Microencapsulation and Its Characteristics and Applications and Manufacturing of Clarithromycin Microcapsules with Mixed Membrane

Hua Cao^{1, †}; Huifang Chen (co first author)^{2, †}; Jianhua Yi (corresponding author)^{3, *}; Hong Xia (corresponding author)^{4, *}; Yang Nie (corresponding author)^{5, *}

¹College of Health Management, Guangdong Lingnan Institute of Technology, Guangzhou, 510663, China

²College of Pharmacy, Guangdong Lingnan Institute of Technology, Guangzhou, 510663, China

³Department of Orthopedics, East Hospital of the First Affiliated Hospital of Sun Yat sen University, Guangzhou, 510700, China

⁴Guangzhou Panyu Central Hospital Gynecology, Guangzhou, 511400, China

⁵School of Pharmaceutical Engineering, Guangdong Food and Drug Vocational College, Guangzhou 510520, China

Abstract: In this paper, the definition, characteristics, applications, wall materials and main preparation methods of microcapsules were described in details. At the same time, the mixed membrane microcapsules were prepared by solvent evaporation method with clarithromycin as model drug, ethyl cellulose and hydroxypropyl methyl cellulose as membrane materials. The optimal preparation conditions were explored, and the slow and controlled release properties of the mixed membrane microcapsules were investigated. The optimal preparation conditions of clarithromycin microcapsules were as following: the concentration of membrane material was 3%, the concentration of ethyl cellulose / hydroxypropyl methyl cellulose was 6:1-7:1, the dosage was 2:1-3:1, the concentration of SDS was 0.1%, the concentration of PVA was 1.0%, and the oil-water ratio was 1:8.

1 Introduction

1.1 Definition of microcapsules

Microcapsule is a kind of micro container or package with polymer or inorganic wall. Microcapsule granulation technology is to embed and seal solid, liquid or gas in a microcapsule to become a solid particle product.

Microencapsulation: coating tiny solid particles, droplets or bubbles with coating film or shell material.

Microcapsule diameter: mm to micron.

Microcapsules are spherical vesicles with certain permeability. The outer layer is a semi permeable membrane and the inner part is a liquid core. In recent years, microcapsule technology has been widely used in the immobilization of microorganisms, animal and plant cells, enzymes and other bioactive substances and chemical drugs. Alginate / polylysine microcapsules are commonly used. Due to the complexity of preparation technology, the long time of encapsulation process, the biological activity of the embedded material is affected, and the price of poly-L-lysine is relatively expensive, so the use of this kind of microcapsules is limited. The basic materials for preparing microcapsules usually contain polyelectrolytes such as proteins, lipids and sugars.

Chitosan is a kind of chitin which the degree of deacetylation is partially removed. The latter has excellent toughness and inertia, and is hydrophilic, non-toxic, porous and uniform. In the meantime, Chitin is abundant in nature.

1.2 Microcapsule function

(1) Powdering, the conversion of liquids, gases, etc. into dry powder.

(2) Reduce volatility and make some volatile substances difficult to volatilize.

(3) Improve the stability of substances (substances easily oxidized, easily decomposed by light, easily affected by temperature or moisture).

(4) Cover up the taste.

(5) Isolate active ingredients.

(6) Controlled release.

[†]These authors contribute equally.

*Corresponding author, E-mail addresses: 2652399240@qq.com (Huifang Chen).

1.3 Wall materials for microcapsules

Table1 Common wall materials for microencapsulation

category	materials used as wall	characteristic
natural polymer materials	Gelatin, Arabic gum, shellac, LAC, starch, dextrin, wax, rosin, sodium alginate, zein, chitosan	It is non-toxic, stable and good film-forming property
semi synthetic polymer materials	Carboxymethyl cellulose, methyl cellulose and ethyl cellulose	It has low toxicity, high viscosity, high solubility after salt formation, but it is easy to hydrolyze and not resistant to high temperature, so it needs to be prepared temporarily
All synthetic polymer materials	Polyethylene, polystyrene, polybutadiene, polypropylene, polyether, polyurea, polyethylene glycol, polyvinyl alcohol, polyamide, polyacrylamide, polyurethane, polymethylmethacrylate, polyvinylpyrrolidone, epoxy resin, polysiloxane	Good film forming and chemical stability

1.4 Manufacturing method

1.4.1 Physical method

Spray drying method, spray freezing method, air suspension method, vacuum evaporation method, complex condensation method and multi space centrifugation method.

1.4.2 Physicochemical method

Water phase separation, oil phase separation, core exchange, extrusion, sharp hole, powder bed method.

1.4.3 Chemical method

Interfacial polymerization in situ polymerization molecular encapsulation radiation encapsulation.

1.4.4 General process of Microencapsulation

A: dispersion of internal phase in medium;
 B: adding film forming material (wall material);
 C: wall material deposition;
 D: wall film curing

1.5 Main application of microcapsules in medicine

Microcapsule is a kind of spherical microcapsule, which is made of natural or synthetic polymer, similar to osmotic membrane, which is an excellent drug delivery carrier.

Microcapsule technology is applied in the field of medicine, which can finish the targeted delivery of drugs [1-4]. Polymer drug microcapsules can control drug release, reduce drug toxicity, increase drug stability and effective utilization, and achieve good medical effect.

Clarithromycin (CLM) is a semi synthetic 14 membered ring macrolide antibiotic [5]. Its acid stability in gastric juice is higher than that of erythromycin, and it has antibacterial effect similar to erythromycin in vitro [6,7], and is mainly used for infections caused by sensitive bacteria [8,9]. The traditional sustained-release and controlled-release clarithromycin preparation has the advantages of large dosage, short retention time in gastrointestinal tract and serious side effects. Ethyl cellulose (EC) is a cellulose derivative with ethoxyl group replacing hydroxyl group, which is a hydrophobic material, and can slow down drug dissolution. Hydroxypropyl methyl fibrin (HPMC) is a non-ionic cellulose ether, soluble in water and most polar organic solvents. Ethyl cellulose (EC) is often mixed with hydrophilic excipients such as hydroxypropyl methylcellulose (HPMC), which act as drug skeleton. The microcapsules with HPMC have better hydrophilicity, which directly affects the in vitro release rate of the microcapsules. Therefore, in this paper, Clarithromycin^[10] was used as the model drug, the mixture of ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) as a mixed membrane material, solvent evaporation method [11-13] was used in the preparation of clarithromycin microcapsules loaded by the mixed membrane. The concentration of membrane material in the dispersed phase was kept at 3%, the concentration of sodium dodecyl sulfate (SDS) was 0.1%, and the concentration of polyvinyl alcohol (PVA) was 1.0%. The effects of dosage, the ratio of ethyl cellulose to hydroxypropyl methyl cellulose in the dispersion phase, and the ratio of oil to water on the performance of microcapsules were investigated by single factor analysis. The sustained and controlled release performance of the microcapsules was tested to obtain the optimal formulation of sustained and controlled release microcapsules [13].

2 Experimental materials and methods

2.1 Drugs and instruments

Clarithromycin intermediate (batch number: 2019-11-mc0134), ethyl cellulose (M70), sodium dodecyl sulfate (SDS), dichloromethane (analytical pure), polyvinyl alcohol (1750-1-50), trichloromethane (analytical pure), hydroxypropyl methyl cellulose (HPMC); digital display DC stepless speed regulation mixer (SXJQ-1, Zhengzhou Changcheng Science Industry and Trade Co., Ltd.), super constant temperature bath (Shanghai Hengping Instrument Factory), constant temperature Magnetic stirrer (HDI-3, Shanghai Meiyongpu Instrument Manufacturing Co., Ltd.), UV Vis spectrophotometry (SP-1900UV type, Shanghai Spectral Instrument Co., Ltd.)

2.2 Methods

ethyl cellulose, hydroxypropyl methyl cellulose and clarithromycin were dissolved in dichloromethane and trichloromethane in a certain proportion to obtain the dispersed phase; SDS and PVA were dissolved in water

at the concentration of 0.1% and 1.0% respectively to obtain the continuous phase; then the dispersed phase was slowly dispersed into the continuous phase with a syringe, and the stirring speed was adjusted to 400 rpm, 1 hour later, the surface of the microcapsules was solidified, the rotating speed was reduced to 100-200 rpm, and the solvent volatilized for 4-5 h. After filtration and washing, the microcapsules were transferred to a drying dish for drying.

3 Result and discussion

3.1 Manufacturing conditions of microcapsules

3.1.1 The influence of the ratio of EC to HPMC: when the concentration of membrane material was 3%, the dosage was 2:1, and the oil-water ratio was 1:8, the microcapsules were prepared with seven different EC / HPMC ratios. The sphericity, particle size, drug loading, encapsulation efficiency and yield of the microcapsules were investigated respectively. The results are shown in Table 2.

Table 2 The proportion selecting of EC and HPMC

EC / HPMC	sphericity	particle size(μm)	drug loading (%)	encapsulation efficiency (%)	yield of clarithromycin microcapsules (%)
1:1	Poor	13.3	26.2	66.2	67.1
2:1	commonly	19.3	29.4	81.3	75.5
3:1	good	24.5	28.3	67.0	80.8
4:1	good	19.1	27.4	64.4	82.8
5:1	good	21.8	26.2	61.1	84.2
6:1	good	24.7	27.0	63.0	88.1
7:1	good	23.7	31.3	83.2	86.9

It can be seen from the table 2 that when the ratio of EC to HPMC is small, the morphology of microcapsules is not ideal, and the drug loading and yield are very low. This is because the solubility of hydroxypropyl methyl fiber in less polar solvent is small, and a large amount of hydroxypropyl methyl cellulose is lost to the continuous phase during the formation of microcapsules. Therefore, the ratio of EC to HPMC in the dispersed phase is 7:1

3.1.2 The influence of oil-water ratio: when the concentration of membrane material is 3%, EC / HPMC is 7:1, and the dosage is 2:1, the influence of oil-water ratio on the sphericity, particle size, drug loading, encapsulation efficiency and yield of clarithromycin microcapsules prepared by the following five groups of different oil-water volume ratios were investigated. The results are shown in Table 3.

Table 3 The influence of Oil-water proportion

oil-water ratio	sphericity	particle size(μm)	drug loading (%)	encapsulation efficiency (%)	yield of clarithromycin microcapsules (%)
1:4	good	36.6	25.3	60	84.2
1:5	good	33.1	26.7	77	84.7
1:6	good	29.7	23.2	66	85.1
1:7	good	26.7	23.1	65	83.2
1:8	good	23.7	29.8	83.1	90.9

It can be seen from the table 3 that the particle size of the microcapsules decreases with the decrease of the oil-water volume ratio. This is because the decrease of

the oil-water volume ratio can make the dispersed phase more easily dispersed in the continuous phase with the help of emulsifier. Therefore, the microcapsules with

smaller particle size and better distribution are prepared. Considering the drug loading and entrapment efficiency, the microcapsules with oil-water volume ratio of 1:8 are finally selected good.

3.1.3 Effect of dosage: when the concentration of

membrane material in dispersed phase is 3%, EC / HPMC is 7:1, oil / water ratio is 1:8, microcapsules are prepared with five different dosages. The sphericity, particle size, drug loading, encapsulation efficiency and yield of microcapsules are investigated respectively. The results are shown in table 4.

Table 4 Dosage Choice

Material / drug ratio(drug dosage)	sphericity	particle size(μm)	drug loading (%)	encapsulation efficiency (%)	yield of clarithromycin microcapsules (%)
1:1	poor	38.0	44	61.2	83.2
2:1	good	23.7	28	83.1	86.9
3:1	good	20.3	22	50.3	68.1
4:1	good	25.8	17	51.7	75.4
5:1	good	36.7	15	52.0	70.9

It can be concluded from the table 4 that the drug loading and entrapment efficiency of microcapsules increase with the increase of drug dosage. This is due to the increase of drug dosage and the decrease of relative amount of drug dissolved in continuous phase per unit volume of continuous phase. However, when the dosage ratio is 1:1, the sphericity of microcapsules becomes worse. The optimum conditions for high yield and high yield were as following: dosage 2:1.

3.2 Sustained release properties of microcapsules

3.2.1 The amount of hydroxypropyl methyl cellulose

(HPMC) directly affects the in vitro release rate of microcapsules. The addition of HPMC can make the microcapsules have better hydrophilicity. However, the amount of HPMC in the dispersed phase should not be too large, which will make the microcapsules form in the initial stage of sustained release. In vitro release tests were carried out on the microcapsules prepared with acetic acid buffer solution as the release medium, when the dosage was 2:1, the oil-water ratio was 1:8, the membrane material concentration was 3%, and the EC / HPMC was 5:1, 6:1 And 7:1, respectively. The cumulative release rate curve within 8 hours was obtained, as shown in Figure 1.

Fig. 1 Effect of EC / HPMC on drug release in vitro

It can be seen from Fig. 1 that when the ratio of EC / HPMC is 6:1, the cumulative release rate of microcapsules in vitro is the highest. The ratio of EC / HPMC is 7:1. Therefore, the ratio of ethyl cellulose to hydroxypropyl methyl fiber in the dispersed phase is the best between 6:1 and 7:1.

3.2.2 The effect of oil / water ratio on the in vitro release performance of the microcapsules was studied. When the dosage was 2:1, the concentration of membrane material was 3%, EC / HPMC was 7:1, and the oil / water ratio was 1:6, 1:7, 1:8, the cumulative release rate curve in 8 hours was obtained, as shown in Figure 2.

Fig. 2 Effect of oil / water ratio on drug release in vitro

It can be seen from Figure 2 that when the oil-water ratio is 1:8, the cumulative release rate of microcapsules in vitro is the highest. This is because when the oil-water ratio is small, the dispersed phase is easy to form uniform emulsion, while when the oil-water ratio is increased, the continuous phase in unit volume contains more dispersed phase, and the collision probability of microcapsules increases, resulting in the adhesion of microcapsules into blocks, which makes it difficult for the obtained microcapsules to form a block in the slow-release

process. The cumulative rate of drug release in vitro is small. Therefore, the optimal ratio of oil to water is 1:8.

3.2.3 Effect of drug dosage on drug release in vitro: three groups of mixed membrane microcapsules with dosage of 2:1, 3:1 and 4:1 were prepared by membrane material concentration of 3%, EC / HPMC of 7:1 and oil-water ratio of 1:8. The cumulative release rate curve within 8 hours was obtained, as shown in Figure 3.

Figure 3 Effect of dosage on drug release in vitro

It can be seen from Figure 3 that the cumulative release rate of microcapsules loaded with drug is the highest when the dosage is 3:1, and the cumulative release rate of microcapsules is the lowest when the dosage is 4:1. This is because the drug loading of microcapsules with 3:1 dosage is higher than that of 4:1 dosage. Considering the preparation conditions, it is concluded that the best dosage is from 2:1 to 3:1.

4 Conclusion

Combined with the factors influencing the preparation of mixed membrane microcapsules with ethyl cellulose and hydroxypropyl methyl cellulose as the mixed membrane materials and the in vitro sustained-release properties of the microcapsules, the optimal preparation process of clarithromycin mixed membrane microcapsules was obtained as following: the concentration of membrane material in the dispersed phase was 3%, the ratio of EC / HPMC in the dispersed phase was 6:1-7:1, the dosage was 2:1 ~ 3:1, the oil-water ratio was 1:8, and the concentration of SDS was in the continuous phase The concentration of PVA was 1.0%.

Author Contributions

[†]Hua Cao and Huifang Chen contribute equally.

Notes

The authors declare no competing financial interest.

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