Drug Delivery Devices
BME Qualifying Exam
Assigned: 10:00 am Thursday, January 18, 2024
Due: 11:59 pm Friday, January 19, 2024
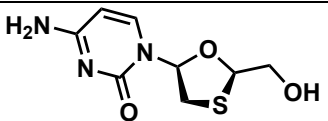### Exam given by S. Rahima Benhabbour

Instructions:

• Write your name and sign the honor code on the Last page only (this is to ensure the exams are graded in a blinded fashion).

• There is no group work allowed. All answers must be completed independently.

• When answering questions, please be concise but thorough. Your answers should reflect your understanding of the concepts, of the problem and the tools needed to address it. Use your own words and justify your answers.

• You must answer all questions for full credit.

• Keep your answers to 10 typed pages (single space) with a font size of 12 pts and margins of no less than 0.75 inches on all sides.

• Grades will take into account both the accuracy of the answers as well as the depth of knowledge shown based on the items listed in the exam study guide.

• You may need to do additional literature search and reading in order to fully answer some of the questions.

Sources in addition to those posted with the qualifying exam information on the BME website that are necessary for completion of this exam:

1. **Noninvasive Characterization of *In Situ* Forming Implant Diffusivity Using Diffusion-weighted MRI:** Hopkins KA, Vike N, Kennedy J, Simmons E, Rispoli J, Solorio L. Journal of Controlled Release. 2019 Sep 10; 309: 289-301.

2. **PLGA *In Situ* Implants Formed by Phase Inversion: Critical Physiochemical Parameters to Modulate Drug Release:** Parent M, Nouvel C, Koerber M, Sapin A, Maincent P, Boudier A. Journal of Controlled Release. 2013; 172: 292-304.

3. **Gelatin Methacryloyl Microneedle Patches for Minimally-invasive Extraction of Skin Interstitial Fluid:** Jixiang Zhu. Small. 2020 April; 16(16):e1905910.

4. **Long-acting PLGA microspheres: Advances in excipient and productanalysis toward improved product understanding:** Bo Wan, Quanying Bao, Diane Burgess. Advanced Drug Delivery Reviews 198 (2023) 114857.

Question 1: Answer all questions below regarding the Hopkins *et al.* Journal of Controlled Release 2019 paper:

1. Explain in details how magnetic resonance imaging (MRI) can be used to quantify changes in *in situ* forming implant (ISFI) diffusivity.
2. In this study, the effect of polymer (PLGA) molecular weight (MW) on drug release kinetics was investigated. Explain what this effect is and give examples based on the data presented in this study.
3. Figure 1 illustrates the in vitro release kinetics of a mock drug, fluoresceine, from two different ISFIs. Why does fluoresceine exhibit a tri-phasic release profile? Explain the difference between the two ISFI systems.
4. Scanning electron microscopy (SEM) can be used to visualize the microstructure of ISFI systems. Why was the implant microstructure analysis by SEM done up to day 10 for the PLGA MW 52 kDa and only up to day 5 for PLGA MW 5 kDa?
5. How would you expect drug release will be in vivo compared to in vitro based on the in vitro vs. in vivo implant shape and microstructure presented in Fig. 9?
6. What factors contribute to the large burst release of fluoresceine? How would you reduce this burst?
7. From the diffusivity analysis, where were different rates seen and what resulted in those differences? Explain with details and support your answer with data.
8. Why did drug release significantly decrease after the first 24 h? Support your answer with a clear rationale and data from the present study or supporting materials.
9. Explain how data from Fig 2A was used to support results from the diffusivity map illustrated in Fig 3-5.
10. Based on the evidence provided in this paper, design an ISFI that can provide sustained release of lamivudine (3TC, see information below) over a period of 90 days. Explain your choice and rationale for the ISFI formulation and what you expect to see both in vitro and in vivo in terms of drug release kinetics.

Drug	Chemical structure	MW (g/mol)	LogP	pKa	Class
Lamivudine (3TC)		229.2	-0.49	4.8	ARV-NRTI

ARV – Antiretroviral
NRTI - Nucleotide Reverse Transcriptase Inhibitors

Question 2: Answer all questions below regarding the Zhu Small 2020 paper:

1. What is the device platform described in this paper? What is its purpose?
2. Describe the design and fabrication of the device presented in Fig. 1.
3. What is the mechanism by which this device achieves its purpose?
4. List all the characteristics of the device described in Fig. 2.
5. What are the factors that influence the MN mechanical properties? Explain why these correlations are observed.

6. In this study, GelMA used as the hydrogel material for the MN fabrication was functionalized with methacrylate groups. How was the degree of methacrylation of GelMA determined? Support your answer with data from this study.
7. How was the MN device optimized to obtain the desired properties, i.e. mechanical, swelling, structural integrity etc.? Support your answer with clear examples and data.
8. What are the different mechanisms of ISF sampling used with MN? What mechanism was used for the GelMA MN described in this paper? How was this mechanism optimized?
9. Describe the experiments and results presented in Fig 3. How was effective fluid extraction determined?
10. How can you further improve ISF extraction using the GelMA MN device?

Question 3: Design.

Using the design principles detailed in the two highlighted papers in Questions 1 and 2 (and any supporting literature) design a drug delivery system (DDS) of your own to treat a specific tumor of your choice. Do not propose an example that has already been reported in the literature.

1. What disease are you targeting?
2. Is your device intended to treat post-surgery tumor recurrence or to treat solid tumors?
2. What tumor model will you use?
3. Will your study be conducted in vitro or in vivo or both?
    a. Which cell lines will you use?
    b. Which drug or treatment will you use?
    c. Chemotherapy or immunotherapy?
4. Describe the mechanism for drug release that you would choose and support the use of specific design aspects:
    a. Which delivery platform (e.g. hydrogel, liposome, ISFI, RBC other?). How is this platform suitable for your application?
    b. How is drug release controlled? What is the target duration of drug release?
    c. Which delivery platform (e.g. liposome, RBC other?). Is this well-informed for your disease application?
    d. Is this a targeted or untargeted drug delivery? What is the rationale for your choice?
    e. What is the route of administration? Why?
5. How will you characterize your DDS? What design metrics do you set for your device to ensure its successful performance?
6. How will you assess drug delivery and tumor killing efficacy?

Question 4: Design based on Bo Wan *et al.* Review

Based on learnings from Wan *et al.* what formulation parameters would you consider when designing a formulation for sustained delivery of a hydrophobic small molecule over 6 months using PLGA microparticles. List 3-5 main studies you would conduct in vitro and in vivo to test your formulation ahead of advancing it to human clinical trials. When you list your studies, you only need to briefly state their rationale and what the main outcomes are from each study (i.e. what major question you are answering with each study you select to conduct).