Research Article

Development And Optimization Of Amoxicillin Trihydrate Minitablets As A Stable And Pediatric-Friendly Alternative To Oral Suspension

Mahesh Patil[1], Sejal Fulzele[1], Shruti Vaidya[1], Suankit Harane[1*], Milind Umekar[2], Vinita Kale[1]

[1]Department of Multidisciplinary Research, Smt. Kishoritai Bhoyar College of Pharmacy Kamptee, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra
[2]Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy Kamptee, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra
*Corresponding author: Suankit.harane92@gmail.com

Abstract

Amoxicillin trihydrate, a widely prescribed β-lactam antibiotic, exhibits hydrolytic instability in aqueous environments, posing stability limitations in conventional powder-for-oral-suspension dosage forms. The present study aimed to develop a stable, mechanically robust, and palatable minitablet formulation of amoxicillin as a dose-flexible alternative for pediatric use. A systematic phase-wise optimization approach was employed to evaluate direct compression, dry granulation, and wet granulation techniques. Wet granulation was identified as the most suitable manufacturing process for high drug loading, providing improved compressibility and mechanical integrity. Subsequent optimization of filler composition, disintegrant distribution and excipient balance resulted in minitablets exhibiting rapid disintegration and satisfactory dissolution performance. The optimized formulation demonstrated friability of 0.36%, disintegration time of 50 seconds, and approximately 90% drug release within 15 minutes. Sensory evaluation confirmed statistically improved palatability following combined sweetener and flavor optimization. Stability studies conducted under ICH-recommended accelerated and long-term conditions showed minimal degradation, maintained assay within 95–105%, and total impurities below pharmacopoeial limits over six months. Solid-state characterization by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) confirmed that the crystalline trihydrate form of amoxicillin was retained in the optimized batch following wet granulation. The developed minitablet formulation provides a stable, dose-flexible, and pediatric-compliant alternative to conventional oral suspension, addressing key limitations related to hydrolytic instability, dosing variability, and in-use shelf-life.

Keywords: Amoxicillin trihydrate; Minitablets; Wet granulation; Pediatric drug delivery; Disintegrant distribution; Palatability; Stability studies; β-lactam antibiotics.

Introduction

Oral liquid antibiotic formulations, particularly dry syrups requiring reconstitution prior to administration, remain widely prescribed in pediatric therapy. Despite their long-standing use, these dosage forms present multiple pharmaceutical and clinical limitations, including reconstitution errors, dosing variability, chemical instability after dilution, storage sensitivity, transportation burden, and palatability concerns. These factors may compromise therapeutic efficacy, adherence, and antimicrobial stewardship, particularly in low-resource and tropical settings (1,2)

β-lactam antibiotics such as amoxicillin and amoxicillin clavulanic acid is especially vulnerable to hydrolytic degradation following reconstitution. Stability studies have demonstrated progressive loss of active content when stored under tropical (30°C) and elevated (40°C) conditions, raising concerns regarding potency during real-world use (3). Inadequate storage practices further exacerbate this problem, with evidence suggesting that a substantial proportion of caregivers store antibiotic suspensions under suboptimal conditions (4). Such instability not only reduces therapeutic effectiveness but may also contribute to antimicrobial resistance.

Dosing accuracy represents another critical limitation of liquid formulations. Pediatric antibiotic dosing is typically weight-based, requiring caregivers to measure specific volumes using spoons or syringes. Studies have reported significant dosing inaccuracies associated with household measuring devices (5,6). Complex dosing schedules, as outlined in product monographs such as CLAVULIN®, further increase the likelihood of measurement errors (7).

Additionally, liquid formulations impose logistical and economic challenges. Their bulk, weight, fragility, and risk of leakage increase transportation and storage costs. A cost-saving investigation in a UK hospital demonstrated that substitution of liquid medicines with acceptable solid oral dosage forms could yield meaningful economic benefits (8).

In response to these challenges, minitablets have emerged as a promising pediatric dosage form. These multiparticulate systems combine the chemical stability of solid dosage forms with dose flexibility, potentially addressing many of the limitations associated with liquid preparations (9).

A recent comprehensive review synthesized key clinical and translational evidence demonstrating favorable acceptability and swallowability of minitablets across pediatric age groups, while highlighting formulation

challenges such as high drug loading, taste masking, and mechanical robustness (10). Complementing this, a bibliometric analysis documented a marked increase in global research activity in pediatric minitablet development and identified critical gaps in high-dose therapeutic areas, particularly antibiotics (11).
Randomized crossover studies have demonstrated high acceptability of 2 mm uncoated minitablets in infants and preschool children, often outperforming syrups, with confirmed safety in neonates and successful administration of multiple minitablets per dose (12–14).
Amoxicillin minitablets have emerged as a promising solid pediatric dosage platform capable of addressing limitations associated with conventional liquid suspensions, including stability, dosing accuracy, and storage constraints. Direct formulation and performance evaluation studies have demonstrated that amoxicillin minitablets can achieve controlled or immediate release profiles with acceptable mechanical strength and in vivo performance (15). Comparative investigations evaluating minitablets against alternative delivery systems such as nanoparticles further confirmed the feasibility of achieving optimized release kinetics while maintaining formulation robustness. Additionally, clinical acceptability and swallowability studies on pediatric minitablets, including film-coated variants, have supported their suitability in young children, reinforcing their potential as scalable antibiotic dosage forms (16). Collectively, these findings support the scientific rationale for continued development of mechanically robust, high drug-loaded amoxicillin minitablets optimized for rapid disintegration and pediatric acceptability.
In the context of global efforts to improve access to child-appropriate antibiotic formulations, amoxicillin remains a cornerstone therapy for pediatric infections, particularly pneumonia. The World Health Organization has emphasized the urgent need to accelerate development of priority pediatric formulations, including flexible solid oral dosage platforms for antibiotics such as azithromycin and nitrofurantoin, while reinforcing optimized delivery strategies for widely used agents like amoxicillin (17). Despite growing evidence supporting minitablets as age-appropriate solid dosage forms, their application in high-dose antibiotic therapy remains limited. Challenges associated with compressibility of antibiotic actives, taste masking of intensely bitter compounds, and multiparticulate dose design continue to restrict widespread commercial translation.
Given the demonstrated limitations of liquid antibiotic formulations and the expanding body of evidence supporting minitablet acceptability, further exploration into pediatric antibiotic minitablet development is warranted. The transition toward robust, stable, and precise solid dosage systems has the potential to enhance therapeutic reliability, improve adherence, reduce healthcare costs, and strengthen antimicrobial stewardship in pediatric populations.

2. Materials and Methods

2.1 Materials

Amoxicillin trihydrate (powder grade and compacted grade) was obtained from Centrient Pharmaceuticals India Pvt. Ltd., India. Microcrystalline cellulose PH101 (MCC PH101) and Crospovidone XL-10 were obtained from JRS pharma, Germany. Lactose monohydrate and lactose DC grade were obtained from DFE Pharma India Pvt Ltd India. Sodium saccharin was obtained from DK Pharma Chem Pvt. Ltd., India. Magnesium stearate was obtained from Roquette India Pvt Ltd, India. Food-grade flavor was obtained from IFF India Pvt. Ltd., India.
Purified water conforming to pharmacopeial specifications was used during granulation. All analytical reagents and solvents used in the study were of analytical grade.

2.2 Methods

2.2.1 Formulation Development of Minitablets

Amoxicillin minitablets containing 50 mg drug per unit were developed using a phase-wise optimization approach. Initial screening batches were prepared by direct compression and dry granulation. Based on preliminary performance, wet granulation was selected as the optimized manufacturing method.
For wet granulation, amoxicillin and intragranular excipients were blended and granulated using purified water. The wet mass was sieved, dried, milled, and blended with extragranular excipients including cross-povidone, sodium saccharin, flavor, and magnesium stearate. The final blend was compressed using 5.5 mm round flat punches on a rotary tablet compression machine.

2.2.2 Evaluation of Minitablets.

Compressed minitablets were evaluated for weight variation, hardness, friability, disintegration time, and drug content. Disintegration testing was performed in distilled water at 25 ± 0.5°C.

In-vitro dissolution studies were carried out using USP Type II (paddle) apparatus at 50 rpm in 900 mL purified water maintained at 37 ± 0.5°C. Samples were withdrawn at specified intervals and analyzed using a validated HPLC method.
The impurity profile was evaluated using a validated HPLC method. Sample solutions were prepared from powdered tablets equivalent to label claim concentration and filtered prior to injection. Acceptance criteria were in accordance with pharmacopeial limits (individual impurity NMT 1.5%; total impurities NMT 3.0%).
The optimized formulation was packed in suitable packaging material and stored under accelerated (40°C/75% RH) and long-term (30°C/75% RH) conditions as per ICH guidelines. Samples were evaluated periodically for physical appearance, assay, dissolution, and related substances.

3. Formulation development of Amoxicillin Minitablets

3.1 Rationale and Conceptual Framework for Development of Amoxicillin Minitablets

Amoxicillin dry syrup (250 mg/5 mL powder for oral suspension) remains one of the most commonly prescribed pediatric antibiotic formulations. Although widely accepted in clinical practice, reconstituted oral suspensions present several inherent limitations associated with handling, stability, dosing accuracy, and storage. The need for precise addition of water during reconstitution introduces variability in final drug concentration. Improper shaking, inaccurate measurement using dosing spoons or cups, and caregiver-dependent administration practices further contribute to potential dosing errors. Moreover, once reconstituted, the suspension typically exhibits limited in-use stability, generally restricted to 14 days under refrigerated conditions (2–8 °C). This constraint increases the risk of degradation, particularly for β-lactam antibiotics such as amoxicillin, which are susceptible to hydrolytic cleavage.
In addition to stability concerns, liquid formulations contain excipients such as aspartame, sorbitol, and sodium benzoate. While these agents improve palatability and preservation, they may pose safety considerations in certain pediatric subpopulations, including children with phenylketonuria or sorbitol intolerance. The aqueous nature of suspensions also increases susceptibility to microbial contamination if storage conditions are not maintained appropriately.
Minitablets represent an emerging multiparticulate solid dosage form designed to address many of these limitations. Typically ranging between 4-5 mm in diameter, minitablets offer several pharmaceutical and clinical advantages. Being solid dosage forms, they eliminate the need for reconstitution and significantly reduce the risk of hydrolytic degradation. The absence of an aqueous environment enhances chemical stability of moisture-sensitive drugs, including β-lactam antibiotics. Furthermore, unit-dose minitablets enable dose flexibility through tablet counting rather than volumetric measurement, thereby improving dosing precision and reducing caregiver-dependent variability.
Minitablets also provide flexibility across age groups. By adjusting the number of units administered, equivalent therapeutic doses can be achieved without modifying formulation strength. This feature is particularly advantageous in pediatric populations where weight-based dosing is common. Additionally, minitablets may be swallowed whole, dispersed in water, or administered with soft food, offering versatility in administration without compromising stability prior to use.
From a manufacturing and regulatory perspective, minitablets offer improved packaging efficiency and transport stability. Unlike reconstituted suspensions, they do not require refrigeration after dispensing for in-use stability, provided moisture protection is maintained. Their solid-state nature also reduces the excipient burden typically required for suspensions, potentially enhancing safety.
To systematically evaluate the feasibility of transitioning from suspension to minitablet dosage form, a conceptual comparative framework was developed. This framework examined equivalence in dose delivery, labeling, packaging, storage, and therapeutic intent while identifying potential improvements in stability, dosing accuracy, and patient convenience.
The conceptual comparison between the existing oral suspension and the proposed minitablet formulation is presented below.
Conceptual Comparison Between Existing Suspension and Proposed Minitablet Formulation

Aspect	Existing Dosage Form (Amoxicillin 250 mg/5 mL Powder for Oral Suspension)	Proposed Dosage Form (Amoxicillin 50 mg Minitablets)
Label Claim	1 mL contains 50 mg amoxicillin trihydrate	Each minitablet contains 50 mg amoxicillin trihydrate
Instructions for	Reconstitution with water; shake before	Swallow whole or disperse in water/soft

Use	use	food
Single Dose Equivalence	5 mL ≡ 250 mg	5 minitablets ≡ 250 mg
Packaging	Glass bottle yielding 100 mL suspension (5 g drug)	Glass/HDPE bottle containing 100 minitablets (5 g drug)
Storage	Refrigeration required; usable for 14 days after reconstitution	Refrigeration recommended; no reconstitution required
Excipients with Known Effects	Aspartame, sorbitol, sodium benzoate	Lactose (if present, declaration required)

Pediatric Weight-Based Dose Conversion (Suspension vs. Minitablets)
Each minitablet contains 50 mg amoxicillin (equivalent to 1 mL of reconstituted suspension).

Weight (kg)	Approx. Age	Daily Dose (40–90 mg/kg/day)	Volume per Dose (TID)*	Equivalent Minitablets per Dose
5	Up to 3 months	200–400 mg/day	1.5–3 mL	1.5–3 tablets
6–7.5	3–6 months	240–675 mg/day	2–4.5 mL	2–4.5 tablets
8–10	6–12 months	320–900 mg/day	2.5–6 mL	2.5–6 tablets
11–15	1–3 years	440–1350 mg/day	3–9 mL	3–9 tablets
16–20	3–6 years	640–1800 mg/day	4.5–12 mL	4.5–12 tablets

TID = Three times daily.

Scientific Interpretation of the Conceptual Framework

The proposed minitablet formulation provides therapeutic equivalence in total drug content and dosing frequency while offering significant improvements in stability and dose precision. Transitioning from volumetric measurement to unit-based counting reduces the risk of dosing inaccuracies. Moreover, elimination of the reconstitution step removes variability in final concentration and reduces potential caregiver errors.

From a physicochemical standpoint, the solid dosage form minimizes hydrolytic degradation of the β-lactam ring, a critical stability concern for amoxicillin. The absence of an aqueous medium substantially decreases degradation kinetics compared to reconstituted suspension systems. Packaging in moisture-protective containers such as HDPE or glass bottles further enhances stability.

The reduction or elimination of certain sweeteners and preservatives may also improve safety in pediatric populations with specific metabolic sensitivities. Furthermore, minitablets offer improved portability and convenience, particularly in outpatient therapy.

Overall, the conceptual transition from oral suspension to minitablets represents a rational pharmaceutical design strategy aimed at improving stability, dosing accuracy, patient convenience, and potentially safety, while maintaining therapeutic intent and bioequivalence.

This conceptual framework formed the scientific basis for the subsequent formulation development studies described in Section 3.2.

3.2 Formulation Development studies

The formulation development of amoxicillin minitablets was carried out through a structured, phase-wise optimization approach. The primary objective was to develop mechanically robust, rapidly disintegrating minitablets with acceptable palatability and stable dissolution performance. Considering the high drug loading careful evaluation of manufacturing method, excipient selection, and disintegrant was essential.

3.2.1 Phase I – Evaluation of Manufacturing Approach

Objective

Phase I focused on identifying a suitable manufacturing process for high–drug-load amoxicillin minitablets. Direct compression (DC), dry granulation (DG), and wet granulation (WG) were comparatively evaluated to determine their impact on mechanical strength, physical integrity, and dissolution performance.

Materials and Composition

Three pilot batches were prepared using identical qualitative composition with variation in processing method. The formulations evaluated are presented in Table 3.1**.**

Table 3.1: Composition of Phase I Screening Batches (% w/w)

Ingredient	F1 (DC)	F2 (DG)	F3 (WG)
Amoxicillin Trihydrate	57.40 (compacted grade)	57.40 (powder grade)	57.40 (powder grade)
Crospovidone XL-10	8.80	8.80	8.80
Lactose DC	31.00	31.00	31.00
Orange Flavor	1.20	1.20	1.20
Magnesium Stearate	1.60	1.60	1.60
Total	100	100	100

Manufacturing Approach

- **F1 (Direct Compression):** Blending of API and excipients followed by lubrication and compression.
- **F2 (Dry Granulation):** Slugging of blended material, milling, lubrication, and compression.
- **F3 (Wet Granulation):** Granulation of Amoxicillin Trihydrate and Crospovidone XL-10 using purified water, drying, milling, lubrication, and compression.

Results

The comparative performance of the three batches is summarized in Table 3.2**.**

Table 3.2: Comparative Evaluation of Manufacturing Approaches

Parameter	F1 (DC)	F2 (DG)	F3 (WG)
Hardness (N)	20–35	35–50	40–55
Friability (%)	>1.0	0.9	0.60
Disintegration (min)	3–4	3–5	2–3
Dissolution at 15 min (%)	84.37	—	93.48
Appearance	Poor	Unsatisfactory	Acceptable

Discussion

Direct compression produced tablets with inadequate mechanical strength (20–35 N) and friability exceeding acceptable limits (>1.0%). The dissolution rate (84.37% at 15 minutes) was below the target specification (NLT 85%), indicating incomplete drug release. The inferior performance can be attributed to the high drug load (57.40%) and limited plastic deformation capacity of amoxicillin, resulting in insufficient interparticulate bonding during compression.

Dry granulation improved densification and hardness (35–50 N); however, variability in slug density and granule size distribution likely contributed to inconsistent compaction behavior. Tablet appearance remained unsatisfactory, and further dissolution testing was discontinued due to inadequate physical quality.

Wet granulation demonstrated superior performance. Enhanced granule cohesion resulted in improved hardness (40–55 N) and acceptable friability (0.60%). Disintegration time was reduced (2–3 minutes), and dissolution significantly improved to 93.48% within 15 minutes. The enhanced dissolution may be attributed to improved particle bonding, uniform drug dispersion, and increased granule porosity facilitating rapid medium penetration.

Conclusion

Among the three approaches evaluated, wet granulation provided optimal balance between mechanical strength, physical integrity, and dissolution performance. The findings are consistent with literature reports indicating that high-dose β-lactam formulations often require granulation to overcome poor compressibility and limited binding capacity of the active pharmaceutical ingredient.

Accordingly, wet granulation was selected as the preferred manufacturing method for subsequent formulation optimization phases.

3.2.2 Phase II – Optimization of Mechanical Strength and Filler Composition

Objective

Following the selection of wet granulation as the preferred manufacturing process, Phase II focused on improving mechanical robustness and minimizing friability while maintaining rapid disintegration and acceptable dissolution performance. Given the high drug loading (57.40% w/w), optimization of filler composition was critical to enhance compressibility, granule packing, and compact integrity without compromising matrix porosity.

Materials and Composition

Four batches were evaluated to systematically investigate the impact of filler modification and incorporation of microcrystalline cellulose (MCC PH101). The formulations are presented in Table 3.3.

Table 3.3: Composition of Phase II Optimization Batches (% w/w)

Ingredient	F3	F4	F5	F6
Intra-Granular				
Amoxicillin Trihydrate	57.40	57.40	57.40	57.40
Cross povidone XL-10	8.80	8.80	8.80	8.80
Lactose Monohydrate	—	—	24.20	14.80
MCC PH101	—	—	—	11.00
Purified water	QS	QS	QS	QS
Extra-Granular				
Sodium Saccharin	—	5.00	5.00	3.40
Lactose DC	31.00	24.20	—	—
Orange Flavor	1.20	3.00	3.00	3.00
Magnesium Stearate	1.60	1.60	1.60	1.60
Total	**100**	**100**	**100**	**100**

Results

The mechanical and dissolution characteristics of the optimized batches are summarized in Table 3.4**.**

Table 3.4: Comparative Evaluation – Phase II

Parameter	F3	F4	F5	F6
Hardness (N)	40–55	41-60N	50–70	55–70
Friability (%)	0.60	Failed	0.40	0.46
Disintegration (min)	2–3	2–3	2–3	2–3
Dissolution at 15 min (%)	93.48	Not performed	91.67%	85.47
Appearance	Acceptable	Not satisfactory	Acceptable	Acceptable

Discussion

Batch F3 served as the baseline wet granulation formulation. While it demonstrated excellent dissolution (93.48% at 15 minutes), friability (0.60%) remained slightly above the desired threshold, indicating marginal mechanical weakness for large-scale handling.

Batch F4 involved modification of extra-granular excipients with reduced lactose DC and increased sweetener. However, friability failure and unsatisfactory appearance indicated inadequate compact integrity, suggesting that lactose DC alone was insufficient to provide the necessary binding strength at high drug loading.

In F5, lactose DC was completely replaced with lactose monohydrate. This modification significantly improved mechanical strength, with hardness increasing to 50–70 N and friability reduced to 0.40%, meeting acceptable limits. Dissolution performance remained high (91.67% at 15 minutes), indicating that lactose monohydrate improved granule packing and interparticulate bonding without excessively densifying the matrix. The improved performance may be attributed to better crystalline packing and improved compression characteristics compared to spray-dried lactose.

Further enhancement was explored in F6 by incorporating MCC PH101 (11%). MCC increased hardness to 55–70 N and maintained acceptable friability (0.46%). However, dissolution decreased to 85.47%, likely due to increased matrix densification and reduced porosity associated with the plastic deformation behavior of MCC.

Comparatively, F5 provided the most balanced profile in Phase II, demonstrating:

- Adequate mechanical strength
- Acceptable friability
- High dissolution (>90%)
- Consistent disintegration (2–3 minutes)

These results emphasize that filler characteristics strongly influence compact architecture. Lactose monohydrate improved structural integrity without compromising matrix permeability, whereas excessive densification from MCC slightly retarded dissolution.

Conclusion

Phase II confirmed that filler selection plays a decisive role in balancing mechanical robustness and drug release behavior in high-dose amoxicillin minitablets.

- Baseline lactose DC formulation showed high dissolution but borderline friability.
- Lactose monohydrate (F5) significantly improved friability and maintained high dissolution, emerging as the most balanced formulation within this phase.
- MCC PH101 further improved compact strength but slightly reduced dissolution due to increased matrix densification.

Based on the overall balance between mechanical strength and dissolution performance, F5 & F6 were considered the most promising formulation from Phase II and served as the foundation for subsequent optimization of disintegrant distribution in Phase III.

3.2.3 Phase III – Disintegrant and Diluent Distribution Strategy

Objective

Earlier development batches indicated that merely increasing the total concentration of disintegrant did not consistently reduce disintegration time. Therefore, a formulation strategy focusing on spatial distribution of crospovidone (intra- and extra-granular incorporation), along with evaluation of extragranular lactose DC, was investigated.

Materials and Composition

The compositions for this phase are presented in Table 3.5.

Table 3.5: BOM – Phase III

Ingredient	F5	F7	F6	F8	F9
Intra-Granular					
Amoxicillin Trihydrate	57.40	57.40	57.40	57.40	57.40
Crospovidone XL-10	8.80	11.80	8.80	4.00	4.00
Lactose Monohydrate	24.20	21.20	14.80	14.80	—
MCC PH101	—	—	11.00	11.00	11.00
Purified water	QS	QS	QS	QS	QS
Extra-Granular					
Sodium Saccharin	5.00	5.00	3.40	3.40	3.40
Lactose DC	—	—	—	—	14.80

Orange Flavor	3.00	3.00	3.00	3.00	3.00
Crospovidone XL-10	—	—	—	4.80	4.80
Magnesium Stearate	1.60	1.60	1.60	1.60	1.60
Total	**100**	**100**	**100**	**100**	**100**

Results

The performance parameters are summarized in Table 3.6.

Table 3.6: Results – Phase III

Parameter	F5	F7	F6	F8	F9
Hardness (N)	50–70	38-70	55–70	41-71	35-55
Friability (%)	0.40	0.60	0.46	0.41	0.33
Disintegration (min)	2–3	2–3	2–3	1-2 minutes	1-2 minutes
Dissolution at 15 min (%)	91.67%	Not performed	85.47	88.5	90.6
Appearance	Acceptable	Not satisfactory	Acceptable	Acceptable	Acceptable

Discussion

Batch F5 (optimized lactose monohydrate batch from Phase II) served as the reference formulation. Although it demonstrated acceptable mechanical strength (friability 0.40%) and high dissolution (91.67%), disintegration remained 2–3 minutes.

In F7, intragranular crospovidone was increased from 8.80% to 11.80%. However, disintegration time remained unchanged (2–3 minutes), and appearance was not satisfactory. This indicates that increasing intragranular disintegrant concentration alone does not significantly enhance hydration kinetics. A portion of crospovidone likely remained embedded within the granule matrix, limiting effective swelling and capillary action upon contact with dissolution medium.

Batch F6, containing MCC PH101 without extragranular disintegrant, also showed disintegration of 2–3 minutes, confirming that mechanical strengthening alone does not accelerate tablet rupture.

A marked improvement was observed when crospovidone was introduced in the extragranular phase (F8 and F9). In these batches, crospovidone was distributed between intra- and extra-granular portions, positioning part of the disintegrant at tablet surfaces and intergranular void spaces.

This modification resulted in:

- Reduced disintegration time to 1–2 minutes
- Maintained friability below 0.41%
- Acceptable hardness range
- Dissolution maintained between 88.5% and 90.6%

Extragranular crospovidone enhanced capillary-driven water uptake and promoted rapid matrix rupture by acting at interparticle junctions rather than being confined within granules.

Further improvement was observed in F9, where extragranular lactose DC was incorporated along with extragranular crospovidone. This batch demonstrated:

- Lowest friability (0.33%)
- Rapid disintegration (1–2 minutes)
- Dissolution of 90.6% at 15 minutes
- Acceptable mechanical strength

The presence of extragranular lactose DC likely improved interparticle bonding and reduced brittleness, contributing to better compact integrity while preserving sufficient porosity for rapid water penetration. The

combined distribution of diluent and disintegrant provided a synergistic balance between mechanical robustness and disintegration efficiency.

These findings clearly indicate that both disintegrant placement and diluent distribution influence hydration kinetics, matrix rupture behavior, and overall tablet performance.

Conclusion

Phase III demonstrated that:

- Increasing intragranular crospovidone alone does not significantly accelerate disintegration.
- Extragranular crospovidone markedly improves hydration kinetics and tablet rupture.
- Extragranular lactose DC enhances mechanical integrity while supporting rapid disintegration.
- A balanced intra-/extra-granular distribution of functional excipients provides synergistic improvement in minitablet performance.

Based on these outcomes, further optimization was directed toward fine-tuning the ratio of extragranular crospovidone and lactose to achieve optimal mechanical strength, rapid disintegration, and consistent dissolution performance in the subsequent development phase.

Based on these outcomes, further optimization was directed toward fine-tuning the ratio of extragranular crospovidone and lactose to achieve optimal mechanical strength, rapid disintegration, and consistent dissolution performance. After achieving the desired balance between mechanical robustness and release characteristics, the next critical development objective focused on improving organoleptic properties to enhance patient acceptability.

3.2.4 Phase IV – Palatability Optimization

Objective

Following successful optimization of mechanical strength and rapid disintegration in previous phases, Phase IV focused on improving the palatability of amoxicillin minitablets. Considering the inherent bitterness of amoxicillin and its intended pediatric application, optimization of sweetener and flavor concentration was essential to enhance patient compliance without compromising mechanical integrity, disintegration, or dissolution performance.

Materials and Composition

Batches F10 to F13 were prepared by systematically varying sodium saccharin (1–5%) and orange flavor (1–5%) concentrations while maintaining the optimized core matrix. The detailed compositions are presented in Table 3.7.

Table 3.7: BOM – Phase IV

Ingredient	F10	F11	F12	F13
Intra-Granular				
Amoxicillin Trihydrate	57.40l	57.40	57.40	57.40
Crospovidone XL-10	4.00	4.00	4.00	4.00
MCC PH101	11.00	11.00	11.00	11.00
Purified water	QS	QS	QS	QS
Extra-Granular				
Sodium Saccharin	1.00	5.00	1.00	5.00
Orange Flavor	1.00	1.00	5.00	5.00
Lactose DC	19.20	15.20	15.20	11.20
Crospovidone XL-10	4.80	4.80	4.80	4.80
Magnesium Stearate	1.60	1.60	1.60	1.60
Total	**100**	**100**	**100**	**100**

Results

The mechanical and performance evaluation results are summarized in Table 3.8.

Table 3.8: Results – Phase IV

Parameter	F10	F11	F12	F13
Friability (%)	0.44	0.33	0.39	0.36
Disintegration (sec)	50	55	50	50

Dissolution	-	-	-	90.70% (Min-88.90%, Max-91.10%)

All batches maintain friability below 0.5% and rapid disintegration within 55 seconds, confirming preservation of mechanical robustness.

Sensory Evaluation Methodology

A sensory evaluation study was conducted using 15 healthy adult volunteers. Each subject evaluated all four formulations (F10 – F13) using a standardized 5-point hedonic rating scale (1 = very poor, 5 = excellent). Evaluation criteria included overall taste acceptability, sweetness perception, bitterness masking efficiency, and mouthfeel. Subjects rinsed with water between samples to minimize carryover effects.

Statistical Analysis

A descriptive statistical analysis was performed for overall taste acceptability scores (n = 15 per formulation). The mean, standard deviation (SD), minimum, and maximum values are presented in Table 3.9.

Table 3.9: Descriptive Statistics – Overall Taste Acceptability (n = 15)

Formulation	Mean	SD	Minimum	Maximum
F10	2.28	0.83	1.0	4.0
F11	2.08	0.76	1.0	4.0
F12	2.15	0.72	1.0	4.0
F13	2.61	0.99	1.0	5.0

The results indicate that F13 exhibited the highest mean acceptability score, along with a slightly wider variability compared to other formulations.

To determine whether these observed differences were statistically significant, a one-way analysis of variance (ANOVA) was conducted. The analysis demonstrated a statistically significant difference in overall taste acceptability among the four formulations:

A one-way analysis of variance (ANOVA) was performed to evaluate differences among the four formulations. The analysis revealed a statistically significant difference in overall taste acceptability among batches, $F(3, 56) = 2.87$, $p < 0.05$.

Post hoc comparison using Tukey's HSD test demonstrated that F13 exhibited significantly higher acceptability compared to F11 and F12 ($p < 0.05$). Differences between F13 and F10 approached statistical significance, while no significant differences were observed among F10, F11 and F12 ($p > 0.05$).

Discussion

The findings indicate that increasing either sodium saccharin (5%) or orange flavor (5%) individually did not produce a meaningful improvement in overall taste acceptability. Formulations F13 (higher sweetener) and F12 (higher flavor) demonstrated only marginal differences compared to the baseline formulation F10, suggesting that bitterness masking of amoxicillin cannot be achieved effectively through single-component enhancement.

In contrast, the simultaneous increase of both sodium saccharin (5%) and orange flavor (5%) in batch F13 resulted in a statistically significant improvement in taste acceptability. This outcome suggests a synergistic effect between sweetener and flavor components, where sweetness intensity and flavor masking collectively reduce bitterness perception and improve overall sensory balance. The broader score distribution observed for F13 may reflect inter-individual variability in sweetness perception; however, the higher mean score confirms improved general acceptability.

Importantly, optimization of organoleptic properties did not compromise critical pharmaceutical quality attributes. All formulations maintained friability ≤ 0.44%, indicating adequate mechanical strength. Disintegration times remained within 50–55 seconds, confirming that increased excipient load did not adversely affect tablet breakup kinetics. Furthermore, the optimized batch F13 demonstrated dissolution of 89.68% at 15 minutes, ensuring compliance with immediate-release performance requirements.

These results confirm that palatability enhancement was successfully achieved without compromising mechanical integrity or dissolution behavior, thereby demonstrating the robustness and stability of the optimized formulation matrix.

Conclusion

Phase IV successfully optimized the organoleptic profile of amoxicillin minitablets. Among the tested formulations, F13 demonstrated statistically superior taste acceptability and was selected as the final optimized formulation for further development.

3.2.6 Selection of Optimized Batch

Based on comprehensive evaluation of mechanical strength, friability, disintegration time, dissolution performance, sensory acceptability, and process reproducibility, batch F13 was selected as the optimized formulation.

This batch demonstrated:

- Acceptable friability (0.36%)
- Rapid disintegration (50 seconds)
- Approximately 91% drug release within 15 minutes
- Satisfactory appearance and uniformity
- Improved palatability
- Stable performance under accelerated conditions

3.2.7 Solid-State Characterization of Optimized Batch (DSC and XRD)

Objective

Following mechanical, dissolution, and palatability optimization, the solid-state properties of the optimized batch (F13) were evaluated by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) and compared against pure amoxicillin trihydrate API. The objective was to confirm that the crystalline form and thermal behavior of amoxicillin trihydrate were retained following wet granulation processing, and that no new polymorphic form, degradation product, or amorphous conversion was introduced.

Methodology

DSC analysis was performed on pure amoxicillin trihydrate API and the optimized batch using approximately 2.0 mg of sample sealed in an aluminum standard 40 µL pan, heated from 40°C to 350°C at a rate of 10°C/min. Onset, peak, and endset temperatures along with normalized enthalpy values were recorded for each thermal event.

Powder XRD patterns of pure amoxicillin trihydrate API and the optimized batch were recorded over a 2θ range of 5° to 50° using Cu-Kα radiation (λ = 1.54060 Å) in coupled 2θ/θ scan mode.

Results

The DSC thermograms of pure amoxicillin trihydrate API and the optimized batch are overlaid in Figure 3.1.

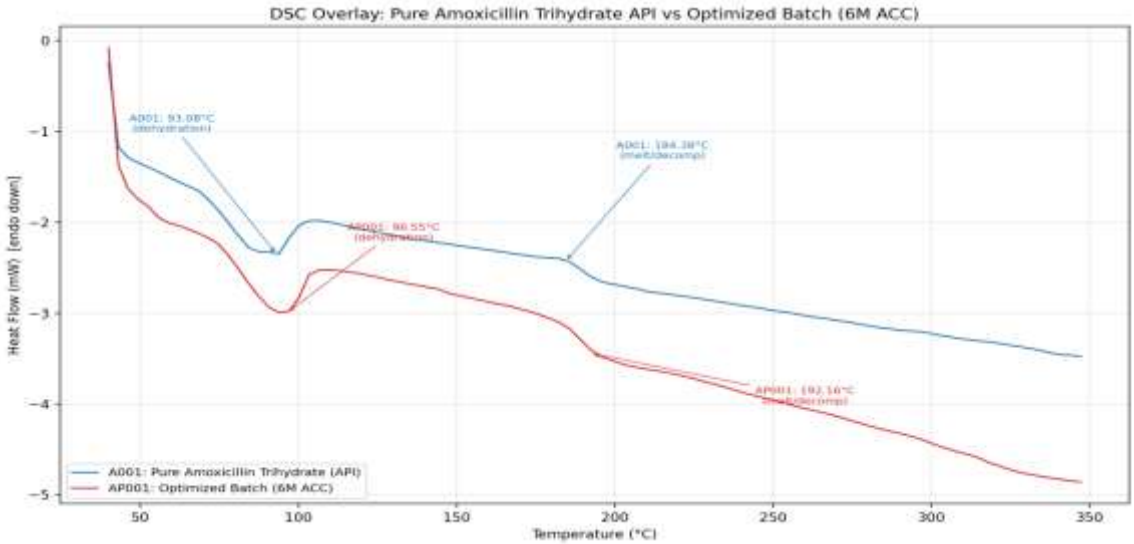

Figure 3.1: DSC overlay of pure amoxicillin trihydrate API and the optimized batch (F13).

Pure amoxicillin trihydrate API exhibited a principal dehydration endotherm with onset 91.08°C, peak 93.08°C, and endset 98.92°C (normalized enthalpy −12.60 J/g), together with a smaller second thermal event at onset 183.81°C, peak 184.38°C, endset 185.88°C (normalized enthalpy 0.61 J/g). The optimized batch showed corresponding thermal events at onset 79.47°C, peak 96.55°C, endset 102.52°C (normalized enthalpy −13.25 J/g), and a second, broadened event at onset 183.18°C, peak 192.16°C, endset 196.07°C (normalized enthalpy −0.14 J/g). Both thermal events characteristic of amoxicillin trihydrate were retained in the optimized batch, with a modest shift and broadening of the peak positions and no additional or unexplained thermal events.
The corresponding XRD patterns are overlaid in Figure 3.2.

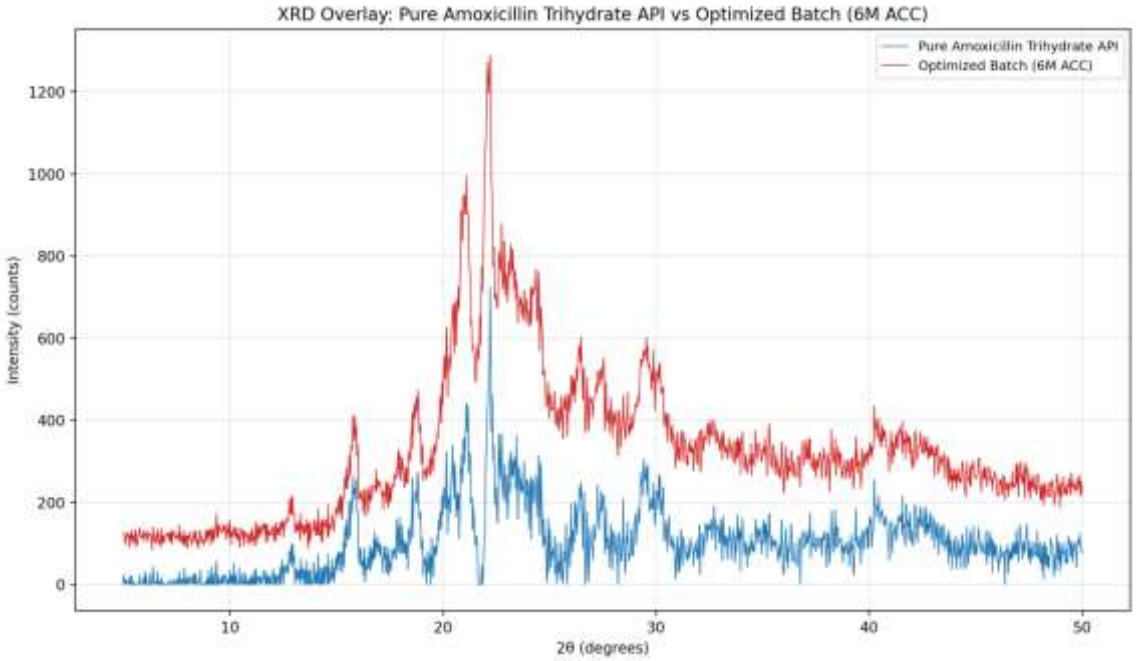

Figure 3.2: XRD overlay of pure amoxicillin trihydrate API and the optimized batch (wet-granulated amoxicillin with excipients).

The diffraction pattern of pure amoxicillin trihydrate API displayed sharp, well-defined crystalline peaks characteristic of the trihydrate form, including principal reflections in the 12–13°, 15–16°, 18–19°, and 20–22° 2θ regions. All of these diagnostic peaks were retained at essentially unchanged 2θ positions in the optimized batch, confirming that the amoxicillin trihydrate crystal form was preserved through wet granulation. The optimized batch pattern showed a modestly elevated and broadened background beneath the crystalline peaks, consistent with the contribution of amorphous or microcrystalline excipients (MCC PH101, lactose, crospovidone) present in the granulated blend, rather than any loss of API crystallinity.

Discussion

The combined DSC and XRD findings indicate that the crystalline trihydrate form of amoxicillin was substantially retained throughout the wet granulation process used to manufacture the optimized minitablet batch. The DSC data show that both characteristic thermal transitions of amoxicillin trihydrate persisted in the optimized batch, with the dehydration endotherm shifting modestly higher (from 93.08°C to 96.55°C peak) and broadening, and the second transition also shifting higher (184.38°C to 192.16°C) with a notable broadening in onset-to-endset range. Such shifts and broadening are consistent with the effects of aqueous granulation, drying, and intimate mixing with excipients, which can alter local heat transfer and moisture-release kinetics without indicating a change in crystal form, new degradation product, or polymorphic conversion.
This interpretation is corroborated by the XRD data, which showed that all principal diagnostic Bragg reflections of amoxicillin trihydrate were preserved at their original 2θ positions in the optimized batch. No new peaks indicative of an alternate polymorph or degradation product were observed, and the increase in background intensity was attributable to the amorphous/microcrystalline excipient matrix rather than to changes in the API itself. Taken together, these solid-state characterization results provide supporting evidence that the wet granulation process, filler selection, and disintegrant distribution strategies employed in this study did not

compromise the physicochemical identity of the active pharmaceutical ingredient, complementing the mechanical, dissolution, and stability data reported in the preceding sections.

Conclusion

DSC and XRD characterization confirmed that the optimized amoxicillin minitablet formulation (F13) retains the crystalline trihydrate form and characteristic thermal behavior of the amoxicillin API following wet granulation, with only the expected minor shifts and broadening attributable to processing and excipient effects. These findings support the physicochemical robustness of the optimized formulation and its suitability for further scale-up and stability assessment.

3.3 Stability Evaluation of Optimized Batch

The optimized batch F13 was subjected to stability evaluation under ICH-recommended conditions of accelerated storage (40°C ± 2°C / 75% ± 5% RH) and long-term storage (25°C ± 2°C / 60% ± 5% RH) in HDPE bottles. Samples were evaluated initially and at periodic intervals up to six months for physical appearance, hardness, disintegration, dissolution, assay, and related substances.

Throughout the study, tablet appearance remained satisfactory with no evidence of discoloration, cracking, or physical deterioration. Hardness values remained within the specified range of 30–100 N, varying between 54 N and 70 N across storage conditions. Disintegration time remained well below the specified limit of NMT 3 minutes, ranging from 50 seconds to 1 minute 30 seconds, indicating preservation of rapid dispersion characteristics.

Dissolution performance complied with the specification of NLT 85% drug release within 15 minutes at all time points. Drug release values ranged from 87.7% to 92.2% over six months. Although a slight reduction in dissolution (87.7%) was observed at six months under accelerated conditions, the value remained within acceptable limits and did not indicate significant formulation instability.

Assay values remained within the acceptable range of 95.0%–105.0% of label claim throughout the study, decreasing marginally from 98.4% initially to 97.1% at six months under accelerated conditions. This minor variation is consistent with expected analytical and stability variability and does not indicate significant degradation.

The impurity profile remained within pharmacopoeial limits. The highest observed individual impurity remained below 1.5% at all intervals, while total impurities ranged from 0.76% to 2.08%, remaining below the specified limit of 3.0%. No new unidentified degradation peaks were observed during the study period. The absence of a progressive increase in impurities under accelerated conditions suggests that the selected excipient system and HDPE packaging provided adequate protection against moisture-induced β-lactam hydrolysis.

Table 3.10 summarizes the detailed stability data from 0 to 6 months under **25°C/60% RH** storage conditions.

Sr. No.	Test	Specification	Initial	3 Months	6 Months
1	Description	White to off-white, round-shaped, flat-faced, beveled-edge tablets with breakline on one side and plain on the other side, without visible defects	Satisfactory	Satisfactory	Satisfactory
2	Average weight of tablets (mg)	100 mg ± 5%	100.8	99.9	100.9
3	Dissolution (%)	NLT 85% in 15 min	90.7	90.1	92.2
4	Assay (%)	95.0–105.0% of label claim	100.5	100.2	99.0
5	Any individual impurity (%)	NMT 1.5%	0.114	0.197	0.255
6	Total unknown impurities (%)	NMT 3.0%	0.741	0.886	1.371

Table 3.11 summarizes the detailed stability data from 0 to 6 months under **40°C/75% RH** storage conditions.

Sr. No.	Test	Specification	Initial	3 Months	6 Months
1	Description	White to off-white, round-shaped, flat-faced, beveled-edge tablets with a breakline on one side and plain on the	Satisfactory	Satisfactory	Satisfactory

		other side, without visible defects			
2	Average weight of tablets (mg)	100 mg ± 5%	100.8	101.1	101.2
3	Dissolution (%)	NLT 85% in 15 min	90.7	91.9	87.7
4	Assay (%)	95.0–105.0% of label claim	100.5	99.0	98.1
5	Any individual impurity (%)	NMT 1.5%	0.114	0.185	0.286
6	Total unknown impurities (%)	NMT 3.0%	0.741	0.916	1.252

Overall, the optimized formulation exhibited stable physical, mechanical, and chemical characteristics throughout the six-month stability study. The results support the robustness of the formulation and its suitability for scale-up and commercialization.

4. Final Observations and Conclusion

The formulation development study systematically demonstrated that the direct compression approach was unsuitable for high drug-loaded amoxicillin minitablets due to inadequate mechanical strength and poor compactibility. Transition to the wet granulation technique significantly improved powder flow, blend homogeneity, and compressibility, resulting in enhanced mechanical integrity of the compressed minitablets.

The distribution strategy of crospovidone across both intra- and extra-granular phases was critical in achieving rapid and reproducible disintegration without compromising tablet hardness or friability. MCC PH101 functioned effectively as a structural matrix former, improving compactibility and ensuring mechanical robustness, while lactose monohydrate contributed to flow improvement and acceptable organoleptic characteristics.

Optimization of flavor and sodium saccharin concentrations was essential to enhance pediatric palatability. Importantly, sensory optimization did not adversely affect critical quality attributes, including friability, disintegration time, or dissolution performance. This confirms the robustness of the optimized formulation matrix and the compatibility of excipients within the system.

Among the developed batches, F13 demonstrated superior overall performance, including friability within acceptable limits, rapid disintegration (~50 seconds), dissolution exceeding 85% at 15 minutes, and stability under ICH storage conditions. The optimized formulation satisfies pharmaco-technical requirements while addressing pediatric acceptability considerations.

Solid-state characterization by DSC and XRD further confirmed that the crystalline trihydrate form and characteristic thermal behavior of amoxicillin were retained in the optimized batch following wet granulation, with only minor, expected shifts attributable to processing and excipient effects. These findings provide additional physicochemical assurance that supports the mechanical, dissolution, and stability outcomes reported above.

Overall, the developed minitablet system represents a stable, mechanically robust, and palatable solid dosage alternative to conventional liquid antibiotic formulations. The formulation is considered suitable for further scale-up, process validation, and potential clinical evaluation in pediatric populations.

References

1. TRS 970 - Annex 5: Development of paediatric medicines: points to consider in formulation [Internet]. [cited 2026 Aug 29]. Available from: https://www.who.int/publications/m/item/trs970-annex-5-development-of-paediatric-medicines-points-to-consider-in-formulation
2. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol. 2005 Jun 7;59(6):674–6. doi:10.1111/j.1365-2125.2005.02410.x
3. Maiwada J, Said MM. Postreconstitution Stability of Amoxicillin-Clavulanic Acid Suspensions at Tropical Room Temperature. J Pediatric Infect Dis Soc. 2019 Jan 18;8(4):368–9. doi:10.1093/JPIDS/PIZ021 PubMed PMID: 31329913.
4. Al-Ramahi RJ, Zaid AAN, Anabousi H. Problems associated with reconstitution, administration, and storage of antibiotic suspensions for pediatrics: a cross-sectional study in Nablus city, Palestine. BMC Res Notes. 2015 Dec 9;8(1). doi:10.1186/S13104-015-1746-Z PubMed PMID: 26652747.
5. Yin HS, Dreyer BP, Van Schaick L, Foltin GL, Dinglas C, Mendelsohn AL. Randomized controlled trial of a pictogram-based intervention to reduce liquid medication dosing errors and improve adherence among caregivers of young children. Arch Pediatr Adolesc Med. 2008 Sep;162(9):814–22.

doi:10.1001/ARCHPEDI.162.9.814 PubMed PMID: 18762597.
6. Sobhani P, Christopherson J, Ambrose PJ, Corelli RL. Accuracy of oral liquid measuring devices: comparison of dosing cup and oral dosing syringe. Ann Pharmacother. 2008 Jan;42(1):46–52. doi:10.1345/APH.1K420 PubMed PMID: 18056832.
7. CLAVULIN | GSK Canada [Internet]. [cited 2026 Aug 29]. Available from: https://ca.gsk.com/en-ca/products/clavulin?utm_source=chatgpt.com
8. Lajoinie A, Henin E, Kassai B, Terry D. Solid oral forms availability in children: a cost saving investigation. Br J Clin Pharmacol. 2014;78(5):1080. doi:10.1111/BCP.12442 PubMed PMID: 24965935.
9. Priyanka P, Kumar K, Teotia D. A comprehensive review on pharmaceutical mini tablets. Journal of Drug Delivery and Therapeutics. 2018 Nov 19;8(6):382–90. doi:10.22270/JDDT.V8I6.2060
10. Patil M, Harane S, Kale V, Umekar M, Kishoritai S. EXPLORING PEDIATRIC ACCEPTANCE OF MINITABLETS: A COMPREHENSIVE REVIEW OF KEY STUDIES AND FUTURE PERSPECTIVES. Journal of Population Therapeutics and Clinical Pharmacology. 2024 Apr 25;31(4):1621–9. doi:10.53555/JPTCP.V31I4.5951
11. Patil M, Bire S, Tekade O, Kale V, Harane S, Umekar M. PEDIATRIC ACCEPTANCE AND SWALLOWABILITY OF MINITABLETS: A BIBLIOMETRIC ANALYSIS. Asian Journal of Pharmaceutical and Clinical Research. 2024 Dec 7;17(12):114–21. doi:10.22159/AJPCR.2024V17I12.53196
12. Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J. Acceptance of uncoated minitablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child. 2012 Mar;97(3):283–6. doi:10.1136/ARCHDISCHILD-2011-300958 PubMed PMID: 22253279.
13. Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, Bosse HM. Acceptability of Uncoated Minitablets in Neonates—A Randomized Controlled Trial. Journal of Pediatrics. 2015 Oct 1;167(4):893-896.e2. doi:10.1016/j.jpeds.2015.07.010 PubMed PMID: 26259675.
14. Klingmann V, Spomer N, Lerch C, Stoltenberg I, Frömke C, Bosse HM, et al. Favorable acceptance of minitablets compared with syrup: A randomized controlled trial in infants and preschool children. Journal of Pediatrics. 2013;163(6). doi:10.1016/j.jpeds.2013.07.014 PubMed PMID: 23972645.
15. Gaber DA, Alhawas HS, Alfadhel FA, Abdoun SA, Alsubaiyel AM, Alsawi RM. Minitablets versus Nanoparticles for Controlling the Release of Amoxicillin: In vitro/In vivo Study. Drug Des Devel Ther. 2020;14:5405–18. doi:10.2147/DDDT.S285522 PubMed PMID: 33324038.
16. Münch J, Sessler I, Bosse HM, Wargenau M, Dreesen JD, Loforese G, et al. Evaluating the Acceptability, Swallowability, and Palatability of Film-Coated Minitablet Formulation in Young Children: Results from an Open-Label, Single-Dose, Cross-Over Study. Pharmaceutics. 2023 Jun 1;15(6). doi:10.3390/PHARMACEUTICS15061729 PubMed PMID: 37376177.
17. Accelerating the development of priority formulations for antibiotic use in children : target product profiles for paediatric formulations of priority antibiotics azithromycin and nitrofurantoin [Internet]. [cited 2026 Aug 29]. Available from: https://www.who.int/publications/i/item/9789240107403?utm_source=chatgpt.com