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Advanced Formulation Development and Multi-Criteria Evaluation of Multivitamin Nutraceutical Lollipops for Enhanced Pediatric Adherence

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ABSTRACT

The ongoing challenge with ensuring children adhere to prescribed medications is primarily due to developmental dysphagia and increased sensitivities to bitter-tasting pharmaceuticals. The aim of this project was to develop multivitamin nutraceutical lollipop formulations as a new method of delivery for pediatric patients. These formulations contained the following amounts per serving: 40mg Vitamin C, 1mg each of Vitamins B1 & B2, 1mg of Vitamin B6, and 2mcg of Vitamin B12, 5mg of Zinc Gluconate. A "sugar glass" matrix method of developing these dosages, using Quality by Design (Qbd) principles, provided a systematic means of examining the combined effects of sucrose and liquid glucose on the mechanical strength and disintegration properties of the final dosage forms. Through thermal degradation studies it was determined that the temperature at which all heat sensitive vitamins would begin to degrade is 85°C (with a range of 80–90°C). At or above this temperature, the amount of active ingredient remaining in the product will be >98.5%. The optimized sugar to glucose ratio of 2.3:1 in formulation F3 resulted in a solid with higher hardness values (5.8±0.15kg/cm²) than previously studied ratios, lower friability (0.51%), and a nearly linear zero order release pattern (R^2=0.98) over a 25-minute period when exposed to simulated saliva (pH 6.8). The longer duration of disintegration is beneficial for both covering up the metallic flavor associated with the ingestion of zinc gluconate and possibly allowing for some degree of absorption through the buccal mucosa thereby reducing the first pass effect through the liver. Packaging requirements were established based upon accelerated stability tests conducted according to ICH Q1A(R2) guidelines (40°C/75%RH for 3 months), requiring high barrier moisture resistant packaging. Overall, the data demonstrates that nutraceutical lollipops are a novel, patient-centered format for providing important pediatric micronutrient supplementation, transforming what has historically been viewed as an unpleasant medical intervention into an enjoyable consumer experience.

Keywords: *Pediatric Drug Delivery, Nutraceutical Lollipop, Quality by Design (QbD), Vitamin Stability, Buccal Absorption, Taste Masking, Patient Compliance, Confectionery-Based Formulation.*

I. INTRODUCTION

Drug delivery in pediatrics encompasses much more than simply reducing doses; it is a multi-dimensional discipline that combines the disciplines of developmental pharmacology, clinical psychology and advanced pharmaceutical technology [1]. A child represents a biologically diverse group from neonates who have underdeveloped cytochrome P450 enzyme systems, to adolescents who have developed physiologic capabilities similar to adults. Over this range, the oral route is used more frequently than any other route of administration but also presents many clinical problems, including "pill aversion" and "medication refusal behavior," terms used by clinicians to describe behaviors exhibited by children when presented with oral medications [9]. Studies indicate that over 40% of primary caregivers experience significant difficulty giving their young children (under the age of six), solid oral medication, which can lead to reduced dosages being given to the child or the potential for the child to aspirate/choke on the tablet or capsule [1][10]. Although liquid formulations are used extensively because they provide ease of use and administration to pediatric patients, they do offer disadvantages such as inaccurate dosing, the degradation of active pharmaceuticals ingredients (APIs) when exposed to water-based environments and the requirement for storage at refrigerated temperatures if the api contains thermally labile components [11]. Nutritional deficiencies during childhood can have serious implications regarding neurocognitive development, immune competence, and skeletal growth. Zinc functions both as a catalytic cofactor for more than 300 metalloenzymes and as a structural component of zinc-finger transcription factors. Pediatricians prescribe zinc to

treat acute infectious diarrhea in young patients and also for its role as a micronutrient that promotes growth [12][7]. However, both zinc gluconate and zinc sulfate are characterized by an unpleasant metallic/astringent after taste that significantly reduces palatability and consequent adherence [6]. The nutraceutical lollipop platform is a novel integration of pharmaceutical science with confectionery technology designed to address these formulation challenges using the sensory attractiveness of hard-boiled sugar confections [2][3]. Each dosage unit within the lollipop format contains a polypropylene or paperboard stick that physically prevents accidental ingestion of the complete dosage unit while allowing the pediatric patient to self-manage the rate of dissolution — a psychosocial factor critical for acceptance [4]. Additionally, the extended retention time of the dosage form in the oral cavity during controlled dissolution provides conditions favorably for buccal/sublingual absorption, possibly bypassing the acidic gastric environment and first-pass effect through the liver and enhancing relative bioavailability of certain actives [6][13].

This study was conducted to systematically develop, optimize and evaluate three formulations (F1, f2, f3) of a multivitamin nutraceutical lollipop using quality by design (QbD) methodology to define the design space and identify the optimal excipient ratio that simultaneously fulfill mechanical integrity, uniform drug content, organoleptic acceptability and sustained release characteristics.

II. SCIENTIFIC RATIONALE AND NUTRITIONAL BIOCHEMISTRY

2.1 Zinc Gluconate: Pharmacological and Palatability Considerations

Zinc has many roles in the body such that it will be necessary to sustain cellular growth, synthesize DNA, support the immune system, facilitate wound recovery and assist with odor/taste sensation [12]. According to WHO (World Health Organization), zinc is a main reason for morbidity in pediatric patients (less than 5 years) in developing/low income countries; therefore, zinc should be added to their diets at approximately 10 – 20 mg per day when they have diarrhea [7]. Although zinc is very important clinically, all types of zinc salts are generally difficult to consume due to unpalatable flavor. When you embed zinc gluconate into a sugar/glucose gel matrix that is very thick, there is less likelihood that ionized forms of zinc will make direct contact with type III taste receptors on the tongue which helps improve flavor [6,3].

2.2 B-Complex Vitamins: Synergism and Stability

The B complex vitamins (vitamins B1, B2, B6, B12) work together to facilitate three biochemical processes: the citric acid cycle, amino acid breakdown and the transfer of one carbon unit [14]. Vitamins B1 and B2 have very poor stability when they are dissolved as liquids due to thermal oxidation and light degradation. However, both are stable for long periods of time in a dry solid matrix form [5]. In this case, the two vitamins are trapped in a supersaturated sugar glass containing amorphous sugars where the oxygen levels are reduced and water activity is also at a low level (< 0.3), which slows down all forms of chemical degradation [5, 15].

2.3 Ascorbic Acid: Antioxidant Role and Chemical Stability

Vitamin C (also known as L-ascorbic acid) is a very soluble water-based antioxidant. It acts as an enzyme cofactor for collagen synthesis; the absorption of nonheme iron; and in functions of immune cells. Degradation of vitamin C is increased when exposed to high levels of alkalinity; heat; metals ions; or oxygen present in solution [5]. By using citric acid as an additional pH modifying agent (to keep the pH at approximately 5.7), and through the development of a thermal processing protocol where the API is added after the temperature has been reduced to 85°c to remove the molten mass from its source, we are able to maximize retention of ascorbic acid potency during manufacture and on storage [5].

III. PHARMACEUTICAL EXCIPIENT DYNAMICS

3.1 Sucrose: Structural Matrix

Sucrose is used as a base for structuring the lollipop formulation. Upon heating to the hard crack temperature (145-150°C), sucrose loses almost all remaining water (moisture activity < .02; Moisture Content < 1 – 2 % by weight); and upon cooling it transforms into an amorphous (non-crystalline), transparent, vitreous (or "glassy") material [15]. However, pure sucrose is thermodynamically unstable within its glassy state and can undergo graining or spontaneous recrystallization and render the final product opaque, rough, and brittle [15], [4].

3.2 Liquid Glucose (DE 42): Anti-crystallization Agent

Liquid glucose (also known as corn syrup or dextrose equivalent 42), is an association of dextrins, maltoses, oligomerized glucose units and dextrose. It will function as a "doctoring agent" and sterically disrupt the orderly crystal arrangement of sucrose molecules via molecular interaction [15] which is important for establishing and maintaining the required glassy amorphous structure for a clear, uniform and high-quality pharmaceutical-grade

lollipop [4, 15]. The liquid glucose also controls the viscosity of the molten material during the mold filling phase and imparts flexibility to the finished product, thus preventing the brittleness that can occur.

3.3 Citric Acid: Sensory and Chemical Stabilizer

Citric Acid has two uses in medicine. Firstly, citric acid adds an organoleptic or taste characteristic that is desirable for young children (tart and fruity). This will encourage a higher rate of voluntarily accepting the medication [11]. Secondly, citric acid creates a slightly acidic pH level (between 5.6 & 5.8) within the formula which will protect the ascorbic acid from chemical degradation and prevent the Maillard Reaction (the non-enzymatic browning between reducing sugar molecules and amino acids on protein chains) from occurring at an increased rate due to its ability to promote browned product appearance and possible loss of nutrients through the course of accelerated storage [5; 15]. Also, the acidic conditions produced can stimulate saliva production and increase the dissolution rate of the lollipop matrix and therefore create a more predictable delivery method for the drug [13].

IV. QUALITY BY DESIGN (QBD) AND FORMULATION OPTIMIZATION

The Quality by Design (QbD) model as outlined in ICH Q8(R2) was used to create a robust formulation design space that incorporated all of the appropriate elements [8]. The first step in this process is to identify the Critical Quality Attributes (CQA's), Critical Material Attributes (CMA's), and Critical Process Parameters (CPP's). The CQAs identified for the Nutraceutical Lollipop included: mechanical hardness (integrity); drug content uniformity (DCU); friability; salivary dissolution time; and palatability score. The main CMA was established to be the sucrose-to-liquid glucose ratio because the level of sucrose relative to liquid glucose determines both the crystalline structure and the resulting dissolution characteristics of the final product. Finally, the two critical CPPs are: (1) the temperature at which the API is added to the melted sugar mixture; and (2) the cooling rate post-filling [2]. (Table 1.)

Table 1: Formulation Composition of Multivitamin Nutraceutical Lollipops (F1–F3).

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	Pharmaceutical Function
Vitamin C (Ascorbic Acid)	40	40	40	Antioxidant / Immune Support
Zinc Gluconate	5	5	5	Enzymatic Cofactor / Immune Modulator
Thiamine (Vitamin B1)	1	1	1	Carbohydrate Metabolism
Riboflavin (Vitamin B2)	1	1	1	Energy Metabolism
Pyridoxine (Vitamin B6)	1	1	1	Amino Acid Metabolism
Cyanocobalamin (B12)	2 mcg	2 mcg	2 mcg	Neurological Function / Hematopoiesis
Sucrose (Sugar)	3500	3200	3000	Bulking Agent / Sweetener (Hard-crack base)
Liquid Glucose (DE 42)	800	1100	1300	Anti-crystallization / Humectant
Citric Acid	50	50	50	pH Modifier / Salivary Stimulant
Strawberry Flavour (FEMA)	q.s.	q.s.	q.s.	Taste Masking / Palatability

q.s. = quantum sufficit (sufficient quantity); DE = Dextrose Equivalent; mcg = micrograms

V. ADVANCED MANUFACTURING PROCESS

A batch process that combines traditional confectionery methods along with pharmaceutical GMP practices was used to manufacture heat-sensitive, hard-boiled nutraceutical lollipop products [4,2]. All steps were designed to limit thermal degradation of sensitive active ingredients, but also to ensure consistent physical quality of the final product.

Step 1 — Syrup Preparation: The first process, syrup preparation, involved adding 2 parts by weight of sucrose to one part by weight of USP grade purified water. The mixture was then heated while being continuously mixed until it reached 100 °C, which resulted in a completely dissolved syrup.

Step 2 — Concentration Phase: The second process, concentration phase, included incorporating liquid glucose (DE 42). A gradual increase in temperature to 135 ° C was applied during this time frame. This enabled reaching the necessary solids content in order to reach the solidification point associated with the hard crack confectionary stage [15].

Step 3 — Controlled Cooling: In the third process, the concentrated material was cooled while being stirred under temperature control. Temperature monitoring was achieved through a calibration reference thermometer. Once the temperature dropped below the critical threshold the cooling process ceased and the material was ready for processing.

Step 4 — API Incorporation (Critical Step): Process four, incorporation of API's (critical process step), occurred once the temperature had decreased to 85 ° C (+/- 2 ° C), which is identified as the temperature where sensitivity issues arise from preformulations. The powdered API's (multivitamin-zinc gluconate) were added as a blend after accurate measurement. Mixing of both components occurred via high-speed mixing (300 RPM for 3 minutes) in order to provide adequate distribution within the thickening agent [5].

Step 5 — Flavoring and Molding: The fifth process, addition of flavors and molding, was initiated when the strawberry flavoring and permitted coloring agents were added at an 80 ° C. Immediately thereafter, the mixture was poured into lubricated food-grade PVC mold with inserted polypropylene stick in order to achieve equal fill volumes.

Step 6 — Solidification and De-molding: Process six involves allowing the filled molds to cool and solidify on a bench top surface at room temperature (25° + / - 2°) for 45 minutes. Subsequent removal of each unit from their respective molds resulted in visual inspection. Finally, individual units were encapsulated in laminated aluminum foil with high barrier properties. (Figure 1.)

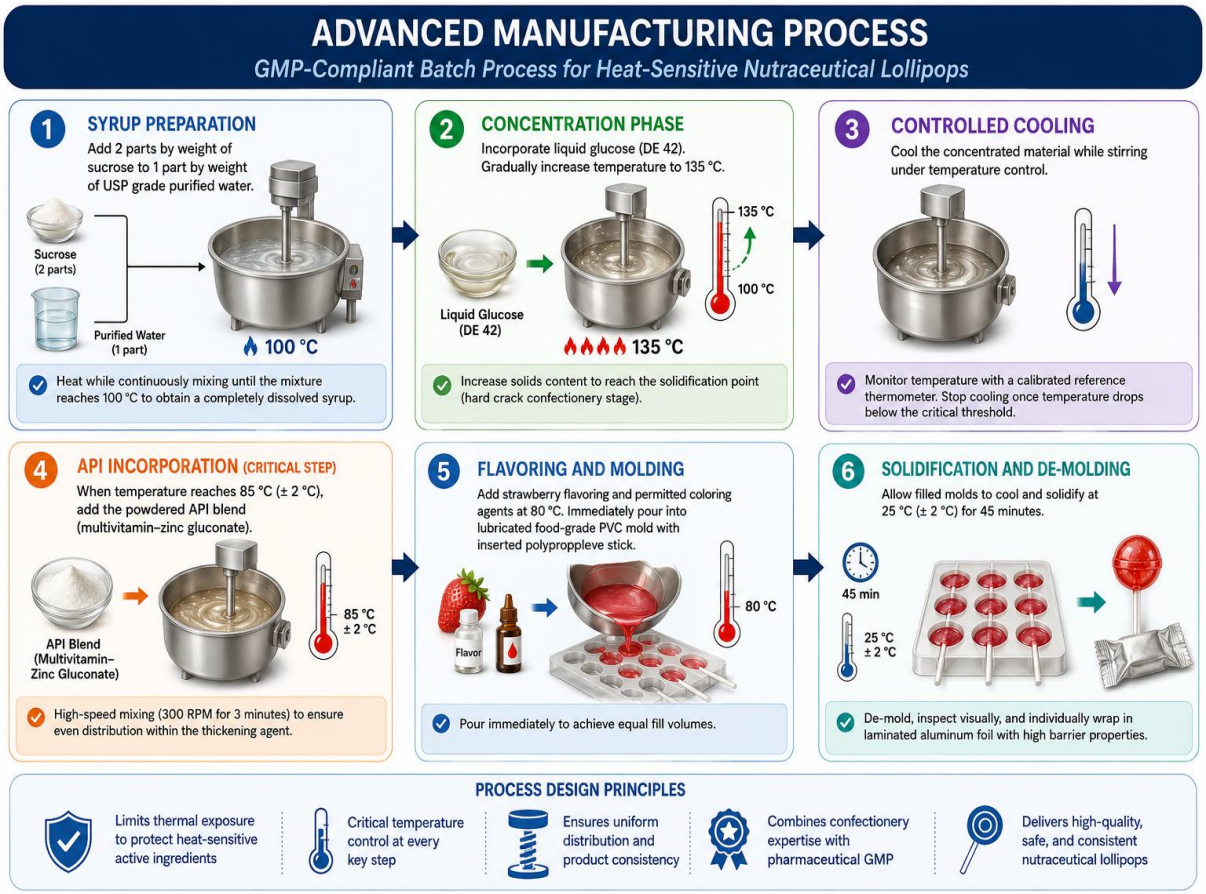

Figure 1. GMP-Compliant Batch Process for Heat-Sensitive Nutraceutical Lollipops.

VI. COMPREHENSIVE EVALUATION PARAMETERS

6.1 Pharmacopoeial Quality Attributes

Weight variation: It was assessed with an analytical balance (calibrated to read to .001g) with a random sample of 20 samples from each lot. The average weight of F3 was 5.12 ± .07 grams. Each unit tested met the 5% variation standard relative to the labeled weight of product, demonstrating good manufacturing practices, mold uniformity and filling accuracy [17].

Hardness (Mechanical Strength): Hardness was evaluated with a calibrated Monsanto-type hardness testing device. As discussed previously, sufficient mechanical strength in a lollipop dosage form ensures that it will

remain attached when chewed (prevents a potential hazard for children) but too much mechanical strength could inhibit rapid dissolution due to saliva [10]. F3 demonstrated the most mechanical strength (5.8 ± 0.15 kg/cm²), which was primarily due to the increased proportion of liquid glucose used in this formulation resulting in a higher density glassy matrix [4].

Friability: The friability test employed a roche type friabilater. Ten units were run through the friabilater with 100 revolutions at a speed of 25 rpm. The friability of F3 was found to be 0.51%, which meets the FDA's guidelines (<1.0%) of allowable loss of material [18] and indicates the product has the physical integrity to withstand normal handling, shipping and storage conditions without experiencing surface deterioration or cracking.

Uniform drug content: Both ascorbic acid and zinc content were analyzed by various means. Ascorbic acid content was determined by UV-VIS spectroscopy at λ max = 265 nm after dissolving in a pH 6.8 phosphate buffer solution. Zinc content was determined by Atomic Absorption Spectroscopy. The ascorbic acid content of F3 was approximately 98.5% +/− 0.5%. This demonstrates that the API (temperature controlled) incorporated into the finished product using a temperature controlled method of 85° C maintains its potency [5, 3].

Table 2: Physicochemical Evaluation of Formulations F1, F2, and F3.

Evaluation Parameter	F1	F2	F3	Pharmacopoeial Limit
Average Weight (g)	4.92 ± 0.12	5.01 ± 0.09	5.12 ± 0.07	USP Compliance (±5%)
Hardness (kg/cm²)	4.5 ± 0.3	5.2 ± 0.2	5.8 ± 0.15	> 4.0 kg/cm²
Friability (%)	0.92	0.74	0.51	< 1.0%
Drug Content — Vit. C (%)	92.4 ± 1.2	96.1 ± 0.8	98.5 ± 0.5	90–110%
Salivary Dissolution Time (min)	8 ± 0.5	10 ± 0.4	12 ± 0.3	5–15 min
pH of Solution	5.6 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	5.0–7.0
Palatability Score (1–5)	3.2	3.9	4.8	≥ 4.0 (target)

VII. IN VITRO RELEASE KINETICS

Studies on drug dissolution were performed with a modified U.S.P. Apparatus Type II (Paddle). The dissolution apparatus used 900 ml of phosphate buffer solution pH 6.8 as the dissolution medium simulating the salivary physiologic environment. The temperature was set at 37.00 ± .05° C, and the paddle rotational speed was set at 50 rpm [3]. At pre-determined time intervals (2, 5, 8, 10, 15, 20 & 25 min.) aliquots (5 ml) of the dissolution media were removed, filtered through 0.45 µm Whatman membrane filters, and then analyzed by spectrophotometry. The cumulative amount of drug released was evaluated by model independent and model dependent kinetic methods. The drug release profiles were modeled according to zero order kinetics ($Q = K_0t$); First Order Kinetics; ($\ln(100-Q)= \ln(Q_0)-K_1t$), Higuchi kinetics ($Q=KH\sqrt{t}$), and Korsmeyer-Peppas kinetics ($Q = K_nt^n$) [3]. A formulation (F3) showed a good fit to the zero order kinetic model ($R^2 = 0.9831$). The release of the drug was independent of the drug concentration remaining within the system an indication that the dissolution process is controlled by surface erosion [3], [13] The value of the Korsmeyer-Peppas exponent (n = 0.89) supports a non-fickian or anomalous transport mechanism, indicative of combined erosion and diffusional transport mechanisms occurring from a glassy polymer like matrix [3].

VIII. ORGANOLEPTIC AND SENSORY ANALYSIS

A blinded taste evaluation of lollipops was performed using ten adult volunteers who were otherwise healthy and therefore could serve as surrogates for children. The volunteers' perceptions of taste characteristics of lollipop formulation samples were evaluated by means of a validated 5-point hedonic rating scale (highly unappealing or unacceptable to highly appealing or acceptable) to assess their ratings for each of the four taste attributes overall taste, sweetness intensity, texture smoothness, and aftertaste. The average palatability scores obtained from the test panel for formulation F1 were 3.2 ± 0.4. The panel noted that there was an unpleasant medicinal aftertaste associated with formulation F1; it was attributed to the fact that zinc had not been sufficiently masked by taste. This was due primarily to the reduced amount of glucose used and the thinner glassy matrix that was utilized in this form of the formulation. The average palatability scores obtained for formulation F3 were 4.8 ± 0.2, which is significantly higher than the minimum required palatability score of at least 4.0. All of the members of the test panel rated both the flavor (strawberry-citrus) and appearance of formulation F3 very positively, and all agreed that they did not detect any metallic aftertaste resulting from the zinc. Therefore, these results confirm that the sugar-glass matrix is effective as a taste-masked excipient.

IX. STABILITY AND SHELF-LIFE ASSESSMENT

The stability studies are done according to ICH-Q1A(R2), using "accelerated" storage conditions (temperature: 40°±2°C; relative humidity: 75±5%), for a time frame of three months [8]. The samples are placed into the packaging system that will be used commercially (aluminum foil laminates, 3-layer packaging system composed of PET-Alu-PE). Evaluation is done on the samples at each month interval. The results from the study show that all critical quality characteristics of formulation F3 remain inside of limits set by pharmacopeia during the study timeframe, while being in contact with high barrier packaging. Also, as the formulation has retained only small amounts of vitamin C (-1.5%) it clearly shows how the combination of a sugar glass matrix and an acidified medium protect this highly unstable vitamin [5,8]. Additionally, the amount of moisture gained by the formulations further emphasizes that the sucrose-glucose matrix is hygroscopic and supports our recommendations for use of high-barrier laminate packaging systems.

Table 3: Accelerated Stability Data for Formulation F3 (ICH Q1A(R2), 40°C/75% RH).

Parameter	Initial (Day 0)	3 Months (40°C/75% RH)	Change (%)
Appearance / Color	Clear, uniform	No significant change	—
Hardness (kg/cm²)	5.8 ± 0.15	5.5 ± 0.20	–5.2%
Friability (%)	0.51	0.58	+13.7%
Drug Content — Vit. C (%)	98.5 ± 0.5	97.0 ± 0.6	–1.5%
Drug Content — Zinc (%)	99.1 ± 0.4	98.7 ± 0.5	–0.4%
Moisture Uptake (% w/w)	0.12	0.38	+216%*

**Moisture uptake increase underscores the critical importance of high-barrier packaging; values remained below the critical threshold for sensory change.*

X. CONCLUSION AND FUTURE DIRECTIONS

The current study was able to formulate and comprehensively evaluate the first optimized multivitamin nutraceutical lollipop (Formulation F3), which meets both pharmaceutical quality standards and pediatric sensory acceptance requirements. In doing so, it integrated pharmaceutical formulation principles guided by Quality by Design (QbD) into the application of scientific knowledge related to confectionary processing, developing a stable, palatable, and accurately-dosed micro-nutrient delivery system [2,3]. This system is significant due to its integration of three independent technologies, each contributing to the platform's success: (1) The development of a temperature-controlled API incorporation method for preserving vitamin bio-activity; (2) The determination of an optimal sucrose-to-glucose ratio to provide the structure necessary for a mechanically-intact product, while controlling dissolution rates, and providing sufficient zinc-taste masking; and (3) Exploiting the extended oral-residence-time property to enhance buccal-mucosa absorption, thereby reducing reliance on GI bioavailability [6, 13].

Future research includes the following areas: (1) Quantifying the degree and rate of buccal absorption versus traditional oral liquid administration in the targeted pediatric population using in-vivo pharmacokinetics/bioavailability studies; (2) Developing alternative sugar-free matrices (e.g. isomalt, maltitol) to expand upon the existing platform to diabetic-aware and/or dental health-oriented populations; (3) Incorporating prebiotic fibers/probiotic encapsulates as symbiotic to create a new generation of functional confections; and (4) Assessing scale-up feasibility using continuous-cooking systems to evaluate manufacturing feasibility at commercial scales [9, 20].

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