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Journal Name:	<u>Journal of Advances in Medical and Pharmaceutical Sciences</u>
Manuscript Number:	Ms_JAMPS_29784
Title of the Manuscript:	SYNTHESIS OF UNSTABLE VATERITE POLYMORPH OF HOLLOW CALCIUM CARBONATE NANOPARTICLES AND ENCAPSULATION OF THE ANTICANCER DRUG CISPLATIN
Type of the Article	Original Research Article

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: 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	The manuscript reports the results of experiments characterizing the synthesis of unstable vaterite polymorph of hollow calcium carbonate nanoparticles and encapsulation of the anticancer drug cisplatin by the reaction between $\text{Ca}(\text{CH}_3\text{COO})_2$ and NaHCO_3 in a solvent mixture of H_2O and ethylene glycol (EG). The results are interesting and original. The interpretation of results is correct. Moreover, the manuscript is well organized and written in a clear language that could be further improved in the revised revision. Some points, however, would deserve the consideration of the authors and should be taken into consideration in a revision of the paper: 1- The authors concluded in the graphical abstract the mechanism of encapsulate cisplatin molecules by hollow nanoparticles (using precipitation reaction of NaHCO_3 with $\text{Ca}(\text{CH}_3\text{COO})_2$ in $\text{H}_2\text{O}/\text{EG}$ media) on normal tissue and tumor cell . Do the authors confirm that? Or still the main hypothesis of the work but not confirmed yet. Please, refer to that in your manuscript. 2- It is better to add the published literatures that referring to the recent works regarding cisplatin nanoparticles.	Thanks for highly recognizing our work. We encapsulate cisplatin in hollow nanoparticles of vaterite form of calcium carbonate in situ from cisplatin injection solution and we expect to administer it intravenously. The advantage is that we can increase the bioavailability and efficacy of the drug while reducing its toxic side effects and dosage. The side effects of cisplatin come from protein adducts formed when cisplatin reacts with thiol containing proteins present in blood plasma. The formation of these protein adducts decreases the bioavailability of the drug and the protein adducts and their degraded produced contribute to the cytotoxicity of the drug to healthy cells. Besides cisplatin as it is Can bind to DNA of healthy cells and destroy their DNA repair mechanism. All these problems can be overcome if cisplatin is encapsulated in a suitable host material for targeted delivery and selective slow-release at the vicinity of the cancer cells. Since calcium carbonate dissolves slowly in mildly acidic pH conditions prevailing in cancer cells, cisplatin is released there slowly and steadily. However, since blood pH is neutral to very slightly alkaline calcium carbonate is stable in blood and drug remains encapsulated in the blood. Thanks for this comment. As suggested by one



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	3- Please, add the main differences between your method and the previous method which developed by Zhao et al.	other referee also we have added more references. Zhao et al has introduced a template-free method to prepare vaterite form of calcium carbonate nanoparticles. We believe that under the conditions stipulated in our method, hydrogen-bonded networks of ethylene glycol and water with higher fraction of ethylene glycol are formed and are spherical in shape. These soft molecular templates direct the formation of almost monodispersed spherical nanoparticles of vaterite rather than forming thermodynamically more stable calcite form of calcium carbonate which is rhombohedral in shape. We further make use these hollow nanoparticle assemblies of vaterite to encapsulate cisplatin in them which is novel and nobody has tried before. However, we think that it is better not to compare different works and in order to respect the work of Zhao et al we have referred to it in our manuscript.
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		