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Thesis Changes Log

Name of Candidate: Yuliya Kan

PhD Program: Materials Science and Engineering

Title of Thesis: Development of Core-Shell Fiber Composite Based on Polyvinyl Alcohol Modified with Graphene Oxide and Silica for Biomedical Applications

Supervisor: Prof. Alexander M. Korsunsky

The thesis document includes the following changes in answer to the external review process.

There were valuable comments and recommendation to the format and style the list of publications and references and reorganization of data. I would like to thank for the careful review of my thesis. I would like to attach the list of replies to the comments
Prof. G. Sukhorukov's, Prof. Y. Kotelevstev' and Prof. E. Marin', Prof. Wei Chih Lin' recommendations were to reorganize the drug delivery chapter and discuss future prospects and add the cell viability tests.
Prof. D. Gorin inquired about the referencing the bands of spectroscopic measurements to support the data.
I confirm that the Thesis structure was reorganized and new references and chapters were added including the assessment of biocompatibility (cell viability assay) and antibacterial efficiency of produced core-shell fiber composite.

Prof. R. Surmenev's comments/remarks on the PhD thesis.

- C1. Usually degree of crystallinity is calculated using DSC (which is also presented in the thesis), XRD allows also revealing nanocrystalline phase which may affect the shape of the amorphous halo, thus calculations of crystallinity can not be estimated correctly.
- C2. Usually GO contains some degree of reduction. Is it clearly visible via Id/Ig bands ration obtained via Raman spectroscopy? I would suggest a brief comment of the degree of reduction of the used GO. I observe that ID/IG ration exceeds 1. In addition, conductivity is an important property while electrospinning is used and GO or rGO behave differently due to different conductivity.
- C3. Based on my experience statistical analysis is required when tensile testing is used, since there are a lot of parameters affecting the results of the measurements. I would recommend providing the results as a mean and a standard deviation to reveal significance of the differences between the groups.

Reply to the Reviewer's comments:
RC1. Dear Professor, thank you for the comment. I clarified the XRD results and exclude the calculations of crystallinity based upon XRD, only DSC results were included in Table 9.
RC2. The I_D/I_G = 1.03 of as-received GO was found, that reports the reduction stage of GO. In the page 80, the ratio of I_D/I_G was compared for GO and PVA-GO and core-shell

PVA-PEG-SiO_2@PVA-GO fibers. The increase of disorders in the structure indicates the reduction trend of GO after being processed with electrospinning.
RC3. Thank you for the valuable comment, I noted that the significant fluctuation arises for the nonuniform specimens and tried to demonstrate the stress-curves of samples considering their cross-section area (Figure 15). The recalculated mechanical parameters were included in Table 10 with a mean value and standard deviations.

Prof. E. Marin's comments:

- C1. As a minus point, since the samples are intended for biomedical applications, *in vitro* testing could have provided additional information on the biocompatibility (cytotoxicity in particular) of the composites and their resistance to bacteria adhesion and proliferation.
- C2. Title: I suggest to use either "a core-shell fiber composite" or "core-shell fiber;
- C3. Table I doesn't show any statistical dispersion of the data, moreover the number of significant digits should be consistent (10.0, 8.4, 8.4, 9.0, using the second column as an example);
- C4. Figure 9(c): the water uptake doesn't present a statistical dispersion;
- C5. The discussion on the Raman results is hard to follow as only 3 bands have been clearly labelled in Fig. 10. Please consider tagging all the major bands;
- C6. In Fig. 10 how can you tell there is a CHX band at 1600 when the G band is exactly at the same position?
- C7. Raman bands for SiO_2 are usually very weak. In this case, I can't really spot them in the fiber results;
- Figure 11 has more labels, but the labelling method is inconsistent: some samples are labelled with band positions, others are labelled with vibrations and sometimes there in no label at all;
- C8. Please note that the x axis labels of Fig. 11a re cut suddenly;
- C9. The FTIR spectra are very similar to each other so differences are hard to spot. Please clearly mark what the readers should focus on;
- C10. As for Raman and FTIR, XRD bands should also be labelled clearly;
- C11. Again, Table 8 and Table 9 will require some statistics;
- C12. The international separator for decimals is ".". I don't know if the same standard applies in this case, but please confirm;
- C13. From Figure 20 (Loading Efficiency), the results are interesting but I can't really trust the trends without some solid statistics, as these materials tend to have a wide dispersion in loading efficiency and release, due to problems in uniformity and distribution;
- C14. At the end of this section, a short comparison with literature data could be an interesting addition, to understand if these mats behave better or worse than those developed by other research groups. A little more focus on the potential application (which could be the best way to use these materials?) would greatly improve the quality of the thesis, with only a little effort.

Reply to Reviewer's comments:
RC1. Thank for the comments. I considered the biomedical application of core-shell fiber composite, the several experiments were added included the results of viability assay for human fibroblasts and antibacterial test with agar disk diffusion assay accompanied with the bacteria response by monitoring the optic density. The results were added in Thesis in *Chapter 4.13 Antibacterial test* and *4.14 Cell viability assay.*
RC2. Core-shell fiber composite as a terminology was actively used throughout the text, unfortunately for thesis title it was accompanied with the detailed description, due to the regulations of title that was established before. I will consider this advise for the future publication.

RC3. Table 1 was fixed, only for core solution the weight ratios of components were left to indicate the input of silica suspension.
RC4. Water uptake results were fixed in Figure 8.
RC5-C9. The Raman section was renovated where the data were clarified in Table 6 with adding the referenced, Figure 9 and Figure 10 were labelled with the band positions, ratios of intensities for D and G bands of GO based composite were calculated, some brief comments were added about the core-shell encapsulated with CHX: the results of Raman do not clearly claim the presence of drug, that is why the additional characterization was provided: TOF-SIMS, Absorbance measurements in Chapter 4.8 and 4.12. The monitoring presence of silica were not obvious indeed, some comments were included in the text to define its presence with FTIR method (p 81).
RC10. Figure 11 was renovated to present the higher resolution of spectra with enlarged inset of research interest. Figure 12 were
RC11. Considering this comment, the measurements of crystallinity were not included in Table 8 because the data were not statically analyzed. only DSC results were included in Table 9.
RC12. The decimal separators were fixed.
RC13. Figure 19 with loading efficiency was supported by the encapsulation efficiency represented in the box chart graph.
RC14. The chapter of Future prospects was included to define the directions of core-shell fiber composite in terms of the wound dressing application.

Prof. Wei Chih Lin selected comments:

- C1. Since the context mentioned that applying the fabricated core-shell fibre mats for drug
- delivery application, it is suggested that a section to introduce drug delivery for wound healing
- application could be indicated in this part.
- C2. Please includes a section related to the antiseptic chlorhexidine (CHX) drug. There is a variety of drugs that could be integrated with the spinning solution. Please address the reason why this drug was selected and why it is crucial to wound healing. A table to indicate the comparison of drugs for wound healing applications could be valuable revealing in the section.
- C3. The core-shell fibre composite in form of a patterned scaffold was fabricated, but there are no sufficient literature reviews on the patterned scaffold. It is suggested to briefly introduce the patterned fibre mats into the study. Moreover, please also describe the importance of patterned fibre mats in drug delivery applications with some citations. Importantly, it is strongly encouraging to mention the advantages of the pattern nanofibers compared with nonwoven or aligned nanofibers in the drug delivery system.
- C4. On page 24, 1st paragraph, the name of the researcher/the research group could be mentioned instead of using the term “author/ reference group” for the statements describing their work.
- C5. On page 26, 2nd paragraph and reference format: [8,12,40,59,60], sometimes the citation format is in form of [6], [8,21], [20]. Please recheck all citation formats and standardized them.
- C6. Please give a brief concussion or discussion about the relationship between the measured viscosity and other results, such as mechanical properties. For example, also, is there any trend for response relative to the added amounts of GO or SiO2, etc.?

- C7. On page 57 in the 1st paragraph, the candidate stated that 14 cm collection distance is the optimal parameter to form bead-free fibre and homogenous fibre coatings. However, from figure S1, the collection distance of 17 cm shows a more uniform fibre distribution than 14 cm.
- C8. It is very nice to apply the ToF-SIMS to study drug loading but unfortunately there are not enough comments and conclusions addressed on page 80.
- C9. If possible, please use two different patterned collectors to fabricate the core-shell fibre composite on page 64 2nd paragraph. Which patterned fibre mats have the potential for drug delivery application? During the drug delivery experiment, which patterned fibre mats you used? Moreover, it states that the topography of fibre mats is a crucial factor in the case of cell adhesion. If possible, it is suggesting conducting a cell cytotoxicity test (at least 3 days) to determine whether the fabricated fibre mats have the potential to exhibit cell growth. The cell cytotoxicity test also could confirm that there is no adverse effect of using graphene oxide in your study.
- C10. Materials and methods should conclude clear description, conclusion should be clarified.

Reply to Reviewer's comments:
RC1. Chapter 1 were expanded by listing the current approaches to treat wound with long-healing case. The area of use was established for developed fiber composite.
RC2. The list of actual studies was attached in p 29 to claim the actuality of chlorhexidine in the wound dressing areas.
RC3. The chapter of Future prospects concluded the findings related with fiber dimension and suggested the future development of fiber composite by increase of its topology and possible alignment of fibers.
RC4-RC5. The statements were formatted carefully, the references were formatted in the same style.
RC6. The viscosity was a challenging, I gave some points about this in Chapter 4.1
RC7. The discussion about the experimental search of optimal tip-target distance was added in p 66. Where I gave the explanation related with how the parameter was selected by the complex of easy detachment of sample, defect-free structure.
RC8. TOF-SIMS results were renovated and brief discussion were included.
RC9. The mechanical test was accordingly refreshed and revised. The new drug release graphs were added to reorganize and focus on the drug delivery application. Also, cell viability was assessed and antibacterial function of fiber mats were included in the new chapters. I appreciate this suggestion to use different type of collector to expand new parameters, I will use this for the next stages of my research.
RC10. I expanded the methodology chapter by giving the detailed explanation of used sample and statistics analysis. Important statements of drug release results were included in the highlights of study in the end of Conclusion.
I appreciate the comments with details about the corrections and better representation of data, some figures I was not managed to add, due to the limited time. I tried to reorganize drug release data for better understanding of my research where the new two Chapters of biocompatibility and in vitro antibacterial function were added to deliver the medicated wound dressing application.