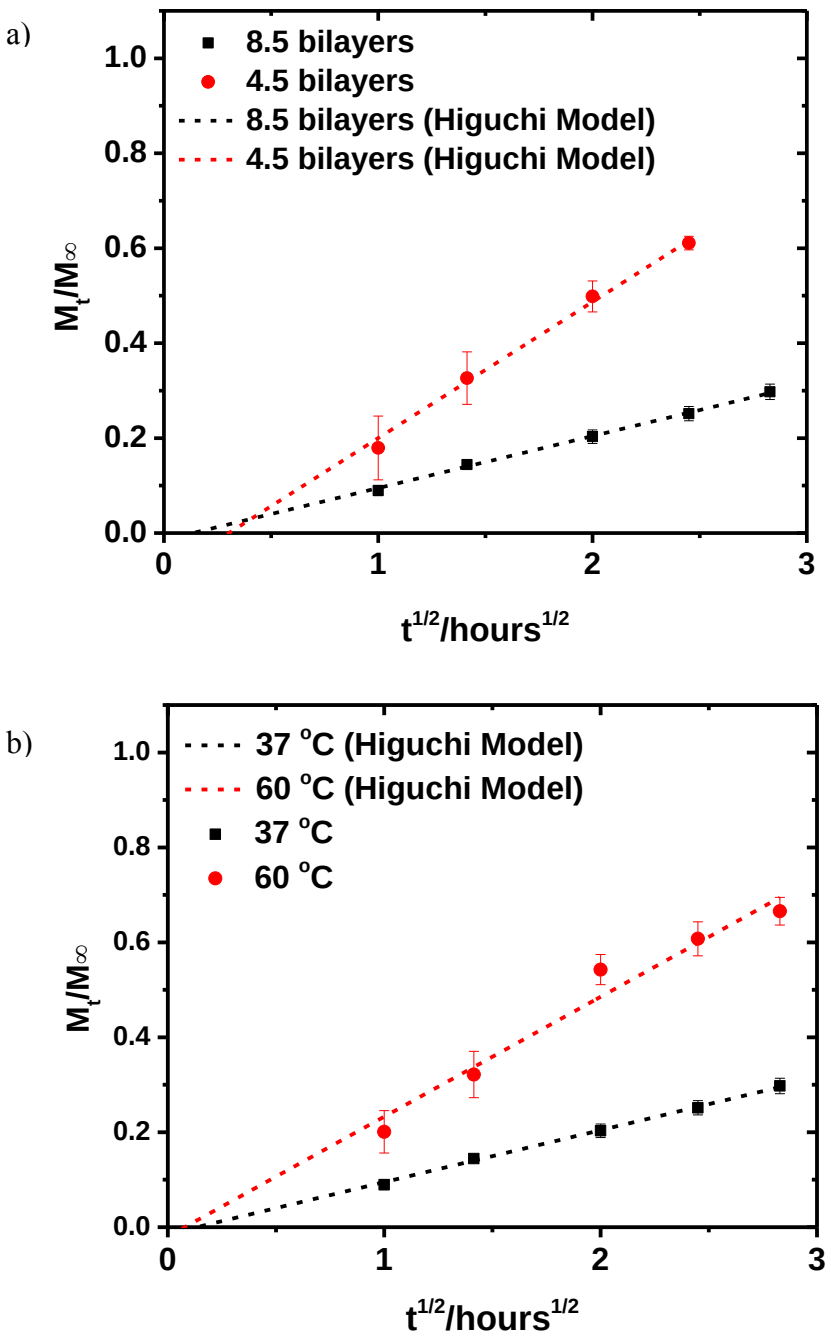
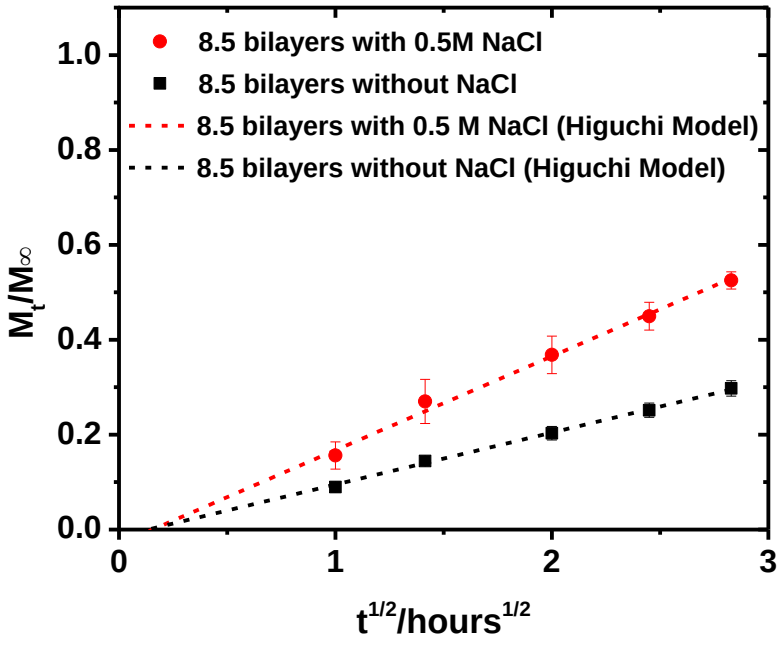


Figure 4-11. Higuchi model fitting exploring a) layer effect, b) salt effect, c) thermo-response of $(PDAC/PSS)_{8.5}$ LbL-coated DXM NPs assembled at 0.5 M NaCl, d) thermo-response of $(PDAC/PSS)_{8.5}$ LbL-coated DXM NPs assembled without NaCl. The slope (k), axis intercept (a) and correlation coefficient (R^2) were shown in Table 1.

c)



d)

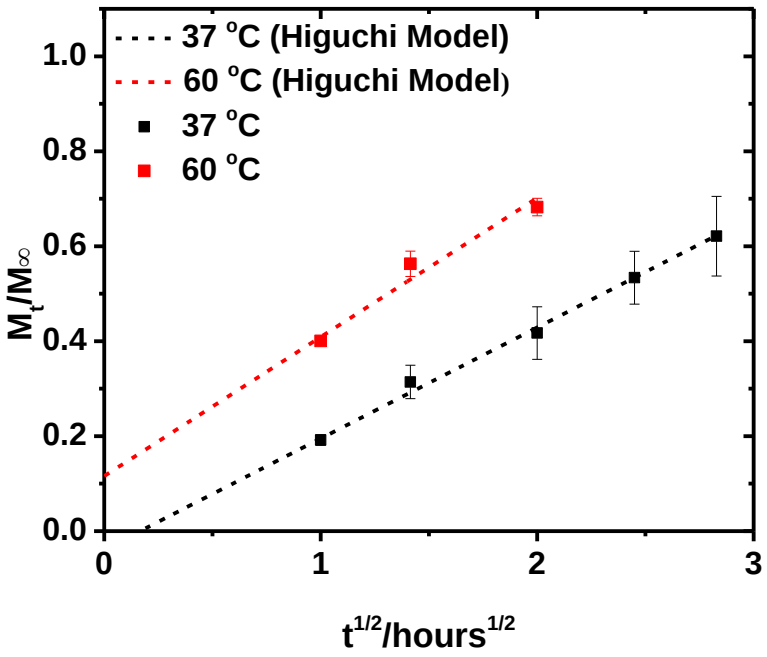


Figure 4-11 Continued

Plots from Higuchi model show good linearity for all release profiles explored, indicating that diffusion is likely to be the main factor controlling DXM release from those delivery systems. Release rate constants are obtained from the slope and correlation coefficients, Table 4-1. The Higuchi constant k_H is associated with the amount of drug per volume, diffusion coefficient, and drug solubility, and its value varied for different delivery systems. An increase in the number of layers appears to decrease the value of k_H. An increase in the ionic strength appears to increase the value of k_H. As temperature increased from 37 ^oC to 60 ^oC, the k_H of LbL-coated DXM NPs assembled at 0.5 M NaCl increased by 21%, whereas the k_H of LbL-coated DXM NPs assembled without NaCl increased by 127%.

Table 4-1. The Higuchi model fitting and release kinetics constants

Sample	Higuchi constant, $k_H^{-1/2}$	A	R^2	Figure reference
$(PDAC/PSS)_{4.5}$ assembled without NaCl, 37 ^oC	0.28 ± 0.01	-0.08 ± 0.03	0.99	Figure 4-11a
$(PDAC/PSS)_{8.5}$ assembled without NaCl, 37 ^oC	0.110 ± 0.004	-0.013 ± 0.007	0.99	Figure 4-11a, 4-11b, 4-11d
$(PDAC/PSS)_{8.5}$ assembled at 0.5 M NaCl, 37 ^oC	0.24 ± 0.01	-0.04 ± 0.01	0.99	Figure 4-11c
$(PDAC/PSS)_{8.5}$ assembled without NaCl, 60 ^oC	0.25 ± 0.03	-0.01 ± 0.07	0.93	Figure 4-11d
$(PDAC/PSS)_{8.5}$ assembled at 0.5M NaCl, 60 ^oC	0.29 ± 0.03	0.11 ± 0.03	0.98	Figure 4-11c

Korsmeyer–Peppas model (Power Law Equation)

The Korsmeyer–Peppas model,[80] or power law equation, $Mt/M_\infty=kt^n$, is a semi-empirical relation describing the general solute release behavior of controlled release systems. $(M_t)/(M_\infty)$ is the fractional drug release, t is the release time, k is a constant incorporating the coupling of solute diffusion and matrix relaxation phenomena, and n is the diffusional exponent, indicating the release mechanism. For release from a swellable sphere, solute release kinetics are dependent on drug diffusion and polymer relaxation. If the polymer swelling front advances faster than the drug diffusion, Fickian diffusion kinetics are expected and is defined by n=0.43. If drug diffusion is much faster than the swelling front advances, zero-order kinetics is expected and is defined by n=0.85.[81] In other words, higher n indicates that the release is more controlled by viscoelastic relaxation of the matrix, whereas lower n indicates that the release is more controlled by pure Fickian-diffusion. Many release behaviors fall between these limiting cases and is defined by n values between 0.43 and 0.85.[82] Because it is valid for the first 60% of the normalized drug release, we were able to fit the release profiles with at least four points (including fixed zero) lying within 60% of fractional release, Figure 4-5b, 4-6b, 4-8c, 4-8d, and 4-10. We obtained different values of exponent n and constant k as summarized in Table 4-2.

Table 4-2. The Korsmeyer–Peppas model fitting and possible mechanism of diffusional release from swellable controlled release systems

Sample	Diffusional exponent, n	Kinetic constant, k/h^{-n}	R^2	Release mechanism	Figure reference
Spherical sample	0.43	--	--	Fickian diffusion	--
	0.43<n<0.85			Anomalous(non-Fickian) transport	--
	0.85			Case-II transport	--
$(PDAC/PSS)_{4.5}$ assembled without NaCl, 37 ^oC	$0.58_{\pm}0.05$	$0.22_{\pm}0.02$	0.99	Non-Fickian diffusion	Figure 4-5b
$(PDAC/PSS)_{8.5}$ assembled without NaCl, 37 ^oC	$0.53_{\pm}0.02$	$0.098_{\pm}0.003$	0.99	Non-Fickian diffusion	Figure 4-5b, 4-6b, 4-8d
$(PDAC/PSS)_{8.5}$ assembled at 0.5 M NaCl, 37 ^oC	$0.57_{\pm}0.02$	$0.194_{\pm}0.005$	0.99	Non-Fickian diffusion	Figure 4-6b, 4-8c
$(PDAC/PSS)_{8.5}$ assembled without NaCl, 60 ^oC	$0.6_{\pm}0.1$	$0.22_{\pm}0.04$	0.94	Non-Fickian diffusion	Figure 4-8d
$(PDAC/PSS)_{8.5}$ assembled at 0.5 M NaCl, 60 ^oC	$0.39_{\pm}0.03$	$0.400_{\pm}0.001$	0.99	Fickian diffusion	Figure 4-8c
$(PDAC/PSS)_4$ assembled at 0.5 M NaCl, 37 ^oC	$0.39_{\pm}0.04$	$0.32_{\pm}0.02$	0.96	Fickian diffusion	Figure 4-10

The Korsmeyer–Peppas model fits the experimental data well with over 95% goodness of fit, enabling a further understanding of possible release mechanisms. Except

for the DXM release at 60 ^{o}C from $(PDAC/PSS)_{8.5}$ LbL nanoshells assembled at 0.5 M NaCl, the values of n are the same, lying between 0.43 and 0.85, indicating a non-Fickian or anomalous transport mechanism. For DXM release at 60 ^{o}C from $(PDAC/PSS)_{8.5}$ LbL-coated DXM NPs assembled at 0.5 M NaCl, the value 0.39 ± 0.03 of n indicates a Fickian transport mechanism. This result may not be reliable due to limited data points.

We next examined the influence of various parameters on kinetic constant k in the power law. An increase in the number of layers appears to decrease the value of k. An increase in the ionic strength appears to increase the value of k. For both $(PDAC/PSS)_{8.5}$ LbL NPs assembled at 0.5 M NaCl and without NaCl, k doubled as temperature increased.

In the power law, k has a specific physical significance $k=6(D/\pi a^2)^{1/2}$ in the case of Fickian-diffusion, where D is the diffusional coefficient and a denotes the radius of a sphere.[83] A decrease in k indicates either an increase in "a" or a decrease in D. As the number of layers increased, the films inner structure remained the same but thickness increased, suggesting an increase in "a". However, the influence on D was hard to conclude. Because PDAC/PSS LbL shell assembled without NaCl is much thinner compared to those assembled at 0.5 M NaCl,[14] as the ionic strength increased, "a" increased. The decrease in k should be associated with D. Upon heating, PDAC-terminated shells swell, resulting in an increase in "a". Thus the increase in k as temperature increased was attributed to an increase in D. The difference of temperature response is hard to be

correlated with either diffusional coefficient or particles radius because the degree of particles swollen upon heating for the respective ionic strength has not been investigated.

These new results allowed us to discuss the interplay of polymer chain mobility and free volume cavities affecting DXM release through PDAC/PSS LbL shells. Here, the rate of DXM release from exponentially growing LbL shells, which exhibits a glass transition, has more changes in polymer chain mobility. If polymer chains served to retard DXM movement through the assemblies, more changes in their mobility might cause more changes in the rate of DXM release. In contrast, the rate of DXM release from exponentially growing LbL shells saw less of a change upon heating, indicating that polymer chain mobility was not a dominant factor here. An increase in polymer chain mobility allows polymer rearrangement, which may lead to a change in the distribution of free volume cavities within the LbL. The difference of such a change in exponentially growing LbL shells and linearly growing LbL shells may explain the difference in the thermo-response of DXM release from these delivery systems. Thus it is interesting to next examine the properties of free volume cavities, including size and concentration, within exponentially growing LbL shells and linearly growing LbL shells at this present temperature window. A more clear explanation of how free volume cavities within LbL shells affect drug release will be discussed.

5. CONCLUSIONS

A thermo-responsive NP-based drug delivery system was developed using PDAC/PSS as the model. The influence of various parameters on DXM release from PDAC/PSS LbL NPs, such as number of layers, ionic strength of the adsorption solution, temperature and outer-most layer, has been investigated. Results disprove the hypothesis that the glass transition of PDAC/PSS LbL nanoshells enhances drug release in this particular DXM NPs-PDAC/PSS system.

DXM NPs at an average size of 201 $\pm$ 96 nm were obtained by a modified solvent evaporation technique and then encapsulated into strong polyelectrolytes of PDAC/PSS using a LbL assembly technique. The successful layer adsorption was demonstrated by ζ –potential, XPS and TEM. By applying the power law to DXM release profiles obtained, DXM release from LbL NPs was estimated to be non-Fickian diffusion. Results have shown a controlled DXM release rate from NPs by tuning number of layers and ionic strength of the adsorption solution. Results have also indicated a more temperature response in the rate of DXM release from linearly growing LbL of PDAC/PSS (assembled without NaCl), which do not exhibit a glass transition, than from exponentially growing LbL of PDAC/PSS (assembled at 0.5 M NaCl), which exhibit a glass transition. Such a difference was attributed to the variation in the change of free volume cavities existing in LbL, suggesting a possible approach to enhance thermo-responsive DXM release from LbL nanoshells by tailoring the properties of cavities. By tailoring the properties of cavities, an ideal thermo-responsive drug delivery

system may be obtained. This thermo-responsive NP-based drug delivery system with tunable permeability may possibly realize an “on” or “off” drug release mechanism in response to temperature, thus providing an alternative approach to delivering therapeutics with reduced toxic effects.

6. FUTURE WORK

Future work will investigate the change in the properties of free volume cavities within exponentially growing PDAC/PSS LbL shells and linearly growing PDAC/PSS LbL shells upon heating, thus elucidating more straightforward causes behind these thermo-responsive drug release phenomena. Characterization tools such as PAS can be used to measure the properties of free volume cavities. Other LbL systems that exhibit glass transition behavior will also be investigated on the properties of free volume cavities and thermo-responsive drug release. Considering factors affecting internal structure of LbL films, such as free volume cavities and polymer chain mobility, an ideal thermo-responsive drug delivery system may be obtained. Furthermore, *in vitro* release studies for investigated thermo-responsive delivery systems will be explored when exposed to an "on" or "off" drug release mechanism in response to heat.

The long term goal in this research is to develop a remotely triggered light-responsive drug delivery system. Near-infrared light (NIR) (650-900 nm) has become an attractive light resource because it is less harmful and allows for penetration of deep tissues. By inserting gold NPs into capsules wall, NIR-induced heat generation on gold NPs will raise the capsules' temperature, which may lead to an enhancement in drug permeability; therefore, remotely triggered NIR-responsive drug release can be achieved. Overall, the present research offers an opportunity in the development of the further combination of hyperthermia therapy with chemotherapy and photothermal therapy in cancer treatment.

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