Synthesis of Multivesicular Liposome-Encapsulated Hydrophobically-Modified Chitosan Gels for Drug Delivery Applications

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Abstract

The encapsulation of drugs into multivesicular liposomes (MVL) offers a novel approach to sustained-release drug delivery.[1] The large size of MVL particles prevents rapid clearance by macrophages and results in the formation of a depot at the site of injection, which causes the drug to release slowly over time. The presence of two transport resistances – the liposomal bilayer and the gel network – is shown to be responsible for the sustained release.

The aim of this work was to prepare multivesicular liposome-encapsulated hydrophobically-modified chitosan gels for drug delivery applications.

Methods

1. Preparation of Multivesicular Liposome (MVL)

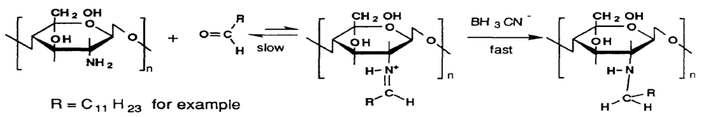
Formation 'water-in-oil' emulsion → Formation 'water-in-oil-in-water' emulsion → Evaporation of organic solvent

Fig. 1. A schematic image of a multivesicular liposome.

Torrent, Ana. "Exparel" *Anestesia* (2012)

2. Synthesis of Hydrophobically-modified chitosan and preparation of MVL-Gel

Hydrophobically modified chitosan was prepared from an alkylation of chitosan.



The hm- chitosan polymer was dissolved in 1% (v/w) acetate solution → The hm-chitosan solution was added drop by drop to MVL solution. → The mixture was left at room temperature for 2 hours before test

Results

Characterization of MVL

Fig. 2. Nikon Eclipse LV100 with Camera System

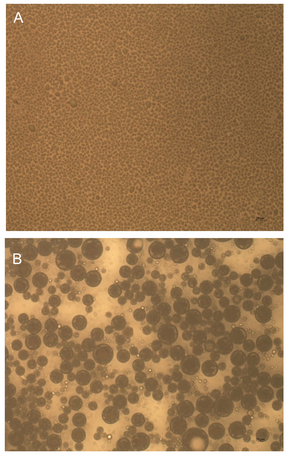


Fig 3. Optical microscope images of the different steps in the preparation of MVL. A)"water-in-oil" emulsion step, B) "water-in-oil-in-water" emulsion step, C) MVL particles after evaporation of organic solvent.

Fig 4. The Tecnai G2 F30 TWIN Transmission Electron Microscope: Displays the size and morphology of the MVL.

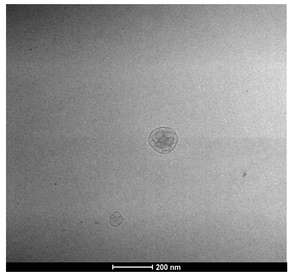
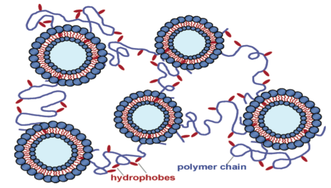


Fig 5. Cryo-TEM Image of MVL

Average particle Size (μm)	Zeta potential (mv)
6	-15.73

Table I. NanoBrook 90Plus Particle Size Analyzer: Determines the size and zeta potential - surface charge - of the MVL.



Lee, Jae-Ho, et al. *Langmuir* 21.1 (2005): 26-33.

Fig 7. Proposed structure of the network formed upon addition of hmc-chitosan to unilamellar liposomes. The hydrophobic part of hmc is shown to be embedded in the bilayer of the liposomes, thus building a connected network of vesicles. Each vesicle acts as a multi-functional cross-link in the network.

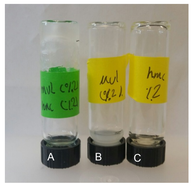


Fig 8. Photograph of (A) 2% hm-chitosan solution+ 2% MVL, (B) 2% MVL and (C) 2% hm-chitosan. At 2 % hm-chitosan, the system is close to the sol-gel transition without the addition of the multivesicular liposome, but it becomes a rigid gel upon the addition of 2% multivesicular liposome with ratio 1:3 (MVL: hmc).

Conclusion

- The MVLs were obtained by double emulsion process.
- The characterization of the MVL morphology was through light microscope as seen in Figure 3.
- Cryo-TEM gives more details of the membrane structure which could be seen in Figure 5.
- The average particle size is 6μm and the zeta potential is -15.7 mV as listed in Table I.
- We observe that the 2% hm-chitosan solution is viscous liquid, while contacting 2% hm-chitosan into 2% MVL solution leads to a gel that is able to hold its own weight under vial inversion.

References

1. Mantripragada, Sankaram. "A lipid based depot for sustained release drug delivery" *SkyePharma Inc.* (2002): 393
2. Liu,James, et.al. "Comparison of Sorafenib-Loaded Poly Acid and DPPC Liposome Nanoparticles." *Wiley* (2015):1187-11

Acknowledgements

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