Preparation of Chitosan / Sodium Alginate Microspheres and Sustained Release in Propranolol Hydrochloride

Yu Yang[1, a, *], Guangrong[1, b] Zhao and Xiaojing[2, c] Wang

Tianjin University, Tianjin, 300071, China

EMAIL: 15822003627@163.com

Keywords: Propranolol hydrochloride; Chitosan; Sodium alginate; Slow release

Abstract: Propranolol hydrochloride is a non-selective adrenergic drug that has been used as a drug for angina pectoris, antihypertensive and many other cardiovascular diseases. Objective: To determine the best process for chitosan / sodium alginate microspheres as a carrier of propranolol hydrochloride sustained release microspheres. Methods: SEM analysis, whether the surface of the microspheres is uniform and smooth, whether there are potholes, and the diameter of the microspheres. The release rate of propranolol hydrochloride adsorbed on the surface of drug-loaded microspheres was measured. Main measurement results: The release rate of propranolol hydrochloride adsorbed on the surface of drug-loaded microspheres reached 59.4% in 5 h. Results: The optimal process parameters were: emulsification time: 5 min, Span-80 dosage: 8 mg, drug loading: 30 mg. Conclusion: This process has prepared propranolol hydrochloride chitosan / sodium alginate microspheres. It is believed that chitosan / sodium alginate microspheres have a good sustained release effect as a carrier of propranolol hydrochloride.

Chinese picture classification number: TQ460.4 Document identification code: an Article ID:

1.Introduction

Propranolol hydrochloride or 1-isopropylamino-3- (1-naphthyloxy) -2-propanol hydrochloride is a non-selective adrenergic blocker that has been used as an angina pectoris and anti-hypertensive agent. Blood pressure medications and many other treatments for cardiovascular disease [1,2]. Its plasma half-life is relatively short, so patients habitually require taking this drug every 6 to 8 hours and taking it several times a day. Frequent administration may reduce patient compliance and treatment efficacy [3].In recent years; microspheres with Chitosan as a carrier have been widely studied. The unique physicochemical properties and safety of chitosan determine the drug release [4]. Firstly, chitosan is a natural polysaccharide with abundant sources in nature and has good biocompatibility. Secondly, the linear polysaccharide properties of chitosan can be chemically modified to graft multifunctional groups, which can be used for embedding and adsorption. The polysaccharide structure is easily recognized by various active enzymes and cells in the body [5,6]. Sodium alginate (SA) is a class of anionic water-soluble polysaccharides extracted from algae in nature. It is mainly polymerized by 1,4-β-D-mannose furanoic acid and 1,4-α-L guluronic acid. Into [7]. Long-chain polymers can be folded to form a porous structure, which is easy to adsorb metal ions and chelate [8,9]. Similar to chitosan, the physical and chemical properties determine that sodium alginate is low in toxicity, degradable and biocompatible. Using gel microspheres formed by sodium alginate and chitosan, the microspheres are made into a special carrier material to embed functional compounds such as proteins and drugs, so as to reduce the continuous dosage and slow drug release effect [10 ~ 15].

2. Research Purpose

Using propranolol hydrochloride as a research drug, a chitosan / sodium alginate microsphere carrier was prepared. The response time method was used to study the emulsification time, span-80, and propranolol hydrochloride. influences. Provide a basis for the development of chitosan / sodium

  DOI: 10.25236/icme.2019.017

alginate propranolol microspheres.

3. Method

3.1 Main instruments and reagents

Propranolol hydrochloride, Pfizer Pharmaceutical Co., Ltd .;
Chitosan, biochemical reagent, deacetylation degree 90% ~ 95%; Sinopharm Chemical Reagent Co., Ltd .;
Sodium alginate, analytical grade, Chengdu Kelong Chemical Reagent Co., Ltd .;
Span-80, analytical grade, Como Chemical Reagent Co., Ltd .;
UV-visible spectrophotometer, TU-1810, General Analysis General Instruments Co., Ltd .;
Scanning electron microscope, SU3500, Hitachi High-tech Co., Ltd .;
Digital thermostatic water bath: Shanghai Yiheng Technology Co., Ltd .;
Infrared spectrometer: Nicolet 6700, American Nicolet company;
Experimental ultrapure water: Milli-Q Academic ultrapure water meter, Millipore, USA
All other reagents were of analytical grade.

3.2 Experimental methods

3.2.1 Preparation of Chitosan / Sodium Alginate Microspheres

Accurately weigh 0.5g of chitosan and 2.0g of sodium alginate into 50mL of 5% hydrochloric acid (V / V) and deionized water. After the above solute is fully dissolved, the two solutions are evenly mixed with ultrasonic waves. Measure 50mL paraffin and add 3mL span-80. As for 50 ° C in the digital constant temperature water bath, continue to stir and mix for 30min, add the chitosan / sodium alginate mixture, and continue stirring for 30min. The mixed solution was taken out, and glutaraldehyde cross-linking agent was added in three batches at room temperature for 30 minutes under ultrasonic shaking to obtain chitosan / sodium alginate microspheres. Add an appropriate amount of methanol to wash the microspheres 3 times, and centrifuge the blank microspheres, and place them in a drying box overnight for later use. Take 50 mL of methanol, add propranolol hydrochloride and blank microspheres, continue to stir for 60 min, and filter to obtain the drug-loaded chitosan / sodium alginate microspheres. Also dry in a dry box overnight.

3.2.2 Determination of drug loading and dissolution

Accurately weigh 50mg of drug-loaded chitosan / sodium alginate microspheres, dissolve with appropriate amount of dichloromethane, add phosphate buffer solution (PBS), maintain pH 6.86, stir with water bath at 50 ° C for 30min, and take the solution through 0.45μm PVDF Immediately after filtration, the absorbance was measured at 290um. The formula for calculating drug load is shown in formula (1) Drug loading = mass of microsphere adsorbed drug / mass of microspheres × 100% (1)

The in vitro dissolution test method of propranolol hydrochloride refers to the dissolution method of propranolol hydrochloride in the "Chinese Pharmacopoeia" (2010 edition). The release solution was a pH 6.86 phosphate buffer solution. The temperature of the water bath simulated the human body temperature of 37.0 ± 0.5 ° C. A batch of 30 min was used to absorb 5 mL of the solution. After filtering through a 0.45 μm membrane, the absorbance at 290 nm was measured six times. concentration.

4. Result

4.1 Preparation of microspheres by response surface method

Using Design-expert V8.0 software, response surface methodology was used to investigate whether the preparation process conditions of drug-loaded chitosan / sodium alginate microspheres interacted and to find the optimal ratio. The emulsification time (5min, 15min), the amount of

span-80 emulsifier (4mL, 8mL), the amount of propranolol hydrochloride (10mg, 30mg), and the level of factor 3 were selected.

Table 1 Analysis of variance of preparation model of drug-loaded chitosan / sodium alginate microspheres

	Squared deviation & SS	Degrees of freedom df	Mean square & MS	F Value	*P* Value Prob > F
Regression model	6.628	3	2.209	6.366	0.0048
A-Emulsification time	0.071	1	0.071	0.204	0.6569
B-Span-80	1.272	1	1.272	3.666	0.0736
C-Medicinal amount	5.284	1	5.284	15.226	0.0013
Residual	5.553	16	0.347	——	——
Lack of fit	4.726	11	0.429	2.599	0.1508
Pure error	0.826	5	0.165	——	——
Total dispersion	12.181	19	——	——	——

It can be seen from Table 1 that the model of drug-loaded chitosan / sodium alginate microspheres fits well, P 0.0048 <0.05. There was no interaction between the three factors, the medicinal amount, the amount of Span-80, and the emulsification time. The fitted equation is: adsorption amount = 3.48 + 0.014 × emulsification time + 0.153 × Span-80 + 0.062 × medicine amount.

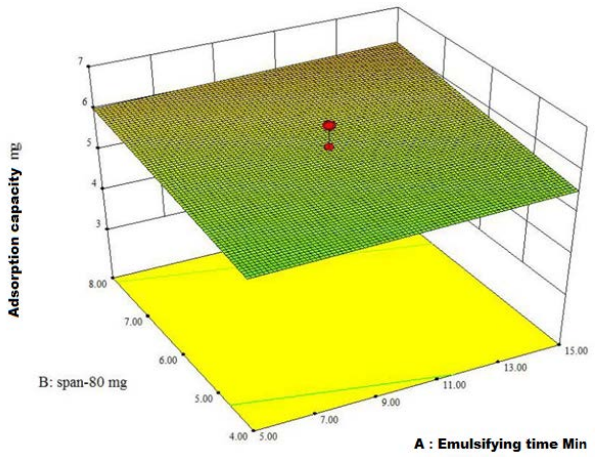

Figure 1. Effect of Span-80 dosage and emulsification time on the adsorption of chitosan / sodium alginate microspheres

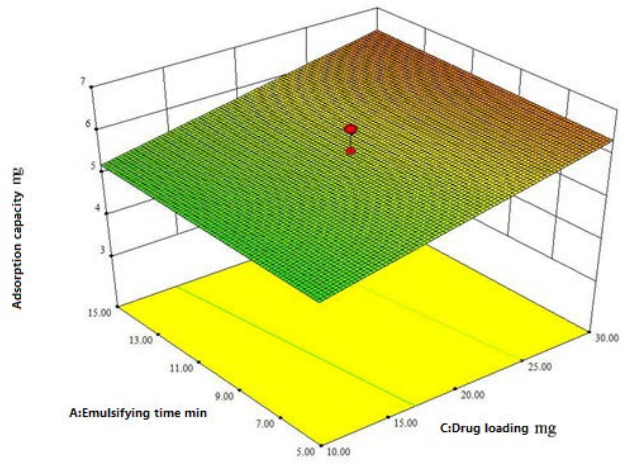

Figure 2. Effect of emulsification time and drug loading on the adsorption of chitosan / sodium alginate microspheres

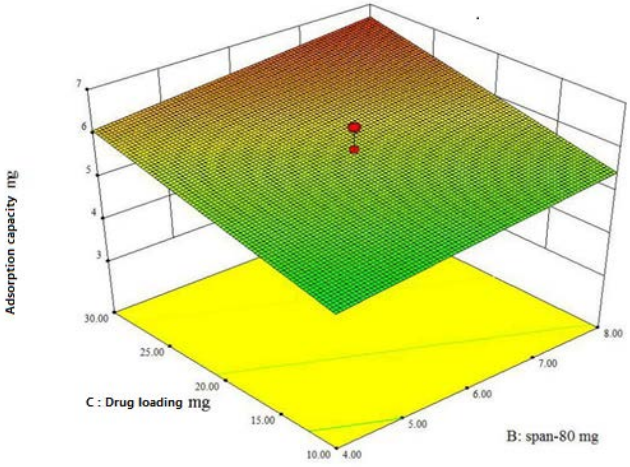

Figure 3. Effect of Span80 dosage and drug loading on the adsorption of chitosan / sodium alginate microspheres

It can be seen from Figures 1 and 2 that when the drug loading is 20 mg, the amount of Span-80 and the emulsification time have little effect on the amount of adsorption. Sodium microsphere adsorption has a great influence. With reference to Figures 1 to 3, the influencing factors of the adsorption amount are ranked as drug loading amount> Span-80 dosage> emulsification time. Therefore, in the process of preparing the microspheres, the amount of the medicament is first considered, thereby reducing costs and reducing losses. Through the optimization of experimental conditions, the best process parameters were selected: emulsification time 5min, Span-80 dosage 8mg, drug loading 30mg. The adsorption amount of propranolol hydrochloride was 6.65 mg.

4.2 SEM analysis of drug-loaded chitosan / sodium alginate microspheres

The blank and drug-loaded chitosan / sodium alginate microspheres were prepared and analyzed by scanning electron microscope SEM. The results are shown in FIG. 4. It can be seen from Figures 4a and 4b that the surface of the blank microspheres is uniform and smooth, with a diameter of 2 ~ 8μm. The drug-loaded microspheres are similar to the blank microspheres (Figures 4c and 4d). 5 ~ 10μm.

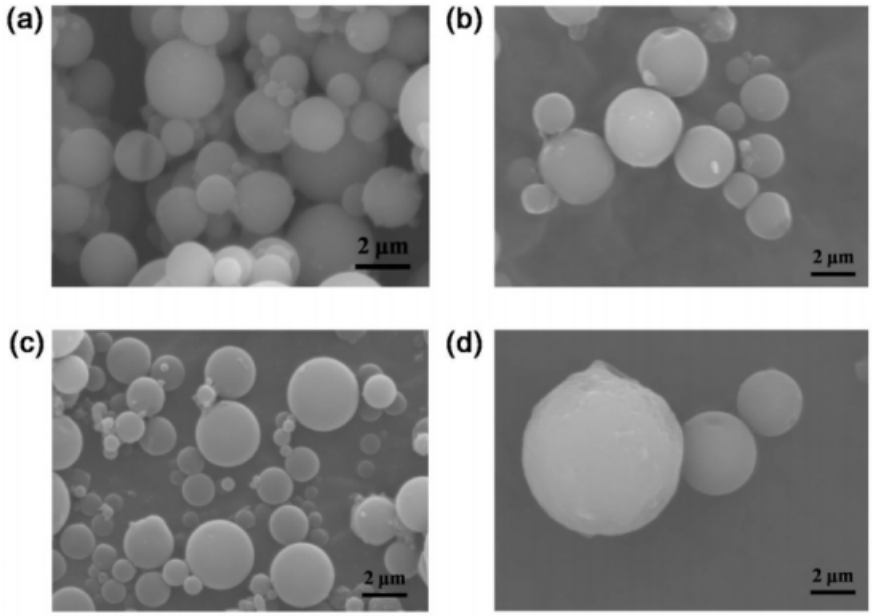

Figure 4. Scanning electron micrographs of blank microspheres (a, b) and drug-loaded microspheres (c d)

5. Discussion

The cumulative release curve of propranolol hydrochloride / sodium alginate microspheres in phosphate buffer solution is shown in the figure below. Within the first 0 to 5 hours, propranolol hydrochloride adsorbed on the surface of drug-loaded microspheres was quickly released to the PBS solution. In the microsphere, more and more fine voids are left on the surface of the microsphere, and the specific surface area of the microsphere is increased. More propranolol hydrochloride in the microsphere is released, so the release rate is faster at this stage, reaching 59.4%. After 5 h, the release rate of propranolol hydrochloride significantly slowed down, possibly due to the swelling and partial dissolution of chitosan / sodium alginate microspheres in PBS, so that the remaining propranolol hydrochloride in the microspheres was completely released. [16]. Therefore, it can be considered that chitosan / sodium alginate microspheres exhibit good sustained-release effect as a carrier of propranolol hydrochloride.

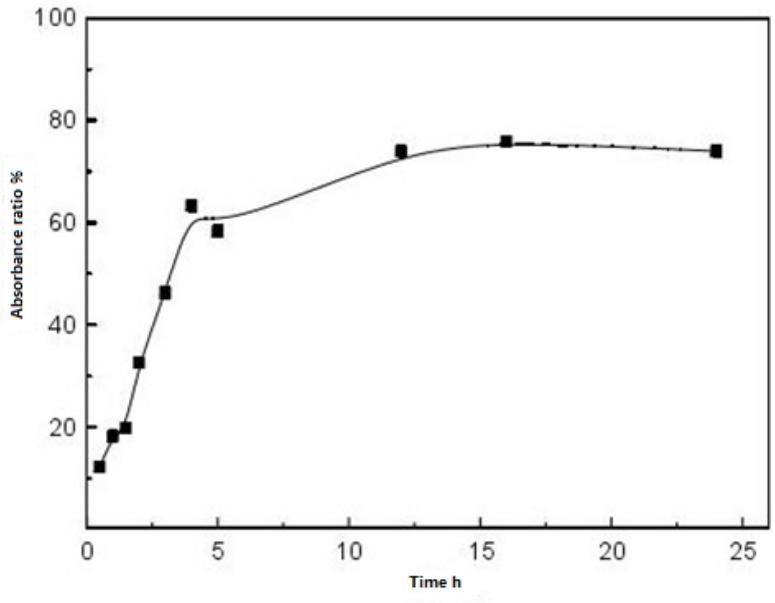

Figure 5 Release curve of drug-loaded microspheres in phosphate buffer solution

Conclusion

The process of preparing chitosan / sodium alginate microspheres by emulsion cross-linking method was investigated. The optimal process parameters were: emulsification time 5 min, Span-80 dosage 8 mg, and drug loading 30 mg.

SEM analysis of propranolol hydrochloride / sodium alginate microspheres. The diameter of the microspheres is 5-10 μm, and the surface is uniform and smooth.

The propranolol hydrochloride adsorbed on the surface of the drug-loaded microspheres was released rapidly and reached 59.4% in 5 hours. As a carrier of propranolol hydrochloride, it exhibited a good sustained-release effect.

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