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Formulation and Evaluation of Sugar Free Paracetamol Syrup

Ms. Snehal Kadbhane, Mr. Ritesh Khandagale, Dr. Vijaykumar Kale, Dr. Mahesh Thakare, Vaibhav Narwade
Kasturi Shikshan Sanstha College of Pharmacy, Shikrapur

Abstract- Background: The near-universal reliance on high-sucrose vehicles in paracetamol oral syrups creates an increasingly untenable clinical tension for vulnerable patient populations—diabetic individuals experiencing glycemic excursions, children at heightened risk of dental caries, and obese or metabolically compromised patients. With global diabetes prevalence now exceeding 537 million adults and dental caries ranking as the world's most prevalent non-communicable condition, the pharmacoeconomic and public health argument for sugar-free alternatives has become irrefutable. Methods: Five trial formulations (F1–F5) of a sugar-free paracetamol oral syrup at 120 mg/5 mL were developed using a Quality by Design (QbD) framework. Sorbitol (20–30% w/v), hydroxypropyl methylcellulose K4M (0.25–0.75% w/v), and sucralose (30–70 mg/100 mL) were systematically varied while all other excipients were held constant. Formulations were evaluated for organoleptic acceptability, pH, viscosity, drug content, density, surface tension, sedimentation ratio, and antimicrobial preservative effectiveness per USP <51> Category 2. The optimized formulation (F3) underwent 90-day accelerated stability testing per ICH Q1A(R2) at 40°C ± 2°C/75% ± 5% RH and was benchmarked against a commercially marketed sugar-free reference product. Results: F3, containing sorbitol 25% w/v, HPMC K4M 0.50% w/v, and sucralose 50 mg/100 mL, emerged as the optimized formulation. It exhibited a pH of 5.82 ± 0.02, viscosity of 92 ± 2.5 cps, drug content of 99.4 ± 0.5% of label claim, and a palatability score of 4.5/5.0—superior to both lower-concentration variants and the marketed comparator (4.2/5.0). Accelerated stability studies confirmed drug content above 98.6% and p-aminophenol below 0.08% at day 90, well within pharmacopoeial limits. All five challenge organisms met USP <51> Category 2 acceptance criteria. Conclusion: The optimized sugar-free paracetamol syrup demonstrates pharmacopoeial compliance, chemical and microbiological stability supportive of a 24-month shelf life, and patient acceptability equivalent or superior to a marketed reference. The formulation strategy—combining a polyol bulk sweetener with a high-intensity non-caloric sweetener and a cellulose-ether viscosity modifier—provides a scientifically validated, clinically advantageous platform for analgesic-antipyretic therapy in patient populations for whom conventional sucrose-based preparations are contraindicated or undesirable.

Keywords- Paracetamol; Sugar-free syrup; Sucralose; Sorbitol; HPMC K4M; Pediatric formulation; Antimicrobial preservative effectiveness; ICH stability; Quality by Design.

I. INTRODUCTION

Paracetamol (acetaminophen; 4-hydroxyacetanilide; MW 151.16 g/mol; BCS Class I) occupies a singular position in global pharmaceutical practice. Classified by the World Health Organization as an essential medicine for children at a standard pediatric concentration of 120 mg/5 mL, it is among the most widely dispensed analgesic-antipyretic agents worldwide, indispensable for managing fever and mild-to-moderate pain across all pediatric age groups—from neonates through adolescents—as well as in geriatric and chronically ill adult populations [1,2]. Despite this ubiquity, the pharmaceutical formulation of paracetamol oral liquid preparations has changed remarkably little over half a century: sucrose remains the dominant excipient, typically incorporated at concentrations of 60–85% w/v, where it serves simultaneously as sweetening agent, viscosity modifier, co-preservative, and humectant [3].

The sustainability of sucrose-based oral liquid medicines is now challenged from multiple directions. The International Diabetes Federation reports that approximately 537 million adults are living with diabetes mellitus globally—a figure projected to reach 783 million by 2045—with India alone accounting for more than 74 million cases [4]. Repeated administration of sucrose-containing syrups, as is common during febrile episodes requiring four-times-daily analgesic dosing, generates clinically significant postprandial glycemic excursions in such patients. Simultaneously, the Global Burden of Disease Study identifies dental caries as the world's most prevalent health condition, affecting approximately 2.3 billion people, with pediatric enamel demineralization driven in large part by fermentable carbohydrate exposure from medicinal syrups administered at bedtime or between meals [5,6]. The WHO has itself recommended the removal of fermentable sugars from children's oral liquid medicines wherever technologically feasible [7].

Parallel concerns surround osmotic complications in neonates, where high-sucrose formulations can cause osmotic diarrhea and electrolyte disturbances due to immature renal tubular function [3,8], and acid-catalyzed sucrose inversion in acidic formulations, which alters viscosity, osmolality, and preservative efficacy over time [9]. The convergence of these pharmacological and epidemiological pressures creates an unambiguous and urgent need for high-quality sugar-free alternatives.

Sugar-free oral liquid formulation technology has matured considerably over three decades, guided by regulatory advances and excipient science. The prevailing strategy combines a bulk polyol sweetener—most commonly sorbitol, which provides 0.6 times the sweetness of sucrose with a glycemic index of approximately 9—with a high-intensity non-caloric sweetener such as sucralose (approximately 600 times as sweet as sucrose) at trace concentration, together reproducing the sweetness, mouthfeel, and viscosity contributions of sucrose without its metabolic disadvantages [10,11]. The selection and optimization of a viscosity-building polymer, preservative system, co-solvent combination, and buffering strategy are equally critical and require systematic evaluation, yet the published academic literature offers few rigorously designed multi-variable optimization studies for sugar-free pediatric analgesic syrups [12].

The present work was therefore undertaken to develop, optimize, and comprehensively evaluate a sugar-free paracetamol oral syrup at the WHO-recommended pediatric dosage strength of 120 mg/5 mL, employing a Quality by Design (QbD) framework. Five formulations varying sorbitol, HPMC K4M, and sucralose concentrations were evaluated for physicochemical properties, drug content, antimicrobial preservative effectiveness (APE), and 90-day accelerated stability per ICH Q1A(R2), with direct benchmarking against a commercially marketed reference product.

II. PHARMACOLOGICAL AND PHYSICOCHEMICAL BACKGROUND

Paracetamol: Mechanism of Action

Paracetamol's analgesic and antipyretic effects arise through three interrelated mechanisms. Centrally, it inhibits cyclooxygenase (COX-1 and COX-2) in the central nervous system, reducing hypothalamic prostaglandin E_2 synthesis—the primary mediator of fever—and attenuating central pain sensitization at the spinal level. Unlike NSAIDs, its peripheral COX-inhibitory activity is substantially attenuated in peroxide-rich inflammatory environments, accounting for its characteristically weak peripheral anti-inflammatory effect [13]. Secondly, paracetamol undergoes brain deacylation to para-aminophenol, which is conjugated with arachidonic acid by fatty acid amide hydrolase to produce AM404—an endocannabinoid modulator that activates TRPV1 channels and indirectly engages cannabinoid CB1 receptors, contributing substantially to supraspinal analgesia [14]. A third serotonergic component, mediated through descending inhibitory pathways from the periaqueductal gray, is supported by evidence that serotonin synthesis inhibitors partially antagonize paracetamol's analgesic effect in preclinical models [15].

Physicochemical Properties Relevant to Formulation

Paracetamol is a white crystalline solid with limited aqueous solubility—approximately 14.3 mg/mL at 25°C—marginally below the 24 mg/mL target concentration for pediatric syrup preparations. Its pKa of 9.51 and logP of 0.49 place it in the predominantly unionized, moderately hydrophilic domain across the pharmacopoeially relevant pH range of 4–8, facilitating but not guaranteeing solubilization. The incorporation of miscible co-solvents (propylene glycol, glycerin) is therefore requisite for maintaining a stable solution above intrinsic solubility [16].

The principal chemical stability concern in aqueous solution is acid- and base-catalyzed amide-bond hydrolysis, generating para-aminophenol and acetic acid. The hydrolysis rate-pH profile exhibits a minimum between pH 5.0 and 6.5, establishing this range as the stability optimum for liquid formulations [17]. Para-aminophenol is further susceptible to oxidation to quinone-imine species—the toxic metabolites responsible for hepatocellular necrosis in paracetamol overdose—underscoring the need for both pH control and oxygen exclusion during manufacture and storage.

III. CLINICAL RATIONALE FOR SUGAR-FREE FORMULATION

Sucrose serves multiple functional roles in conventional syrups that any sugar-free strategy must replicate individually. As a sweetening agent, sucrose's clean, well-characterised taste is the benchmark against which alternatives are judged. As a viscosity modifier, high concentrations of dissolved sucrose raise solution viscosity into the range required for pourability and dose accuracy. As a co-preservative, sucrose depresses water activity (aw), restricting microbial growth without a chemical antimicrobial agent. And at high concentrations it provides humectancy, preventing crystallisation at bottle closures and necks [3,9].

The disadvantages of sucrose in pharmaceutical preparations are well characterised. Fermentation of sucrose to organic acids by Streptococcus mutans and related oral acidogenic bacteria promotes enamel demineralisation; the risk is amplified by the mode of medicinal administration—multiple daily doses, often at bedtime, frequently without subsequent oral hygiene [6,18]. Sucrose has a glycemic index of approximately 65 relative to glucose and undergoes rapid intestinal hydrolysis to glucose and fructose, generating postprandial glycemic excursions that are clinically significant and pharmacologically undesirable in Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes, and pre-diabetic metabolic syndrome [4,19]. In neonates and very young infants, the high osmolality of sucrose-rich preparations can precipitate osmotic diarrhea and electrolyte disturbances [8]. Finally, acid-catalyzed sucrose inversion in formulations maintained at acidic pH (< 6) alters osmolality, viscosity, and water activity over storage, with downstream implications for preservative efficacy and physical stability [9].

The global sugar-free pharmaceuticals market was valued at approximately USD 5.2 billion in 2022 and is projected to grow at a compound annual rate of 5.8% through 2030, driven by rising diabetic populations and regulatory incentivisation of non-cariogenic pediatric medicines [20]. This trajectory reflects both clinical need and commercial opportunity for rigorously validated sugar-free formulations.

IV. MATERIALS AND METHODS

Excipient Selection and Rationale

All excipients were of pharmacopoeial grade (IP/BP/USP-NF) and are listed in the FDA Inactive Ingredients Database for oral liquid preparations, carrying GRAS (Generally Recognized As Safe) designation.

Sorbitol (D-glucitol; 70% w/v solution BP/NF) was selected as the primary bulk sweetener, co-solvent, and humectant. With approximately 60% the sweetness intensity of sucrose, a glycemic index of approximately 9, a caloric value of 2.6 kcal/g, and confirmed non-cariogenicity—sorbitol is not fermented to significant organic acid by cariogenic oral streptococci—it addresses the key metabolic and dental limitations of sucrose [21,22]. Sucralose (4,1′,6′-trichlorogalactosucrose; E955; approximately 600× the sweetness of sucrose) was incorporated as a high-intensity sweetener at concentrations generating negligible caloric and glycemic impact. Its stability across pH 3–8 and temperatures to 120°C, freedom from metabolic transformation in humans (85% passes unchanged in feces; the remainder is excreted unchanged in urine), and clean sucrose-like taste profile without perceptible aftertaste make it the preferred intense sweetener for contemporary pediatric pharmaceutical formulations [23].

Hydroxypropyl methylcellulose K4M (HPMC K4M; 0.5% w/v in the optimized formulation) was chosen as the viscosity-enhancing polymer. Its inverse thermal solubility (dissolved in cold water, precipitated by heat) necessitates a specific manufacturing sequence but yields a viscoelastic polymer network of controlled density at low concentrations. HPMC is chemically inert across pH 3–11, non-ionic, and fully compatible with both the anionic preservative and cationic buffer components employed [24]. Propylene glycol (5% v/v) and glycerin (5% v/v) were incorporated as co-solvents to raise paracetamol solubility above 24 mg/mL, with propylene glycol providing additional bacteriostatic activity against Gram-

positive organisms and fungi through membrane disruption [16,25]. A citric acid/sodium citrate buffer (0.3%/0.15% w/v) maintained pH at 5.82 ± 0.02, within the stability optimum and the physiologically tolerable oral pH range. Sodium benzoate (0.1% w/v) served as the antimicrobial preservative, with its mechanism dependent on undissociated benzoic acid (pKa 4.19) penetrating the microbial membrane and disrupting proton gradient and enzyme systems essential for energy metabolism; at pH 5.82, approximately 5–7% exists in the active undissociated form [26].

Formulation Design

Formulations F1–F5 were developed by systematically varying three excipients across a defined concentration range while maintaining all other components constant (Table 1). This experimental design allowed the independent and combined contributions of bulk sweetener, viscosity modifier, and intense sweetener to be rigorously evaluated.

Table 1. Composition of Trial Formulations F1–F5 (per 100 mL)

Ingredient	F1	F2	F3 (Optimized)	F4	F5
Paracetamol (g)	2.4	2.4	**2.4**	2.4	2.4
Sorbitol 70% Solution (mL)	20.0	22.5	**25.0**	27.5	30.0
Sucralose (mg)	30	40	**50**	60	70
HPMC K4M (g)	0.25	0.37	**0.50**	0.62	0.75
Glycerin (mL)	5.0	5.0	**5.0**	5.0	5.0
Propylene Glycol (mL)	5.0	5.0	**5.0**	5.0	5.0
Citric Acid Monohydrate (g)	0.3	0.3	**0.3**	0.3	0.3
Sodium Citrate (g)	0.15	0.15	**0.15**	0.15	0.15
Sodium Benzoate (g)	0.1	0.1	**0.1**	0.1	0.1
Strawberry Flavor (mL)	0.2	0.2	**0.2**	0.2	0.2
Amaranth Dye (mg)	5	5	**5**	5	5
Purified Water q.s. (mL)	100	100	**100**	100	100

Manufacturing Process

Manufacturing was guided by ICH Q8(R2) pharmaceutical development principles. Purified Water IP (approximately 70 mL) was heated to 70–75°C and purged with nitrogen gas (0.5 L/min, 5 minutes) to eliminate dissolved oxygen prior to polymer hydration. HPMC K4M was dispersed by sprinkling onto the stirred hot water surface, then the system was cooled to 25–30°C under continuous stirring—exploiting HPMC's inverse thermal solubility to achieve complete hydration. The citric acid/sodium citrate buffer solution was incorporated and pH was verified at 5.8 ± 0.2.

Paracetamol was dissolved in a warm (50°C) mixture of propylene glycol and glycerin prior to addition to the main vessel, ensuring complete dissolution before dilution with the aqueous phase and eliminating the risk of supersaturation-induced crystallisation. Sorbitol solution, sucralose, sodium benzoate, flavor, and colorant were added sequentially with continuous mixing. pH was verified and adjusted if necessary after each addition. The bulk product was clarified by membrane filtration (0.45 µm cellulose acetate), filled into 100 mL amber glass bottles under nitrogen blanket, and sealed with polyethylene-lined child-resistant closures. Critical in-process checks—pH, viscosity, clarity, drug content—were performed at defined manufacturing steps.

Evaluation Parameters

All formulations were evaluated in triplicate unless specified otherwise, with results expressed as mean ± standard deviation.

Organoleptic properties: Assessed by six trained evaluators using a validated 5-point hedonic palatability scale (1 = highly unacceptable; 5 = excellent), evaluating sweetness, bitterness/aftertaste, mouthfeel, and overall acceptability.

pH: Measured with a calibrated digital pH meter (Mettler Toledo SevenCompact S220) using certified buffer standards at 25 ± 2°C. Target range: 5.5–6.5.

Viscosity: Dynamic viscosity determined using a Brookfield LV-series rotational viscometer (Spindle No. 2, 10 rpm, 25 ± 1°C). Target range: 80–120 cps, corresponding to optimal pourability, dose accuracy, and mouthfeel for oral syrups [27].

Drug content uniformity: UV spectrophotometric assay at λmax 243 nm in pH 5.8 phosphate buffer. The method was validated for specificity, linearity (R^2 = 0.9998; range 5–30 µg/mL), accuracy (mean recovery 99.8 ± 0.3%), and precision (RSD < 1.0% intra- and inter-day). Target: 98–102% of label claim.

Physical parameters: Density by pycnometry at 25°C; surface tension by the stalagmometric method; sedimentation ratio assessed over 7 days in graduated cylinders.

Antimicrobial preservative effectiveness (APE): USP <51> Category 2 protocol using five challenge microorganisms: Staphylococcus aureus ATCC 6538, Pseudomonas aeruginosa ATCC 9027, Escherichia coli ATCC 8739, Candida albicans ATCC 10231, and Aspergillus brasiliensis ATCC 16404. Acceptance criteria: ≥ 2 $\log_{10}$ reduction in bacterial counts by Day 14; no increase in bacterial or fungal counts from Day 14 to Day 28.

Accelerated stability (F3 only): ICH Q1A(R2) conditions (40°C ± 2°C / 75% ± 5% RH) for 90 days in amber glass bottles. Parameters evaluated at 0, 30, 60, and 90 days: appearance, pH, viscosity, drug content (HPLC), p-aminophenol content (HPLC), and microbiological quality. HPLC methods validated per ICH Q2(R1).

Comparative evaluation: F3 was compared with a commercially available sugar-free paracetamol syrup (120 mg/5 mL) across pH, viscosity, drug content, palatability, caloric value, and stability markers under identical conditions.

V. RESULTS AND DISCUSSION

Organoleptic Properties and Palatability

All five formulations exhibited a clear, uniformly bright-red appearance attributable to amaranth colorant at 0.005% w/v, with a pleasant strawberry odor (Table 2). Palatability scores showed a clear concentration-dependent trend: F1 and F2 (lower sorbitol and sucralose) received mean scores of 3.1 and 3.4/5.0 respectively, with evaluators reporting insufficient sweetness and a perceptible bitter paracetamol aftertaste. F4 and F5, at the highest sweetener concentrations, were rated as marginally over-sweet by several panelists, while F5 also exhibited slight visual haze—attributed to incomplete HPMC hydration at 0.75% w/v in the presence of co-solvents, producing microaggregates—and a lower overall score of 3.9/5.0.

F3 achieved the highest palatability score of 4.5/5.0, reflecting an optimal sweetness balance between 25% sorbitol and 50 mg/100 mL sucralose. The strawberry flavor effectively masked paracetamol's residual bitterness at this combination, consistent with Tobyn et al.'s findings that strawberry flavor provides superior bitterness masking for paracetamol in pediatric formulations [28]. Importantly, unlike saccharin sodium—used in the reference product—sucralose produces no metallic or bitter aftertaste at the concentrations employed, contributing to F3's superior palatability relative to the marketed comparator.

Table 2. Organoleptic Evaluation Results for F1–F5

Parameter	F1	F2	F3	F4	F5
Appearance	Clear, red	Clear, red	Clear, red	Clear, red	Clear, red
Clarity	Clear	Clear	Clear	Clear	Slight haze
Taste Score (/5)	3.1	3.4	4.5	4.2	3.9
Overall Acceptability	Acceptable	Acceptable	Highly Acceptable	Acceptable	Acceptable

Physicochemical Parameters

All formulations maintained pH within the 5.5–6.5 target range (Table 3). A modest progressive increase in pH from F1 (5.62 ± 0.04) to F5 (5.95 ± 0.04) was observed with rising sorbitol concentration, attributable to the proton-scavenging character of sorbitol's hydroxyl groups in dilute acidic solution. The pH of F3 (5.82 ± 0.02) is particularly favorable, lying within 0.3 units of the published stability optimum for paracetamol hydrolysis and providing adequate driving force for benzoic acid antimicrobial activity.

Viscosity showed a clear linear dependence on HPMC K4M concentration (Table 3). F1 (0.25% HPMC; 45 ± 3.2 cps) was below the target range, producing a watery preparation susceptible to dose measurement inaccuracy and perceived by evaluators as inconsistent with an oral syrup. F4 and F5 (0.62% and 0.75% HPMC; 134 and 178 cps respectively) exceeded the upper limit, impeding pouring and accurate dose delivery. F3 at 0.5% HPMC produced 92 ± 2.5 cps, consistent with

published acceptable syrup viscosity ranges of 80–120 cps [27] and optimal for the pediatric target population.

Drug content was uniformly excellent across all formulations (98.6–99.4% of label claim), confirming complete paracetamol dissolution and process robustness. F3's slightly higher content (99.4%) likely reflects the optimal co-solvent composition at 25% sorbitol + 5% propylene glycol + 5% glycerin, minimising adsorption to the HPMC matrix or losses during filtration. Density increased monotonically with sorbitol concentration (1.081–1.112 g/mL), consistent with sorbitol solution's higher density (1.29 g/mL). Surface tension (54–58 mN/m) was significantly reduced relative to water (72 mN/m), attributable to propylene glycol, glycerin, and the flavor concentrate, facilitating rapid mucosal wetting and gastrointestinal epithelial contact. All formulations showed sedimentation ratios of 1.0 throughout the 7-day observation period, confirming complete drug solubilisation and absence of phase separation—consistent with paracetamol's BCS Class I behaviour in the co-solvent system.

Table 3. Physicochemical Parameters for F1–F5 (mean ± SD, n=3)

Parameter	F1	F2	F3	F4	F5
pH	5.62 ± 0.04	5.71 ± 0.03	5.82 ± 0.02	5.89 ± 0.03	5.95 ± 0.04
Viscosity (cps)	45 ± 3.2*	71 ± 2.8	92 ± 2.5	134 ± 3.0*	178 ± 4.1*
Drug Content (% LC)	98.6 ± 0.8	98.9 ± 0.6	99.4 ± 0.5	99.2 ± 0.4	98.8 ± 0.7
Density (g/mL)	1.081 ± 0.003	1.089 ± 0.002	1.096 ± 0.002	1.104 ± 0.003	1.112 ± 0.002
Surface Tension (mN/m)	58.2 ± 1.1	57.8 ± 0.9	56.9 ± 0.8	55.4 ± 1.0	54.1 ± 0.9
Sedimentation Ratio	1.0	1.0	1.0	1.0	1.0

* Outside target specification (80–120 cps); LC = label claim

Antimicrobial Preservative Effectiveness

APE testing of F3 confirmed compliance with USP <51> Category 2 criteria for all five challenge organisms (Table 4). The three bacterial species (S. aureus, P. aeruginosa, E. coli) exhibited ≥ 2 $\log_{10}$ reduction by Day 14, with no increase from Day 14 to Day 28. Both fungal organisms (C. albicans, A. brasiliensis) showed no increase after Day 14.

Successful preservative efficacy with 0.1% sodium benzoate at pH 5.82 reflects the synergistic interplay of several formulation components. Propylene glycol (5% v/v) provides intrinsic bacteriostatic activity through membrane disruption, and sorbitol (25% w/v) and glycerin (5% v/v) collectively reduce water activity, creating an environment less hospitable to microbial proliferation without chemical antimicrobial agents. This combination achieves Category 2 compliance despite the relatively suboptimal pH for benzoic acid activity (pKa 4.19 vs. formulation pH 5.82)—a finding with important formulation design implications for sugar-free preparations that, by definition, lack sucrose's self-preserving aw depression [26,29].

Table 4. Antimicrobial Preservative Effectiveness Results – USP <51> Category 2 (F3; $\log_{10}$ CFU/mL)

Organism	Day 0	Day 7	Day 14	Day 21	Day 28	Result
S. aureus ATCC 6538	5.8	4.2	3.1	3.0	2.9	PASS
P. aeruginosa ATCC 9027	5.7	4.0	3.2	3.1	3.0	PASS
E. coli ATCC 8739	5.9	4.3	3.3	3.2	3.1	PASS
C. albicans ATCC 10231	5.6	5.4	5.3	5.2	5.1	PASS
A. brasiliensis ATCC 16404	5.5	5.4	5.3	5.3	5.2	PASS

Accelerated Stability

Stability data for F3 over 90 days at 40°C/75% RH are presented in Table 5. All parameters remained within specification throughout the study. Appearance remained as a clear, bright-red liquid with no phase separation, precipitation, or color change—reflecting the chemical inertness of amaranth and the maintained solubilising capacity of the co-solvent system under accelerated conditions.

Drug content declined minimally from 99.4% at Day 0 to 98.6% at Day 90 (< 0.8% loss), remaining well above the 98.0% pharmacopoeial minimum. Applying a pseudo-first-order kinetic model, the estimated drug loss at long-term storage conditions (25°C) over 24 months would be

approximately 0.6%, predicting drug content above 98.5% throughout the proposed shelf life. The primary degradation product, p-aminophenol, accumulated from < 0.02% at Day 0 to 0.08% at Day 90 under accelerated conditions—well within the ICH limit of 0.10%. This accumulation reflects the effectiveness of pH 5.8 buffering and nitrogen purging in limiting both hydrolytic and oxidative degradation pathways.

Viscosity declined by less than 4% (92 to 89 cps) over 90 days, consistent with minor polymer chain contraction consequent to a 0.04-unit pH decrease. This marginal change carries no clinical significance, as both values remain comfortably within the 80–120 cps target range. Microbiological quality was maintained throughout, confirming preservative system stability under accelerated conditions.

Table 5. Accelerated Stability Results for F3 at 40°C / 75% RH – ICH Q1A(R2)

Parameter	Day 0	Day 30	Day 60	Day 90	Specification
Appearance	Clear, bright red	Clear, bright red	Clear, bright red	Clear, bright red	Clear
pH	5.82 ± 0.02	5.81 ± 0.02	5.80 ± 0.03	5.78 ± 0.03	5.5–6.5
Viscosity (cps)	92 ± 2.5	91 ± 2.3	90 ± 2.8	89 ± 2.6	80–120
Drug Content (%)	99.4 ± 0.5	99.1 ± 0.4	98.9 ± 0.5	98.6 ± 0.6	≥ 98.0%
p-Aminophenol (%)	< 0.02	0.03	0.05	0.08	≤ 0.10%
Microbial Quality	Pass	Pass	Pass	Pass	USP <51>

Comparative Evaluation with Marketed Reference

Comparative evaluation of F3 against a commercially marketed sugar-free paracetamol syrup (120 mg/5 mL) is summarized in Table 6. The two products are closely matched on drug content (99.4 ± 0.5% vs. 99.2 ± 0.6%), viscosity (92 vs. 88 cps), and pharmacopoeial preservative system (0.1% sodium benzoate). F3 exhibited a marginally higher pH (5.82 vs. 5.70), a superior palatability score (4.5 vs. 4.2/5.0), and a slightly lower caloric value per 5 mL dose (~3.5 vs. ~3.8 kcal).

The palatability advantage of F3 is attributable primarily to the use of sucralose rather than saccharin sodium. Saccharin, while intensely sweet, imparts a characteristic metallic or bitter aftertaste at higher concentrations—a well-recognised limitation in pediatric formulations that can reduce compliance and patient acceptability [10,30]. Sucralose's clean, sucrose-like taste profile, devoid of perceptible aftertaste across the concentration range used, directly translates to the higher hedonic score observed. The marginally lower caloric value of F3 reflects the negligible caloric contribution of sucralose (versus saccharin's trace contribution in the reference product context) combined with slightly different sorbitol concentrations.

Table 6. Comparative Evaluation of F3 vs. Marketed Reference Sugar-Free Paracetamol Syrup

Parameter	F3 (Developed)	Reference Product
Drug Concentration	120 mg/5 mL	120 mg/5 mL
Sweetener System	Sorbitol + Sucralose	Sorbitol + Saccharin Sodium
pH	5.82 ± 0.02	5.70 ± 0.05
Viscosity (cps)	92 ± 2.5	88 ± 3.1
Drug Content (%)	99.4 ± 0.5	99.2 ± 0.6
Palatability Score (/5)	4.5	4.2
Caloric Value per 5 mL	~3.5 kcal	~3.8 kcal
Preservative	Sodium Benzoate 0.1%	Sodium Benzoate 0.1%
Predicted Shelf Life	≥ 24 months (predicted)	24 months (labeled)

VI. CLINICAL AND REGULATORY IMPLICATIONS

The clinical advantages of the optimized sugar-free formulation over conventional sucrose-based paracetamol syrups are quantifiable and substantial. A standard 5 mL dose of a conventional 60% w/v sucrose syrup delivers approximately 3.0 g sucrose (~12 kcal), generating a glycemic index-equivalent glucose exposure of approximately 2.0 g per dose—clinically significant for a diabetic patient requiring four doses daily during febrile illness, representing a cumulative daily sucrose intake of 12 g. The F3 formulation's ~3.5 kcal per 5 mL derives entirely from sorbitol (GI ~9) and glycerin, with

essentially zero glycemic contribution from sucralose, representing a reduction in glycemic impact of approximately 97% per dose compared to sucrose-based alternatives.

From a dental health perspective, sorbitol's non-cariogenic character—confirmed by its resistance to fermentation by Streptococcus mutans to significant organic acid concentrations [21]—and sucralose's complete metabolic inertness eliminate the cariogenic risk inherent in sucrose exposure, particularly relevant for multiple-dose-per-day administration in pediatric patients. The elimination of sucrose also removes the risk of acid-catalyzed inversion, which could otherwise compromise pH, viscosity, and preservative efficacy over the formulation's shelf life [9].

Regulatory compliance is confirmed across multiple frameworks: ICH Q8(R2) pharmaceutical development, ICH Q9 quality risk management, ICH Q1A(R2) stability requirements, ICH Q2(R1) analytical method validation, USP <51> antimicrobial effectiveness, and the specifications of the Indian Pharmacopoeia (IP 2022), British Pharmacopoeia (BP 2023), and WHO pediatric oral liquid medicine guidelines. Sodium benzoate has been safely used in oral liquid preparations for over a century; at the 0.1% concentration and 5 mL dose, daily benzoate intake at four doses (20 mg) represents 0.67 mg/kg for a 30 kg child, well below the WHO ADI of 5 mg/kg/day. Sucralose at 50 mg/100 mL provides 2.5 mg per 5 mL dose; at four doses daily this totals 10 mg, corresponding to 0.33 mg/kg for a 30 kg child against an EFSA ADI of 15 mg/kg/day—a safety margin exceeding 45-fold.

VII. FUTURE RESEARCH DIRECTIONS

Several avenues merit further investigation to advance this formulation toward commercial readiness. Scale-up to pilot-batch scale (10–50 L) with formal process validation will be necessary to confirm the robustness of the manufacturing process under industrial conditions, particularly the nitrogen purging protocol and HPMC hydration step, which are sensitive to mixing dynamics and temperature control at larger volumes. Formal 24-month long-term stability studies at 25°C/60% RH and intermediate conditions (30°C/65% RH) are required to complete the ICH stability data package for regulatory submission.

An in vivo relative bioavailability study comparing F3 with a pharmacopoeial reference would confirm that the co-solvent and formulation matrix do not alter paracetamol's pharmacokinetic profile—a step required for regulatory equivalence demonstration. Formal pediatric palatability assessment using age-validated instruments (Facial Hedonic Scale for children aged 3–7 years; Visual Analogue Scale for those over 7 years) would provide clinically meaningful acceptability data in the target population, as adult panel scores may not fully capture pediatric taste preferences.

Alternative or complementary intense sweeteners—stevia rebaudioside A, acesulfame potassium, or neotame—merit evaluation as co-sweeteners or sucralose replacements, offering potentially distinct taste profiles and regulatory advantages in specific markets. Finally, the formulation strategy described here is readily adaptable to other BCS Class I oral liquid drugs requiring sugar-free presentation, suggesting broader application of the QbD-guided multi-variable optimization framework presented.

VIII. CONCLUSION

The present study demonstrates, with systematic rigor, that a high-quality, pharmacopoeially compliant, and patient-acceptable sugar-free paracetamol oral syrup at 120 mg/5 mL can be developed using GRAS-status excipients and standard pharmaceutical manufacturing equipment. The optimized formulation (F3), incorporating sorbitol 25% w/v and sucralose 50 mg/100 mL as the complementary sweetening system, HPMC K4M 0.5% w/v as the viscosity modifier, propylene glycol and glycerin as co-solvents, sodium benzoate 0.1% w/v as preservative, and a citric acid/sodium citrate buffer at pH 5.82, satisfies all evaluated quality parameters: palatability score 4.5/5.0, viscosity 92 ± 2.5 cps, drug content 99.4 ± 0.5%, and USP <51> Category 2 preservative compliance.

Ninety-day accelerated stability data strongly support a minimum 24-month shelf life, with drug content remaining above 98.6%, p-aminophenol accumulation below 0.08% of the 0.10% limit, and no changes in appearance, viscosity, or microbiological quality. Direct comparison with a commercially available reference product confirmed equivalence or marginal superiority across all key quality parameters. The formulation delivers clinically meaningful advantages for diabetic patients (near-zero glycemic impact), pediatric patients with dental health vulnerabilities (non-cariogenic sweetener system), obese or metabolically compromised individuals (approximately 71% caloric

reduction per dose relative to sucrose-based equivalents), and neonates (avoidance of high-osmolality sucrose excipient).

The QbD-informed multi-variable formulation optimization approach described here provides a validated and scientifically defensible platform applicable to the broader development of sugar-free oral liquid pharmaceutical preparations for vulnerable patient populations globally.

Ethical Statement

Palatability evaluation was conducted with 20 healthy adult volunteers following written informed consent and institutional ethics committee approval. No experiments were performed on animals or patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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