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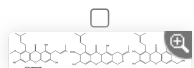
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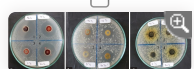
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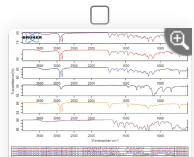
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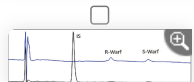
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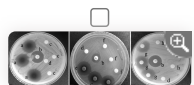
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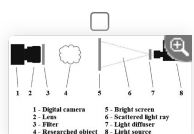
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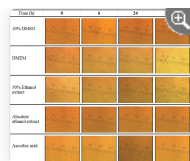
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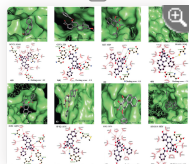
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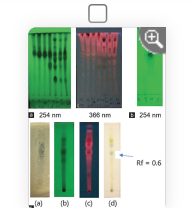


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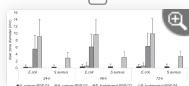


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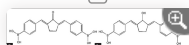
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Characterization and *in vitro* release of inhalation quercetin solid lipid microparticles: Effect of lipid

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ABSTRACT

This study purposes to develop solid lipid microparticles (SLM) inhalation delivery system for respiratory diseases with Quercetin as the active agent. Quercetin has various functions, such as for antioxidant, anti-inflammatory, immunomodulator, and antivirus. SLM is formed from a mixture of lipids and surfactants, namely, Glyceryl Behenate as solid lipid, Poloxamer 188 as the surfactant, and production of SLM using the melt o/w emulsification technique and was dried using freeze dryer. The effect of lipid concentration was studied in this research. Quercetin SLM was characterized by moisture content, Fourier transform infrared, particle size, yield, drug loading, and encapsulation efficiency. The SLM particles produced were spherical in shape and had a smooth surface with sizes of F1, F2, and F3 were 1.79 μm , 1.88 μm , and 1.91 μm , respectively. According to the target particle size of inhalation, Quercetin SLM had good flowability according to Carr's Index (F1 = 12.73% \pm 0.38, F2 = 14.28% \pm 0.65, F3 = 14.65% \pm 0.62), in which the highest drug loading and EE of F3 were 10.94% and 88.48%, respectively. *In vitro* release study showed that in 630 min about 31%–33% Quercetin released indicated sustained release following Higuchi kinetics and quercetin release rate was not affected by the amount of lipid. To sum up, quercetin SLM demonstrates its potential as an inhalation delivery system and it is recommended to study its stability.

Key words: Antivirus, glyceryl behenate, inhalation, quercetin, respiratory disease, solid lipid microparticle

INTRODUCTION

Solid lipid microparticle (SLM) is a controlled drug delivery system to improve the bioavailability and distribution of drugs in the body.^[1] It has a solid form with a size of

1–1000 m, composed of a solid fat core, and stabilized by surfactants.^[2] SLM has advantages, such as controlled release, safe protection of active agent against chemical and physical degradation, and reduced side effects. Based on the advantages mentioned, this system can be used as a delivery system targeted at the lungs.^[3]

Lungs are vital organs in the human body that have the probability to be attacked by respiratory diseases, including virus that causes infection. At the end of 2019, cases of pneumonia of unknown cause appeared in Wuhan.^[4] A few weeks later, in January 2020, a new virus that attacked the

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respiratory tract had been identified, namely SARS-CoV-2.^[5] Natural compounds with diverse chemical structures can provide an alternative approach for the discovery of new antiviral. In fact, many polyphenolic compounds have been found to have antiviral effects against SARS-CoV-2 which can inhibit the 3-3CLpro and PLpro enzymes. Research that has been done^[6] shows that Quercetin has been found to be active against infection.^[7] Quercetin is a polyphenolic compound that has various functions, such as antioxidant, anti-inflammatory, immunomodulator, and has anti-pathogenic and antiviral properties. Among several antioxidant compounds, flavonoids are considered to be able to inhibit SARS-CoV-2 infection. Antioxidants are compounds that can absorb or neutralize free radicals to prevent degenerative diseases.^[6]

A dry powder inhaler is an inhalation drug delivery system which has more advantages than Nebulizers and MDI, in which it is more environmentally friendly, the formulation is more stable, the dose is wider, and it can improve patient adherence.^[8] An effective and optimal inhalation therapy is 1–5 m to reach lower airway.^[9]

Various researchers have conducted research related to SLM drug delivery system targeted at the lungs with low water-soluble active agent, such as quercetin, which allows the study of the potential use of SLM as a quercetin carrier for pulmonary delivery. There are researches in drug formulations, one of which is by considering the solid lipid concentration in SLM as a promising carrier.^[10]

Glyceryl behenate as a lipid component and poloxamer 188 as a surfactant are very promising because they have a high ability to entrap lipophilic drugs such as quercetin. Besides that, it can produce small particle sizes because they have a smaller surface tension but concentration and technique for producing SLM need to be considered.^[11] Melt o/w emulsification technique shows that quercetin SLM can be formulated as a dry powder which is suitable for the delivery of inhaled drugs, apart from that it is easier and can provide good entrapment results.

This research is to optimize quercetin in SLM system for inhalation delivery. This study compares the amount of solid lipid used to evaluate the *in vitro* characteristics and release aspects.

MATERIALS AND METHODS

Materials

Quercetin was purchased from Tcchemicals (Japan), Glyceryl behenate (Compritol 888 ATO) was purchased from Gattefose (France), Poloxamer 188 was purchased from Sigma-Aldrich (USA), Aquadest, Methanol, and other chemicals (pharmaceutical grade).

Methods

Preparation of solid lipid microparticles

SLM was prepared using the o/w emulsification technique. Poloxamer 188 was dissolved using 250 ml of distilled water, then poloxamer 188 and Glyceryl Behenate were heated on a hot plate to a temperature of 70°C. After reaching the temperature of 70°C, Poloxamer 188 was poured into the *Glyceryl Behenate* oil phase which had melted first and has been mixed with quercetin until homogeneous. The emulsion was resulted at ultra-turrax5000 rpm for 1 min and continued at 10,000 rpm for 4 min. The results of Ultra-Turrax were then sonicated for 5 min, the samples were allowed to reach room temperature, then dried with freeze-dry for 27–30 h. The formulation of SLM is shown in Table 1.

Fourier transform infrared spectrophotometer

The raw materials, SLM Formula 1, Formula 2, and Formula 3 as much as 10 mg were placed alternately on the Fourier transform infrared (FTIR) lens, and then infrared absorption was observed. Results of the spectra obtained were compared with the literature.^[12]

Moisture content

The moisture content was tested with Mettler Toledo Moisture Analyzer.

Yield

Yield was determined by comparing the total weight of the SLM that had been obtained toward the weight of the SLM-forming material. The yield was calculated using the formula:

$$\%Yield = \frac{\text{solid lipid microparticle(SLM) weight}}{\text{Total quercetin and excipient weight}} \times 100$$

Drug loading and encapsulation efficiency

The determination of drug loading and encapsulation efficiency began with the making of a standard curve of Quercetin. Quercetin, as much as 10 mg, was dissolved in 100 ml of methanol (100 ppm) as the main standard. Then, the standard working solutions for 2, 4, 6, 8, and 10 ppm were made. After that, the maximum wavelength was determined by scanning the wavelength of 370–375 nm. Quercetin standard curve was made and the regression equation was determined as $y = bx + a$. Then, the 50 mg SLM sample was weighed, dissolved in 10 ml of methanol, stirred

Table 1: Quercetin solid lipid microparticle formula

Formula	Quercetin (%)	Glyceryl behenate (%)	Poloxamer 188 (%)
F1	0.4	2.2	0.5
F2	0.4	2.4	0.5
F3	0.4	2.6	0.5

for 2 h, and centrifuged at 2500 rpm for 10 min. The resulting supernatant was analyzed by UV-VIS spectrophotometry at 370 nm. Quercetin concentration was determined, drug Loading and encapsulation efficiency in SLM were calculated using the formula:

$$\text{Drug Loading}(\%) = \frac{\text{mass of Quercetin in SLM powder}}{\text{mass of SLM powder}} \times 100$$

$$\text{Entrapment Efficiency}(\%) = \frac{\text{mass of Quercetin in SLM powder}}{\text{mass Quercetin in formula}} \times 100$$

Particle size

Particle size analysis was performed using an optical microscope and measured using Optical lab software. The sample was placed on object-glass. In addition, 300 particles were measured and the average particle diameter was calculated.^[9]

Solid lipid microparticles morphology

The surface morphology examination of SLM was carried out using a scanning electron microscope (SEM). The sample was placed on a pan of aluminum coated with a thin layer of gold for 120 s and observed with an SEM microscope at 10 kV.^[13] Micrographs were obtained at magnifications of 500, 1000, and $\times 1500$.

Bulk and tapped density

Bulk density was determined by weighing a number of SLM powder, then put into a measuring cup without compaction. The weight of the powder in the measuring cup was weighed and calculated using the formula:

$$\text{Bulk Density} = \frac{\text{Weight of powder (gr)}}{\text{Volume of powder (ml)}}$$

The tapped density was determined by filling the SLM into a measuring cup, then the measuring cup containing SLM powder was compacted using a motorized tapping device for 1 min ($\times 500$) and the final volume of the powder was observed.

$$\text{Tapped Density} = \frac{\text{Weight of powder (gr)}}{\text{Volume occupied after tapping (ml)}}$$

In vitro release study

Quercetin release from SLM was carried out in phosphate buffer saline pH 7.4 using a thermoshaker at 37°C. SLM equivalent to 15 mg of quercetin was weighed and then put in 100 ml of phosphate buffer saline pH 7.4 and rotated at 100 rpm. Samples were taken (5 ml) and replaced with the release medium of 5 ml of phosphate buffer saline pH 7.4 ± 0.5 .^[14] Samples were taken at minutes 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 390, 450, 510, 570, and 630. Samples were filtered using 0.45 μm pore size millipore membrane filter. The absorbance of the sample was

observed using UV-Vis spectrophotometry at a wavelength of 370 nm. The level of quercetin was determined by using the absorbance value of the sample into the quercetin standard curve equation that had been made previously.^[14]

RESULTS AND DISCUSSION

Solid lipid microparticles characterization

Fourier transform infrared

The analysis results of the FTIR spectra of the three formulas [Figure 1 and Table 2] still showed the presence of functional groups of quercetin, glyceryl behenate, and poloxamer 188 and there was no change in the structure of the compound in the formula. Therefore, it can be considered that there is no chemical interaction between the ingredients that can cause drug degradation and there is no chemical interaction between lipids and surfactants. A solid lipid microsphere is therefore confirmed to have formed.

Physical characteristics of solid lipid microspheres

Results of quercetin SLM moisture content, yield, drug loading, and encapsulation efficiency of formula 1, formula 2, and formula 3 are shown in Table 3. Regarding moisture content, all formulas showed good moisture content, which was $< 5\%$. After analyzing the data using one-way ANOVA, sig. 0.009 was obtained. The result of sig. < 0.05 signified that there was a significant difference between the three formulas. Among the 3 formulas, formula 3 had high moisture content because it had a higher lipid content associated with high hydrophobicity.

The production of SLM with the quercetin using the melt o/w emulsification technique resulted in a yield of SLM approaching 100% [Table 3]. According to the study of

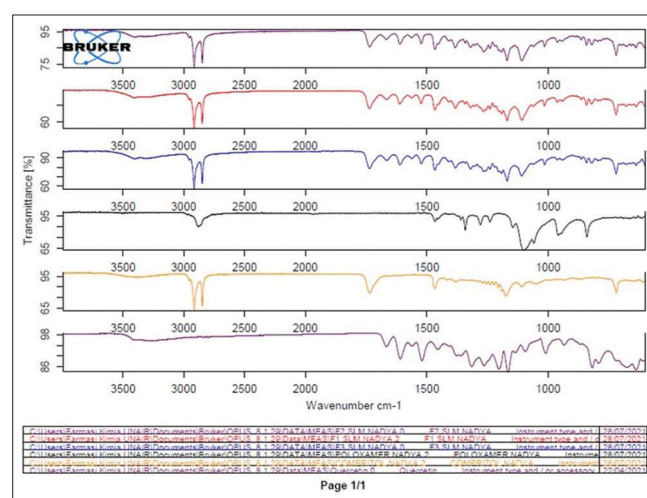


Figure 1: Spectra overlay of drug, excipients, and solid lipid microparticles formula. Dark Purple: Solid lipid microparticles Formula 2; Red: Solid lipid microparticles Formula 1; Blue: Solid lipid microparticles Formula 3; Black: Poloxamer; Yellow: Compritol; Light purple: Quercetin

Table 2: Wavenumber of drug, excipients, and solid lipid microparticle formula

Functional group	Wavenumber (cm ⁻¹)					
	Compritol	Poloxamer	Quercetin	F1	F2	F3
Stretching CH	2914.49			2912.00	2912.23	2913.46
Stretching CH ₃	2848.08	2879.64		2848.16	2848.46	2848.52
COOR/ester	1733.14			1736.61	1736.76	
CH ₂	1465.66	1466.07		1465.05	1456.77	1409.98
CH		1359.33				
Phenol			1202.36			
Stretching CO/secondary OH	1174.76			1167.46	1169.57	
Ether, stretching CO		1100.28	1165.29	1108.42	1108.86	1110.37
CH ₂	719.46	840.59	818.55	720.10	720.30	720.01

Mezzena *et al.*,^[8] the group of SLM formula using melt o/w emulsification shows SLM recovery that is close to 100%. In this research, the freeze-dry drying technique was continued to remove water. Freeze-dry drying was chosen because it did not use high temperatures so that the stability of the medicinal ingredients was maintained. Yield is a determining factor for the success of a method used, indicating that the method is effective and efficient.^[15] The results of statistical analysis using one-way ANOVA obtained sig. 0.097 > 0.05 so it could be considered that there was no significant difference between the three formulas.

Table 3 shows that formula 2 has the highest drug loading and entrapment efficiency. This is due to the influence of the amount of lipid concentration, in which the higher the lipid concentration used will affect the increase in drug loading and entrapment efficiency. After analyzing the data using one-way ANOVA, the data result obtained sig > 0.05. Therefore, it could be considered that there was no significant difference in drug loading between the three formulas and entrapment efficiency [Figures 2 and 3].

Particle size

Results of particle size showed that the quercetin SLM in the three formulas was 1.79 ± 0.13–1.91 ± 0.11. After analyzing the data using one-way ANOVA, sig. 0.040 < 0.05 was obtained thus it could be concluded that there was a significant difference between the three formulas, namely F3 with the largest particle size but still in the range of particle size for inhalation preparation. The particle size obtained is in accordance with the optimal particle size of 1-5 μm to reach the bottom of the lung.^[9] Furthermore, the diameter of the SLM depends on the stirring speed during manufacture; the higher the stirring speed, the smaller the size obtained, in addition to the use of drying techniques that as well will have an impact on the small particle size obtained.^[16] As for the polydispersity index, the result was < 0.6 so that the Quercetin SLM particles were homogeneous [Table 4 and Figure 4].

Quercetin solid lipid microparticles morphology

SEM results of formula 1, formula 2, and formula 3 in Figure 5 showed morphology of Quercetin SLM. They were

Table 3: Results of MC, yield, DL and EP of quercetin solid lipid microparticle formulas

Formula	MC (%)	Yield (%)	Drug loading	Entrapment efficiency
F1	1.44 ± 0.21	88.45 ± 1.39	8.57 ± 0.77	58.41 ± 4.10
F2	0.96 ± 0.04	95.16 ± 1.75	10.42 ± 1.06	87.72 ± 5.15
F3	1.55 ± 0.12	93.74 ± 1.01	10.94 ± 0.50	88.48 ± 4.20

MC: Moisture content, DL: Drug loading, EP: Encapsulation efficiency

Table 4: Particle size and polydispersity index of quercetin solid lipid microparticle

Formula	Particle size (μm)	PDI
F1	1.79 ± 0.13	0.0033
F2	1.88 ± 0.04	0.0033
F3	1.91 ± 0.11	0.0033

PDI: Polydispersity index

Table 5: Flow properties of quercetin solid lipid microparticle

Parameters	Formula 1	Formula 2	Formula 3
Bulk density	0.277	0.153	0.116
Tapped density	0.211	0.119	0.126
Hausner ratio	1.146	1.167	1.171
Carr's index	12.73% ± 0.38	14.28 ± 0.65	14.65 ± 0.62
Flowability	Good	Good	Good

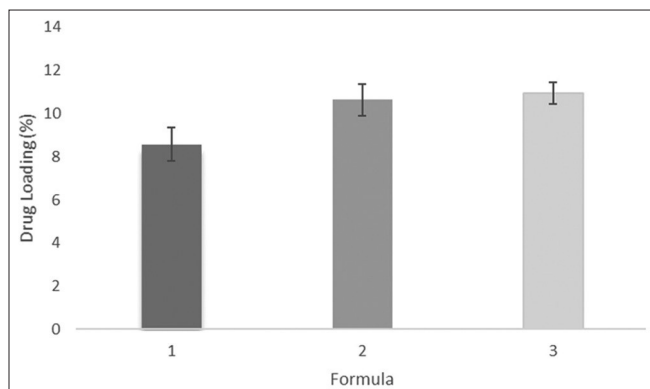
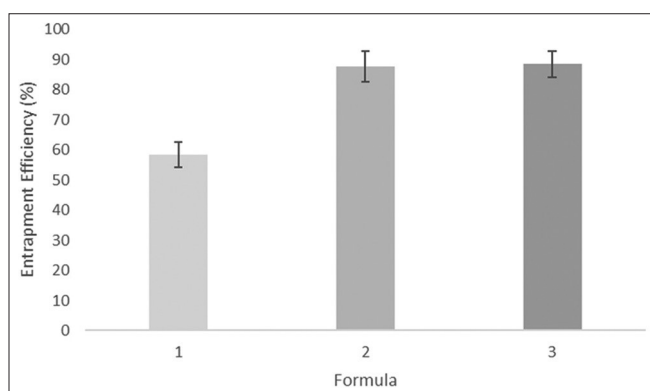
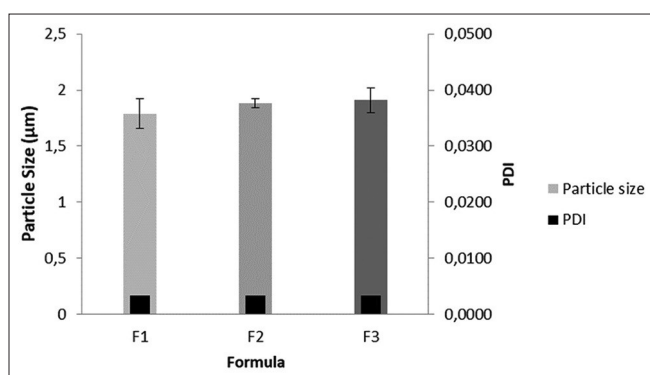
round and spherical. F2 produced the best morphology by showing the most smooth and spherical SLM. However, the morphology of F1 and F3 looked like needle crystals, but quercetin outside SLM was rather in a larger amount compared to F2. Hence, it is recommended that further observations need to be made using powder X-ray diffraction. The morphological description shows the use of *glyceryl behenate* as a lipid carrier affects the shape of the SLM.^[17]

Flow properties

Table 5 shows that the flow properties of the three formulas were included in the good category. Aerosolization of powders can be optimized by reducing powder bulk density.^[18,19] However, some researchers emphasize that

Table 6: Regression equation model of quercetin release kinetics from solid lipid microparticle

Formula	Order 0	Order I	Higuchi	Korsmeyer–Peppas
F1	$Y=0.0456x + 3.8323$	$Y=0.0017x + 0.6233$	$Y=1.3109x-3.4712$	$Y=0.5829x-0.1928$
F2	$Y=0.0433x + 4.7511$	$Y=0.0011x + 0.8821$	$Y=1.278x-2.3128$	$Y=0.5974x-0.1901$
F3	$Y=0.434x + 5.2797$	$0.0015x + 0.7529$	$Y=1.2285x-1.4905$	$Y=0.5219x-0.0079$

**Figure 2:** Drug loadings of quercetin solid lipid microparticles. Data was the average of three replications**Figure 3:** Entrapment efficiency of quercetin solid lipid microparticles**Figure 4:** Particle size and polydispersity index of quercetin solid lipid microparticles

lower bulk density of SLM powder can be beneficial for lung deposition. Glyceryl behenate lipid showing bulk density of 0.1–0.2 is considered favorable for powder aerosolization. After analyzing the data using one-way ANOVA,

sig. 0.013 < 0.05 was obtained and it could be considered that there was a significant difference between the three formulas. F2 and F3 meet the criteria for aerosolized powders which have advantages for deposition in the lungs. Based on confidence interval value, flow ability is 5%–12% (excellent); 12%–18% (good); 18%–21% (fair); and 21%–25% (poor).^[13]

In the release test, the release profile, release kinetics, and release rate were observed. The release of the drug from SLM is influenced by several factors, such as formula, physicochemical properties, particle size, drug-polymer interactions, and shape. Phenomenon of mechanism includes release kinetics such as diffusion.^[18] In addition, to obtain optimal release results, the release medium must reach a sink condition.

In Figure 6, it can be seen that the release of quercetin from SLM had started to release at the 30 min and it could be seen that the release of formulas 1, 2, and 3 was constant and slow and the percentage of the amount released between minutes was not so high. Release of drugs occurs via diffusion mechanism showed by the glyceryl behenate crystalline behavior. The lack of a regular lipid matrix composition allows high drug encapsulation.

Results of *in vitro* release kinetics of quercetin in SLM in Tables 6 and 7 showed that the formulation followed the release kinetics of the Higuchi model (R^2 was close to 1). The Higuchi release model is a release model where the amount of drug released depends on time. The longer the duration of the release, the more drug are released.^[20] To find out about the drug released as a whole, it takes longer than the total time of testing that has been carried out. After analyzing the data related to the release profile and release rate using one-way ANOVA, sig. 0.476 and 0.648 were obtained. The result of sig. was >0.05, so it could be concluded that there was no significant difference between the three formulas.

CONCLUSION

This research investigated the SLM system which has the potential as a carrier of lipophilic active agent such as quercetin which has the potential for lung delivery. This system has several advantages due to the use of lipids in the formulation such as, high tolerability, controlled release, protection of drug against harsh exposure and reducing side effects that can be caused, which is expected to obtain inhaled particles with a diameter suitable for pulmonary

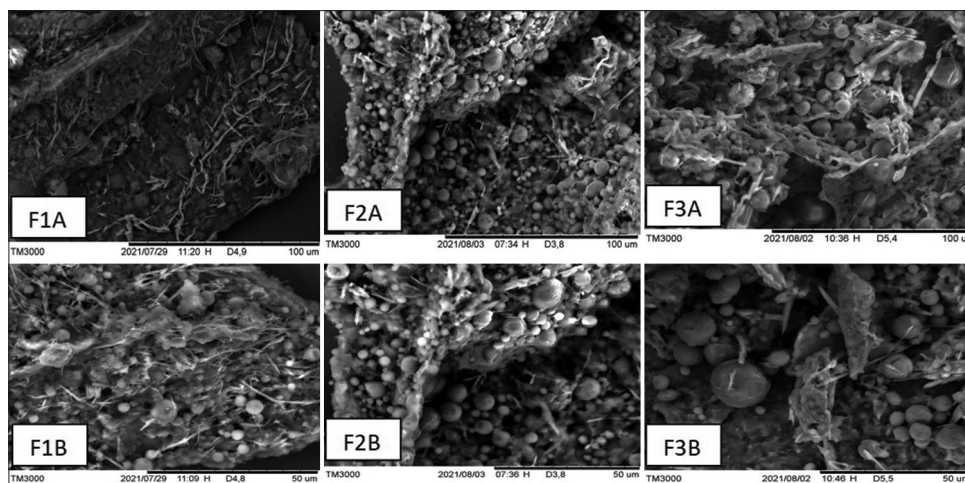


Figure 5: Quercetin solid lipid microparticles morphology with scanning electron microscope observations of solid lipid microparticles Formula F1, F2 and F3 at magnifications of A: $\times 1000$ and B: $\times 1500$

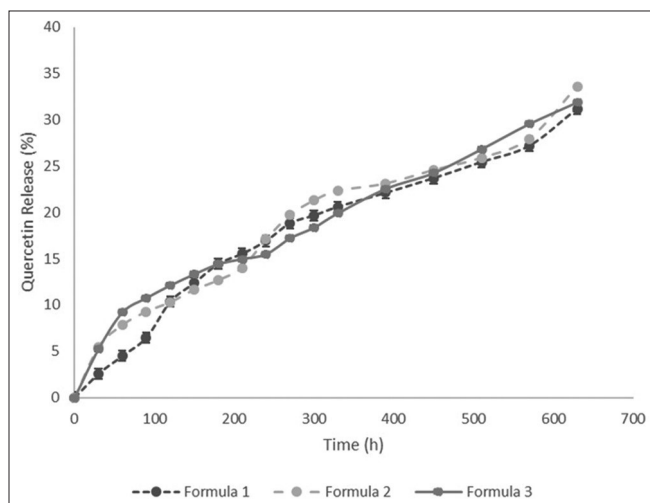


Figure 6: Quercetin release profile from solid lipid microparticles. The data were the three replications

Table 7: Relationship coefficient value (R^2) of quercetin release kinetics model

Formula	Order 0 (R^2)	Order I (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)
F1	0.9429	0.6805	0.9769	0.9336
F2	0.9659	0.8814	0.9685	0.9765
F3	0.9628	0.6184	0.9791	0.9940

administration. This study indicated that the composition of the formulation and the technique of producing SLM affected the physicochemical properties of the SLM and release profile of the drug. Formula 3 obtained Quercetin SLM with the best physical characteristics (moisture content, particle size, yield, drug loading, and entrapment efficiency). For further study, it is recommended to examine mass median aerodynamics related testing and *in vivo* study.

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Conflicts of interest

There are no conflicts of interest.

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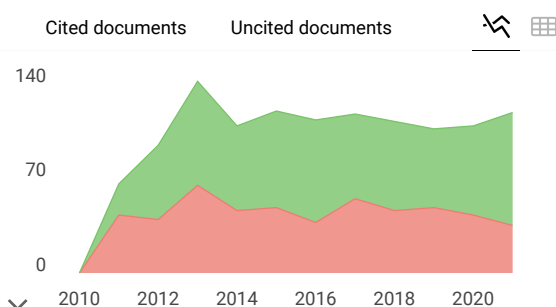
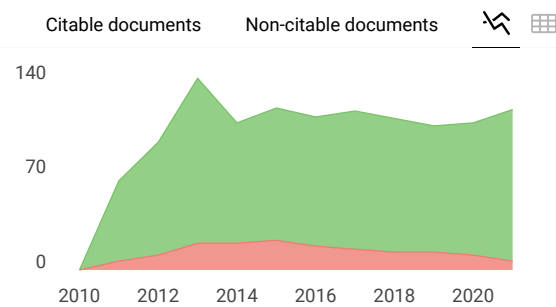
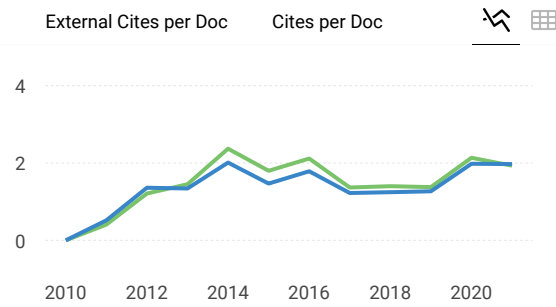
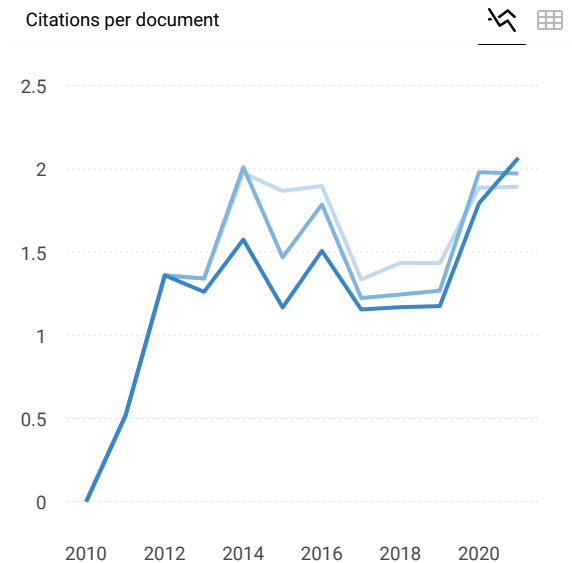
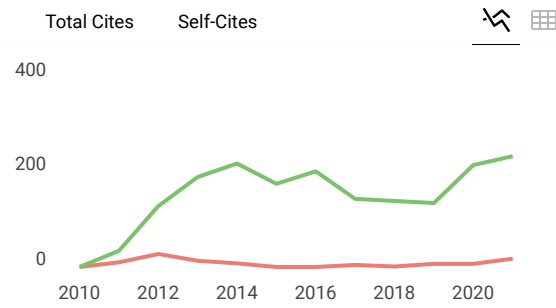
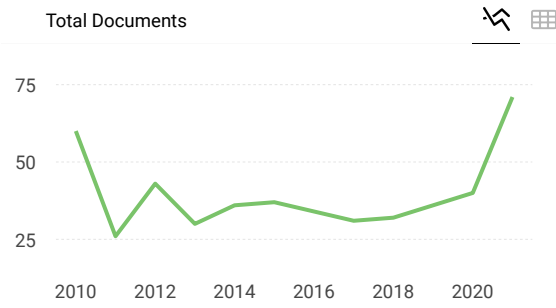
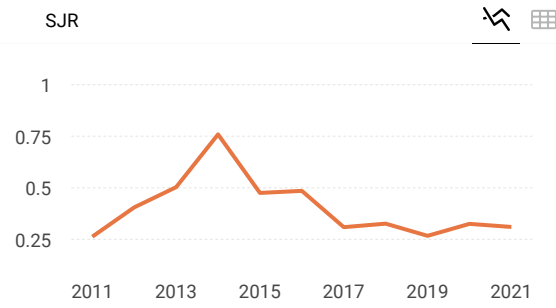
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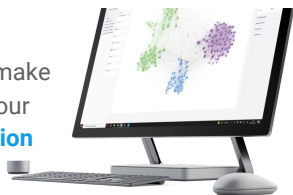
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