

Influence of Packaging Material and Design on the Microbial Quality and Cost Structure of Nonsterile Pharmaceutical Products

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ABSTRACT

Background: Pharmaceutical product safety requires packaging that limits microbial entry while remaining cost-effective. **Objectives:** This study evaluated the influence of nonsterile oral pharmaceutical products' (paracetamol) packaging choice on microbial safety and product cost, and demonstrated the propensity to contamination over a 6-day active use period. **Materials and Methods:** A total of 160 packages of 100 mL paracetamol syrup samples were analysed across four experimental configurations combining different package materials and orifice diameters. A longitudinal, single-group time-series design was adopted for multiple-packaged paracetamol tablets to track contamination. Total viable aerobic counts (colony forming unit/millilitres) were determined using the standard pour plate technique after 48 hr of incubation. **Results:** Statistical evaluations: Two-Way Analysis of Variance, independent-samples *t*-tests, variance partitioning, and Pearson correlation coefficients at a significance threshold of $\alpha \leq 0.05$, indicated significant main effects for experimental configuration ($F=34.86$, $p<0.001$) and active-use-time ($F=288.77$, $p<0.001$), with a significant interaction effect ($F=8.19$, $p<0.001$). Pooled by material type, glass showed a significantly more effective contamination barrier compared to plastic. Regression modelling for the 6-day active exposure of tablets package revealed a significant positive linear trend ($F_{1,38}=72.28$, $p<0.0001$). Cost analysis showed glass carries a substantial pricing premium compared to plastic. **Conclusion:** Contamination containment in nonsterile products is not restricted to the use of preservatives alone. A clear trade-off exists between product costs and preservation performance. This challenges the current lack of descriptive label procedures for product active use based on package type and design.

Keywords: Contamination, Cost, Nonsterile, Orifice Diameter, Packaging Material, Total Viable Aerobic Counts.

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INTRODUCTION

The preservation of product integrity prior to, during, and after storage is a fundamental challenge in the manufacturing of pharmaceutical and consumer goods products. Microbial contamination, particularly by aerobic pathobionts and spoilage organisms, leads to rapid degradation of perishable matrices, shortens product shelf-lives, and presents significant public health risks (Marsh and Bugusu, 2007). To mitigate these

vectors, manufacturing frameworks rely heavily on the use of preservatives and the barrier properties of container housings (Marsh and Bugusu, 2007).

Standards for microbial requirements are critical to the quality, safety, and efficacy of pharmaceutical products. The microbiological quality of pharmaceutical products when in active use is critical yet often overlooked in safety ratings. While sterile products require absolute freedom from viable microorganisms, Non-Sterile Pharmaceutical Products (NSPPs), such as oral solids (tablets), liquids, and topical creams, are permitted to harbour a limited, controlled bioburden devoid of pathogenic organisms (European Directorate for the Quality of Medicines and HealthCare, 2023; United States Pharmacopeial Convention, 2026). Regulatory frameworks establish strict microbiological attributes for NSPPs prior to their release for commerce. However,



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once a container is opened and enters the "active-use" phase, maintaining product quality becomes a dynamic challenge. This transition from a controlled manufacturing facility to variable consumer environments significantly escalates the risk of microbial contamination and subsequent proliferation, jeopardizing patient safety.

Globally, microbiological contamination remains one of the leading drivers of substandard pharmaceuticals and product recalls (Ratajczak *et al.*, 2021; Sandle, 2026). An estimated 1 in 10 pharmaceutical products in commerce in low- and middle-income countries are substandard due to microbial overgrowth resulting from unhygienic manufacturing (World Health Organization, 2017). Substandard essential medicines have been associated with an annual global death toll of 72,000 to 169,000 children due to pneumonia, causing \$30.5 billion in annual economic losses (Ozawa *et al.*, 2018). This threat is disproportionately higher in Africa due to vulnerability driven by decentralized manufacturing facilities, tropical climates that accelerate bioburden proliferation, and historically fragmented regulatory frameworks (Ndomondo-Sigonda *et al.*, 2017). The heaviest burden of this quality deficit is felt in Sub-Saharan Africa, where substandard and contaminated antimalarial products contribute to an additional 116,000 malaria deaths annually (World Health Organization, 2017).

Specification of microbiological limits, often supplemented by preservatives, has become the standard domain to ensure the safety of liquid NSPPs throughout their shelf life under sealed conditions. However, a microbial quality evaluation of nonsterile dosage forms found that up to 50% were heavily contaminated (Mugoyela and Mwambete, 2010). Such independent post-market surveillance data continues to expose severe discrepancies between theoretical quality standards and shelf-ready pharmaceuticals.

This disposition places NSPPs when in active use, at high-quality risk, considering the critical regulatory blind spot that unsealing and repeated use of multidose products presents. The product active-use phase introduces a highly variable, unmonitored environment (Długaszewska *et al.*, 2015). The vulnerability of such unsealed products to repeated contamination through human activities and unhygienic environments is high.

This study seeks to evaluate the microbiological quality of paracetamol syrup (liquid NSPPs) and tablets (solid NSPPs) vis-à-vis the role of package design and product cost during post-unsealing active use. The study evaluates the isolated and interactive effects of packaging material, orifice diameter metrics, and temporal active-use windows on both Total Viable Aerobic Counts (TVAC) and systemic product cost structures.

MATERIALS AND METHODS

Materials

The study utilized 180 commercial 100 mL paracetamol syrup products across four different brands, alongside 10 bulk packages of paracetamol tablets (1 pack by 1,000 tablets) (solid NSPPs). All samples were sourced from the open market by hospital management and held under identical storage conditions within hospital general stores. Additional laboratory materials included nutrient agar powder (Sigma-Aldrich); 90 by 15 mm disposable sterile petri dishes (DSPD) (Eisco); *Staphylococcus aureus* (ATCC 6538) standard reference strain (Microbiologics); BioLogics sonicator 150VT; an IKA vortex mixer III; standard Pyrex laboratory glassware; and a BINDER incubator BD 23. All glassware and sample collection bottles were autoclaved prior to use.

Experimental Design

For the liquid format, a completely randomized 4 x 4 full factorial experimental design with replication was implemented. Two independent architectural variables were evaluated: product package material and geometric orifice diameter. This structure created four distinct configuration groups: group 1: Glass containers with a 1.8 cm orifice diameter; group 2, glass containers with a 2.4 cm orifice diameter; group 3, plastic containers with a 1.5 cm orifice diameter; group 4, plastic containers with a 2.8 cm orifice diameter.

Bacterial contamination was monitored longitudinally across four operational milestones: day 0, 2, 4, and 6. Measured dependent variables were the Total Viable Aerobic Count (TVAC), expressed in Colony-Forming Units per milliliter (CFU/mL), and the fixed container unit cost in USD. To ensure robust statistical power, $n=40$ independent replicates were prepared per factor combination, producing $n=640$ total microbial observations and $n=160$ cost evaluations.

The solid format study utilized a longitudinal, single-group time-series design tracking $n=10$ independent replicates, gathering $n=40$ total observations across the identical 6-day timeframe.

Sample Collection and Preparation Protocols

Using a single proportion sample size determination technique, 45 liquid containers per brand were procured. Because ten plastic units suffered microbiological compromise during pre-test holding, exactly 160 intact liquid packages advanced to the study (40 units per brand). Single-blind labels were applied to all containers to eliminate analytical bias. In-patient volunteers were recruited based on prescribed medication requirements and tracked over a minimum six-day hospital stay.

To replicate real-world consumer handling, hospital dispensary personnel unsealed the bulk tablet containers on Day 0, while

nursing staff administered the liquid syrups to the volunteers. On days 0, 2, 4, and 6, operators wearing personal protective equipment extracted 10 mL liquid samples via sterile syringes and harvested 10 random tablets using a flame-sterilized spatula. Samples were transferred aseptically and stored at 4°C.

Test samples were prepared in triplicate using the following homogenization sequences:

Liquid NSPP

10 mL of sample was mixed with distilled water by vortex at 500 RPM for 1 min. This was diluted to a total volume of 100 mL and sonicated at 500 RPM for 5 min.

Solid NSPP Tablets

Ten tablets were weighed on an electronic balance (Model WT-G) to determine the average unit weight. The tablets were allowed to disintegrate in distilled water for 5 min, shaken, diluted to a 100 mL solution, and sonicated for 2 min to dislodge embedded microbial cells.

Culture Media, Inoculation, and Incubation

Culture media was prepared according to standard procedures by suspending 23 g of nutrient agar powder in 1,000 mL of distilled water. The mixture was heated on a water bath with intermittent agitation, boiled for 1 min, and autoclaved at 121°C for 15 min under 15 psi of pressure. The molten medium was cooled to roughly 45°C under a laminar airflow hood.

Plating was executed at the Natural Chemotherapeutic Research Institute in Kampala using a standard pour plate technique (Baird *et al.*, 2000; USP, 2007). Under flame-aseptic conditions, a sterile pipette introduced 1 mL of processed sample solution into a petri dish, followed by 25 mL of molten agar. The plates were allowed 30 to 40 min to solidify. Negative controls, Medium Sterility Tests (MST), and Growth Promotion Tests (GPT) inoculated with *S. aureus* were conducted to verify sterility and viability. Inverted plate sets were incubated at 35°C for exactly 48 hr.

Microbial Counting

Visual growth assessments were completed at 12-hr intervals throughout the 48-hr incubation window. Final colony counting using the colony counter against a dark background followed regulatory procedures (Baird *et al.*, 2000; USP, 2007). Experimental sets that displayed background growth in the MST baseline were discarded. Final quantitative values were calculated using the standard compendial equation:

$$\text{CFU/mL} = \frac{\text{number of colonies (CFU)}}{\text{Volume plated (mL) x Dilution Factor}}$$

Quality Control and Ethical Clearance

Ethical clearance for the study was obtained from the IRE-committee of Mbarara University of Science and Technology

(Reference number DOS-11/16). Consent was administered with full interpretation in English and Runyankore languages to each volunteer at Mbarara Regional Hospital. Inclusion criteria for the liquid NSPP required volunteers to be in-patients with valid prescribed medications which must be administered while patient is within the hospital and under the supervision of a nursing staff; volunteer and product must be within the hospital setting for a minimum of six (6) days; and shelf life of product must be valid as referenced by manufacturer's expiration date.

Statistical Analysis

Data values are presented as mean±Standard Deviation (SD) with a significance threshold set a priori at $\alpha \leq 0.05$. Main and interactive effects for the liquid formats were isolated via a two-way Analysis of Variance (ANOVA). Pairwise simple main effects of orifice dimensions at day 6 were isolated via independent-samples t-tests with a Bonferroni adjustment. A nested ANOVA variance partitioning model evaluated packaging cost contributions. Linear dependencies were mapped using Pearson correlation coefficients (*r*). Computations were executed in a Python 3.10 runtime environment using SciPy, Statsmodels, and Matplotlib.

RESULTS

Liquid NSPPs

Primary Factorial Analysis: Experimental Group and Storage Time

A Two-Way ANOVA with replication was executed using a fully crossed design (4 experimental configurations×4 time points) with a sample size of $n=40$ replicates per cell, totalling $n=640$ observations. The dependent variable was the total viable aerobic count (CFU/mL). The statistical threshold for significance was set a priori at $\alpha \leq 0.05$. The primary ANOVA revealed highly significant main effects for both the experimental group composition ($F=34.86$, $p<0.001$) and active use time ($F=288.77$, $p<0.001$). Crucially, the interaction effect between experimental group and active use time was also highly significant ($F=8.19$, $p<0.001$) (Figure 1).

Isolated Substrate Analysis: Pooled Material Dynamics

In a secondary 2×4 ANOVA evaluating material (glass vs. plastic) and active use time, the main effect of material type was highly significant ($F=56.93$, $p<0.001$), with glass configurations maintaining a lower overall bacterial load. The material against active use time interaction profile was also significant ($F=7.31$, $p=0.001$), capturing a clear divergence between the material vs. contamination curves during the later stages of product exposure (Figure 2).

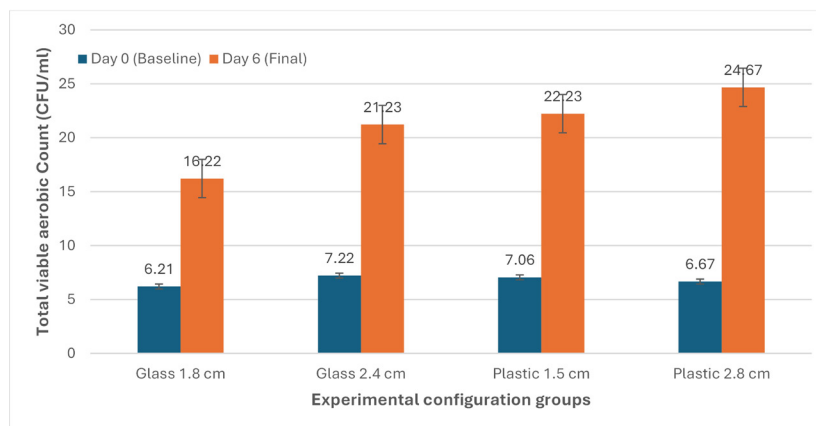


Figure 1: Interaction effect in the liquid NSPPs study between experimental groups and contamination by total aerobic count on active use day 0 and 6.

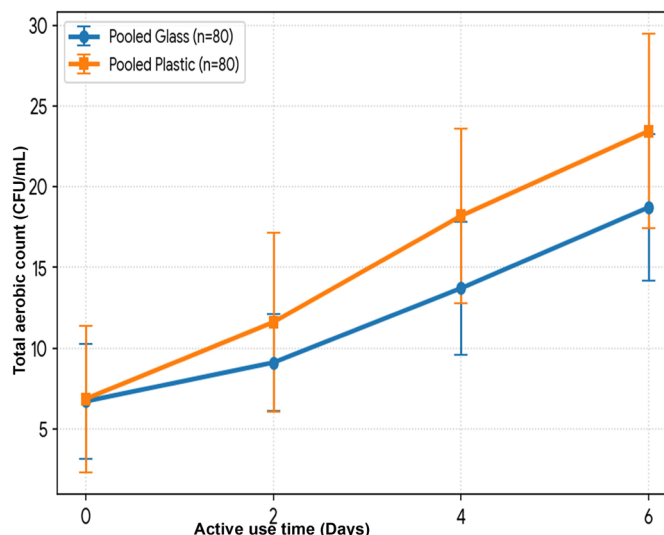


Figure 2: Material substrates (glass vs. plastic) pooled performance as barrier in a secondary 2×4 analysis of contamination by total aerobic count against active use time (Day 0 to 6).

Pairwise Orifice Effects at Day 6 Milestone

Within glass substrates, increasing the aperture from 1.8 cm (Group 1: $M=16.22 \pm 5.00$ CFU/mL) to 2.4 cm (Group 2: $M=21.23 \pm 4.00$ CFU/mL) caused a significant jump in aerobic counts ($p < 0.001$). Within plastic substrates, increasing the aperture from 1.5 cm (Group 3: $M=22.23 \pm 6.00$ CFU/mL) to 2.8 cm (Group 4: $M=24.67 \pm 6.00$ CFU/mL) also caused a statistically significant increase in contamination ($p=0.042$) (Figure 3).

Financial Cost Structures and Variance Partitioning

Day 0 baseline alignment by Pearson correlation testing in Figure 4 showed no significant linear relationship between packaging cost and initial baseline contamination ($r=-0.11$, $p=0.066$), indicating that initial microbial counts are independent of product cost.

In Figure 5, a Day 6 final alignment indicated a highly significant negative (A) and positive (B) correlation between packaging cost and final aerobic count ($r=-0.703$, $p < 0.001$). This confirms that capital investment in packaging directly explains 49.4% ($R^2=0.494$) of the variance in final shelf-life preservation success.

In Figure 6, group 4 increases unit costs by \$0.82 USD compared to group 3 yet exhibited more overall microbial contamination (24.67 CFU/mL). This demonstrates that increasing expenditure without considering geometric constraints can lead to poor outcomes in both cost and product safety.

Solid NSPPs

Figure 7 shows analytical model incorporated four discrete time intervals with ten replicates (n) per group for a total of

$n=40$ individual observations. The calculated linear model was governed by the regression equation $y=0.9349x+0.6108$, which revealed a significant positive linear trend ($F_{1,38}=72.28$, $p<0.0001$). The slope coefficient ($m=0.9349$) establishes that the aerobic population expanded at an average rate of 0.9349×10^2 CFU/mL per day during the study.

DISCUSSION

The performance of a container as a product package is primarily governed by two architectural metrics: the chemical composition of the substrate barrier and the physical dimensions of the dispensing closure or orifice (reference). Substrates such as borosilicate glass offer high hermeticity and excellent gas barrier properties, preventing the migration of volatile components and environmental contaminants (Robertson, 2012). However, glass packaging presents economic and logistical challenges, including higher procurement costs and increased shipping weights. Conversely, synthetic polymers like plastic offer lightweight, flexible, and cost-effective alternatives, but often present higher inferior structural defences over extended timelines (Siracusa, 2012). Furthermore, the physical orifice diameter represents a critical structural constraint. While wider dispensing apertures improve consumer utility and product flow dynamics, they exponentially expand the surface area vulnerable to environmental exposure, accelerating microbial entry. Finding an optimal balance between protective performance and financial

feasibility requires appropriate modelling sequenced to microbial containment during active use of product.

Primary Factorial Analysis for Liquid NSPPs

In this study, analysis with replication executed using a fully crossed design confirms that the velocity of aerobic microbial contamination across the 6-day tracking window is structurally dependent on the chosen packaging configuration (Figure 1).

To isolate the raw performance of the barrier substrate, the orifice dimensions were pooled to perform a secondary evaluation for material (glass vs. plastic) versus active use time. An independent-samples t -test applied at the final day 6 milestone confirmed that the pooled glass units ($M=18.73$, $SD=5.16$ CFU/mL, $n=80$) exhibited a significantly lower aerobic burden than pooled plastic units ($M=23.45$, $SD=6.09$ CFU/mL, $n=80$; $t=-5.30$).

Pairwise simple main effects testing on Day 6 isolated the exact impact of changing the orifice diameter within each material tier at the final Day 6 tracking window. Within glass and plastic substrates, increasing the aperture caused significant ($p\leq 0.05$) increase in microbial contamination (Figure 3).

Liquid NSPPs Financial Cost Structures and Parametric Correlation

Because package unit pricing operates as a fixed manufacturer's parameter within each configuration, within-group variance was zero. A nested variance partitioning model was used across the

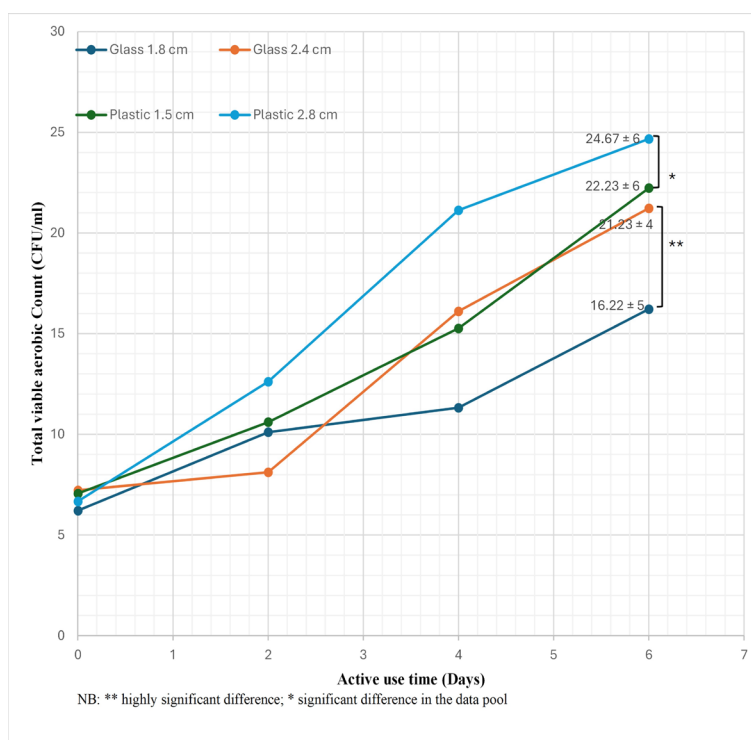


Figure 3: The liquid NSPPs cross design 4 x 4 (experimental configuration groups vs active use time) analysis of contamination by total aerobic count against active use time (Day 0 to 6).

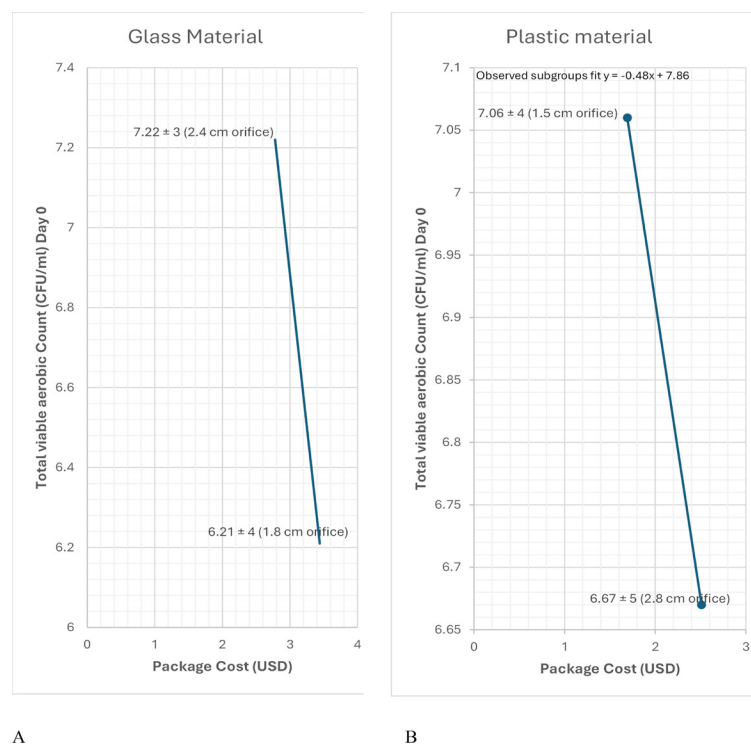


Figure 4: Multi-panel parametric linear mapping of the experimental configuration groups for day 0 baseline alignment of the liquid NSPPs cost against contamination by total aerobic count.

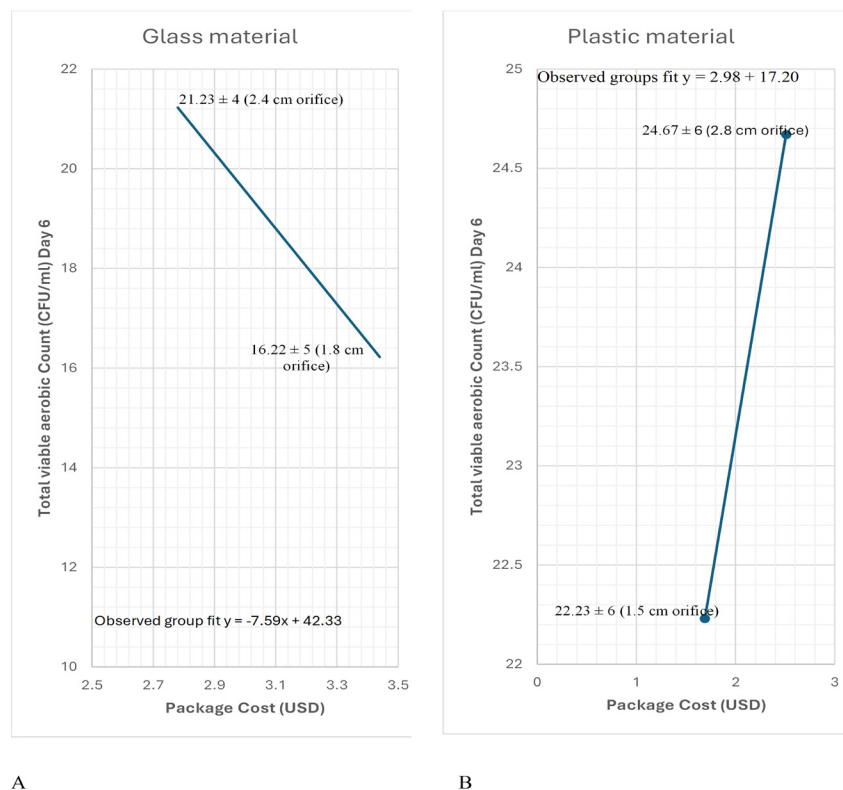


Figure 5: Multi-panel parametric linear mapping of the experimental configuration groups for day 6 alignment of the liquid NSPPs cost against contamination by total aerobic count.

160 units to quantify how cost in manufacturing decisions drives expenses. The baseline choice of raw package material substrate of the container (glass vs. plastic) emerged as the primary cost driver, explaining 64.81% (SS=40.80) of systemic financial variation ($t=17.06$, $p<0.001$). Modifying the orifice diameter acted as a secondary driver, accounting for the remaining 35.19% (SS=22.16) of cost variance in this study.

To determine whether product cost profiles can serve as a predictive proxy for microbial shelf-life outcomes, parametric linear mapping on Day 0 baseline alignment showed that initial product microbial counts are independent of product cost (Figure 4). However, day 6 final alignment showed a significant ($p\leq 0.05$) negative ($y=-7.59x+42.33$) and positive ($y=2.98x+17.20$) correlation between product cost and microbial contamination in Figure 5A and 5B respectively. This is a base for the justification of capital investment in packaging the product, as it substantially contributes to microbial quality of the product.

Liquid NSPP Operational Trade-offs: The Pareto Frontier

Package material

The empirical findings of this study demonstrated a clear, statistically significant ($\alpha=0.05$) relationship between physical package orifice, microbial containment on a long-term active use duration, and product cost constraints. The primary data analysis confirmed that microbial contamination over time is not uniform across package container configurations, as evidenced by the significant interaction effect ($p<0.001$) in Figure 3. This non-parallel development indicates that different packaging designs actively change the rate of microbial contamination rather than just shifting the baseline.

The package material substrate analysis shows that glass functions as a fundamentally superior hermetic barrier compared to

synthetic plastic polymers. This performance gap widens as active use progresses, likely because plastics are susceptible to micro-permeability and environmental gas transmission over time (Siracusa, 2012). Thus, plastic consistently trends higher in microbial contamination than glass packaged product. This overall shift suggests that the higher microbial presence in day 0, likely due to manufacturing process and storage; and perhaps on day 6, by the plastic package material, may not necessarily be due to their wider orifice diameter alone. It could have been enhanced by the plastic material's surface properties: microscopic porosity, chemical composition, or charge, that are more favourable to microbial adherence and survival. This visual distinction shows plastic to generally permit higher microbial contamination overall, regardless of the opening or orifice size.

Package orifice

Conversely, looking at material type alone oversimplifies the system. The main effects testing on Day 6 highlighted the critical role of geometric constraints, showing that larger orifice diameters significantly increase microbial exposure (Figure 1). Interestingly, the cost impact relatable to the orifice sizes was opposite for the two package materials. While the wider openings indicated reduced costs in glass, it correlates with increased costs in plastic material (Figure 6).

Analysis of package design showed impact on cost and contamination of the liquid NSPPs. The negative relationship between product cost and microbial contamination ($y=-0.48x+7.86$) in plastic packaging (Figure 4B), presents a different material-specific dynamic in Figure 4. Despite utilizing a wider opening, the higher-cost plastic packaged product option successfully maintained a lower initial microbial load ($M=6.67$) than its cheaper, narrower counterpart ($M=7.06$), apparently during storage. This contradiction implies that the added cost of

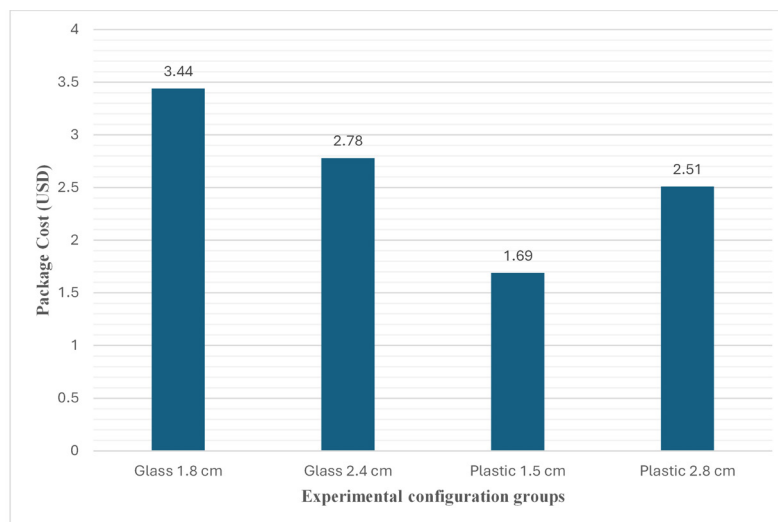


Figure 6: The main effects testing on Day 6 comparative cost analysis across experimental configuration groups of the liquid NSPPs.

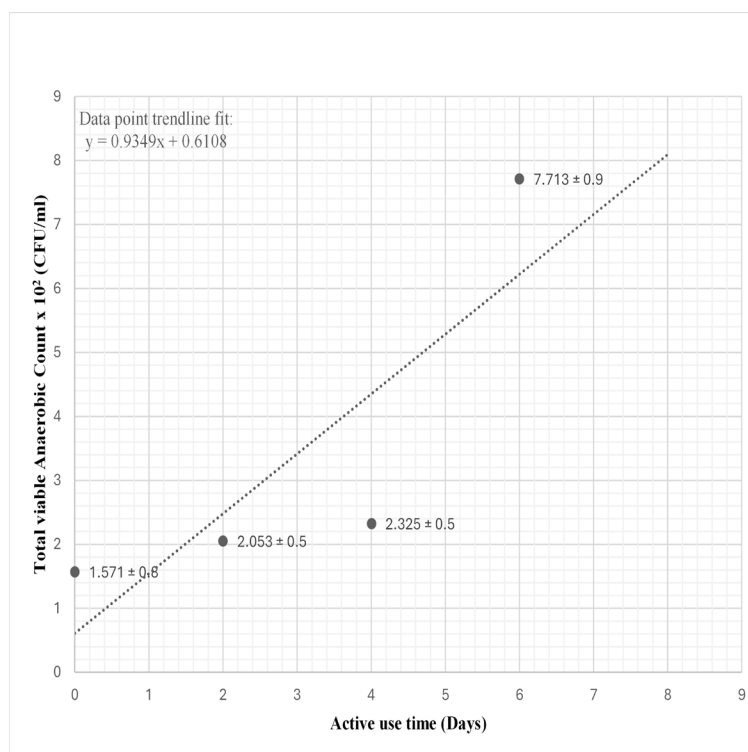


Figure 7: Relationship between active use time (Day 0 to 6) and contamination as total viable aerobic count (10^2 CFU/mL), using the Ordinary Least Squares (OLS) linear regression analysis in the solid NSPPs study.

the plastic container does not stem from geometric restriction, but perhaps from enhanced material quality which provided a more resilient barrier during storage. Premium polymers often incorporate advanced antimicrobial surface coatings, higher density resins that minimize microscopic structural porosity, or superior anti-static properties that prevent the electrostatic attraction of dust-borne microbes during flight or handling (Ebnesajjad, 2012).

The statistical findings demonstrate that package orifice diameter has a significant, positive linear relationship with microbial presence when analyzing packaging materials independently. These outcomes suggest that larger orifice diameters likely accelerate gas exchange or increase ambient exposure, thereby creating a more favourable environment for rapid microbial contamination over a 6-day period. Isolating the package substrates revealed that both glass and plastic package materials are highly sensitive to physical dimension changes.

In the pooled package material (glass vs. plastic) over time a steeper slope was observed in the glass packaging ($\beta=5.27$) compared to plastic ($\beta=3.97$) which indicates that microbial contamination in glass package containers may be more sensitive to changes in opening size (Figure 2). This is because glass is inherently an absolute barrier material thus, gas exchange is confined strictly to the package orifice aperture (Siracusa, 2012). Conversely, the overall higher baseline of microbial presence in plastic package

suggests that its surface properties might have independently promoted contamination, regardless of the orifice size. This is in consistence with previous report that showed that polymer-based films often exhibit minor background oxygen transmission rates directly through the walls (Caleb *et al.*, 2013). These results ultimately indicate that minimizing orifice dimensions is a critical design factor in reducing the propensity to violate microbiological quality, maintain product microbial integrity, and reduce product spoilage, while the choice of package material substrate acts as an important baseline modifier. As such, fixing product cost without considering the package material and geometric constraints for preservation, can lead to poor outcomes in product safety or quality.

Primary Analysis for Solid NSPPs

The relationship between exposure (active use) duration (Days) and contamination as total viable aerobic count (10^2 CFU/mL) was evaluated using Ordinary Least Squares (OLS) linear regression analysis (Figure 7). The model demonstrated a robust explanatory power, with an overall coefficient of determination (R^2) of 0.6554, indicating that active use duration accounts for 65.54% of the total variance observed within the individual replicate measurements. This confirms a statistically linear relationship between active use time and aerobic bacterial contamination of the product. However, the correlation trendline intercept $c=0.6108$, at Day 0 estimated at 0.6108×10^2 CFU/mL of

microbial count indicates that the model baseline profile remains within compendia limits and acceptable microbial quality for oral solid dosage forms (USP, 2024). This was also the case throughout the period of study for all the products.

A visual assessment of the regression plot demonstrates distinct contamination phases that deviate from strict linearity. Because of the sharp exponential acceleration between day 4 and 6, it may be prudent to consider ambient environment dynamics a substantive driver of the real-time contamination phases. However, the straight-line equation acts as a generalized summary rather than a perfect depiction of the extent this, or other dynamics might have affected product contamination in this study.

CONCLUSION

This study confirms packaging material and orifice diameter as cardinal for microbial preservation. Glass provides superior protection against bacteria but costs more. Orifice diameter is crucial for maintaining quality during active use, while time acts as a strong driver of contamination. Trade-offs by manufacturers in this regard, must balance safety, integrity, and supply chain costs. As such, Package designs must minimize product exposure to optimize quality. Furthermore, environmental challenge tests are vital for quality control. These tests highlight the need for necessary storage and handling label instructions peculiar to package types. Implementing policies in this perspective will improve long-term product quality.

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ABBREVIATIONS

ANOVA: Analysis of Variance; **CFU/mL:** Colony-Forming Units per Millilitre; **GPT:** Growth Promotion Test; **MST:** Medium Sterility Test; **NSPPs:** Nonsterile Pharmaceutical Products;

TVAC: Total Viable Aerobic Count; **USD:** United States Dollar; **USP:** United States Pharmacopeia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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