



Development of a child-friendly oral drug formulation using liposomal multilamellar vesicle technology

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ABSTRACT

Many medicines are only available in solid dosage forms suitable for adults, and extemporaneous compounding is required to prepare formulations for children. However, this common practice often results in inaccurate dosing and unpleasant taste, reducing the medication adherence. Here, we report the development of a new method to prepare and compound child-friendly oral formulations based on a liposomal multilamellar vesicle (MLV) platform. MLVs composed of a phospholipid (DSPC) and cholesterol (55/45, molar ratio) were prepared using the standard thin film hydration method with 300 mM citric acid (pH 2), followed by an addition of aqueous sodium carbonate to adjust the exterior pH to 8–10 for creating a transmembrane pH gradient. Weak-base drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ), could be actively and completely loaded into the MLVs at a drug-to-lipid ratio of 15–20 wt%. This technique formulated weak-base drugs from the powder or tablet form into a liquid preparation, and the complete drug encapsulation would prevent contact between the drug molecules and the taste buds. The gradient MLV formulation could be preserved by lyophilization and stored at room temperature for at least 8 weeks. Upon reconstitution with water, the MLV formulation could completely encapsulate CQ at 20 wt%, which was comparable to the freshly prepared MLVs. The CQ-loaded MLV formulation could be stored at 4 °C for 2 weeks without drug leakage. In vitro release studies indicated that MLV could retain CQ in the simulated saliva, but released up to 50% and 30% of the drug in the simulated gastric and intestinal fluids, respectively. The orally delivered MLV-CQ formulation displayed higher CQ absorption in mice, with a 2-fold increase in the area under the curve (AUC) of the plasma profile compared to CQ solution. Our data suggest that the new MLV method could serve as a platform to prepare child-friendly oral formulation for weak-base drugs.

1. Introduction

Most medicines are only available in solid dosage forms such as tablets and capsules, which are difficult for children to swallow (British National Formulary for Children, 2022; Preventing). Extemporaneous compounding of those adult dosage forms are required for paediatric use. This typically involves dividing an adult dosage form into smaller doses, which is then grinded up into powder and mixed with food or liquid, such as water, milk or juice. Unfortunately, this common practice is associated with poor medication adherence (World Health

Organization, 2012; Nunn, 2003). First, the dosage is often not accurate, posing safety and efficacy concerns for many drugs that have a narrow therapeutic window. Second, many drugs exhibit an unpleasant taste that cannot be effectively masked by food or flavoured liquids. Often, children spit out or refuse to take the medicine, leading to failure of therapy (Cram et al., 2009).

Tang et al. (2017) were the first to show that liposomal small unilamellar vesicles (SUVs) were an effective platform for preparing child-friendly drug formulations. They encapsulated a highly bitter drug, mefloquine (Mef), in the aqueous core of SUV liposomes to disperse the

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drug in a solution form for easy swallowing and also to prevent direct contact of Mef molecules with the taste buds in the mouth, leading to complete masking of the taste. Upon oral ingestion, SUV liposomes effectively released the payload in the acidic gastric fluid as well as in the bile salt containing intestinal fluid, resulting in slightly increased oral absorption compared to the standard suspension formulation. However, the manufacturing of the SUV liposomes was tedious, time consuming, expensive, and challenging for scale-up. The method involved hydrating a thin lipid film composed of cholesterol and a phospholipid (DSPC) with aqueous ammonium sulfate to prepare liposomal multilamellar vesicles (MLVs), followed by membrane extrusion to reduce the particle size and lamellarity, yielding liposomal SUVs. Then, the SUVs were dialyzed against 10% sucrose to create a transmembrane gradient. Finally, the drug was mixed with the SUVs and incubated to facilitate the active loading into the SUV core (Tang et al., 2017). The membrane extrusion and dialysis procedures are particularly challenging for scale-up. Based on this previous study, here, we focused on developing an alternative liposomal technology that did not require membrane extrusion and dialysis and therefore, would be much easier for scale-up manufacturing. We explored the possibility of creating a transmembrane pH gradient for liposomal MLVs by simply adding an alkaline in the external phase and using this MLV formulation for active loading of weak base drugs to prepare child-friendly oral drug formulations. Here, we report the development and optimization of this MLV technology and characterization of its *in vitro* and *in vivo* properties for formulating and delivering a highly bitter drug, chloroquine (CQ). CQ is an essential paediatric medicine for the treatment of rheumatoid arthritis (Rynes, 1988); lupus erythematosus (Tsakonas et al., 1998; Ruiz-Irastorza et al., 2006; James et al., 2007; Sisó et al., 2008; Pauli et al., 2020) and malaria. It is a weak-base quinine drug and is only available in the adult tablet form (Aralen) (CDC, 2007), and therefore, was selected as a model drug for this study.

2. Materials and methods

2.1. Materials

1,2-distearoyl-*sn*-glycero-3-phosphatidylcholine (DSPC) was purchased from Avanti Polar lipids (Alabaster, AL). Cholesterol (Chol), chloroquine diphosphate (CQ), hydroxychloroquine sulfate (HCQ), Nile Blue (NB), citric acid monohydrate, sodium carbonate (Na₂CO₃), phosphoric acid, phosphate buffered saline (PBS), concentrated hydrochloric acid and sodium taurocholate hydrate were purchased from Sigma Aldrich (St. Louis, MO). Hydroxychloroquine tablets (200 mg/tablet) were purchased from Regency Medical Centre Pharmacy (Vancouver, BC, Canada). All chemical reagents and organic solvents were of analytical grade.

2.2. Simulated fluids

Simulated saliva (SS, pH 6.5) was prepared by titrating 10 mM PBS (pH 7.4) with 1 M phosphoric acid. Simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 6.8) were both purchased from RICCA Chemical Company (Arlington, TX). Sodium taurocholate hydrate (3 mM) was added to the simulated intestinal fluid to mimic bile salt in the intestine.

2.3. Preparation of liposomal multilamellar vesicles (MLVs)

MLVs were prepared using the thin film hydration method as previously described (Yu et al., 2020). The mixture of cholesterol/DSPC (45/55, molar ratio) was dissolved at a total lipid concentration of 30 mg/mL in chloroform in a round-bottomed flask. Chloroform was removed using rotary evaporation at 60°C and a rotation speed of 400 rpm to obtain a thin lipid film. The lipid film was dried under high vacuum for 30 min to remove residuals of chloroform. The film was then

hydrated with 2 mL of 300 mM citric acid (pH 2). The MLV suspension was heated at 40 °C and sonicated for 30 min to obtain a homogeneous and milky liquid preparation. Particle size, polydispersity index (PDI) and zeta potential of the MLVs were measured by dynamic light scattering (DLS) using Zetasizer NanoZS (Malvern Instruments, Malvern, UK). For lyophilization, MLVs prepared in citric acid (pH 2) with 30% sucrose, were aliquoted into 200 µL and freeze dried overnight at -90 °C and 0.12 mBar, using FreeZone® Triad™ freeze dry system (LAB-CONCO, Kansas City, MO). The samples were sealed and stored at room temperature for stability monitoring.

2.4. Active loading of drugs

Approximately 34–40 µL of sodium carbonate (300 mg/mL) was added to 200 µL of the liposomal MLVs to bring up the exterior pH to 8–10. CQ and HCQ-powder were dissolved in distilled water at a final concentration of 10 mg/mL. HCQ-tablet (200 mg) was first grinded into fine powder and dissolved in distilled water at 10 mg/mL. Loading of the drugs was performed at drug-to-lipid (D/L) ratios ranging from 5% – 30% (w/w) by mixing the drug solution with the MLVs containing a pH gradient, followed by incubation at the room temperature for 1 h and quench on ice for 2 min to terminate the loading process. Unencapsulated drug was removed by size exclusion chromatography (SEC) on a Sephadex-G25 column (GE Healthcare, Milwaukee, WI). Drug and lipid concentrations in samples were quantitatively analysed by UPLC as described below. The drug encapsulation efficiency was calculated by the following equation where D/L_{before} and D/L_{after} denote drug-to-lipid ratios before and after SEC, respectively.

$$\text{Encapsulation efficiency (\%)} = \frac{(D/L)_{\text{After}}}{(D/L)_{\text{Before}}} \times 100 \quad (1)$$

Alternatively, the MLVs were centrifuged at 10,000 g for 10 min and the supernatant containing unencapsulated drug was analysed by UPLC. The result was then compared with the total drug concentration in the MLVs to obtain the EE.

2.5. Cryogenic transmission electron microscopy (CryoTEM)

Empty and CQ-loaded MLVs (30 mg lipid/mL) at 20% D/L ratio (w/w) were deposited onto a glow-discharged copper grid, vitrified using a FEI Mark IV Vitrobot (FEI, Hillsboro, OR, USA), and imaged using a 200 kV Glacios microscope equipped with a Falcon III camera at the UBC High Resolution Macromolecular Cryo-Electron Microscopy facility (Vancouver, BC, Canada).

2.6. Ultra performance liquid chromatography (UPLC)

Concentrations of drugs and lipids were simultaneously quantified by a ACQUITY UPLC H-Class System (Waters, Milford, MA) (Böttger et al., 2022). The mobile phase was composed of solvent A: 0.1% trifluoroacetic acid (TFA) in water and solvent B: 0.1% TFA in methanol. CQ and HCQ were quantified by a photodiode array (PDA) detector at wavelengths of 342 and 342, respectively. DSPC and Chol were quantified by an evaporative light scattering (ELS) detector. Concentrations of drugs and lipids were measured by integrating the peak area under the curve and compared to the standard curves. For plasma CQ quantitation, a Waters QDa mass spectrometry detector was used. The ionization was carried out at 250 °C (source temperature) using a cone voltage of 65 V, and concentration of CQ was determined by integrating the single ion recognition (SIR) peak for the singly charged molecular ion (*m/z* 319.8) acquired at a capillary voltage of 0.5 V.

2.7. Storage stability study

MLVs prepared in citric acid with 30% sucrose were lyophilized and

stored at room temperature. At selected timepoints (1, 2, 3, 4 and 8 weeks), the lyophilized MLVs was reconstituted with Milli-Q water. Sodium carbonate was then added into the MLVs to create a transmembrane pH gradient as described above, followed by loading with CQ at a D/L of 20 wt%. The drug loading efficiency was measured using the centrifugation method. The prepared CQ-loaded MLVs were stored in the liquid form at 4 °C. At different timepoints, CQ encapsulation efficiency was determined using the centrifugation method.

2.8. *In vitro* drug release

MLVs loaded with CQ at 20% D/L (w/w) were mixed with different simulated gastrointestinal fluids at 1:1 (v/v), incubated at 37°C with shaking (150 rpm). At selected time points, 200 µL of the mixture was collected, and the released drug was removed by SEC. Drug and lipid concentrations of MLVs, before and after SEC, were measured using UPLC. Drug release (%) was obtained by equation (2):

$$\text{Drug release (\%)} = \left(1 - \frac{(D/L)_{\text{After}}}{(D/L)_{\text{Before}}} \right) \times 100 \quad (2)$$

2.9. Animals

Female CD1 mice (18–20 g, 6–7 weeks old) were purchased from The Jackson Laboratory (Bar Harbor, ME). All the *in vivo* studies were conducted in accordance with an established protocol (A18-0177) approved by the Animal Care Committee of the University of British Columbia (Vancouver, BC, Canada).

2.10. Pharmacokinetics

MLV-CQ or free CQ (dissolved in saline) was administered through oral gavage to mice at 10 mg CQ/kg (50 mg lipid/kg). At 0.5, 1, 3, 4, 6 and 24 h, blood was collected through either the saphenous vein or cardiac puncture and was quickly transferred into an EDTA-coated tube. Plasma was isolated by centrifugation at 4 °C for 10 min at 10,000 g. Forty-five µL of plasma was mixed with 300 µL ethanol, vortexed for 30 s, placed on ice for 30 min, and centrifuged twice at 12,500 rpm for 5 min. The supernatant (280 µL) was collected, lyophilized, and reconstituted in 45 µL ethanol. Ten µL of the sample was then injected into the UPLC to measure CQ concentration. Pharmacokinetics parameters and AUC were analyzed using PK solver (Zhang *et al.*, 2010) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA), respectively.

2.11. Statistical Analysis.

All data are expressed as mean ± SD. Statistical analysis was performed with GraphPad Prism version 8.0. Comparison between two groups were made by unpaired *t*-test, and one-way ANOVA was used for comparisons among three or more groups.

3. Results and discussion

Liquid formulations are desirable for paediatric use because they are easy to swallow and flexible for dosage adjustment for precise dosing. However, dispersing drug molecules in a liquid often introduce unpleasant tastes, leading to poor medication adherence for children. The most efficient taste masking method for liquid formulations is encapsulating the drug in small particles (low µm or smaller), which forms a barrier to prevent direct contact between the drug molecules with the taste buds. These particles must be consisting of safe materials and provide high encapsulation efficiency, which directly correlates with the taste masking effect. Tang *et al.* (2017) used Generally Regarded as Safe (GRAS) materials (a phospholipid, DSPC, and cholesterol) to prepare

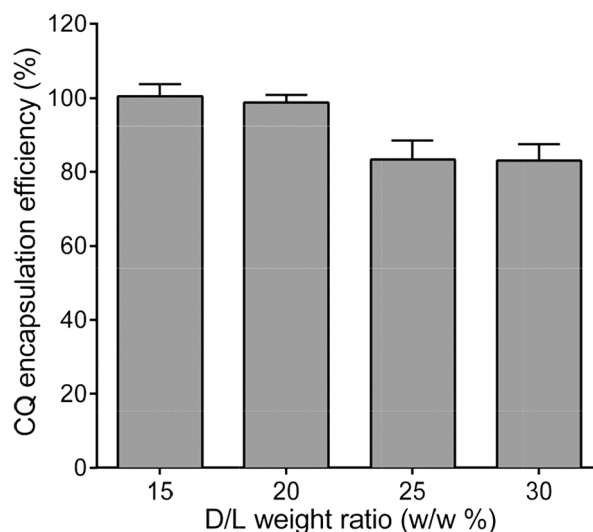


Fig. 1. Loading efficiency of CQ into the MLVs at different drug-lipid ratios (D/L). Data = mean ± SD (n = 3).

SUV liposomes and utilized the active loading technique to achieve complete encapsulation of Mef, a highly bitter drug, producing a liquid formulation without any bitter taste determined by an e-tongue. The active loading of drugs into the SUV liposomes relied on the transmembrane gradient created through the dialysis method, which is not scalable. Additionally, the rationale for using the SUV conformation of liposomes was because SUVs have a large aqueous core and thus, provide high capacity for drug encapsulation. However, the standard method for producing SUVs involves tedious membrane extrusion, a process that tends to introduce inconsistency and challenges for scale-up manufacturing. In this study, we explored using simple and scalable techniques to load a weak-base drug into MLV liposomes for producing child-friendly oral formulations.

3.1. Preparation of drug-loaded MLVs

MLV liposomes were spontaneously formed by hydrating DSPC and cholesterol with 300 mM citric acid (pH 2), without the tedious membrane extrusion process. A transmembrane pH gradient was created by adding aqueous Na₂CO₃ to the MLVs to bring the external pH to 8–10. To demonstrate whether this technology could provide active and complete loading of CQ, the gradient MLVs were mixed with CQ at a range of D/L, incubated at room temperature for 1 h before analysis of EE. As shown in Fig. 1, complete (>95%) drug encapsulation was determined at D/L of 15–20% (w/w). Drug entrapment efficiency decreased to ~80% as the D/L increased to 25% (w/w) (Fig. 1), indicating saturation of drug loading. It was long thought that drugs could not be actively loaded into MLVs due to the limited aqueous space between the lipid bilayers. To the best of our knowledge, we are the first group developing an active loading method for MLV liposomes. Additionally, the MLVs were prepared using simple and scalable techniques and provided complete

Table 1
Characterization of empty and CQ loaded MLVs. Data = mean ± SD (n = 3).

| Formulation | D/L ratio (w/w)% | Size (nm) | PDI | Encapsulation efficiency (%) | ξ potential (mV) |
|-------------|------------------|--------------|---------------|------------------------------|------------------|
| Empty-MLV | – | 251.5 ± 0.25 | 0.49 ± 0.015 | – | 5.52 ± 0.30 |
| MLV-CQ | 20% | 240.4 ± 4.95 | 0.366 ± 0.036 | 98.77 ± 2.07 | –4.93 ± 0.23 |

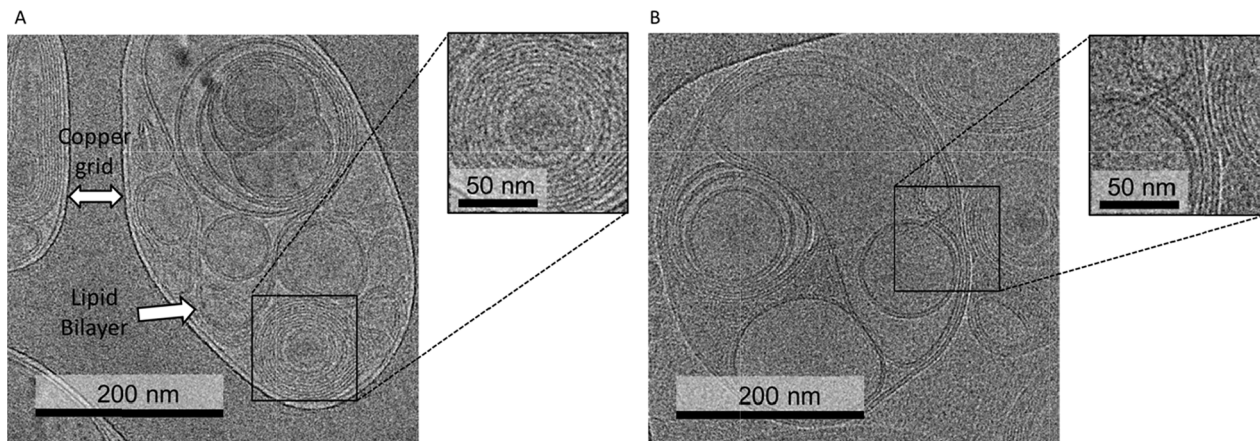


Fig. 2. Cryo-TEM images of (a) empty MLV and (B) MLV-CQ at a D/L of 20 wt%.

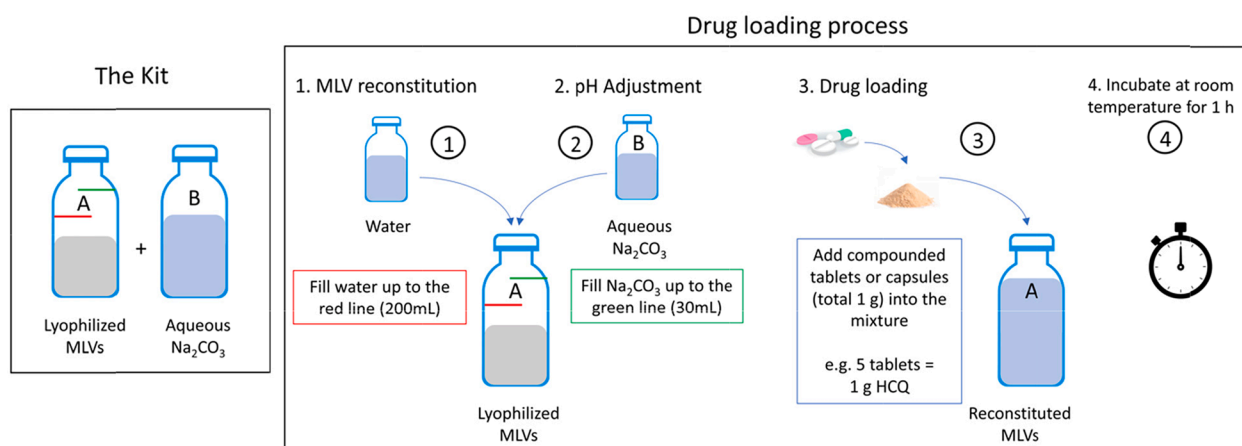


Fig. 3. Schematic diagram of the MLV kit and the procedures of formulation compounding. the kit includes a bottle of lyophilized MLVs (A) and a bottle of aqueous Na_2CO_3 (B). Step 1: reconstitution of MLVs with a pre-determined volume of water, Step 2: pH adjustment to 8–10 using a pre-determined volume of aqueous Na_2CO_3 , Step 3: Compounding a tablet/capsule into powder and adding it into MLVs with thorough mixing. Step 4: Mixture incubated at room temperature for 1 h before use.

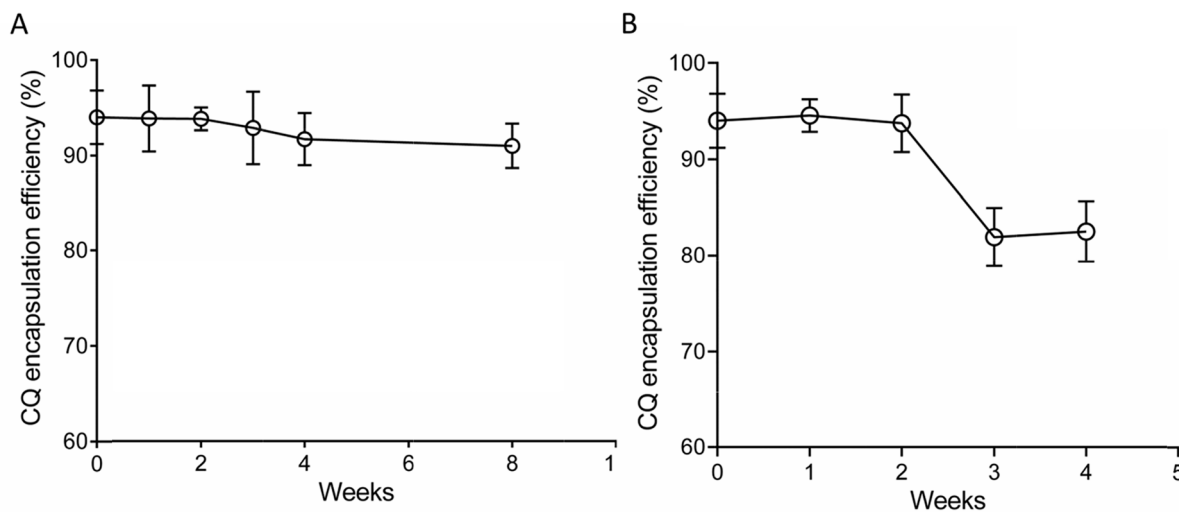


Fig. 4. CQ encapsulation efficiency in MLV products under different conditions: (A) Lyophilized MLVs were stored at room temperature for up to 8 weeks. CQ was actively loaded into the MLVs after reconstitution and pH adjustment, and the encapsulation efficiency was measured; (B) MLV-CQ was prepared and stored at 4 °C for up to 4 weeks, and the CQ encapsulation efficiency was determined. Data = mean \pm SD (n = 3–4).

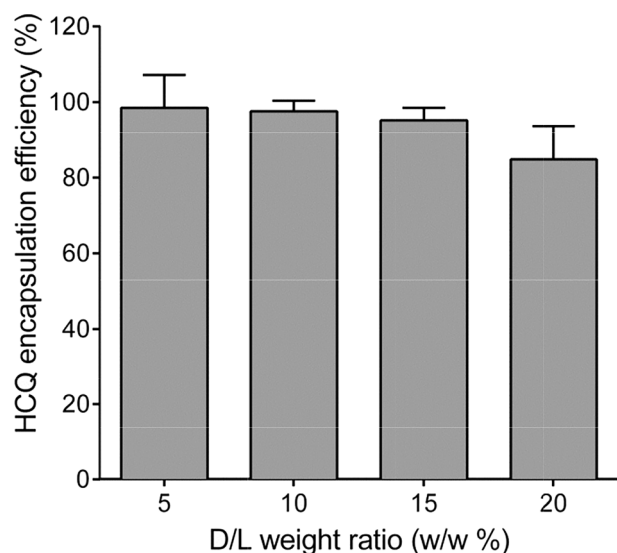


Fig. 5. HCQ encapsulation efficiency into MLVs by compounding an HCQ adult tablet into a liquid preparation using the MLV kit at a range of drug-to-lipid (D/L) ratios. Data = mean \pm SD (n = 3).

encapsulation for weak-base drugs. Besides CQ, we successfully encapsulated other weak-base small molecules such as HCQ and NB into the MLV liposomes at the same D/L (Figure S.1 and table S.1 in supplementary) demonstrating that this could serve as a platform technology.

Empty and CQ-loaded MLVs were characterized by DLS and displayed comparable size (\sim 250 nm), PDI (0.3–0.5) and zeta potential (\pm 5 mV) (Table 1 and Figure S.2 A,B in supplementary). The high PDI was expected as there was no membrane extrusion in the preparation to control the particle size. The relatively small size of these MLV formulations could be caused by the gradient introducing method that might promote lipid rearrangements. The multilamellar morphology of MLVs and variable particle size distribution were further confirmed by cryo-TEM images (Fig. 2). Unlike the previously reported SUV-Mef structure (Tang *et al.*, 2017); no electron-dense drug aggregates were shown inside the MLVs.

3.2. Development of a user kit for simple preparation of stable liquid drug formulation

We envisioned that this MLV platform could be used as a universal taste-masking liquid for weak-base drugs. The drug-free MLVs in the lyophilized form will be provided along with aqueous Na_2CO_3 in the pharmacy or to the care giver as a kit with a user instruction. First, the MLVs will be reconstituted with a fixed amount of water, followed by an addition of a fixed volume of the aqueous Na_2CO_3 to increase the external pH to 8–10. A fixed amount of the drug powder (15–20 wt%) will be mixed with the MLVs and then incubated at room temperature for 1 h before use, as shown in Fig. 3.

To examine whether this approach is feasible, we lyophilized MLVs prepared in 300 mM citric acid (pH 2) with 30% sucrose into dry powder, which was then stored at room temperature for up to 8 weeks. At different time points, the lyophilized MLVs were reconstituted in MilliQ water, adjusted for pH (8–10) using aqueous Na_2CO_3 , mixed with 20 wt% CQ, incubated at room temperature for 1 h, and measured for drug encapsulation efficiency using the centrifugation method. As shown in Fig. 4A, the lyophilized MLVs could be stored at room temperature for at least 8 weeks and still provided $>$ 90% encapsulation efficiency for CQ, indicating that the lyophilized MLV product exhibited good storage stability at room temperature and was ready for use to prepare a child-friendly liquid formulation following simple procedures. Additionally, the prepared MLV-CQ was stable for 2 weeks upon storage at 4 °C. As shown in Fig. 4B, the CQ encapsulation efficiency was maintained at $>$ 94% for 2 weeks at 4 °C, but decreased to \sim 80% in 3 weeks. The data suggest that once a paediatric formulation is prepared using this MLV kit, patients can store this formulation at 4 °C for up to 2 weeks.

3.3. Compounding a hydroxychloroquine tablet into a liquid formulation using the MLV kit

Next, we examined whether the MLV kit could be used to compound a commercially available HCQ tablet into a liquid formulation. CQ tablets are not available in Canada, and therefore, we acquired HCQ tablets as an alternative for the study. Extemporaneous compounding of an adult dosage form into a liquid preparation is commonly practiced by pharmacists and care givers when a child-friendly dosage form is not commercially available. As discussed earlier, this common practice often leads to poor medication adherence due to inefficient taste masking.

The tablet (200 mg HCQ/tablet) was grinded into fine powder and dissolved in MilliQ water at a final concentration of 10 mg HCQ/mL.

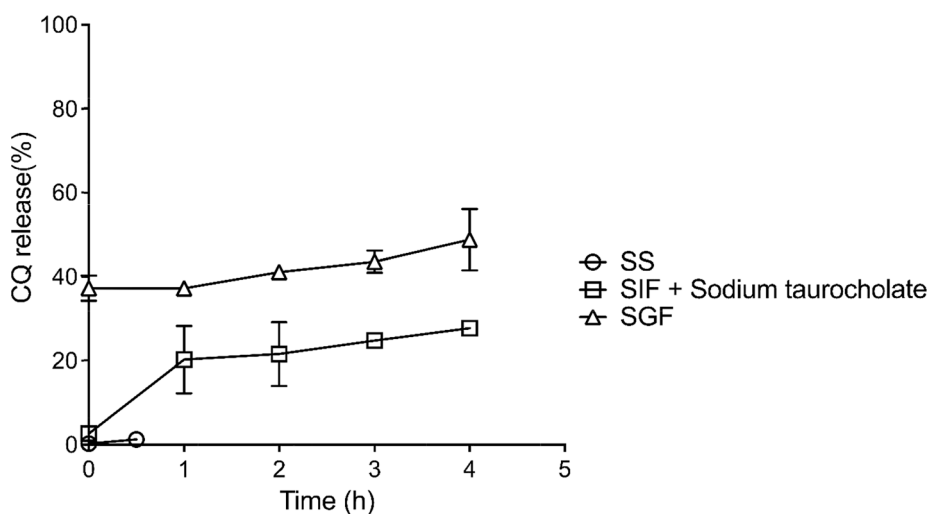


Fig. 6. In vitro drug release profiles of MLV-CQ (20%, w/w) in simulated saliva (SS), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF) supplemented with 3 mM sodium taurocholate. Data = mean \pm SD (n = 3). SD bars are within some data symbols.

MLVs containing a pH gradient were prepared and mixed with the HCQ suspension at a range of D/L ratios (5–20 wt%), followed by incubation at room temperature for 1 h before measurement of HCQ encapsulation efficiency. As shown in Fig. 5, MLV-HCQ prepared at a D/L of 15 wt% displayed almost complete drug encapsulation efficiency, while the efficiency decreased to ~ 85% when the D/L increased to 20 wt%. The data suggest that the MLV kit could be employed to support effective compounding of a child-friendly liquid formulation from an adult tablet following easy procedures.

We acknowledge that the compounding work might be challenging to some care givers even with written instructions, while that has been part of the training for pharmacists and routinely performed in pharmacy around the world. Therefore, for short-term use medicines, it would be practical to ask the pharmacist to perform the compounding, while for drugs used for chronic diseases, care givers can purchase reusable compounding tools and get trained by their pharmacist to compound the formulation for their child. This approach has been in practice for decades. Compounding a tablet into fine powder with some size variation will still allow the drug to be sufficiently released and dissolved in the medium and then actively partitioned into the MLV core for loading. We acknowledge that this process could introduce variation to the formulation similar to that with the standard compounding that has been practiced for decades. However, it is believed that this variation is tolerable compared to no child-friendly formulation available, which will completely fail the therapy.

3.4. *In vitro* drug release studies

We then examined whether CQ could be released from the MLV formulation in gastrointestinal fluids after oral delivery and performed drug release studies in simulated saliva (SS), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF) supplemented with 3 mM sodium taurocholate to mimic the oral and gastrointestinal conditions, respectively. MLV-CQ were incubated with various simulated fluids at 37 °C while shaking at 150 rpm. Drug release was measured by comparing CQ concentration before and after SEC at the selected time-points. As shown in Fig. 6, when incubating MLV-CQ with SS, there was no drug release for 30 min, indicating that CQ would be retained inside the MLVs within the oral cavity. As we have previously established that the unpleasant taste of a compound was depending on the concentration of the free or released form of drug, the data suggest that this MLV delivery system providing 100% retention of CQ would completely mask the bitter taste. Since the formulation transition time through the oral cavity would be short, we only monitored drug release for 30 min. We then examined drug release in SGF (pH 1.2). As shown in Fig. 6, the formulation displayed an instant burst release (~38%) upon incubation with SGF with a cumulative CQ release of ~ 50% after 4 h. This burst release can be explained by the extremely acidic pH in SGF, where the phosphate groups (pKa ~ 3) of the DSPC would be protonated, resulting in imbalance between the hydrophobicity and hydrophilicity of the phospholipid and ultimately causing instability in the lipid bilayer (Tang *et al.*, 2017). Finally, CQ release was evaluated in SIF supplemented with 3 mM sodium taurocholate, a bile salt commonly found in the intestines. MLV-CQ displayed 20% drug release after 1 h incubation in SIF, and then the release gradually increased to 30% in 4 h, as shown in Fig. 6. The bile salt could act as a surfactant to disrupt the liposomal membrane for drug release as demonstrated and suggested previously (Tang *et al.*, 2017). The data indicate that when MLV-CQ were administered orally, the MLV could retain CQ, preventing its contact with the taste buds and masking the bitter taste. After transition to the stomach and intestine, CQ could be effectively released in the gastrointestinal tract due to the acidic environment and the presence of bile salt surfactants.

3.5. Pharmacokinetics

A Pharmacokinetics study was conducted to examine and compare

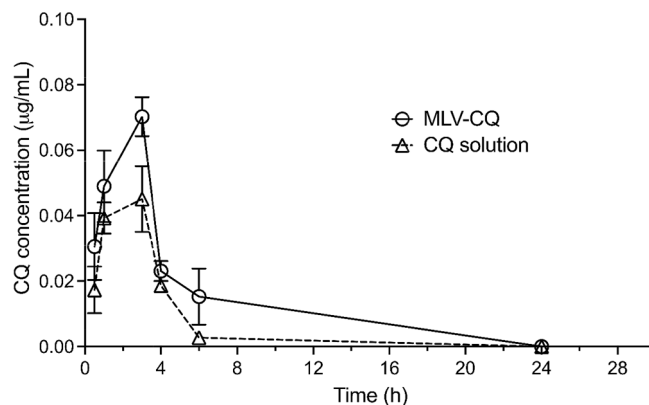


Fig. 7. Pharmacokinetic profiles of MLV-CQ and free CQ administered orally to female CD-1 mice at 10 mg CQ/kg. Data = mean \pm SD (n = 3–5).

Table 2

Pharmacokinetic parameters of MLV-CQ and CQ solution after oral administration in female CD-1 mice at 10 mg/kg.

| | CQ solution | MLV-CQ |
|--|-------------------|------------------|
| C_{max} ($\mu\text{g/mL}$) | 0.045 \pm 0.010 | 0.07 \pm 0.006 |
| T_{max} (h) | 3 | 3 |
| AUC_{0-24} ($\mu\text{g/mL}\cdot\text{h}$) | 0.18 \pm 0.014 | 0.36 \pm 0.079 |

the oral delivery of MLV-CQ and CQ aqueous solution *in vivo*. CD-1 mice were orally dosed with MLV-CQ (liquid) or CQ solution at 10 mg/kg, and the plasma was collected at 0.5, 1, 3, 4, 6 and 24 h post administration, to measure CQ concentration. After oral administration, CQ concentration in plasma increased gradually reaching C_{max} at 3 h and completely eliminated from plasma at 24 h, for both MLV-CQ and CQ solution. As shown in Fig. 7 and Table 2, the plasma profiles of MLV-CQ and CQ solution were comparable; however, MLV-CQ displayed 1.75 and 2-fold higher C_{max} and AUC, respectively, compared to CQ solution, suggesting enhanced drug absorption with MLVs. This data is in line with previous reports demonstrating that lipids are effective absorption enhancers (Rezhdo *et al.*, 2016).

4. Conclusion

We have developed a MLV platform technology for making child-friendly oral liquid formulations for weak-base drugs. This platform could be developed into a kit available to pharmacists and care-givers to support compounding of adult solid dosage forms into a paediatric formulation. There is a high demand for such solutions to address the issue of medication adherence that leads to failure of therapy in this special population.

CRediT authorship contribution statement

Nojoud A.L. Fayez: Investigation, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Roland Böttger:** Investigation, Methodology, Formal analysis, Visualization. **Sreemoyee Ghosh:** Investigation, Methodology, Formal analysis, Visualization. **Yushi Nakajima:** Investigation. **Po-Han Chao:** . **Elham Rouhollahi:** Investigation. **Anne Nguyen:** Investigation. **Pieter R. Cullis:** Project administration, Supervision. **Domink Witzigmann:** Investigation, Visualization. **Shyh-Dar Li:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Nojoud AL FAYEZ has patent pending to NanoStar. Roland Böttger has patent pending to NanoStar. Sreemoyee Ghosh has patent pending to NanoStar. Shyh-Dar Li has patent pending to NanoStar.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2022.122107>.

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