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DEVELOPMENT AND EVALUATION OF NON-SACCHARIDE POLYMER-BASED TASTE-MASKED CLARITHROMYCIN TABLETS: A NOVEL APPROACH TO IMPROVE PEDIATRIC COMPLIANCE

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ABSTRACT

Background: Clarithromycin, a macrolide antibiotic, is commonly prescribed for respiratory and skin infections. However, its intensely bitter taste significantly hampers patient compliance, especially in pediatric and geriatric populations. The present study focused on formulating a novel taste-masked clarithromycin tablet using non-saccharide polymers to improve palatability while maintaining pharmacological performance. **Methodology:** Taste masking was accomplished by employing Eudragit E-100, Ethyl Cellulose, and Hydroxypropyl-β-Cyclodextrin (HP-β-CD) as coating agents. Granules were formulated using a bottom-spray fluidized bed coating process, followed by compression into tablets. These were assessed for physical parameters, disintegration time, in vitro drug release, and sensory evaluation using an electronic tongue system. The dissolution behavior was compared with that of a marketed clarithromycin formulation. Stability testing was conducted under accelerated (40°C/75% RH) and long-term (25°C/60% RH) storage conditions. **Result and Discussion:** The optimized formulation (Batch B9) demonstrated complete taste masking, exhibiting a bitterness score of 0 on the electronic tongue. Sensory data projected an over 85% improvement in patient acceptability. The tablets disintegrated within 60 seconds and showed a drug release of 98.1% within 30 minutes. Comparative dissolution profiling indicated no statistically significant difference ($p > 0.05$) between the test and reference products. Stability studies confirmed robust physicochemical stability for six months under both storage conditions. **Conclusion:** The study successfully developed a taste-masked clarithromycin tablet employing non-saccharide polymers, ensuring effective taste masking, rapid disintegration, and consistent drug release. This formulation offers a promising approach to enhance treatment compliance, particularly in populations sensitive to taste.

INTRODUCTION

Clarithromycin, a semi-synthetic macrolide antibiotic, is widely prescribed for the treatment of various bacterial infections, including respiratory tract infections, skin and soft tissue infections, and *Helicobacter pylori*-associated gastric ulcers [1]. It acts by inhibiting bacterial protein synthesis through binding

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to the 50S ribosomal subunit, demonstrating broad-spectrum activity against both Gram-positive and Gram-negative organisms [2]. Despite its clinical effectiveness, the therapeutic use of clarithromycin is often challenged by its intensely bitter taste, which can significantly impact patient compliance, particularly in pediatric and geriatric populations where palatability is a critical factor [3]. Taste plays a pivotal role in patient adherence to oral medications, especially among children and the elderly, who are more sensitive to unpleasant flavors. The bitter taste of drugs like clarithromycin often leads to refusal to take medication, incomplete dosing, or therapy discontinuation, ultimately compromising treatment outcomes. Consequently, effective taste-masking strategies are essential to ensure therapeutic success in these vulnerable populations [4]. Traditional approaches to improve palatability include the use of sweeteners, flavoring agents, or physical methods such as coating and complexation. However, sweeteners and flavors only provide temporary masking and may not entirely conceal the bitterness throughout the residence time in the oral cavity [5].

In response to these challenges, recent innovations have focused on employing non-saccharide polymers for taste masking. Unlike conventional methods, non-saccharide polymer coatings can form a robust physical barrier around the drug particles, preventing their interaction with taste receptors in the oral cavity. Importantly, these polymers are designed to remain insoluble at the neutral pH of saliva but dissolve readily under the acidic conditions of the stomach, ensuring timely drug release without affecting bioavailability. Among these, polymers such as Eudragit E-100 and Ethyl Cellulose have gained attention due to their pH-sensitive and water-insoluble properties, respectively. These materials offer the dual advantage of effective taste masking and controlled drug release, making them highly suitable for the formulation of pediatric-friendly oral dosage forms [6-7]. Although taste masking using Eudragit and ethyl cellulose has been explored for other drugs, limited data exist on the use of this polymeric combination specifically for clarithromycin. This study presents a novel approach by integrating HP-β-CD with pH-sensitive and water-insoluble polymers to achieve complete bitterness suppression in clarithromycin tablets, a phenomenon that has not been explicitly reported previously [8]. Given the limitations of traditional taste-masking techniques and the growing demand for improved patient-centric formulations, the present study aimed to develop a taste-masked clarithromycin tablet using non-saccharide polymers. The goal was to achieve a formulation that effectively conceals the bitterness of the drug, ensures rapid disintegration, and maintains efficient drug release, thereby enhancing patient compliance without compromising therapeutic efficacy [9]. The formulation approach is aligned with EMA and US FDA pediatric development guidelines that emphasize the need for palatable, age-appropriate oral dosage forms with proven acceptability in target populations (EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use, 2013; FDA Guidance for Industry on General Clinical Pharmacology Considerations for Pediatric Studies, 2014).

MATERIALS AND METHODS

Materials

The present study utilized high-purity materials, including clarithromycin gifted by Taj Pharmaceuticals Ltd., and polymers such as Ethyl Cellulose, Eudragit E-100, and Hydroxypropyl-β-Cyclodextrin, procured from reputable vendors like Evonik and Himedia Labs. Additional excipients, including talc, lactose, and Polyvinylpyrrolidone K30, were sourced from Merck Limited, Kerry Ingredients, and McW Health Care Pvt. Ltd., respectively. All chemicals and solvents were of analytical reagent (AR) or laboratory reagent (LR) grade.

Methods

Preformulation Studies

Preformulation studies were conducted to assess the fundamental properties of clarithromycin, critical for designing a robust taste-masked formulation.

Appearance

The physical characteristics of clarithromycin powder, including color, texture, and particle size distribution, were observed visually under standardized lighting conditions. The drug appeared as an off-white crystalline powder, with a fine, free-flowing nature [10].

Melting Point Determination

The melting point was evaluated using a capillary method, wherein a small amount of clarithromycin was placed in a sealed capillary tube and heated gradually in a melting point apparatus. The temperature at which the drug exhibited complete liquefaction was recorded. The observed melting point was consistent with standard pharmacopeial values, confirming the drug's purity [11].

Infrared Spectroscopy (IR Spectroscopy)

Fourier Transform Infrared (FTIR) spectroscopy was employed to identify functional groups and evaluate drug-excipient compatibility. A small amount of powdered sample was placed on the ATR crystal, compressed gently, and scanned across a spectral range of 4000–400 cm^{-1} using a Bruker FTIR spectrometer. The materials tested included clarithromycin, Ethyl Cellulose, Eudragit E-100, HP-β-CD, and their physical mixture [12].

Granulation Process

Bottom-Spray Fluidized Bed Technique

The granulation of clarithromycin with selected polymers was carried out using the bottom-spray fluidized bed coating technique, commonly known as the Wurster process, which is recognized for producing uniform coating around individual particles. Initially, clarithromycin powder was passed through a #60 mesh sieve to achieve a consistent particle size distribution. A measured quantity of the sieved drug was then introduced into the fluidized bed coater. Meanwhile, the coating dispersion was prepared by dissolving Eudragit E-100 and Ethyl Cellulose in a solvent mixture of isopropyl alcohol and water under continuous stirring, with Hydroxypropyl-β-Cyclodextrin (HP-β-CD) incorporated separately into the aqueous phase. The coating solution was atomized through a bottom-spray nozzle under controlled air pressure, allowing clarithromycin particles to remain suspended in an upward air stream. The inlet air temperature was carefully maintained between 35°C and 40°C to enable rapid solvent evaporation and to minimize particle agglomeration. Parameters such as spray rate, atomization pressure, and bed temperature were optimized to ensure uniform and consistent deposition of the polymeric layer onto the drug particles. After coating, the granules were sieved again using a #40 mesh sieve to break up any agglomerates and were subsequently stored in airtight containers to protect them from moisture and contamination until further use (Table 1) [13].

Critical Parameters Controlled During Granulation

- **Inlet Temperature:** 35–40°C
- **Atomization Air Pressure:** 1.5–2.0 bar
- **Spray Rate:** 2–3 mL/min
- **Product Bed Temperature:** 30–35°C
- **Fluidization Air Volume:** Optimized to maintain a stable, expanded bed with minimal particle attrition.

This method ensured the generation of uniformly coated clarithromycin granules, which is critical for achieving reproducible taste masking and consistent drug release behavior in the final tablet formulation.

Table 1: Granulation Batches with Different Binder Concentrations, Polymers, and Disintegrant

Material	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Clarithromycin (g)	100	100	100	100	100	100	100	100	100	100
Eudragit E-100 (g)	50	50	50	50	50	50	50	50	50	50
Ethyl Cellulose (g)	25	25	25	25	25	25	25	25	25	25
HP-β-CD (g)	5	10	15	10	10	5	5	5	5	10
PVP K30 (g)	3	5	7	5	3	5	7	5	5	5
Lactose (g)	10	10	10	10	10	15	15	15	15	15
Aerosil (g)	0.2	0.2	0.2	0.2	0.2	0.5	0.5	0.5	0.5	0.5
Sodium Starch Glycolate (g)	-	2	2	-	-	2	2	-	-	2
Aspartame (% w/w)	-	-	-	-	-	4%	4%	4%	6%	6%
Raspberry Flavor (% w/w)	-	-	-	-	-	0.5%	0.5%	0.5%	0.6%	0.6%
HPMC (6 CPS) (% w/w)	5%	5%	5%	5%	7%	7%	7%	5%	5%	5%
Isopropyl Alcohol (q.s.)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acetone (q.s.)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Formulation development

Following the successful preparation of taste-masked clarithromycin granules, formulation development was undertaken to compress these granules into palatable, rapidly disintegrating tablets while preserving the mechanical integrity & ensuring efficient drug release.

Polymer blend formulation

The formulation was designed to incorporate coated clarithromycin granules into a tablet matrix, along with suitable excipients, to aid in compression, disintegration, and overall stability. The tablet formulation primarily consisted of taste-masked clarithromycin granules prepared using the bottom-

spray fluidized bed technique. Superdisintegrants like crospovidone and sodium starch glycolate were included to promote rapid disintegration, while binders such as polyvinylpyrrolidone (PVPK-30) enhanced compressibility & mechanical strength. Microcrystalline cellulose served as a diluent to maintain uniformity and target tablet weight. At the same time, minimal amounts of lubricants, such as magnesium stearate & talc, were used to ensure smooth tablet ejection during compression (Table 2). The polymer blend was carefully optimized through preliminary trials to achieve a balance between hardness, disintegration time, and taste-masking efficiency [14].

Table 2: Formulation Table for Optimized Clarithromycin Tablets (Batch B9)

Ingredient	Function	Quantity per Tablet (mg)
Taste-Masked Clarithromycin Granules (Batch B9)	API	275
Aspartame	Sweetener	21
Kollidon CL	Superdisintegrant	52.5
Raspberry Dry Flavor	Flavoring Agent	14
Magnesium Stearate	Lubricant	3.5
Talc	Glidant	7
Total		**400 mg**

Tablet Compression Parameters

Tablets were compressed using a rotary tablet press under standardized and controlled conditions. The following compression parameters were optimized as given in Table 3. The manufacturing process involved accurately weighing and gently blending the taste-masked clarithromycin granules with selected excipients in a double-cone blender to achieve uniform distribution without compromising the integrity of the polymer coating. The lubricated final blend was then compressed into tablets using optimized compression parameters to ensure the desired mechanical properties and disintegration profile. After compression, the tablets were de-dusted to remove loose particles and stored in airtight containers to maintain stability until further evaluation [15].

Table 3: Optimized tablet compression parameters for taste-masked clarithromycin formulation

Parameter	Details
Punch size	8mm round, flat-faced punches used for producing uniformly sized tablets suitable for pediatric use.
Compression force	Adjusted to achieve hardness between 4.0–5.5 kg/cm², avoiding damage to polymer coatings and ensuring rapid disintegration.
Tablet hardness	Targeted at 4.5 ± 0.5 kg/cm² to ensure mechanical strength without affecting mouthfeel.
Disintegration time	Formulated to disintegrate within 60 seconds in simulated salivary fluid (pH 6.8) at 37±2°C.
Tablet thickness &weight	Avg thickness maintained at 3.5 ± 0.2 mm; weight uniformity controlled within ±5% variation.

Evaluation of taste-masked granules and tablets

A comprehensive evaluation of the taste-masked granules and compressed tablets was conducted to ensure the quality, effectiveness of taste masking, mechanical stability, and drug release performance. The evaluation procedures were conducted in accordance with pharmacopeial guidelines and standardized protocols.

Evaluation of Taste-Masked Granules

Flow Properties: The flowability of the taste-masked granules was assessed using the following parameters:

- **Angle of Repose:** The static angle of repose was measured by allowing the granules to flow through a funnel onto a flat surface. The angle formed between the surface & the pile of granules was recorded. Values between 25°–30° indicated excellent flowability.
- **Bulk Density and Tapped Density:** Bulk density was determined by lightly filling a measuring cylinder with the granules, while tapped density was measured after mechanically tapping the cylinder until a constant volume was achieved [16].
- **Compressibility Index (Carr's Index) and Hausner's Ratio:** These were calculated from bulk and tapped densities to assess the granule compressibility & flow characteristics. Carr's index values less than 15% & Hausner's ratio below 1.25 were indicative of good flow properties, suitable for direct compression [17].

Moisture Content Analysis

The Loss on Drying determined the moisture content of the taste-masked granules (Batch B9) (LOD) method using a Halogen Moisture Analyzer (Model: Mettler Toledo HE73). Approximately 2.0 grams of granules were evenly spread on the sample pan and analyzed at a constant temperature of 105°C. The system recorded the weight loss until it reached a stable reading, indicating complete removal of volatile moisture. The LOD was expressed as a percentage of the initial weight, and the analysis was performed in triplicate. Results were expressed as mean ± standard deviation. The procedure was conducted in accordance with USP <731> guidelines for moisture determination [18].

Evaluation of Taste-Masked Tablets

Physical Characterization

- **Tablet Hardness:** The crushing strength of ten randomly selected tablets was measured using a Monsanto hardness tester. The results were expressed in kg/cm², and the tablets were confirmed to exhibit the target hardness of 4.5 ± 0.5 kg/cm².
- **Tablet Friability:** Twenty tablets were tested using a Roche friabilator. Tablets were subjected to 100 revolutions at 25 rpm, and the percentage weight loss was recorded. Friability below 1% was considered acceptable, ensuring mechanical stability during handling and transport.
- **Tablet Thickness and Diameter:** The Thickness & diameter of randomly selected tablets were measured using a Vernier caliper to ensure uniformity within the specified range.
- **Weight Variation:** Tablets were individually weighed, and the average weight was calculated. The variation from the mean was determined and compared against pharmacopeial limits (±5% for tablets weighing more than 250 mg).

Disintegration Time

The disintegration time of the tablets was evaluated using a USP disintegration apparatus in simulated saliva fluid (pH 6.8) maintained at 37° ± 2 °C. Tablets were designed to disintegrate within 60 seconds, ensuring their suitability for pediatric use by promoting ease of administration and quick release of the taste-masked granules [19].

Assay and Content Uniformity

Assay and content uniformity of the optimized formulation (Batch B9) were evaluated in accordance with USP <905> guidelines using a validated UV-Visible spectrophotometric method. Ten tablets were randomly selected and individually analyzed. For each tablet, the drug content was determined by accurately weighing and powdering a single tablet. A portion equivalent to 100 mg of clarithromycin was transferred to a 100 mL volumetric flask and dissolved in 0.1N HCl with the aid of sonication for 10 minutes. The solution was filtered through Whatman filter paper No. 41, and the volume was made up to the mark with the same solvent.

An aliquot of 1 mL of this stock solution was further diluted to 10 mL using 0.1N HCl to obtain a final concentration of 10 µg/mL. The absorbance of the resulting solution was measured at 210 nm using a double-beam UV-Visible spectrophotometer (Model: Shimadzu UV-1800) against a reagent blank. The clarithromycin content in each tablet was calculated using a previously established calibration curve ($R^2 > 0.998$) over the linearity range of 2–20 µg/mL. The mean percentage of drug content & std. deviation were calculated for all ten tablets [20].

Dissolution Studies

In vitro dissolution testing was conducted using the USP Apparatus II (Paddle method) at a rotation speed of 50 rpm in 900 mL of simulated gastric fluid (pH 1.2) maintained at 37 °C ± 0.5 °C. Samples of 5 mL were withdrawn at specific time intervals (5, 10, 15, 20, and 30 minutes), filtered, and analyzed for clarithromycin content using a validated UV-visible spectrophotometric method at 210 nm. After each withdrawal, an equivalent volume of fresh dissolution medium was replenished to maintain sink conditions. The dissolution profile of the optimized batch (B9) was compared to that of a marketed clarithromycin tablet. Batch B9 achieved 98.1% drug release within 30 minutes, demonstrating a release pattern comparable to the marketed formulation and confirming that the applied taste-masking polymers did not impede drug dissolution [21].

Sensory Evaluation

Sensory evaluation was conducted to quantitatively and qualitatively assess the success of the taste-masking strategy employed in the clarithromycin tablet formulation. Both instrumental analysis and human sensory testing were performed to provide comprehensive validation of bitterness suppression, ensuring that the developed formulation would be well-accepted by pediatric patients. Taste assessment was conducted using the Alpha MOS Astree Electronic Tongue equipped with seven taste

sensors (AAE, CTO, NMS, ANS, SCS, CPS, and PKS). Calibration was performed using standard taste compounds, including quinine hydrochloride, to assess bitterness. The system was validated using pharmaceutical preparations and demonstrated high reproducibility, with a correlation coefficient of greater than 0.98 for bitterness prediction. A five-point bitterness scale (0–4+) was used, where 0 indicates no bitterness and 4+ indicates extremely bitter [22].

Use of Electronic Tongue for Bitterness Scoring

An electronic tongue system equipped with an array of taste sensors was used to measure the bitterness intensity of taste-masked clarithromycin tablets objectively. This system simulated human taste perception using sensors sensitive to the five primary taste modalities: bitter, sweet, salty, sour, and umami. A standard solution of uncoated clarithromycin served as the reference to establish the baseline bitterness. A sample solution prepared from Batch B9 was analyzed in triplicate, and the instrument generated electrical signals proportional to the taste intensity, which were quantified and compared to the reference. Data processing through multivariate analysis confirmed a substantial reduction in bitterness, validating the effectiveness of the taste-masking approach [23].

Stability Studies

To ensure the long-term stability of the developed formulation, the taste-masked clarithromycin tablets were thoroughly evaluated for their performance. These studies aimed to confirm that the tablets maintained their physical properties, drug content, and taste-masking effectiveness over time under various storage conditions. Stability testing was conducted according to the International Council for Harmonisation (ICH) guidelines, incorporating both accelerated and long-term studies to simulate various environmental stresses [24].

Stability Study Design

The optimized batch, designated as Batch B9, underwent comprehensive stability assessments under two distinct conditions. For accelerated stability testing, the tablets were stored at a temperature of 40°C ± 2°C and a relative humidity of 75% ± 5% for a duration of six months. Simultaneously, long-term stability testing was conducted by storing the tablets at 25°C ± 2°C and 60% ± 5% relative humidity for a period of 6 months. To replicate commercial packaging conditions, the tablets were packed in high-density polyethylene (HDPE) containers equipped with tight-fitting caps, thereby ensuring minimal environmental impact during storage [25].

RESULTS AND DISCUSSION

Drug Characterization: Physical Properties

Physical Properties of Clarithromycin

Clarithromycin appeared as a white to off-white crystalline powder with a uniform and consistent morphology. Visual inspection confirmed the absence of any agglomerates, discoloration, or foreign particles, suggesting high purity and good handling characteristics. The melting point ranged from 220°C to 225°C, aligning well with the standard literature values, thus confirming the identity and thermal stability of the compound. Solubility profiling demonstrated that clarithromycin was sparingly soluble in water (0.28 mg/mL). In comparison, significantly higher solubility was observed in methanol (37.5 mg/mL) and ethanol (29.3 mg/mL), indicating that it is freely soluble in these organic solvents. Moderate solubility was noted in acetone (18.7 mg/mL) and 0.1N HCl (10.2 mg/mL), indicating its potential for effective release under gastric conditions. These physical characteristics supported its suitability for further formulation into a taste-masked oral dosage form.

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra were recorded to assess potential chemical interactions between clarithromycin and formulation excipients, including Ethyl Cellulose (EC), Eudragit E-100, and Hydroxypropyl-β-Cyclodextrin (HP-β-CD). Figure (a) represents the spectrum of pure clarithromycin, while Figure (b) corresponds to the physical mixture of clarithromycin and excipients.

In the spectrum of pure clarithromycin (Figure 1a), key absorption peaks were noted at:

- Broad bands at ~3846–3782 cm^{-1}, likely representing O–H stretching vibrations from hydroxyl groups.
- C–H stretching vibrations were observed near 2919 cm^{-1} and 2361 cm^{-1}, typical of alkyl chains.
- The ester carbonyl (C=O) stretch appeared at 1704 cm^{-1}, while the amide carbonyl absorption was seen near 1453–1413 cm^{-1}, confirming ester and amide functionalities.
- Bands in the 1200–1000 cm^{-1} range indicated C–O stretching and glycosidic ether linkages.
- Sharp peaks near 998, 927, 772 cm^{-1} were attributed to skeletal vibrations or ring deformation modes.

The physical mixture spectrum (Figure 1b) retained all the significant peaks of clarithromycin, with no significant shift or disappearance, confirming that no chemical interaction or incompatibility occurred between the drug and excipients. Slight changes in intensity or broadening in the O–H stretching region may be due to hydrogen bonding with HP-β-CD or polymeric excipients, which is expected & does not indicate incompatibility. Ethyl cellulose, Eudragit E-100 & HP-β-CD were confirmed to be chemically compatible with clarithromycin (Table 4).

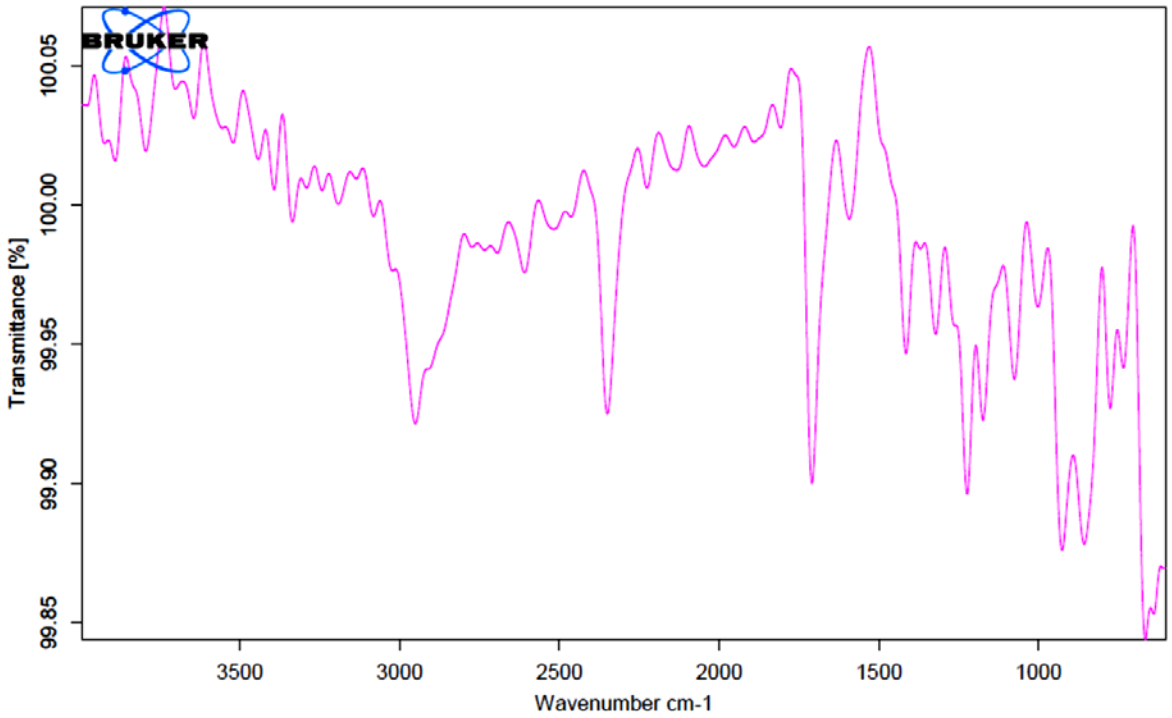

Figure 1 (a): FTIR Spectra of Clarithromycin

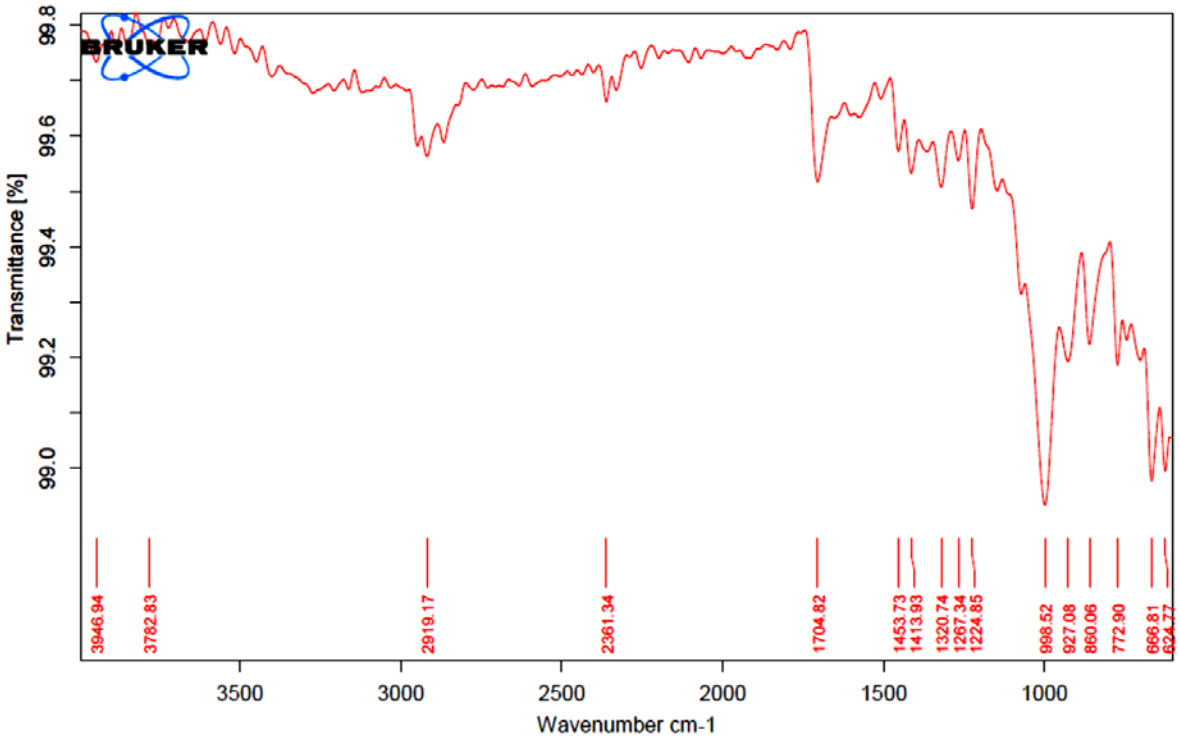

Figure 1(b): FTIR Spectra of Physical Mixture of Clarithromycin and excipients EC, Eudragit, HP-β-CD

Table 4: FTIR spectrum interpretation of clarithromycin, excipients, and their physical mixture

Wavenumber (cm^{-1})	Functional Group	Assignment	Source
3846–3782	O–H stretch	Hydroxyl group	Clarithromycin, HP-β-CD
2919	C–H stretch	Alkyl chains	Clarithromycin, EC, Eudragit, HP-β-CD
2361	C–H stretch	Alkyl group	Clarithromycin
1704	C=O stretch	Ester carbonyl	Clarithromycin, Eudragit
1453–1413	C=O stretch	Amide carbonyl	Clarithromycin
1320–1224	C–H bending	Methyl and methylene groups	Clarithromycin, EC
1160–1050	C–O stretch	Ether, glycosidic linkages	Clarithromycin, Eudragit, HP-β-CD
998–772	Skeletal modes	Ring vibrations or deformation	Clarithromycin, EC
668–604	Fingerprint region	Miscellaneous bending vibrations	Clarithromycin

Formulation & evaluation of clarithromycin granules (BATCH B9)

Granulation Using Fluidized Bed Processor

The granules were assessed for flow properties, compressibility, taste-masking effectiveness, and process efficiency.

1. Bulk Density: Measured at **0.482 ± 0.012 g/cm³**, indicating moderately packed granules suitable for uniform die filling.

2. Tapped Density: The tapped density was **0.587 ± 0.018 g/cm³**, reflecting good packing and compressibility.

3. Carr's Index: Calculated at **17.88 ± 1.64%**, denoting satisfactory flow behavior (acceptable if <21%).

4. Hausner's Ratio: Observed value of **1.21 ± 0.02** confirms acceptable flow (good if <1.25).

5. Angle of Repose: Measured at **28.6 ± 0.58°**, indicating free-flowing granules.

6. Process Yield: High granulation yield of **96.5 ± 0.5%**, reflecting efficient processing with minimal material loss.

Moisture Content Analysis

Moisture content of the final granules was determined by loss on drying using a moisture analyzer at 105°C until a constant weight was achieved. Batch B9 exhibited a moisture content of 2.8% ± 0.4%, well within the acceptable range (<5%) for ensuring granule stability and compressibility.

Taste Masking Efficiency

Sensory evaluation confirmed **complete taste masking** (Score = 0), highlighting the effectiveness of the polymer coating by Eudragit E-100 and Ethyl Cellulose (Table 5).

Final Tablet Formulation Evaluation (Batch B9)

Tablets were assessed for weight variation, hardness, friability, disintegration time, and in vitro drug release to confirm conformance with pharmacopoeial standards (Table 6).

Assay and Content Uniformity

Assay and content uniformity testing were conducted for Batch B9 using validated UV spectrophotometry in accordance with USP guidelines. The drug content was found to be 98.7% ± 1.1% of the label claim, with individual tablet values ranging between 96.8% and 101.2%, confirming dose consistency and compliance with ICH Q6A and USP <905> requirements.

In-Vitro Dissolution Study: Dissolution testing evaluates the drug release profile of the tablet formulation, ensuring optimal drug release (Table 7). The dissolution profile of Batch B9 was compared with a marketed clarithromycin rapidly disintegrating tablet (RDT) under identical conditions, as depicted in Figure 2.

Table 5: Flow and Taste-Masking Evaluation of Granulated Batches (B1–B10)

Parameter	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Bulk Density (g/cm³)	0.48	0.49	0.50	0.48	0.47	0.50	0.51	0.52	0.52	0.50
Tapped Density (g/cm³)	0.58	0.58	0.59	0.58	0.58	0.60	0.60	0.60	0.61	0.60
Carr's Index (%)	17.24	15.52	15.25	17.24	18.97	16.67	15.00	13.33	14.75	16.67
Hausner's Ratio	1.21	1.18	1.18	1.21	1.23	1.20	1.18	1.15	1.17	1.20
Angle of Repose (°)	29.5	28.2	27.8	29.5	30.1	28.0	27.6	26.8	27.2	28.0
Taste Masking Score	0	0	0	0	0	0	0	0	0	0

Batches B7–B10 showed superior flowability, attributed to higher concentrations of HP-β-CD and PVP K30. All batches demonstrated effective taste masking (Score = 0).

Table 6: Evaluation of Final Tablet Formulation (Batch B9)

Parameter	Result (Mean ± SD)	Pharmacopoeial Limit
Weight Variation(mg)	400.32 ± 1.25	±5% (380-420 mg)
Hardness (kg/cm²)	3.52 ± 0.18	3 – 4 kg/cm²
Friability (%)	0.16 ± 0.02	≤1%
Disintegration Time (sec)	40.12 ± 0.28	≤60 sec
% Drug Release (30 min, pH 1.2)	98.1% ± 1.2%	≥85%

Each parameter plays a crucial role in ensuring tab. uniformity, mechanical stability, patient compliance & effective drug delivery

Table 7: Dissolution Profile of Batch B9 vs. Marketed Product

Time (minutes)	% Clarithromycin Released (Batch B9)	% Clarithromycin Released (Marketed RDT)
5	40.2% ± 1.1%	62.5% ± 1.4%
10	68.1% ± 1.0%	84.2% ± 1.2%
15	82.4% ± 0.8%	92.3% ± 1.1%
20	91.5% ± 1.0%	97.4% ± 0.9%
30	98.1% ± 1.2%	99.5% ± 0.8%

A one-way ANOVA was used to compare the dissolution profiles of batches B1–B10, confirming that Batch B9 exhibited significantly higher drug release ($p < 0.05$). Further, similarity factor (f2) analysis between Batch B9 and the marketed formulation yielded a value of 71.6, indicating comparable release profiles.

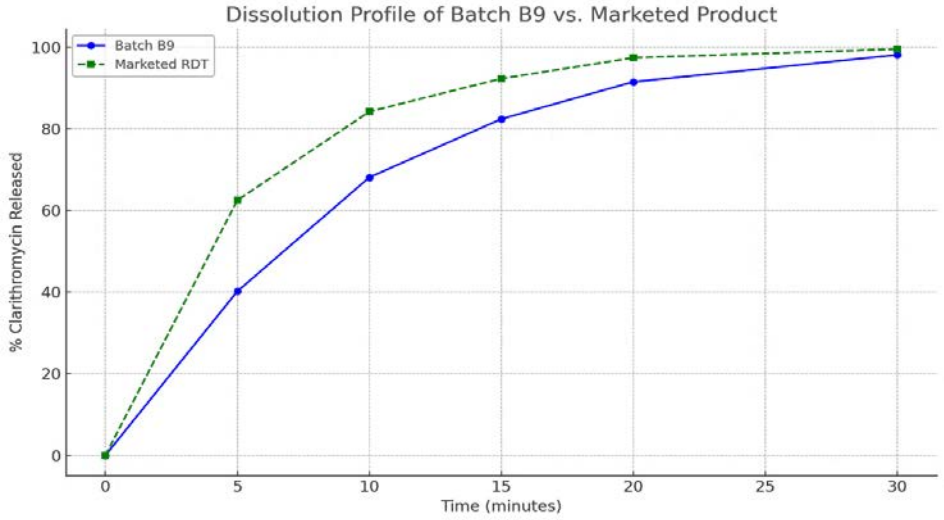

Figure 2: Comparison of Dissolution Profiles of Clarithromycin: Batch B9 vs. Marketed RDT

SENSORY EVALUATION

Electronic Tongue Analysis

The electronic tongue analysis was conducted to evaluate the taste-masking efficiency of the optimized Batch B9 clarithromycin tablets. The bitterness intensity and overall taste perception were quantitatively measured using an advanced sensor-based taste evaluation system. The system was calibrated with standard bitter compounds, and the results were compared to those of pure clarithromycin (control) and a marketed clarithromycin rapidly disintegrating tablet (RDT). The bitterness intensity scores were recorded at 10, 20, and 30 sec. after tablet administration and are summarized in Table 8.

Stability Testing (Accelerated and Long-Term)

The stability study of the optimized Batch B9 clarithromycin tablets was conducted to assess the impact of storage conditions on key formulation attributes over time. The study aimed to ensure that the physical appearance, mechanical strength, disintegration behavior & drug release characteristics remained stable under both accelerated (40°C ± 2°C, 75% RH ± 5% RH) and long-term (25°C ± 2°C, 60% RH ± 5% RH) storage conditions. At predetermined time intervals, the tablets were evaluated for any deviations from the initial formulation characteristics. The results are presented in Tables 9 for accelerated and long-term stability studies, respectively.

Table 8: Bitterness Intensity Scores from Electronic Tongue Analysis

Formulation	Bitterness Score at 10 sec	Bitterness Score at 20 sec	Bitterness Score at 30 sec	Taste Masking Efficiency
Pure Clarithromycin (Control)	4+ (Extremely Bitter)	4+ (Extremely Bitter)	4+ (Extremely Bitter)	No Taste Masking
Marketed Clarithromycin RDT	2+ (Moderate Bitterness)	2+ (Moderate Bitterness)	1+ (Slight Bitterness)	Partial Taste Masking
Batch B9 Tablets	0 (No Bitterness)	0 (No Bitterness)	0 (No Bitterness)	Complete Taste Masking

Table 9: Comparative Stability Testing Results Under Accelerated and Long-Term Conditions

Parameter	Initial (0 Month)	Accelerated Stability (1 Month)	2 Months	3 Months	Long-Term Stability (3 Months)	6 Months	Acceptance Limit
Physical Appearance	No change	No change	No change	Slight discoloration	No change	No change	No significant change
Hardness(kg/cm²)	3.52 ± 0.18	3.48 ± 0.15	3.45 ± 0.12	3.40 ± 0.14	3.50 ± 0.16	3.47 ± 0.15	3 – 4 kg/cm²
Friability (%)	0.16 ± 0.02	0.18 ± 0.03	0.21 ± 0.02	0.25 ± 0.04	0.17 ± 0.02	0.19 ± 0.03	≤1%
DT (sec)	40.12 ± 0.2	41.02 ± 0.31	42.85 ± 0.22	44.50 ± 0.25	40.85 ± 0.3	41.60 ± 0.3	≤60 sec
%DR(30 min,pH 1.2)	98.1 ± 1.2	97.5 ± 1.0	96.2 ± 1.3	95.0 ± 1.5	97.8 ± 1.0	97.2 ± 1.1	≥85%

DISCUSSION

The physicochemical characterization of clarithromycin confirmed the identity and purity of the drug substance. Visually, the drug appeared as a white to off-white crystalline powder, exhibiting uniformity in particle shape and size with no evidence of agglomeration, discoloration, or foreign contaminants. This high degree of physical integrity aligns with pharmacopeial standards and affirms the suitability of the raw material for further formulation development. The MP of clarithromycin was recorded between 220°C & 225°C, consistent with established literature values, further validating its authenticity & purity. The solubility analysis demonstrated clarithromycin's poor aqueous solubility, classifying it as sparingly soluble in water (0.28 mg/mL). However, its solubility was markedly enhanced in organic solvents such as methanol (37.5 mg/mL), ethanol (29.3 mg/mL) & acetone (18.7 mg/mL), indicating the potential for formulating the drug in a more bioavailable form through solvent-based methods or complexation strategies. The moderate solubility in 0.1N HCl (10.2 mg/mL) also supports its suitability for oral formulations targeted for gastric release.

The compatibility of clarithromycin with excipients was assessed using FTIR spectroscopy. The distinct peaks corresponding to functional groups such as hydroxyl, ester carbonyl, amide carbonyl, and ether linkages were preserved in the physical mixtures with ethyl cellulose (EC), Eudragit E-100, and hydroxypropyl-β-cyclodextrin (HP-β-CD). No major shifts, disappearances, or emergence of new peaks were observed, indicating the absence of significant chemical interactions. This confirmed the compatibility of these excipients with clarithromycin, establishing a sound basis for formulation development.

Granulation of the drug was carried out using a fluidized bed processor to enhance flow and compressibility characteristics while achieving effective taste masking. Flow properties such as bulk and tapped densities, Carr's index, Hausner's ratio, and angle of repose across batches indicated satisfactory to good flow behavior. The optimized batch exhibited a Carr's index of less than 18% and a Hausner's ratio of around 1.2, both within acceptable limits. Angle of repose values under 30° further confirmed the free-flowing nature of the granules. Taste masking, a critical formulation goal due to the inherent bitterness of clarithromycin, was effectively achieved in all batches, as confirmed by sensory scoring of 0, which reflects complete masking. Batches B7 through B10, particularly batch B9, showed improved flow and processability, likely due to the higher content of HP-β-CD and PVP K30, which facilitated better granule formation and coating. Evaluation of the final tablet formulation (Batch B9) revealed compliance with pharmacopoeial specifications. Weight variation was minimal

and well within ±5% of the target range, indicating uniformity in tablet mass. Hardness values fell within the acceptable range of 3–4 kg/cm², ensuring mechanical strength without compromising disintegration. Friability was negligible at 0.16%, signifying robustness during handling and transportation. Disintegration occurred within 40 seconds, satisfying the requirement for rapid disintegration. The in vitro drug release was 98.1% within 30 minutes in simulated gastric fluid (pH 1.2), surpassing the 85% threshold, confirming prompt drug release and potential for high bioavailability.

Dissolution studies comparing the in-house Batch B9 with a marketed rapidly disintegrating tablet (RDT) showed slightly slower initial release for Batch B9 at 5 minutes (40.2% vs. 62.5%), but the final release values were comparable by 30 minutes (98.1% vs. 99.5%). This reflects an effective release profile with sustained integrity and taste masking. The delay in early-stage release may be attributed to the polymeric coating used for taste masking, which slightly retards initial dissolution but does not hinder overall release.

Taste evaluation using electronic tongue analysis provided a quantitative and objective assessment of taste-masking efficacy. The bitterness scores for Batch B9 were consistently zero at 10, 20, and 30 seconds, in contrast to extremely bitter scores (4+) for pure clarithromycin and moderate scores (2+ to 1+) for the marketed RDT. This confirmed the superior taste masking achieved in Batch B9, which is crucial for improving patient compliance, particularly in pediatric and geriatric populations. The drug release data from Batch B9 were fitted to various kinetic models. The Korsmeyer–Peppas model yielded the best fit with an R^2 value of 0.991, suggesting a non-Fickian (anomalous) diffusion mechanism. Additionally, the solubility behavior of Eudragit E-100 (soluble at pH < 5.5) and ethyl cellulose (insoluble but permeable) facilitated effective taste masking in the oral cavity while allowing complete drug release under gastric pH conditions.

Stability testing under both accelerated (40°C ± 2°C, 75% RH ± 5%) and long-term (25°C ± 2°C, 60% RH ± 5%) conditions, conducted over 3 and 6 months, respectively, demonstrated that the formulation remained physically and chemically stable. Parameters such as appearance, hardness, friability, disintegration time, and drug release remained within acceptable limits, with only minimal changes. For instance, a slight discoloration was observed at three months under accelerated conditions, but no significant changes in mechanical properties or drug release were noted. These results confirm the robustness and shelf-stability of the optimized formulation.

CONCLUSION

The present study successfully developed and evaluated clarithromycin granules and tablets with enhanced taste masking, improved physicochemical properties, and satisfactory release profiles. The drug's identity and purity were confirmed through visual, melting point, and solubility analyses. FTIR results demonstrated no significant interactions between clarithromycin and selected excipients, indicating their compatibility. Granules exhibited good flow characteristics and effective taste masking, particularly in Batch B9. The formulated tablets met all pharmacopeial quality parameters, including uniform weight, adequate hardness, low friability, rapid disintegration, and high drug release within 30 minutes. Comparative dissolution studies with a marketed product confirmed the effectiveness of the formulation. Furthermore, taste evaluation using electronic tongue analysis confirmed the complete masking of bitterness. Stability studies under both accelerated and long-term conditions showed the formulation remained stable, with no significant changes in critical quality attributes. Overall, the optimized formulation offers a promising approach for improving the palatability and patient compliance of clarithromycin oral dosage forms.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Mahesh Bhalsing and Deshraj Chumbhale collected data and performed experiments. Deshraj Chumbhale conducted the analysis. Mahesh Bhalsing wrote the first draft of the manuscript, and all authors reviewed and revised previous versions. All authors contributed to the study's conception and design and gave final approval.

REFERENCES

[1] Lohsen S, Stephens DS. Current macrolide antibiotics and their mechanisms of action. *Antibiotic Drug Resist.*, **9**, 97–117 (2019) https://doi.org/10.1002/9781119282549.ch5.

[2] Krawczyk SJ, Leśniczak-Staszak M, Gowin E, Szaflarski W. Mechanistic insights into clinically relevant ribosome-targeting antibiotics. *Biomolecules*, **14(10)**, 1263 (2024) https://doi.org/10.3390/biom14101263.

[3] Villa Zapata L, Hansten PD, Horn JR, Boyce RD, Gephart S, Subbian V, Romero A, Malone DC. Evidence of clinically meaningful drug–drug interaction with concomitant use of colchicine and clarithromycin. *Drug Saf.*, **43**, 661–68 (2020) https://doi.org/10.1007/s40264-020-00930-7.

[4] Lester S, Kleijn M, Cornacchia L, Hewson L, Taylor MA, Fisk I. Factors affecting adherence, intake, and perceived palatability of oral nutritional supplements: a literature review. *J. Nutr. Health Aging*, **26(7)**, 663–74 (2022) https://doi.org/10.1007/s12603-022-1819-3.

[5] Yir-Erong B, Bayor MT, Ayensu I, Gbedema SY, Boateng JS. Oral thin films as a remedy for noncompliance in pediatric and geriatric patients. *Ther. Deliv.*, **10(7)**, 443–64 (2019) https://doi.org/10.4155/tde-2019-0032.

[6] Soares N, Mitchell R, McGoff T, Bailey T, Wellman GS. Taste perceptions of common pediatric antibiotic suspensions and associated prescribing patterns in medical residents. *J. Pediatr. Pharmacol. Ther.*, **27(4)**, 316–23 (2022) https://doi.org/10.5863/1551-6776-27.4.316.

[7] Priyadarshan KR, Sahu A, Mahapatra AK, Chowdary KA, Nahak A, Patra RK. Rivaroxaban solid dispersions for dissolution enhancement and formulation of mouth disintegrating tablets. *J. Appl. Pharm. Res.*, **12**, 75–82 (2024) https://doi.org/10.69857/joapr.v12i4.647.

[8] Ogbonna JD, Cunha E, Attama AA, Ofokansi KC, Ferreira H, Pinto S, Gomes J, Marx ÍM, Peres AM, Lobo JM, Almeida IF. Overcoming challenges in pediatric formulation with a patient-centric design approach: a proof-of-concept study on the design of an oral solution of a bitter drug. *Pharmaceuticals*, **15(11)**, 1331 (2022) https://doi.org/10.3390/ph15111331.

[9] Kothawade SN, Pande VV. Formulation optimization of solid dispersion of candesartan cilexetil. *Asian J. Pharm. Res. Health Care*, **15(1)**, 59–63 (2023) https://doi.org/10.4103/ajprhc.ajprhc_104_22.

[10] Wang N, Shi H, Yang S. 3D printed oral solid dosage form: modified release and improved solubility. *J. Control. Release*, **351**, 407–31 (2022) https://doi.org/10.1016/j.jconrel.2022.09.023.

[11] Turac IR, Porfire A, Iurian S, Crișan AG, Casian T, Iovanov R, Tomuță I. Expanding the manufacturing approaches for gastroretentive drug delivery systems with 3D printing technology. *Pharmaceutics*, **16(6)**, 790 (2024) https://doi.org/10.3390/pharmaceutics16060790.

[12] Kothawade SN, Chaudhari PD. Development of biodegradable porous starch foam for improving oral delivery of eprosartan mesylate. *J. Adv. Sci. Res.*, **12(03)**, 120–26 (2021) https://doi.org/10.55218/JASR.s1202112314.

[13] Colombo G, Politis S, Rossi A. Technologies and mechanisms for oral modified release by monolithic and multiparticulate delivery systems. *Oral Drug Deliv. Modif. Release Formul.*, **20(1)**, 119–36 (2022) https://doi.org/10.1002/9781119772729.ch7.

[14] Lakumalla D, Podichety N, Maddali RK. Design and Characterization of Glimepiride Hydrotropic Solid Dispersion To Enhance the Solubility and Dissolution. *J. Appl. Pharm. Res.*, **12**, 68–78 (2024) https://doi.org/10.18231/j.joapr.2024.12.2.68.78.

[15] Ghazi N, Liu Z, Bhatt C, Kiang S, Cuitino A. Investigating the effect of APAP crystals on tablet behavior manufactured by direct compression. *AAPS PharmSciTech*, **20**, 1–4 (2019) https://doi.org/10.1208/s12249-019-1369-0.

[16] Kadota K, Terada H, Fujimoto A, Nogami S, Uchiyama H, Tozuka Y. Formulation and evaluation of bitter taste-masked orally disintegrating tablets of high memantine hydrochloride loaded granules coated with polymer via layering technique. *Int. J Pharm*, **604**, 120725 (2021) https://doi.org/10.1016/j.ijpharm.2021.120725.

[17] Ranmal SR, Lavarde M, Wallon E, Issa S, Taylor WR, Nguyen Ngoc Pouplin JL, Tuleu C, Pensé-Lhéritier AM. Responsive sensory evaluation to develop flexible taste-masked paediatric primaquine tablets against malaria for low-resource settings. *Pharmaceutics*, **15(7)**, 1879 (2023) https://doi.org/10.3390/pharmaceutics15071879.

[18] Chiarugi I, Biagi D, Nencioni P, Maestrelli F, Valleri M, Mura PA. Taste masking of dexketoprofen trometamol orally disintegrating granules by high-shear coating with glyceryl distearate. *Pharmaceutics*, **16(2)**, 165 (2024) https://doi.org/10.3390/pharmaceutics16020165.

[19] Hu S, Liu X, Zhang S, Quan D. An overview of taste-masking technologies: approaches, application, and assessment methods. *AAPS PharmSciTech***, 24(2)**, 67 (2023) https://doi.org/10.1208/s12249-023-02520-z.

[20] Shirwar M, Birajdar S, Garad S, Kumbhar S. Development and validation of novel UV-visible spectrophotometric method for estimation of tepotinib in bulk and in pharmaceutical formulation. *Int. J. Pharm. Pharm. Sci.*, 15(9), 32–36 (2023) https://dx.doi.org/10.22159/ijpps.2023v15i9.48431.

[21] Lex TR, Rodriguez JD, Zhang L, Jiang W, Gao Z. Development of in vitro dissolution testing methods to simulate fed conditions for immediate release solid oral dosage forms. *AAPS J.*, **24(2)**, 40 (2022) https://doi.org/10.1208/s12248-022-00690-5.

[22] Boniatti J, Tappin MR, da S Teixeira RG, de AV Gandos T, Rios LP, Ferreira IA, Oliveira KC, Calil-Elias S, Santana AK, da Fonseca LB, Shimizu FM. In vivo and in vitro taste assessment of artesunate–mefloquine, praziquantel, and benznidazole drugs for neglected tropical diseases and pediatric patients. *AAPS*

PharmSciTech, **23**, 1–0 (2022) https://doi.org/10.1208/s12249-021-02162-z.

[23] Guedes MD, Marques MS, Guedes PC, Contri RV, Kulkamp Guerreiro IC. The use of electronic tongue and sensory panel on taste evaluation of pediatric medicines: a systematic review. *Pharm. Dev. Technol.*, **26(2)**, 119–37 (2021) https://doi.org/10.1080/10837450.2020.1860088.

[24] Siafaka P, Ipekci E, Caglar EŞ, Okur NU, Buyukkayhan D. Current status of pediatric formulations for chronic and acute children's diseases: applications and future perspectives. *Medeni Med. J.*, **36(2)**, 152–62 (2021) https://doi.org/10.5222/MMJ.2021.78476.

[25] Scrivens G. Prediction of the long-term dissolution performance of an immediate-release tablet using accelerated stability studies. *J. Pharm. Sci.*, **108(1)**, 506–15 (2019) https://doi.org/10.1016/j.xphs.2018.10.025.