RESEARCH PAPER

Approaches to Improve The Palatability of Metronidazole : Focus on Cyclodextrin Complexation

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ABSTRACT
Metronidazole is an antimicrobial agent of the nitroimidazole class, largely employed in therapy against infections caused by anaerobic bacteria and protozoa. However, its highly bitter taste often results in poor patient compliance, particularly among children and el-derly individuals. The development of effective taste-masking strategies becomes thus essential to improve palatability and ensure adherence to treatment. Among the available approaches, cyclodextrin inclusion complexation has proven as a safe and efficient method for masking the un-pleasant taste of metronidazole. Due to their hydrophilic outer surface and hydrophobic center cavity, cyclodextrins (CDs) are cyclic oligosaccharides that may include the bitter medicinal molecule via non-covalent host-guest interactions. This complexation reduces the amount of free medication in saliva, thus lessening interactions with taste receptors, while per-mitting sufficient drug release in the digestive system. In the present review, the physicochemical and organoleptic characteristics of metronidazole, the principles of cyclodextrin inclusion complexation, as well as various manufacturing methods, such as kneading, co-evaporation, spray-drying, and lyophilisation, will be presented. This review further covers the analytical and characterisation techniques, such as phase-solubility analysis, DSC, FTIR, XRD, and NMR, used for the confirmation of the formation of complexes, as well as data from sensory and in vitro evaluation, summarizing the relation between the complexation efficiency and the respective taste masking performance. Recent developments will be highlighted, including βand hydroxypropyl-β-cyclodextrin nanofibrous and film formulations. In all, cyclodextrin complexation is a practical, efficacious, and scalable approach to formulate palatable metronidazole products, with perspectives for future development and optimization using computer-aided tools and novel oral delivery systems.

Keywords: - Metronidazole**,** Taste masking**,** Cyclodextrin complexation**,** β-Cyclodextrin (β-CD)**,** Hydroxypropyl-β-cyclodextrin (HP-β-CD)**,** Oral drug delivery**,** Patient compliance.

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1. INTRODUCTION

The oral route is the most commonly and widely used for the drug administration because it is convenient, safe, cost-effective and easy to administer[1]. But due to unpleasant taste of many active pharmaceutical ingredients, it is more challengable to develope acceptable formulations[2]. Bitter or metallic taste of drug is problematic especially among pediatric and geriatric population, where poor palatabilty reduces patient compliance which results in incomplete dosing[3]. So, taste masking is essential in modern formulation developments[4].

Metronidazole, belongs to the nitroimidazole class which is used as an antimicrobial agent for infections such as amoebiasis, giardiasis, trichomoniasis and other anaerobic bacterial diseases[5]. Though it gives better antimicrobial action but it exhibits a strong, persistent bitter and metallic taste which remains detectable even at low concentrations[6]. This affects the patient adherence, particularly in oral dosage forms

such as syrups, suspensions, chewable tablets, and other oral formulations[7]. Therefore, it is essential to improve the palatability of metronidazole to improve patient acceptability and therapeutic effectiveness[8].

There are various taste-masking strategies have been used in pharmaceutical developments like polymer coating, ion-exchange resins, solid dispersion systems, microencapsulation, and the use of flavoring or sweetening agents[9]. But it has some limitations such as it does not mask the taste sufficiently and also requires complex procedures. Sometimes it also causes instability in formulations and undesirable drug release[10]. But in the case of cyclodextrin inclusion complexation which is a simple, scalable, and effective approach for masking bitterness without alteration in drug performance[11].

Cyclodextrins including α, β and γ-cyclodextrins are cyclic oligosaccharides composed of six to eight α-(1,4)-linked D-glucopyranose units[12]. Their distinctive toroidal shape, with a hydrophilic outside and a hydrophobic inside, lets them trap hydrophobic drug molecules using non-covalent interactions such van der Waals forces, hydrogen bonding, and hydrophobic association[13]. This complexation effectively reduces drug interaction with taste receptors while maintaining solubility and controlled release properties[14].

β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) are the most commonly used cyclodextrins because they are safe, accepted by regulatories, and it has capability to hold the other molecules[15]. Beyond taste masking, cyclodextrin complexation may enhance the physicochemical properties of metronidazole, such as solubility, chemical stability, and bioavailability[16]. The complexation process can also be reversed, which means that drugs can be released in the stomach while keeping bitterness from getting into the mouth[17]. This review provides a detailed overview of metronidazole taste masking through cyclodextrin inclusion complexation. It covers all the physicochemical and organoleptic properties of metronidazole, the mechanism of cyclodextrin-based complex formation, manufacturing methods, and characterization techniques. Additionally, a summary of new developments and creative uses of metronidazole–cyclodextrin systems in current oral drug delivery platforms is provided[18].

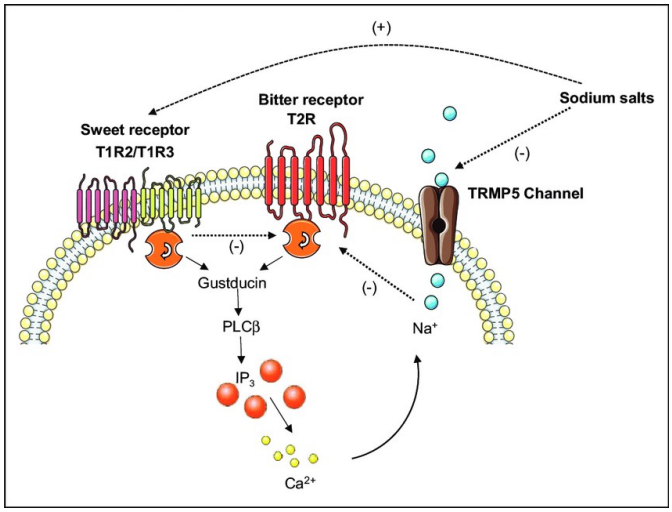

Figure 1. Schematic showing the anatomy of taste buds and how tastants (including bitter drugs) interact with taste-receptor cells, which send signals via afferent nerves to the brain.

2. METRONIDAZOLE — A BRIEF OVERVIEW

2.1. Chemical Name, Structure, and Molecular Formula

Metronidazole is chemically known as 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, and it belongs to the family of nitroimidazole derivatives[19]. It is a low–molecular-weight compound with a chemical formula of $C_6H_9N_3O_3$ and a molecular weight of 171.15 g/mol. As a solid, metronidazole is a crystalline powder, white to pale yellow in color, odorless, and of a strong bitter taste[20]. It is very soluble in alcoholic solvents such as ethanol, acetone, and chloroform, but poorly soluble in water at room temperature[21].

Table 1. Physicochemical Properties of Metronidazole

Property	Description
Chemical name	1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole
Molecular formula	$C_6H_9N_3O_3$
Molecular weight	171.15 g/mol
Appearance	White to pale-yellow crystalline powder
Odor	Odorless
Taste	Strongly bitter and metallic
Melting point	159–163 °C
Solubility	Sparingly soluble in water; freely soluble in ethanol and chloroform
pKa	~2.6
Partition coefficient (log P)	0.1–0.2
BCS classification	Class II (low solubility, high permeability)
Stability	Stable under normal storage; degrades under light exposure and alkaline conditions
Therapeutic category	Antiprotozoal and antibacterial

2.2. Pharmacological Classification

Metronidazole belongs to a class of nitroimidazole antimicrobials, with both antiprotozoal and antibacterial action[22]. Because of its wide therapeutic relevance, affordability, and favorable clinical history, it continues to be widely prescribed and remains first-line therapy for several anaerobic and protozoal infections[23].

2.3. Mechanism of Action

Metronidazole is a prodrug and exerts its effect only after bioreductive activation in susceptible microorganisms[24]. This occurs through a one electron reduction of the nitrogens on the side chain of metronidazole, creating a very reactive nitrogen species that then interacts with the DNA of the microorganism. The interaction results in breaks in the DNA strands and helix disruptions and prevents the DNA from being synthesized, ultimately resulting in cell death[25]. Even though the detailed intracellular pathways are still under investigation, DNA damage remains the widely accepted primary lethal mechanism[26].

2.4. Pharmacokinetic Profile

Oral administration of metronidazole is rapidly absorbed and nearly completely bioavailable (~90–100%) such that oral and intravenous routes are clinically interchangeable[27]. Maximum plasma concentrations usually occur within 1–2 hours and metronidazole exhibits extensive penetration into body tissues, including cerebrospinal fluid[28].
Metabolism predominantly occurs in the liver through hydroxylation and glucuronidation to produce metabolites with partial antimicrobial activity[29]. Renal excretion is the primary method of elimination, with a half-life of around 8–10 hours, increasing in hepatic dysfunction or special patient groups[30].

2.5. Organoleptic Properties

Metronidazole has an intensely bitter, metallic aftertaste even at low concentrations[31]. Reports describe unpleasant taste as one of the leading patient complaints when using oral therapy. Because of its very low bitterness threshold, it is difficult to formulate acceptable liquid and chewable dosage forms, making advanced taste-masking approaches quite necessary[32].

2.6. Clinical Uses

Indications for metronidazole include infections caused by anaerobic bacteria and protozoa: amoebiasis, giardiasis, trichomoniasis, bacterial vaginosis, intra-abdominal infections, and selected periodontal diseases[33]. These include immediate-release tablets, dispersible tablets, and suspensions. For pediatric patients, the prodrug metronidazole benzoate, with its reduced bitterness, remains preferred for liquid formulations due to improved sensory acceptance[34]. Shelf-stable oral suspensions, such as 250 mg/5 mL, are in wide use around the world, especially in low resource settings where palatability and storage stability are major formulation concerns[35]

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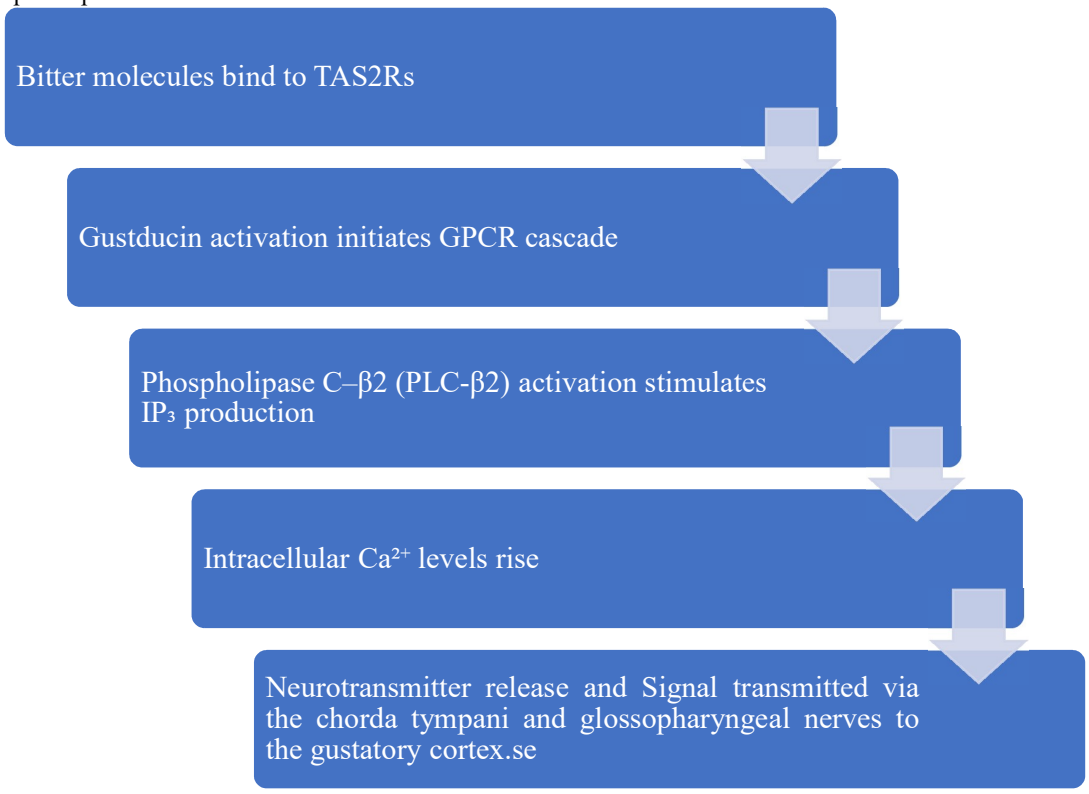
3. TASTE MASKING: CONCEPT AND MECHANISM

3.1. Concept of Taste Masking

Taste masking can be defined as the modification of the API in order to suppress the unpleasant taste Upon exposure:



Even extremely small quantities dissolved in saliva can trigger bitterness because bitter taste thresholds are often in the micromolar range[42]. Metronidazole's bitterness threshold is approximately 0.001 mg/mL, contributing to its strong perceptibility during oral administration.

without impairing its therapeutic efficacy or bioavailability[36]. This is of particular importance in pediatric and geriatric patients where bitter taste directly reduces medication adherence with a negative impact on treatment success[37].

Metronidazole has a strong bitter and metallic taste, requiring special formulation strategies to avoid the interaction of drugs with taste receptors by physical entrapment, chemical complexation, or sensory modulation[38].

3.2. Physiology of Taste Perception

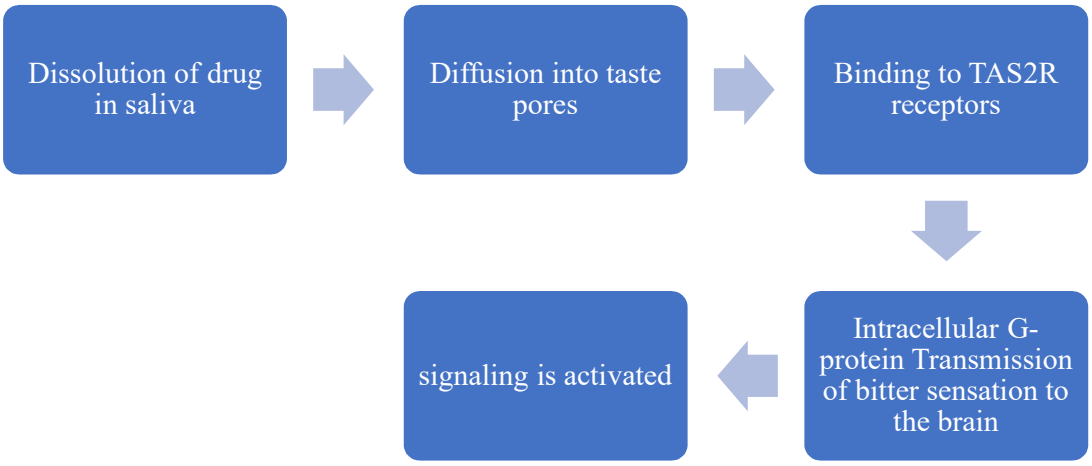
Within the human oral cavity, there are 2,000-5,000 taste buds, mainly distributed on the fungiform, foliate, and circumvallate papillae. Each taste bud contains 50-100 TRCs that are capable of detecting five basic taste modalities: sweet, sour, salty, bitter, and umami[39].

Taste Receptors and Signal Pathway:

Bitterness perception is mediated via TAS2R (Type 2 taste receptors), a subclass of G-protein-coupled receptors (GPCRs) located on type II TRCs[40 - 41].

3.3. Mechanism of Bitterness Perception

Bitterness detection involves[43]:



The intensity and duration of bitterness depend on:

a) Drug solubility in saliva
b) Affinity for TAS2Rs
c) Residence time in oral cavity

Thus, aim of taste-masking methods is to restrict dissolution in saliva or block receptor interaction[44].

3.4. General Approaches to Taste Masking

Taste masking strategies are broadly classified into physical, chemical, biochemical, and sensory approaches[45-46].

A. Physical Methods

These minimize drug exposure to taste buds through either creating a barrier or delaying release.

a) Coating Techniques:
- Polymers including Eudragit E100, ethyl cellulose, shellac, cellulose acetate phthalate are soluble in gastric fluid without dissolution in saliva [47].
- Eudragit-coated metronidazole granules are reported to significantly enhance palatability in pediatric patients[48].

b) Microencapsulation:
- Drug particles are encapsulated in microcapsules 10–1000 µm in diameter, which are made up of gelatin, PVP, alginate, PEG[49].
- Microencapsulation controls the dissolution in saliva, which improves the taste, of high benefit in metronidazole suspensions[50].

B. Chemical Approaches:

These alter the drug's physicochemical behavior.

a) Inclusion Complexation
- Cyclodextrins and ion-exchange resins, which can form stable complexes with metronidazole, prevent free drug release in the mouth [51].
- Inclusion complexes of cyclodextrin are specifically effective due to the hydrophobic cavity shielding the drug from taste receptors [52].

b) Prodrug Approach
- Chemical modification into less bitter derivatives improves palatability.
- Example: Metronidazole benzoate, used widely in pediatric suspensions, reconverts to its active form of metronidazole post-administration[53].

c) Biochemical Approaches
- Modulate biological pathways related to taste.
- Compounds such as miraculin or AMP alter receptor responsiveness.
- Flavors such as menthol and vanillin mask bitterness through sensory distraction [54].

d) Sensory Approaches
- Masking by overshadowing bitterness through:

i. Sweeteners: sucrose, sucralose, aspartame, saccharin
ii. Flavors: mint, chocolate, fruit flavors
iii. Cooling agents: menthol, xylitol, WS-3

A combination of sweeteners + flavors has reported synergistic enhancement in metronidazole oral suspensions [55-56].

4. VARIOUS TECHNIQUES USED FOR TASTE MASKING OF METRONIDAZOLE

Metronidazole is a nitroimidazole antibiotic that possesses a strongly bitter and metallic taste, which seriously influences patient compliance, especially for pediatric and geriatric patients. Various techniques were tried for improving palatability: physical coating, chemical complexation, microencapsulation, ion-exchange resin adsorption, use of cyclodextrins, and flavor/sweetener combinations. These methods aim to avoid the interaction of the drug with the taste receptors on the tongue, either by reducing the drug's

solubility in saliva or by chemically entrapping the drug until it reaches the stomach.

4.1. Coating Techniques[57]

Coating is one of the most commonly employed physical methods for the taste masking of bitter drugs. This approach involves coating the drug particles with a layer of polymer or lipid material, acting as a barrier between the drug and the taste buds.Polymer Coating.

a) Polymer Coating

- Polymers used include Eudragit E100, cellulose acetate phthalate (CAP), ethyl cellulose, and shellac.
- The polymer layer is insoluble in saliva at pH 6.8 but is soluble in the pH 1.2 of the gastric fluid to effect release immediately upon swallowing.
- Metronidazole granules coated with Eudragit E100 showed significant taste masking without compromising dissolution rate in the gastric medium.

A. Lipid Coating

- The hydrophobic film could also be formed by lipid-based materials such as glyceryl monostearate, stearic acid, and hydrogenated oils.
- Lipid coating not only masks the taste but can also enhance drug stability and flow properties.
- These coatings depend on the formulation requirement, as coatings are applied through fluid-bed coating, solvent evaporation, or melt coating techniques.

4.2.Microencapsulation[57,61]

- Microencapsulation is a process where particles of drug are entrapped in a polymeric or lipidic matrix to form microspheres or microcapsules, whose size varies from 1 µm up to several hundred micrometers.
- The core of metronidazole is coated with coating material(s) such as ethyl cellulose, alginate, gelatin, or PVP. The microcapsules prevent drug dissolution in saliva but release the drug rapidly in gastric fluid (pH 1–2).
- In one study, metronidazole microcapsules prepared with ethyl cellulose showed effective bitterness suppression and acceptable mouthfeel.
- Evaporation of the solvent and coacervation-phase separation methods are mostly applied in preparing such microcapsules.
- Microencapsulation also improves stability, reduces dose dumping, and provides for sustained release formulations.

4.3. Ion-Exchange Resin Complexation[58,62]

Ion-exchange resins are high-molecular-weight polymers possessing ionic functional groups that are capable of forming reversible complexes with ionizable drugs. Metronidazole is a slightly basic drug, so it can interact with carboxylic acid or sulfonic acid-containing resins such as Amberlite IRP 64 or Indion 204.

- Oral administration: the drug-resin complex, being undissociated in saliva, does not interact with taste buds.
- Once the complex reaches the acidic environment of the stomach, the drug is released by means of an ion exchange with gastric H^+ ions.
- Ion-exchange complexation offers a number of advantages, including chemical stability, low cost, and suitability for liquid suspensions.

  In one such study, El-Khordagui et al. prepared a metronidazole–resin complex that exhibited outstanding taste-masking efficiency, releasing its entire drug content within 30 minutes in simulated gastric fluid.

4.4.Prodrug Formation[57]

Chemical modification of metronidazole results in less bitter prodrugs that are bioconverted in vivo to the parent drug.

- The most common prodrug involved in pediatric oral suspensions is metronidazole benzoate, which is an esterified derivative.
- It is poorly soluble in saliva, thereby minimizing contact with taste buds, but is readily hydrolyzed by esterases in the gastrointestinal tract to release active metronidazole.
- Other derivatives, like metronidazole phosphate, have been investigated for administration either by injection or orally.
- This approach offers permanent masking of bitterness, yet in addition requires extra synthetic and stability studies.

4.5.Inclusion Complexation with Cyclodextrins[59,60]

- Cyclodextrins are cyclic oligosaccharides that may form inclusion complexes with a variety of drug molecules. They have a hydrophobic cavity which can accommodate the nonpolar parts of the drug and a hydrophilic outer surface, thus enhancing aqueous solubility.
- Most commonly used for taste masking are β-Cyclodextrin and hydroxypropyl-β-cyclodextrin.
- The bitter molecule of metronidazole fits into the hydrophobic cavity, preventing its interaction with taste buds.

- This complex dissociates in the acidic gastric medium, which ensures rapid release and absorption of the drug.

Methods of Complex Formation

Common techniques include:

A. Kneading method: simple & inexpensive; mixing drug & CD with a small quantity of solvent.
B. Co-evaporation: both components dissolved and solvent evaporated under vacuum.
C. Spray-drying and freeze-drying (lyophilization) - produce complexes with high inclusion efficiency.

4.6.Solid Dispersion Method[63]

- Carrier matrix such as mannitol, PEG 4000, or PVP K30, which modifies its rate of release.
- The amount of the drug released into saliva can be reduced by adjusting the carrier ratio and solubility.
- Metronidazole–PEG solid dispersions exhibited reduced bitterness and increased dissolution rate, useful in the preparation of orally disintegrating tablets.

4.7.Use of Sweeteners and Flavour Modifiers[57]

Adding sweeteners and flavoring is the easiest way of reducing bitterness, even as they are often applied in combination with other methods of bitterness reduction.

- Common sweeteners: sucrose, aspartame, sucralose, saccharin sodium.
- Flavours: orange, mint, banana, chocolate, and vanilla.
- Cooling agents, including menthol and xylitol, improve mouthfeel and contribute to a reduction of bitterness.
- The combination of sweeteners, flavors, and cyclodextrin complexation in formulation form has been reported to provide a synergistic masking effect, especially in pediatric oral liquids and chewable tablets.

4.8.Nanoparticle and Film-Based Delivery Systems[64]

Recent developments in the field of nanotechnology have presented nanofibers, nanoparticles, and oral thin films as useful vectors for taste masking. The encapsulation of metronidazole by cyclodextrin-based nanofibers and electrospun films has shown improved taste masking in addition to rapid drug release under gastric conditions. Hydroxypropyl-β-cyclodextrinloaded orodispersible films show reduced bitterness and better patient acceptability.These systems represent next-generation oral delivery platforms that combine taste masking, flexibility, and convenience.

Different methods are developed for the taste masking of metronidazole, from traditional coating and prodrug formation to advanced complexation and nanofiber approaches. Among all, cyclodextrin inclusion complexation presents the most balanced combination of simplicity, safety, scalability, and effectiveness. By entrapping the drug within the hydrophobic cavity, cyclodextrin prevents interaction with taste receptors and thus improves palatability without affecting bioavailability. Future studies need to focus on computational modeling and molecular docking to further enhance the taste masking and stability of nanofibers containing metronidazole.

5. EVALUATION METHODS FOR TASTE MASKING

Assessment of the effectiveness of taste masking is an important procedure in oral formulation development, especially for drugs like metronidazole, which have a strong bitter taste and poor palatability. An effective taste-masked product should decrease or avoid bitterness when administered without compromising its therapeutic efficacy and bioavailability[65]. There are various assessment methodologies employed, ranging from:

- sensory in-vivo methods,
- In-vitro dissolution-based and analytical approaches,
- Advanced instrument-based taste-simulation systems[66].

5.1. Sensory (In-Vivo) Taste Evaluation

Sensory evaluation by human assessors remains one of the most direct and clinically relevant techniques for determining taste masking efficiency since it reflects human perception[67]. The bitterness intensity is evaluated by a trained human panel, typically comprising 5–10 participants, who use standardized rating scales such as:

- Hedonic scale
- Visual Analog Scale (VAS)
- Numerical bitterness intensity score (0–5 or 0–10)

In this testing method, the sample is kept in the oral cavity for a predetermined period of time (10–30 seconds) and is then spat out[68]. Though sensory evaluation gives the closest realistic estimate, the limitations include ethical considerations, safety concerns, variability of taste sensitivity, and restricted repeatability[69]. Therefore, it is normally used after initial non-human evaluation methods.

5.2. In-Vitro Evaluation Techniques

In-vitro methods are widely used because of ethical convenience, reproducibility, and suitability for early-stage screening.

a) Simulated Salivary Dissolution Testing:

This technique estimates the amount of drug released to simulated salivary fluid (SSF) during a short residence time, i.e., 1–2 minutes[70]. Parameters assessed in this method include:

- Burst release
- Dissolved drug concentration at 30s and 60s
- Comparison with bitterness threshold levels

Lower release means higher efficiency in taste masking.

b) Determination of the Threshold for Bitterness:

This method determines the minimum concentration that can be detected as bitter by humans[71]. If the concentration of the dissolved drug does not exceed the predetermined bitterness threshold, the formulation is said to be adequately masked.

5.3. Analytical and Instrument-Based Methods

Objective instrumental methods have been developed to overcome the subjectivity associated with human taste panels.

a) Electronic Tongue (E-Tongue):

The E-tongue performs gustatory recognition by using lipid/polymer-based sensors of taste together with chemometric pattern-matching algorithms. It allows the reproducible comparison of bitterness reduction between formulations[72].

- Advantages: high reproducibility, rapid measurement, correlation with sensory scoring.
- Limitations: high instrument cost, technical expertise is required.

b) Spectrophotometric Assessment:

UV-visible spectrophotometry is able to quantify the drug concentration released into artificial saliva[73]. Because bitterness perception increases with dissolved fraction, a lower absorbance indicates better masking.

5.4 Texture and Palatability Evaluation

Overall palatability for dosage forms such as orally disintegrating tablets (ODTs), suspensions, and chewables includes:

- Mouthfeel Grittiness
- Disintegration behaviour
- Aftertaste persistence

Even a chemically masked product may fail patient acceptability if the texture or aftertaste is unpleasant[74].

Table 2. Evaluation Methods for Taste-masking

Evaluation Method	Type	Description	Advantages	Disadvantages
Human Taste Panel	In-vivo	Trained volunteers evaluate bitterness intensity using hedonic or numerical scales.	Closest to real perception; provides direct sensory feedback; suitable for final validation.	Ethical concerns; inter-individual variability; limited repeatability; exposure to active drug.
Bitterness Threshold Determination	In-vivo	Determines minimum concentration at which the drug becomes perceptible as bitter.	Useful reference value for formulation comparison; simple and low cost.	Requires human participation; subjective scoring; may not detect aftertaste or delayed release.
Simulated Saliva Dissolution Test	In-vitro	Measures drug release in artificial saliva over short intervals (10–60 seconds).	Ethical alternative; good for early screening; relates to physiological dissolution.	Cannot fully replicate mouth conditions like enzymes or salivary flow; indirect sensory relevance.
UV-Visible Spectrophotometric Analysis	In-vitro Analytical	Quantifies released drug concentration in simulated saliva based on absorbance.	Fast, simple, accurate, and cost-effective; suitable for batch comparison.	Only measures concentration—not sensory perception; requires calibration curve.
Electronic Tongue (E-Tongue)	Instrumental	Uses sensor arrays and pattern recognition to simulate taste receptor response.	High reproducibility; eliminates human bias; sensitive to subtle	High cost, requires technical expertise; calibration needed; limited availability.

			formulation changes.	
HPLC-Based Release Profiling	In-vitro Analytical	Measures precise drug release profile using chromatographic separation.	Highly accurate; useful for complex formulations containing multiple excipients.	Time-consuming; expensive instrumentation; does not directly measure sensory experience.
Palatability and Mouthfeel Testing	Sensory	Evaluates texture, grittiness, aftertaste, and disintegration characteristics.	Useful for pediatric/ODT formulations; assesses comfort during administration.	Subjective; difficult to quantify; often requires human testing.
In-Vitro Ion-Exchange Evaluation	Mechanistic	Used when taste masking involves ion exchange resins to assess binding and release.	Helps predict drug release rate; useful for resin-based techniques.	Not applicable to all dosage forms; cannot estimate final sensory acceptability.

6. ROLE OF CYCLODEXTRINS IN TASTE MASKING OF METRONIDAZOLE

Among the most promising pharmaceutical excipients for improving the palatability of bitter active ingredients like metronidazole are cyclodextrins. Because they are capable of forming non-covalent inclusion complexes, they mask unpleasant tastes effectively without affecting therapeutic performance[75]. This approach is especially favorable in pediatric and geriatric formulations because taste is a major factor affecting treatment compliance[76].

6.1. Cyclodextrin Structure and Inclusion Behavior

The cyclodextrins are cyclic oligosaccharides of α-(1→4) linked glucose monomers. They have a toroidal shape that is essentially a truncated cone[77]. Outer surfaces are hydrophilic, while the inner cavity is hydrophobic; this enables selective entrapment of the lipophilic regions of drug molecules. Three main types exist:

Table 3. Evaluation Methods for Taste-masking

Type	No. of glucose units	Relative cavity size
α-CD	6	Small
β-CD	7	Medium (best fit for metronidazole)
γ-CD	8	Large

β-CD and its hydrophilic derivative HP-β-CD display strong affinity for metronidazole because of complementary size and polarity[78]. The inclusion complex results in a reversible host-guest system that transiently sequesters drug molecules, thus limiting the amount of drug presented to taste receptors[79].

6.2. Mechanism of Taste Masking by Cyclodextrins

Masking of drugs via cyclodextrin is mediated through the reduction of free metronidazole concentration in saliva. The inclusion complex remains intact during the short oral residence time and prevents direct interaction with TAS2R bitter taste receptors[80].

In the gastrointestinal tract, the dilution of the complex, change in pH, and enzymatic interactions bring about its dissociation, therefore allowing normal absorption of the drug and hence therapeutic effect[81]. Thus, CDs provide masking during administration while preserving pharmacokinetics.

6.3. Advantages of Using Cyclodextrins for Metronidazole Taste Masking

Cyclodextrins offer multiple formulation benefits[82,83]:

Table 4. Advantages of Using Cyclodextrins

Advantages	Explanation
Highly effective masking of intense bitterness	Suitable for strongly unpalatable drugs
No negative impact on drug release profile	Complex dissociates naturally in GI conditions
Improved solubility and stability	CDs enhance aqueous solubility and protect from degradation
Broad dosage form compatibility	ODTs, suspensions, chewables, pediatric formulations

Unlike coating or sweetening methods, CD complexation offers both taste masking and physicochemical enhancement**.**

6.4. Types of Cyclodextrins Used for Metronidazole

Optimal fitting and stability allows for a preference of β-Cyclodextrin for solid formulations, while HP-β-CD was ideal for liquid formulations, improving solubility and preventing precipitates[84].

Table 5. Techniques for Taste-masking

Technique	Notes
Kneading	Simple, economical, moderate efficiency
Co-precipitation	better uniformity compared with kneading
Spray drying	It produces fine amorphous complexes with high performance.
Lyophilization	Highest inclusion efficiency and palatability gains

Spray drying and lyophilization generally provide superior interaction and taste masking outcomes[85].

Selection depends on dosage form design:

- β-CD : tablets, granules, ODT systems
- HP-β-CD : suspensions, dispersible formulations

6.5. Formulation and Processing Considerations

Several preparation techniques are utilized:

6.6. Stoichiometry of Cyclodextrin–Drug Complexes (1:1 and 1:2)

A. 1:1 Complex:

- One Cyclodextrin molecule binds one drug molecule[86].
  i.e. Drug + CD □ Drug·CD

Hydrophobic cavity (inside) – Hydrophilic rims (outside)

Figure 2. 1:1 Drug-Cyclodextrin inclusion complex

B. 1:2 Complex:

- Two CDs associate with one drug molecule[87].
  i.e. Drug + 2CD □ Drug·$(CD)_2$
- Two CD molecules co-operatively encapsulate different parts of the drug

Figure 3. 1:2 Drug-Cyclodextrin inclusion complex

Metronidazole can form either structure depending on formulation conditions and cavity interaction.[87]

Table 6. Stoichiometry used for Taste-masking

Stoichiometry	Taste Masking	Drug Release
1:1	Good	Rapid
1:2	Excellent masking (more shielding)	May slightly delay release if binding is too strong

Formulators try to balance taste reduction and release kinetics.
Experimental Determination Methods[89,90]:
Table 7. Experimental Determination Methods

Method	Purpose
Phase-Solubility (Higuchi–Connors model)	Suggests stoichiometry and stability constant $K_{1:1}$
Job's Continuous Variation Plot	Identifies molar ratio producing maximum complexation
Spectroscopy & Calorimetry (NMR, ITC, MS)	Confirms structure, affinity, and stoichiometry
Solid-State Tests (FTIR, DSC, XRD)	Supportive evidence of complex formation

The most definitive stoichiometry confirmation usually comes from NMR + ITC binding analysis..

7. RECENT RESEARCH AND PATENTS (2018–2025) — SUMMARY AND NOVEL TRENDS

In the last six to eight years, research on the taste masking of metronidazole has evolved from classical coating and sweetening methods to advanced molecular engineering and smart drug delivery constructs. Emerging approaches emphasize not only bitterness suppression but also improved solubility, stability, and patient-centric design[91].
There is an identifiable trend towards increasing dependence on cyclodextrin-based systems, polymeric nanocarriers, 3D-printed personalized dosage forms, and electrospun nanofiber matrices in a number of academic publications and patent filings. These platforms are designed to effectively mask taste during oral exposure, without compromising the restoration of rapid release and therapeutic availability post-administration[92,93].
Running in parallel with academic advancement, patent landscapes indicate an increasing industrial focus on scalable microencapsulation technologies, coated multiparticulate granules, and hybrid complexation–coating systems that are more adapted to regulatory acceptance and mass produc-tion[94].
7.1 Summary Table of Representative Studies (2019–2025)

Table 8. Summary Table of Representative Studies

Year	Technique	Key Findings
2019	Electrospun nanofibrous webs of metronidazole/HP-β-CD complex	The human panel testing showed significant bitterness reduction, fast oral dissolution, and improved handling properties[95].
2022	Metronidazole-cyclodextrin complex loaded into chitosan nanoparticles	Demonstrated superior solubility, decreased free medication concentration in simulated saliva, and enhanced physicochemical stability[96].
2024	Extrusion-based 3D-printed tablets with polymer taste-masking shell	Enabled personalized pediatric dosing, fast gastric release, and effective barrier-based bitterness control[97].
2025	Cyclodextrin-modified nanogels (nGels) for oral delivery	Exhibited high drug encapsulation efficiencies, delayed oral exposure, and controlled release profile[98].

7.2. Current Challenges and Limitations

Despite promising progress, there are formulation and translational barriers to modern research.
a) Balancing Taste Masking and Drug Release:
Strong host–guest binding (e.g., high cyclodextrin stability constants) or thick barrier coatings can lead to delayed gastric release or incomplete drug liberation[99].
The formulation challenge is achieving masking during 5–15 seconds of oral residence while ensuring immediate post-swallow dissociation.
b) Recrystallization and Solid-State Stability:

Spray-dried complexes, amorphous dispersions, and electrospun fiber systems may undergo phase separation or API recrystallization during storage, leading to loss of taste masking and altered dissolution[100]. Stability is affected by humidity, temperature, and excipient miscibility.

c) Scalability in Manufacturing:

Processes such as electrospinning, kneading, and freeze-drying provide high-quality mask-ing at laboratory scale but face hurdles in industrial implementation. In contrast, spray-drying, hot-melt extrusion, and fluid-bed coating are more scalable yet may require formulation optimization to match laboratory performance[101],[102].

d) Analytical Challenges in Complex Systems:

The multicomponent formulations, such as cyclodextrins + polymer + nanoparticle + nanofiber, require combined analytical strategies to confirm:

- Inclusion complex formation
- Molecular interaction strength
- Drug spatial distribution
- Salivary release kinetics

Using tools like NMR, ITC, DSC, XRD, HPLC, and E-tongue benchmark testing remains necessary[103],[104].

e) Variability-Ethical and Biological in Sensory Evaluation:

Human taste perception varies based on age, genetics, cultural exposure, and sensory sensitivity. Ethical constraints limit pediatric testing, forcing reliance on electronic tongue systems and simulated saliva models, which require stronger clinical correlation[105].

f) Regulatory and Excipients Limitations:

Novel excipients, high cyclodextrin content, or advanced manufacturing (e.g., 3D-printed paediatric drugs) may trigger additional regulatory scrutiny for safety, leachables, stability, and pediatric acceptability standards[106,109].

g) Cost and Accessibility Constraints

Advanced nanotechnology-based or customized manufacturing platforms may not be cost-feasible for low-cost essential medicines like metronidazole. Scalable and cost-effective solutions remain necessary, especially for low-resource healthcare markets[107,108].

8. FUTURE PERSPECTIVES

Future research directions in taste masking of metronidazole are shifting toward predictive science, hybrid formulation systems, and scalable smart manufacturing technologies. These

advancements aim not only to improve palatability but also to enhance formulation efficiency, stability, and accessibility, particularly for pediatric and geriatric populations.

a) Computational Methods for Rational Design:

Emerging computational approaches—including molecular docking, host–guest simulation, quantitative structure–activity relationship (QSAR) modeling, and AI-assisted binding predictions—enable rapid screening of cyclodextrin derivatives and determination of op-timal stoichiometry (1:1 vs. 1:2 complexes) before laboratory validation[110].

Integrating these tools with high-throughput phase-solubility screening and automated design-of-experiments (DoE) systems may significantly accelerate formulation optimization and reduce experimental cycles.

b) Hybrid, Multi-Mechanism Systems:

Future formulations are expected to incorporate two or more taste-masking mechanisms, like:

CD inclusion complexation + polymer overcoating[111].

The orally disintegrating matrices embedded with CD-loaded nanoparticles.Sensory modulators carrying nanogels based on CD.

Such hybrid systems may deliver stronger and more consistent masking while maintaining fast post-swallow release. The challenge will be to maintain manufacturability and avoid unnecessary formulation complexity.

c) Improved predictive in-vitro models and sensors:

Innovations in microfluidic saliva environment simulators, dynamic dissolution platforms with shear flow, and next-generation electronic tongue sensors are expected to enable better prediction of real-world taste perception. Emerging organ-on-chip taste receptor models may replace or substantially reduce reliance on large-scale human sensory panels, addressing ethical and variability concerns.

d) Scalable Manufacturing Innovations:

Translating laboratory methods into commercial manufacturing remains a bottleneck. Future progress is expected in:

- Continuous electrospinning systems
- Roll-to-roll nanofiber or film processing
- Precision particle engineering through spray-drying
- Hot-melt extrusion and automated encapsulation platforms

Integration of Process Analytical Technology (PAT), real-time quality monitoring, and industrial automation will be essential for GMP compliance and reproducibility.

e) Personalized and On-Demand Dosing:

Technologies such as pharmaceutical 3D printing, semi-solid extrusion, and modular micro-fabrication may enable customized dose strength, formulation texture, and patient-preferred flavor profiles, making treatment more acceptable for children and special populations.

Further research is required to establish regulatory frameworks, product consistency standards, and long-term physical stability for printed medicines.

f) Regulatory Science and Harmonized Guidelines:

Harmonized standards are required in order to define acceptable assessment frameworks for:

- Taste masking efficiency
- Human taste panel ethics and design
- Electronic tongues–human sensory correlations
- Stability testing requirements

Collaboration between FDA, EMA, WHO, and International Pediatric Formulation Con-sortium (IPFC) is anticipated to shape unified global regulatory pathways.

g) Focus on cost-effective and low-resource solutions: For metronidazole—a widely used essential medicine-future strategies must prioritize affordability, scalability, and global accessibility. Low-cost solutions such as:

- β-cyclodextrin complexation with simple granulation
- Solvent-free encapsulation

Minimal excipient systems are critical for implementation in the low-income regions.

Practical recommendations for future studies:

- Apply a step-by-step development workflow
- computational modeling → phase-solubility screening → in-vitro simulated saliva release → e-tongue → small-scale human panel validation.

Target moderate binding constants ($K \approx 10^2$–10^3 M^{-1}) for cyclodextrin complexes to ensure balance between effective masking and rapid gastric release. Incorporate early accelerated stability studies to minimize recrystallization and taste-masking failure over shelf life. Consider process scale-up feasibility during early formulation design, especially in systems involving nanoparticles, fibers, or hybrid architecture.

9. Conclusion

Metronidazole remains one of the most important drugs in treating anaerobic and protozoal infections; however, its potent bitter taste is a serious drawback to compliance. Cyclodextrin inclusion complexation has proved one of the best approaches to solve this problem. By temporarily enclosing the drug within its hydrophobic cavity, cyclodextrins can reduce bitterness in the mouth without affecting the drug's absorption or therapeutic action.

New techniques, such as spray drying, lyophilization, electrospinning, and nanogel formation, have been added over the years for increasing the efficiency and stability of these complexes. Moreover, these advances enable the development of more patient-friendly dosage forms, including orodispersible films, buccal strips, and personalized units. Improved evaluation methods, such as electronic tongue analysis and simulated saliva dissolution, now allow more reliable assessment of taste-masking performance.

In all, complexation with cyclodextrin represents a pragmatic, patient-centered strategy for improving the palatability of metronidazole. Further innovations in computational design, scalable manufacturing, and standardized palatability testing should continue to enable the development of next-generation, easier-to administer formulations that are more acceptable to patients and ultimately more effective at enhancing treatment outcomes.

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