International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 473-479 www.ijprajournal.com ISSN: 2456-4494

# Formulation and Evaluation of Effervescent Granules of Ibuprofen

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Date of Submission: 10-07-2024 Date of Acceptance: 20-07-2024

**ABSTRACT:** Recently, fast-dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better compliance. Usually, elderly people experience difficulty in swallowing the tablet. The object of this investigation was to formulate and evaluate effervescent granules of ibuprofen, to increase its dissolution rate to get rapid analgesic and antipyretic effects. In particular, the invention relates to a new, clearly dissolving ibuprofen effervescent formulation and a process for the Preparation of this formulation.

Ibuprofen or (t)2-(4-isobutylphenyl)-propionic acid.

Five formulas (F1-F5) of effervescent ibuprofen granules were formulated by the wet granulation method. Croscarmellose sodium, Powder of banana and other ingredients were used in the formulation of effervescent granules. Evaluation studies were carried out for all five Formulas, these include: (compatibility study, flow ability study, % of drug content, effervescent time and in vitro dissolution study.The results show that the formulated granules have good flow properties with suitable bulk density for the uniting dose. FTIR study shows that there is no drug interaction with other ingredients in the formula. Ibuprofen was successfully formulated and evaluated as effervescent granules by using a combination of Croscarmellose sodium and Banana powder.

**Keywords**: Ibuprofen, Effervescent, Granules, Wet granulation

## I. INTRODUCTION:

The oral dosage forms are the most popular way of taking medication despite having some Disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in Liquid form. So, Effervescent tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to Drunk immediately. Effervescent granules are soluble, dissolve quickly and provide a palatable formula which can avoid the bad bitter taste of drugs. It is convenient, stable dosage forms. [1]

Effervescent powders used as Saline cathartics were available in the eighteenth century and were subsequently listed in the official compendia as compound Effervescent powders. There were commonly known as 'Seidlitz powders'. Effervescent mixtures have been moderately popular over the years since along with the medicinal value of the particular preparations, they offered the public a unique dosage form that was interesting to prepare. [2] Effervescent tablet have major advantage that the drug product is already in solution at the Time it is consumed. Thus the absorption is faster and more complete than with conventional Tablet.

Ibuprofen is a propionic acid derivative it's a non-steroidal anti-inflammatory agent used for treating Rheumatoid arthritis and osteoarthritis. Ibuprofen considers Insoluble substance in water (0.078µg/ml) with pKa 4.5. Due to The low solubility of ibuprofen, the dissolution profile of Ibuprofen may be considering the rate-limiting step for the Absorption process of the ibuprofen drug.[3] This study aimed to enhance the release profile of ibuprofen by Using the wet granulation method to prepare effervescent granules of ibuprofen.

### 1.1 In vitro Dissolution Studies [4, 5]

Dissolution behaviour is investigated by in vitro dissolution research. The in-vitro disintegration investigation can be utilized to demonstrate the bioavailability or bioequivalence of the drug product through in vitro-in vivo correlation(IVIVC). The medication in the gastrointestinal fluid, on other hand ,flows freely through the biomembranes at a rate greater than dissolves or is released from the dosage form if absorption of the drug is dissolution rate limited. In a solid dispersion system, a specially created in-vivo dissolving research will be necessary to determine the absorption rate, and consequently its

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 473-479 www.ijprajournal.com ISSN: 2456-4494

bioavailability, and to eventually prove the bioequivalency.

**1.2 Solubility studies**

Studies on solubility are conducted to determine the solubility behavior exhibited by solid dispersion system in various solvent systems and body fluids. [6, 7]

**1.3 Preformulation studies of Ibuprofen**

The preformulation studies include the physicochemical characterization of the drug and excipients which are useful in formulation or dosage form. [8]

**1.3.1 General characteristics** [9, 10]

Ibuprofens chemical name is (RS)-2-(4-isobutylphenyl) propionic acid and its structure shown in Figure1. The medication is often supplied as the racemic substance , however in certain nations, including Finland(FI), formulations that exclusively include the S-enantiomer, dexibuprofen, are accessible. While other salts, esters, and other compounds are also employed, ibuprofen is typically administered as the free acid. These consist of meglumine derivatives, guaiacol and pyridoxine esters, sodium and lysine salts, and isobutanolammonium. Unless otherwise specified , ibuprofen is assumed to be the free acid in the racemic form thoughout this monograph.

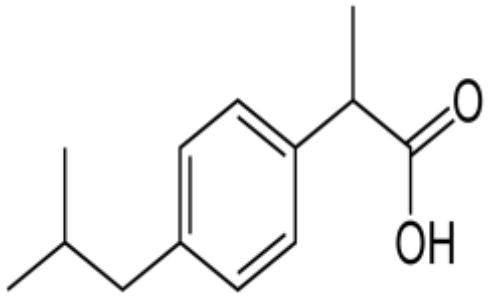


Fig. 1: structure of ibuprofen

**1.3.2. Therapeutic indication and therapeutic index**

One well-known and frequently used non steroidal anti-inflammatory drugs (NSAID) is ibuprofen. The racemic substance is thought to be a nonselective inhibitor of cyclooxygenase (COX). [10] The S-enantiomer has been shown to selectively inhibit COX-1, but R- ibuprofen's pharmacodynamic effectiveness is minimal. Racemic ibuprofen and its S-enantiomer are mostly used to treat soft tissue disorders, rheumatoid arthritis, osteoarthritis, spondylitis, headaches, migraines, and mild to moderate pain associated with dysmenorrhea, surgery, and dental pain. [10,11] Additionally, ibuprofen has antipyretic qualities. Considered to be one of the safest NSAIDs on the market is ibuprofen.[12]

**1.3.3. Pharmacokinetic properties** [13]

**1.3.3.1 Absorption and permeability**

Permeability was observed because NSAIDs promote their own transport. This observation may help to explain the GI adverse effect and GI membrane damage that occur when high dosages of ibuprofen are taken orally or over an extended period of time. .[13] Like other NSAIDs ibuprofen and its enantiomers have been shown to have high permeability in rats due to promotion of their own transport by NSAIDs, which has resulted in increased GI permeability.[14] This finding may help to explain the GI adverse effect and GI membrane damage that occur when high dosages of ibuprofen are taken orally or over an extended period of time. In CaCo-2 cell culture, ibuprofen and its enantiomers have also been shown to have high permeability.[14]

**1.3.4. Pharmacokinetics**

Ibuprofen's linear pharmacokinetics in the 200–400 mg dosing range have been documented. Nonlinearity has been shown at doses greater than 400 mg; however, this is more likely the result of altered plasma protein binding than of decreased absorption.[13,14]It has also been shown that there is dose linearity in the absorption of S-ibuprofen in the 200–600 mg dosing range. Ibuprofen is well linked to plasma proteins (99%). The primary pharmacodynamically active moiety, S-ibuprofen, is known to undergo a systemic unidirectional inversion from R-ibuprofen.15 Apart from the broad enantiomeric metabolic inversion of the active S-ibuprofen, no pharmacologically active metabolites of ibuprofen are known to exist.Two inactive primary metabolites, 2-hydroxy-2-methylpropyl and 2-carboxypropyl phenylpropionic acid, are produced via hepatic biotransformation, which are excreted either free or as conjugates in urine.[15]

**1.4. Physicochemical Characteristics**

**1.4.1. Solubility**

In the literature only data at 208 ℃ or room temperature were found.[15]BCS classification requires data on the solubility at 378℃, these values were experimentally determined, for each media in

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 473-479 www.ijprajournal.com ISSN: 2456-4494

triplicate. Ibuprofen drug substance was suspended in medium and stirred for 24 hr. at 378 ℃ and then stored for a further 24 hr. without agitation. In each case sediment on the bottom of the flask was observed. The ibuprofen concentration in the clear supernatant was determined by UV analysis.[16]

Table 1: Solubility data of ibuprofen

| Solvent | Solubility |
|---|---|
| Water | **Poorly soluble** |
| Poorly soluble Phosphate buffer 6.8 | **Slightly soluble** |
| Phosphate buffer 7.2 | **Slightly soluble** |
| Phosphate buffer 7.4 | **Slightly soluble** |
| Methanol | **Soluble** |

*Solubility of drug was performed in both polar and non-polar solvent

**1.4.2. Polymorphism**

Ibuprofen does not exhibit genuine polymorphism. However, it has a tendency towards slight crystal lattice modification, which may affect also its dissolution behavior.[17]

**1.4.3. pKa**

The pKa of ibuprofen is in the range of 4.5-4.6[17]

## II. MATERIALS AND METHODS

**2.1. Materials:**

**Ibuprofen, citric acid tartaric acids , Sodium Bicarbonate, hydroxyl propyl methylcellulose (HPMC E5), Microcrystalline cellulose , Croscarmellose sodium.**

**2.2. Methods:**

Effervescent granules of ibuprofen were prepared by two different methods.

**2.2.1. Method-I:**

Acid granulation and base granulation, the two distinct stages of granulation used in method-I, were based on dry granulation.

Step-I: Weigh the citric and tartaric acids, then combine them and pass through sieve No. 40#. Binding agent pvp-k-30 was dissolved in IPA in the second stage. Citric acid and tartaric acid were mixed with the above mentioned organic solvent. The obtained wet mass passed through sieve No.20# and kept in tray dried at 600$^{o}$C for 1 hour.

Step-II: In base granulation firstly the sodium bicarbonate, sodium carbonate were mixed together and then pass through sieve No. 40#. The binding agent, pvp-k-30 ,was dissolved in IPA, an organic solvent, in the second step. The base components, sodium bicarbonate and sodium carbonate, were mixed with the above mentioned organic solvent. The obtained wet mass passed through sieve No.20# and kept in tray dried at 600$^{o}$C for 1 hour. The two types of granules acid and base were mixed after drying at room temperature. Following the well-mixing of the two granules, ibuprofen and a lubricant such as sodium benzoate were added.

**2.2.2. Method: II**

**Formulation of effervescent granules of ibuprofen**

The wet granulation method was used to prepare the effervescent Granules of ibuprofen.[18] The quantity of each ingredient used is shown in table 2. According to geometrical dilution, all ingredients of the formulation will be mixed thoroughly to maintain good Distribution of the drug with other ingredients, and then pass the Powder through sieve no 20 after that suitable amount of binding Agent added the powder mixture to fabricate a moist mass. Then Moisten mass was passed through sieve no. 20 to get granules. These Granules were be dried at 40 $^{o}$C overnight in a hot air oven.

Table.2 **Formula used to prepare the effervescent Granules of ibuprofen**

| **Ingredients(mg)** | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Ibuprofen<br>Citric acid | 600<br>217 | 600<br>217 | 600<br>217 | 600<br>217 | 600<br>217 |
| Tartaric acid | 434 | 434 | 434 | 434 | 434 |
| Sodium bicarbonate | 738 | 738 | 738 | 738 | 738 |
| Saccharine | 15 | 15 | 15 | 15 | 15 |

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Volume 9, Issue 4 July-Aug 2024, pp: 473-479 www.ijprajournal.com ISSN: 2456-4494

| | | | | | |
|---|---|---|---|---|---|
| Croscarmellose sodium | - | 5 | - | - | 5 |
| Banana powder | - | - | 5 | - | 5 |
| Microcrystalline cellulose | - | - | - | 5 | - |
| HPMC In alcohol 2% | 5 | 5 | 5 | 5 | 5 |

## III. EVALUATION OF EFFERVESCENT GRANULES OF IBUPROFEN

### 3.1. Fourier transforms infrared spectroscopy (FTIR) study

FTIR spectroscopy was employed to determine ibuprofen's compatibility with additional compound. Using a potassium bromide disc with a wavelength of 4000-400 cm-1, the FTIR spectra of ibuprofen, each component of the formula ,and the chosen formula were recorded.[19]

### 3.2. Flow ability study

### 3.2.1. Bulk density and tapped density

Two types of density were determined (bulk density (BD) and Tapped density (TD). In a 100 ml measuring cylinder, an appropriate amount of granules was weighted and put; then the Initial volume was recorded. After that, the measuring cylinder was tapped at the height of 2.5 cm at 2-second intervals until no further Change was noted in the volume.[20] From the equation below, bulk density and tapped density were calculated.

$$BD = \frac{\text{Granules weight}}{\text{Packing volume}}$$

$$TD = \frac{\text{Granules Weight}}{\text{Tapped volume of the packing}}$$

Carr's index for ibuprofen granules was measured to evaluate the bulk density and tapped density.[21]The values of Carr's index of ibuprofen granules were compared with references as shown in table 3.

$$\text{Carr's index} = \frac{[(TD - BD) * 100]}{TD}$$

Hausner's ratio of ibuprofen granules was calculated by using the equation below. Hausner's ratio which is less than 1.25 shows good flowing properties more than higher ones. Hausner's ratios which are from 1.25 to 1.6 show moderate flowing properties. Hausner's ratio which is more than 1.6 will show more cohesive powders.[22]

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

### 3.2.2. The angle of repose determination

To estimate the flow properties of ibuprofen granules, the funnel method was used to measure the angle of repose. When granular materials are poured onto a horizontal plane; a conical pile will be formed. The internal angle between the surface of the pile and the the horizontal surface is known as the angle of repose. The tan of the angle of repose was measured by height (H) of the cone and diameter of the base cone (D). [23] The values of the angle of repose were compared with references as shown in table 4.

$$\tan\theta = \frac{H}{0.5*D}$$

**Table 3: Flow properties and compressibility index**

| Flow characters | Carr's index |
|---|---|
| Excellent | 1-10 |
| Good | 11-15 |
| Fair | 16-20 |
| Passable | 21-25 |
| Poor | 26-31 |
| Very poor | 32-37 |
| Very, very poor | >38 |

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**Table 4: Flow properties of the angle of repose**

| The angle of repose value | Flow properties |
|---|---|
| <20<br>20-30 | Excellent<br>Good |
| 30 34 | Passable |
| >40 | Very poor |

### 3.3. Effervescence time:

The effervescent time of ibuprofen granules was measured by adding one dose of granules to a glass containing 250 ml of water when a clear solution is obtained the effervescent time will be recorded.[24]The arithmetic mean of triplicate readings was recorded.

### 3.4. Dissolution study:

The dissolution study of ibuprofen granule was done by using the USP type II dissolution test apparatus. The dissolution test was performed by using a dissolution medium made of phosphate buffer with pH 6.8 and at a temperature of 37±0.5°C and 50 rpm. A sample of 5 ml will be drawn every 1 min interval and then replenished with 5 ml to maintain the constant volume. After that, the sample was filtered through Whitman filter paper, and then the absorbance of the sample was measured at 260 nm. Then the amount of drug released was calculated from a previously prepared calibration curve of ibuprofen.[25]

## IV. RESULTS AND DISCUSSION:

The results of the flow-ability study are shown in table 5. The values of bulk density were in the range of 0.45-0.51. The tapped density values of the prepared granules were in the range of 0.52-0.59. The values of the angle of repose were found in range 25.2–28.98. While the result of the carr′s index of the prepared granules was in the range of 12.1-14.03. Hausner′s ratio values were found in the range of 1.13-1.16. The results indicate that all five formulas had good flow properties. The good flow properties may be attributed to the successful method of preparation by wet granulation.[26]

**Table 5: Flow properties of ibuprofen effervescent granules**

| Formula no. | Bulk density | Tapped density | Angle of repose | Carr′s index | Hausner′s ratio | Flow property |
|---|---|---|---|---|---|---|
| **F1** | 0.5±0.15 | 0.57±0.12 | 28.98±0.9 | 12.28±0.13 | 1.14±0.03 | Good |
| **F2** | 0.49±0.20 | 0.57±0.09 | 27.9±0.16 | 14.03±0.15 | 1.16±0.04 | Good |
| **F3** | 0.45±0.18 | 0.52±0.11 | 27.72±0.1 | 13.46±0.18 | 1.15±0.72 | Good |
| **F4** | 0.51±0.08 | 0.58±0.12 | 25.2±0.18 | 12.1±0.99 | 1.13±0.11 | Good |
| **F5** | 0.51±0.12 | 0.59±0.13 | 26.88±0.8 | 13.55±0.12 | 1.51±0.89 | Good |

## 4. EVALUATION OF EFFERVESCENT TABLETS

### 4.1. Thickness

Thickness of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

### 4.2. Hardness test

The hardness of the core tablets and coated tables were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm2.

### 4.3. Friability test

Twenty tablets were weight and placed in the friability test apparatus and apparatus was

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rotated at 25 rpm for 4 min. After revolution the tablets were de-dusted and weight. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

### 4.4. Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. Solution time required for 2 tablets to dissolve in 180ml of water at Room Temperature. The pH of solution can measured by pH meter, pH of solution prepared by putting tablets into water was affected by storage condition due to liberation of co2.Water content titration method used to determine the water content. In contrast to drying method, this is a specific method if no side reactions occur only water will be determined. While using drying method some problem occurs like apart from water, other volatile components of the sample and decomposition products are also determined. Titration method is rapid (few minutes), can be validated & therefore fully documented. With the Karlfischer (KF) titration both free and bound water can be determined e.g. surface water as crystals or the water content inside them. The method works over a wide concentration range from ppm upto 100% and supplies reproducible and correct result.

### 4.5. Content Uniformity

Twenty tablets were randomly selected from each batch and individually selected. The average weight and standard deviation of 20 tablets was analyzed. Tablets contain not less than 90% and not more than 110% of labelled amount of Ibuprofen.

## V. CONCLUSION

Ibuprofen was prepared and satisfactorily assessed as effervescent granules by the wet granulation method using a different concentration of polymers .Citric acid ,tartaric acid ,sodium bicarbonate, saccharine, croscarmellose, banana powder, microcrystalline cellulose, and HPMC in ethanol alcohol were used to properly manufacture ibuprofen effervescent granules. Following the preparation of five distinct formulations, namely F1, F2, F3, F4 and F5 was evaluated for preformulation studies, formulation study ,and in-vitro evaluation experiments were conducted.

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