



SDI Review Form 1.6

PART 1:

Journal Name:	Ophthalmology Research: An international Journal
Manuscript Number:	MS: 2012/ OR/ 2442
Title of the Manuscript:	Formulation and physical characterization of a novel sustained-release ophthalmic delivery system for sparfloxacin: the effect of the biological environment

General guideline for Peer Review process is available in this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)

- This form has total 9 parts. Kindly note that you should use all the parts of this review form.



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PART 2: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	1.The author cannot predict the type of phase solubility diagram. He needs more points to get the best fitting. Only one point showed a significant increase in solubility (0.01 mM). 2.From the apparent $K_{1:1}$, it is clear that the binding is weak and the efficiency of CD to solubilize the drug is very low (1:20 CD/Drug molar ratio). Also one cannot predict the stoichiometry from the slope. Non linear regression may be needed to fit the data for such prediction. 3.The phase solubility diagram needs to be done in buffered water (pH 7) to compare with the findings in the dissolution and formulation works. 4.The author cannot have strong evidence that the prepared complex is real complex and improve the drug solubility unless he prepared the physical mixture of the drug and CD, off course after treating each component separately with the same procedure (e.g. lyophilizing with the same solvent) before mixing together. 5.The decrease in the intensity of peak by DSC as explained by the author (due to partial formation of complex) needs to be checked by preparing the physical mixture by simple mixing without mortar and pestle. If the phenomena remains most probable the decrease in the DSC peak is due to formation of	1- There were other points showed the increase in the solubility but not illustrated for curve simplification, as it was repeated several times using different molar concentrations. The phase solubility curve was modified to show more points in the paper Fig 3 page 10. 2-The apparent stability constant of sparfloxacin-cyclodextrin complex was calculated from the slope of the initial straight portion of the phase solubility diagram with the assumption of 1:1 stoichiometry 3-Really phase solubility diagram was performed only in water as it is mentioned in various research papers. 4- I did not use the lyophilization process to prepare the complex throughout my work . The physical mixture as mentioned in all research papers is prepared by simple mixing of the two components without any previous treatments. 5-The physical mixture in my experiment was prepared simply by mixing both ingredients (in the same molar ratio used for complex) with the aid of mortar and pestle just for mixing without grinding. To be honest, I am not sure what was happened



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	complex during running the DSC (e.g. due to heating in the presence of high content of water in the components). 6.Using the IR to prove complexation, the author needs to compare the spectra of the complex with the physical mixture not with that for the drug. 7.Also SEM scan for the freeze dried drug and CD alone to be run to prove change in morphology. Use the two components without treatment may lead to inadequate conclusions. 8.In case of dissolution, it is most probable if the author used the freeze dried drug and CD to prepare the physical mixture the difference in the %release will dimensioned between the complex and the physical mixture. 9.From the process point of view, using physical mixture rather than using freeze drying technique to prepare the complex is better. So I recommend to prepare the same formulas (FM1, FM2, FM3 and FM4) using just the physical mixture not the complex. Most probable this will lead to the gels.	actually during the DSC running process, but I am just trying to explain the results on the base of the intensity of the drug peak which was sharp before complexation. In addition if the complex was formed during DSC running of the physical mixture, why the drug peak did not disappeared completely as in case of the prepared complex. 6- I already compared IR spectra of complex with the pure components (drug, CYD), and with the physical mixture. It was illustrated by 4 IR spectra in Fig 5 page 13. Spectrum (c) is the physical mixture. 7- I did not use the lyophilization process to prepare the complex throughout my work. 8- The physical mixture in my experiment was prepared simply by mixing pure untreated ingredients (in the same molar ratio used for complex) with the aid of mortar as mentioned in many lectures. The physical mixture prepared from the treated components may reveal different results. 9-I did not use the freeze drying technique at all, but I used spray drying one. Which was proved to provide many advantages such as high efficiency in perfect complex formation, rapid technique, and controlled particle size yield. In addition, you have indicated in all your comments to prepare physical mixture from the
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	10. The data of LVR in the text and table different. Needs correction. 11. The difference in LVR values between FP2 and FM2 needs explanation. 12. Need more discussion on LVR, Breakdown stress and phase transition time. 13. The difference in the Hardness between FP3 and FM3 is insignificant, both are very small compare with the others, so no need for more explanation. Comparison of FP3 and FM3 with the others is worthy. 14. Conclusion needs to be summarised and focused on the suitable formulation. The detail discussion can be moved to "Result and Discussion" section.	drug and complexing agent after treatment by the same technique used to prepare the complex. I am not in manufacturing process, but I think it is easier to prepare the formulation from the complex (which prepared just by one process) instead of using the physical mixture that prepared after treating each individual component separately by the same process). 10- Corrected in table 11-Explanation and reference were inserted. 12- Corrected 13- Both are very small compared with others, but there was still a difference between the both, FM3 hardness was decreased to less than half FP3 hardness, I think it is worthy to be explained. 14- a summarised paragraph was added
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<u>Minor</u> REVISION comments	1. Table (9) changed to table (3) and Table (1)) to Table (4) in the text. 2. Reference 1, change Omaria to Omari, Daraghmeha to Darghmeh, Zughulc to Zughul, Chowdhryd to Chowdhry, Leharded to Leharne, and Badwana to Badwan. 3. Table (3), uniform the range by (-) or by (to) 4. Page 17, line 597, add "on" before $T_{sol/gel}$. 5. Page 17, line 605, ca^{+2} to Ca^{+2}. 6. Present the $K_{1:1}$ by 105 no need to be 105.0228 M^{-1}.	1-Corrected 2- Corrected 3- Corrected 4- Corrected 5- Corrected 6- Corrected
<u>Optional/General</u> comments	The manuscript needs more discussion and data elaboration. Strong evidence for complex formation is not presented Use of physical mixture instead of inclusion complex might lead to the same formulations.	Corrected I think all 3 used techniques confirmed the complex formation. I am not sure, may be reveal similar results or not.