Impact of Manufacturing Process on Critical Quality Attributes of Multivesicular Liposomes

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PURPOSE

Multivesicular liposome (MVL) is a lipid-based drug delivery system that provides sustained release of drugs with short half-lives. For example, once bupivacaine (BPV), with a short half-life ($t_{1/2}$=2.7 hours), was encapsulated into MVL, sustained release characteristics ($t_{1/2}$=34 hours) was obtained. Structurally, MVL consists of a series of non-lamellar liposomes arranged in honeycomb structure with non-concentric aqueous chambers. To date, three MVL-based drug products have been approved by the FDA; DepoCyt (cytarabine), DepoDur (morphine sulfate), and Exparel (bupivacaine). The objective of this study was to identify the critical process parameters during the manufacturing of bupivacaine-loaded MVL and to evaluate their impact on the critical quality attributes of the MVL products, such as morphology and drug release characteristics.

METHODS

MVLs were manufactured using two amphipathic phospholipids, tricaprylin and cholesterol, via a double-emulsion method. BPV, an amino-amide local anesthetic, with a pKa of 8.4 was selected as the model drug. A pH gradient method was utilized for the encapsulation of BPV inside the MVL. The effect of process conditions such as emulsification time, shear rate, pH, osmolality, rate of solvent removal, etc. was evaluated to produce stable and uniform MVLs with optimum drug encapsulation efficiency. The morphology and size distribution of the prepared MVLs were determined using confocal laser scanning microscopy (CLSM) and laser diffraction techniques, respectively. The drug encapsulation efficiency and the stability of MVL were determined using HPLC-UV method.

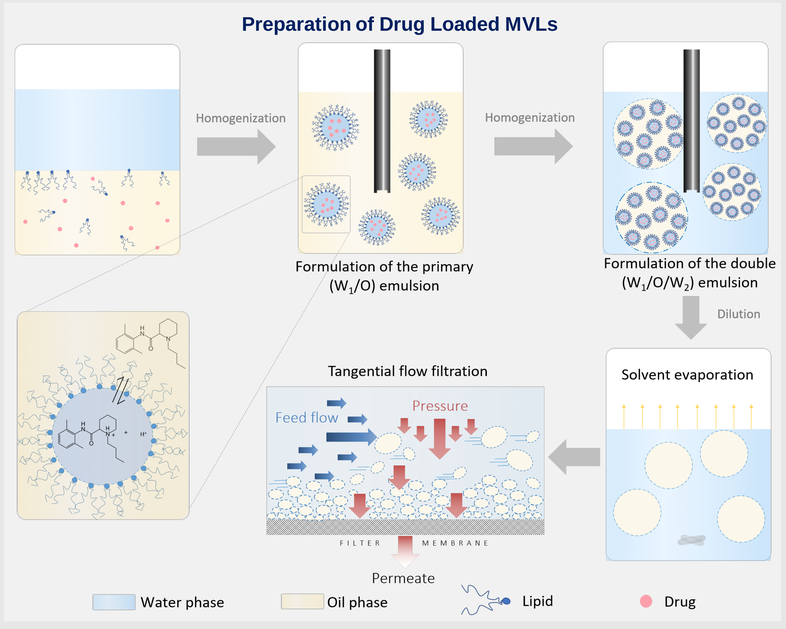

Figure 1. Schematics showing the manufacturing process of the MVLs, including formation of the W_1/O primary emulsions, $W_1/O/W_2$ double emulsions, solvent evaporation, and tangential flow filtration for purification and buffer exchange.

RESULTS

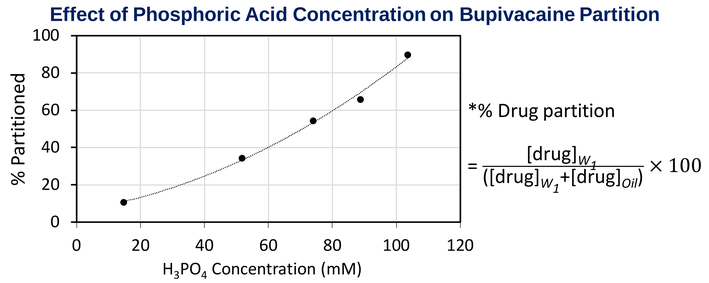

Figure 2. Bupivacaine (30 mg/ml, 104 mM) partition between chloroform and the initial water phase (W_1) at various concentrations of phosphoric acid.

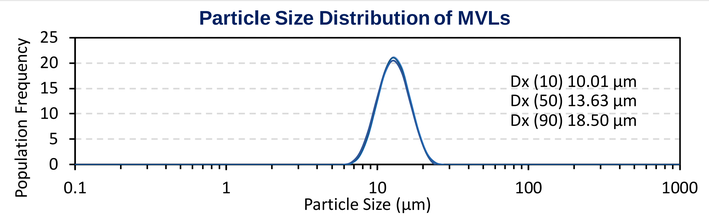

Figure 3. Particle size distribution of MVLs by Laser diffraction

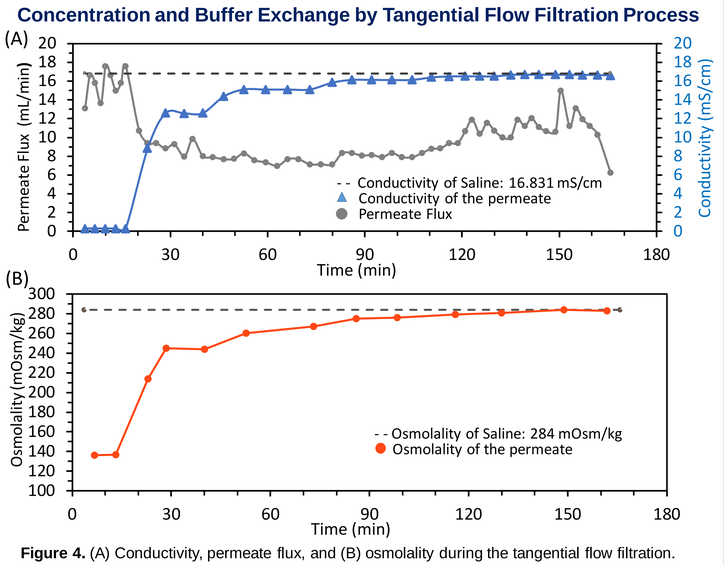

Figure 4. (A) Conductivity, permeate flux, and (B) osmolality during the tangential flow filtration.

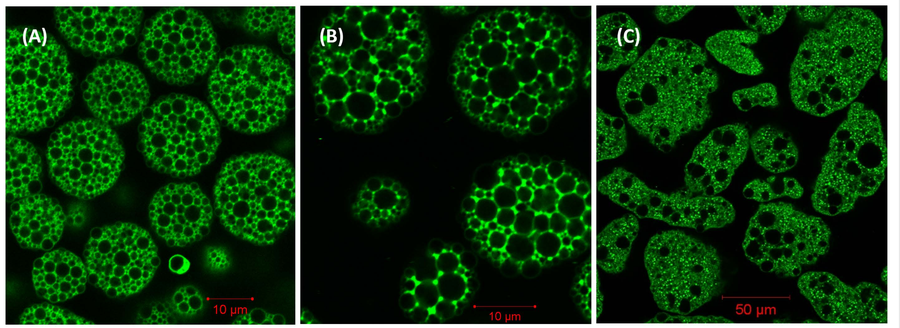

Figure 5. Confocal images of MVLs manufactured under different conditions: (A) 9000 RPM for 30 min during W_1/O step; (B) 7000 RPM for 30 minutes during W_1/O step; (C) MVL with damaged internal structure if W_1 and W_2 aqueous phases were not maintained isotonic. These results showed demonstrated the critical roles of the shear rate of the first water-in-oil emulsifying step and osmotic pressure balance in controlling the MVL internal structures.

Critical formulation and process parameters impacting critical quality attributes of MVL

- pH of the internal aqueous phase (low pH favors BPV transfer)
- Concentration of phosphoric acid (Figure 2)
- Osmolality balance between internal and external aqueous phases (Figure 5)
- Shear rate and duration
  - W_1/O emulsion step: controlling the size of inner vesicle droplets
  - $W_1/O/W_2$ step: a low shear rate to prevent fusion of W_1/O emulsion

CONCLUSIONS

This study provided an improved understanding on impact of the manufacturing process on the quality of MVLs (e.g., morphology, stability and drug loading). This understanding may be useful for comparative evaluation of key physicochemical characteristics between a potential generic drug and the reference listed drug.

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