Annals of Materials Science & Engineering

Open Access

Austin Publishing Group

Research Article

Study on Enteric Vacant Capsules Based on Hydroxypropyl Methylcellulose Phthalate-55S

Liping L*
College of Biological & Environmental Sciences, Zhejiang Wanli University, Ningbo, China

***Corresponding author:** Liu Liping, College of Biological & Environmental Sciences, Zhejiang Wanli University, Ningbo, 315100, China

Received: June 04, 2021; **Accepted:** June 25, 2021; **Published:** July 02, 2021

Abstract

The formulation and preparation technology of enteric cellulose hollow capsules were studied, and its properties were evaluated. The enteric cellulose hollow capsules were prepared with hydroxypropyl methylcellulose phthalate~55S (Hp55S) as film~forming material, agar as molding agent and hydroxypropyl methylcellulose (HPMC) as disintegration regulator. The preparation process was as follows: (1) At room temperature, 9~16 phr of Hp55S was dissolved in 30~50 phr of dilute ammonia solution with pH of 10~11 to obtain transparent Hp55S glue solution; (2) Put 1.2~1.6 parts of agar into 50~70 parts of water, heat and boil to obtain agar solution. 1~7 phr of HPMC, 0.12~0.16 phr of KCl and 0.1~0.2 phr of Tween~80 were poured into agar solution to disperse evenly, and then the temperature of gel solution was reduced to 50~55 °C to obtain agar/HPMC mixed gel solution; (3) The Hp55S solution was heated to 50~55 °C and then poured into agar/HPMC solution to obtain composite cellulose solution. The temperature of the solution was kept at 50~55 °C. (4) Enteric cellulose hollow capsules were prepared by dipping in glue, shaping, drying, trimming and assembling. The results showed that the enteric cellulose hollow capsules met the quality requirements of "enteric coated hollow capsules" in Chinese Pharmacopoeia. Compared with the traditional formula and preparation process of enteric coated hollow capsules, it avoids the use of organic solvents and multiple molding process. The enteric cellulose hollow capsule greatly reduces the preparation cost from the formula to the process, which is green, safe and environmental friendly, and has good application value.

Keywords: Hydroxypropyl methylcellulose phthalate-55S (Hp55S); Hydroxypropyl Methylcellulose (HPMC); Agar; Non organic solvents; One-step molding process; Enteric cellulose hollow capsules

Introduction

Vacant capsules can be divided into gastric type, enteric type and colon type, respectively corresponding to the human stomach, small intestine and colon regional administration. The enterosoluble vacant capsules have the characteristics of stable in the stomach and disintegrating in the small intestine of human body [1]. It is especially suitable for filling drugs which are easily damaged by enzymes or acid in the stomach and produce strong irritation to gastric mucosa [2]. There are three processes for the preparation of drug enteric capsules: (1) Firstly, the drug particles or pellets are coated with enteric coated materials, and then they are filled into ordinary vacant capsules [3,4]; (2) The enteric coating solution is sprayed on the outer layer of the capsule filled with drugs [5]. (3) The drug is directly filled into the enteric empty capsules [6-8]. The first and second enteric coated drug capsules are actually made by uniformly spraying the intestinal solution on the surface of drug particles or capsules through coating process. The process has the problem of potential impact of coating solvents on drugs. The third preparation of drug enteric capsule is to fill the drug directly into the enteric empty capsule. The third preparation of drug enteric capsule is that the drug is directly filled in the enterosoluble vacant capsule, which can avoid the potential influence of organic solvent in the coating solution on the filling drug. Therefore, it is necessary to develop enterosoluble vacant capsules.

At present, the enterosoluble vacant capsules usually use gelatin or hydroxypropyl methylcellulose as raw materials to prepare blastocysts, and then the enteric coated materials are used to coat the outer layer of blastocysts [9]. This technology has the following problems:

- The preparation process is complex [10]. Generally, vacant blastocysts are prepared, and then the blastocysts are inserted into the enteric coated solution for coating again. This requires a customized professional production line.

- There are a lot of organic solvents in the enteric coating solution. The commonly used enteric coating materials, such as cellulose phthalate series [11] and acrylic resin series [12], are usually insoluble in water, but easily soluble in ethanol, acetone or mixed organic solvents. The coating material is attached to the outer layer of vacant blastocyst by the volatilization of organic solvent. A large number of organic solvents have great safety risks to operators and production workshops.

In order to solve the above technical problems, a common cellulose enteric coated materia---hydroxypropyl methylcellulose phthalate-55S (Hp55S) was selected as the membrane material of enteric cellulose vacant capsules. This material has good acid stability and has been widely used as pharmaceutical excipients [13,14].

Citation: Liping L. Study on Enteric Vacant Capsules Based on Hydroxypropyl Methylcellulose Phthalate-55S. Ann Materials Sci Eng. 2021; 5(1): 1038.

According to the characteristic that Hp55S could be dissolved in the medium with pH more than 5.5 [15], ammonia solution was selected to dissolve Hp55S to prepare Hp55S glue. Ammonia is a weak basic substance, which has little effect on the stability of Hp55S and can be removed by volatilization in the subsequent drying process of capsules. Agar was used as a gelling agent of Hp55S gum, agar also had good acid stability [16], which could promote the solidification of Hp55S glue on the mold.

In this study, the preparation of Hp55S glue solution does not use organic solvent, and there is no hidden danger of organic solvent in the production process. The enteric vacant capsules can be prepared by one-step dipping process, and the ordinary vacant capsule production line can meet the preparation requirements [8]. The enteric cellulose vacant capsules prepared has the stability of no swelling and no disintegration in simulated gastric juice for 2 hours, and complete disintegration in simulated intestinal fluid within 30 minutes, and has sufficient pliability and has good tolerance to the environment.

Materials and Methods

Raw materials and chemicals

Hydroxypropyl methylcellulose phthalate (Hp55S, 202004027, Zhejiang Deqing Weikang Biotechnology Co., Ltd.); Hydroxypropyl methylcellulose (HPMC, E4 type, 20190911, Zhejiang prospect Pharmaceutical Co., Ltd.); κ- carrageenan (refined gum, 0909, Zhaoqing Haixing Biotechnology Co., Ltd.); Jieleng gum (TW-JY800 type, m200707, Zhejiang Tianwei Biochemical Engineering Co., Ltd.); Agar strip (food grade, content 99%, Henan Runcheng Chemical Industry Co., Ltd.); Tween-80 (CP, 20190322, Sinopharm Group Chemical Reagent Co., Ltd.); Ammonia (AR, Sinopharm Group Chemical Reagent Co., Ltd.); Glycerin(Food grade, Lianyungang Youjin food additive development Co., Ltd); Potassium chloride (food grade); Ketoprofen enteric-coated capsules(No.190402, Peking University Pharmaceutical Co., Ltd).

(1) Preparation of Hp55S glue solution: To dissolve Hp55S in water containing ammonia, mix well and place overnight to obtain a clear and transparent glue solution with pH value of 6.5~6.8.

(2) Preparation of HPMC/agar glue solution: The agar was soaked in water and heated until clear and transparent. HPMC, KCl and Tween-80 were mixed evenly, the mixture was dispersed in agar solution, and the mixed glue was cooled to 50 ^{0}C.

(3) Preparation of enteric cellulose glue: the temperature of Hp55S glue was raised to 50^{0}C, and then it was poured into HPMC/agar glue at the same temperature, and then mixed evenly. The enteric cellulose glue was obtained by keeping the temperature at 50^{0}C. The glue solution was used to make capsule within 6~24 hours.

(4) Preparation of capsule: Under the environment temperature of 22~25 ^{0}C and relative humidity of 50~65 %, the mold of No.1 capsule was immersed in the enteric cellulose glue solution of 45~50 ^{0}C. The dipping speed was 3 molds/min, and it was turned up and down 540^{0} for shaping. The capsules were dried in an oven at 28~35 ^{0}C for 2 h, and then removed from the capsule mold. After cutting and nesting, the enteric cellulose vacant capsules were obtained. Record the solidification time of the glue on the mold surface (subject to the glue on the mold does not stick to the hand) [10]. The defective products such as shrinkage head, bubble eye, bark wrinkle and damage in the capsules were removed, and the qualified rate of the prepared capsules was calculated [17].

Determination of properties of glue solution and hollow capsules

Properties of glue solution: Viscosity of glue (cP): DV-VIS-COMETER (Brookfield) was selected. The rotor S62 was preheated and the number of turns was adjusted to twist 30~70 % at a certain temperature.

pH value of glue : It was determined by pH meter-8601, AZ instrument Corp.).

Color of glue: Tu-1810 UV-Vis spectrophotometer (Beijing puxi General Instrument Co., Ltd.) was used to determine the absorbance value of glue at 540nm wavelength.

Properties of hollow capsule: Capsule film thickness (mm): Six points on the capsule shell were randomly selected to measure, and the average value was taken.

Moisture content (%): MB35 moisture analyzer (OHAUS Instrument Co., Ltd.) was selected for determination. The capsule (the cap body of the vacant capsule separated) was put in the moisture analyzer for 2 h under 105^{0}C.

Gastric stability and intestinal disintegration: Four use tablet analyzer (SY-2D, Shanghai Huanghai drug testing instrument Co., Ltd.) was used. Six vacant capsules were filled with talcum powder. According to the method of "enterosoluble vacant gelatin capsules" in Chinese Pharmacopoeia 2020 edition [18].

Brittleness and tightness: According to the method of "enterosoluble vacant gelatin capsules" in Chinese Pharmacopoeia 2020 edition [18].

SEM: The enteric vacant capsule film was directly pasted on the conductive tape and adhered to the sample table. The surface structure of the film was observed by GSM 6360 scanning electron microscope (Japan Electronics Co., Ltd.) to analyze whether the components were compatible.

IR: The samples were dried and ground into powder under liquid nitrogen. KBr tablet pressing method was used and Vertex 70 Fourier infrared spectrometer (Bruker Instruments Co., Ltd.) was used to determine the compatibility of the components.

DSC: DSC 131 EVO differential scanning calorimetry (Sataram Instruments Co., Ltd.) was used to scan the film from 35^{o}C to 250^{o}C with nitrogen flow 20 mL·min-1 and heating rate 10^{o}C·min^{-1} to judge the compatibility of components and the thermal stability of the membrane.

Mechanical property: Enteric cellulose hollow capsule film was prepared by tape casting method. Thickness×width×length of the film strip was 0.11×10×100 mm, and the tensile rate was 10 mm·min^{-1}. The shear strength and elongation of the film strip were measured by WOW-05 electronic universal testing machine (Jinan Chuanbai Instrument Equipment Co., Ltd.) under the environment of 25^{o}C and RH 50% [19].

Water vapor permeability rate: The film (30×30×0.11 mm) was fixed with paraffin wax at the mouth of conical flask containing anhydrous calcium chloride. To weigh it and put it in SYW-350B drug stability test box (Ningbo southeast Instrument Co., Ltd.) at 25°C and RH 75%. After 24h, take it out and weigh again to calculate the water vapor permeability.

$$Water\ vapor\ transmission\ rate\ /\ g\ /\ m^2 \times 24hr = \frac{\Delta m}{A.t}$$

Where: Δm/g - the amount of water absorbed by calcium chloride; A/m^2-film area; t/24h [20].

Dissolution of ketoprofen enteric capsules: Ketoprofen enteric capsules were obtained by fillings containing ketoprofen (No.190402, Peking University Pharmaceutical Co., Ltd) with Hp55S capsules and Hp55S/HPMC capsules. Each capsule contained 50 mg ketoprofen. The dissolution was determined according to the method of "ketoprofen enteric capsules" in Chinese Pharmacopoeia (2020 Edition) [21].

Results and Discussion

Preparation of Hp55S glue solution

The dissolution of Hp55S material is the key to the preparation of Hp55S glue solution. Weigh 16g of Hp55S was put into 100mL of water containing different amounts of ammonia, mix well and place to observe the effect of the amount of ammonia on the dissolution of Hp55S. The results were shown in Table 1.

It could be seen from Table 1 that when the amount of ammonia water was lower, the dissolution time of Hp55S was longer; on the contrary, when the amount of ammonia was more, the dissolution time of Hp55S was shorter, and the color of the glue solution was darker. When the temperature of the glue was increased from 25°C to 50°C, the color of the glue was turned white and the pH value was increased slightly. It indicates that ammonia in the glue may volatilize a little during heating. The results showed that the amount of ammonia needed to dissolve 16g of Hp55S was 2.4~2.6 mL, and the pH value of the Hp55S gel was 6 ~7 at 25°C and 6~6.5 at 50°C.

Selection of gel-forming agent

Because cellulose gel itself has no coagulability, k-carrageenanand low acyl gellan gum are usually chosen as gel-forming agent [22,23] to promote the solidification of the colloid in the preparation of cellulose vacant capsules. It has been rarely reported that agar is chosen as gel-forming agent for plant vacant capsules. The effects of three kinds of gel-forming agent (dosage of 1.2g) on the gel properties and capsule formability of Hp55S were investigated and compared. The results were shown in Table 2.

The compatibility of commonly used k-carrageenan and low acyl gellan gum with Hp55S was poor, so it was difficult to make a uniform appearance glue. At the same time, k- carrageenan lost gel characteristics in Hp55S solution. Agar had good compatibility with Hp55S solution, which could form a uniform transparent gel. This is because agar has more extensive pH tolerance. Therefore, agar was chosen as coagulant of Hp55S gel on capsule mold.

Table 1: Effect of ammonia dosage on solubility and gel properties of Hp55S.

Ammonia/ mL	pH value of aqueous solution	Speed of dissolution and deaeration/h	Glue solution/25°C			Glue solution/50°C		
			Appearance/A_{540nm}	Viscosity/ cP	pH value	Appearance/A_{540nm}	Viscosity/ cP	pH value
2	10	Insoluble	/	/	/	/	/	/
2.2	10.5	>8	Clarity transparency/ 0.047	748	5.5	White transparent/ 0.127	339	4.8
2.4	10.5	4.5	Yellowish transparent/ 0.053	711	6.5	Yellowish transparent/ 0.061	332	6
2.6	10.7	4	Yellowish transparent/ 0.055	654	7	Yellowish transparent/ 0.087	283	6.5
2.8	11	2.5	Yellow transparent/ 0.058	624	7.5	Yellow transparent/ 0.137	256	7.2

Table 2: Effect of different gel-forming agent on the gel properties and capsule formability of Hp55S.

Gel-forming agent	Properties of glue			Dipping process		Capsule thickness		Yeild/%
	De foaming	Appearance/50°C	Viscosity/cP, $_{50°C}$	Glue flowing	Shaping time/s	Wall/mm	Top/mm	
k-Carrageenan	Hard	Non uniform With flocs	/	/	/	/	/	/
Low acyl gellan gum	Hard	With flocs mushy	/	/	/	/	/	/
Agar	Easy	Uniform Transparency	544±10	No	4~6	0.11	0.16	>95%

Table 3: Effects of the mass ratio of Hp55S and HPMC on the properties of glue solution and vacant capsules.

Hp55S/HPMC /m/m	Properties of glue			Dipping process		Capsule thickness		Yeild/%	Disintegration time/ min	
	Defoaming	Appearance/50°C	Viscosity/cP, $_{50°C}$	Glue flowing	Setting time/s	Wall /mm	Top /mm		pH1.2	pH6.8
16/0	Easy	Uniform transparency	544	No	4~6	0.11	0.16	>95	>120	25~60
5-Nov	Easy	Uniform Slightly white	613	No	4~6	0.11	0.16	>95	>120	14~52
6-Oct	Easy	Uniform Slightly white	639	No	4~6	0.12	0.17	>95	>120	10~35
7-Sep	Easy	Uniform Slightly white	685	No	3~5	0.11	0.17	>95	>120	7~25
8-Aug	Hard	mushy	/	/	/	/	/	/	/	/

Table 4: Effect of agar dosage on properties of Hp55S/HPMC glue solution and vacant capsule.

Agar dosage/g	Viscosity/cP, $_{50^oC}$	Setting time/s	Capsule thickness		Yeild/%	Disintegration time/min	
			Wall/mm	Top/mm		pH1.2	pH6.8
1.2	600	4~6	0.11	0.16	>95	film a little swollen	8~21
1.4	652	4~6	0.11	0.15	>95	>120	8~20
1.6	685	3~5	0.12	0.18	>95	>120	7~25
1.8	743	2~3	0.12	0.17	>95	>120	9~31
2	773	2~3	0.12	0.18	>95	>120	10~35

Table 5: Effect of incubation time on properties of glue.

Incubation time/h	Viscosity/cP, $_{50^oC}$	Color/$A_{540, 50^oC}$
6	742±14	2.112±0.005
9	856±12	2.342±0.005
12	984±2	2.347±0.006
24	1135±23	2.382±0.004
36	2170±17	2.370±0.007
48	2860±44	2.340±0.009

Compositeing of film materials for enteric cellulose vacant capsules

enteric cellulose vacant capsules prepared with Hp55S as membrane material and agar gel were very stable in simulated gastric juice, but the disintegration time in intestinal juice was about 25~60 min. In addition, the raw material cost of Hp55S was high. Therefore, HPMC and Hp55S were selected to shorten the disintegration time of the capsules in intestinal juice and reduce the preparation cost of the capsules. The effect of the mass ratio of Hp55S/ HPMC (total was 16g) on the properties of gel and capsule was shown in Table 3.

enteric cellulose hollow capsule prepared from Hp55S and agar gel was stable in simulated gastric juice, but the disintegration time in intestinal juice was about 25~60 min, and the cost of raw material was high. Therefore, HPMC was selected as the disintegration regulator of enteric hollow capsules in intestinal liquid and the cost of raw materials was reduced. The effects of the mass ratio of Hp55S/HPMC (total mass was 16g) on the properties of the glue solution and hollow capsules were investigated. The results were shown in Table 3.

With the increase of HPMC content in the ratio of Hp55S/ HPMC, the compatibility of the two kinds of cellulose in solution decreased. When HPMC content was more than 50%, the viscosity of the gel increased sharply and it was difficult to form a uniform gel. According to the uniformity of the gel, the stability of the capsule in gastric juice and the disintegration time in intestinal juice, the mass ratio of Hp55S/HPMC should be controlled in the range of 10/6~9/7.

Effect of agar dosage

Agar can promote the formation of composite Hp55S/HPMC glue solution on the mold, and has good stability in gastrointestinal fluid.

The amount of agar mainly affects the viscosity of the glue, the molding speed of the composite Hp55S/HPMC glue solution on the mold, and the disintegration time of the capsule in the intestinal fluid. According to the experimental results, the amount of agar added in every 100 mL of gel solution was 1.4~1.6 g, and the molding time of

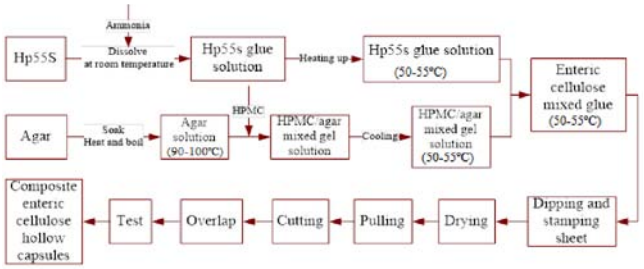

Figure 1: Preparation process of enteric cellulose glue and hollow capsules.

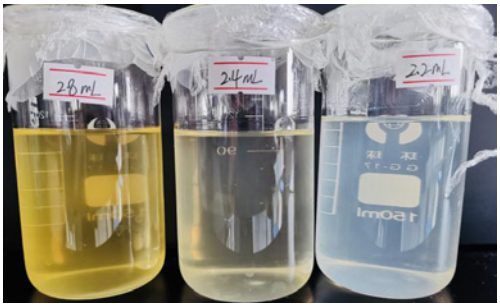

Figure 2: Effect of ammonia dosage on the color and transparency of Hp55S glue (50°C).

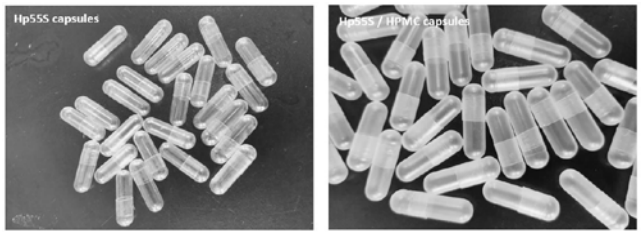

Figure 3: Appearance of Hp55S capsules and Hp55S/HPMC capsules corresponding to formula 1 and 2 of Table 7.

the prepared gel on the mold was 3~6 s at room temperature. The obtained capsules were stable in gastric juice for more than 2 hours and disintegrated in intestinal fluid within 25 minutes (Table 4).

Effect of incubation time on properties of composite glue solution

The formula was as follows: 9g Hp55S, 7g HPMC, 1.6g agar, 0.16g KCl, 0.2g Tween-80, 1.3mL ammonia water and 100mL water. The prepared glue was incubated at 50°C, and the effects of incubation time on the viscosity and color of the glue were determined.

It could be seen from Table 5 that the color of the glue solution

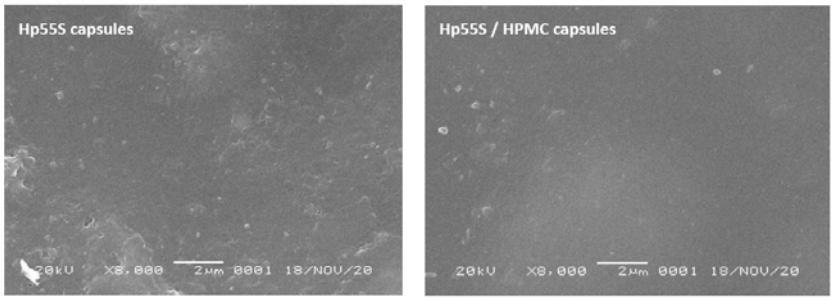

Figure 4: SEM images of Hp55S capsules and Hp55S/HPMC capsules corresponding to formula 1 and 2 of Table 7.

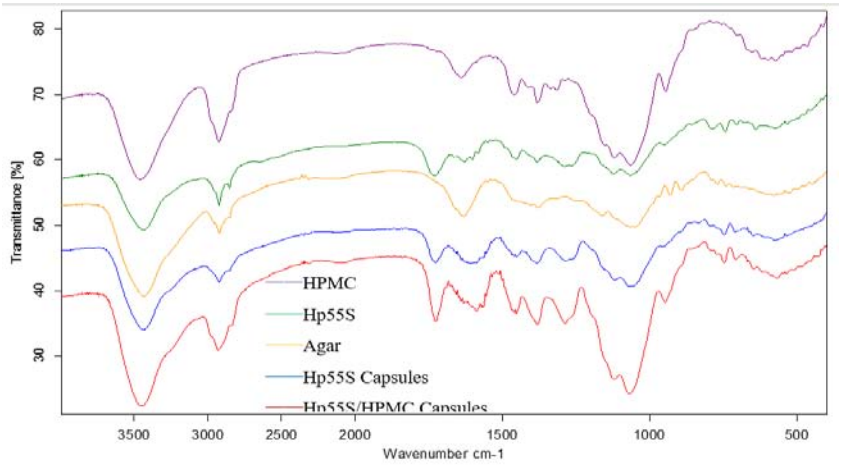

Figure 5: Infrared spectrum of Hp55S capsules and Hp55S/HPMC capsules corresponding to formula 1 and 2 of Table 7.

Table 6: Effect of glue temperature on preparation of vacant capsules during dipping (1#mould).

Temperature/°C	Viscosity/cP	Uniformity	Capsule thickness /mm		Yield/%	Reasons for unqualified capsules
			Wall	Top		
45	906±11	Uniform transparency	0.12	0.18	>92	wall too thick
50	685±4	Uniform whitening	0.11	0.17	>95	/
55	544±3	Uniform whitening	0.11	0.16	>80	top too thin

Table 7: To preparation of enteric cellulose vacant capsules with different formulations (1#mould).

No	Formula							Viscosity/cP, 50°C	Setting time/s	Yield/%	Capsule thickness Wall/top /mm	Degree of tightness /10 pills	Brittleness /50 pills	Disintegration time/min	
	Hp55S/g	HPMC /g	Agar /g	Ammonia /mL	KCl /g	Tween-80 /g	H_2O /mL							pH1.2	pH6.8
1	16	0	1.2	2.4	0.12	0.2	100	644±4	4~6	>95	0.11/0.16	0/10	0/50	>120	25~60
2	9	7	1.6	1.35	0.16	0.2	100	626±2	2~4	>95	0.12/0.17	0/10	0/50	>120	9~25
3	10	6	1.6	1.5	0.16	0.2	100	686±4	3~4	>95	0.11/0.16	0/10	0/50	>120	13~36
4	11	5	1.6	1.65	0.16	0.2	100	755±3	2~4	>95	0.11/0.17	0/10	0/50	>120	19~47

was basically stable, but the viscosity of the glue solution tended to increase with the extension of incubation time. The reason may be that the evaporation of water or the volatilization of ammonia would lead to the partial precipitation of Hp55S in the glue solution. Therefore, it was better to use the glue within 24 hours.

Effect of temperature of glue solution on capsule formation during dipping

The temperature of the glue solution is also the key point for the preparation of vacant capsules. The temperature will affect the viscosity of the glue solution and thus the thickness of the capsule film. The formula was: 9g Hp55S, 7g HPMC, 1.6g agar, 0.16g KCl, 0.05g tween-80, 1.3mL ammonia and 100mL water. The effects of 45°C, 50°C and 55°C glue solution on the preparation of vacant capsule embryo were investigated. The results were shown in Table 6.

The glue viscosity decreases with the increase of temperature. At 45~50 °C, the color of the glue was uniform, the viscosity was

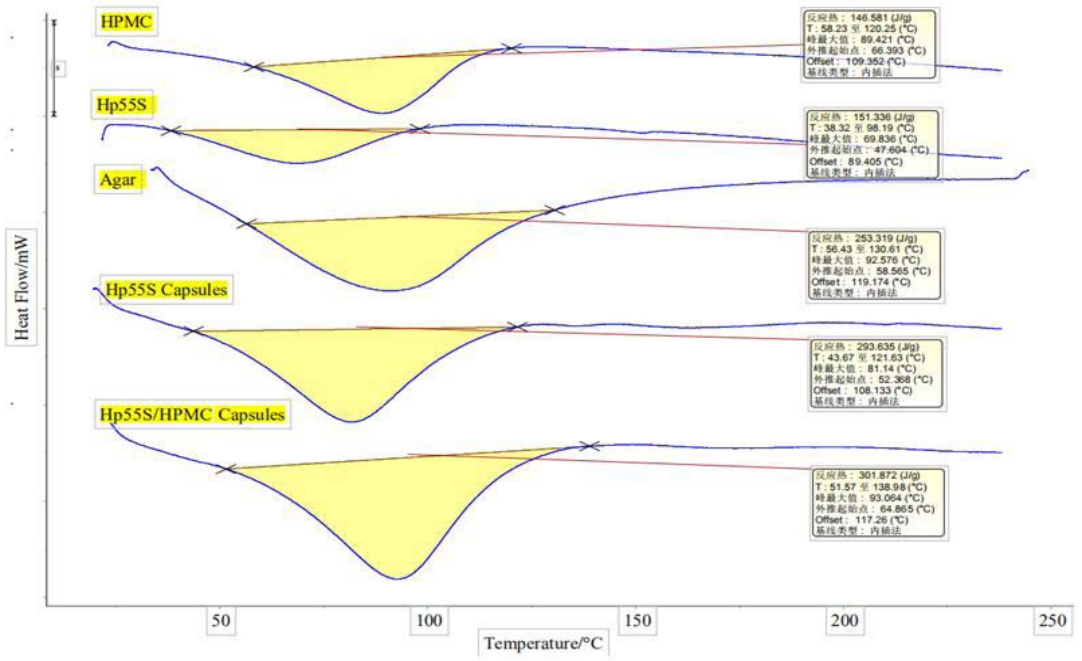

Figure 6: DSC of Hp55S capsules and Hp55S / HPMC capsules corresponding to formula 1 and 2 of Table 7.

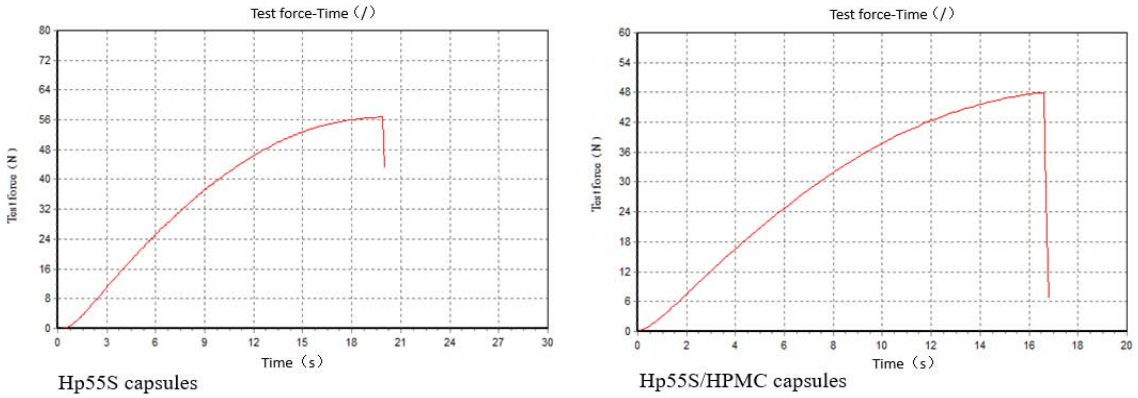

Figure 7: Mechanical test of enteric cellulose films.

appropriate, and the thickness of the prepared capsule film was appropriate (0.11~0.12 mm). At 55°C, the color of the glue turned white and the viscosity was low. Some of the obtained capsules appeared top thin, shrunken head, rupture, and decreased rate of capsule formation. Therefore, the temperature of glue solution should be controlled at 45~50 °C.

The glue viscosity generally decreases with increasing temperature, because the dissolution temperature of HPMC is generally within 50°. It could be seen from experiments that when the temperature of the glue solution was 45~50 °C, the color of the glue solution was uniform, the viscosity was suitable, and the thickness of the prepared capsule film was suitable (0.11~0.12 mm). However, when the temperature of the glue was 50°C, the color of the glue was white and the viscosity was low, the qualified rate of capsules prepared with glue at this temperature was reduced, and the tops of some capsules collapsed and broken. Therefore, the temperature of the glue solution should be controlled between 45°C and 50°C in the dipping process.

Preparation and determination of enteric cellulose vacant capsules

Four batches of enteric cellulose vacant capsules with different formulations were prepared according to Table 7.

The enteric cellulose vacant capsules prepared according to formula 1 and formula 2 in Table 7 were expressed as Hp55S capsules and Hp55S/HPMC capsules respectively.

Appearance characterization of enteric cellulose vacant capsules: The appearance of Hp55S capsules and Hp55S / HPMC capsules were as follows:

Under the magnification 8000 electron microscope, the white colloidal particles in the SEM image may be caused by incomplete agar dissolution. The SEM images of Hp55S/HPMC capsules were

Table 8: Mechanical properties test of enteric cellulose films.

Samples	Thickness× width×length/mm	Maximum force/N	Tensile rate/%	Tensile strength/MPa
Formula 1: Hp55S capsule film	0.11×10×100	57.37±0.90	2.67±0.29	50.51±2.24
Formula 2: Complex Hp55S/HPMC capsule film	0.11×10×100	47.33±2.34	3.0±0.5	43.03±2.13

Table 9: Comparison of water vapor permeability of enteric cellulose films of formula 1 and 2 (n=5).

Samples	Hp55S capsule film	Hp55S/HPMC capsule film
Water vapor permeability/g/(m^2.24h)	207.13±33.42	292.82±24.78

Table 10: Dissolution comparison of ketoprofen enteric capsules (n=6).

Dissolution medium	Sample	Hp55S capsules	Hp55S/HPMC capsules
Dissolution/%	In simulated gastric liquid (pH=1)	0.31±0.11	0.114±0.023
	In simulated intestinal liquid (pH=7.2)	88.39±0.033	89.54±0.028

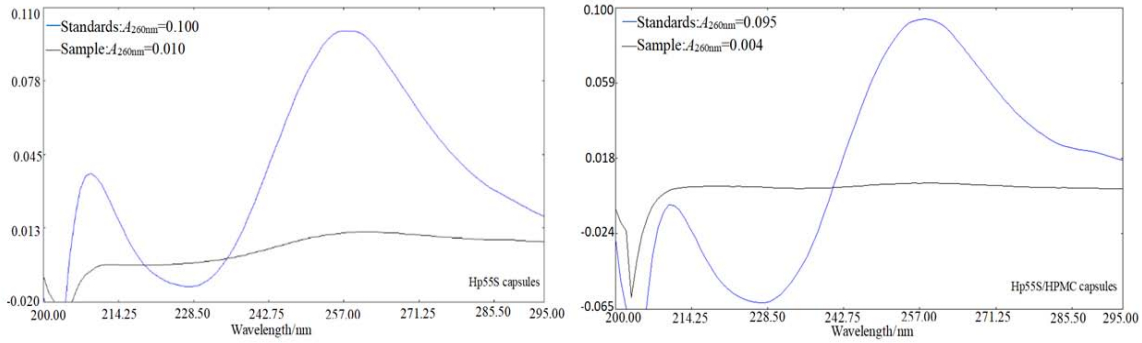

Figure 8: UV spectrum of ketoprofen standard solution of 1.55 ug/mL and ketoprofen enteric capsules filled with two kinds of hollow capsules in simulated gastric liquid (pH1.0) for 2 h.

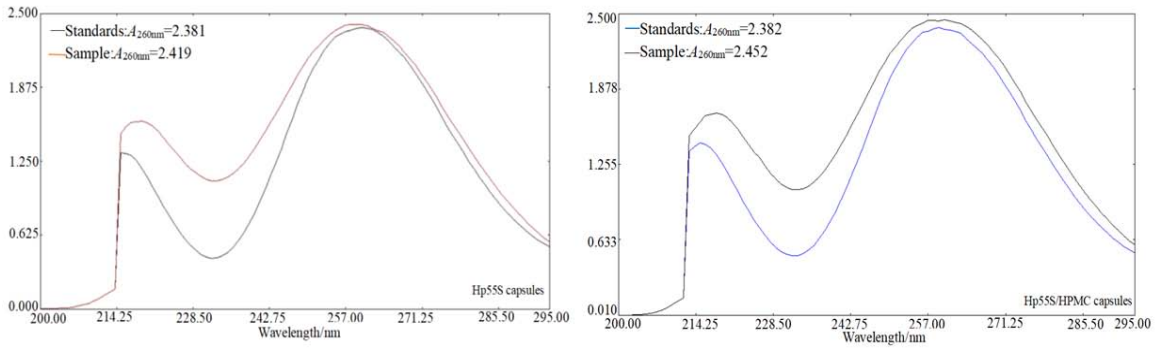

Figure 9: UV spectrum of ketoprofen standard solution of 43.4 ug/mL and ketoprofen enteric capsules filled with two kinds hollow capsules in simulated intestinal liquid (pH7.2) for 45min.

smooth and uniform, indicating that Hp55S, HPMC and agar had good compatibility.

IR spectrum: It could be seen from the infrared spectrum that the infrared spectrum of the Hp55S capsule was the superposition of the two main components of Hp55S and agar, indicating that the two components had good compatibility. The IR spectrum of Hp55S/HPMC capsules included the IR spectrum information of Hp55S, HPMC and agar, which also reflect that these three components were compatible.

According to the DSC curve, the exothermic peak temperature of Hp55S and agar were 69.84°C and 92.58°C, respectively, and the proportion of agar in Hp55S capsule was about 7%, while the exothermic peak temperature of enteric vacant capsule of Hp55S capsule was 81.14°C, which showed that the thermal stability of Hp55S capsule was improved. The exothermic peak temperature of composite Hp55S/HPMC capsules was 93.08, while the corresponding temperatures of three main components of Hp55S, HPMC and agar were 69.84°C, 89.42°C and 92.58°C, respectively. The results showed that the three components were not only compatible, but also the intermolecular force between the three components were enhanced, which improved the stability of the composite Hp55S/

HPMC capsules.

From the comparison of the endothermic peaks, Hp55S/ HPMC capsules were more stable than Hp55S capsules.

Mechanical test of enteric cellulose vacant capsules: The remaining glue solution (45~50 ^{0}C) after the capsule preparation in Table 7 was 15g glue solution per plate. The glue solution was poured onto a 20×20 cm polytetrafluoroethylene plate, and the capsule film was prepared by the casting method. Place the film in an oven at 30 ^{0}C to dry for 1.5~2 hours, uncover and store the membrane in a drug stable box at 20~25 ^{0}C and RH 50% for use. The mechanical properties and water vapor permeability of the membrane were measured.

It could be seen from Table 8 and Figures 1-7 that the maximum force and tensile strength of Hp55S capsule film were higher than those of Hp55S/HPMC capsule film, but the tensile rate of Hp55S/ HPMC capsule film was better than that of Hp55S capsule film. The results showed that the Hp55S/HPMC capsules had more toughness than Hp55S capsules.

Water vapor permeability: It can be seen from Table 9 that the water vapor transmission rate of composite Hp55S/HPMC enteric vacant capsule film was higher than that of Hp55S enteric vacant capsule film. This is due to the HPMC [24,25] in the composite enteric vacant capsule membrane. It is suggested that the composite Hp55S/ HPMC enteric vacant capsules should be sealed and preserved.

Determination of dissolution of ketoprofen enteric capsules: According to the ultraviolet visible spectrophotometry (general rule 0401, Chinese Pharmacopoeia, 2020 Edition), the sample solution, standard solution and blank solution were scanned in the wavelength range of 200~300 nm, and the spectrograms 8 and 9 were obtained.

According to Figure 8 and Figure 9, the absorbance of ketoprofen enteric capsules was determined at 260nm wavelength, and the dissolution amount of ketoprofen in each capsule was calculated. The results are shown in Table 10.

It could be seen from Table 10 that the drug dissolution of ketoprofen enteric capsules prepared by two kinds of Hp55S and Hp55S/HPMC vacant capsules was much less than 10% in simulated gastric liquid (pH1), indicating that the two kinds of Hp55S and Hp55S/HPMC vacant capsules had no leakage to drugs. The drug dissolution was more than 85% in the simulated intestinal fluid (pH7.2) within 45 min, which indicated that the Hp55S and Hp55S/ HPMC vacant capsule could rapidly disintegrate and release the drug in the intestinal fluid, which met the requirements of Chinese Pharmacopoeia [26].

Conclusions

In the preparation of enteric cellulose vacant capsules with Hp55S as film-forming material, the key problems to be solved are: the preparation of Hp55S gel (aqueous gel), the influence of formula composition on the disintegration time of enteric cellulose vacant capsules in gastrointestinal tract, and the preparation cost of products. In this paper, Hp55S and HPMC were used as the composite membrane material of vacant capsule, and agar was selected as the setting agent for capsule formation. The composite cellulose glue was prepared by dissolving Hp55S in aqueous solution containing ammonia. The enteric cellulose vacant capsules which were stable in gastric juice and disintegrated in intestinal juice within 35 min were prepared by using the general production line of vacant capsules. All the indexes of the enteric cellulose vacant capsule met the quality standard of the Chinese Pharmacopoeia. Compared with the current production process of enteric vacant capsules, the most prominent feature of this study is to avoid the use of organic solvents and the secondary dip molding process. The enteric cellulose vacant capsule studied in this paper has the characteristics of simple formula, feasible process, controllable cost and good product stability, which has practical application value.

Declarations

Ethical Approval: The authors declare compliance with the ethical approval.

Consent to Participate: Agree

Consent to Publish: Agree

Funding: This work was supported by innovation and entrepreneurship training program for Zhejiang university students in 2020 (S202010876038), and Zhejiang province's first-class discipline "bioengineering" student innovation program (CX2020004).

Availability of data and materials: The authors guarantee the authenticity of the experimental data.

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