

Orodispersible Tablets: Patient Friendly Formulations in Pediatrics

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Abstract—The development of patient-friendly dosage forms has become a growing priority in pediatric pharmacotherapy due to challenges associated with swallowing conventional tablets and capsules. Orodispersible tablets (ODTs), also known as fast-dissolving or melt-in-mouth tablets, have emerged as an effective solution to enhance compliance, safety, and therapeutic efficacy in children. These formulations disintegrate rapidly in the oral cavity without water, offering advantages for pediatric, geriatric, and dysphagic patients.

Simultaneously, herbal medicine continues to play a vital role in pediatric healthcare, particularly when synthetic drugs pose higher risks of adverse effects. However, poor solubility, stability, and low bioavailability of herbal bioactives often limit their effectiveness. Nanotechnology-based delivery systems—such as nanoemulsions, liposomes, solid lipid nanoparticles, and nanocrystals—offer promising solutions by improving the solubility and absorption of phytoconstituents. Incorporating such nano-herbal systems into ODTs can further enhance patient compliance and therapeutic outcomes.

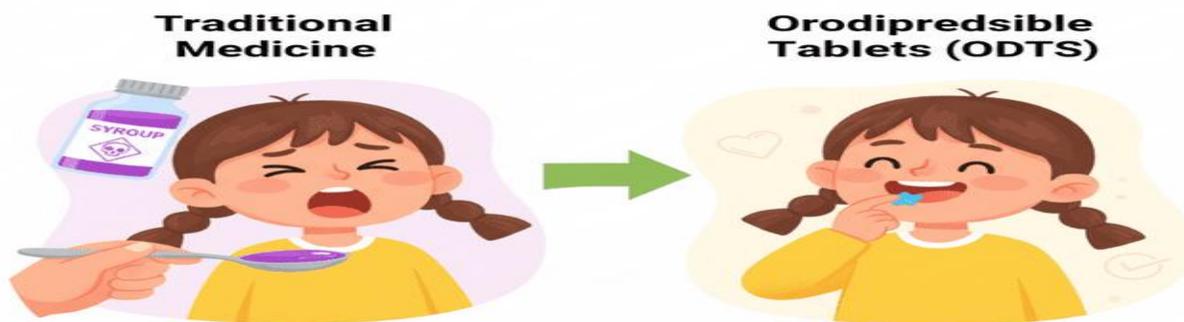
Despite these advancements, challenges remain in optimizing formulation methods, ensuring stability, achieving dose uniformity, and addressing regulatory concerns. Future directions include the integration of personalized medicine, microbiome-based therapies, and smart packaging technologies. The convergence of

nanotechnology and herbal ODTs represents a promising frontier in developing safe, effective, and patient-friendly formulations for pediatric use.

Index Terms—Orodispersible tablets, Pediatrics, Herbal medicine, Nanotechnology, Bioavailability, Pediatric drug delivery

I. INTRODUCTION

1.1 Background of Oral Drug Delivery in Pediatrics
Oral drug delivery is the most widely used route for medication administration owing to its convenience, safety, and cost-effectiveness. In pediatric practice, it is particularly favored because it avoids invasive methods such as injections, which are often associated with pain, fear, and poor acceptance among children. Liquid formulations such as syrups and suspensions are traditionally preferred in younger populations; however, they present stability issues, unpleasant taste, bulkiness during transportation, and the risk of dosing errors. Solid oral dosage forms, particularly tablets and capsules, remain the most stable and widely distributed formulations but are not always suitable for children due to age-specific physiological and behavioral constraints.



1.2 Challenges with Conventional Dosage Forms (Tablets, Capsules, Syrups)

Children, especially those below six years, face significant difficulties in swallowing conventional tablets and capsules, leading to poor acceptance and non-adherence. The large size, hard texture, and risk of choking are critical barriers. Syrups, though easier to administer, have their own limitations such as short

shelf-life, requirement of preservatives, and frequent dosing. Furthermore, issues of palatability due to bitterness or unpleasant drug taste remain a major hurdle in pediatric compliance. The need for water to ingest conventional formulations also poses challenges in emergency situations and in regions with limited access to clean drinking water.

CHALLENGES WITH CONVENTIONAL TABLETS



1.3 Importance of Patient Compliance in Pediatrics

Therapeutic success in pediatric patients is closely linked to compliance. Unlike adults, children depend entirely on caregivers for medication administration, and any resistance due to taste, difficulty in swallowing, or fear of choking can result in skipped doses or incomplete treatment. Poor compliance may

lead to therapeutic failure, disease progression, or the need for higher doses, which increases the risk of adverse drug reactions. Thus, the design of pediatric formulations must prioritize not only pharmacokinetics and stability but also ease of administration, palatability, and acceptability to ensure optimal therapeutic outcomes.

IMPROVED COMPLIANCE = HEALTHY CHILDREN



1.4 Emergence of Orodispersible Tablets (ODTs) as a Solution

Orodispersible tablets (ODTs), also known as fast-dissolving or melt-in-mouth tablets, have been developed to address the shortcomings of conventional pediatric dosage forms. These tablets disintegrate rapidly in the oral cavity, typically within 30–60 seconds, without the need for water. This

unique feature makes ODTs highly suitable for children, elderly patients, and individuals with dysphagia. They combine the stability and dose accuracy of solid dosage forms with the ease of administration and improved palatability of liquid formulations. Moreover, ODTs allow faster onset of action and reduce the risk of choking, making them highly patient-friendly in pediatric care.



1.5 Aim and Scope of the Review

The aim of this review is to provide a comprehensive overview of orodispersible tablets (ODTs) with an emphasis on their relevance in pediatric pharmacotherapy. The scope includes a detailed discussion of formulation considerations, excipients, and taste-masking strategies tailored for children. It will also explore manufacturing technologies, evaluation parameters, marketed pediatric ODTs, and regulatory perspectives. Furthermore, the review highlights current challenges, innovations such as nanotechnology-enabled ODTs, and future opportunities in personalized pediatric medicine. By consolidating current evidence, this article seeks to underline the significance of ODTs as patient-friendly formulations capable of bridging critical gaps in pediatric drug delivery.

II. ORODISPERSIBLE TABLETS (ODTs): AN OVERVIEW

2.1 Definition and Regulatory Descriptions (FDA, EMA, WHO)

The FDA defines orally disintegrating tablets as solid dosage forms that disintegrate rapidly—typically within seconds—when placed on the tongue, distinguishing them from chewable or conventional tablets.[1]

The European Pharmacopoeia (EMA) defines ODTs as uncoated tablets that disperse rapidly in the oral cavity, typically within three minutes.[2]

The WHO recognizes the oral route as the gold standard for pediatrics and mentions ODTs as innovative platforms overcoming swallowing difficulties and improving patient compliance

2.2 Characteristics and Essential Requirements of ODTs

ODTs must combine the stability and accurate dosing of solid forms with the ease of administration of liquid forms: they should disintegrate rapidly in the mouth, without water, and be safe, palatable, and easy to manufacture.[9,3]

Essential physical attributes include appropriate tablet size, weight, low friability, acceptable hardness, rapid wetting, fast disintegration, and chemical stability. Palatability—especially flavor and mouthfeel—is critical for pediatric use.[4]

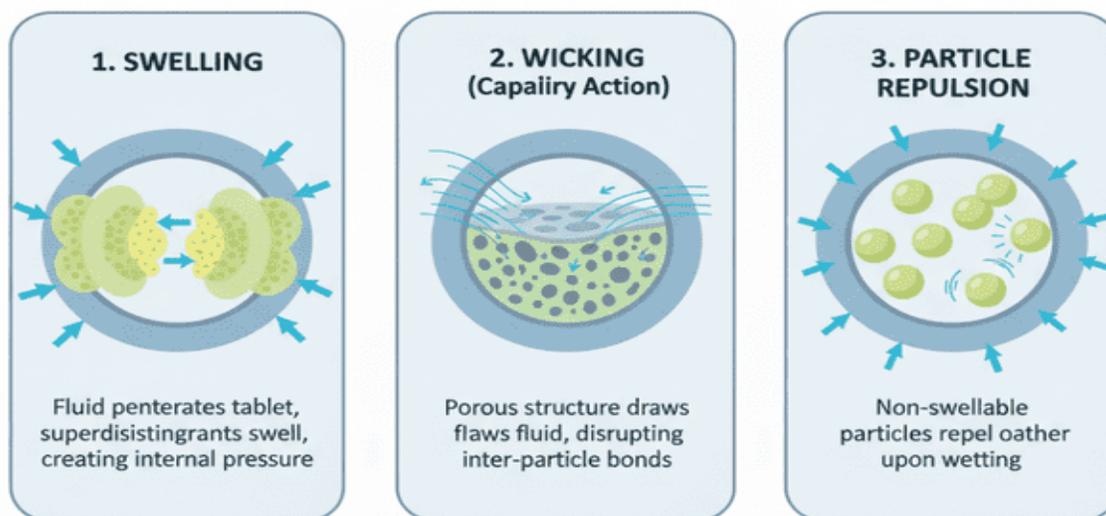
ESSENTIAL CHARACTERISTICS OF ODTs



2.3 Mechanism of Disintegration in the Oral Cavity
 Disintegration primarily depends on the action of superdisintegrants. Mechanisms include:
 Swelling, where penetration of fluid causes internal pressure that breaks the tablet apart.
 Wicking (porosity and capillary action), drawing fluid into the tablet to disrupt inter-particle bonds and disintegrate it.
 Particle/particle repulsive forces, where non-swellable particles repel each other upon wetting.

Heat of wetting (air expansion)—exothermic disintegration stress in certain materials.[6,7]
 A study evaluating wetting time, absorption ratio, and disintegration time revealed that the disintegration efficacy depends heavily on the type of disintegrant used. For instance, sodium citrate (osmotic mechanism) resulted in fastest wetting and disintegration versus slower performance with swellable disintegrants like sodium starch glycolate.[8]

MECHANISMS OF ODT DISINTEGRATION



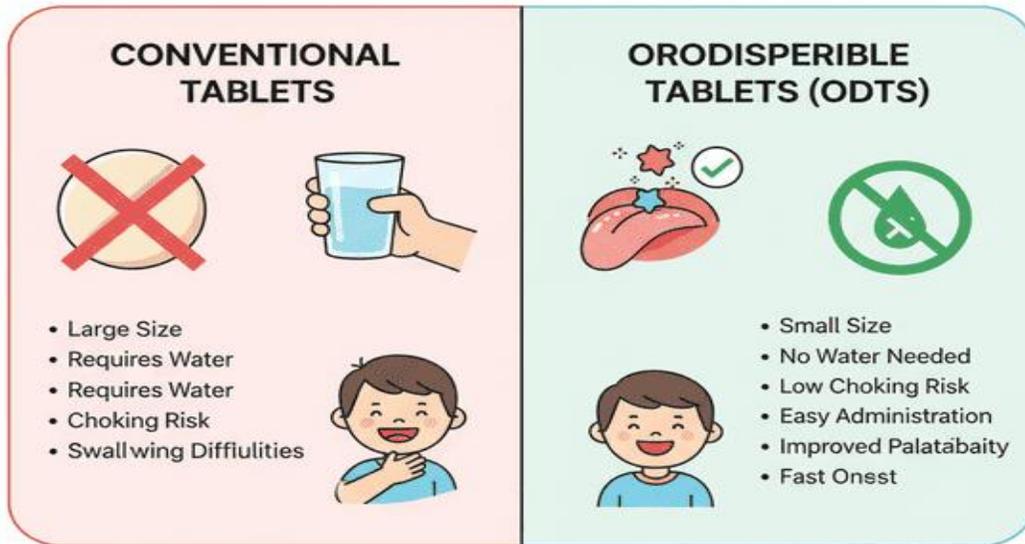
2.4 Comparison with Conventional Oral Dosage Forms

ODTs offer notable advantages over conventional tablets, capsules, and syrups: they are easier to administer (no water needed), reduce choking risk, provide accurate dosing, and ensure better stability and portability.

They also permit rapid onset of action due to fast disintegration and potential partial buccal absorption,

which may bypass first-pass metabolism and enhance bioavailability.[3,9]

Despite these benefits, ODTs have limitations: inflexible dosing—requiring multiple strengths, fragility that impacts handling, challenging taste masking, and strict storage requirements to maintain stability.[5,6]



2.5 Advantages of ODTs in Pediatric Practice

Ease of administration: Particularly beneficial for children with difficulty swallowing, ODTs dissolve rapidly in the mouth without water.

Improved compliance: Palatability, mouthfeel, rapid disintegration, and low choking risk make ODTs more acceptable to children and caregivers.

Mini-tablets for personalization: Mini-ODTs (4 mm for toddlers, up to 10 mm for adolescents) enable flexible dosing and are well-accepted even by neonates.

Potential for improved bioavailability: Fast disintegration and absorption via the oral mucosa may yield quicker therapeutic effects and higher systemic availability.

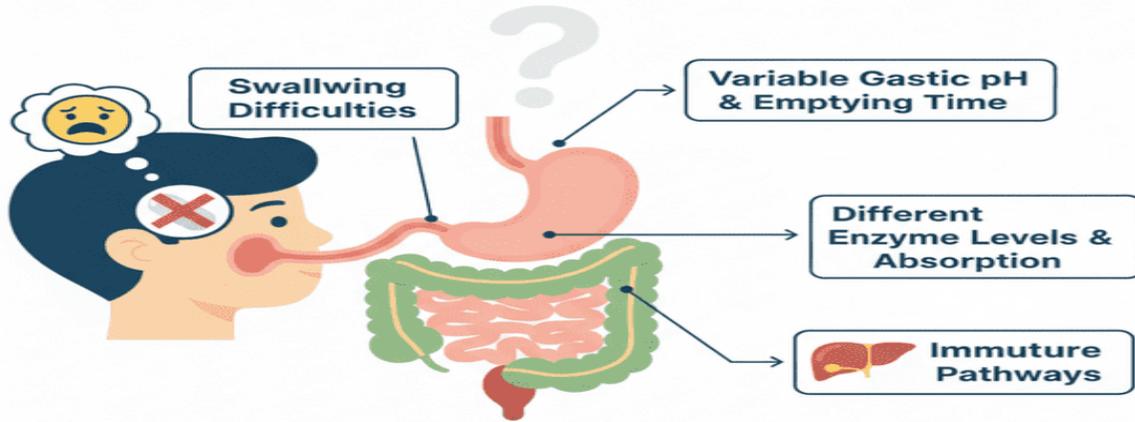
Avoids hospitalization and additional aids: ODTs allow safe home administration without professional support or water. [3,9,10,12]

III. PEDIATRIC DRUG DELIVERY: CHALLENGES AND REQUIREMENTS

3.1 Anatomical and Physiological Considerations in Children

Children undergo rapid developmental changes, affecting pharmacokinetics and pharmacodynamics significantly. Age-dependent variations in gastrointestinal pH, gastric emptying time, digestive enzyme production, and metabolic pathways influence drug absorption and bioavailability.[13] Additionally, differences in body composition (e.g., body fat and water percentage), organ maturation, and transporter/enzyme expression add complexity to pediatric dosing regimens.[14]

PEDIATRIC ANATOMICAL CONSIDERATIONS



Age-Dependent Changes Affecting Absorption & Metabolism

3.2 Dysphagia and Swallowing Difficulties

Swallowing solid dosage forms presents a significant barrier in young children. The lack of coordination and underdeveloped swallowing mechanisms can cause choking, aspiration, or outright refusal of medication.

Oropharyngeal dysphagia (OPD) in children—including conditions like cerebral palsy, anatomical anomalies (e.g., cleft palate), prematurity, and reflux disorders—exacerbates these challenges and heightens the risk of morbidity.[15]

DYSPHAGIA AND SWALLOWING DIFFICULTIES IN CHILDREN



3.3 Taste and Palatability Issues

Unpleasant taste remains one of the most frequent reasons for non-compliance in pediatric patients. Nearly 90% of pediatricians in the US report that bitter or off-putting flavors significantly hinder treatment adherence. Liquid formulations often require extensive use of sweeteners, flavoring agents, and colorants to mask undesirable flavors. However, taste preference varies by age and individual genetics, making effective masking a persistent challenge.[17,19,29]

3.4 Dose Accuracy and Flexibility in Pediatrics

Pediatric dosing often necessitates high precision and flexibility due to wide-ranging body weights and age-related metabolic differences. Liquid dosage forms (syrups, solutions) are commonly used to allow adjustable dosing, but they come with drawbacks such as dosing errors, measurement inaccuracies, stability concerns, and portability limitations.[27,28,29] Compounding adult drugs into pediatric doses introduces potential safety risks due to inconsistent quality control.[28]

3.5 Safety Concerns and Risk of Choking

Safety is a prime concern in pediatric formulations. Large or hard tablets may lead to choking or aspiration. Moreover, excipients used to improve stability, taste, or appearance must be carefully evaluated for pediatric toxicity. Agents like benzyl alcohol, propylene glycol, and some preservatives have been associated with adverse effects in neonates and infants when used in inappropriate amounts. [16,17] Ensuring excipient safety across developmental stages is essential.

3.6 Need for Innovative Pediatric-Friendly Formulations

Given these multifaceted challenges—ranging from anatomical and physiological factors to taste, dosage flexibility, and safety—there is a critical need for innovative, age-appropriate dosage forms. Orally dispersible formats such as ODTs, mini-tablets, oral films, and multiparticulate systems offer promise by enhancing swallowability, enabling dose flexibility, and improving patient compliance.[19,30,31] Nonetheless, improvements in formulation design, regulatory guidance, and manufacturing are required

to enable widespread adoption of truly child-centered medications.[18,19,32]

IV. FORMULATION CONSIDERATIONS FOR PEDIATRIC ODTs

4.1 Selection of Active Pharmaceutical Ingredients (APIs)

The choice of API for pediatric ODTs is a critical factor in formulation success. Solubility and stability play decisive roles in determining the bioavailability of the drug when administered in orodispersible form. Water-soluble APIs generally provide rapid onset of action, whereas poorly soluble drugs may require particle size reduction, solid dispersion, or nanotechnology-based approaches to achieve adequate dissolution rates. Stability during storage is another challenge, especially for moisture-sensitive compounds.

Taste remains a major barrier in pediatric compliance since many APIs (e.g., antibiotics, antipyretics, and anti-epileptics) have inherently bitter or metallic flavors. Therefore, early-stage assessment of taste acceptability and potential for masking is essential. Pediatric-specific dosing also requires precise adjustment, as children's pharmacokinetic profiles differ significantly from adults. APIs intended for ODTs must therefore allow safe miniaturization into lower strengths or divisible/multiple-unit dosing systems.[17]

4.2 Excipients in ODT Formulation

Superdisintegrants-

Superdisintegrants facilitate rapid disintegration of ODTs in the oral cavity, usually within 30–60 seconds. Commonly used agents include croscopovidone, sodium starch glycolate, and croscarmellose sodium. These work through mechanisms such as swelling, capillary action, and wicking, enabling quick breakdown without excessive bulk or grittiness.

Fillers and Diluents-

Fillers provide mechanical strength and enhance palatability. Mannitol is particularly popular due to its negative heat of solution, imparting a cooling sensation and pleasant mouthfeel. Microcrystalline cellulose (MCC) contributes to compressibility and stability. Other options include lactose, sorbitol, and isomalt.

Binders and Lubricants-

Binders (e.g., polyvinylpyrrolidone, starch paste, hydroxypropyl methylcellulose) provide structural integrity, while lubricants such as magnesium stearate reduce tablet friction during compression. However, excessive lubricant may delay disintegration, which is undesirable in ODTs.

Flavoring Agents, Sweeteners, and Taste-Masking Agents

Children's formulations must prioritize palatability. Natural and artificial flavorings (orange, strawberry, vanilla) are commonly used. Sweeteners such as

aspartame, sucralose, and xylitol improve taste acceptability. In some cases, taste-masking polymers (e.g., Eudragit®) or cyclodextrin complexes are added to reduce bitterness.

Coloring Agents and Preservatives-

Coloring improves acceptability, but only pediatric-safe dyes approved by regulatory agencies should be employed. Preservatives (e.g., parabens, benzoates) may be required in certain formulations but must be carefully considered for safety in neonates and infants.[20]



4.3 Pediatric Safety of Excipients

Excipients considered inert in adults may not be safe for children due to immature metabolic and detoxification pathways. For instance, propylene glycol, benzyl alcohol, and sorbitol have been linked to toxicity in neonates. The FDA's Inactive Ingredient Database (IID) and the Safety and Toxicity of Excipients for Paediatrics (STEP) database provide essential guidance for evaluating excipient acceptability in children. Manufacturers must carefully balance functionality with safety, considering dose thresholds and cumulative exposure across multiple medicines.

4.4 Strategies for Taste Masking

Taste masking is vital in pediatric ODTs to ensure compliance:

Polymeric Coating – APIs can be coated with pH-dependent polymers (e.g., Eudragit® E) to prevent taste perception in the mouth.

Complexation – Cyclodextrin complexes encapsulate bitter drugs, reducing exposure of the API to taste buds.

Ion-Exchange Resins – APIs bound to resins are released in the stomach but not in saliva, reducing bitterness (e.g., resinate technology for antibiotics).

Flavoring and Sweetening – Effective use of intense sweeteners (aspartame, sucralose) and child-friendly flavors enhances acceptability.

Microencapsulation/Nanoparticles – Advanced technologies reduce drug particle exposure to taste buds while maintaining rapid disintegration.[21]



TASTE-MASKING STRATEGIES

V. TECHNOLOGIES FOR MANUFACTURING ODTs

5.1 Conventional Methods

Direct

Direct compression is the most widely used and cost-effective method for manufacturing ODTs. It involves blending APIs with excipients (e.g., superdisintegrants, diluents, lubricants) and compressing them into tablets. The process is simple, scalable, and compatible with existing tablet manufacturing infrastructure. However, it is limited by the need for APIs and excipients with adequate flowability and compressibility.

Molding-

Molding involves dissolving or dispersing the drug in a solvent (usually water or ethanol) and molding it into

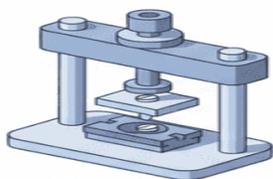
Compression-

tablets, followed by drying. Molded ODTs are porous and rapidly soluble but have low mechanical strength, making packaging and handling more challenging.

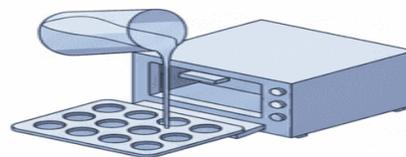
Spray Drying-Spray drying creates porous particles by atomizing a drug-excipient solution into hot air. The resulting powder is compressible and forms rapidly dispersing tablets. Spray drying allows taste masking and solubility enhancement but involves higher production costs.

Freeze-Drying (Lyophilization)-Freeze-drying produces highly porous tablets that dissolve in seconds upon contact with saliva. A drug solution or suspension is frozen and sublimated under vacuum, leaving behind a fragile, sponge-like structure. Lyophilized ODTs (e.g., Zydys®) show excellent patient compliance but require specialized packaging to protect against fragility and moisture sensitivity.

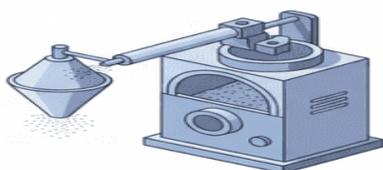
CONVENTIONAL ODT MANUFACTURING METHODS



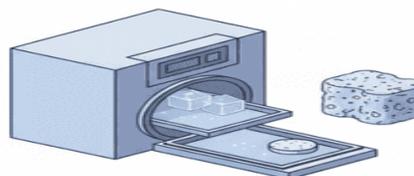
1. Direct Compression



2. Molding



3. Spray Drying



4. Freeze-Drying (Lyophilization)

5.2 Novel and Patented Technologies

Zydis® Technology- Developed by R.P. Scherer (Catalent), Zydis® tablets are produced by freeze-drying a drug solution/suspension in preformed blisters. They disintegrate within 2–5 seconds. Advantages include rapid dispersion and suitability for heat-sensitive APIs. Limitations are high cost, moisture sensitivity, and low drug-loading capacity.

Orasolv® and **Durasolv®**- Orasolv® (Cima Labs) uses effervescent disintegration with taste-masked particles compressed at low force. Durasolv® is a modification using conventional tableting at higher compression force for improved mechanical strength. Durasolv® allows smaller, stronger tablets but has limited drug loading (<500 mg).

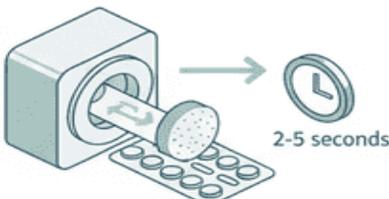
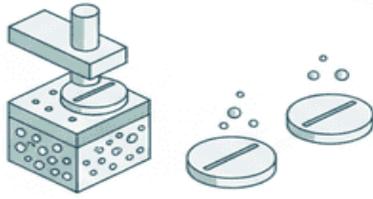
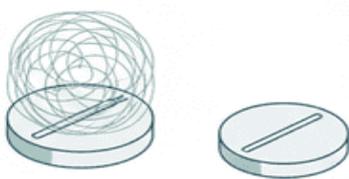
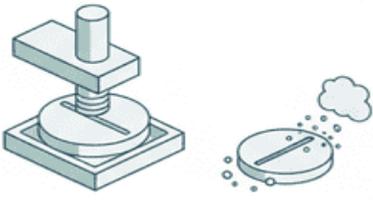
WOWTAB®- Developed by Yamanouchi Pharma, WOWTAB®

(“Without Water” tablet) uses a combination of highly soluble saccharides and insoluble excipients to balance strength and fast disintegration. It is moisture sensitive and requires protective packaging.

Flashtab® and **FlashDose®**- **Flashtab®** (Ethypharm) involves compressing coated drug microgranules with disintegrants and excipients to yield robust ODTs. **FlashDose®** uses cotton candy process technology, where flash-melted sugar is spun into a floss matrix that is then compressed. This provides rapid disintegration and a sweet taste but requires specialized equipment.[22]

Advatab®, Lyoc®, and Pharmaburst® Systems- **Advatab®** integrates taste-masked drug particles into a tablet with rapid disintegration. **Lyoc®** uses freeze-drying of drug suspensions, similar to Zydis®, but allows higher drug loading. **Pharmaburst®** is a co-processed excipient system enabling rapid disintegration via direct compression.

NOVEL AND PATENTED ODT TECHNOLOGIES

<p>ZYDIS® TECHNOLOGY </p>  <p>FAST DISSOLUTION Ultra-porous tablet, fast disintegration, enhanced patient compliance</p>	<p>ORASOLV®/DURASOLV® </p>  <p>FAST DISSOLUTION Masked drug particles, compressed effervescent granules, pricked the sponges and enhanced patient compliance</p>
<p>WOWTAB® </p>  <p>LIGHT COMPRESSION Special sugar springer include in string the preferred of light compression enhanced patient compliance</p>	<p>Flashtab®/FlashDose® </p>  <p>FAST DISSOLUTION Drug microgranules, to within all compression compressed on light powder FAST DISPERSION</p>

5.3 Comparative Analysis of Technologies

Technology	Advantages	Limitations	Cost/Feasibility
Direct Compression	Simple, low cost, scalable	Limited to APIs with good compressibility	Low
Molding	Good mouthfeel, rapid disintegration	Poor mechanical strength	Low–Moderate
Spray Drying	Solubility enhancement, taste masking	High processing cost, stability issues	Moderate–High
Freeze-Drying (Zydis®, Lyoc®)	Ultra-fast disintegration, good for heat-sensitive drugs	Fragile tablets, expensive packaging	High
Orasolv®/Durasolv®	Improved taste masking, conventional tableting	Limited drug load	Moderate
WOWTAB®	Balanced strength and disintegration	Moisture sensitive	Moderate
Flashtab®/FlashDose®	Fast dispersion, improved palatability	Special equipment needed	High
Advatab®, Pharmaburst®	Direct compression, robust	Excipients may be costly	Moderate

VI. EVALUATION OF ORODISPERSIBLE TABLETS

6.1 General Tablet Evaluation Tests

Although ODTs have unique features, they must comply with standard tablet quality assessments to ensure uniformity, strength, and accuracy:

Weight Variation Test – Ensures uniformity of dosage units. According to pharmacopeial standards (USP, BP, IP), the percentage deviation allowed depends on tablet weight. Variability beyond limits indicates poor die filling or mixing.

Hardness Test – Determines the mechanical strength of ODTs. Unlike conventional tablets, ODTs require a

balance between sufficient strength to withstand handling and friability, while still ensuring rapid disintegration. Typically, hardness is lower than standard tablets.

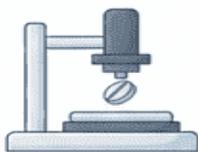
Friability Test – Conducted using a Roche friabilator to assess resistance to abrasion and breakage. ODTs are prone to friability due to porosity, especially when manufactured via lyophilization. A friability loss of <1% is generally acceptable.

Content Uniformity – Ensures each tablet contains the intended API dose within pharmacopeial limits (85–115% of label claim). This is critical for pediatric dosing, where under- or overdosing can have serious consequences.

GENERAL TABLET EVALUATION TESTS



WEIGHT VARIATION



HARDNESS TEST



FRIABILITY TEST



**CONTENT
UNIFORMITY**

6.2 Specific Tests for ODTs

Wetting Time – Measures the time required for a tablet to become completely wet in a small volume of simulated saliva. Short wetting times (10–30 sec) indicate good patient acceptability.

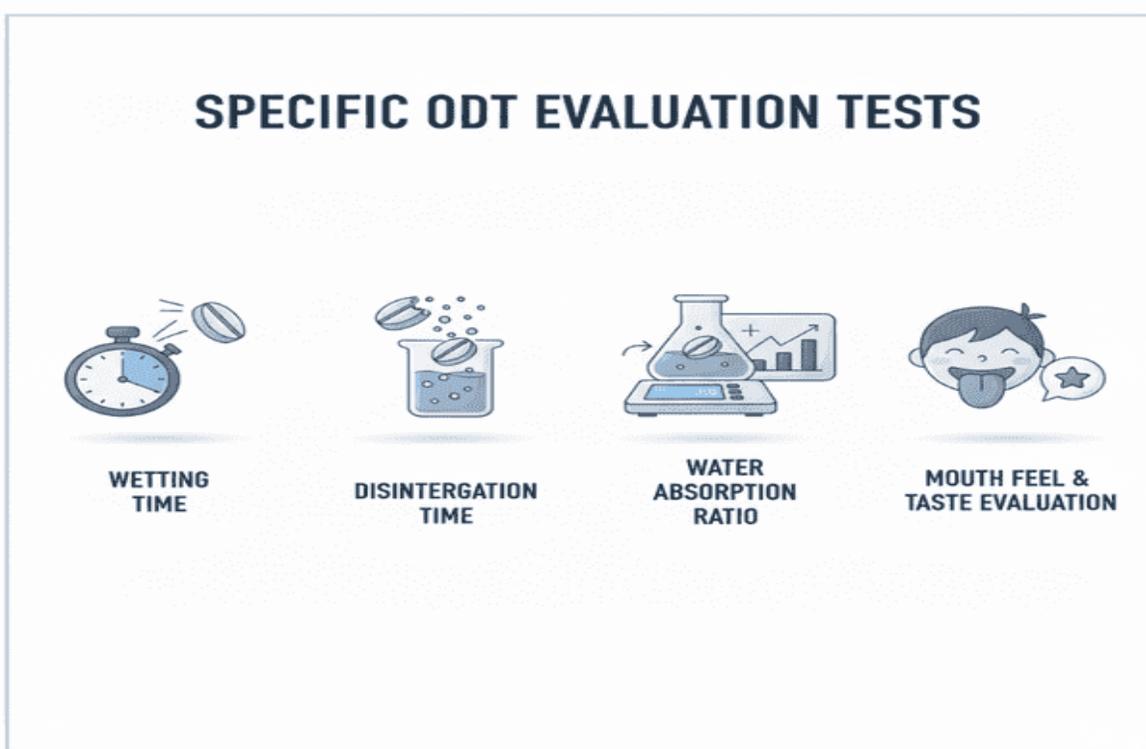
Disintegration Time (In Vitro and In Vivo) – ODTs must disintegrate rapidly without water, ideally within 30 seconds (per European Pharmacopoeia). In vivo disintegration is often faster due to tongue and saliva interaction.

Water Absorption Ratio (R) – Indicates the capacity of the tablet to absorb water, calculated by weight difference before and after water absorption. A high R value correlates with rapid disintegration.

Mouth Feel Evaluation – Assesses patient-perceived texture, grittiness, or irritation. Pediatric patients prefer smooth, non-gritty formulations. Mannitol and sorbitol are often used to improve mouthfeel.

Taste Evaluation – Since palatability strongly affects compliance, taste masking must be evaluated. This can be done using electronic taste sensing systems (e-tongue) or sensory panels with ethical considerations in pediatrics.[21]

Dissolution Studies – In vitro dissolution testing ensures rapid drug release and predicts bioavailability. Methods include USP Apparatus 2 (paddle method) or modified dissolution setups with small volumes mimicking saliva.



6.3 In Vivo Evaluation and Bioequivalence Studies in Pediatrics

In vivo evaluation is essential for confirming disintegration, dissolution, and absorption performance in real conditions. Pediatric in vivo testing poses ethical and methodological challenges; thus, surrogate models such as adult volunteers or in silico simulations are often employed initially.

Pharmacokinetic Studies – Assess parameters such as C_{max} , T_{max} , and AUC to compare ODTs with

conventional formulations. Faster T_{max} is usually observed with ODTs due to pre-gastric absorption.

Bioequivalence Studies – Regulatory agencies (FDA, EMA) require demonstration of bioequivalence for ODTs compared to reference listed drugs. In children, such studies must minimize invasiveness while ensuring accurate sampling.

Patient-Centered Outcomes – Compliance, palatability, ease of use, and caregiver feedback are crucial endpoints for pediatric ODTs, beyond traditional pharmacokinetics.[17]

VII. CLINICAL APPLICATIONS OF ODTs IN PEDIATRICS

7.1 Use in Common Pediatric Conditions

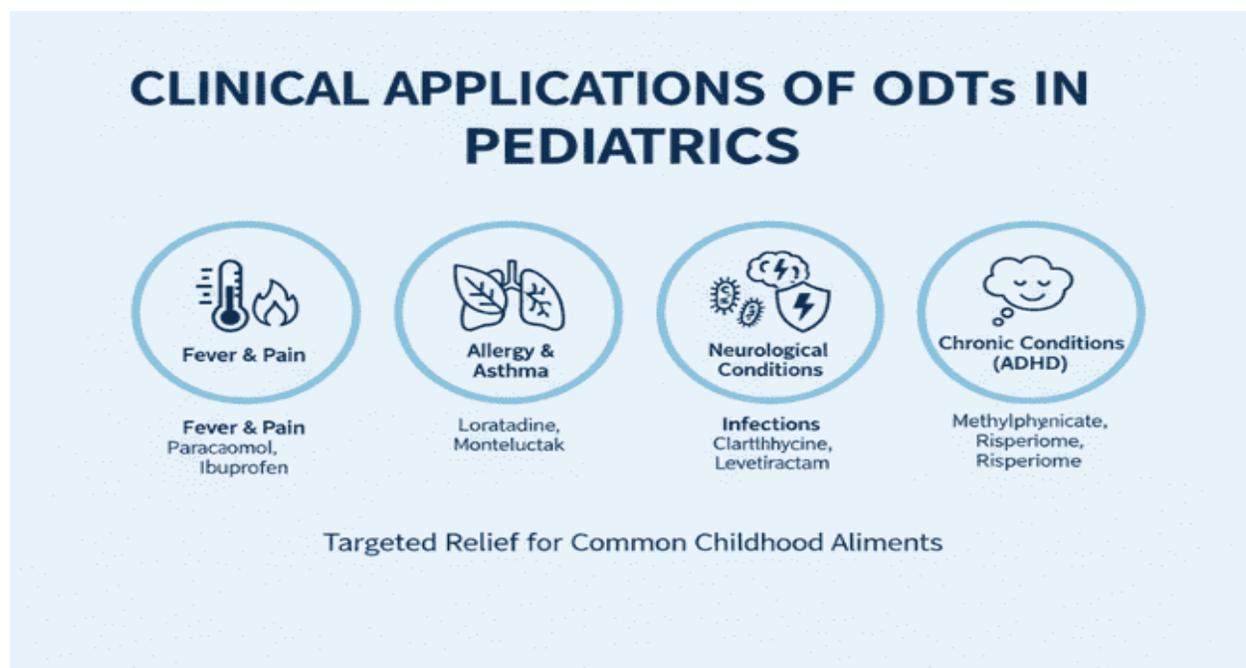
Fever and Pain-Antipyretics such as paracetamol (acetaminophen) and analgesics like ibuprofen are frequently prescribed in children. ODT formulations improve compliance in children with fever or pain who cannot swallow conventional tablets or refuse bitter syrups. Studies have demonstrated that ibuprofen ODTs are bioequivalent to liquid formulations, with the added advantage of portability and dosing convenience.

Allergy and Asthma-ODTs are widely used for allergic rhinitis and asthma-related conditions. Antihistamines such as loratadine ODT (Claritin RediTabs®) and cetirizine ODT (Zyrtec-D®) offer rapid onset and child-friendly dosing. Montelukast ODT (Singulair®) is available in 4 mg and 5 mg doses specifically for pediatric asthma, with demonstrated efficacy in improving symptoms and treatment adherence.

Neurological Conditions (Epilepsy, Seizure Disorders)-

Children with epilepsy often require long-term therapy, where compliance is crucial. ODT formulations of lamotrigine (Lamictal ODT®) and levetiracetam have been introduced to improve administration in pediatric patients with dysphagia or poor cooperation. These formulations ensure accurate dosing and reduce caregiver stress.

Infections (Antibiotics, Antivirals)- Certain pediatric antibiotics, such as clarithromycin ODT (Klacid® OD), have been developed to improve palatability and compliance, particularly in respiratory tract infections. Antiviral agents like oseltamivir ODTs are under development for influenza treatment in children to avoid liquid formulation stability issues. **Chronic Conditions (ADHD, Psychiatric Disorders)-** ODTs are increasingly used in psychiatric and behavioral conditions where swallowing difficulties or compliance barriers exist. Methylphenidate ODT (Cotempla XR-ODT®) is approved for ADHD in children aged 6–17 years, providing extended-release properties with convenient administration. Similarly, risperidone ODT (Risperdal M-Tab®) is used for irritability in autism and other psychiatric conditions in pediatric patients.[23]



7.2 Nutraceuticals and Herbal ODTs in Children

Beyond pharmaceuticals, nutraceuticals and herbal supplements are increasingly being developed as ODTs for pediatric populations. Examples include

multivitamin ODTs, vitamin D and calcium ODTs, and herbal-based formulations such as echinacea or ginger ODTs for immunity and digestive health. These products improve compliance compared to syrups or

chewables and are particularly beneficial for children requiring long-term supplementation. While evidence

is still limited, ODT-based nutraceuticals have potential in preventive pediatric health.



7.3 Marketed Pediatric ODT Products (Global Examples)

Drug / Product	Indication	Brand (Region)
Paracetamol ODT	Fever, pain	Calpol Fastmelts® (UK, India)
Ibuprofen ODT	Fever, pain	Nurofen Meltlets® (Europe)
Loratadine ODT	Allergy	Claritin RediTabs® (US, EU)
Cetirizine ODT	Allergy	Zyrtec-D® (US)
Montelukast ODT (4 mg, 5 mg)	Pediatric asthma, allergies	Singulair® (Global)
Lamotrigine ODT	Epilepsy	Lamictal ODT® (US, EU)
Clarithromycin ODT	Infections	Klacid® OD (Asia, EU)
Methylphenidate XR-ODT	ADHD	Cotempla XR-ODT® (US)
Risperidone ODT	Psychiatric disorders	Risperdal M-Tab® (Global)
Multivitamin & Calcium ODTs	Nutritional supplementation	Various brands (Global nutraceuticals)

VIII. REGULATORY AND SAFETY PERSPECTIVES

8.1 Regulatory Definitions and Guidelines (FDA, EMA, ICH)

The development of ODTs for pediatric populations is guided by multiple regulatory authorities.

FDA defines ODTs as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within seconds, when placed upon the tongue". EMA specifies that ODTs must disintegrate in less than 3 minutes, though most marketed products disintegrate within 30 seconds.

ICH E11(R1) provides a harmonized framework for clinical investigation of pediatric medicines,

emphasizing appropriate formulation development, safety, and ethical standards.

8.2 Pediatric Investigation Plans (PIPs)

In the European Union, a Pediatric Investigation Plan (PIP) is mandatory for new medicines or new indications, routes, or formulations of existing

medicines intended for children. The PIP ensures that pediatric-specific studies are conducted early in drug development. ODTs are often prioritized in PIPs due to their patient-friendly nature. Non-compliance with PIP requirements can result in marketing authorization delays or denials.



8.3 Biopharmaceutics Classification System (BCS) and ODT Relevance

The BCS classification (Classes I–IV) strongly influences ODT formulation strategies.

BCS Class I drugs (high solubility, high permeability) are ideal candidates for ODTs as they rapidly dissolve in saliva and are absorbed in the GI tract.

BCS Class II drugs (low solubility) require solubility enhancement techniques (nanoparticles, solid dispersions) in ODTs.

BCS Class III and IV drugs present additional challenges due to permeability and solubility limitations.

Understanding the interplay between BCS classification and ODT performance helps streamline regulatory approval by predicting bioequivalence and in vivo outcomes.[24]

8.4 Labeling Requirements for Pediatric Medicines

Regulatory agencies emphasize clear and age-appropriate labeling for pediatric formulations. Labels must include:

Pediatric dosage forms and age-specific dosing instructions.

Warnings regarding choking hazards.

Information on excipients with known safety concerns in children (e.g., aspartame, benzyl alcohol).

Special instructions for administration without water.

The Pediatric Research Equity Act (PREA, US) and EU Paediatric Regulation (2006/1901/EC) mandate pediatric-specific labeling to ensure safe and effective use in children.

8.5 Safety Assessment of Excipients in Children

Excipients generally considered safe in adults may pose risks in children due to differences in metabolism and organ maturity.

Inactive Ingredient Database (IID, FDA) provides maximum safe levels of excipients for pediatric populations.

Examples of concern include:

Benzyl alcohol → linked to "gassing syndrome" in neonates.

Propylene glycol → causes hyperosmolality in infants.
Aspartame → contraindicated in phenylketonuria (PKU).

Pediatric ODT development requires careful excipient risk-benefit analysis and justification.[25]



8.6 Ethical Considerations in Pediatric Trials

Conducting clinical trials in children raises ethical challenges:

Informed Consent & Assent – Parents/guardians must provide consent; children may give assent depending on age and maturity.

Minimization of Risk – Trial design must reduce invasive procedures (e.g., sparse sampling PK studies).

Age-Appropriate Formulations – Trials should test formulations intended for actual pediatric use (e.g., ODTs vs tablets).

Global Harmonization – ICH E11 encourages alignment across regions to reduce redundant trials and ensure equitable pediatric drug development.[26]

IX. CURRENT MARKET TRENDS AND INDUSTRY INSIGHTS

9.1 Global market size and growth of ODTs

Multiple analysts report robust double-digit growth for ODTs through the next decade, though absolute dollar estimates vary by methodology. Recent reports estimate the 2024–2025 global ODT market at roughly USD 10–22 billion, projecting ~8–12% CAGR to ~USD 30–64 billion by 2034–2035. Discrepancies reflect scope (Rx vs OTC), therapeutic mix, and technology licensing. Overall drivers include pediatric and geriatric demand, taste-masking advances, and CDMO platforms.

Pediatric relevance: oral solid forms remain the dominant route in children, reinforcing ODT uptake for age-appropriate formulations.



9.2 Pediatric pharmaceutical market needs

Key pediatric needs shaping ODT pipelines include: (i) age-appropriate palatability and mouthfeel; (ii) flexible, accurate dosing; (iii) safe excipients; and (iv) ease of administration without water—critical for home and school settings. Recent pediatric drug-delivery reviews and industry briefs highlight persistent formulation gaps and the opportunity for ODTs to improve adherence.[31,32]

9.3 Key pharmaceutical companies in ODT development

The ODT space blends originator pharma, technology holders, and CDMOs:

Catalent (Zydis®): freeze-dried ODT platform; >20 launched products across ~60 countries; widely used for taste-sensitive pediatric APIs.

Adare Pharma Solutions (AdvaTab®; Microcaps® taste-masking): direct-compression ODTs; active

collaborations for next-gen manufacturing (e.g., 3D printing).

SPI Pharma (Pharmaburst® 500): co-processed ODT excipient system used in dozens of commercial products; enables fast disintegration via direct compression.

Ethypharm (Flashtab®, Lyoc®/Pharmalyoc): lyophilized and compression-based ODT technologies; widely referenced in ODT manufacturing literature.[36]

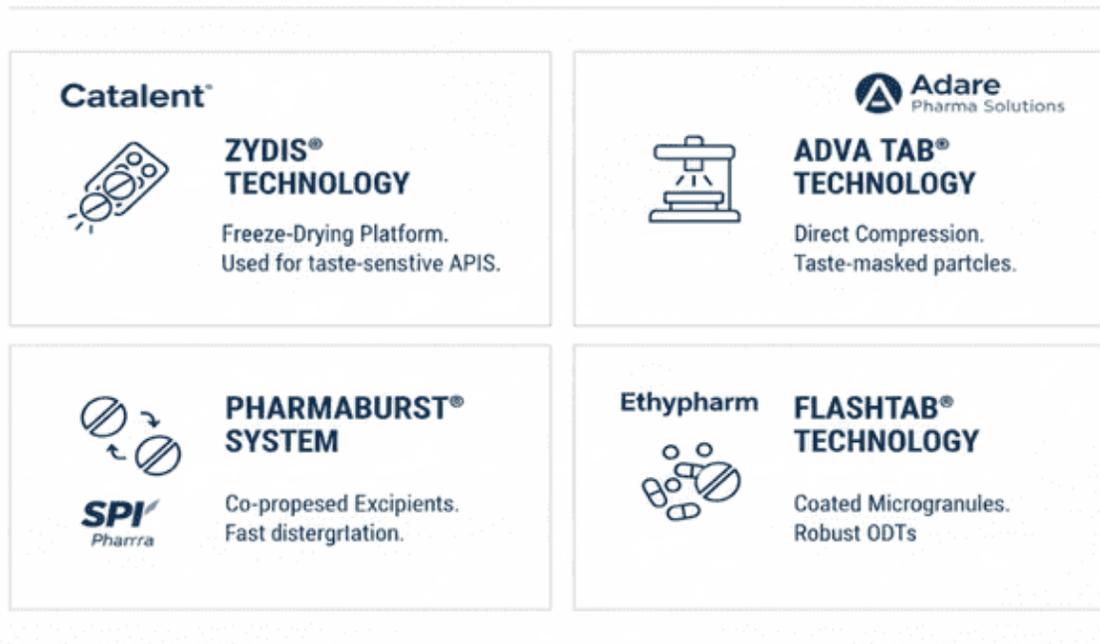
CIMA Labs legacy tech (OraSolv®, DuraSolv®): effervescent and non-effervescent direct-compression ODTs; foundational IP referenced across later filings.

Astellas/Yamanouchi (WOWTAB®): sugar-moldability approach enabling robust, fast-disintegrating tablets; further evolved to WOWTAB-DRY.[11]

Biovail/Fuisz (FlashDose® “cotton-candy” process): shear-form matrix spun to create highly porous ODTs.[33]

KEY PHARMACEUTICAL COMPANIES IN ODT DEVELOPMENT

Leading Platforms & Their Innovators



Driven by Pediatric & Geriatric Demand, and Continuous Innovation

9.4 Patent landscape of ODT technologies

The ODT patent estate spans lyophilization, direct compression with co-processed excipients, effervescent systems, and shear-form matrices. Illustrative (non-exhaustive) entries you can cite in a table:

Platform exemplars:

Zydis® (freeze-drying; multiple families since the 1990s). Secondary literature and filings broadly document process elements and constraints (e.g., cost/throughput trade-offs).

OraSolv®/DuraSolv® (CIMA): direct compression; effervescence or robust tablet matrices. [34]

Pharmaburst® (SPI): co-processed polyol excipient; U.S. patents including 7,118,765; later disclosures in ODT excipient filings.

WOWTAB® (Astellas/Yamanouchi): low/high-moldability saccharides; U.S./AU families from late 1990s–2000s.

FlashDose®/“cotton-candy” (Fuisz/Biovail): spun floss matrices enabling rapid disintegration.[35]

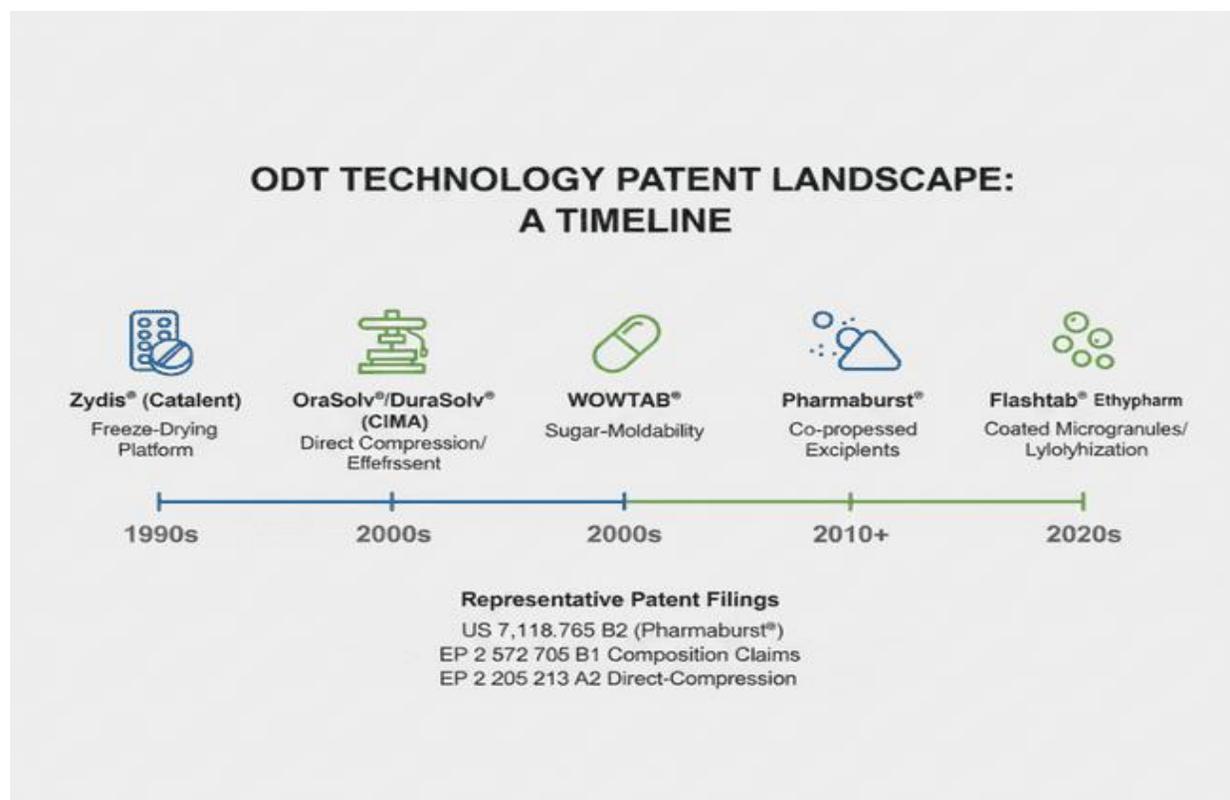
Lyoc®/Pharmalyoc (Ethypharm/Pharmalyoc): emulsion-based lyophilization variant; economic limitations noted vs Zydis.[36]

Recent representative filings:

EP2572705B1 “Orodispersible tablets” (composition/process claims for palatability and mechanical strength via conventional methods).

EP2205213A2 (direct-compression ODTs with calcium silicate and high diluent load).

Assorted Ethypharm assignments (low-dose orodispersible opioids, etc.), illustrating continued incremental innovation.



9.5 Economic aspects and cost-effectiveness

Economic value of ODTs in pediatrics arises from

- (i) higher adherence → fewer treatment failures
- (ii) lower administration burden for caregivers/health systems
- (iii) potential bioequivalence with improved patient-reported outcomes. Formal pharmacoeconomic data are still emerging, but disease-specific models and HTA-style analyses support value when ODTs improve adherence or reduce waste:

Psychiatry:

model-based evaluation found olanzapine ODT cost-effective vs alternatives in Morocco (first-line schizophrenia), highlighting ODTs' potential to reduce overall costs via adherence/relapse impacts.[37]

Gastroenterology:

budesonide ODT (eosinophilic esophagitis) showed cost-effectiveness vs no treatment in Austria and other settings.[38]

Manufacturer economics:

lyophilization (e.g., Zydis/Lyoc) can carry higher COGS and specialized packaging vs direct-

compression platforms (AdvaTab/Pharmaburst), but may unlock differentiation (very fast disintegration, fragile-patient suitability). Many sponsors deploy ODTs for lifecycle management (patent/market exclusivity extensions) or label expansions into pediatric age bands.[34]

X. FUTURE DIRECTIONS AND INNOVATIONS

10.1 Nanotechnology-enabled ODTs

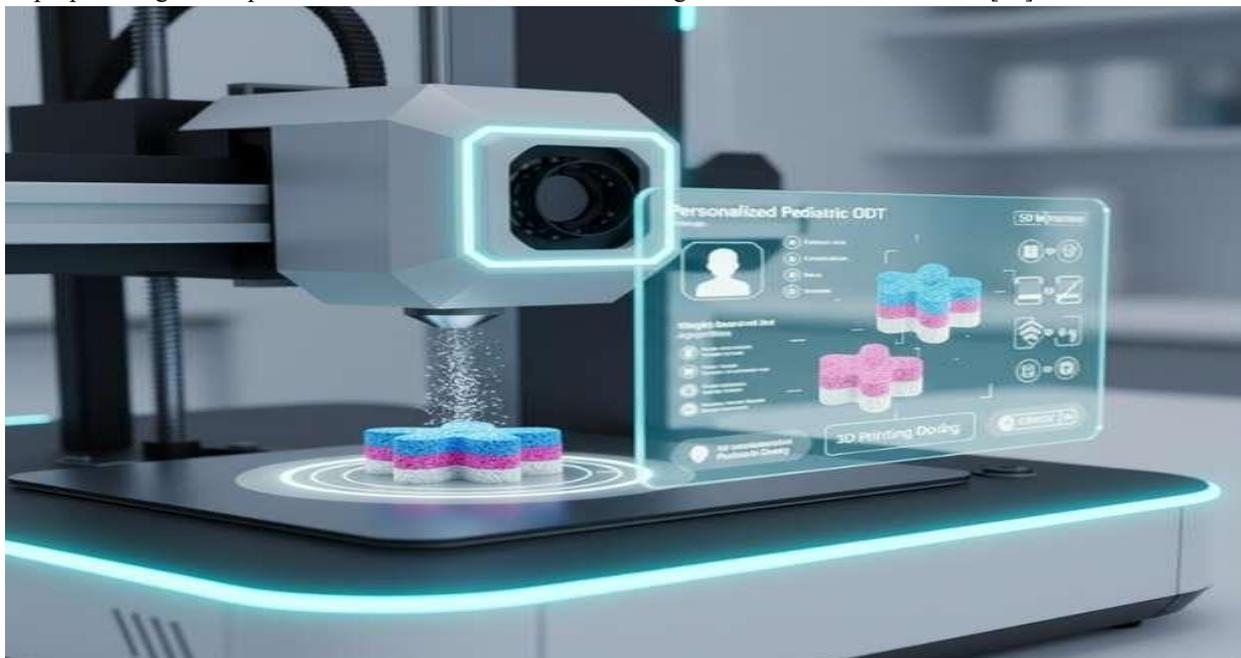
Platforms. Incorporating nanoemulsions, liposomes, nanocrystals, and solid lipid nanoparticles (SLNs) into ODT matrices can boost apparent solubility, dissolution, and mucosal residence—especially for BCS II/IV and many bitter herbal actives. SLNs/NLCs protect labile phytoconstituents, enable taste-masking via encapsulation, and can be spray-dried or lyophilized into ODT-ready powders.[39,40] Use-cases. Poorly soluble APIs (e.g., anti-infectives, anticonvulsants) and botanicals (polyphenols, terpenoids) are candidates for nano-enabled ODTs; barriers include long-term physical stability, scale-up with QbD/CMC control, and pediatric excipient safety margins.[41]



10.2 3D printing of ODTs for pediatrics

What's new. Additive manufacturing (binder jetting, fused deposition modeling, semi-solid extrusion) can produce highly porous, fast-disintegrating tablets with age-tailored doses, shapes, and textures—useful for step-up dosing and special-needs children. Recent

work demonstrates individualized ODTs and pediatric-oriented printable feeds.[42,43] Gaps. Regulatory pathways (process validation, batch definition), print-to-print variability, and acceptable pediatric polymers/inks remain active areas of guidance and standardization.[43]



10.3 Personalized medicine approaches

Dose personalization via mini-unit ODTs (mini-tablets within sachets/sticks) and on-demand 3D-printed ODTs can match weight- or phenotype-based regimens and support titration without liquids or

splitting. Evidence shows strong pediatric acceptability of mini-units and a clear path to individualized dosing algorithms when combined with EMR-linked order sets.[44,45]



10.4 Smart packaging and dose personalization

Electronic smart blisters log date/time of tablet removal and can trigger caregiver prompts—closing the loop for home-use ODTs (fever, allergy, ADHD). Usability studies and new trials (e.g., MEMS®/AARDEX systems; Cere®Pak) show feasibility for adherence monitoring and titration feedback. Integration with NFC/BT and clinician dashboards enables truly adaptive pediatric dosing.[46]

evidence is still developing, so quality standards and excipient vigilance are key.[2]

10.5 Integration of ODTs into nutraceuticals and functional foods

Convergence of nutraceutical ODTs (vitamins, minerals, probiotic/herbal actives) with child-friendly flavors and clean-label excipients is accelerating, leveraging nano-encapsulation to stabilize sensitive botanicals and mask taste—while preserving the ODT's water-free administration advantage. Pediatric

10.6 Role of artificial intelligence and predictive modeling in formulation design

From trial-and-error to ML. Machine-learning models now predict ODT disintegration time, hardness, and dissolution from API/excipient features and process parameters, shortening design cycles and guiding excipient screens. Explainable AI has been applied specifically to ODT disintegration; recent datasets (~2,000 formulations) have enabled generalizable prediction of disintegration times across tablet types.[47,48]

Next steps. Multiscale models that pair ML with PBPK/physiologically relevant pediatric GI conditions (saliva volume, pH) could de-risk pediatric BE strategies and accelerate personalized ODT development.[49]



XI. CHALLENGES AND LIMITATIONS

11.1 Stability Issues (Moisture Sensitivity, Friability)
Orodispersible tablets (ODTs) are highly porous to enable rapid disintegration; however, this porosity also makes them prone to moisture uptake, mechanical

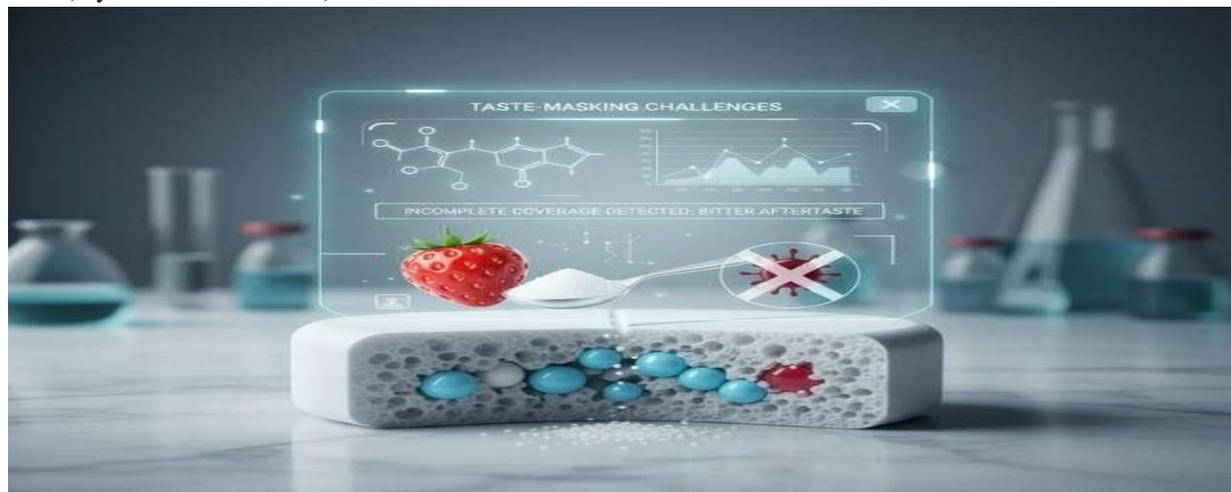
fragility, and friability. Moisture ingress can lead to premature swelling, compromised hardness, and reduced shelf-life. Lyophilized ODTs (e.g., Zydis®) require specialized blister packaging to prevent degradation. While direct compression methods yield stronger tablets, balancing mechanical strength with fast disintegration remains a persistent challenge.



11.2 Taste-Masking Limitations

Taste is a major determinant of pediatric compliance, and many APIs (antibiotics, antiepileptics, antihistamines) have strong bitterness or metallic aftertaste. Techniques such as coating, ion-exchange resins, cyclodextrin inclusion, and sweeteners/flavors

improve palatability but may not fully mask unpleasant taste. Coating can delay disintegration, while complexation may reduce bioavailability. Hence, achieving a balance between rapid disintegration, complete taste-masking, and drug release kinetics remains an unresolved limitation.



11.3 Dose Limitations (for High-Dose Drugs)

ODTs are generally restricted to low- to moderate-dose drugs (<500 mg) due to limitations in tablet size, porosity, and patient acceptability. High-dose medications often lead to large, fragile, and unpalatable tablets, unsuitable for children. This constrains their application to drugs requiring lower

doses (e.g., antihistamines, analgesics) or necessitates splitting into multiple ODTs, which may negatively impact compliance. Emerging approaches such as nanocrystals and 3D printing may partially overcome dose-loading barriers, but widespread applicability remains limited.



11.4 Scale-Up and Cost of Production

Although technologies like direct compression are cost-effective, advanced ODT manufacturing methods (e.g., lyophilization, spray drying, 3D printing)

significantly increase production costs due to specialized equipment, stringent packaging requirements, and high rejection rates. For resource-limited healthcare systems, cost remains a barrier to

the widespread adoption of pediatric ODTs. Furthermore, technology transfer from laboratory to industrial scale often faces hurdles in maintaining disintegration performance and mechanical strength across larger batch sizes.

11.5 Acceptance and Compliance Studies in Real-World Pediatrics

Despite strong laboratory and clinical trial evidence, real-world acceptability studies are limited. Factors such as taste preferences across age groups, cultural differences in formulation acceptance, and caregiver perceptions influence compliance but are often underreported. Children with neurological or swallowing impairments may still face challenges with ODTs. Longitudinal studies on adherence, palatability, and therapeutic outcomes in diverse pediatric populations are needed to validate the real-world impact of ODTs.

XII. CONCLUSION

Orodispersible tablets (ODTs) have emerged as one of the most promising solutions to overcome long-standing barriers in pediatric drug delivery. By combining the stability and dosing accuracy of solid dosage forms with the ease of administration and palatability of liquids, ODTs address critical challenges such as swallowing difficulties, poor compliance, and caregiver burden. Their rapid disintegration in the oral cavity without the need for water makes them particularly suitable for young

children, emergency situations, and patients with dysphagia.

Over the past two decades, significant progress has been made in the formulation science of ODTs, with advances in excipient functionality, taste-masking strategies, and novel manufacturing technologies such as lyophilization, spray drying, and 3D printing. Clinical applications now extend across a wide range of pediatric conditions, including fever, allergy, infections, epilepsy, and chronic neurological and psychiatric disorders. Real-world studies suggest that ODTs improve treatment adherence, therapeutic outcomes, and patient/caregiver satisfaction, although more longitudinal pediatric data are required.

Importantly, ODTs represent a bridge between patient needs and formulation science. While scientific advances have enabled flexible, palatable, and safe dosage forms, challenges such as dose limitations, cost-effective scale-up, excipient safety, and global regulatory harmonization remain. Addressing these will be key to ensuring that ODTs are accessible to children worldwide, including in low-resource settings.

Looking forward, the integration of nanotechnology, personalized medicine, smart packaging, and AI-driven predictive modeling is expected to transform ODTs into truly next-generation pediatric formulations. By aligning pharmaceutical innovation with the unique physiological, psychological, and practical needs of children, ODTs hold the potential to set new standards in pediatric therapeutics and improve healthcare outcomes globally.



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XIV. AUTHORSHIP STATEMENT

All authors contributed substantially to the conception, design, literature review, drafting, and critical revision of this manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

XV. CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to the publication of this review article.

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