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# International Journal of Drug Delivery Technology

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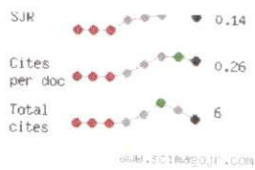
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## Development of Carrageenan Polymer for Encapsulation of Ciprofloxacin HCL: In Vitro Characterization

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### ABSTRACT

This study reported the properties of microspheres based Carrageenan polymers with Ciprofloxacin HCl antibiotic as a model for dry powder inhalation (DPI). Microspheres Ciprofloxacin-Carrageenan was prepared through ionic gelation process which is a widely used microencapsulation technique in the pharmaceutical industry. Microspheres formula consists of formula using 0.5 and 1% carrageenan polymer and 0.2 and 0.6% KCl crosslinker which was named as F1, F2, F3 and F4. Microspheres were characterized for their yield, morphology, entrapment efficiency, drug loading and particle size. Results revealed that ionic gelation technique was a suitable technique for preparation of microspheres as most of the formulations were small in size, spherical in shape with a good yield of 46% to 89%. Based on the data of various evaluations such as drug entrapment efficiency, drug loading and particle size, formula F3 was found as the best DPI formula. Microspheres were successfully prepared and this study can be concluded that the developed microspheres of ciprofloxacin HCl-Carrageenan can be used for pulmonary system to improve the release mechanism and drug bioavailability.

**Keywords:** Microspheres, Ciprofloxacin HCl, Carrageenan, Characteristics.

### INTRODUCTION

Ciprofloxacin HCl is a wide spectrum antibacterial agent for positive and negative gram bacteria. Ciprofloxacin HCl is especially active for Gram negative germs including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin HCl has moderate activity against Gram positive bacteria such as Streptococcus pneumonia and Enterococcus. The use of Ciprofloxacin HCl has been used for airway infections (but not pneumococcal pneumonia), urinary tract, digestive system (including typhoid fever), gonorrhea and septicemia by sensitive organisms<sup>1</sup>

In oral route, Ciprofloxacin HCl was absorbed in body by 70% after administration. Ciprofloxacin was then metabolized in the liver about 15% then excreted 40-50% from oral dose<sup>2</sup> therefore suggested an alternative route. The other route is pulmonary route. The pulmonary route needs small dosage and small particle size of <5  $\mu\text{m}$  therefore microspheres were as an alternative for delivery system. Microspheres were chosen because the use of fewer dosages, small size and can be used for prolonged therapeutic effects<sup>3</sup>. Carrageenan polymer was selected in this research because it is a natural polymer that is biodegradable, economical and widely used for encapsulation<sup>4</sup>. Kappa carrageenan is one of carrageenan type which has many advantages. To form microspheres gel for carrageenan, monovalent crosslinker was needed, such as  $\text{K}^+$ ,  $\text{Na}^+$  and  $\text{Li}^+$ <sup>5</sup>. The most crosslinker used for kappa carrageenan is potassium chloride (KCl). KCl was

used because it can form a gel that was stable, elastic, cohesive and transparent<sup>6</sup>. This study used ionotropic gelation method with aerosolization technique because of simple and easy. Aerosolization techniques were used because they can produce small and uniform particle sizes<sup>7,8</sup>. In this research, development of optimized microspheres preparations will be done by study the physical characteristics of ciprofloxacin HCl-carrageenan microspheres at different concentration of carrageenan polymer and KCl crosslinker. Physical characteristics included morphology, yield, particle size, drug loading and entrapment efficiency.

### MATERIALS AND METHODS

#### Materials

Ciprofloxacin HCl (Zinjang Ltd), Kappa-Carrageenan (KCN), KCl (Merck), Maltodextrin (Zhuceng Ltd), Aquadestillata (Bratachem). All composition and reagent

Table 1: Microspheres formula of Ciprofloxacin HCl-carrageenan.

Formula	Ciprofloxacin HCl	Carrageenan	KCl
F1	1%	0.5%	0.2%
F2	1%	0.5%	0.6%
F3	1%	1%	0.2%
F4	1%	1%	0.6%

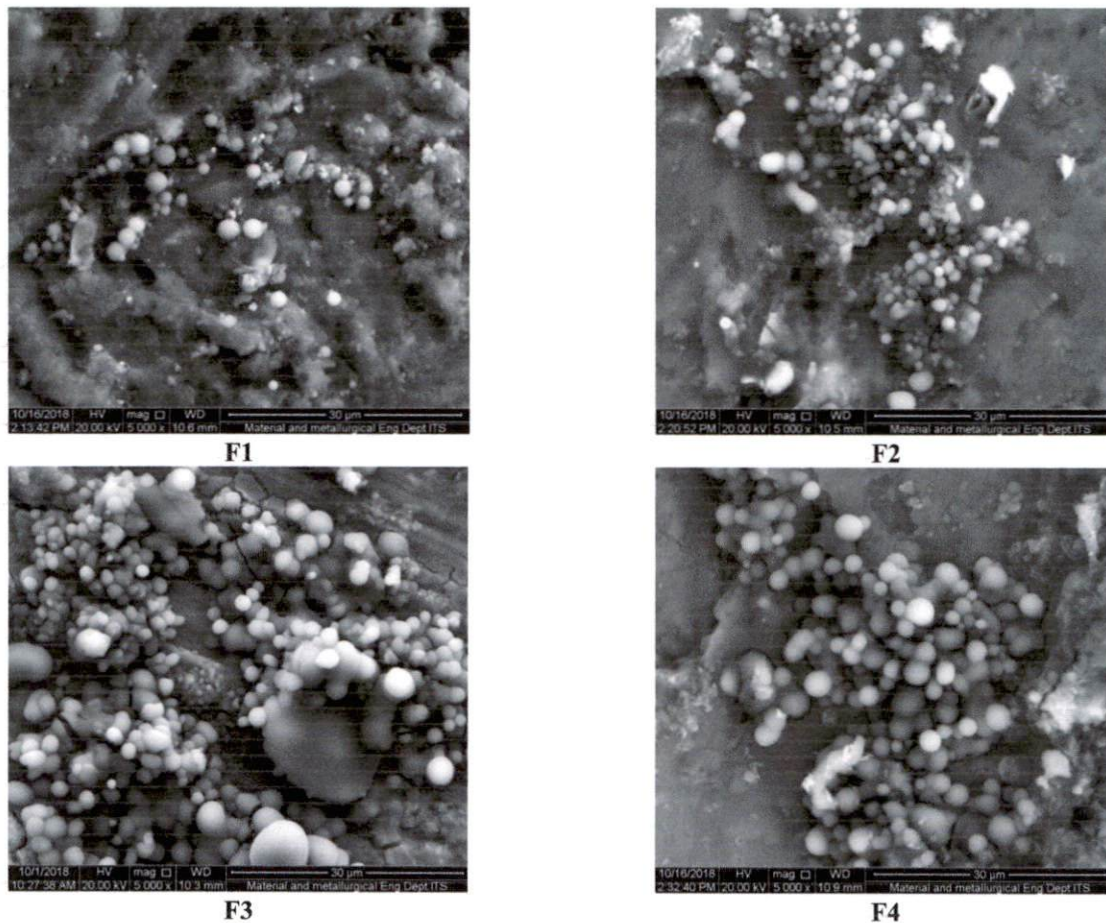


Figure 1: Scanning Electron Microscope of Microspheres F1, F2, F3 and F4 (at 5000x) For particle size distribution, figure 2 to 5 illustrated that small sizes of range between 0.6 to 4 μm were resulted.

Table 2: Characteristic physics of microspheres ciprofloxacin-carrageenan.

Formula	Particle size (μm)	Yield (%)	Drug loading (%)	Entrapment efficiency (%)
F1	1.41	34.62	13.49	10.54
F2	1.59	46.11	13.81	11.09
F3	1.62	67.05	15.97	24.71
F4	1.67	89.33	18.90	28.69

use pharmaceutical grade.

**Methods**

*Preparation of microspheres by ionic gelation method*

Ciprofloxacin HCl, Carrageenan and KCl were firstly each dissolved in water. Ciprofloxacin and KCl were then mixed and the solutions were sprayed into Carrageenan solution. Mixture of solution was stirred for 2 hours using a magnetic stirrer at 1000 rpm. Formed solution was separated using centrifuge, then it was filtered to collect microspheres. Wet microspheres obtained were put into freeze dryer for 48 hours at -50°C.

*Physical characterization of microspheres*

**Morphology**

Surface morphology of microspheres was examined using Scanning Electron Microscope (SEM). The sample was mounted on an aluminum SEM sample holder, coated with a thin layer of gold for 120 seconds and then observed with a SEM microscope at 10 kV<sup>9</sup>.

**Particle size**

Microspheres were put on object glass and 300 particles were measured using optical microscope. Particle were then grouped, determined smallest and largest particle size of all samples, and grouping into several intervals and classes. Average diameter was determined and calculated using below equation:

$$\text{Diameter average} = \frac{\sum nd}{\sum n}$$

n = number of microparticles observed

d = size of the microparticles<sup>10</sup>.

**Yield**

Yield was determined by comparing total weight of microspheres with weight of microparticles forming material. Yields close to 100% indicated that the method used in preparation is efficient to produce microspheres. Yield was calculated using below equation:

$$\% \text{ yield} = \frac{\text{Weight of dry microspheres}}{\text{Total weight material}} \times 100\%$$

**Drug loading**

Weighted of microspheres (50 mg) and microspheres were put in a 50 ml of PBS solution pH 7.4, then it was left for

24 hours by continued stirring for 2 hours. The solution was filtered and then measured the absorbance in a UV-Vis spectrophotometer at wavelength of 268 nm using a regression from the standard curve. Drug loading was calculated using below equation:

$$\text{Drug loading} = \frac{\text{Weight of drug}}{\text{Weight of microspheres}} \times 100\%^{12}$$

*Entrapment efficiency*

Entrapment efficiency was calculated using below equation:

$$\text{Entrapment efficiency} = \frac{\text{Drug content in microspheres}}{\text{Theoretical drug content in formula}} \times 100\%^{13}$$

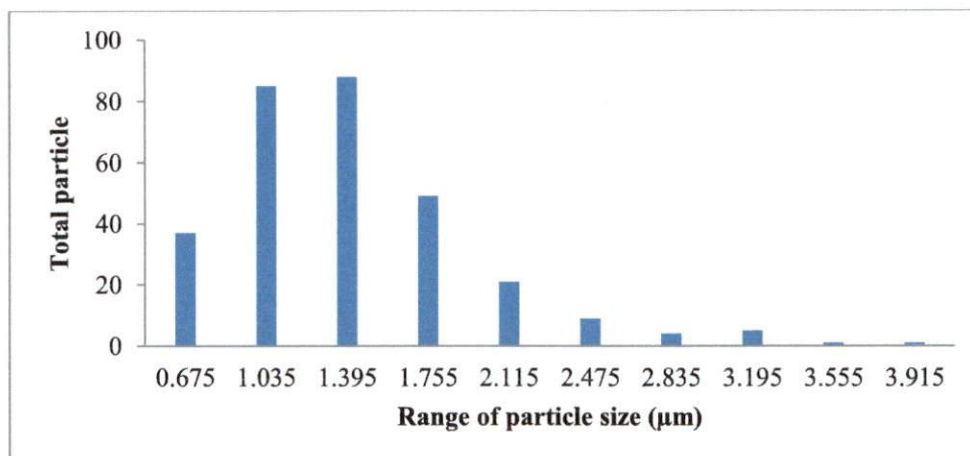


Figure 2: Histogram of particle size distribution F1.

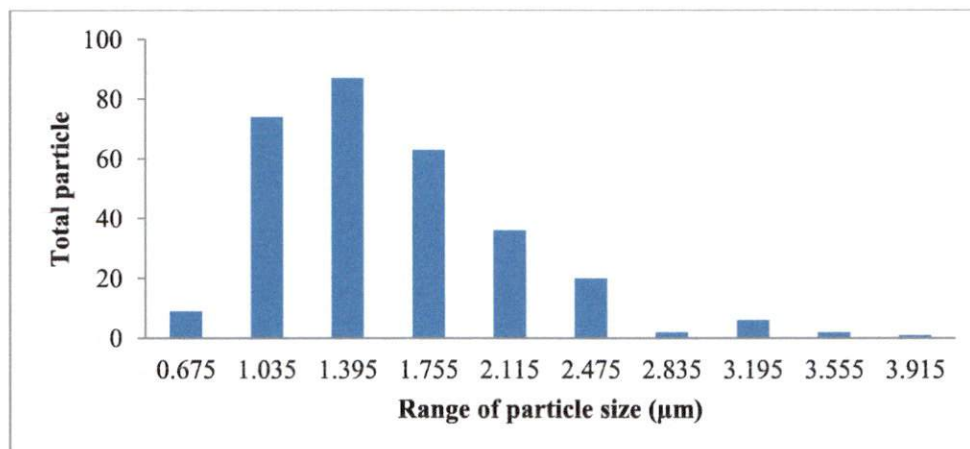


Figure 3: Histogram of particle size distribution F2.

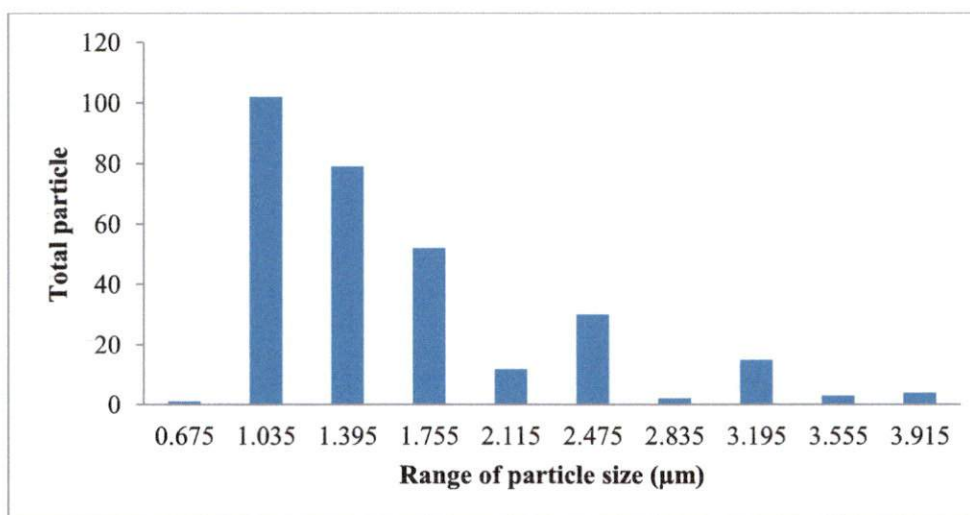


Figure 4: Histogram of particle size distribution F3.

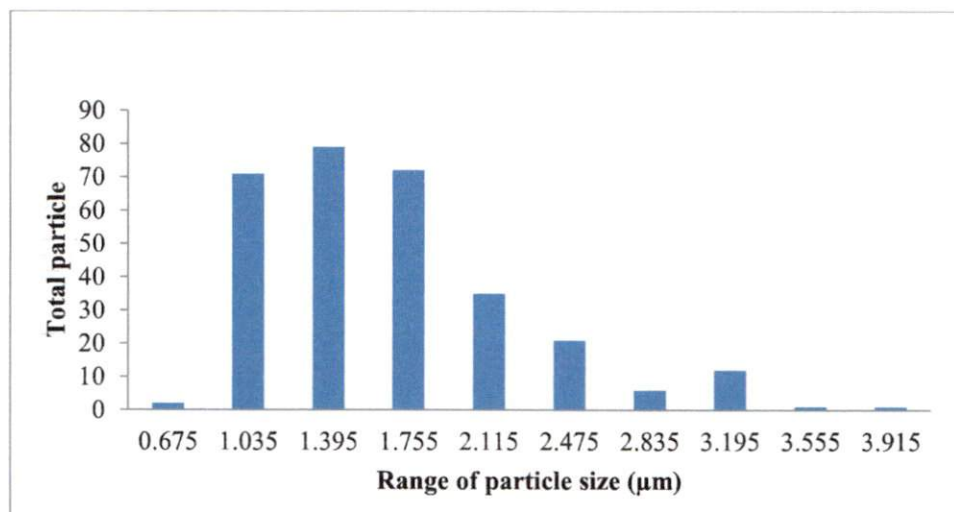


Figure 5: Histogram of particle size distribution F4.

**RESULT**

Result of characteristics of microspheres produced form aerosolization technique can be seen in their morphology in Figure 1. In terms of average of particle size, yield, drug loading and entrapment efficiency, ciprofloxacin HCl-carragenan microspheres of all formulas were shown at Table 2.

**DISCUSSION**

Microspheres were made by ionic gelation using non-organic solvents which was distilled water. Ciprofloxacin HCl is easily soluble in water, stable at room temperature 25°C and at pH 4-7. Ionotropic gelation methods were used because they are very simple and easy process to design a carrier as controlled release<sup>11,12</sup>. The results of examination of particle morphology using Scanning Electron Microscope (SEM) of F1 to F4 were had round spherical shape and smooth surface. Measurement of particles of F1 to F4 was less than 4µm with average of about 1.4 to 1.6µm. The particle size of smaller than 5 µm was desirable to be deposited in the alveoli. Particles of more than 10 µm will quickly disappear in the upper airways due to swallowing or coughing<sup>13</sup>. Yield value showed the smallest value that was for F1 of 34.62 % and the highest was F4 of 89.33%, which means this method was an efficient method to produce ciprofloxacin HCl-carragenan microspheres. Entrapment efficiency had the lowest value of 10.54 % and the highest at 28.69%. Drug loading had values ranging from 13% to 18%. These results showed that the higher concentration of the polymer and crosslinker showed entrapment efficiency and drug loading was also increased. This was because an increase concentration of the polymer increased the degree of crosslink in the microspheres to bind the drug into helical forms of the carragenan microspheres. In addition, increase of polymer also increased the drug encapsulation. Thus, drug loading and entrapment efficiency of F4 were the highest<sup>14</sup>.

**CONCLUSION**

This study can be concluded that the Ciprofloxacin HCl-Carrageenan microspheres resulted round spherical shape

with smooth surface. Increasing concentration of carrageenan polymers (0.5 to 1.0%) and KCl crosslinker (0.2 to 0.6%) increased particle size, yield, entrapment efficiency and drug loading. The further study of in vitro release was recommended to complete study of in vitro microspheres characterization.

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