Pharmacy Education (2023) 23(4) 27 - 31
https://doi.org/10.46542/pe.2023.234.2731

ICMHS 2022 SPECIAL EDITION

RESEARCH ARTICLE

Carbomer and ethyl cellulose optimisation in the preparation of mucoadhesive microspheres ciprofloxacin hydrochloride

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Keywords
Carbomer
Ciprofloxacin hydrochloride
Ethyl cellulose
Microsphere
Mucoadhesive

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Abstract

Background: Ciprofloxacin hydrochloride (CH) is an antibiotic used to treat urinary tract infections. CH has a short half-life and low bioavailability. Microspheres combined with a mucoadhesive system can increase the residence time of the drug in the stomach to increase the bioavailability of CH. **Objective:** This research was conducted to obtain the best amount of carbomer as a polymer mucoadhesive and ethyl cellulose as a matrix polymer based on factorial design. **Method:** The factorial design 2^2 was used to determine the amount of carbomer and ethyl cellulose to produce optimum mucoadhesive microspheres. Three responses were observed in this study: particle size, entrapment efficiency, and mucoadhesive strength. **Result:** The resulting entrapment efficiency was 69.0%, particle size was 404.52 nm, and mucoadhesive strength was 64.3 grams, with drug loading and yield values of 19.13% and 99.8%, respectively. **Conclusion:** The optimum formula with the highest response value is the formula containing 300 mg carbomer and 1000 mg ethyl cellulose.

Introduction

Ciprofloxacin hydrochloride is a second-class fluoroquinolone antibiotic that has a broad antibacterial spectrum. Ciprofloxacin effectively treats urinary tract infections (UTIs) (Shahidulla & Fatima, 2019). The recommended daily dose of ciprofloxacin in treating UTIs is 500 mg, given twice in divided doses (Brown, 2006). In oral administration, the bioavailability is low, around 70-82%. Primary drug absorption occurs in the stomach (Olivera *et al.,* 2010). Ciprofloxacin has a short half-life of about three to four hours, so it needs to be administered repeatedly. Repeated oral administration of ciprofloxacin causes discomfort and patient noncompliance (Begg *et al*., 2000).

Reducing the frequency of drug administration can improve patient compliance (Srivastava *et al*., 2013). Extending the drug's residence time increases the drug's bioavailability in systemic circulation so that the goal of reducing the frequency of drug administration can be achieved.

The mucoadhesive system uses a gastro-retentive drug delivery system approach to prolong the residence time of drugs in the digestive tract (Makwana *et al*., 2012). Mucoadhesive systems can be combined with microspheres drug carrier systems to extend gastrointestinal drug release (Kaurav *et al*., 2012). The microsphere-forming matrix polymer used in this study was ethyl cellulose, and the mucoadhesive polymer used was carbomer.

Ethyl cellulose is a hydrophobic polymer used as a matrix to control the drug release rate. Carbomer was used in this study because of its high mucoadhesive strength and low toxicity (Kaurav *et al*., 2012).

Factors that affect the size and shape of the microspheres are the concentration and type of polymer used (Deb *et al*., 2011). The higher the polymer

concentration, the larger the size of the resulting microspheres. The higher polymer concentration will also affect the entrapment efficiency and mucoadhesive strength. Based on this, optimising the concentration of carbomer and ethyl cellulose is necessary to obtain the optimum particle size, the highest entrapment efficiency, and mucoadhesive strength.

Methods

Design

The materials used in this study were ciprofloxacin hydrochloride (Shangyu Jingxin Pharmaceutical, Co. Ltd), ethyl cellulose (Shanghai Honest Chem. Co. Ltd), carbomer 940, acetone, span 80, liquid paraffin, petroleum ether in pharmaceutical grade, purchased from PT.BrataChem (Indonesia), and Wistar rats' gastric juice.

The instruments used in this study were UV-Vis spectrophotometer (Genesys 10s, Thermo Scientific), FTIR (Alpha Bruker), four blades propeller mixer (IKA Labortechnik), Scanning Electron Microscope (Hitachi TM3000), texture analyser (TA-TX2, Stable Micro System), hot plate magnetic stirrer (Ika c-mag HS7).

Microspheres were prepared by solvent evaporation technique. First, ethyl cellulose was dissolved in acetone. Ciprofloxacin hydrochloride and carbomer were added to the ethyl cellulose solution. The mixture was then stirred using a magnetic stirrer for 30 minutes to produce an internal phase solution. Liquid paraffin and span 80 were prepared in a certain amount into an external phase solvent. The internal phase solution was emulsified into the external phase solution and then stirred with a four-blade propeller mixer at 1000 rpm for 45 minutes. The microspheres formed were filtered, washed using petroleum ether, dried at room temperature, and stored in a desiccator. The mucoadhesive microspheres formula used in this study are shown in Table I.

Table I: The formula of mucoadhesive microspheres

Material	Composition			
	F1	F2	F3	F4
Ciprofloxacin hydrochloride	0.5 g	0.5 g	0.5 g	0.5 g
Carbomer	0.1 g	0.3 g	0.1 g	0.3 g
Ethylcellulose	0.75 g	0.75 g	1.0 g	1.0 g
Acetone	9 mL	9 mL	9 mL	9 mL
Liquid paraffin	70 mL	70 mL	70 mL	70 mL
Span 80	1.5 mL	1.5 mL	1.5 mL	1.5 mL

Assessment

Particle size measurements were carried out using an optical microscope equipped with an ocular micrometre and an objective with a sample of 50 particle microspheres. Microspheres were placed on the object glass and dripped with distilled water. The particle size measurement was done by calculating the average and coefficient of variation.

The maximum wavelength was determined by measuring the absorption of the selected standard at a wavelength of 200-400 nm using a UV spectrophotometer.

The measurement of entrapment efficiency was carried out by weighing a certain number of microspheres equivalent to 50 mg of ciprofloxacin hydrochloride and dissolved in 50 ml of 0.1 N HCL. The suspension was sonicated for approximately two hours and then filtered. The filtrate was analysed to determine the drug content with a UV spectrophotometer at the maximum wavelength.

Mucoadhesive strength testing was carried out using the Texture analyser. The freshly excised pieces of gastric tissue of Wistar rats were washed with 0.9% physiological NaCl solution then the tissues were attached to the plates in the position of mucosa facing up. A certain number of microspheres were attached to the gastric tissue and left in contact for 20 minutes. The device was run, and the probe was adjusted to apply pressure. Then, it was withdrawn from the probe at a test speed of 0.5 mm/sec. The instrument recorded the curve between the time and the required force until the microspheres separated from the tissue surface (Thirawong *et al.,* 2007).

The optimum formula was determined by analysing the results of particle size, entrapment efficiency, and mucoadhesive strength as a research response.

The optimum formula was then verified using a one-sample *t-test* on the three responses. Characterisation of the optimum formula includes the determination of drug loading, yield, surface morphology analysis using scanning electron microscopy (SEM), and The Fourier transform infrared (FTIR) analysis.

Results

Evaluation of the microspheres provided the results as shown in Table II. The results of the entrapment efficiency test showed that the F4 formula has the highest average entrapment efficiency of 69.58%. The results of the post hoc analysis (LSD) showed that the entrapment efficiency was F4 > F2 > F1 > F3. Entrapment efficiency data were analysed using Design Expert 11.0.

Table II: The evaluation results of mucoadhesive microspheres

Evaluation	Results			
	F1	F2	F3	F4
Entrapment efficiency (%) + SD	49.5 + 0.426	55.3 ± 2.035	42.3 ± 0.888	69.6 ± 2.132
Particle size (μm) ± SD	377.9 +10.11	397.6± 10.485	383.5± 10.699	405.0± 10.82
Mucoadhesive strength (g) ± SD	35.8+ 1.76	42.0 +1.637	60.8 + 0.723	63.5 + 1.401

The F4 microspheres had the largest average particle size of 404.95m. Based on the results of the post hoc analysis (LSD), the resulting particle size is F4 > F2 > F3 > F1.

The results of the mucoadhesive strength test showed that F4 microspheres had the highest average mucoadhesive strength of 63.47g. Based on the results of post hoc analysis (LSD), it can be concluded that the mucoadhesive strength produced is F4 > F3 > F2 > F1.

The optimum formula was determined based on the highest response value that met the pre-determined criteria with a desirable value close to one. The optimum area can be seen in the overlay plot in Figure 1. The optimum formula with the highest desirability value is F4, with 300 mg of carbomer and 1000 mg of ethyl cellulose.

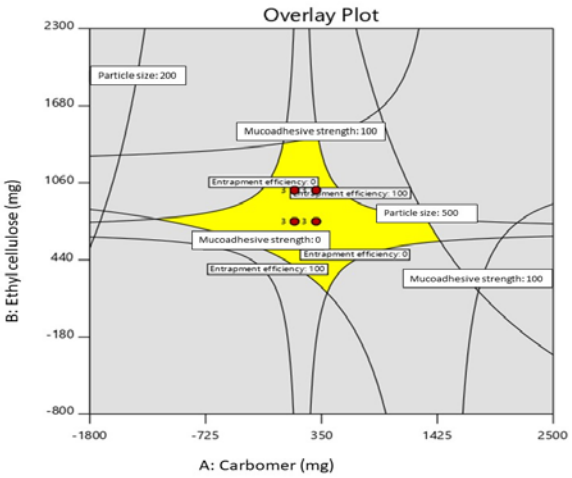

Figure 1: The overlay plot

The optimum formula that was selected based on the results of the design expert was verified by performing three replications which included entrapment efficiency, particle size, and mucoadhesive strength.

The results of verifying the optimum formula of the three responses showed a significance value of > 0.05, indicating that the predictive and observational results were not significantly different.

Determination of drug loading and yield of the mucoadhesive microsphere from the optimum formula resulted in a drug loading of 19.13% + 0.28 and a yield of 99.8% + 0.12.

The results of the FTIR test can be seen in Figure 2. The –CH2 bending was found at a wave number of 1,446.89 cm^{-1}, which is the group in the carbomer and ethyl cellulose. The C=O stretching group, which is the functional group of the carbomer, was found at wave number 1265.13 cm^{-1}. The C-O ester group was found at a wave number of 1089.15 cm^{-1}, which indicated the group from the ethyl cellulose. The overlay results showed that there was no significant peak shift in the mucoadhesive microspheres of ciprofloxacin hydrochloride which indicated that there was no interaction between the active drug ingredient (ciprofloxacin hydrochloride) and the polymers used (carbomer and ethyl cellulose) during preparation.

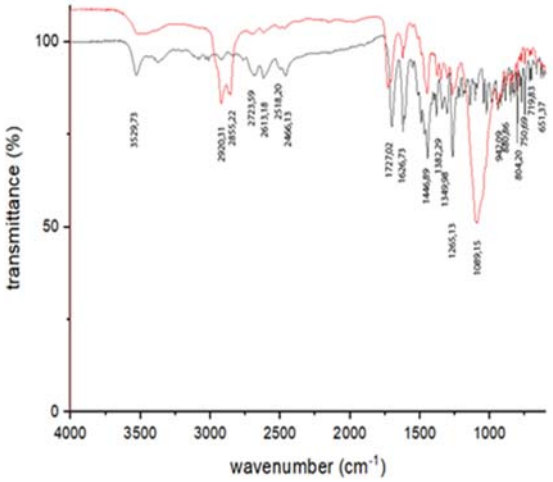

Figure 2: The overlay FTIR spectra of mucoadhesive microspheres and pure ciprofloxacin HCl

The characterisation of the shape and surface morphology of the mucoadhesive microspheres of ciprofloxacin hydrochloride at a magnification of 100 times is shown in Figure 3. In this figure, the shape of the mucoadhesive microspheres is close to spherical, the surface morphology looks porous.

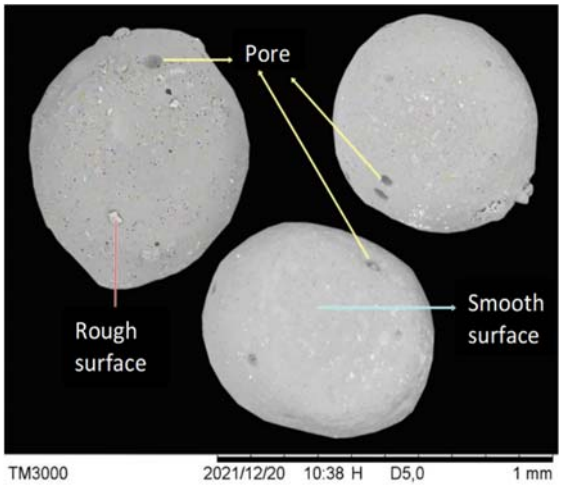

Figure 3: The SEM analysis of mucoadhesive microspheres ciprofloxacin hydrochloride

Discussion

Based on Table II, F4 gave the highest entrapment efficiency of 69.6%, with 300 mg of carbomer and 1000 mg of ethyl cellulose. Analysis of entrapment efficiency in this study showed that the dominant factor in determining entrapment efficiency was the amount of carbomer. Carbomer has a higher viscosity than ethyl cellulose; therefore, if the emulsion has a higher viscosity, the density between the particles is also getting bigger, resulting in a larger droplet particle size. The larger the droplet size, the larger the adsorbed drug, thus increasing the entrapment efficiency (Kyada *et al*., 2014).

Based on Design Expert, the final equation in terms of coded factors was obtained:

*Entrapment efficiency = +54.17 + 8.26*A + 1.79*B + 5.37*AB …… (Equation 1)*

The difference in the particle size is influenced by the differences in carbomer and ethyl cellulose amount used in each formula. The polymer-to-drug ratio affects the size of the resulting microspheres. The higher the polymer concentration, the more the emulsion viscosity will increase, so the resulting droplets become larger.

Based on the analysis of the results of the particle size measurements using factorial design, the following final equation in terms of coded factors was obtained:

*Particle size= +390.98 + 10.30*A + 3.24*B + 0.4393*AB…… (Equation 2)*

The factorial design analysis showed that the higher the polymer concentration, the larger the particle size due to the nature of the solution being more viscous depending on the high concentration of polymer used. The increased viscosity indicates the more significant density of the particles in the liquid. Dense particles will have attractive forces between larger particles. In the emulsion system, the resulting droplets will also be more extensive.

The highest mucoadhesive strength was found in F4 with a mucoadhesive strength of 63.5 g. The higher the polymer-to-drug ratio, the stronger the mucoadhesive strength due to the interaction between the –COOH (carboxyl) group of the polymer and the sialic acid in the mucin (Carvalho *et al*., 2010)

The increasing carbomer concentration and ethyl cellulose increase the mucoadhesive value.

The final equation in terms of coded factors of mucoadhesive strength is:

*Mucoadhesive strength = + 50.53 + 2.20*A + 11.62*B – 0.8833*AB …… (Equation 3)*

The FTIR spectra of the microspheres showed the same peak as pure ciprofloxacin hydrochloride, indicating that the functional group in pure ciprofloxacin hydrochloride was also present in mucoadhesive microspheres. These data suggest no significant peak shift in the mucoadhesive microspheres of ciprofloxacin hydrochloride. Therefore, it means no interaction between the active drug ingredient (ciprofloxacin hydrochloride) and the polymers used (carbomer and ethyl cellulose) during preparation.

Conclusion

Increasing carbomer and ethyl cellulose concentration within microspheres can increase entrapment efficiency, particle size, and mucoadhesive strength. The interaction between these factors can increase entrapment efficiency and particle size but can reduce mucoadhesive strength. The optimum formula of ciprofloxacin hydrochloride mucoadhesive microspheres obtained consists of 300 mg carbomer and 1000 mg ethyl cellulose.

Acknowledgement

This study was supported by the Faculty of Pharmacy University of Jember.

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