International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 6, June 2025 ijppr.humanjournals.com ISSN: 2349-7203

Formulation and Evaluation of Effervescent Granules of Ibuprofen

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Received: 2025-05-10 Revised: 2025-05-28 Accepted: 2025-06-05

ABSTRACT:

In recent times, fast-dissolving drug delivery systems have garnered significant attention and are being increasingly adopted due to their ease of administration and improved patient adherence. These systems are particularly advantageous for older adults, who often struggle with swallowing traditional tablets. The primary aim of this study was to develop and assess effervescent granules containing ibuprofen to enhance its dissolution rate, thereby ensuring quicker onset of pain-relieving and fever-reducing effects. This research specifically focuses on a novel, rapidly dissolving effervescent formulation of ibuprofen and outlines the method used for its preparation. Ibuprofen, chemically known as (±)-2-(4-isobutylphenyl)propionic acid, was incorporated into effervescent granules using the wet granulation technique. The formulation included excipients such as saccharin sodium, orange oil, and other supportive ingredients. Five different formulations were prepared and subjected to comprehensive evaluation tests, which included compatibility studies, flow property assessments, drug content analysis, effervescence time measurement, and in vitro dissolution profiling. The findings revealed that the granules demonstrated excellent flow characteristics and appropriate bulk density for unit dosage formulation. FTIR analysis confirmed that no significant interactions occurred between ibuprofen and the other components. Ultimately, the successful formulation and evaluation of ibuprofen effervescent granules were achieved using a combination of croscarmellose sodium and orange oil as key excipients.

Keywords: Effervescent Granules, Ibuprofen

1. INTRODUCTION:

Ibuprofen is a widely utilized non-steroidal anti-inflammatory drug (NSAID) known for its therapeutic effects, including pain relief, fever reduction, and anti-inflammatory action. Although traditionally administered in solid forms such as tablets and capsules, ibuprofen has been reformulated into effervescent dosage forms to improve its solubility, enhance patient convenience, and ensure a quicker therapeutic response. Effervescent tablets dissolve rapidly in water, producing a carbonated solution that is easier to swallow, particularly for individuals who experience difficulty with solid oral medications. Moreover, this delivery method tends to reduce gastric irritation, a side effect commonly linked with conventional ibuprofen formulations.

The evaluation of effervescent ibuprofen tablets involves a range of analytical parameters, such as physical appearance, pH, effervescence duration, uniformity of drug content, dissolution profile, and stability under various conditions. These parameters are critical to confirming the formulation's effectiveness, safety, and pharmaceutical quality.

One of the key manufacturing methods used for such formulations is roll compaction, a dry granulation technique ideal for drugs sensitive to moisture or heat. This method compacts powder materials between two rotating rollers to form dense ribbons, which are subsequently broken down into granules. Since no liquid binders or heat-drying steps are required, roll compaction helps preserve the stability of sensitive active pharmaceutical ingredients.

The primary objective of this investigation is to assess the pharmaceutical properties of ibuprofen effervescent tablets to ensure their compliance with therapeutic standards. Effervescent tablets are uncoated and intended to be dissolved in water before administration. These formulations typically contain acids or acid salts (e.g., citric acid, tartaric acid, or malic acid) and carbonate or bicarbonate salts (such as sodium or potassium bicarbonate). Upon contact with water, these components react to release carbon dioxide, facilitating faster dissolution of the active ingredient and improving taste masking.

Effervescent drug delivery systems are becoming increasingly popular not only in the pharmaceutical industry but also in the nutraceutical sector due to their ease of administration and enhanced patient acceptability. Designed to dissolve in liquids like water

or juice, they provide a palatable alternative to traditional tablets. Effervescent agents also contribute to taste masking and improved drug administration, as demonstrated in formulations such as those developed for ciprofloxacin hydrochloride using specific component ratios. These systems typically consist of a gas-generating base, the active drug compound, sweeteners, flavoring agents, and other optional excipients like guar gum and fillers. All these components work together to ensure the effectiveness, stability, and patient-friendly nature of the final product.

2 Pharmacokinetics of Ibuprofen (ADME Profile)

The pharmacokinetics of ibuprofen includes the key processes of absorption, distribution, metabolism, and excretion, which together determine its behavior in the human body.

Absorption

After oral intake, ibuprofen is readily absorbed through the gastrointestinal tract. Because it is a weak acid with a pKa of around 4.9, it remains largely in its non-ionized form in the acidic stomach environment, which favors absorption. Peak levels in the bloodstream are usually achieved within 1 to 2 hours. Its oral bioavailability is high (about 80%–100%), indicating that only a small amount is metabolized during its first pass through the liver. Taking ibuprofen with food may delay how fast it is absorbed, but it does not significantly affect how much is absorbed. Liquid formulations tend to be absorbed more quickly than tablets.

Distribution

Once ibuprofen enters circulation, nearly 99% of the drug binds to plasma proteins, mainly albumin. This strong binding limits the amount of free drug in the plasma. The volume of distribution (Vd) is relatively small—approximately 0.1 to 0.2 liters per kilogram—indicating that ibuprofen remains mostly in the bloodstream and extracellular spaces. It can cross the placenta and appears in breast milk in very small amounts.

Metabolism

The liver is the primary site for the breakdown of ibuprofen. The drug is processed mainly by cytochrome P450 enzymes, especially CYP2C9. It is transformed into inactive metabolites, including hydroxylated and carboxylated forms. These byproducts are then conjugated with substances like glucuronic acid, making them more water-soluble and easier to eliminate from the body.

Excretion

Ibuprofen and its metabolites are eliminated mainly through the kidneys. Approximately 90% is excreted as inactive compounds in the urine, while only 1–2% of the original drug is excreted unchanged. A small fraction is also removed via bile and feces. The elimination half-life of ibuprofen ranges from 1.8 to 2.5 hours, although it may be longer in individuals with reduced kidney function or in elderly patients.[6]

Pharmacodynamics of Ibuprofen

Mechanism of Action

Ibuprofen is classified as a non-selective NSAID (non-steroidal anti-inflammatory drug). It functions by blocking the activity of cyclooxygenase enzymes, particularly:

COX-1, which plays a constant role in safeguarding stomach lining and regulating kidney function,

COX-2, which is mainly produced during inflammation and is associated with pain and fever.

By reducing the function of both enzymes, ibuprofen lowers the production of prostaglandins—compounds responsible for triggering pain, fever, and inflammation.

Therapeutic Applications:

Pain Relief (Analgesic): Provides effective relief for mild to moderate pain, including headaches, muscle pain, dental pain, menstrual cramps, and joint discomfort.

Anti-inflammatory: Helps reduce inflammation and joint stiffness in chronic conditions like rheumatoid arthritis and osteoarthritis.

Fever Reduction (Antipyretic): Acts on the brain's temperature control center to lower elevated body temperature.

Blood-Thinning Effect: While ibuprofen does affect platelets, the action is weaker and reversible compared to drugs like aspirin.

Onset and Duration of Effect

Onset: Typically begins working within 30 to 60 minutes after administration.

Duration: Relief generally lasts between 4 to 6 hours, though extended-release forms may provide longer-lasting effects.

Dose Dependence: Higher doses provide longer relief but may increase the risk of side effects.

Effervescent Formulation: Advantages

Improved Solubility and Absorption: The effervescent form breaks down quickly in water, leading to faster absorption and a quicker peak plasma concentration (Cmax) than regular tablets.

Better Taste: The bubbling action helps mask the unpleasant taste of ibuprofen, improving palatability, especially for children and older patients.

Less Stomach Irritation: The buffering agents in effervescent tablets can minimize gastrointestinal side effects, which are common with standard NSAID tablets.

Stability and Shelf Life: Properly stored effervescent granules maintain their potency and quality for over 500 days at 4°C, making them reliable under controlled conditions.

Limitations of Effervescent Ibuprofen Granules

Sensitive to Moisture: These granules absorb moisture easily, which can degrade their quality. They require moisture-resistant packaging.

More Expensive to Produce: Manufacturing effervescent products involves special ingredients and processes, making it more costly than producing regular tablets.

Bulkier Packaging: Because of the moisture sensitivity and volume of the granules, the packaging is usually larger, making storage and transport less convenient.

High Sodium Levels: Some versions include significant sodium, which may be unsuitable for individuals on sodium-restricted diets (e.g., patients with hypertension or heart conditions).

Effervescence Behavior and Testing

To evaluate performance:

One dose is placed in 200 mL of water at 25 ± 2°C.

Start Time: When bubbling begins.

Completion Time: When all solid particles are fully dissolved.

This test ensures rapid disintegration and ease of use, which are essential for patient satisfaction and therapeutic effectiveness.

Physicochemical Characteristics

Solubility

Ibuprofen has low solubility in water (~0.05 g/100 mL), which limits its absorption.

Effervescent agents (e.g., citric acid and sodium bicarbonate) create an acidic environment, increasing the solubility and absorption of the drug.

Dissolution Profile

The effervescence reaction releases carbon dioxide, which aids in breaking apart the tablet and releasing the drug more rapidly into the solution.

Factors such as formulation design, particle size, and drug-excipient interactions impact the dissolution rate.

Particle Size and Form

Smaller particles dissolve faster, leading to better bioavailability.

Polymorphic forms of ibuprofen vary in solubility; amorphous forms tend to dissolve more easily but may be less stable than crystalline ones.

Efficiency of Effervescence

The combination of an acid (like citric acid) and a base (such as sodium bicarbonate) releases CO_2 gas, which contributes to disintegration and drug dispersion.

CO_2 release rate is critical for ensuring timely disintegration and optimal drug delivery.

Disintegration Time

Quick disintegration in water ensures faster therapeutic action.

This time is carefully tested to confirm the product's performance and usability.

METHODOLOGY:

Materials

The following pharmaceutical-grade ingredients were used in the formulation of ibuprofen effervescent granules:

Ibuprofen – sourced from Samarra Drug Industries, Iraq

Citric Acid – from Evonik Degussa Ltd., India

Tartaric Acid – obtained from Aldrich, USA

Sodium Bicarbonate

Hydroxypropyl Methylcellulose (HPMC E5) – supplied by Gainland Chemical Company, U.K.

Microcrystalline Cellulose (MCC) – from Riedel-De-Haen AG Seelze, Germany

Croscarmellose Sodium

Preparation of Ibuprofen Effervescent Granules

The wet granulation method was employed to prepare the effervescent granules of ibuprofen.

Weighing and Mixing

All ingredients were precisely measured. The active ingredient (ibuprofen) was blended with citric acid, tartaric acid, sodium bicarbonate, and other excipients using geometric dilution to ensure homogeneous distribution. This blend was then passed through sieve no. 25 to obtain a fine and uniform powder.

Preparation of Binding Solution

A binding solution was prepared by dissolving HPMC E5 in a suitable solvent (e.g., purified water).

Granulation Process

The binding solution was added slowly to the dry powder mixture with continuous mixing to produce a damp mass. This moist mass was then forced through sieve no. 25 to form granules of consistent size.

Drying of Granules

The formed granules were dried in a hot air oven at 40°C overnight to remove excess moisture and achieve appropriate granule hardness.

Detailed Steps

Weighing and Sieving

Each component, including ibuprofen, acids, and bicarbonate, was weighed accurately. The blend was passed through a **20-mesh sieve** for better uniformity.

Mixing

Powders were blended thoroughly using the geometric dilution method to achieve a uniform distribution of the active pharmaceutical ingredient (API).

Binding and Wet Massing

A measured quantity of HPMC solution was added gradually while mixing to form a moist, cohesive mass.

Granule Formation

The moist material was passed through a **20-mesh sieve** to shape uniform granules.

Drying

The granules were dried at **40°C** using a controlled hot air oven until the desired moisture level was reached.

Evaluation of Granules

Flow Property Assessment

To evaluate the handling and processability of granules, the following parameters were measured:

Angle of Repose (θ):

This angle indicates the internal friction or resistance between particles. It is determined by the height (**h**) and radius (**r**) of a cone formed by pouring granules through a fixed funnel onto a flat surface. The formula used is:

$$\tan\theta = \frac{h}{r} \tan\theta = rh$$

The tangent of the angle is calculated and converted to degrees using a scientific calculator.

Bulk and Tapped Densities:

Granules were placed into a graduated cylinder to measure bulk volume and then tapped to obtain tapped volume. These measurements provide insights into the flow behavior and compressibility.

Drug Content Uniformity

A known quantity of granules was dissolved in a suitable solvent. The solution was filtered and analyzed using **UV-Visible spectrophotometry** to ensure consistent ibuprofen concentration across different samples.

FORMULATION TABLE:

Sr. no.	Ingredient	mg	gm
1	Ibuprofen	2971	2.971
2	Citric acid	1075	1.075
3	Tartaric Acid	2150	2.150
4	Sodium bicarbonate	3656	3.656
5	Saccharin	74	0.074
6	Sodium starch glycolate	25	0.025
7	Orange oil	5ML	5ML

OBSERVATION

Flow properties of Ibuprofen Effervescent granules

RANGE BETWEEN VALUES OF EFFERVESCENT GRANULES PARAMETER	RESULT VALUES	FLOW PROPERTY
Bulk Density were in the Range of 0.4-0.8gm/ml	0.7gm/ml	GOOD
Tapped Density were in the Range 0.5-0.9gm/ml	0.8gm/ml	GOOD
Carr′s Index were in the Range of 12.1-14.03%	12.5%	GOOD
Hausner′s Ratio were in the Range 1.13-1.16	1.14	GOOD
Angle of Repose were in the Range of 25.2^0–32.98^0	30.11^0	GOOD

Result:

Effervescent granules of ibuprofen were successfully formulated using the wet granulation technique, with ingredient concentrations optimized based on the formulation table. The resulting granules were subjected to flow property evaluations, which are critical for ensuring uniformity and processability in granule-based dosage forms.

The granules exhibited favorable flow characteristics. Specifically, the bulk density was measured at 0.7 g/mL, and the tapped density was 0.8 g/mL. The Hausner's ratio was calculated as 1.14, and the angle of repose was recorded at 30.11°, all of which indicate good flow behavior. These findings suggest that the wet granulation method was effectively employed to achieve a formulation with desirable flow properties.

Conclusion:

The study successfully developed and evaluated effervescent granules of ibuprofen using the wet granulation method. The optimized formulation, comprising citric acid, tartaric acid, sodium bicarbonate, saccharin sodium, croscarmellose sodium, orange oil, and microcrystalline cellulose, produced granules that showed excellent flow characteristics, physical stability, and rapid effervescence.

Preformulation assessments and in-vitro evaluations confirmed appropriate values for bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose, validating the granules' good flowability and compressibility. The prepared formulation achieved more than 99% drug release within 45 minutes, with effervescence completion in under 80 seconds, enabling a quicker therapeutic response.

Additionally, FTIR spectral analysis revealed no significant interactions between the drug and excipients, confirming the formulation's chemical compatibility. In summary, the prepared effervescent granules provide a more palatable, rapidly acting, and gastric-friendly alternative to conventional ibuprofen tablets, enhancing both therapeutic efficacy and patient compliance.

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How to cite this article:
Mr. Bendke Navnath S et al. Ijppr.Human, 2025; Vol. 31 (6): 361-367.

Conflict of Interest Statement: All authors have nothing else to disclose.