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Research Article

KETOPROFEN-CARBOXYMETHYL CHITOSAN MICROPARTICLES PREPARED BY SPRAY DRYING: OPTIMIZATION AND EVALUATION

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ABSTRACT

Objective: The aim of this research was to investigate the effect of two operating parameters (inlet temperature and pump speed) of laboratory spray dryer to optimize the production of ketoprofen-carboxymethyl chitosan (CM chitosan) microparticles and the effect of carboxymethyl chitosan concentration on microparticles characteristics.

Methods: Microparticles with various concentration of CM chitosan were prepared by ionic gelation with $CaCl_2$, then dried by spray drying with various inlet temperature and pump speed. The obtained microparticles were evaluation for particle size, drug entrapment efficiency and drug release.

Results: The results showed that inlet temperature at 100°C and pump speed at 9.0 ml/min was known to be the optimum condition since the drying process was relatively faster and it could produce the most yield. The obtained CM chitosan microparticles have irregular and hollow shape with the size of 1.1 – 2.1 µm. As carboxymethyl chitosan concentration increased, mean particle size and drug entrapment efficiency of the drugs increased. In simulated intestinal fluid media pH 6.8, the release rate of ketoprofen from microparticles was delayed up to 0.43 times slower than ketoprofen powder.

Conclusion: The optimal condition for spray drying in this study was at pump speed 9.0 ml/min with inlet temperature 100°C, since it gave the most yield compare to other conditions. The size of ketoprofen-CM chitosan microparticles were between the range of 1.1 – 2.1 µm with high drug entrapment. In general, microparticles of CM chitosan could delay ketoprofen release in simulated intestinal fluid media.

Keywords: Microparticles, Spray drying, Ketoprofen, Carboxymethyl chitosan.

INTRODUCTION

Microparticles are small particles with size range from 1 to 1000 µm, contained drug that is entrapped or encapsulated in polymeric, waxy, and other protective materials that is biodegradable synthetic polymer or modified natural product. Microparticles could be developed for reducing local high concentration of drug that may lead to irritation or toxic effect; sustained release, controlled release and drug targeted [1].

One of the chitosan derivates, carboxymethyl (CM) chitosan, is favorable to be developed as microparticles. Besides nontoxic, biodegradable, biocompatible, CM chitosan is a water-soluble polymer due to the CM group. Compared with chitosan that is soluble in acidic condition, CM chitosan is more advantageous especially for materials that are unstable to pH acid. These polymers can form solid particles through crosslinking between divalent cations Ca^{2+} and carboxyl ion (COO^-) of CM chitosan [2,3]. Factors affecting microparticles formation is the number of crosslinker, the polymer viscosity, *homogeneity*, type of polymer, polymer concentration, and the ratio of drug-polymer [4,5].

Spray drying generally could produce spherical particles with smooth surfaces and range of size from a few to tens micron with narrow size distribution. Spray drying technique proved to be fast, simple and reliable to produce microspheres. Factors that influence the formation of microparticles are inlet temperature, gas flow rate, pump speed, nozzle diameter. Increasing pump speed and inlet temperature can improve the yield and size of microparticles [4,6,7].

Ketoprofen, a non-steroidal anti-inflammatory drug has a short half-life (1.5-4 hrs) so it must frequently be given to maintaining fixed levels in the blood. This drug has side-effects on gastrointestinal tract due to inhibition of cyclooxygenase-1, which can be reduced when given in modified drug delivery systems to improve bioavailability and reduce side-effects, therefore ketoprofen is appropriate to develop in microparticles [8,9].

This study was conducted to determine the effect of inlet temperature, pump speed on spray drying and CM chitosan amount on the physical characteristics and release profiles of ketoprofen-CM chitosan microparticles prepared by ionic gelation then spray dried.

METHODS

Materials

Ketoprofen pharmaceutical grade was obtained from PT. Kimia Farma, CM chitosan with degree of substitution 81.9%, 96.5% degree of deacetylation from China Eastar Group Co., Ltd., $CaCl_2.2H_2O$ pro analysis from Merck and all other reagents are pharmaceutical grade.

Methods

Preparation of ketoprofen-CM chitosan microparticles

Microparticles of ketoprofen-CM chitosan (drug-polymer ratio=2:5) with polymer concentration 0.25%, 0.375% and 0.50% were prepared by ionic gelation. CM chitosan was dissolved in aquadest then added to ketoprofen solution while stirring with a magnetic stirrer. Afterward, $CaCl_2$ solution was added drop-wise into ketoprofen-CM chitosan solution and continuously stirred for 3 hrs. Particles formed in the liquid media were dried by Spray dryer (SD-Basic Lab Plant UK Ltd.) at certain condition.

Optimization condition of spray drying

The particles in the liquid medium were dried at various conditions with different inlet temperature and pump speed as listed in Table 1. Formula

of microparticles dried was ketoprofen:CM chitosan:$CaCl_2$=0.4:1:0.4 and prepared as described in preparation method. The yield was calculated from obtained particles weight divided by total mass weight. All experiment was carried out in triplicate.

Particle size evaluation

Particle size evaluation was done for 300 particles using an optical microscope (Olympus C41, US) with magnification ×1000.

Particle morphology evaluation

Particles surface and morphology of particles were observed by scanning electron microscope (SEM) (Inspect S50 type FP2017/12, Japan) in different magnification.

Drug loading and entrapment efficiency

Ketoprofen microparticles were dissolved in phosphate buffer pH 6.8 then filtered. The solution was assayed for drug content by ultraviolet-visible (UV-Vis) spectrophotometer (Carry 50 Conc., USA) at a wavelength of 259 nm. The drug loading and entrapment efficiency was calculated by the following formula:

$$\text{Drug loading} = \frac{\text{Drug amount}}{\text{Particle weight}} \times 100$$

$$\text{Entrapment efficiency} = \frac{\text{Actual drug amount}}{\text{Theoritically drug amount}} \times 100$$

***In vitro* drug release**

In vitro drug release test was performed by Dissolution Tester (Erweka DT-700, Germany) with a basket in 900 ml simulated intestinal fluid media pH 6.8 at 37°C, 50 rpm. A volume of 5 ml sample were taken at predetermined time during 3 hrs and assayed by UV-Vis spectrophotometer at a wavelength of 259 nm.

Table 1: Experimental design for optimization of spray drying

Pump rate (ml/minutes)	Inlet temperature (°C)		
	80	100	120
3.5	P I	P III	P V
9.0	P II	P IV	P VI

Table 2: Yield value (%) and size of particle dried at various condition

Condition	Yield (%)	Size (µm)
P I	11.25±0.61	1.40
P II	14.82±0.60	1.86
P III	13.95±0.56	1.78
P IV	17.66±0.76	2.10
P V	4.30±0.06	1.19
P VI	13.48±0.41	1.59

RESULTS AND DISCUSSION

In this study, microparticles of ketoprofen-CM chitosan were prepared with ionic gelation using $CaCl_2$ as crosslinker, then spray dried in various condition. Ionic gelation is based on the ability of polyelectrolytes (polymer) to crosslink in the presence of counter ions (crosslinker) to form hydrogel particles which are stabilized by electrostatic interactions [5].

Table 2 shows the yield of spray drying with various condition. The results show that at the same inlet temperature, increasing the pump speed led to improve yield. It can be due to the larger particles formed at higher pump rate and hence that the microparticles are more easily captured by the cyclone [6,7].

Yield product was also affected by inlet temperature alteration. At the same pump speed, drying with inlet temperature 100°C gave higher yield product than drying at 80°C and 120°C. Increasing inlet temperature will also increase outlet temperature thus particles become drier and non-sticky hence improving yield as well [6]. In other hand, drying at 120°C produce less yield than at 100°C. It can be explained that particles are too dry and small so could not fall down into the reservoir tube. Statistical analysis factorial design with general linear model (univariate) in SPSS 17 (α=0.01) indicate there was the influence of each of inlet temperature and pump rate, and there was an interaction effect between the two variables.

From SEM image at Fig. 1, it appeared that the particles morphology were non-spheris with hollow. It can be due to the composition of polymer and crosslinker ($CaCl_2$) that could not build optimal bond on the particle surface. Furthermore with the pressure and hot temperature during spray drying process, the droplets were depressed so sunken particles formed.

Particle size evaluation of particles produced by different condition of spray drying process gave result as stated in Table 2. At same inlet temperature, increasing pump speed of 3.5-9.0 ml/minutes led to an enlargement in particle size since faster pump rate at the same pressure will produce larger droplets so particles formed also enlarge [6,7]. At the same pump speed, particles dried at inlet temperature of 100°C were larger than particles dried at 80°C due to agglomeration of particles at high temperature [6,10]. However, in this study, particles dried at 120°C had the smallest size compared to others.

Further, microparticles with different CM chitosan concentration were prepared with spray drying condition: Inlet temperature 100°C and pump speed 9.0 ml/minutes. Drying process of particles with CM chitosan concentration 0.5% (F3) could not succeed since the mixture was too viscous. Particles with CM concentration 0.25% (F1) and 0.375% (F2) had average particle size 1.60 µm and 1.90 µm respectively.

Drug loading and entrapment efficiency of microparticles were high, and it was observed that higher polymer concentration improved

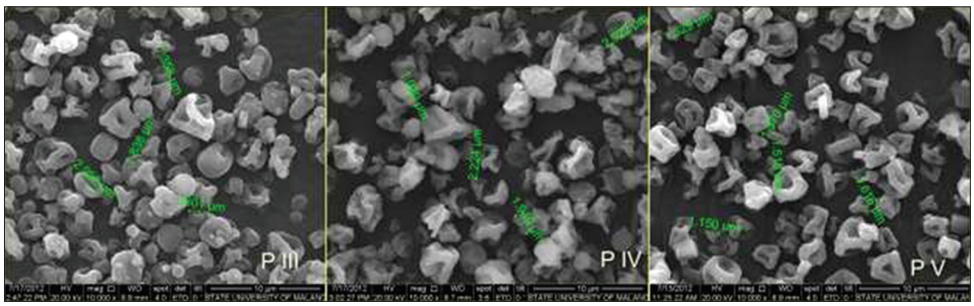

Fig. 1: Scanning electron microscope of ketoprofen-carboxymethyl chitosan dried at different condition: 100°C, pump rate 3.5 ml.minutes (P III), 9 ml/minutes (P IV); 120°C, 3.5 ml/minutes (P V) (magnification ×10,000)

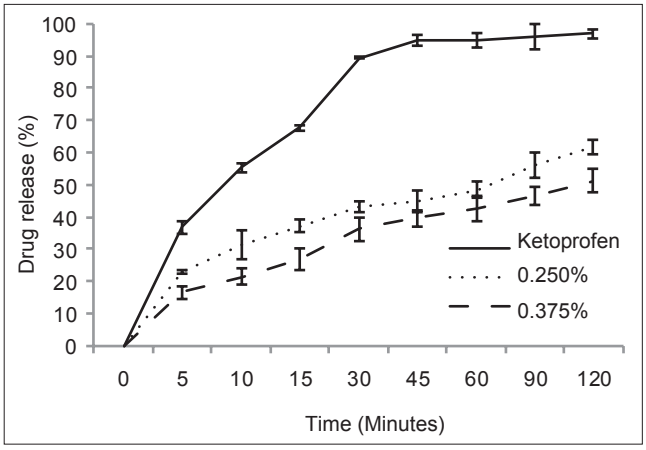

Fig. 2: Drug release from carboxymethyl chitosan microparticles in simulated intestinal fluid media pH 6.8

Table 3: Drug loading and EE and slope of microparticles with different polymer concentration and dried in condition: Inlet temperature 100°C and pump speed 9.0 ml/minutes

Polymer concentration (%)	Drug loading (%)	EE (%)	Slope mg/ ml.minutes^{½}
0.250	20.73±0.12	93.23±0.52	5.9157±0.5001
0.375	21.98±0.40	98.86±1.82	5.5152±0.3886

EE: Entrapment efficiency

the entrapment efficiency (Table 3). Nonetheless, the polymer concentration increment was limited since formula with high polymer concentration could not be dried successfully.

Fig. 2 presented that *in vitro* release in simulated intestinal fluid media pH 6.8, microparticles of ketoprofen-CM chitosan gave retarded release with slope value 5.9157±0.5001 mg/ml.minutes^{½} and 5.5152±0.3886 mg/ml.minutes^{½} for F1 and F2, since ketoprofen gave slope value of 12.7154±0.3752 mg/ml.minutes^{½} (Table 3).

From statistical analysis ANOVA (p=0.05), release rate between ketoprofen and ketoprofen-CM chitosan microparticles was significantly different, however there was no significant difference as polymer concentration increase from F1 to F2. From the result, it was indicated that ketoprofen release from CM chitosan microparticles could be delayed up to 0.43 times slower compared to ketoprofen itself.

CONCLUSION

The optimal condition for spray drying in this study was at pump speed 9.0 ml/minutes with inlet temperature 100°C, since it gave the most yield compared to other condition. The size of ketoprofen-CM chitosan microparticles were between the range of 1.1-2.1 µm. As polymer concentration increase, the particle size enlarged and entrapment efficiency enhanced. In general, microparticles of CM chitosan could delay ketoprofen release in simulated intestinal fluid media.

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