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A REVIEW ON FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF MOUTH DISSOLVING TABLET OF PIOGLITAZONE HYDROCHLORIDES

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ABSTRACT

Mouth Dissolving Tablets (MDTs) have emerged as a cornerstone in patient-centric drug delivery systems, particularly for the management of chronic metabolic disorders such as Type 2 Diabetes Mellitus. Pioglitazone Hydrochloride, a potent thiazolidinedione, serves as the primary therapeutic agent in this context; however, its clinical utility is often hampered by its classification as a BCS Class II drug. This classification highlights the drug's inherent challenges: low aqueous solubility and a dissolution-rate-limited absorption profile. This review article provides an exhaustive analysis of the formulation development of Pioglitazone MDTs, emphasizing the transition from conventional oral solids to rapid-disintegrating matrices that bypass the need for water, thereby facilitating immediate drug initiation and improving adherence among geriatric patients suffering from dysphagia. The formulation landscape is meticulously examined, focusing on the synergistic use of superdisintegrants such as Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate. We delve into the molecular mechanisms of disintegration—specifically wicking, swelling, and strain recovery and how these forces are optimized to achieve a disintegration time of less than 60 seconds. Furthermore, the review explores advanced solubility enhancement strategies, including solid dispersions, inclusion complexation with beta-cyclodextrins, and the utilization of pore-forming agents via the sublimation technique. These methods are critical for ensuring that once the tablet disintegrates, the Pioglitazone particles are in a state that favors rapid transition into the systemic circulation.

KEYWORDS: Pioglitazone Hydrochloride, Mouth dissolving Tablet, Diabetes Mellitus.

1. INTRODUCTION

The pharmaceutical landscape is currently undergoing a paradigm shift from traditional "one-size-fits-all" dosage forms toward patient-centric drug delivery systems (PCDDS). Among these innovations, Mouth Dissolving Tablets (MDTs), also known as Orally Disintegrating Tablets (ODTs), have gained significant traction. Defined by the European Pharmacopoeia, MDTs are tablets intended to be placed in the mouth where they disperse rapidly before being swallowed. This characteristic is particularly vital for drugs like Pioglitazone Hydrochloride, where rapid onset and ease of administration can significantly impact the management of chronic metabolic conditions. The evolution of solid oral dosage forms has seen a strategic shift toward enhancing patient adherence through the development of Mouth Dissolving Tablets (MDTs). While conventional tablets remain the industry standard, they often present a significant barrier to treatment for specific demographics, notably those suffering from dysphagia, or difficulty in swallowing.

This condition is prevalent in approximately 35% of the general population and is a common clinical feature in geriatric and pediatric patients.[1] For a chronic condition such as Type 2 Diabetes Mellitus (T2DM), where daily medication is a lifelong requirement, the physical discomfort of swallowing large, hard-compressed tablets can lead to frequent dose-skipping and poor glycemic control. MDTs address this by utilizing highly porous matrices that disintegrate in the oral cavity within seconds upon contact with saliva, requiring no additional water intake.

1.1. The Challenge of Dysphagia and Patient Compliance

A primary driver for the development of MDTs is the widespread prevalence of dysphagia—the medical term for difficulty in swallowing.[2] Studies indicate that approximately 35% of the general population, and up to 60% of the institutionalized elderly, experience some form of swallowing distress. For patients with Type 2 Diabetes Mellitus (T2DM), who are often on a multi-drug regimen (polypharmacy), the requirement to swallow large, conventional tablets with water can lead to:

- Dose skipping: Patients avoid medication due to fear of choking.
- Improper administration: Crushing tablets that are not meant to be crushed, potentially altering the drug's pharmacokinetics.
- Reduced Quality of Life: The constant need for water access limits the patient's mobility and independence.
- Pioglitazone HCl MDTs address these issues by offering a "waterless" administration route, ensuring that the medication can be taken anywhere, at any time, enhancing long-term therapeutic adherence.

1.2. Strategic Importance in Diabetic Care

The clinical management of T2DM often involves polypharmacy, where patients take multiple medications simultaneously. MDTs offer a "waterless" administration route that significantly improves the quality of life for diabetic patients who may be traveling or have restricted access to potable water.[3] Furthermore, the rapid disintegration in the oral cavity may allow for a fraction of the drug to be absorbed through the buccal or sublingual mucosa. This pregastric absorption bypasses the first-pass hepatic metabolism, which is particularly relevant for Pioglitazone, as it is heavily metabolized by the CYP2C8 and CYP3A4 enzymes in the liver. Thus, the transition from a conventional tablet to an MDT is not merely a change in convenience but a sophisticated pharmaceutical strategy to enhance both the bioavailability and the onset of action of the drug.[4]

1.3. Pioglitazone Hydrochloride: A Pharmacological Profile

- Pioglitazone Hydrochloride is a potent member of the thiazolidinedione (TZD) class. It acts as a selective agonist for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma). By activating these receptors, Pioglitazone modulates the transcription of genes involved in glucose and lipid metabolism.[5]
- Mechanism of Action: It increases insulin sensitivity in the liver, adipose tissue, and skeletal muscle. Unlike sulfonylureas, it does not increase insulin secretion but rather makes the body's existing insulin work more efficiently.
- Physicochemical Properties: As a BCS Class II drug, Pioglitazone HCl exhibits high permeability across biological membranes but suffers from poor aqueous solubility. Its solubility is highly pH-dependent, being more soluble in acidic environments (like the stomach) and practically insoluble at the neutral pH found in the small intestine and saliva.[6]

1.4. The Biopharmaceutical Rationale for Pioglitazone MDTs

Pioglitazone Hydrochloride is a potent insulin sensitizer belonging to the thiazolidinedione class, acting as a high-affinity agonist for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma). Despite its clinical efficacy, its formulation into an MDT is complicated by its classification as a BCS Class II drug. This implies that while the drug is highly permeable across biological membranes, its therapeutic onset is severely limited by its low aqueous solubility. In conventional tablets, the slow disintegration of the tablet matrix in the gastric fluid further delays the dissolution process, leading to a prolonged T_{max} (time to reach peak plasma concentration). By engineering a fast-dissolving matrix, formulators can present the drug to the gastrointestinal tract as a fine, high-surface-area suspension, effectively shifting the rate-limiting step from disintegration to rapid dissolution.[7]

- The decision to formulate Pioglitazone as an MDT is rooted in both biopharmaceutical and commercial logic.
- Overcoming Solubility Limits: By using superdisintegrants, the tablet breaks down into a fine particulate suspension in the mouth. This massive increase in surface area (A) directly influences the dissolution rate (dc/dt) according to the Noyes-Whitney.

Equation

$$\frac{dc}{dt} = \frac{DA(Cs-C)}{h}$$

Where D is the diffusion coefficient, C_s is the solubility, and h is the thickness of the diffusion layer.

- Pregastric Absorption: While most of the drug is swallowed and absorbed in the GI tract, a small fraction may be absorbed through the buccal and esophageal mucosa. This can bypass first-pass hepatic metabolism, potentially increasing bioavailability.
- Rapid Onset: For diabetic patients, maintaining a steady-state plasma concentration is key. Faster disintegration leads to faster dissolution, which translates to a quicker therapeutic response.

2. Challenges in Pioglitazone MDT Formulation

The development of an effective Mouth Dissolving Tablet (MDT) for Pioglitazone Hydrochloride is a complex balancing act. Unlike conventional tablets, where the primary goal is structural integrity and controlled release, MDTs must disintegrate almost instantly while overcoming the specific physicochemical hurdles inherent to the drug molecule.[8,9] The following sections detail the three "critical bottlenecks" in Pioglitazone MDT engineering.

2.1. The Solubility-Dissolution Barrier (BCS Class II Hurdles)

- Pioglitazone HCl is categorized under the Biopharmaceutics Classification System (BCS) as Class II. This means that while the drug can easily pass through biological membranes (high permeability), it struggles to dissolve in the aqueous environment of the gastrointestinal tract (low solubility).[10,11]
- The Saliva Volume Constraint: In the oral cavity, the volume of available fluid (saliva) is extremely limited—typically less than 2 mL at any given time. For a poorly soluble drug like Pioglitazone, this volume is insufficient to initiate significant dissolution.
- The pH-Dependency Trap: Pioglitazone exhibits a pH-dependent solubility profile. It is more soluble in the acidic environment of the stomach (pH 1.2) but becomes nearly insoluble at the near-neutral pH of saliva (pH 6.8). Formulators must, therefore, ensure that the tablet doesn't just "sit" as a hard mass on the tongue but breaks into a high-surface-area suspension that can be rapidly swallowed.[12]

2.2. Physicochemical Barriers: The BCS Class II Challenge

The formulation of Pioglitazone into an MDT is a direct response to its classification under the Biopharmaceutics Classification System (BCS) as Class II. This indicates that while the drug molecules can easily permeate through the lipophilic membranes of the gastrointestinal tract, they struggle to enter the aqueous systemic environment due to poor water solubility.[13]

- Lipophilicity: With a Log P value of approximately 2.3, Pioglitazone is highly lipophilic. While this favors absorption once in solution, it causes the raw drug powder to resist wetting, often floating on the surface of aqueous media rather than dissolving.
- The Dissolution Rate-Limiting Step: Because the permeability is high, the rate at which the drug enters the bloodstream is entirely dependent on how fast it dissolves. In an MDT, the goal is to use superdisintegrants to bypass the "disintegration lag," forcing the drug into a fine suspension to maximize the surface area available for dissolution.[13]

2.3. Molecular Geometry and Crystalline Nature

Pioglitazone HCl typically exists in a stable crystalline form, characterized by a rigid molecular lattice held together by strong intermolecular forces.

- Thermal Footprint: The high melting point of the crystalline drug (approx. 193°C) reflects its high lattice energy.
- Formulation Impact: To create an effective MDT, researchers often employ Solid Dispersion or Sonocrystallization to break this lattice. By disrupting the crystalline order and converting the drug into an amorphous state, formulators can lower the energy barrier required for the drug to break free and dissolve, leading to the rapid clinical onset desired in diabetic emergency or maintenance therapy.[14]

Table 1: Physicochemical and Pharmacological Characterization of Pioglitazone HCl for MDT Formulation.

Functional Parameter	Technical Specification	Strategic Formulation Implication
Therapeutic Classification	Thiazolidinedione (TZD)	Requires advanced taste-masking due to inherent acridity.
Biopharmaceutics (BCS)	Class II (Low Solubility/High Permeability)	Dissolution rate is the primary rate-limiting step for absorption.
Molecular Mechanism	Selective PPAR-gamma Receptor Agonist	Modulates genomic transcription for insulin sensitization.
Solubility Profile	pH-Dependent (Basic Nature)	High risk of drug precipitation at neutral salivary pH (6.8).
Clinical Rationale	Insulin Sensitization Therapy	High chronic compliance required; ideal for waterless MDT delivery.

2.4. Organoleptic Challenges: The Bitter Taste

Patient compliance is heavily influenced by the organoleptic properties (taste, smell, and mouthfeel) of the dosage form.[15] Pioglitazone HCl possesses an inherently bitter and acrid taste.

- Prolonged Exposure: Because MDTs are designed to dwell in the oral cavity during the disintegration process (30–60 seconds), the taste buds are exposed to the drug for a longer duration than with a conventional tablet that is swallowed immediately.[16]
- The Grittiness Factor: If the excipients or the drug particles are too large or do not dissolve quickly, the patient experiences a "sandy" or "gritty" sensation, which is a common cause for pediatric and geriatric patient rejection.

Table 2: Common Taste Masking Strategies for Pioglitazone.

Strategy	Mechanism	Pros/Cons
Sweeteners & Flavors	Overpowers the bitter signal to the brain.	Simple; but may not be effective for highly bitter drugs.
Polymer Coating	Physical barrier (e.g., Eudragit) prevents drug-tongue contact.	Highly effective; but can delay disintegration time.
Inclusion Complexation	Using Beta-Cyclodextrin to "hide" the drug molecule.	Improves solubility and masks taste simultaneously.
Ion-Exchange Resins	Drug binds to a resin and is only released in stomach pH.	Excellent taste masking; requires complex processing.

2.5. The "Strength vs. Speed" Paradox (Mechanical Integrity)

The most significant engineering challenge in MDT formulation is achieving a tablet that is porous enough to melt yet strong enough to handle.

- The Porosity Requirement: To achieve a disintegration time of <30 seconds, the tablet matrix must be highly porous. This allows saliva to be "wicked" into the center of the tablet via capillary action.
- The Fragility Issue: High porosity is usually achieved by using low compression forces during manufacturing. However, low compression results in tablets with low mechanical strength (Hardness). Such tablets often break during packaging, shipping, or even when the patient tries to push them out of a blister pack.
- Hygroscopicity: Many of the superdisintegrants used (like Sodium Starch Glycolate) are hygroscopic. They tend to absorb moisture from the atmosphere, which can lead to the tablet becoming soft or "mushy" over time, compromising its stability.[17]

2.6. Technical Specifications Comparison

The following table highlights the difference between a "Standard Tablet" and the "Target MDT" for Pioglitazone, illustrating the technical gap formulators must bridge.

Table 3: Conventional vs. MDT Specification Comparison.

Feature	Conventional Pioglitazone Tablet	Target Pioglitazone MDT
Disintegration Time	15 – 30 Minutes	< 30 Seconds
Water Requirement	200 mL (one glass)	None (Saliva only)
Hardness Range	5.0 – 8.0 kg/cm2	2.5 – 4.0 kg/cm2
Friability Target	< 1.0%	< 1.0% (Difficult to achieve)
Porosity	Low (Dense matrix)	High (Porous matrix)
Flavor Profile	Usually unflavored	Strongly masked / Sweetened

3. Advanced Manufacturing Technologies for Pioglitazone MDTs

The transition from a conventional compressed tablet to a high-performance Mouth Dissolving Tablet (MDT) requires specialized engineering. For a drug like Pioglitazone HCl, which is limited by its poor solubility, the manufacturing process must not only ensure rapid disintegration but also enhance the drug's surface area for faster dissolution.[18]

3.1. Direct Compression Method

Direct compression is the most common and cost-effective technique used in the industry. It involves the dry blending of the drug with high-efficiency super disintegrants and direct-compression fillers (like spray-dried Mannitol or Microcrystalline Cellulose).

- Process Flow: **Sifting → Blending → Lubrication → Compression**.
- Advantages: It is ideal for heat-sensitive drugs like Pioglitazone and maintains the stability of the drug as no moisture or heat is involved (unlike wet granulation).
- The Superdisintegrant Strategy: Formulators typically use a concentration of 2% to 5% of agents like Crospovidone. This creates a matrix that "wicks" saliva into the tablet core, causing it to fragment into millions of tiny particles within seconds.[19]

3.2. Sublimation Technique

To achieve the ultra-fast disintegration times (often <15 seconds) required for premium MDTs, the Sublimation method is employed. This process focuses on creating a "honeycomb" or highly porous structure.

- Mechanism: Volatile ingredients such as Camphor, Menthol, Thymol, or Ammonium Bicarbonate are added to the tablet blend.
- Removal: After the tablets are compressed, they are subjected to a vacuum or mild heating (around 45°C–60°C). The volatile agent "sublimes"—meaning it turns from a solid directly into a gas leaving behind empty pores where the crystals used to be.
- Result: When the patient places the tablet on the tongue, saliva is sucked into these empty pores via capillary action, leading to near-instantaneous melting.

3.3. Solid Dispersion and Spray Drying

Because Pioglitazone is a BCS Class II drug, simply breaking the tablet is often not enough; the drug itself must be made more soluble.

- Solid Dispersion: Pioglitazone is dispersed in a hydrophilic carrier (like PEG 6000 or PVP K-30). This converts the drug from a crystalline state to an amorphous state, which dissolves much faster.
- Spray Drying: The drug-carrier solution is sprayed into a hot air chamber, creating fine, spherical, highly porous particles. These "engineered" particles are then mixed with superdisintegrants and compressed. This dual approach ensures that once the tablet melts, the drug is released in a form that the body can absorb almost immediately.[20]

3.4. Mass Extrusion and Molding

While less common for Pioglitazone, the Molding technique involves moistening the drug-excipient blend with a solvent (like Ethanol/Water) to form a wet mass.

- Process: This mass is pressed into mold plates to form tablets under very low pressure. The solvent is then removed by air-drying.

- Outcome: These tablets have extremely high porosity much higher than compressed tablets but are often very fragile, requiring specialized "peel-off" blister packaging to prevent breakage.

Table 4: Comparison of MDT Manufacturing Techniques.

Method	Principle	Disintegration Time	Key Benefit for Pioglitazone
Direct Compression	High-efficiency disintegrants	30–60 Seconds	Low cost; high stability.
Sublimation	Removal of volatile pore-formers	10–25 Seconds	Maximum porosity for "instant" melt.
Spray Drying	Evaporation of solvent to form pores	20–40 Seconds	High surface area; enhanced solubility.
Lyophilization	Freeze-drying a drug solution	< 10 Seconds	Best for heat-sensitive and highly bitter drugs.
Molding	Solvent-moistened mass drying	5–15 Seconds	Extremely rapid; gentle on the drug.

4. Stability Studies and Regulatory Requirements

For any pharmaceutical product, particularly a sensitive dosage form like a Mouth Dissolving Tablet (MDT), stability testing is a critical phase of development. Because MDTs are engineered to be highly porous and often contain hygroscopic (moisture-attracting) superdisintegrants, they are inherently more susceptible to environmental degradation than conventional tablets.[21]

4.1. Stability Challenges Specific to Pioglitazone MDTs

The primary stability concerns for Pioglitazone HCl MDTs involve physical integrity and chemical potency:

- Moisture Sensitivity: Superdisintegrants like Sodium Starch Glycolate (SSG) or Croscarmellose Sodium (CCS) function by absorbing water. If exposed to high humidity during storage, the tablets may "autodisintegrate" or become soft and mushy, losing their mechanical strength.
- Polymorphic Transitions: Since Pioglitazone is often formulated as a solid dispersion to increase solubility, there is a risk that the drug may revert from its high-energy amorphous state back to its stable, low-solubility crystalline state over time.[22]
- Thermal Stability: Methods like sublimation involve volatile components (e.g., Camphor). If the storage temperature is too high, residual volatile agents might cause gas pressure within the packaging or further alter the tablet’s porosity.

4.2. Parameters Evaluated During Stability

During the 6-month accelerated stability study, samples are withdrawn at intervals (e.g., 0, 1, 3, and 6 months) and tested for:

- Physical Appearance: Checking for discoloration, spotting, or swelling.
- Hardness and Friability: Ensuring the tablet maintains its "Strength vs. Speed" balance.
- Disintegration Time: Confirming that the "mouth-dissolving" property has not slowed down.
- Drug Content (Assay): Ensuring the Pioglitazone HCl remains within 95%–105% of the labeled amount.
- In Vitro Dissolution Profile: Comparing the release rate to the initial (Month 0) data.

4.3. Packaging Strategies for MDTs

Standard plastic containers are usually insufficient for MDTs. To protect the Pioglitazone matrix from moisture and light, specialized packaging is required:[23]

- Blister Packaging: This provides a 100% barrier to moisture, light, and oxygen. It is the preferred choice for porous MDTs.
- Strip Packaging: Uses aluminum foils to provide similar protection but is less common for fragile tablets.
- Desiccants: Small silica gel packets are often included in bulk containers to absorb any residual moisture.

4.4. Regulatory Requirements and Labeling

Regulatory bodies like the FDA (USA) and EMA (Europe) have specific requirements for products labeled as "Orally Disintegrating" or "Mouth Dissolving":

- Tablet Size: The FDA recommends that MDTs should not exceed a weight of 500 mg to ensure they can dissolve comfortably in the mouth.
- Disintegration Limit: The FDA guidance suggests an in vitro disintegration time of 30 seconds or less.
- Labeling: Labels must clearly state that the tablet should not be chewed or swallowed whole, and usually include instructions to "place on the tongue and allow to dissolve."

5. Pre-formulation and Drug-Excipient Compatibility Studies

Pre-formulation is the foundational stage of pharmaceutical development, where the physical and chemical properties of a drug substance are characterized in isolation and in combination with potential excipients. For Pioglitazone Hydrochloride, this phase is critical because its BCS Class II nature makes it highly sensitive to the microenvironment of the tablet matrix.[24] If an excipient is incompatible, it could lead to the formation of degradation products or, more commonly, a physical interaction that locks the drug into a crystalline state, further reducing its already limited solubility.

5.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR serves as the "chemical fingerprinting" tool for the formulation. In the context of Pioglitazone MDTs, the primary goal is to ensure that the functional groups responsible for the drug's antidiabetic activity—specifically the thiazolidinedione ring and the pyridine ring—do not undergo chemical shifting when blended with superdisintegrants.

- Spectral Analysis: Pioglitazone HCl typically exhibits a distinct sharp peak near 1740 cm^{-1} representing the C=O stretching of the diketone group and a peak around 1240 cm^{-1} for C-O-C stretching.[25]
- Interpretation: During compatibility studies, a 1:1 physical mixture of the drug and each excipient (e.g., Crospovidone, Mannitol, Magnesium Stearate) is stored at 40^{o}C/75% RH for four weeks. If the FTIR spectra of these aged mixtures show no disappearance of existing peaks or appearance of new peaks, the ingredients are deemed chemically compatible. This ensures that the rapid disintegration intended for the MDT will actually result in the release of active, non-degraded Pioglitazone.

5.2. Differential Scanning Calorimetry (DSC) Analysis

DSC is an indispensable thermo-analytical technique used to study the thermal transition of Pioglitazone HCl during the pre-formulation and formulation stages. By measuring the heat flow required to increase the temperature of a sample relative to a reference, researchers can identify melting points, glass transition temperatures (T_g), and potential drug-excipient incompatibilities.

The Crystalline "Fingerprint"

Pure Pioglitazone HCl exists in a highly organized crystalline lattice, which requires a specific amount of energy (enthalpy of fusion) to break. This is represented in a DSC thermogram as a sharp endothermic peak at approximately 193°C. The sharpness of this peak is a direct indicator of the drug's purity and crystalline nature.

The Amorphous Transition in MDTs

- In the development of high-performance Mouth Dissolving Tablets, the goal is often to "mask" this crystalline peak by forming a Solid Dispersion or an Inclusion Complex. When Pioglitazone is successfully integrated into a carrier like PEG 6000 or beta-cyclodextrin:
- Peak Disappearance: The characteristic endothermic peak at 193°C disappears entirely.
- Scientific Inference: This indicates that the drug is no longer in a crystalline state but has been molecularly dispersed within the carrier matrix, reaching an amorphous state.
- Therapeutic Advantage: Amorphous Pioglitazone possesses higher internal energy and lower thermodynamic stability, which facilitates near-instantaneous dissolution in the limited volume of saliva available in the oral cavity.[26]

Table 5: DSC Thermal Parameters of Pioglitazone HCl Formulations.

Sample Formulation	Onset Temp (°C)	Peak Temp (°C)	Enthalpy (ΔH in J/g)	Physical State Inference
Pure Pioglitazone HCl	190.2	193.5	-112.4	Purely Crystalline
Physical Mixture (Drug+Excipients)	188.5	192.1	-95.8	Crystalline (No interaction)
beta-Cyclodextrin Complex	No Peak	No Peak	Negligible	Amorphous Inclusion Complex
Solid Dispersion (PEG 6000)	No Peak	No Peak	Negligible	Amorphous Solid Dispersion
Final MDT Formulation	No Peak	No Peak	Negligible	Optimized Amorphous Form

5.3. X-Ray Powder Diffraction (XRPD)

To complement DSC, XRPD is used to confirm the "crystallinity index" of the formulation. A crystalline drug like Pioglitazone produces sharp, intense "Bragg peaks" at specific 2-theta angles.

- Structural Verification: If the final MDT powder shows a "halo" pattern (a broad, flat hump) instead of sharp peaks, it confirms that the manufacturing process—such as spray drying or mass extrusion has successfully bypassed the drug's natural crystal lattice.
- Stability Prediction: XRPD data is often used to prove that the drug did not "re-crystallize" during storage. Re-crystallization is a major failure mode for MDTs, as it would cause the "fast-dissolving" tablet to perform like a slow-dissolving conventional tablet over time.

5.4. Solubility and pH-Dependency Profiling

A deep dive into pre-formulation must include pH-solubility profiling. Pioglitazone is a weakly basic drug, meaning its solubility increases as the pH decreases.[27]

- The Saliva Challenge: Saliva has a pH of approximately 6.8, where Pioglitazone's solubility is at its lowest**[28]**. Pre-formulation studies often involve testing "Solubilizing Agents" (like Citric Acid or Tartaric Acid) that can temporarily lower the micro-environmental pH within the tablet as it dissolves[29]
- Saturation Solubility Studies: This involves adding an excess amount of the drug to various media (0.1 N HCl, Phosphate Buffer 6.8, and Water) and shaking them for 24–48 hours. The concentration is then measured via UV-

Spectrophotometry. These values provide the "baseline" that the MDT formulation must exceed to be considered successful.[30]

Table 6: Summary of Pre-formulation Characterization.

Technique	Property Measured	Significance for Pioglitazone MDT
FTIR	Molecular Functional Groups	Ensures no chemical degradation during blending.
DSC	Melting Point / Enthalpy	Confirms transition from crystalline to amorphous state.
XRPD	Crystal Lattice Pattern	Quantitative proof of drug dispersion in the matrix.
pH Solubility	Solubility vs. pH	Determines the need for pH-modifying excipients.
SEM	Particle Morphology	Analyzes drug-excipient surface area and flowability.

CONCLUSION

The development of Pioglitazone Hydrochloride Mouth Dissolving Tablets represents a significant clinical advancement in the management of Type 2 Diabetes Mellitus, particularly for patients facing the challenges of dysphagia and treatment non-compliance. This review has demonstrated that the inherent solubility limitations of Pioglitazone as a BCS Class II drug can be effectively mitigated through strategic formulation engineering. By utilizing high-efficiency superdisintegrants such as Crospovidone and Croscarmellose Sodium, in conjunction with advanced manufacturing techniques like sublimation and solid dispersion, it is possible to create a tablet matrix that achieves a disintegration time of less than 30 seconds. The successful conversion of the drug from its crystalline lattice to a high-energy amorphous state, as confirmed by DSC and XRD analysis, remains the cornerstone for ensuring rapid dissolution and improved oral bioavailability.

Looking toward the future, the pharmaceutical industry is poised to move beyond traditional compression toward 3D printing (ZipDose technology) and nanofiber-based orodispersible films, which offer even greater porosity and dosing precision. Furthermore, the increasing shift toward natural, biodegradable superdisintegrants derived from mucilages and gums highlights a move toward more sustainable and biocompatible drug delivery systems. Ultimately, the integration of rigorous in vitro evaluation parameters—from wicking time to mathematical kinetic modeling—ensures that these MDTs are not only a convenience for the patient but a robust, stable, and bioequivalent alternative to conventional therapy. Continued research into long-term stability and Level A IVIVC correlation will be essential to transition these innovative laboratory formulations into large-scale commercial success.

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