

# Innovative Formulation Techniques for Orodispersible Tablets: A Review of Recent Advancements

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**Abstract:** *Orodispersible tablets (ODTs) represent a significant advancement in drug delivery systems, offering improved patient compliance and convenience. This systematic review explores innovative formulation techniques for ODTs, focusing on their evolution, challenges, and future trends. The review covers traditional methods such as direct compression, freeze drying, and melt granulation while examining the impact of advanced strategies like super-disintegrants, effervescent techniques, and solid dispersions. Comprehensive characterization and evaluation methods, including physical property assessments and in vitro-in vivo studies, are discussed to underscore quality control measures and regulatory compliance.*

*Emerging technologies, including nanotechnology and 3D printing, are highlighted for their potential to revolutionize ODT development through enhanced solubility, bioavailability, and personalized medicine applications. Challenges such as stability issues, patient compliance factors, regulatory hurdles, and scalability of innovative techniques are critically analyzed.*

*The review identifies key research gaps, particularly in the formulation of high-dose drugs and biologics. It emphasizes the role of artificial intelligence (AI) and machine learning (ML) in optimizing formulation processes. The integration of these tools promises to streamline development timelines and improve consistency.*

*This review concludes that ODTs, supported by continuous innovation and interdisciplinary research, hold immense promise for transforming patient-centric drug delivery and addressing unmet therapeutic needs..*

**Keywords:** Orodispersible Tablets, Drug Delivery Systems, Innovative Formulation Techniques, Patient Compliance, Nanotechnology in ODTs, 3D Printing in Medicine, Super-disintegrants, Personalized Medicine

## I. INTRODUCTION

Orodispersible tablets (ODTs) are solid dosage forms designed to disintegrate rapidly in the oral cavity, typically within seconds, without the need for water [1]. These tablets address the challenges faced by individuals with dysphagia, such as elderly patients, children, and individuals with specific medical conditions, providing an easy and effective means of drug administration [2].

The importance of ODTs in drug delivery lies in their ability to enhance patient compliance and improve therapeutic outcomes. By offering a palatable and convenient dosage form, they are particularly beneficial for populations with swallowing difficulties [3]. Additionally, ODTs allow for a quicker onset of action due to their rapid disintegration and absorption, often bypassing first-pass metabolism partially when drugs are absorbed through the oral mucosa [4].

This systematic review aims to explore the advancements and challenges associated with innovative formulation techniques for ODTs. The scope encompasses a comprehensive analysis of both traditional and modern formulation

methods, evaluating their contributions to the field and the barriers faced during development. The review also highlights innovative approaches, such as the use of super-disintegrants, effervescent techniques, and solid dispersion methods, along with their impact on enhancing the efficacy and acceptability of ODTs.

Furthermore, the discussion includes the characterization and evaluation parameters critical for the success of ODTs, such as physical property assessments and in vitro and in vivo evaluations [5]. The ultimate goal is to provide insights into current trends and future directions in ODT formulation, supporting researchers and pharmaceutical developers in optimizing their approaches for effective drug delivery solutions.

**II. HISTORICAL PERSPECTIVE AND TRADITIONAL FORMULATION TECHNIQUES**

The development of orodispersible tablets (ODTs) has undergone significant evolution, reflecting advancements in pharmaceutical sciences. The concept of ODTs originated in the late 20th century, driven by the need to address swallowing difficulties among specific populations, including geriatric and pediatric patients [6]. Early formulations primarily relied on conventional techniques such as wet granulation and direct compression, using basic excipients to achieve acceptable disintegration times and palatability [7].

Initially, traditional methods lacked the precision to ensure consistent drug release profiles and stability, leading to variability in therapeutic outcomes. However, the pharmaceutical industry soon recognized the potential of ODTs as a patient-centric dosage form, spurring innovations in excipient selection and manufacturing processes [8]. Key milestones included the introduction of disintegrants like sodium starch glycolate and croscopovidone, which significantly improved the rapid disintegration properties of tablets [9].

The transition from traditional to modern techniques was characterized by the integration of more sophisticated technologies, such as freeze-drying and lyophilization, which enhanced the physical and mechanical properties of ODTs. These methods allowed for the development of highly porous tablets with superior disintegration times, catering to a broader range of active pharmaceutical ingredients (APIs) [10]. Similarly, advancements in melt granulation and solid dispersion techniques enabled the inclusion of poorly soluble drugs, addressing a major limitation of early formulations [11].

The historical evolution of ODTs underscores the importance of learning from traditional practices while embracing innovative approaches. Modern formulation techniques draw heavily on the lessons of the past, particularly the need for patient-centric designs and robust quality control measures [12]. This blend of historical knowledge and contemporary science forms the foundation for the ongoing development of ODTs as a versatile and practical drug delivery system.

**Table 1.** Comparison of Traditional and Modern ODT Formulation Techniques

Aspect	Traditional Techniques	Modern Techniques
Methods	Wet granulation, direct compression	Freeze drying, lyophilization, melt granulation
Excipients Used	Basic disintegrants	Advanced super-disintegrants, polymers
Disintegration Time	Slower (30-60 seconds)	Faster (<30 seconds)
Drug Compatibility	Limited to soluble APIs	Includes poorly soluble APIs
Stability	Moderate	Enhanced through advanced technologies

**III. FORMULATION TECHNIQUES FOR ORODISPERSIBLE TABLETS**

The formulation of orodispersible tablets (ODTs) has advanced significantly, integrating diverse techniques to enhance their efficacy, stability, and patient acceptability. Key methods such as direct compression, freeze drying, and melt granulation are widely utilized, each with distinct advantages and limitations.

**3.1 Direct Compression**

Direct compression is the most straightforward and economical method for manufacturing ODTs, involving the compression of powdered ingredients directly into tablets without the need for additional granulation steps [13]. The technique relies heavily on excipients that provide both compressibility and rapid disintegration properties.

Key excipients used in direct compression include microcrystalline cellulose, which imparts structural integrity, and croscopovidone, a super disintegrant that ensures quick tablet dispersion upon contact with saliva [14]. This technique has advantages, including minimal processing steps, reduced production costs, and compatibility with heat-sensitive drugs. Despite its benefits, direct compression faces challenges, such as achieving uniform drug distribution in low-dose formulations and maintaining tablet stability for moisture-sensitive drugs [15]. However, continuous advancements in excipient technology have mitigated these issues, making direct compression a preferred technique for the mass production of ODTs.

### 3.2 Freeze Drying and Lyophilization

Freeze drying, also known as lyophilization, is a sophisticated method that produces ODTs with highly porous structures, facilitating rapid disintegration in the oral cavity [16]. This technique involves freezing the tablet formulation and sublimating the solvent under vacuum, leaving behind a porous matrix.

Benefits of freeze drying include superior disintegration times, enhanced patient compliance, and compatibility with a wide range of APIs, including heat-sensitive drugs [17]. Notable examples include Zydis® formulations, which use freeze-dried matrices for optimal drug delivery [18].

However, freeze-drying is associated with high production costs and requires specialized equipment. The fragility of the resulting tablets also poses challenges in handling and packaging. Despite these limitations, freeze-drying remains a gold standard for high-performance ODTs, particularly in therapeutic areas where rapid onset of action is critical [19].

### 3.3 Melt Granulation

Melt granulation is a novel technique in which a binder with a low melting point is used to agglomerate powdered ingredients into granules under heat [20]. These granules are subsequently compressed into tablets, offering enhanced tablet cohesion and stability.

One of the significant advantages of melt granulation is its ability to improve the solubility and bioavailability of poorly water-soluble drugs. Additionally, this method does not require the use of water or solvents, making it suitable for moisture-sensitive APIs [21]. Polyethylene glycol and poloxamers are commonly used binders in this process, contributing to the tablet's disintegration and dissolution properties [22].

While melt granulation offers numerous advantages, it requires precise control over temperature and binder concentration to prevent the degradation of heat-sensitive drugs. Nevertheless, its ability to produce robust tablets with improved drug delivery profiles has established melt granulation as a promising technique in ODT formulation [23].

**Table 2.** Comparison of Key ODT Formulation Techniques

Technique	Advantages	Challenges	Applications
Direct Compression	Cost-effective, minimal steps, heat-sensitive drugs	Drug distribution issues, moisture sensitivity	Widely used for mass production
Freeze Drying	Rapid disintegration, heat-sensitive APIs	High-cost, fragile tablets	Critical applications like Zydis®
Melt Granulation	Improved solubility, solvent-free process	Requires precise temperature control	Poorly soluble and moisture-sensitive drugs

## IV. INNOVATIVE APPROACHES IN ODT FORMULATION

The development of innovative techniques in orodispersible tablet (ODT) formulation has expanded the range of drugs that can be incorporated into this dosage form, addressing the limitations of traditional methods. This section highlights key advancements, including the use of super-disintegrants, effervescent techniques, and solid dispersion technologies.

#### 4.1 Use of Super-disintegrants

Super-disintegrants are specialized excipients designed to facilitate the rapid breakdown of tablets into smaller particles upon contact with saliva, enabling swift drug release and absorption [24]. Commonly used super-disintegrants include croscarmellose sodium, sodium starch glycolate, and crospovidone, each functioning through swelling, capillary action, or both [25].

The incorporation of super-disintegrants has been a game-changer in ODT formulation, significantly reducing disintegration time while maintaining tablet integrity during handling and packaging. Comparative studies reveal that crospovidone exhibits superior performance due to its high capillary activity and water-wicking properties [26].

Despite their advantages, super-disintegrants must be carefully optimized in formulations to prevent adverse effects, such as excessive friability or poor taste masking. The ongoing development of next-generation disintegrants with enhanced functionalities ensures continued advancements in this domain [27].

#### 4.2 Effervescent Techniques

Effervescent techniques rely on the reaction between an acid (e.g., citric acid) and a carbonate or bicarbonate base (e.g., sodium bicarbonate) in the presence of saliva, releasing carbon dioxide gas [28]. This gas facilitates tablet disintegration and drug dispersion, making effervescent formulations ideal for drugs requiring rapid onset of action.

The key advantage of this approach lies in its ability to mask unpleasant drug tastes, as the effervescence enhances the sensory experience. Additionally, the technique promotes the dissolution of poorly water-soluble drugs by creating a microenvironment conducive to solubilization [29].

Challenges associated with effervescent formulations include stability issues due to moisture sensitivity and the need for specialized packaging. However, advancements in moisture-resistant excipients and packaging materials have mitigated these concerns, enabling broader application of this technique [30].

#### 4.3 Solid Dispersion Techniques

Solid dispersion techniques involve dispersing the drug in a polymer matrix to enhance its solubility and bioavailability [31]. Polymers such as polyethylene glycol, polyvinylpyrrolidone, and hydroxypropyl methylcellulose are commonly employed for this purpose.

The primary benefit of solid dispersion is its ability to improve the dissolution rate of poorly soluble drugs, thereby increasing their bioavailability. Case studies have demonstrated significant improvements in the pharmacokinetic profiles of drugs formulated using this technique [32]. For instance, the incorporation of itraconazole into a solid dispersion matrix has led to enhanced therapeutic efficacy [33].

However, challenges such as drug-polymer incompatibility and the stability of amorphous forms require careful consideration during formulation development. Recent advancements in carrier materials and process optimization have addressed many of these issues, making solid dispersion a valuable tool in ODT development [34].

**Table 3.** Comparison of Innovative ODT Formulation Techniques

Technique	Advantages	Challenges	Applications
Super-disintegrants	Rapid disintegration, minimal tablet friability	Optimization challenges, taste masking issues	Widely used in direct compression
Effervescent Techniques	Taste masking, rapid onset of action	Moisture sensitivity, specialized packaging	Fast-acting drugs, patient-friendly designs
Solid Dispersion	Improved solubility and bioavailability	Stability concerns, polymer compatibility issues	Poorly soluble APIs

### V. CHARACTERIZATION AND EVALUATION OF ORODISPERSIBLE TABLETS

Comprehensive evaluation of orodispersible tablets (ODTs) is essential to ensure their efficacy, safety, and patient acceptability. Characterization techniques primarily focus on assessing physical properties and evaluating performance through in vitro and in vivo methods.

### 5.1 Physical Properties Assessment

The physical properties of ODTs significantly impact their performance and user experience. Key parameters include hardness, friability, disintegration time, and dissolution rate.

- **Hardness:** This parameter measures the tablet's mechanical strength, ensuring it can withstand handling and transportation. Optimal hardness prevents breakage while allowing rapid disintegration [35]. Tests are conducted using hardness testers to achieve consistent quality.
- **Friability:** Friability assesses the tablet's ability to resist chipping and abrasion. Tablets are subjected to controlled tumbling in a friability, with weight loss not exceeding 1% considered acceptable [36].
- **Disintegration Time:** Rapid disintegration is critical for ODTs to ensure prompt drug release. The United States Pharmacopeia (USP) specifies that ODT should disintegrate within 30 seconds under standard conditions [37].
- **Dissolution Rate:** This test evaluates the rate and extent of drug release in simulated physiological conditions. Dissolution testing helps predict in vivo drug performance and is particularly important for poorly soluble APIs [38].

### 5.2 In Vitro and In Vivo Evaluation

Evaluating the bioavailability and performance of ODTs requires both in vitro and in vivo methods.

- **In Vitro Methods:** Disintegration and dissolution tests are primary in vitro tools for assessing the functionality of ODTs. Advanced techniques, such as imaging and spectroscopy, are also employed to study tablet structure and drug release kinetics [39]. These tests provide valuable insights into the formulation's behaviour under simulated conditions.
- **In Vivo Methods:** Human pharmacokinetic studies assess the absorption, distribution, metabolism, and excretion (ADME) of the drug. Parameters such as maximum concentration (Cmax) and time to reach Cmax (Tmax) are critical indicators of the formulation's effectiveness [40]. Additionally, taste evaluation studies are conducted to ensure patient acceptability.

Combining in vitro and in vivo data provides a comprehensive understanding of an ODT's performance. Correlation studies, such as in vitro-in vivo correlation (IVIVC), further enhance the predictive value of in vitro tests, reducing the reliance on extensive clinical trials [41].

**Table 4.** Key Parameters in ODT Characterization and Evaluation

Parameter	Purpose	Methodology	Regulatory Standards
Hardness	Ensures mechanical strength	Hardness tester	4–6 kg/cm <sup>2</sup> for optimal strength [35]
Friability	Evaluates resistance to chipping	Friabilator testing (1% weight loss limit)	≤ 1% loss in weight [36]
Disintegration Time	Measures rapid dispersion in saliva	USP disintegration tester	≤ 30 seconds [37]
Dissolution Rate	Assesses drug release profile	USP dissolution apparatus	API-specific criteria [38]
In Vivo Evaluation	Determines bioavailability and therapeutic efficacy	Pharmacokinetic studies	Based on Cmax, Tmax, and AUC parameters [40]

## VI. CHALLENGES IN FORMULATING ORODISPERSIBLE TABLETS

Formulating orodispersible tablets (ODTs) presents unique challenges due to the specific requirements for rapid disintegration, taste masking, and stability. These challenges are critical in determining the commercial and therapeutic success of ODTs.

- **Stability Issues with Active Pharmaceutical Ingredients (APIs):** Many APIs used in ODTs are susceptible to degradation due to their exposure to environmental factors such as moisture, light, and temperature. Moisture sensitivity is particularly problematic in formulations employing effervescent techniques or super-

disintegrants [42]. Protective packaging, such as blister packs with desiccants, is often required, increasing production costs [43].

- **Patient Compliance Factors:** Ensuring patient compliance is another significant challenge. Achieving a balance between tablet size, taste, and mouthfeel is critical, particularly for pediatric and geriatric populations. Taste masking of bitter drugs remains a significant obstacle, requiring advanced coating techniques or the incorporation of sweeteners and flavouring agents [44]. However, excessive use of such agents can impact the disintegration time and stability of the formulation.
- **Regulatory Hurdles in Formulation Development:** ODT formulations must comply with stringent regulatory standards, which vary across regions. Parameters such as disintegration time, content uniformity, and dissolution rates are tightly regulated. Demonstrating bioequivalence for generic ODTs is particularly challenging, requiring extensive in vitro and in vivo studies [45]. Navigating these regulations often involves significant time and financial investment, delaying product launch.
- **Process Optimization and Scale-Up:** Transitioning from small-scale laboratory formulations to large-scale manufacturing poses difficulties in maintaining consistency and quality. Factors such as compression force, granule size, and environmental conditions must be precisely controlled to avoid batch-to-batch variations [46]. The scalability of advanced techniques like freeze drying is limited due to high equipment and operational costs.
- **Taste Masking and Palatability:** Developing ODTs with acceptable taste and palatability is a persistent challenge. Bitter APIs require effective taste-masking strategies that do not compromise disintegration and dissolution profiles [47]. Innovative methods, such as microencapsulation and ion exchange resins, are increasingly used to address this issue.

Table 5. Key Challenges in ODT Formulation

Challenge	Description	Solutions/Strategies
Stability Issues	APIs sensitive to moisture, light, or heat	Moisture-resistant excipients, advanced packaging [43]
Patient Compliance	Balancing taste, size, and disintegration	Taste-masking agents, flavor enhancers [44]
Regulatory Hurdles	Varying standards for disintegration, bioequivalence	Comprehensive in vitro and in vivo studies [45]
Process Optimization	Ensuring batch-to-batch consistency during scale-up	Advanced manufacturing controls, automation [46]
Taste Masking	Managing bitterness without affecting drug release	Microencapsulation, ion exchange resins [47]

## VII. FUTURE TRENDS AND INNOVATIONS IN ODT DEVELOPMENT

The convergence of novel formulation strategies, advanced materials, and personalized medicine approaches marks the future of orodispersible tablet (ODT) technology. These innovations aim to enhance ODTs' therapeutic efficacy, patient compliance, and versatility.

### 7.1 Emerging Technologies in Formulation Science

The adoption of nanotechnology in ODT formulation has opened new avenues for improving drug solubility and bioavailability. Nanocrystals and nanoemulsions are being incorporated into ODTs to address the challenges associated with poorly soluble drugs [48]. Additionally, 3D printing technology enables precise control over drug loading and release profiles, facilitating the development of complex dosage forms tailored to individual needs [49].

Advanced manufacturing methods, such as continuous manufacturing and hot-melt extrusion, are also being explored for their potential to streamline production and enhance scalability [50].

**7.2 Potential for Personalized Medicine Applications**

Personalized medicine is gaining traction in ODT development, particularly for drugs requiring precise dosing or tailored formulations. Techniques like 3D printing allow for the creation of patient-specific ODTs with customized drug combinations and release profiles [51]. This approach is particularly beneficial for pediatric and geriatric populations, where individualized therapy is often necessary.

**7.3 Research Gaps and Future Directions**

Despite significant advancements, several gaps remain in ODT research. The long-term stability of innovative formulations, especially those utilizing nanotechnology or biologics, requires further investigation [52]. Additionally, expanding the applicability of ODTs to high-dose drugs and biologics remains a challenge.

Future research should also focus on integrating artificial intelligence (AI) and machine learning (ML) to optimize formulation design and predict drug behaviour in vivo. These tools can significantly reduce development timelines and costs by identifying optimal formulation parameters and predicting potential stability issues [53].

**Table 6.** Future Trends in ODT Development

Trend/Innovation	Description	Potential Benefits
Nanotechnology	Use of nanocrystals and nano-emulsions to enhance solubility	Improved bioavailability broader drug applicability [48]
3D Printing	Customised ODTs with precise drug loading and release profiles	Personalised medicine, complex formulations [49]
Continuous Manufacturing	Streamlined production processes	Enhanced scalability, cost reduction [50]
AI and ML Integration	Predictive tools for formulation optimization	Reduced development time, improved consistency [53]
Biologics in ODTs	Formulating large molecules like peptides and proteins	Expanding ODT applicability to new therapeutic areas [52]

**VIII. CONCLUSION**

The evolution of orodispersible tablets (ODTs) has revolutionized drug delivery by addressing patient compliance, particularly in populations with swallowing difficulties. This systematic review highlights the transition from traditional to innovative formulation techniques, emphasizing the role of advanced technologies and materials in overcoming formulation challenges.

Key findings underscore the significance of direct compression, freeze drying, and melt granulation as foundational techniques. The integration of super-disintegrants, effervescent mechanisms, and solid dispersion methods has further enhanced the functionality of ODTs. Comprehensive characterization protocols, including physical and in vitro assessments, ensure consistent quality and performance, addressing regulatory demands.

Emerging technologies, such as nanotechnology and 3D printing, are paving the way for personalized medicine, allowing for tailored drug delivery systems with enhanced bioavailability and therapeutic efficacy. However, challenges such as stability issues, scalability of advanced techniques, and regulatory hurdles remain barriers to widespread adoption.

Future directions should focus on bridging research gaps, particularly in the formulation of high-dose drugs and biologics. The integration of artificial intelligence (AI) and machine learning (ML) into formulation science offers promising solutions for optimizing development processes and predicting formulation outcomes.

In conclusion, ODTs hold immense potential to transform patient-centric drug delivery. Continued innovation, supported by interdisciplinary research, is essential to address existing challenges and expand the scope of ODT applications in therapeutic domains.

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#### **Conflict of Interest**

The authors confirm that there are no competing interests with any institutions, organizations, or products that may influence the findings or conclusions of this manuscript.

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