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	Status	Comments	Phase entry date	Days in review
1	Editorial Review	-	22/Nov/20 17:48	--
3	Technical Modification	Remark	24/Nov/20 18:18	2 [2]
5	Editorial Review	-	01/Dec/20 02:51	9 [7]
	--do--	-	02/Dec/20 04:15	10 [1]
7	Peer Review	-	06/Dec/20 21:27	14 [4]
	--do--	-	02/Jan/21 19:45	41 [27]
9	Technical Modification	Remark	03/Jan/21 17:23	42 [1]
11	Editorial Review	-	06/Jan/21 12:06	45 [3]
13	Peer Review	-	13/Jan/21 18:17	52 [7]

	--do--	-	18/Jan/21 07:59	57 [5]
	--do--	-	21/Jan/21 18:57	60 [3]
	--do--	-	30/Jan/21 06:59	69 [12]
16	Editorial Review	-	31/Jan/21 08:11	70 [1]
18	Under revision	Remark	31/Jan/21 20:58	70 [0]
20	Editorial Review	-	19/Mar/21 03:11	117 [47]
22	Peer Review	-	22/Mar/21 11:28	120 [3]
24	Editorial Review	-	09/Apr/21 14:38	138 [18]
26	Technical Modification	Remark	11/Apr/21 17:03	140 [2]
28	Editorial Review	-	16/Apr/21 02:05	145 [5]
30	Editorial review	-	17/Apr/21 09:09	146 [1]
32	Manuscript charges	-	28/Sep/21 09:28	310 [164]
34	Technical check	-	28/Sep/21 09:37	310 [0]
	--do--	-	02/Oct/21 12:38	314 [4]

andang miatmoko <andang-m@ff.unair.ac.id>

[RPS]:Article for revision:RPS_232_20

2 messages

Research in Pharmaceutical Sciences <editor@rpsjournal.net> Mon, Feb 1, 2021 at 3:58 AM
Reply-To: editor@jrps.ir
To: andang-m@ff.unair.ac.id

If you cannot see this page properly, please **click here.**

Dear Dr. Miatmoko,

NOTE: This e-mail is sent to you as one of the contributing authors. If you are not corresponding author, please co-ordinate with the author designated by your group as the corresponding author for this manuscript

Status of the manuscript titled 'Characterization and distribution of niosomes containing ursolic acid coated with chitosan layer' submitted by Dr. Andang Miatmoko has been changed and a copy of the mail is as;

Dear Dr. Miatmoko

With reference to your manuscript entitled 'Characterization and distribution of niosomes containing ursolic acid coated with chitosan layer', please review the comments of the referees from our site https://www.journalonweb.com/jrps. The manuscript would be reconsidered after requisite modifications as per the comments and instructions provided by the journal.

If you wish to continue with the publication process, kindly make the changes using **track change mode** according to the comments and upload the revised manuscript from the site along with the point to point clarifications to the comments indicating clearly where in the manuscript the changes have been carried out. Do check the FAQ related to replying to the comments and uploading a file. The contributors' form/images should be sent separately to the Administrative Office of the journal.

The journal allows four weeks for the revision of the manuscript. If we do not hear from you within this period, we will consider it your non-desire to continue the article with us. Please also note that submission of revised article does not guarantee i ts final acceptance by the journal.

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Dear Author

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to consider my decision.

[REVIEWER1]:

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[REVIEWER 2]:

Thank you for considering me as a reviewer for article entitled" characterization and distribution of niosomes containing ursolic acid coated with chitosan layer". After review of this article, my comments and questions are as below:

The article is written very poorly. It sho uld be rewrite. The discussion is very weak. It cannot be considered for publication in this format.

This system was developed to increase bioavailability of ursolic acid. However , nearly 70 % of drug was released in GI. How do the author explain the benefit of ursolic acid loading in noisome and chitosan coated noisomes?

Please demonstrate the structure of niosomes remains unchanged in acidic media used for coating.

Prepare SEM after and before coating with chitosan

Please use table to show the result of physicochemical characteristics of drug instead of figures

Please determine the major characteristics bonds of each component of formulation in FTIR study and then discuss about the changes of these peaks in final formulation

The visual observation isn't sufficient for stability study. To demonstrate stability of formulation, particle size, zeta potential and encapsulation efficiency should be studied

The plasma concentration profile is required to compare bioavailability of formulations. The concentration at one point is not sufficient

---

[REVIEWER 3]:

The authors prepared Ursolic acid niosomes coated with chitosan and the effect of different ratios of formulation component on physical characteristic and stability of niosomes were evaluated.

I think this is a well-written manuscript and has some interesting results. In my opinion, the manuscript is suitable for publication however comments below may be helpful for the minor revision before publication.

In “in vivo study” did the Nio-UA-Cou-6 or UA-CS-Cou-6 contained the UA and Cou-6, simultaneously? Did the author loaded Cou-6 in to the niosomes as the same way of UA?

I think this should be mentioned in the manuscript.

Some typos need to be fixed:

Lines 286-288: Coumarin-6

Lines 311, 348: Cholesterol

Line 315: polydispersity index

Line 382: amount

Line 386: weas

Line 388: (Wang et.al., 2017)

Line 394, 396: ursolic acid

The representation of “encapsulation efficiency “is not uniform throughout the manuscript

Double spaces must be checked throughout the manuscript.

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Thank you for submitting your valuable work to Research in Pharmaceutical Sciences journal. For further process of your manuscript please consider the following comment.

1- Please provide cover letter/first page according to INSTRUCTION TO THE AUTHOR section. Your cover letter should include the following parts:

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2- In the reference section, please reduce the number of references to 35.

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-Please insert the Latin characters (A,B,..), out of the figure on the top of the left corner.

-If a figure has different parts including different graphs or images, therefore different Capital/UPPERCASE letters in Times New Roman, solid black or white (depends on background color), and bold must be assigned to each part at

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Thank you in advance for your cooperation

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Dear Dr. Miatmoko,

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Yours sincerely,
Jaber Emami
Research in Pharmaceutical Sciences
Remarks:

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Reply to the reviewers' comments

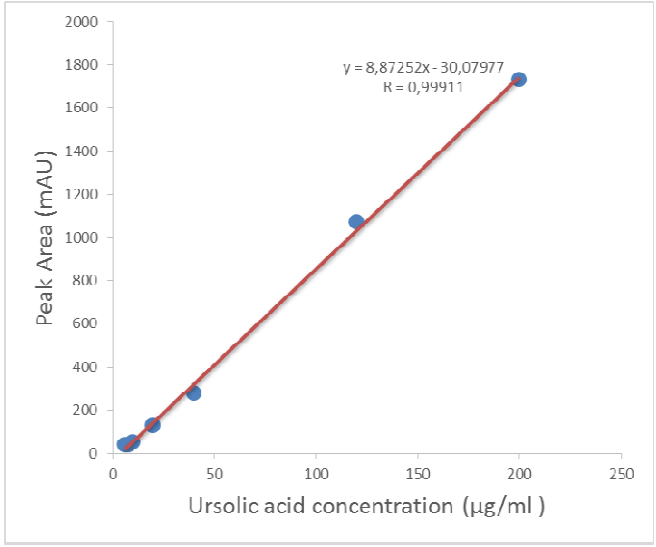
Reviewer Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
		We have changed "chemotherapy agent" with "cancer therapy" in the abstract section	Page 1: line 7
		We have added the keyword of cancer	Page 2: line 26
		There was mistaken in inputing the data, which the written average data is replication 1 data, so, we have changed the average zeta potential from -43.96 to -46.23 as the following: Page 13 line 257: "The addition of chitosan to the sample also increased the ζ-potential value from -46.32 ± 3.56 mV" We have also corrected the abstract as the following: Page 1 line 19: "which increased from -46 mV to -21 mV"	Page 13: line 257 Page 1: line 19
		There were mistaken in writing the results information. The figure 5A-C represents the cumulative UA released from the niosomes; however, the information written in the results section of **The in vitro release of Ursolic Acid from niosomes with chitosan layers** stating about the release efficiency, which these two parameters are different. So, we have revised the manuscript according to cumulative drug release (%) appropriately, as the following: Page 14-15 line 291-295: "The cumulative UA release from Nio-UA after the test lasting 360 minutes was 19.77% on 0.1 N HCl pH 1.2, 13.67% on PBS pH 6.8, and 12.76% on PBS pH 7.4 media. Meanwhile, the cumulative UA released from Nio-UA-CS was 14.27% in 0.1 N HCl pH 1.2, 15.29% in PBS pH 6.8, and 16.27% in PBS pH 7.4 media. Based on these results, the relative high cumulative drug release for Nio-UA was occurred at gastric pH 1.2."	Page 14-15: line 291-295
		We have change the term of "release efficiency" to drug release in the	Page 20: line 398

		discussion section as the following: Page 20 line 398: “The results obtained indicated that the highest drug release of Nio-UA” Page 20 line 407: “In contrast, at pH 6.8 and 7.4, the cumulative UA release of Nio-UA-CS”	Page 20: line 407
		In the method section, we stated the use of cumulative drug release and release efficiency data to compare the effect of chitosan addition on UA release from niosomes; however, the results were similar in their trends. Moreover, the figure 5A-C only represents the cumulative drug release. So, we deleted the release efficiency analysis and revise the references by deleting the reference number 24 in the Page 9 line 169-174. Page 23-27: the number of references have been revised from 35 to 34 references	Page 9: line 169-174 (deleted) Page 23-27; the number of reference has been reordered

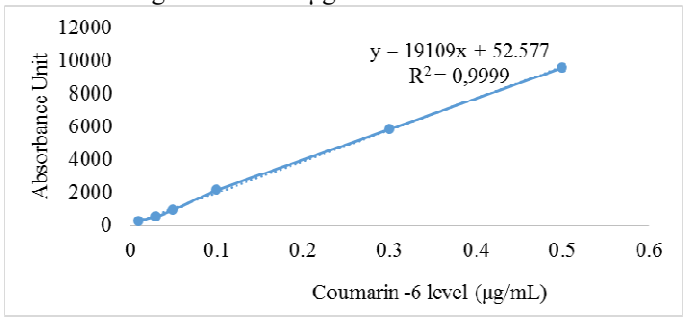
Reply to the reviewers' comments

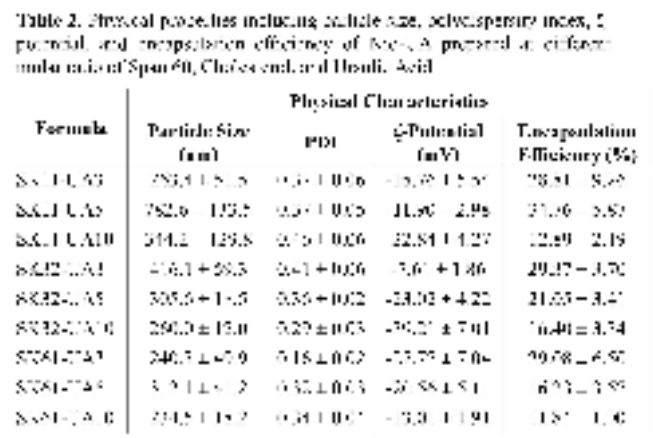
Reviewer Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
1	The introduction section is too long but does not provide enough justification about the novelty and contribution of the current work compared to previously published reports for example as stated by respected reviewer UA liposome (ref 19 and 32) have been previously reported. . what are the novelty and priority of the current work compared to UA liposomes?	Many thanks for the comments. In this study, we focused on the use of niosomes that composed of cholesterol and span 60, which are more economically used carriers than liposomes, to deliver ursolic acid systemically through oral administration. In the previous study the use of liposomes loaded ursolic acid composed of soy phosphatidylcholine was administered via intragastric administration (ref. no. 19) and intravenous infusion (ref. no. 32). However, it has been known that the use of phospholipids may be damaged by gastrointestinal enzymes, thus by using niosomal carriers, it is intended to obtain more stable drug carriers to deliver drug entering systemic blood circulation. We have revised the introduction as the following: We have deleted some sentences in Page 3: line 31-33, line 36-39, Page 4: line 62, line 69-74, Page 5: line 86-88, line 93. We have added a sentence in Page 5 line 93-95 as the following: "….., niosomes have been developed to provide more economically used and stable drug carriers against gastrointestinal environments than liposomes for an oral chemotherapy"	Page 3: line 31-33, line 36-39 Page 4: line 62, line 69-74 Page 5: line 86-88, line 93 Page 5 line 93-95
1	Pls define the abbreviation BW	Many thanks. BW means body weight, we have changed the BW with body weight in Page 3 line 47 as the following: "…8,330 mg / Kg body weight"	Page 3 Line 47
1	Pls define all of the abbreviations for the first time	Many thanks. Cps means centipoise, we have revised the sentence in Page 6 line 110 as the following: "…19 centipoise (cps) chitosan"	Page 6 line 110
1	Preparation of noisome should be defined in details lipid phase was dissolved in organic acid and other procdeure should be provide in detail	Many thanks. In this study, the cholesterol and Span 60 each was dissolved in chloroform, while the ursolic acid was dissolved in methanol. We have added some details in Page 6-7 line 119-124 as the following: "At first, cholesterol and Span 60 were dissolved in chloroform, while UA was dissolved in methanol. Niosome-loading UA (Nio-UA) was prepared with various drug-surfactant-cholesterol mole ratios, as shown in Table 1. UA was then passively trapped in the niosomes using a thin film method by completely evaporating the organic solvents using a rotary vacuum evaporator at 60ºC."	Page 6-7 line 119-124
1	Define PBS	Many thanks. PBS refers to phosphate buffered saline and we have revised the sentence as the following: "…by adding phosphate buffered saline (PBS)"	Page 7 line 124

<table>
<tr><td>1</td><td>Niosome loading UA was changed into Nio-UA</td><td>Many thanks, in this section we meant niosome loading UA for Nio-UA and Nio-UA-CS. We have revised the subheading as the following:
“Characterization of Nio-UA and Nio-UA-CS”</td><td>Page 7 line 134</td></tr>
<tr><td>1</td><td>the abbreviation of EE should be defined when the word is presented for the first time</td><td>Many thanks, we have revised the use of EE as the following:
“…this affects the percentage of drug entrapment efficiency/EE (24,25)”

“…Based on the results obtained, the EE was further calculated using equation 1”</td><td>Page 4 line 69
Page 5 line 79
Page 8 line 149</td></tr>
<tr><td>1</td><td>particle size zeta potential and ee should be reported in stability study</td><td>Many thanks for the comment. In this study, we just observed the visual stability of the samples during the time period of study referring to reference no. 41. Further study by evaluation of particle size, zeta potential, and EE should be needed, however, we focused on choosing the optimal formula for loading UA in niosomes and this visual observation may reflect the comprehensive results of physical stability during the storage</td><td>-</td></tr>
<tr><td>1</td><td>pls provide the range of linearity and precision and accuracy of HPLC method</td><td>The linearity curve for determining Ursolic acid level by HPLC was obtained within the range of 6-200 µg/mL with correlation coefficient of 0.999111
 

<table>
<tr><th>Concentration (µg/mL))</th><th>Peak area (mAU)</th></tr>
<tr><td>6</td><td>37.29115</td></tr>
<tr><td>8</td><td>40.71617</td></tr>
<tr><td>10</td><td>52.87971</td></tr>
<tr><td>20</td><td>128.66783</td></tr>
</table></td><td>Page 10 line 199-200</td></tr>
</table>

		40 | 279.52829 We have added a sentence in the method section Page 10 line 199-200 as the following: "The linear calibration curve was prepared within the UA level range of 6-200 µg/mL with correlation coefficient of 0.9991"	
1	pls define these abreviations for the first time pls provide the details for preparation of curcumin (correction:coumarin) loaded noisomes	Many thanks for the comments. We have revised the sentences as the following: Page 10 line 209-210: "..Coumarin-6 labelled Nio-UA (Nio-UA-Cou-6), while Coumarin-6 labelled Nio-UA-CS (Nio-UA-CS-Cou-6)" We have added the sentences as the following: Page 10 line 210-212: "The Nio-UA-Cou-6 and Nio-UA-CS-Cou-6 were prepared by adding about 0.3 mg Coumarin-6 into formula presented in Table1, and then produced by the same niosomes preparation method."	Page 10: line 209-210, line 210-212
1	pls insert the title for treatment protocol for example in vivo efficacy	Many thanks. The title of study protocol is Uji Biodistribusi Niosom Asam Ursolat Pada Mencit (Biodistribution study of Ursolic Acid Niosomes in Mice) We have added the title into the method section page 10 line 204 as the following: "..based on the study protocol entitled "Biodistribution study of Ursolic Acid Niosomes in Mice" that have been approved.."	Page 10 line 204
1	pls provide the range of linearity and precision and accuracy	The linearity curve for determining Coumarin-6 level by a fluorometer was obtained within the range of 0.01-0.5 µg/mL with correlation coefficient of 0.9999  	Page 11 line 225-226

		<table><tr><th>Coumarin-6 Level (µg/mL)</th><th>AU</th></tr><tr><td>0.01</td><td>229</td></tr><tr><td>0.03</td><td>527</td></tr><tr><td>0.05</td><td>937</td></tr><tr><td>0.1</td><td>2150</td></tr><tr><td>0.3</td><td>5840</td></tr><tr><td>0.5</td><td>9550</td></tr></table> We have added a sentence in the method section Page 11 line 225-226 as the following: “The linear calibration curve was prepared within the Coumarin-6 level range of 0.01-0.50 µg/mL with correlation coefficient of 0.9999”	
1	it is suggested that provide the physical properties of noisome in the table instead of figs	Many thanks for the comment. We have changed the figure 1 into Table 2 as the following:  We have also re-ordered the figure number	Table 2
1	it is suggested report the results of stability studies includinf particle size zeta potential and ee in table and omit the figure 2	Many thanks for the comment. In this study, we just observed the visual stability of the samples during the time period of study referring to reference no. 41. Further study by evaluation of particle size, zeta potential, and EE should be needed, however, we focused on choosing the optimal formula for loading UA in niosomes and this visual observation may reflect the comprehensive results of physical	-

		stability during the storage	
1	pls report which formulation was used to coat with chitosan and use its abbreviation in the legend of fig 3	Many thanks for the comment. We have added a sentence in Page 14 line 272 as the following: "..and this formula was used for further evaluations." We have also revised the legend of Fig 3 in Page 30 line 606 as the following: "…prepared at a molar ratio of Cholesterol:Span 60:UA= 60:40:10 (SK32-UA10) before and after addition.."	Page 14 line 272 Page 30 line 606
1	FTIR spectra should also be added in method section	Many thanks for the comment. We have added it in the method section as the following: **"Fourier-transform infrared (FTIR) spectroscopy of liposomes** The FTIR profiles of niosomes were analyzed using an FTIR spectrometer (Bruker Spectrometer Alpha II, Germany). The samples were examined at wavenumbers of 4000–450 cm^{-1}. The results were then compared to the literatures."	Page 8 line 157-160
2	The article is written very poorly. It should be rewrite. The discussion is very weak. It cannot be considered for publication in this format.	Many thanks for the comments. In the discussion section, we have discussed and explained about the physical properties of niosomes affected by different Cholesterol, Span 60, and Ursolic Acid molar ratio as the main supporting idea for characterization of niosomes. In addition, we have also given information regarding the chitosan layer addition into niosomes and how it could affect the physical properties, morphology, as well as in vitro and in vivo evaluation as supporting information for characterization and distribution of niosomes after chitosan coating, for the use of niosomes as an oral chemotherapy. We are very welcome if the comment can be more specific thus we can improve the quality of the manuscript.	-
2	This system was developed to increase bioavailability of ursolic acid. However , nearly 70 % of drug was released in GI. How do the author explain the benefit of ursolic acid loading in noisome and chitosan coated noisomes?	In our study, about 15-20% ursolic acid was released at a-6 hour release study with about nearly 10% was released in the first hour in a 0.1 N HCl pH 1.2 media stimulating gastric acid. Therefore, considering the stomach emptying time, which is about 30 minutes, it can be seen that niosomes could stably encapsulated ursolic acid, either with or without chitosan layer. However, about the question of nearly 70 % of drug was released in GI, we have no results reporting this value.	-
2	Please demonstrate the structure of niosomes remains unchanged in acidic media used for coating.	According to the results of physical characterizations of niosomes, after chitosan coatings, there were changes of particle size, polydispersity index, and zeta potential, which indicate that chitosan coating affected the physical properties of the vesicles as presented in Table 2; however, according to the SEM results, there were relative unchanged structure of niosomes compared to that of after chitosan coating. The niosomes after chitosan coating still remained as intact vesicles, as shown in Figure 3.	-
2	Prepare SEM after and before	Many thanks. We have added SEM pictures of Nio-UA and Nio-UA-CS as Figure 3	Figure 3

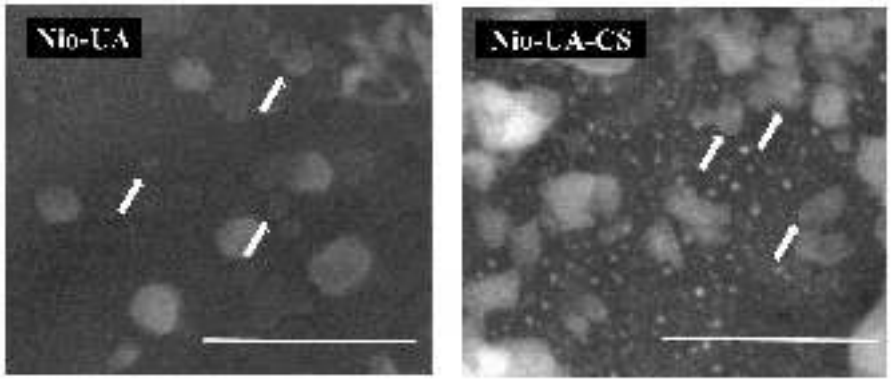
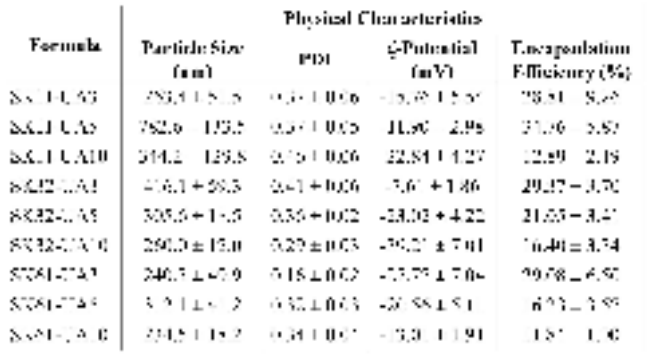
	coating with chitosan	in this following figure:  **Figure 3.** Scanning electron photomicroscopy of niosomes loading Ursolic Acid without (Nio-UA) and with chitosan addition (Nio-UA-CS) (scale bar= 5 μm). White arrows indicate the vesicles. We have re-ordered the figure numbers. Moreover, we have added the method for photomicroscopy assessment in Page 8 Line 162-166 as the following: **"Evaluation of niosome vesicles morphopology by scanning electron microscopy (SEM)** In order to evaluate the morphology of the vesicles, the niosomes i.e. Nio-UA and Nio-UA-CS were air-dried onto SEM stubs with carbon tape by sputter-coating with iridium at a thickness of 20 nm to eliminate electron charging. SEM images were then taken on a Scanning Electron Microscope". We have added a sentence explaining the SEM images of Nio-UA and Nio-UA-CS in Page 14 line 284-286 as the following: "In addition, the SEM images show that the addition of chitosan layer in Nio-UA-CS resulted in less spheroidal vesicles than that of without chitosan coating (Nio-UA) as presented in Figure 3".	Page 8 Line 162-166 Page 14 line 284-286 Page 30 line 609-611
2	Please use table to show the result of physicochemical characteristics of drug instead of figures	Many thanks for the comment. We have changed the figure 1 into Table 2 as the following:	Table 2 Page 13 Line 247-263

		Table 2. Physical properties including particle size, polydispersity index, ζ potential, and encapsulation efficiency of Niosomes prepared at different formulations of Span 60, Cholesterol and Ursolic Acid  We have also re-ordered the figure number The use of Figure 1 was also be replaced with Table 2 in the section of physical characteristics of Ursolic acid niosomes (page 13 Line 247-263).	
2	Please determine the major characteristics bonds of each component of formulation in FTIR study and then discuss about the changes of these peaks in final formulation	Many thanks for the comment. We have added the explanation about the spectra identification of each component of niosomes in Page 15 line 295-304 as the following: "According to the infra-red spectroscopy analysis, it has been shown that UA has specific absorption bands of alcohol group (-OH stretching: 2924 cm^{-1}), high intensity of carbonyl spectra absorption (-C=O: 1695 cm^{-1}), and aromatic ring (C=C: 1455 cm^{-1}) as shown in Figure 4. On the other hand, spectra measurement of niosomes component, such as Span 60 showed specific bands of hydroxyl groups (-OH), alkyl groups (-CH), and esters (R-CO-OR') at 3425, 2918, and 1738 cm^{-1}, respectively. While, Cholesterol had absorption bands of hydroxy groups (-OH: 3447 cm^{-1}), aromatic carbon (CH-CH: 2931 cm^{-1}), and carboxylate group (R-CO-OH: 1704 cm^{-1}). The measurement of Chitosan spectra showed that it has absorption bands of –OH, primary –NH, and –C-O-C-, and C-N at 3433, 3433 (overlapped), 1155, and 1323 cm^{-1}, respectively. After niosomes formation with chitosan coating,…"	Page 15 line 295-304
2	The visual observation isn't sufficient for stability study. To demonstrate stability of formulation, particle size, zeta potential and encapsulation	Many thanks for the comment. In this study, we just observed the visual stability of the samples during the time period of study referring to reference no. 41. Further study by evaluation of particle size, zeta potential, and EE should be needed, however, we focused on choosing the optimal formula for loading UA in niosomes and this visual observation may reflect the comprehensive results of physical	-

	efficiency should be studied	stability during the storage.	
2	The plasma concentration profile is required to compare bioavailability of formulations. The concentration at one point is not sufficient	In this study, we observed the single point bio-distribution after oral administration of niosomes. It is intended that niosomes would improve drug delivered to systemic circulation reaching tissue target i.e. liver. The results showed that the use of niosomes enhanced oral absorption of niosomes carried ursolic acid into blood plasma and a high niosomes accumulation was observed in liver, referring to Coumarin-6 levels in plasma and fluorescence intensity in the liver section. The plasma level profile would provide complete data since it reflects absorption as well as elimination phases that occur together, however, this study aimed for evaluating whether the niosomes system enhanced drug absorption as well as tissue distribution specifically for tissue target through an oral administration. In addition, there are many papers reporting the single point bio distribution as a parameter to show the successful of drug delivery using nano carriers (3–5) 1. Jadon PS, Gajbhiye V, Jadon RS, Gajbhiye KR, Ganesh N. Enhanced Oral Bioavailability of Griseofulvin via Niosomes. AAPS PharmSciTech [Internet]. 2009;10(4):1186–92. Available from: http://www.springerlink.com/index/10.1208/s12249-009-9325-z 2. Bagheri A, Chu BS, Yaakob H. Niosomal drug delivery systems: Formulation, preparation and applications. World Appl Sci J. 2014;32(8):1671–85. 3. Onishi H, Fukasawa A, Miatmoko A, Kawano K, Ikeuchi-Takahashi Y, Hattori Y. Preparation of chondroitin sulfate-adipic acid dihydrazide-doxorubicin conjugate and its antitumour characteristics against LLC cells. J Drug Target. 2017;25(8):747–53. 4. Hattori Y, Shibuya K, Kojima K, Miatmoko A, Kawano K, Ozaki K-I, et al. Zoledronic acid enhances antitumor efficacy of liposomal doxorubicin. Int J Oncol. 2015;47(1):211–9. 5. Miatmoko A, Kawano K, Yoda H, Yonemochi E, Hattori Y. Tumor delivery of liposomal doxorubicin prepared with poly-L-glutamic acid as a drug-trapping agent. J Liposome Res [Internet]. 2017;27(2):99–107. Available from: http://www.tandfonline.com/doi/full/10.3109/08982104.2016.1166511 6. Wang M, Zhao T, Liu Y, Wang Q, Xing S, Li L, et al. Ursolic acid liposomes with chitosan modification: Promising antitumor drug delivery and efficacy. Mater Sci Eng C [Internet]. 2017;71:1231–40. Available from: http://dx.doi.org/10.1016/j.msec.2016.11.014	-
3	In “in vivo study” did the Nio-UA-Cou-6 or UA-CS-Cou-6 contained the UA and Cou-6,	Many thanks for the comment. We have added the sentences as the following: Page 11 line 211-212: “The Nio-UA-Cou-6 and Nio-UA-CS-Cou-6 were prepared by adding about 0.3 mg	Page 11 line 211-212

	simultaneously? Did the author loaded Cou-6 in to the niosomes as the same way of UA?	Coumarin-6 into formula presented in Table1, and then produced by the same preparation method."	
3	Some typos need to be fixed: Lines 286-288: Coumarin-6 Lines 311, 348: Cholesterol Line 315: polydispersity index Line 382: amount Line 386: weas Line 388: (Wang et.al., 2017) Line 394, 396: ursolic acid The representation of "encapsulation efficiency "is not uniform throughout the manuscript Double spaces must be checked throughout the manuscript.	Many thanks. We have revised all typos. We have revised the citation as the following: Page 21 line 459: "..thereby slowing drug release(17)." We have replaced "entrapment" with "encapsulation" We have formatted the manuscript in double space writing.	Page 21 line 459
Editor	1- Please provide cover letter/first page according to INSTRUCTION TO THE AUTHOR section. Your cover letter should include the following parts:Title, Name of Authors, Affiliations, Address, Corresponding Autho r, Running Title, Funding Information, Acknowledgments, Conflict of Interest, ORCID for all authors, Author Contribution.	We have prepared the cover letter according to the author guideline	-
Editor	2- In the reference section, please reduce the number of references to 35.	We have reduced the references to 35 articles, as presented in the reference section	Page 29 Line 611
Editor	4- You are kindly requested to modify all the graph (all parts) according to the following comments: - All characters including words, letters, and digits must be written	We amended accordingly	-

	in Times New Roman, un-bold, non-italic with solid black color. -An appropriate legend with unit must be defined for both X and Y axes, unit should be provided in parentheses. -All lines in a graph including X and Y axes, lines around the columns, error bars, …. must be in solid black color with 1 pt thickness. -Please insert the Latin characters (A,B,..), out of the figure on the top of the left corner. -If a figure has different parts including different graphs or images, therefore different Capital/UPPERCASE letters in Times New Roman, solid black or white (depends on background color), and bold must be assigned to each part at the top left corner of the part and then each Latin characters should be defined in the figure legend.		
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