

Orodispersible Tablets (ODTs): Innovations, Formulation Strategies, and Future Prospects in Patient-Centric Drug Delivery

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Abstract: The oral route remains the gold standard for drug delivery due to its non-invasive nature and high patient compliance; however, its efficacy is significantly hindered by dysphagia, affecting approximately 30% of adults and a higher proportion of pediatric and geriatric populations. Orodispersible Tablets (ODTs) have emerged as a paramount solution to this challenge, engineered to undergo rapid disintegration in the oral cavity—typically in under 30 seconds—without the need for water.

This review provides a comprehensive analysis of the innovative formulation strategies and manufacturing technologies that define the ODT landscape. It explores the critical role of superdisintegrants and the "disintegration-mechanical strength paradox," where high porosity must be balanced with structural integrity. We evaluate diverse manufacturing paradigms, ranging from cost-effective Direct Compression to advanced Lyophilization (Zydis® technology) and the burgeoning potential of 3D Printing for personalized dosing. Furthermore, the study addresses the clinical advantages of ODTs, including pre-gastric absorption which can bypass hepatic first-pass metabolism to enhance bioavailability. By integrating considerations of taste-masking, stability, and regulatory requirements, this review positions ODTs as a cornerstone of patient-centric drug delivery, offering a roadmap for future innovations in biologics and AI-optimized pharmaceutical design.

Keywords - Orodispersible Tablets (ODTs), Fast-Dissolving Tablets (FDTs), Mouth-Dissolving Tablets (MDTs), Patient-Centric Drug Delivery

1. Introduction

1.1. The Oral Route: Preference and Pitfalls

The oral route of administration remains the most preferred for drug delivery due to its non-invasiveness, convenience, high patient compliance, and cost-effectiveness [1]. However, this route is not without challenges. A significant portion of the patient population, notably pediatric, geriatric, and dysphagic (swallowing difficulty) patients, often struggles with the ingestion of conventional tablets and capsules. Studies suggest that 30% of adults and a higher percentage of elderly and children report difficulty in swallowing solid dosage forms, leading to reduced compliance, medication refusal, and potentially ineffective therapy [2].

1.2. Defining the Need for Orodispersible Tablets (ODTs)

To address the pervasive issue of dysphagia and enhance compliance, particularly in patient groups with special needs, the concept of Orodispersible Tablets (ODTs)—also known as Fast Dissolving Tablets (FDTs) or Mouth Dissolving Tablets (MDTs)—emerged. The European Pharmacopoeia (Ph. Eur.) defines an ODT as an uncoated tablet intended to be placed in the mouth where it disperses rapidly before being swallowed. The United States Pharmacopeia (USP) requires ODTs to disintegrate rapidly, typically within less than one minute (30 seconds is a common target), in the oral cavity without the aid of water [3]. This innovative dosage form combines the convenience of a solid unit dose with the ease of administration seen in liquids.

1.3. Scope of the Review

This review critically analyzes the unique characteristics, advantages, challenges, advanced formulation technologies, and the future potential of Orodispersible Tablets, positioning them as a cornerstone of patient-centric drug delivery strategies in modern pharmaceuticals [4].

2. Ideal Characteristics and Advantages of ODTs

The success and rapid commercial adoption of ODTs are due to a unique blend of properties that satisfy patient, clinical, and commercial needs.

2.1. Enhanced Patient Compliance and Convenience

- ✓ **Water-Free Administration:** ODTs eliminate the need for water, making them ideal for individuals who are traveling, prone to motion sickness, bedridden, or in situations where water is unavailable (e.g., soldiers, astronauts).
- ✓ **Suitability for Special Populations:** They are invaluable for pediatric patients (who resist swallowing solid forms), geriatric patients (who often have reduced saliva production and difficulty coordinating swallow reflexes), and psychiatric patients who may feign swallowing [5].
- ✓ **Non-Residue Mouth Feel:** An ideal ODT disintegrates into fine, smooth particles, ensuring minimal grittiness and an agreeable sensation in the mouth.

2.2. Clinical and Pharmacokinetic Benefits

- ✓ **Rapid Onset of Action:** Due to the rapid disintegration and dissolution, the drug is quickly available for absorption. A portion of the drug can be absorbed through the oral mucosa, pharynx, and esophagus (pre-gastric absorption) as the saliva is swallowed.
- ✓ **Potential for Increased Bioavailability:** Pre-gastric absorption allows the drug to bypass the hepatic first-pass metabolism, which can lead to increased systemic bioavailability, particularly for drugs that are extensively metabolized by the liver (e.g., certain antipsychotics, opioids) [6].
- ✓ **Protection from Gastric Degradation:** Drugs prone to degradation in the acidic environment of the stomach or by intestinal enzymes benefit from the immediate swallowing of the dispersed drug, which minimizes residence time in the harsh GI environment.

2.3. Commercial Advantages

ODTs offer significant opportunities for Product Differentiation and Life Cycle Management (LCM). Converting a blockbuster drug to an ODT formulation can extend its patent life, differentiate it from generic competition, and open up new markets focused on patient convenience [7].

3. Challenges in ODT Formulation and Development

Despite the clear benefits, formulating a successful ODT involves overcoming complex trade-offs between rapid disintegration, mechanical strength, taste, and stability.

3.1. The Disintegration-Mechanical Strength Paradox

The most critical challenge is balancing the requirement for rapid disintegration (requiring a highly porous, low-density tablet structure) with the need for adequate mechanical strength (hardness) to withstand manufacturing stresses (compression, ejection), packaging, shipping, and patient handling.

- **High Friability:** Tablets designed for rapid disintegration often have low density and are fragile (high friability), necessitating specialized, often expensive, blister packaging rather than bulk bottles [8].
- **Compression Force:** Increasing the compression force improves hardness but compresses the pore structure, thereby slowing down the ingress of saliva and increasing the disintegration time.

3.2. Taste-Masking of Bitter APIs

Since the drug is released directly into the oral cavity, an unpleasant or bitter taste is a major impediment to patient acceptance, especially in pediatric populations. Effective taste-masking is non-negotiable for most therapeutic agents suitable for ODTs [9].

- **Techniques Employed:**
 - **Microencapsulation/Coating:** Coating drug particles with taste-masking polymers (e.g., Eudragit E-100).
 - **Inclusion Complexation:** Using cyclodextrins to trap the drug molecule and prevent its interaction with oral taste receptors.
 - **Granulation:** Incorporating the drug into rapidly dissolving granules containing intense sweeteners and flavors.

3.3. Hygroscopicity and Stability

The highly porous structure and the use of hydrophilic excipients (like superdisintegrants and water-soluble fillers) render ODTs highly susceptible to moisture and humidity. Water absorption can lead to:

- ❖ **Loss of Integrity:** Softening or deformation of the tablet structure.
- ❖ **Slower Disintegration:** The pre-swelling of the disintegrant reduces its ability to absorb saliva rapidly.
- ❖ **Chemical Degradation:** Increased degradation rate for moisture-sensitive drugs. Special blister packaging (aluminum-aluminum) is essential to mitigate this [10].

3.4. Limitation on Drug Loading and Dose

The tablet size must be small enough for comfortable swallowing of the dispersed mass. This typically restricts the maximum weight of an ODT to under 500 mg. Consequently, drugs requiring high doses (e.g., certain antibiotics or high-strength analgesics) are often unsuitable candidates for ODT formulation.

4. Formulation Components and Mechanism of Disintegration

The rapid action of ODTs is dictated by the selection and proportion of specialized excipients, especially superdisintegrants.

4.1. Superdisintegrants: The Core of ODTs

Superdisintegrants are excipients included in small amounts (1-10% w/w) that facilitate the fast break-up of the tablet upon contact with saliva. Their primary mechanisms of action include:

- ❖ **Swelling:** Absorbing water and rapidly increasing in volume (e.g., Croscarmellose Sodium, Sodium Starch Glycolate).
- ❖ **Wicking/Capillary Action:** Creating channels (wicking) to draw water into the tablet matrix (e.g., Crospovidone).
- ❖ **Deformation:** Recovering from deformation during compression, leading to tablet disintegration (e.g., Crospovidone) [11].

Superdisintegrant	Mechanism of Action	Special Feature
Croscarmellose Sodium (Ac-Di-Sol)	Swelling and Wicking	Swells 4-8 times in less than 10 seconds.
Crospovidone (Polyplasdone)	Wicking/Capillary Action	Swells minimally but acts primarily by rapid water uptake.
Sodium Starch Glycolate (Explotab)	Swelling	Highly hydrophilic, but concentration must be optimized to avoid gelling.

4.2. Bulking Agents and Diluents

These excipients constitute the majority of the tablet mass and are crucial for the rapid dissolution and porous structure. They should be highly water-soluble to facilitate fast breakdown.

- Mannitol: The most widely used due to its high water solubility, low hygroscopicity, and negative heat of solution, which imparts a pleasant, cooling sensation in the mouth (desirable for patient comfort) [12].
- Lactose, Maltodextrin, Xylitol: Also used for bulk, sweetness, and dissolution enhancement.

4.3. Other Essential Excipients

- Sweeteners and Flavors: Essential for taste masking (e.g., sucralose, aspartame, saccharin).
- Binders: Used sparingly or low-melting point binders are used (e.g., PEG, Gelatin) to maintain adequate mechanical strength without compromising disintegration.
- Lubricants: Required for tablet ejection (e.g., Sodium Stearyl Fumarate is preferred over Talc or Magnesium Stearate, which can impart hydrophobicity).

5. Manufacturing Technologies for ODTs

The physical state and performance of an ODT are heavily dependent on the manufacturing technique, with the trend shifting towards methods that create high porosity and low density.

5.1. Direct Compression (DC)

- Principle: The most simple and cost-effective method. It involves blending the drug with specialized excipients (co-processed fillers/superdisintegrants) and compressing the blend directly into tablets.
- Advantage: Fast, economical, requires few processing steps, and avoids heat and moisture.
- Limitation: Requires APIs and excipients with excellent flow and compressibility, which can limit drug loading and formulation options [13].

5.2. Freeze Drying (Lyophilization)

- Principle (Patented Technology: Zydis®): An aqueous solution or suspension of the drug and matrix formers (e.g., gelatin, mannitol) is filled into blister pockets and frozen. The water is subsequently removed by sublimation under vacuum, leaving behind a highly porous, amorphous, or microcrystalline sponge-like matrix [14].
- Advantage: Produces the fastest disintegration times (often <5 seconds), suitable for heat-sensitive drugs.
- Limitation: Very poor mechanical strength, requires specialized, expensive equipment, and special blister packaging; high manufacturing cost.

5.3. Sublimation

- Principle: A volatile solid substance (e.g., camphor, urea, ammonium carbonate) is incorporated into the tablet matrix. After compression, the volatile component is removed by sublimation, generating a network of fine, highly porous channels that enhance water uptake.
- Advantage: Creates high porosity and rapid disintegration using conventional tableting equipment.
- Limitation: Requires a secondary drying step, and residual subliming agent can be a concern.

5.4. Novel and Emerging Technologies

- Spray Drying: Atomizing an API/excipient solution into a hot chamber to produce fine, spherical, porous powders which are then compressed. Offers good particle properties and homogeneity.
- Mass Extrusion: Softening the drug blend using a solvent-binder system and extruding the mass, followed by cutting and drying. Suitable for high-dose ODTs.
- 3D Printing (Additive Manufacturing): Emerging technology enabling the precise, layer-by-layer deposition of drug and excipients. This offers unprecedented control over tablet geometry, porosity, and internal structure, paving the way for personalized ODT formulations with customized release profiles and doses [15].

6. Evaluation and Regulatory Aspects of ODTs

Rigorous quality control testing is necessary to ensure the clinical effectiveness and regulatory compliance of ODT formulations.

6.1. Pharmacopeial Requirements and Quality Tests

- ❖ **Disintegration Time:** The most crucial test. Ph. Eur. mandates a disintegration time of 3 minutes; however, industry standards and FDA guidance often target <30 seconds. Testing is done using the standard USP disintegration apparatus with saliva substitute or water
- ❖ **Wetting Time and Water Absorption Ratio:** Measures the time taken for a drop of water to completely wet the tablet surface and the amount of water absorbed, correlating directly with the efficiency of superdisintegrants and porosity [16].
- ❖ **Uniformity of Dosage Units:** Ensures consistent drug content in each tablet.
- ❖ **Dissolution Testing:** Used to assess the rate and extent of drug release, critical for predicting in vivo performance.

7. Marketed ODT Formulations and Therapeutic Applications

The ODT market is rapidly expanding, driven by the geriatric population and the demand for convenient dosage forms.

- ❖ **Neurological/Psychiatric Agents:** Antipsychotics (e.g., Risperidone, Olanzapine, Zydys® technology) and anti-epileptics are major ODT candidates, as patients in acute distress or those non-compliant benefit most from ease of administration.
- ❖ **Pain Management:** Analgesics and Triptans (for migraines, e.g., Maxalt-MLT®) use ODTs to achieve rapid onset of action, crucial for treating acute pain episodes.
- ❖ **Gastrointestinal/Antiemetics:** Ondansetron ODT is highly effective for chemotherapy-induced nausea and vomiting, as it can be administered quickly without inducing further gagging or emesis.
- ❖ **Antihistamines and Allergies:** Used for rapid relief of acute allergic reactions.

Leading marketed products include Claritin® RediTabs (Loratadine), Maxalt-MLT® (Rizatriptan), and Zofran® ODT (Ondansetron), often leveraging patented technologies to optimize performance.

8. Future Directions and Conclusion

8.1. Targeted Innovations

The future of ODT technology lies in addressing current limitations through advanced science:

- ❖ **Sustained-Release ODTs:** Integrating taste-masked drug microparticles/pellets with controlled-release coatings into the ODT matrix, allowing for both rapid disintegration and prolonged drug effect.
- ❖ **Biologics and Macromolecules:** Exploring ODTs for the delivery of protein/peptide-based therapies, which are typically degraded in the GI tract, by exploiting the pre-gastric absorption route [18].
- ❖ **AI and Machine Learning (ML):** Utilizing computational tools to optimize formulation design by predicting the best blend of superdisintegrants, fillers, and compression parameters to achieve the optimal balance between hardness and disintegration time.

8.2. Conclusion

Orodispersible Tablets have successfully transitioned from a niche dosage form to a mainstream pharmaceutical solution, fundamentally changing drug administration for patient populations struggling with dysphagia. The core success of ODTs rests on the delicate balance achieved between superior mechanical integrity and ultra-rapid disintegration, facilitated by advanced formulation science, particularly the intelligent use of superdisintegrants and sophisticated manufacturing techniques like lyophilization and HME.

As the global geriatric population continues to grow and patient-centricity becomes the industry standard, ODTs—supported by emerging technologies like 3D printing and AI-driven optimization—will remain an area of intense research and commercial innovation, solidifying their role as a key strategy in modern drug delivery.

References

1. Aulton, M. E., & Taylor, K. (2017). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. Elsevier Health Sciences.
2. Sastry, S. V., Nyshadham, J. R., & Fix, J. A. (2000). Recent technological advances in oral drug delivery – a review. *Pharmaceutical Science & Technology Today*, 3(4), 138-145.
3. Food and Drug Administration (FDA). (2008). *Guidance for Industry: Orally Disintegrating Tablets*. Center for Drug Evaluation and Research (CDER).
4. Pahwa, R., Piplani, M., Sharma, P. C., Kaushik, D., & Nanda, S. (2010). Orally disintegrating tablets: Friendly to pediatrics and geriatrics. *Archives of Applied Science Research*, 2(2), 35-48.
5. Ivanovska, V., Rademaker, C. M., van Dijk, L., & Mantel-Teeuwisse, A. K. (2014). Pediatric drug formulations: a review of challenges and progress. *Pediatrics*, 134(2), 361-372.
6. Ashish, P., Harsoliya, M. S., Pathan, J. K., & Shruti, S. (2011). A review-Formulation of orally disintegrating tablet. *International Journal of Pharmaceutical & Biological Archives*, 2(2), 608-613.
7. Klancke, J. (2003). Dissolution testing of orally disintegrating tablets. *Dissolution Technologies*, 10(2), 6-8.
8. Dutta, P. K., & Dutta, J. (2016). Excipients for Orally Disintegrating Tablets: A Review. *Journal of Pharmaceutical Sciences and Research*, 8(8), 820.
9. Sharma, S., & Lewis, S. (2010). Taste masking technologies: a review. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2(2), 6-13.
10. Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandira, R. M. (2009). Fast dissolving tablet: An overview. *Journal of Chemical and Pharmaceutical Research*, 1(1), 163-177.
11. Mohanachandran, P. S., Sindhumol, P. G., & Kiran, T. S. (2011). Superdisintegrants: an overview. *International Journal of Pharmaceutical Sciences Review and Research*, 6(1), 105-109.
12. Gupta, A., Mishra, A. K., Gupta, V., & Bansal, P. (2010). Recent trends of fast dissolving tablet-an overview of formulation technology. *International Journal of Pharmaceutical & Biological Archives*, 1(1), 1-10.
13. Nagar, M., Nagar, M., & Chopra, V. (2011). Formulation and evaluation of mouth dissolving tablets of antipsychotic drugs. *International Journal of Research in Pharmacy and Chemistry*, 1(3), 483-496.
14. Seager, H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. *Journal of Pharmacy and Pharmacology*, 50(4), 375-382.
15. Khaled, S. A., Burley, J. C., Alexander, M. R., & Roberts, C. J. (2014). Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *International Journal of Pharmaceutics*, 461(1-2), 105-111.
16. Bi, Y., Sunada, H., Yonezawa, Y., Danjo, K., Otsuka, A., & Iida, K. (1996). Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. *Chemical and Pharmaceutical Bulletin*, 44(11), 2121-2127.
17. Bandari, S., Mittapalli, R. K., & Gannu, R. (2014). Orodispersible tablets: An overview. *Asian Journal of Pharmaceutics*, 2(1).
18. Al-Khattawi, A., & Mohammed, A. R. (2013). Compressed orally disintegrating tablets: excipients evolution and formulation strategies. *Expert Opinion on Drug Delivery*, 10(5), 651-663.