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# STUDY OF SOLUBILITY OF DRUG BY SOLID DISPERSION TECHNIQUE AND FORMULATION INTO SOLID ORAL DOSAGE FORM.

[1]Rutuja Yeole , [2]Ruchita Shinde, [3]Rhutik Mandwade , [4]Hemant Kale .

SVS Institute of Pharmacy, Mungase, Malegaon.

## ABSTRACT

Ibuprofen is considered as the most important Non-steroidal anti-inflammatory drug and widely used for treatment of major and minor pain, arthritis etc. The present work has been done to formulate tablet of Ibuprofen, the drug having low aqueous solubility, by solid dispersion technique for enhancement of solubility.

According to the biopharmaceutical classification system, BCS class II drugs are classified as drugs having low solubility and high permeability, therefore the barrier to their absorption is dissolution and solubility of the drug. Ibuprofen is BCS class II drug. According to our studies we found that, solid dispersion is the promising tool which can help to increase the solubility of the drug.

As these drugs have low solubility and high permeability, increase in the solubility of such drugs can probably improve the onset of action of the drug. In our project we have selected a drug belonging from BCS class 2 that is Ibuprofen and tried to enhance the solubility by solid dispersion technique. As a result, we found that solubility of the drug before processing **24.6192 mcg/ml** was found to be and the solubility of the same drug after processing **32.8394 mcg/ml** was found to be of SD ratio 1:3 which shows that the solubility of the drug is enhanced by folds with the help of solid dispersion technique.

In the present work, Solubility of pure drug was determined. Different solid dispersion ratios using mannitol as a carrier were prepared and their solubility was determined and compared with standard. The SD ratio having optimized solubility was selected for tablet formulation. The tablets were formulated by wet granulation method using Croscarmellose sodium as superdisintegrant.

The tablets were evaluated for physical parameters, disintegration time, hardness, thickness, weight

variation, friability, and in vitro drug release. All the physical parameters were in acceptable limit of pharmacopeial specification.

**Keywords:** Ibuprofen, BCS Classification, solubility, Solid dispersion, wet granulation UV spectroscopy etc.

## INTRODUCTION

Oral route is most convenient, popular and easy to administration. Because of the greater stability, smaller bulk, accurate dosage and easy production. According to BCS classification drugs are divided into four classes depend on in-vitro solubility and in-vivo permeability. As, we are more concerned about the drug that comes under BCS Class II of biopharmaceutical classification; drugs belonging to this class have low solubility and high permeability so the dissolution rate becomes the governing parameter for bioavailability.

**Table no.1: BCS Classification**

| Sr. No. | Class | Solubility | Permeability | Example |
|---|---|---|---|---|
| 1 | Class I | High | High | Metoprolol, Paracetamol |
| 2 | Class II | Low | High | Ibuprofen, Aceclofenac |
| 3 | Class III | High | Low | Cimetidine |
| 4 | Class IV | Low | Low | Bifonazole |

### SOLUBILITY:

Solubility is defined as maximum amount of solute dissolve in given amount of solvent.

### PROCESS OF SOLUBILISATION:

The processes of solubilisation involve the breaking of intermolecular or inter ionic bonds in the solute. Interaction between the solvent and solute molecule and ion. The molecule solid break away from the bulk.

### IMPORTANCE OF SOLUBILITY:

Therapeutic effect of a drug is depend on the bioavailability and solubility of drug molecules. Solubility is most important parameter to obtain desired concentration of drug in systemic circulation for showing pharmacological response. Solubility plays major role in oral dosage forms and as well as in parental formulation. Poorly water soluble drug required high doses to reach plasma concentration after orally administration. Water is used as universal vehicle and solvent of choice for liquid dosage forms. More than 40% drugs are practically insoluble in water such as ibuprofen.

Solubility also plays a major role for other dosage forms like parenteral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bio-availability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist.

**FACTORS AFFECTING SOLUBILITY:**

- **Temperature**: the solubility of a given solute in a given solvent depends on temperature. Depending on nature of solute the solubility will decrease or increase with the temperature.
- **Pressure**: The pressure dependence of solubility is typically weak. The pressure dependence of solubility does occasionally have practical significance.
- **Molecular Size**: Molecular size will affect the solubility. The large molecules have less solubility.
- **Particle size**: The size of the solid particle influences the solubility, because as particle become smaller.

**TECHNIQUES FOR SOLUBILITY ENHANCEMENT:**

Improvement of solubility techniques can be categorized by physical modification, chemical modification and other techniques.

**I. Physical modification:**

1. Particle size reduction

- Nano suspension
- Micronization

2. Modification of the crystal habit

- Polymorphs form
- Amorphous form
- Co-crystallization

3. Drug dispersion in carriers

- Eutectic mixture
- Solid dispersion
- Solid solution
- Cryogenic technique

**II. Chemical modification:**

1. Change of pH
2. Use of buffer
3. Derivatization
4. Complexation
5. Salt formation

**III. Miscellaneous methods**

1. Superficial fluid process
2. Surfactant
3. Solubilizer
4. Co solvency

- **Particle size reduction:**

The solubility of drug is intrinsically depending on particle size, as the particle size become smaller, the surface area to volume ratio increases.

- **Micronization:**

Micronization increases the dissolution of drug does no increases equilibrium solubility. Mocronization of drugs is done by milling technique using jet mill, rotor stator colloid mill.

- **Nano suspension:**

Nano suspension technique is used for poorly soluble drugs that are insoluble in both water and oil. Pharmaceutical nano suspension is a biphasic system it consist nanos sized drug particle stabilized by surfactant.

- **Supercritical fluid process:**

Supercritical fluids are fluids where temperature and pressure are greater than its critical temperature and critical pressure.

- **Cryogenic technique:**

Cryogenic technique is used to enhance dissolution rate of drugs at very low temperature. Cryogenic invention can defined as the type of injection device such as capillary, pneumatic etc location of nozzle and the composition of cryogenic fluid.

- **Micelle solubilisation:**

Concentration of surfactant exceeds their critical micelle concentration (CMC range of 0.05 -0.10 % for most surfactant). Micelle formation occurs when micelles are entered in drugs.

- **Hot melt method (fusion method):**

It is a direct melting method. The melting or fusion method discovered by sekiguchi and obi to prepare fast release solid dispersion dosage form. In this method, physical mixture of drugs and water soluble carrier are heated directly. Hot plate important and essential technique method is for formation of solid dispersion.

- **Solid dispersion:**

Solid dispersion method is used to investigate medication solubility and formulate solid oral dosage form. Solid dispersion is described as the solid dispersion of one or more active substances (hydrophobic) in a hydrophilic carrier (hydrophilic) generated by melting (fusion) and solvent evaporation. A hydrophilic matrix and a hydrophobic medication are among the components of the finished product. Solid dispersion method is used to investigate medication solubility and solid oral dosage form.

**Advantages of solid dispersion:**

1) Solid dispersion produces particles with smaller particle size, with increasing surface area and dissolving rate. Bioavailability is improved.
2) The solid dispersion carrier has a significant impact on the wettability of the dispersion particle. Improved wettability leads to higher solubility which improves bioavailability.
3) Drugs are shown as supersaturated solution in solid dispersion.

**Disadvantages of solid dispersion:**

1) The main disadvantage of solid dispersion is their instability.
2) The moisture and temperature have more of decline effect on solid dispersion than on physical mixture.
3) Solid dispersion is difficult in handling.

**Selection of carrier:**

A carrier should posses the following properties to be suitable for increasing the dissolution rate of drugs.

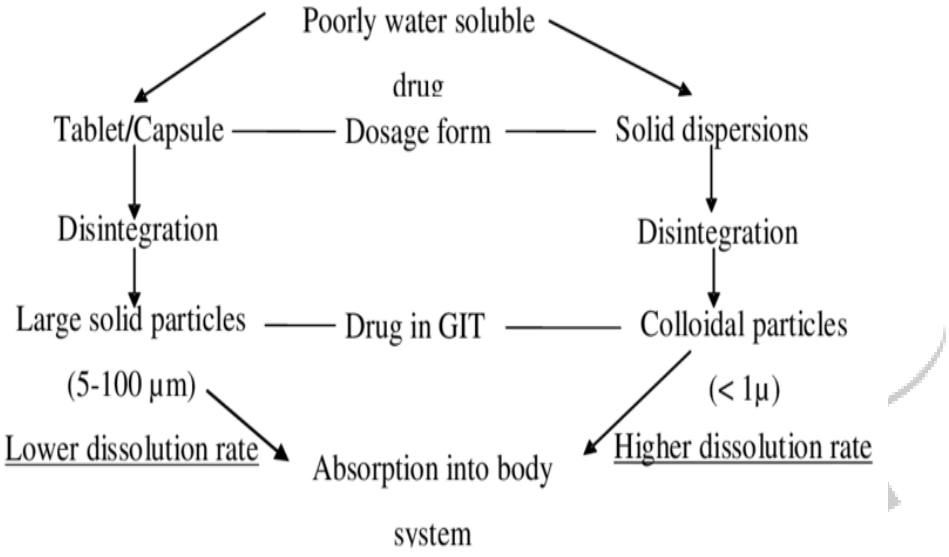
- Carrier should be freely water soluble with high rate of dissolution.
- Non-toxic in nature.
- Pharmacologically inert.

- Heat stability with low melting point.
- Enhance aqueous solubility of drug.

**Commonly used carriers:**

- Sugar, polyols and their polymers.
- Organic acid and their derivatives
- Cellulose derivatives
- Polyacrylate and polymethacrylate
- Urea
- Polyethylene glycol (PEG)

**Mechanism of Bioavailability Enhancement:**




**Applications of solid dispersion:**

1. It increases the solubility of poorly soluble drugs and thus increases the dissolution rate, which enhances the absorption and bioavailability of the drug.
2. For stabilization of the unstable drugs against various decomposition procedures like hydrolysis, oxidation etc.
3. For reducing the side effect of certain drugs.
4. Masking of unpleasant taste and smell of the drugs.
5. To avoid undesirable incompatibilities.
6. To obtain a homogeneous distribution of small amount of drugs in solid.

**Common methods used for preparation of solid dispersion:**

- Fusion method
- Solvent method
- Melting solvent method
- Supercritical fluid method
- Electro spinning method
- Solvent evaporation method
- Melt extrusion method
- Melt agglomeration method
- Lyophilisation method

**1. Fusion method:**

The first solid dispersion created for pharmaceutical application were prepared by the fusion method. When starting material are crystalline the fusion method referred to as the melt solvent.

**Advantages:**

- The main advantage of direct melting method is its simplicity and economy.
- In addition, melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

**Disadvantages:**

- Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible when they mix well at the heating temperature.
- When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion.
- In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions.

**2. Solvent method:**

The first step in the solvent methods is the preparation of a solution containing both matrix and material and drug. The second step involved removal of solvent in the resulting in the formation of solid dispersion. Mixing at the molecular level is preferred. To reduce the drug particle size in the solid dispersion.

**Advantages:**

- The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

**Disadvantages:**

- The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of the drug are some of the disadvantages of this method.

**3. Melting solvent method:**

In this method drug is first dissolved in a suitable liquid solvent solution is then in cooperated directly into melt of polyethylene glycol obtainable below 700C without removing the liquid solvent. It has been shown that 5-10 %( w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

**Advantages:**

- In this method that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

**4. Supercritical fluid methods:**

Supercritical fluid methods are mostly applied with carbon dioxide, which is used as either a solvent for drug and matrix or as an ant solvent. When supercritical C02 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed.

The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as "solvent free". Thetechnique is known as Rapid Expansion of Supercritical Solution.

**Advantages:**

- The supercritical anti solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.
- The general term for this process is precipitation with compressed anti oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO2 is used or Aerosol Solvent Extraction System, and solution Enhanced Dispersion by supercritical fluids.

**5. Electro spinning method:**

Electros pining is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimetre scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attaching to reservoir containing a polymer solution or melt and a conductive collection screen.

**6. Solvent evaporation method:**

Solvent evaporation method consists of the solubilisation of the drug and carrier in a volatile solvent that is latter evaporated19-21. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature22. A basic process of preparing solid dispersions of this type consists of dissolving the drug and thy polymeric carrier in a common solvent, such as ethanol, chloroform mixture of ethanol and dichloromethane.

**7. Melt agglomeration method:**

This technique has been used to prepare where in the binder acts as a carrier. In addition, are prepared either by Heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. A rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a high binder content can be incorporated in the agglomerates.

**8. Lyophillization techniques:**

Lyophillization has been thought of a molecular mixing technique. The drug and carrier are codissolved in a common solvent, Frozen and sublimed to obtain a lyophilized molecular dispersion.

**9. Melt extrusion method:**

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry.

**10. Kneading technique:**

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

**11. Co-precipitation method:**

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

**12. Co-grinding method:**

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixtures pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

- **Applications of solid dispersion**

1. It increases the solubility of poorly soluble drugs and thus increases the dissolution rate, which enhances the absorption and bioavailabilty of the drug.
2. For stabilization of the unstable drugs against various decomposition procedures like hydrolysis, oxidation etc
3. For reducing the side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. To avoid undesirable incompatibilities.
6. To obtain a homogeneous distribution of a small amount of drug in solid state.
7. Dispensing of liquid (up to 10%) or gaseous compounds in a solid dosage.

8. Formulation of sustained release dosage form.

## PLAN OF WORK

- Literature Survey
- Selection of Drug
- Collection of drug, polymers & other excipients.
- Construction of standard calibration curve for purity determination.
- Construction of standard calibration curve for solubility determination.
- Preparation of solid dispersion using 4 different ratios.
- Solubility determination of SD ratios and comparison with standard.
- Formulation using solid dispersion.
- Formulation developments

1. Preformulation Study:

   Determination of λmax.

   Determination of purity of standard drug.
2. Evaluation of granules:

   Angle of repose

   Bulk density

   Tapped density

   Carr's compressibility index

   Hausner's ratio
3. Formulation of tablet by wet granulation method
4. Evaluation of tablet

   Disintegration

   Hardness

   Weight variation

   Friability

   Dissolution test

## LITERATURE SURVEY

1. **Shweta U. Kannao, B. V. Bakade** Studied the solid dispersion technique for solubility enhancement of weakly water soluble drug. Oral drug delivery is the most common and preferred method due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble in water. Therapeutic effectiveness of drug depends upon bioavailability & ultimately on the solubility of drug molecules. According to their study solid dispersion utilized to describe the dosage form whereby the drug is dispersed in inert matrix. It is a useful method because of of its capability to solve the solubility problem using solid dispersion.

2. **Hemanta Kumar Sharma, Prosun Kanti Ghosh** Were studied different methods used for preparation of solid dispersion and also studied different types of carriers
used for solid dispersion technique. He found that Solid dispersion systems have been extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling.

3. **Rupali S. Joshi, Nilima S. Pawar, Sameer S. Katiyar, Devendra B. Zope, Amol T. Shinde** Studied the development and validation of UV Spectrophotometric methods for simultaneous estimation of paracetamol and ibuprofen in pure and tablet dosage form. Simultaneous equation and determination of 'Q' value using this methods simultaneous estimation of paracetamol and ibuprofen in pure and tablet dosage form had been developed and are validated according to ICH guidelines and adopted for routine analysis of both drugs.

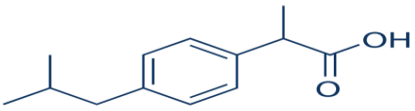
4. **Beenakumari, Harish Kumar bishnoi** Studied the solid dispersion technique: Its type and mechanism of enhancement of solubility by solid dispersion. In the process of solid dispersion there is dispersion of one or more active pharmaceutical ingredient in a carrier at solid state so, solid dispersion method as many benefits over conventional dosage form. For preparation of solid dispersions various factors are considered such as selection of carrier & methods of physicochemical characterisation.
5. **Bhumika Kumar** Solid dispersion is an effective way of improving the dissolution rate of poorly water soluble drugs and hence its bioavailability. The water soluble carriers used in preparation of solid dispersion enhance the dissolution rate of the poorly water soluble drugs. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by melting (fusion) method, solvent or melting solvent method. When the solid dispersion comes in a contact with the aqueous medium, the inert carrier

dissolves and the drug is released, the increased surface area produces a higher dissolution rates thus increasing the bioavailability of the poorly soluble drugs.

## THEROTICAL BACKGROUND

### DRUG PROFILE:

**Structure:**




**IUPAC Name:** 2-[4-(2-methylpropyl) phenyl] propanoic acid.

**Formula:** $C_{13}H_{18}O_2$

**Molecular mass:** 206.28 gm/mol

**Bioavailability:** 80-100 %

**Protein binding:** 90-99 %

**Half life:** 2-4 hrs

Ibuprofen is the propionic acid dewrivative and non steroidal anti inflammatory drug (NSAID) with anti inflammatory, analgesic and antipyretic effect. Ibuprofen inhibits the activity of cyclooxygenase I and II, resulting in a decreased formation of precursor of prostaglandins and thromboxanes. Ibuprofen also cause decrease in the formation thromboxane A2 synthesis by thromboxane synthase there by inhibit platelet aggregation. It is used to treat mild to moderate pain.

### EXCIPIENT PROFILE:

**1. Mannitol:**

**Synonym:** D-mannitol, Mannite, Manna sugar, Osmitrol etc.

**Chemical name:** D-mannitol 4 Empirical Formula.

**Molecular Formula:** $C_6H_{14}O_6$

**Category:** Sweetening agent, in tablet and capsule used as diluents.

Mannitol is type of sugar alcohol used as sweetener and medication. It is used as low calorie sweetener as it is poorly absorbed by intestine. Mannitol is used in pharmaceutical products as a sweetening agent, tablets and capsule diluents and in this research mannitol used as carrier.

**2. Croscarmellose Sodium**:

**Synonym:** Carboxymethyl cellulose, Crosslinkedcarboxymethylcellulose sodium, Solutab etc.

**Chemical Name:**

**Molecular Formula:** $C_8H_{16}NaO_8$

**Category:** super disintegrant, used in food as emulsifier.

It is synthetic ie. Inorganic compound. Croscarmellose sodium act as an enzyme to breakdown the tablet's contents to easier digestion making it faster for the effects. It act as an superdisintegrant and mainly used in pharmaceutical production ie. Tablet formation.

**3. Talc:**

**Synonym:** Talcum powder, soapstone, steatite

**Chemical name:** Hydrous magnesium silicate

**Molecular formula:** $Mg_3Si_4O_{10}(OH)_2$

**Category:** lubricant, glidant.

Talc is a clay mineral. Talc is in the powdered form, often combined with the corn starch, it is used as the baby powder. Talc has been widely used as the conventional dosing form.

**4. Magnesium stearate:**

**Synonym:** Magnesium salt, magnesium distearate, stearic acid etc.

**Chemical name:** Magnesium octadecanoate

**Molecular formula:** $Mg(C_{18}H_{35}O_2)2$

**Category:** Emulsifier, binder, thickener, anticaking agent, lubricant, antifoaming agent etc.

Magnesium stearate is a salt that forms when stearate molecules bond with a magnesium ion. It is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. it is also used in barrier creams.

# MATERIALS AND METHODS:

**Materials:**

Ibuprofen purchased from Research Lab Fine Chem Industries, Mumbai. Talc, Magnesium stearate, Starch, Mannitol and Crosscarmellose Sodium were purchased from Loba Chemie Pvt Ltd, Mumbai.

**Methods:**

**1. PREPARATION OF STANDARD CALIBRATION CURVE OF IBUPROFEN:**

**Requirements:**

- Apparatus: Beaker, 100ml volumetric flask, 10ml volumetric flask, pipettes, funnel, whatmann filter paper, glass rod etc.
- Chemicals: Standard Ibuprofen, NaOH, distilled water etc.

**Selection of wavelength:**

The dilution was obtained to the concentration 100mcg/ml for ibuprofen and the solution was scanned in UV range of 200-400nm in 10mm cell against solvent blank (NaOH). The study of spectrum revealed that ibuprofen shows well defined lambda max at 230nm. This wavelength selected for development of standard calibration curve of ibuprofen.

**Assay Procedure:**

- Preparation of standard stock solution:

1. Prepare standard stock solution of ibuprofen by dissolving 100 mg of standard ibuprofen in sodium hydroxide.
2. Transfer the solution into 100 ml of volumetric flask and make up the volume upto 100 ml.
3. Measure the absorbance at 230 nm.

- Preparation of different dilutions of stock solution:

**1.** Prepare 5 different dilution of stock solutions having concentration 1 mg/ml, 3 mg/ml, 5 mg/ml, 10 mg/ml and 15 mg/ml.
**2.** To measure the absorbance of each stock solution at 230 nm.
**3.** Finally standard calibration curve vs absorbance was constructed

**2. SOLUBILTY DETERMINATON OF IBUPROFEN:**

**Requirements:**

- Apparatus: Beaker, 100ml volumetric flask, 10ml volumetric flask, pipettes, funnel, whatmann filter paper, glass rod etc.
- Chemicals: Standard Ibuprofen, NaOH, distilled water etc.
- Instrument: UV Spectroscopy

**Selection of wavelength:**

The dilution was obtained to the concentration 100mcg/ml for ibuprofen and the solution was scanned in UV range of 200-400nm in 10mm cell against solvent blank (water). The study of spectrum revealed that ibuprofen shows well defined lambda max at 200nm. This wavelength selected for development of standard calibration curve of ibuprofen.

## 3. STANDARD CALIBRATION CURVE OF IBUPROFEN:

**Assay procedure:**

- Preparation of standard stock solutions:

1. Prepare standard stock solution of ibuprofen by dissolving 100 mg of standard ibuprofen in purified water.
2. Transfer the solution into 100 ml of volumetric flask and make up the volume upto 100 ml.
3. Measure the absorbance at 230 nm.

- Preparation of different dilution of stock solutions:

1. Prepare 5 different dilution of stock solution having concentration 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml and 30 mg/ml.
2. To measure the absorbance of each stock solution at 230 nm.
3. And to construct calibration curve vs absorbance.
4. 50 mg of standard ibuprofen dissolved in 50 ml of distilled water.
5. The resulting solution was kept in sonicator for mixing for 30 min.
6. Then the solution filtered through whatmann filter paper.
7. To measure absorbance of resulting solution at 200 nm.
8. The measured absorbance of this solution was insert on standard calibration curve of ibuprofen.

## 4. PREPARATION OF SOLID DISPERSION:

**Fusion Method:**

Solid dispersion were prepared by fusion method using mannitol as carrier. The solid dispersion were prepared at weight ratio of 1:1, 1:2, 1:3, 1:4 (drug:carrier). The required amount of carrier and standard ibuprofen was melted in beaker on water bath and mixed thoroughly. Then the molten mixture is cooled down at room temperature and stored in desicator for further use.

**Practicing the determination and comparative testing with standard of solubility of 3 different ratios of solid dispersion:**

- Solid dispersion equivalent to 50mg of standard ibuprofen was dissolved in 50ml of distilled water.
- Then resulting solution was kept in sonicator for mixing for 30minutes, and then filtered through whatmannn filter paper.
- The absorbance of resulting solution was measured at 200nm.
- The measured absorbance of this solution was interpolated on standard calibration curve of ibuprofen.

**Table No. 2: Equivalent Drug Calculation**

| Sr. No. | Solid dispersion ratio | Solid dispersion to 50mg drug ibuprofen |
|---|---|---|
| 1 | 1:1 | 100mg |
| 2 | 1:2 | 150mg |
| 3 | 1:3 | 200mg |
| 4 | 1:4 | 250mg |

## FORMULATION OF TABLET

**Requirements:**

- Apparatus: Mortar Pestle, Beaker, Sieves, Glass rod, Funnel, Burette Stand, Measuring Cylinder etc.
- Chemicals: Standard Ibuprofen, Croscarmellose Sodium, Starch Paste, Talc, Magnesium Stearate etc.
- Instruments: Tablet Compression Machine, Dissolution Apparatus, Disintegration Apparatus, Friabilator, Hardness Tester (Monsanto), Weighing Balance etc.

**Table No. 3: Formula**

| Sr. no. | Ingredients | Quantity (for 1 tablet ) gm | Quantity (for 20 tablet) gm |
|---|---|---|---|
| 1 | SD. Ibuprofen | 0.400 | 8 |
| 2 | Croscarmellose sodium | 0.08 | 0.16 |
| 3 | Starch paste | | |
| 4 | Talc | 0.01 | 0.2 |
| 5 | Magnesium stearate | 0.01 | 0.2 |

**Wet Granulation method:**

- Weighing, milling and mixing of the API's with powder excipients.
- Preparation of binder solution (starch paste).
- Starch paste mixed with powder to damp mass.
- Screening of the dampened powder in to granules using 6 to 12 mesh screen.
- Then drying of moist granules in hot air oven.
- Sizing the granulation by dry screening using 14 to 20 mesh screens mixing of the dried granules with lubricant and disintegrant by using mortar and pestle.

- Then the final compressed granules into the tablet by using compression machine.

## EVALUATION OF GRANULES

### 1. Angle of Repose:

The angle of repose the material is the angle of dip relative to the horizontal plane to which a material can be piled without depression. Angle of repose was determined by using fixed funnel method. The material poured through a funnel that can be raised vertically until a maximum cone height was obtained. The radius of the heap was measured and it was calculated by using formula. $Ø = \tan^{-1} h/r$

### 2. Bulk density:

It is defined as the weight of many particles of the materials divided by the total volume they occupy. The total volume include particle volume, interparticle void volume, and internal pore volume.

Bulk density = weight of powder/ volume of powder

### 3. Tapped density:

It is the ratio of the weight of powder to the minimum volume of occupied in measuring cylinder. Tapped density is determined by placing a graduated cylinder containing known mass of drug or formulation on mechanical tapper apparatus which is operated at fixed number of taps.

Tapped density = weight of powder /minimum volume of powder

### 4. Carr's index:

Is an indication of the ease with which a material which can be induced to flow is given by compressibility of the granules was determined by Carr's compressibility index which is calculated by using formula

Carr's index = tapped density – bulk density/ tapped density × 100

### 5. Housner's ratio:

It is the ratio of tapped density to bulk density and is an indirect index of ease of powder flow. Lower housner ratio indicate the better flow properties. It can calculated by using formula,

Housner's ratio = tapped density/ bulk density

## EVALUATION OF TABLETS

### 1. Uniformity of weight:

This test is done by sampling and weighing 20 tablets at random and average weight is calculated. IP limit for weight variation in case of tablets weighing up to 120mg ±10%, 120 mg to 300 mg is ±7.5 % and more than 300 mg is ±5 %.

**2. Tablet thickness:**

The thickness and diameter of the tablet was determined by usning a Vernier Calliper or by hand gauge. Tablet thickness should be control within 5% or less of standard value.

**3. Hardness test:**

The strength of tablet is expressed as tensile strength kg/cm$^2$. The tablet crushing load which is the force required to break a tablet into pieces by compression. It was determined by using Monsanto Hardness Tester.

**4. Friability test:**

The Roche friabilator was used to determined friability. Pre weighed tablets were placed in friabilator and rotated at speed of 25rpm for 4 minutes or upto 100 revolution. The percentage of weight loss was calculated by using formula

% Friability = initial weight – final weight/ initial weight × 100S

**5. Disintegration test:**

6 tablets were placed individually in each test tube of disintegration test apparatus. The water was maintained at a temperature of 37$^0$C ± 0.5$^0$C and time taken for entire tablet to disintegrate completely was noted.

**6. Content uniformity:**

20 tablets were powdered and equivalent to 100 mg of Ibuprofen was weighed and transferred in to 100 ml of volumetric flask. 5 ml methanol was added and shaken for 10 minutes. Then the volume makeup to 100 ml with 6.8 pH phosphate buffer. Then the solution was filtered and diluted suitably.

## RESULT AND DISCUSSION

Ibuprofen orally fast dissolving tablet were prepared by using weight granulation method and carried out by using super disintegrating agent and other excipients mentioned in formulation table.

**Determination of lambda max:**

The lamda max of ibuprofen was found to be 230nm in Sodium hydroxide and 200nm in distilled water.

**1. Standard calibration curve of Ibuprofen: (In NaOH)**

**Observation Table:**

**Table No. 4: Spectrometric data of Ibuprofen**

| Sr. No. | Concentration (mcg/ml) | Stock solution (mcg/ml) | Sodium Hydroxide (mcg/ml) | Absorbance |
|---|---|---|---|---|
| 1 | 1 | 0.1 | 9.9 | 0.0193 |
| 2 | 3 | 0.3 | 9.7 | 0.0401 |
| 3 | 5 | 0.5 | 9.5 | 0.4360 |
| 4 | 10 | 1.0 | 9.0 | 0.6011 |
| 5 | 15 | 1.5 | 8.5 | 0.8314 |

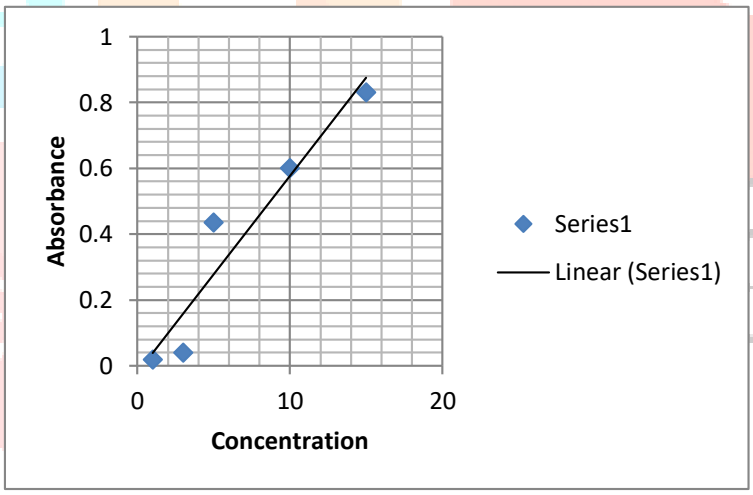



Fig. Standard calibration curve of Ibuprofen

**2. Standard calibration curve of Ibuprofen: (In Distilled water)**

**Observation Table:**

**Table No. 5: Spectrometric data of solubility determination**

| Sr.No. | Concentration (mcg/ml) | Stock solution (mcg/ml) | Distilled Water (mcg/ml) | Absorbance |
|---|---|---|---|---|
| 1 | 10 | 1 | 9 | 0.1331 |
| 2 | 15 | 1.5 | 8.5 | 0.2548 |
| 3 | 20 | 2 | 8 | 0.3810 |
| 4 | 25 | 2.5 | 7.5 | 0.6718 |

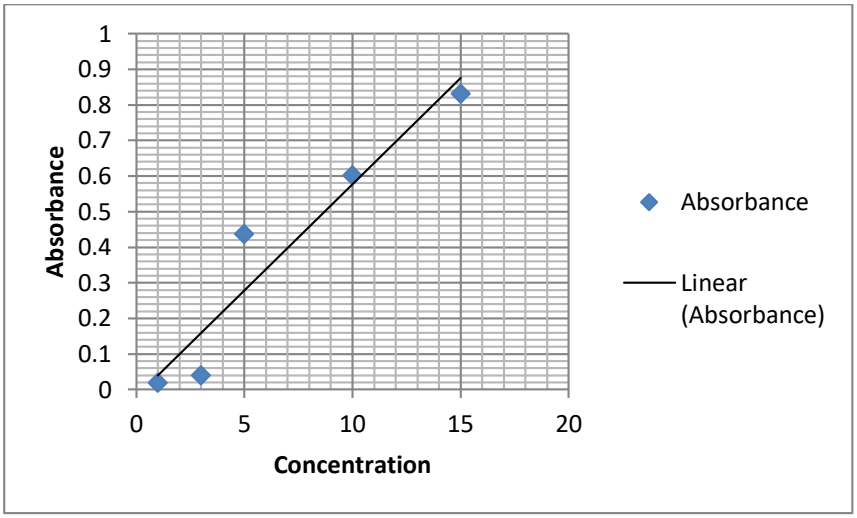



Fig. Standard calibration curve of Ibuprofen

### 3. Solubility studies of Solid Dispersion ratios of Ibuprofen:

**Table No. 6: Spectrometric data of SD Ibuprofen**

| Sr.No. | S.D. Ratio | Absorbance |
|---|---|---|
| 1 | 1:1 | 0.6894 |
| 2 | 1:2 | 0.7328 |
| 3 | 1:3 | 0.8870 |
| 4 | 1:4 | 0.7472 |

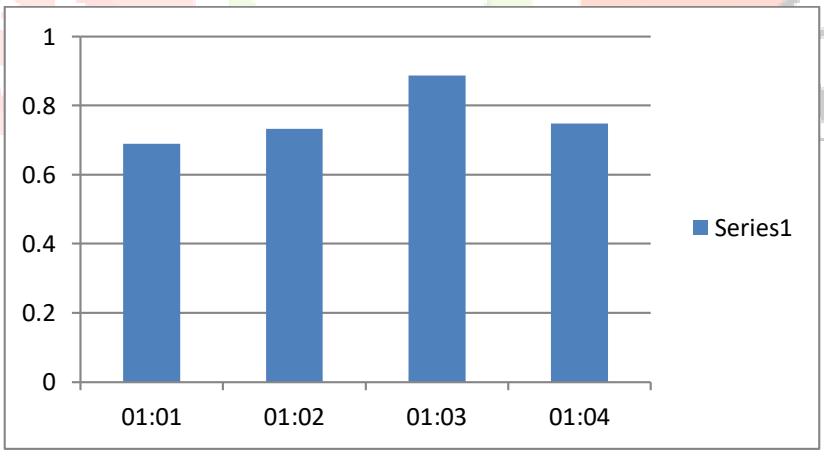



Fig. Absorbance of S. D. Ratios

## 4. Spectrometric data of Standard Ibuprofen and Solid Dispersion Ratios:

**Table No. 7: Spectrometric data of Standard and SD ratios**

| Sr. No. | Solid Dispersion ratio | Absorbance | Concentration (mcg/ml) |
|---|---|---|---|
| 1 | Standard Ibuprofen | 0.6017 | 24.61921 |
| 2 | 1:1 | 0.6894 | 27.14607 |
| 3 | 1:2 | 0.7328 | 28.39653 |
| 4 | **1:3** | **0.8870** | **32.83941** |
| 5 | 1:4 | 0.7472 | 28.81143 |

The absorbance of ratio 1:3 was found to be 0.8870 so it has more concentration of Ibuprofen compared to standard and all other SD ratios. So we selected it for formulation of tablet.

**Pre compression evaluation:**

Mass of Granules: 8gm

Bulk Volume: 22ml

**Table No. 8: Pre compression evaluation**

| Sr. no. | Parameters | Results |
|---|---|---|
| 1 | Angle of repose | $28.98^0$ |
| 2 | Bulk density | 0.3636gm/ml |
| 3 | Tapped density | 0.3809gm/ml |
| 4 | Carr's index | 4.54% |
| 5 | Housner's ratio | 104.75 |

**Post compression evaluation:**

**Table No. 10: Post compression evaluation**

| Sr. No. | Parameters | Results |
|---|---|---|
| 1 | Appearance | White |
| 2 | Thickness | 3mm |
| 3 | Hardness | 4.5kg/cm$^2$ |
| 4 | Friability | 0.6% |
| 5 | Weight variation | 5% |
| 6 | Disintegration | 20min |

## CONCLUSION

In the present work solubility of pure drug was determined and then the series of solid dispersion containing Ibuprofen drug were prepared using mannitol as a carrier in 4 different ratios by using suitable solvent. From 4 ratios one best ratio of SD was selected showing great increase in solubility. Solid dispersion made by fusion method. The excipient material was added into the solid dispersion includes superdisintegrant, lubricant, binder and mixed completely. SD tablet were prepared by wet granulation method.

SD tablet of ibuprofen were subjected to disintegration, hardness, weight variation, friability, in vitro drug release. The formulation has shown good drug release without compressibility problems. From this study, it can be concluded that solubility and ultimately dissolution rate of Ibuprofen could be enhanced by tablet containing solid dispersion technique. Tablets prepared by the ratio 1:3 (ibuprofen: mannitol), showed great increase in solubility of ibuprofen.

The proposed spectrophotometric methods are simple, rapid, accurate, precise, and economic. The standard curve prepared shown very linearity hence it was used for further analysis. This solid dispersion method can be successfully used for estimation and comparison of solubility of Ibuprofen in pure and tablet dosage form.

Here we have succeeded in formulating Ibuprofen tablets with enhanced in extent of its solubility which are cost effective and have patient compliance

## REFERENCES


1. Indian Pharmacopoeia. Vol. I & II, published by Indian Pharmacopoeia Commission, Ghaziabad, 2018 Pg No.321, 1217, 1521.
2. USP The official Compendia of Standards Vol. I, II and III 2008 Pg. No.2372
3. British Pharmacopoeia Vol I, published by Medicines Commission London 1988 Pg. No. 27, 15687.
4. Indian L. Lachman, H. Liebarman And J. L.Kanig. The Theory and Practice Of Industrial Pharmacy. Lea and Febigar.3rd Edition, 1986
5. Beena Kumari Harish Bishnoi .Solid Dispersion its types and mechanism of enhancement of solubility by solid dispersion. Acta Pharmaceuticals Sinica B. February 2014; 4(1): 18-2.
6. Yong-ChulPyo 1 Dong-Hyun Kim 1Sang-Eun Lee 1Jin-Ki Kim 2.Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubilityof Poorly Water-Soluble Drugs and Application to Anticancer Drugs**.**
7. Kumar B. Solid Dispersion- A Review. Pharma Tutor. 2017; 5(2): 24-29
8. Vinoth P, Rajalakshmi A N, Stephen P. Orodispersibleliquisolid compacts: A novel approach to enhance solubility and bioavailability. PharmaTutor; 2018; 6(6):28-35.http://dx.doi.org/10.29161/PT.v6.i6.2018.2
9. Shweta U. Kannao et al. Solid Dispersion – A Technique for Solubility Enhancement of Weakly Water Soluble Drug –A Review. Indo American Journal of Pharm Research.2014;4(06).
10. Hemanta Kumar Sharma, Nayanmoni Boruah ProsunKanti Ghosh. Different Methods Used In Solid Dispersion. IOSR Journal Of Pharmacy.8( 7):28-38 28
11. Ghulammurtaza. Solubility enhancement of simhastatin: areview. Acta Poloniae Pharmaceutica. 69 (4).
12. Sandip Sapkal*, Mukesh Babhulkar, Ashish Rathi, Gautam Mehetre and Mahesh Narkhede. Dissolution Rate Enhancement In Solid Dispersion. International Journal of PharmTech Research.Jan-Mar 2013; 5(1).
13. www.wikipedia.org
14. www.drugbank.ca
15. www.pharmgkb.org
16. Rupali joshi, Nilima pawar, samor katiyar Development and validation of UV spectrophotometric methods for simultaneous estimation of Paracetamol and Ibuprofen in pure and tablet dosage form. Pelagia Research Library Der Pharmacia Sinica, 2011, 2 (3): 164-171. www.pelagiaresearchlibrary.com.
17. R.Margretchandira1,Debjit Bhowmik1 , Rahul Yadav1 , B.Jayakar1 , K. P. Sampath Kuma. Formulation and Evaluation The Oral Tablets Ibuprofen. Pharmacy journal. 2012; 1.www.thepharmajournal.com
18. Yanbin Huanga,na.Fundamental aspects of solid dispersion technology for poorly soluble drug.

Acta Pharmaceutica SinicaB.February2014;4(1):18-25

19. Ketan T Savjani, Anuradha K Gajjar & Jignasa K Savjani. Drug Solubility; Importance And Enhancement Techniques. 8 May 2012.
20. AnshuSharma, C. P. Jain. Solid Dispersion: A Promising Techinique To Enhance Solubility of Poorly Water Soluble Drug. International Journal Of Drug Delivery. 2011.
21. Sandeep Kumar, Pritam Singh. Various Techniques For Solubilty enhancement: aoverview, the pharma innovation journal. 2016 january.
22. Sneha Jagtap, Chandrakant Magdum, Dhanra jJadge, Rajesh Jagtap, Solubility Enhancement: A Review.2018; 10
23. MOTRIN ® (Ibuprofen) – FDA, 05/25/2006
24. M. Radi, Y. Ramli, M. Elkarhane, A. Elalami, K. K. Karrouchi, A. Bekkali, B. Benaji, S Issaili And K. Bakhous. Optimization and Validation Of Method For Determination Of Ibuprofen By Hplc In Different Pharmaceutical Forms, Tablet, Syrup, Gel, Suppositories. 2014.
25. Rabia Bhushra, Muhammad Harris Shoaib, Nouseen Aslam, Durriya Hashmat And Masud Rehman. Formulation And Development And Optimization Of Ibuprofen Tablet By Direct Compression Method. 5th June 2014.
26. Suja C Jayan, Navaneet Krishna Manoj, Neetu Chacko And Sheena K. K. Formulation And Evaluation Ibuprofen Tablet Using Gum Of Anacardium Occidentale As Binding Agent.
27. Naveed Aslam Dogar, Isam Ullah Khan, Bilal Bashir, Naeem Ashghar Khan, Spectrometric Determination Of Ibuprofen In Visible Region Of Spectrum. March – April 2013; 2.
28. Syed Umer Jan, Gul Majid Khan And IzharHussin. Formulation Development And Investigation Of Ibuprofen Controlled Release Tablet With Hydrophilic Polymer And The Effect Co-Exipients On Drug Release Patterns. October 2012; 25.
29. Rakesh D Parmar, Dr. Pankaj Kapuparaand Dr.Ketan Shah. Development & Validation of Absorbance Correction Method for Simultaneous Estimation of Paracetamol, Ibuprofen Dextromethorphan. Journal of Chemical and Pharmaceutical Research. 2018.
30. Dr. (Mrs) D. Nagavalli. A Validation, Estimation of Ibuprofen and Formulation in Pure and In Dosage Form by UV Spectrophotometry and RP-HPLC. May-2012.
31. Narendra Nyolaand Govinda Samy Jeyabalan. Simultaneous Estimation of Ibuprofen and Formotidine in Pure And Combination Dosage Form By RP-HPLC. Journal Of Applied Pharmaceutical Science. 02/05/2012.
32. Patil RM, Maniyar AH, Kale MT, Akarte AM, Baviskar DT, Solid Dispersion: Strategy toenhance solubility, Int.J Pharm Sci. Review & Reasearch. 2011; 8(2): 66-7
33. Banker GS, Rhodes CT. Modern pharmaceutics. 4th Ed. New York: Marcel Dekker; 2002.
34. Aulton ME. Pharmaceutics: The science of dosage form design. 2nd Ed. London; 2002.
35. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: Importance and Enhancementtechniques.

ISRN Pharmaceutics 2012; 1-10

36. Mohammad Ali. Dabbagh. Behzad Taghipour. Investigation of Solid Dispersion Technique in Improvement of Physicochemical Characteristics of Ibuprofen Powder. Iranian Journal of Pharmaceutical Sciences Spring 2007; 3(2): 69-76
37. Madhuri Newa. Krishna Hari. Jong Oh Kim. Jong Seob IM. Jung Ae KIM. Bong Kyu YOOCS et al. Enhancement of Solubility, Dissolution and Bioavailability of Ibuprofen in Solid Dispersion Systems. Chem. Pharm. Bull. 2008; 56(4) 569—574.