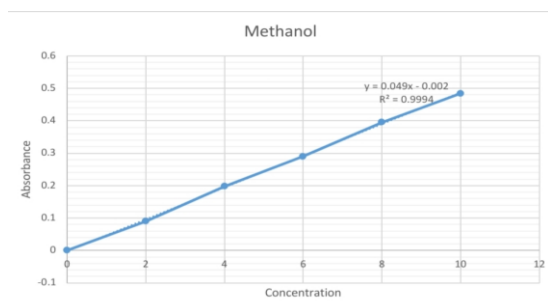


Figure 7: BEER LAMBERT'S PLOT OF THE DRUG IN METHANOL

In MethanolicHCl: Beer Lambert's plot of drug sample that was prepared in MethanolicHCl. A linear relationship was obtained between concentration (2.5-7.5 µg/ml) and the absorbance of the drug in methanolicHCl with an R2 value of 0.9998 at 285 nm is shown in calibration curve shown in **Fig. 8** and line equation, $y = 0.0683x - 0.0025$.

TABLE 7: ABSORBANCE VALUE FOR DIFFERENT CONCENTRATION OF DRUG IN METHANOLIC HCL

Sr. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0.000
2	2.5	0.165
3	3.7	0.248
4	5.0	0.341
5	6.2	0.421
6	7.5	0.510

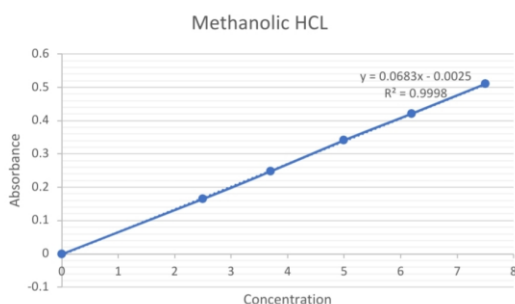


Figure 8: BEER LAMBERT'S PLOT OF THE DRUG IN METHANOLIC HCL

In Phosphate buffer (pH 7.4): Beer Lambert's plot of the drug was prepared in Phosphate buffer (pH 7.4). A linear relationship was obtained between concentration (2-10 µg/ml), and the absorbance of the drug in phosphate buffer (pH 7.4) with an R2 value of 0.9983 at 285 nm is shown in calibration curve shown in **Fig. 9** and line equation, $y = 0.034x + 0.0068$.

TABLE 8: ABSORBANCE VALUE FOR DIFFERENT CONCENTRATION OF DRUG IN PHOSPHATE BUFFER (pH 7.4)

Sr. No.	Concentration(µg/ml)	Absorbance (nm)
1	0	0.000
2	2	0.078
3	4	0.146
4	6	0.215
5	8	0.282
6	10	0.340

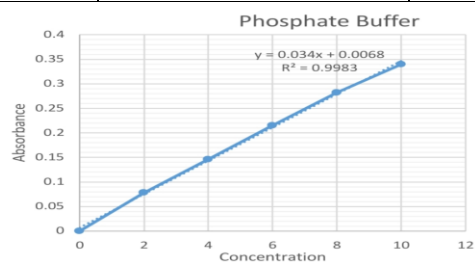


Figure 9: BEER LAMBERT'S PLOT OF THE DRUG IN PHOSPHATE BUFFER pH 7.4

Differential Scanning Calorimetry (D.S.C.) Study of Drug:

The endotherm of melting corresponds to the portion of the DSC curve that's far from the baseline and later returns to it. Melting is a process that change a substance from solid to liquid. This happens once the internal energy of the solid increase, generally by the application of heat that will increase the substance's temperature to the melting point. In DSC, as the temperature increases, the sample reaches its melting temperature (Tm). The melting process leads to an endothermic peak in the DSC curve. DSC studies were performed for drug sample. The DSC thermogram drug sample is presented in **Fig. 10** and interpretation is shown



in **Table 9**. Thermogram of DSC of the drug shows melting in the range between 230 - 235 °C, and also the sharp peak was seen at 235.9 °C. So, it shows endothermic reaction. The following figure shows the endothermic peak of the drug with height -35.63 mW

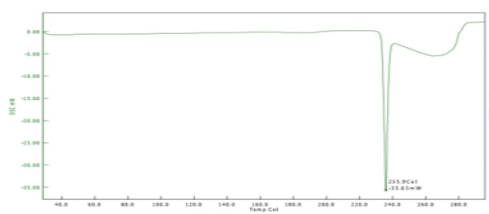


Figure 10: DSC THERMOGRAM OF DRUG

TABLE 9: INTERPRETATION OF DSC OF DRUG

Name of substance	Melting Point	Inference
Mefenamic Acid	235.9 C	Sharp endothermic peak obtained and it matches with official standard.

Partition Coefficient (K_p): The permeability coefficient was found to be 5.10, indicating that the drug sample is lipophilic and of a high class (value 5-6), and the results are shown in **Table 10**. It is worth noting that this log P = 0 means the compound is equally soluble in water and the partitioning solvent. If the compound has log P = 5, then the compound is 100,000 times more soluble in the partitioning solvent. A log P = 2 means that the compound is 100 times more water-soluble, i.e. Quite hydrophilic. Therefore, from the result obtained, the drug is 1000 times more soluble in the partitioning solvent (octanol).

TABLE 10: COMPARISON OF THE RESULT OF PARTITION COEFFICIENT (K_p) DRUG SAMPLE WITH THE REPORTED STANDARDS

Sr. no.	Observed value	Reported standard
1	5.10	5.12

5. Discussion

In the present work, the preformulation study of mefenamic acid drug was done. Preformulation studies

play significant role in anticipating formulation problems and identifying a logical path in both liquid and solid dosage form. This study shows a satisfactory result for all characterization such as organoleptic properties, melting point, calibration curve, Solubility Studies, UV, FTIR, DSC, partition coefficient, etc. Reported standard and all results match with each other

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