M7008

Assessing In Vitro Drug Release from Multivesicular Liposome: Comparison of Reverse Dialysis and Rotary Shaking Methods

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PURPOSE

- Bupivacaine (BPV), an amide type local anesthetic, has a relatively short half-life ($t_{1/2\text{-BPV}}$) ~ 2.7 hours. BPV, when encapsulated in a multivesicular liposome (MVL) formulation, exhibits sustained release characteristics
- Multivesicular liposomes (MVLs) consist of a non-lamellar honeycomb structure with non-concentric aqueous chambers
- Significantly increased elimination $t_{1/2\text{-BPV}}$ ~ 34 hours is observed, which is likely influenced by various physicochemical parameters of the MVL such as:
  - MVL vesicle morphology and size (both external and internal physical dimension)
  - Rate of drug partitioning between hydrophilic (aqueous phase) and lipophilic (lipid bilayers) components
- It is *hypothesized* that alteration of MVL morphology over time influences the in vitro drug release rate

OBJECTIVES

- Characterize the vesicle size and morphology of the BPV-MVL complex formulation
- Conduct in vitro drug release in 50 mM PBS with and without Human Serum Albumin (HSA) over a period of 7 days - expected complete drug release profile (5 times the $t_{1/2\text{-BPV}}$)
- Analyze the effect of different parameters such as a) agitation, b) temperature, c) dissolution medium , and d) dissolution set-up on the in vitro drug release rate

METHODS

- MVL vesicle size – Laser diffraction (Malvern Mastersizer 3000)
- MVL vesicle morphology – Cryo-scanning electron microscopy (Tescan MIRA 3)
- In vitro dissolution set-up and drug release detection techniques:
- Rotary shaker mechanism (Thermo Scientific™ Tube Revolver / Rotator)

Dissolution media	50 mM PBS (pH 7) with varied concentrations of HSA				
Temperature	37°C	*Rotation*	12 rpm	*Dilution of model drug*	17 x

HPLC Column	Agilent ZORBAX SB-CN – 4.6x150 mm, 5µm		
Mobile phase	40% Acetonitrile + 0.01% Trifluoroacetic acid; pH 2.8		
Flow rate	1 mL/min	*Temperature*	30°C
λ_{BPV}	263 nm	*Retention time*	~ 2.1 min

- Reverse dialysis (USP II apparatus – Teledyne Hanson Research)

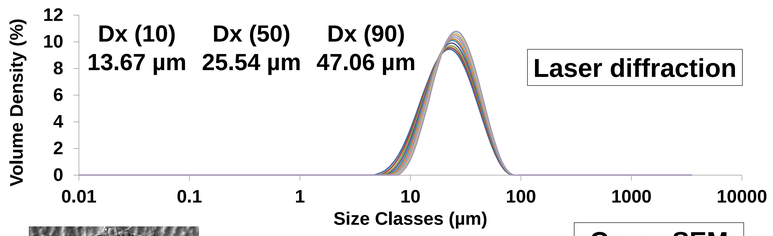
Dissolution media	50 mM PBS (pH 7)		
Temperature	37°C and 40°C	*Rotation*	120 rpm and 240 rpm

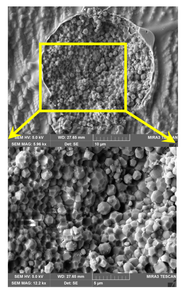
Dialysis cartridges	10-100 kDa (MWCO) conditioned with SDS
Drug detection	In situ UV-Vis fiber optic probe
Dilution of model drug	17x

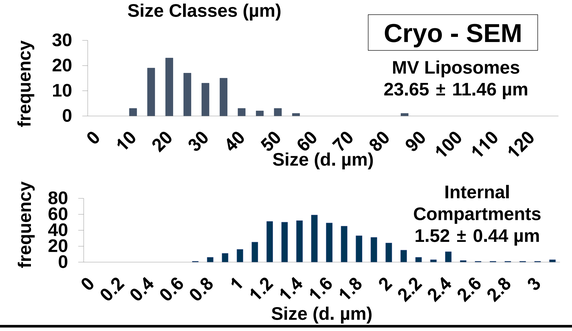
Rotary shaker device

Reverse Dialysis - USP II apparatus

RESULTS: MVL Vesicle Size and Morphology

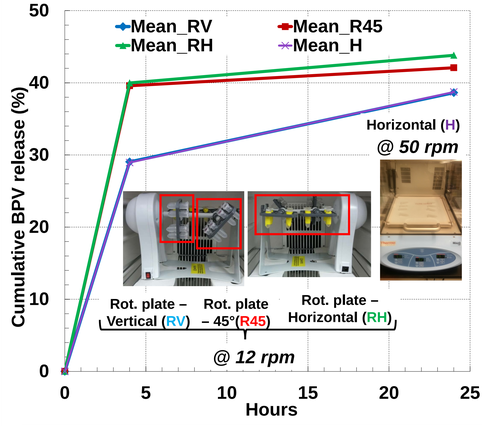






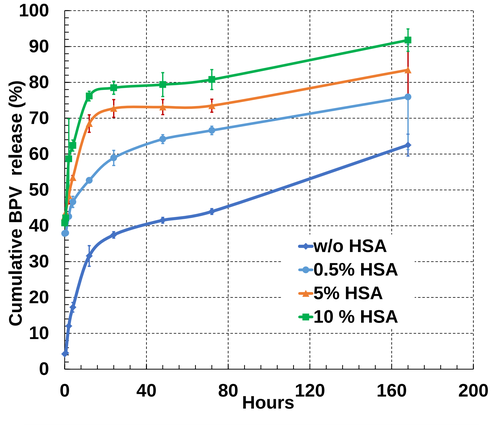
RESULTS: In vitro Drug Release – Rotary Shaker - HPLC

Effect of Orientation of Agitation



Initial release in RH and R45 orientations is more compared to the RV and H orientations

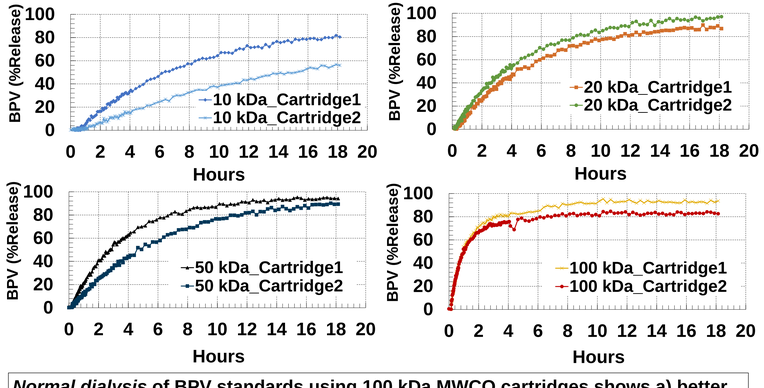
Effect of Composition of Dissolution Media



Presence of HSA in 50 mM PBS caused accelerated release of BPV from the MVLs under RH rotation

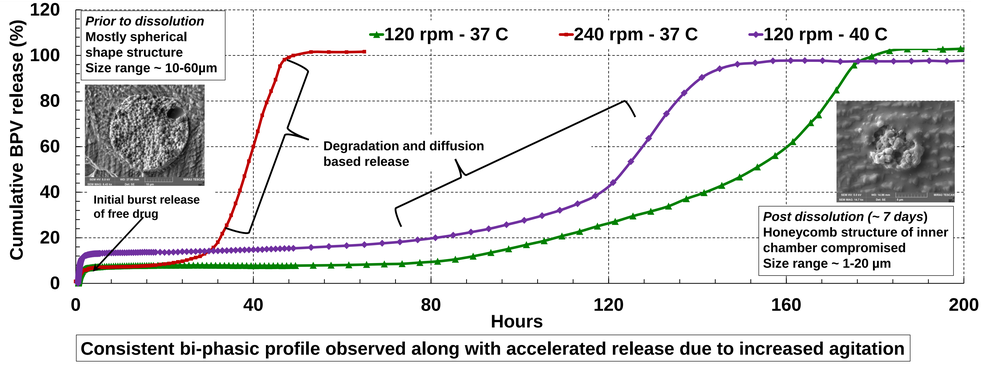
RESULTS: In vitro Drug Release – Reverse Dialysis USP II-in situ UV

Determination of MWCO of Dialysis Cartridges



Normal dialysis of BPV standards using 100 kDa MWCO cartridges shows a) better detection of initial release of BPV (~2 h) and b) 100% release of BPV

Effect of Agitation Speed and Temperature on the In vitro Drug Release Profile (100 kDa cartridges)



Consistent bi-phasic profile observed along with accelerated release due to increased agitation

CONCLUSIONS

- BPV MVLs are monodisperse spherical particles with complex internal compartment morphology
- In vitro release – Rotary shaker ⟶ Orientation of agitation and presence of HSA influence BPV release
- In vitro release – Reverse dialysis – USP II coupled with in-situ UV fiber optic ⟶ Discern both an initial diffusion burst release (~ 2 – 4 hr) followed by secondary release likely triggered by physical degradation of MVLs. It also provides the advantage of continuous monitoring of the BPV release profile.
  - -- Temperature ↑ initial release ↑ -- Agitation speed ↑ Total BPV release duration ↓

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