

Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres

by Andang Miatmoko

Submission date: 03-Apr-2023 10:18AM (UTC+0800)

Submission ID: 2054035525

File name: 5_artikel.pdf (590.21K)

Word count: 4732

Character count: 24648



Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres

Tekla Kalalo¹, Andang Miatmoko², Hanafi Tanojo³, Tristiana Erawati², Dewi Melani Hariyadi², Noorma Rosita^{2*}

¹Master Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

²Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

³Genepharma, Inc., Santa Clara, California, USA

*Corresponding author: noorma-r@ff.unair.ac.id

Submitted: 20 December 2021

Accepted: 3 February 2022

Published: 31 August 2022

Abstract

Background: Quercetin is a flavonoid compound that has anti-inflammation activity. However, poor stability presents significant problems for the formulation into dosage forms. Microspheres are one of the potential lung delivery systems because of their ability to encapsulate various types of drugs, protect drugs from environmental effects and can release drugs in a sustained release. **Objective:** In the present study, the microsphere inhalation system of the anti-inflammation drug, quercetin was developed and evaluated to achieving the targeted delivery of these drugs to the lung. **Method:** The drug-loaded ca-alginate microspheres were prepared by aerosolization ionic gelation technique followed by freeze-drying. **Result:** The result of this study showed that particle size was less than 2 μ m, the yield ranged from 41.33-76.14%, drug loading was less than 6%, entrapment efficiency ranged from 74.153% - 93.805% and flow properties showed that all formula had an excellent flow. Spherical microspheres were demonstrated by formulations containing 1 and 1.5% sodium alginate. A drug release study showed that the highest drug release of 30.649% was from the formulation with 2.5% sodium alginate, and the lowest drug release of 26.625% was from the formulation with 2% sodium alginate. A stability study at temperatures of 25°C and 40°C for 28 days showed a decrease in drug loading and entrapment efficiency but an increase in particle size. The formulation containing 1.5% sodium alginate showed the optimal formula. **Conclusion:** These findings indicated that quercetin ca-alginate microspheres are the potential for inhalation to be delivered to the lung.

Keywords: quercetin, microspheres, physical characteristic, release, stability

How to cite this article:

Kalalo, T., Miatmoko, A., Tanojo, H., Erawati, T., Hariyadi, D. M. & Rosita, N. (2022). Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 9(2), 107-114. <http://doi.org/10.20473/jfiki.v9i22022.107-114>

INTRODUCTION

Acute pulmonary injury (ALI) is an inflammatory disease characterized by the overproduction of inflammatory factors in lung tissue, followed by non-cardiogenic dyspnea, severe hypoxemia, and pulmonary oedema, leading to high morbidity and mortality (Huang *et al.*, 2015). ALI is also experienced by COVID-19 patients. Anti-inflammatory drugs are an alternative to avoid spikes in cytokine levels (cytokine storms) in an effort to combat COVID-19.

Quercetin is a flavonoid compound that has been shown to have anti-inflammatory effects. Research showed that quercetin increased the expression of IL-10 and Heme-oxygenase 1 by inhibiting the activation of the NLRP3 inflammasome and the secretion of inflammatory factors. These results suggest that quercetin may be a good candidate for direct lung delivery for the treatment of COVID-19 (Saeedi-Boroujeni & Mahmoudian-Sani, 2021).

The inhalation route provides many advantages over the oral route, as the high surface area with fast absorption because of increased vascularity can avoid the first pass effect, reduce dose, decrease systemic absorption and reduce side effects (Paranjpe & Müller-Goymann, 2014). However, the use of quercetin is still limited because quercetin shows low physical stability, rapid hydrolysis in aqueous solution, and is unstable because of oxygen and light (Cunico *et al.*, 2020). One approach to improve the limitations in terms of the stability of quercetin is to produce microspheres.

Biodegradable polymers are often used in the manufacture of microparticles, both microspheres and microcapsules, as a support for the delivery of bioactive compounds to their targets (Soni *et al.*, 2010). Microspheres are multiparticulate drug delivery systems designed to produce controlled drug delivery, to increase bioavailability, stability, and target drugs to specific sites. In addition, microspheres can protect drugs from environmental effects such as humidity, heat, and oxidation, and mask unpleasant tastes and odours, making them very suitable for unstable compounds such as quercetin (Uyen *et al.*, 2020).

Sodium alginate is a natural polymer used for the manufacture of microparticles. The advantages of using sodium alginate polymer are that it is non-toxic, biodegradable, biocompatible, and relatively inexpensive (S *et al.*, 2015). Sodium alginate can be crosslinked in an aqueous solution with divalent cations (e.g. Ca^{2+} , Ba^{2+} and Sr^{2+}) to form hydrogels (Kyzioł *et al.*, 2017). Ca^{2+} is the most often used ion because it has non-toxic properties (Hariyadi & Hendradi, 2020a).

Characterization and study of the release of a microsphere are influenced by several factors, such as the type of polymer used, polymer concentration, polymer ratio, type of crosslinker, the concentration of crosslinker, and the method of manufacture. Athamneh *et al.* (2019) find that the morphology of sodium alginate-hyaluronic acid microspheres is spherical, and the size distribution of different microspheres is found depending on the composition of the polymer solution, its dynamic viscosity, and the stirring rate during the ionic gelation process. Hariyadi *et al.* (2019) produced microspheres ranging in size from $1.23 \mu\text{m}$ - $1.43 \mu\text{m}$ by manufacturing ciprofloxacin microspheres with alginate polymer for inhalation delivery with several polymer concentrations and aerosolization techniques. The higher the alginate concentration, the particle size also increases. An increase follows in alginate content in the diameter of the microspheres, which increases the viscosity of the alginate solution used so that large alginate droplets are formed when adding alginate solution to the crosslinking solution and causing the resulting microspheres to be more significant. In addition to particle size, Alipour *et al.* (2010) found the effect of the drug to polymer mass ratio for drug loading and entrapment efficiency of sodium alginate-paclitaxel microspheres for inhalation. Drug loading and encapsulation efficiency of microparticles depend on the manufacturing conditions. Among all the formulations made, maximum drug loading and encapsulation efficiency of up to 61% are obtained, with the highest mass ratio of paclitaxel to alginate and the highest external oil phase volume. These results are following the results of other researchers who study the effect of the mass ratio of the drugs to the polymer, the volume of the external oil phase and CaCl_2 to mass ratio of alginate in the production of microparticles using alginate (Alipour *et al.*, 2010).

This study aimed to formulate quercetin in calcium alginate microspheres system using sodium alginate as a polymer and calcium chloride as a crosslinker. Increasing the concentration of sodium alginate was carried out to see its effect on physical characteristics, release and physical stability.

MATERIALS AND METHODS

Materials

Materials used in this research (Table 1) are quercetin, sodium alginate pharmaceutical grade (Sigma-Aldrich inc), CaCl_2 , aquadest, ethanol 95%, and maltodextrin (Bratachem Chemistry).

Table 1. The formula of microsphere quercetin-alginate

Component	F1	F2	F3	F4
Quercetin	0.2%	0.2%	0.2%	0.2%
Sodium Alginate	1%	1.5 %	2%	2.5%
CaCl ₂	5.5%	5.5%	5.5%	5.5%
Maltodextrin	5%	5%	5%	5%

The drug-loaded ca-alginate microspheres were prepared by aerosolization ionic gelation technique followed by freeze-drying. Solution of sodium alginate was made separately with different concentrations of as much as 100 mL of aquadest and then stirred using a magnetic stirrer. Quercetin (0.2 gram in 20 mL ethanol) was added to the sodium alginate solution, which had been formed slowly and then stirred using a magnetic stirrer until it is homogeneous. A 5.5 % CaCl₂ solution was prepared as a cross-link in 100 mL of distilled water. Quercetin alginate solution was sprayed using aerosol spray into CaCl₂ solution with a distance of 8 cm from the solution's surface and a pressure of 40 psi while stirring with a magnetic stirrer for two hours at a speed of 1000 rpm. The microspheres formed were separated from the CaCl₂ solution by centrifugation at 2500 rpm for six minutes and then washed with aquadest. The microspheres were resuspended in 5% maltodextrin solution as a lyoprotectant. The quercetin microsphere suspension was dried by freeze-dryer at -50°C for 96 hours.

Physical characterization of microspheres

Morphology

The shape and surface of the ca-alginate quercetin microspheres were observed by scanning electron microscopy (SEM) (Hariyadi & Hendradi, 2020a).

Particle size

Particle size measurements were carried out using an optical microscope and the optic lab software (Hariyadi & Hendradi, 2020b).

Yield

Yielding close to 100% indicates that the method used in the preparation of microspheres produces the maximum number of microspheres (Kumar & Suresh, 2018). The quercetin microspheres were weighed, and the percentage yield of the prepared microspheres was calculated using the following formula:

$$yield = \frac{microsphere\ mass}{mass\ of\ polymer + drug + lyoprotectant} \times 100\%$$

The amount of quercetin trapped in the microsphere system was determined directly by calculating the total concentration in the microspheres against the theoretical content of quercetin added to the formula. The quercetin P-ISSN: 2406-9388 E-ISSN: 2580-8303

content was determined by dissolving 100 mg of quercetin-na alginate microspheres in 100 mL of phosphate buffer pH 7.4 under sonication for 60 minutes until the microspheres were completely dissolved. After that, the sample was filtered and analyzed spectrophotometrically at a wavelength of 370 nm. The experiment was replicated three times (Hazra et al., 2015).

$$DL = \frac{Drug\ mass\ in\ microspheres}{Microspheres\ sample\ mass} \times 100\%$$

$$EE = \frac{Experimental\ drug\ mass\ in\ sample}{Hypothetical\ drug\ mass} \times 100\%$$

Flow properties

Bulk density dan tapped density

Bulk density was carried out by inserting quercetin ca-alginate microsphere powder into a 100 mL graduated cylinder and weighed, then the initial volume was noted (before it was compressed). After that, the quercetin ca-alginate microsphere powder in a 100 mL graduated cylinder was compressed using a motorized tapping device, tapping 500 times and observing the final volume of the powder. Then the bulk density and tapped density were calculated using the following formula:

$$bulk\ density = \frac{mass\ powder\ (gram)}{initial\ volume\ (ml)}$$

$$tapped\ density = \frac{mass\ powder\ (gram)}{tapped\ volume\ (ml)}$$

Carr index dan hausner ratio

Carr's index and Hausner ratio can be determined after performing bulk density and tapped density tests, using the following formula:

$$carr's\ index = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100\%$$

$$Hausner\ ratio = \frac{tapped\ density}{bulk\ density}$$

Drug release study

Drug release from ca-alginate microspheres was determined in phosphate buffer saline solution (pH 7.4). The release study was carried out using a thermoshaker at 37°C at 100 rpm. A number of microspheres equivalent to 30 mg of quercetin were weighed, and the sample was put in 100 ml of phosphate buffer saline solution (pH 7.4) and then put in a thermoshaker that had reached a temperature of 37°C and rotated at a speed of 100 rpm. Samples were taken (5 mL). Samples were taken by replacing the release medium with 5 mL of PBS solution (pH 7.4). Samples were taken after 30 minutes, 1 hour, 1 hour, 30 minutes, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, and 10 hours. At each sampling, the release medium was replaced with the same medium. Samples were filtered using 0.45 μm Millipore filter paper. The absorbance of the sample was observed using a UV-Vis

spectrophotometer at a wavelength of 370 nm. The level of quercetin was determined by entering the absorbance value of the sample into the quercetin standard curve equation that had been made previously (Hariyadi & Hendradi, 2020a).

Stability study

An accelerated stability test was carried out on calcium alginate quercetin microspheres. The microsphere powder was put into a vial. These bottles were stored in a room with a temperature of 25°C ± 2°C and 40°C ± 2°C, RH 75 ± 5% for 28 days. Microsphere organoleptic changes, drug loading and powder morphology were observed to check the stability of dry powder inhalation. Quercetin calcium alginate microspheres were declared stable

when organoleptically, they did not change color and did not agglomerate, the morphology of the microspheres remained spherical, the particle size remained constant and the drug loading did not decrease (Aashigari *et al.*, 2019).

RESULTS AND DISCUSSION

Based on the result of morphology and shape, formula 1 and 2 had a spherical shape and smooth surface (Figure 1). These results indicate that the two formulae are formed into a system of microspheres, this is expected to facilitate microsphere uptake by alveolar macrophage (Vishwa *et al.*, 2021).

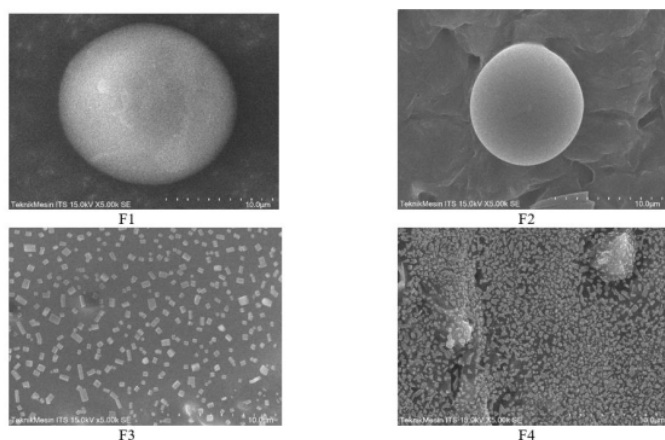


Figure 1. Surface morphology of a quercetin-loaded calcium alginate microsphere (Magnification 5000x)

Table 1. Characteristics of quercetin calcium alginate microspheres

Formula	Particle size (µm)	Yield (%)	Drug Loading (%)	Entrapment efficiency (%)
1	1.267 ± 0.081	40.80 ± 1.11	5.42 ± 0.105	74.15 ± 1.613
2	1.357 ± 0.092	57.68 ± 3.97	5.49 ± 0.311	92.95 ± 3.333
3	1.433 ± 0.006	58.83 ± 4.92	4.07 ± 0.074	92.16 ± 6.265
4	1.743 ± 0.120	54.55 ± 2.94	4.11 ± 0.182	93.81 ± 4.220

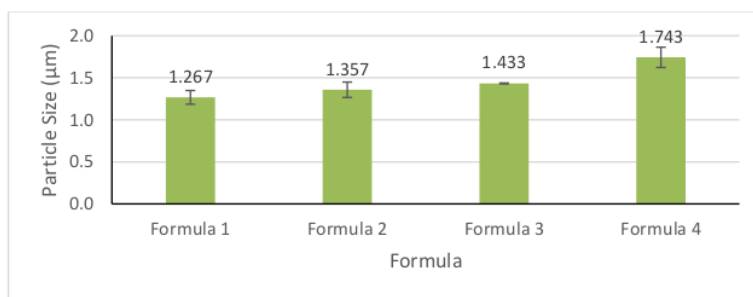


Figure 2. Histogram of particle size of quercetin-calcium alginate microspheres with increasing polymer concentration F1 (1% sodium alginate) F2 (1.5% sodium alginate), F3 (2% sodium alginate) and F4 (2.5% sodium alginate). Data are the mean of three replications ± SD

31 Particle size plays an important role in the phagocytosis of micron-sized particles in lung delivery. Based on Table 1, particles obtained for all formulae were F1 (1.1267 μ m), F2 (1.357 μ m), F3 (1.433 μ m) and F4 (1.743 μ m). The one way ANOVA statistical test for particle size distribution showed that the value of sig = 0.003 < 0.05, which means that there is a significant difference between the formulae. Results indicated that the four formulae's particle size fulfills the optimal particle size for delivery to the lungs, which is < 6 μ m (Vishwa *et al.*, 2021). Based on the results obtained, there was an increase in particle size along with an increase in the concentration of sodium alginate. This is because when the concentration of sodium alginate increases, the viscosity increases, which causes the droplet size of the microspheres to become larger. The polydispersity index (PDI) for all formulae showed a value close to 0, which means that the particle size distribution is homogeneous.

Calculation of the yield obtained in the four formulae was F1 (40.80%), F2 (57.68%), F3 (58.83%) and F4 (54.55%) (Table 1). Based on the one-way ANOVA statistical test results, the value of sig = 0.003 < 0.05, which means that there is a significant difference. Yielding close to 100% indicated that the method used in the preparation of microspheres efficiently produces the maximum number of microspheres (Kumar & Suresh, 2018). Based on the results obtained, it can be seen that the higher the concentration of sodium alginate, the higher the yield. This is because the higher the concentration, the greater the amount of sodium alginate required, so to obtain more microspheres.

Based on Table 1, the drug loading obtained from the four formulae is F1 (5.428%), F2 (4.495%), F3 (4.075%) and F4 (4.112%). The one-way ANOVA statistical analysis showed the value of sig = 0.000 < 0.05, which means that there is a significant difference. From the results obtained, it can be seen that the higher the sodium alginate drug loading concentration, the smaller the drug loading obtained. This is because the viscosity of the resulting solution increases the concentration of sodium alginate, which causes many droplets that cannot load quercetin into the system. Meanwhile, for encapsulation efficiency, the results obtained were F1 (74.153%), F2 (92.952%), F3 (92.166%) and F4 (93.805%). Based on the results of the one-way ANOVA statistic, it showed that the value of

sig = 0.004 < 0.05, which means that there is a significant difference. The highest entrapment efficiency is on F4. The increasing concentration of sodium alginate will increase the viscosity of the solution, causing the droplet size to be larger, resulting in an increase in entrapment efficiency (Hariyadi *et al.*, 2019).

The flow properties test was determined by means of Carr's index and the Hausner's ratio. Carr's index results obtained from the four formulas based in Table 2 include F1 (8.703), F2 (7.963), F3 (6.427) and F4 (9.7), while the Hausner ratio obtained from the four formulae include F1 (1.092), F2 (1.082), F3 (1.069), and F4 (1.107).

8 The results obtained for the value of Carr's index and Hausner's ratio show that the four formulae are included in the excellent category. These results indicated that the carrier particles, such as microspheres, offer the potential to increase the flow of fine drug particles and help obtain uniform fine drug particles into the inhalation device.

The quercetin release test from the microspheres was carried out for 600 minutes using a thermoshaker. After each sampling, the media volume was replaced as much as the sampled volume to keep the media in sync. Until the 600th minute, the following was the amount of quercetin released from the microspheres: F1 (30.64%), F2 (29.35%), F3 (25.62%) and F4 (28.65%) (Table 3). Based on these results, it can be seen that the higher the concentration of sodium alginate, the lower the release. The one-way ANOVA statistical analysis shows that the value of sig = 0.040 < 0.05, which means that there is a significant difference between the formulae. An increase in sodium alginate concentration can cause an increase in viscosity so that the formed microspheres are thicker and have a denser surface so that the release of quercetin from the microspheres takes longer because the rate of diffusion of the release medium into the microspheres decreases.

The stability of quercetin ca-alginate microspheres was carried out at two different temperatures, 25°C and 40°C, for 28 days. Based on the results obtained for particle size, there was an increase in particle size in the four formulae at both 25°C and 40°C (Tables 6 and 7). However, the particle size in the four formulae is still > 6 μ m, which is a particle size requirement for inhalation delivery (Vishwa *et al.*, 2021).

Table 2. Flow properties of quercetin ca-alginate microspheres

Formula	F1	F2	F3	F4
Bulk Density	0.199 ± 0.061	0.149 ± 0.037	0.217 ± 0.014	0.194 ± 0.054
Tapped Density	0.218 ± 0.066	0.162 ± 0.041	0.233 ± 0.018	0.217 ± 0.066
Carr's index	8.703 ± 2.384	7.963 ± 2.426	6.427 ± 2.414	9.7 ± 4.357
Hauster ratio	1.092 ± 0.030	1.082 ± 0.031	1.069 ± 0.028	1.107 ± 0.053

Table 3. Release study of quercetin ca-alginate microspheres

Sampling time (minute)	Cumulative quercetin release (%)			
	F1	F2	F3	F4
30	14.66 ± 1.584	22.924 ± 3.795	17.507 ± 3.079	16.984 ± 0.620
60	15.116 ± 2.121	26.748 ± 4.405	19.275 ± 2.702	20.403 ± 1.633
90	17.066 ± 1.615	24.719 ± 3.590	20.333 ± 3.192	21.088 ± 2.092
120	17.97 ± 1.781	24.711 ± 1.394	20.183 ± 2.647	22.698 ± 2.414
150	19.526 ± 0.910	24.907 ± 1.868	20.825 ± 1.029	21.615 ± 2.934
180	21.29 ± 0.496	24.214 ± 3.515	20.84 ± 2.030	22.138 ± 0.990
240	22.747 ± 1.307	25.775 ± 4.331	22.383 ± 3.578	23.011 ± 2.025
300	23.772 ± 1.643	26.137 ± 3.227	22.930 ± 1.881	24.145 ± 1.022
360	25.418 ± 1.928	25.991 ± 3.662	23.94 ± 3.845	24.847 ± 0.727
420	26.748 ± 2.910	26.853 ± 3.651	24.496 ± 2.900	24.723 ± 1.689
480	28.712 ± 1.777	28.099 ± 4.727	26.114 ± 4.173	26.627 ± 2.564
540	29.757 ± 2.404	27.902 ± 4.551	25.371 ± 2.068	27.185 ± 3.190
600	30.649 ± 1.886	29.358 ± 1.654	25.625 ± 2.544	28.65 ± 3.016

Table 4. Stability study of drug loading at 25°C

Formula	Drug Loading (%)			
	Temperature (25°C)			
	D0	D7	D15	D28
1	5.428	5.349	5.432	5.211
2	4.495	4.795	4.088	4.157
3	4.075	3.991	3.963	4.047
4	4.112	3.991	3.989	4.116

Table 5. Stability study of drug loading at 40°C

Formula	Drug Loading (%)			
	Temperature (40°C)			
	D0	D7	D15	D28
1	5.428	5.030	4.518	4.421
2	4.495	4.463	4.158	4.089
3	4.075	4.061	4.033	3.964
4	4.112	4.006	3.992	3.978

Table 6. Stability study of particle size (µm) at 25°C

Formula	D0	D7	D15	D28
1	1.267	1.718	1.971	2.11
2	1.357	1.573	2.071	2.435
3	1.433	1.639	2.145	2.549
4	1.743	2.378	2.625	2.65

Table 7. Stability study of particle size (µm) at 40°C

Formula	D0	D7	D15	D28
1	1.267	1.512	1.768	1.976
2	1.357	1.784	1.691	1.92
3	1.433	1.722	1.779	1.953
4	1.743	1.745	1.79	1.955

Table 8. Stability study of entrapment efficiency at 25°C

Formula	Entrapment efficiency (%)			
	Temperature (25°C)			
	D0	D7	D15	D28
1	76.277	75.688	76.864	73.728
2	91.724	89.906	76.662	77.960
3	95.674	93.405	92.757	94.701
4	96.063	95.401	94.739	92.380

Table 9. Stability study of entrapment efficiency at 40°C

Formula	Entrapment efficiency (%)			
	Temperature (40°C)			
	D0	D7	D15	D28
1	76.277	71.181	63.929	62.557
2	91.724	83.673	77.960	76.662
3	95.674	95.026	94.377	92.757
4	96.063	95.732	95.401	95.073

The stability of quercetin ca-alginate microspheres was carried out at two different temperatures, namely 25°C and 40°C, for 28 days. Based on the results obtained for particle size, there was an increase in particle size in the four formulae at both 25°C and 40°C (Tables 6 and 7). However, the particle size in the four formulae is still > 6 μm which is a particle size requirement for inhalation delivery (Vishwa *et al.*, 2021).

Drug loading and entrapment efficiency of quercetin ca-alginate microsphere stability test at 25°C and 40°C decreased levels in the four formulae (Tables 4 and 5). This was because, during storage, quercetin was degraded due to the influence of temperature and storage time, so that quercetin was released from the system, namely microspheres, resulting in a decrease in drug loading and encapsulation efficiency (Tables 8 and 9).

CONCLUSION

The quercetin-loaded ca-alginate microspheres were prepared by aerosolization ionic gelation technique followed by freeze drying. From the result, there are three things that can be concluded, that is an increase in the concentration of sodium alginate (1%, 1.5%, 2% and 2.5%) caused an increase in particle size, yield, and entrapment efficiency, while the drug loading decreased; an increase in the concentration of sodium alginate (1%, 1.5%, 2% and 2.5%) caused the release of quercetin from the microspheres to be slower; and increasing the concentration of sodium alginate (1%, 1.5%, 2% and 2.5%) in the stability test for 28 days caused a decrease in drug loading levels and entrapment efficiency, while the particle size increased.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Result showed that optimal formula containing 1.5% sodium alginate produced spherical, very good flow and small particle size fulfills dry powder inhaler characteristics with high loadings and efficiency. The optimum quercetin-ca alginate microspheres may be potential for lung inhalation delivery.

ACKNOWLEDGMENT

This research is part of the Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia.

AUTHOR CONTRIBUTIONS

Conceptualization, N.R.; Methodology, D.M.H.; Validation, A.M.; Formal Analysis, T.K.; Investigation, T.K.; Resources, D.M.H.; Data Curation, T.K.; Writing - Original Draft, T.K.; Writing - Review & Editing, N.R.; Visualization, T.E.; Supervision, H.T.; Funding Acquisition, D.M.H.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

REFERENCES

- Aashigari, S., Goud, R. G. & Raju Potnuri, N. (2019). Stability Studies of Pharmaceutical Products. *World Journal of Pharmaceutical Research*; 8; 479-492. doi: 10.20959/wjpr20191-13872.
- Alipour, S., Montaseri, H. & Tafaghodi, M. (2010). Preparation and Characterization of Biodegradable Paclitaxel Loaded Alginate Microparticles for Pulmonary Delivery. *Colloids and Surfaces B: Biointerfaces*; 81; 521-529. doi: 10.1016/j.colsurfb.2010.07.050.

- Athamneh, T., Amin, A., Benke, E., Ambrus, R., Leopold, C. S., Gurikov, P. & Smirnova, I. (2019). Alginate and Hybrid Alginate-Hyaluronic Acid Aerogel Microspheres as Potential Carrier for Pulmonary Drug Delivery. *Journal of Supercritical Fluids*; 150; 49–55. doi: 10.1016/j.supflu.2019.04.013.
- Cunico, L. P., Cobo, A. M., Al-Hamimi, S. & Turner, C. (2020). Solubility and Thermal Degradation of Quercetin in Co2-Expanded Liquids. *Molecules*; 25; 1-10. doi: 10.3390/molecules25235582.
- Hariyadi, D. M. & Hendradi, E. (2020a). Optimization Performance and Physical Stability of Ciprofloxacin HCLCA Alginate Microspheres: Effect of Different Concentration of Alginate and CACL2. *International Journal of Drug Delivery Technology*; 10; 89–94.
- Hariyadi, D. M. & Hendradi, E. (2020b). Optimization Performance and Physical Stability of Ciprofloxacin HCLCA Alginate Microspheres: Effect of Different Concentration of Alginate and CACL2. *International Journal of Drug Delivery Technology*; 10; 89–94.
- Hariyadi, D. M., Hendradi, E. & Kurniawan, T. D. (2019). Alginate Microspheres Encapsulating Ciprofloxacin HCl: Characteristics, Release and Antibacterial Activity. *International Journal of Pharma Research and Health Sciences*; 7; 3020–3027. doi: 10.21276/ijprhs.2019.04.02.
- Hazra, M., Dasgupta, M. D., Mandal, T., Bhuniya, S. & Ghosh, M. (2015). Designing Polymeric Microparticulate Drug Delivery System for Hydrophobic Drug Quercetin. *Saudi Pharmaceutical Journal*; 23; 429–436. doi: 10.1016/j.jsps.2015.01.007.
- Huang, R., Zhong, T. & Wu, H. (2015). Quercetin Protects Against Lipopolysaccharide-Induced Acute Lung Injury in Rats Through Suppression of Inflammation and Oxidative Stress. *Archives of Medical Science*; 11; 427–432. doi: 10.5114/aoms.2015.50975.
- Kumar, K. R. & Suresh, G. (2018). Development and Characterization of Alginate Microspheres Containing Olmesartan by Ionotropic Gelation Method. *International Journal of Pharmaceutical Sciences and Drug Research*; 10; 335-341. doi: 10.25004/IJPSDR.2018.100420.
- Kyziół, A., Mazgala, A., Michna, J., Regiel-Futyr, A., & Sebastian, V. (2017). Preparation and Characterization of Alginate/Chitosan Formulations for Ciprofloxacin-Controlled Delivery. *Journal of Biomaterials Applications*; 32; 162–174. doi: 10.1177/0885328217714352.
- Paranjpe, M. & Müller-Goymann, C. C. (2014). Nanoparticle-Mediated Pulmonary Drug Delivery: a Review. *International Journal of Molecular Sciences*; 15; 5852–5873. doi: 10.3390/ijms15045852..
- Saeedi-Boroujeni, A. & Mahmoudian-Sani, M. R. (2021). Anti-Inflammatory Potential of Quercetin in COVID-19 Treatment. *Journal of Inflammation (United Kingdom)*; 18; 1-9.
- Soni, M. L., Kumar, M. & Namdeo, K. P. (2010). Sodium Alginate Microspheres for Extending Drug Release: Formulation and In Vitro Evaluation. *International Journal of Drug Delivery*; 2; 64–68. doi: :10.5138/ijdd.2010.0975.0215.02013.
- Uyen, N. T. T., Hamid, Z. A. A., Tram, N. X. T. & Ahmad, N. (2020). Fabrication of Alginate Microspheres for Drug Delivery: a Review. *International Journal of Biological Macromolecules*; 153; 1035–1046. doi: 10.1016/j.ijbiomac.2019.10.233.
- Vishwa, B., Moin, A., Gowda, D. V., Rizvi, S. M. D., Hegazy, W. A. H., Abu Lila, A. S., Khafagy, E. S. & Allam, A. N. (2021). Pulmonary Targeting of Inhalable Moxifloxacin Microspheres for Effective Management of Tuberculosis. *Pharmaceutics*; 13; 1–17. doi: 10.3390/pharmaceutics13010079.

Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres

ORIGINALITY REPORT

14%

SIMILARITY INDEX

10%

INTERNET SOURCES

8%

PUBLICATIONS

0%

STUDENT PAPERS

PRIMARY SOURCES

1	ejournal.stitpn.ac.id Internet Source	2%
2	doaj.org Internet Source	1%
3	Xiaojun Ma, Ivan Vacek, Anthony Sun. "Generation of Alginate-Poly-L-Lysine-Alginate (APA) Biomicrocapsules: the Relationship Between the Membrane Strength and the Reaction Conditions", Artificial Cells, Blood Substitutes, and Biotechnology, 2009 Publication	1%
4	www.scielo.br Internet Source	1%
5	Moumita Hazra, Dalia Dasgupta Mandal, Tamal Mandal, Saikat Bhuniya, Mallika Ghosh. "Designing polymeric microparticulate drug delivery system for hydrophobic drug quercetin", Saudi Pharmaceutical Journal, 2015	1%

6	clock.uclan.ac.uk Internet Source	1 %
7	www.escort-ireland.com Internet Source	1 %
8	ijpsr.com Internet Source	<1 %
9	journals.plos.org Internet Source	<1 %
10	Suvakanta, Dash, Murthy Padala Narsimha, Deb Pulak, Chakraborty Joshabir, and Das Biswajit. "Optimization and characterization of purified polysaccharide from <i>Musa sapientum</i> L. as a pharmaceutical excipient", <i>Food Chemistry</i> , 2013. Publication	<1 %
11	Tamara Athamneh, Adil Amin, Edit Benke, Rita Ambrus, Claudia S. Leopold, Pavel Gurikov, Irina Smirnova. "Alginate and hybrid alginate-hyaluronic acid aerogel microspheres as potential carrier for pulmonary drug delivery", <i>The Journal of Supercritical Fluids</i> , 2019 Publication	<1 %
12	"Natural Polymeric Materials based Drug Delivery Systems in Lung Diseases", Springer Science and Business Media LLC, 2023 Publication	<1 %

13 Nguyen Thi Thanh Uyen, Zuratul Ain Abdul Hamid, Nguyen Xuan Thanh Tram, Nurazreena Ahmad. "Fabrication of alginate microspheres for drug delivery: A review", International Journal of Biological Macromolecules, 2020
Publication

14 Antonio Ribeiro, Marlene Lopes, Bárbara Abrahim-Vieira, Pedro Fonte et al. "Probing insulin bioactivity in oral nanoparticles produced by ultrasonication-assisted emulsification/internal gelation", International Journal of Nanomedicine, 2015
Publication

15 Muhammad Adnan Zia, Muhammad Sohail, Muhammad Usman Minhas, Rai Muhammad Sarfraz et al. "HEMA based pH-sensitive semi IPN microgels for oral delivery; a rationale approach for ketoprofen", Drug Development and Industrial Pharmacy, 2020
Publication

16 mail.oap-lifescience.org
Internet Source

17 www.hindawi.com
Internet Source

18 www.ijnrd.org
Internet Source

19	www.jpsbr.org Internet Source	<1 %
20	kb.psu.ac.th Internet Source	<1 %
21	repositorio.tec.mx Internet Source	<1 %
22	repository.usd.ac.id Internet Source	<1 %
23	wjpr.s3.ap-south-1.amazonaws.com Internet Source	<1 %
24	www.journalijar.com Internet Source	<1 %
25	coek.info Internet Source	<1 %
26	fdocuments.in Internet Source	<1 %
27	mro.massey.ac.nz Internet Source	<1 %
28	patents.glgoo.top Internet Source	<1 %
29	1library.net Internet Source	<1 %
30	Shigao Yang, Wen Liu, Shuai Lu, Yong-zhen Tian, Wei-yun Wang, Tie-jun Ling, Rui-tian Liu.	<1 %

"A Novel Multifunctional Compound Camellikaempferoside B Decreases A β Production, Interferes with A β Aggregation, and Prohibits A β -Mediated Neurotoxicity and Neuroinflammation", ACS Chemical Neuroscience, 2016

Publication

31

ebin.pub

Internet Source

<1 %

32

www.atlantis-press.com

Internet Source

<1 %

33

Amal H. El-Kamel, Doaea H. Al-Shora, Yousry M. El-Sayed. "Formulation and pharmacodynamic evaluation of captopril sustained release microparticles", Journal of Microencapsulation, 2008

Publication

<1 %

34

Ying-Lin Wang, Jin-Jia Hu. "Sub-100-micron calcium-alginate microspheres: Preparation by nitrogen flow focusing, dependence of spherical shape on gas streams and a drug carrier using acetaminophen as a model drug", Carbohydrate Polymers, 2021

Publication

<1 %

35

Adebolu Adewole Adeagbo, Gbenga Alebiowu. "Evaluation of Cocoa Butter as Potential Lubricant for Coprocessing in Pharmaceutical

<1 %

Tablets", Pharmaceutical Development and Technology, 2008

Publication

36

L.Sze Tu, F Dehghani, N.R Foster.
"Micronisation and microencapsulation of pharmaceuticals using a carbon dioxide antisolvent", Powder Technology, 2002

Publication

<1 %

Exclude quotes Off

Exclude matches Off

Exclude bibliography On

Effect of Sodium Alginate Concentration on Characteristics, Stability and Drug Release of Inhalation Quercetin Microspheres

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8
