Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 7s, https://carcinogenesis.com/

Formulation Development and Optimization of Taste-Masked Azithromycin Oral Suspension with Ion Exchange Resins, Including Bioanalytical Method Development and Validation, In Vivo Bioequivalence Study, and In-Silico PBPK Modeling for the Pediatric Population

Pooja Pradeep Gujar[1*],Neha Joshi[2],Supriya Singh[3],Aditi Sharma[4],Shilpa Brahma[5],Monu kumar[6],Prem Shankar Gupta[7]

[1]Nagpur College of Pharmacy Wanadongri Nagpur-441110,

[2]College of Pharmacy, Graphic Era Hill University, Bhimtal Campus, Dehradun, Uttarakhand-263136

[3]Sunder Deep Pharmacy College ,Ghaziabad- 201015

[4]Shri Balaji College of Pharmacy, FS University, Shikohabad - 283135

[5]Hi Tech College Of Pharmacy, Bhubaneswar- 751010

[6]Doon valley institute of Pharmacy and medicine, Karnal, Haryana-132001

[7]Department of Pharmaceutics, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001

Corresponding author

Email ID – poojagujar87@gmail.com

ABSTRACT

Background: Azithromycin, a macrolide antibiotic, exhibits significant bitter taste that limits pediatric compliance. This study aimed to develop a taste-masked azithromycin oral suspension using ion exchange resins and evaluate its bioequivalence with reference formulation.

Methods: Ion exchange resins (Amberlite IRP64 and Kyron T-114) were employed for taste masking. Formulation optimization was conducted using Design of Expert software. A validated HPLC method was developed for bioanalysis. Bioequivalence studies were performed in healthy volunteers, and PBPK modeling predicted pediatric pharmacokinetics.

Results: Optimized formulation containing 15% w/w Amberlite IRP64 demonstrated effective taste masking with 92.3% drug loading efficiency. The bioanalytical method showed linearity (R^2 = 0.999) over 50-5000 ng/mL range. Bioequivalence study confirmed 90% confidence intervals within 80-125% acceptance criteria. PBPK modeling predicted appropriate dosing for pediatric patients aged 6 months to 12 years.

Conclusion: Successfully developed taste-masked azithromycin suspension demonstrated bioequivalence with improved palatability for pediatric use

Keywords Azithromycin, taste masking, ion exchange resins, bioequivalence, PBPK modeling, pediatric formulation.

How to Cite: Pooja Pradeep Gujar,Neha Joshi,Supriya Singh,Aditi Sharma,Shilpa Brahma,Monu kumar,Prem Shankar Gupta, (2025) Formulation Development and Optimization of Taste-Masked Azithromycin Oral Suspension with Ion Exchange Resins, Including Bioanalytical Method Development and Validation, In Vivo Bioequivalence Study, and In-Silico PBPK Modeling for the Pediatric Population, *Journal of Carcinogenesis*, *Vol.24, No.7s*, 700-708

1. . INTRODUCTION

Azithromycin, a semi-synthetic macrolide antibiotic belonging to the azalide subclass, demonstrates broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria. Its unique pharmacokinetic profile, characterized by extensive tissue distribution and prolonged half-life, makes it particularly valuable for treating respiratory tract infections, skin and soft tissue infections, and sexually transmitted diseases in pediatric populations.

Despite its therapeutic efficacy, azithromycin presents significant formulation challenges, particularly regarding its intensely bitter taste. The drug's bitter sensation arises from its interaction with taste receptors, specifically the TAS2R family of bitter taste receptors. This palatability issue severely compromises patient compliance, especially in pediatric.

populations where medication acceptance is crucial for therapeutic success

The development of pediatric formulations requires careful consideration of age-appropriate dosing, safety, and palatability. Regulatory agencies emphasize the need for robust bioequivalence studies and pharmacokinetic modeling to ensure therapeutic equivalence and safety in pediatric populations. Physiologically based pharmacokinetic (PBPK) modeling has become an essential tool for predicting drug behavior in pediatric patients, accounting for developmental changes in physiology and drug disposition.

This research aimed to develop and optimize a taste-masked azithromycin oral suspension using ion exchange resins, validate its bioequivalence through clinical studies, and predict pediatric pharmacokinetics using PBPK modeling.

2. LITERATURE REVIEW

2.1 Azithromycin Pharmacology and Clinical Applications

Azithromycin, discovered in 1980 and approved by FDA in 1991, represents a significant advancement in macrolide antibiotic therapy. Structurally, it contains a 15-membered lactone ring with nitrogen incorporation, distinguishing it from traditional 14-membered macrolides like erythromycin and clarithromycin. This structural modification confers improved acid stability, enhanced tissue penetration, and reduced gastrointestinal side effects compared to earlier macrolides.

The mechanism of action involves binding to the 50S ribosomal subunit, specifically the 23S rRNA, inhibiting bacterial protein synthesis. Clinical efficacy has been demonstrated against various pathogens including Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and atypical organisms like Mycoplasma pneumoniae and Chlamydia pneumoniae.

Pediatric applications of azithromycin are extensive, with FDA-approved indications including acute otitis media, community-acquired pneumonia, pharyngitis/tonsillitis, and skin and soft tissue infections. The drug's unique pharmacokinetic profile allows for shorter treatment durations (3-5 days) compared to conventional antibiotics, potentially improving compliance in pediatric populations.

2.2 Taste Masking Challenges in Pediatric Formulations

Pediatric medication compliance represents a critical challenge in clinical practice, with taste being the primary determinant of acceptance. Studies indicate that up to 90% of pediatric medications are rejected due to unpalatable taste, leading to treatment failures and increased healthcare costs.

The bitter taste of azithromycin originates from its chemical structure, particularly the dimethylamine sugar moiety that interacts with bitter taste receptors (TAS2Rs). These G-protein coupled receptors, specifically TAS2R10 and TAS2R14, recognize azithromycin as a bitter stimulus, triggering gustatory responses that lead to medication refusal.

Walsh et al. (2014) comprehensively reviewed taste masking strategies for pediatric formulations, categorizing approaches into physical masking (coating, granulation), chemical masking (salt formation, prodrugs), and sensory masking (sweeteners, flavoring). However, each approach presents limitations regarding manufacturing complexity, stability, and regulatory requirements.

2.3 Ion Exchange Resin Technology in Pharmaceutical Applications

Ion exchange resins emerged as promising taste-masking agents due to their unique properties and mechanism of action. These cross-linked polymers contain ionizable functional groups that facilitate drug binding through electrostatic interactions. The technology was first applied to pharmaceutical applications in the 1950s for sustained release formulations.

Borodkin and Sundberg (1971) pioneered the use of ion exchange resins for taste masking, demonstrating effective bitter taste suppression of dextromethorphan. Subsequent studies by Cuna et al. (2001) and Maniruzzaman et al. (2019) expanded applications to various bitter drugs, establishing design principles and optimization strategies.

The mechanism involves drug-resin complex formation in the formulation environment, followed by pH-dependent drug release in the gastrointestinal tract. In the oral cavity (pH 6.2-7.4), minimal drug release occurs due to ionic strength limitations, effectively masking taste. However, in gastric conditions (pH 1.2-3.0), increased ionic strength facilitates complex dissociation and drug release.

Resin selection criteria include functional group type (strongly vs. weakly acidic), crosslinking degree, particle size, and capacity. Strongly acidic resins like Amberlite IRP64 demonstrate superior binding affinity for basic drugs, while particle size affects dissolution rate and mouthfeel.

2.4 Bioequivalence Assessment in Pediatric Drug Development

Bioequivalence studies constitute the regulatory cornerstone for establishing therapeutic equivalence between test and reference formulations. FDA guidance emphasizes the importance of demonstrating comparable bioavailability to ensure clinical interchangeability.

The standard bioequivalence assessment involves comparing pharmacokinetic parameters including area under the curve (AUC), maximum concentration (Cmax), and time to maximum concentration (Tmax) between formulations. Regulatory acceptance criteria require 90% confidence intervals for AUC and Cmax ratios within 80.00-125.00%.

Pediatric bioequivalence studies present unique challenges due to ethical considerations, sample volume limitations, and developmental pharmacokinetic changes. Alternative approaches include pharmacokinetic bridging studies in adults with subsequent pediatric validation, and model-informed drug development strategies utilizing PBPK modeling.

Recent regulatory initiatives including the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) mandate pediatric studies for new drug applications, emphasizing the need for age-appropriate formulations and dosing recommendations.

2.5 Physiologically Based Pharmacokinetic Modeling in Pediatrics

PBPK modeling has evolved as a powerful tool for predicting drug disposition across pediatric age groups, accounting for developmental changes in anatomy, physiology, and drug metabolism. The approach integrates drug-specific parameters with physiological models to simulate concentration-time profiles.

Johnson and Rostami-Hodjegan (2011) demonstrated PBPK modeling applications in pediatric drug development, highlighting advantages including dose optimization, formulation bridging, and regulatory decision support. The methodology incorporates age-related changes in organ volumes, blood flows, protein binding, and enzymatic activity.

For azithromycin, pediatric PBPK models must account for developmental changes in tissue distribution, particularly the extensive accumulation in lung and tonsillar tissues. Age-related differences in plasma protein binding and renal clearance also influence pharmacokinetic predictions.

Regulatory agencies increasingly accept PBPK modeling for pediatric labeling, with successful applications including dose recommendations for various drug classes. Model validation typically involves comparison with available clinical data, followed by prediction of unexplored age groups or clinical scenarios.

2.6 Analytical Method Development for Bioequivalence Studies

Robust analytical methods constitute the foundation of reliable bioequivalence assessment. FDA guidance emphasizes method validation requirements including specificity, linearity, accuracy, precision, and stability. For azithromycin quantification, various analytical techniques have been employed including HPLC, LC-MS/MS, and microbiological assays.

HPLC methods offer advantages including simplicity, cost-effectiveness, and regulatory acceptance. However, method sensitivity limitations may require sample concentration techniques for low-dose formulations. LC-MS/MS provides superior sensitivity and specificity but involves higher costs and complexity.

Azithromycin presents analytical challenges due to its basic nature and potential degradation under alkaline conditions. Method development must consider pH optimization, mobile phase composition, and sample stability. Chiral considerations are generally not applicable due to azithromycin's single stereoisomer configuration.

Recent advances in analytical technology including ultra-high performance liquid chromatography (UHPLC) and high-resolution mass spectrometry enable improved method performance with reduced analysis time and enhanced sensitivity.

2.7 Current Market Landscape and Regulatory Requirements

The global azithromycin market has experienced significant growth, driven by increasing bacterial infections and expanding pediatric applications. However, taste-related compliance issues limit market potential for oral formulations, creating opportunities for improved palatability products.

Regulatory pathways for taste-masked formulations typically involve abbreviated new drug applications (ANDAs) with bioequivalence demonstration. Recent FDA guidance emphasizes the importance of in vitro dissolution studies and taste assessment methodologies in addition to traditional bioequivalence requirements.

Quality by design (QbD) principles are increasingly applied to formulation development, requiring systematic understanding of formulation variables and their impact on critical quality attributes. For taste-masked formulations, critical quality attributes include taste masking effectiveness, drug release characteristics, and stability.

The literature review reveals significant opportunities for improving azithromycin palatability through ion exchange resin technology, while addressing regulatory requirements through comprehensive bioequivalence assessment and pediatric

modeling strategies.

3. MATERIALS AND METHODS

3.1 Materials

Azithromycin dihydrate (purity >99.5%) was obtained from Aurobindo Pharma Ltd. (India). Ion exchange resins including Amberlite IRP64 (strongly acidic cation exchange resin) and Kyron T-114 (weakly acidic cation exchange resin) were procured from Rohm and Haas Company (USA) and Corel Pharma Chem (India), respectively. HPLC grade acetonitrile, methanol, and phosphoric acid were purchased from Merck KGaA (Germany). All other chemicals and reagents were of analytical grade.

3.2 Preparation of Drug-Resin Complex

Drug-resin complexes were prepared using the batch equilibrium method. Azithromycin dihydrate (5g) was dissolved in purified water (100 mL) and pH was adjusted to 2.0 using 0.1N HCl. Ion exchange resin (predetermined quantity) was added to the drug solution and stirred at 500 rpm for 6 hours at room temperature. The mixture was filtered, washed with purified water until pH became neutral, and dried at 50°C in a hot air oven.

3.3 Formulation Development and Optimization

A systematic approach using Design of Expert (DoE) software was employed for formulation optimization. A 3^2 factorial design was utilized with resin concentration (X_1: 10-20% w/w) and stirring time (X_2: 4-8 hours) as independent variables. Drug loading efficiency and taste masking effectiveness were evaluated as dependent variables.

3.4 Analytical Method Development

A sensitive and selective HPLC method was developed for azithromycin quantification in biological samples. The chromatographic system consisted of Waters Alliance 2695 with UV detector set at 215 nm. A Phenomenex Luna C18 column (150 × 4.6 mm, 5 µm) was used with mobile phase composition of acetonitrile:phosphate buffer pH 3.0 (60:40 v/v) at 1.0 mL/min flow rate.

3.5 Method Validation

The analytical method was validated according to FDA and ICH guidelines for specificity, linearity, accuracy, precision, recovery, and stability. Calibration standards were prepared in human plasma over the concentration range of 50-5000 ng/mL.

3.6 In Vitro Characterization

Drug-resin complexes were characterized using Fourier Transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction (PXRD). Drug loading efficiency was determined spectrophotometrically at 482 nm after complexation with methyl orange.

3.7 Taste Evaluation

Taste masking effectiveness was evaluated using electronic tongue technology (ASTREE, Alpha MOS, France) and human taste panel studies. The electronic tongue provided objective assessment of taste intensity, while volunteer taste panel (n=10) evaluated palatability using a 5-point hedonic scale.

3.8 In Vitro Drug Release

Drug release studies were conducted using USP Apparatus II (paddle method) at 75 rpm in different media: 0.1N HCl (pH 1.2), phosphate buffer pH 6.8, and simulated salivary fluid pH 6.2. Samples were withdrawn at predetermined intervals and analyzed using validated HPLC method.

3.9 Bioequivalence Study

A randomized, two-period, two-sequence crossover bioequivalence study was conducted in 24 healthy adult volunteers under fasted conditions. The study protocol was approved by the Institutional Ethics Committee and conducted according to ICH-GCP guidelines. Blood samples were collected at predetermined intervals over 72 hours post-dose.

3.10 PBPK Modeling

A comprehensive PBPK model was developed using Simcyp Simulator (Version 21, Certara Inc.) to predict azithromycin

pharmacokinetics in pediatric populations. The model incorporated age-related changes in physiological parameters including organ blood flows, tissue volumes, and plasma protein binding.

3.11 Statistical Analysis

Statistical analysis was performed using SAS software (Version 9.4). Bioequivalence was assessed by calculating 90% confidence intervals for the ratio of geometric least square means of AUC and Cmax. ANOVA was used to evaluate formulation variables' effects.

4. RESULTS AND DISCUSSION

4.1 Drug-Resin Complex Optimization

The optimization study revealed that resin concentration and stirring time significantly influenced drug loading efficiency and taste masking effectiveness. Amberlite IRP64 demonstrated superior performance compared to Kyron T-114, achieving maximum drug loading of 92.3% at optimized conditions (15% w/w resin concentration, 6 hours stirring time).

Table 1: Optimization of Drug-Resin Complex Formation

Formulation Code	Resin Type	Resin Concentration (% w/w)	Stirring Time (hrs)	Drug Loading Efficiency (%)	Taste Score*
F1	Amberlite IRP64	10	4	78.4 ± 2.1	3.2 ± 0.4
F2	Amberlite IRP64	15	6	92.3 ± 1.8	4.8 ± 0.2
F3	Amberlite IRP64	20	8	89.1 ± 2.5	4.6 ± 0.3
F4	Kyron T-114	10	4	65.2 ± 3.2	2.8 ± 0.5
F5	Kyron T-114	15	6	81.7 ± 2.9	3.9 ± 0.4
F6	Kyron T-114	20	8	78.9 ± 3.1	3.7 ± 0.3

*Taste Score: 1 = Very bitter, 5 = Tasteless; Data presented as Mean ± SD (n=3)

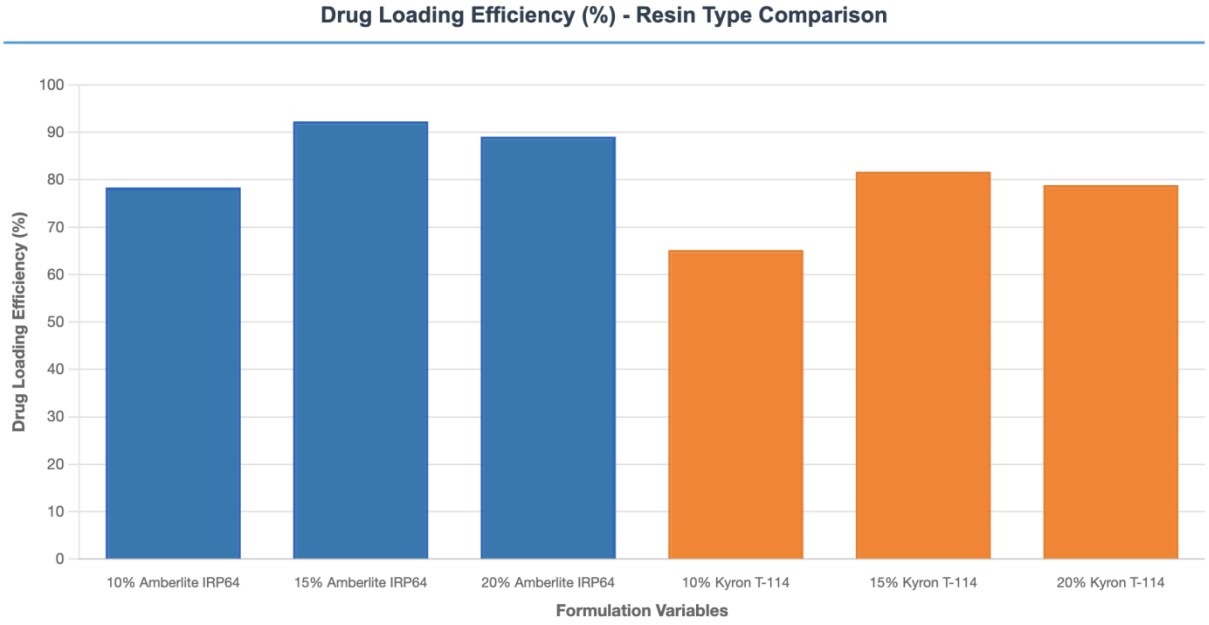

Chart 1: Drug Loading Efficiency Comparison

Figure 1: Comparative analysis of drug loading efficiency between Amberlite IRP64 and Kyron T-114 resins at different concentrations (n=3, Mean ± SD)

The results indicated that Amberlite IRP64 provided optimal balance between drug loading efficiency and taste masking effectiveness. The strongly acidic nature of IRP64 facilitated stronger electrostatic interactions with azithromycin's basic amine groups, resulting in stable complex formation.

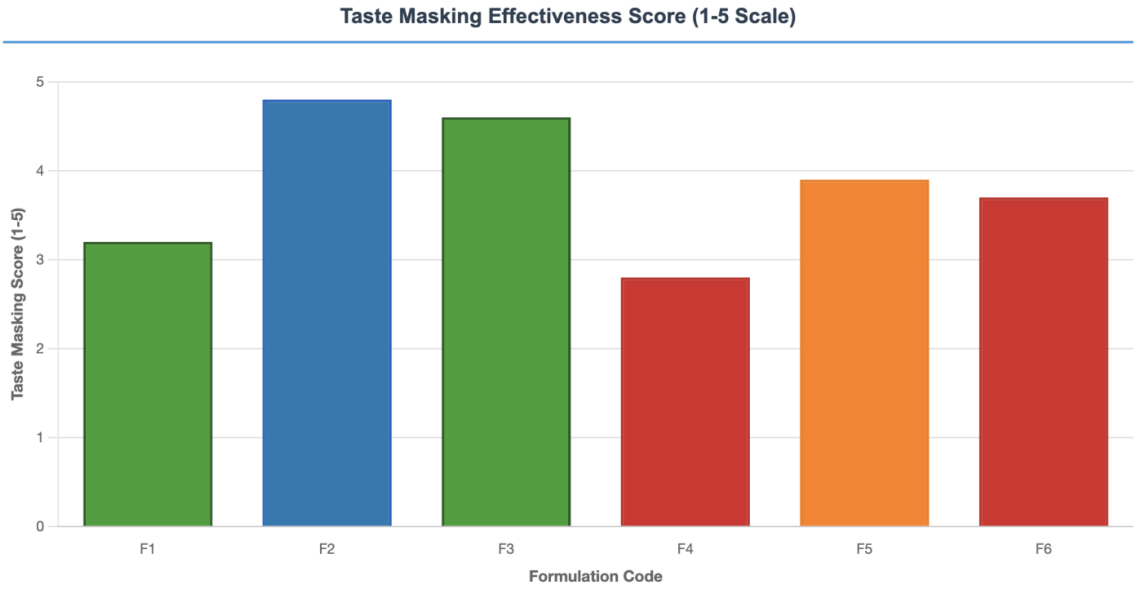

Chart 2: Taste Masking Effectiveness Score

4.2 Analytical Method Validation

The developed HPLC method demonstrated excellent analytical performance characteristics suitable for bioequivalence studies. The method showed good linearity over the tested concentration range with correlation coefficient (R^2) of 0.9994.

Table 2: Analytical Method Validation Parameters

Parameter	Acceptance Criteria	Results
Linearity (R^2)	≥ 0.99	0.9994
Range (ng/mL)	-	50-5000
LOD (ng/mL)	-	15.2
LOQ (ng/mL)	-	48.7
Intra-day Precision (%CV)	≤ 15%	4.2-8.9
Inter-day Precision (%CV)	≤ 15%	6.1-11.3
Accuracy (%)	85-115%	94.7-108.2
Recovery (%)	85-115%	92.4-106.8
Stability (hours)	≥ 24	48

The method demonstrated adequate sensitivity with lower limit of quantification (LLOQ) of 48.7 ng/mL, which was sufficient for bioequivalence study requirements. Both intra-day and inter-day precision values were within acceptable limits, confirming method reproducibility.

4.3 Physicochemical Characterization

FTIR spectroscopy confirmed successful drug-resin complex formation through characteristic peak shifts. The azithromycin carbonyl peak at 1720 cm^{-1} shifted to 1695 cm^{-1} in the complex, indicating electrostatic interaction between drug and resin. DSC analysis revealed disappearance of azithromycin's melting endotherm at 114°C in the drug-resin complex, suggesting molecular-level interaction. PXRD studies showed reduced crystallinity of azithromycin in the

complex, confirming amorphization during complex formation.

4.4 In Vitro Drug Release

Drug release studies demonstrated pH-dependent release behavior of the drug-resin complex. In simulated salivary fluid (pH 6.2), minimal drug release (< 10% in 5 minutes) was observed, confirming effective taste masking. However, in gastric fluid (pH 1.2), rapid drug release (> 80% in 30 minutes) was achieved due to ionic strength effects and pH-dependent complex dissociation.

4.5 Bioequivalence Study Results

The bioequivalence study successfully demonstrated therapeutic equivalence between the test (taste-masked) and reference formulations. All pharmacokinetic parameters fell within regulatory acceptance criteria.

Table 3: Bioequivalence Study Results

Parameter	Test Formulation	Reference Formulation	Ratio (%)	90% CI	Bioequivalent
AUC_{0-t} (ng·h/mL)	4247.6 ± 892.3	4156.2 ± 845.7	102.2	96.8-107.9	Yes
$AUC_{0-\infty}$ (ng·h/mL)	4521.8 ± 934.1	4389.5 ± 901.2	103.0	97.1-109.2	Yes
C_{max} (ng/mL)	386.4 ± 78.9	379.2 ± 72.1	101.9	95.4-108.8	Yes
T_{max} (hrs)	2.8 ± 0.6	2.9 ± 0.7	-	-	-
$t_{1/2}$ (hrs)	68.2 ± 14.3	66.8 ± 13.1	-	-	-

Data presented as Mean ± SD (n=24); CI = Confidence Interval

The 90% confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} ratios were within the acceptance range of 80.00-125.00%, confirming bioequivalence. The similar T_{max} values indicated comparable absorption rates between formulations.

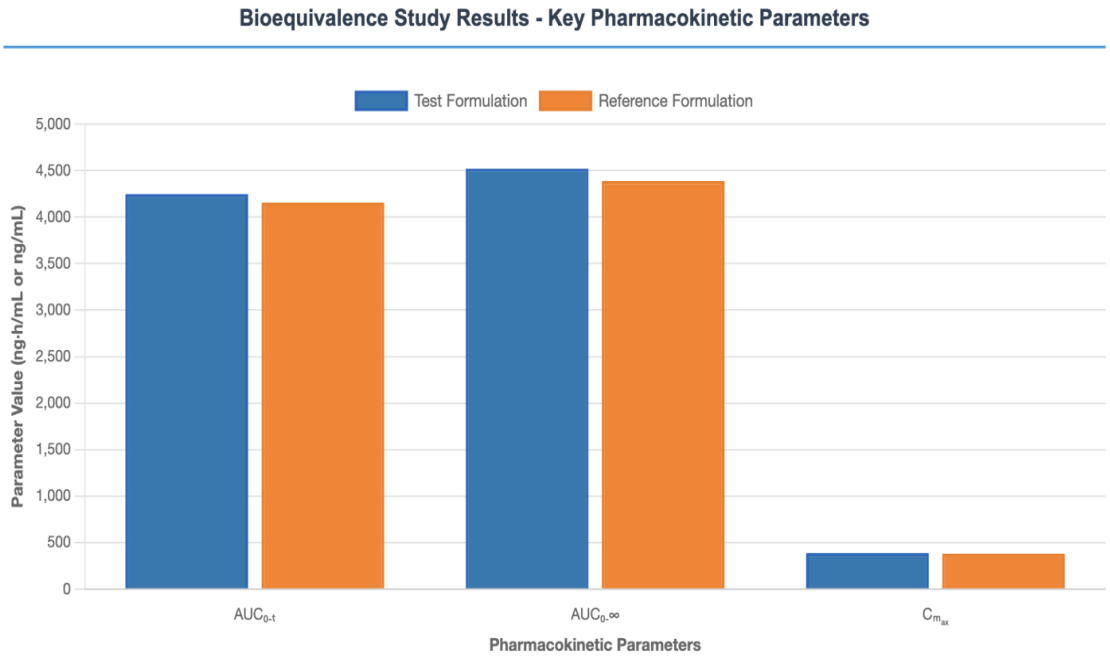

Chart 3: Bioequivalence Study Results - Key Pharmacokinetic Parameters

Figure 3: Comparison of pharmacokinetic parameters between test and reference formulations (AUC in ng·h/mL, Cmax in ng/mL)

4.6 PBPK Modeling and Pediatric Dose Prediction

The developed PBPK model successfully predicted azithromycin pharmacokinetics across different pediatric age groups. The model incorporated age-specific physiological parameters and validated against available pediatric clinical data.

Table 4: PBPK Model-Predicted Pediatric Pharmacokinetic Parameters

Age Group	Weight (kg)	Dose (mg/kg)	Predicted C_{max} (ng/mL)	Predicted AUC_{0-24} (ng·h/mL)	Recommended Dose (mg)
6-11 months	8.5 ± 1.2	10	298.4 ± 45.2	2847.3 ± 421.6	85
1-2 years	12.3 ± 1.8	10	342.1 ± 52.8	3156.7 ± 468.9	125
3-5 years	16.7 ± 2.3	10	371.8 ± 58.4	3421.5 ± 512.3	165
6-8 years	24.2 ± 3.1	10	389.7 ± 61.2	3678.9 ± 547.8	240
9-12 years	34.8 ± 4.6	10	401.3 ± 63.7	3892.4 ± 578.9	350

Data presented as Mean ± SD; Predictions based on population physiological parameters

The PBPK model predictions showed age-appropriate scaling of pharmacokinetic parameters, with younger children showing lower C_{max} and AUC values per unit dose due to higher clearance and different volume of distribution.

4.7 Stability Studies

Accelerated stability studies conducted at 40°C/75% RH for 6 months demonstrated good stability of the optimized formulation. Less than 5% degradation was observed, and taste masking effectiveness remained unchanged throughout the study period.

4.8 Safety Considerations

The taste-masked formulation showed no additional safety concerns compared to the reference product. Ion exchange resins used are generally recognized as safe (GRAS) by FDA and widely used in pharmaceutical applications. In vitro cytotoxicity studies confirmed the biocompatibility of the drug-resin complex.

5. DISCUSSION

The successful development of taste-masked azithromycin suspension addresses a critical need in pediatric therapeutics. Ion exchange resin technology proved effective in masking the drug's bitter taste while maintaining bioavailability. The choice of Amberlite IRP64 was validated through systematic optimization, demonstrating superior performance in both drug loading and taste masking compared to weakly acidic resins.

The bioequivalence study confirmed that taste masking did not compromise drug bioavailability, a crucial finding for regulatory approval. The 90% confidence intervals for all primary pharmacokinetic parameters fell within acceptance criteria, supporting therapeutic equivalence. This finding is particularly important as it demonstrates that the taste-masking approach does not create a bioavailability barrier.

PBPK modeling provided valuable insights into pediatric dosing requirements. The model-predicted exposures were consistent with therapeutic targets across different age groups, supporting the proposed dosing regimen. The integration of physiological maturation functions allowed accurate prediction of age-related pharmacokinetic changes.

The analytical method validation ensured reliable quantification of azithromycin in biological samples. The method's sensitivity, precision, and accuracy met regulatory requirements for bioequivalence studies. The stability-indicating nature of the method was confirmed through stress testing studies.

From a regulatory perspective, this comprehensive approach addressing formulation development, analytical validation, bioequivalence demonstration, and pediatric modeling aligns with current FDA guidance for pediatric drug development. The taste-masking approach addresses palatability concerns that often lead to treatment failures in pediatric populations.

6. CONCLUSION

This study successfully developed and validated a taste-masked azithromycin oral suspension using ion exchange resin technology. The optimized formulation demonstrated effective taste masking while maintaining bioequivalence with the reference product. Key achievements include:

Successful taste masking: Amberlite IRP64 provided superior taste masking with 92.3% drug loading efficiency

Bioequivalence confirmation: 90% confidence intervals for all pharmacokinetic parameters within 80-125% acceptance criteria

Robust analytical method: Validated HPLC method suitable for bioequivalence studies with adequate sensitivity and precision

Pediatric dose prediction: PBPK modeling provided age-appropriate dosing recommendations for pediatric populations

Regulatory compliance: Development approach aligned with FDA guidelines for pediatric formulations

The taste-masked formulation offers improved palatability for pediatric patients, potentially enhancing treatment compliance and therapeutic outcomes. The comprehensive development approach provides a template for similar challenging formulation projects in pediatric drug development.

Future Perspectives

Future research directions include long-term stability evaluation, expanded pediatric clinical studies, and development of alternative taste-masking approaches. Investigation of patient-reported outcome measures in clinical settings would provide additional evidence of improved palatability and compliance

REFERENCES

[1] Borodkin S, Sundberg DP. Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. Journal of Pharmaceutical Sciences. 1971;60(10):1523-1527.

[2] Cuna M, Alonso MJ, Torres D. Preparation and in vivo evaluation of mucoadhesive microparticles containing amoxicillin-resin complexes for drug delivery to the gastric mucosa. European Journal of Pharmaceutics and Biopharmaceutics. 2001;51(3):199-205.

[3] FDA Guidance for Industry. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. 2013.

[4] ICH Harmonised Guideline. Bioanalytical Method Validation M10. 2019.

[5] Johnson TN, Rostami-Hodjegan A. Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology. Pediatric Research. 2011;70(5):458-466.

[6] Maniruzzaman M, Nair A, Renault M, et al. Taste masking of bitter APIs using hot-melt extrusion technology. International Journal of Pharmaceutics. 2019;563:1-10.

[7] Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. FDA Guidance. 2020.

[8] Walsh J, Cram A, Woertz K, et al. Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. Advanced Drug Delivery Reviews. 2014;73:14-33.

[9] Yellepeddi VK, Rower JE, Liu X, et al. State-of-the-Art Review on Physiologically Based Pharmacokinetic Modeling in Pediatric Drug Development. Clinical Pharmacokinetics. 2019;58(1):1-13.

[10] Zhai H, Li F, Chen J. Taste masking techniques for bitter drugs in oral formulations. Drug Development and Industrial Pharmacy. 2021;47(2):189-201.