Young Postdoc Position: Theoretical and experimental study of polymer nanocoatings for prefilled syringes.

General Context: BD Medical Pharmaceutical Systems (BDM PS) is designing and manufacturing syringes for parenteral use. Those syringes are prefilled with a drug and can be used once for injection into the patient body. The drug solution contained in the syringe barrel is usually expelled from the syringe through a needle, by pushing a rod with an elastomeric stopper at the end to avoid leakage. In order to ensure smooth displacement of the stopper during injection, the inner wall of the syringe is usually coated with a polydimethylsiloxane (PDMS) lubricant.

When drug is in contact with PDMS, PDMS elution from the syringe walls into the drug can occur, and silicone droplets (called subvisible particles) with size inferior to 300 µm can be found in drug. An upper specification limit for the amount of particles in syringes is given by standards for prefilled syringes, and pharmaceutical company must comply with these standards to put drugs in prefilled syringes on the market. In a worst-case setting, complete elution of the PDMS coating in solution can lead to incomplete injections, where the drug is not fully transferred to the patient's body. Another risk with biotech drugs made of biomolecules is the aggregation of proteins with silicon subvisible particles that could potentially be a risk for the patient (Kotarek J., 2016), for example by triggering unwanted immune reaction.

To mitigate those risks, BDM PS has developed an innovative solution (Roberto A. Depaz, 2014) based on well-accepted prefilled syringe technology. By creating a cross-linked silicone barrier on the top of regular PDMS, subvisible particles generation is greatly decreased, and incomplete injection risks are strongly limited.

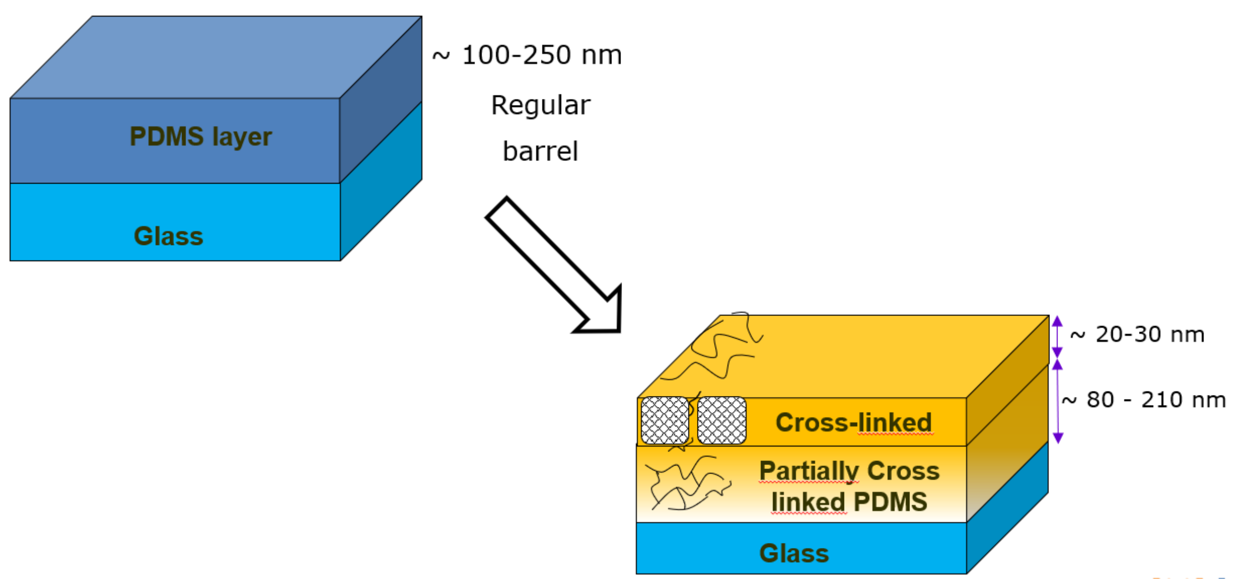

Figure 1: Structure of the cross-linked silicone

Specific context of work: Several important questions, however, remain open on the impact of this technology on the resulting coating/substrate system:

- While the cross-linked layer is functionally well characterized, further investigation is needed to understand the spatial structure of the coating in terms of bulk and surface mechanical properties and chemistry before and after cross-linking (Mills et al., 2008). A combined experimental and modeling work on model surfaces and eventually on actual syringes, with out-of-the-box thinking for surface and interface characterization at the nanoscale (Jongsoo Kim, 2000) will allow to develop a phenomenological model of the coated surface/substrate.
- The coating structure and syringe functional properties are highly dependent on the product and process parameters that are used to generate the cross-linked silicone layer. To determine the influence of the processing conditions on the surface morphology and microstructure of the coating layer, a chemomechanical model that accounts for the interplay, at the nanoscale, between molecular diffusion and deformation (both in the PDMS and the cross-linked layers) will be derived from the basic principles of continuum mechanics and the thermodynamics of nonequilibrium processes. The resulting hierarchy of free-boundary problems will be solved, analytically where possible, numerically otherwise, with values for the various parameters that enter the theory inferred from the experiments alluded to in the first bullet, and its predictions compared with experimental measurements."
- The "barrier effect" caused by the cross-linked layer between non-crossed linked silicone and the drug is known to greatly decrease subvisible particles generation and limit elution of the silicone in solution. However, the physical and/or chemical mechanisms of this "barrier effect" remain unknown. By extending the above theory, we will attempt (if the time allows) to develop a continuum model for the post-processing interactions between the cross-linked layer and the fluid mixture containing the drugs to be delivered.

The developed nanoscale models may also be used to numerically analyze the multi-scale character of the process, thus allowing for a better understanding of the impact of the process on these features. The validity of the models will be assessed with the help of corresponding industrial trials. Such results will allow to make the manufacturing process more robust and help in a future scaling-up of the technology. This, in turn, will increase the process throughput and will lead to upgrades on the technology currently used in production. Most parts of the proposed work will be carried out between the Laboratory of Solid Mechanics (LMS), Ecole Polytechnique and BDM PS, Grenoble.

Keywords: nanofilms and nanomechanics / prefilled syringe / multi-physics theoretical modeling / numerical modeling.

Required Skills: The postdoc candidate should:

- have a PhD in mechanical engineering, mechanics, soft-matter physics or a closely-related field,
- have the ability to develop mechanical and coupled models and at the same time to propose innovative strategies to validate those models in at an experimental environment,
- be interested in working on a rigorous theoretical and numerical modeling combined with experimental work,

- be open-minded, autonomous, and have demonstrated ability to work on complex topics in cross-functional teams.

Acquired skills: By pursuing the above-described postdoc, the student is expected to acquire a strong combined knowledge of experimental methods (e.g., image correlation techniques, AFM and SEM measurements) as well as of a rigorous theoretical multiphysics modeling. This knowledge together with the novelty of the project can equally provide industrial and academic opportunities after the end of the appointment.

Funding: The postdoc will be funded by BDM PS for a period of one year with competitive salary.

Starting date: The position is expected to start not earlier than October, 2019 but the search may continue beyond that date until a suitable candidate is found.

Requirements: The candidate should be expected to defend in the following months or not have more than one year since the defense of the PhD thesis.

Postdoc supervisors: Prof. Kostas Danas and Prof. Michel Jabbour (LMS, Ecole Polytechnique) and Carole Braley (BDM PS)

Place: Solid Mechanics Laboratory, Ecole Polytechnique, France

Contact info: Interested candidates are kindly requested to contact by email Prof. K. Danas (konstantinos.danas@polytechnique.edu) and Prof. M. Jabbour (michel.jabbour@polytechnique.edu) with at least 3 references (letters or contact names), a fully detailed CV with publication record and a 1-page (max) motivation letter.

Bibliography

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