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Smart Orodispersible Drug Delivery of Metoclopramide: Role of Nanocomposites and Functional Polymers in Taste Masking and In Vitro Evaluation

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Abstract: *Orodispersible drug delivery systems (ODTs) have emerged as a patient-centric approach to enhance compliance, particularly in pediatric, geriatric, and dysphagic populations. Metoclopramide, a widely used antiemetic and gastroprokinetic agent, presents formulation challenges due to its inherently bitter taste and the need for rapid onset of action. This review focuses on the integration of nanocomposite encapsulation and functional polymer-based strategies to develop advanced orodispersible formulations of metoclopramide. Nanocomposites offer a promising platform for drug encapsulation, enabling improved taste masking, enhanced stability, and controlled drug release. Simultaneously, functional polymers such as ion-exchange resins, hydrophilic matrices, and pH-responsive materials play a critical role in minimizing drug–taste receptor interaction while maintaining rapid disintegration and dissolution profiles. The review critically examines formulation approaches, excipient selection, and processing techniques influencing tablet performance. Furthermore, it highlights key in vitro evaluation parameters including disintegration time, wetting time, dissolution behavior, and taste masking efficiency. Comparative analysis of conventional and nanotechnology-driven systems underscores the superiority of nanocomposite-assisted formulations in achieving optimal balance between palatability and bioavailability. Challenges related to scalability, regulatory considerations, and reproducibility are also discussed. Overall, this review provides a comprehensive understanding of current advancements and future prospects in designing smart orodispersible drug delivery systems for metoclopramide, emphasizing the synergistic role of nanocomposites and polymers in overcoming critical formulation barriers.*

Keywords: Metoclopramide; Orodispersible Tablets; Nanocomposites; Taste Masking; Functional Polymers

I. INTRODUCTION

Overview of Orodispersible Drug Delivery Systems (ODDS)

Orodispersible drug delivery systems (ODDS), also known as orally disintegrating tablets (ODTs), are advanced solid dosage forms designed to disintegrate rapidly in the oral cavity without the need for water (1). These systems rely on optimized combinations of superdisintegrants, porous matrices, and hydrophilic excipients that facilitate rapid water uptake through mechanisms such as wicking, swelling, and deformation, ultimately leading to fast drug release (2,3). Recent advancements (2020–2025) have expanded ODDS beyond conventional formulations to include co-processed excipients, nanostructured carriers, and additive manufacturing approaches such as 3D printing, enabling improved performance and dose personalization (4–6).

From a biopharmaceutical perspective, ODDS enhance patient compliance, particularly among pediatric, geriatric, and dysphagic populations, while also offering rapid onset of action and potential improvement in bioavailability through

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pregastric absorption (7,8). Consequently, ODDS have become an integral component of patient-centric pharmaceutical design and modern oral drug delivery strategies (9).

Clinical relevance of rapid-onset antiemetics

Rapid pharmacological intervention is essential in the management of acute nausea and vomiting, particularly in conditions such as chemotherapy-induced nausea, postoperative emesis, and gastrointestinal motility disorders (10). Metoclopramide, a dopamine D_2 receptor antagonist with additional serotonergic modulation, is widely utilized due to its combined antiemetic and gastroprokinetic effects (11). The therapeutic efficacy of metoclopramide is strongly dependent on rapid systemic availability, making fast-dissolving formulations highly desirable (12).

ODDS provide a suitable delivery platform by enabling rapid disintegration and dissolution in the oral cavity, leading to faster onset of action and improved clinical outcomes (13). Additionally, ease of administration without water enhances patient compliance in emergency and ambulatory settings (14).

Limitations of conventional metoclopramide dosage forms

Despite its clinical importance, metoclopramide presents several formulation challenges that limit the effectiveness of conventional dosage forms. A major limitation is its intensely bitter taste, which significantly reduces patient acceptability, particularly in orally disintegrating systems (15,16). Conventional taste-masking approaches such as sweeteners and flavoring agents are often insufficient for highly water-soluble and bitter drugs (17).

Furthermore, traditional tablets may exhibit delayed onset due to gastrointestinal disintegration and hepatic first-pass metabolism, while liquid formulations suffer from issues related to dose inaccuracy, stability, and patient compliance (18,19). These challenges necessitate the development of advanced delivery systems capable of improving palatability, pharmacokinetic performance, and overall therapeutic efficacy (20).

Rationale for nanocomposite and polymer-based approaches

To address these limitations, nanocomposite-based drug delivery systems and functional polymer technologies have emerged as promising strategies. Nanocomposites, consisting of nanoscale drug carriers embedded within polymeric or inorganic matrices, provide effective encapsulation that reduces drug interaction with taste receptors, thereby enhancing taste masking (21,22).

Recent studies (2022–2025) have demonstrated that polymeric nanocapsules and hybrid nanocomposites can significantly reduce bitterness while maintaining rapid drug release profiles (23–25). Functional polymers such as polymethacrylates (e.g., Eudragit), ion-exchange resins, and pH-responsive materials further enhance taste masking by forming drug–polymer complexes that suppress drug release in the oral cavity but allow rapid release in gastric conditions (26,27).

The integration of nanotechnology with polymer science enables the development of hybrid delivery systems exhibiting improved encapsulation efficiency, controlled release behavior, enhanced bioavailability, and superior patient compliance (28).

Scope and objectives of the review

The present review aims to provide a comprehensive and critical evaluation of smart orodispersible drug delivery systems of metoclopramide, focusing on nanocomposite encapsulation and polymer-based taste masking strategies. It systematically examines formulation approaches, excipient selection, and processing techniques influencing ODDS performance (29).

Furthermore, the review highlights key in vitro evaluation parameters, including disintegration time, dissolution kinetics, and taste masking efficiency, which are essential for optimizing formulation quality (30). Emphasis is also placed on recent advancements in nanotechnology-driven systems, regulatory considerations, and future perspectives to guide the development of next-generation patient-centric formulations.

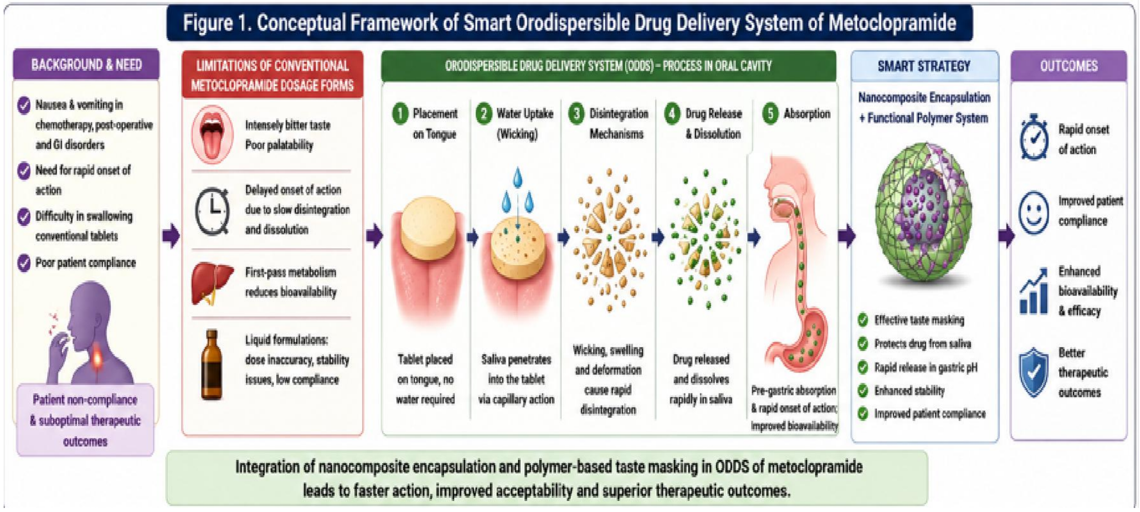

Figure 1: Conceptual Framework of Smart Orodispersible Drug Delivery System of Metoclopramide Integrating Nanocomposite Encapsulation and Polymer-Based Taste Masking

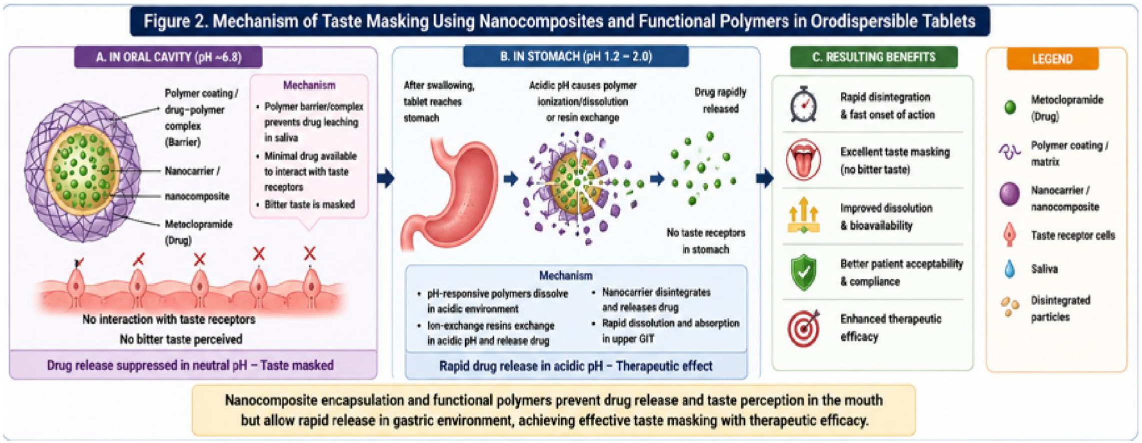

Figure 2. Mechanism of Nanocomposite- and Polymer-Mediated Taste Masking in Orodispersible Metoclopramide Tablets: Oral Suppression and Gastric Release Dynamics

II. BIOPHARMACEUTICAL PROFILE OF METOCLOPRAMIDE

Physicochemical Properties (Solubility, pKa, log P)

Metoclopramide hydrochloride is a substituted benzamide derivative characterized by high aqueous solubility and moderate lipophilicity, which significantly influence its absorption and distribution behavior (31). The drug exhibits pH-dependent solubility, remaining highly soluble in acidic environments due to protonation of its amine functional group (32). The reported pKa of metoclopramide is approximately 9.0–9.4, indicating that it predominantly exists in an ionized form under physiological pH conditions (33).

The partition coefficient (log P) of metoclopramide ranges between 2.5 and 3.0, suggesting moderate lipophilicity that supports membrane permeability while maintaining sufficient aqueous solubility for rapid dissolution (34). These physicochemical properties collectively classify metoclopramide as a Biopharmaceutics Classification System (BCS) Class I drug, exhibiting high solubility and high permeability (35). This profile makes it a suitable candidate for orodispersible drug delivery systems, where rapid dissolution and absorption are critical (36).

Pharmacokinetics and Bioavailability

Metoclopramide is rapidly absorbed following oral administration, with peak plasma concentrations typically achieved within 1–2 hours (37). The drug exhibits an oral bioavailability of approximately 70–80%, which is influenced by hepatic first-pass metabolism (38). It is widely distributed throughout the body, including penetration across the blood–brain barrier, which is essential for its central antiemetic action (39).

Metabolism primarily occurs in the liver via conjugation reactions, including sulfation and glucuronidation, while renal excretion accounts for the elimination of both unchanged drug and metabolites (40). The elimination half-life of metoclopramide ranges from 5 to 6 hours in healthy individuals but may vary depending on renal function (41).

From a formulation perspective, the relatively short onset time and moderate half-life necessitate dosage forms that enable rapid drug release and absorption, reinforcing the suitability of orodispersible systems for improving therapeutic efficiency (42).

Mechanism of Action (D_2 Receptor Antagonism and Prokinetic Effect)

Metoclopramide exerts its pharmacological action primarily through antagonism of dopamine D_2 receptors located in the chemoreceptor trigger zone (CTZ) of the central nervous system, thereby suppressing nausea and vomiting (43). In addition to its central antiemetic action, metoclopramide enhances gastrointestinal motility by promoting acetylcholine release in the enteric nervous system (44).

The drug also exhibits weak antagonistic activity at 5-HT_3 receptors and agonistic effects at 5-HT_4 receptors, contributing to its prokinetic properties (45). These combined mechanisms accelerate gastric emptying, increase lower esophageal sphincter tone, and improve intestinal transit (46).

The dual central and peripheral actions of metoclopramide underscore the importance of rapid systemic availability, as delayed absorption may compromise therapeutic efficacy, particularly in acute emetic conditions (47).

Challenges: Bitterness, Stability, and First-Pass Metabolism

Despite its favorable pharmacokinetic profile, metoclopramide presents several formulation-related challenges. One of the most significant limitations is its intensely bitter taste, which is attributed to rapid dissolution in saliva and subsequent interaction with taste receptors (48). This issue is particularly critical in orodispersible systems, where the drug is exposed directly in the oral cavity (49).

Stability concerns also arise due to the drug's susceptibility to environmental factors such as light, temperature, and moisture, which may lead to degradation and reduced shelf-life (50). Additionally, hepatic first-pass metabolism significantly reduces systemic drug availability, contributing to variability in therapeutic response (51).

To overcome these limitations, advanced formulation strategies such as nanocomposite encapsulation and polymer-based taste masking have been explored. These approaches aim to reduce drug–taste receptor interaction, enhance stability, and optimize drug release kinetics, thereby improving overall formulation performance (52–60).

III. FUNDAMENTALS OF ORODISPERSIBLE DRUG DELIVERY SYSTEMS

• Definition and Classification (ODTs, Films, Granules)

Definition

Orodispersible drug delivery systems (ODDS) are solid dosage forms engineered to disintegrate rapidly in the oral cavity (typically ⩽30 – 60 s) in the presence of saliva, without the need for water, resulting in prompt drug release (61,62). Regulatory bodies such as the FDA define orally disintegrating tablets (ODTs) as solid oral dosage forms that disintegrate rapidly when placed on the tongue, generally within seconds (63).

Classification of ODDS

a) Orodispersible Tablets (ODTs)

- Most widely used ODDS due to ease of manufacturing and stability (64).
- Prepared by techniques such as direct compression, lyophilization, sublimation, and spray drying (65).

- Incorporate superdisintegrants and porous excipients to facilitate rapid breakup (66).

b) Orodispersible Films (ODFs)
- Thin polymeric films that dissolve on the tongue, providing ultra-fast disintegration and improved patient acceptability (67).
- Suitable for low-dose drugs and enable dose uniformity through solvent casting or hot-melt extrusion (68).

c) Orodispersible Granules and Powders
- Multi-unit particulate systems designed to disperse rapidly in saliva (69).
- Offer flexibility in dosing and improved stability compared to liquid formulations (70).

d) Emerging Systems
- Include nanocomposite-loaded ODTs, 3D-printed ODDS, and hybrid polymer-based systems (71).
- Enable precision dosing, controlled release, and enhanced taste masking (72).

• Disintegration Mechanisms (Wicking, Swelling, Deformation)

Rapid disintegration in ODDS is governed by a combination of physicochemical processes:

a) Wicking (Capillary Action)
- Water is drawn into the porous matrix of the tablet via capillary forces (73).
- Leads to weakening of interparticulate bonds and initiation of disintegration (74).

b) Swelling Mechanism
- Superdisintegrants (e.g., sodium starch glycolate) absorb water and swell (75).
- Swelling generates internal pressure, causing tablet rupture (76).

c) Deformation Recovery Mechanism
- Particles compressed during tableting regain their original shape upon hydration (77).
- This recovery induces stress within the matrix, promoting disintegration (78).

d) Combined Mechanisms
- In practical formulations, these mechanisms act synergistically, resulting in rapid disintegration and drug release (79).

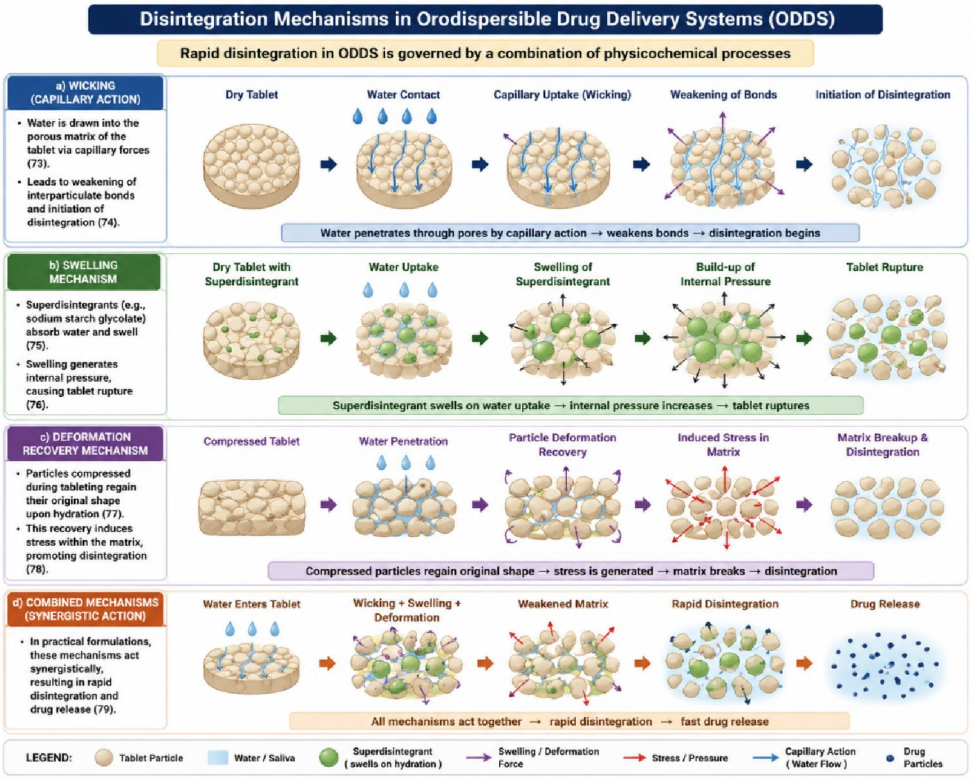

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Figure 3: Disintegration Mechanisms in Orodispersible Drug Delivery Systems: Wicking, Swelling, Deformation, and Synergistic Action

Table 1: Advantages of Orodispersible Drug Delivery Systems (ODDS) over Conventional Oral Dosage Forms

S. No.	Advantage	Description	Reference
1	Improved Patient Compliance	Particularly beneficial for pediatric, geriatric, and dysphagic patients	(80)
2	Rapid Onset of Action	Fast disintegration leads to quicker dissolution and absorption	(81)
3	No Requirement of Water	Enables administration in emergency or ambulatory conditions	(82)
4	Enhanced Bioavailability	Partial pregastric absorption may reduce first-pass metabolism	(83)
5	Better Patient Acceptability	Taste-masked formulations improve palatability	(84)
6	Reduced Risk of Choking	Eliminates swallowing difficulties associated with conventional tablets	(85)

• Critical Quality Attributes (CQAs)

For successful formulation of ODDS, several critical quality attributes must be optimized:

a) Disintegration Time

- Should be ⩽30 seconds for optimal performance (86).

b) Mechanical Strength (Hardness & Friability)

- Tablets must be strong enough to withstand handling yet disintegrate rapidly (87).

c) Wetting Time and Water Absorption Ratio

- Indicators of tablet hydration efficiency (88).

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d) Drug Content Uniformity

- Ensures dose accuracy and therapeutic consistency (89).

e) Dissolution Profile

- Should demonstrate rapid and complete drug release (90).

f) Palatability (Taste Masking Efficiency)

- Critical for patient acceptance, especially in bitter drugs like metoclopramide (61).

g) Stability

- Formulations must maintain integrity under temperature and humidity variations (62).

IV. TASTE MASKING: PRINCIPLES AND CHALLENGES

• Physiology of Taste Perception

Taste perception is a complex sensory process mediated by specialized taste receptor cells located within taste buds on the tongue, primarily concentrated in fungiform, foliate, and circumvallate papillae (91). These receptor cells detect five primary taste modalities—sweet, sour, salty, bitter, and umami—through distinct molecular pathways involving G-protein coupled receptors (GPCRs) and ion channels (92).

Bitter taste perception is particularly significant in pharmaceutical sciences, as it serves as a protective mechanism against potentially toxic substances. Bitter compounds interact mainly with T2R receptors, a family of GPCRs that trigger intracellular signaling cascades involving gustducin activation, calcium release, and neurotransmitter signaling to the brain (93).

In the context of oral drug delivery, rapid dissolution of a drug in saliva leads to immediate interaction with these taste receptors, resulting in perception of bitterness. Therefore, effective taste masking strategies must either prevent drug dissolution in saliva or block interaction with taste receptors, thereby minimizing sensory detection (94).

• Mechanisms of Bitterness in Metoclopramide

Metoclopramide exhibits pronounced bitterness primarily due to its high aqueous solubility and rapid dissolution in saliva, which facilitates immediate interaction with taste receptors (95). The presence of ionizable functional groups in its molecular structure enhances its solubility under physiological pH conditions, increasing its availability in dissolved form for receptor binding.

Additionally, the drug's moderate lipophilicity enables efficient interaction with the hydrophobic binding pockets of T2R receptors, further intensifying the bitter taste perception. The rapid release of free drug molecules in the oral cavity leads to a high local concentration, exceeding the bitterness threshold and resulting in strong sensory response.

These characteristics make metoclopramide a challenging candidate for orodispersible formulations, necessitating advanced taste masking approaches such as polymer coating, ion-exchange complexation, and nanocomposite encapsulation to effectively reduce drug–receptor interaction without compromising drug release in the gastrointestinal tract.

Overview of taste masking strategies:

Table 2: Overview of Taste Masking Strategies in Orodispersible Drug Delivery Systems

S. No.	Strategy Type	Approach	Mechanism of Taste Masking	Key Materials/Examples	Advantages	Limitations
1	Physical Methods	Coating	Forms a barrier around drug particles to prevent interaction with taste receptors	Polymer coatings (Eudragit, ethyl cellulose)	Effective for highly bitter drugs; controlled release possible	May delay drug release if coating is too thick
		Encapsulation	Drug is entrapped within micro/nanocarriers,	Nanoparticles, liposomes, microspheres	Enhances stability and taste masking	Complex formulation and scale-up

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			reducing exposure to saliva		simultaneously	challenges
2	Chemical Methods	Complexation	Drug forms complexes with carriers, reducing free drug concentration in saliva	Ion-exchange resins, cyclodextrins	Highly effective for soluble bitter drugs	Possible incomplete drug release in GI tract
		Prodrug Approach	Chemical modification of drug to reduce bitterness	Ester prodrugs, derivatives	Eliminates bitterness at molecular level	Requires metabolic conversion; regulatory complexity
3	Organoleptic Methods	Flavors	Masks unpleasant taste using sensory perception	Fruit flavors, mint, vanilla	Simple and cost-effective	Not effective alone for highly bitter drugs
		Sweeteners	Competes with bitter taste perception	Aspartame, sucralose, saccharin	Improves palatability	Limited masking efficiency for strong bitterness

• Limitations of conventional methods

Conventional taste masking strategies, including organoleptic approaches (flavors and sweeteners), simple polymer coating, and basic complexation techniques, exhibit several limitations that restrict their effectiveness, particularly for highly bitter and water-soluble drugs such as metoclopramide.

a) Incomplete Masking of Intense Bitterness

Traditional methods such as sweeteners and flavoring agents primarily act by modulating sensory perception rather than eliminating drug–receptor interaction, making them insufficient for drugs with low bitterness thresholds. Highly soluble drugs dissolve rapidly in saliva, leading to immediate exposure to taste receptors and persistent bitterness despite masking attempts.

b) Premature Drug Release in Oral Cavity

Conventional coating and complexation techniques may fail to fully prevent drug release in saliva. Thin or imperfect polymer coatings can allow drug diffusion, while weak drug–carrier complexes may dissociate in the oral environment, resulting in inadequate taste masking.

c) Compromise Between Taste Masking and Drug Release

A critical challenge lies in balancing effective taste masking with rapid drug release. Increasing coating thickness or strengthening drug–polymer interactions may improve masking but can delay disintegration and dissolution, adversely affecting onset of action—especially problematic in orodispersible systems.

d) Limited Efficiency for Highly Water-Soluble Drugs

Conventional approaches are less effective for drugs with high aqueous solubility, as rapid dissolution increases the concentration of free drug in saliva beyond the bitterness threshold. This is particularly relevant for metoclopramide, where fast dissolution intensifies taste perception.

e) Stability and Manufacturing Constraints

Some taste masking techniques, such as coating and complexation, may introduce stability issues related to moisture sensitivity, temperature variation, and polymer degradation. Additionally, processes like microencapsulation may involve complex manufacturing steps, affecting scalability and reproducibility.

f) Variability in Patient Perception

Taste perception is inherently subjective and influenced by age, genetics, and physiological conditions. As a result, organoleptic methods may show inconsistent performance across different patient populations, limiting their universal applicability.

V. FUNCTIONAL POLYMERS IN TASTE MASKING

Classification of Polymers (Natural, Synthetic, Semi-Synthetic)

Functional polymers play a pivotal role in modern taste masking strategies by modulating drug release and minimizing interaction with taste receptors. These polymers can be broadly classified based on their origin and chemical characteristics:

a) Natural Polymers

Natural polymers such as chitosan, alginate, gelatin, and starch derivatives are widely used due to their biocompatibility, biodegradability, and low toxicity (96). These polymers can form hydrogels or viscous matrices that entrap drug molecules, thereby reducing their availability in saliva. However, variability in physicochemical properties and batch-to-batch inconsistency may limit their reproducibility (97).

b) Semi-Synthetic Polymers

Semi-synthetic polymers, including cellulose derivatives (e.g., HPMC, CMC, HPC), offer improved stability and controlled functionality compared to natural polymers (98). Their tunable viscosity and swelling behavior enable effective modulation of drug release, making them suitable for both taste masking and controlled delivery applications (99).

c) Synthetic Polymers

Synthetic polymers such as polymethacrylates (Eudragit), polyvinylpyrrolidone (PVP), and polyethylene glycol (PEG) are extensively used due to their well-defined structure and reproducible performance (100). These polymers are particularly effective in taste masking due to their ability to form coatings or matrices that prevent drug release in the oral cavity while allowing release under specific physiological conditions (101).

Ion-Exchange Resins and Polymeric Complexes

Ion-exchange resins represent a highly effective class of functional polymers used for taste masking of ionic drugs. These resins form drug–resin complexes (resinates) through reversible ionic interactions, thereby reducing the concentration of free drug available for interaction with taste receptors (102).

In the oral cavity, the absence of competing ions limits drug release, ensuring effective taste masking. Upon reaching the gastrointestinal tract, exchange with physiological ions (e.g., Na^+, H^+, Cl^-) facilitates rapid drug release (103).

Polymeric complexation using materials such as cyclodextrins and polymethacrylates further enhances taste masking by encapsulating drug molecules within molecular cavities or forming insoluble complexes (104). These approaches are particularly advantageous for highly soluble drugs like metoclopramide, where conventional methods fail to adequately suppress bitterness (105).

pH-Sensitive and Stimuli-Responsive Polymers

pH-sensitive polymers are designed to exhibit differential solubility based on environmental pH, making them ideal for taste masking applications. For example, Eudragit E remains insoluble at salivary pH (~6.8) but dissolves rapidly in acidic gastric conditions, enabling selective drug release (106).

Stimuli-responsive polymers, including thermo-responsive and enzyme-sensitive systems, further enhance formulation performance by enabling site-specific or condition-triggered drug release (107). These polymers prevent premature drug release in the oral cavity while ensuring rapid availability in the gastrointestinal tract, thereby optimizing both palatability and therapeutic efficacy (108).

Hydrophilic vs Hydrophobic Polymer Matrices

The selection of polymer matrix significantly influences drug release behavior and taste masking efficiency:

a) Hydrophilic Polymers

Hydrophilic polymers such as HPMC and PVP rapidly hydrate and form gels upon contact with saliva (109). While they facilitate quick disintegration, their high water affinity may allow partial drug release in the oral cavity, potentially compromising taste masking efficiency.

b) Hydrophobic Polymers

Hydrophobic polymers such as ethyl cellulose and polymethacrylates provide superior taste masking by limiting water penetration and drug diffusion (110). These polymers act as effective barriers, preventing drug release in saliva while enabling controlled release in gastric conditions.

c) Hybrid Systems

Combining hydrophilic and hydrophobic polymers allows optimization of both disintegration time and taste masking, resulting in balanced formulation performance (111).

Role in Controlled Release vs Immediate Disintegration

Functional polymers play a dual role in modulating drug release behavior:

a) Controlled Release Systems

Polymers such as ethyl cellulose and high-viscosity HPMC are used to sustain drug release, ensuring prolonged therapeutic action (112). However, excessive retardation of drug release may delay onset of action, which is undesirable in orodispersible formulations.

b) Immediate Release Systems

In ODDS, polymers must ensure minimal drug release in the oral cavity while allowing rapid release in the gastrointestinal tract (113). This requires precise selection of polymer type, concentration, and physicochemical properties.

c) Balancing Functionality

The challenge in designing ODDS lies in achieving a balance between effective taste masking and rapid disintegration, which can be accomplished through optimized polymer combinations and advanced formulation strategies (114–120).

VI. NANOCOMPOSITE-BASED DRUG DELIVERY SYSTEMS

Nanocomposite-based drug delivery systems represent an advanced class of hybrid formulations in which drug molecules are incorporated within nanoscale carriers embedded in polymeric or inorganic matrices, enabling multifunctional performance including taste masking, controlled release, and enhanced bioavailability (121,122). These systems combine the high surface area and permeability advantages of nanotechnology with the structural and release-controlling properties of polymers, resulting in improved physicochemical and biopharmaceutical performance. Based on composition, nanocomposites can be broadly classified into polymer-based systems, lipid–polymer hybrid systems, and inorganic–organic hybrid nanocomposites, each offering distinct advantages in terms of drug loading, stability, and release kinetics (123).

Among the various nanocarrier systems, polymeric nanoparticles such as nanospheres and nanocapsules are widely utilized due to their biodegradability and ability to provide controlled drug release. These systems, typically formulated using polymers such as PLGA, chitosan, and polyvinylpyrrolidone, effectively encapsulate drug molecules and minimize their diffusion into saliva, thereby contributing to efficient taste masking (124,125). Lipid-based systems,

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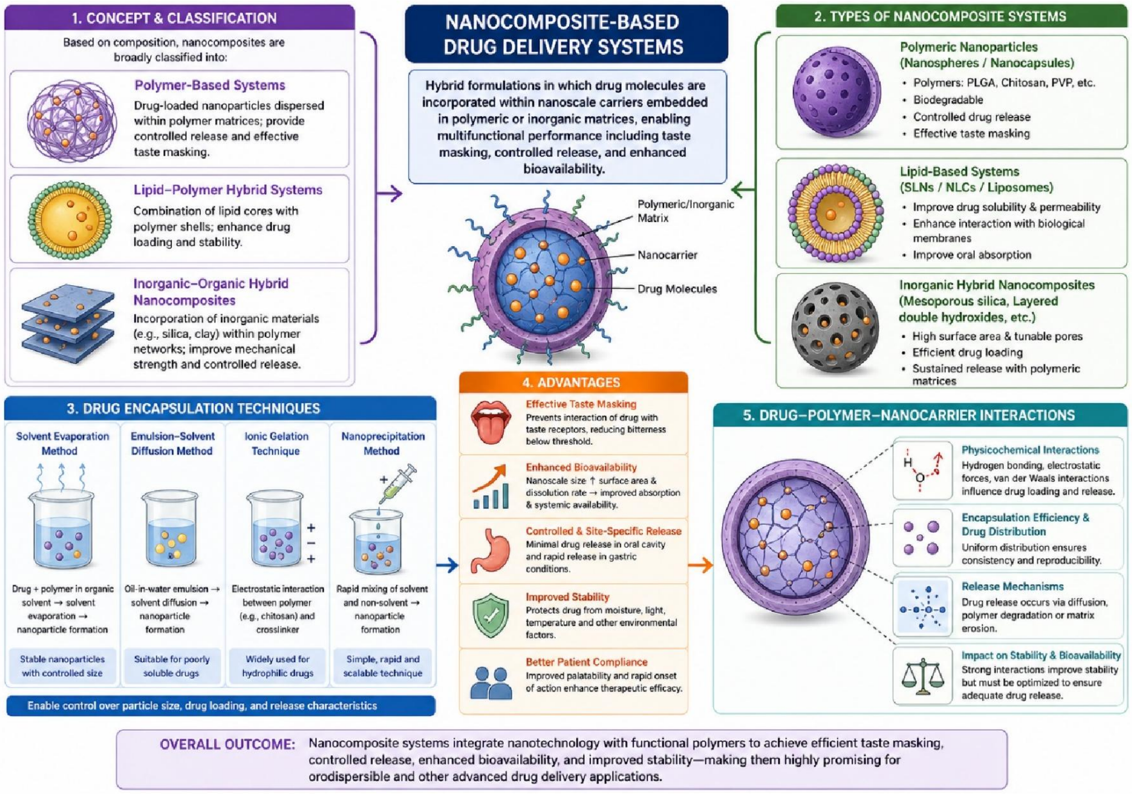
including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, further enhance drug solubility and permeability due to their lipidic nature, which facilitates interaction with biological membranes and improves oral absorption (126,127). Inorganic hybrid nanocomposites, such as mesoporous silica nanoparticles and layered double hydroxides, provide high surface area and tunable pore structures, enabling efficient drug loading and sustained release when combined with polymeric matrices (128,129).

The encapsulation of drugs within nanocomposites is achieved through various techniques that allow precise control over particle size, drug loading, and release characteristics. Methods such as solvent evaporation, emulsion–solvent diffusion, ionic gelation, and nanoprecipitation are commonly employed depending on the physicochemical properties of the drug and polymer (130–133). These techniques enable the formation of stable nanosystems with uniform particle distribution and high encapsulation efficiency, which are critical parameters influencing formulation performance (134).

Nanocomposite systems offer significant advantages in both taste masking and bioavailability enhancement. Encapsulation of drug molecules within nanocarriers prevents direct interaction with taste receptors in the oral cavity, thereby reducing bitterness below perceptible thresholds (135). Additionally, the nanoscale size of these carriers increases surface area and dissolution rate, leading to improved drug absorption and systemic availability (136). Polymer matrices further enable controlled and site-specific drug release, ensuring minimal release in the oral cavity and rapid release in gastric conditions, which is essential for orodispersible drug delivery systems (137). Moreover, nanocomposites enhance drug stability by protecting active pharmaceutical ingredients from environmental degradation factors such as moisture, light, and temperature (138). These combined advantages contribute to improved patient compliance and therapeutic efficacy (139).



1. CONCEPT & CLASSIFICATION

Based on composition, nanocomposites are broadly classified into:

Polymer-Based Systems
Drug-loaded nanoparticles dispersed within polymer matrices; provide controlled release and effective taste masking.

Lipid–Polymer Hybrid Systems
Combination of lipid cores with polymer shells; enhance drug loading and stability.

Inorganic–Organic Hybrid Nanocomposites
Incorporation of inorganic materials (e.g., silica, clay) within polymer networks; improve mechanical strength and controlled release.

NANOCOMPOSITE-BASED DRUG DELIVERY SYSTEMS

Hybrid formulations in which drug molecules are incorporated within nanoscale carriers embedded in polymeric or inorganic matrices, enabling multifunctional performance including taste masking, controlled release, and enhanced bioavailability.

2. TYPES OF NANOCOMPOSITE SYSTEMS

Polymeric Nanoparticles (Nanospheres / Nanocapsules)
- Polymers: PLGA, Chitosan, PVP, etc.
- Biodegradable
- Controlled drug release
- Effective taste masking

Lipid-Based Systems (SLNs / NLCs / Liposomes)
- Improve drug solubility & permeability
- Enhance interaction with biological membranes
- Improve oral absorption

Inorganic Hybrid Nanocomposites (Mesoporous silica, Layered double hydroxides, etc.)
- High surface area & tunable pores
- Efficient drug loading
- Sustained release with polymeric matrices

3. DRUG ENCAPSULATION TECHNIQUES

Solvent Evaporation Method	Emulsion–Solvent Diffusion Method	Ionic Gelation Technique	Nanoprecipitation Method
Drug + polymer in organic solvent → solvent evaporation → nanoparticle formation	Oil-in-water emulsion → solvent diffusion → nanoparticle formation	Electrostatic interaction between polymer (e.g., chitosan) and crosslinker	Rapid mixing of solvent and non-solvent → nanoparticle formation
Stable nanoparticles with controlled size	Suitable for poorly soluble drugs	Widely used for hydrophilic drugs	Simple, rapid and scalable technique

Enable control over particle size, drug loading, and release characteristics

4. ADVANTAGES

Effective Taste Masking
Prevents interaction of drug with taste receptors, reducing bitterness below threshold.

Enhanced Bioavailability
Nanoscale size ↑ surface area & dissolution rate → improved absorption & systemic availability.

Controlled & Site-Specific Release
Minimal drug release in oral cavity and rapid release in gastric conditions.

Improved Stability
Protects drug from moisture, light, temperature and other environmental factors.

Better Patient Compliance
Improved palatability and rapid onset of action enhance therapeutic efficacy.

5. DRUG–POLYMER–NANOCARRIER INTERACTIONS

Physicochemical Interactions
Hydrogen bonding, electrostatic forces, van der Waals interactions influence drug loading and release.

Encapsulation Efficiency & Drug Distribution
Uniform distribution ensures consistency and reproducibility.

Release Mechanisms
Drug release occurs via diffusion, polymer degradation or matrix erosion.

Impact on Stability & Bioavailability
Strong interactions improve stability but must be optimized to ensure adequate drug release.

OVERALL OUTCOME: Nanocomposite systems integrate nanotechnology with functional polymers to achieve efficient taste masking, controlled release, enhanced bioavailability, and improved stability—making them highly promising for orodispersible and other advanced drug delivery applications.

Figure 4: Integrated Overview of Nanocomposite Drug Delivery Systems Illustrating Structural Classification, Encapsulation Strategies, and Drug–Polymer–Nanocarrier Interactions

The overall performance of nanocomposite systems is governed by complex interactions between the drug, polymer, and nanocarrier. Physicochemical interactions such as hydrogen bonding, electrostatic forces, and van der Waals interactions play a critical role in determining drug loading, encapsulation efficiency, and release behavior (140). Uniform distribution of the drug within the nanocarrier ensures consistent formulation performance and reproducibility (141). Drug release from nanocomposites typically occurs through mechanisms such as diffusion, polymer degradation, or matrix erosion, depending on the system design (142–144). While strong drug–polymer interactions can enhance stability, they must be carefully optimized to ensure adequate drug release and bioavailability (145–150).

VII. FORMULATION STRATEGIES FOR ORODISPERSIBLE TABLETS

The formulation of orodispersible tablets (ODTs) requires a strategic balance between rapid disintegration, mechanical strength, and effective taste masking, which is achieved through the careful selection of formulation techniques and excipients. Among the various approaches, direct compression is the most widely employed method due to its simplicity, cost-effectiveness, and scalability. This technique utilizes superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate to facilitate rapid tablet breakup through mechanisms including wicking and swelling, while maintaining adequate tablet hardness and friability (151,152). The success of direct compression largely depends on the use of co-processed excipients that enhance flow properties and compressibility, ensuring uniform tablet formation and consistent performance (153).

Freeze-drying (lyophilization) is another advanced technique that produces highly porous and rapidly disintegrating tablets. In this method, the drug is dispersed in a suitable matrix and frozen, followed by sublimation of the solvent under reduced pressure to create a sponge-like structure (154). The resulting tablets exhibit extremely fast disintegration due to high porosity and rapid water uptake; however, they are often mechanically fragile and require specialized packaging, which can increase production costs (155).

Techniques such as spray drying and sublimation further enhance tablet porosity and disintegration behavior. Spray drying involves the formation of porous particles by rapid solvent evaporation, resulting in improved wettability and dissolution characteristics (156). Sublimation, on the other hand, incorporates volatile substances such as camphor or ammonium bicarbonate into the tablet matrix, which are later removed to create a porous structure that facilitates rapid disintegration (157). These methods are particularly useful in optimizing the balance between mechanical strength and disintegration efficiency.

The incorporation of nanocomposites into the ODT matrix represents a novel strategy for enhancing both taste masking and drug delivery performance. Nanocomposite systems, including polymeric nanoparticles and lipid-based carriers, can be uniformly dispersed within the tablet matrix to prevent premature drug release in the oral cavity while enabling rapid release under gastric conditions (158,159). This approach not only improves palatability but also enhances drug stability and bioavailability, making it highly suitable for drugs with poor taste and solubility challenges.

The selection of superdisintegrants and excipients is a critical determinant of ODT performance. Superdisintegrants play a key role in ensuring rapid tablet breakup, while excipients such as diluents, binders, and lubricants influence compressibility, stability, and mouthfeel (160). The use of multifunctional excipients and co-processed materials allows for optimization of multiple formulation parameters simultaneously, thereby improving overall tablet performance. Additionally, the integration of taste masking agents, polymers, and nanocarriers into the formulation further enhances patient acceptability and therapeutic efficiency (161-165).

VIII. EVALUATION OF ORODISPERSIBLE TABLETS

The evaluation of orodispersible tablets (ODTs) involves a comprehensive assessment of both pre-compression and post-compression parameters to ensure optimal performance, quality, and patient acceptability.

- **Pre-compression Studies**

Pre-compression parameters are critical for ensuring uniform die filling and consistent tablet quality. These include flow properties and compressibility of the powder blend. Flowability is typically assessed using parameters such as angle of repose, Carr's index, and Hausner's ratio, which indicate the ability of the powder to flow smoothly during tableting. Good flow properties are essential to prevent weight variation and ensure content uniformity. Compressibility studies evaluate the ability of the powder to consolidate into a stable compact under pressure, which directly influences tablet hardness and mechanical integrity.

• Post-compression Parameters

a) Hardness and Friability

Tablet hardness determines the mechanical strength of ODTs, ensuring they can withstand handling, packaging, and transportation. Friability testing evaluates the tendency of tablets to crumble or break under mechanical stress. An optimal balance between hardness and friability is essential, as excessive hardness may delay disintegration, while low hardness may compromise tablet integrity.

b) Disintegration and Wetting Time

Disintegration time is one of the most critical parameters for ODTs and typically should be within 30 seconds. Wetting time measures the time required for saliva or aqueous medium to penetrate the tablet matrix, which directly correlates with disintegration behavior. Faster wetting and disintegration indicate better performance of superdisintegrants.

c) Water Absorption Ratio

The water absorption ratio reflects the ability of the tablet to absorb saliva, which facilitates rapid swelling and disintegration. It is calculated based on the weight difference before and after water uptake. Higher water absorption generally corresponds to faster tablet disintegration.

• In Vitro Dissolution Studies

Dissolution studies are performed to evaluate the rate and extent of drug release from the ODT. These studies are typically conducted using USP dissolution apparatus under simulated physiological conditions. Rapid and complete drug release is essential for achieving fast onset of action. Dissolution profiles also help in understanding drug release kinetics and ensuring batch-to-batch consistency.

• Taste Evaluation Methods

a) Electronic Tongue

The electronic tongue is an advanced analytical tool that mimics human taste perception using sensor arrays. It provides objective and reproducible data for evaluating taste masking efficiency and is particularly useful in formulation development.

b) Human Sensory Panel

Human taste evaluation involves trained volunteers who assess bitterness, mouthfeel, and overall palatability. Although subjective, it remains the gold standard for taste assessment. Ethical considerations and safety protocols must be followed during such studies.

• Stability Studies (ICH Guidelines)

Stability studies are conducted according to ICH guidelines (Q1A) to evaluate the effect of environmental factors such as temperature, humidity, and light on the formulation. Both accelerated (40°C ± 2°C / 75% RH ± 5%) and long-term conditions (25°C ± 2°C / 60% RH ± 5%) are used to assess changes in physical appearance, drug content, disintegration time, and dissolution profile. Stability testing ensures the formulation maintains its quality, safety, and efficacy throughout its shelf life.

IX. COMPARATIVE ANALYSIS: CONVENTIONAL VS NANOCOMPOSITE SYSTEMS

Table X. Comparative Analysis of Conventional vs Nanocomposite-Based Orodispersible Drug Delivery Systems

S. No.	Parameter	Conventional Systems	Nanocomposite-Based Systems	Scientific Interpretation	Reference
1	Taste Masking Efficiency	Limited; relies on sweeteners, flavors, or basic coating; often	High efficiency due to encapsulation preventing receptor interaction	Reduced drug exposure in saliva improves masking	(166,167)

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		insufficient			
2	Drug Release Kinetics	Rapid but uncontrolled; possible premature release in oral cavity	Controlled and site-specific release (minimal oral, rapid gastric release)	Polymer–nanocarrier systems enable pH-responsive delivery	(168,169)
3	Bioavailability	Moderate; affected by first-pass metabolism	Enhanced due to improved solubility and permeability	Nanoscale carriers increase surface area and absorption	(170,171)
4	Stability	Susceptible to environmental degradation	Improved due to protective encapsulation	Nanocarriers protect against moisture, light, and oxidation	(172)
5	Patient Compliance & Acceptability	Moderate due to bitterness and swallowing difficulty	High due to improved palatability and ease of use	Better taste masking enhances adherence	(173)
6	Dose Uniformity	May vary in conventional systems	Highly uniform due to nanoparticle dispersion	Ensures reproducibility and consistent dosing	(174)
7	Manufacturing Complexity	Simple and cost-effective	Complex; requires specialized techniques	Trade-off between simplicity and performance	(175)
8	Scalability	Easily scalable	Challenging at industrial scale	Requires process optimization and validation	(176)
9	Therapeutic Efficiency	Adequate but limited by pharmacokinetics	Superior due to optimized delivery and absorption	Improved PK leads to better outcomes	(177)
10	Application Scope	Limited to conventional delivery	Advanced targeted and patient-centric systems	Enables next-generation drug delivery	(178)

X. REGULATORY AND QUALITY CONSIDERATIONS

• Guidelines for Orodispersible Tablets (FDA, EMA)

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide specific guidance for the development and evaluation of orodispersible tablets (ODTs). According to FDA guidance, ODTs are defined as solid oral dosage forms that disintegrate rapidly in the oral cavity, typically within 30 seconds, without the need for water (179). Similarly, the European Pharmacopoeia specifies that orodispersible tablets should disperse or disintegrate within 3 minutes, emphasizing the importance of rapid disintegration and patient acceptability (180).

Regulatory expectations for ODTs include evaluation of critical parameters such as disintegration time, mechanical strength, dissolution profile, and palatability, along with appropriate taste masking strategies for bitter drugs (181). Additionally, excipients used in ODT formulations must comply with safety and regulatory standards, particularly for special populations such as pediatric and geriatric patients (182).

• ICH Quality Guidelines (Q8, Q9, Q10)

The International Council for Harmonisation (ICH) provides a comprehensive framework for pharmaceutical development through guidelines such as ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System).

ICH Q8 emphasizes a science- and risk-based approach to formulation development, encouraging the identification of critical quality attributes (CQAs) and critical process parameters (CPPs) that influence product performance (183). ICH Q9 focuses on systematic risk assessment and management to ensure product quality and patient safety throughout the product lifecycle (184). ICH Q10 establishes a robust pharmaceutical quality system that integrates development, manufacturing, and continuous improvement processes (185).

Together, these guidelines support a holistic and systematic approach to the design and control of ODT formulations, ensuring consistent quality and regulatory compliance (186).

• Scale-Up and Manufacturing Challenges

Despite significant advancements in formulation technologies, the scale-up of ODTs, particularly those incorporating nanocomposite systems, presents several challenges. One of the primary issues is maintaining uniformity in drug distribution and nanoparticle dispersion during large-scale production (187). Variability in particle size, mixing efficiency, and compression parameters can significantly affect product performance and reproducibility.

Additionally, techniques such as lyophilization and nanoparticle synthesis are often associated with high production costs and complex processing requirements, limiting their industrial scalability (188). Mechanical fragility of ODTs, sensitivity to environmental conditions (humidity and temperature), and packaging constraints further complicate manufacturing processes (189). Addressing these challenges requires optimization of formulation parameters and adoption of advanced manufacturing technologies (190).

• Quality by Design (QbD) Approach

The Quality by Design (QbD) approach has emerged as a key strategy for the systematic development of pharmaceutical formulations, including ODTs. QbD involves defining the Quality Target Product Profile (QTPP) and identifying critical material attributes (CMAs) and process parameters that influence product quality (191).

Through the use of statistical tools such as Design of Experiments (DoE) and response surface methodology, QbD enables optimization of formulation variables and establishment of a design space within which consistent product quality can be achieved (192). This approach enhances process understanding, reduces variability, and facilitates regulatory flexibility.

In the context of nanocomposite-based ODTs, QbD plays a crucial role in optimizing parameters such as nanoparticle size, polymer concentration, and disintegration behavior, ensuring reproducible and high-quality formulations (193–195).

XI. CHALLENGES AND LIMITATIONS

• Scale-Up and Reproducibility Issues

The transition from laboratory-scale formulation to industrial-scale production of orodispersible tablets, particularly those incorporating nanocomposite systems, presents significant challenges. Maintaining uniformity in nanoparticle size distribution, drug loading, and dispersion within the tablet matrix becomes increasingly complex at larger scales. Variations in processing conditions such as mixing, drying, and compression can lead to batch-to-batch inconsistencies, ultimately affecting product quality and performance. Furthermore, ensuring reproducibility of nanocarrier synthesis and integration into the formulation requires precise control over critical process parameters, which may not always be feasible in large-scale manufacturing environments.

• Cost and Material Constraints

The development of advanced nanocomposite-based drug delivery systems often involves the use of specialized polymers, lipids, and nanocarriers, which can significantly increase production costs. Techniques such as lyophilization, nanoparticle fabrication, and advanced coating processes require sophisticated equipment and infrastructure, further adding to the economic burden. Additionally, the availability and scalability of high-quality raw materials may be limited, particularly for novel or proprietary excipients. These cost-related challenges can hinder the widespread industrial adoption of such advanced formulations.

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• Regulatory Hurdles for Nanotechnology-Based Systems

Nanotechnology-based drug delivery systems face complex regulatory challenges due to their unique physicochemical properties and lack of standardized evaluation frameworks. Regulatory agencies require comprehensive characterization of nanocarriers, including particle size distribution, surface properties, and potential toxicity, which increases the complexity of approval processes. The absence of universally accepted guidelines specific to nanomedicine further complicates regulatory pathways, leading to extended development timelines and uncertainty in approval outcomes. Additionally, demonstrating safety, efficacy, and quality consistency for nanocomposite systems requires extensive data and validation.

• Long-Term Stability Concerns

Long-term stability remains a critical concern in the development of nanocomposite-based orodispersible formulations. Nanoparticles are inherently prone to aggregation, sedimentation, or structural changes over time, which can alter drug release profiles and reduce formulation efficacy. Environmental factors such as temperature, humidity, and light exposure may further accelerate degradation of both the drug and the carrier system. Ensuring physical, chemical, and microbiological stability throughout the product's shelf life requires careful optimization of formulation components, packaging, and storage conditions. These stability challenges must be addressed to ensure consistent product performance and regulatory compliance.

XII. FUTURE PERSPECTIVES

• Personalized Orodispersible Formulations

The future of orodispersible drug delivery systems is increasingly aligned with the concept of personalized medicine, where formulations are tailored to meet individual patient needs. Personalized ODTs can be designed based on patient-specific factors such as age, weight, disease condition, and genetic profile, enabling optimized dosing and improved therapeutic outcomes. This approach is particularly beneficial for populations with variable pharmacokinetics, including pediatric and geriatric patients. Customization of taste, dosage strength, and release profile further enhances patient compliance and treatment efficacy, making personalized orodispersible formulations a promising direction in patient-centric drug delivery.

• AI-Driven Formulation Design

Artificial intelligence (AI) and machine learning (ML) are emerging as powerful tools in pharmaceutical formulation development. AI-driven models can analyze large datasets to predict optimal combinations of excipients, polymers, and process parameters required for achieving desired product attributes. In the context of ODTs, AI can assist in optimizing disintegration time, taste masking efficiency, and drug release kinetics, significantly reducing trial-and-error experimentation. Predictive modeling and data-driven decision-making not only accelerate formulation development but also improve reproducibility and scalability, thereby enhancing overall efficiency in pharmaceutical research and manufacturing.

• Advanced Nanocarrier Systems (Stimuli-Responsive and Targeted Delivery)

The development of advanced nanocarrier systems represents a significant advancement in orodispersible drug delivery. Stimuli-responsive nanocarriers, which respond to environmental triggers such as pH, temperature, or enzymatic activity, enable controlled and site-specific drug release. These systems can effectively prevent drug release in the oral cavity while ensuring rapid release in the gastrointestinal tract, thereby improving both taste masking and therapeutic performance. Additionally, targeted delivery systems offer the potential to direct drugs to specific tissues or organs, enhancing therapeutic efficacy while minimizing systemic side effects. The integration of such smart nanocarriers into ODT formulations is expected to revolutionize oral drug delivery strategies.

• Integration with 3D Printing Technologies

Three-dimensional (3D) printing has emerged as a transformative technology in pharmaceutical manufacturing, offering unprecedented flexibility in the design and fabrication of dosage forms. In the context of ODTs, 3D printing enables precise control over tablet architecture, porosity, and drug distribution, allowing the development of highly customized formulations with rapid disintegration properties. This technology supports on-demand manufacturing of

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personalized dosage forms, reducing production time and enabling decentralized healthcare solutions. Furthermore, the combination of 3D printing with nanocomposite-based systems opens new avenues for the development of complex, multi-functional drug delivery platforms with enhanced performance and patient acceptability.

XIII. CONCLUSION

• Summary of Key Findings

The present review highlights the significant advancements in the design and development of smart orodispersible drug delivery systems (ODDS) for metoclopramide, emphasizing the integration of nanocomposite encapsulation and functional polymer-based taste masking strategies. Conventional formulations, although effective, are limited by issues such as poor palatability, rapid drug release in the oral cavity, and suboptimal bioavailability. In contrast, nanocomposite-based systems demonstrate superior performance by enabling efficient taste masking, controlled drug release, and enhanced stability. The role of functional polymers in modulating drug release and minimizing drug–taste receptor interaction has been identified as a critical factor in achieving optimal formulation performance. Furthermore, advanced formulation techniques and evaluation strategies contribute to the development of robust and patient-centric ODT systems.

• Clinical and Industrial Relevance

From a clinical perspective, the development of smart ODDS offers significant benefits in improving patient compliance, particularly among pediatric, geriatric, and dysphagic populations. Rapid disintegration and enhanced bioavailability ensure faster onset of action, which is crucial for the effective management of nausea and vomiting. Industrially, the incorporation of nanotechnology and advanced polymers presents opportunities for the development of next-generation pharmaceutical products with improved therapeutic efficiency. However, challenges related to scalability, cost, and regulatory compliance must be addressed to facilitate successful translation from laboratory to commercial production. The adoption of systematic approaches such as Quality by Design (QbD) further supports the development of reproducible and high-quality formulations.

• Final Outlook on Smart ODDS for Metoclopramide

The future of metoclopramide delivery lies in the continued evolution of smart, multifunctional ODDS that integrate nanotechnology, advanced polymers, and innovative manufacturing techniques. Emerging trends such as personalized medicine, AI-driven formulation design, and 3D printing are expected to further enhance the precision and efficiency of drug delivery systems. With ongoing research and technological advancements, nanocomposite-based orodispersible formulations have the potential to overcome existing limitations and establish a new standard in oral drug delivery. Overall, smart ODDS represent a promising and transformative approach for improving the therapeutic performance and patient acceptability of metoclopramide and similar pharmaceutical agents.

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