



Formulation of Effervescent Ibuprofen

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ABSTRACT

This research is a formulation of the drug Ibuprofen as an effervescent tablet by two methods (direct compression and wet granulation). The bitter taste was masked by saccharine as sweetening agent with guar gum and Tragacanth gum, furthermore the effervescent effect of citric acid, tartaric acid and sodium bicarbonate lead to improve the taste of the drug beside increase the effect of formula. Also the Guar gum with Tragacanth gum were used as binder agent lead to hide the taste. The strawberry with banana which was used as flavoring agent also enhances the palatability. The formulated tablets were passed all the fundamental testes in the monograph. This study was found that formulating the ibuprofen as effervescent tablet by wet granulation method concentration and die cavity twenty is the suitable one and that might be lead to increase the drug effectiveness, therapeutic effect as well as increase patient acceptability as effervescent tablet.

Keywords: Tablets, Ibuprofen, effervescent, patient acceptability, Taste.

INTRODUCTION

Tablet formulations may be rendered effervescent for several reasons, including improvement of their disintegration characteristics, increase dissolution rate and thus enhance liberating the ciprofloxacin HCl beside together with sweetener, flavor and guar to mask the taste.¹

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agent for ciprofloxacin HCl (in ratio 1:2:3:4).² It comprise effervescent base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition by other non-active material such as sweeteners, flavoring agent, guar gum and fillers. Thus all that contributes in success the formula.^{1-3-4.}

Ibuprofen

is a medication in the nonsteroidal anti-inflammatory drug (NSAID) fig(1) class that is used for treating pain, fever, and inflammation.⁵ This includes painful menstrual periods, migraines, and rheumatoid arthritis.⁵ About 60% of people improve with any given NSAID, and it is recommended that if one does not work then another should be tried.⁶ It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.⁵

Common side effects include heartburn and a rash.⁶ Compared to other NSAIDs it may have fewer side effects such as gastrointestinal bleeding.⁶ It increases the risk of heart failure, kidney failure, and liver failure.⁵ At low doses, it does not appear to increase the risk

of myocardial infarction; however, at higher doses it may. Ibuprofen can also result in worsened asthma.⁶ While it is unclear if it is safe in early pregnancy,⁵ it appears to be harmful in later pregnancy and therefore is not recommended.⁷ Like other NSAIDs, it works by inhibiting the making of prostaglandins by decreasing the activity of the enzyme cyclooxygenase.⁴ Ibuprofen might be a weaker anti-inflammatory than other NSAIDs.⁶

Ibuprofen was discovered in 1961 by Stewart Adams and marketed as Brufen.⁸ It is available under a number of trade names, including Advil and Motrin.⁵⁻⁹ It was first marketed in 1969 in the United Kingdom and in the United States in 1974.⁵⁻⁷ It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.⁹ It is available as a generic medication.⁵ The wholesale cost in the developing world is between 0.01 and 0.04 USD per dose.¹⁰ In the United States it costs about 0.05 USD per dose.⁵

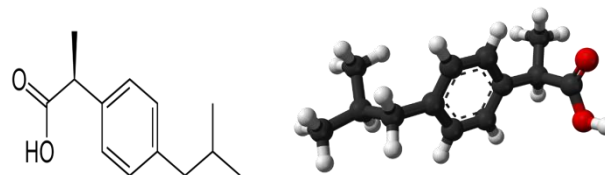


Figure 1: Chemical and 3 D Structure of Ibuprofen

Medical uses

Ibuprofen is used primarily to treat fever (including postimmunisation fever), mild to moderate pain (including pain relief after surgery), painful menstruation, osteoarthritis, dental pain, headaches, and pain from kidney stones. About 60% of people respond to any NSAID; those who do not respond well to a particular one may respond to another.¹¹ It is used for

inflammatory diseases such as juvenile idiopathic arthritis and rheumatoid arthritis.¹⁰⁻¹³ It is also used for pericarditis and patent ductus arteriosus.

Adverse effects

Adverse effects include nausea, dyspepsia, diarrhea, constipation, gastrointestinal ulceration / bleeding, headache, dizziness, rash, salt and fluid retention, and hypertension.¹⁰⁻¹³ Infrequent adverse effects include esophageal ulceration, heart failure, hyperkalemia, renal impairment, confusion, and bronchospasm.¹³ Ibuprofen can exacerbate asthma, sometimes fatally.¹⁴ Ibuprofen may be quantified in blood, plasma, or serum to demonstrate the presence of the drug in a person having experienced an anaphylactic reaction, confirm a diagnosis of poisoning in hospitalized patients, or assist in a medico-legal death investigation. A monograph relating ibuprofen plasma concentration, time since ingestion, and risk of developing renal toxicity in overdose patients has been published.¹⁵

Interactions

Drinking alcohol when taking ibuprofen may increase the risk of stomach bleeding.¹⁶ According to the US Food and Drug Administration, "ibuprofen can interfere with the antiplatelet effect of low-dose aspirin, potentially rendering aspirin less effective when used for cardio-protection and stroke prevention." Allowing sufficient time between doses of ibuprofen and immediate-release (IR) aspirin can avoid this problem. The recommended elapsed time between a dose of ibuprofen and a dose of aspirin depends on which is taken first. It would be 30 minutes or more for ibuprofen taken after IR aspirin, and 8 hours or more for ibuprofen taken before IR aspirin. However, this timing cannot be recommended for enteric-coated aspirin. But, if ibuprofen is taken only occasionally without the recommended timing, the reduction of the cardio-protection and stroke prevention of a daily aspirin regimen is minimal.¹⁷

Overdose

Ibuprofen overdose has become common since it was licensed for OTC use. Many overdose experiences are reported in the medical literature, although the frequency of life-threatening complications from ibuprofen overdose is low.¹⁸ Human response in cases of overdose ranges from absence of symptoms to fatal outcome despite intensive-care treatment. Most symptoms are an excess of the pharmacological action of ibuprofen, and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely, more severe symptoms, such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalemia, hypotension, bradycardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression, and cardiac arrest have been reported.¹⁹ The severity of symptoms varies with the ingested dose and the time elapsed; however, individual sensitivity also plays an important

role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs.

Correlation between severity of symptoms and measured ibuprofen plasma levels is weak. Toxic effects are unlikely at doses below 100 mg/kg, but can be severe above 400 mg/kg (around 150 tablets of 200 mg units for an average man),²⁰ however, large doses do not indicate the clinical course is likely to be lethal.²¹ A precise lethal dose is difficult to determine, as it may vary with age, weight, and concomitant conditions of the individual person. Therapy is largely symptomatic. In cases, presenting early, gastric decontamination is recommended. This is achieved using activated charcoal; charcoal adsorbs the drug before it can enter the systemic circulation. Gastric lavage is now rarely used, but can be considered if the amount ingested is potentially life-threatening, and it can be performed within 60 minutes of ingestion. Emesis is not recommended.²² The majority of ibuprofen ingestions produce only mild effects and the management of overdose is straightforward. Standard measures to maintain normal urine output should be instituted and renal function monitored.²⁰ Since ibuprofen has acidic properties and is also excreted in the urine, forced alkaline diuresis is theoretically beneficial. However, because ibuprofen is highly protein-bound in the blood, renal excretion of unchanged drug is minimal. Forced alkaline diuresis is, therefore, of limited benefit.²³ Symptomatic therapy for hypotension, gastrointestinal bleeding, acidosis, and renal toxicity may be indicated. On occasion, close monitoring in an intensive-care unit for several days is necessary.

Mechanism of action

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandin H₂ (PGH₂). PGH₂, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A₂ (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indometacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilatation, and subsequent heat dissipation. Inhibition of COX-1 instead would be responsible for unwanted effects on the gastrointestinal tract.²⁴ However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different



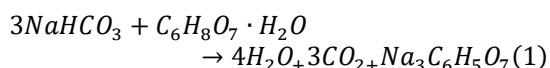
degrees of analgesia and gastric damage.²⁵ Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive inter conversion to the S-enantiomer *in vivo*. The S-enantiomer is believed to be the more pharmacologically active enantiomer.²⁶ The R-enantiomer is converted through a series of three main enzymes. These enzymes include acyl-CoA-synthetase, which converts the R-enantiomer to (-)-R-ibuprofen I-CoA; 2-arylpropionyl-CoA epimerase, which converts (-)-R-ibuprofen I-CoA to (+)-S-ibuprofen I-CoA; and hydrolase, which converts (+)-S-ibuprofen I-CoA to the S-enantiomer. In addition to the conversion of ibuprofen to the S-enantiomer, the body can metabolize ibuprofen to several other compounds, including numerous hydroxyl, carboxyl and glucuronyl metabolites. Virtually all of these have no pharmacological effects²⁷.

Method

Formulation of Tablets

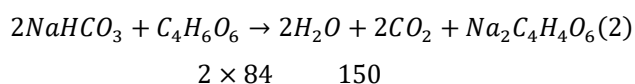
Tablets were prepared by two methods. In the two Methods: The ratios of the effervescent ingredients were taken as (1:2:3.4) respectively for citric acid: tartaric acid: sodium bicarbonate according to the following equation.

Citric acid:



3 × 84 210

Tartaric acid:



2 × 84 150

From the above equations the ratio of effervescent ingredients used was (1:2:3.4) for the citric acid tartaric acid: sodium bicarbonate².

Wet Granulation

The most widely used and most general method of tablet preparation is the Wet Granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluents, and disintegrant are mixed or blended well.²⁻²⁸

Specific amount of ibuprofen and saccharin were weighed and were divided into two pestles in equal amount and well mixed to each one of pestles effervescent base was added Citric and Tartaric acid in one and sodium bicarbonate in another one to avoid reaction then the binder combination (Guar and Poly vinyl pyrrolidone) was

added slowly after dissolving in a very small amount of water and then the mixture was blended continuously to make the paste, granulated using mesh (10), and then put in oven for drying for twenty hours. The mixture was passed through mesh (14) after drying using mesh (14). The micro crystalline cellulose when added before granulation used as disintegrant and after granulation as glident. Talc powder and magnesium stearate were added as lubricant and glident. Granules were compressed into two types one tablet 250 mg (0.25 gm active ingredient) by 20mm die and 125 mg (0.125 gm ingredient) by 13mm die as divided dose.⁽²⁾⁽²⁸⁾

Calculations:

Formula (1) (high binder concentration):

Guar: 1% & PVP: 4% (w/w)

Formula (2) (low binder concentration):

Guar: 0.005% & PVP: 2% (w/w)

- Guar with poly Vinyl pyrrolidone as binder indifferent ratios for the two formulae.
- Saccharin was used from three to five time of active ingredient and the best one it was used in ratio five times to active ingredient.
- Saccharine itself can be used as a binder.
- Tablet weight in these two formulae 1600 mg and 2000 mg can be used in two tablets to be easy to carry, handle, and stand packaging and transportation.
- Micro crystalline cellulose (Avicil) 5% is used as disintegrating agent and glident and lubricant.
- Mg stearate and Talc powder combinations as lubricant and glident.
- Vanillin was used as flavoring agent.

Direct Compression

As its name implies, Direct Compression consists of compression of tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as the method of tablet manufacture was reserved for small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet.²⁻²⁸ Ibuprofen is mixed with lactose to improve compression characteristic then NaHCO₃ and saccharine sodium four times (active ingredient) were added to active ingredient and mixed well and named (A). In another mortar, specified amount of tartaric acid and citric acid were weighed accurately and named (B). Then (A) and (B) were mixed in third mortar and specified amount of banana and vanillin flavor was added and then the whole mixture was passed through a sieve for more mixing. One percent of guar is used in dry form for all formula, vanillin was

added as flavor agent. The powder was put in an oven for drying and then tableting machine²⁻²⁸.

Determination of uniformity of weight

20 tablets from effervescent tablet were weighed individually with an analytical weighing balance. The average weights for each effervescent tablet and the percentage deviation from the mean value were obtained²⁹.

Assay

The assay was carried out using titrimetric methods and the highly sensitive High Performance Liquid Chromatography²⁸ (HPLC Agilent 1100 series, USA). For the Titrimetry methods, standard procedure using 1998 BP was followed²⁹. With the HPLC, twenty tablets from prepared tablets were weighed and powdered. An accurately weighed portion of the powder, equivalent to about 1200mg of Ibuprofen, to a suitable container, 100.0ml of internal standard solution was added and shaken for 10 minutes. The powder was centrifuged and the supernatant clear solution obtained was use in the assay preparation.

This was subjected to Liquid chromatography by separately injection of equal volumes (about 5 μ L) of the standard preparation, the assay preparation, and the 4-isobutylacetophenone standard solution into the Chromatograph, the chromatograms was recorded including the responses of the major peaks and the quantity, in mg of ibuprofen $C_{13}H_{18}O_2$ in each tablet was calculated by the formula

$$100(C/W) (RU/RS)$$

where C=concentration mg/ml of USP ibuprofen RS in the standard preparation; A is the average weight, in mg, of a Tablet; W is the weight in mg of tablet powder taken to prepare the assay preparation; and RU/RS are the ratios of the ibuprofen peak response to the valerophane peak

response obtained from the Assay preparation and the standard preparation, respectively.

Hardness test

The crushing strength was determined with a tablet hardness tester (Monsant, U.K). Four tablets were randomly selected from effervescent tablet and then the pressure at which each tablet crushed was recorded and the hardness value obtained.²⁹

Friability test

Ten tablets of effervescent ciprofloxacin HCl were weighed and subjected to abrasion by employing a Roche friabilator (ErwekaGmbH, Germany) at 25 rev-min for four minutes. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.²⁹

Dissolution test

The tablets were dissolved in sink condition and the time of dissolution of effervescent tablet was recorded by stop watch.²⁹

pH adjustment

The effervescent tablets were dissolved and then filtered and the pH of resultant solution was read by pH meter.²⁹



Figure 2: newly formulated effervescent Ibuprofen granules and tablets

RESULTS AND DISCUSSION

Table 1: Summary of the Quality Control Tests Undertaken on the two types of the Ibuprofen Effervescent Tablets

Effervescent Tablet	Friability	Hardness (Kg/cm ²)	Deviation %	pH	Assay %	Mean of Dissolution Time (min)
Direct Compression	1.9	5.5	1.045	6.02	98	2.42
Wet Granulation 13mm tablet	1.0	7.80	1.22	6.15	97	4.09
Wet Granulation 20mm tablet	0.9	6.2	0.84	6.17	96	2.8

In wet granulation method we can omit the binder when we use saccharin in any formula when it use with a very

low quantity of water. The problem of bitterness of soluble drug (Ibuprofen) can be overcome by using

saccharin from four to six time's active ingredient in effervescent formula. Effervescent tablet formula can be used to enhance solubility and might increase the palatability and mask taste and bioavailability and activity. Flavoring agent (vanillin) might mask taste beside good odor. Wet granulation is very good for production of effervescent tablet rather than dry compression method. Guar 1% is very strong binder when it was used in combination with PVP 4% in formula. All tablets passed the requirement of monograph this agree with Ahmed *et al*²⁸. Ten times dilution were needed for binder (0.1 guar gum and 0.4 PVP) with saccharin to avoid very hardness value in compression in previous method in which we use guar 1% dry lactose PVP 1% we find weight granulation method give good compressibility rather than direct compression table (1) this result agree with Nicole *et al*⁽²⁾ and Ahmed *et al*²⁸.

The use of MCC is work as lubricant which intended to reduce the friction during tablet rejection between the wall of tablet and the wall die cavity in which the tablet was formed furthermore has glidant effect and disintegrating action. This agrees with Nicole *et al*².

CONCLUSION

1. The study managed to improve the palatability of the Ibuprofen solution, via the utilization of saccharin sodium and vanillin flavor and using effervescent formula. Formulation into effervescent tablet is suitable for larger dose size which has difficulty in production of a convention tablet due to the difficulty in swallowing, besides enhancing solubility, which masking the taste and may leads to higher bioavailability and compression.

2. Formulating tablet as wet granulation method (when it is possible and applicable) is better than in direct compression method because of good distribution active ingredient.

3. The effervescent formula is needed and sometimes it is a must to enhance palatability of certain drugs.

4. The correlation can be made between dissolution rate of effervescent Ibuprofen tablets as an indication for its effectiveness without in vivo studies and effervescent base can be used to relief precipitation of any residual to drugs.

5. Wet granulation method (when it is applicable) is better than the direct compression method; this might be good distribution of active ingredient.

7. The effervescent tablets which prepared by wet granulation method (punch13) two tablets must be used to give 200 mg active ingredient (Ibuprofen) or four tablets to give 400 mg.

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