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PRE FORMULATION STUDY OF DEXKETOPROFEN TROMETAMOL

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Keywords:

Non-Steroidal anti-inflammatory drugs (NSAID), Ketoprofen, Dexketoprofen trometamol, UV spectroscopy, FTIR spectroscopy

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ABSTRACT: The research aims to do a pre-formulation study on powdered drug of Dexketoprofen Trometamol to know its physical, chemical and pysico-chemical properties. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely used for pain relief and inflammation reduction. Dexketoprofen Trometamol, a highly soluble Non-Steroidal Anti-Inflammatory Drug (NSAID) is tromethamine salt of Dexketoprofen (Active enantiomer of ketoprofen). It works by blocking the action of cyclo-oxygenase in the body. It is widely used for its analgesic and anti-inflammatory properties in the treatment of acute pain and musculoskeletal disorder and post operative pain. Dexketoprofen trometamol was subjected to microscopy, X-ray diffraction, UV-Visible spectroscopic analysis and FTIR spectroscopic analysis for its properties to study. The drug was also subjected to some physical examination to examine its organoleptic properties and subjected to some chemical analysis to determine its chemical properties. The research showed micro-sized particle size ranges (1-10µm) of drug with its hydrophilic nature and UV analysis of drug showed its λ max peak of absorbance at 259nm. The X-ray diffraction study and Melting point study showed that the powder has sharp melting point of 95-98oC that stated that the drug Dexketoprofen Trometamol have crystalline property. The partition coefficient of Dexketoprofen trometamol was found to be less than 1 that showed its highly hydrophilic nature. Due to trometamol salt form of the drug, it has higher onset of action. The Drug Dexketoprofen trometamol have shorter half life of about 100 minutes then it is used in frequent dosing, so it may be main field of research to use in controlled drug release and extended drug release.

INTRODUCTION:

Drug Identification: The drug was to be identified by using UV-visible spectrophotometer by using 0.1N hydrochloric acid (0.1NHCl) as a reagent. The drug was also subjected to Infrared spectroscopy (Fourier transform infrared spectroscopy- FTIR) by using potassium bromide buffer (KBr) with methanol as solvent.

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Determination of Peak by using UV-Visible spectroscopy (λmax Determination): UV-visible spectrophotometer is generally used for structural information of various drugs to obtain specific information on the chromophoric part of the molecules in solution when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. The UV spectrum is generally recorded as a plot of absorbance versus wavelength. Double beam UV-visible spectrophotometer (Shimadzu, UV1800) was used to know the λ max of drug.

Preparation of Standard Solution of 0.1N HCl: The standard solution of 0.1N HCl was prepared by

dissolving 8.4 ml concentrated HCl in a volumetric flask containing 1000ml (1L) distil water.

Preparation of Stock Solution: Required 100mg of powdered drug of Dexketoprofen trometmol was dissolved in the prepared 100 HCl solution.1 ml of drug and HCl solution is diluted with 100 ml of 0.1N HCl solution.

Determination of λ_{max}: The UV was to make auto zero using standard solution of Hydrochloric acid. The sample cuvette of UV was emptied and then filled with prepared stock solution. The peak in UV is captured and noted the wavelength at which peak of absorbance appears.

Spectroscopy Analysis: The drug was also subjected to Infrared spectroscopy (Fourier transform infrared spectroscopy- FTIR) by using potassium bromide buffer (KBr) with methanol as solvent. The FTIR involves analyzing a sample to identify its chemical composition. First, the sample was placed in Attenuated total reflectance (ATR) cell. The instrument was turned on, and a background scan was performed to account for ambient conditions. The sample was then placed in the spectrometer; an ATR crystal was also placed for easy measurement. The machine passes infrared light through the sample, detects how it absorbs the light at different wavelengths.

The spectrum of spectroscopy was recorded, and graph was plotted.

Pre-formulation Studies: Pre-formulation study provides important information for formulation design. Every drug has its chemical and physical properties which have to be considered before development of dosage form. It is the study of the physical and chemical properties of the drug before formulation process. These studies focus on those physicochemical properties of the drug that could affect its performance and development of an efficacious dosage form. A complete understanding of these properties may provide a framework for formulation design. The obtained drug sample was identified by various analytical techniques such as, UV spectroscopy, melting point etc [1]. Objective of pre-formulation study is to develop the stable, effective and safe dosage form by establishing compatibility with the other ingredients and establish physicochemical parameter of dosage form. Among these properties, drug solubility, partition coefficient, dissolution rate, plays important role in pre-formulation study [2].

Physicochemical Parameters:

Organoleptic Properties:

- Color
- Odour
- Taste

Bulk Characterization Studies:

- Crystal property
- Polymorphism
- Particle shape and size
- pH determination
- Melting point and Boilimg point

Solubility Analysis:

- Solubility determination
- PKa determination
- Partition coefficient

Organoleptic Property [3, 4]:

Color: The color was to be analyzed by visual examination. A small amount of drug is placed on white surface and was thoroughly spread evenly for clear visual examination.

Odour: The odour of Dexketoprofen Trometamol was to be analyzed by olfactory perception. A minute quantity of drug is taken in a petri dish for analysis and analyzed by olfactory perception.

Taste: The Dexketoprofen Trometamol placed on Petri-dish was tasted.

Bulk Characterization:

Crystal Property (Crystallography) [3]: Crystal property determination is the process of studying the structure and properties of crystals. The study of the structure, properties, and symmetries of crystals of a compound is to be done in crystallography. This study is to be done to examine that the taken drug Dexketoprofen Trometamol have either crystal property or amorphous nature.

- By microscopy

- Visual Inspection
- Differential scanning Calorimetry
- X-ray Diffraction

Polymorphism: Polymorphism is the ability of a substance to crystallize into more than one form. This can happen when a substance is exposed to changes in temperature or pressure.

The different forms of a substance are called polymorphs. The polymorphic study of drug was also done by X-ray diffraction crystallography [5].

Particle size: Particle size is either determined by sieving or by microscopy.

By Sieving:

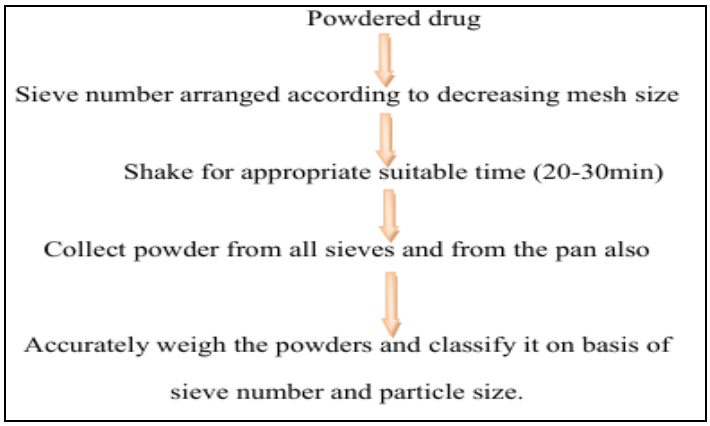

FIG. 1: PARTICLE SIZE DETERMINATION BY SIEVING

By Microscopy:

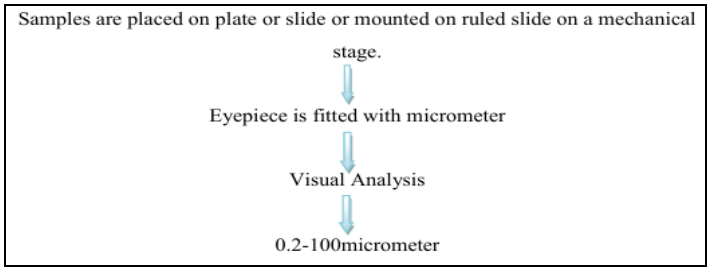

FIG. 2: PARTICLE SIZE DETERMINATION BY MICROSCOPY

Particle Shape Determination: By microscopy, shape of particles can also be determined which may be acicular, Columnar, Equant, Flake, Lath and plate.

pH Determination:

- By using standard pH paper.
- 25+-2°C
- By potentiometrically
- Glass electrode
- Reference electrode
- pH meter

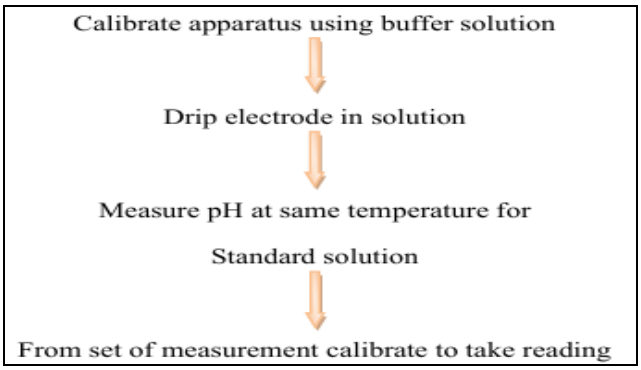

FIG. 3: pH DETERMINATION POTENTIOMETRICALLY

Melting Point: Melting point determination is a laboratory procedure that measures the temperature at which a substance changes from a solid to a liquid melting point was determined by using melting point apparatus. Capillary tube is taken and seals one end of capillary tube by heating its end on direct flame. Dexketoprofen Trometamol drug is placed on dry paper and open end of tube is tapped on pile and then tube is tapped on palm by closed end. The closed end of tube is inserted in melting point apparatus and thermometer was also placed inside it. Temperature of apparatus was raised and through watch the capillary was analyzed till melting of powder occurs and the temperature at which powder starts melting was noted [6].

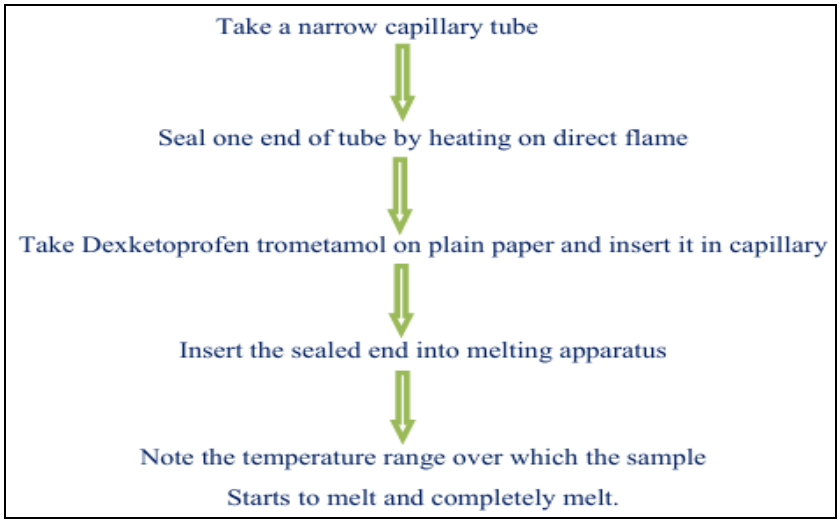

FIG. 4: PROCESS OF MELTING POINT DETERMINATION

Boiling Point Determination:

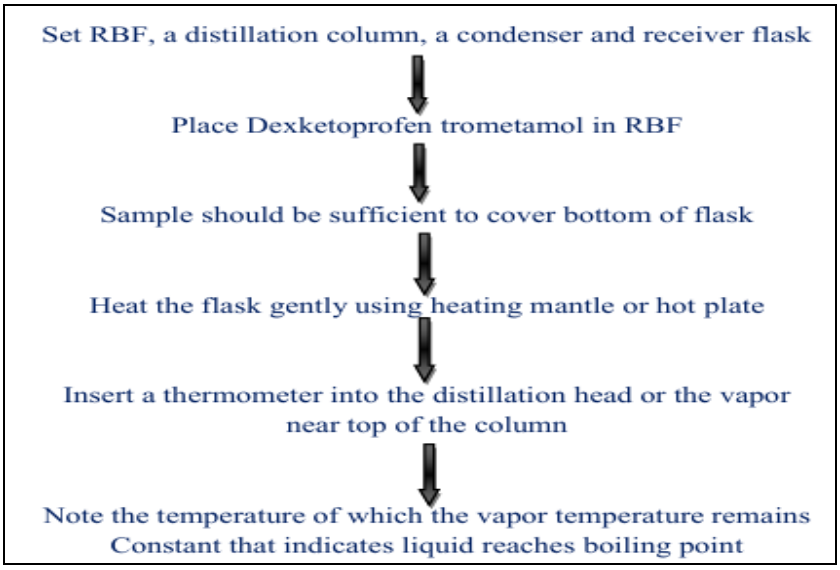

FIG. 5: REPRESENTING BOILING POINT DETERMINATION TECHNIQUE

Solubility Analysis Solubility: Solubility is the ability of a substance (solute) to dissolve in a solvent to form a homogeneous solution. The solubility of Dexketoprofen trometamol was determined by shake flask method.

A pinch of powder was dissolved in 10ml each of different solvents like Methanol, Ethanol, Distil water, Chloroform, Acetone, Benzene, Toluene, Petroleum ether, n-Octanol, Diethyl ether, 0.1N HCl *etc*. by shaking the flask for about 15 minute and place the flask in rest condition for 5 minutes and watched visually by naked eye to detect either the powder is dissolved or not [7, 8].

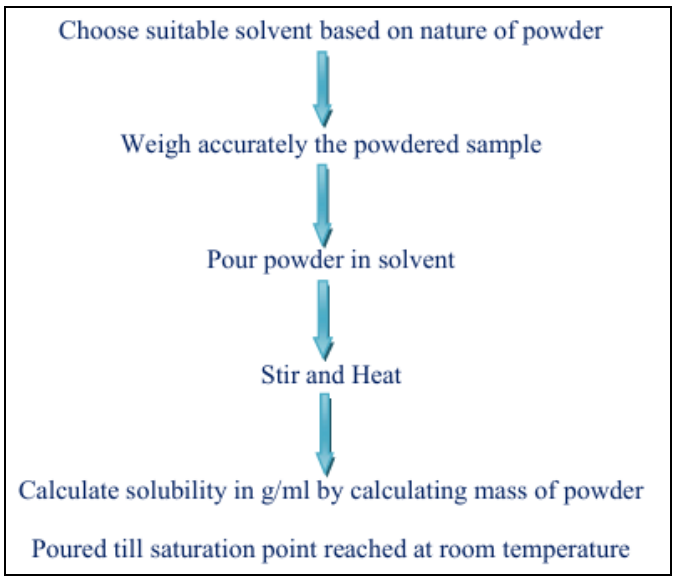

FIG. 6: REPRESENTING QUANTITATIVE SOLUBILITY DETERMINATION PROCEDURE

FIG. 7: SOLUBILITY DETERMINATION OF DEXKETOPROFEN TROMETAMOL IN VARIUOS SOLVENTS

Partition Coefficient: The partition coefficient is a measure of the relative solubility of a compound in two immiscible solvents, typically an organic solvent (octanol) and water. It describes that how a compound distributes itself between the two phases at equilibrium [9, 10].

- Take 25 ml of Distil water and 25ml of n-Octanol in a separate beaker.
- Take 100mg of Dexketoprofen trometamol.
- Dissolve both the solvent and Dexketoprofen trometamol in a separating funnel.
- Shake vigorously manually by covering the opening with cap for 20 minute.
- Place the separating funnel at tripod stand for 24 hours to rest and separate both oil phase and water phase.
- After 24 hours the phase were separated in separate beakers.
- The concentration of Dexketoprofen trometamol was determined by UV spectroscopy.

Partition coefficient was determined by following equation:

Partition coefficient = Concentration of drug in organic phase / Concentration of drug in aqeuous phase

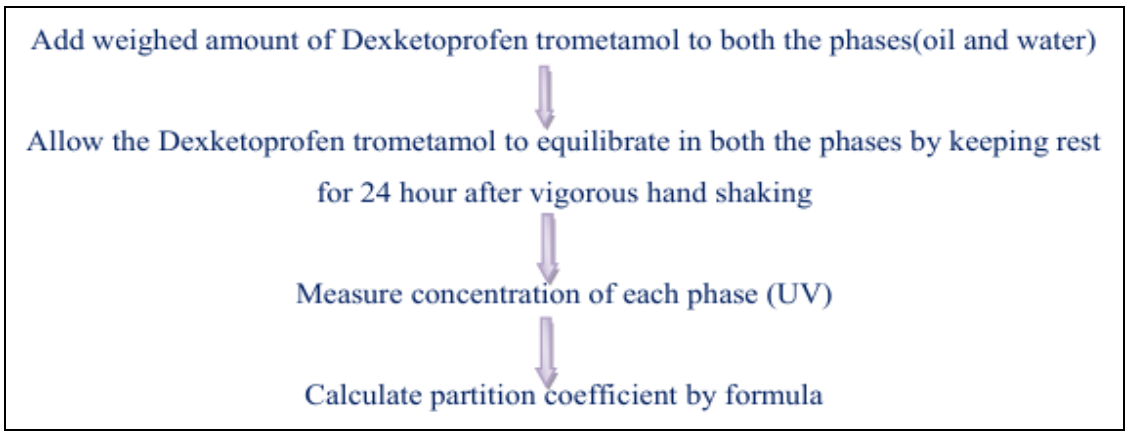

FIG. 8: PARTITION COEFFICIENT DETERMINATION PROCEDURE

FIG. 9: DETERMINATION OF PARTITION COEFFICIENT OF DEXKETOPROFEN TROMETAMOL USING SEPARATING FUNNEL

Preparation of Calibration Curve of Dexketoprofen Trometamol Using 0.1N HCl Solution [10, 11]: Preparation of standard solution of 0.1N HCl-The standard solution of 0.1N HCl was prepared by dissolving 8.4ml concentrated HCl in a volumetric flask containing 1000ml (1L) distil water.

Preparation of Appropriate Dilution: From the prepared stock solution of 0.1N HCl, 10 ml of the solution was taken in 100 ml of volumetric flask, and the volume was made up to 100 ml with freshly prepared 0.1 N HCl solution. From these 02, 04, 06, 08, and 10 ml of sub-stock solution was pipette out into 10 ml volumetric flask and the volume was made up to the mark with 0.1 N HCl. This dilution gives 0.2, 0.4, 0.6, 0.8 and 1 mg/ml concentration of Dexketoprofen Trometamol, the obtained concentration was further diluted to sub-stock using pipette out into 10ml volumetric flask to prepare 20, 40, 60, 80, 100 µg/ml solution. Further dilution using 10ml of 0.1 N HCl gives 2, 4, 6, 8, 10µg/ml.

Data Analysis: The absorbance was measured at 259 nm using UV/Visible spectrophotometer against 0.1 N HCl as blank. The study was carried out in triplicate.

Data Interpretation: The absorbance was plotted against concentration of Dexketoprofen Trometamol.

Preparation of Caliberation Curve of Dexketoprofen Trometamol Using Methanol:

Preparation of Stock Solution: A precise amount of 100 mg of Dexketoprofen Trometamol was carefully weighed and transferred into a 100 ml volumetric flask. The substance was dissolved in methanol, and the volume was adjusted to the mark with methanol to obtain a solution with a concentration of 1000 µg/ml.

Subsequently, 10 ml of this solution was accurately measured using a pipette and diluted to 100 ml with methanol. From this diluted solution, another 10 ml was pipetted out and further diluted to 100 ml in a separate volumetric flask using methanol, resulting in a stock solution with a concentration of 10µg/ml.

Preparation of Curve: From these 2, 4, 6, 8 and 10 ml of sub-stock solution was pippetted out into 10 ml volumetric flask and the volume was made up to the mark with methanol, the resulting concentration gives 02, 04, 06, 08, 10µg/ml concentration of Dexketoprofen Trometamol solution.

The absorbance was measured at 259 nm using UV/Visible spectrophotometer against methanol as blank. The study was carried out in triplicate. The absorbance was plotted against concentration of Dexketoprofen trometamol.

RESULT AND DISCUSSION:

Peak determination by UV-spectroscopy: The peak of absorbance of spectra of Dexketoprofen trometamol was obtained at 259 nm, which was plotted in graph.

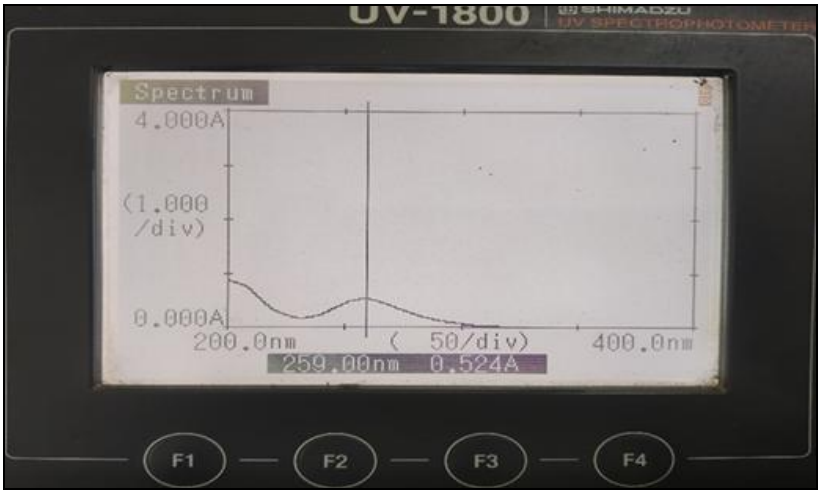

FIG. 10: GRAPH SHOWING PEAK OF ABSORBANCE OF DEXKETOPROFEN TROMETAMOL

Plotting of Graph for FTIR Spectra of Dexketoprofen Trometamol:

TABLE 1: IR FREQUENCIES OF DEXKETOPROFEN TROMETAMOL

Functional group	Characteristic wave number	Wavenum be observed
CN stretching	2500-2400	2412.86
CH bending	1600-1400	1552.59
-C-	1300-1250	1278.14
enes	950-900	909.59

The graph of spectra was plotted using ATR cell for powder sample, the graph of FTIR spectra was plotted.

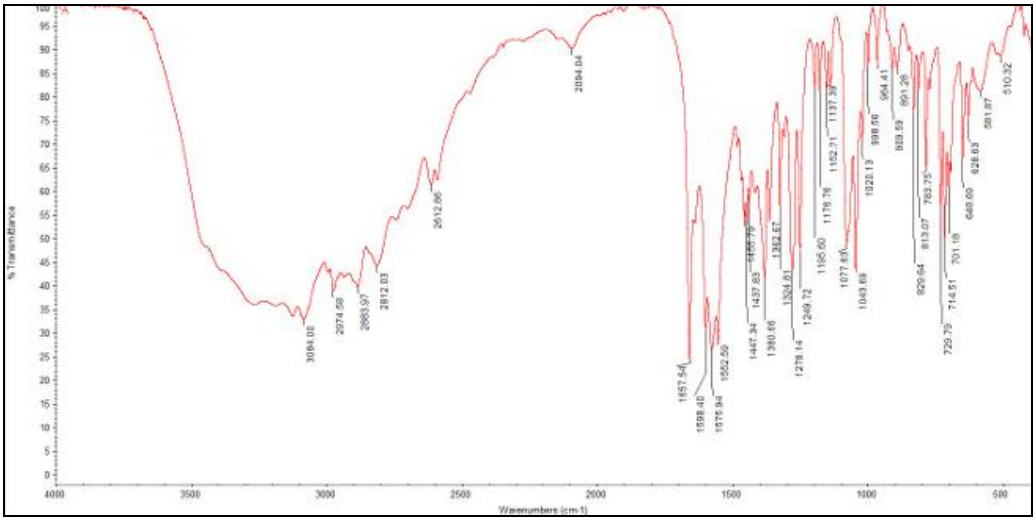

FIG. 11: FTIR SPECTRUM OF DEXKETOROFEN TROMETAMOL POWDERED DRUG

Result of Preformulation Studies of Dexketoprofen Trometamol:

Colour: The colour of dried powder of Dexketoprofen Trometamol was found to be Milky White.

Odour: The odour of the Dexketoprofen trometamol was found to be Very unpleasant, that may cause sneezing in some allergic patient.

FIG. 12: DRY POWDER OF DEXKETOPROFEN TROMETAMOL

Taste: The Bittertaste of Dexketoprofen trometamol was observed.

Crystal Property: After crystallographic analysis of powder. It was found that the powder shows crystal property. The crystallograph study showed that Dexketoprofen trometamol has crytstalline nature.

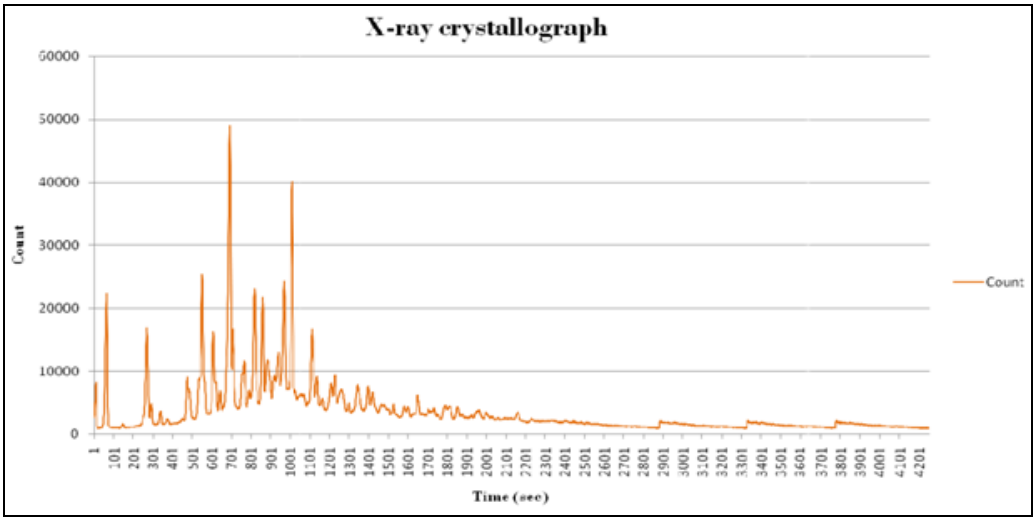

FIG. 13: GRAPH SHOWING X-RAPH SHOWING X-RAY CRYSTALLOGRAPHY OF POWDERED DRUG OF DEXKETOPROFEN TROMETAMOL

Particle size and Shape: The particle size of Dexketoprofen Trometamol was found to be lies between 1-10 µm.

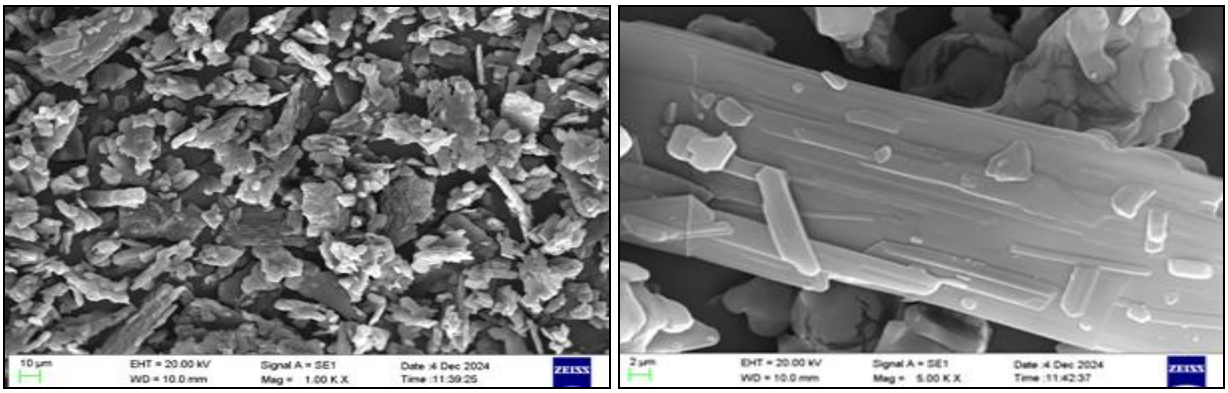

FIG. 14: HR-SEM IMAGE SHOWING PARTICLE SIZE OF DEXKETPROFEN TROMETAMOL UNDER 1000 X AND 5000 X RESOLUTION

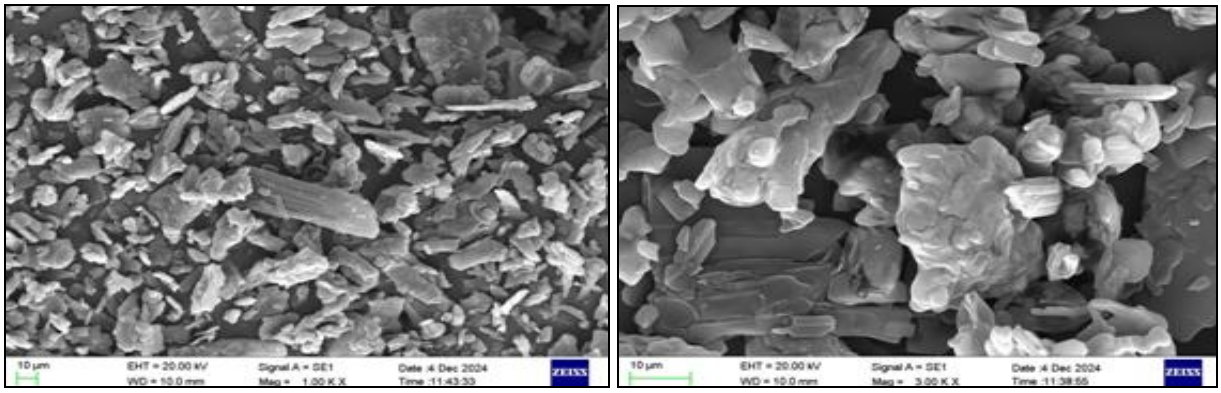

FIG. 15: HR-SEM IMAGE OF DEXKETOPROFEN TROMETAMOL UNDER 1000 X AND 3000 X RESOLUTION

Melting Point: The melting point of Dexketoprofen Trometamol was determined by melting point apparatus and was noted that its starts melting at 95°C and its melting point range is 95-98°C.

The melting point is recorded in triplet to get accuracy of the result. The powder showed sharp melting point then it was observed that Dexketoprofen trometamol was of crystalline nature.

TABLE 2: TABLE SHOWING MELTING POINT OF DEXKETOPROFEN TROMETAMOL

S. no.	Reading
1	95°C
2	98°C
3	96°C

Solubility: The solubility of drug was determined in different type of solvents-

TABLE 3: TABLE SHOWING SOLUBILITY OF DEXKETOPROFEN TROMETAMOL IN VARIOUS SOLVENTS

S. no.	Solvent	Status
1	Distilwater	Soluble
2	Ethanol	Soluble
3	0.1NHCl	Soluble
4	Acetone	Soluble
5	Diethylether	Insoluble (particles sediment)
6	Benzene	Soluble
7	Methanol	Soluble
8	Choloroform	Soluble (milkywhite solution)
9	Toluene	Soluble
10	n-Octanol	Soluble
11	Diethylether	Insoluble

Calibration curve of different concentration of Dexketoprofen trometamol in 0.1 NHCl: The calibration curve of dexketoprofen trometamol µg/ml at λmax 259nm.

TABLE 4: CHART SHOWING CONCENTRATION VS ABSORBANCE DATA FOR SOLUTIONS OF DIFFERENT CONCENTRATION OF DEXKETO-PROFEN TROMETAMOL IN 0.1N HCL AT SPECIFIC WAVELENGTH

S. no.	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.218
3	4	0.422
4	6	0.628
5	8	0.842
6	10	1.080

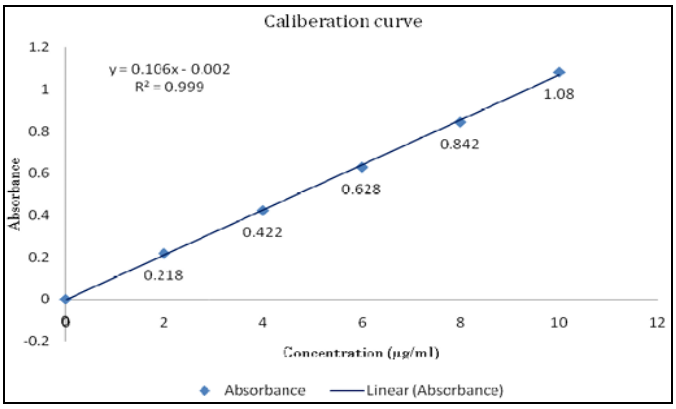

FIG. 16: CALIBRATION CURVE OF DEXKETOPROFEN TROMETAMOL USING 0.1N HCL

Preparation of Calibration Curve of Dexketoprofen Trometamol in Methanol:

TABLE 5: TABLE SHOWING ABSORBANCE AT DIFFERENT CONCENTRATION OF DEXKETO-PROFEN TROMETAMOL IN METHANOL AT SPECIFIC WAVELENGTH OF 259NM

S. no.	Concentration (µg/ml)	Absorbance
1	2	0.179
2	4	0.376
3	6	0.568
4	8	0.761
5	10	0.972
6	12	1.158

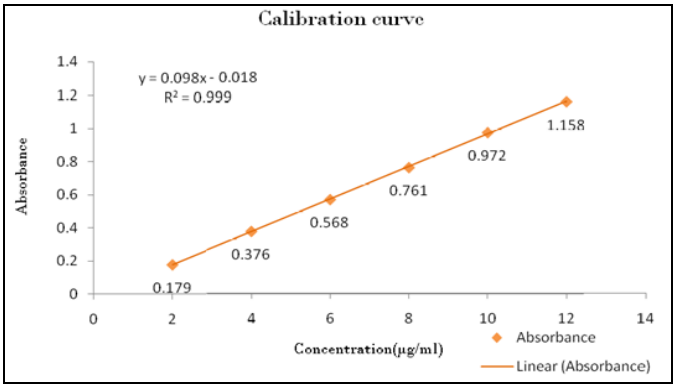

FIG. 17: GRAPH SHOWING CALIBRATION CURVE OF DEXKETOPROFEN TROMETAMOL IN METHANOL

CONCLUSION: The prefomulation and identification test was successfully done on Dexketoprofen trometamol. The physiochemical characterization revealed that drug posses' favorable high solubility in aqueous phase and greater solubility in ethanolic solvents while insolubility in ethers.

The research showed micro-sized particle size ranges (1-10µm) of drug with its hydrophilic nature and UV analysis of drug showed its λ_{max} peak of absorbance at 259nm. The X-ray diffraction study and Melting point study showed that the powder has a sharp melting point of 95-98^{o}C that stated that the drug Dexketoprofen Trometamol has crystalline property. The partition coefficient of Dexketoprofen trometamol was found to be less than 1 that showed its highly hydrophilic nature. Due to the trometamol salt form of the drug, it has higher onset of action. The Drug Dexketoprofen trometamol has a shorter half-life of about 100 minutes than it is used in frequent dosing, so it may be main field of research to use in controlled drug release and extended drug release.

Partition Coefficient: The partition coefficient of Dexketoprofen trometamol was found to be 0.82. That shows that Dexketoprofen trometamol was of hydrophilic nature. That stated that dexketoprofen trometamol was freely soluble in water.

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CONFLICT OF INTEREST: Nil

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