

Performance and drug deposition of kappa carrageenan microspheres encapsulating ciprofloxacin HCl: Effect of polymer concentration

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ORIGINAL ARTICLE

Performance and drug deposition of kappa-carrageenan microspheres encapsulating ciprofloxacin HCl: Effect of polymer concentration

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ABSTRACT

It has been known that in respiratory disease, antibiotic is selected for respiratory diseases or lung infections and this research focused on ciprofloxacin HCl as a model. The aim was to evaluate the effect of kappa-carrageenan polymer concentrations on characteristics, release, and drug deposition in the lung. Ciprofloxacin HCl-carrageenan microspheres were produced with kappa carrageenan (0.75%, 0.50%, and 0.25%) as polymer and KCl (1.5%) as crosslinker. Physical characteristics were included morphology, size, moisture content, swelling index, mucoadhesivity, drug loading, entrapment efficiency, and yield. Freeze-dried microspheres were inhaled by animal, and drug deposition was observed. Results showed that dried, smooth, and spherical microspheres of size of 1.34 to 1.70 μm and loading of 15.63% to 38.72%. Entrapment efficiency and yield were 25.38%–51.61% and 52.53%–63.19%, respectively. Mucoadhesivity was 0.0059–0.0096 kg force, and release in 24 h was 74.38%–81.02%. Release kinetics demonstrated Higuchi mechanism. Increasing carrageenan concentration affected size, loading, and efficiency but did not influence adhesivity, yield, and release. Higher amount of polymer caused the lower deposit on the lungs. Respirable size of ciprofloxacin HCl-kappa carrageenan microspheres was successfully achieved target site and prolonged residence time in lungs.

Key words: Ciprofloxacin HCl, deposition, kappa carrageenan, lung delivery, microspheres, release, respiratory disease

INTRODUCTION

Respiratory tract infection is an infectious respiratory disease that occurs in both upper and lower respiratory tract. This can cause a wide spectrum of diseases, ranging

from mild-to-severe infection to death, which is influenced by causative pathogens, environmental, and host factors. Bacteria that can cause infection in the human respiratory tract are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.^[1] *Staphylococcus aureus* contained in the respiratory tract will enter the lungs causes irritation of the respiratory tract from the pharynx to the lungs.^[2] Antibiotics can be used to treat respiratory infections, and their use refers to the results of sputum culture.^[3]

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Ciprofloxacin is a fluoroquinolone class antibiotic that is active both against Gram-negative and some Gram-positive bacteria.^[4] Ciprofloxacin can be used by oral twice a day. However, only 0.5%–5% can enter the systemic circulation and of these levels, only 10% can reach target organ. Thus, delivery system is needed by changing the route or modifying the release to increase efficacy and reduce side effects of antibiotics.^[5]

Inhalation drug experiences rapid absorption because the wide of the absorption surface, avoiding first-pass metabolism in the liver, can be administered directly into the bronchi, and the lesser amount of drug. Advantages of this require a lower dose along with minimal drug side effects.^[1] Microspheres are one of the delivery systems which can deliver large amounts of drug and slower clearance in the lungs, therefore, it can increase effectiveness.

Microsphere is a small spherical particle (1 µm to 1000 µm). Mechanism of drug release is mediated by diffusion, swelling, and degradation of the matrix.^[6] For the inhalation route, the particle size ranges from 1 µm to 5 µm. If it is greater than 5 µm, the particles will only reach the oropharynx, whereas if it is smaller than 1 µm, the particles will come out with expired air.^[7] Spherical has good flow properties that allow drug to reach respiratory tract. Microencapsulation can increase drug bioavailability and sustained release to target therapy.^[8] Release is influenced by various factors.^[9] Hariyadi *et al.* entrapped ciprofloxacin HCl in alginate microspheres using CaCl₂.^[10] Hariyadi *et al.* also investigated ciprofloxacin-carrageenan microspheres with high concentration of drug and low concentration of KCl,^[11] however, the entrapment efficiency was less than 30%. Kinetics and micromeritics of those microspheres were also studied (unpublished paper).

Carrageenan has been used for encapsulation of drug and pharmaceutical purposes.^[12-15] Carrageenan has different types which produce distinct gel and solution for specific texturing applications.^[15]

This study encapsulated ciprofloxacin HCl using kappa carrageenan produced by ionic gelation method and administered to mice using nose-only inhalation method as modification of Kaur's method, and the lung tissue was collected using the cryotome technique.^[16] The animals were observed for drug deposition. Carrageenan-ciprofloxacin HCl microspheres were designed with 0.75%, 0.50%, and 0.25% polymer; 5% maltodextrin; and 1.5% KCl using aerosolization technique. This research investigated the effect of polymer concentration on characteristics includes size, morphology, entrapment efficiency, loading, yield, mucoadhesive, and release. Drug deposition in the lungs was also observed.

MATERIALS AND METHODS

Materials

Ciprofloxacin HCl (Interbath); Kappa-Carrageenan (Danisco Cultor); KCl (Solvay Chemicals International); Na₂HPO₄ p.a (Merck); KH₂PO₄ p.a (Merck); NaCl p.a (Merck); KCl p.a (Merck); Maltodextrin (PT Bratachem); HCl p.a (Merck); Aquademineralisata (PT. Bratachem).

Microspheres preparations

Microspheres were made by aerosolization with modification, by spraying solution with a spray diameter of 35 µm, distance of 8 cm, and pressure of 40 psi.^[10,11] Formula is shown in Table 1. Ciprofloxacin-carrageenan solution was sprayed on the KCl solution and stirred for 2 h at 1000 rpm. Microspheres were washed for 6 min by centrifugation at 2500 rpm and freeze dried for 24 h at -80°C.

Evaluation of microspheres

Particle size and morphology

Size was characterized by optical microscope and software with a magnification of × 100. For morphology, scanning electron microscope (SEM) was used.

Entrapment efficiency and drug loading

Entrapment efficiency was calculated from ciprofloxacin contained in microspheres, as below equation:

$$\% EE = \frac{\text{ciprofloxacin mass in the microspheres (mg)}}{\text{ciprofloxacin mass in the formula (mg)}} \times 100\% .^{[9]}$$

Loading was calculated from the total microspheres obtained compared to the total weight of microspheres.

In vitro release

Ciprofloxacin release from microspheres was carried out in phosphate-buffered saline (PBS) pH 7.4 ± 0.05 at 37°C. Sample was shaken at 100 rpm. A 5.0 ml of sample was taken from the PBS at 10 min up to 1440 min, and 5 ml media was replaced in each interval. Sample was filtered using 0.45 µm millipore paper. Cumulative ciprofloxacin HCl released from microspheres was obtained by below equation:

$$\% \text{ Ciprofloxacin HCl cumulative} = \frac{\text{Ciprofloxacin mass in the 100 ml of media (mg)}}{\text{ciprofloxacin mass (mg)}} \times 100\%$$

Release profile was shown by the value of b (slope) of the regression equation.

Mucoadhesive examination

Mucoadhesivity was performed using TA-XT stage plus texture analyzer (Stable Micro Systems, Godalming, UK).

Drug deposition and lung irritation

Wistar rats which met inclusions criterias were used, including male rats, 150-200 grams, healthy and no defects

or wounds on their body. Minimum number of animals in each group was 6 rats. Animal experiments were done according to the animal handling protocols and have passed the ethical clearance by Ethical committee of Universitas Airlangga with Reference No. 038/HRECC.FODM/II/2019.

Drugs administration to animal

Ciprofloxacin dosage inhalation for animals is 20 mg/Kg BW.^[17] Microspheres given to rats were calculated from drug loadings. Administration of microspheres by nose only exposure were applied using modified tool as same principle as DPI tool [Figure 1]. The apparatus was adopted from Kaur.^[16] Microspheres were flown and inhaled by rats through their nose.^[16]

Drug deposition examination

Microspheres were labeled with rhodamine B and were inhaled by previous method. Rats were euthanized and lungs were taken. Lungs were rinsed with normal saline then sliced longitudinally horizontally with a thickness of 6 μm using a cryotom (Tissue-Tek Cyro3, Sakura) at a temperature of -59°C at the Anatomical Pathology Laboratory, Integrated Central Surgical Building at Soetomo Hospital. The cryostat preparations were stored at -15°C-20°C until further analysis. Drug deposition observation was carried out using Fluorescence Microscope (FS × 100, Olympus) with a magnification of ×42 and an exposure time of 1/1.2 ms and using a red filter.

Data analysis

For physical characteristics and drug release, statistical

data analysis was performed using one-way ANOVA with a confidence degree of 95% ($\alpha = 0.05$). Drug deposition was observed using a fluorescent microscope and intensity was compared. Data analysis of the intensity quantitatively used imageJ software and compared statistically with the Kruskal–Wallis nonparametric analysis.

RESULTS AND DISCUSSIONS

Particle size and morphology of microspheres

Particle size of all formulas was obtained below 5 μm as shown in Figure 2. This size corresponds to the desired size to achieve alveoli site. If it is greater than 5 μm, particles will only reach the oropharynx, whereas if it is smaller than 1 μm, the particles will come out with expired air.^[18]

Based on statistical analysis, the increase in polymer concentration showed a significant difference to the particle size.

Morphological observations of the microspheres using SEM can be seen in Figure 3. It was showed that formulas formed spherical microspheres and smooth surfaces.

Yield

Microspheres' yield was seen in Figure 4 and showed at about 52.53%–63.19%.

Table 1: Ciprofloxacin HCl-carrageenan microspheres

Formula	Components			
	Ciprofloxacin (%)	Kappa-carrageenan (%)	KCl (%)	Maltodextrin (%)
F1	0.5	0.75	1.5	5
F2	0.5	0.50	1.5	5
F3	0.5	0.25	1.5	5

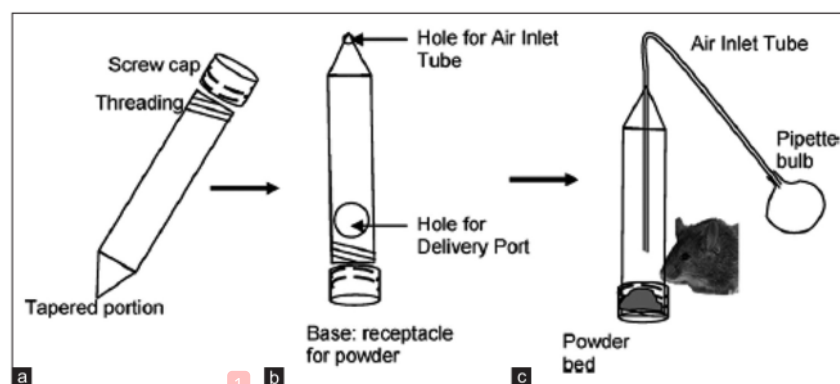


Figure 1: Inhalation Drug Apparatus [16]: (a) A tapered poly(propylene) centrifuge tube of capacity 15 ml that formed the powder fluidization or aerosol generation chamber; (b) Flexible, C-Flex tubing to introduce a turbulent fluidizing air stream into the chamber; (c) a rubber pipette bulb that provided the source of turbulent air when pressed and released.

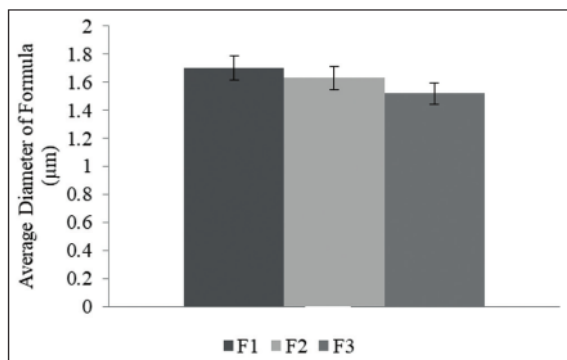


Figure 2: Size of ciprofloxacin HCl-carrageenan microspheres

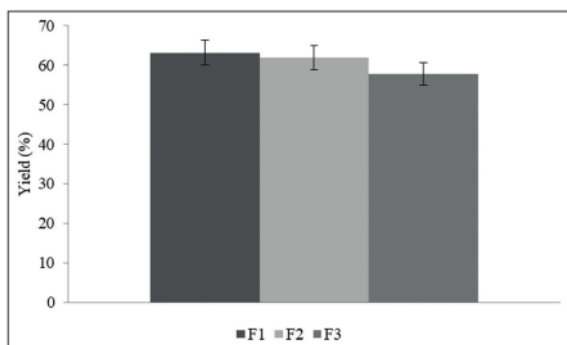


Figure 4: Microspheres yield

1.4 Entrapment efficiency and drug loading

Entrapment efficiency of microspheres and drug loading was presented in Figure 5.

F1 had the highest entrapment efficiency and drug loading. This was due to the highest concentration of F1 polymer. Increasing polymer concentration increased entrapment and drug loading which will cause high polymer solution viscosity and produce large droplets and sizes and cross-linking points on the polymer chain increased to bind drugs so that entrapment efficiency and drug loading increased.^[19,20] Meanwhile, F3 had the smallest entrapment efficiency and drug loading because due to smallest polymer concentration caused low viscosity and results in small droplets and a reduced cross-link point on the polymer chain. Thus, small efficiency and drug loading were found. Addition of maltodextrin may cause small entrapment efficiency and loading due to ability of maltodextrin to form hydrogen bonds which can force the intermolecular bonds between K⁺ with sulfate groups and carrageenan polymer oxygen, thereby causing a decrease in cross-link point of the polymer.^[9]

In vitro release study

Release of all microspheres formula is shown in Figure 6.

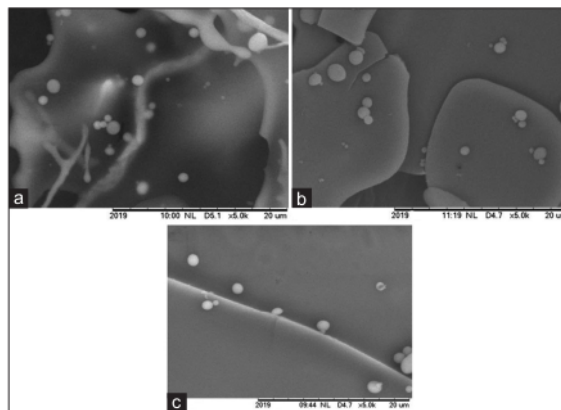


Figure 3: Morphological of ciprofloxacin HCl-carrageenan microspheres Formula 1 (a), Formula 2 (b), and Formula 3 (c) with a magnification of ×5000

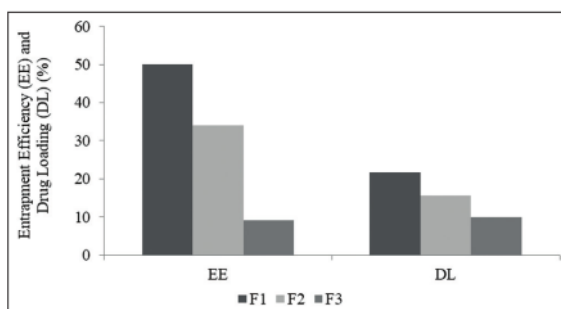


Figure 5: Entrapment efficiency and drug loading of ciprofloxacin-carrageenan microspheres

Cumulative drug release up to 1440 min from F1 to F3 was 71% to 77.96%. This was in line with the expectation of slow-release modification. Statistical showed that there was no significant difference in the cumulative regardless of each formula. This could be because differences in concentration between formulas of 0.25% still did not make a significant difference at the use of 1.5% KCl. Thus, it is recommended to optimize other factors that may influence the release. Based on statistical analysis, there was no significant difference toward all slopes.

Release kinetics

Release kinetics model showed that kinetics follows zero order with the highest *r* value [Table 2]. Zero-order kinetics model stated that drug release occurs through a solid gel layer which has a constant thickness with respect to the time associated with the swelling process of carrageenan and erosion rate of the gel layer.^[21] In consequence, sustain release of microspheres in carrageenan matrix can be applied.

F1, F2, F3, and F4 showed no significant differences between amount of polymer and release rate. This could be because of the small differences in concentration used did not make a difference.

Table 2: Coefficient of the relation (R) of the kinetics model

Formula	Order 0 (R ²)	Order 1 (R ²)	Higuchi (R ²)	Korsmeyer-Peppas (R ²)
F1	0.9994	0.9940	0.9723	0.9359
F2	0.9996	0.9855	0.9777	0.9372
F3	0.9996	0.9900	0.9770	0.9370

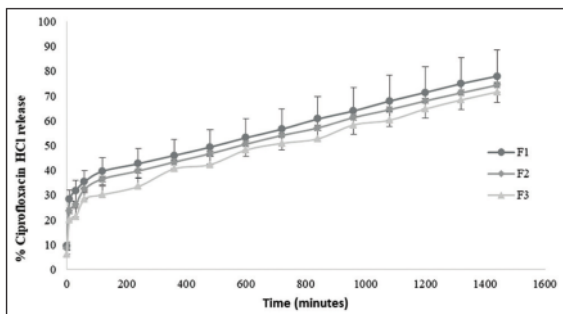


Figure 6: Release of ciprofloxacin HCl from microspheres

Mucoadhesivity of microspheres

Mucoadhesivity of microspheres formula is shown in Figure 7.

F1 had the highest mucoadhesive compared to others, however, no significant difference between formulas. The most optimized formula was formula with high carrageenan because formula provided high drug loading and entrapment efficiency, spherical, small, and smooth surface microspheres which were not cause irritation to the respiratory tract.

Drug deposition of microspheres

Observations of drug deposition in the trachea at 1st and 4th h can be observed in Figure 8. It can be seen that intensity was higher in Formula 3 compared to others in the 1st h. For the 4th h, intensity became more even in Formulas 1 and 2. For Formula 3, intensity was fainter than the 1st h [Table 3]. It was indicated that there was a significant difference in drug deposition in trachea.

Observations of drug deposition in bronchioles at the first and the 4th h can be seen in Figure 9.

It can be seen that intensity was greater in Formula 3 compared to others [Figure 10]. For the 4th h, intensity became more even in Formulas 1 and 2. In Formula 3, intensity was fainter than 1st h [Table 4]. It was indicated that there was a significant difference in drug deposition.

Observations of drug deposition in the alveoli at the 1st and the 4th h can be seen in Figure 11.

Highest intensity in alveoli at 1 h was Formula 3. For the 4th h, highest intensity was Formula 1 and decreased in Formula 3. On the other hand, in Formula 3, intensity

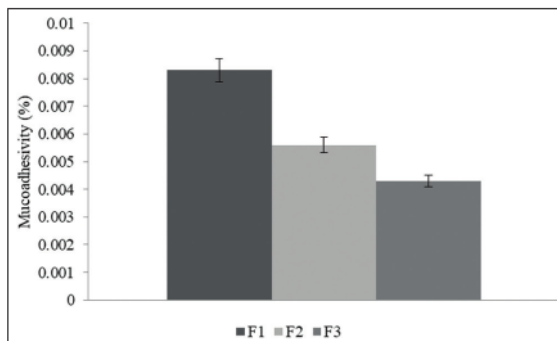


Figure 7: Mucoadhesivity of microspheres

was fainter than the 1st h [Table 5]. It was indicated that a significant difference in drug deposition was found. Based on all results, the distribution of microspheres intensity in rat lungs at the one and 4 h was seen clearly.

Drug inhalation in the form of DPI uses nose-only method because simple no need for anesthesia, no surgery, and quite effective.^[12] Observation of deposition using fluorescence microscopy was a sensitive method.^[21]

Results of F1 and F2 observation, it can be seen that at 1st h, the red luminescence weak in the trachea, bronchi, and alveoli. In F3, the red luminescence was higher and had spread to the lower lungs. Furthermore, an increase in polymer concentration showed significant difference in the intensity. This may occur because with a concentration of 0.75% and 0.5%, microspheres hold release of rhodamine, therefore, at the 1st h, only a little rhodamine was released and red luminescence was only visible around the walls of the trachea and bronchioles.

Increase in polymer concentration caused larger size, which means thicker matrix and more polymers that entrap the drug produced longer drug release. Therefore, at the 1st h, formula with smallest polymer concentration produced more luminescence than formula with higher concentration.

At the 4th h, F3 luminescence had started to fade and intensity was the lowest, while in F1 and F2, the intensity was higher than 1st h. This may occur because a lot of rhodamine was released from microspheres enter into the lower lungs and alveoli.

The ideal size range for inhalation system is 1–5 μm, therefore, all formulas were included as particles

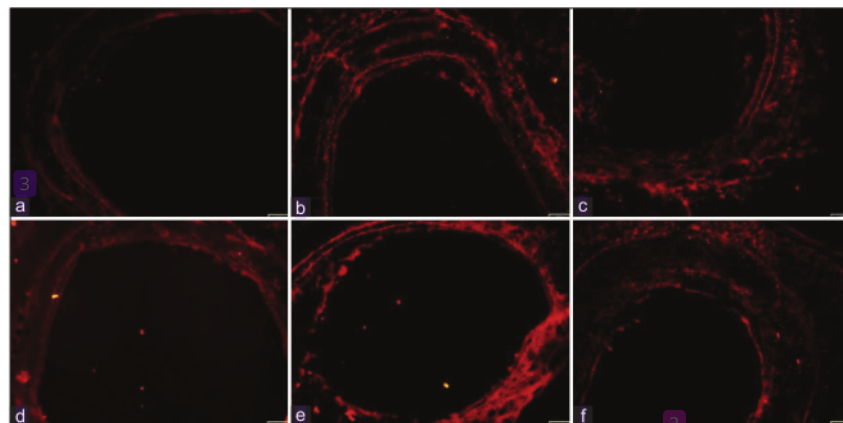


Figure 8: Observation of ciprofloxacin HCl-carrageenan microspheres in the trachea at 1st h of Formula 1 (a), Formula 2 (b), Formula 3 (c) and 4th h of Formula 1 (d), Formula 2 (e), Formula 3 (f)

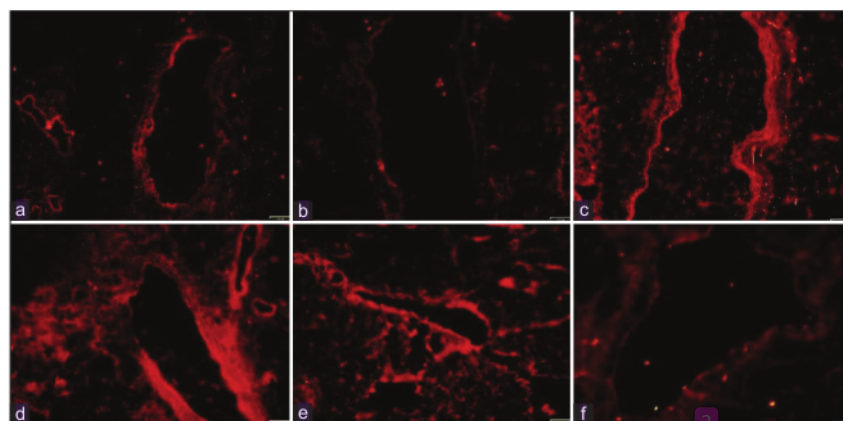


Figure 9: Observation of ciprofloxacin HCl-carrageenan microspheres in rat bronchioles at the 1st h of Formula 1 (a), Formula 2 (b), Formula 3 (c) and the 4th h of Formula 1 (d), Formula 2 (e), Formula 3 (f)

which capable of entering the lower respiratory system. Microspheres were able to deliver drugs to the lower lungs. Further research is needed to determine whether ciprofloxacin reaches the lungs with sufficient concentration levels to kill bacteria.

CONCLUSION

Increased polymer concentration carrageenan kappa influenced physical characteristics of the ciprofloxacin-kappa carrageenan microspheres but had no effect on mucoadhesive, release rate, and release profile. The use of carrageenan was capable of delivering microspheres to the lower lung. Carrageenan concentration affected drug deposition in the lungs. The higher the carrageenan levels, the slower the drug deposition in the lungs. It is suggested to evaluate more quantitatively the ciprofloxacin HCl concentration in the blood that is separated from the microspheres.

Table 3: Intensity in the trachea at 1st and 4th h

Formula	Mean intensity ± SD	
	1 st h	4 th h
F1	7.4056 ± 0.908	12.085 ± 0.1589
F2	11.944 ± 1.934	24.932 ± 6.084
F3	40.083 ± 6.879	5.354 ± 0.717

SD: Standard deviation

Table 4: Intensity in the bronchioles at 1st and 4th h

Formula	Mean intensity ± SD (intensity unit)	
	1 st h	4 th h
F1	8.414 ± 0.911	31.407 ± 7.378
F2	19.7024 ± 3.4765	25.973 ± 5.913
F3	35.1182 ± 3.894	9.458 ± 1.994

SD: Standard deviation

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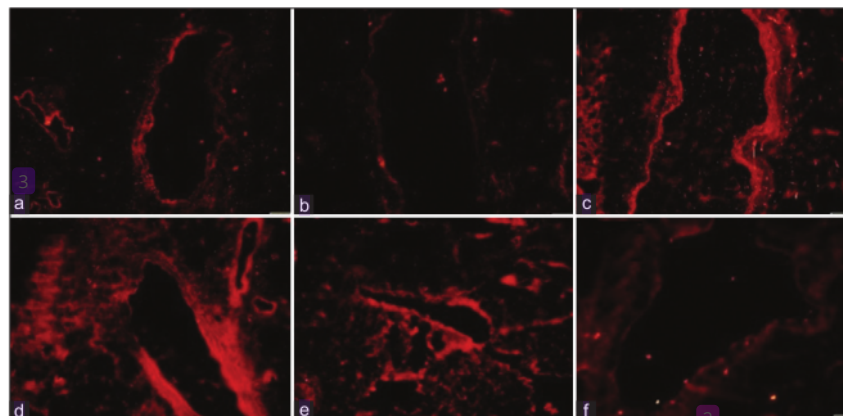


Figure 10: Observation of ciprofloxacin HCl-carrageenan microspheres in rat bronchulus at the 1st h of Formula 1 (a), Formula 2 (b), Formula 3 (c) and the 4th h of Formula 1 (d), Formula 2 (e), Formula 3 (f) with a ×42 magnification red filter fluoresce

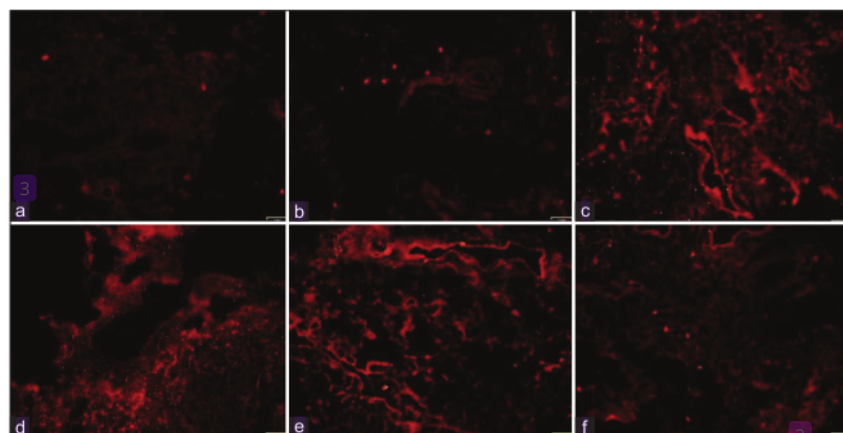


Figure 11: Observation of ciprofloxacin HCl-carrageenan microspheres in the alveoli of rats at the 1st h of Formula 1 (a), Formula 2 (b), Formula 3 (c) and 4th h of Formula 1 (d), Formula 2 (e), Formula 3 (f)

Table 5: Intensity in the alveoli at 1st and 4th h

Formula	Mean intensity unit±SD	
	1 st h	4 th h
F1	4.212±1.325	21.487±6.541
F2	4.169±1.079	16.992±1.813
F3	15.376±2.520	8.251±2.824

SD: Standard deviation

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Conflicts of interest

There are no conflicts of interest.

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