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Research Article

Formulation And Evaluation Of Celecoxib Effervescent Tablet

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ABSTRACT

Effervescent tablets offer a promising alternative for drug delivery, providing rapid disintegration and enhanced dissolution rates. Celecoxib, a nonsteroidal anti-inflammatory drug, is commonly used for the treatment of pain and inflammation associated with osteoarthritis, rheumatoid arthritis, and other conditions. Effervescent formulations of celecoxib have garnered attention due to their potential to improve drug delivery efficiency and patient compliance. This research explores the development and evaluation of celecoxib effervescent tablets. Efforts have been made to optimize formulation parameters such as effervescent agents, binders, disintegrants, and active pharmaceutical ingredients to ensure rapid disintegration and dissolution. Comparative studies with conventional dosage forms have demonstrated the superiority of celecoxib effervescent tablets in terms of onset of action, bioavailability, and patient acceptance. Despite being the most popular method of medication administration, oral dosage forms have drawbacks compared to other methods, such as the risk of slow drug absorption. This issue can be addressed by administering drugs in liquid form, potentially allowing for lower doses. However, the instability of many drugs in liquid form limits its use. An alternative approach is the use of the effervescent technique to develop dosage forms that accelerate drug disintegration and dissolution, typically applied in quick-release preparations. With the advancement of pharmaceutical techniques, effervescent tablets are increasingly utilized to modify drug release behavior, including in sustained and controlled release preparations and pulsatile drug delivery systems.

INTRODUCTION

An effervescent tablet is a pharmaceutical dosage form designed to rapidly dissolve in water, releasing carbon dioxide bubbles and creating a fizzy or effervescent solution. These tablets typically contain a combination of acid and base compounds that react when exposed to water, generating carbon dioxide gas. This reaction helps in the dispersion and dissolution of the tablet's active ingredients, facilitating faster absorption in the body.

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Effervescent tablets offer several advantages over conventional dosage forms, including:

I. Rapid disintegration: Effervescent tablets dissolve quickly in water, allowing for faster drug absorption and onset of action compared to traditional tablets or capsules.

II. Enhanced drug delivery: The effervescence generated by these tablets helps in dispersing the drug particles uniformly, leading to enhanced dissolution and bioavailability.

III. Convenient dosage form: Effervescent tablets are easy to administer and do not require swallowing whole, making them suitable for individuals with swallowing difficulties or children.

IV. Improved taste: Effervescent tablets often have a pleasant taste due to the carbonation, which can help mask the taste of bitter or unpleasant drugs, enhancing patient compliance.

1. Stability:

Effervescent tablets can be individually packaged to prevent exposure to moisture, increasing their shelf life and stability compared to liquid formulations.(1,2,3,4) Overall, effervescent tablets offer a versatile and effective approach to drug delivery, suitable for a wide range of therapeutic applications.

Celecoxib :

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that belongs to the class of selective cyclooxygenase-2 (COX-2) inhibitors. It is primarily used for the treatment of pain, inflammation, and swelling associated with various conditions such as osteoarthritis, rheumatoid arthritis, acute pain, menstrual cramps, and ankylosing spondylitis. Unlike traditional NSAIDs, which inhibit both cyclooxygenase enzymes (COX-1 and COX-2), celecoxib selectively targets COX-2, thereby reducing inflammation and pain without affecting the protective functions of COX-1 in the stomach lining. Celecoxib works by inhibiting the production of prostaglandins, which are chemicals in the body that promote inflammation, pain, and fever. By blocking COX-2, celecoxib helps alleviate symptoms of inflammation and pain, providing relief to individuals with various musculoskeletal disorders. Celecoxib is available in various formulations, including capsules, tablets, and oral suspensions, and is typically taken orally with or without food. It is important to follow the prescribed dosage and instructions provided by healthcare professionals to minimize the risk of side effects, which may include gastrointestinal ulcers or bleeding, cardiovascular events, and kidney problems. Overall, celecoxib is an effective medication for managing pain and inflammation associated with various conditions, offering a selective and targeted approach to treatment with a reduced risk of gastrointestinal side effects compared to traditional NSAIDs.(5,6,7,8) Effervescent tablets offer several potential benefits when formulated with celecoxib, a nonsteroidal anti-inflammatory drug (NSAID). Some of these benefits may include:

I. Rapid Onset of Action:

Effervescent formulations generally disintegrate and dissolve more quickly in the gastrointestinal tract compared to conventional tablets or capsules. This can lead to faster absorption of celecoxib, potentially resulting in a more rapid onset of action for pain relief.

II. Improved Patient Compliance:

Effervescent tablets are often preferred by patients who have difficulty swallowing traditional tablets or capsules. Their fizzy nature and pleasant taste can make them easier and more enjoyable to take, improving overall adherence to the prescribed medication regimen.

III. Enhanced Bioavailability:

Effervescent formulations can enhance the solubility and dissolution rate of poorly water-soluble drugs like celecoxib. This improved dissolution may lead to higher drug concentrations in the bloodstream, thereby increasing the drug's bioavailability and therapeutic efficacy.(9,10,11)

IV. Reduced Gastrointestinal Side Effects:

Selective COX-2 inhibitors like celecoxib are associated with a lower risk of gastrointestinal complications compared to non-selective NSAIDs. Effervescent formulations may further decrease the risk of gastrointestinal irritation or ulceration by reducing the time the drug spends in the stomach and minimizing direct contact with gastric mucosa.

V. Customizable Dosage Forms:

Effervescent tablets offer flexibility in dose adjustment, allowing for the formulation of different strengths tailored to individual patient needs. This customization can optimize therapeutic outcomes while minimizing the risk of adverse effects associated with over- or under-dosing.

VI. Enhanced Product Stability:

Effervescent tablets can be individually packaged in moisture-resistant packaging, protecting the drug from environmental degradation and maintaining its stability over time. This can prolong the shelf life of the medication and ensure its efficacy until the time of consumption.

Overall, celecoxib effervescent tablets have the potential to offer a convenient, effective, and well-tolerated dosage form for the management of pain and inflammation associated with various conditions, contributing to improved patient outcomes and satisfaction.(12,13,14)

Excipients :

a. Citric Acid:

Provides the acidic component necessary for the effervescence reaction when combined with a carbonate or bicarbonate salt.

b. Sodium Bicarbonate (NaHCO3):

A carbonate salt that reacts with citric acid to release carbon dioxide gas, resulting in effervescence and tablet disintegration.

c. Tartaric Acid:

Another acidulant option that can be used in combination with carbonate or bicarbonate salts to generate effervescence.

d. Carbonate Salts (e.g., Sodium Carbonate, Potassium Carbonate):

React with acids to release carbon dioxide gas and create effervescence.

e. Sweeteners (e.g., Aspartame, Sucralose):

Used to improve the taste of the effervescent tablet.

f. Flavoring Agents (e.g., Fruit flavors):

Enhance the palatability of the tablet.

g. Colorants:

Provide aesthetic appeal and aid in tablet identification.

h. Binders (e.g., Polyvinylpyrrolidone, Povidone):

Help to hold the tablet ingredients together during compression.(15,16,17,18,19)

i. Lubricants (e.g., Magnesium Stearate, Sodium Stearyl Fumarate):

Prevent sticking of tablet ingredients to the tablet press.

j. Disintegrants (e.g., Crospovidone, Sodium Starch Glycolate):

Aid in the rapid disintegration of the tablet upon contact with water, promoting drug dissolution and absorption.

Content table:

Ingredient	F1(mg)	F2(mg)	F3(mg)	F4(mg)
Celecoxib	100	100	100	100
Nahco3	40	40	40	40
Citric Acid	37	-	18	12
Tartaric Acid	-	37	19	25
Crospovidone	15	15	15	15
Gelatin	6	6	6	6
Starch	4	4	4	4
Talc	8	8	8	8
Lactose	30	30	30	30
Total	240	240	240	240

Preformulation Studies :

1. Bulk density :

Bulk density is a measure of the mass of a powder divided by its bulk volume. It is typically expressed in grams per milliliter (g/mL) or grams per cubic centimeter (g/cm^3). Bulk density is determined by weighing a known volume of the powder and calculating the ratio of mass to volume.

The formula for bulk density is:

Bulk Density=Bulk Volume of Powder/Mass of Powder

Bulk volume is the total volume occupied by the powder, including the spaces between individual particles. It can be determined by pouring the powder into a graduated cylinder or measuring cup and tapping it gently to settle the powder. Bulk density is an important parameter in powder characterization and pharmaceutical formulation. It provides information about the packing properties of the powder, which can influence factors such as powder flow, compaction behavior, and storage stability. By measuring bulk density, scientists can optimize powder formulations and manufacturing processes to ensure consistent quality and performance of the final product.(20,21)

2. Tapped Density :

Tapped density is a measure of the mass of a powder divided by its tapped volume. It is typically expressed in grams per milliliter (g/mL) or grams per cubic centimeter (g/cm^3). Tapped density is determined by subjecting a powder sample to a specified tapping procedure to settle the particles and reduce the void spaces between them. The tapping procedure involves placing a measured volume of the powder into a graduated cylinder or other suitable container and subjecting it to a specified number of taps under controlled conditions. The container is tapped until no further volume change is observed, indicating that the powder has reached its maximum tapped density.

The formula for tapped density is:

Tapped Density=Tapped Volume of Powder/Mass of Powder

Tapped volume is the volume occupied by the powder after tapping, which is typically lower than the bulk volume due to the reduction in void spaces between particles. Tapped density is an important parameter in powder characterization, particularly in the pharmaceutical industry. It provides information about the packing properties of the powder and its ability to settle under compaction. Tapped density measurements are used to assess powder flow, compressibility, and dosage form uniformity, and to optimize formulation and manufacturing processes.(22,23,24)

3. Carr's Index :

Carr's Index, also known as the Carr Index or Carr's Compressibility Index, is a measure used in pharmaceutical and powder technology to assess the flow properties of granular or powdered

materials. It's named after Ralph J. Carr, who introduced it in 1965.

The formula for Carr's Index is:

Carr's Index=Bulk Density−Tapped Density/Bulk Density×100%

Where:

- **Bulk Density:**

The density of the powder in its loosest packed state.

- **Tapped Density:**

The density of the powder after tapping or compacting.

Carr's Index provides an indication of the flowability of powders. A lower Carr's Index value indicates better flow properties, while a higher value suggests poor flowability.

Here's what the values generally represent:

- Less than 10%: Excellent flowability
- 11% to 15%: Good flowability
- 16% to 20%: Fair flowability
- More than 21%: Poor flowability

This index is particularly important in industries where powders or granular materials are handled, such as pharmaceuticals, food processing, and chemical engineering, as poor flow properties can lead to problems in manufacturing processes and dosing accuracy.(25,26)

4. Hausnour Ratio :

The Hausner Ratio is calculated as the ratio of tapped density to bulk density:

Hausner Ratio=Tapped Density/Bulk Density

Like Carr's Index, the Hausner Ratio provides insight into the flowability of powders. A higher Hausner Ratio indicates poorer flow properties, while a lower ratio suggests better flowability.

The interpretation of Hausner Ratio values is similar to that of Carr's Index:

- Less than 1.25: Excellent flowability
- 1.25 to 1.34: Good flowability
- 1.35 to 1.45: Fair flowability
- More than 1.45: Poor flowability

Both Carr's Index and Hausner Ratio are commonly used in tandem to comprehensively evaluate the flow properties of powdered or granular materials in various industries.(27,28)

5. Angle of Repose:

The angle of repose is another important parameter used to assess the flow properties of granular or powdered materials. It refers to the maximum angle at which a pile of material remains stable without slumping or cascading. To measure the angle of repose, you typically pour a sample of the material onto a flat surface, allowing it to form a cone-shaped pile naturally. Then, you measure the angle between the surface and the slope of the cone. This angle is the angle of repose. The angle of repose can vary depending on factors such as particle size, shape, and moisture content. Materials with larger particle sizes or irregular shapes tend to have larger angles of repose, indicating poorer flow properties, while materials with smaller, smoother particles tend to have smaller angles of repose, indicating better flow properties. In industries dealing with bulk solids like pharmaceuticals, food processing, agriculture, and mining, the angle of repose is a critical parameter for designing equipment and optimizing processes involving the handling, storage, and transportation of granular or powdered materials. The formula for calculating the angle of repose involves trigonometry. The tangent of the angle of repose (θ) is equal to the ratio of the height (*h*) of the cone formed by the material to the radius (r) of the base of the cone. Mathematically, it can be expressed as:

$$\tan(\theta)=r/h$$

So, to find the angle of repose (θ), you can use the arctangent function:

$$\theta=\arctan(r/h)$$

Where:

- θ is the angle of repose.
- h is the height of the cone formed by the material.

- r is the radius of the base of the cone.

This formula allows you to calculate the angle of repose based on the measurements of the pile of material formed during the experiment.(29,30,31)

Table of Preformulation Study:

Parameter	F1	F2	F3	F4
Bulk Density(G/Cm³)	17.5	17	19.5	15.5
Tapped Density(G/Cm³)	12.5	11.5	10	9.5
Angle Of Repose	29.24	32.09	28.14	33.75
Carr`s Index (%)	28.57	32.35	48.71	35.48
Hausner`S Ratio	1.4	1.47	1.95	1.63

Direct Compression Method:

The Direct Compression Method is a common technique used in pharmaceutical manufacturing to produce tablets. It is a preferred method when the active pharmaceutical ingredient (API) and excipients have good flow properties and compressibility.

Here's an overview of the Direct Compression Method:

1. **Blend Preparation:**

The first step involves blending the active pharmaceutical ingredient (API) with various excipients such as diluents, binders, disintegrants, and lubricants. These excipients are selected based on their functionality to ensure proper flow, compression, and disintegration of the tablet.

2. **Mixing:**

The blended powders are thoroughly mixed to ensure homogeneity. Proper mixing ensures uniform distribution of the API and excipients throughout the blend, which is essential for consistent tablet quality.

3. **Compression:**

Once the blend is adequately mixed, it is compressed directly into tablets using a tablet press. No additional processing steps such as granulation or drying are required, which makes the process more straightforward and cost-effective.

4. **Tablet Evaluation:**

After compression, the tablets undergo various quality control tests to ensure they meet the required specifications for parameters such as weight variation, thickness, hardness, friability, disintegration time, and dissolution rate.(32,33,34,35,36)

Advantages of the Direct Compression Method include:

- Simplified manufacturing process: It eliminates the need for additional processing steps such as granulation, which reduces manufacturing time and costs.
- Preservation of API potency: Since there are no high-temperature or moisture-sensitive processes involved, the method helps preserve the potency of heat or moisture-sensitive APIs.
- Reduced risk of content non-uniformity: With fewer processing steps, there's less risk of content non-uniformity due to segregation or degradation of ingredients.
- However, the Direct Compression Method may not be suitable for all formulations, especially those with poor flow or compressibility properties. In such cases, alternative methods like wet granulation or dry granulation may be preferred.(37,38)

Evaluation Parameters :

1. **Weight Variation :**

The tablet weight variation test is a quality control procedure in pharmaceutical manufacturing to ensure consistency in tablet weights within a batch. It involves randomly selecting tablets, weighing them individually, calculating the

average weight, and comparing individual tablet weights to the average. Acceptance criteria are set based on regulatory standards. If tablets fall within the acceptable range, the batch passes; otherwise, corrective actions are taken.

The Indian Pharmacopoeia (IP) provides specific criteria for the tablet weight variation test. According to IP standards:

1. For tablets weighing 80 mg or less: The individual tablet weight should be within ±10% of the average weight.
2. For tablets weighing more than 80 mg: The individual tablet weight should be within ±7.5% of the average weight. These criteria ensure that the tablets consistently deliver the intended dose and meet the quality standards set by the IP. Any tablets falling outside of these specified limits may require investigation and corrective action.(39)

2. Friability :

Friability is a measure of the tendency of tablets to crumble or break when subjected to mechanical stress or friction during handling, packaging, and transportation. It is an essential parameter in pharmaceutical quality control to ensure that tablets maintain their structural integrity throughout their shelf life. The friability test involves placing a sample of pre-weighed tablets into a friabilator, a rotating drum-like apparatus. The tablets are tumbled within the apparatus for a specified duration, typically 4 minutes, at a defined speed. After tumbling, the tablets are re-weighed to determine the amount of weight loss due to abrasion and breakage. The USP specifies acceptance criteria for tablet friability, typically requiring that the weight loss should not exceed a certain percentage, usually 1% or less. This limit ensures that the tablets remain intact and maintain their intended dosage form throughout handling and use. In summary, the friability test assesses the durability of tablets and their ability to withstand mechanical stress, helping to ensure product quality and patient safety.(40)

3. Hardness:

Tablet hardness, also known as tablet crushing strength, is a crucial parameter in pharmaceutical manufacturing and quality control. It refers to the resistance of a tablet to undergo breakage or crumbling under applied pressure. Hardness is essential because it influences various factors, including tablet disintegration, dissolution, packaging, and handling. The tablet hardness test is typically conducted using a tablet hardness tester, which applies pressure to the tablet until it fractures. The force required to break the tablet is measured in units such as kiloponds (kp) or Newtons (N). Acceptable hardness values vary depending on factors such as the formulation, manufacturing process, and intended use of the tablet. However, common industry standards and pharmacopeias often provide guidelines for acceptable hardness ranges for different types of tablets.(41)

4. Effervescent Time :

To perform the effervescent time test for effervescent tablets, start by preparing the necessary equipment, including a stopwatch, beaker or glass, and a thermometer if temperature control is required. Ensure that the water used for testing is at the specified temperature, typically room temperature or as specified in the formulation. Once prepared, fill the beaker or glass with the specified volume of water and record the initial temperature if required. Drop one effervescent tablet into the water and immediately start the stopwatch upon tablet immersion. Observe the tablet as it dissolves and releases gases, noting the time taken for the tablet to completely dissolve and for effervescence to cease. Record the effervescent time in minutes and seconds accurately. Repeat the test with additional tablets from the same batch to ensure consistency and reliability of results. If required, perform

multiple tests on different batches. Calculate the average effervescent time if multiple tests are performed and compare the results against acceptance criteria provided by regulatory standards or internal quality control specifications.(42)

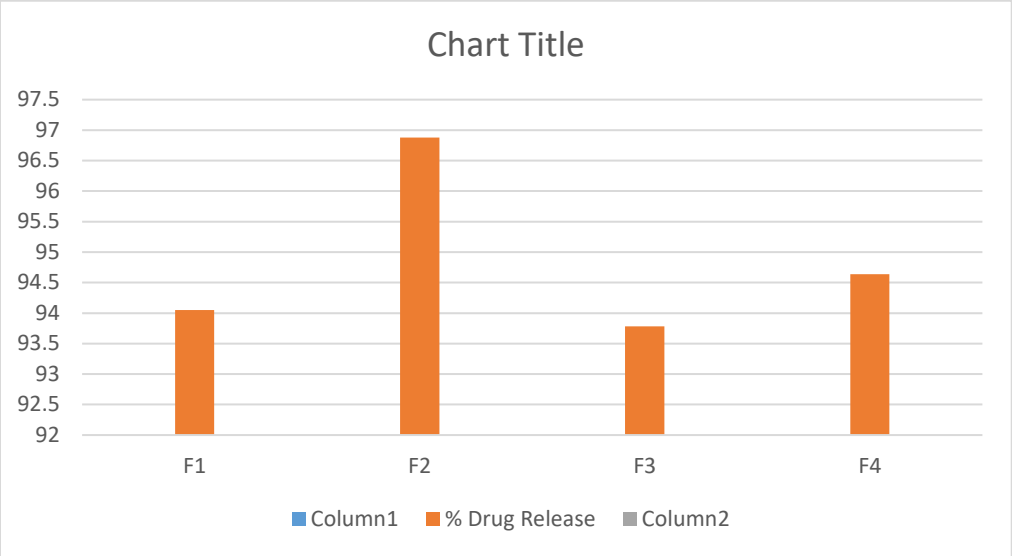
5. PH of Content :

To conduct the pH test on effervescent content, begin by assembling the necessary equipment, including a pH meter, pH electrode, beakers, and calibrated pH buffers spanning the expected pH range of the sample. Calibration of the pH meter is crucial; follow the manufacturer's guidelines and use standard pH buffer solutions to ensure accurate readings. Next, prepare the effervescent content sample as per the specified method, ensuring it accurately represents the content to be tested. If needed, dissolve the effervescent tablet or powder in distilled water to create a homogeneous solution. Submerge the pH electrode into the solution, allowing the pH reading to stabilize on the meter display before recording it to the nearest 0.1 unit. Following measurement, verify the accuracy of the pH meter by cross-checking it against the calibrated pH buffers. If necessary, conduct replicate measurements on the same sample to confirm result consistency, averaging the pH values if multiple measurements are taken. Subsequently, compare the measured pH value against the acceptance criteria outlined in relevant pharmacopeial standards or internal quality control specifications for effervescent formulations. Evaluate any deviations from these criteria to determine their significance regarding product quality and stability. Finally, thoroughly document the test results, including the measured pH value, any deviations from acceptance criteria, and specifics of the effervescent content solution tested. Ensure proper labeling and traceability of the sample throughout the testing process to maintain quality assurance standards. Following these steps diligently ensures an accurate assessment of the pH of effervescent content, facilitating compliance with regulatory standards and internal quality control requirements.(43)

6. Dissolution Test :

To perform the dissolution test for effervescent tablets, begin by assembling the necessary equipment, including a dissolution apparatus suitable for effervescent tablets, dissolution medium (usually water), temperature-controlled bath, and sampling apparatus. Set up the dissolution apparatus according to the specified method outlined in relevant pharmacopeial standards or internal protocols tailored for effervescent tablets. Ensure that the dissolution medium matches the intended use conditions and is appropriate for evaluating the dissolution behavior of the effervescent tablets. Prepare the effervescent tablet samples accurately by weighing or measuring the required amount and place them into the dissolution vessels at the predetermined time points or conditions as per the test method. Initiate the dissolution test by immersing the dissolution vessels containing the effervescent tablets into the temperature-controlled bath. Operate the dissolution apparatus under predefined conditions, including rotation speed and sampling intervals, and maintain the temperature and agitation of the dissolution medium to ensure uniform dissolution of the effervescent tablets. At specified time intervals, withdraw samples from the dissolution vessels using the sampling apparatus. Filter or centrifuge the samples to remove any undissolved particles or gas bubbles, and analyze them for the concentration of the active ingredient or relevant dissolution marker using an appropriate analytical method. Calculate the percentage of the active ingredient dissolved from the effervescent tablets at each time point using the measured concentrations, and plot dissolution profiles to visualize the dissolution behavior over time. Compare the dissolution profiles and results

obtained from the effervescent tablets against the acceptance criteria specified in relevant pharmacopeial standards or internal quality control specifications. Document all aspects of the dissolution test, including the test conditions, sample preparation details, sampling procedure, analytical results, and any deviations from acceptance criteria. Proper labeling and traceability of the effervescent tablet samples throughout the testing process are essential to maintain quality assurance standards. Following these steps meticulously ensures accurate assessment of the dissolution behavior of effervescent tablets, providing valuable insights into their performance and quality.(44)



Graph of %Drug Release

EVALUTION TABLE:

Parameter		F1	F2	F3	F4
Weight Variation(%)	Upper Limit	5.87	4.03	8	3.9
	Lower Limit	10.31	-5.79	-12.1	-5.8
Friability (%)		1.4	1.2	3.4	1.6
Hardness(Kg)		2.3	2.1	2.3	2.5
THICKNESS(Mm)		3.1	3.1	3.1	3.1
Effervescent Time (Min)		3.16	3.57	4.25	5.10
Ph OF CONTENT		6.41	6.42	6.37	6.35
Dissolution (% Drug Release)		94.05	96.88	93.78	94.64

RESULT AND DISCUSSION:

The oral pharmaceutical dosage forms such as capsules and conventional tablets are formulated to be chewed or swallowed. Mostly childrens and old peoples have difficulties in chewing and swallowing these dosage forms. As a effervescent pharmaceutical dosage form , 100mg celecoxib is not available in this form . Since it is better tolerated by patients and better results in faster recovery. So, we decided to formulate and evaluate the 100mg celecoxib effervescent tablet. In the effervescent products acid and alkali resources are required for effervescent reaction, so they were used in all batches of formulation Then, pH of solution, solubility and effervescent time were tested. Formulations containing tartaric acid (F2) were considered as a excellent due to good %

drug release , limited weight variation & hardness and faster disintegration.

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41. Advances in Tablet Manufacturing Processes: A Review" by Muhammad Akram and Murtaza Abid (International Journal of Pharmaceutical Sciences and Research)
42. Pharmaceutical Formulation and Development Textbooks: Textbooks such as "Pharmaceutical Dosage Forms: Tablets" by Larry L. Augsburger and Stephen W. Hoag may provide detailed information on effervescent tablet formulation, testing, and quality control.
43. European Pharmacopoeia (Ph. Eur.): The European Pharmacopoeia offers standards for pharmaceutical products in European countries. You can refer to the Ph. Eur. general chapter 2.2.3 "pH Measurement" for information on pH testing methods and acceptance criteria.
44. European Pharmacopoeia (Ph. Eur.): The European Pharmacopoeia offers standards for pharmaceutical products in European countries. You can refer to the Ph. Eur. general chapter 2.9.3 "Dissolution Test for Solid Dosage Forms" for information on dissolution testing methods and acceptance criteria.

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