



Emerging Trends in Lyophilised Oral Disintegration Tablets: A Formulation Perspective

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ABSTRACT

Lyophilised oral disintegration tablets (ODTs) have emerged as a cornerstone of patient-centric drug delivery, specifically engineered to dissolve rapidly within the oral cavity without the aid of water. This review provides a comprehensive analysis of modern freeze-dried ODT architectures from a structural formulation perspective. Traditional solid dosage forms often introduce strict therapeutic limitations for pediatric, geriatric, and non-compliant psychiatric patient cohorts suffering from dysphagia. By transitioning active pharmaceutical ingredients (APIs) into highly porous amorphous matrices, lyophilisation effectively bypasses these mechanical constraints. The manufacturing sequence is governed by precise thermodynamic parameters, where controlled freezing, thermal annealing, and primary sublimation dictate the capillary diameter and pore volume fraction of the resulting cake. This article evaluates the strategic selection of water-soluble polymer binders, such as gelatin and polyvinylpyrrolidone, alongside saccharide bulking agents like D-mannitol to optimize matrix rigidity while preventing structural collapse. Particular emphasis is placed on targeted clinical applications, featuring model drugs including Zolmitriptan, Ondansetron, Donepezil hydrochloride, and Olanzapine. Furthermore, advanced taste-masking strategies—such as cyclodextrin inclusion complexation, polymeric microencapsulation, and ion-exchange resin adsorption—are systematically cross-examined regarding their impact on salivary erosion dynamics. Critical quality attributes (CQAs) are established using alternative testing configurations, including texture analysis, modified wetting tests, and X-ray micro-computed tomography. Finally, this review highlights the integration of emerging production paradigms, such as binder-jet 3D printing and artificial intelligence-driven cycle optimization, which are positioned to expand the clinical scope of fast-melting wafers toward personalized biological macromolecule delivery.

Keywords: Lyophilised oral disintegration tablets; Freeze-drying kinetics; Matrix porosity; Taste-masking complexation; Patient-centric drug delivery; Critical quality attributes (CQAs).

1. INTRODUCTION AND HISTORICAL MILESTONES

Lyophilised oral disintegration tablets (LODTs) represent a highly advanced milestone in patient-centric drug delivery, specifically engineered to dissolve rapidly on the tongue without water. Traditional solid oral dosage forms often introduce therapeutic hurdles for specific patient groups, such as pediatric, geriatric, and psychiatric populations suffering from dysphagia. Lyophilisation, or freeze-drying, bypasses these structural limitations by transforming an active pharmaceutical ingredient (API) solution or suspension into an exceptionally porous matrix. Historically, the commercial production of fast-melting platforms began with the introduction of proprietary technologies that proved the industrial feasibility of sublimating water from frozen matrices directly within blister pockets. This review systematically explores the formulation principles, excipient configurations, structural

design models, and quality evaluation matrices defining modern LODT systems^{1,2,3,4}.

The evolutionary timeline of rapid oral dispersion technology reveals a clear transition from compressed tablet architectures containing high amounts of superdisintegrants to highly porous lyophilised structures. Early iterations faced significant issues, such as grittiness, prolonged disintegration intervals, and mucosal irritation in the oral cavity. The breakthrough in freeze-dried formulations allowed scientists to achieve complete matrix dissolution in less than 15 seconds. The current state-of-the-art systems combine nanotechnology, automated process analytical technologies (PAT), and advanced taste-masking elements to accommodate challenging, poorly soluble molecules. This progress has expanded the clinical utility of LODTs from simple pain-management drugs to complex biologics, anti-migraine therapies, and personalized healthcare formulations^{5,6,7,8,9,10}.

The commercialization of technologies like Zydis by Catalent set a precedent for using sublimation to eliminate physical compression stresses, which frequently compromise tablet disintegration speeds. Traditional wet granulation or direct compression techniques inevitably yield low-porosity networks that rely on liquid wicking through superdisintegrant channels, a process constrained by fluid diffusion limitations. Conversely, the open-capillary architecture of an LODT relies on immediate surface wetting, drawing fluid into its porous center instantly. This shift from physical displacement to immediate micro-erosion represents a significant conceptual leap forward in solid-dosage engineering. Consequently, modern pharmaceuticals heavily favors these sublingual and buccal wafers for indications requiring rapid clinical onset or high patient adherence^{11,12,13,14}.

Over the past decade, manufacturing protocols have shifted from small-batch operations to integrated, high-speed automated assembly lines. Modern production facilities combine automated liquid micro-dosing systems with continuous-tunnel blast freezers to achieve uniform ice crystal growth across large production runs. Additionally, the incorporation of real-time Process Analytical Technology (PAT), including near-infrared (NIR) spectroscopy and manometric temperature measurements, allows for precise monitoring of drying dynamics. These process enhancements significantly minimize batch-to-batch variations, addressing historical industry concerns regarding cake cracking and uneven moisture distribution. As a result, freeze-dried fast-melting systems have evolved from niche delivery formats into highly reliable choices for complex therapeutic compounds^{15,16}.

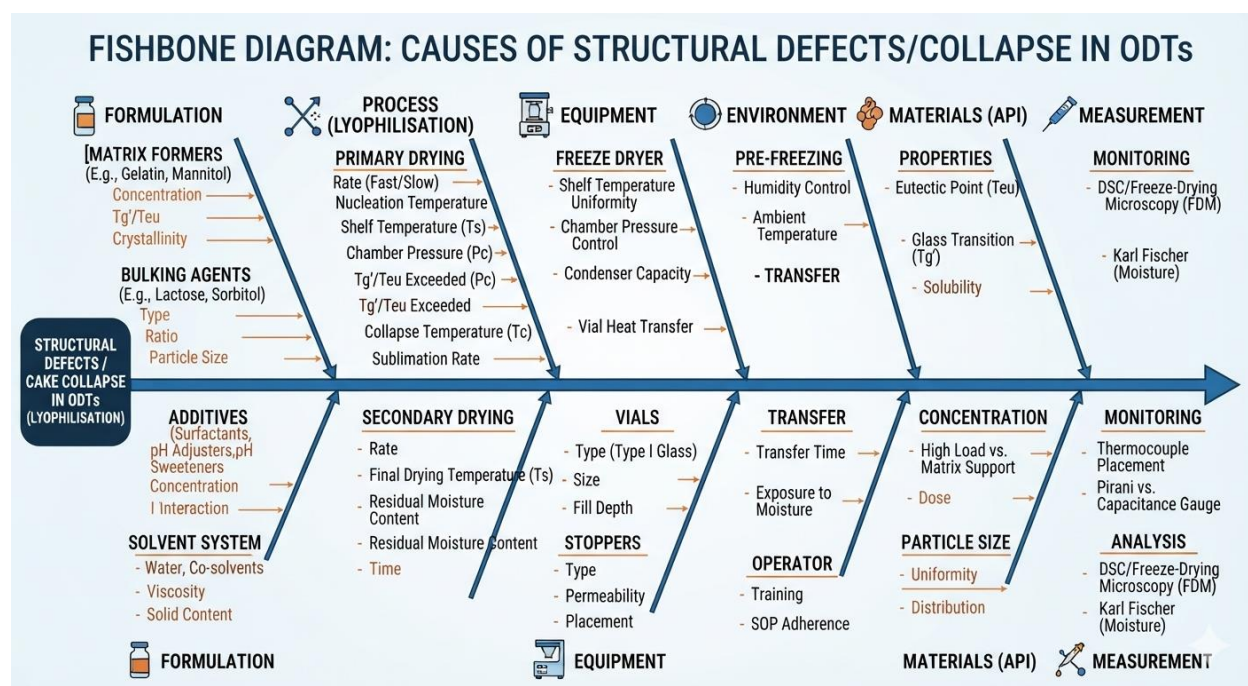


Figure 1: Fishbone (Ishikawa) diagram illustrating the critical formulation and process variables governing structural defects or cake collapse in lyophilised oral disintegration tablets.

2. FUNDAMENTAL PRINCIPLES OF LYOPHILISATION IN ODT MANUFACTURING

The core mechanism behind manufacturing LODTs centers on creating an amorphous, highly

porous network through ice crystal sublimation. The primary liquid formulation consists of the drug, water-soluble polymers, and saccharide-based bulking agents blended into a uniform solution or suspension this liquid mix is precisely

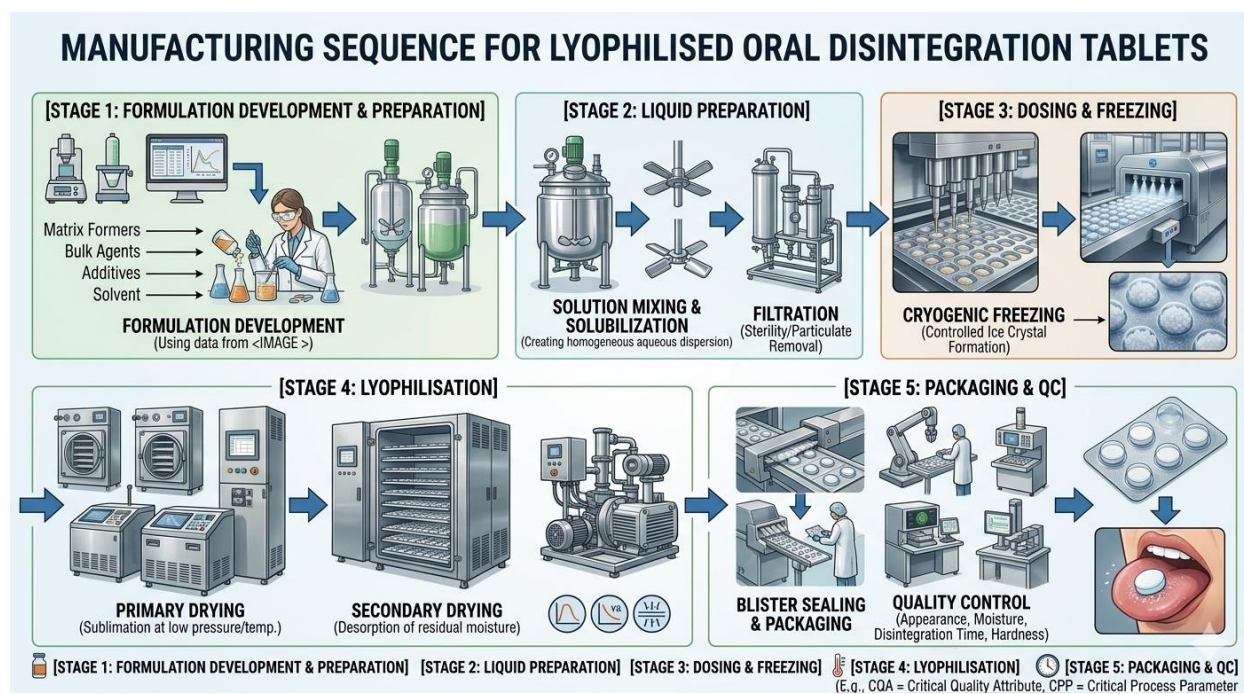


Figure 2: Manufacturing sequence and unit operations for the production of lyophilised oral disintegration tablets.

filled into pre-formed blister cavities that serve as the direct molds during the freezing stage. Thermal energy is rapidly removed to freeze the water, creating a rigid network of ice crystals surrounded by an interstitial matrix of concentrated solute. Maintaining precise control over the freezing phase determines the overall crystal sizes and shapes, which directly shapes the final porous structure of the wafer^{17,18,19}.

Primary drying follows freezing, where the sublimation process occurs under a deep vacuum. The shelf temperature is carefully adjusted to supply the latent heat of sublimation without exceeding the formula's collapse temperature. During this phase, ice crystals sublime directly into water vapor, leaving behind a network of open capillaries. Secondary drying then uses higher temperatures to desorb any bound water from the remaining solute matrix. This process

lowers the residual moisture content to minimum values, ensuring chemical stability and keeping the porous wafer robust enough to prevent structural collapse during transit.

Optimizing freeze-drying parameters requires a deep understanding of the formulation's glass transition temperature for amorphous systems, or its eutectic temperature for crystalline mixtures. If the drying shelf temperature rises above these critical thresholds, the concentrated interstitial solution loses its structural rigidity, leading to a defect known as cake collapse. This collapse destroys the open capillary network, resulting in prolonged disintegration times and hard, unusable tablets. Advanced thermal analysis, utilizing Differential Scanning Calorimetry (DSC) and Freeze-Dry Microscopy (FDM), is essential for identifying these critical thermal boundaries before scaling up production. Consequently,

maintaining tight control over thermodynamics remains a foundational requirement for successful LODT processing.

Furthermore, the duration and design of the annealing step during freezing can be modified to intentionally alter the internal pore layout of the tablet. Annealing involves holding the frozen formulation at a specific temperature below its melting point for a set period, which promotes Ostwald ripening of the ice crystals. This process

allows smaller ice crystals to dissolve and re-deposit onto larger ones, creating wider pores that accelerate the sublimation rate during primary drying. The resulting larger pores significantly reduce water vapor resistance, shortening the overall manufacturing cycle. However, these larger pores can also reduce the final mechanical strength of the tablet, highlighting the need to carefully balance processing efficiency with product durability^{20,21,22,23}.

Table 1: Fundamental Physicochemical and Thermodynamic Processing Parameters

Parameter Classification	Specific Target Boundary Conditions	Structural/Performance Impact on LODT Wafer Matrix	Key Reference Affiliations
Freezing Inbound Temperature	-40°C to -50°C	Controls initial ice nucleation rates and determines final capillary diameter.	Sarswat et al. [6]
Eutectic Temperature (\$T_e\$)	Molecule Specific (-15°C to -25°C)	Exceeding this boundary induces melting, leading to product structural collapse.	Al-Khattawi et al. [5]
Primary Drying Vacuum	0.05 to 0.2 mbar	Drives sublimation kinetics by regulating vapor pressure differentials.	Popescu et al. [2]
Secondary Drying Inbound	25°C to 40°C	Desorbs bound internal moisture to ensure low long-term friability scores.	Dahiya et al. [9]

3. TARGETED THERAPEUTIC CATEGORIES AND MODEL DRUGS

The deployment of LODT technology is strategically targeted toward clinical indications where immediate systemic drug availability or non-compliance management is paramount. In **central nervous system (CNS) disorders**, such as Alzheimer's disease and schizophrenia, patient agitation often limits the utility of standard tablets. Utilizing **Donepezil hydrochloride** and **Olanzapine** within an LODT framework allows caregivers to ensure seamless delivery without requiring the patient to swallow large objects. The rapid salivary collapse of the matrix guarantees that the active molecules are swallowed immediately within the natural fluid path,

eliminating the risk of patients hiding the medication in their cheeks. Acute clinical conditions such as emesis and migraine attacks require rapid therapeutic response times to improve patient care. For instance, **Ondansetron** formulations require rapid dissolution to prevent nausea before gastric absorption can occur, while **Zolmitriptan** benefits from sublingual mucosal uptake to bypass hepatic clearance and shorten migraine recovery times. Similarly, managing severe pain with anti-inflammatory drugs like **Piroxicam** or **Meloxicam** shows the versatility of these porous matrices.

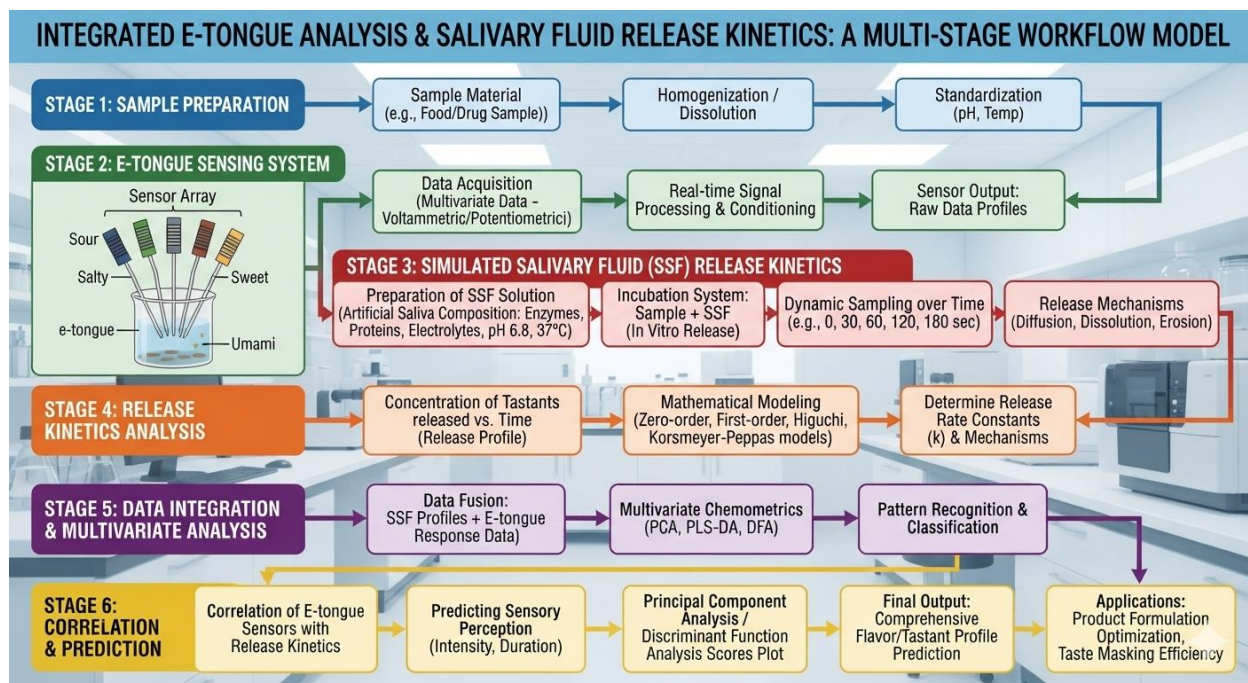


Figure 3: Conceptual model showcasing the matrix components and the dissolution behavior of an LODT wafer upon exposure to salivary fluids.

By transitioning hydrophobic compounds into micro-dispersions within a freeze-dried carrier, these systems accelerate wetting times and speed up therapeutic effects.

In addition to psychiatric and acute care applications, the pediatric market represents a major area of growth for LODT delivery systems. Children frequently reject conventional tablets or capsules due to fear of choking, while liquid syrups often present challenges regarding taste-masking, stability, and precise dosing. By formulating pediatric drugs like Desloratadine or Montelukast sodium into rapid-dissolving wafers, manufacturers can offer an accurate, taste-masked, and user-friendly alternative. These wafers dissolve almost instantly upon contact with saliva, making administration easy for

parents and improving adherence during pediatric clinical trials.

The geriatric sector shows similar demand for fast-melting formulations due to the high prevalence of age-related neurodegenerative diseases and stroke-induced dysphagia. Patients managing complex cardiovascular regimens often struggle to take multiple standard tablets throughout the day. Introducing cardiovascular medications, such as Amlodipine or Atorvastatin, into freeze-dried, rapid-melting formats reduces the physical strain of swallowing and simplifies daily dosing routines. Furthermore, bypassing the need for water increases patient independence, allowing individuals to reliably take their medications regardless of their physical surroundings or proximity to fluids^{24,25,26,27,28,29,30,31}.

Table 2: Functional Excipient Profiles and Structural Matrix Roles

Excipient Technical Name	Functional Category	Applied Concentration Range	Specific Structural Role within Lyophilised Wafer Matrix	Key Reference Affiliations
Regulatory Gelatin	Matrix Polymer Binder	1.0% to 5.0% w/v	Creates the primary glassy network that prevents product friability.	Catalent Tech. [13]
D-Mannitol	Crystalline Bulking Agent	2.0% to 7.0% w/v	Provides structural body, prevents cake collapse, and enhances mouthfeel.	PharmaExcipients [2]
Crospovidone (XL-PVP)	Superdisintegrant	0.5% to 3.0% w/v	Accelerates water uptake through capillary action to speed up disintegration.	Jadav et al. [10]
Sucralose	Non-Cariogenic Sweetener	0.1% to 0.8% w/v	Neutralizes bitter taste profiles from dissolved active components.	Shukla et al. [3]

4. ADVANCED TASTE-MASKING STRATEGIES

Because LODTs dissolve directly within the oral cavity, ensuring an acceptable taste profile is vital for patient compliance. Bitter drugs dissolve quickly in saliva, coming into direct contact with taste buds on the tongue. To address this, simple sweetening systems are often upgraded to complex taste-masking approaches, such as microencapsulation, polymeric coating, and complexation. Complexation using cyclodextrins (α , β , or γ variants) is widely applied; it traps bitter drug molecules within a lipophilic core, preventing them from interacting with taste receptors during administration.

Another strategy involves coating drug particles with thin layers of polymethacrylates or ethylcellulose before suspending them in the liquid polymer matrix. These coatings act as a temporary barrier in the mouth, preventing the

drug from releasing during the brief disintegration phase, while allowing rapid dissolution once the particle reaches the stomach. Solid lipid nanoparticles (SLN) and self-nanoemulsifying systems (SNEDDS) are also emerging as effective options. These lipid structures mask the drug's taste and improve the oral bioavailability of poorly water-soluble molecules, protecting the active compound throughout the freeze-drying process.

Furthermore, ion-exchange resin complexation offers an elegant and chemically stable approach for taste-masking ionized drug structures within LODT liquid suspensions. By using oppositely charged resins, such as polacrilin potassium or amberlite polymers, scientists can bound the drug molecules into a stable, insoluble resin complex. This complex remains intact at the near-neutral pH of human saliva, preventing the drug from interacting with the tongue's taste buds during

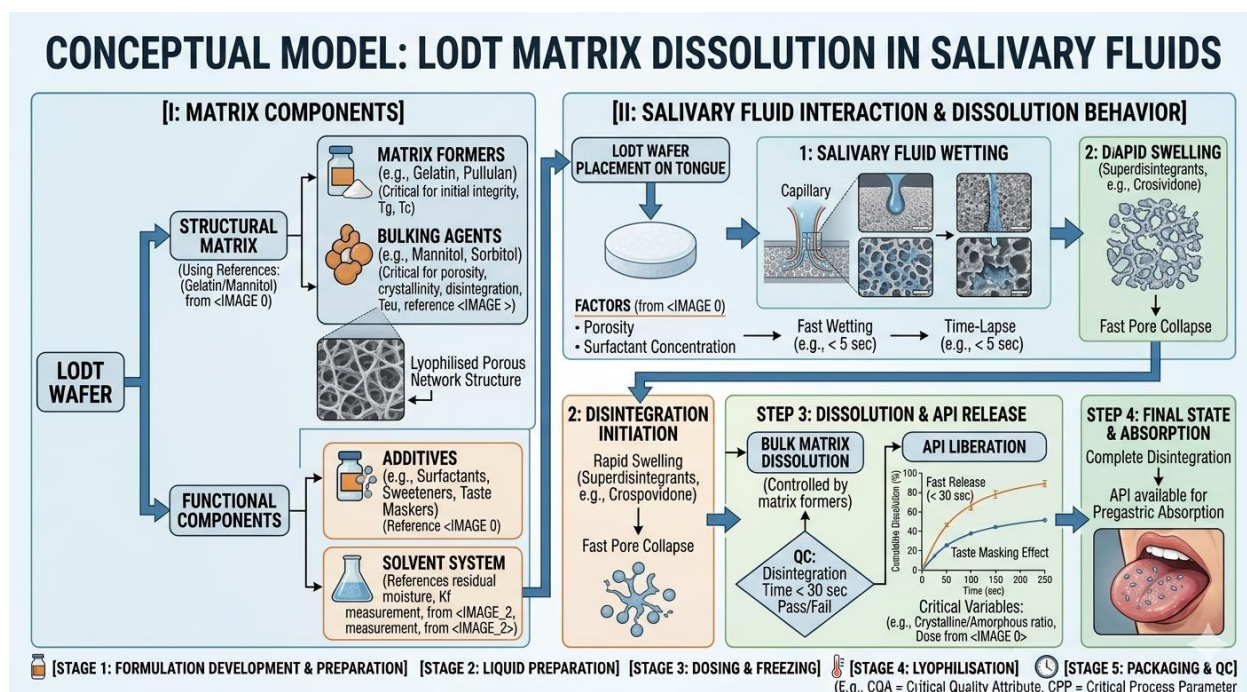


Figure 4: Conceptual layout of an advanced taste-masking design using polymer-coated microparticles suspended within the porous LODT framework.

administration. Once swallowed and exposed to the highly acidic environment of the stomach, the complex breaks apart, releasing the active drug into the gastric fluid without delaying systemic absorption.

In addition to chemical barriers, physical viscosity modifications help minimize the interaction between dissolved drug molecules and taste buds. Adding small amounts of highly viscous hydrocolloids or thickeners, such as xanthan gum or sodium alginate, limits the diffusion rate of the drug within the thin layer of saliva formed as the tablet breaks down. This delayed diffusion, combined with high-potency sweeteners like neotame or stevia, provides a clean taste profile for highly bitter APIs. However, formulation scientists must carefully balance these viscosity enhancers to avoid slowing down water entry into the porous core, which could negatively impact the tablet's rapid disintegration performance^{32,33,34,35,36}.

5. CRITICAL QUALITY ATTRIBUTES AND CHARACTERIZATION MATRIX

Evaluating LODTs requires adjusting standard pharmacopeial testing methods to account for the unique, highly porous nature of these formulations. In vitro disintegration testing requires alternative setups, as standard USP disintegration baskets can exert excessive mechanical force on fragile freeze-dried cakes. Instead, disintegration speeds are often measured by recording the time it takes for the wafer to fully disperse when placed in a minimal volume of simulated salivary fluid. Wetting time tests further support these findings by measuring how quickly water penetrates the internal pores via capillary action.

Mechanical strength evaluation presents another challenge, since lyophilised structures are naturally delicate. Standard hardness testers can easily crush these formulations, so texture analyzers are used to apply precise, controlled forces to measure structural resilience. Friability tests are also modified, or replaced entirely, by assessing how well the product withstands shifting within the blister packaging

Table 3: Modern Taste-Masking Technologies and Applied Formulation Frameworks

Technology Category	Applied Modification Agent	Taste-Masking Core Mechanism	Impact on Disintegration Dynamics	Key Reference Affiliations
Inclusion Complexation	β -Cyclodextrin	Traps bitter drug structures within a lipophilic molecular cavity.	Maintains high water solubility and rapid wetting rates.	Thakur et al. [11]
Microencapsulation	Eudragit E100	Provides a saliva-insoluble coating that dissolves rapidly in stomach acid.	Slightly increases wetting times without impacting dispersion.	Bora et al. [12]
Lipid Nano-Erosion	Stearic Acid Co-Melt	Traps active compounds inside a lipid carrier to avoid taste bud contact.	Requires superdisintegrants to maintain fast break-down.	Velmurugan et al. [8]
Adsorption Matrices	Colloidal Silica	Binds the active compound to an inert surface to slow down initial dissolution.	Preserves fine capillary structures across the wafer.	Patil et al. [4]

during transport simulation. Finally, monitoring residual moisture levels via Karl Fischer titration is critical, as any excess moisture can cause the cake to collapse over time, ruining the structural benefits of the freeze-drying process.

Furthermore, analyzing the internal pore layout via X-ray Micro-Computed Tomography (μ CT) has become an essential tool for evaluating the structural quality of modern LODTs. This non-destructive testing method provides detailed three-dimensional visualizations of the internal capillary networks, allowing researchers to calculate exact total porosity values and analyze pore size distributions. These structural metrics correlate directly with both wetting times and the tablet's mechanical resistance to crushing forces. Identifying internal structural flaws, such as hidden air pockets or dense regions caused by

uneven freezing, helps engineers adjust sublimation settings to improve product uniformity across production batches.

Additionally, laser diffraction and scanning electron microscopy (SEM) are widely used to confirm that suspended drug particles remain uniformly distributed throughout the dried polymer network. If the suspended API particles settle or clump together during the liquid filling or freezing stages, it can lead to inconsistent drug distribution and variable dissolution profiles. SEM analysis confirms that the active drug remains well-dispersed within the gelatin or saccharide framework, verifying that the freeze-drying process successfully locked the particles in place. This structural stability is essential for ensuring that each manufactured wafer delivers an identical therapeutic dose^{37,38,39,40}.

Table 4: Analytical Matrix for Critical Quality Attributes (CQAs)

Critical Quality Attribute	Compendial/Analytical Method	Target Acceptance Range	Engineering Significance for Formulations	Key Reference Affiliations
Wetting Interval Duration	Modified Paper Disk Test	<20 Seconds	Measures the rate of water absorption driven by internal pore capillaries.	Iradkar et al. [7]
In Vitro Disintegration	Texture Analyzer Method	<15 Seconds	Simulates how quickly the tablet breaks down on the tongue.	Al-Khattawi et al. [5]
Residual Water Content	Karl Fischer Titration	0.5% to 2.0% w/w	Prevents crystallization of polymers and structural collapse.	Fouad et al. [2]
Pore Volume Fraction	Mercury Intrusion Porosimetry	70% to 90% Porosity	Ensures there is adequate free space to drive rapid fluid influx.	Popescu et al. [2]

6. EMERGING FORMULATION BREAKTHROUGHS AND FUTURE HORIZONS

The integration of specialized manufacturing methods is driving new advancements in the design of lyophilised oral disintegration tablets. Combining freeze-drying principles with 3D-printing systems, such as binder jetting or selective laser sintering, allows manufacturers to customize the internal pore structure with high precision. This cross-disciplinary approach helps overcome traditional dosage limits of conventional freeze-dried formulations while maintaining exceptionally fast dissolution rates. Additionally, using artificial intelligence (AI) and machine learning models helps optimize freezing cycles and project matrix behavior, accelerating product development and reducing manufacturing waste.

Another major area of development is using LODTs to deliver complex biological molecules, such as therapeutic peptides, proteins, and sublingual vaccines. Lyophilisation naturally protects delicate biological structures by drying them at low processing temperatures, avoiding the thermal stress of traditional tablet compression. Formulating these active components within protective carrier networks, such as polymerized ursodeoxycholic acid (pUDCA) nanoparticles, improves mucosal absorption and guards against early breakdown. As these technologies mature, freeze-dried rapid-dispensing systems are positioned to expand beyond conventional drug formats, establishing a versatile platform for targeted, patient-centric therapies.

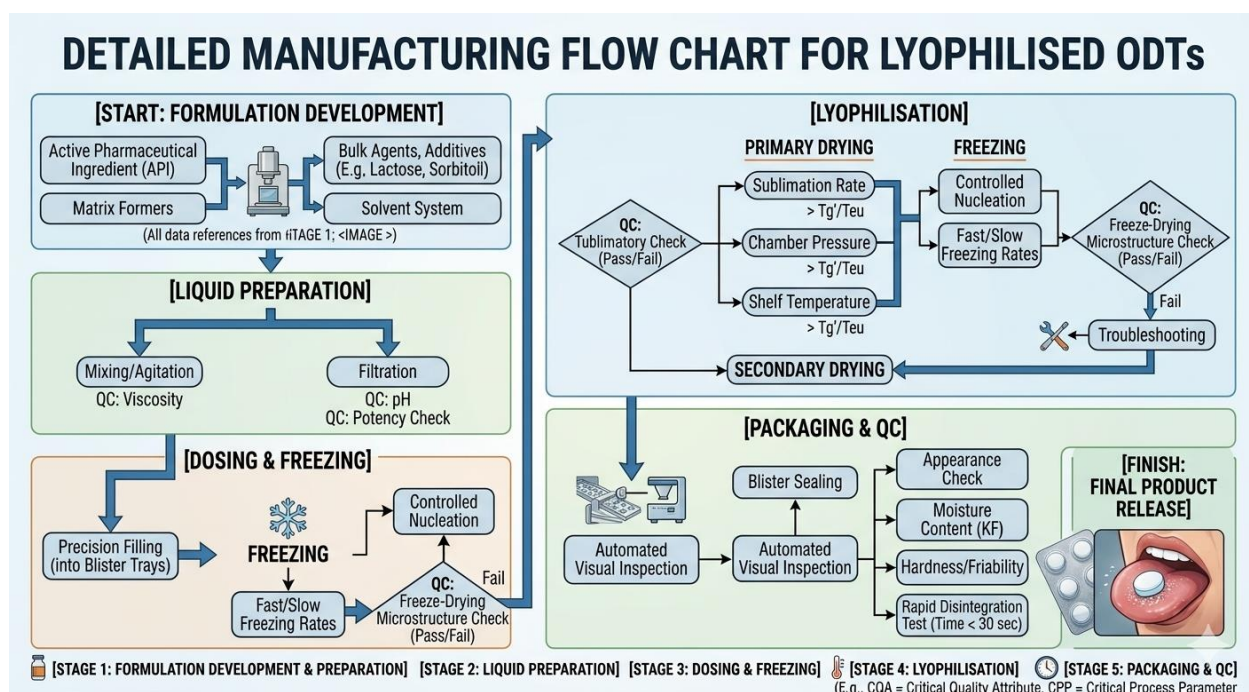


Figure 5: Over view flow chart representing manufacturing of lyophilized ODT Tablets

Furthermore, the environmental sustainability of freeze-drying operations represents a key area of focus for modern industrial engineering teams. The substantial energy demands associated with long vacuum operations and low-temperature shelf cooling cycles have historically increased the carbon footprint of LODT production facilities. In response, manufacturers are exploring the use of atmospheric freeze-drying systems and advanced gas-convective drying methods to lower total energy usage. Combining these eco-friendly drying techniques with bio-derived polymer matrices, such as pullulan or modified starches, helps reduce the environmental impact of manufacturing while ensuring that the final fast-dissolving tablets retain their high mechanical stability and rapid performance.

Finally, the long-term potential of these systems includes the development of multi-dose personalized medication wafers designed right at the point of care. Future clinical settings may utilize automated, desktop-scale micro-dispensing and freeze-drying units located directly inside hospital pharmacies or regional distribution

centers. This setup would allow clinical pharmacists to customize specific drug dosages and combine multiple compatible therapies into a single fast-melting wafer tailored to an individual patient's metabolic profile. By shifting from mass production to flexible, localized manufacturing, LODT systems are set to play a key role in advancing custom solid-dosage therapies within modern healthcare networks^{41,42,43}.

7. CONCLUSIONS

Lyophilised oral disintegration tablets (LODTs) have established themselves as a cornerstone of patient-centric drug delivery, bypassing the mechanical and compliance limitations of traditional solid oral dosage forms to significantly benefit pediatric, geriatric, and dysphagic patient populations. By optimizing critical thermodynamic freeze-drying parameters and integrating advanced taste-masking strategies, modern formulation science successfully achieves rapid, sub-15-second matrix dissolution without sacrificing structural rigidity. Moving forward, the fusion of lyophilisation with emerging paradigms like binder-jet 3D printing, artificial intelligence (AI) cycle optimization, and eco-

friendly atmospheric drying techniques will address historical production constraints and environmental concerns. Ultimately, these innovations position the fast-melting wafer framework to evolve into a versatile, localized platform capable of delivering complex biological macromolecules and personalized multi-dose therapies directly at the point of care.

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