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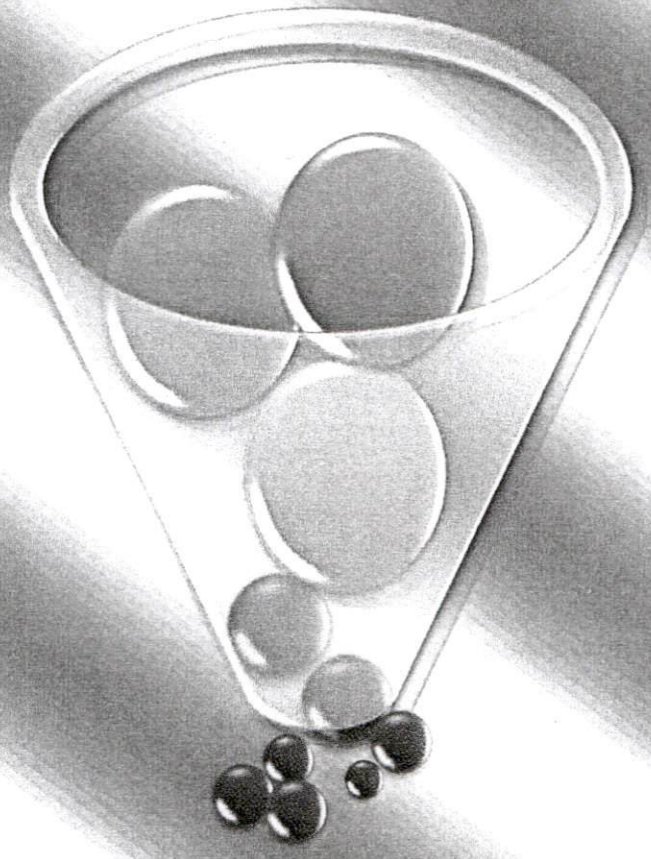

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DAFTAR ISI

PHYSICAL CHARACTERIZATION AND IN VITRO RELEASE STUDY ON THEOPHYLLINE-CHITOSAN MICROPARTICLES (EFFECT ON CROSSLINKING TIME AND METHOD OF PREPARATION)

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ABSTRACT

Microparticles of theophylline using chitosan as polymer and tripolyphosphate as crosslinker were prepared by ionic gelation (IG) methods. In this study, microparticles were prepared by two different of IG methods : orifice ionic gelation (OIG) and emulsification ionic gelation (EIG) with different crosslinking time. The obtained microparticles were evaluated for its particles size, entrapment efficiency and in vitro release in CO_2 free water. The particle size of microparticles were in the range of 987 – 1687 µm. Microparticles prepared by OIG had larger size than microparticles prepared by EIG and the size grew larger as crosslinking time longer. Both methods with different crosslinking time resulted similar and relatively high entrapment efficiency (± 60%). The release profile indicated that microparticles prepared by OIG had more retarded release compare to EIG's particles.. This result will be further studied to decrease the size in nanoparticles range by developing the preparation methods.

Keywords : *microparticle, theophylline, chitosan, ionic gelation*

INTRODUCTION

Microspheres or microparticles can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They made of polymeric, waxy or other protective materials that is biodegradable synthetic polymers and modified natural product. Microparticles are small in size and therefore have large surface to volume ratios. Entrapping drug in microparticles has advantages such as taste and odor masking, protection drugs against the environment, improvement flow properties etc. Microparticles product also could reducing the possibility of local high concentrations which could result in irritation or toxic effects and permitting more reproducible absorption (Swarbrick and Boylan, 1994 ;

Birnbaun and Peppas, 2004)

Theophylline is a xanthine derivate which is used as bronchodilator. The side effect encountered with theophylline is gastrointestinal irritation. The half life of theophylline is relatively short (6 hours) and varies depend on age, disease, smoking, etc. Modified release preparations are used as they can reduced adverse effect and the need of frequent dosing, especially in patient with a rapid theophylline clearance (Sweetman, 2005) .

Chitosan, a homopolymer composed of β- (1, 4)-linked N-acetyl glucosamine is biodegradable and biocompatible polymer. Chitosan has been widely used as carrier for drugs, proteins carriers (Ko et al, 2002). Due to free amino groups in chitosan which has a positive charge, it could react with many negatively charged polymers, and multi/polyanions such as sulphate, tripolyphosphate, and citrate. (Sinha et al, 2004). Chitosan microparticles prepared with tripolyphosphate (TPP) could prolong drug release period. TPP is nontoxic and multivalent anions made it possible to interact with chitosan by ionic bonding between amino groups of chitosan and negatively charged counter ion of TPP (Ko et al, 2002). Microparticles of chitosan could be prepared by ionic gelation methods, either by orifice ionic gelation or emulsification ionic gelation. The amount of TPP affected the entrapment efficiency in entrapment of insulin and tetanus toxoid (Bhumkar and Varsha, 2006). The objective of this work was to investigated the effect of preparation methods and crosslinking time on the physical characteristics and drug release. In this study, TPP-chitosan microparticles of theophylline were prepared by ionic gelation methods with various crosslinking time with drug-polymer ratio 1 : 1.

MATERIALS AND METHODS

Materials

Theophylline *pharmaceutical grade* obtained from Kimia Farma, chitosan *pharmaceutical grade* (degree of deacetylation 86,63%, viskositas 5,6 cps, Vital House), sodium

tripolyphosphate pentabasic p.a (Sigma-Aldrich). All other chemicals were reagent grade.

Preparation of the microparticles by orifice ionic gelation

Chitosan was dissolved in 4% (v/v) acetic acid solution. Theophylline (140 mesh) was dispersed homogenously in chitosan solution. The dispersion of drug-polymer was extruded drop wise through syringe fitted with a 23 G needle size (0.20 – 0,25 inch) into 20 ml 15% TPP solution (pH 5). The droplet was immersed for various times to allow the reaction. The obtained microparticles were filtered and washed with cold water then dried at 40°C.

Preparation of the microparticles by emulsification ionic gelation

Chitosan was dissolved in 4% acetic acid solution. Theophylline was dispersed homogenously in chitosan solution in 4 % acetic acid. Drug-polymer dispersion was added to 50 ml palm oil while stirring at 400 rpm for 20 minutes. Then TPP solution (in 4% acetic acid solution, pH 5) was added dropwise. The emulsion was stirred at 400 rpm for various time to allow the crosslinking. The microparticles was filtered and washed with washbenzene, then was rinsed with water. The obtained microparticles was dried at 40ºC and evaluated further.

Particle size analysis

The particle size analysis of 300 particles were evaluated by optical microscope (magnification 40X)

Entrapment efficiency of microparticles

Entrapment efficiency was studied by dissolving microparticles in CO_2water. The amount of drug content was determined by spectrophotometer at 270,94 nm. All the experiments were carried out in triplicate. Entrapment efficiency (EE) was calculated by equation:

$$\text{EE}\ (\%) = \frac{W1}{W2} \times 100\%$$

Where is W_1 is the weight of drug in the microparticles, W_2 is initial weight of drug.

In vitro drug release

Theophylline release from microparticles was evaluated in CO_2 free water using

dissolution test apparatus with basket (900 ml, 37°C, 50 rpm, n=3). At predetermined time intervals, 5 ml samples were withdrawn and analyzed by UV spectrophotometer (λ= 270,94 nm).

RESULTS AND DISCUSSION

TPP-chitosan microparticles of theophylline were prepared by ionic interaction gelation between positively charged amino group of chitosan and a negatively charged counter ion of TPP ($P_3O_{10}^{-5}$) (Ko et al, 2002). The interaction between cations of chitosan and anions of TPP are mainly controlled by the charge density of both cation and anion which is determined by the pH solution. (Shu and Zhu, 2001). In this experiment, chitosan is dissolved in 4% acetic acid (pH 5) to generate free amino groups and TPP solution was adjusted to pH 5 with acetic acid solution. Ionic interaction between TPP and chitosan may exist only at a certain pH region, as for TPP/chitosan is 1,9 - 7,5. Since TPP is weak acid, the ionization degree increased at higher pH. At its original pH 8,6, TPP is dissociated into OH^- and TPP ions and in lower pH, TPP is dissociated into TPP ions. The ionization degree of chitosan decreased at pH higher than 6,0 near pKa of chitosan 6,3 (Shu and Zhu, 2001). Therefore microparticles prepared in acidic was dominated with ionic interaction.

In this work, microparticles of theophylline-chitosan were prepared by ionic gelation, either orifice ionic gelation or emulsification ionic gelation. The obtained microparticles prepared by OIG methods has smoother and spherical shape, since the particles obtained from EIG has irregular shape and roughness in its surface. The diameter of particle prepared by OIG was larger than EIG's particle. The size of particle prepared by OIG was depend on the needle diameter and as the contact time was extended, the diameter became larger. Whereas the particle size of EIG's was affected mainly by stirring speed (Table 1).

The entrapment efficiency of the particles was in the range of 57.11% to 62.09% or approximately 60 % regardless of

Table 1. Particle size of chitosan microparticles of theophylline

Contact time (minute)	Particle size (μm)	
	OIG	EIG
15	1505.7	-
30	1597.2	1052.3
45	1687.9	-
60	1621.2	1101.5
90	-	986.9
120	-	1079.2

Table 2. Entrapment efficiency (EE) of microparticles of theophylline (n = 3)

Contact time (minute)	Entrapment efficiency (%)	
	OIG	EIG
15	62.09±0.16	-
30	59.15±0.79	61.09±0.82
45	58.39±0.70	-
60	58.41±0.96	59.20±0.83
90	-	62.91±1.72
120	-	57.11±1.25

methods of preparation and contact time. This relatively low entrapment efficiency was due to solubility of drug in immersion media and water that caused loss of drug during hardening/cross linking and washing process (Table 2).

In vitro drug release was evaluated in CO_2 free water media for 3 hours for microparticles and theophylline substance. The results as shown in Figure 1 and Figure 2 indicated that all the microparticles had retarded release during the first 1 hour compared to theophylline substance. As for EIG's particles, after 1 h the matrix for already swelled and the amount of drug release was as high as theophylline substance.

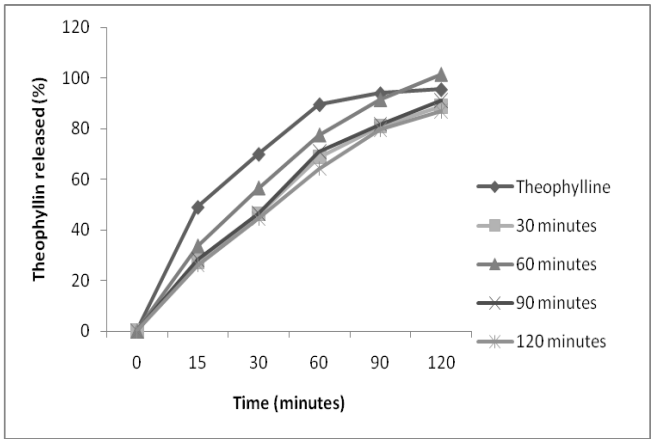

Figure 1. Release profile of theophylline from chitosan microparticles prepared by EIG in CO_2 free water media

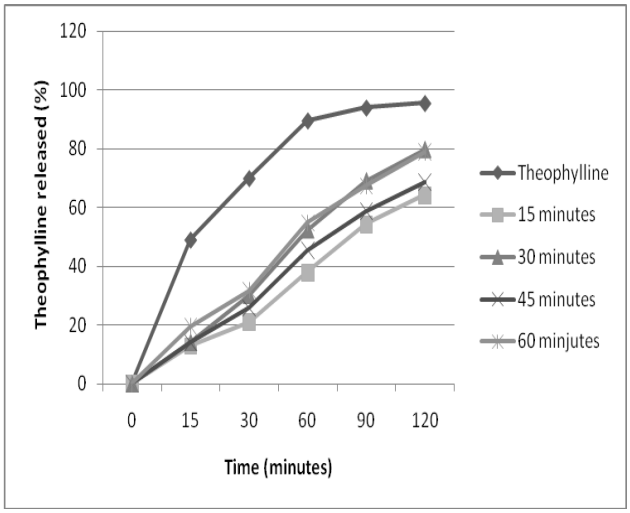

Figure 2. Release profile of theophylline from chitosan microparticles prepared by OIG in CO_2 free water media

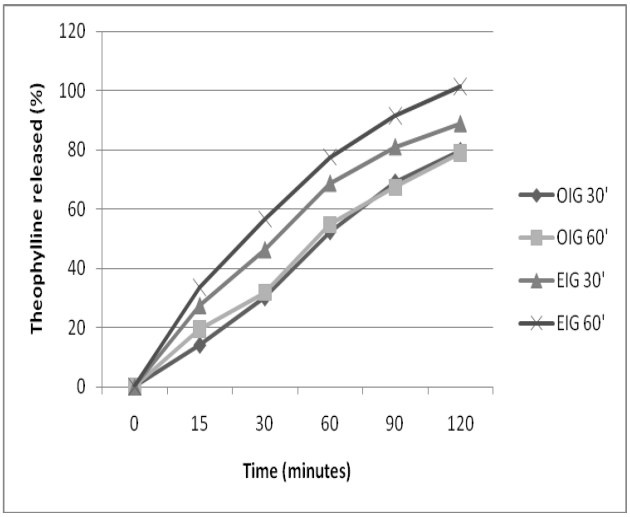

Figure 3. Comparison release profile of theophylline from chitosan microparticles prepared by OIG and EIG in CO_2 free water media

In related with OIG's particles, it was known that the particles had more retarded release compared to EIG's with the same contact time (Figure 3). The result indicated that the particles obtained from OIG formed strong wall and high density of cross linking between TPP-chitosan resulted in less swelling ability. Therefore the drug release decreased. Since EIG formed porous wall, thus the drug released faster than OIG's particles (Figure 3).

CONCLUSIONS

Microparticles prepared by OIG methods had smoother and more spherical shape compare to EIG's particles. The drug release from chitosan microparticles of OIG's had more retarded release compare to EIG's particles.

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