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SOLUBILITY ENHANCEMENT OF IBUPROFEN AND ACETYL SALICYLIC ACID AFTER COMMINUTION

Aisha Liaqat[*1], Omer Mahmood Mumtaz[2], Anum Zaeem[3], Zunaira Tahir[4], Subat Mirza[5], Wali Ullah Shahid[6], Rabia Javaid[7]

*[1]*Department of Pharmacy, Minhaj University Lahore, Pakistan*
[2]*Department of Pharmacy, Minhaj University Lahore, Pakistan/ Punjab University College of Pharmacy*
[3,4,5,6,7]*Punjab University College of Pharmacy, University of the Punjab, Lahore*

[*1]aishaliaqat.pharma@mul.edu.pk

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Corresponding Author: *
Aisha Liaqat

Abstract

The poor solubility of potential drug molecules is a significant problem in the design of pharmaceutical formulations. It is well known, however, that the solubility of crystalline materials is enhanced when the particle size is reduced to submicron levels and this factor can be expected to enhance drug product bioavailability. The aim of our study was to enhance to solubility of acetylsalicylic acid and ibuprofen by shake flask method and also by reducing particle size, for this purpose we make dilutions of stock solution and saturated solution and find their absorbance. Our data clearly shows that after shaking and particle size reduction, solubility of our studied class 2 drugs is increased.

INTRODUCTION

The solubility of a substance refers to the amount of substance that passes into solution to achieve a saturated solution at constant temperature and pressure. Solubility is expressed in terms of maximum volume or mass of the solute that dissolve in a given volume or mass of a solvent. Pharmacopoeias give solubility in terms of the "number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid". There are different terms established to distinguish solubility such as "intrinsic solubility", "kinetic solubility" and "apparent solubility". The intrinsic solubility is measured to indicate solubility. Intrinsic solubility corresponds to the equilibrium solubility at thermodynamic equilibrium of the pure uncharged compound/drug. The term intrinsic refers to the fact that the species in solution is the same as that of the solid form. Measurements are taken at two temperatures, first at 4°C to ensure physical and chemical stability for short-term storage. A minimum in aqueous solubility can be observed at 4°C because of a maximum of water density. The second temperature of interest is 37°C, to support biopharmaceutical evaluation (Savjani, Gajjar, & Savjani, 2012)

Solubility is the property of a solid, liquid, or gaseous chemical substance called *solute* to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution (Lachman, Lieberman, & Kanig, 1976).

Solubility is based on the highest-dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water (Lachman et al., 1976).

The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important, since 85% of the most sold drugs in the USA and Europe are orally administered.

All drugs have been divided into four classes: class I—high soluble and high permeable, class II—low soluble and high permeable, class III—low soluble and high permeable and class IV—low soluble and low permeable.

Table no.1: Descriptive terms for solubility

S. no.	Descriptive terms	Parts of solvent required to dissolve one part of solute
1.	Very soluble	Less than 1
2.	Freely soluble	More than 1 but less than 10
3.	Soluble	More than 10 but less than 30
4.	Sparingly soluble	More than 30 but less than 100
5.	Slightly soluble	More than 100 but less than 1000
6.	Very slightly soluble	More than 1000 but less than 10,000
7.	Very slightly soluble or practically Insoluble	More than 10,000

Background

Determining compound solubility is an essential tool for early stages of the drug discovery process, as well as for lead optimization. Low solubility can lead to unpredictable and unreliable results during *in vitro* testing, thereby increasing the development costs. Solubility issues at the later stages of the drug discovery may lead to poor bioavailability, underestimated toxicity and other obstacles, lowering the chances of a given drug candidate for success. Solubility can be measured either as a kinetic or thermodynamic value. Typically, for early-stage drug discovery the kinetic solubility method is used, as it is fast and well suited for HTS format. In this case,(Stuart & Box, 2005)

Solid compounds are first dissolved in DMSO and then linear serial dilutions of each compound are added to an aqueous buffer and observed for precipitate formation when the compound is not completely soluble. Precipitate appearance can be evaluated by light scattering (laser nephelometry method). For better precision, the solution can be subjected to high-speed centrifugation or filtration using special solubility filter plates and then the compound concentration is measured in the saturated solution directly by UV or LC-MS using separately built calibration curves. Thermodynamic solubility is important for lead optimization and drug formulation stages. It is usually determined for pure compounds: crystalline powders, amorphous substances and liquids. In this modification of solubility assay long (24 hours or more) incubations are required. Measurements are usually performed by the shake flask method with UV-Vis or LC-MS detection.

Measuring of solubility:

In pharmaceutical practice, one important task is to measure the solubility of solids in liquids.

The following precautions serve as guidelines when running solubility tests:

- The solvent and the solute must be pure.
- The sample is removed for analysis after confirmation of saturation.
- Sample separation from saturated solution with un-dissolved solute must be reliable and satisfactory.

- The method used to analyze the solution must be reliable and reproducible.
- Temperature must be adequately controlled.
- Traditionally, the equilibrium solubility at a given pH and temperature is determined by the shake flask method (Glomme, März, & Dressman, 2005).

Apparatus:

SOLUBILITY DETERMINATION BY SHAKE-FLASK METHOD

Sample preparation:
An excess amount of drug is added to the solubility medium. The added amount should be enough to make a saturated solution in equilibrium with the solid phase. In the case of acidic or basic drugs dissolved in an unbuffered solubility medium, further addition of the solid could change the pH of the solution and consequently the solubility of the drug.(Veith & Comstock, 1975)

Equilibration:
Depending on the dissolution rate and the type of agitation used, the equilibration time between the dissolved drug and the excess solid could be varied. Equilibration is often achieved within 36 h. To ensure the equilibration condition, the dissolution profile of the drug should be investigated. The shortest time needed for reaching the plateau of drug concentration against time could be considered a suitable equilibration time. Any significant variation of the dissolution profile after reaching the equilibration should be inspected, since there are a number of possibilities including degradation of the drug as well as its polymorphic transformation. Both of these affect the solubility values of a drug dissolved in the dissolution media. Vertexing or sonicating the sample prior to equilibration could reduce the equilibration time. To overcome the poor wettability of low soluble drugs, one may use small glass microspheres or sonication (TONG, 2007)

Separation of phases:
Two common methods used for phase separations of saturated solutions are filtration and centrifugation. Filtration is the easiest method; however, the possible sorption of the solute on the filter should be considered as a source of error in solubility determinations, especially for very low soluble drugs. Prerinsing the filter with the saturated solution could reduce the sorption of the solute on the filter by saturating the adsorption sites. Centrifugation or ultracentrifugation is preferred in some cases, and the higher viscosity of the saturated solutions, i.e., in mixed solvents, should be considered as a limitation. A combination of filtration and centrifugation could also be used

Analysis of saturated solution and the excess solid:
UV spectrophotometric analysis is the most common and the easiest analytical method in solubility determination experiments. The next is the high-performance liquid chromatography (HPLC) methods in both the isocratic and gradient elution modes. The HPLC analysis could also detect the possible impurities or degradation products if a highly selective method was used. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) of the residual solid separated from the saturated solution confirm the possible solid-phase transformations during equilibration.

Data analysis:
The collected data could be compared with the previously reported data to ensure the accuracy of the experimental procedure employed. Any mistake in the dilution step, any miscalculations, or using uncalibrated instruments, such as uncalibrated balances, temperature variations, and some other factors, could result in different solubility values for a given drug dissolved in a solvent at a fixed temperature.

Ball Mill
Ball milling is size reduction technique used for the production of microparticles .A ball mill comprises a vessel or vial filled with balls, or rods, constructed from a variety of materials such as ceramic, agate, silicon nitride, sintered corundum, zirconia, chrome steel , tungsten carbide or plastic polyamide .The material to be milled is placed inside the vessel, which is made to rotate or vibrate at a particular speed or frequency. The movement of the vessel causes the balls to cascade or move in a particular pattern, colliding with each other and with the opposing inner wall of the vessel. Size reduction of the drug particles is effected from the impact they receive from the balls as well as attritive forces arising from the movement of the balls relative to each other. The ball mill may be modified to conical and tapered shape .If balls of different sizes are used as they segregate according to size and provide progressively finer grindings as the material flow axially**.**

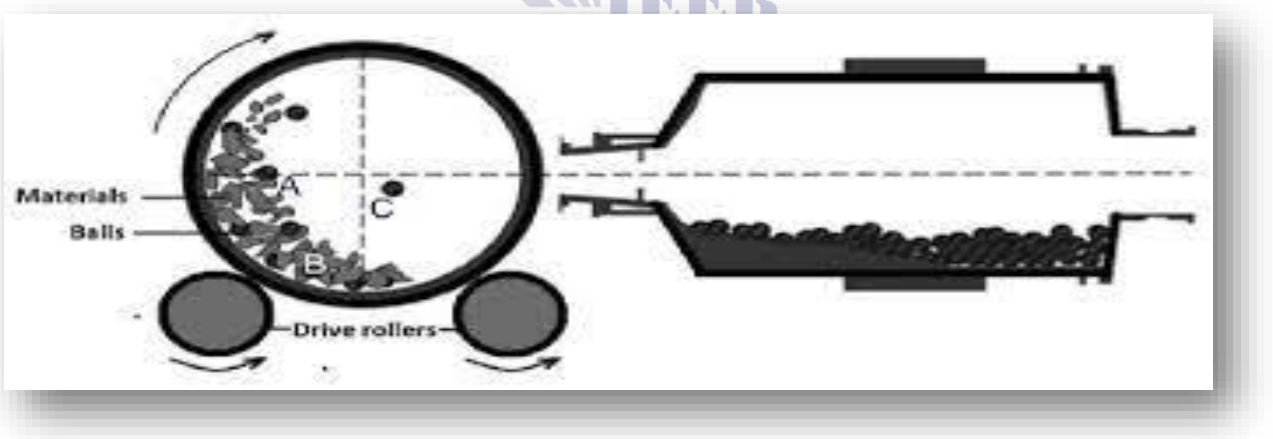


Fig:Schematic diagram of Ball Mill.The balls makeup grinding media and derive rollers help to rotate the milling chamber

The quantities of the balls and starting material determine the extent of fill of the vessel and the intensity of the milling process. Typically, the vessel is filled by the balls and starting material to 50% and 25% of the total volume of the vessel. In the case of a rotating vessel, rotation is usually carried out at 50–85 % of the critical speed, defined as the speed at which the balls cease to cascade owing to the centrifugal force imparted by the rotating vessel. The critical speed may be estimated based on the following relationship Critical speed (rpm) =54/√Rft
Where Rft is the diameter of the vessel measured in feet. As the rotational speed of the vessel decreases, attrition plays a more dominant role in particle size

reduction relative to impaction and compression, yielding finer particles at the expense of longer processing times. Apart from the speed of rotation or vibration, the size, density and hardness of the balls affect the rate and extent of particle size reduction. Decreasing the size and/or increasing both the density and hardness of the balls often increase the rate and extent of particle size reduction . The use of ball milling as a micronization technique for enhancing drug solubility is well supported by literature dating as far back as the 1970s.

Use of a ball mill to prepare the glass solutions was found to be effective in producing a single homogenous amorphous phase, and the dissolution rates were also found to be higher when compared to the glass solutions of the same drugs prepared by spray drying. This suggests the applicability of ball milling technique to produce homogenous amorphous preparations of poorly soluble drugs, and can be an important approach to improve the solubility of such drugs (Dai, Pollock-Dove, Dong, & Li, 2008)

Apart from its comminution function, ball milling also serves as an intensive mixing technique capable of producing co-ground drug-excipient mixtures comprising amorphous drug forms intimately mixed with suitable hydrophilic excipients at the molecular level. This interaction between the drug and hydrophilic excipient enhances the wetting and dissolution of the drug. Despite the efficiency of ball milling for size reduction it is less amendable to scale up. By a flow through method, with vibrating balls or discs in the milling chamber, milling efficiency can be improved. External jacketing for heat removal allows the mill to be used continuously and will limit the rise in temperature within the milling chamber.

Ultraviolet (UV):

Ultraviolent-visible spectrophotometer investigates the interaction of light radiation with matter in the ultra violet (200-400) and visible (400-800) range.

The spectrophotometer consists of light source, a sample compartment and a detector. Monochromator is a device that used to separate light into its component wavelength.

Furthermore, the method of spectrophotometer is to use absorbance of light by an analyte,

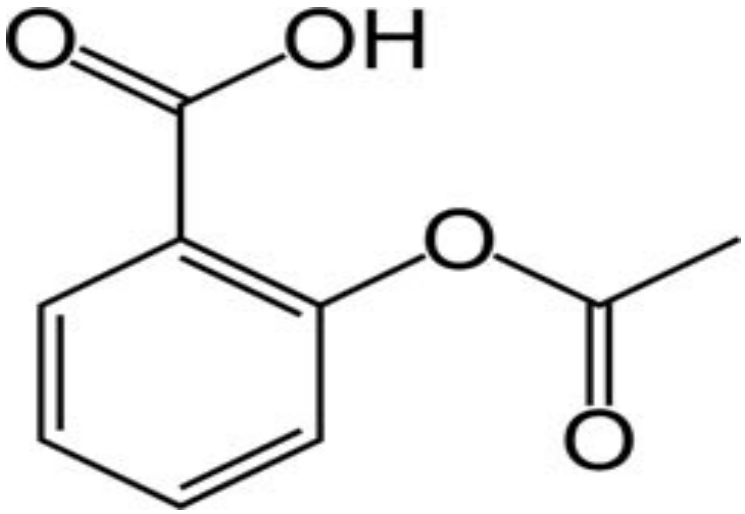
At a certain wavelength to determine the unknown concentration, the instruments is UV/Vis Spectrophotometer use UV light and visible port of electromagnetic spectrum.

Sample data collection was optimized with UV detection at 274 for acetyl salicylic acid and at 224 for ibuprofen (Zlatkis & Kim, 1976).

Characteristics of studied drugs

Acetylsalicylic acid (Aspirin)

Aspirin is an orally administered non-steroidal anti-inflammatory agent. Acetylsalicylic acid binds to and acetylates serine residues in cyclooxygenases, resulting in decreased synthesis of prostaglandin, platelet aggregation, and inflammation. This agent exhibits analgesic, antipyretic, and anticoagulant properties.



Chemical structure of acetylsalicylic acid.

Solubility

Values for solubility of ASA were obtained from several standard references. The European Pharmacopeia (Ph. Eur.)16 states that ASA is slightly soluble in water (according to Ph. Eur. General Notices, 100–1000 mL of solvent per gram of solute). The USP3 specifies its solubility as being one part solute in 300 parts solvent (water). A summary of literature values for the aqueous solubility of ASA is given in Table 2

Review of the data published on the solubility of ASA reveals that the solubility data vary from study to study, that the sample preparation method was not always appropriate or described clearly, or that the values are irrelevant to BCS because of the study parameters.

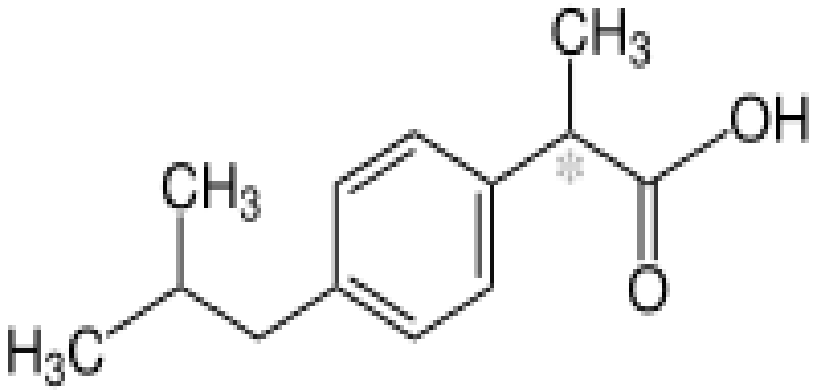
Table 2. Aqueous Solubility Values for Acetylsalicylic Acid Taken from the Literature

Solubility of Acetylsalicylic Acid in Water	References
Slightly soluble (15°C–25°C) (100–1000 mL of solvent/g of solute)	16
Slightly soluble*a*	14
1 in 300*a*	17
1 in 300*a*	14
1 in 300 (25◦C)	18
1 in 100 (37◦C)	18
4.6 mg/mL*a*	8
3.33 mg/mL*a*	14
3 mg/mL (25◦C)	19
10 mg/mL (37◦C)	19

a Temperature not specified.

Ibuprofen

Ibuprofen is a commonly used non-steroidal anti-inflammatory (NSAID) drug which is available both by prescription and over-the-counter. Ibuprofen is considered to be among the safest NSAIDs and is generally well tolerated but can, nevertheless, rarely cause clinically apparent and serious acute liver injury.



Chemical structure of Ibuprofen

Solubility

Ibuprofen is practically insoluble in water, but very soluble in most organic solvents like ethanol (66.18 g/100 mLat 40 °C for 90% EtOH), methanol, acetone and dichloromethane (Brayfield, 2014)

Materials and Methodology

Ingredients

Acetylsalicylic Acid
Ibuprofen

Method

The purpose of our project was to check the solubility enhancement of drugs (Ibuprofen and Acetyl salicylic acid) in water. We used UV spectrophotometer for checking absorbance of the drugs before and after milling. 200g of each drug was milled using Ball mill. Values of the absorbance obtained before and after milling were tabulated and a calibration curve was plotted (concentration vs absorbance). The tools used for the Data Analysis were MICROSOFT EXCEL and MICROSOFT WORD.

Preparation of Stock Solution:

For the determination of solubility stock solution is prepared by adding **0.1g** of drug into **100ml** of water. Then different dilutions are made of this solution like **2µl, 4µl, 6µl, 8µl, 10µl, 12µl** .We find the absorbance of that dilutions by UV spectrophotometry and then plot a graph between concentration and absorbance. For further evaluation the preserved stock solution is set to shake flask apparatus for 72 hours and again note absorbance of dilutions.

Preparation of Saturated Solution:

We also made the saturated solution of drugs by adding **10g** of drug into **50ml** of water and then set this flask to shake flask apparatus for 72 hours and also find the absorbance of that saturated solution. We also checked the absorbance of the different dilutions made out of the saturated solution by serial dilution method.

Serial dilution:

Serial dilutions are made by making the same dilution step over and over, using the previous dilution as the input to the next dilution in each step. Dilution is a process of making the solution weaker or less concentrated. We did our dilutions by taking 1ml of the stock solution and making it up to 10ml. Then we took 1ml from this solution and raised it up to 10ml and so on.

Determination of absorbance:

We determined the absorbance by using UV spectrophotometer. First we calculated the absorbance of the blank. Then we adjusted the wavelength according to our drugs (ibuprofen and acetyl salicylic acid i.e., 274 and 224 respectively). We took the required volume of the sample using micro-pipettes. The cells were filled at least $3/4^{th}$ for accurate absorbance values.

Milling:

We performed milling of the drugs (Acetyl salicylic acid , Ibuprofen) using Ball mill. We measured the Tap and the Bulk density before milling by taking average of 3 readings. Then 200g of drug was milled for 20

minutes .Then again tap and bulk density of the powder was measured (Dai et al., 2008).

Calibration curve:

Calibration curves are used to understand the instrumental response to an analyte, and to predict the concentration of analyte in a sample. The standard solution for drug concentration 2, 4, 6, 8, 10 ,12 µg/ml was prepared from stock solution. The absorbance of solution of acetyl salicylic acid and ibuprofen were measured at 274 and 224 respectively and a calibration curve was plotted between absorbance vs concentration to get the linearity and regression equation.

Discussion:

Now we discuss the calibration curve results of acetylsalicylic acid and ibuprofen, both for stock and saturated solution.

Before Comminution

Acetyl Salicylic Acid:

Bulk Density:

Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	89	0.561
2	50	85	0.588
3	50	82	0.609

Average Bulk Density = 0.561+0.588+0.609

=0.586 g/ml

Tap Density:

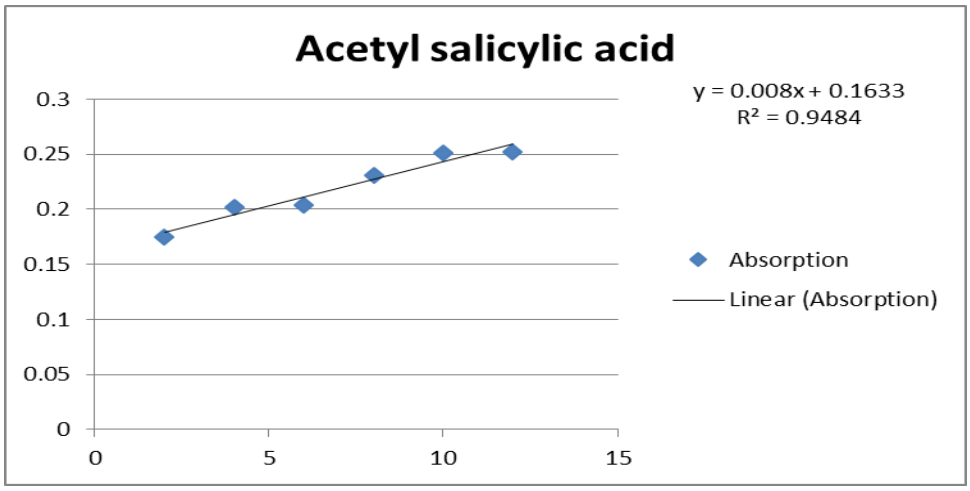
Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	71	0.704
2	50	69	0.724
3	50	69	0.724

Average Tap Density= 0.704+0.724+0.724/3

= 0.717 g/ml

Calibration curve:

Concentration (µl)	Absorbance (nm)
2	0.175
4	0.202
6	0.204
8	0.231
10	0.251
12	0.252



This is a curve between absorbance and concentration of acetyl salicylic acid

Ibuprofen:

Bulk Density:

Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	98	0.510
2	50	97	0.515
3	50	99	0.505

Average bulk density= 0.510+0.515+0.505/3
= 0.510 g/ml

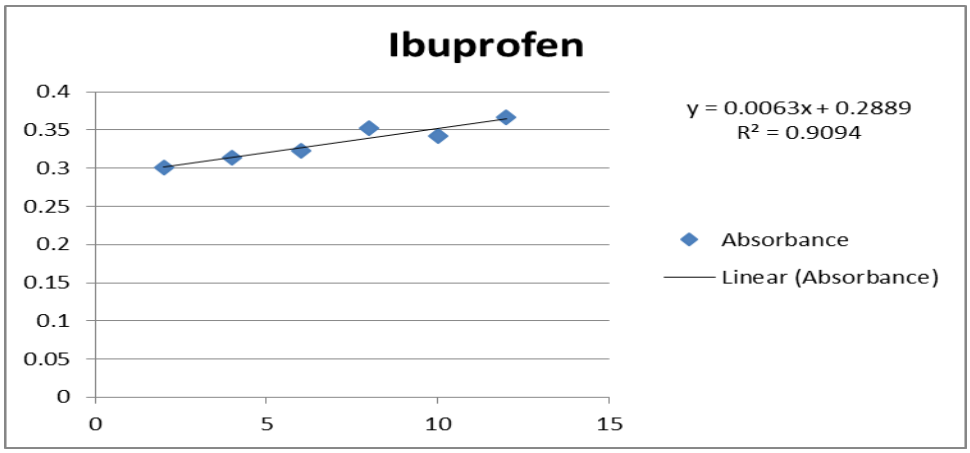
Tap Density:

Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	84	0.595
2	50	86	0.581
3	50	85	0.588

Average Tap Density= 0.595+0.581+0.588/3
= 0.588 g/ml

Calibration Curve:

Concentration (µl)	Absorbance (nm)
2	0.301
4	0.314
6	0.323
8	0.352
10	0.342
12	0.367



This is a calibration curve between absorbance and concentration of ibprofen

After Comminution:
Ibuprofen:
Bulk Density:

Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	100	0.50
2	50	96	0.52
3	50	97	0.51

Average Bulk Density= 0.50+0.52+0.51/3

= 0.51 g/ml

Tap Density:

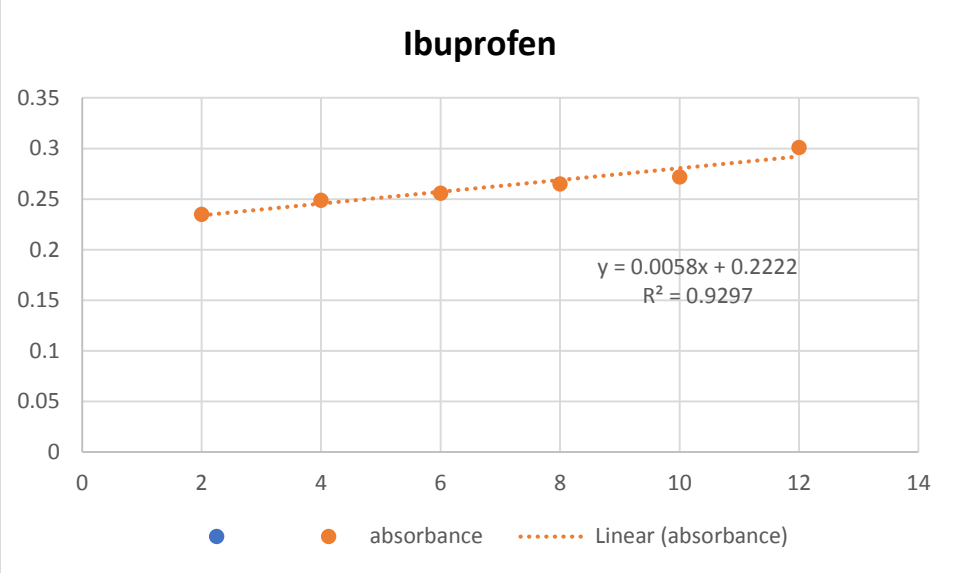
Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	86	0.58
2	50	81	0.61
3	50	80	0.625

Average Tap density= 0.58+0.61+0.625/3

= 0.605 g/ml

Calibration Curve:

Concentration (µl)	Absorbance (nm)
2	0.235
4	0.249
6	0.256
8	0.265
10	0.272
12	0.301



This is a calibration curve between absorbance and concentration of ibprofen

Acetyl Salicylic Acid:

Bulk Density:

Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	69	0.724
2	50	66	0.757
3	50	68	0.735

Average bulk Density= 0.724+0.757+0.735/3

= 0.738 g/ml

Tap Density:

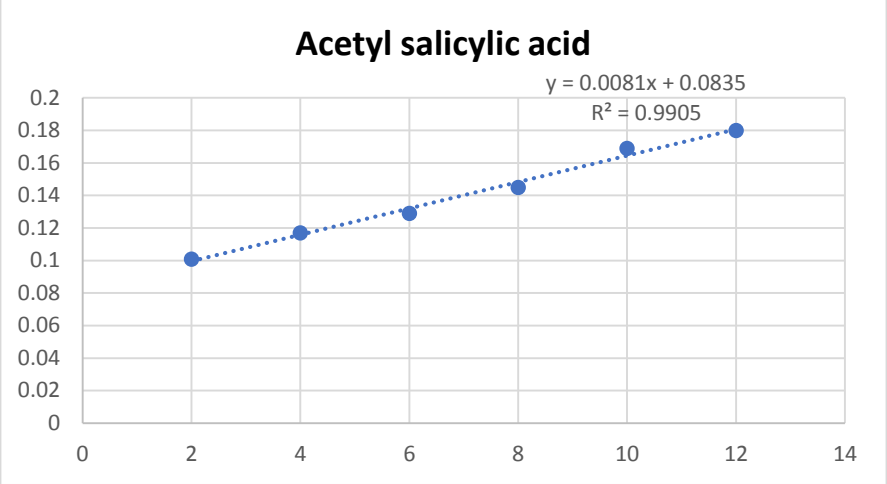
Sr no.	Mass (g)	Volume (ml)	Density (g/ml)
1	50	60	0.833
2	50	62	0.806
3	50	63	0.793

Average tap density= 0.833+0.806+0.793/3

= 1.9 g/ml

Calibration Curve:

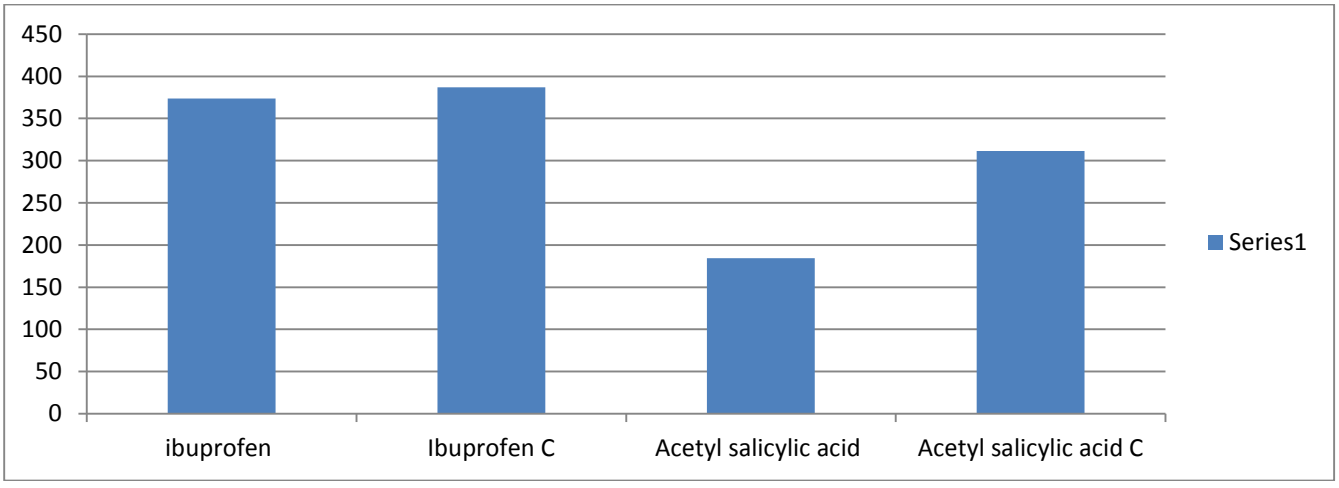
Concentration (µl)	Absorbance (nm)
2	0.101
4	0.117
6	0.129
8	0.145
10	0.169
12	0.180



This is a calibration between absorbance and concentration of acetyl salicylic acid

Solubility:

Drug	Abs:1	Abs:2	Absorbance	Drug µg/ml	Dilution factor	Medium	Drug released mg/ml	% release mg/ml
Ibuprofen	0.199	0.165	0.182	74.74603175	10	50	37.37301587	373.7301587
Ibuprofen C	0.222	0.231	0.2265	77.36206897	10	50	38.68103448	386.8103448
Acetyl salicylic acid	0.141	0.122	0.1315	36.85	10	50	18.425	184.25
Acetyl salicylic acid C	0.502	0.49	0.496	62.2654321	10	50	31.13271605	311.3271605



Take Ibuprofen and Acetyl salicylic acid powder. Then **tap** and **bulk** densities which were **0.510 g/ml**

and **0.588 g/ml** respectively for **Ibuprofen** while **1.903g/ml** and **0.738 g/ml** respectively for **Acetyl Salicylic Acid** were calculated. Then **stock solution** was made of both the drugs by serial dilution method and found their absorbance. Then take **100mg** of the drug (ibuprofen) and dissolved it in **100ml** of water. This was our stock solution for ibuprofen, and we did similar for acetyl salicylic acid. Then different solution i.e. **2µl, 4µl, 6µl, 8µl, 10µl and 12µl** were prepared by dissolving respective µl of stock solution and make up to the mark till 1ml (1000µl).

Futher, prepare a **saturated solution** of both the powders by taking **10 grams** of each ibuprofen and acetyl salicylic acid and dissolving it in **50ml** of water. Put those solutions on an orbital shaker for 72 hours and after that filtered the solutions using Whattman paper no. 40. After 72 hours the solution was filtered. After that the absorbance of the filtrate was checked and also of the dilutions made using the filtrate. The **absorbance** after dilution for ibuprofen was **0.182nm** and that of acetyl salicylic acid was **0.1315nm**.

200gm of drug was taken for milling purpose. The drug was milled in Ball Mill for 20 minutes and the tap and bulk densities were measured. Then **tap** and **bulk** densities which were **0.605 g/ml** and **0.51 g/ml** respectively for **Ibuprofen** while **0.717g/ml** and **0.586 g/ml** respectively for **Acetyl Salicylic Acid** were calculated. Then **stock solution** was made of both the drugs by serial dilution method and found their absorbance. Then take **100mg** of the drug (ibuprofen) and dissolved it in **100ml** of water. This was our stock solution for ibuprofen, and we did similar for acetyl salicylic acid. Then different solution i.e. **2µl, 4µl, 6µl, 8µl, 10µl and 12µl** were prepared by dissolving respective µl of stock solution and make up to the mark till 1ml (1000µl). Futher, prepare a **saturated solution** of both the powders by taking **10 grams** of each ibuprofen and acetyl salicylic acid and dissolving it in **50ml** of water. Put those solutions on an orbital shaker for 72 hours and after that filtered the solutions using **Whattman paper no. 40.** After **72 hours** the solution was filtered. After that the absorbance of the filtrate was checked and also of the dilutions made using the filtrate. The **absorbance** after dilution for ibuprofen was **0.2265nm** and that of acetyl salicylic acid was **0.496nm**.

The **percentage drug released** for ibuprofen before milling was **373.7301**% and of acetyl salicylic acid was **18.425**% while the percentage release after comminution was **386.8103**% for ibuprofen and **311.327**% for acetyl salicylic acid.

By using the absorbance values of the solutions and adding the formulas in Ms.Excel we made a graph to calculate the percentage drug released. The graph and values show that the solubility of ibuprofen as well as acetyl salicylic acid was increased after comminution.

Results:

This study indicated that the solubility of the drugs was enhanced by particle size reduction and the technique used was proven to be effective in increasing solubility. The percentage drug release was also increased after comminution.

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