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Pediatric Oriented Development and Evaluation of Bismuth Subsalicylate for the Management of Diarrheal Therapy

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Abstract: *Pediatric drug delivery is a specialized field challenged by physiological heterogeneity and poor patient adherence, primarily due to the unpleasant taste of active pharmaceutical ingredients (APIs) and swallowing difficulties associated with conventional solid dosage forms. Bismuth Subsalicylate (BSS) is a well-established antidiarrheal agent with antimicrobial, antisecretory, and anti-inflammatory properties; however, its inherent chalky and bitter profile limits its acceptability in children. This study aimed to develop, optimize, and characterize a stable, palatable chocolate-based drug delivery system for BSS to improve pediatric compliance. Preformulation studies, including UV-Visible spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC), confirmed drug purity and excipient compatibility. A 32 factorial design was implemented to optimize the formulation, varying cocoa butter (X1) and lecithin (X2) concentrations as independent variables. Optimized batch F7 was evaluated for physical appearance, weight uniformity, thickness, surface pH, drug content, and in vitro release.*

Analytical results identified the λmax of BSS at 323 nm in 0.1 N HCl. Compatibility studies indicated no significant chemical interactions between BSS and the chocolate matrix components (cocoa butter, milk powder, and saccharin). Formulation F7 exhibited a uniform weight (1.03 ± 0.04 g) and a surface pH (5.7–6.7) compatible with the oral mucosa. Drug content analysis revealed high uniformity (93.8 ± 0.3%), and in vitro dissolution studies showed a cumulative drug release of 90.0 ± 2.1% within 60 minutes, adhering to first-order kinetics (R2=0.9998). Accelerated stability testing (28 days at 45 ± 2°C and 75 ± 5% RH) confirmed the formulation's structural and chemical integrity. The findings suggest that chocolate-based delivery systems are a viable, patient-centric platform for administering bitter APIs to the pediatric population.

Keywords: Pediatric drug delivery, Bismuth Subsalicylate, Medicated chocolate, Taste masking, Factorial design, Diarrhea, Patient compliance

I. INTRODUCTION

Pediatric drug delivery remains one of the most challenging and specialized areas in pharmaceutical sciences. Unlike the adult population, children represent a highly heterogeneous group characterized by significant physiological, biochemical, and developmental variations. These differences profoundly influence drug pharmacokinetics—absorption, distribution, metabolism, and excretion (ADME)—and therapeutic responses. Oral drug delivery is the preferred route due to its convenience and safety; however, pediatric patients often exhibit poor compliance due to the bitter taste of drugs, difficulty in swallowing tablets (dysphagia), and the fear of medication. Consequently, there is an urgent need for age-appropriate, palatable dosage forms that integrate therapeutic efficacy with patient acceptability [1-3].

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Diarrhea is a leading cause of illness and death among children worldwide, particularly in developing nations where sanitation and healthcare access may be limited. The condition is characterized by an increase in the frequency, volume, or liquidity of stool compared to an individual's normal pattern. In pediatric patients, the rapid loss of fluids and electrolytes can lead to life-threatening dehydration and malnutrition. Etiological factors include viral pathogens like Rotavirus and bacterial infections such as Escherichia coli and Salmonella. Pathophysiologically, diarrhea involves a disruption in the balance of intestinal fluid absorption and secretion, manifesting as secretory, osmotic, or inflammatory diarrhea. Effective management requires not only efficacious drugs but also high patient adherence to complete the dosing regimen [1,4,5].

Bismuth Subsalicylate (BSS) is a well-established antidiarrheal agent with multi-mechanistic actions, including antimicrobial, antisecretory, and anti-inflammatory properties. In the gastrointestinal tract, BSS hydrolyzes into bismuth oxychloride and salicylic acid. The salicylate component reduces intestinal inflammation by inhibiting prostaglandin synthesis, while the bismuth component exerts antimicrobial effects against enteric pathogens and coats the mucosa to reduce fluid loss. Despite its clinical effectiveness, BSS possesses an unpleasant, chalky, and bitter taste that often leads to medication refusal in children [3,4,6].

Chocolate-based drug delivery systems offer an innovative solution to these challenges. Chocolate is a complex lipid-based matrix primarily composed of cocoa butter, cocoa solids, and sweetening agents. Its unique melting behavior close to human body temperature (34–37°C) allows for rapid disintegration in the oral cavity without the need for water. Crucially, the lipid-rich nature of cocoa butter facilitates effective taste masking by coating drug particles and preventing their interaction with taste receptors. Furthermore, the lipid matrix of chocolate may enhance the solubility and bioavailability of poorly water-soluble drugs (BCS Class IV) by mimicking the mechanisms of self-emulsifying drug delivery systems (SEDDS) [6-8].

Recent literature supports the potential of medicated chocolates. Pahwa et al. (2019) emphasized the need for robust techniques to ensure dose uniformity and stability in such matrices. Prasad et al. (2020) identified milk chocolate as a highly effective carrier for taste-masking, provided the API particle size is appropriately reduced. Additionally, the positive psychological connotations of chocolate can help reframe a child's perception of medicine, reducing medical anxiety [9,10].

The present research was envisaged to develop and optimize a stable, palatable pediatric chocolate formulation of BSS. By utilizing a 3^2 factorial design, this study seeks to optimize the concentrations of cocoa butter and lecithin to achieve desirable physical properties and release profiles. The ultimate goal is to provide a patient-centric delivery platform that improves compliance and therapeutic outcomes in pediatric antidiarrheal therapy [9-12].

II. MATERIALS AND METHODS [5-9]

2.1 Materials

Bismuth Subsalicylate (Pharma grade) was selected as the active pharmaceutical ingredient (API). The chocolate base and excipients included Cocoa Butter (Pharma/Cosmetic grade), Milk Powder, Sugar Powder (Sucrose), Cocoa Powder (Food grade), and Lecithin (LR grade). Saccharin was used as an intense sweetening agent. All chemicals used were of analytical or laboratory reagent grade.

2.2 Preformulation Studies

BSS was standardized through description (visual color/texture), melting point determination via the capillary tube method, and semi-quantitative solubility testing in various solvents (0.1 N HCl, ethanol, and methanol).

2.3 Analytical Method Development

A standard calibration curve of BSS was generated in 0.1 N HCl using a double-beam UV-Visible spectrophotometer (Shimadzu UV-1800). The wavelength of maximum absorption (λmax) was determined by scanning a 10 μg/mL solution between 200 and 400 nm. Working solutions (5–25 μg/mL) were analyzed to establish linearity.

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2.4 Drug-Excipient Compatibility Studies

Compatibility was assessed using FTIR spectroscopy and DSC. FTIR spectra of BSS and physical mixtures with cocoa butter, milk powder, and saccharin were recorded in the range of 4000–400 cm-1 to detect peak shifts or disappearance. DSC thermograms were recorded under a nitrogen environment (0–400°C at 10°C/min) to observe thermal transitions.

2.5 Phase Solubility Studies

Solubility enhancement was studied according to the Higuchi and Connors method. Excess BSS was added to 10 mL of 0.1 N HCl containing increasing concentrations of the chocolate carrier components. Samples were shaken for 72 hours at 37°C, filtered, and analyzed spectrophotometrically.

2.6 Formulation and Optimization

Medicated chocolates were prepared using the melt molding method. Cocoa butter was melted at 40–45°C. BSS was dispersed uniformly into the molten base with continuous stirring. Cocoa powder, milk powder, and saccharin were then incorporated. The homogeneous mass was sonicated to remove entrapped air and poured into pre-lubricated molds to solidify.

A 3^2 factorial design was employed to optimize the formulation. The independent variables were Cocoa butter concentration (X1) and Lecithin concentration (X2), while drug release, drug content, and moisture content served as dependent variables. Nine batches (F1–F9) were prepared (Table 1).

Table 1. Formulation design for bismuth subsalicylate anti diarrheal chocolate

Formulation batch	Bismath subsalicylate (mg)	Coca butter (mg)	Lecithin (mg)	Sugar (mg)	Coca powder (mg)	Preservative (mg)
F1	87	250	10	480	200	10
F2	87	250	20	470	200	10
F3	87	250	30	460	200	10
F4	87	250	10	455	200	10
F5	87	275	20	445	200	10
F6	87	275	30	435	200	10
F7	87	300	10	430	200	10
F8	87	300	20	420	200	10
F9	87	300	30	410	200	10

2.7 Evaluation of Medicated Chocolate [7-12]

2.7.1 Physical Appearance

The prepared medicated chocolates were visually inspected for colour, surface smoothness, gloss, shape, and the presence of cracks, air bubbles, or blooming. A uniform and defect-free appearance indicates proper formulation, good manufacturing quality, and acceptable aesthetic characteristics essential for patient compliance.

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2.7.2 Weight Uniformity

Weight uniformity was determined by individually weighing three randomly selected medicated chocolate units using an analytical balance, and the average weight was calculated. This test ensures uniform distribution of the drug and excipients, consistent dosing, and reproducibility of the manufacturing process.

2.7.3 Thickness

The thickness of the medicated chocolates was measured at three different positions using a calibrated micrometer screw gauge, and the average value was recorded. Uniform thickness ensures consistent drug loading, mechanical integrity, dissolution behaviour, and overall quality of the formulation.

2.7.4 Surface pH

Surface pH was measured by placing 1 mL of distilled water on the chocolate surface for one minute, followed by measurement with a calibrated combined glass electrode. The test evaluates compatibility with the oral cavity and helps minimize the risk of irritation during administration.

2.7.5 Drug Content

Drug content was determined by dissolving accurately weighed medicated chocolate (1.1 g) in 10 mL of 0.1 N HCl and analysing the solution at 323 nm using a UV–Visible spectrophotometer. The test confirms uniform drug distribution and ensures dosage accuracy throughout the formulation.

2.7.6 In Vitro Dissolution Study

The in vitro dissolution study was carried out using a USP dissolution apparatus containing 900 mL of 0.1 N HCl maintained at 37 ± 0.5°C with a paddle speed of 50 rpm. Samples were analysed at predetermined intervals to evaluate the drug release profile and dissolution characteristics of the formulation.

2.7.7 Disintegration Test:

The disintegration time of the medicated chocolate was evaluated by placing one chocolate unit in 900 mL of distilled water maintained at 37 ± 0.5°C under gentle agitation. The time required for complete disintegration without any visible solid residue was recorded. The test was performed in triplicate, and the mean disintegration time was calculated.

2.7.8 Release Kinetics and Stability Testing

Release data were fitted into Zero order, First order, Higuchi, and Korsmeyer-Peppas models. Accelerated stability studies for the optimized batch (F7) were performed at room temperature and at 45 ± 2°C / 75 ± 5% RH for 28 days.

III. RESULTS

3.1 Preformulation and Analytical Data

BSS was confirmed as a white, bitter, amorphous powder with a melting point of < 360°C. UV analysis showed a characteristic λmax at 323 nm. The standard calibration curve exhibited high linearity ($R^2 = 0.9982$) with the equation $y = 0.0284x + 0.148$ (Fig. 1).

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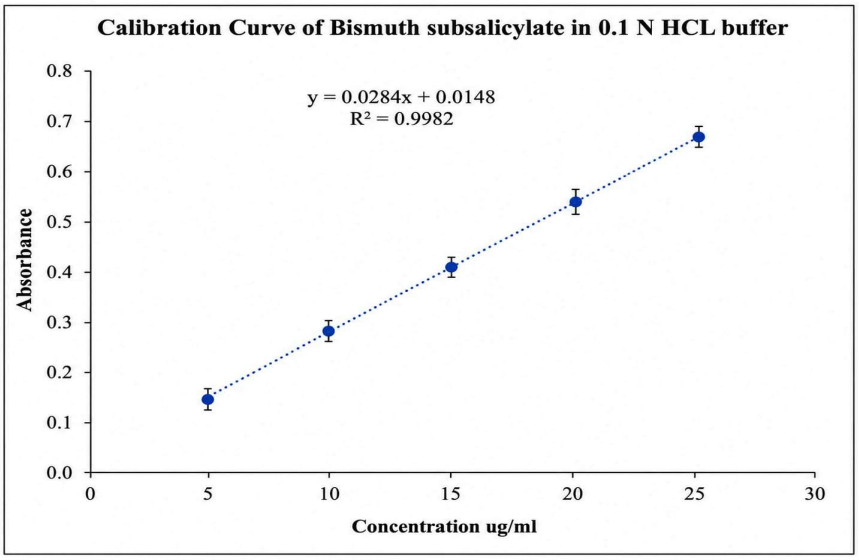

Fig 1. Standard Calibration Curve of Bismuth subsalicylate in 0.1N HCL Phosphate buffer

3.2 Compatibility and Phase Solubility

FTIR analysis of the pure drug showed peaks at 3230.91 cm-1 (O-H) and 683.79 cm-1 (BI-O), which remained intact in drug-excipient mixtures, indicating no chemical interaction (Fig. 2).

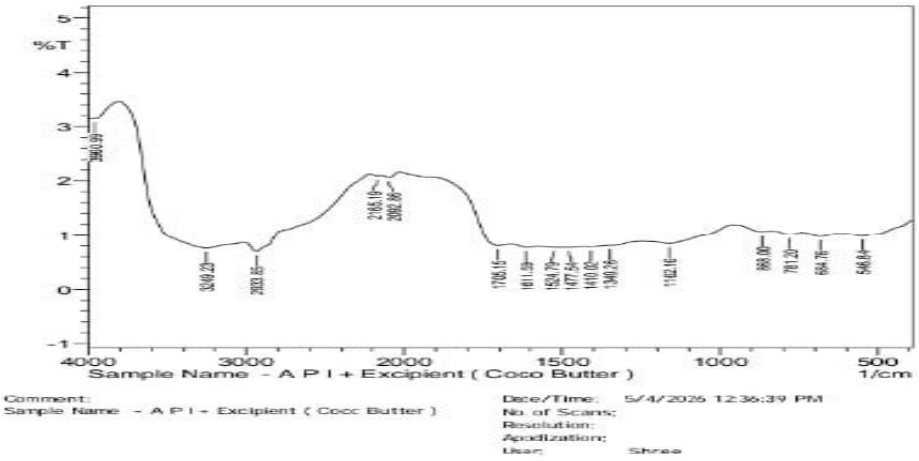

Fig 2. FTIR Spectrum of Drug and Excipient Mixture

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DSC thermograms of BSS showed a sharp melting peak at 154.99°C; the formulation mixture showed a slight shift to 229.48°C, confirming thermal stability (Fig. 3). Phase solubility studies showed a Bs-type curve, where BSS solubility increased linearly with chocolate carrier concentration due to 1:1 molar complex formation.

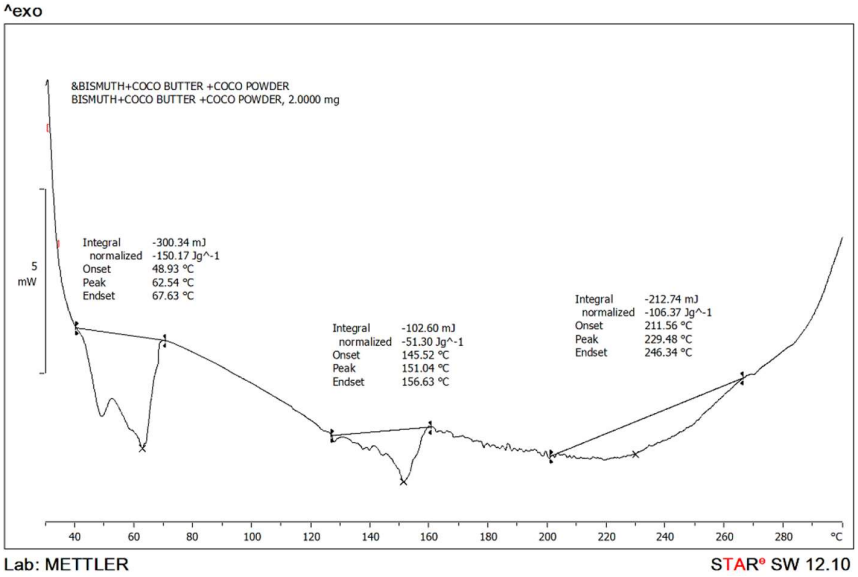

Fig 3. DSC thermogram of drug and mixture

3.3 Characterization of Factorial Batches

All batches (F1–F9) appeared brown and smooth. Weights were uniform (~1.0 g), and surface pH values (5.7–6.7) were compatible with salivary pH. Drug content ranged from 90.2% to 97.1%, with optimized batch F7 showing 93.8%.

Table 2. Evaluation of All the Formulation Batches

Formulation Batches	Physical Appearance	Weight of Chocolate	Thickness (nm)	DI Time (Sec)
F1	Brown	1.01 ± 0.03	4 ± 0.04	6 min 2 sec±0.32
F2	Brown	0.99 ± 0.02	4.3 ±0.00	5 min 1 sec±0.35
F3	Brown	1.00± 0.34	4.5 ±0.02	4 min 8 sec±0.37
F4	Brown	1.2 ± 0.4	4.2 ± 0.02	5 min 3 sec±0.32
F5	Brown	1.00 ± 0.02	4.6 ± 0.01	6 min 6 sec±0.35
F6	Brown	0.98 ± 0.03	4.8± 0.03	3 min sec±0.37
F7	Brown	1.03 ± 0.04	4.5 ± 0.06	4 min 45 sec±0.31
F8	Brown	1.0± 0.02	4.7 ± 0.02	5 min 29 sec±0.36
F9	Brown	1.05 ± 0.03	5.0 ± 0.04	3 min 45 sec±0.34

3.4 In Vitro Drug Release and Kinetics

All formulations released 60–70% of the drug within 10 minutes. Optimized batch F7 achieved 90.0 ± 2.1% cumulative release at 60 minutes (Table 3). Kinetic analysis revealed that F7 best followed First Order Kinetics (R^2 = 0.9998), indicating drug release is proportional to the remaining concentration (Table 4).

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Table 3. In vitro Drug Released of F1 to F9 Formulation

Formulation Batch	Time in Min						
	0	10	20	30	40	50	60
F1	0	14.2± 0.6	26.9± 1.2	42.4 ± 1.4	54.8± 1.6	70.5 ± 1.7	82.2 ± 1.9
F2	0	12.7 ± 0.5	23.81 ± 1.0	37.5 ± 1.2	49.3 ± 1.5	64.8 ± 1.6	76.5 ± 1.8
F3	0	9.4± 0.4	18.9 ± 0.8	28.7 ± 1.0	41.9± 1.3	52.8± 1.4	67.1± 1.6
F4	0	15.9 ± 0.6	30.1 ± 1.3	46.0± 1.5	59.4 ± 1.7	75.1 ± 1.8	88.3 ± 2.0
F5	0	11.1 ± 0.5	23.2 ± 1.0	34.0 ± 1.1	46.8± 1.4	61.0 ± 1.5	73.2± 1.7
F6	0	8.9± 0.4	17.0 ± 0.7	27.3 ± 0.9	36.9± 1.1	48.6± 1.3	61.4 ± 1.5
F7	0	16.41 ± 0.7	31.8 ± 1.3	49.1 ± 1.6	63.1± 1.8	79.0 ± 1.9	90.0± 2.1
F8	0	13.3 ± 0.6	25.1± 1.1	38.5 ± 1.3	53.7± 1.6	66.2± 1.7	80.8 ± 1.9
F9	0	10.1 ± 0.4	20.2 ± 0.9	29.8 ± 1.0	42.5 ± 1.12	54.1± 1.4	68.0 ± 1.6

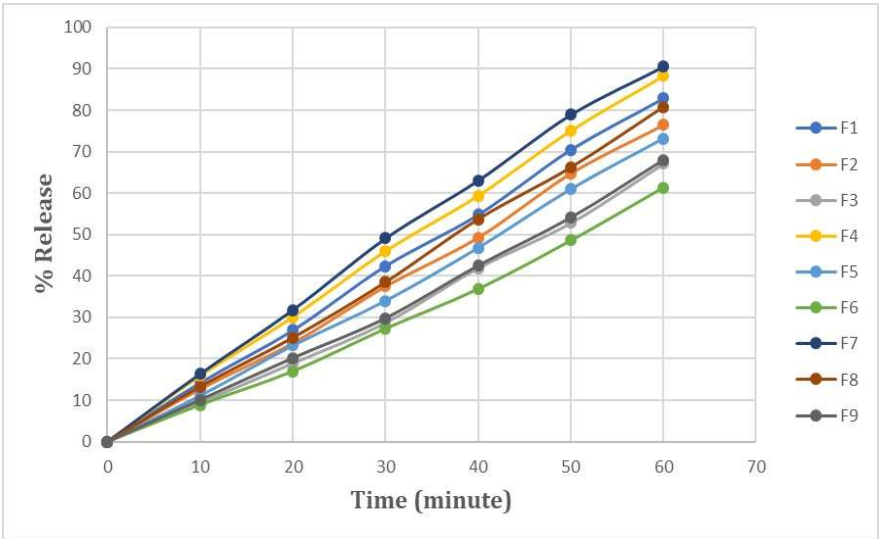

Fig 4. % Drug release at different at different time interval

Table 4. Model Fitting Release of Optimized Batches

Formulation Batch	Zero Order R2	First Order R2	Higuchi Model R2	Kores Meyer Peppas Model R2	Hixson Crowel Model R2	Best Fitted Model
F7	0.9985	0.9998	0.9915	0.9284	0.9738	First Order Kinetic

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Fig 5. First Order Kinetic of Optimized Batch

3.5 Stability Studies

Stability testing of F7 showed no significant reduction in appearance, drug content (retained at ~90%), or disintegration time (20 min 14 sec) over 28 days under room and accelerated conditions. Batch F7 was deemed stable for the duration of the study.

Table 5. Stability Study for F7 Formulation

Stability (Room Temp)	Appearance	Drug Content	Disintegration Time
0 Day	Brown	90.0± 2.1	20 min 14 sec±0.35
7 Days	Brown	90.0± 3.4	20 min 14 sec±0.31
14 Days	Brown	90.0± 2.3	20 min 14 sec±0.29
21 Days	Brown	90.0± 4.2	20 min 14 sec±0.25
28 Days	Brown	90.0± 3.1	20 min 14 sec±0.23

IV. DISCUSSION

The development of a medicated chocolate for Bismuth Subsalicylate addressed the critical pediatric issues of palatability and swallowability. The use of a cocoa butter base (X1) provided a lipophilic matrix that effectively masked the drug's bitter taste, which is consistent with findings by Prasad et al. (2020) regarding the efficacy of lipid carriers in pediatric formulations.

Phase solubility results indicated that the chocolate components improved BSS solubility through 1:1 molar complexation, aiding uniform dispersion within the fatty matrix. Factorial design analysis demonstrated that increasing cocoa butter levels generally increased the thickness of the units. Lecithin (X2) was instrumental in stabilizing the dispersion and improving consistency. Optimized batch F7 was selected for its high drug content (93.8%) and superior release profile (90% in 60 min), ensuring that therapeutic levels are reached efficiently.

The observation of first-order kinetics in F7 suggests that drug release occurs as the drug dissolves out of the lipid matrix into the dissolution medium. Stability data confirmed that F7 maintained its integrity under stress, although the literature (Patel et al., 2022) suggests that moisture-resistant packaging remains critical for long-term lipid-based stability. The surface pH (5.6–6.0) of the optimized batch was ideally matched to the natural oral environment, minimizing irritation. This study demonstrates that chocolate is not merely a confection but a functional pharmaceutical excipient capable of transforming pediatric therapy.

V. CONCLUSION

The study successfully developed a stable and palatable chocolate-based pediatric formulation of Bismuth Subsalicylate. Through a 3^2-factorial design, batch F7 was identified as the optimized formulation, offering high dose uniformity (93.8%), favorable surface pH, and efficient drug release (90% in 60 min) following first-order kinetics. The formulation effectively addressed the inherent bitterness of BSS, providing a patient-friendly alternative to conventional syrups and

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tablets. This novel delivery platform has significant potential to improve treatment adherence and health outcomes in children suffering from acute diarrhea.

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