Development & Evaluation of Fast Dissolving Tablet of Ramipril

Km Bhagyalaxmi*, Shailendra Patel, Dr. Arun Patel, Narayan yadav
Shree Ram Group of Institutions, Near ITI, Madholtal, Karmeta
Jabalpur Madhya Pradesh, 482002

***Corresponding Author: Km. Bhagy Laxmi**
Shree Ram Group of Institutions, Near ITI, Madholtal, Karmeta
Jabalpur Madhya Pradesh, 482002

Email Id: goldijaiswal7376@gmail.com
Contact: 7706842001

Abstract
Oral drug administration is the preferred route for drug delivery, accounting for 50-60% of all dosage forms. Solid dosage forms, particularly tablets and capsules, are widely accepted due to their ease of administration, precise dosing, suitability for self-medication, pain avoidance, and high patient compliance. Despite their advantages, some patients have trouble in swallowing these forms, necessitating the use of water. Tablets, a common solid dosage form, consist of active substances and excipients compressed into a solid dose, often coated with polymers to enhance swallowability, control release rates, and protect from environmental factors. Compressed tablets dominate the market, with significant use in delivering precise dosages to specific sites via oral, sublingual, rectal, or intravaginal administration. Capsules, similarly popular, provide an alternative solid dosage form. This review comprehensively examines the formulation, advantages, challenges, and patient considerations of tablets and capsules in oral drug delivery, highlighting their critical role in modern therapeutics.

Keyword: Solid dosage forms, Polymers, control release dosage, Capsules, Excipients.

Introduction
Oral drug administration is widely accepted, accounting for 50-60% of all dosage forms. Solid dosage forms, such as tablets and capsules, are particularly popular due to their ease of administration, precise dosing, suitability for self-medication, pain avoidance, and, most importantly, patient compliance. However, a significant drawback for some patients is the difficulty in swallowing these forms, where drinking water plays a crucial role in the process (1).

A tablet is a solid pharmaceutical dosage form composed of a mixture of active substances and excipients, typically in powder form, compressed into a solid dose. Excipients may include diluents, binders, glidants, lubricants, disintegrants, sweeteners, Flavors, and pigments. Tablets are often coated with a polymer to improve swallowability, control the release rate of the active ingredient, protect the tablet from environmental factors, or enhance its appearance.
Compressed tablets are the most popular dosage form, with about two-thirds of prescriptions dispensed as solid dosage forms, half of which are tablets. Tablets can be designed to deliver a precise dosage to specific sites and can be taken orally, sublingually, rectally, or intravaginally. Tablets can come in various shapes, colors, and sizes, with some being stamped for identification. The size of tablets can range from a few millimeters to about a centimeter. Tablets designed to dissolve or disintegrate, such as cleaning and deodorizing products, are also common. The term "pill" originally referred to a soft mass rolled into a ball shape but is now commonly used to describe tablets and capsules (2).

1.1 Tablet Properties

- Tablets can be made in nearly any shape, but most are round, oval, or capsule-shaped due to patient preferences and manufacturing requirements. Unusual shapes can be harder to swallow and more prone to chipping.
- Tablet diameter and shape are determined by the tooling used in production—a die and punches.
- The main guideline in tablet pressing is ensuring the correct amount of active ingredient in each tablet, requiring well-mixed ingredients. If homogeneity cannot be achieved through simple blending, granulation may be necessary (2).

1.2 Methods of Preparation

There are two basic techniques for granulating powders for tablet compression: wet granulation and dry granulation. Powders that mix well can be directly compressed into tablets.

1.2.1 Wet Granulation

Wet granulation involves using a liquid binder to agglomerate the powder mixture lightly. The amount of liquid must be controlled to avoid overly hard or soft granules. Aqueous solutions are safer than solvent-based systems but may not suit drugs prone to hydrolysis.

Procedure:

- Weigh and mix the active ingredient and excipients.
- Add the liquid binder-adhesive to the powder blend and mix thoroughly.
- Screen the damp mass through a mesh to form granules.
- Dry the granules using a tray-dryer or fluid-bed dryer.
- Screen the dried granules to create uniform size.
- Use low shear or high shear wet granulation processes, or fluid bed granulation for close control.

1.2.2 Dry Granulation

Dry granulation forms granules by lightly compacting the powder blend under low pressures. This method is suitable for moisture- and heat-sensitive products and can be done using a tablet press with slugging tooling or a roller compactor. It is simpler and cheaper than wet granulation but may produce more fine granules.

1.2.3 Direct Compression

Direct compression involves compressing the powdered material without altering its physical nature. This method is simple, avoids granulation and drying steps, minimizes material handling, and optimizes bioavailability.

Procedure:

- Mix the drug or drug mixture in powder form with necessary diluents, glidants, and lubricants.
- Pass the powder through a suitable sieve.
- Compress the powder into tablets (1).

1.3 Tablet Evaluation Methods

1. Analytical Determination of Tablet Content:

- Measure weight variation by weighing each tablet and calculating the percent difference from the intended amount. According to USP 24/NF19, each tablet should be within 90-110% of the theoretical weight.

2. Tablet Hardness:

- Tablets must withstand mechanical stress during packaging, shipping, and handling. USP 24/NF19 outlines a standard friability test. Hand-operated testers like Strong Cobb, Pfizer, and Stokes are useful. Tablets typically have a hardness of 4-8 kg, with variations for different types.

3. Tablet Disintegration:

- Use a simple apparatus with a 10-mesh screen in a beaker with 1000 ml of water, stirred magnetically. Record the time for tablets to disintegrate, aiming for 15-30 minutes.

4. Tablet Dissolution:

- Dissolution rate is crucial for drug absorption and is more indicative of drug availability than disintegration time. Most pharmacies lack the equipment for these tests (2).

1.4 Fast Dissolving Tablets

Fast Dissolving Tablets offer advantages such as improved patient compliance, convenience, bioavailability, and rapid onset of action. They increase solubility by reducing the drug's effective particle size and enhancing wetting. These tablets disintegrate/dissolve quickly in the mouth without water and are sufficiently strong (3).

1.5 Characteristics and Development Challenges of Fast Disintegrating Tablets

1. Fast Disintegration
2. Taste of Active Ingredient
3. Moisture Sensitivity

1.6 HPLC Method

High-performance liquid chromatography (HPLC) is an instrumental analytical chemistry technique used to separate, identify, and quantify components in a mixture. It involves passing a liquid sample over a solid adsorbent material in a column, with each analyte interacting differently with the adsorbent chromatography and Its Impact on Analytic Flow.

The interaction strength between the analyte and the stationary phase significantly affects the analytic flow in chromatography. Weak interactions cause the analyte to elute quickly from the column, whereas strong interactions result in longer elution times (4).

Types of Chromatography

1. Normal-phase chromatography
2. Reversed-phase chromatography
3. Reversed-phase ion-pair chromatography
4. Ion-exchange chromatography
5. Bio affinity chromatography

Hypertension

Hypertension (HTN), also known as high blood pressure or arterial hypertension, is a chronic medical condition where the pressure in the arteries is persistently elevated. This increased pressure forces the heart to work harder to pump blood through the vessels. Blood pressure is measured using two values: systolic (pressure during heart contraction) and diastolic (pressure when the heart is relaxed). Normal resting blood pressure ranges from 100-140 mmHg systolic and 60-90 mmHg diastolic. Hypertension is diagnosed when blood pressure consistently measures at or above 140/90 mmHg (5).

Signs and Symptoms

- Hypertension often has no symptoms and is usually identified through screening or when seeking healthcare for unrelated issues.
- Some individuals with high blood pressure may experience headaches (particularly in the morning and at the back of the head), light-headedness, vertigo, tinnitus, altered vision, or fainting episodes. These symptoms may be related more to anxiety than the hypertension itself (6).

Primary Hypertension

Primary (essential) hypertension accounts for 90–95% of all cases and generally has no identifiable cause. Blood pressure typically increases with age, making the risk of developing hypertension higher later in life. Recommendations from the US National High BP Education Program (2002) for preventing hypertension include maintaining a normal body weight, reducing dietary sodium, engaging in regular aerobic physical activity, limiting alcohol consumption, and eating a diet rich in fruits and vegetables. Effective lifestyle changes can reduce blood pressure as effectively as antihypertensive medication, with combinations of lifestyle modifications yielding even better results.

Secondary Hypertension

Secondary hypertension is less common (5-10% of cases) and is caused by identifiable conditions such as kidney or endocrine diseases. Increased resistance to blood flow due to structural narrowing of small arteries and arterioles, or decreased peripheral venous compliance, often characterizes primary hypertension. Other contributing factors may include disturbances in renal salt and water handling, abnormalities in the sympathetic nervous system,

endothelial dysfunction, and vascular inflammation. Secondary hypertension is more common in preadolescent children, often due to renal disease, while primary hypertension is more common in adolescents and is linked to obesity and family history. Diagnostic tests help identify secondary hypertension causes and assess potential damage to the heart, eyes, and kidneys (7).

ACE Inhibitors (Angiotensin Converting Enzyme Inhibitors)

ACE inhibitors were the first class of antihypertensive agents developed based on a clear understanding of the pathophysiological mechanisms of arterial hypertension, a condition now recognized as a leading cause of morbidity and mortality worldwide.

Effects of Angiotensin II

- Vasoconstriction: Leads to increased blood pressure and hypertension.
- Kidney effects: Constriction of the efferent arterioles increases glomerular perfusion pressure.
- Heart effects: Promotes ventricular remodelling and hypertrophy, potentially leading to congestive heart failure.
- Hormonal effects: Stimulates the adrenal cortex to release aldosterone, causing sodium and water retention, which increases blood volume and pressure (8).

Types of ACE Inhibitors

ACE inhibitors can be categorized based on their molecular structure:

- Sulfhydryl-containing agents: e.g., Captopril
- Dicarboxylate-containing agents: e.g., Enalapril, Ramipril, Lisinopril, Benazepril, Fosinopril (9).

Drug Profile: Ramipril

IUPAC Name: (2S,3aS,6aS)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino} propanoyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid.

Pharmacokinetic Data

- Bioavailability: 13%
- Protein binding: 50%
- Half-life: 2 to 4 hours

Chemical Data

- Formula: $C_{23}H_{32}N_2O_5$
- Molecular Mass: 416.511 g/mol
- Melting Point: 106-108 °C

Description

Ramipril is an ACE inhibitor used to treat high blood pressure and congestive heart failure. It is marketed under various brand names worldwide, such as Altace in the United States and Rami tens in Canada (10). As a prodrug, ramipril is converted to its active form, ramiprilat, by liver enzymes. Ramiprilat is primarily excreted by the kidneys, with a variable half-life of 8-18 hours, which can be prolonged in cases of heart, liver, or kidney failure. Ramipril is

indicated for hypertension, congestive heart failure, post-myocardial infarction heart failure, and prevention of cardiovascular events in high-risk patients. The drug's dissolution rate from solid dosage forms affects its absorption, with poorly water-soluble drugs potentially having erratic or incomplete gastrointestinal absorption.

Medical Use

Indications for Ramipril include:

- Hypertension
- Congestive heart failure
- Post-heart attack in patients showing clinical signs of heart failure
- Prevention of heart attack, stroke, cardiovascular death, or the need for revascularization procedures in patients over 55 years
- Diabetic nephropathy with microalbuminuria (11).

Contraindications

Ramipril should not be used in patients with renovascular disease, severe renal impairment (particularly in those with a single kidney or bilateral renal artery stenosis), volume depletion, a history of angioedema related to ACE inhibitors, during pregnancy, or in those with hypotension.

Adverse Effects

- Low blood sugar in diabetic patients, causing symptoms such as sweating or shakiness
- Dry cough
- Dizziness and light-headedness due to low blood pressure
- Fatigue, especially initially
- Dry mouth, particularly early on
- Signs of infection (fever, chills, persistent sore throat)
- Yellowing of the eyes or skin, dark urine
- Stomach or abdominal pain
- Neutropenia (low white blood cell count)
- Impotence (erectile dysfunction)

Mechanism of Action

ACE inhibitors work by blocking the action of angiotensin-converting enzyme (ACE), which reduces the production of angiotensin II and decreases the breakdown of bradykinin. This leads to the relaxation of arteriole smooth muscle, reducing total peripheral resistance and lowering blood pressure as the blood flows through widened vessels. The inhibition of bradykinin breakdown is also responsible for the common side effect of a dry cough. Ramipril is a prodrug that is metabolized into its active form, ramiprilat, by liver esterase enzymes. Ramiprilat is primarily excreted by the kidneys, with a variable half-life of 3–16 hours, which can be prolonged in cases of heart, liver, or kidney failure (12).

Excipients Profile (13).

Sodium Starch Glycolate
- Functional category: Tablet disintegrant
- Chemical name: Starch carboxymethyl ether, sodium salt
- Description: White to off-white, odorless, tasteless, free-flowing powder
- Typical properties:
  - Density: 1.5 g/cm³
  - Bulk volume: 1.4 g/cm³
  - pH: 5.5-7.5
  - Solubility: Disperses in cold water at 2% w/v, forming a highly saturated layer; insoluble in organic solvents.

Cros povidone
- Functional category: Tablet disintegrant
- Chemical name: 1-Ethyl-2-pyrrolidone homopolymer
- Description: White to creamy-white, odorless, tasteless hygroscopic powder
- Typical properties:
  - Bulk density: 0.3-0.4 g/cm³
  - Tapped density: 0.4-0.5 g/cm³
  - Solubility: Practically insoluble in water and most common organic solvents.

Microcrystalline Cellulose
- Functional category: Adsorbent, suspending agent, diluent
- **Chemical name: Cellulose**

Description: White to off-white, odorless, tasteless crystalline powder composed of porous particles
- Typical properties:
  - Bulk density: 0.337 g/cm³
  - Tapped density: 0.478 g/cm³
  - Solubility: Slightly soluble in 5% w/v sodium hydroxide solution.

Magnesium Stearate
- Functional category: Tablet and capsule lubricant
- Chemical name: Magnesium stearate
- Description: White powder with a faint characteristic odor and taste
- Typical properties:
  - Bulk volume: 3.0-8.4 ml/g
  - Helium density: 1.03-1.08 g/cm³
  - Solubility: Slightly soluble in benzene and warm ethanol (95%).

Talc
- Functional category: Tablet and capsule lubricant
- Chemical name: Hydrous magnesium silicate

- Description: White or grayish-white, odorless crystalline powder
- Typical properties:
  - Tapped density: 48-62.5 lb/ft³
  - Solubility: Insoluble in organic solvents, cold acids, and dilute alkalis.

5. Materials and methods

5.1Materials

5.1.1-Chemicals and reagents

All the material used in the formulation, evaluations and other experiments are listed below. The chemical used were of laboratory reagent grade and were used as they were procured. The distilled water was used in all experiment.

Table no-1 List of chemicals and reagents

S.No.	MATERIAL	SUPPLIER
1	Ramipril	Alkam pharmaceutical Ltd, baddi
2	Sodium starch glycolate	Himedia, Mumbai
3	Cross povidone	Himedia, Mumbai
4	Lactose	Himedia, Mumbai
5	Microcrystalline cellulose	Himedia, Mumbai
6	Magnesium stearate	Himedia, Mumbai
7	Talc	Himedia, Mumbai

5.1.2 INSTRUMENTS

Table no-2 List of Instrument and Apparatus

S.No.	INSTRUMENTS	MANUFACTURER
1	Tablet compression Machine	Single punching machine
2	Friability test apparatus	Roche friabilator
3	Tablet disintegration Tester	Model-911 Make-E1.
4	UV Spectrophotometer	EI double beam UV-VIS UV/Visible model 1372.
5	HPLC System	Younglin quaternary gradient Acme 9000
6	FTIR system	IR affinity 1 shimadzu
7	Dissolution tester	Electro lab (USP XX111)
8	Electronic balance	Sartorius (India)

Methods

5.2 Identification and Characterization of Ramipril

5.2.1 Identification of Ramipril by FTIR

During the preparation of fast-dissolving tablets, the drug and excipients may interact due to their close proximity, potentially leading to drug instability. Pre-formulation studies assessing drug-excipient interactions are thus critical for selecting appropriate excipients. FTIR spectroscopy was used to evaluate the compatibility between Ramipril and the chosen excipients. The pure drug and the drug-excipient mixtures were scanned separately, with the results presented in Table (9), Table 10, and Figures 2 and 4.

5.2.1.2 Physicochemical Characteristics

- Melting Point: The melting point of pure Ramipril was measured and found to be 106˚C at room temperature, as specified in the certificate of analysis, confirming the drug's purity.
- Solubility: The solubility of the drug was assessed by dissolving it in various solvents. Results are shown in Table (8).

5.2.2 Formulation

5.2.2.1 Direct Compression Method (Mehta M, 2009)

Five different batches of tablets were prepared using the direct compression method, with different combinations shown in Table 3. Direct compression involves compressing tablets directly from a blend of ingredients and suitable excipients, ensuring uniform flow into the die cavity to form a compact tablet. The drug powder was mixed with super disintegrants, MCC as a diluent, aspartame, talc as a glidant, and magnesium stearate as a lubricant. All ingredients were passed through a #60 mesh, and then a pinching machine was used to compress the tablets, each containing 20 mg of Ramipril, with an average weight of 250 mg per tablet.

Table no-5 Composition of fast dissolving tablet of ramipril

Ingredients (mg)	**Formulation codes**				
	FDT1	**FDT2**	**FDT3**	**FDT4**	**FDT5**
Ramipril	20	20	20	20	20
Crosspovidone	55	55	55	55	55
Sodium starch glycolate	50	55	60	65	70
Microcrystalline cellulose	90	90	90	90	90
Lactose	30	25	20	15	15
Talc	2.5	2.5	2.5	2.5	2.5
Mg. Stearate	2.5	2.5	2.5	2.5	2.5

5.2.2.2 Evaluation of tablets: -

Precompressions parameters

5.2.2.2(1) Bulk density (14)

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The accurate weighed amount sample taken in 50ml measuring cylinder of borosil measured the volume of parking and tapped 50 time on plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formulation shown in table no-9

LBD =Mass of powder / Volume of packing

TBD= Mass of powder / Tapped volume of packing

5.2.2.2(2) Angle of repose (1).

The frictional forces in loose powder or granules can be measured by the angle of respose. this is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plan. Result showed in table no (9).

$\tan \theta = h/r$

$\theta = \tan^{-1}(h/r)$

where θ= angle of repose

h=height

r=radius

Table No-5.4: Relationship between angles of repose

S.No.	Angle of Repose (°)	Type of Flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very Poor

5.2.2.2(3) Percentage compressibility index (United States of pharmacopeia 2007)

Percentage compressibility of powder mix was determined by Carr's Compressibility Index calculated by following formulation. Shown in table no (9).

% Carr's Index= (TBD-LBD) ×100/TBD

Where, TBD= Tapped bulk density

LBD= Loose bulk density

Table No-5 grading of the powder for this flow property according to Carr's index

%Compressibility	Flow ability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

5.2.2.3 Post-Compression Parameters

5.2.2.3.1 Thickness Uniformity (15).

The study aimed to check the uniformity of tablet thickness. The thickness of the tablets was measured at three different points using a digital caliper, and the average thickness of the three readings was calculated. The results are shown in Table (10).

5.2.2.3.2 Hardness Test (16).

Tablet hardness, which indicates the tablet's ability to withstand mechanical shocks during handling, was determined using a Monsanto hardness tester. The hardness is expressed in kg/cm². The mean and standard deviation (SD) values were also calculated and are presented in Table 10.

5.2.2.3.3 Friability Test (17).

The friability test assesses the effect of friction and shocks, which can cause tablets to chip, cap, or break. A Roche Friabilator was used for this test. A pre-weighed sample of ten tablets was placed in the friabilator, which was operated for 100 revolutions. After 100 revolutions, the tablets were dusted and reweighed. The friability percentage is calculated using the formula:

\ [\text {Friability (\%)} = \frac {\text {Initial weight – Final weight}}{\text{Initial weight}} \Times 100 \] Results are shown in Table 10.

5.2.2.3.4 Water Absorption Ratio and Wetting Time (18)

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was placed on the paper, and the time required for complete wetting was measured. The water absorption ratio is calculated using the formula:

\ [R = \ frac {W_a - W_b} {W_b} \times 100 \]

where \ (W_a \) is the weight of the tablet after water absorption and \ (W_b \) is the weight of the tablet before water absorption. Results are shown in Table (10).

5.2.2.3.5 Disintegration Studies (16)

In vitro disintegration time was determined using a dissolution apparatus at 50 rpm. Phosphate buffer with pH 6.8 (600 ml) was used as the disintegration medium at a temperature of 37±2˚C. The time taken for complete disintegration of the tablet, with no mass remaining in the apparatus, was measured in seconds. Results are shown in Table (10).

5.2.2.3.6 In Vitro Dissolution Studies (19).

In vitro release studies were conducted using a tablet dissolution test apparatus. The dissolution studies for all formulations are shown in Table (11).

Table no 5 Parameter for *In vitro* dissolution

Dissolution medium	900ml of buffer pH6.8
Temperature	37ºC±1ºC
rpm	50
Drug content	Weight of tablet equivalent to 250mg of Ramipril
Volume with drawn	1ml
λ_{max}	210nm
Berr's range	10-60µg/ml

5.3 Calibration Curve of Ramipril Using UV Spectrophotometry

5.3.1 Preparation of Stock Solution:

A stock solution of ramipril was prepared by dissolving 100 mg of standard ramipril in 100 ml of methanol. This solution was further diluted to achieve a concentration of 10 µg/ml, and its UV absorption at 210 nm was used for subsequent calibration.

5.3.2 Preparation of Working Standard Solutions:

From the stock solution, a series of working standard solutions (10, 20, 30, 40, 50, and 60 µg/ml) were prepared by dilution with methanol. Each solution was scanned at 210 nm, and a calibration curve was constructed using the absorption values, with a reagent blank for reference.

5.4 HPLC Method Development for Ramipril

5.4.1 Mobile Phase Selection:

The mobile phase selection involved optimizing chromatographic conditions to achieve symmetrical peaks and efficient separation. Various combinations were tested, and a 60:40 mixture of methanol and acetonitrile (Mobile Phase A) was chosen, supplemented with a solution of sodium acetate, ammonium acetate, glacial acetic acid, and water (Mobile Phase B).

5.4.2 Method Development Steps:

- Preparation of Mobile Phase: Mobile Phase A was prepared by mixing methanol and acetonitrile in a 60:40 ratio, filtered before use. Mobile Phase B involved dissolving specific chemicals in water and adding glacial acetic acid.
- Wavelength Selection: A solution of ramipril was prepared and scanned over a UV range, identifying an absorption peak at 238 nm.
- Selection of Chromatographic Variables: Different chromatographic conditions were tested to optimize peak shape and retention time, with constant parameters selected for consistency.
- Preparation of Standard Solutions: A stock solution of ramipril was prepared and diluted to create working solutions ranging from 0 to 30 µg/ml.
- Calibration Curve Preparation: Each standard solution was injected three times, and the mean peak areas were used to plot a calibration curve. The resulting regression equation was derived from this curve.
- System Suitability: Chromatographic conditions were validated by injecting replicates of a 10 µg/ml standard solution, ensuring peak and column performance met predefined criteria.

5.5 Analysis of Tablet Formulation

5.5.1 Assay of Tablet Formulation: Twenty tablets were individually weighed, crushed, and an equivalent of 100 mg of ramipril was dissolved in mobile phase. The solution was filtered, and from this, a 10 µg/ml solution of ramipril was prepared. Tablet formulation analysis involved calculating the amount of ramipril per tablet using the calibration curve method, repeated six times for accuracy.

5.6 Validation Parameters

5.6.1 Linearity

Linearity of the analytical procedure refers to its ability, within a specified range, to produce results that are directly proportional to the analyte concentration in the sample. A calibration curve was constructed by analyzing six different concentrations (10-60 µg/ml) of ramipril, with each concentration tested three times. Mean areas were calculated and correlations were determined. Response factors were derived by dividing the area under the curve (AUC) by the respective concentration.

5.6.2 Precision

5.6.2.1 Repeatability: Repeatability was assessed by preparing standard dilutions and analysing three replicates of each dilution on the same day. This process was repeated on different days and by different analysts, and the results were statistically analysed (see table no 21).

5.6.2.2 Intermediate Precision: Intermediate precision, reflecting within-laboratory variation (across different days, analysts, and equipment), was evaluated. Standard dilutions were prepared and analyzed in triplicate by different analysts using the established methods. Statistical analysis was conducted and the results are presented (see tables no 22, 23).

5.6.3 Accuracy

Accuracy was validated through recovery studies, where known amounts of standard drug (at 80%, 100%, and 120% levels) were added to sample solutions and the recovery was determined. Results are detailed in tables no (19, 20).

5.6.4 Limit of Quantification (LOQ)

The LOQ, defined as the lowest concentration of the analyte that can be accurately quantified, was determined using the formula LOQ = 10 (σ/S), where σ is the standard deviation of the response and S is the slope of the calibration curve. Results are shown in table no 26.

5.6.5 Limit of Detection (LOD)

The LOD, which is the lowest concentration of the analyte that produces a detectable response, was calculated using the formula LOD = 3.3 (σ/S), where σ is the standard deviation of the response and S is the slope of the calibration curve. Results are presented in table no (24).

6. Summary and conclusion

6.1 Precompression parameter of different formulation

Formulation code	FDT 1	FDT2	FDT 3	FDT 4	FDT 5
Bulk Density (gm/cm³)	0.85	0.78	0.69	0.64	0.66
Tapped Density (gm/cm³)	0.98	0.88	0.75	0.68	0.77
Angle of Repose (θ˚)	25.33	24.43	26.33	23.23	25.64
Compressibility Index%	11.93	12.64	10.94	13.27	12.76

6.2 Post compression parameter of different formulation

Formulation code	FDT1	FDT2	FDT 3	FDT 4	FDT 5
Thickness(mm) (n=3)	2.6±0.03	2.7±0.01	27.±0.02	2.6±0.03	2.7±0.01
Hardness(n=3) (kg/cm³	3.4±0.25	3.9±0.27	3.5±0.26	3.7±0.25	3.8±0.24
Friability (%)(n=10)	0.52	0.42	0.42	0.43	0.44
Disintegrating time(sec)(n=3)	32±0.220	31±0.200	31±0.220	29±o.320	29±0.320

Water absorption ratio (n=3)	62.00±0.89	64.00±0.24	65.00±0.91	68.00±0.85	67.00±0.32
Wetting Time(sec)(n=3)	37±1.09	35±1.07	33±1.23	29±0.30	35±1.94
uniformity of weight (n=10)	245±1.18	248.91±2.06	249±1.34	250±1.79	251±1.78

6.3 % Drug release of Different Batches

Batches % DRUG RELEASE

% drug release					
TIME (min.)	**FDT1**	**FDT2**	**FDT3**	**FDT4**	**FDT5**
2	8.25	8.25	8.56	8.99	7.99
4	12.35	12.54	14.23	15.57	11.89
6	25.11	23.78	21.98	30.89	20.34
8	28.77	29.74	31.23	35.90	25.76
10	55.64	59.88	65.10	75.13	60.43
12	76.99	70.10	82.82	90.15	79.16

6.4 Summary of validation parameter

S. no	**Parameter**	**Limits**	**Observed value**	
1	system suitability	%RSD should be NMT 2	Rt	0.659
			Th-	0.757
			Taili	0.669
2	Linearity	correlation coefficient 0.999	0.999	
3	Assay	% purity 98-100%	99.99%	
4	LOD&LOQ		0.802µg/ml & 1.4 µg/ml	
5	Accuracy	% recovery range is 99-100	99.90-100.0	
6	Day to day precision	%RSD should be NMT 2	Rt Rt	0.794 1.037
			Aera Aera	1.494 1.0007
7	Analyst to analyst	%RSD should be NMT 2	Rt Rt	1.037 1.032
			area Aera	0.7605 0.9901

7. CONCLUSION

Fast Dissolving Tablets (FDTs) represent a significant advancement in drug delivery systems, providing a solution to several limitations associated with conventional dosage forms such as tablets or capsules. These novel dosage forms are designed to disintegrate and dissolve quickly in the mouth, usually within a matter of seconds, without the need for water or chewing. FDTs offer multiple advantages over traditional oral formulations, making them an attractive option for both patients and pharmaceutical manufacturers.

Key Advantages of FDTs

1. **Improved Patient Compliance**: FDTs are especially beneficial for patients who have difficulty swallowing conventional tablets, such as paediatric, geriatric, or bedridden patients. This ease of administration enhances patient compliance, particularly for those with dysphagia (difficulty swallowing) or for individuals with conditions requiring chronic medication administration.
2. **Convenience**: The need for water is eliminated with FDTs, making them highly convenient for use in situations where water may not be readily available, such as during travel or for emergency treatments.
3. **Rapid Onset of Action**: Due to the fast disintegration and dissolution of the tablet in the mouth, the drug becomes available for absorption much quicker than with conventional tablets, which must pass through the gastrointestinal tract. This rapid onset of action is particularly useful for drugs used to treat conditions requiring immediate relief, such as hypertension or pain.
4. **Improved Bioavailability**: FDTs can improve bioavailability by allowing partial absorption of the drug in the oral cavity through the buccal mucosa before reaching the gastrointestinal tract. This can reduce the extent of first-pass metabolism, which is particularly beneficial for drugs that undergo significant hepatic degradation.

Mechanisms Enhancing Solubility in FDTs

The compression process in tablet manufacturing plays a crucial role in enhancing the solubility and bioavailability of the active pharmaceutical ingredient (API). Specifically, in FDTs, compression reduces the particle size of the drug, which increases the surface area exposed to the dissolving medium, thereby accelerating dissolution. Additionally, compression improves wetting properties, which promotes rapid disintegration and dissolution of the tablet in the oral cavity.

Several excipients are typically employed in FDT formulations to facilitate rapid disintegration, including super disintegrants like croscarmellose sodium, crospovidone, or sodium starch glycolate. These excipients swell in the presence of saliva, allowing the tablet to break apart quickly, releasing the drug into the solution.

Study Findings on Formulation FDT4

Among the formulations tested, FDT4 demonstrated superior performance in key quality control parameters:

1. **Percent Drug Release**: FDT4 exhibited the highest percentage of drug release within a short period, indicating efficient dissolution and bioavailability. This suggests that FDT4 is capable of delivering the drug in a more efficient manner compared to other formulations, ensuring that therapeutic concentrations are achieved rapidly in the systemic circulation.

2. **Compressibility Index**: The compressibility index, a measure of powder flowability, was found to be optimal in FDT4. A lower compressibility index indicates better flow properties, which is essential for the uniformity and consistency of the tablet during the manufacturing process.
3. **Hardness**: Tablet hardness is a critical parameter that affects both disintegration and dissolution. FDT4 exhibited an ideal balance between hardness and friability, meaning it was hard enough to withstand handling and packaging yet soft enough to disintegrate quickly in the mouth.
4. **Disintegration Time**: The disintegration time for FDT4 was significantly shorter than for other formulations, which is a key feature for fast-dissolving tablets. The quick breakdown of the tablet ensures that the drug is rapidly available for absorption, contributing to the faster onset of therapeutic action.

Potential Applications of Ramipril FDTs

Ramipril, an angiotensin-converting enzyme (ACE) inhibitor commonly used in the management of hypertension and heart failure, is a good candidate for FDT formulations. The rapid dissolution of Ramipril in FDT form could provide a quicker onset of action, which is particularly beneficial in hypertensive crises where blood pressure needs to be controlled rapidly. Moreover, the convenience of not requiring water makes it more likely that patients will adhere to their treatment regimens, particularly in populations with difficulty swallowing or limited access to water.

7.1 Formulation Studies

- This study successfully formulated Fast Dissolving Tablets of Ramipril to achieve immediate drug release and enhance bioavailability.
- Various formulation parameters such as thickness, hardness, friability, content uniformity, and in vitro disintegration were evaluated.
- Formulation F4, which included super disintegrant crospovidone, exhibited rapid disintegration, minimal wetting time, and the highest drug release among tested formulations.
- Based on in vitro disintegration time, wetting time, and drug release, Formulation F4 was identified as the optimal choice.

7.2 Future Directions and Investigations

While FDT4 containing Ramipril has demonstrated promising in vitro characteristics, further investigations are required to confirm its in vivo efficacy. Pharmacokinetic and pharmacodynamic studies are necessary to evaluate how well the drug is absorbed, distributed, metabolized, and excreted when delivered via FDTs compared to conventional tablets.

Additionally, the formulation needs to be optimized to ensure stability, uniformity, and efficacy over time. This might involve adjusting the concentration of excipients, optimizing the compression process, or modifying the disintegration and dissolution profiles to align with the desired therapeutic outcomes.

7.3 Analytical Study

Simplicity of the Method: The analytical method developed for the determination of Ramipril is straightforward, minimizing the complexity of both sample and mobile phase preparation. This simplicity makes it easily adoptable for routine analysis in quality control laboratories. The approach does not require sophisticated instruments or extensive operator training, enhancing its utility in various settings.

Rapid Analysis: The method allows for quick analysis of Ramipril, reducing the time required for both qualitative and quantitative assessment. Speed is crucial for large-scale manufacturing environments, where rapid turnaround times in quality control can significantly improve productivity and efficiency. This is particularly valuable for pharmaceutical companies handling high sample volumes.

Accuracy and Precision: The method exhibits high levels of accuracy, ensuring that the measured concentrations of Ramipril are close to the true values. Precision is demonstrated by the method's ability to consistently produce similar results when repeated under identical conditions, reflecting its reliability and robustness for both intra- and inter-day studies.

Cost-Effectiveness: The method is designed to be economical by using readily available reagents and minimizing the use of expensive solvents and chemicals. The lower costs of reagents, combined with the simplicity of the procedure, make it a cost-effective option for routine drug analysis in pharmaceutical dosage forms, benefiting small laboratories and large pharmaceutical manufacturers alike.

Specificity of the Method: The analytical method is highly specific to Ramipril, ensuring that the drug can be accurately identified and quantified in the presence of other components, such as excipients or impurities. This specificity minimizes the risk of interference from other substances that may be present in the formulation, making it suitable for complex dosage forms.

Reproducibility: The method demonstrates excellent reproducibility, meaning it can yield consistent results when applied under varying conditions or by different analysts. This property is crucial for establishing a standardized method that can be replicated across different laboratories, contributing to the method's robustness.

Method Optimization – Key Parameters: During method development, optimization of several critical parameters was necessary, including the pH of the mobile phase, its composition, and the flow rate. pH influences the ionization state of Ramipril, affecting its retention time and peak shape. The composition of the mobile phase determines the separation efficiency, and the flow rate influences the analysis time and resolution.

Enhanced Sensitivity: The method demonstrates enhanced sensitivity, meaning it can detect even very low concentrations of Ramipril. This is important for both quality control and pharmacokinetic studies where precise measurements of trace amounts are needed. Enhanced sensitivity ensures that even slight variations in drug concentration can be accurately quantified, improving the method's utility in dosage optimization.

Reliability for Pharmaceutical Dosage Forms This method is highly reliable for analyzing Ramipril in its pharmaceutical dosage forms, such as tablets or capsules. The ability to accurately determine drug content and purity is essential in quality control to ensure compliance with regulatory standards and guarantee the safety and efficacy of the drug product.

Advantages Over Traditional Methods: Compared to traditional analytical techniques, this method offers numerous advantages, including reduced analysis time, fewer preparation steps, and greater precision. Its simplicity in mobile phase preparation and sample handling, combined with its speed and cost-effectiveness, makes it superior for routine pharmaceutical analysis. The method's high sensitivity and specificity further enhance its applicability for a wide range of pharmaceutical formulations.

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