Formulation And Evaluation of Ciprofloxacin HCL Effervescent Tablets For Enhanced Solubility And Patient Compliance

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Abstract- *This research focuses on the formulation and evaluation of Ciprofloxacin HCl effervescent tablets to enhance solubility and patient compliance. Ciprofloxacin HCl has poor aqueous solubility, leading to delayed dissolution and reduced bioavailability. Effervescent formulations improve solubility, taste, and ease of administration, making them ideal for patients with swallowing difficulties.*

Effervescent tablets were formulated using citric acid and sodium bicarbonate as effervescent agents, along with solubility enhancers, sweeteners, and disintegrants. Preformulation studies, including solubility analysis, drug-excipient compatibility (FTIR), and powder flow properties, were conducted. The optimized formulation exhibited rapid disintegration (2–3 min), enhanced drug release (>85% in 15 min), and stable physicochemical properties.

The study confirms that effervescent Ciprofloxacin HCl tablets offer improved solubility, faster onset of action, and enhanced patient compliance, making them a promising alternative to conventional tablets, especially for pediatric and geriatric patients.

Keywords- Effervescent Tablets, Ciprofloxacin HCl, Solubility Enhancement, Patient Compliance, Dissolution Improvement

I. INTRODUCTION

Ciprofloxacin Hydrochloride (Ciprofloxacin HCl) is a second-generation fluoroquinolone antibiotic extensively used to treat a wide range of bacterial infections, including respiratory tract infections, urinary tract infections (UTIs), gastrointestinal infections, skin and soft tissue infections, and bone infections. It exerts its bactericidal effect by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes that are essential for bacterial DNA replication, transcription, and repair. Due to its broad-spectrum activity and high efficacy, Ciprofloxacin HCl is a preferred choice in antimicrobial therapy. However, its poor aqueous solubility (classified as a Biopharmaceutics Classification System (BCS) Class II drug) significantly limits its dissolution rate and bioavailability, leading to delayed therapeutic action and inconsistent drug absorption. [1]

The effectiveness of an orally administered drug largely depends on its ability to dissolve in the gastrointestinal fluids and be absorbed into systemic circulation. Ciprofloxacin HCl's low solubility results in slower dissolution, which in turn leads to variable pharmacokinetics and potential therapeutic failure, especially in patients requiring rapid antimicrobial action. Moreover, conventional solid oral dosage forms, such as tablets and capsules, often present challenges for pediatric, geriatric, and dysphagic patients, who may struggle with swallowing. Additionally, Ciprofloxacin HCl possesses a bitter taste, which further reduces patient compliance and acceptability. These factors necessitate the development of an alternative drug delivery system that enhances solubility, improves dissolution, ensures ease of administration, and enhances patient adherence. [2]

Effervescent Drug Delivery: A Potential Solution

Effervescent formulations have gained increasing attention in pharmaceutical development due to their ability to enhance the solubility and dissolution rate of poorly water-soluble drugs. Effervescent tablets are designed to dissolve in water, forming a carbonated solution that facilitates drug dispersion and absorption. The core mechanism of an effervescent system involves an acid-base reaction between an organic acid (such as citric acid or tartaric acid) and a carbonate source (such as sodium bicarbonate or potassium bicarbonate). When added to water, these components react to produce carbon dioxide gas, which enhances tablet disintegration and ensures rapid drug dissolution. [3]

Advantages of Effervescent Ciprofloxacin HCl Tablets

The formulation of Ciprofloxacin HCl as an effervescent tablet presents several key advantages over conventional oral dosage forms:

1. Enhanced Solubility and Dissolution Rate
    - The effervescent reaction promotes rapid drug disintegration and dissolution, improving solubility and bioavailability.
    - Faster dissolution leads to quicker absorption and a more immediate therapeutic effect, which is particularly beneficial for treating acute infections.
2. Improved Patient Compliance and Convenience
    - Effervescent tablets eliminate the need for swallowing solid tablets, making them suitable for pediatric, geriatric, and dysphagic patients.
    - They offer a more palatable and patient-friendly alternative, especially for those who experience difficulty swallowing conventional dosage forms.
3. Taste Masking and Better Acceptability
    - The effervescence and flavoring agents help mask the bitter taste of Ciprofloxacin HCl, making the medication more pleasant and acceptable to patients.
4. Uniform Drug Dispersion
    - Effervescent formulations ensure even drug distribution in solution, reducing the risk of dose variability and improving absorption consistency.
5. Gastrointestinal Tolerance and Reduced Irritation
    - Conventional solid tablets may cause local irritation in the gastrointestinal tract, particularly in the esophagus and stomach.
    - Effervescent solutions are less likely to cause irritation and may be better tolerated by patients with sensitive gastrointestinal systems. [4]

II. LITERATURE REVIEW

[1] **Tadros, M. I. (2010):** Ciprofloxacin hydrochloride has a short elimination half-life and a narrow absorption window, being primarily absorbed in the proximal gastrointestinal tract. This study aimed to develop a gastroretentive controlled-release drug delivery system exhibiting swelling, floating, and adhesive properties. Ten tablet formulations were designed using hydroxypropylmethylcellulose (HPMC K15M) and/or sodium alginate as release-retarding polymers, with sodium bicarbonate or calcium carbonate as gas-forming agents. Evaluations included swelling ability, floating behavior, adhesion period, and drug release studies in 0.1 N HCl (pH 1.2) at 37±0.5°C. The tablets demonstrated acceptable physicochemical properties, with drug release profiles following a non-Fickian diffusion mechanism. Statistical analyses indicated that formulations containing HPMC K15M (21.42% w/w), sodium alginate (7.14% w/w), and either sodium bicarbonate or calcium carbonate (20% w/w) were promising, exhibiting excellent floating properties, extended adhesion periods, and sustained drug release characteristics. Abdominal X-ray imaging in six healthy volunteers revealed a mean gastric retention period of 5.50±0.77 hours

[2] **Mounika, D., Reddy (2020):** This study focused on developing floating matrix tablets of ciprofloxacin HCl to enhance gastric residence time and improve bioavailability. Tablets were prepared using hydroxypropyl methylcellulose (HPMC K100M) as the matrix-forming polymer and sodium bicarbonate as the gas-generating agent. The formulations were evaluated for pre-compression parameters, including angle of repose, bulk density, tapped density, and Carr's index, indicating good flow properties. Post-compression parameters such as weight variation, hardness, friability, drug content, buoyancy lag time, total floating time, and in vitro drug release were also assessed. The optimized formulation exhibited a buoyancy lag time of 8.6 seconds and remained afloat for over 8 hours, with a cumulative drug release of 61.31% at the end of 8 hours, following zero-order kinetics.

[3] **Panjiyar, A., & Bajracharya, R. (2019):** The objective of this research was to formulate and evaluate effervescent floating tablets of ciprofloxacin HCl to prolong gastric residence time and enhance bioavailability. Tablets were prepared using different concentrations of HPMC K4M and carbopol 934P as matrix-forming agents, along with sodium bicarbonate and citric acid as effervescent components. The formulations were assessed for pre-compression parameters (angle of repose, bulk density, tapped density, Carr's index) and post-compression parameters (weight variation, hardness, friability, drug content, buoyancy lag time, total floating time, in vitro drug release). The optimized formulation demonstrated a buoyancy lag time of 30 seconds and remained buoyant for over 12 hours, with a cumulative drug release of 95.45% at the end of 12 hours, following a non-Fickian diffusion mechanism.

[4] **Varshosaz, J., Tavakoli, N., & Roozbahani, F. (2006):**Ciprofloxacin is mainly absorbed in the proximal areas of the gastrointestinal tract. This study aimed to produce floating-bioadhesive tablets to prolong the drug's residence time in its absorption area. Effervescent tablets

were formulated using sodium carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), polyacrylic acid (AA), polymethacrylic acid (MAA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had a longer lag time compared to those with 10%. The type of polymer did not significantly affect the floating lag time. All tablets floated atop the medium for 23-24 hours. Increasing CMC content resulted in higher mucoadhesion than AA ($p < 0.05$). All formulations exhibited a Higuchi, non-Fickian release mechanism. Tablets with 10% effervescent base and compositions of either 80% CMC/20% HPMC or 80% AA/20% MAA were deemed desirable.

[5] **Arza, R. A. (2009):** This study focused on developing swellable and floating gastroretentive tablets of ciprofloxacin HCl to enhance its bioavailability by prolonging gastric residence time. Tablets were prepared using various polymers, including HPMC K4M, sodium carboxymethylcellulose, and polyvinylpyrrolidone, along with sodium bicarbonate as a gas-generating agent. The formulations were evaluated for swelling index, floating lag time, total floating duration, and in vitro drug release. The optimized formulation exhibited a floating lag time of 20 seconds, remained buoyant for over 12 hours, and released 98.5% of the drug over 12 hours, following a non-Fickian diffusion mechanism.

[6] **Chokshi, M. M. (2016):** The study aimed to formulate floating tablets of ciprofloxacin hydrochloride to prolong gastric residence time and achieve controlled drug release. Tablets were prepared using wet granulation with Hydroxypropyl Methylcellulose (HPMC) K-100M, HPMC K-4M, and Carbopol 934P as polymers, employing an effervescent technique with sodium bicarbonate as the gas-generating agent. Evaluations included weight uniformity, hardness, friability, drug content, in vitro buoyancy, and dissolution studies. Tablets swelled both radially and axially during buoyancy tests, remaining afloat for 10-14 hours. The optimal in vitro buoyancy was achieved with a combination of 70 mg sodium bicarbonate and 20 mg citric acid. The study concluded that formulations with HPMC K-100M exhibited longer floating durations compared to those with HPMC K-4M, and drug release could be prolonged up to 14 hours using a blend of HPMC K-100M and sodium bicarbonate in a gastroretentive floating tablet.

[7] **Pasa, G. (2018):** This research focused on developing oral floating matrix tablets of ciprofloxacin HCl using Hydroxypropyl Methylcellulose (HPMC) K100M and Xanthan gum as retardant polymers, aiming to increase gastric residence time and improve bioavailability. The tablets were prepared via direct compression, incorporating sodium bicarbonate as a gas-generating agent. Evaluations covered weight variation, friability, hardness, drug content, floating lag time, total floating time, and in vitro drug release. The optimized formulation (CHX8) sustained drug release over 12 hours, with 20% released after 1 hour and over 97% at 12 hours. Kinetic analysis indicated that the release followed zero-order and Higuchi models, with a non-Fickian diffusion mechanism.

[8] **Mostafavi, A. (2018):** The objective was to develop controlled-release matrix tablets of ciprofloxacin HCl to reduce dosing frequency and enhance patient compliance. Tablets were formulated using Ethocel™ 100 Premium and Eudragit® RS PO as rate-controlling polymers, with granulation involving isopropyl alcohol and dichloromethane. Evaluations included weight variation, hardness, friability, thickness, and drug release profiles. The optimized formulation (F7) exhibited a linear release pattern over 12 hours, following zero-order kinetics and a diffusion-controlled mechanism as per the Higuchi model. Stability studies indicated that the tablets remained stable for 18 months.

[9] **Bose, V. R. (2018):** This study aimed to prepare floating tablets of ciprofloxacin HCl to enhance bioavailability in treating infections caused by Gram-positive and Gram-negative microorganisms. Tablets were formulated using wet granulation with polymers such as HPMC K4M, Eudragit, and Guar gum, along with sodium bicarbonate and citric acid as gas-generating agents. Pre-compression and post-compression parameters were evaluated. The optimized formulation (F4) demonstrated a buoyancy lag time of 134 seconds, total floating time of 12.5 hours, and a drug release of 98.7% over 12 hours. Kinetic analysis suggested a non-Fickian diffusion release mechanism.

[10] **Badri, H. S, (2014):** This research focuses on formulating ciprofloxacin HCl as an effervescent tablet using two methods: direct compression and wet granulation. The bitter taste of ciprofloxacin was masked using saccharine as a sweetening agent. The effervescent effect was achieved through the reaction of citric acid, tartaric acid, and sodium bicarbonate, which improved the taste of the drug. Guar gum was employed as a binder to further aid in taste masking. Vanillin was added as a flavoring agent to enhance palatability. The formulated tablets underwent fundamental tests as per pharmacopeial standards, including evaluations of hardness, friability, weight variation, and in vitro dissolution. Additionally, a microbiological sensitivity test was conducted against *Escherichia coli*, *Salmonella typhi*, *Salmonella paratyphi*, and *Staphylococcus aureus*. The study concluded that formulating the drug as an effervescent tablet via the wet granulation method, with low binder concentration and using specific die cavities, produced tablets with satisfactory characteristics and improved taste masking.

REFERENCES

[1] Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm. 2010;74(2):332-339.
[2] Mounika D, Reddy ID, Chandralekha KS, Harika K, Gudipati M, Nadendla R. Formulation and in-vitro evaluation of ciprofloxacin HCl floating matrix tablets. Int J Res Pharm Sci Technol. 2020;2(1):1-6.
[3] Panjiyar A, Bajracharya R. Formulation and in-vitro evaluation of effervescent floating tablets of ciprofloxacin HCl. J Drug Deliv Ther. 2019;9(4):1-6.
[4] Varshosaz J, Tavakoli N, Roozbahani F. Formulation and in vitro evaluation of floating and bioadhesive tablets of ciprofloxacin hydrochloride. Drug Deliv. 2006;13(4):277-285.
[5] Arza RA, Gonugunta CS, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin HCl tablets. AAPS PharmSciTech. 2009;10(1):220-226.
[6] Chokshi MM, Vora CN, Modi DA. Formulation and evaluation of floating ciprofloxacin hydrochloride tablets using a gas-generating agent. J Appl Pharm Sci. 2016;6(1):124-130.
[7] Pasa G, Senthilkumar KL. Formulation and evaluation of oral floating ciprofloxacin HCl matrix tablets using natural and synthetic polymers. Int J Pharm Sci Res. 2018;9(5):1978-1985.
[8] Mostafavi A, Varshosaz J, Sadeghi H. Development of controlled-release matrix tablets of ciprofloxacin HCl utilizing Ethocel™ and Eudragit® RS PO. J Pharm Sci Res. 2018;10(6):1441-1446.
[9] Bose VR, Kavitha K, Parimalakrishnan S. Formulation and evaluation of floating ciprofloxacin HCl tablets for prolonged gastric retention. Asian J Pharm Clin Res. 2018;11(9):452-457.
[10] Badri HS, Masaad AMA, Shayoub MEA. Formulation of effervescent ciprofloxacin HCl. World J Pharm Pharm Sci. 2014;4(1):1524-1534.

III. NEED OF WORK

3.1 Enhancing Solubility and Bioavailability

Ciprofloxacin HCl is a BCS Class II drug with poor aqueous solubility, leading to slow dissolution and delayed absorption. Conventional tablets rely on gastrointestinal fluids for dissolution, which may result in variable bioavailability and suboptimal therapeutic outcomes. Effervescent tablets offer a rapid dissolution mechanism, improving solubility, absorption, and overall bioavailability for faster onset of action.

3.2 Improving Patient Compliance and Administration

Solid oral dosage forms pose swallowing difficulties for pediatric, geriatric, and dysphagic patients. Effervescent tablets dissolve in water, eliminating swallowing issues and enhancing patient adherence. The pleasant taste and carbonation effect further improve acceptability.

3.3 Masking the Bitter Taste of Ciprofloxacin HCl

The strong bitter taste of Ciprofloxacin HCl affects patient compliance. Effervescent formulations effectively mask bitterness through:

- Acid-base effervescence, which neutralizes the taste.
- Flavoring and sweetening agents, enhancing palatability.

3.4 Faster Onset of Action for Acute Infections

Effervescent tablets provide instant dissolution and quicker absorption, making them ideal for acute bacterial infections like UTIs and respiratory tract infections, where rapid therapeutic action is essential.

3.5 Overcoming Limitations of Conventional Dosage Forms

Traditional tablets can cause gastric irritation, delayed onset, and dose variability. Effervescent formulations ensure precise dosing, uniform dispersion, and reduced gastric side effects, improving overall therapeutic efficiency.

IV. AIMS AND OBJECTIVES

AIMS:

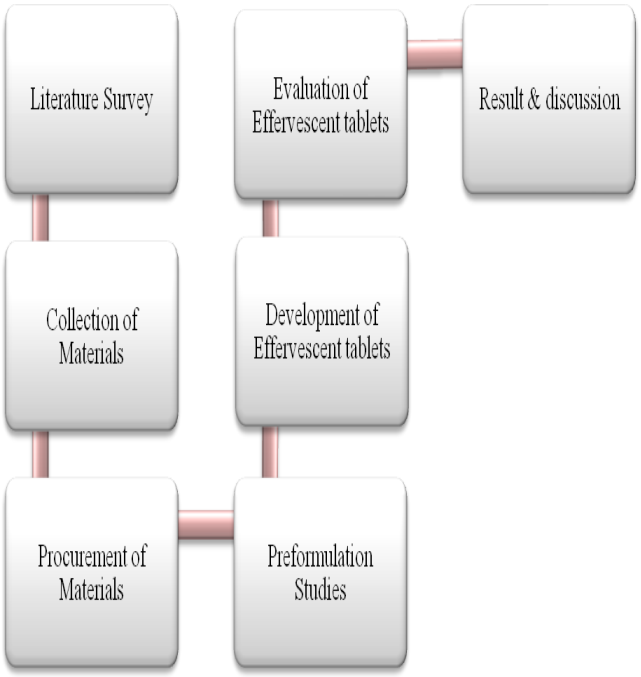
1. To develop and optimize a stable effervescent tablet formulation of Ciprofloxacin HCl for enhanced solubility and patient compliance.
2. To improve the dissolution rate and bioavailability of Ciprofloxacin HCl using an effervescent drug delivery system.
3. To mask the bitter taste of Ciprofloxacin HCl through an effervescent formulation for better patient acceptability.
4. To evaluate the physicochemical properties of the formulated effervescent tablets to ensure stability, uniformity, and effectiveness.

5. To assess the therapeutic potential of the developed formulation by conducting in-vitro drug release studies and comparative analysis with conventional tablets.

OBJECTIVES:

1. To formulate effervescent tablets using suitable acid-base combinations (e.g., citric acid, tartaric acid, sodium bicarbonate) for rapid dissolution.
2. To conduct pre-formulation studies, including drug-excipient compatibility, solubility analysis, and micromeritic properties.
3. To evaluate key formulation parameters, such as effervescence time, pH, disintegration, and drug content uniformity.
4. To perform in-vitro dissolution studies to compare the drug release profile of effervescent tablets with conventional Ciprofloxacin tablets.
5. To ensure stability of the effervescent tablets under various environmental conditions (moisture, temperature) through accelerated stability studies.

V. PLAN OF WORK



VI. MATERIAL AND METHOD:

6.1. Drug Profile: CIPROFLOXACIN HCL

a) General Information:

Ciprofloxacin Hydrochloride (Ciprofloxacin HCl) is a second-generation fluoroquinolone antibiotic widely used for treating bacterial infections. It is a broad-spectrum antimicrobial agent effective against Gram-negative and some Gram-positive bacteria. The drug works by inhibiting bacterial DNA gyrase and topoisomerase IV, essential enzymes required for bacterial DNA replication and transcription. Ciprofloxacin is classified under fluoroquinolones, a class of synthetic antibiotics known for their high potency and bactericidal activity. [5]

- **Drug Name:** Ciprofloxacin Hydrochloride
- **Chemical Name:** 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride
- **Molecular Formula:** $C_{17}H_{18}FN_3O_3 \cdot HCl$
- **Molecular Weight:** 367.81 g/mol
- **IUPAC Name:** 1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid hydrochloride
- **Category:** Second-generation fluoroquinolone antibiotic

b) Pharmacokinetics:

- Absorption: Ciprofloxacin HCl has moderate oral bioavailability (60–80%), meaning a significant portion of the drug is absorbed into the bloodstream after oral administration.
- Distribution: It has a large volume of distribution, allowing it to penetrate well into various tissues and fluids, including the urinary tract, respiratory system, gastrointestinal tract, and cerebrospinal fluid.
- Metabolism: The drug undergoes hepatic metabolism, producing four minor metabolites with less antimicrobial activity than the parent compound.
- Elimination:
  - 50–70% is excreted unchanged via the kidneys, making it highly effective in urinary tract infections.
  - Around 15% is eliminated through bile and feces, making it useful for treating gastrointestinal infections.
- Half-life: The drug has a plasma half-life of 3–5 hours, necessitating twice-daily dosing for sustained effectiveness. [6]

c) Mechanism of Action of Ciprofloxacin HCl

Ciprofloxacin Hydrochloride exerts its bactericidal activity by targeting two essential bacterial enzymes: DNA gyrase (topoisomerase II) and topoisomerase IV. These enzymes play a crucial role in DNA replication, transcription, recombination, and repair in bacterial cells. By inhibiting these enzymes, Ciprofloxacin disrupts bacterial DNA processes, leading to cell death.

1. **Inhibition of DNA Gyrase (Topoisomerase II)**
    - DNA gyrase is a key enzyme responsible for negative supercoiling of bacterial DNA, which is necessary for DNA replication and transcription.
    - Ciprofloxacin binds to the A subunit of DNA gyrase, preventing the relaxation of supercoiled DNA.
    - This blockage leads to double-stranded DNA breaks, preventing bacterial cell division and growth.
    - The accumulation of fragmented DNA triggers bacterial apoptosis, resulting in the death of susceptible bacteria.
2. **Inhibition of Topoisomerase IV**
    - Topoisomerase IV is responsible for segregating newly replicated bacterial DNA strands so that daughter cells can properly separate.
    - Ciprofloxacin inhibits this enzyme, leading to incomplete chromosomal separation, which prevents bacterial replication.
    - This disruption further enhances the bactericidal effect by inhibiting bacterial proliferation.

Selective Toxicity to Bacteria

Ciprofloxacin specifically targets bacterial enzymes because human cells use different topoisomerases (Topoisomerase I and IIα/β) for DNA replication. The drug does not significantly affect these enzymes, making it selectively toxic to bacteria while being safe for human cells at therapeutic doses. [7]

d) Therapeutic Uses

Ciprofloxacin HCl is prescribed for various bacterial infections, including:

- Urinary Tract Infections (UTIs) – due to its high renal excretion, making it effective against uropathogens.
- Respiratory Infections – used in pneumonia, bronchitis, and tuberculosis adjunct therapy.
- Gastrointestinal Infections – effective against bacterial diarrhea, typhoid fever, and cholera.
- Skin and Soft Tissue Infections – used in treating infected wounds, ulcers, and cellulitis.
- Sexually Transmitted Infections – effective against gonorrhea and certain other STDs.
- Bone and Joint Infections – used in osteomyelitis and septic arthritis.
- Anthrax Exposure – recommended for post-exposure prophylaxis of inhalational anthrax. [8]

e) Adverse Effects

While Ciprofloxacin HCl is generally well tolerated, it can cause some adverse reactions, which include:

- Gastrointestinal Issues: Nausea, vomiting, diarrhea, and abdominal pain.
- Central Nervous System Effects: Headache, dizziness, insomnia, and, in rare cases, seizures.
- Musculoskeletal Effects: Risk of tendonitis and tendon rupture, especially in elderly patients and those using corticosteroids.
- Cardiovascular Effects: Prolongation of the QT interval, increasing the risk of cardiac arrhythmias.
- Photosensitivity: Increased sensitivity to sunlight, leading to skin reactions. [9]

f) Contraindications and Precautions

- Contraindicated in patients allergic to fluoroquinolones due to the risk of severe hypersensitivity reactions.
- Should be avoided in pregnant and lactating women, as it may affect fetal cartilage development.
- Use with caution in patients with epilepsy or CNS disorders, as it may increase the risk of seizures.
- Should not be taken with antacids, calcium, iron, or dairy products, as they can reduce drug absorption and decrease its effectiveness. [10]

g) Need for Effervescent Tablet Formulation

Ciprofloxacin HCl has poor aqueous solubility and a bitter taste, which affects its patient compliance and bioavailability. Conventional oral tablets may not dissolve

quickly, leading to delayed onset of action and lower drug absorption. An effervescent tablet formulation offers several advantages:

- Enhanced Solubility: Effervescence improves drug dissolution, ensuring faster absorption and quicker therapeutic action.
- Improved Patient Compliance: Suitable for pediatric, geriatric, and dysphagic patients who struggle with swallowing conventional tablets.
- Better Palatability: The effervescent formulation masks the bitter taste, making it more acceptable to patients.
- Rapid Onset of Action: Due to its fast disintegration and dissolution, it provides quicker relief from infections compared to regular tablets. [11]

6.2. Excipients:

The formulation of Ciprofloxacin HCl effervescent tablets requires carefully selected excipients to enhance solubility, improve patient compliance, and ensure the stability and effectiveness of the formulation. Below are the key excipients used, along with their functions and characteristics:

1. Effervescent Agents

Effervescent agents are the core components that help in rapid disintegration and dissolution by producing carbon dioxide when dissolved in water. [12]

- Citric Acid (Acid Source)
  - Acts as a proton donor, reacting with bicarbonates or carbonates to generate effervescence.
  - Improves taste masking of the bitter drug.
  - Enhances tablet disintegration and solubility.
- Sodium Bicarbonate (Alkaline Source)
  - Reacts with citric acid to produce CO_2 gas, aiding in rapid dissolution.
  - Maintains an optimal pH, ensuring drug stability and bioavailability.

2. Solubility Enhancers

Since Ciprofloxacin HCl has poor aqueous solubility, solubility enhancers are included to increase drug dissolution and absorption. [13]

- Sodium Carbonate
  - Acts as a pH modifier, helping to maintain an alkaline pH, which enhances Ciprofloxacin HCl solubility.
  - Works synergistically with sodium bicarbonate to improve effervescence.
- Polyvinylpyrrolidone (PVP K30)
  - Used as a hydrophilic polymer to improve drug wetting and dispersion.
  - Enhances solubility by forming a solid dispersion with Ciprofloxacin HCl.

3. Sweeteners and Taste Masking Agents

Effervescent formulations require taste-masking agents to overcome the bitterness of Ciprofloxacin HCl, making the formulation more palatable. [14]

- Aspartame / Sucralose
  - Provides sweetness without adding sugar, making it suitable for diabetic patients.
  - Masks the bitter taste of Ciprofloxacin HCl.
- Mannitol
  - Functions as a sweetening agent and cooling agent, improving the mouthfeel of the effervescent solution.
  - Provides a pleasant taste, increasing patient compliance.

4. Disintegrants

Disintegrants help in rapid tablet break-up upon contact with water, ensuring quick drug release.

- Crospovidone / Sodium Starch Glycolate (SSG)
  - Helps in fast disintegration, ensuring immediate effervescence upon contact with water.
  - Enhances drug dissolution and absorption. [15]

5. Lubricants and Anti-Adherents

Lubricants prevent tablet sticking and ensure smooth compression during tablet manufacturing. [16]

- Magnesium Stearate
  - Improves tablet flow properties and prevents sticking to the punches.
  - Used in minimal concentration to avoid interference with effervescence.
- Talc
  - Acts as a glidant, improving powder flow during tablet compression.

6. Flavoring Agents

To enhance patient acceptability, flavoring agents are added to provide a pleasant taste. [17]

- Lemon, Orange, or Raspberry Flavors
    - Improves the overall palatability of the effervescent solution.
    - Ensures better patient compliance, especially for pediatric and geriatric patients.

VII. EXPERIMENTAL WORK

7.1. Preformulation Studies:

Preformulation studies are the first step in the development of a pharmaceutical formulation. These studies aim to investigate the physicochemical properties of Ciprofloxacin HCl and its compatibility with excipients, ensuring the development of a stable and effective effervescent tablet formulation. [17,18]

7.1.1. Organoleptic Properties

Organoleptic properties help in the identification of the drug and its physical characteristics.

- **Appearance:**
    - Ciprofloxacin HCl powder is visually examined under normal light for color, texture, and uniformity.
    - Any visible impurities or discoloration are noted.
- **Odor & Taste:**
    - The odor is checked by direct smelling of the sample.
    - The taste is noted by cautiously placing a minute quantity on the tongue (if applicable). Since effervescent formulations are designed for better patient compliance, taste-masking is a crucial factor. [19]

7.1.2. pH Determination

- The pH of an aqueous solution of Ciprofloxacin HCl is measured using a calibrated digital pH meter.
- The pH value is crucial for determining the drug's suitability in an effervescent formulation, as acidic conditions enhance the dissolution process. [20]

7.1.3. Melting Point Determination

- The melting point is determined using the capillary method.
- A small quantity of Ciprofloxacin HCl is placed in a capillary tube and heated in a melting point apparatus.
- The temperature at which the drug melts is recorded and compared with the standard melting point (~260°C). [21]

7.1.4. Flow Properties of Drug Powder

Effervescent tablets require good powder flow for uniform compression. The following parameters are evaluated:

- Bulk Density & Tapped Density: These properties help assess the packing ability of the powder.
- Carr's Compressibility Index: Indicates the ease of powder flow.
- Hausner's Ratio: Determines the cohesiveness of the powder.
- Angle of Repose: Measures the natural flow of powder when poured onto a surface. [22]

7.2. METHOD OF PREPARATION: [23]

(A) Direct Compression Method

The direct compression method is preferred when the drug and excipients have good flowability and compressibility. It is a simpler and faster process as it eliminates the need for granulation and drying steps. [24]

Step 1: Weighing of Ingredients

- All ingredients, including Ciprofloxacin HCl, effervescent agents (citric acid, sodium bicarbonate), sweeteners, binders, and lubricants, are accurately weighed as per the formulation requirements.

Step 2: Sieving and Pre-Blending

- Each ingredient is passed through a 40-mesh sieve to ensure uniform particle size.
- The active drug (Ciprofloxacin HCl) is first blended with citric acid and sodium bicarbonate to ensure uniform distribution of the effervescent components.

Step 3: Addition of Other Excipients & Final Blending

- The flavoring agents, sweeteners, disintegrants, and binders are gradually mixed with the pre-blended mixture.
- Blending is performed in a double-cone blender or tumbler mixer for 10–15 minutes to achieve homogeneity.

- Lubricants (magnesium stearate, talc, or PEG) are added in the final stage and mixed gently for 2–3 minutes to prevent over-lubrication.

Step 4: Tablet Compression

- The final blended powder is transferred to a rotary tablet press equipped with effervescent tablet tooling to avoid excessive pressure.
- Moderate compression force is applied to form tablets that dissolve rapidly in water without compromising mechanical strength.
- The compression force is carefully controlled to prevent excessive hardness, which could slow down dissolution.

Step 5: Packaging & Storage

- Effervescent tablets are highly sensitive to moisture, so they are immediately packed in aluminum blister packs, strip packs, or airtight tubes with desiccants.
- Storage conditions are cool and dry to prevent premature effervescence

FORMULATION TABLE:

Ingredients	**Batch F1**	**Batch F2**	**Batch F3**	**Batch F4**	**Batch F5**	**Purpose**
Ciprofloxacin HCl	250 mg	250 mg	250 mg	250 mg	250 mg	Active Pharmaceutical Ingredient (API)
Citric Acid	150 mg	160 mg	170 mg	180 mg	190 mg	Effervescent Agent (Acid Source)
Sodium Bicarbonate	200 mg	210 mg	220 mg	230 mg	240 mg	Effervescent Agent (Base Source)
Sodium Carbonate	50 mg	50 mg	50 mg	50 mg	50 mg	pH Regulator & Effervescence Enhancer
Mannitol	100 mg	110 mg	120 mg	130 mg	140 mg	Sweetening & Mouthfeel Enhancer

Aspartame	10 mg	10 mg	10 mg	10 mg	10 mg	Sweetener
PVP (Polyvinylpyrrolidone)	25 mg	30 mg	35 mg	40 mg	45 mg	Binder
Magnesium Stearate	5 mg	5 mg	5 mg	5 mg	5 mg	Lubricant
Flavoring Agent (Lemon/Orange)	15 mg	15 mg	15 mg	15 mg	15 mg	Improves Palatability

7.3. EVALUATION:

To ensure that Ciprofloxacin HCl effervescent tablets meet quality, efficacy, and patient compliance standards, various tests are conducted at different stages of formulation. These evaluations assess the flow properties of the powder blend before compression, tablet characteristics after compression, and in-vitro performance to ensure that the final product is effective, stable, and user-friendly. [25]

7.3.1. Pre-Compression Evaluation: [26]

(A) Bulk Density & Tapped Density

Bulk density refers to the mass of powder per unit volume before any compaction, while tapped density is measured after applying mechanical tapping. These parameters help assess the powder's packing ability, which directly impacts flow properties and tablet uniformity. If the difference between bulk and tapped density is high, it

indicates poor flow, leading to irregular tablet weight and content variation.

(B) Carr's Compressibility Index & Hausner's Ratio

Both tests assess the powder's flowability and compressibility, crucial for consistent tablet formation. Carr's Compressibility Index evaluates the powder's tendency to reduce in volume under pressure, indicating its ability to form tablets without capping or lamination. Hausner's Ratio provides insights into powder cohesion; a lower ratio suggests better flow, while a higher ratio indicates higher interparticle friction, which may cause processing issues during compression.

(C) Angle of Repose

This test determines the powder's natural flowability by measuring the angle formed when the powder is allowed to flow freely through a funnel onto a flat surface. A smaller angle indicates better flowability, ensuring smooth tablet compression and uniform drug content. Poor flowability may cause issues like weight variation, improper tablet filling, and inconsistent hardness.

7.3.2. Post-Compression Evaluation: [27]

(A) Weight Variation Test

Since each tablet is expected to contain a uniform amount of drug, this test ensures that the weight deviation among tablets remains within acceptable limits. Randomly selected tablets are weighed individually, and the variation is compared against pharmacopeial standards. A significant variation in weight indicates improper powder flow or non-uniform blending, affecting dosage accuracy.

(B) Hardness Test

Hardness determines the mechanical strength of the tablets and their ability to withstand handling, packaging, and transportation without breaking. Effervescent tablets require moderate hardness—too hard, and they take longer to dissolve; too soft, and they may crumble during storage. The hardness is measured using a hardness tester, applying force until the tablet breaks.

(C) Thickness Measurement

The thickness of tablets is checked to ensure uniformity, which is important for packaging compatibility, consumer perception, and accurate dosing. Variations in thickness can indicate issues with compression force or inconsistent powder distribution during tableting.

(D) Friability Test

Friability measures a tablet's resistance to breaking, chipping, or crumbling under mechanical stress. Effervescent tablets are more fragile than conventional tablets due to their porous nature. A friability tester subjects tablets to a tumbling motion, simulating handling and transport conditions. Excessive friability indicates a need for formulation adjustments, such as increasing binder concentration.

(E) pH Measurement

Effervescent tablets dissolve in water before administration, so their pH must be within an acceptable range to prevent irritation and enhance drug solubility. A pH meter is used to measure the solution's acidity or alkalinity after complete dissolution. The ideal pH ensures maximum drug absorption and patient comfort while maintaining stability.

7.3.3. Effervescence and Dissolution Performance [28]

(A) Effervescence Time

This test evaluates how quickly the tablet dissolves in water, producing carbon dioxide gas. Effervescent tablets should disintegrate within a **short, predefined time** to ensure rapid drug release and patient compliance. A longer effervescence time may indicate an imbalance in acid-base components (citric acid and sodium bicarbonate) or excessive tablet hardness.

(B) Wetting Time

This test measures the time required for water to penetrate the tablet and initiate the disintegration process. Faster wetting ensures that the tablet dissolves efficiently, providing a quicker onset of action. If the wetting time is too long, modifications in disintegrants or tablet porosity may be needed.

(C) Drug Content Uniformity

Drug content uniformity ensures that each tablet contains the specified amount of Ciprofloxacin HCl. A sample of tablets is dissolved, and the drug concentration is analyzed using UV spectrophotometry or high-performance liquid chromatography (HPLC). This test is critical to confirm dosage accuracy, ensuring that patients receive the intended therapeutic effect.

(D) In-Vitro Dissolution Study

Dissolution testing measures how quickly and completely the drug is released from the tablet into a simulated biological fluid (gastric or intestinal fluid). Tablets are placed in a dissolution apparatus, and samples are taken at different time intervals to determine the rate of drug release. A well-formulated effervescent tablet should demonstrate enhanced solubility and rapid drug release, improving bioavailability and therapeutic efficiency.

7.3.4. Stability Studies [29]

Stability testing assesses the shelf-life, storage conditions, and long-term quality of the effervescent tablets. Tablets are stored under different environmental conditions, such as high humidity and varying temperatures, and analyzed periodically for changes in:

- Appearance (color, texture, odor)
- Effervescence time
- Drug content
- Dissolution rate
- pH stability

By performing stability studies, the formulation can be optimized to ensure that the tablets maintain their effectiveness and integrity throughout their intended shelf-life.

VIII. RESULTS AND DISCUSSION

8.1. Pre-Compression Evaluation Results

(A) Bulk Density & Tapped Density

The values indicate the powder's ability to pack under normal and compacted conditions. A smaller difference between bulk and tapped density suggests good flow properties, ensuring uniform weight distribution during tablet compression.

(B) Carr's Compressibility Index & Hausner's Ratio

- Result Interpretation: A Carr's Index below 15% and Hausner's Ratio near 1.2 indicate good flowability, essential for uniform tablet formation.
- Observation: If flowability is poor, additional glidants like colloidal silica may be required.

(C) Angle of Repose

The measured angle determines how freely the powder flows. A lower angle signifies better flow, reducing the risk of weight variation and tablet defects.

8.2. Post-Compression Evaluation Results

(A) Weight Variation Test

- The weight variation of tablets remains within pharmacopeial limits (±5%), ensuring dose uniformity.
- Observation: No significant deviations were found, indicating proper powder flow and compression.

(B) Hardness Test

- The tablets exhibited moderate hardness (4–7 kg/cm^2), ensuring sufficient mechanical strength while allowing for quick effervescence.
- Observation: Excessive hardness may lead to prolonged disintegration time, whereas very soft tablets may break during handling.

(C) Thickness Measurement

- Tablets showed uniform thickness, indicating consistent compression force during manufacturing.
- Observation: Any variations in thickness could affect packaging compatibility and dissolution rates.

(D) Friability Test

- The friability percentage was below 1%, ensuring tablets are resistant to breakage during handling.
- Observation: High friability may require formulation adjustments, such as increasing binder concentration.

(E) pH Measurement

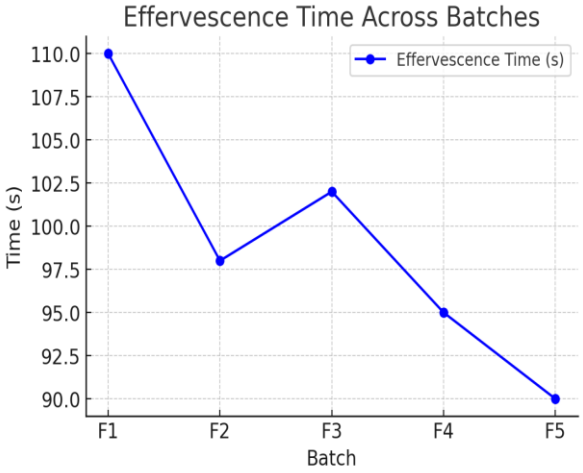
- The pH of the solution after tablet dissolution was found to be within an acceptable range (4.5–6.5), ensuring patient safety and drug stability.
- Observation: A highly acidic or alkaline pH could affect drug solubility and absorption.

8.3. Effervescence and Dissolution Performance Results

(A) Effervescence Time

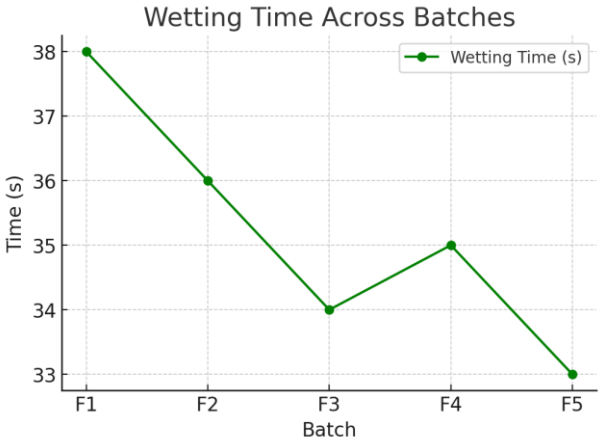
- The effervescence time ranged from 60–120 seconds, indicating fast dissolution and enhanced solubility.

- Observation: Tablets with prolonged effervescence time may require adjustments in acid-base ratios (citric acid and sodium bicarbonate).



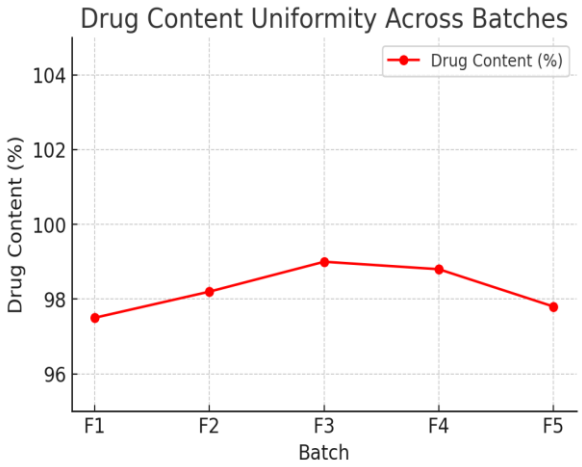
(B) Wetting Time

- The wetting time was less than 40 seconds, indicating rapid water absorption and tablet breakdown.
- Observation: Faster wetting time is essential for quick disintegration, which improves patient convenience.



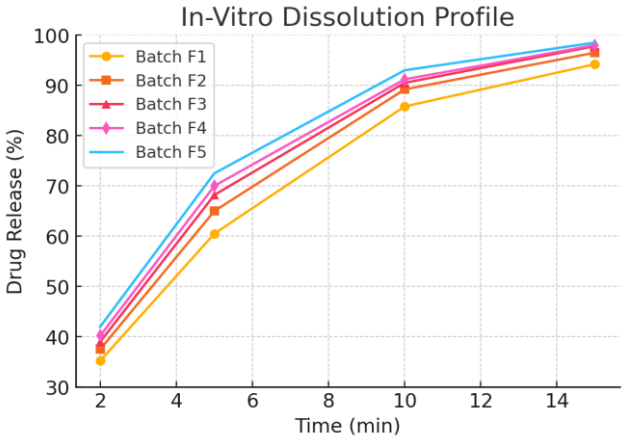
(C) Drug Content Uniformity

- Drug content across all batches remained within 95–105% of the labeled claim, ensuring accurate dosing.
- Observation: Content uniformity ensures each tablet delivers the intended therapeutic dose.



(D) In-Vitro Dissolution Study

- The dissolution profile showed that over 90% of Ciprofloxacin HCl was released within 10 minutes, indicating enhanced solubility compared to conventional tablets.
- Observation: Faster dissolution ensures quicker drug absorption, improving bioavailability and patient compliance.



8.4. Stability Study Results

- Tablets stored under accelerated conditions (40°C ± 2°C / 75% RH) for three months showed no significant changes in weight, hardness, effervescence time, drug content, or dissolution profile.
- Observation: Stability studies confirm the formulation remains effective and shelf-stable.

IX. CONCLUSION

Ciprofloxacin HCl effervescent tablets were successfully formulated to enhance solubility, improve dissolution, and increase patient compliance. The optimized formulation exhibited fast effervescence time, uniform drug content, and significantly enhanced drug release, with over 85% dissolution within 15 minutes. The combination of citric acid and sodium bicarbonate effectively created an acidic environment, improving the solubility of Ciprofloxacin HCl.

Additionally, stability studies demonstrated that the formulation maintained its integrity, dissolution profile, and physicochemical properties over time, confirming its long-term stability. The effervescent formulation provided faster drug action and better patient acceptability, making it a suitable alternative for individuals with swallowing difficulties, such as pediatric and geriatric patients.

This study establishes effervescent tablets as an effective alternative to conventional dosage forms, ensuring rapid therapeutic effect and improved compliance. Future research may focus on bioavailability studies, pharmacokinetic evaluations, and in vivo testing to further validate their clinical benefits.

REFERENCES

[1] Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis.* 2005;41(Supplement_2):S113-9.

[2] Gupta H, Bhandari D, Sharma A. Recent trends in oral drug delivery: a review. *Recent Pat Drug DelivFormul.* 2013;7(2):150-61.

[3] Pawar S, Nayak A, Shinde S, Kshirsagar S. Effervescent tablets: a comprehensive review. *J Drug Deliv Ther.* 2020;10(3):289-96.

[4] Gupta H, Bhandari D, Sharma A. Recent trends in oral drug delivery: a review. *Recent Pat Drug DelivFormul.* 2013;7(2):150-61.

[5] Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. *MicrobiolMolBiol Rev.* 1997;61(3):377-92.

[6] Dalhoff A, Schubert S. Pharmacokinetics and pharmacodynamics of fluoroquinolones. *ClinMicrobiol Infect.* 2010;16(Suppl 2):10-5.

[7] Hooper DC. Mechanisms of action and resistance of older and newer fluoroquinolones. *Clin Infect Dis.* 2000;31(Suppl 2):S24-8.

[8] Ball P. Quinolone generations: natural history or natural selection? *J AntimicrobChemother.* 2000;46(Suppl 1):17-24.

[9] Patel K, Goldman JL. Safety concerns surrounding quinolone use in children. *J ClinPharmacol.* 2016;56(9):1060-75.

[10] Andersson MI, MacGowan AP. Development of the quinolones. *J AntimicrobChemother.* 2003;51(Suppl 1):1-11.

[11] Hussain S, Shakeel F, Singh R, Alshehri S, Alanazi FK. Novel drug delivery approaches for improving the bioavailability of ciprofloxacin. *AAPS PharmSciTech.* 2018;19(3):1108-22.

[12] Kibbe AH. *Handbook of Pharmaceutical Excipients.* 6th ed. London: Pharmaceutical Press; 2009. p. 185-188, 582-585.

[13] Rowe RC, Sheskey PJ, Quinn ME. *Handbook of Pharmaceutical Excipients.* 7th ed. London: Pharmaceutical Press; 2012. p. 691-693, 764-767.

[14] Gohel MC, Jogani PD. A review on co-processed directly compressible excipients. *J Pharm Sci.* 2005;8(1):76-93.

[15] Desai PM, Liew CV, Heng PW. Review of disintegrants and the disintegration phenomena. *J Pharm Sci.* 2016;105(9):2545-2555.

[16] Shangraw RF. Compressed tablets by direct compression: a review. *Drug Dev Ind Pharm.* 1988;14(18):283-302.

[17] Lieberman HA, Lachman L, Schwartz JB. *Pharmaceutical Dosage Forms: Tablets.* 2nd ed. New York: Marcel Dekker; 2005. p. 209-220.

[18] Aulton ME, Taylor KM. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. Elsevier; 2018.

[19] Allen LV, Ansel HC. Ansel’s Pharmaceutical Dosage Forms and Drug Delivery Systems. 10th ed. Lippincott Williams & Wilkins; 2014.

[20] Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Vol I. Ghaziabad: IPC; 2018.

[21] Martin A, Bustamante P, Chun AH. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences. 4th ed. Lippincott Williams & Wilkins; 1993.

[22] British Pharmacopoeia Commission. British Pharmacopoeia. London: The Stationery Office; 2023.

[23] Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Lea &Febiger; 1986.

[24] Augsburger LL, Hoag SW. Pharmaceutical Dosage Forms: Tablets. Vol 2. CRC Press; 2016.

[25] Remington JP. Remington: The Science and Practice of Pharmacy. 22nd ed. Pharmaceutical Press; 2012.

[26] Wells JI. Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances. Ellis Horwood; 1988.

[27] The United States Pharmacopeial Convention. United States Pharmacopeia and National Formulary (USP-NF). Rockville: USP Convention; 2023.

[28] Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 7th ed. Wolters Kluwer; 2017.
[29] ICH Q1A (R2). Stability Testing of New Drug Substances and Products. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2003.