

Comprehensive Review on Effervescent Tablets of Flunarizine Dihydrochloride.

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Date of Submission: 01-04-2026

Date of Acceptance: 10-04-2026

Abstract

Effervescent drug delivery systems have emerged as an innovative approach to enhance the performance of orally administered drugs, particularly those with poor solubility. Flunarizine dihydrochloride, a calcium channel blocker used in migraine prophylaxis, exhibits low aqueous solubility and undergoes extensive first-pass metabolism, resulting in limited bioavailability. Effervescent tablets offer a promising solution by rapidly generating carbon dioxide upon contact with water, leading to faster disintegration, improved dissolution, and enhanced absorption. This review highlights the formulation strategies, mechanism, excipients, manufacturing techniques, and evaluation parameters of effervescent tablets with a focus on flunarizine dihydrochloride. Additionally, the advantages, limitations, and future perspectives of effervescent drug delivery systems are discussed. These systems provide improved patient compliance, rapid onset of action, and better therapeutic outcomes, making them a suitable alternative to conventional dosage forms.

Keywords

Effervescent tablets, Flunarizine dihydrochloride, Drug delivery system, Bioavailability, Migraine, Solubility enhancement

I. Introduction

Oral drug delivery remains the most widely accepted and preferred route due to its convenience, cost-effectiveness, and high patient compliance. However, conventional oral dosage forms often face challenges such as poor solubility, variable absorption, and first-pass metabolism.^[1]

Flunarizine dihydrochloride is a BCS Class II drug characterized by low solubility and high permeability. Its therapeutic effectiveness is often

limited due to dissolution rate-dependent absorption. Therefore, there is a need for advanced drug delivery systems that can enhance its solubility and bioavailability.^[2-4]

Effervescent tablets represent one such novel approach that converts a solid dosage form into a rapidly dissolving solution, thereby improving drug performance and patient acceptability.^[5]

II. Overview of Migraine and Role of Flunarizine

Migraine is a chronic neurological disorder characterized by recurrent headaches, often associated with nausea, vomiting, and sensitivity to light and sound. It significantly impacts the quality of life and productivity of affected individuals.

Flunarizine dihydrochloride is widely used in migraine prophylaxis due to its calcium channel blocking activity. It reduces neuronal excitability and prevents vasospasm, thereby decreasing the frequency and severity of migraine attacks.

Despite its effectiveness, the drug suffers from poor aqueous solubility and delayed onset of action when administered in conventional tablet form, highlighting the need for improved formulations.^[6,7]

III. Effervescent Tablets: Concept and Mechanism

Effervescent tablets are uncoated solid dosage forms containing a mixture of acids (e.g., citric acid, tartaric acid) and carbonates or bicarbonates (e.g., sodium bicarbonate). Upon contact with water, these components react to release carbon dioxide gas, resulting in rapid tablet disintegration and formation of a solution.^[8]

➤ Mechanism of Effervescence

The reaction typically involves:

Citric acid + Sodium bicarbonate → Sodium citrate + CO₂ + Water

Tartaric acid + Sodium bicarbonate → Sodium tartrate + CO₂ + Water

This effervescence enhances drug dissolution, improves taste masking, and facilitates faster absorption.^[9]

IV. Advantages of Effervescent Tablets

Effervescent tablets offer several benefits over conventional dosage forms:

- Improved solubility and bioavailability
- Rapid onset of action
- Enhanced patient compliance
- Suitable for paediatric and geriatric patients
- Uniform drug distribution in solution
- Reduced gastric irritation
- Taste masking of bitter drugs

These advantages make them particularly suitable for drugs like flunarizine with solubility limitations.^[10]

V. Limitations of Effervescent Tablets

Despite their benefits, effervescent tablets have certain drawbacks^[11]:

- High sensitivity to moisture
- Complex and costly manufacturing process
- Requirement of special packaging (e.g., moisture-resistant tubes)
- Not suitable for all drugs
- Need for water before administration
- Possible gastric discomfort due to CO₂ release

VI. Formulation Components of Effervescent Tablet

Effervescent tablets consist of several essential components:

- Active Pharmaceutical Ingredient (API): Provides therapeutic effect
- Acid source: Citric acid, tartaric acid
- Alkaline source: Sodium bicarbonate
- Binders: Improve tablet integrity
- Diluents: Increase bulk
- Sweeteners and flavours: Enhance palatability
- Lubricants and glidants: Improve flow and compression
- Desiccants: Prevent moisture absorption

Each component plays a crucial role in ensuring tablet stability and performance.^[12]

VII. Manufacturing Techniques

Various methods are used in the preparation of effervescent tablets^[13]:

7.1 Wet Granulation

Improves flow properties and compressibility
Suitable for large-scale production

7.2 Dry Granulation

Ideal for moisture-sensitive drugs
Involves slugging or roller compaction

7.3 Direct Compression

Simple and cost-effective
Requires good flow and compressibility of powders.

7.4 Advanced Techniques

- Fluidized-bed granulation
- Hot-melt granulation
- High-shear granulation

These techniques ensure uniformity, stability, and optimal tablet performance.

VIII. Evaluation of Effervescent Tablets

Evaluation is essential to ensure quality, safety, and efficacy. Key parameters include:

- **Pre-compression parameters:** Angle of repose, bulk density, tapped density, Carr's index, hausner's ratio
- **Post-compression parameters:**
 - 1) Weight variation
 - 2) Hardness
 - 3) Friability
 - 4) Thickness
- **Functional parameters:**
 - 1) **Effervescent time:** Effervescent time measures the duration for a tablet to completely dissolve and release gas in water.
Procedure: Add one tablet into 200 mL purified water at 20 ± 1 °C. Record the time until a clear solution is formed. Take the average of three measurement.
 - 2) **pH of solution:** The pH of the effervescent solution is measured immediately after complete dissolution using a pH meter.
Procedure: Dissolve one tablet in 200 mL purified water at 20 ± 1 °C. Record the pH value to ensure proper formulation and patient safety.
 - 3) **Water absorption ratio:** The water absorption ratio will be determined to measure the tablet's capacity to absorb moisture, promoting faster disintegration. It will be calculated using the formula:
$$R = (W_a - W_b) / W_b \times 100$$

Where; W_a = Weight of tablet after water absorption and W_b = Weight of tablet before water absorption

A higher R value will indicate greater moisture uptake and a faster disintegration rate.

- 4) **Wetting time:** Wetting time will be assessed to evaluate the tablet's ability to absorb moisture, which influences its disintegration behaviour. Each tablet will be placed on absorbent paper in a Petri dish containing a small quantity of water, and the time required for complete wetting will be recorded.
- 5) **Drug content:** Ten tablets will be powdered, and an accurately weighed portion will be dissolved in a suitable solvent at a predetermined pH. The solution will be filtered and analyzed using a UV-visible spectrophotometer. The procedure will be performed in triplicate, and the average value will be used to determine drug content uniformity among the tablets.

These tests confirm the consistency and performance of the formulation.^[14-16]

IX. Application to Flunarizine Dihydrochloride

Flunarizine dihydrochloride exhibits Poor water solubility, High lipophilicity (log P ~6.17), Extensive hepatic metabolism.

Effervescent formulation can:

- Enhance dissolution rate
- Improve bioavailability
- Provide faster therapeutic action
- Improve patient compliance

Thus, effervescent tablets represent a promising approach for effective delivery of flunarizine in migraine management.^[17]

X. Future Perspectives

Recent advancements in effervescent technology focus on:

- Moisture-resistant formulations
- Novel excipients for stability
- Effervescence-assisted solubilization
- Integration with nanotechnology

These innovations may further enhance the applicability of effervescent systems for poorly soluble drugs.

XI. Conclusion

Effervescent tablets are an effective and patient-friendly drug delivery system that addresses the limitations of conventional oral dosage forms. For drugs like flunarizine dihydrochloride, which suffer from poor solubility and bioavailability,

effervescent formulations provide significant advantages in terms of rapid dissolution, improved absorption, and enhanced therapeutic efficacy.

This review highlights the importance of effervescent technology as a promising strategy for optimizing drug delivery and improving patient outcomes in migraine therapy.

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