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Study of Solubility of Drug by Solid Dispersion Technique and Formulation into Solid Oral Dosage Form.

Rutuja Yeole[1], Ruchita Shinde[2], Rhutik Mandwade[3], Hemant Kale[4].
SVS Institute of Pharmacy, Mungase, Malegaon.
Corresponding Author: Prof. Vaishali S. Hire.

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ABSTRACT: Ibuprofen is considered as non steroidal anti-inflammatory drug used to treating pain, fever and inflammation. It also treats menstrual periods pain, migraines and rheumatoid arthritis. to enhance the solubility of ibuprofen practically or poorly water soluble and freely soluble in acetone, chloroform, ethanol and ether. The solid dispersion method is used to make ibuprofen which has poor water solubility. According to BCS classification ibuprofen is classified in class II drug. Hence according to our study, we found that solid dispersion technique which can help in increase the solubility of drug. As a result we found that solubility of ibuprofen drug before processing 24.6192 mcg/ml and solubility of same drug after processing 32.8394 mcg/ml. Solid dispersion ratio shows that solubility of ibuprofen drug is enhanced or increased by solid dispersion technique. The tablets were evaluated for physical parameter, disintegration time, hardness, thickness, weight variation, friability etc.
KEYWORDS: Solubility, Solid dispersion, BCS classification, Ibuprofen, Weight granulation.

I. 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.

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.

FACTORS AFFECTING SOLUBILITY:
1) **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.
2) **Pressure**: The pressure dependence of solubility is typically weak. The pressure dependence of solubility does occasionally have practical significance.
3) **Molecular Size**: Molecular size will affect the solubility. The large molecules have less solubility.
4) **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.

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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
5. hydrotrophy

- **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, which are termed metastable polymorphic forms. As a result, delivering the medicine in an amorphous form to boost the particle solubility.

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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)
- Polyvinyl pyrrolidone (PVP)

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.

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.

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.

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

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to as "solvent free". The technique is known as Rapid Expansion of Supercritical Solution.

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. Normally, the resulting films are pulverized and milled 20, 23.

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 co dissolved 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:

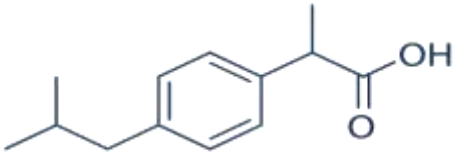
Physical mixture of drug and carrier is mixed for some time employing a blender at a particularspeed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixtures pulverized. Then the sample is collected and kept at room temperature in a screw capped 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
9. Reduction in the inactivation of drugs like morphine and progesterone in pre systemic circulation

DRUG PROFILE:

Structure:



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

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

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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.

II. MATERIALS AND METHODS:

Materials:
Ibuprofen purchased from Research Lab Fine Chem Industries, Mumbai. Talc, Magnesium stearate, Starch were purchased from Loba Chemie Pvt Ltd, Mumbai.

Methods:

1. Preparation of Solid Dispersion:

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.

2. Formulation of Tablet:

Table no. 1:

SR.NO	INGREDIENTS	QUANTITY (For 1 tablet)mg	QUANTITY (For 20 tablets)mg
1	SD. Ibuprofen	800	16000
2	Croscarmellose sodium	16	320
3	Starch paste	5	100
4	Talc	8	160
5	Magnesium stearate	2	40
		831mg	16620mg

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.

$Ø = \tan^{-1}$

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

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the minimum volume of occupied in measuring cylinder. Tapped density is determined by placing a graduated cylinder contaiong knowmn 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 37^0C ± 0.5^0C 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.

III. 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 Λ max:

The lamda max of ibuprofen was found to be 230 nm in NaOH and 200 nm in H_2O.

Pre compression evaluation:

Table no. 2

Sr. no.	Parameters	Results
1	Angle of repose	33.49^o
2	Bulk density	0.4957 mg/ml
3	Tapped density	0.5748mg/ml
4	Carr's index	0.06748%
5	Housner's ratio	1.1329

Post compression evaluation:

Table no. 3

Sr. No.	Parameters	Results
1	Appearance	White
2	Thickness	3mm
3	Hardness	4.4 kg/cm^2
4	Friability	0.6%

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5	Weight variation	5%
6	Disintegration	20 min

IV. 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 four different ratios. From four ratios one best ratio of solid dispersion was selected showing grate increase in solubility. The excipient material was added into the solid dispersion includes super disintegrant, lubricant, binder and mixed completely. Solid dispersion tablet were prepared by wet granulation method. The formulation has shown good drug release without compressibility.

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