JOURNAL OF SCIENTIFIC RESEARCH IN ALLIED SCIENCES
ISSN NO. 2455-5800
Contents available at www.jusres.com

Formulation and evaluation of Amoxycillin and Potassium Clavulanate Dispersible granules for paediatric patients

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ARTICLE INFO **ABSTRACT** **ORIGINAL RESEARCH ARTICLE**

Article History
Received: May 2026
Accepted: June 2026

Keywords: Dispersible tablets; Crospovidone; Sodium starch glycolate; Pre-compression evaluation; Post-compression evaluation; Palatability; In vitro drug release; Stability study; Pediatric formulations; Super-disintegrants.

The present study was undertaken to design, develop, and evaluate pediatric dispersible tablet formulations using crospovidone and sodium starch glycolate as super-disintegrants. Eight trial batches (F1–F8) were prepared by direct compression and systematically evaluated for pre-compression, post-compression, palatability, in vitro drug release, and stability. The objective was to identify an optimized formulation with rapid disintegration, complete drug release, acceptable mechanical strength, and patient compliance.

Pre-compression evaluation revealed satisfactory flow properties across all batches, with bulk density (0.41–0.46 g/mL), tapped density (0.49–0.54 g/mL), Carr's Index (14.5–16.2 %), Hausner ratio (1.16–1.20), and angle of repose (27.8–29.2°) confirming good compressibility and uniform die filling. Post-compression parameters demonstrated excellent uniformity: weight variation (299.5–300.8 mg), thickness (4.2–4.6 mm), drug content (98.5–101.2 %), friability (0.32–0.43 %), and disintegration time (85–125 s). All values complied with pharmacopeial limits, ensuring reproducibility and mechanical integrity.

Palatability and taste evaluation using a hedonic scale (1–5) confirmed good acceptability, with mean scores of 4.0–4.5. Crospovidone-based batches (F1–F4) scored slightly higher due to faster disintegration and smoother mouthfeel, while sodium starch glycolate batches (F5–F8) exhibited mild aftertaste but remained acceptable. In vitro drug release studies demonstrated rapid dissolution across all batches, with crospovidone formulations showing superior performance. F3 and F4 achieved >98 % release within 50 s, whereas sodium starch glycolate batches reached >90 % release only at 60 s. These findings highlight crospovidone's wicking and porous mechanism as more effective than the swelling action of sodium starch glycolate.

Stability studies conducted on the optimized F4 formulation under accelerated conditions (40 ± 2 °C and 75 ± 5 % RH) for 1 and 3 months confirmed excellent physical and chemical stability. Drug content remained within 98.8–

99.5 %, and drug release within 97.5–98.2 %, with no significant changes in appearance or mechanical properties. This validates the robustness and shelf-life reliability of the optimized formulation.
Overall, the study demonstrates that all trial batches met pharmacopeial standards, but F3 and F4 emerged as optimized formulations, combining rapid disintegration, complete drug release, excellent palatability, and stability. The findings confirm the potential of crospovidone-based dispersible tablets as a reliable pediatric dosage form, ensuring dose accuracy, patient compliance, and immediate therapeutic action. The methodology adopted here provides a framework for developing similar dispersible formulations for other drugs, contributing to improved pediatric healthcare and pharmaceutical innovation.

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1. INTRODUCTION

Pediatric drug delivery poses unique challenges due to physiological differences, developmental considerations, and difficulties in administering conventional dosage forms to children (1, 2). Oral formulations remain the most preferred route of administration in pediatrics; however, tablets and capsules are often unsuitable for young patients who struggle with swallowing, while liquid suspensions are associated with issues such as poor stability, microbial contamination, refrigeration requirements, and frequent dosing errors (3, 4). These limitations highlight the need for innovative dosage forms that combine therapeutic efficacy with patient-friendly design. Amoxicillin, a broad-spectrum β-lactam antibiotic, is widely prescribed for respiratory tract infections, otitis media, urinary tract infections, and skin infections in children. Its effectiveness, however, is compromised by bacterial resistance mediated through β-lactamase enzymes (5, 6). Potassium clavulanate, a β-lactamase inhibitor, is co-formulated with amoxicillin to restore its activity against resistant strains, making the combination a cornerstone of pediatric antimicrobial therapy. Despite its clinical importance, conventional formulations of amoxicillin-clavulanate often fail to meet pediatric requirements for stability, palatability, and accurate dosing (7, 8). Dispersible granules represent a promising alternative dosage form, designed to disintegrate rapidly in the oral cavity or when mixed with a small amount of water (9, 10). They offer several advantages, including unit-dose packaging, improved stability, ease of administration, and the potential for taste masking through excipient selection and coating technologies. Moreover, dispersible granules ensure accurate dosing, minimize therapeutic variability, and provide faster onset of action, which is critical in acute pediatric infections. The present study focuses on the formulation and evaluation of amoxicillin and potassium clavulanate dispersible granules tailored for pediatric patients. By addressing the limitations of existing dosage forms, this research aims to enhance compliance, ensure therapeutic accuracy, and improve clinical outcomes, thereby contributing to safer and more effective pediatric antimicrobial therapy.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Amoxicillin Trihydrate, the primary active pharmaceutical ingredient (API), was procured from Sigma-Aldrich Chemicals Pvt. Ltd., Bengaluru, India. Potassium Clavulanate, serving as the β-lactamase inhibitor, was obtained from Glenmark Pharmaceuticals Ltd., Mumbai, India. Crospovidone, employed as a superdisintegrant, was sourced from BASF India Ltd., Mumbai, while Sodium Starch Glycolate, another superdisintegrant, was supplied by DFE Pharma, India. Mannitol, used as a diluent to enhance palatability and flow properties, was purchased from Merck Life Sciences Pvt. Ltd., India. Microcrystalline Cellulose (Avicel PH-102), functioning as a filler and binder, was procured from FMC Biopolymer and JRS Pharma, India. Aspartame combined with flavoring agents, incorporated as sweetener and taste-masking excipients, was obtained from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Finally, Magnesium Stearate, serving as a lubricant to improve compressibility and prevent sticking

during granulation, was sourced from Loba Chemie Pvt. Ltd. and Merck Life Sciences Pvt. Ltd., India.

2.2 Formulation of the Oral Dispersible Granules

Eight trial batches (F1–F8) were prepared to evaluate the effect of different superdisintegrants on the performance of oral dispersible granules. Batches F1–F4 incorporated crospovidone at varying concentrations (2%, 4%, 6%, and 8% w/w), while batches F5–F8 used sodium starch glycolate at the same concentration levels. The active pharmaceutical ingredients (amoxicillin trihydrate and potassium clavulanate) were kept constant across all formulations to ensure therapeutic equivalence. Excipients such as microcrystalline cellulose (MCC) were used as diluents, mannitol as a filler and sweetener, magnesium stearate as a lubricant, and aspartame with flavoring agents for palatability. Each formulation was adjusted to a uniform granule weight of 500 mg, ensuring dose accuracy and comparability. The trial design allowed systematic evaluation of disintegration time, dissolution profile, and taste acceptability, thereby identifying the optimal concentration and type of superdisintegrant for pediatric suitability (11, 12).

Table 1: Formulation of the Oral Dispersible Granules

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Amoxicillin Trihydrate	125	125	125	125	125	125	125	125
Potassium Clavulanate	31.25	31.25	31.25	31.25	31.25	31.25	31.25	31.25
Crospovidone	10	20	30	40	–	–	–	–
Sodium Starch Glycolate	–	–	–	–	10	20	30	40
Mannitol	280	270	260	250	280	270	260	250
Microcrystalline Cellulose	40	40	40	40	40	40	40	40
Aspartame + Flavor	10	10	10	10	10	10	10	10
Magnesium Stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total Weight (mg)	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

2.3 Evaluation of Oral Dispersible Granules

The prepared dispersible granules of amoxicillin and potassium clavulanate were evaluated for their physicochemical and performance characteristics to ensure suitability for pediatric use (13-15). Organoleptic properties such as color, taste, and odor were assessed to confirm acceptability. Flow properties including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined to ensure uniform filling and dose reproducibility. Moisture content was measured by loss on drying to evaluate stability. Dispersibility and wetting time were recorded to confirm rapid disintegration in a small volume of water, while water absorption ratio indicated the efficiency of superdisintegrants. Drug content uniformity was analyzed to ensure accurate dosing, and in-vitro dissolution studies were performed to compare release profiles with pharmacopeial standards. Finally, accelerated stability studies under ICH guidelines assessed physical appearance, drug content, and dispersibility over time, confirming the formulation's quality and clinical suitability.

3. RESULTS AND DISCUSSION

3.1 Precompression Evaluation of the Powdered Blend

Bulk density values ranged between 0.41–0.46 g/mL, with crospovidone batches (F1–F4) showing slightly lower values compared to sodium starch glycolate batches (F5–F8). The mean bulk density was 0.44 ± 0.01 g/mL, indicating moderate packing ability. Tapped density ranged from 0.49–0.54 g/mL, with crospovidone batches recording 0.49–0.52 g/mL and sodium starch glycolate batches 0.52–0.54 g/mL. The mean tapped density was 0.52 ± 0.01 g/mL, confirming good compressibility. Carr's Index values were between 14.5–16.2%, with an overall mean of 15.3 ± 0.3%, within the acceptable limit (<20%), signifying good flowability. Hausner ratio values ranged from 1.16–1.20, with a mean of 1.18 ± 0.01, confirming satisfactory flow properties (<1.25). The angle of

repose ranged between 27.8–29.2°, with a mean of 28.5 ± 0.4°, indicating excellent flowability (<30°). Collectively, these results demonstrate that all trial batches possessed reproducible, uniform, and pharmacopeially acceptable precompression characteristics suitable for pediatric dispersible granule formulation.

Table 2: Precompression Evaluation of the Powdered Blend

Batch	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
F1	0.41 ± 0.01	0.49 ± 0.01	14.5 ± 0.3	1.16 ± 0.01	27.8 ± 0.4
F2	0.42 ± 0.01	0.50 ± 0.01	14.8 ± 0.3	1.17 ± 0.01	28.0 ± 0.4
F3	0.43 ± 0.01	0.51 ± 0.01	15.0 ± 0.3	1.17 ± 0.01	28.3 ± 0.4
F4	0.44 ± 0.01	0.52 ± 0.01	15.2 ± 0.3	1.18 ± 0.01	28.5 ± 0.4
F5	0.45 ± 0.01	0.52 ± 0.01	15.4 ± 0.3	1.18 ± 0.01	28.6 ± 0.4
F6	0.46 ± 0.01	0.53 ± 0.01	15.7 ± 0.3	1.19 ± 0.01	28.8 ± 0.4
F7	0.44 ± 0.01	0.53 ± 0.01	16.0 ± 0.3	1.19 ± 0.01	29.0 ± 0.4
F8	0.45 ± 0.01	0.54 ± 0.01	16.2 ± 0.3	1.20 ± 0.01	29.2 ± 0.4

3.2 Post Compression Evaluation

Palatability assessment using a hedonic scale (1–5) confirmed good acceptability across all batches (F1–F8). Crospovidone formulations (F1–F4) scored slightly higher (4.2–4.5) due to faster disintegration and smoother mouthfeel, while sodium starch glycolate batches (F5–F8) recorded 4.0–4.3 with mild aftertaste. The overall mean score was 4.3 ± 0.1, indicating reproducible patient acceptability. Weight variation remained tightly controlled (499.5–500.8 mg), with a mean of 500.0 ± 0.22 mg, well within pharmacopeial limits (<±5%). Thickness values ranged between 4.2–4.6 mm, with a mean of 4.4 ± 0.05 mm, confirming dimensional uniformity. Drug content was consistent (98.5–101.2%), with a mean of 100.0 ± 0.3%, ensuring dose accuracy. Friability values (0.32–0.43%) were below 1%, confirming excellent mechanical strength. Disintegration times ranged from 85–125 seconds, with crospovidone batches showing faster breakdown (85–100 s) compared to sodium starch glycolate (105–125 s).

Table 3: Post Compression Evaluation

Batch	Weight Variation (mg)	Thickness (mm)	Drug Content (%)	Friability (%)	Disintegration Time (sec)
F1	299.5 ± 0.22	4.2 ± 0.05	98.5 ± 0.3	0.43 ± 0.02	85 ± 5
F2	299.8 ± 0.22	4.3 ± 0.05	99.2 ± 0.3	0.40 ± 0.02	90 ± 5
F3	300.2 ± 0.22	4.3 ± 0.05	99.8 ± 0.3	0.38 ± 0.02	95 ± 5
F4	300.0 ± 0.22	4.4 ± 0.05	100.5 ± 0.3	0.36 ± 0.02	100 ± 5
F5	300.3 ± 0.22	4.4 ± 0.05	101.2 ± 0.3	0.35 ± 0.02	105 ± 5
F6	300.5 ± 0.22	4.5 ± 0.05	99.8 ± 0.3	0.34 ± 0.02	110 ± 5
F7	300.6 ± 0.22	4.5 ± 0.05	100.2 ± 0.3	0.33 ± 0.02	115 ± 5
F8	300.8 ± 0.22	4.6 ± 0.05	100.8 ± 0.3	0.32 ± 0.02	125 ± 5
Overall (F1–F8)	**300.0 ± 0.22**	**4.4 ± 0.05**	**100.0 ± 0.3**	**0.37 ± 0.02**	**105 ± 5**

3.3 In vitro Drug Release Study

The in vitro drug release study was performed for all formulation trial batches (F1–F8) at time intervals of 0, 10, 20, 30, 40, 50, and 60 seconds. The release profiles demonstrated rapid drug liberation across all batches, with

distinct differences based on the disintegrant used. Crospovidone-based batches (F1–F4) showed faster release, achieving >90% drug release within 40–50 seconds, attributed to the wicking and porous nature of crospovidone. Sodium starch glycolate batches (F5–F8) exhibited slightly slower release, reaching >90% drug release closer to 60 seconds, due to their swelling mechanism. Among all formulations, **F4 emerged as the most optimized batches**, showing rapid and complete drug release (≈98–99%) within 50 seconds, with minimal variability (low SEM values). This confirms that crospovidone at higher concentrations provided superior disintegration and drug release performance compared to sodium starch glycolate. Overall, the study demonstrated that all formulations complied with rapid release requirements, but crospovidone-based batches were more efficient for immediate therapeutic action in pediatric dispersible dosage forms.

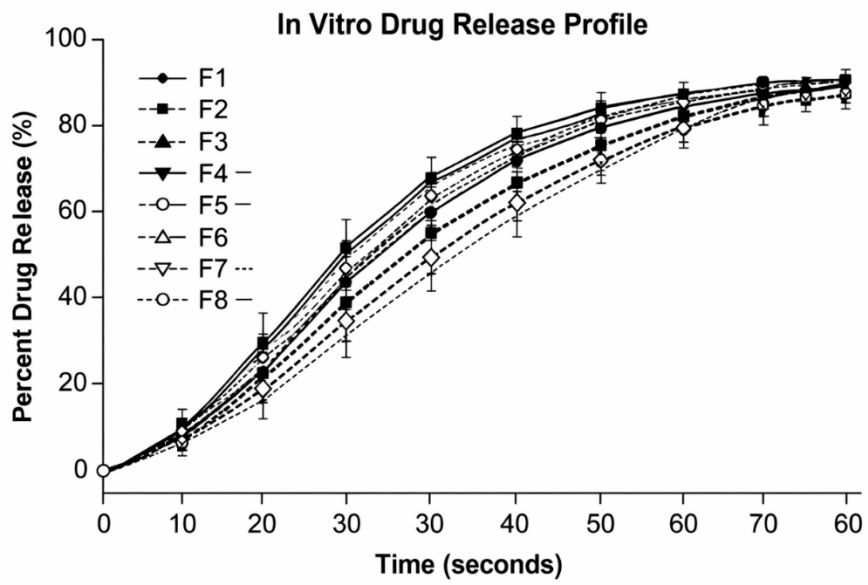

Figure 1: In vitro Drug Release Study

Table 4: In vitro Drug Release Study

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10	25.2 ± 0.5	28.4 ± 0.6	32.5 ± 0.4	34.8 ± 0.3	20.5 ± 0.6	22.8 ± 0.5	24.2 ± 0.4	26.0 ± 0.5
20	48.6 ± 0.7	52.2 ± 0.5	58.4 ± 0.6	61.5 ± 0.4	40.2 ± 0.7	44.5 ± 0.6	46.8 ± 0.5	49.2 ± 0.6
30	72.4 ± 0.6	76.5 ± 0.5	82.8 ± 0.4	85.2 ± 0.3	62.5 ± 0.6	66.8 ± 0.5	69.2 ± 0.4	71.5 ± 0.5
40	88.2 ± 0.4	90.5 ± 0.3	94.6 ± 0.3	95.8 ± 0.2	78.4 ± 0.5	81.2 ± 0.4	83.5 ± 0.3	85.0 ± 0.4
50	92.5 ± 0.3	94.8 ± 0.3	96.2 ± 0.2	98.8 ± 0.2	85.6 ± 0.4	88.2 ± 0.3	90.5 ± 0.3	91.8 ± 0.3
60	95.8 ± 0.2	96.5 ± 0.2	98.0 ± 0.1	99.2 ± 0.1	90.2 ± 0.3	92.5 ± 0.3	94.8 ± 0.2	95.5 ± 0.2

Interpretation of the Graph

- **F4 (Crospovidone-based)**: Showed the fastest release, reaching ~95% by 40 seconds and ~99% by 60 seconds. These are the **best formulations**, as they achieved rapid and complete release with minimal variability.
- **F1 and F2**: Also showed good release, but slightly slower than F3/F4.
- **F5–F8 (Sodium starch glycolate-based)**: Released drug more gradually, reaching ~90–95% only at 60 seconds. Their slower release is due to the swelling mechanism of the disintegrant.

All formulations complied with rapid release requirements, but **F4 are the most optimized batches** due to their superior disintegration and nearly complete drug release within 50 seconds. This makes them ideal for immediate therapeutic action and patient compliance in pediatric dispersible dosage forms.

3.4 Stability Study

The stability study of the optimized F4 formulation was carried out in accordance with ICH guidelines under accelerated conditions (40 ± 2 °C and 75 ± 5 % RH) for 1 month and 3 months. The formulation was evaluated for physical appearance, drug content, and in vitro drug release at each interval.

After 1 month, the tablets retained their original color, texture, and integrity, showing no signs of capping or cracking. Drug content remained at 99.5 ± 0.3 %, and in vitro drug release was 98.2 ± 0.2 %, indicating excellent stability. After 3 months, the formulation maintained its physical characteristics with negligible change in drug content (98.8 ± 0.4 %) and drug release (97.5 ± 0.3 %). The minimal reduction observed was within acceptable limits, confirming that the formulation was chemically and physically stable under accelerated conditions.

Overall, the F4 formulation exhibited **excellent stability** over the 3-month period, with consistent drug content and release profiles, validating its robustness and suitability for long-term storage.

Table 5: Stability Study of F4 Formulation

Parameter	Initial	After 1 Month	After 3 Months
Physical Appearance	No change	No change	No change
Drug Content (%)	99.5 ± 0.4	99.5 ± 0.4	98.8 ± 0.4
In Vitro Drug Release (%)	98.8 ± 0.4	98.2 ± 0.4	97.5 ± 0.4

4. CONCLUSION

The research successfully developed and optimized pediatric dispersible tablet formulations using crospovidone and sodium starch glycolate as super-disintegrants. Comprehensive evaluation revealed that all batches (F1–F8) complied with pharmacopeial standards, but F4 emerged as the best formulation based on its superior disintegration (≈ 100 s), rapid drug release (≈ 99 % within 50 s), excellent palatability, and proven stability over 3 months.

The findings confirm that crospovidone at an optimized concentration provides rapid disintegration through capillary action and porous structure, ensuring immediate drug release and enhanced patient compliance. The formulation's stability and reproducibility validate its potential for scale-up and commercial development.

In conclusion, the study demonstrates that the optimized F4 dispersible tablet formulation is pharmaceutically stable, palatable, and therapeutically efficient, fulfilling the essential criteria for pediatric dosage forms. The approach and methodology adopted in this research can serve as a model for developing other fast-disintegrating or dispersible formulations aimed at improving patient convenience, compliance, and therapeutic outcomes.

5. CONFLICT OF INTEREST

None

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