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Review Article

Orally Disintegrating Tablets: A Comprehensive Review of Formulation Strategies, Excipient Technology and Quality Evaluation

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Orally disintegrating tablets (ODTs) have emerged as a highly patient-centric solid dosage form, offering significant advantages over conventional oral tablets, particularly for pediatric, geriatric, dysphagic, and critically ill patients. These solid dosage forms are specifically designed to disintegrate or dissolve rapidly in the oral cavity within 30 seconds or less without the need for water, thereby facilitating ease of administration and improving medication adherence. The global ODT market has witnessed considerable growth driven by rising demand for convenient drug delivery and technological innovations in excipient science. This review comprehensively examines the scientific principles underlying ODT design, including the role of superdisintegrants, diluents, taste-masking agents, and lubricants. Manufacturing methodologies—namely direct compression, freeze-drying, sublimation, spray drying, and molding—are critically appraised with respect to their advantages, limitations, and industrial applicability. The review further addresses quality evaluation parameters encompassing pre-compression characterization, post-compression testing, wetting behavior, disintegration kinetics, dissolution profiling, drug content uniformity, and accelerated stability assessment per ICH guidelines. Regulatory frameworks governing ODT approval, including guidance from the US FDA and European Medicines Agency, are also discussed. Emerging trends such as nanotechnology-based ODTs, 3D-printed oral films, and co-processed excipients are highlighted as frontiers shaping the future of this dosage form. This review aims to serve as a consolidated reference for pharmaceutical scientists engaged in the rational development and optimization of ODT formulations.

Keywords: Orally Disintegrating Tablets, Superdisintegrants, Fast Dissolving Dosage Forms, Direct Compression, Taste Masking, Patient Compliance, Wetting Time, Disintegration, Dissolution, ICH Stability.

INTRODUCTION

The oral route of drug administration remains the most widely accepted and preferred mode of drug delivery worldwide owing to its simplicity, non-invasiveness, patient acceptability, and cost-effectiveness. Conventional oral solid dosage forms, including standard compressed tablets and hard gelatin capsules, are easy to manufacture at industrial scale and well-established in clinical practice. However, a substantial subset of patients encounters significant difficulties in swallowing these conventional dosage forms, a condition clinically referred to as dysphagia. Epidemiological estimates indicate that dysphagia affects approximately 8 to 22 percent of the general population and is considerably more prevalent among elderly patients, pediatric cohorts, and individuals with neurological or psychiatric conditions. Dysphagia and swallowing difficulties frequently result in non-compliance, dose dumping, or outright refusal of medication, thereby compromising therapeutic outcomes and escalating healthcare costs. In acute clinical scenarios such as emesis, epileptic episodes, or anaphylaxis, patients may be physically incapable of swallowing a conventional tablet, underscoring the need for alternative delivery strategies that circumvent this limitation. Orally disintegrating tablets (ODTs) were

developed specifically to address these clinical challenges. ODTs are solid pharmaceutical dosage forms engineered to disintegrate instantaneously upon placement in the oral cavity, releasing the drug for absorption via the oral mucosa or gastrointestinal tract following ingestion of the resulting dispersion with saliva. Since their introduction in the 1980s with freeze-dried formulations, ODTs have undergone substantial technological evolution and currently represent one of the fastest-growing segments in pharmaceutical dosage form development. The clinical relevance of ODTs extends beyond mere convenience. For antiemetic agents, anti-epileptics, analgesics, anxiolytics, and drugs indicated in acute migraine or Parkinson's disease, the rapid disintegration property of ODTs translates directly into faster onset of therapeutic action, improved pharmacokinetic profiles, and enhanced patient outcomes. Additionally, the elimination of the swallowing requirement significantly reduces medication errors associated with non-compliance in chronic disease management. This review provides a comprehensive and updated account of the scientific, technological, and regulatory dimensions of ODT formulation. It synthesizes current knowledge on excipient selection, manufacturing techniques, evaluation methodologies, regulatory considerations, and future directions, aiming to serve as a definitive reference for pharmaceutical researchers and industry practitioners engaged in ODT development.

2. Definition and Regulatory Classification of ODTs

The United States Food and Drug Administration (US FDA) defines orally disintegrating tablets as solid dosage forms that disintegrate rapidly, generally within 30 seconds or less, when placed on the tongue. Upon contact with saliva, the tablet undergoes rapid physical disintegration, forming a suspension or dispersion that can be swallowed without the requirement for additional liquid intake. This FDA definition, established under the Guidance for Industry on Orally Disintegrating Tablets (2008), distinguishes ODTs from chewable tablets, effervescent tablets, and buccal or sublingual tablets, which operate through different mechanisms of drug release. The European Pharmacopoeia (Ph. Eur.) refers to a broadly analogous dosage form as "orally dispersible tablets," defining them as uncoated or film-coated tablets intended to be placed in the mouth where they disperse rapidly before swallowing. The Ph. Eur. specifies that tablets should disperse within 3 minutes using the disintegration test for uncoated tablets, though pharmacopeial refinements continue to evolve. The Indian Pharmacopoeia (IP) acknowledges mouth-dissolving tablets as a distinct category with defined disintegration criteria aligned with international standards. These regulatory frameworks collectively underscore that ODTs constitute a distinct pharmaceutical dosage form class subject to specific quality and performance requirements, separate from conventional oral solid dosage forms. Proprietary technologies for ODT manufacturing include the Zydis® technology (freeze-drying), OraSolv® and DuraSolv® platforms (direct compression-based), FlashDose® (cotton candy process), and WOWTab® (wet granulation with sugar alcohols). Each platform is associated with unique performance attributes and patent portfolios, contributing to the commercially diverse ODT landscape.

3. Advantages and Limitations of Orally Disintegrating Tablets

3.1 Therapeutic and Patient-Centric Advantages

ODTs offer a range of clinically significant advantages that collectively differentiate them from conventional oral dosage forms:

- Administration without water renders ODTs suitable for use in diverse settings including travel, emergency care, and postoperative recovery wards where water access is restricted.
- Rapid disintegration and dissolution facilitate faster drug absorption, which is particularly beneficial in acute therapeutic scenarios requiring immediate pharmacological intervention.
- Improved patient compliance: Elimination of the swallowing barrier promotes consistent medication intake in chronic therapy, directly improving adherence rates and therapeutic outcomes.

- Suitability for vulnerable populations: Pediatric patients with underdeveloped swallowing reflexes and geriatric patients with age-related dysphagia represent primary beneficiary groups for ODT therapy.

- Reduced risk of aspiration and choking, particularly relevant for neurologically impaired patients, bedridden individuals, and those with pharyngeal disorders.

- Potential for partial pre-gastric absorption through oral and esophageal mucosae, which may reduce first-pass hepatic metabolism and enhance systemic bioavailability for select drugs.

- Enhanced drug stability compared to liquid formulations, with the added benefit of portability and ease of dose identification inherent to solid dosage forms.

3.2 Formulation and Manufacturing Challenges

Despite their considerable clinical utility, ODTs present several technological challenges that must be systematically addressed during formulation development:

- Mechanical fragility: The highly porous tablet matrix and low compaction forces required to achieve rapid disintegration compromise tablet hardness, making ODTs susceptible to breakage during handling, transit, and dispensing. Unit-dose blister packaging is typically mandatory.

- Hygroscopicity: Many ODT excipients, including sugar alcohols and superdisintegrants, are hygroscopic, necessitating moisture-controlled manufacturing environments and secondary packaging with desiccants.

- Taste acceptability: Since the dosage form disintegrates in the oral cavity, the drug is directly exposed to taste receptors. Bitter, astringent, or otherwise objectionable-tasting drugs require effective and carefully validated taste-masking strategies.

- Drug loading constraints: ODTs are generally limited to relatively low drug doses (typically below 400 mg) due to constraints on tablet weight and the need to maintain acceptable disintegration time and mouthfeel.

- Scalability and cost: Certain ODT manufacturing technologies such as freeze-drying involve high capital investment and operational costs, limiting their application to high-value pharmaceutical products.

4. Excipient Selection in ODT Formulation

Excipient selection is the cornerstone of successful ODT development. Each excipient category fulfills a specific functional role, and their interactions collectively determine the disintegration behavior, mechanical properties, palatability, and stability of the final dosage form.

4.1 Superdisintegrants

Superdisintegrants are pharmacologically inactive excipients employed at relatively low concentrations (typically 2–15% w/w) to achieve rapid tablet disintegration. Their mechanism of action distinguishes them from traditional disintegrants: superdisintegrants promote tablet breakup through rapid and extensive swelling, wicking (capillary absorption), or deformation recovery upon exposure to aqueous media such as saliva.

Crospovidone (PVPP)

Crospovidone is a cross-linked homopolymer of N-vinyl-2-pyrrolidone that functions principally via a wicking mechanism, rapidly drawing moisture into the tablet matrix through capillary action. Its low gel formation tendency and excellent water absorption capacity make it one of the most efficient superdisintegrants in ODT formulations. Crospovidone demonstrates pH-independent activity, broad compatibility with drugs and excipients, and minimal interaction with active pharmaceutical ingredients. Published literature consistently identifies crospovidone as producing the shortest disintegration times among commonly used superdisintegrants at equivalent concentrations.

Croscarmellose Sodium (CCS)

Croscarmellose sodium is an internally cross-linked sodium carboxymethylcellulose derivative. It promotes disintegration through a dual mechanism: rapid swelling upon hydration generates mechanical stress within the tablet matrix, while simultaneous wicking action ensures thorough moisture penetration. Croscarmellose sodium is particularly effective in directly compressed formulations and exhibits good compressibility characteristics. Its performance is influenced by moisture content and compression force, parameters that must be carefully controlled during manufacturing.

Sodium Starch Glycolate (SSG)

Sodium starch glycolate is a modified cross-linked starch derivative characterized by rapid and extensive swelling in aqueous media. While highly effective at low concentrations, SSG exhibits electrolyte sensitivity that may reduce its disintegration efficiency in formulations containing significant ionic excipients. Additionally, excessive SSG concentrations can lead to viscous gel formation, paradoxically retarding drug release. Optimization of SSG concentration within the range of 4–8% w/w is generally recommended to balance swelling efficacy and dissolution performance.

4.2 Diluents and Bulking Agents

Diluents serve as the primary matrix-forming component in ODT formulations, providing bulk, compressibility, and importantly, an acceptable mouthfeel upon tablet disintegration. In ODTs, the sensory attributes of diluents are as critical as their pharmaceutical functionality.

Mannitol

Mannitol (D-mannitol) is widely regarded as the gold standard diluent for ODT formulations. Its low hygroscopicity, chemical inertness across a broad pH range, negative heat of solution (producing a distinctive cooling sensation upon dissolution in the mouth), and excellent mouthfeel make it uniquely suited for oral disintegrating dosage forms. Mannitol is available in several grades varying in particle size distribution and flow properties, allowing formulators to tailor compressibility and disintegration performance. Furthermore, mannitol contributes to taste modulation by partially masking the bitterness of incorporated drugs.

Microcrystalline Cellulose (MCC)

Microcrystalline cellulose is a partially depolymerized cellulose with exceptional compressibility and binding properties, enabling the production of mechanically robust tablets even at low compression forces. MCC also promotes disintegration through its capacity to absorb water and swell. In combination with mannitol, MCC creates a tablet matrix balancing mechanical integrity and rapid disintegration—a critical design objective in ODT formulation. Grades such as Avicel PH-101 and PH-102 are commonly employed, with particle size selection guided by flow and compressibility requirements.

Lactose

Spray-dried lactose, in its monohydrate or anhydrous form, is used as a diluent in ODT formulations. Its rapid dissolution in saliva contributes to fast disintegration, and its sweet taste improves palatability. However, lactose is contraindicated in lactose-intolerant patients and those with galactosemia, limiting its universal applicability.

4.3 Taste-Masking Agents

Taste masking represents one of the most challenging and commercially significant aspects of ODT formulation technology. The direct contact between the disintegrating tablet and oral taste receptors necessitates effective and validated taste modification strategies for drugs with unpleasant organoleptic properties.

Sweeteners

High-intensity artificial sweeteners including aspartame, acesulfame potassium, sucralose, and saccharin sodium are routinely incorporated into ODT formulations to impart sweetness and neutralize bitterness. Aspartame, with a sweetening potency approximately 200 times that of sucrose, is particularly valued for its clean sweet taste without a metallic or bitter aftertaste. Saccharin sodium offers high sweetness intensity but may leave a slight bitter

or metallic aftertaste at elevated concentrations. Combination sweeteners are frequently employed to achieve a balanced, natural sweetness profile.

Flavoring Agents

Natural and artificial flavoring agents including mint, orange, strawberry, cherry, and bubblegum flavors are incorporated to mask residual bitterness and enhance the overall sensory experience. Flavor selection is guided by the drug's intrinsic taste characteristics, target patient population, and compatibility with other excipients. Encapsulated flavor systems may be employed to protect volatile aromatic compounds and ensure shelf-life stability of the flavor profile.

Polymer Coating and Ion-Exchange Resins

For drugs with intensely bitter or objectionable taste, polymer microencapsulation using ethylcellulose, Eudragit® E100, or cellulose acetate phthalate provides a physical barrier around drug particles, preventing drug-receptor contact in the oral cavity while permitting dissolution post-swallowing in the gastrointestinal tract. Ion-exchange resin complexation (drug-resin complexes using Amberlite IRP-69 or IRP-88) represents another physicochemical taste-masking strategy that reduces free drug availability in saliva, significantly diminishing taste perception.

4.4 Lubricants and Glidants

Lubricants reduce interparticulate and die-wall friction during tablet compression, preventing sticking and ensuring smooth tablet ejection. However, hydrophobic lubricants can impair disintegration and dissolution if used at excessive concentrations or mixed for prolonged periods. Magnesium stearate is the most widely used lubricant, typically incorporated at concentrations of 0.25–1.0% w/w in ODT formulations. Its hydrophobic nature necessitates careful blending time optimization to minimize adverse effects on disintegration. Sodium stearyl fumarate offers comparable lubrication with a lesser hydrophobic impact on tablet surfaces, making it preferable for moisture-sensitive ODT formulations. Colloidal silicon dioxide (Aerosil®) functions as a glidant, improving powder flowability and reducing segregation during blending.

5. Manufacturing Methods for Orally Disintegrating Tablets

The selection of an appropriate manufacturing method is governed by the physicochemical properties of the drug and excipients, target disintegration time, mechanical performance requirements, economic considerations, and scalability. The principal manufacturing technologies employed for ODT production are described below.

5.1 Direct Compression

Direct compression is the predominant manufacturing method for ODTs due to its operational simplicity, minimal processing steps, economic efficiency, and compatibility with thermolabile or moisture-sensitive drugs. The method involves direct blending of all components—including the active pharmaceutical ingredient, superdisintegrants, diluents, sweeteners, flavoring agents, and lubricants—followed by compression on conventional rotary tablet presses without prior granulation. The success of direct compression is contingent upon the use of excipients with inherently good flow and compressibility characteristics, eliminating the need for pre-processing granulation steps. Co-processed excipients specifically designed for direct compression, such as F-Melt® (a combination of mannitol, microcrystalline cellulose, crospovidone, and calcium silicate), have been commercially developed to further enhance ODT performance. Direct compression is particularly suited for pilot-scale and commercial-scale ODT manufacturing, offering advantages in content uniformity, batch-to-batch reproducibility, and reduced exposure of drugs to elevated temperatures or solvents.

5.2 Freeze-Drying (Lyophilization)

Freeze-drying involves the preparation of an aqueous drug-excipient solution or suspension that is filled into pre-formed blister cavities and subjected to freezing followed by primary drying under reduced pressure through sublimation of ice. The resulting tablet is highly porous, with a network of fine interconnecting channels that facilitate almost instantaneous disintegration upon contact with saliva. The Zydis® technology represents the most commercially successful application of freeze-drying

for ODT manufacturing. Freeze-dried ODTs demonstrate extremely rapid disintegration times, often within 5 to 10 seconds, which is unmatched by compression-based technologies. However, the method is associated with high capital investment in specialized lyophilization equipment, low production throughput, limitations in drug loading capacity, and the requirement for unit-dose blister packaging to protect the mechanically fragile tablets. These factors restrict the application of freeze-drying to high-value pharmaceutical products where superior disintegration performance justifies the manufacturing cost.

5.3 Sublimation Technique

The sublimation technique incorporates volatile solid materials—most commonly camphor, menthol, ammonium bicarbonate, or urethane—into the tablet formulation during compression. Following compression, these volatile excipients are removed by sublimation under mild vacuum or heating conditions, creating a porous tablet matrix with enhanced water penetration capacity and rapid disintegration. The degree of porosity and resultant disintegration time can be modulated by adjusting the type and concentration of the volatile agent. While technically straightforward, sublimation requires additional processing infrastructure and careful handling of volatile compounds to ensure workplace safety and batch consistency.

5.4 Spray Drying

Spray drying involves the atomization of a drug solution or suspension containing dissolved or dispersed excipients into a stream of heated gas, producing fine, spherical, highly porous particles upon rapid solvent evaporation. These particles are subsequently compressed into tablets. The spray drying process can simultaneously achieve drug-excipient co-processing, particle engineering, and taste masking (through polymer coating during drying). Spray drying technology enables the production of free-flowing granules with enhanced compressibility, facilitating ODT manufacturing on conventional tablet presses. The method requires sophisticated process control and investment in spray drying equipment but offers flexibility in particle design.

5.5 Melt Granulation

Melt granulation utilizes low-melting-point binders such as polyethylene glycol, Gelucire®, or poloxamers that melt during granulation, binding drug and excipient particles through liquid bridges that solidify upon cooling. The resulting granules exhibit excellent flow and compressibility. This solvent-free process is particularly advantageous for moisture-sensitive drugs and eliminates the need for aqueous or organic solvents. However, the thermal processing requirement limits applicability to thermostable drug substances.

5.6 Tablet Molding

Tablet molding involves compacting a moistened powder mass of drug and water-soluble excipients into tablet-shaped molds. Upon drying, the resulting tablets exhibit low density and high porosity, enabling rapid dissolution. Molded tablets typically disintegrate faster than compressed tablets but possess significantly lower mechanical strength, necessitating specialized handling and packaging. This technique finds limited commercial application but has been explored for ODTs containing highly water-soluble drugs and excipients.

6. Evaluation Parameters for Orally Disintegrating Tablets

Comprehensive and systematic evaluation of ODTs is essential to confirm compliance with regulatory specifications, ensure consistent manufacturing quality, and predict clinical performance. Evaluation encompasses pre-compression characterization of the powder blend, post-compression testing of tablet physical attributes, and functional performance assessment.

6.1 Pre-Compression Evaluation

Pre-compression characterization assesses the flowability and compressibility of the powder blend prior to tableting, as these properties directly influence die-fill uniformity, tablet weight consistency, and content uniformity.

- Angle of Repose: Determined by allowing the powder to flow through a funnel onto a flat

surface and measuring the angle of the formed cone relative to the horizontal. Values below 30° indicate excellent flow; values above 45° indicate poor flow properties.

- Bulk Density: Calculated as the ratio of the mass of powder to its uncompacted bulk volume. Lower bulk density generally indicates greater porosity and compressibility potential.

- Tapped Density: Measured after a standardized number of mechanical taps, reflecting the minimum achievable powder volume under gravitational packing. Tapped density is consistently greater than bulk density.

- Carr's Compressibility Index (CI): Computed from the formula CI (%) = [(Tapped Density − Bulk Density) / Tapped Density] × 100. CI values of 5–15% indicate excellent compressibility; values exceeding 35% indicate very poor flow.

- Hausner's Ratio: Defined as the ratio of tapped density to bulk density. Values approaching 1.00 indicate good flow; values greater than 1.25 indicate cohesive powders with poor flow characteristics.

6.2 Post-Compression Evaluation

6.2.1 Physical Parameters

Tablet thickness, determined using a calibrated vernier caliper, ensures dimensional uniformity for packaging compatibility and dose delivery consistency. Tablet hardness, measured using a calibrated hardness tester (e.g., Erweka TBH or Schleuniger), quantifies the diametral crushing force in Newtons (N) or kiloponds (kP). For ODTs, a balance between sufficient hardness for handling (typically 30–100 N) and rapid disintegration must be optimized. Weight variation, assessed per pharmacopeial specifications, verifies uniformity of tablet mass, which is a surrogate indicator of content uniformity for directly compressed tablets. Friability, determined using a Roche friabilator at 25 rpm for 4 minutes, quantifies tablet abrasion resistance; ODTs are expected to exhibit friability below 1.0% w/w per general pharmacopeial guidance.

6.2.2 Wetting Time and Water Absorption Ratio

Wetting time is a functional parameter specific to ODTs that reflects the tablet's capacity to absorb moisture rapidly. In a validated method, a tablet is placed on tissue paper saturated with purified water, and the time required for complete surface wetting is recorded. A short wetting time (typically below 60 seconds) correlates strongly with rapid in vivo disintegration. The water absorption ratio is concurrently calculated as: Water Absorption Ratio (%) = [(Wâ − W^b) / W^b] × 100, where W^b and Wâ denote tablet weight before and after wetting, respectively. Higher water absorption ratios are generally associated with more porous tablet matrices and faster disintegration.

6.2.3 Disintegration Time

Disintegration time is the most critical quality attribute of ODTs and is routinely measured using the USP disintegration apparatus with simulated saliva fluid (pH 6.8 phosphate buffer) at 37 ± 0.5°C. Per FDA guidance, ODTs should disintegrate in the mouth within 30 seconds. Pharmacopeial disintegration tests provide a standardized in vitro surrogate for in vivo oral disintegration performance. Alternative methodologies include the texture analysis method and the hydrodinamic flow cell method for more precise characterization of disintegration kinetics.

6.2.4 Drug Content Uniformity

Drug content uniformity ensures that each tablet delivers the intended therapeutic dose within acceptable variability limits. Tablets are individually extracted and assayed using validated UV-Vis spectrophotometric, HPLC, or other analytical methods appropriate for the specific drug substance. Per USP <905>, the relative standard deviation of content should not exceed 6.0% in a sample of 10 tablets, with all individual values falling within 85–115% of the label claim.

6.2.5 In Vitro Dissolution Studies

Dissolution testing, conducted using USP Apparatus II (paddle method) typically in phosphate buffer pH 6.8 at 37 ± 0.5°C and 50 rpm, evaluates the rate and

completeness of drug release from ODTs. Given the rapid disintegration profile of ODTs, dissolution testing must employ appropriate analytical sampling intervals (e.g., 2, 5, 10, 15, 30, and 45 minutes). Dissolution profiles are characterized using similarity factor ($f2 \geq 50$ for equivalence) when comparing formulations or assessing scale-up changes. In vitro dissolution data serve as a predictive indicator of in vivo drug absorption, particularly for rapidly dissolving, highly soluble drugs classified under BCS Class I.

7. Stability Studies

Stability testing of ODTs is conducted in accordance with ICH Q1A(R2) guidelines to establish shelf life and define storage conditions that maintain product quality throughout the intended use period. Accelerated stability studies are performed at 40°C ± 2°C and 75% relative humidity ± 5% RH for a minimum of six months, while long-term stability studies are conducted at 25°C ± 2°C and 60% RH ± 5% RH for a period of 12 to 24 months or longer. Critical stability-indicating parameters monitored during the study period include physical appearance (color, texture, and surface integrity), tablet hardness and friability, disintegration time, drug content assay, related substance and degradation product profiles (by stability-indicating HPLC methods), moisture content (by Karl Fischer titration), and dissolution performance. For ODTs, moisture uptake is a particularly sensitive stability indicator, as hygroscopic excipients can cause significant changes in mechanical strength and disintegration behavior upon exposure to humidity. Photostability testing per ICH Q1B is additionally required for drugs susceptible to light-induced degradation. Packaging compatibility studies are integral to stability programs for ODTs, evaluating the performance of primary packaging materials (typically aluminum/aluminum or aluminum/PVC-PVDC blisters with or without desiccants) under stress conditions to confirm adequate moisture and light protection throughout the product shelf life.

8. Regulatory Considerations for ODT Development

The regulatory pathway for ODT development and approval is informed by guidance documents from multiple global health authorities. The US FDA Guidance for Industry: Orally Disintegrating Tablets (2008) provides foundational criteria distinguishing ODTs from other oral dosage forms and outlines specific labeling requirements emphasizing the rapid in-mouth disintegration characteristic. The FDA guidance specifies that the disintegration performance claim must be supported by appropriate clinical data demonstrating in-mouth disintegration within 30 seconds. In the European Union, the European Medicines Agency (EMA) Guideline on Pharmaceutical Development of Medicines for Paediatric Use (2013) specifically addresses ODTs as preferred dosage forms for pediatric populations, recognizing their clinical advantages. The European Pharmacopoeia monograph for orally dispersible tablets specifies compliance with the disintegration test using the standard disintegration apparatus in water at 37°C. Bioequivalence (BE) studies for generic ODT products typically follow standard BE guidance for immediate-release solid oral dosage forms. However, where ODTs demonstrate pre-gastric absorption or significantly different pharmacokinetic profiles compared to conventional tablets, additional BE study designs or in vitro-in vivo correlation (IVIVC) data may be required by regulatory authorities. Scale-up and post-approval changes (SUPAC) guidance further provides a framework for managing manufacturing changes without necessitating full BE studies.

9. Emerging Technologies and Future Perspectives

The field of ODT technology continues to evolve rapidly, driven by advances in pharmaceutical engineering, materials science, and patient-centered drug delivery design. Several emerging technological platforms hold significant promise for expanding the capability and performance of ODTs.

9.1 Nanotechnology-Based ODTs

Integration of nanotechnology into ODT formulations offers transformative potential for enhancing drug bioavailability, dissolution rate, and therapeutic efficacy. Drug nanoparticles, nanosuspensions, lipid-based nanocarriers, and cyclodextrin inclusion complexes incorporated into ODT matrices can substantially improve dissolution kinetics for poorly water-soluble (BCS Class II and IV) drugs, a category

representing a growing proportion of new chemical entities. Nanocrystal technology, in particular, has demonstrated remarkable success in enhancing the bioavailability of BCS Class II drugs when incorporated into ODTs, combining nanotechnology benefits with ODT patient-compliance advantages.

9.2 Co-Processed Excipients

Co-processed excipients are prepared by simultaneously processing two or more pharmacopeial excipients at the physical or particle level to achieve functional synergy exceeding that of individual components. Examples include Ludiflash® (mannitol, crospovidone, polyvinyl acetate), F-Melt® (mannitol, microcrystalline cellulose, crospovidone, calcium silicate), and Pharmaburst® (mannitol, sorbitol, crospovidone, silicon dioxide). These multifunctional excipients simultaneously address compressibility, disintegration, flow, and mouthfeel, simplifying formulation development and enabling high-speed direct compression of ODTs.

9.3 Three-Dimensional (3D) Printing

Additive manufacturing or 3D printing technologies, including binder jetting, fused deposition modeling, and inkjet printing, are being actively investigated for ODT fabrication. The first FDA-approved 3D-printed tablet, Spritam® (levetiracetam), produced using ZipDose® Technology (Aprecia Pharmaceuticals), demonstrated that 3D printing can produce ODTs with extremely rapid dissolution at high drug doses (up to 1000 mg), challenging the traditional dose loading limitations of ODT technology. The inherent flexibility of 3D printing also enables the production of personalized dosage forms with patient-specific doses, geometries, and disintegration profiles.

9.4 Orally Dissolving Films and Hybrid Systems

Orally dissolving films (ODFs) represent an evolution of the ODT concept, offering ultra-thin, flexible, fast-dissolving matrices that may be preferable for certain patient populations. Hybrid systems combining ODT technology with controlled-release mechanisms—such as pulsatile release, biphasic release, or abuse-deterrent formulations—represent an active area of formulation innovation. Additionally, bioenhancer-incorporated ODTs utilizing compounds such as piperine, quercetin, or pharmaceutical absorption promoters are being explored to improve systemic drug availability and reduce interpatient pharmacokinetic variability.

CONCLUSION

Orally disintegrating tablets represent a scientifically sophisticated and clinically validated evolution in oral solid dosage form technology, addressing a broad spectrum of patient-related and therapeutic challenges associated with conventional tablets and capsules. By enabling drug administration without water and facilitating rapid disintegration in the oral cavity, ODTs have meaningfully improved medication adherence, patient quality of life, and therapeutic outcomes across diverse clinical indications and patient populations. The rational design of ODTs demands a thorough understanding of excipient science, manufacturing processes, and evaluation methodologies. Superdisintegrants remain the linchpin of ODT formulation, with the choice and concentration of crospovidone, croscarmellose sodium, or sodium starch glycolate critically determining disintegration performance. Complementary excipients including mannitol, microcrystalline cellulose, and high-intensity sweeteners synergistically contribute to mechanical robustness, palatability, and stability. Direct compression, supported by co-processed excipient technology, has emerged as the preferred industrial manufacturing platform for its simplicity, scalability, and cost-effectiveness. Rigorous evaluation through pre-compression characterization, post-compression physical testing, wetting time, disintegration assessment, dissolution profiling, and ICH-compliant stability studies ensures that ODTs consistently meet quality, safety, and efficacy requirements throughout their shelf life. Regulatory frameworks from the US FDA, EMA, and other global authorities continue to evolve in parallel with technological advancements, providing clearer pathways for ODT development and approval. The future of ODT technology is poised for significant expansion through the integration of nanotechnology, co-processed multifunctional excipients, 3D printing, and hybrid controlled-release systems. These innovations will progressively overcome current limitations related to drug loading capacity, dose flexibility, and bioavailability

enhancement, broadening the therapeutic scope of ODTs. Continued interdisciplinary research bridging pharmaceutical sciences, materials engineering, and clinical pharmacology will be essential to fully realize the potential of next-generation orally disintegrating dosage forms in improving global patient health outcomes.

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