UF UNIVERSITY of FLORIDA

Department of Materials Science and Engineering

210A Rhines Hall
P.O. Box 116400
549 Gale Lemerand Dr.
Gainesville, FL 32611
Phone: 352-846-3336
Fax: 352-846-3355
Email: lgower@mse.ufl.edu

RE: Response letter to review of Manuscript ID: applsci-994886

Manuscript ID: applsci-994886
Type of manuscript: Article
Title: Liquid-Solid Core-Shell Microcapsules of Calcium Carbonate Coated Emulsions and Liposomes
Authors: Mark Bewernitz, Archana Lovett, Laurie Gower *
Received: 25 October 2020

Dear Editor and Reviewers at MDPI at Applied Biosciences and Bioengineering:

We thank the reviewers for the careful attention that was paid in reviewing our paper, and which we believe has led to enhancements in the revised version. We have addressed the Major and Minor concerns by providing point-by-point explanations and clarifications below, where each reviewer and revision has been addressed individually. Individual reviewers' comments are highlighted with the explanation written below.

An important point that we'd like to communicate which applies to more than one revision point: We are not proposing a specific core-shell microcapsule for a specific application. We believe the information we're reporting may be applied to many applications, not just biomedical. We did not focus on one because we think our report may be beneficial to a whole array of nano/microcapsule applications, such as industrial catalyst, environmental pesticide, skin and hair care products, as well as pharmaceutical. Studies such as cellular viability, uptake, intracellular release is crucial to specific cellular drug delivery and clearance but is beyond the scope of what we intended to report here, and, we believe, is not necessary to be included for our report to be valuable to this journal's readership. Other important properties, such as polydispersity and encapsulation efficiency are substrate specific. They will vary as the size and surface properties of the vast array of emulsions and liposomes vary. Our system was a model system, similar to many emulsions and liposomal microcapsule systems in use, to demonstrate proof of principle. The reported method of core-shell coating synthesis is meant to be a baseline starting point to researchers who will then tailor the methods to their specific application and synthesis conditions. We believe that the value of our studies is the demonstration that smooth continuous shells can be deposited on and removed from emulsion and liposomal microcapsules under benign conditions, and thereby provide the baseline "recipe" to do so. We envision this as an additional tool that many in the field may find useful to their specific applications but that specific applications may need further study. We agree with the suggestions put forth by the reviewers relating to measurement of size, PDI, and other studies and agree that these additional studies would be valuable to the report, but is not necessary until a specific application is targeted. Unfortunately, this study has been concluded as the graduate student has graduated and is no longer in a position to follow up this report with additional studies. We believe that, even in the absence of the suggested studies, that our report will be valuable and relevant to the

scientific community, and should be publishable after having addressed most of the pertinent comments below.

Reviewer 1

- Study 1) model drug release profile, 2) cell viability, 3) cellular uptake and 4) intracellular drug release of the degradable microcapsules.

Cell viability, uptake, release is very important for biomedical applications involving drug release applications. However, we are not focused specifically on biomedical applications, as mentioned above. The method and technique we report may require cell viability or may not, depending on the application that the reader envisions for their applications. The scope of our report is very broad. We are sharing our knowledge on this technique in hopes that some applications in either industry or medicine may find it useful. Given the broad potential and the non-specific application of our coating method, we did not focus on the cellular response to uptake, which is beyond the capability of our lab. But hopefully researchers who read this manuscript may be inspired to further the research in that direction.

- Size distribution (e.g. polydispersity, aggregation, and agglomeration, etc.) of the final products (microcapsules) is needed to be evaluated.

We agree that size distribution properties are important to evaluate for reports regarding whole microcapsule designs for specific applications. We are not reporting a specific microcapsule for a specific application but rather a method to apply to a diverse array of microcapsule types. That is why we chose two representative model particle systems, emulsions and liposomes. The PILP process of coating is directed by the substrate which is coated. The polydispersity of the substrate would largely direct the polydispersity of the resultant coated substrates, for example. Aggregation and agglomeration depend largely on the polydispersity and size of the coated emulsions or liposomes, any additional functionalization of the calcium carbonate shell which a tailored microcapsule may possess, and the conditions of the surrounding bulk solution. Given the vast array of potential applications for our reported technique it may be difficult for us to accommodate all of them and do them justice.

- **SEE LINES 447-464**

- Authors should explain how uniform-sized particles can be obtained (e.g. using syringe filters, centrifugation, etc.) and why these microcapsules have been produced in different sizes (diameters).
The explanation has been added to the text. This explanation has been added to the results section.

- **SEE LINES 267-272**

Reviewer 2

1) Introduction Section. Please provide further information regarding the state of the art of previously described core-shell nanoparticle systems. Please discuss the main differences and advantages regarding previously reported methodologies and the system described here by the authors.

To address your concerns, we have added additional text and citations to allow the reader to learn the state of the art of the field with respect to improvements to Pickering emulsions and liposomal microcapsules. There have been many proposed methods to address limitations. I added text to highlight differences in our approach and to highlight how our method may fit into the current research focus.

- **SEE LINES 79-102**

2) Results and Discussion section. The authors mention that the particles display "little polydispersity in diameter". Further data regarding the size distribution of the microcapsules should be provided in the manuscript. In particular, DLS will provide a more accurate indication of the size distribution of the nanoparticles in solution. The associated PDI values need to be reported and discussed.

We agree with the reviewer's assessment. We corrected a confusion. There is polydispersity present. We have corrected this and added additional text which was suggested by the other reviewer as well.

- **SEE LINES 267-272**
- **SEE LINES 447-464**

We agree that DLS would have been superb to add to this study. Unfortunately, this study has been concluded a few years ago and we are not longer in the position to follow up with your suggestion. We believe that the PILP process, being a coating process, will yield core-shell particles that match the polydispersity of the substrate particle its coating. Therefore, we contend that the report is valuable to share with the scientific community even when lacking this study.

3) The encapsulation efficiency of the system should be evaluated.

We agree. However, this study has been finished for a few years at this point and we are not in a position to continue the experiment. As described in the additional text, the encapsulation efficiency is expected to vary with different emulsion or liposome substrates, and should depend on whatever entrapment of active agent is already encapsulated with the substrate particles. The coating method would not be anticipated to alter this. Desirable efficiencies may be obtained in different applications and contexts by adjusting the materials and methods to suite the new application. We believe our information is still valuable to the scientific community even if lacking in encapsulation efficiency. We have added text to address your comment.

- **SEE LINES 447-464**

Thank you for your time and consideration,

Sincerely,

Laurie Gower

Laurie Gower, Ph.D.
Professor of Materials Science & Engineering