International Journal of Medical, Medicine and Health Sciences
ISSN: 2517-9969
Vol:9, No:6, 2015

Numerical Investigation of Thermally Triggered Release Kinetics of Double Emulsion for Drug Delivery Using Phase Change Material

Yong Ren, Yaping Zhang

***Abstract*—**A numerical model has been developed to investigate the thermally triggered release kinetics for drug delivery using phase change material as shell of microcapsules. Biocompatible material n-Eicosane is used as demonstration. PCM shell of microcapsule will remain in solid form after the drug is taken, so the drug will be encapsulated by the shell, and will not be released until the target body part of lesion is exposed to external heat source, which will thermally trigger the release kinetics, leading to solid-to-liquid phase change. The findings can lead to better understanding on the key effects influencing the phase change process for drug delivery applications. The facile approach to release drug from core/shell structure of microcapsule can be well integrated with organic solvent free fabrication of microcapsules, using double emulsion as template in microfluidic aqueous two phase system.

***Keywords*—**Phase change material, drug release kinetics, double emulsion, microfluidics.

I. Introduction

THE microcapsule has attracted increasing attention in the past decade because of the intrinsic core/shell structure, whereas the microscale liquid droplet, solid particle or gas bubble is surrounded by a shell, which works as a physical barrier to separate the core from the outside environment. Microcapsules are good candidates for encapsulating, transporting, or releasing functional materials, and they have consequently been widely used in variety of applications, including food and beverage industry [1], [2], cosmetic components [3], [4], biochemical sensors [5], [6], chemical catalyst reactions [7], [8] and oil recovery [9]. They also act as an important role especially in pharmaceutical industry, for instance, the drug can be encapsulated in the core/shell structure of microcapsule, and will be released with certain external stimulus in human body [10]-[12]. One of the major classes of microcapsules has microcapsule core in liquid form, while shell in solid form, which can overcome a shear stress. Conventional microcapsule fabrication methods include interfacial polymerization [13], [14], polymer phase separation [15], [16], as well as electrospraying [17], [18]. Nonetheless, these approaches usually lead to microcapsules with polydisperse sizes and structures, results in highly variable loading levels, and poorly controlled release kinetics [19]. For instance, shape and size of drug delivery vesicles have significant impacts on the initial burst effect and the drug release kinetics [20]-[23]. Thus the use of microcapsules can be severely limited in a number of real industrial applications. The advances in microfluidics offer an alternative solution to the microcapsule synthesis. Microfluidics refers to the science and technology that process or control small amounts of fluids using devices with characteristic dimensions of tens to hundreds of micrometers, and it offers a number of advantages such as low fabrication cost; short analysis time and high integration of multiplexing functions on a chip [24]. The technology can be applied to address the problems encountered by conventional microcapsule fabrication methods, because it offers good control over the flows of multiple fluids by adjusting geometry of device, and the flow rate, using microfluidic multiphase system, which can be applied in a wide variety of applications. For example, it can facilitate drug encapsulation and release using emulsion droplets as a template to fabricate core-shell microspheres, or capsules [25]-[27]. As one of promising approaches, double emulsions can be fabricated by microfluidics to produce drops of the core material as inner phase within drops of another fluid as middle phase, which is subsequently suspended in a continuous fluid as outer phase. The middle phase is solidified to create solid shell of the microcapsules. The droplet size is determined by the shear forces, which can be carefully tuned in a microfluidic device via control over the device geometry configurations and the flow conditions. Compared to the counterparts made by conventional methods, microfluidic double emulsion can be used as template to fabricate microcapsules with good monodispersity, and compositions and morphologies in controlled manner.

Investigations have been conducted to study the release kinetics involved in the process as microcapsules release their encapsulated contents at a prescribed rate when they are subject to a specific stimulus – such as pH change due to chemical reaction [28], a temperature change [29], or an external stress [30]. The release can also be facilitated by solid-to-liquid phase change. For instance, polystyrene undergoes a solid-to-liquid phase change as it can absorb hydrocarbon oil, thus it has been used to fabricate shell of microcapsules for oil recovery applications [30]. Despite that, the fabrication process requires organic solvent, and droplets often need to be washed repeatedly to remove any remaining oil phase prior to being used as microcapsule. This hinders the microfluidic biomedical applications such as drug delivery. An organic-solvent free

Y. Ren is with the Department of Mechanical, Materials & Manufacturing Engineering, The University of Nottingham, Ningbo, China (corresponding author; phone: 86-574-88189064; e-mail: yong.ren@ nottingham.edu.cn).
Y. Zhang is with the Department of Electrical and Electronic Engineering, The University of Nottingham, Ningbo, China.

approach to fabricate droplets is thus needed. This problem can be well addressed by aqueous two-phase systems (ATPS), which can be used to form the double emulsion as template to fabricate microcapsules [31]. However, solid-to-liquid phase change will become challenging in absence of oil phase. In this paper, we present a thermally triggered release approach for drug delivery using phase change material (PCM) in ATPS. As a biocompatible material, n-Eicosane in water solution is used as the PCM to fabricate the shell of the microcapsule. The melting range of n-Eicosane is 309-310 K, slightly higher than the average body temperature of 309 K. We assume the average temperature in blood vessel is same as the average body temperature, this implies the PCM shell of microcapsule will remain in solid form after the drug is taken, so the drug will be encapsulated by the shell, and will not be released until the target body part of lesion is exposed to external heat source, which will thermally trigger the release kinetics, leading to solid-to-liquid phase change. A numerical model is developed in the paper, and release kinetics is investigated for better understanding on the key effects influencing the phase change process for drug delivery applications.

II. Numerical Model

A. Governing Equations

The basic equations governing the fluid motion and the heat transfer are mass conservation, momentum conservation and energy equations as,

$$\nabla \cdot v = 0 \tag{1}$$

$$\nabla \cdot \rho v v = -\nabla p + \nabla \cdot \tau \tag{2}$$

$$\nabla \cdot v\rho E + p = k\nabla \cdot \nabla T + \nabla \cdot \tau \cdot v \tag{3}$$

where v, ρ, p, τ, E, k, and T represent fluid velocity, density, pressure, shear stress, energy, thermal conductivity and temperature, respectively. The equations are solved by computational fluid dynamics (CFD) software Ansys Fluent using finite volume technique. Our simulation is based on the following assumptions to simplify the problem. Fluid continuum is assumed because of low Knudsen number in the computational domain of blood vessel which surrounds the microcapsule with drug encapsulated in core and shell made by PCM, as shown in Fig. 1 (a). We assume the blood possesses the same property as that of water. The inner phase in core is water as well. Fluid is assumed to be Newtonian and incompressible. Only the space nearby the microcapsule in the blood vessel is considered in our model to reduce the computational cost. The symmetry boundary condition is applied on each surface of domain of blood vessel with size of 1 mm. Constant temperature is applied at the interface between core and shell, and the interface between the shell and the blood vessel. Fluid properties are assumed to be independent on temperature. Buoyancy effects are neglected as density is assumed to be constant. The fluid-particle nature of n-Eicosane in water solution is simplified by assuming a homogenous liquid with physical properties dependent on the concentration of PCM. No volume change is assumed during the phase change process. The interaction among the microcapsules and the interaction between microcapsule and wall of blood vessel are ignored.

Phase change process is assumed to take place within melting range of temperature between 309-310 K, and the solid-to-liquid transition of PCM shell is modeled by adopting the solidification/melting approach. For temperatures below and above the melting range, the specific heat of the PCM shell is weighted average of the specific heats of the water solution and n-Eicosane material. For temperatures in the melting range, specific heat is the weighted average of fluid specific heat and the corresponding effective specific heat of the n-Eicosane material based on its latent heat. This effective specific heat is obtained using the latent heat and the melting range. The computational domain is meshed by Ansys ICEM 14.0, and the generated grids are illustrated in Fig. 1(b). The grid size sensitivity study has been conducted, and it is found the solution can reach convergence with grid size of 0.07, 0.01, and 0.02 mm, for blood vessel, shell and core, respectively.

B. Materials

The n-Eicosane particles are dissolved in the carrier fluid of water to form the PCM. The volumetric concentration of PCM of 15% was applied for all the simulations. The latent heat of n-Eicosane is 230kJ/kg. The properties of PCM mixture of shell, such as viscosity, and density can be calculated by [32],

$$\mu_b/\mu_f = (1-c-1.16c^2)^{-2.5} \tag{4}$$

$$\rho_b = c\cdot\rho_p + (1-c)\cdot\rho_f \tag{5}$$

where the subscripts b, f and p stand for bulk, fluid and particle (PCM), respectively. The properties of fluid and n-Eicosane particles, as well as the combined properties of PCM mixture of shell are listed in Table I.

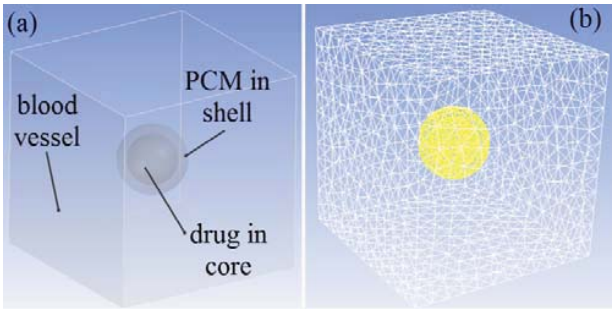

Fig. 1 (a) The numerical model of the double emulsion for drug release (b) The mesh generated by Ansys ICEM 14.0

TABLE I
Material Properties in the Simulation

	Density (kg/m3)	Cp (kJ/kg-K)	k (W/m-K)	Viscosity (N-s/m2)
n-Eicosane	946.4	1.973	0.15	
Water	998	4.179	0.613	0.000855
Mixture	989.41	3.862	0.5246	0.001388

III. Results and Discussion

The model was first validated by adopting a circular channel filled with same PCM under constant heat flux condition, and the simulation results were compared with experiments on PCM fluid flow in the same geometry with the same thermal conditions [33]. Good agreement was found. Subsequently, the mesh of microcapsule in blood vessel was used in the study. Time lapse images of phase change process when thickness of PCM shell is 0.05 mm at heated temperature of 313 K are demonstrated in Fig. 2. Initially, the shell is at solid state, thus it can protect the encapsulated substance in the core, as the temperature of 313 K is higher than melting range, it takes only 0.06 s to complete the solid-to-liquid phase change process. Finally, the encapsulated substance such as drug can be released from core to the blood vessel.

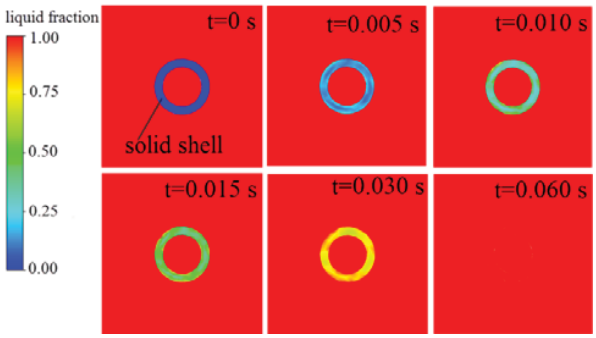

Fig. 2 Time lapse images of phase change process when thickness of PCM shell is 0.05 mm at heated temperature of 313 K

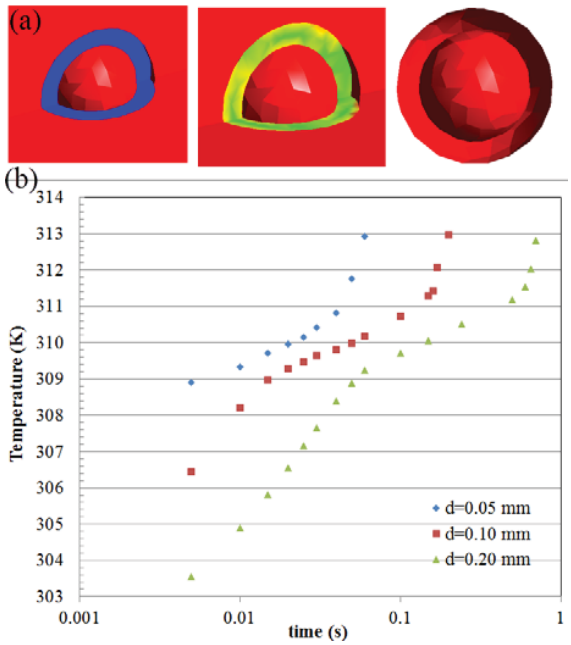

Fig. 3 (a) Isometric view of the 3D phase change simulation results at t=0, 0.02 s and 0.06 s, respectively (from left to right) when thickness of PCM shell is 0.05 mm at heated temperature of 313 K. (b) Evolution of volumetrically average temperature of PCM shell with different thicknesses

The wall thickness effect is also investigated. Fig. 3 (a) shows the isometric view of the phase change process at different time. The volumetrically average temperature of PCM shell with different thicknesses was numerically calculated, three cases were studied, with wall thickness d=0.05, 0.1 and 0.2 mm, respectively. The evolution of temperature indicates that the microcapsule with smallest thickness can require shortest time to complete the phase change process, as shown in Fig. 3 (b). Nusselt number was investigated to compare the heat transfer performance. The dimensionless number is dependent on three parameters including heat transfer coefficient, wall thickness and thermal conductivity. As shown in Fig. 4, highest Nusselt number is found when d=0.05 mm, indicating that it has the highest effectiveness of the convective heat transfer process taking place between core and shell, and also between the shell and the blood vessel.

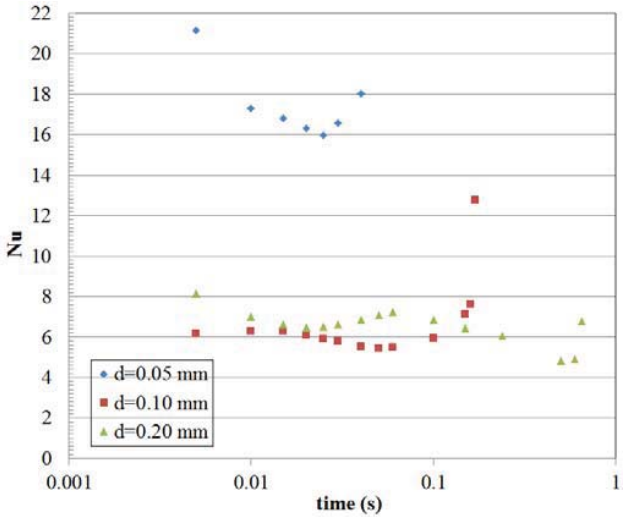

Fig. 4 Nusselt number for different thicknesses of PCM shell

IV. Conclusion

The thermally triggered kinetics to release drug from microcapsule with core/shell structure has been numerically investigated. Phase change material is used to fabricate the shell and the shell can be liquefied in the absence of non-biocompatible organic solvent such as oil. Heat transfer in phase change process is studied. The shell thickness effect on release kinetics has been investigated. Microcapsule with small thickness can require short time to complete the phase change process. However, mechanical property of shell may be compromised with small thickness. This will be investigated in future. The study provide the new insight to understand the underlying physics in the thermally triggered phase change process by a facile and biocompatible approach, which can be well used for biochemical applications including drug delivery.

Acknowledgment

The authors acknowledge the funding support from the conference attendance grant, and the Sandpit Research Award offered by Faculty of Science and Engineering, University of

Nottingham Ningbo China.

REFERENCES

[1] A. Madene, M. Jacquot, J. Scher, and S. Desobry, "Flavour encapsulation and controlled release – a review,"*Int. J. Food Sci. Technol.*vol.41, no.1, pp.1-21, 2006.

[2] D. J. McClements, E. A. Decker, and J. Weiss, "Emulsion-based delivery systems for lipophilic bioactive components," *J. Food Sci.*vol.72, pp.109-124, 2007.

[3] R. Karnik , F. Gu , P. Basto , C. Cannizzaro , L. Dean , W. Kyeimanu, R. Langer, and O.C. Farokhzad, "Microfluidic platform for controlled synthesis of polymeric nanoparticles,"*NanoLett.*vol.8, no.9, pp. 2906, 2008.

[4] K. Saskia, L. Peter, S. Ute, and N. Hiroshi, *Fragrance Journal*, vol.33, pp. 51, 2005.

[5] M. J. McShane, J. Q. Brown, K. B. Guice, and Y. M. Lvov, "Polyelectrolyte Microshells as Carriers for Fluorescent Sensors: Loading and Sensing Properties of a Ruthenium-Based Oxygen Indicator," *Nanoscience and Nanotechnology*, vol.2, pp. 411-416, 2002.

[6] L. I. Kazakova , L. I. Shabarchina, G. B. Sukhorukov,"Co-encapsulation of enzyme and sensitive dye as a tool for fabrication of microcapsule based sensor for urea measuring," *Phys. Chem.Chem. Phys.*vol.13, pp.11110, 2011.

[7] S. L. Poe, M. Kobaslija, and D. T. McQuade, "Mechanism and application of a microcapsule enabled multicatalyst reaction," *J. Am. Chem. Soc.* vol.129, pp.9216, 2007.

[8] C. Ramaraoa, S. V. Ley, S. C. Smith, I. M. Shirley, and N. DeAlmeidac, "Polyurea encapsulated palladium acetate: a robust and recyclable catalyst for use in conventional and supercritical media," *Chem. Commun.* vol.13, pp.1132, 2002.

[9] J. Sheng, "Modern Chemical Enhanced Oil Recovery: Theory and Practice," *Gulf Professional Publishing*, 2010.

[10] C. H. Choi , J. H. Jung , D. W. Kim , Y. M. Chung, and C. S. Lee, "Novel one-pot route to monodisperse thermosensitive hollow microcapsules in a microfluidic system," *Lab Chip*vol.8, pp.1544, 2008.

[11] B. G. De Geest, A. G. Skirtach, A. A. Mamedov, A. A. Antipov, N. A. Kotov, S. C. De Smedt, and G. B. Sukhorukov, "Ultrasound-triggered release from multilayered capsules," *Small*, vol.3, pp.804, 2007.

[12] T. He , K. Zhang , X. Mu , T. Luo , Y. Wang , and G. Luo, "A modified microfluidic chip for fabrication of paclitaxel-loaded poly (l-lactic acid) microspheres," *Microfluid. Nanofluid*. vol.10, pp.1289, 2011.

[13] K. Bouchemal, S. Briancon , E. Perrier, H. Fessi , I. Bonnet, andN. Zydowicz, "Synthesis and characterization of polyurethane and poly(ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification,"*Int. J. Pharm*, vol. 269, pp.89, 2004.

[14] T. Dobashi, F. J. Yeh, Q. C. Ying, K. Ichikawa, and B. Chu, "Experimental Investigation on the Structure of Microcapsules," *Langmuir*, vol.11, pp.4278, 1995.

[15] A. Loxley, and B. Vincent, "Preparation of Poly(methylmethacrylate) Microcapsules with Liquid Cores.," *J. Colloid Interface Sci.*, vol.208, pp.49, 1998.

[16] P. J. Dowding, R. Atkin, B. Vincent, and P. Bouillot, "Oil core-polymer shell microcapsules prepared by internal phase separation from emulsion droplets. I. Characterization and release rates for microcapsules with polystyrene shells," *J. Am. Chem. Soc.*vol.20, pp.11374, 2004.

[17] R. Bocanegra , A. G. Gaonkar , A. Barrero , I. G. Loscertales ,D. Pechack , and M. Marquez, "Production of Cocoa Butter Microcapsules Using an Electrospray Process," *Journal of Food Science*, vol.70, pp.8, 2005.

[18] H. Chen, Y. Zhao, Y. Song, and L. Jiang, "One-step multicomponent encapsulation by compound-fluidic electrospray," *J. Am. Chem. Soc.*, vol.130, pp.7800, 2008.

[19] S. S. Datta, A. Abbaspourrad, E. Amstad, J. Fan, S. Kim, M. Romanowsky, H.C. Shum, B. Sun, A. S. Utada, M. Windbergs, S. Zhou, D. A. Weitz, "Double Emulsion Templated Solid Microcapsules: Mechanics And Controlled Release," *Advanced Materials*, vol.26, no.14, pp.2205, 2014.

[20] C. Berkland, M. King, A. Cox, K. Kim, D. Pack, "Precise control of PLG microspheresize provides enhanced control of drug release rate," *J Control Release*, vol.82, pp.137–47, 2002.

[21] D. Klose, F. Siepmann, K. Elkharraz, S. Krenzlin, and J. Siepmann, "How porosity and size affect the drug release mechanisms from PLGA-based microparticles,"*Int JPharm*, vol.314, pp.198–206, 2006.

[22] A. Budhian, S.J. Siegel, and K.I. Winey, "Haloperidol-loaded PLGA nanoparticles: systematic study of particle size and drug content," *Int. J. Pharm.*vol.336, pp.367–75, 2007.

[23] G. J. S. Dawes, L. Fratila-Apachitei, K. Mulia, I. Apachitei, G. J. Witkamp, J. Duszczyk, "Size effect of PLGA spheres on drug loading efficiency and release profiles,"*J Mater Sci – Mater Med*, vol.20, pp.1089–94, 2009.

[24] G.M. Whitesides, "The origins and the future of microfluidics," *Nature*, vol. 442, no.7101, pp.368-373, 2006.

[25] H.C. Shum, D. Lee, I. Yoon, T. Kodger and D.A. Weitz, "Double Emulsion-Templated Monodisperse Phospholipid Vesicles," *Langmuir*, vol. 24, pp.7651–7653, 2008.

[26] C.I. Zoldesi, P. Steegstra and A. Imhof, "Encapsulation of emulsion droplets by organo-silica shells," *J. Colloid Interface Sci.*, vol.308, pp. 121–129, 2007.

[27] Y. Ren, Z. Liu and H.C. Shum, "Breakup dynamics and dripping-to-jetting transition in a Newtonian/shear-thinning multiphase microsystem," *Lab Chip*, vol.15, no.1, pp.121 – 134, 2015.

[28] S. H. Kim , J. W. Kim , J. C. Cho , and D. A. Weitz,"Double-emulsion drops with ultra- thin shells for capsule templates," *Lab Chip*, vol.11, pp.3162, 2011.

[29] S. Zhou, J. Fan, S. S. Datta, M. Guo, X. Guo, and D. A. Weitz, "Thermally switched release from nanoparticle colloidosomes," *Adv. Func. Mater.*, vol.23, pp.5925, 2013.

[30] A. Abbaspourrad, N. J. Carroll, S. H. Kim, and D. A. Weitz, "Polymer microcapsules with programmable active release," *J. Am. Chem.Soc.*, vol.135, pp.7744, 2013.

[31] Y. Song, A. Sauret, and H. C. Shum, "All-aqueous multiphase microfluidics," *Biomicrofluidics*, vol.7, pp.061301, 2013.

[32] R. Sabbah, M. M. Farid, and S. Al-Hallaj, "Micro-channel Heat Sink with Slurry of Water with Micro-encapsulated Phase Change Material: 3D-Numerical Study," *Applied Thermal Engineering*, vol. 29, no. 2-3, pp. 445-454, 2009.

[33] B. Chen, X. Wang, R. Zeng, Y. Zhang, X. Wang et al., "An Experimental Study of Convective Heat Transfer with Microencapsulated Phase Change Material Suspension: Laminar Flow in a Circular Tube under Constant Heat Flux," *Experimental Thermal Fluid Science*, vol. 32, pp. 1638-1646, 2008.

Yong Ren obtained Ph.D. degree in mechanical engineering from the Hong Kong Polytechnic University (HKPU) in 2013. Prior to pursuing his Ph.D. degree, he had worked as a mechanical engineer in industry. His dissertation focuses on investigation of centrifugal microfluidic flow and mixing with applications in cell culture and cell lysing, and the research can lead to automated bio-sample preparation and nucleic acid analysis for lab-on-a-chip applications. Before joining the University of Nottingham Ningbo China as assistant professor, he worked as a research assistant at HKPU, followed by postdoctoral research associate at microfluidics and soft matter group of University of Hong Kong. He has broad range of academic interests including microscale fluid dynamics, heat and mass transfer, CFD, multiphase flow, bio-MEMS device fabrication, biomaterial synthesis, and biomedical applications using the technology of droplet microfluidics and centrifugal microfluidics.