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Review Article

Advances in Orally Disintegrating Tablets (ODTs): Formulation Strategies and Future Prospects

Joseph Eze, Mercy Agu, Nnaemeka Okoli, Francis Okoli, Joshua Agbo

Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

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For Correspondence:

Joseph Eze, Pharmacist & Lead Researcher at Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

Abstract

Objective: This review critically evaluates recent advances in orally disintegrating tablet (ODT) technologies, with emphasis on innovative formulation and manufacturing strategies developed to overcome the limitations of conventional ODT approaches, particularly for poorly soluble and high-dose drug substances.

Data Sources: A comprehensive narrative literature review was conducted using PubMed, Scopus, and ScienceDirect, supplemented by relevant articles identified from Google Scholar, reference lists of selected publications, and other authoritative pharmaceutical sources. Relevant pharmaceutical literature and regulatory guidelines were reviewed, with a primary emphasis on emerging technologies published between 2015 and 2026.

Summary Of Contents: While ODTs have significantly improved patient compliance, especially among pediatric and geriatric populations, formulation challenges persist for Biopharmaceutics Classification System (BCS) Class II and IV drugs and high-dose active pharmaceutical ingredients. This review explores emerging technologies such as fused deposition modeling (FDM), selective laser sintering (SLS), and binder jetting 3D printing, which enable enhanced control over tablet architecture, porosity, and disintegration behavior. Additionally, the incorporation of nanotechnology-driven systems, including nanocrystals and spray-dried amorphous solid dispersions, has shown promise in improving drug dissolution and oral bioavailability. Critical quality attributes, including disintegration time, mechanical strength, and moisture sensitivity, are evaluated, with particular attention to formulation performance under tropical climatic conditions (ICH Zone IVb). Prospects emphasize a shift toward point-of-care personalized medicine and the potential for mucoadhesive ODTs in biologics delivery, while identifying current barriers to large-scale commercial adoption and the evolving regulatory landscape for biowaivers.

Conclusion: The convergence of advanced manufacturing technologies and rational formulation design positions next-generation ODTs as a promising platform for patient-centric drug delivery, while emphasizing the need for scalable, robust, and climate-resilient manufacturing strategies.

Keywords: Orally disintegrating tablets, 3D printing, nanotechnology, bioavailability, patient compliance, BCS classification.

Introduction

Orally disintegrating tablets (ODTs), also known as orodispersible tablets, are solid dosage forms designed to disintegrate or dissolve rapidly in the oral cavity, typically within seconds, upon contact with saliva, without the need for water or chewing.[1,2] This technology has become increasingly significant since the 1990s, evolving from early lyophilization-based products to diverse manufacturing methods that improve stability, palatability, and scalability.[3]

The primary clinical need for ODTs stems from difficulties in patient adherence linked to traditional solid oral dosage forms, especially in vulnerable populations. Dysphagia (difficulty swallowing) affects up to 35% of the general population and 60% of elderly institutionalized patients, leading to risks such as choking, aspiration, and reduced adherence.[2,4] ODTs resolve these issues by offering ease of administration for pediatric, geriatric, psychiatric, paralyzed, bedridden, and post-stroke patients, as well as those with nausea or behavioral disorders.[1,3] Studies indicate that ODTs improve compliance rates by up to 20% compared to traditional tablets, while providing quicker therapeutic onset for acute conditions [such as migraine and nausea] due to possible pre-gastric absorption and reduced first-pass metabolism.[1,5]

Market projections indicate strong growth, with the global ODT sector expected to expand significantly through 2034, fueled by the rising demand for patient-centric formulations.[6-8] The market was valued at approximately USD 13.4–15.7 billion in 2024–2025 and is projected to reach USD 28–32 billion by 2034, with a CAGR of 8.0–8.2%.[6,7] This growth is driven primarily by innovations in taste masking, 3D printing, and applications for special populations [3,9]

In addition to the compliance benefits, ODTs improve therapeutic outcomes. They have a rapid disintegration time of 30 seconds or less, based on the FDA Guidance for Industry[10] and increased bioavailability for certain drugs.[2] They are particularly advantageous for administration in situations requiring mobility or in resource-limited environments where access to water may be restricted.[1]

Overview of ODT Technology

Definition and Significance

ODTs are defined by regulatory bodies such as the FDA as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue," with a recommended disintegration time of ≤30 seconds and tablet weight ≤500 mg.[2] Unlike conventional tablets, ODTs form a suspension or solution in saliva that is easily swallowed, eliminating the need for additional fluids.[1]

ODTs overcome swallowing difficulties, improve patient adherence, and enable a rapid onset of action. Marketed examples include olanzapine (Zyprexa Zydis®) and rizatriptan for psychiatric and migraine indications, demonstrating enhanced bioavailability and reduced side effects.[1] ODTs also enable dose flexibility in special populations and cost-effective treatment through better compliance.[4] The ability of ODTs to solve dysphagia in vulnerable patients fits well with how drug developers use biopharmaceutical knowledge to make medicines work better. A critical framework guiding such optimization is the Biopharmaceutical Classification System (BCS), which categorizes drugs according to their solubility and permeability characteristics and informs API selection, formulation design, and regulatory considerations for ODTs.[11]

The Biopharmaceutics Classification System (BCS) classifies drugs according to their aqueous solubility and intestinal permeability. This system serves as a key foundation for developing orally disintegrating tablets (ODTs) and for making biowaiver decisions.[11] The system groups drugs into four major classes:

a. BCS Class I drugs (high solubility and high permeability, e.g., paracetamol): ODTs are especially beneficial in this class. Their rapid disintegration enables immediate dissolution and swift systemic absorption, free from significant solubility limitations.[2,5]

b. BCS Class II drugs (low solubility and high permeability, e.g., ibuprofen): these drugs benefit from advanced ODT formulation approaches by the incorporation of solubilizing agents, nanotechnology, or solid dispersions. For instance, a proliposome tablet formulation of diclofenac sodium (using lipid-based solubilization) demonstrated 1.95-fold higher bioavailability compared to a plain enteric-coated tablet, based on pharmacokinetic studies in animal models.[12] Similarly, a nanosuspension of ibuprofen (employing nanotechnology) achieved approximately 2-fold higher relative bioavailability compared to a marketed oral suspension, with improved Cmax (14.8 µg/mL vs. 7.03 µg/mL) and faster Tmax (36 min vs. 112 min) in in vivo rat studies.[13,14]

c. BCS Class III drugs (high solubility and low permeability): these drugs offer both opportunities and challenges for ODT development. Their rapid disintegration and prolonged mucosal contact can be combined with permeation enhancers to improve absorption. However, achieving consistently high bioavailability remains challenging. Biowaivers may still be applicable when comparing ODTs to immediate-release formulations, if significant oral cavity absorption does not occur.[11]

d. BCS Class IV drugs (low solubility and low permeability): they are less frequently developed as ODTs. Nevertheless, emerging formulation techniques such as solid dispersions provide potential strategies to overcome these dual limitations.[2,13]

The Biopharmaceutics Classification System (BCS) guides excipient selection for ODTs to a large extent. For instance, super disintegrants are commonly used to ensure rapid tablet breakup, while surfactants or other solubilizing agents are often incorporated for Class II drugs to overcome solubility limitations. It also shapes the regulatory pathways, with particular focus on achieving in vitro disintegration times of less than 30 seconds (per FDA guidance) and conducting appropriate bioequivalence studies.[2,11]

Formulation Strategies

Formulation of orally disintegrating tablets (ODTs) requires careful selection and optimization of components to achieve rapid disintegration (typically ≤30 seconds), acceptable mechanical strength, pleasant mouthfeel, and efficient drug release while maintaining stability and palatability.[1,2] The primary components include the active pharmaceutical ingredient (API), excipients (such as diluents, binders, and lubricants), and super disintegrants, which are essential for rapid breakup in the oral cavity.

Active Pharmaceutical Ingredients [APIs]

APIs suitable for ODTs should exhibit favorable physicochemical properties, including low to moderate dose (generally <50 mg to avoid bulkiness and ensure rapid disintegration), good stability in the presence of saliva (pH ~6-7), and compatibility with excipients [3] Low-molecular-weight drugs with reasonable aqueous solubility are preferred, as they facilitate quick dissolution upon disintegration. Examples of marketed or studied APIs in ODTs include analgesics/antipyretics (paracetamol, ibuprofen), antihistamines (loratadine, cetirizine), anti-migraine agents (rizatriptan), antipsychotics (olanzapine), anti-emetics (ondansetron), and others such as donepezil hydrochloride, salbutamol sulphate, clopidogrel bisulfate, and bromhexine hydrochloride.[2,4] For poorly soluble APIs (BCS Class II/IV), strategies like micronization, solid dispersions, or complexation with cyclodextrins are employed to improve dissolution without compromising disintegration.[13]

Excipients

Excipients in ODTs perform multiple roles, including providing bulk, ensuring compressibility, enhancing flow, and supporting rapid disintegration while contributing to mouthfeel through sweetness and cooling sensation.[1,15]

1. Diluents/Fillers

Water-soluble polyols such as mannitol (Pearlitol®), sorbitol, or xylitol serve as preferred diluents or fillers due to their pleasant sweetness, low hygroscopicity, and rapid dissolution in the oral cavity. Mannitol-based co-processed excipients, including Parteck® ODT, Ludiflash®, and Pharmaburst®, offer improved compressibility, high porosity, and fast disintegration, making them especially suitable for direct compression ODT formulations.[15,16,25]

2. Binders

Binders ensure tablet integrity during and after compression. Commonly used binders include polyvinylpyrrolidone (PVP K-30), pregelatinized starch, and hydroxypropyl cellulose[15]. In modern direct compression ODT formulations, co-processed excipients often incorporate binders to provide multifunctional performance, reducing the need for separate binder addition[15]

3. Lubricants

Lubricants prevent the sticking of the tablet lend to punches and dies during tableting. Magnesium stearate or sodium stearyl fumarate are widely used (typically 1-2% w/w). Hydrophobic lubricants must be used cautiously, as excessive levels or prolonged blending time can delay disintegration and dissolution by forming a hydrophobic film on the tablet surface .[16]

4. Glidants, Sweeteners, and Flavors

Glidants such as colloidal silicon dioxide improve powder flow. Sweeteners (e.g., aspartame, sucralose) and flavors enhance the sensory profile and patient acceptability. [15,16.] These excipients are particularly important for ensuring a pleasant mouthfeel and masking any bitter taste of the active pharmaceutical ingredient

5. Recent advances emphasize the use of multifunctional co-processed excipients that combine several functions into a single ingredient. Examples Prosolv® ODT G2 (a combination of mannitol, microcrystalline cellulose, and super-disintegrants), which enables direct compression by improving flow, compatibility, and disintegration while reducing the number of individual additives required.[15,16]

6. Super-disintegrants

Super-disintegrants are essential for achieving the rapid disintegration required for ODTs (typically ≤30 seconds). They function at low concentrations (usually 1–10% w/w) through mechanisms such as swelling, wicking (capillary action), or strain recovery/deformation.[17]

- Swelling-based: Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) expand upon hydration, generating disruptive force.
- Wicking-based: Crospovidone draws water into the tablet pores rapidly without significant volume change.
- Deformation/strain recovery: Creates fissures to facilitate breakup.[17]

Synthetic super-disintegrants provide consistency and high efficiency, whereas natural alternatives (e.g., plant mucilages, gums, and modified starches) are gaining interest for their biocompatibility, lower cost, and eco-friendliness, and in some studies, superior swelling indices and equivalent or better disintegration performance when optimized.[17,18] However, natural options may exhibit higher batch-to-batch variability compared to synthetics, limiting their use in commercial products requiring tight disintegration specifications.[17]

The following table compares various natural and synthetic super-disintegrants, including their sources or descriptions, mechanisms, typical concentrations in ODT formulations, and key notes or examples (drawn from recent reviews and studies, 2020-2026):

Table 1: Overview of synthetic versus natural super-disintegrants: mechanisms, typical concentrations in ODT formulations, and representative examples from recent studies [2020-2026]

Category	Super-disintegrant	Source/Description	Mechanism	Typical Concentration in ODTs [% w/w]	Examples
Synthetic	Crospovidone (e.g., Polyplasdone XL)	Cross-linked polyvinylpyrrolidone	Wicking, swelling, strain recovery	2-6 (optimal ~4-5)	Fastest DT often <15 s; high efficiency in direct compression[2]
Synthetic	Sodium Starch Glycolate (SSG)	Modified starch derivative	Swelling	2-8 (up to 10)	Good swelling; gelling risk at high levels; common in many ODTs[17]
Synthetic	Croscarmellose Sodium (CCS, e.g., Ac-Di-Sol)	Cross-linked carboxymethylcellulose	Wicking + swelling	2-5	Expands 4-8x; DT <30 s; widely used benchmark[17]

Natural	Plantago ovata Mucilage/Ispaghula Husk	Seed mucilage/husk from Plantago ovata	Swelling	3-15 (optimal 8-12)	High swelling index; superior to SSG in some studies; eco-friendly[17,18]
Natural	Guar Gum	From Cyamopsis tetragonoloba seeds	Swelling	4-10	Rapid action; often out performs some synthetics[18]
Natural	Fenugreek Seed Mucilage	From Trigonella foenum-graecum	Swelling	1-6 (optimal ~6)	DT ~20-25 s; better than SSG/CCS in select formulations[17]
Natural	Banana Powder	Dehydrated banana pulp	Swelling + wicking	2-6 (optimal 4)	Natural sweetness; good for palatability[18]

Note: Natural super-disintegrants often show comparable or superior performance to synthetics in eco-friendly formulations but may exhibit higher batch variability[17,18]

Taste-Masking Techniques

Taste masking is a critical aspect of formulating orally disintegrating tablets (ODTs), as these dosage forms disintegrate rapidly in the oral cavity, leading to direct and prolonged contact between the active pharmaceutical ingredient (API) and taste receptors. Bitter or unpleasant-tasting APIs can significantly reduce patient compliance, particularly in pediatric, geriatric, and dysphagic populations.[2,19] Effective taste masking must achieve a balance between suppressing bitterness during the brief disintegration phase (typically <30 seconds) and ensuring rapid drug release post-swallowing for optimal bioavailability. Common strategies include complexation, coating, and flavoring, often used in combination for synergistic effects.[1,2]

Complexation involves forming inclusion complexes or ionic interactions that encapsulate or bind the API, preventing its interaction with taste buds while allowing release in the gastrointestinal tract. Cyclodextrins, particularly β-cyclodextrin and hydroxypropyl-β-cyclodextrin, are widely used for inclusion complexation due to their ability to host hydrophobic or bitter APIs in their cavity, thereby reducing bitterness perception.[2] For instance, ibuprofen-β-cyclodextrin complexes prepared via spray drying have demonstrated effective taste masking in ODTs, improving solubility and palatability without compromising disintegration.[2] Ion-exchange resins (e.g., Kyron T-114 or Amberlite) form drug-resin complexes through electrostatic binding, especially effective for ionizable bitter drugs like dextromethorphan hydrobromide or levocetirizine. These complexes release the drug via ionic exchange in the stomach, providing excellent masking with minimal impact on bioavailability when optimized.[2,19]

Coating techniques create a physical barrier around API particles or granules to prevent dissolution in saliva while permitting release in the acidic gastric environment. Fluid-bed coating or layering with pH-dependent polymers such as Eudragit E100 (gastric-soluble), ethylcellulose, hydroxypropyl methylcellulose (HPMC), or polyvinyl acetate is common. These polymers are insoluble at salivary pH (~6-7) but dissolve rapidly in the stomach (pH <5), ensuring taste suppression during oral residence and quick release thereafter. Studies on high-dose memantine hydrochloride ODTs using enteric-coated granules via layering have shown successful bitterness suppression, as confirmed by electronic tongue evaluation, while maintaining acceptable disintegration time and mechanical strength.[20] Mass extrusion followed by coating with similar polymers has also been applied to bitter drugs like tramadol hydrochloride, enabling incorporation into ODTs.[2]

Flavoring represents an organoleptic approach that overpowers or competes with unpleasant tastes through the addition of sweeteners (e.g., aspartame, sucralose, mannitol) and flavors (e.g., peppermint, fruit essences, yogurt powder). This method is often combined with physical techniques for enhanced efficacy. For example, incorporating citric acid, yogurt flavor, and aspartame in olopatadine ODTs has been shown to suppress bitterness in a dose-dependent manner via gustatory sensation tests.[1] Natural sweeteners like ammonium glycyrrhizinate or skimmed milk powder can also contribute to masking while improving mouthfeel.[21] Combined physical (e.g., coating) and organoleptic (e.g., flavoring) strategies have proven particularly effective for highly bitter APIs, such as propiverine hydrochloride, where they improve overall palatability without prolonging disintegration.[21]

Advanced approaches integrate these methods, such as spray-dried microspheres, hot-melt extrusion, or solid dispersions, to achieve dual masking and bioavailability enhancement.[2] Sensory evaluation using human panels, electronic tongues, or visual analog scales remains essential to confirm masking efficacy, ensuring the formulation meets regulatory and patient acceptance criteria.[19] Overall, the choice of technique depends on the API's bitterness intensity, dose, solubility, and compatibility, with hybrid strategies offering the most robust solutions for ODTs. While ion-exchange resins provide elegant masking for cationic drugs, they are limited for anionic or neutral molecules; coating remains universal but risks delayed release [19,20]

Manufacturing, Quality Control, and Stability of Orally Disintegrating Tablets (ODTs)

Orally disintegrating tablets (ODTs) are designed to disintegrate rapidly in the oral cavity, typically within seconds, without the need for water. Their manufacture requires careful balancing of porosity, mechanical strength, dose uniformity, and stability. From an industrial perspective, manufacturing approaches must also satisfy scalability, cost control, and regulatory robustness.

Conventional Manufacturing Techniques

-Direct Compression

Direct compression (DC) remains the dominant commercial manufacturing route for ODTs due to its operational simplicity, low capital investment, and compatibility with existing tablet production infrastructure.[2] The process involves blending the active pharmaceutical ingredient (API) with directly compressible excipients and superdisintegrants such as crospovidone or sodium starch glycolate, followed by low-to-moderate compression forces to preserve tablet porosity.[2,1]

From a regulatory standpoint, DC is highly favorable: the method is well understood, reproducible, and supported by extensive pharmacopeial precedent. Its main limitations are formulation-driven rather than technological. High drug loading or poorly flowing APIs can compromise compressibility and disintegration performance, necessitating careful excipient optimization.[2]

-Lyophilization

Lyophilization (freeze-drying) produces highly porous ODTs by sublimation of water from a frozen drug–polymer matrix, yielding exceptionally rapid disintegration due to capillary action within the sponge-like structure .[1,19] While this method achieves superior in-mouth dispersion, its commercial utility is constrained by high production costs, long cycle times, low throughput, and the mechanical fragility of the final dosage form. As a result, lyophilized ODTs require specialized blister packaging and are less suited to large-scale, cost-sensitive markets .[1]

Overall, conventional technologies are characterized by high regulatory readiness and scalability, but their performance is tightly coupled to excipient selection and formulation design.

Advanced Manufacturing Techniques

-Spray drying

Spray drying is employed primarily as a particle-engineering step rather than a final tableting process. By converting API–polymer solutions into amorphous, highly porous microparticles, spray drying can enhance dissolution rates and improve powder flow before compression.[20,24] This approach is particularly valuable for poorly soluble APIs but introduces solvent handling, higher equipment costs, and additional validation requirements. Compared with DC, spray drying offers functional advantages but reduced economic efficiency at scale.

-Melt granulation

Melt granulation utilizes low-melting binders (e.g., PEG-based excipients) to agglomerate powders without water or organic solvents. The technique improves flowability and compressibility while avoiding moisture exposure, making it attractive for moisture-sensitive APIs.[2,21] However, thermal exposure and added process complexity limit its universal applicability, and regulatory familiarity remains lower than for DC.

In comparison with conventional methods, advanced techniques provide functional flexibility but impose greater manufacturing and regulatory burdens, reinforcing the continued dominance of DC for commercial ODT products.

Quality Control Parameters

Quality control testing of ODTs focuses on attributes that directly influence patient experience and product robustness:

Hardness must be sufficient to withstand handling while preserving porosity for rapid liquid penetration.[2,1]

Friability is critical due to the relatively low mechanical strength of ODTs; values below 1% weight loss are generally required.[2]

Wetting time reflects the rate of saliva penetration into the tablet matrix and correlates strongly with disintegration performance.[2]

Disintegration time is the defining functional parameter and must comply with pharmacopeial expectations for orodispersible dosage forms.[1]

Table 2: Evaluation Parameters and Pharmacopoeial Considerations for ODTs [1,2,19]

Acceptance Range / Guidance	Parameter	Relevance
Disintegration time	Typically, ≤60 s†	Ensures rapid in-mouth dispersion
Friability	<1% weight loss	Maintains integrity during handling
Hardness	Optimized (≈30–50 N)‡	Balances strength and porosity
Wetting time	Typically, <60 s§	Predictor of disintegration behavior
Content uniformity	85–115% of label claim	Dose accuracy and patient safety

Footnotes:

† European Pharmacopoeia defines orodispersible tablets as dispersing within minutes; most commercial ODTs target <60 s for patient acceptability.

‡ No fixed pharmacopeial limit; values are formulation-dependent.

§ Informational parameter widely used during development.

Drug Loading and Stability

Drug Loading Constraints

High drug loading remains a fundamental limitation in ODT formulation. Because rapid disintegration depends on a sufficient proportion of functional excipients, increasing API content reduces available disintegrant capacity and can compromise tablet porosity, disintegration time, and mouthfeel.[2,1] For many APIs, practical loading thresholds are governed less by dose potency than by sensory acceptability and mechanical stability.

Stability and Hygroscopicity Considerations

Stability represents a critical challenge for ODTs, particularly in humid and tropical environments. Many excipients used to promote rapid disintegration, such as superdisintegrants and amorphous sugars, are inherently hygroscopic. Moisture uptake can lead to premature softening, reduced mechanical integrity, delayed disintegration, or physical transformation of amorphous components.[2,21]

Stability assessment of ODTs follows general principles outlined in ICH Q1A(R2) guideline, with particular emphasis on humidity stress due to the dosage form's high surface area and porosity.[22,23] Accelerated and long-term studies are essential to establish shelf life, while photostability testing may be required depending on API sensitivity.

From a regulatory and practical standpoint, stability risks are mitigated primarily through high-barrier packaging systems, such as aluminum–aluminum blister packs, and through careful excipient selection to minimize moisture sorption. [2,1] These strategies are especially important for products intended for distribution in hot and humid climates, where environmental exposure can rapidly degrade ODT performance.

Manufacturing of ODTs requires integration of formulation science, process engineering, and regulatory strategy to reconcile rapid disintegration with mechanical and environmental stability. Conventional technologies, particularly direct compression remains the most commercially viable due to scalability and regulatory maturity, while advanced techniques offer targeted functional benefits at increased cost and complexity. Rigorous quality control and stability management are essential to ensure consistent clinical performance, particularly in moisture-challenged environments. These considerations provide a robust foundation for subsequent discussion of emerging technologies and future development pathways.

While conventional QC parameters ensure the robustness of mass-produced ODTs, they must be adapted to evaluate the unique porous architectures provided by emerging technologies like 3D printing.

Novel Technologies (The "Advances")

The shift toward personalized medicine has catalyzed significant advancements in Orally Disintegrating Tablet (ODT) formulation, moving away from "one-size-fits-all" industrial standards to address specific patient needs, such as pediatric dosing and swallowing difficulties.[24] The primary drivers of this revolution have been identified as 3D printing and nanotechnology, which offer unprecedented control over dose titration, release profiles, and the solubility of poorly water-soluble drugs.[25]

3D Printing: Detailed analysis of Fused Deposition Modeling (FDM) and Selective Laser Sintering (SLS).

Three-dimensional printing (3DP), or additive manufacturing, enables the fabrication of solid dosage forms layer-by-layer according to digital computer-aided design (CAD) models.[26]

3D Printing has matured since its origins in the 1980s, enabling new pharmaceutical manufacturing methods. The first FDA-approved 3D-printed drug – Spritam® (levetiracetam ODT) – was approved in 2015, produced by a powder-bed binder-jet process that gave it an ultra-porous, fast-disintegrating structure.[32] This success with Spritam, which disintegrates in (~11 s), has driven interest in other printing technologies like Fused Deposition Modeling (FDM) and Selective Laser Sintering (SLS) for personalized oral solids.[27,34]

-Fused Deposition Modeling (FDM): This is one of the most accessible and affordable 3DP techniques, utilizing thermoplastic filaments that are heated and extruded layer by layer through a nozzle according to a CAD design. In the context of ODTs, FDM is often combined with hot-melt extrusion (HME) to incorporate active pharmaceutical ingredients (APIs) into polymers like PVA or cellulose derivatives.[28,30]

However, FDM typically produces dense, fused structures that favor extended-release (ER) kinetics rather than rapid disintegration.[24] To achieve ODT performance, researchers have explored structural modifications, such as reducing infill density or printing "miniprintlets," to increase the surface-area-to-volume ratio and facilitate faster media penetration.[26]

Challenges: The process requires high temperatures (often 180 °C – 400 °C), which can degrade thermolabile drugs. FDM often produces dense structures that lead to extended-release rather than rapid disintegration.[24]

-Selective Laser Sintering (SLS): Unlike FDM, SLS uses a laser to selectively fuse (sinter) particles within a powder bed. Porosity has been identified as a key advantage of selective laser sintering (SLS) for orally disintegrating tablet applications, as modulation of laser scanning speed enables the production of highly porous orally disintegrating printlets (ODPs) that rapidly absorb water via capillary action and disintegrate almost instantly. [29] Studies show that ODPs containing ondansetron can achieve a disintegration time of approximately 15 seconds, comparable to commercial ODTs but with the added benefit of being a solvent-free process.[29,31]

Challenges: Many pharmaceutical polymers do not absorb laser energy at the common blue-diode wavelength (445 nm), requiring the addition of absorbance enhancers like Candurin®. High laser energy

may also cause thermal degradation of sensitive active ingredients.[24]

Table 3: Comparative Summary of FDM vs. SLS

Feature	Fused Deposition Modeling (FDM)	Selective Laser Sintering (SLS)
Input Material	Drug-loaded Filament (requires HME first)	Powder Mixture (Drug + Polymer + Flow aids)
Principal Mechanism	Extrusion of molten material	Laser fusion of powder particles
Tablet Structure	Dense, hard, low porosity	Highly porous, brittle, "sponge-like."
Best Used for	Extended Release (ER), high mechanical strength tablets, gastric-resistant tablets.	Orally Disintegrating Tablets (ODT), immediate release, high-solubility drugs.
Heat Stress	High (Applied twice: during HME and Printing)	Low to Moderate (Laser applies heat for microseconds)
Solvents	Solvent-free (Dry process)	Solvent-free (Dry process)
Disintegration Time	Slow (Minutes to Hours) unless modified	Fast (Seconds to Minutes)

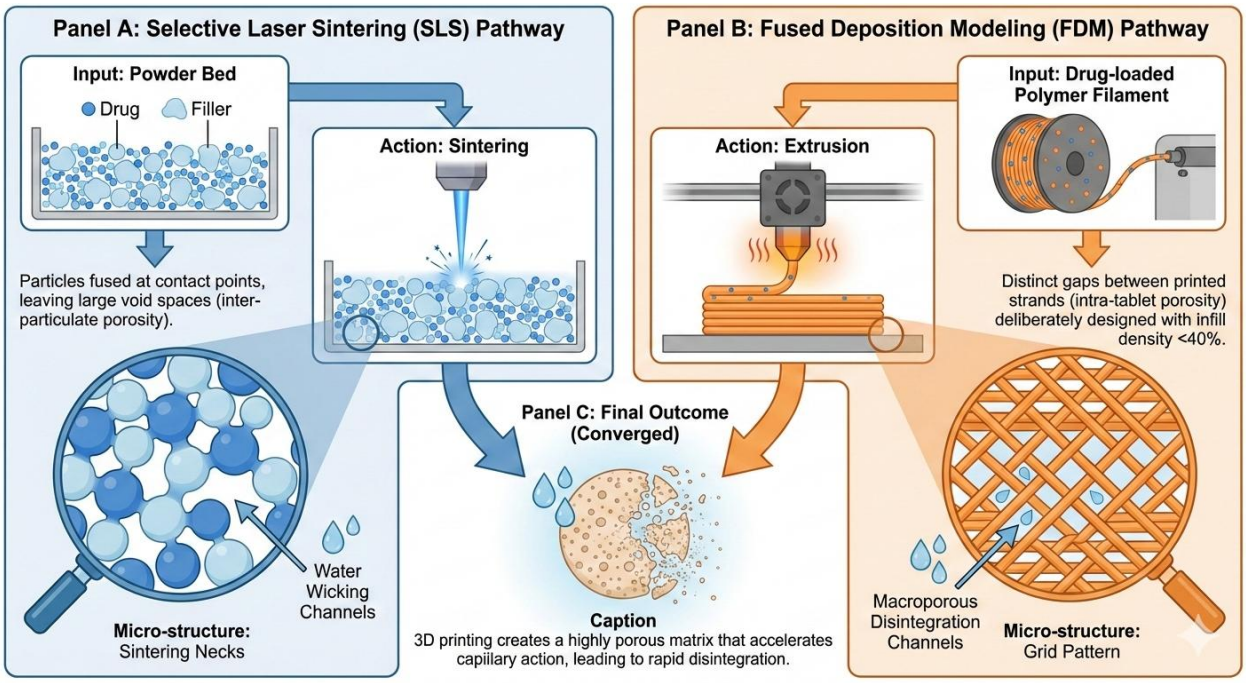

Figure 1: Comparative pathways for SLS and FDM 3D printing in ODT manufacturing. (Note: Image generated/assisted by AI and verified for technical accuracy by the authors)

Binder Jetting Three-Dimensional Printing (BJ-3DP): Binder jetting is a powder-based 3DP technique in which a liquid binder is selectively deposited onto a powder bed to bind particles according to a digital design.[30,31]The process operates at ambient or near-ambient temperatures, making it suitable for heat-sensitive APIs. Tablets produced via BJ-3DP typically exhibit high internal porosity, enabling rapid disintegration without reliance on high levels of superdisintegrants.[31,32,43]

BJ-3DP has been successfully applied to fabricate fast-disintegrating and dispersible tablets, including multicompartment dosage forms with spatial separation of APIs while maintaining acceptable mechanical strength [32] Despite these advantages, formulation sensitivity, limited throughput, and evolving regulatory frameworks currently restrict large-scale adoption.[31-33] At present, BJ-3DP is best positioned for personalized medicine and small-batch manufacturing rather than high-volume commercial ODT production.

Nanotechnology: Nanocrystals and Solid Dispersions for BCS Class II/IV drugs.

A major challenge in oral drug delivery is the low aqueous solubility of many new drug candidates, especially those classified under the Biopharmaceutics Classification System (BCS) Class II and IV. These drugs' poor dissolution rates limit their oral bioavailability and clinical effectiveness. Nanotechnology-based formulation strategies—especially nanocrystals and solid dispersions—have emerged as promising approaches to overcome such limitations and are increasingly being explored in advanced oral dosage forms, including Orally Disintegrating Tablets (ODTs).[34]

a.) ***Nanocrystals***: These are pure drug particles with a crystalline structure and sizes typically between 200 and 500 nm. Nanosizing drastically increases the surface area available for dissolution, which, according to the Ostwald–Freundlich equation, enhances saturation solubility. The integration of nanocrystals into 3DP "printlets" using the melting solidification printing process (MESO-PP) operates at low temperatures (~42 °C), preventing aggregation or thermal degradation of the nanosystem.[35]

Key features of nanocrystal formulations include:

i. High drug loading since most of the mass is API.

ii. Faster dissolution kinetics, driven by increased surface area.

iii. Greater concentration gradients at the absorption site, stimulating uptake.

iv. Potential to reduce food effects in oral absorption.

b.) ***Solid Dispersions:*** Solid dispersions (SDs) disperse poorly soluble drugs within a hydrophilic matrix (usually polymers), thus improving drug wettability, reducing crystallinity, and enhancing dissolution. These systems have been shown to significantly boost the dissolution rates and predicted bioavailability of poorly water-soluble APIs.[36]

Solid dispersions offer several key benefits:

i) Strong increase in dissolution rate due to increased surface area and wettability.

ii) Ability to sustain supersaturation in physiological fluids.

iii) Compatibility with multiple downstream processing techniques such as spray drying, freeze drying, and hot melt extrusion.

Stability remains a core challenge for solid dispersions, especially due to potential recrystallization of the API and phase separation over time. The choice of polymer and manufacturing method strongly influences performance outcomes.[36]

Comparative Evaluation with Conventional Methods

While conventional ODT technologies (such as lyophilization and direct compression with superdisintegrants) remain highly effective for many immediate-release products, the emerging technologies discussed above present distinct advantages:

Customization: 3D printing allows for dose personalization and complex geometries not feasible with traditional tablets.[37,42]

Porosity Control: Additive processes can generate highly porous structures that enhance disintegration independently of chemical disintegrants.[38]

Targeted Solubility Enhancement: Nanotechnology can markedly increase dissolution of poorly soluble drugs beyond the extent achievable with simple micronization.[39]

Table 4: A Comparative Summary of Conventional and Novel Technologies for Orodispersible Tablet Manufacturing.

Technology	Key Advantage	Key Limitation	Scalability	Regulatory Readiness
Direct compression	Low cost, high throughput	Limited dose flexibility	High	High
Lyophilization	Very fast disintegration Moderate High	Fragile tablets, high cost	Moderate	High
FDM	Dose personalization	High temperature, dense structure	Low–Moderate	Emerging
SLS	High porosity, solvent-free	Material constraints, cost	Low–Moderate	Emerging
BJ-3DP	Ambient processing, high porosity	Throughput, formulation sensitivity	Low	Emerging
Nanotechnology-based ODTs	Enhanced dissolution	Stability, excipient burden	Moderate	Moderate

The future of ODTs lies in a multiscale alliance between 3DP and nanotechnology. While SLS provides the optimal macroscopic porous architecture required for rapid disintegration, nanocrystals and solid dispersions address the microscopic solubility challenges of modern APIs. Together, these novel technologies enable the production of highly specialized, "patient-centric" medications that can be manufactured on demand in clinical settings.

Barriers To Commercial Adoption

Despite the clinical promise of additive manufacturing, its integration into large-scale pharmaceutical production faces significant hurdles. While conventional direct compression can produce over 1,000,000 units per hour, 3D printing technologies like FDM and SLS are limited by low production throughput and high capital equipment costs. Furthermore, the lack of standardized high-speed quality control methods for personalized 'printlets' remains a primary bottleneck for widespread industrial adoption.[39-41]

Stability and Regulatory Perspectives

Performance in Tropical Climates (Zone IVb)

The performance of orally disintegrating tablets (ODTs) in tropical regions represents a critical consideration for drug delivery effectiveness and therapeutic reliability. Nigeria is classified under ICH Stability Zone IVb**,** characterized by persistently high temperature and relative humidity. These environmental conditions present significant challenges for ODTs, which are intentionally formulated with high porosity and hydrophilic excipients to enable rapid disintegration.[44,45]

Exposure to elevated humidity can lead to moisture uptake by commonly used superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate. This moisture absorption may reduce tablet hardness, increase friability, and alter disintegration behavior during storage, potentially compromising dose accuracy and patient experience.[22,46] From a therapeutic perspective, such changes may result in inconsistent drug release or delayed onset of action, particularly in populations where ODTs are relied upon for ease of administration.

Advanced ODT systems, including freeze-dried and three-dimensional (3D) printed tablets, are especially sensitive to humid environments due to their highly porous internal structures. Structural weakening or partial collapse of these matrices under tropical storage conditions may negatively affect both mechanical integrity and in vivo performance.[47] Consequently, stability evaluation under **30 °C ± 2 °C / 75 % ± 5 % RH** remains essential for ensuring that ODTs retain acceptable quality throughout their shelf life in Zone IVb settings.[44]

To support consistent therapeutic performance, formulation strategies such as careful excipient selection, optimization of tablet porosity, and the use of moisture protective packaging are essential. These approaches are particularly relevant in tropical regions where climate-controlled storage and distribution may be limited.[45,47]

NAFDAC and Global Regulatory Frameworks

Regulatory oversight of ODTs in Nigeria is provided by the National Agency for Food and Drug Administration and Control (NAFDAC)**,** which adopts pharmacopoeial standards consistent with British and European practices while emphasizing stability requirements appropriate for tropical climates.[49] For manufacturers, compliance with these requirements is central to ensuring product quality, patient safety, and market authorization.

Globally, regulatory definitions of ODTs vary. The U.S. Food and Drug Administration (FDA) generally defines ODTs as tablets that disintegrate within approximately 30 seconds in the oral cavity, while the European Pharmacopoeia permits longer disintegration times under general tablet testing criteria.[50,51] In practice, NAFDAC aligns more closely with European Pharmacopoeial standards but requires robust stability data generated under ICH Zone IVb conditions**.**

For drug delivery scientists, these regulatory expectations highlight the importance of designing ODTs that balance rapid disintegration with sufficient mechanical strength and environmental resilience. While current regulatory testing methods, such as disintegration time, hardness, friability, and stability studies, are generally adequate for conventional ODT formulations, they also provide a workable framework for assessing newer technologies, including 3D-printed ODTs, when supported by appropriate formulation justification and stability data.[49,52]

Rather than posing a barrier to innovation, the Nigerian regulatory framework encourages practical, compliance-driven formulation design**,** particularly for products intended for use in hot and humid environments. Early consideration of regulatory requirements during formulation development can therefore facilitate smoother product registration and improve the likelihood of successful clinical use.

The Biowaiver Challenge for Novel ODTs

A critical regulatory gap exists regarding BCS-based biowaivers for 3D-printed ODTs. In conventional manufacturing, biowaivers are granted based on in vitro dissolution. However, for 3D-printed ODTs, the internal micro-architecture, specifically the infill density and grid patterns, directly dictates the disintegration kinetics. Because minor Computer-Aided Design (CAD) adjustments can significantly alter drug release, NAFDAC and global regulators may require exhaustive in vivo bioequivalence studies rather than simple dissolution profiles, thereby increasing the time and cost of registration.[39-41]

Future Prospects and Research Gaps

The future development of orally disintegrating tablets (ODTs) is progressively shifting from conventional mass-production models toward patient-centric and potentially personalized drug delivery systems**,** driven by the need to improve dosing accuracy, patient adherence, and therapeutic outcomes.[48,53] This transition is particularly relevant for pediatric, geriatric, and

dysphagic populations, where conventional solid dosage forms may be unsuitable.

One of the most prominent emerging directions is point-of-care three-dimensional (3D) printing of ODTs. Technologies such as fused deposition modeling (FDM) offer the ability to fabricate dosage forms with precisely controlled geometry, porosity, and drug distribution, enabling on-demand production of individualized doses.[48,53] In principle, this approach could reduce dosing inaccuracies associated with tablet splitting and allow rapid adjustment of therapy in clinical settings.

Nonetheless, several research gaps must be addressed before widespread adoption is feasible, including the establishment of robust quality assurance frameworks**,** clear batch-definition concepts, regulatory acceptance pathways, and cost-effectiveness, particularly in low- and middle-income countries.

The delivery of biologics, including peptides and small proteins, via ODT platforms represents a significant but underexplored frontier in pharmaceutical research. Future investigations may focus on developing mucoadhesive ODT systems for sublingual or buccal administration to enhance systemic bioavailability by partially bypassing hepatic first-pass metabolism. However, transitioning these systems from the laboratory to clinical practice faces substantial translational hurdles, such as enzymatic degradation within the oral cavity, inherent molecular instability, and restricted mucosal permeability. Furthermore, the lack of validated *in vitro–in vivo* correlation (IVIVC) models remains a critical barrier to standardizing these novel delivery systems.[40,48] While these challenges currently restrict immediate clinical application, they provide a vital pathway for long-term innovation in non-invasive biologic delivery.

Sustainability has also emerged as a strategically important consideration in ODT development, particularly in tropical and resource-limited settings. There is growing interest in the use of eco-friendly and locally sourced excipients**,** including natural superdisintegrants derived from Nigerian starch sources such as *Manihot esculenta* (cassava) and *Dioscorea rotundata* (yam). Experimental studies have demonstrated that modified *Dioscorea rotundata* starch can function effectively as a tablet disintegrant, supporting its potential role in locally optimized ODT formulations.[53] This aligns with broader efforts to evaluate the functionality of natural Nigerian excipients in solid oral dosage forms to reduce reliance on imported synthetics.[54]

Collectively, these future directions highlight the need for integrated research approaches that align formulation innovation with regulatory feasibility, climate resilience, and therapeutic relevance. Addressing these gaps will be essential for translating next-generation ODT technologies into practical and accessible drug delivery solutions.

Conclusion

Orally disintegrating tablets remain an important drug delivery platform for improving patient compliance and therapeutic accessibility, particularly among pediatric, geriatric, and dysphagic populations. Advances in formulation science and manufacturing technologies have expanded the potential applications of ODTs, yet their successful use in tropical regions depends on careful attention to stability, packaging, and regulatory compliance. The integration of 3D printing technologies offers an unprecedented path toward personalized dosing and optimized tablet architectures that can handle higher drug loads without compromising disintegration kinetics. Furthermore, leveraging nanotechnology-based systems such as nanocrystals and solid dispersions effectively addresses the solubility hurdles characteristic of BCS Class II and IV molecules.

In ICH Zone IVb environments such as Nigeria, moisture sensitivity directly influences product quality and clinical reliability.[46] Future research must therefore prioritize the synergy between these advanced fabrication methods and moisture-protective excipient selection to ensure structural integrity remains intact from production to patient. By integrating climate-appropriate formulation strategies with established regulatory frameworks, ODTs can be developed as robust, effective, and patient-friendly dosage forms suitable for widespread use in tropical and developing country settings.[44,46]

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