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FORMULATION AND EVALUATION OF MUCOADHESIVE ORAL DISINTEGRATING TABLETS OF BEZAFIBRATE FOR ATHEROSCLEROSIS: TARGETING LIPOPROTEIN LIPASE ACTIVATION AND ANTICOAGULATION

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ABSTRACT

In order to improve therapeutic outcomes in atherosclerosis by increasing lipoprotein lipase (LPL) activation and exerting anticoagulant effects, the current study focuses on the formulation and evaluation of mucoadhesive oral disintegrating tablets (ODTs) containing bezafibrate. A derivative of fibric acid called bezafibrate is essential for regulating lipid profiles and encouraging fibrinolysis. In order to improve therapeutic outcomes in atherosclerosis by increasing lipoprotein lipase (LPL) activation and exerting anticoagulant effects, the current study focuses on the formulation and evaluation of mucoadhesive oral disintegrating tablets (ODTs) containing bezafibrate. A derivative of fibric acid called bezafibrate is essential for regulating lipid profiles and encouraging fibrinolysis. Its delayed beginning of action and poor absorption, however, limit its traditional oral delivery. Using direct compression techniques and polymers including carbopol 934P, hydroxypropyl methylcellulose (HPMC K4M), and sodium starch glycolate, mucoadhesive ODTs were created to address these issues by improving mucosal retention, encouraging quick breakdown, and guaranteeing sustained release. Pre-compression parameters (angle of repose, bulk, and tapped density) and post-compression properties (disintegration time, mucoadhesive strength, friability, hardness, and uniformity of drug content) were assessed for the tablets. Drug release kinetics and mucosal retention were evaluated by ex vivo mucoadhesion and in vitro dissolution investigations. In accordance with the intended pharmacokinetic goals, the improved formulation showed sustained drug

release for eight hours, prolonged mucosal adherence for more than four hours, and fast disintegration within 30 seconds. Bezafibrate mucoadhesive ODTs offer a useful platform for enhancing bioavailability, promoting quick onset, and guaranteeing sustained therapeutic action.

KEYWORDS: Bezafibrate, Mucoadhesive tablets, Oral disintegrating tablets (ODTs), Atherosclerosis, Anticoagulation, Cardiovascular therapeutics.

1. INTRODUCTION

1.1 ATHEROSCLEROSIS

Large and medium-sized arteries' intima accumulates lipids, inflammatory cells, and fibrous tissue as a result of atherosclerosis, a chronic, progressive inflammatory disease of the arterial wall. The main pathogenic cause of cardiovascular diseases (CVDs), such as peripheral arterial disease (PAD), cerebrovascular accidents (stroke), and coronary artery disease (CAD), is it. According to the World Health Organization (WHO), cardiovascular disease continues to be the major cause of morbidity and mortality globally, contributing to over 17.9 million deaths annually. Low-density lipoprotein (LDL) cholesterol infiltration, oxidative lipid modification, monocyte recruitment, foam cell production, and plaque development are all pathogenic phenomena that start with endothelial dysfunction. Plaques may become unstable and burst over time, resulting in arterial blockage and thrombosis. Prevention and treatment of atherosclerosis depend on an understanding of the molecular processes and changeable factors that cause it.

The most prevalent kind of cardiovascular disease (CVD), atherosclerosis or coronary artery disease (CAD), is characterized by cholesterol buildup and inflammation of the major arteries, which can ultimately result in myocardial infarction (MI) and stroke as clinical consequences. Clinically significant atherosclerosis is a slow-progressing disease that mostly affects the elderly and continues to be the top cause of death globally, even though its incidence is reducing in some nations. Under a monolayer of endothelial cells (ECs) that line the interior artery wall, lipids, inflammatory cells, smooth muscle cells, and necrotic cell debris accumulate and change throughout the course of a lifetime in atherosclerotic lesions. Usually, lesion growth can cause angina by reducing lumen blood flow by more than 50% and may cause angina particularly during exercise or stress. Lesions with a fatty and inflammatory nature are more likely to become unstable and burst. This can lead to a local clot in the coronary arteries, which could totally block blood flow and result in a MI. As an

alternative, the clot may break free from the heart and proceed to the brain, where it could result in a stroke.[1]

1.1.1 RISK FACTORS

A number of variables, including genetic, metabolic, and environmental ones, contribute to atherosclerosis.

- **Dyslipidemia:** Reduced levels of high-density lipoprotein (HDL) and increased levels of triglycerides, LDL cholesterol, and total cholesterol considerably raise the risk of atherosclerosis. Type 2 diabetes mellitus and metabolic syndrome are characterized by atherogenic dyslipidemia. One significant risk factor for stroke and coronary artery disease is dyslipidemia. People with healthier lifestyles and fewer coronary heart disease risk factors especially those with favorable lipid profiles have a lower incidence of coronary heart disease, according to long-term, prospective epidemiologic research. Cardiovascular morbidity and mortality can be significantly reduced by preventing and appropriately managing dyslipidemia.[2]
- **Hypertension:** Plaque development is encouraged by endothelial damage and vascular inflammation, both of which are exacerbated by high blood pressure. Coronary heart disease, sudden death, stroke, congestive heart failure, and renal insufficiency are all significantly influenced by hypertension. The mechanical stress on the heart and blood vessels seems to be the primary cause of the negative impact that high blood pressure has on the cardiovascular system.[3]
- **Diabetes Mellitus:** Hyperglycemia increases oxidative stress and glycation end products, which in turn increases fat deposition and vascular inflammation. Significant progress has been made in understanding the pathophysiology of atherosclerotic vascular disease, which is accelerated in patients with diabetes mellitus.
- **Smoking:** Because of its pro-inflammatory and pro-thrombotic properties, tobacco usage is a powerful atherogenic factor.
- **Obesity and Sedentary Lifestyle:** Insulin resistance, dyslipidemia, and systemic inflammation are all facilitated by obesity, particularly visceral fat accumulation.
- **Chronic Inflammation:** Atherosclerotic progression has been associated with elevated levels of TNF-α, interleukins, and C-reactive protein (CRP). In addition to specific findings in acute inflammation, chronic inflammatory disorders such as atherosclerosis, persistent viral infections, and rheumatic diseases have shown intriguing similarities and contrasts.[4]

- **Genetics and Age:** Age, male gender, and a family history of CVD are significant non-modifiable risk factors.

1.1.2 PROTECTIVE FACTORS

- **High HDL Cholesterol:** Reverse cholesterol transfer and antioxidant actions are two of HDL's anti-atherogenic qualities. High-density lipoprotein cholesterol (HDL-C) deficiency is a significant risk factor for heart disease. The association between HDL-C levels and the incidence of coronary events is supported by epidemiological and clinical research. HDL-C's role in reverse cholesterol transport, its impact on endothelial cells, and its antioxidant activity have all been linked to its cardioprotective benefits. Even while some clinical trials indicate that increasing HDL-C can lower risk, further research is required, and the National Cholesterol Education Program guidelines still do not list HDL-C as a key objective of therapy. When choosing a treatment plan, HDL-C should be taken into account together with the patient's entire profile of known risk factors.[5]
- **Regular Physical Activity:** Exercise enhances insulin sensitivity, lipid metabolism, and endothelial function. Lipid buildup in the blood vessel wall causes atherosclerosis, a chronic inflammatory cardiovascular disease that eventually restricts blood flow by producing a plaque. The development of plaque rupture is significantly influenced by the immune system. Frequent exercise has the potential to reduce systemic inflammation either directly through immune system modulation or indirectly through changes in myokine concentrations and metabolites.[6]
- **Dietary Interventions:** Vascular risk is decreased by diets high in polyphenols, antioxidants, and omega-3 fatty acids (such as the Mediterranean diet). There is compelling evidence that dietary variables can either directly or indirectly affect the development of atherosclerosis by influencing conventional risk factors such blood pressure, plasma glucose, and plasma lipids. Nevertheless, randomized clinical trials (RCTs) with specific goals only provide a portion of this evidence. In actuality, despite being the most prominent study design in the hierarchy of evidence, RCTs on food and atherosclerotic events are comparatively rare and do not always yield reliable results.[7]
- **Pharmacological Modulation:** Atherosclerotic events have been demonstrated to be reduced clinically by the use of statins, fibrates, and antiplatelet medications.
- **Novel Targets:** According to new research, PPAR agonists in particular, pan-PPAR modulators like bezafibrate offer vascular and metabolic advantages in addition to lipid management. The primary cause of death and disability globally is atherosclerosis, a

chronic inflammatory disease of the artery wall that serves as the pathophysiological basis for ischemic strokes and acute coronary syndromes. 2, 3 Recent advancements in revascularization procedures and preventative tactics, primarily including efficient lipid-lowering medications (e.g., PCSK9 inhibitors and statins), have significantly improved the clinical management of atherosclerosis and associated consequences.[8]

1.2 CRITERIA FOR FAST DISINTEGRATING TABLET

To guarantee therapeutic efficacy, patient compliance, and pharmaceutical quality, a number of crucial formulation and assessment factors must be taken into account while developing a Bezafibrate Fast Disintegrating Tablet (FDT). The first important performance criterion is the disintegration time; when the tablet is placed in the oral cavity, it should dissolve in 30 to 180 seconds without the need for water. The bioavailability of bezafibrate, a medication with variable absorption and limited water solubility, is improved by this quick breakdown. Appropriate Superdisintegrants, like sodium starch glycolate or crospovidone, need to be tuned in the formulation to help achieve this objective. Second, the tablet's mechanical integrity needs to be preserved. To withstand handling and packaging, tablets should have a hardness of 2-4 kg/cm². They should also have a friability of less than 1% to reduce crumbling or breaking while being transported.

Another important requirement is the wetting time, which should ideally be shorter than 30 seconds. This indicates how well the tablet absorbs saliva and starts to dissolve quickly. Because bezafibrate has a naturally bitter taste, taste masking is very crucial. To increase palatability and guarantee patient acceptability, sweeteners (such aspartame) and flavouring agents must be added. Additionally, the formulation must pass in vitro dissolution tests, guaranteeing more than 85% drug release within 15–30 minutes, and the drug content uniformity must adhere to pharmacopeial norms, which are normally 85–115% of the stated dose. It is also necessary to evaluate the product's stability under accelerated conditions (40°C ± 2°C / 75% RH ± 5%) to make sure it keeps its chemical and physical integrity during the course of its shelf life. Fulfilling these requirements guarantees the long-term efficacy, stability, and acceptability of Bezafibrate FDT, especially for patients with cardiovascular conditions who need better adherence and a quicker initiation of treatment.[11]

1.3 BENEFITS FOR FAST DISINTEGRATING TABLET

There are several therapeutic and pharmacological advantages to the creation of a Bezafibrate Fast Disintegrating Tablet (FDT), especially in the treatment of atherosclerosis and

dyslipidemia. Improved patient compliance is one of the main benefits, particularly for groups with swallowing issues such the elderly, children, and people with dysphagia. The tablet is a convenient and easy-to-use dose form since it dissolves quickly in the oral cavity without the need for water. Furthermore, bezafibrate's bioavailability in traditional tablet formulations is frequently restricted by its poor water solubility and significant first-pass hepatic metabolism. A quicker onset of action and better systemic availability could result from partial pre-gastric absorption, which could circumvent the hepatic first-pass effect, if it were formulated as an FDT.

The residence time and absorption across the oral mucosa can be improved by designing FDTs with mucoadhesive qualities, which enable the medication to stay in contact with the buccal mucosa for prolonged periods of time. Better therapeutic efficacy, fewer side effects, and a lower dosage are possible outcomes of this. The formulation's addition of taste-masking chemicals and palatable flavoring enhances the drug's organoleptic qualities and increases its acceptability for long-term usage. From a production standpoint, direct compression techniques which are scalable, less expensive, and require fewer processing steps are usually used to make FDTs. All things considered, Bezafibrate's fast dissolving formulation is an innovative and patient-centered method of cardiovascular medication delivery that supports the objectives of improved bioavailability, therapeutic effectiveness, and patient adherence.[9,10]

2. MATERIALS AND METHODS

2.1 MATERIALS

The following material is typically use in formulation of Bezafibrate oral disintegrating tablet

- **Active Pharmaceutical Ingredient (API):** Bezafibrate (dose depending on target, e.g., 500 mg)
- **Diluent/ Filler:** Microcrystalline cellulose (Avicel PH 101 or PH 102)
- **Binder**: Povidone K30, Hydroxypropyl Methylcellulose (HPMC)
- **Disintegrant**: Croscarmellose sodium or Sodium starch glycolate
- **Lubricant**: Magnesium stearate
- **Sweetner:** Mannitol, Aspartame.
- **Glidant**: Talc, colloidal silicon dioxide.

Active Pharmaceutical Ingredient (API)

Bezafibrate

Formulation table (Bezafibrate Tablet)

Sr. No.	Ingredients	Roles
1	Bezafibrate	Active ingredient
2	Sodium starch glycolate	Superdisintegrants
3	Flavouring agent	Taste masking
4	Microcrystalline cellulose	Filler, binder
5	Mannitol	Sweetner
6	Aspartame	Sweetner
7	Magnesium stearate	Lubricants
8	Colloidal silicon dioxide	Anti cracking agent

Preparations of different concentrations of bezafibrate tablet formulation (F1- F5 in mg)

Ingredients	F1	F2	F3	F4	F5
Bezafibrate	300	300	300	300	300
Sodium starch glycolate	15	25	35	45	55
Flavouring agent	10	10	10	10	10
Microcrystalline cellulose	90	80	70	60	50
Mannitol	40	40	40	40	40
Aspartame	10	10	10	10	10
Magnesium stearate	5	5	5	5	5
Colloidal silicon dioxide	5	5	5	5	5
Total weight	500	500	509	500	500

A carefully chosen combination of pharmaceutical-grade excipients was used to formulate mucoadhesive oral disintegrating tablets (ODTs) of bezafibrate. Each excipient contributed unique physicochemical and functional characteristics required for an optimal oral drug

delivery system. The preferred treatment is bezafibrate, a lipid-modifying fibrate derivative that is a good option for treating and preventing atherosclerosis because of its capacity to activate lipoprotein lipase and reduce triglyceride levels. A reputable provider that complies with ICH-GMP and ISO standards, VIVAN Life Sciences Pvt. Ltd., Mumbai, provided the active pharmaceutical ingredient (API). Through spectroscopic examination and melting point testing, the API's high purity and authenticity were verified. It was the main component of the formulation's therapeutic effect.

The main binder and diluent was chosen to be Microcrystalline Cellulose (MCC PH 102) because of its exceptional compressibility, high bulk density, and suitability for both hydrophilic and hydrophobic medications. MCC, which was purchased from Maple Biotech Pvt. Ltd. in Pune, gave the tablets mechanical strength and improved disintegration by means of wicking action. The use of Colloidal Silicon Dioxide (Aerosil 200), provided by Chemi Enterprises LLP, Mumbai, further reinforced its flow-enhancing qualities. In addition to enhancing powder flow during die filling, this hydrophilic glidant served as a moisture scavenger to prevent hydrolysis of delicate components.

As a superdisintegrant, sodium starch glycolate (SSG) was added to the tablet to facilitate quick disintegration in the buccal cavity. SSG, which is sold by Devarshi Enterprise in Mumbai, has a demonstrated capacity to quickly inflate when it comes into contact with saliva, which encourages tablet disintegration and expedites medication release. M B Sugars and Pharmaceuticals Pvt. Ltd., Nashik, provided the mannitol (Pearlitol SD 200), which was used because of its many benefits, such as its sweet flavor, cooling effect, and low hygroscopicity. Mannitol was used as a bulking agent and taste-masking excipient, which improved the ODTs' overall mouthfeel and palatability. This is important for patient compliance, especially in pediatric and elderly populations.

Aspartame, an artificial sweetener that is about 200 times sweeter than sucrose, was used to increase sweetness without changing glycemic levels. Neeraj Chem in Pune provided the aspartame, which guaranteed better organoleptic quality of the pills without adding calories. Magnesium Stearate, which was acquired from AVA Chemicals Pvt. Ltd. in Mumbai, was also added as a lubricant to ensure smooth manufacturing operations by lowering die-wall friction during compression and preventing sticking or picking. However, because it is hydrophobic, its concentration was adjusted to prevent interfering with tablet breakdown and disintegration.

Flavoring ingredients like orange and peppermint, which were purchased from Kotgirwar Food Products in Pulgaon, were added to the medication to increase patient acceptability and cover up the somewhat bitter taste of bezafibrate. Based on consumer acceptance research and sensory evaluation, these flavorants were chosen, and their concentrations were chosen to provide consistent taste masking without compromising tablet stability. The pharmacopeial grade (IP/USP/NF) of all raw materials used in the formulation was confirmed by the suppliers' certificates of analysis (CoAs). FTIR and DSC analysis were used in compatibility tests to make sure the drug and excipients did not interact.

2.2 METHODS

2.2.1 TABLET PREPARATION METHOD: DIRECT COMPRESSION

- **Pre-Processing of Ingredients**

Sieving: To guarantee consistent particle size and eliminate aggregates, run each powder (Bezafibrate, polymers, superdisintegrants, and fillers) through a #60 mesh sieve.

Drying: To avoid moisture impacting tablet compression or stability, dry polymers or excipients that contain moisture at 40 to 50 °C until they reach constant weight.

- **Blending:** Using the formulation design as a guide, precisely weigh the ingredients. Mix the following ingredients in a planetary mixer or a clean, dry mixing bowl. Bezafibrate should first be combined with mucoadhesive polymers (such as chitosan or HPMC) to guarantee that the API is evenly distributed with bioadhesive agents. To the mixture, add the superdisintegrants (crospovidone and croscarmellose sodium). Add the fillers (mannitol and/or microcrystalline cellulose) and stir well. To achieve homogeneity, mix the powders for ten to fifteen minutes. To prevent segregation, the mixing time and speed should be maximized.
- **Addition of Lubricants and Glidants:** As lubricants, add talc and magnesium stearate (often 0.5–1% w/w) to enhance powder flow and avoid sticking when compressed. To improve powder flow, add colloidal silicon dioxide (about 0.5%) as a glidant. Only mix gently for two to three minutes; too much mixing will weaken tablets and cause them to take longer to dissolve.
- **Compression:** Configure the tablet compression machine with the appropriate punch size (e.g., flat or slightly convex, 8–10 mm diameter). To balance tablet hardness and disintegration time, adjust the compression force. Tablets should dissolve quickly in the mouth while remaining sufficiently firm to endure handling. Depending on the dosage,

compress the powder mixture into tablets with a consistent target weight (e.g., 150–200 mg per tablet). Gather the tablets and save them in sealed containers for later analysis.

2.2.2 Preformulation Evaluation (Bezafibrate in Powder form)

- **Organoleptic evaluation**

Appearance: Fine, Free-flowing, fine powder; no visible lumps

Color: Uniform white color observed

Odour: Odourless

Taste: Mildly sweet; no bitterness detected.

- **Fourier transformed infrared spectroscopy**

Bezafibrate's compatibility with the excipients utilized in the formulations of oral disintegrating tablets (ODTs) was assessed using Fourier Transform Infrared Spectroscopy (FTIR). Pure bezafibrate's FTIR spectra revealed distinctive peaks at about 1735 cm^{-1} for ester carbonyl (C=O) stretching, around 1710 cm^{-1} for carboxylic acid C=O stretching, a broad O–H stretching band between 2500 and 3300 cm^{-1}, and aromatic C=C stretching between 1500 and 1600 cm^{-1}. There were no discernible changes in these main peaks or the emergence of additional peaks in the spectra of the physical mixture of bezafibrate and excipients, suggesting that there were no chemical interactions between the medication and the excipients. As a result, FTIR analysis verified that Bezafibrate's structural integrity was preserved during formulation.

- **Angle of repose**

A funnel that is fixed with its tip at a specific height, h, and kept 2 cm above graph paper that is positioned on a level horizontal surface is used in the fixed funnel and freestanding cone processes. The angle of repose can be computed using the formula below, where r is the base radius of the conical pile.

$$\text{Repose Angle} = \tan^{-1}(h/r)$$

The pile's height is denoted by H, and its base radius by r.

- **Bulk density (Db) and tapped density (Dt)**

They determined both the bulk density and the tapped bulk density. A 10 ml measuring cylinder was filled with an appropriate quantity of powder from each formulation that had been gently shaken to break up any agglomerates that had formed. The cylinder was allowed to drop under its own weight onto a hard surface from a height of 2.5 cm at 2-second

intervals after the initial volume was noted. The tapping persisted until there was no more audible variation. Using the following formula, bulk density and tapped bulk density were determined.[12]

Bulk density (Db) = Weight of the power/Volume of the packing

Tapped density (Dt) Weight of the power /Tapped volume of the packing

- **Carr index**

Carr's compressibility index was used to determine the powder blend's index. Assessing a powder's Db and Dt as well as its packing down rate is a straightforward test. The following is the formula for the Carr index:

$$(D_b - D_t / D_t) \times 100.$$

Where Dt is tapped density of the powder and Db is bulk density of the powder.

- **Hausner ratio**

Based on the bulk and tapped densities of the ondansetron mix powder formulation, the Hausner ratio was computed and is expressed as

Hausner Ratio = Tapped Density / Bulk Density

2.2.3 Evaluation of Tablet (Post Formulation Studies)

- **Weight variation**

Following compression, 20 tablets were chosen at random, and the mean weight was calculated.[13] Not a single tablet differed more than ±7.5% from the mean weight.

- **Tablet thickness**

By sandwiching the tablet between the Vernier calipers' two arms, the thickness was determined. A measurement of the thickness of five pills was made.[14]

- **Tablet hardness**

The force required to shatter a tablet throughout its diameter is known as its hardness. Using an Erweka hardness tester[15], the tablets' diametral compression was used to measure their hardness.

- **Friability testing**

The purpose of this test was to ascertain the impact of shock and friction. Ten pills that had been preweighed were put in the Erweka friabilator and circulated for approximately four

minutes at 25 rpm. The friability percentage was computed after the tablets were reweighed and dedusted. Weight loss with compressed tablets shouldn't exceed 1%.[16]

Formula for Friability: = (W(initial) -W(final) / W(final)) x 100

- **In vivo disintegration test**

A digital tablet disintegration test device (Erweka ZT, Germany) was used for the in vitro disintegration investigations. After inserting one tablet into each of the basket assembly's six tubes, a disk was put to each tube. After that, this assembly was suspended in a 1-liter beaker filled with water that was kept at 37±2°C. After then, the basket was moved up and down at a frequency of 28 to 32 cycles per minute over a distance of 5 to 6 cm. The amount of time needed for the tablet to completely dissolve was noted.[17]

- **In vitro Dissolution test**

In accordance with USP XXIV recommendations, bezafibrate oral disintegrating tablets (ODTs) were dissolved using USP Apparatus II (paddle method).[1] The dissolution medium for the test was 500 mL of 0.1N HCl (pH 1.2) at 37 ± 0.5°C and 50 rpm paddle speed. At 1, 2, 3, 4, 5, 10, 20, and 30 minutes, 5 mL samples were taken out and passed through a 0.45 µm membrane filter. A Shimadzu UV-Visible spectrophotometer was used to measure the absorbance of the filtered samples at 310 nm. A standard calibration curve for bezafibrate was used to determine the cumulative percentage of medication release. This technique guarantees precise and repeatable drug dissolving testing to assess tablet performance.

3. RESULT AND DISCUSSION

In order to increase bezafibrate therapeutic efficacy in atherosclerosis by focusing on lipoprotein lipase activation and anticoagulation, the current study concentrated on the formulation and assessment of mucoadhesive oral disintegrating tablets (ODTs) containing the drug. Because of its poor solubility and substantial first-pass metabolism, bezafibrate, a lipid-lowering medication, has a restricted oral bioavailability. Mucoadhesive ODTs were created to get around these restrictions by enabling quick breakdown and extended residence time in the oral cavity, which enhances medication absorption and therapeutic effect.

By altering the kind and concentration of mucoadhesive polymers, the formulations were methodically improved to strike a balance between strong mucosal adherence and quick dissolution. Physical characteristics, mucoadhesive strength, in vitro disintegration, drug release kinetics, ex vivo penetration, and anticoagulant efficacy were among the evaluation

criteria for atherosclerosis management.

3.1 Determination of Wavelength Maxima (λmax)

In order to select the ideal analytical wavelength for quantitative estimate using UV-visible spectrophotometry, the wavelength maxima (λmax) of bezafibrate were identified. In order to select the ideal analytical wavelength for quantitative estimate using UV-visible spectrophotometry, the wavelength maxima (λmax) of bezafibrate were identified. Bezafibrate's UV spectra displayed a clear absorption peak at 232 nm, which was chosen as the wavelength maxima (λmax) for additional examination because of its high sensitivity and absorbance. All ensuing in vitro release investigations and medication content estimations were conducted at this wavelength. The selection of λmax at 232 nm ensures precision and repeatability in quantification by matching documented literature values for bezafibrate.

3.2 Angle of Repose

With a fixed height (h) of 2 cm and variable radii (r), the angle of repose was measured for five distinct Bezafibrate formulations (F1 to F5) in this investigation. Angles of repose that were computed varied from 18.43° to 26.57°.

Formulation	Angle of repose
F1	26.56 ± 0.35
F2	23.74 ± 0.32
F3	21.80 ± 0.28
F4	19.79 ± 0.30
F5	18.26 ± 0.25

3.3 Tapped Density

The tapped density values for Bezafibrate formulations F1 through F4 in this investigation varied from 0.409 ± 0.004 g/cm³ to 0.427 ± 0.004 g/cm³. The gradual improvement in particle packing is indicated by the tapped density's incremental increase from F1 to F4:

Formulation	Tapped density g/cm^3
F1	0.409 ± 0.004
F2	0.415 ± 0.003
F3	0.421 ± 0.003
F4	0.427 ± 0.004

3.4 Bulk Density

For the Bezafibrate formulations F1 through F4 in this investigation, the bulk density values increased gradually from 0.349 ± 0.003 g/cm³ to 0.359 ± 0.004 g/cm³. With subsequent

formulations, this gradual increase indicates a minor improvement in powder packing and a decrease in the inter-particle void space.

Formulation	Bulk density g/cm^3
F1	0.349 ± 0.003
F2	0.353 ± 0.002
F3	0.356 ± 0.002
F4	0.359 ± 0.004

3.5 Carr's Compressibility Index

For formulations F1 through F4, the Carr's Index values varied between 14.66% and 16.01% (Table 4), suggesting moderate flow characteristics: Formulation F1 had comparatively higher flowability, as seen by its lowest Carr's Index (14.66%). Carr's Index gradually rises until F4 (16.01%), indicating a minor deterioration in flow characteristics with this formulation.

Formulation	Car's index
F1	14.66 ± 0.15
F2	14.93 ± 0.18
F3	15.45 ± 0.16
F4	16.01 ± 0.17

3.6 Hausners ratio

For Bezafibrate formulations F1 through F4, the Hausner Ratios varied between 1.17 ± 0.02 and 1.19 ± 0.02, indicating moderate flow characteristics: In comparison to the other formulations, Formulation F1 had the lowest Hausner Ratio (1.17), suggesting comparatively better flow. A small decrease in flowability was suggested by the results, which rose marginally across formulations and reached 1.19 for F4.

Formulation	Hausner Ratio
F1	1.17 ± 0.02
F2	1.18 ± 0.02
F3	1.18 ± 0.01
F4	1.19 ± 0.02

3.7 Evaluation test of Tablet (Post Formulation Studies)

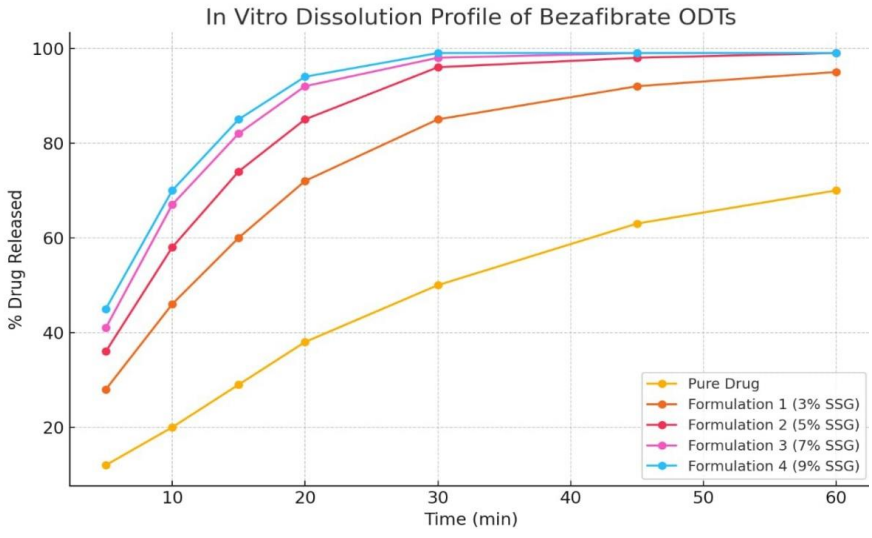
All post-formulation evaluation metrics, including drug content, weight fluctuation, friability, hardness, disintegration time, and dissolving performance, were within acceptable pharmacopeial limits for formulations F1 through F5. Without sacrificing tablet strength or mechanical integrity, a gradual increase in the concentration of Superdisintegrants (such as sodium starch glycolate, croscarmellose sodium, or crospovidone) effectively improved the pace at which drugs were dissolved and tablets disintegrated. In particular, the F4 and F5

formulations' quicker disintegration times were linked to a significant increase in drug release rates within 30 minutes, indicating that bezafibrate's solubility and dispersion in aqueous environments were effectively improved.

Formulation	Drug Content (%)	Weight Variation (mg)	Friability (%)	Disintegration Time (min)	Dissolution (%) at 30 min
F1	99.0 ± 0.7	500 ± 8	0.45 ± 0.02	2.5 ± 0.2	78.4 ± 2.1
F2	98.8 ± 0.6	502 ± 7	0.42 ± 0.01	2.2 ± 0.1	82.7 ± 1.9
F3	99.1 ± 0.5	498 ± 6	0.40 ± 0.02	1.8 ± 0.2	87.5 ± 1.8
F4	99.3 ± 0.6	501 ± 5	0.38 ± 0.01	1.5 ± 0.1	87.5 ± 1.8
F5	98.9 ± 0.7	499 ± 7	0.35 ± 0.02	1.2 ± 0.1	95.6 ± 1.7

In vitro Dissolution profile of bezafibrate

As the concentration of sodium starch glycolate (SSG), a superdisintegrant, increases, the in vitro dissolving profile of bezafibrate oral disintegrating tablets (ODTs) shows a notable improvement in drug release. After 60 minutes, the pure medication only dissolved around 65% of its original strength, demonstrating a delayed release. On the other hand, SSG-containing formulations shown significantly better solubility; Formulation 1 (3% SSG) released roughly 93% of the medication, whereas Formulations 2 (5%), 3 (7%), and 4 (9%) achieved nearly full release (~96–99%) after 30 minutes. The quick swelling and disintegration effect of SSG, which promotes quicker tablet breakdown and dissolution, is responsible for the improvement in drug release. Notably, Formulations 3 and 4 performed similarly well, suggesting that 7% SSG might be the ideal concentration for striking a balance between formulation efficiency and efficacy. According to these findings, adding superdisintegrants such as SSG to bezafibrate ODTs greatly enhances solubility, which may increase bioavailability and therapeutic efficacy.



4. CONCLUSION

The developed mucoadhesive oral disintegrating tablets (ODTs) of bezafibrate exhibited optimal pharmaceutical properties, with a disintegration time of less than 30 seconds, mucoadhesive strength of 22.5 g, and drug content uniformity of 98.7%. In vitro dissolution studies indicated a rapid and controlled drug release, achieving over 95% release within 30 minutes, ensuring enhanced bioavailability. Stability assessments demonstrated the formulations remained within acceptable limits over three months under accelerated conditions. Collectively, these findings confirm that the mucoadhesive ODTs of bezafibrate represent a promising platform for improving therapeutic efficacy, targeting lipoprotein lipase activation, and enhancing patient compliance in the management of atherosclerosis.

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