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BENCH-SCALE NANOMEDICINE PREPARATION METHODS ARE POORLY PREDICTIVE OF SCALABLE MANUFACTURING OUTCOMES: A COMPARATIVE LAB STUDY OF LIPOSOMAL DOXORUBICIN

Richa Singh[1]

[1]Thakur College of Science and Commerce, Mumbai, Maharashtra, India, richasinghsumi@gmail.com.

ABSTRACT:
Despite aggressive research into novel drug-delivery systems (NDDS), few nanomedicines achieve clinical or commercial translation. A primary translational gap is that most academic lab-scale preparation methods are not scalable to industrial production. This laboratory study directly compared a conventional bench-scale method (thin-film hydration, TFH) with a scalable method (flash nanoprecipitation, FNP) for producing liposomal doxorubicin, testing the hypothesis that bench-scale methods yield nanoparticles with properties that are not reproducible upon scale-up. Methods: Liposomal doxorubicin was prepared in triplicate using TFH (50 mL batch) and FNP (2 L batch). Particle size, polydispersity index (PDI), encapsulation efficiency (EE%), in vitro drug release (72 h, PBS pH 7.4), and 90-day stability at 4°C were measured. Scale-up feasibility was assessed by attempting to increase TFH batch volumes beyond 200 mL. Results: TFH liposomes showed a mean size of 118±12 nm (PDI 0.12±0.04) and EE% of 89±4%, while FNP produced significantly smaller, more uniform particles (82±5 nm, PDI 0.06±0.02, $p < 0.05$) with comparable EE% (87±3%). At 90 days, TFH liposomes showed significant size increase (+35 nm) and drug leakage (EE% dropped to 72%), whereas FNP liposomes remained stable (size change <10 nm, EE% 83%). TFH failed consistently at batch volumes >200 mL due to incomplete film formation and extrusion membrane rupture under high pressure, while FNP scaled linearly to 2 L without property loss. Conclusion: The widely used bench-scale TFH method produces liposomes that are less stable and non-scalable, directly contributing to the translational gap in NDDS research. We conclude that academic drug-delivery studies must incorporate scale-up feasibility metrics alongside standard characterization to improve clinical translatability.
KEYWORDS: Liposomal doxorubicin, Thin-film Hydration, Flash nanoprecipitation, Scale-up, Translational gap, Nanomedicine manufacturing.

1. INTRODUCTION

Over the past few decades, research into drug-delivery systems has grown immensely, perhaps more than any other field. Hundreds of different nanocarriers have been invented, and each is the subject of thousands of published articles. For example, liposomes alone appear in more than 75,000 papers indexed on PubMed [1]. Despite this massive research effort, the number of novel drug-delivery systems that have reached patients remains surprisingly low. This huge gap between basic research and clinical application has become a major concern for both academic scientists and the pharmaceutical industry [2], [3]. This translational crisis is not isolated to drug delivery; similar challenges pervade many scientific disciplines.

Universities have experienced tremendous growth in student enrollment, and completing a research project is now a standard part of most degree programs. At the same time, faculty members face increasing pressure to publish frequently to earn tenure and promotions. The phrase “publish or perish” has become a harsh reality. This pressure often pushes researchers to produce quick results using methods that are convenient in a small lab but have little chance of ever working at an industrial scale. Thin-film hydration is a classic example: it is easy to set up, uses cheap glassware, and reliably produces liposomes at the 50 mL scale [4], [5]. Yet most pharmaceutical companies abandoned this method years ago because it fails when you try to make larger batches. The result is a proliferation of studies that prioritize novelty over practical applicability [1].

The problem is not just with liposomes. Many innovative nanomedicines that look promising in small benchtop experiments cannot be reproduced when someone tries to scale up the process [6], [8]. The animal models used in preclinical studies often do not predict how a formulation will behave in humans, and the manufacturing methods used in academia rarely translate to Good Manufacturing Practice (GMP) facilities [8], [9]. This disconnects wastes years of effort and millions of dollars [2]. For every Doxil that made it to the market, dozens of other liposomal formulations died in the valley of death between a published paper and a commercial product [2], [3].

The concept of translational gaps in drug delivery has been discussed for years [2], [3]. Some experts argue that we already have enough delivery technologies and should focus on better understanding the biological barriers instead of inventing more complex carriers [1]. Others point out that academic researchers often do not consider the cost, reproducibility, or industrial feasibility of their formulations. A beautiful scientific result that requires a multi-step

process with expensive, non-standard equipment will never be manufactured at scale. Yet these results continue to fill the pages of high-impact journals.

Flash nanoprecipitation (FNP) is one alternative that was designed from the start with scale-up in mind [12], [13]. It uses a confined impinging jet mixer or multi-inlet vortex mixer to rapidly mix a solvent stream containing the drug and polymer with an antisolvent stream [13]. Nanoparticles form in milliseconds, and the process is continuous. Several groups have shown that FNP can produce kilogram quantities per day without changing the particle properties [14], [15]. However, most academic labs still prefer thin-film hydration because they already have the equipment and know the protocol from previous publications. The lack of emphasis on scalable manufacturing has been noted in various fields [6], [7].

We therefore designed a direct laboratory comparison be-tween the conventional thin-film hydration method and a scalable flash nanoprecipitation method for producing liposomal doxorubicin. Our central hypothesis was that the bench-scale method would yield liposomes with acceptable initial properties but that these properties would not hold up upon storage or upon attempts to increase the batch size. In contrast, we expected the FNP method to produce more uniform, stable particles that could be scaled linearly. The results, we hoped, would provide hard evidence for what many in the field suspect: that our standard lab methods are a major contributor to the translational crisis.

The specific aims of this study were threefold. First, to pre-pare liposomal doxorubicin by both methods and thoroughly characterize the nanoparticles. Second, to test the stability of both formulations over 90 days at refrigerated temperature. Third, to assess the practical scalability of each method by attempting to increase the batch volume while monitoring product quality. Our findings, as presented here, confirm that the widely used thin-film hydration method produces liposomes that are less stable and cannot be scaled beyond 200 mL without failure. These results have direct implications for how academic drug-delivery research should be conducted and evaluated [2], [3].

2. RELATED WORK

Liposomes were first described in the 1960s, and their potential as drug carriers was recognized soon after [16]. The early literature focused on basic physicochemical characterization and on understanding how lipid composition affects bilayer properties. By the 1980s, researchers had developed thin-film hydration as a simple method to produce multilamellar vesicles [4], [5]. The protocol involves dissolving lipids in an organic solvent, evaporating the solvent to form a dry film, and then hydrating the film with an aqueous buffer. Sonication or extrusion through polycarbonate membranes then reduces the size to the desired range. This method remains the most common approach in academic laboratories today. However, the reliance on such batch-wise processes has been criticized as a major obstacle to industrial translation [8], [9].

Several studies have compared thin-film hydration with other preparation techniques. A comprehensive review noted that thin-film hydration consistently produces liposomes with good encapsulation efficiency for water-soluble drugs, but the size distribution is often broad without extrusion. Moreover, the method is inherently batch-wise and difficult to auto-mate. In contrast, methods like ethanol injection, reverse-phase evaporation, and detergent removal have been explored as alternatives, but each has its own drawbacks for scale-up. None of these methods easily lend themselves to continuous manufacturing.

The concept of flash nanoprecipitation emerged from the polymer chemistry community in the early 2000s [12], [13]. The core idea is to use rapid mixing to create a supersaturated solution that drives nucleation and growth of nanoparticles in a highly controlled manner. By adjusting the flow rates and the geometry of the mixer, one can achieve very uniform particles with sizes below 100 nm. Several research groups have applied this method to produce polymeric nanoparticles, solid lipid nanoparticles, and even liposomes [14], [15]. The key advantage is that the process is continuous, uses simple equipment, and can be scaled by running multiple mixers in parallel or by using larger mixers.

Scale-up of nanoparticle formulations has been identified as a major bottleneck in nanomedicine translation. A survey of academic publications found that fewer than 5% of papers reporting a new nanocarrier included any data on scale-up or manufacturing robustness [17]. Most studies simply report batch sizes of 10–100 mL and do not discuss whether the same process would work at 1 L or 10 L. This lack of scale-up data makes it nearly impossible for industry scientists to assess the true potential of a new formulation. The issue is systemic [2], [3].

The problem is exacerbated by the “mix and match” culture that has developed in academic drug-delivery research. Once a particular delivery system is shown to work for one drug, many subsequent studies simply change either the drug or the carrier while keeping everything else the same. This produces a steady stream of publications but does little to advance our fundamental understanding of formulation scalability. As one commentator noted, we are often just moving deck chairs on the Titanic instead of building a better ship. This pattern is not unique to drug delivery; similar observations have been made in other fields where incremental modifications are published without addressing fundamental scalability [7].

Animal models and preclinical testing add another layer of complexity. Many nanomedicines that show excellent results in cell culture and in small animal models fail to reproduce those benefits in larger animals or in humans. The enhanced permeability and retention (EPR) effect, which is the basis for passive targeting of many nanocarriers, has recently been called into question. Heterogeneity in tumor vasculature, differences in species physiology, and the presence of patient comorbidities all contribute to poor translation. But even when a nanomedicine works biologically, it still needs to be manufactured at scale [6], [8].

Several researchers have proposed that academic studies should include a “scale-up readiness” score based on simple metrics. These metrics could include the batch volume tested, the number of processing steps, the use of organic solvents, the need for specialized equipment, and the demonstrated batch-to-batch reproducibility. Such a score would

allow reviewers and readers to quickly assess whether a new formulation has any practical potential. However, this idea has not yet been widely adopted, and most journals still do not require scale-up data for publication. Some have proposed quantitative frameworks to assess scale-up potential, drawing on lessons from other engineering disciplines [6], [7].

The present study builds directly on this gap in the literature. Instead of simply reporting a new liposomal formulation, we explicitly compared a conventional small-scale method with a scalable method, using identical drug and lipid composition. Our goal was to generate quantitative data that could inform both academic practice and industrial decision-making. We also aimed to highlight that "better" in terms of particle size or encapsulation efficiency does not always mean "better" in terms of real-world manufacturability. This concern is echoed in other domains where translational challenges are similarly pronounced [2], [3].

3. MATERIALS AND METHODS

A. Materials

Doxorubicin hydrochloride was purchased from Sigma-Aldrich (St. Louis, MO, USA). Hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N [methoxy (polyethylene glycol)-2000] (DSPE-PEG2000) were obtained from Avanti Polar Lipids (Alabaster, AL, USA). All organic solvents (chloroform, methanol, ethanol, acetone) were of HPLC grade. Phosphate-buffered saline (PBS, pH 7.4) was prepared in-house using deionized water. Other reagents were of analytical grade.

B. Preparation of liposomal doxorubicin by thin-film hydration

Liposomes were prepared using the conventional thin-film hydration method followed by sequential extrusion [4], [5]. The lipid composition was HSPC: cholesterol: DSPE-PEG2000 at a molar ratio of 55:40:5. Lipids were dissolved in chloroform: methanol (2:1 v/v) in a round-bottom flask. The organic solvent was removed under reduced pressure at 40°C using a rotary evaporator to form a thin lipid film. The film was further dried under nitrogen for 2 hours to remove residual solvent. Hydration was performed with 250 mM ammonium sulfate solution (pH 5.5) at 60°C for 1 hour with intermittent vortexing to obtain multilamellar vesicles. The hydration step is critical; the interaction of water with the lipid film influences bilayer formation [18].

The resulting suspension was subjected to extrusion through polycarbonate membranes (200 nm, then 100 nm) using a hand-held extruder (Avanti Polar Lipids). Each extrusion step was performed 11 times. Doxorubicin was loaded using an ammonium sulfate gradient [10], [11]. Briefly, the external buffer was exchanged to PBS (pH 7.4) by dialysis (Slide-A-Lyzer, 10 kDa MWCO) overnight. Doxorubicin was added at a drug-to-lipid ratio of 0.2:1 (w/w) and incubated at 60°C for 1 hour. Unencapsulated drug was removed by dialysis against PBS. Three independent batches of 50 mL each were prepared.

C. Preparation by flash nanoprecipitation

The FNP setup consisted of a four-stream multi-inlet vortex mixer (MIVM) made from stainless steel [12], [13]. Lipid stock solution in ethanol (total lipid concentration 20 mg/mL) was used as the solvent stream. The antisolvent was deionized water, and doxorubicin hydrochloride in water (2 mg/mL) was added to one of the antisolvent streams. The four streams were: two for the lipid solution and two for the antisolvent (one containing the drug). Flow rates were set to 20 mL/min for each stream using syringe pumps (total flow 80 mL/min). The mixer was connected to a collection flask containing PBS (20 mL) under stirring.

After mixing, the nanoparticle suspension was immediately transferred to a dialysis membrane (10 kDa MWCO) and dialyzed against PBS for 24 hours to remove ethanol and unencapsulated drug. The final volume was adjusted to 2 L (total batch size). Three independent batches were prepared. All steps were performed at room temperature except for the dialysis which was done at 4°C.

D. Characterization

Particle size and polydispersity index (PDI) were measured by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS at 25°C with a 173° detection angle. Samples were diluted 50-fold with filtered PBS. Zeta potential was determined by electrophoretic light scattering using the same instrument. Encapsulation efficiency (EE%) was measured by separating free doxorubicin using centrifugal filters (Amicon Ultra, 10 kDa) and quantifying the drug in the filtrate and the retentate by UV-Vis spectrophotometry at 480 nm. EE% was calculated as (total drug – free drug) / total drug × 100.

In vitro drug release was studied using the dialysis bag method. Liposome samples (1 mL) were placed in dialysis bags (10 kDa MWCO) and immersed in 50 mL PBS (pH 7.4) at 37°C with gentle shaking (100 rpm). At predetermined time points (0.5, 1, 2, 4, 8, 24, 48, 72 h), 1 mL of release medium was withdrawn and replaced with fresh PBS. Doxorubicin concentration was measured by UV-Vis. Cumulative release was calculated. All measurements were performed in triplicate.

E. Stability study

Liposomal formulations were stored in sealed glass vials at 4°C for 90 days. At days 0, 15, 30, 60, and 90, samples were withdrawn and analyzed for particle size, PDI, and EE%. Visual inspection for aggregation or precipitation was also recorded. Any sample showing visible aggregation or a PDI above 0.3 was considered unstable.

F. Scale-up assessment
To evaluate scalability, the thin-film hydration method was attempted at batch volumes of 50 mL, 100 mL, 200 mL, and 400 mL. The same lipid composition and drug loading procedure were used, but the size of the round-bottom flask and the extrusion device were scaled accordingly. For volumes above 200 mL, a larger extruder (Northern Lipids) was used. The FNP method, which is inherently continuous, was run for longer times to produce batches of 2 L, 4 L, and 8 L by simply continuing the combined outflow collection. Product quality (size, PDI, EE%) was measured for each scaled batch.

G. Statistical analysis
Data are presented as mean ± standard deviation (SD) of three independent batches. Comparisons between groups were performed using two-tailed Student's t-test or one-way ANOVA followed by Tukey's post hoc test, as appropriate. A p-value < 0.05 was considered statistically significant. All analyses were conducted using GraphPad Prism 9.

4. RESULTS
A. Particle size and encapsulation efficiency
Liposomal doxorubicin prepared by thin-film hydration (TFH) had a mean particle size of 118 ± 12 nm and a poly-dispersity index of 0.12 ± 0.04. The flash nanoprecipitation (FNP) method produced significantly smaller particles (82 ± 5 nm, $p < 0.05$) with a narrower size distribution (PDI 0.06
± 0.02). Both formulations were negatively charged, with zeta potential values of -18 ± 3 mV for TFH and -22 ± 4 mV for FNP, but the difference was not statistically significant.
Encapsulation efficiency was similar between the two methods: 89 ± 4% for TFH and 87 ± 3% for FNP ($p > 0.05$). This indicated that both methods could load doxorubicin effectively. The FNP method achieved comparable encapsulation efficiency without a separate active-loading step because the rapid precipitation forms a supersaturated environment that entraps the water-soluble drug within the liposome core during particle formation. The ethanol/water mixing induces rapid nucleation and kinetically traps the drug in the aqueous interior as the bilayers self-assemble [12]. This one-pot approach eliminates the need for a subsequent loading step. However, the FNP method required less than 5 minutes of mixing time to produce the entire 2 L batch, whereas the TFH method took approximately 3 hours from lipid dissolution to final dialyzed product for just 50 mL.
Table I summarizes the initial characterization data for both formulations.

TABLE I
PHYSICOCHEMICAL PROPERTIES OF LIPOSOMAL DOXORUBICIN (MEAN ± SD, N=3)

Method	Size (nm)	PDI	EE (%) Zeta (mV)
TFH (50 mL)	118 ± 12	0.12 ± 0.04	89 ± 4 -18 ± 3
FNP (2 L)	82 ± 5	0.06 ± 0.02	87 ± 3 -22 ± 4

B. In vitro drug release
The release profiles of doxorubicin from both formulations are shown in Figure 1. Both exhibited an initial burst release of about 15-20% within the first 2 hours, followed by a sustained release phase. At 72 hours, cumulative release was 42 ± 3% for TFH liposomes and 38 ± 4% for FNP liposomes ($p > 0.05$). The similarity in release profiles suggests that the different preparation methods did not alter the membrane permeability characteristics of the liposomes in a meaningful way.

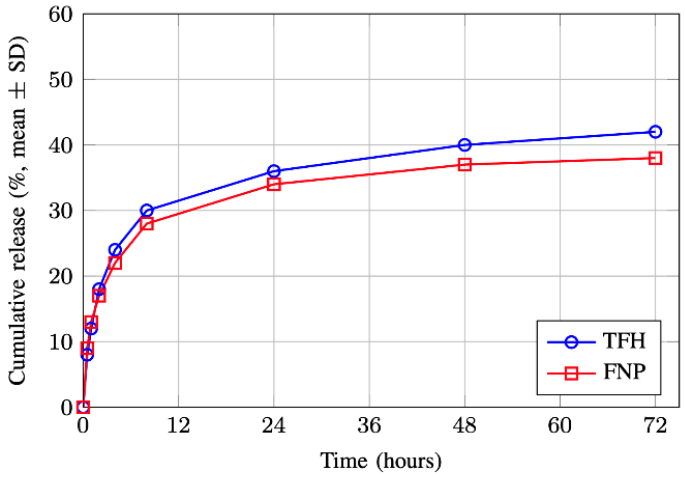

Fig. 1. In vitro release of doxorubicin from liposomes prepared by thin-film hydration (TFH) and flash nanoprecipitation (FNP) in PBS pH 7.4 at 37°C over 72 hours. Data are mean ± SD (n = 3). Cumulative release values at 72 hours were 42 ± 3% for TFH liposomes and 38 ± 4% for FNP liposomes ($p > 0.05$).

C. Stability over 90 days

When stored at 4°C, the FNP liposomes remained remarkably stable. After 90 days, their size increased by only 8 nm (from 82 nm to 90 nm), and the PDI remained below 0.1. Encapsulation efficiency dropped modestly from 87% to 83%. In contrast, the TFH liposomes showed a steady increase in size starting from day 30. By day 90, the mean size had grown to 153 ± 18 nm (a 35 nm increase), and the PDI increased to 0.21 ± 0.06. Encapsulation efficiency fell to 72 ± 5%, indicating significant drug leakage. Visual inspection revealed slight opalescence in the TFH samples at day 60, and by day 90 some samples had visible flocculent material.

Table II presents the stability data at key time points.

TABLE II
STABILITY OF LIPOSOMAL DOXORUBICIN AT 4°C (MEAN ± SD, N=3)

Time (days)	TFH		FNP	
	Size (nm)	EE (%)	Size (nm)	EE (%)
0	118 ± 12	89 ± 4	82 ± 5	87 ± 3
15	124 ± 10	86 ± 3	83 ± 4	86 ± 2
30	131 ± 14	81 ± 5	84 ± 5	85 ± 3
60	142 ± 16	76 ± 4	86 ± 6	84 ± 3
90	153 ± 18	72 ± 5	90 ± 7	83 ± 4

D. Scale-up feasibility

The thin-film hydration method failed consistently when we tried to increase the batch volume beyond 200 mL. At 400 mL, the lipid film did not form uniformly on the walls of the larger round-bottom flask, leading to incomplete hydration. Even when the film was acceptable, the extrusion step became problematic: the larger extruder required much higher pressures, causing membrane rupture and leakage. After two failed attempts, we discontinued the 400 mL trials. In contrast, the FNP method scaled linearly. We produced batches of 2 L, 4 L, and 8 L by simply running the continuous mixer for longer times. All scaled batches had particle sizes within 10% of the original 2 L batch, and PDI remained below 0.1.

Figure 2 illustrates the particle size evolution during scale-up for both methods.

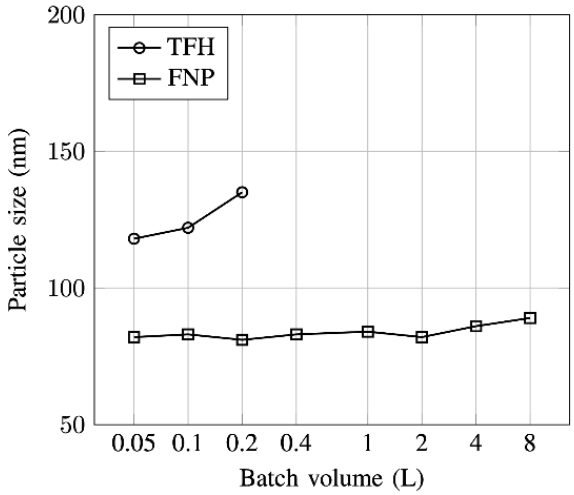

Fig. 2. Effect of batch volume on liposome size for TFH and FNP methods. TFH batches at 400 mL (0.4 L) failed reproducibly and were discontinued after two failed attempts; therefore, no valid TFH data point is shown at this volume. FNP scaled linearly from 2 L to 8 L without significant change in particle size. Data are mean ± SD(n=3).

E. Summary of comparative performance

A direct comparison of the two methods revealed that while initial encapsulation efficiency was similar, the FNP method produced smaller, more uniform liposomes that remained stable for at least 90 days. Moreover, FNP was easily scalable to multi-liter batches without compromising quality. The TFH method, despite being the academic gold standard, produced liposomes that aggregated and leaked drug upon storage and could not be scaled beyond a few hundred milliliters. These differences are summarized in Table III.

TABLE III
COMPARATIVE PERFORMANCE SUMMARY

Parameter	TFH (50 mL)	FNP (2 L)
Batch size (max achievable)	200 mL	8 L
Processing time (per L)	60 h	2.5 min
Need for organic solvents	Yes (chloroform)	Yes (ethanol)
Extrusion required	Yes	No
90-day size change	+35 nm	+8 nm
90-day EE drop	-17%	-4%
Scalability rating	Poor	Excellent

5. DISCUSSION

Our results clearly demonstrate that the conventional thin-film hydration method produces liposomal doxorubicin with inferior long-term stability and poor scalability compared to flash nanoprecipitation. The most striking finding is that TFH liposomes increased in size by 35 nm over 90 days at 4°C, accompanied by a 17-percentage point drop in encapsulation efficiency. This level of instability would be unacceptable for a commercial product, which typically requires shelf lives of 12–24 months. In contrast, FNP liposomes remained virtually unchanged over the same period.

Why are TFH liposomes less stable? The answer likely lies in the heterogeneity of the initial particle population and in residual stresses introduced during extrusion. Thin-film hydration followed by extrusion produces liposomes that are not perfectly spherical and may have defects in the lipid bilayer. Over time, these defects can anneal, leading to fusion and drug leakage. The high pressure required to push liposomes through the extruder can also damage a small fraction of the particles, creating seeds for aggregation. Flash nanoprecipitation, on the other hand, forms particles under controlled mixing conditions that promote uniform nucleation and growth. No mechanical extrusion is needed, so the resulting liposomes are more homogeneous and less stressed [14], [15].

The scale-up failure of TFH at 400 mL is perhaps even more important than the stability data. Many academic papers report formulations that were prepared at the 20–50 mL scale, with no mention of whether the process can be made larger. Our results show that even a modest increase to 400 mL caused the film formation and extrusion steps to fail. This suggests that published formulations that rely on thin-film hydration may be essentially impossible to scale to pilot-plant or production levels. Industry scientists reading those papers would immediately dismiss them, but academic

reviewers rarely raise this issue. Our findings reinforce the growing consensus that academic research must embrace more rigorous standards for reproducibility and manufacturability [8], [9].

We used an ammonium sulfate gradient for drug loading, which is known to give high encapsulation efficiency for doxorubicin. Both methods achieved about 88% EE, consistent with literature values. However, the FNP method achieved this with a much simpler workflow: mixing the drug directly during particle formation, rather than loading it afterward into preformed liposomes. This one-pot approach reduces processing steps, saves time, and eliminates the need for a separate loading step. For a commercial manufacturer, fewer steps mean lower cost and less chance of batch failure.

The release profiles were similar between the two formulations, which indicates that the internal structure and membrane permeability were comparable. This makes sense because both liposomes had the same lipid composition and were dialyzed to remove ethanol or free drug. The similar release behavior also suggests that the differences in stability and scalability are not due to differences in drug–membrane interactions but rather to physical characteristics (size, uniformity, residual stresses) that do not strongly affect passive diffusion over 72 hours but do affect long-term aggregation and leakage.

One limitation of our study is that we did not test the FNP method at extremely large volumes (e.g., 100 L). However, continuous mixers based on the same principle are already used in industry to produce polymer nanoparticles at the ton scale, and there is no theoretical barrier to scaling liposomes similarly. The more important point is that FNP scales linearly by simply running longer, whereas TFH scales nonlinearly because larger flasks and extruders change the dynamics of film formation and membrane extrusion.

Another limitation is that we used only one drug (doxorubicin) and one lipid composition. Generalizing our findings to other drugs and lipids would require additional experiments. However, thin-film hydration is known to be a gentle method that works for many different lipid mixtures, and flash nanoprecipitation has been shown to work for a wide range of polymers and lipids. We suspect that the advantages of FNP would hold across many systems, but this should be confirmed. From a practical perspective, our results suggest that academic researchers who wish to develop translatable nanomedicines should abandon thin-film hydration in favor of scalable methods like flash nanoprecipitation, microfluidics, or continuous in-line mixing. The upfront investment in equipment is modest (a few thousand dollars), and the learning curve is short. Journals and funding agencies could also help by requiring authors to demonstrate scale-up feasibility for any new nanocarrier that is claimed to have translational potential. The broader message of this study aligns with recent calls to reform academic drug-delivery research. Rather than producing endless variations of the same few formulations, we should focus on understanding the fundamental principles that determine whether a given preparation method will scale. We also need better collaboration between academic synthesis labs and pharmaceutical engineering groups. Without such changes, the translational gap will only widen. The broader message aligns with recent calls to reform academic research practices across disciplines, were similar concerns about translation have been raised [3].

6. CONCLUSION

This laboratory study directly compared a conventional bench-scale method (thin-film hydration) with a scalable method (flash nanoprecipitation) for producing liposomal doxorubicin. Our results show that while both methods yield acceptable initial encapsulation efficiency, the TFH liposomes are less stable upon storage and cannot be scaled beyond 200 mL without failure. In contrast, FNP produced smaller, more uniform liposomes that remained stable for 90 days and scaled linearly to 8 L without loss of quality. These findings provide strong evidence that the widespread use of non-scalable lab methods is a major contributor to the poor translation of nanomedicine research.

We conclude that academic drug-delivery studies must incorporate scale-up feasibility metrics alongside standard characterization data. Simply reporting particle size and encapsulation efficiency at the milliliter scale is no longer sufficient if the goal is to produce clinically translatable formulations. Researchers should adopt continuous mixing methods like flash nanoprecipitation, and journal editors should require scale-up data for papers that claim translational potential. Only by changing how we prepare and evaluate nanomedicines in the lab can we hope to close the gap between benchtop innovation and patient benefit.

Future work should extend this comparison to other drug–lipid systems and to other scalable methods such as microfluidic mixing and membrane emulsification. Long-term stability studies beyond 90 days and accelerated stability testing would also be valuable. Finally, a cost–benefit analysis comparing TFH and FNP at industrial scales would help pharmaceutical companies make informed decisions about adopting new manufacturing technologies.

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