

KEYNOTE FORUM

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Lipid Nanoparticles Formulations from Bench Scale To Industrial Scale

Purpose: Lipid nanoparticles are self-assembling vesicles obtained by hydrating a mixture of non-lipids and cholesterol and are suitable as carriers of drugs and biopharmaceuticals. It is desirable to be able to accurately control size and polydispersity of the vesicles as this can impact on biological outcome. Moreover, its crucial to formulate these nanoparticles in a scalable method that can be used in industrial settings. One approach that has been successful for lipid-based systems is the use of microfluidics (MF). In this study we compared a MF-based method with traditional methods such as thin film hydration (TFH) method and heating method using niosomes as a model nanoparticles.

Method: Niosomes using MF were prepared on a NanoAssemblr□. Monopalmitin, cholesterol and dicetyl phosphate were dissolved in ethanol at specific molar ratios. The lipids and aqueous buffer were injected into separate chamber inlets of the micromixer. The flow rate ratio (FRR; ratio between aqueous and solvent streams) and the total flow rate (TFR) of both streams were controlled by syringe pumps. An established TFH and heating methods were used to prepare niosomes followed by extrusion through an Avanti-polar miniextruder. The particles generated from these methods were compared for their size and potential by dynamic light scattering and morphology using atomic force microscopy.

Results and Discussion: The size of niosomes produced by MF was controlled by altering the FRR and TFR in both the lipid and aqueous phases (Table 1). In contrast, niosomes prepared by the TFH method and heating method were large, polydisperse and required a post-manufacturing extrusion size reduction step (around 4μm ± 0.2 before extrusion). A stability study was performed on NISV generated by both methods, at four temperatures (4, 25, 37 and 50°C) for 4 weeks, and the vesicles were shown to be stable in terms of size and polydispersity index (PDI) (Table 2).

Conclusion: Stable, controlled size niosomes, were manufactured by MF in seconds. The TFH method

and heating method also produced stable niosomes, but the process took several hours and the resulting vesicles were polydisperse and required an extrusion step to control the size. Studies are on-going to determine the drug entrapment efficiency and biological impact of controlled size vesicles.

Table 1: Characteristics of NISV prepared at different flow ratios between the aqueous and the lipid phase through MF. *Progressed to stability studies. n=3

FRR Aqueous/solvent	Size (nm)	PDI	Z potential (mV)
1:1	187.8	0.12	-27.2
3:1	166.1	0.05	-21.4
5:1	120.6	0.16	-19.2

Table 2: Characteristics of NISV prepared by TFH and MF stored at 4°C for four weeks. n=3

	Microfluidics		TFH	
Time (weeks)	Size (nm)	PDI	Size (nm)	PDI
0	166.1	0.05	110.6	0.18
1	170.7	0.05	110.8	0.18
2	171.8	0.06	111.5	0.21
3	171.9	0.07	111.4	0.24
4	172.0	0.06	111.2	0.23

Biography

Mohammad Obeid is an Assistant professor at the Faculty of pharmacy, Yarmouk University, Irbid, Jordan. He is the head of pharmaceutics and pharmaceutical technology department and specialized in designing lipid based nanoparticles as a delivery system. He was successfully developed stable nanoparticles and tested their efficacy in the delivery of different therapeutic agents such as siRNA, curcumin, doxorubicin and various types of antibiotics and vaccines. The aim of his work is to prepare these nanoparticles at industrial scale for large batches production.

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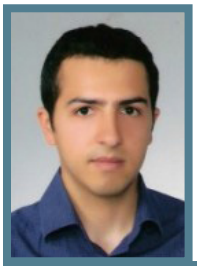

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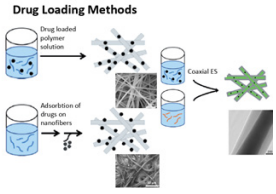
Novel Strategies for Nanofiber based Controlled Release Drug Delivery Systems

Controlled drug delivery systems have many advantages compared to conventional drug delivery systems such as, reduced drug level fluctation and adverse effects, need of fewer drug administration and improved patient complience. Electrospinning method has gained popularity in pharmaceutical area due to its ability to produce nanofiber based drug delivery systems with a wide variety of polymers and drugs. In addition to their unique properties, nanofiber based drug delivery systems have many routes of drug administration. In nanofiber based drug delivery systems, it is possible to provide controlled drug release profiles by using suitable polymer or suitable coating methods. One of these methods is the preparation of effervescent floating drug delivery systems. In the first part of the study, nanofiber formulations containing sodium bicarbonate were prepared and controlled release of the active substance was achieved. Sodium bicarbonate discs were embedded inside the nanofibers and gas bubbles were created in acidic medium. These gas bubbles provided the system to float in the stomach. Simultaneously, the active substance was released from the nanofibers with a controlled release profile. Another method is the coating outside of the nanofibers with a hydrophobic polymer layer to achive controlled release of the active substance. For this purpose, parylene types C and N were used as coating material with two different amounts. It was found that the increasing of coating material decreased the released active substance from the nanofibers. In addition, parylene type C was found more effective in case of delaying the release of active substance. Both of parylene types were found successful for preventing the burst release of active substance from the nanofibers. It is especially important to provide controlled release for the oral and transdermal systems. With the systems developed in this study, it is possible to provide controlled release of the active substance for both drug delivery routes.



Recent Publications

1. Tort, S., Han, D., & Steckl, A. J. (2020). Self-inflating floating nanofiber membranes for controlled drug delivery. International Journal of Pharmaceutics, 579, 119164.

2. Tugcu-Demiröz, F., Saar, S., Tort, S., & Acartürk, F. (2020). Electrospun Metronidazole-Loaded Nanofibers for Vaginal Drug Delivery. Drug Development and Industrial Pharmacy, 1-37.

3. Tort, S., Demiröz, F. T., Cevher, Ş. C., Sarıbaş, S., Özoğul, C., & Acartürk, F. (2020). The effect of a new wound dressing on wound healing: Biochemical and histopathological evaluation. Burns, 46(1), 143-155.

4. Tort, S., Demiröz, F. T., Yıldız, S., & Acartürk, F. (2019). Effects of UV exposure time on nanofiber wound dressing properties during sterilization. Journal of Pharmaceutical Innovation, 1-8.5.

5. Eskitoros-Togay, Ş. M., Bulbul, Y. E., Tort, S., Korkmaz, F. D., Acartürk, F., & Dilsiz, N. (2019). Fabrication of doxycycline-loaded electrospun PCL/PEO membranes for a potential drug delivery system. International journal of pharmaceutics, 565, 83-94.

Biography

Serdar Tort has completed his master of science thesis, which is related with development of controlled release tablet of morphine, in 2011 from Gazi University. Then, he received his Ph.D degree in 2016 from the same faculty in the area of nanofiber wound dressings for acute/chronic wound healing. He has completed his postdoctoral studies between 2018-2019 at the University of Cincinnati, developing nanofiber based controlled drug release systems. He also works on nanoparticular controlled drug delivery systems, 3D printing systems and novel dosage forms.