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# Entrapment of Ibuprofen by Multilamellar Liposomes for Aerosol Drug Delivery Towards Sustained Release Upon Pulmonary Administration

**Ange Imanishimwe, Adam Taylor, Manal Almalki, and Edward P.C. Lai***

## Abstract

**Purpose:** Ibuprofen, a drug commonly used for treatment of inflammation and pain, has a short half-life which requires that the patient takes multiple doses a day to see a lasting effect in the cardiovascular system. Multilamellar liposomes (MLLs) have previously been shown to be effective nanocarriers in prolonging the administration cycle of similar drugs. The aim of this research is to entrap ibuprofen in MLLs and to evaluate these ibuprofen-loaded MLLs for sustained drug release during pulmonary delivery.

**Methods:** MLLs were prepared by the lipid hydration method wherein a thin film of ibuprofen and lecithin was heated past the critical temperature for efficient hydration. Stability test of the MLLs entrapping ibuprofen was confirmed by an incubation test at room temperature over 24 hours. To simulate physiological conditions expected in the lung, a surfactant (tween 20) was added to test the stability of the ibuprofen-entrapped MLLs. Then, any release of ibuprofen from the MLLs was determined by capillary electrophoretic analysis.

**Results:** Ibuprofen was successfully loaded into the MLLs with a diameter of 892-1713 nm at a high efficiency of 92%. There was no release of ibuprofen from the MLLs during the stability test under incubation at room temperature over 24 hours. However, sustained release of ibuprofen from the loaded MLLs at a rate of 0.09 mg/mL/hour was observed under physiological conditions expected in the lungs.

**Conclusions:** Our results suggest that MLLs could protect ibuprofen during administration in a pulmonary delivery system. Drying in a phosphate-buffered saline preserved the integrity of MLLs for long-haul transportation as well as long-term storage.

**Keywords:** ibuprofen, entrapment, multilamellar liposomes, pulmonary delivery, sustained release, capillary electrophoresis

## Introduction

Discovered in 1950, ibuprofen has proven to be one of the most powerful anti-inflammatory drugs for various types of fever, inflammation, and pain [1]. However, this drug has some disadvantages such as poor water solubility. Its short half-life of 2-4 hours, due to oxidative metabolism in the human body [2, 3] requires patients to take a high dosage of 1600 mg once (or two 800-mg tablets) daily to see a lasting therapeutic effect [4]. Accidental overdoses can damage the kidneys and may develop gastrointestinal ulcers in vulnerable patients. Among solutions to overcome these drawbacks, drug delivery system is proposed to be a viable candidate because of the awareness that nanocarriers

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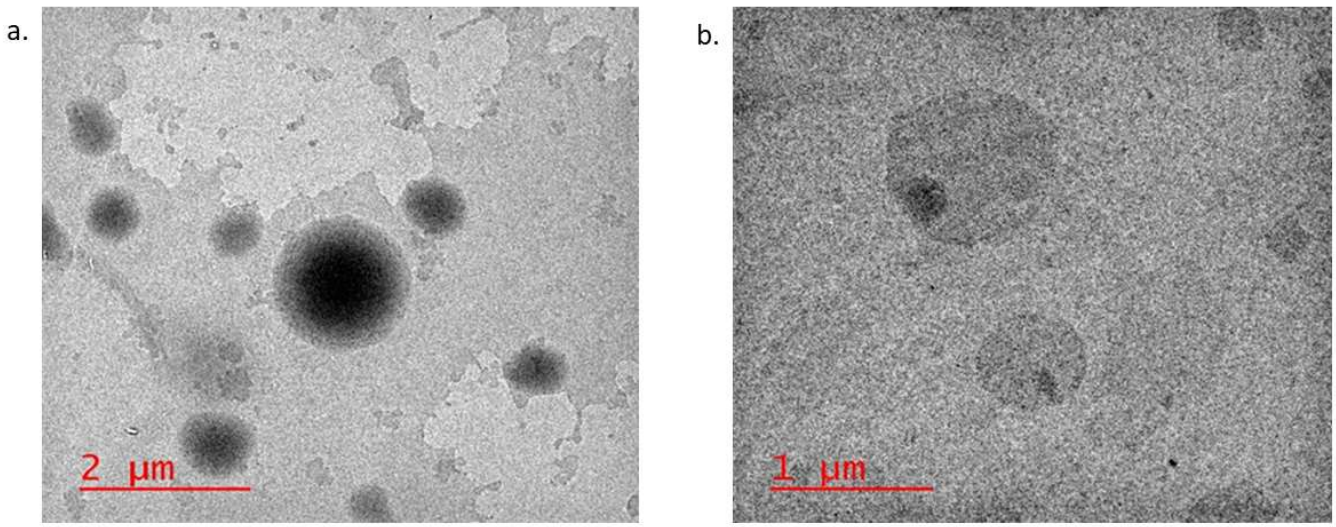


**Figure 3:** TEM micrographs: (a) ibuprofen-entrapped multilamellar liposomes, and (b) multilamellar liposomes.

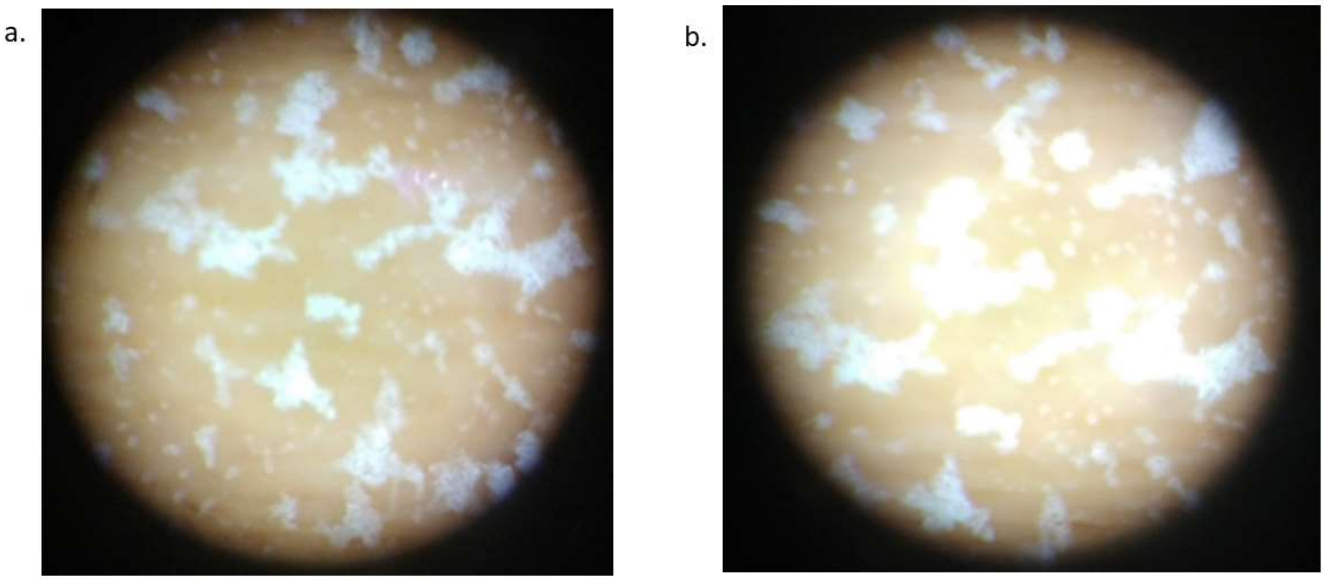


**Figure 4:** Stereo micrographs: (a) ibuprofen-entrapped multilamellar liposomes, and (b) multilamellar liposomes. White stain of salts (KH2PO4 and NaCl from phosphate-buffered saline) can be seen deposited on clusters of circular liposomes.

sipping up from the multilamellar structure of liposomes in a process similar to efflorescence [41]. These air-dried IMLLs could offer a cost-efficient way of long-term storage and long- haul delivery.

The delivery of liposome-encapsulated drugs depends on the structure and characteristics of the liposomes, the size and nature of the drug molecules, and their mutual interactions. In general terms, the release of drugs from multilamellar liposomes can be slower than that from unilamellar liposomes as it involves traversing only a single bilayer. An ibuprofen release test was performed to investigate the stability of the IMLLs during incubation at room temperature over a period of 24 hours. In order to obtain the time profile of ibuprofen release from the IMLLs, CE-UV was applied to measure the peak areas for ibuprofen in the PBS supernatants that were collected every 2 hours, as typified in Figure 5. Those peak areas were converted to concentrations of ibuprofen in the supernatant samples using the linear regression equation from the standard calibration curve presented above. Based on the release profile shown in Figure 6, there was no significant changes in ibuprofen concentration due to release of ibuprofen from the IMLLs for as long as 24 hours. The

Imanishimwe A, et al., J Pharm Pharmacol Res 2024
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steady concentration of approximately 1.3 mg/mL ibuprofen represented just 8% of the initial concentration that was not entrapped by the liposomes during formation of IMLLs. This can be explained by several factors. The first one is based on the influence of lipid alkyl chain length wherein the longer the alkyl chain is, the longer the retention of entrapped hydrophobic drug in the MLLs becomes. Mohammed et al. have demonstrated how the ability of liposomes to retain poorly water-soluble drug correlates with the alkyl chain length of the lipid component, with longer retention in the order C24PC > DSPC > DMPC > PC [42]. The second could be the phase transition temperature (Tc) of the lipid excipients within the bilayer because as the alkyl hydrocarbon chain length increases, the van der Waals interactions between the lipid chains become stronger requiring more energy to disrupt the ordered packing, and therefore the phase transition temperature increases. Hence, the high Tc, the lesser the drug loss, and the longer the drug retention. Yadav et al. stated that lipids with a long acyl chain length are commonly used because a high phase transition temperature enables the drug to be retained due to strong van der Waals interactions. Anderson et al. also found that DSPC liposomes have the greatest encapsulation efficiency and drug retention over 48 hr at 37°C (85±10%) compared to DMPC liposomes which had (54±4%) at 37°C despite both systems being in the ordered gel phase [43]. The third could be the van der Waals interactions between the longer lipid chains where the increased lipid phase area within the liposomes enhancing the drug binding and bilayer stability [44]. These results are similar to previous reports that ibuprofen entrapped in liposomes containing soybean lecithin had shown good stability for the treatment of osteoarthritis [45]. In addition, Aisha et al. portrayed how liposomes prepared from soybean lecithin are highly stable at pH 5.5 and 7.4.

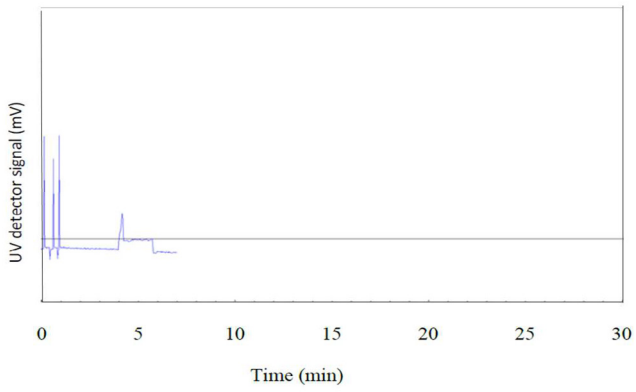


**Figure 5:** Typical electropherogram for CE-UV analysis of PBS supernatant from IMLLs stability test after 6 hours. Area of ibuprofen peak = 59±1 mV.min at migration time = 4.1±0.1 min.

## Loading capacity and entrapment efficiency of IMLLs

Multiplying the volume of IMLLs suspension by the steady-state concentration obtained by CE-UV analysis above, the free mass of ibuprofen in the IMLLs suspension

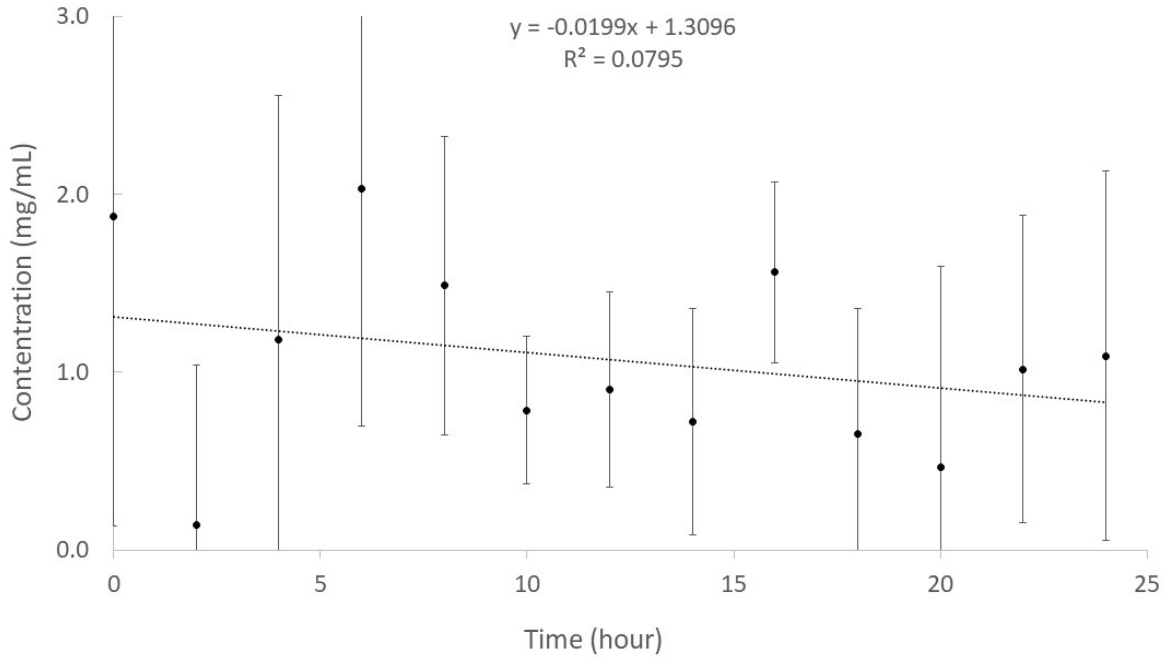


**Figure 6:** Release profile of ibuprofen from IMLLs to PBS supernatant.

Imanishimwe A, et al., J Pharm Pharmacol Res 2024
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was calculated. The loading capacity and entrapment efficiency of IMLLs were next determined by converting the concentration into a free mass and using the this formula:

$$Entrapmentefficiency = \frac{/nitialmassof\ /\ BU - Freemassof\ /\ BU}{/nitialmassof\ /\ BU} * 100\%$$

;

$$Entrapmentefficiency = \frac{/nitialmassof\ /\ BU - Freemassof\ /\ BU}{/nitialmassof\ /\ BU} * 100\%$$

The IMLLs were found to have a loading capacity of 920 mg/g that represented a reasonable mole ratio of 3.1 between ibuprofen and lecithin, considering the molecular length of 1.03-1.30 nm for ibuprofen and thickness of 2.5-3.5 nm for the hydrophobic tails in a lipid bilayer [46]. Similarly, Eloy et al. reported that the encapsulation efficiency of hydrophobic drugs strongly depends on the length and packing density of the liposome acyl chains hosting them, whereas an increased loading capacity requires an increase in the bilayer lipophilic volume by choosing longer alkyl chain lipids [47]. The ibuprofen encapsulation or entrapment efficiency of 92% initially during preparation of IMLLs is similar to the 82% previously reported for paclitaxel in nanostructured lipid carriers [48] Chaves et al. had also reported a similar high entrapment efficiency of 93.3% for curcumin and 91.3% for cholecalciferol in multilamellar liposomes. These results suggest that a popular supplement dosage (1200 mg) of soy lecithin could entrap ibuprofen (1100 mg) just under the maximum daily dose (1200 mg) allowed for over-the-counter pain relievers [49, 50].

### *In vitro* release studies of ibuprofen from IMLLs/ tween 20

In another stability test of the IMLLs under conditions expected in the lungs, polyoxyethylene sorbitan monolaurate (Tween 20) was chosen from among other chemicals to simulate the effect of lung surfactant [51, 52]. Tween 20 is a polysorbate surfactant approved by the US FDA for use as an additive in pharmaceutical preparations, and polysorbate surfactants facilitate nanoparticulates to cross the blood- brain barrier [53]. The final concentration of Tween 20 was similar to the concentration of lung surfactant normally present. It was found that tween 20 allowed some ibuprofen leaking out from IMLLs to the PBS supernatant, as evidenced by the profile shown in Figure 7. The release rate was estimated to be 0.09±0.01 mg/mL/hour approximately, which is statistically significant in terms of 0.55% release per hour. Fortunately, this low release rate may be considered physiologically insufficient to cause non-cardiogenic pulmonary edema [54]. Preliminary biodistribution studies performed by Shah *et al* after the delivery of ibuprofen to mice by aerosol had demonstrated ibuprofen is rapidly transported from the lungs into the blood serum with minimum retention in lung tissue and bronchoalveolar lavage fluid [55].

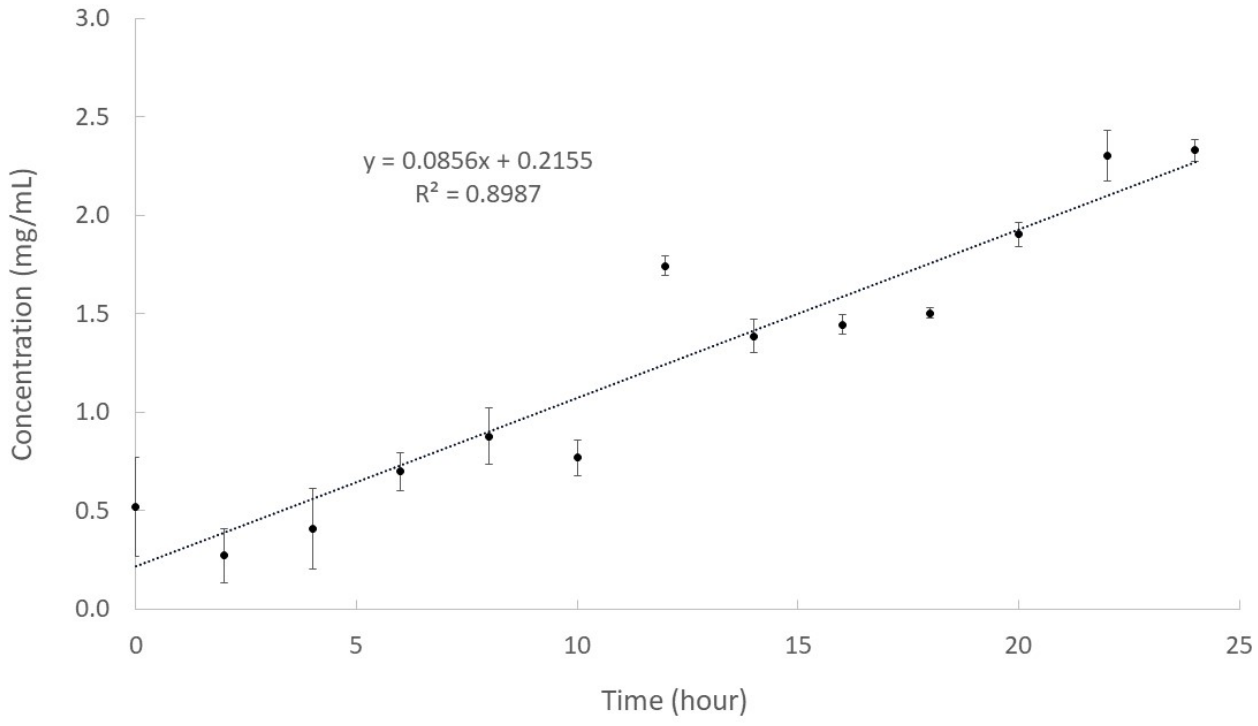


**Figure 7:** Release profile of ibuprofen from IMLLs to PBS supernatant containing tween 20.

Imanishimwe A, et al., J Pharm Pharmacol Res 2024
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An investigation was last conducted to better understand the mechanism by which ibuprofen was released in the presence of tween 20 surfactant. Both IMLLs and IMLLs/tween20 were analyzed again by CE-UV. For IMLLs, a peak was observed at a longer migration time (8.7 min) as shown in Figure 8(a) which suggested that the liposomes were negatively charged. However, when IMLLs/tween 20 were analyzed, a peak was observed at a short migration time (6.4 min, closer to that for a neutral marker) in Figure 8(b). In addition to osmotic swelling of the IMLLs by the surfactant, [56] it can be hypothesized that the hydroxyl groups of tween 20 (a non-ionic surfactant) molecules covered the negatively charged phosphate head groups via hydrogen bonding. The surface lipid bilayer was probably disrupted by the fatty acid ester moiety of tween 20 to slowly release ibuprofen from the liposome [57]. This observation is similar to the previous report that in vitro polyphenols released from lipid vehicles demonstrated slower kinetics when compared to the free polyphenols in phosphate buffer solution at pH 7.4 [58]. From these results, it can be concluded that MLLs could protect ibuprofen during administration in a pulmonary delivery system. The drug release performance can be controlled by tuning the lamellarity and other physicochemical properties (membrane rigidity/fluidity, curvature, stress and permeability) of IMLLs [59]. In chemistry and chemical physics, a mesophase is a state of matter intermediate between liquid and solid. Biological structures such as the lipid bilayers of cell membranes are examples of mesophases.

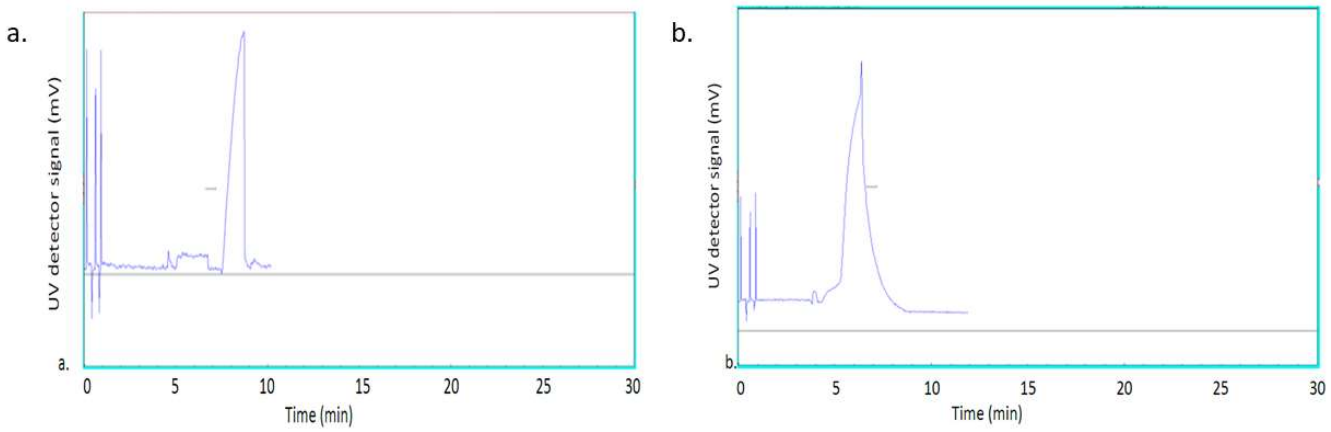


**Figure 8:** CE-UV electropherograms: (a) IMLLs (migration time = 8.6±0.2 min, peak area = 365±2 mV.min), and (b) IMLLs/tween 20 (migration time = 6.4±0.2 min, peak area = 831±5 mV.min).

## Conclusion

In the present work, ibuprofen-entrapped multilamellar liposomes were successfully formed with a spherical shape that measured 892-1713 nm in diameter. By comparison, multilamellar lecithin liposomes without ibuprofen entrapment had a diameter in the range of 674-1106 nm. Sufficient entrapment of ibuprofen in MLL was attained, promising for new and novel pharmaceutical applications. The stability test of IMLLs showed there was no observable release of ibuprofen over 24 hours. However, repeating the stability test in the presence of tween 20 attained a small release of ibuprofen from the IMLLs at a rate of 0.09 mg/mL/hour. Pulmonary administration of IMLLs can deliver ibuprofen directly to epithelial cells in the lungs for local therapy, bypassing the gastrointestinal route altogether. In order for liquid formulations of IMLLs to be administered to the pulmonary region by intranasal drug delivery, [60, 61] they will have to be nebulized. We will test their stability during nebulization [62, 63] and verify that the nebulization process itself does not result in a burst of ibuprofen. It is expected that microencapsulation of ibuprofen by MLLs can offer bioavailability, control release, target delivery, mask bitter taste, provide stability, increase efficacy, and minimize side effects [64]. Our future work would focus on conducting more release experiments, in cell lines and animals, to investigate how the ibuprofen will be released from the multilamellar liposomes into the biological system. It would be interesting to study whether IMLLs interact with angiotensin conversion enzyme 2 receptors and look for evidence that ibuprofen can help alleviate some symptoms of chronic obstructive pulmonary disease.

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Imanishimwe A, et al., J Pharm Pharmacol Res 2024
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## Author Contributions

Conceptualization: AI, AT, EPCL Writing Original Draft Preparation: AI Review & Editing: EPCL

Visualization: AI Supervision: EPCL

Co-supervision: AT, MA

**Conflicts of Interest:** The authors declare no conflict of interest.

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