Executive Summary

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UGC Reference No.: F-47-1084/14/General/67/WRO/XII Plan
Date- 16.03.2017

Period of project : 2 years

Title of research project: "Study of molecular interaction of various water soluble drugs at different temperature and different concentration."

1. Introduction:

Ultrasonic studies provide wealth information about the state of the liquid. Ultrasonic measurement has been adequately employed to understand the nature of the molecular interactions in liquid system. Ultrasonic and other related thermo acoustical parameters provide useful information regarding the structure of molecules, molecular order, molecular packing, inter and intra-molecular interaction etc [1, 2]. The study and understanding of thermodynamic and transport properties of liquid mixtures are more essential for their application in various fields.

Study of intermolecular interaction in liquid system have been made by various methods like Ultraviolet, Dielectric constant, Infrared, Raman Effect, Nuclear Magnetic Resonance and Ultrasonic method. Now a day ultrasonic method has become a powerful tool in providing information regarding the physic-chemical properties of liquid system [3, 6].

Ultrasonic investigations of liquid mixtures consisting of polar and non-polar components are of equally important for understanding intermolecular interactions between molecules [7, 8]. Ultrasound waves are known for their wide range of applications in various fields like industry, medicine, material testing, depth gauges (SONAR) and cleaning [9, 10].

Physicological properties of drugs are of great interest to understand ‘drug action’ at the molecular level. It is necessary to know what a drug does to the body and what the body does to the drug that is ‘pharmadynamics’ and ‘pharmakinetics’. For drug action, it is necessary to consider the bonds formed by drug molecules which are generally influenced by thermal agitation and chemical environment. Therefore now a days, many researchers have concentrated on ultrasonic investigation of various drugs such as cefotaxime sodium, combiflame [11], colimax [12] etc to understand the molecular interaction. At lower concentration solute-solute interactions predominate which weakened at higher concentration thus causing the solute- solvent interaction to dominate was estimated in case of cetrizine, loratidine and chlorpheniramine by researchers [13].

N Jayamadhuril et al (June 2012) have studied three hydrate drugs – levofloxacin hemihydrate, tacrolimus monohydrate and lisinoprildihydrate in their aqueous solutions at 30 and 40^0C by measuring ultrasonic velocity, density and viscosity. As a function of temperature.

A. N. Sonar et al has been studied , ultrasonic measurements of the drug Parvon-spas as a solute has been reported which is a kind of narcotic-analgesic drug that selectively relieves pain by acting on the central nervous system (CNS) or on the peripheral pain mechanics, without significantly altering consciousness.

2. Need of research:

From the ultrasonic velocity (U), density (ρ), viscosity (η) and acoustic and thermodynamic parameter measurements of water soluble drugs at different temperature and different concentration gives idea of activeness of drugs.

Over the last ten years the number of poorly soluble drugs has steadily increased. It is estimated that 40% of the drugs produced by the pharmaceutical companies or industries have solubility problems . By studying the literature, it states that 60% of all the drugs synthesized are now a day poorly soluble.Poor solubility in water correlates with poor bioavailability. If drug solubility is not improved, then it will not be able to be absorbed from the gastrointestinal tract into the bloodstream and reach the site of action .Drug solubility in the aqueous environment of the gastrointestinal (GI) tract is one of the primary factors influencing the rate and extent of drug absorption and therefore determining the overall bioavailability, but also impacts other pharmaceutical properties such as speed of onset of action and fed/fasted variation. It is very much difficult to bring a new chemical entity (NCE) in the market. It takes to much cost *i.e.* $897 million, on average or nearly doubles to $1.7 billion when you factor in the costs of failed prospective drugs and nearly about 10 to 20 years. To solve the problems of absorption of poorly soluble drugs, various recent novel techniques such as particle size reduction via sonocrystallisation, super critical fluid (SCF), micronisation via nanoparticle nanoemulsion, nanosuspension, spray freezing into liquid, commercialized nanotechnologies biorise technology, diffucap's technology and Do-coops technology have been reviewed in this article. These novel technologies can be utilized for oral delivery of hydrophobic drugs.

In recent years, immense research efforts have been devoted to activeness of drug. Now a day, local delivery of drug is attracted to many researches because of its applications. Local delivery is considered to have an excellent potential and is an alternative to traditional therapy in many diseases. Since low dosage is required with lesser side effects So present work is focused to develop a sustained release dosage form of drugs for diseases.

3.OBJECTIVES OF THE PROJECT: -

Measurement of ultrasonic velocity (U), density (ρ), viscosity (η), study of acoustical parameters, study of effect of pH these are the objectives of project. Achievement of these objectives in described in detail

01) To measure velocity (U):

Ultrasonic interferometer method is used to measure ultrasonic velocity (U) of given liquid or liquid mixtures. This is a simple and direct device to determine ultrasonic velocity with high degree of accuracy. The ultrasonic velocity is calculated by the following relation.

$$U = f \times \lambda \qquad (1)$$

where $\lambda = 2d/N$ = wavelength of the ultrasonic waves in the liquid mixture and f is the frequency of the generator (2 MHz).

02) To measure density (ρ):

The density (ρ) of the liquid mixture was determined by a specific gravity bottle of 25 ml capacity. The specific gravity bottle with the liquid mixture was immersed in a temperature controlled water bath. The density was determined using the relation.

$$\rho_2 = \frac{w_2}{w_1}\rho_1 \qquad (2)$$

where w_1, w_2, ρ_1, and ρ_2 are the mass of distilled water, mass of liquid mixtures, density of distilled water, and density of liquid mixture, respectively.

03) To measure viscosity (η):

Ostwald viscometer method is used in determining the viscosity (η) in given liquid or liquid mixtures. This method is a simple and direct method to determine the viscosity in liquids in high degree of accuracy.

$$\therefore \ \eta_2 = \frac{\rho_2 t_2}{\rho_1 t_1}\eta_1 \quad (3)$$

04) To study acoustical parameters:

(i) The adiabatic compressibility (β) has been calculated from the ultrasonic velocity (U) and density (ρ) of the medium using the equation as:

$$\beta = \frac{1}{U^2} \qquad (4)$$

(ii) To measure free length (L_f) this is the distance between the surfaces of the neighboring molecules. This suggests that there is weak molecular interaction between drug and water molecules. Intermolecular free length can be calculated by following equation

$$L_f = K_T \sqrt{\beta} \qquad (5)$$

(iii) To study acoustical parameters such as acoustic impedance (Z) which is important parameter in ultrasonic investigation because it is directly proportional to molecular interaction which is present in water soluble drugs. Specific acoustic impedance (Z) supports the possibility of strong interaction between unlike molecules.

$$Z = \rho U \qquad (6)$$

05) Study of effect of pH:

Study of effect of pH on molecular interaction of water soluble drugs because water soluble drugs are very sensitive to changes in pH.

06) Study of the effect of moderate temperature and various concentrations of water soluble drugs which give information of molecular interaction between water soluble drugs. The study will help us to know the molecular interactions so as to decide effectiveness of drug.

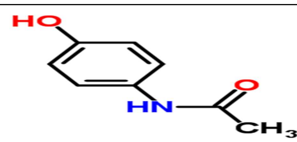
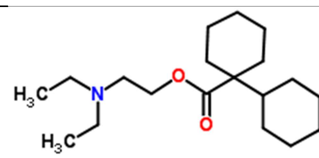
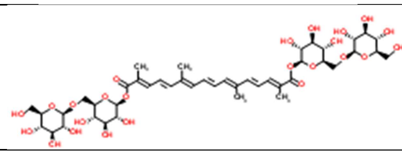
Measurement of ultrasonic velocity (U), density (ρ), viscosity (η), study of acoustical parameters, study of effect of pH and study of effect of moderate temperature and various concentration these are the objectives of project which are achieved using ultrasonic tools such as ultrasonic interferometer, specific gravity bottle and Ostwald viscometer. Such achieved objects focus the light on the knowledge of intermolecular interaction present in drugs.

4. Methodology:

Drugs will be dissolved in distilled water of various moderate concentrations. Effect of pH will be studied. Ultrasonic velocities (U), density (ρ), viscosity (η) were measured with the help of ultrasonic interferometer. Densities of prepared sample were carried out with the help of specific gravity bottle and digital balance. Ostwald viscometers were used to measure viscosity. Abbe refractrometer were used to measure refractive index of sample. Various acoustic and thermodynamic parameters such as adiabatic compressibility (b), intermolecular free length (L_f), specific acoustic impedance (Z), apparent molal compressibility (f_k), solvation number (Sn) and relative association (Ra) etc. were calculated by using ultrasonic velocities (U), density (ρ), viscosity (η) measured parameters.

From such calculated and measured parameters molecular interaction, effectiveness of drug, drug properties for pharmaceutical science and drug release pattern will be obtained.

MATERIALS USED IN THE PRESENT STUDY

Sr. No.	Drug Name	Structure	Molecular Formula	Molecular Weight
01.	Paracetamol		$C_8H_9NO_2$	151.165 g/mol
02.	Colicure		$C_{19}H_{35}NO_2$	309.487
03.	Crocin		$C_{44}H_{64}O_{24}$	976.965

5. FORMULATIONS FOR RESEARCH

Ultrasonic Velocity (U)

In the present investigation a variable path ultrasonic interferometer (Mittal enterprises, New Delhi Model M-81) is used to measure the ultrasonic velocity in liquid and liquid mixtures. It is single frequency generator that is 2 MHz. Ultrasonic velocity determined by interferometer method is considered as more reliable and precise. The ultrasonic velocity is calculated by the following relation.

Ultrasonic Velocity (U) = Frequency (f) ×Wavelength (λ)

The expression used to determine the ultrasonic velocity is

$U = f\,\lambda$ (m / sec) 2.1

Where, ‘f’ is the frequency of the generator which is used to excite the crystal. In the present investigation, a constant frequency 2 MHz interferometer was employed and hence value of $'f'$ is 2×10^6 Hz.

$$U = f\,\lambda$$

$$= 2\times10^6 \times 2d$$

$$= 4d\times10^6 \text{ cm/sec}$$

$$= 4d\times10^4 \text{ m/sec}$$

Where, d is the distance of micrometer moved between two consecutive maximum.

Density

The density of a material is defined as its mass per unit volume. The symbol of density is ‘ρ’ (the Greek letter rho).

$$\rho = \frac{M}{V} \qquad 2.2$$

where M is mass of solution

V is volume of solution

For the present investigation specific gravity bottle is used for determination of density of liquid and liquid mixture at different concentration and at different temperature. The knowledge of the density of liquid mixtures is necessary for calculation of other properties like viscosity and thermo acoustical parameters.

Viscosity

In the present investigation Ostwald viscometer method is used for determination of viscosity of liquid and liquid mixture at different concentrations and at different temperatures. Viscosity is a measure of the resistance of a fluid which is being deformed by either shear stress or extensional stress. In simple words viscosity is "thickness". Thus, water is "thin" having a lower viscosity, while honey is "thick" having a higher viscosity.

$$\eta_2 = \frac{\rho_2 t_2}{\rho_1 t_1} \eta_1 \qquad 2.3$$

where t_2 = mean time flow for solution in sec

t_1 = mean time flow for water

ρ_2 = density of solution gm/cm^3

ρ_1 = density of water

η_1 = viscosity of water

As R.H.S. quantities of above equation are known, viscosity of liquid that is η_2 can be calculated. This resultant viscosity is called absolute viscosity of experimental liquid.

Refractive Index (n_D)

Refractive indices were measured using thermostatically controlled Abbe refractometer with an accuracy less than 0.0001units.Water was circulated in to the prism of the refractometer by a circulation pump connected to an external thermostated water bath. The sample mixture was directly injected in to the prism assembly of the instrument using a syringe. Finally, mixtures were prepared in all cases by an electronic balance with an accuracy of 0.1 mg. A minimum of three independent readings were taken for each composition and the average value was considered in all the calculations. Calibration was performed by measuring the refractive indices of doubly distilled water and propyl alcohol at defined temperatures. The change of refractive index over the composition range was obtained by

$$\delta n_D = n_D - (x_1 n_{D1} + x_2 n_{D2}) \qquad 3.4$$

Where n_D is the refractive index of the mixture and n_{D1} and n_{D2} are the refractive indices of the pure compounds.

Adiabatic Compressibility (β)

Adiabatic compressibility is a measure of intermolecular association or dissociation or repulsion. Singh and Kalsh [14], showed that the adiabatic compressibility should be independent of temperature and pressure for unassociated and weekly associated molecules and it is time dependent for other molecules. It also determines the orientation of the solvent molecules. The structural arrangement of the molecule affects the adiabatic compressibility. It can be calculated using the following equation [15].

$$\beta = \frac{1}{U^2\rho} \qquad (kg^{-1}ms^{2}) \qquad 2.4$$

Where, U is the ultrasonic velocity and ρ is the density of the solution.

Specific Acoustic Impedance (Z)

There is some relation between acoustics and electricity. One of the most fruitful of these has been the direct impedance analogy. Acoustic pressure P_a is the analogue of voltage, acoustic velocity U is the analogue of current and specific acoustic impedance Z is the analogue of resistance. Specific acoustic impedance (Z) is defined by Ohms analogue [15].

$$Z = \frac{\rho_a}{U} \qquad 2.5$$

Beyer and Letcher [16] considered the case of plane harmonic wave and obtained a relation for Z as

$$Z = \rho U \qquad 2.6$$

Where, ρ is the density and U is the ultrasonic velocity.

Intermolecular Free Length (L_f)

Intermolecular free length is the distance between the surfaces of the neighboring molecules. It is calculated using the formula given by Jacobson [16].

$$L_f = \frac{K}{\sqrt{U^2\rho}} = K\sqrt{\beta} \quad \text{(m)} \qquad 2.7$$

Where, K is Jacobson's constant. This constant is a temperature dependent parameter which is calculated by the formula as fallows

$K = (93.875 + 0.375T)\ 10^{-8}$

6. OUTCOME OF PROJECT

- Ultrasonic investigation of molecular interaction in water soluble paracetamol has been carried out at a wide range of temperature and pH. The experimentally obtained parameters such as ultrasonic velocity, density, viscosity, refractive index and other acoustical parameters gives valuable information regarding molecular interaction present in solution. Ultrasonic velocity and refractive index increases with pH.
- The density and viscosity decreases with increase in pH. Acoustic parameters such as adiabatic compressibility, intermolecular free length are found to be decreased. On the contrary specific acoustic impedance is found to be higher as pH increases.
- The present study of molecular interaction of water soluble paracetamol using ultrasonic investigation provides important information about the physiological system and used to understand the mechanism of their metabolism in the living system.
- It can be concluded from the above study that the interferometer technique requires minimum efforts. It is a direct method and has its own identity and significance in material science, which can gives an idea about effectiveness of solvent. Change in temperature affects compressibility of solution, which in turn affects molecular interaction in liquid mixtures and solutions. Structural relaxation process occurs and in such a situation molecules gets rearranged due to co-operative process.
- When drug is added in water, ions attracted certain drug molecules towards it by moving with a violent twist in the bulk of ions due to the force of electrostriction. Thus, the conclusion drawn from all the studies is that the studied drug paracetamol when added water acts as structure breaker for the system as a function of temperature. Calculated acoustic and thermodynamic parameters also support the existence of drug solvent interactions.
- The results obtained from these studies can thus be helpful for pharmacological applications of drugs as well as to understand form kinetic processes such as transport of drug across biological membranes, drug action and physicochemical properties. Complex formation produces displacement of drug molecules.
- The chemical interaction may involve the association due to solute - solvent and solute - solute interaction. In recent years, immense research efforts have been devoted to activeness of drug. Now a day, local delivery of drug is attracted to many researchers because of its applications. Local delivery is considered to have an excellent potential and is an alternative to traditional therapy in many diseases. Since low dosage is required with lesser side effects.

- In recent year ultrasonic tool is used to study physicochemical interactions in drugs. Physicochemical studies on molecular interactions of *curcumin* with mono and divalent salts at different temperature were carried out by Archana Pandey to study the molecular interaction of antioxidant with metal ions.
- In some recent publications, efforts have been made to correlate biological activity with calculated physical parameters with the help of densities and ultrasonic velocities for mixtures at different temperatures. But a molecular interaction study of the water soluble drugs with varying pH has not been investigated so far.
- Therefore the present investigation reports on the water soluble drugs with varying pH. Water soluble drugs are chosen for present investigation are crocin, paracetamol and colicure.

7. APPLICATIONS OF STUDY

The interaction of ions and antioxidants provide important information about mechanism of their metabolism in living system and play a key role in the wide range of biochemical process such as immunology, biosynthesis, pharmacology and medicine. The interaction of ions and antioxidant provides important information about physiological system and used to understand the mechanism of their metabolism in living system.

8. **CONTRIBUTION TO THE SOCIETY**

- Ultrasonic investigation of molecular interaction in water soluble paracetamol, crocin and colicure solution have been carried out at a wide range of concentration, temperature and pH. The experimentally obtained parameters such as ultrasonic velocity, density, viscosity, refractive index and other acoustical parameters gives valuable information regarding molecular interaction present in solution. Ultrasonic velocity and refractive index increases with pH. The density and viscosity decreases with increase in pH. Acoustic parameters such as adiabatic compressibility, intermolecular free length are found to be decreased. On the contrary specific acoustic impedance is found to be higher as pH increases.
- The present study of molecular interaction of water soluble paracetamol, crocin and colicure using ultrasonic investigation provides important information about the physiological system and used to understand the mechanism of their metabolism in the living system. It can be concluded from the above study that the interferometer technique requires minimum efforts. It is a direct method and has its own identity and significance in material science, which can gives an idea about effectiveness of solvent. Change in temperature affects compressibility of solution, which in turn affects molecular interaction in liquid mixtures and solutions. Structural relaxation process occurs and in such a situation molecules gets rearranged due to co-operative process. When drug is added in water, ions attracted certain drug molecules towards it by moving with a violent twist in the bulk of ions due to the force of electrostriction. Thus, the conclusion drawn from all the studies is that the studied drug *paracetamol, crocin and colicure* when added water act as structure breaker for the system as a function of temperature. Calculated acoustic and thermodynamic parameters also support the existence of drug solvent interactions.
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- The results obtained from these studies can thus be helpful for pharmacological applications of drugs as well as to understand pharmacokinetics processes such as transport of drug across biological membranes, drug action, and physicochemical properties. Calculated acoustic and thermodynamic parameters also support the existence of drug–solvent interactions. The

results obtained from these studies are helpful for pharmacological applications of drugs, transport of drugs across biological membranes.

- The knowledge of pharmacological applications of drugs as well as pharmacokinetics processes such as transport of drug across biological membranes, drug action, and physicochemical properties is need of pharma society. Ultrasonic investigation of molecular interaction in water soluble paracetamol, crocin and colicure solution have been carried out at a wide range of concentration, temperature and pH may provide useful information to pharma society.

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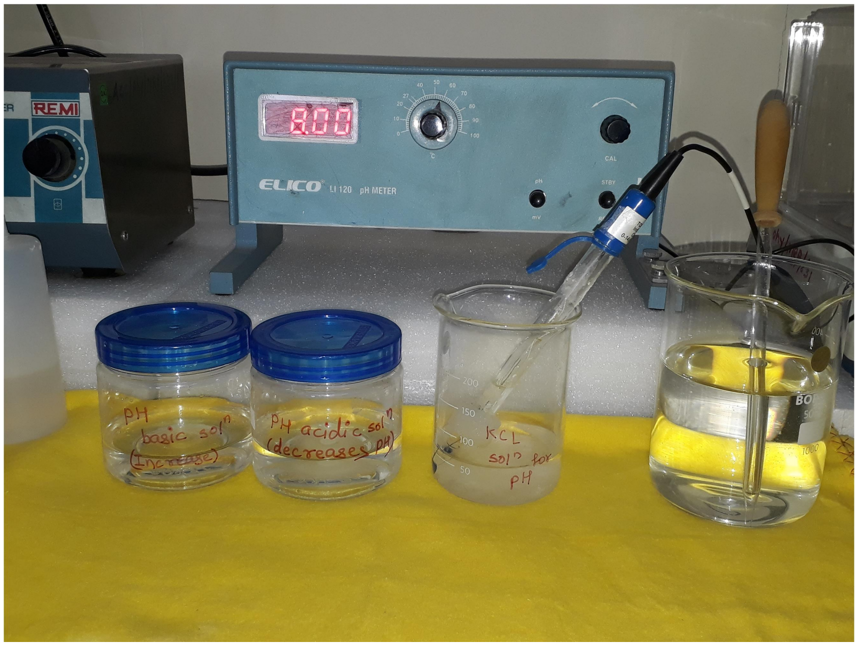
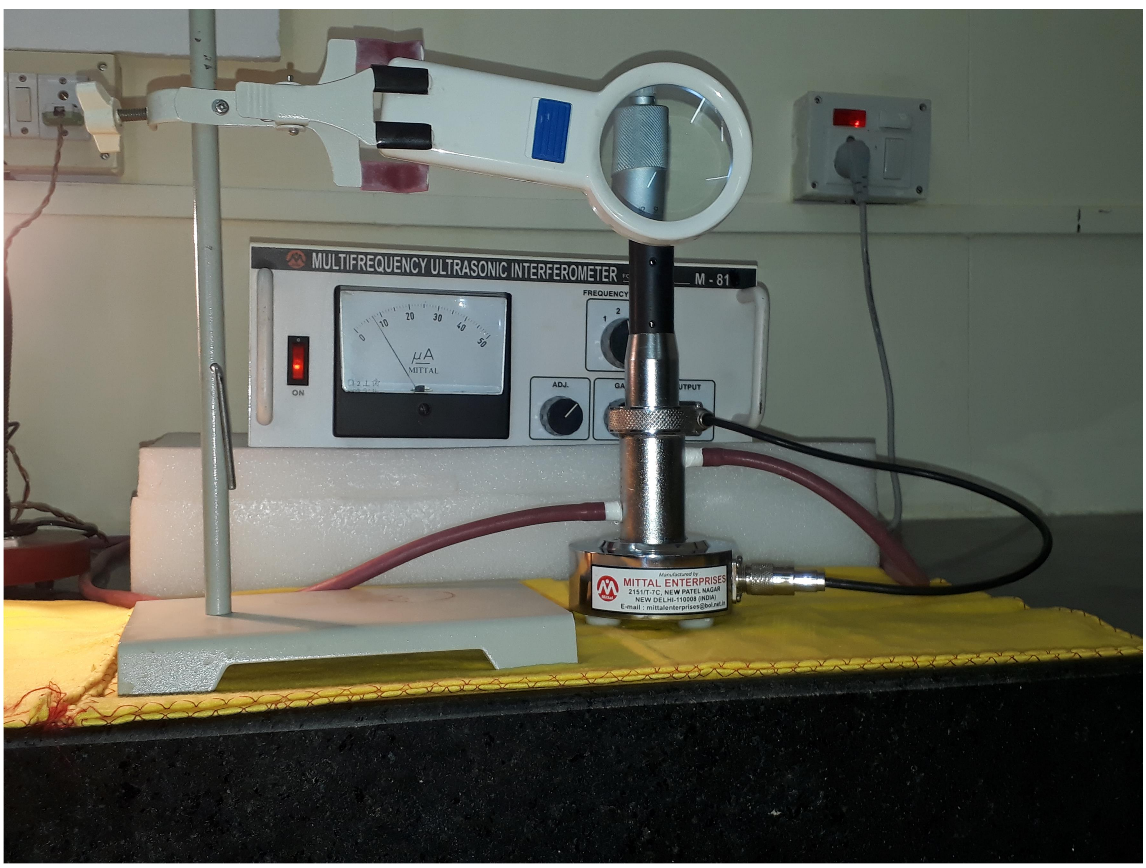
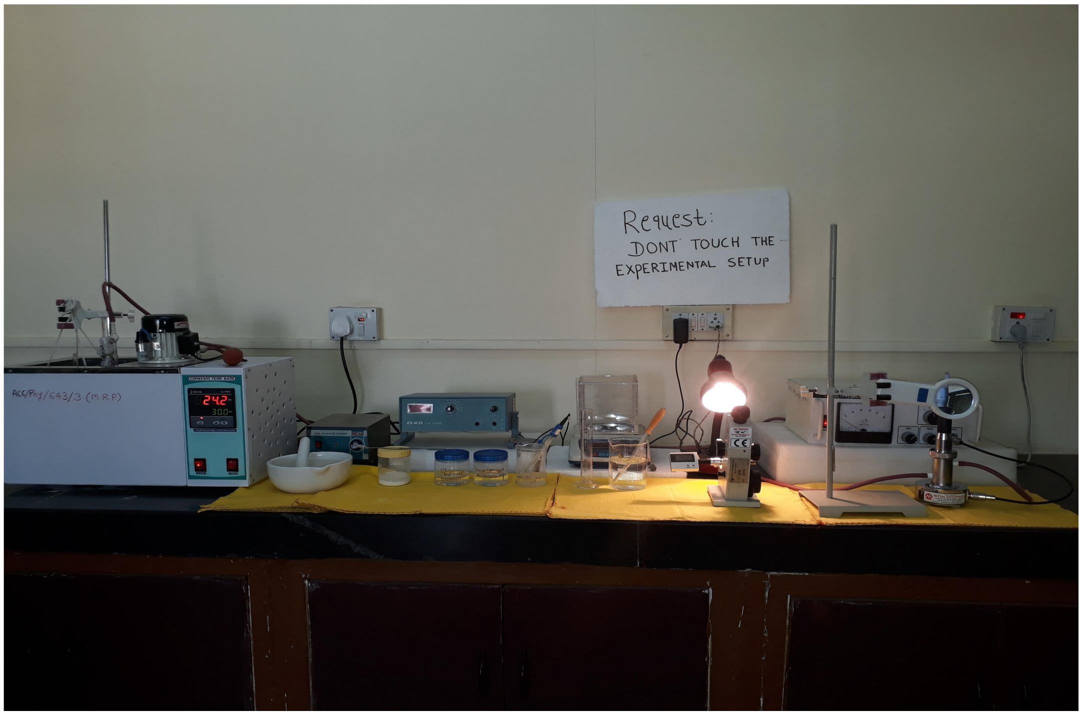
Photographs of experimental work of project



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