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Evaluation of PhD thesis – Mgr Jana Kubackova

The PhD dissertation titled “Preparation of pharmaceutical formulations based on polymeric and lipid carriers” deals with a topic of high relevance and timeliness for pharmaceutical sciences. As an increasing number of newly developed active substances suffer from low bioavailability or unfavorable pharmacokinetics, it is important to investigate formulations that can improve both. Polymeric and lipid-based carriers certainly have the potential to become viable formulation approaches and provide a fertile ground for research.

The thesis is based on three apparently unrelated studies, presented in Chapters 4, 5 and 6. The first study (Chapter 4) investigated PLGA particles containing Rhodamine B for the targeting of intracellular receptors in macrophages. The second study (Chapter 5) was concerned with the encapsulation of indomethacin into lipidic nanoparticles. The third study (Chapter 6) explored the formulation of an oligonucleotide into a self-emulsifying system intended for oral delivery.

On the one hand, the variety of topics addressed in this dissertation demonstrates the ability of the candidate to identify problems of scientific significance and practical relevance, to apply experimental skills in many different areas, and to analyze literature and experimental data from several corners of pharmaceutical sciences. On the other hand, I can’t help feeling that the dissertation leaves too many loose ends. In a PhD dissertation, it is always a question whether there is more value in addressing one topic fully or several topics partially.

Upon reading the thesis, the following questions came to my mind:

1. Regarding the opening motivation of Chapter 4, could the candidate please specify which disease is caused by liver-resident macrophages, and what are the currently established treatment approaches, if they exist? Which drugs are used, and do they have any side effects or unfavourable pharmacokinetic profile that can be solved by encapsulation into PLGA particles?

2. In order to evaluate a new drug carrier, it is common to compare it against some reference (e.g. currently used formulation, non-encapsulated drug, or another experimental formulation published in the literature). How did the PLGA particles perform in this regard?

3. It is mentioned in the concluding parts of Chapter 4 that PLGA particles are suitable as “macrophage-specific carriers”. However, macrophages will eat almost anything you drop to the well plate – this is their job! The difficult thing is to target a specific organ in the body. Did you compare macrophages that reside in different organs (lungs, spleen, liver…) and did you really achieve specific uptake of the PLGA particles by only one type of macrophages (Kupffer cells) and not by the others?

4. The title of Chapter 4 refers to “nanocarriers… targeting intracellular receptors”. Which receptors did you target, how did you prove that the targeting was successful, and which particles did you use as a negative control? Which targeting moiety did you attach to the surface of your particles in order to achieve intracellular receptor targeting?

5. In Chapter 5, what exactly was the objective of this study? Which route of administration did you have in mind, and what are the currently used formulations available on the market or reported in the literature? Which problems or limitations of existing formulations did you aim to overcome, and what were your target CQA values?

6. How much indomethacin was actually contained in the final nanoparticles?

7. What do you consider to be the most important scientific conclusions of the work presented in Chapter 5 with regard to the state of the art?

8. In Chapter 6, what was the sequence of the oligonucleotide and which treatment or disease was it intended for?

9. What is the ultimate target of the oligonucleotide in the body? Does it need to decomplex from the DDAB or DOTAP complexes in order to reach the target and perform its biological function?

10. By what mechanism do you envisage that the oligonucleotide permeates across the Caco-2 cells? Is it by some kind of transcytosis?

11. Can it be expected that endonucleases present in the Caco-2 cells would partially digest the oligonucleotides, and was this somehow taken into consideration when evaluating the permeation experiments?

Regarding the formal aspects of the work, my observation is that the thesis is generally well written and logically structured. In summary, I believe that the PhD thesis of Jana Kubackova meets the basic requirements and therefore, I recommend that the dissertation should proceed to a public defence.

Piscataway, May 25, 2021

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