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Study on the preparation technology of Omeprazole Vesicles

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Abstract

We present a study on the process of converting omeprazole into omeprazole vesicles by a film dispersion method. Using the encapsulation efficiency as an index, the formulation and technology of the omeprazole vesicles are optimized by a single factor experiment and a central composite design-response surface method. The optimized formulation and technology are as follows: the ratio of Tween-80 to cholesterol is 3:1, the hydration time is 65 min, the hydration temperature is 30 ºC, the hydration solvent pH is 11, and the dosage is 100 mL. Under such conditions, the average particle diameter of the obtained omeprazole vesicles is 70 nm, and the encapsulation efficiency is 92.40%, which is close to the theoretical value of 93.43%. Transmission electron microscope (TEM) characterization revealed that the omeprazole vesicles are of regular spherical shape, and the IR and TG characterization results showed that the omeprazole was encapsulated by the vesicles. The release time of pure omeprazole drug in simulated human intestinal fluid (pH=6.8) is about 70 minutes, and the release time of omeprazole vesicles is about 75 minutes, with a release rate of 33.19%.

Keywords: Omeprazole; vesicles; encapsulation efficiency; central composite design-response surface method.

Introduction

In the 1970s, vesicles were first reported in the field of cosmetic applications [1]. Following in-depth research and the application of new drug delivery systems, people gradually noticed that the structure of the vesicles is similar to that of cell membranes, both of which are bi-molecules. The layered structure has excellent biocompatibility characteristics, for example it can influence toxicity in the body, promote the targeting of drugs, and can further regulate the distribution and release of a drug in the human body, as well as greatly increasing the bioavailability [2]. Vesicles mainly include lipid vesicles, non-ionic surfactant vesicles (niosomes), polymer vesicles, anionic and cationic surfactant vesicles and fatty acid vesicles. Lipid vesicles are microstructures composed of natural or synthetic lipids with a closed bilayer molecular layer [3]. Non-ionic surfactant vesicles are single or multiple layers formed by non-ionic surfactants and cholesterol, which can be used as drug carriers [4-5]. Polymer vesicles are a kind of hollow structured polymer aggregate formed by the self-assembly of amphiphilic block copolymers in solution [6]. Anionic and cationic surfactant vesicles are composed of anionic and cationic surfactants that can form spontaneous vesicles [7]. A two closed lipid vesicle colloidal dispersion is a fatty acid salt solution formed from fatty acids having amphipathic structures similar to liposomes [8]. Current studies on vesicles involve their use as functionalized carriers of anti-tumor drugs, transdermal delivery systems, diagnosis and imaging, etc. [9-10].

Omeprazole is a representative drug of the first generation of proton pump inhibitors. It is widely used in the treatment of gastric ulcers and duodenal ulcers because of its strong acid inhibitory effect, high specificity, and prolonged life-time [11-13]. Omeprazole belongs to the family of benzimidazole derivatives. It is a white or off-white crystalline powder with a pKa value of about 4, *i.e.* a weakly alkaline fat-soluble compound. It is slightly soluble in water, has poor solubility in water/acid, and due to the presence of the sulfoyl group, it readily decomposes in acid, yet is stable in neutral or alkaline environments. Therefore, during the preparation process, the technological conditions need to be strictly controlled [14-16]. After

omeprazole is made into vesicles, it becomes wrapped in the vesicle bilayer which improves its water solubility and improves its biology. Utilization of such vesicles can reduce the dosage, and enhance the release characteristics *versus* omeprazole alone.

In view of the above considerations, omeprazole is prepared using five common vesicles, namely lipid vesicles, non-ionic surfactant vesicles, polymer vesicles, anionic and cationic surfactant vesicles and fatty acid vesicles. Among them, non-ionic surfactant vesicles (omeprazole vesicles) have the highest encapsulation efficiency. Therefore, this article uses Tween-80 and cholesterol as raw materials, using the encapsulation efficiency as an index, the formulation and technology of omeprazole vesicles are optimized by the central composite design-response surface method. Moreover, the structure of the vesicles was characterized in order to improve the bioavailability of omeprazole, and reduce its usage, thereby providing the basis for the preparation of omeprazole in other dosage forms.

Materials and methods

2.1 Materials

The following were employed: a DF-101S type thermostatic magnetic stirrer; an intelligent low-speed centrifuge; a TECNIAG2 SPIRIT BIOTWIN type dynamic light diffuser; a PHS-3C type pH meter; a MD34 dialysis bag; a dialysis bag special clip; a JEM-F200 transmission electron microscope; a JD200-4 electronic balance; a THZ-82A type gas bath constant temperature oscillator; an RE52C rotary evaporator; a KQ5200B ultrasonic cleaner; a UV-2700 UV-Spectrophotometer.

The following reagents were employed: Methanol (CH_3OH); potassium hydrogen phosphate anhydrous ($K_2HPO_4 \cdot 3H_2O$); sodium chloride (NaCl); omeprazole ($C_{17}H_{19}N_3O_3S$); potassium hydroxide (KOH); cholesterol ($C_{27}H_{46}O$); polysorbate($C_{24}H_{44}O_6$); sodium hydroxide (NaOH), potassium phosphate monobasic (KH_2PO_4).

2.2 Experimental method

2.2.1 Preparation of an omeprazole standard curve

Accurately weigh 0.012 g of omeprazole drug, and dissolve it in a small amount of

methanol, then put into a 200 mL small volumetric flask, continue to add a small amount of methanol, ultrasonically cool to room temperature, dilute the omeprazole with a small amount of methanol solution, prepare omeprazole drug solutions at various concentrations of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 μg/mL. The absorbance of omeprazole was then measured at a wavelength of 305 nm. The abscissa is the concentration of omeprazole and the ordinate is the absorbance. A linear curve is drawn. Y=0.0361x-0.0059 (R2=0.9998) is the obtained standard curve. Over the concentration range of 1-10 μg/mL, there is a near linear relationship between the absorbance and concentration.

2.2.2 Preparation of omeprazole vesicles

Use the commonly used film dispersion method [17]: Take 120 mL of Tween-80 methanol solution and 120 mL of cholesterol methanol solution and put them into the prepared round-bottom flask, and rotate the round-bottom flask repeatedly to evaporate the methanol completely, thereby making the substance form a uniform non-ionic surfactant film in the round bottom flask. Then add 120 mL omeprazole buffer solution, put it in a gas bath constant temperature oscillator at a temperature of 37 °C and rotation speed of 200 r/min for hydration for 1 h. After the hydration was completed, ultrasonication was performed for 300 s and then the system was filtered (0.45 μm). The obtained liquid comprises omeprazole vesicles.

2.2.3 Determination of the encapsulation efficiency of the omeprazole vesicles

Take 5 mL methanol solution and 5 mL omeprazole vesicle solution and mix them thoroughly in a beaker. After 2 h of ultrasound, place in a centrifuge for 30 min, with the rotation speed set at 3000 r/min. 1 mL of the supernatant was taken, which was diluted with a small amount of methanol to determine the absorbance a1, and the total mass of omeprazole in the vesicle solution was calculated at a2. Then 5 mL of omeprazole vesicle solution was directly put into a centrifuge, and 1 mL of supernatant was taken. After dilution with a small amount of methanol, absorbance b1 was measured, and the mass meter of omeprazole encapsulated by omeprazole vesicle was calculated as b2. The encapsulation rate of omeprazole vesicles is equal to the percentage of the mass of omeprazole encapsulated by omeprazole vesicles (b2) and the total mass of omeprazole in the omeprazole vesicle solution

(a2) [18].

2.2.4 Single factor

According to the preparation method for the omeprazole vesicles in section 2.2.2, the experimental conditions are a mass ratio of Tween-80 and cholesterol (1:1, 2:1, 3:1, 4:1, 5:1), hydration time (50, 70, 90, 110, 130 min.) and hydration temperature (25, 30, 35, 40, 45 °C). The evaluation index is the encapsulation efficiency of the omeprazole vesicles, and the experiment was repeated 3 times to determine the best preparation conditions.

2.2.5 Star point design experiment

Take the hydration temperature, hydration time and feed ratio as the inspection factors, and use the encapsulation efficiency of the omeprazole vesicles as indicators. According to the principle of star point design, three factors are set in five levels, represented by +α (α=1.682), +1, 0, -1, -α, according to the single factor research results, the central point value is used to select the hydration temperature, hydration time and feed ratio [19].

2.2.6 Representation of the omeprazole vesicles

Determination of particle diameter: After the test product is filtered using 0.45 μm filter membrane, it is scanned by dynamic laser light scattering. The wavelength of the scanning laser is 632.8 nm, and the scanning time is 3 min. The intensity and diameter of omeprazole vesicles is then measured.

TEM was employed to investigate the appearance and morphology of the omeprazole vesicles. The omeprazole vesicles were prepared according to the best process. After observing the appearance, drop the prepared omeprazole vesicles on the grid on the surface of the fiber membrane and use. After staining with 1% an aqueous solution of phosphotungstic acid for 2 min, it was placed in a transmission electron microscope, with the electron beam voltage at 200 kV [20].

2.2.7 Infrared spectroscopy and thermogravimetric analysis of the omeprazole vesicles

For the infrared spectroscopy: Take an appropriate amount of omeprazole, blank vesicles, and produce a physical mixture of blank vesicles and omeprazole drugs (mass ratio 2:1), the

samples were mixed with KBr according to the mass ratio of 1:100, grinded and then pressed as tablets, and the infrared scanning conducted; the wave number range is 4000~500 cm^{-1}. Origin software was used to process the infrared spectroscopic data.

Thermogravimetric analysis: Herein, we employed the method of Mansaray *et al* [21], whereby samples of omeprazole and blank vesicles were physically mixed (mass ratio 2:1). Then omeprazole vesicles 3~5 mg were placed in the crucible separately, the N_2 rate was 50 mL/min, with a heating rate of 10 ºC/min over range 30~800 ºC. The thermal decomposition curve of the sample was then measured. STARe V13.0 software was used to process the thermogravimetric analysis data.

2.2.8 Sustained release of omeprazole vesicles in a simulated human environment.

Fill a dialysis bag with 3 mL of omeprazole vesicle solution, then put the dialysis bag into 250 mL of buffer (pH=6.8), and allow to stand for 4 h. This releases omeprazole that is not in the vesicles. The buffer solution was used to determine the absorbance and the quality of the omeprazole in the buffer solution was calculated. After the quality of omeprazole in the buffer did not change, the dialysis bag with omeprazole vesicles was transferred to a fresh 250 mL buffer (buffer temperature 37 ºC) and the rotation speed was set to 60 r/min. The release of omeprazole was determined, and a 3 mL of the solution sample was taken at an interval of 5 min. After that, 3 mL of the new buffer solution was added [22]. Using this process, the absorbance of omeprazole vesicles at the maximum absorption peak was measured using an ultraviolet spectrophotometer, and the cumulative release of omeprazole in simulated intestinal fluid environment (pH=6.8) was obtained by subsequent calculation.

Results and Discussion

3.1 Single factor experiment results

3.1.1 The effect of feed ratio on the encapsulation efficiency of the omeprazole vesicles

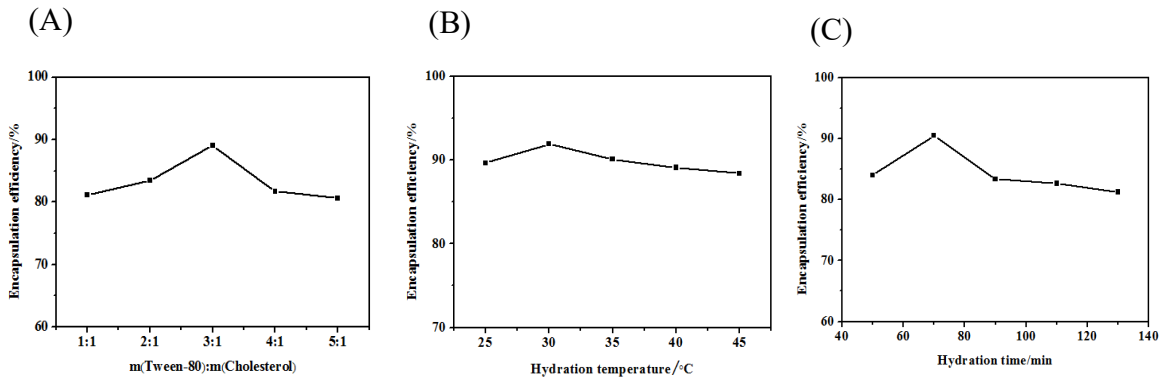

Figure 1. The effect of feed ratio (A), hydration temperature (B) and hydration time (C) on the encapsulation efficiency of the omeprazole vesicles.

As shown in Figure 1 (A), for the continuous increase of Tween-80, the encapsulation efficiency of omeprazole vesicles first increased and then returned to about the same level. This is because omeprazole is encapsulated by the Tween-80. At the beginning, a small amount of Tween-80 was added, and only a small amount of omeprazole was encapsulated, and so most omeprazole remained not encapsulated. Therefore, the encapsulation rate will be relatively low; when the amount of Tween-80 is within a certain range, as the amount of Tween-80 added increases, the amount of omeprazole encapsulated will also increase, and the encapsulation rate will gradually increase. When the amount of Tween-80 is too large and the amount of cholesterol is small, the fluidity of the membrane will be strengthened. Cholesterol has the effect of reducing the fluidity of the membrane. There is no way to form a constant vesicle, which will reduce the encapsulation efficiency. Therefore, it is best to prepare omeprazole vesicles with a feed ratio of Tween-80 and cholesterol mass ratio of 3:1.

3.1.2 The effect of hydration temperature on the encapsulation efficiency of the omeprazole vesicles.

As shown in Figure 1(B), on increasing the hydration temperature, the encapsulation efficiency of the omeprazole vesicles first increased and then decreased. When the hydration temperature is 25 °C, it can be seen from the figure that the encapsulation efficiency of the omeprazole vesicles has not reached the maximum. When the hydration temperature reaches

30 °C, it can be gleaned from the figure that the encapsulation efficiency of the prepared omeprazole vesicles has reached the maximum. When the hydration temperature is higher than 30 °C, it can be seen from the figure that the encapsulation rate of omeprazole vesicles begins to decrease. This is because omeprazole is not readily encapsulated when the temperature is too high, which leads to a reduction in the encapsulation efficiency. Thus, the best hydration temperature for preparing omeprazole vesicles is 30 °C.

3.1.3 Effect of hydration time on the encapsulation efficiency of omeprazole vesicles.

As shown in Figure 1(C), as the hydration time continues to increase, the encapsulation efficiency of the omeprazole vesicles first increases and then decreases. When the hydration time is 50 mins, it can be seen from the figure that the encapsulation efficiency of the omeprazole vesicles has not reached the maximum. Given the hydration time is short, the omeprazole has not completely been encapsulated by the omeprazole vesicles. When the hydration time is 70 mins, it can be seen from the figure that the encapsulation efficiency of the omeprazole vesicles reaches the maximum. Clearly, as the hydration time continues to increase, more omeprazole was encapsulated. When hydration time exceeded 70 mins, the encapsulation rate of omeprazole vesicles began to decline. With the increase of hydration time, the originally hydrated vesicles were destroyed under the constant agitation, and so the encapsulation efficiency of the omeprazole vesicles began to decline. Therefore, the optimal hydration time for the preparation of these omeprazole vesicles is 70 mins.

3.2 Central composite design-response surface method results.

3.2.1 Central composite design research results.

Design Expert 8.05 software was used to perform binomial fitting for the data in Table 1 [23], and a variance analysis was conducted on the model. The binomial fitting equation was obtained as follows:

$Y=93.81+0.78A-2.02B-1.01C+2.31AB-0.96AC+0.083BC-1.40A^2-1.96B^2-4.25C^2$ ($P<0.0001$, $R^2=0.9335$).

Table 1. Comparison of star point design code value and actual value

Serial number	Coded value			Actual value			Y/%
	A	B	C	Feed ratio	Hydration temperature /℃	Hydration time/minutes	
1	0.000	0.000	-1.682	3.00	30.00	36.36	83.61
2	-1.682	0.000	0.000	1.32	30.00	70.00	86.88
3	0.000	0.000	0.000	3.00	30.00	70.00	93.05
4	0.000	1.682	0.000	3.00	38.41	70.00	84.99
5	-1.000	-1.000	1.000	2.00	25.00	90.00	89.27
6	1.000	1.000	-1.000	4.00	35.00	50.00	90.05
7	1.000	-1.000	1.000	4.00	25.00	90.00	86.45
8	-1.000	-1.000	-1.000	2.00	25.00	50.00	92.29
9	0.000	0.000	0.000	3.00	30.00	70.00	93.47
10	-1.000	1.000	1.000	2.00	35.00	90.00	83.53
11	0.000	-1.682	0.000	3.00	21.59	70.00	90.72
12	-1.000	1.000	-1.000	2.00	35.00	50.00	79.79
13	0.000	0.000	0.000	3.00	30.00	70.00	94.09
14	0.000	0.000	1.682	3.00	30.00	103.64	79.14
15	1.000	-1.000	-1.000	4.00	25.00	50.00	86.88
16	0.000	0.000	0.000	3.00	30.00	70.00	94.32
17	1.682	0.000	0.000	4.68	30.00	70.00	92.02
18	1.000	1.000	1.000	4.00	35.00	90.00	83.52
19	0.000	0.000	0.000	3.00	30.00	70.00	93.78
20	0.000	0.000	0.000	3.00	30.00	70.00	94.27

3.2.2 Model fitting and variance analysis

The results of the variance analysis are shown in Table 2. From the results of the

quadratic polynomial fitting, the model $P<0.0001$ indicates that the fitted model is extremely significant. The loss of the quasi item $P<0.05$ and the correlation coefficient $R^2=0.9335$, indicate that the quadratic polynomial equation model has a high degree of fitting to the data, with only a small error. Thus, the model is reliable, and can be used as an analysis and test model for the omeprazole vesicle preparation process. The terms A (feed ratio), B (hydration temperature), and C (hydration time) have no significant effects, while the quadratic terms B^2 and C^2 have significant effects. It can be seen that there is no simple relationship between each influencing factor and the wrapping rate; the size relationship between each influencing factor is B>C>A.

Table 2. Variance analysis results.

Source	Sum of Squares	df	Mean square	F Value	p-value Prob>F	Significant
Model	433.92	9	48.21	15.61	< 0.0001	***
A Feed ratio	8.33	1	8.33	2.70	0.1316	*
B Hydration temperature	55.93	1	55.93	18.10	0.0017	**
C Hydration time	13.86	1	13.86	4.49	0.0602	*
AB	42.69	1	42.69	13.82	0.0040	**
AC	7.37	1	7.37	2.39	0.1534	*
BC	0.054	1	0.054	0.018	0.8970	*
A^2	28.22	1	28.22	9.14	0.0128	**
B^2	55.55	1	55.55	17.98	0.0017	**
C^2	260.83	1	260.83	84.44	< 0.0001	***
Residual	30.89	10	3.09	—	—	—
Lack of Fit	29.65	5	5.93	23.88	0.0017	**
Pure Error	1.24	5	0.25	—	—	—
Cor Total	464.81	19	—	—	—	—

Note: *** means the difference is extremely significant ($P<0.01$); ** means the difference is significant ($P<0.05$); * means the difference insignificant ($P>0.05$).

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3.2.3 Response surface analysis

Design-Expert 8.05 software was used to draw a three-dimensional surface diagram between the encapsulation efficiency, feed ratio, hydration temperature and hydration time of the omeprazole vesicles, and the results are shown in Figure 2.

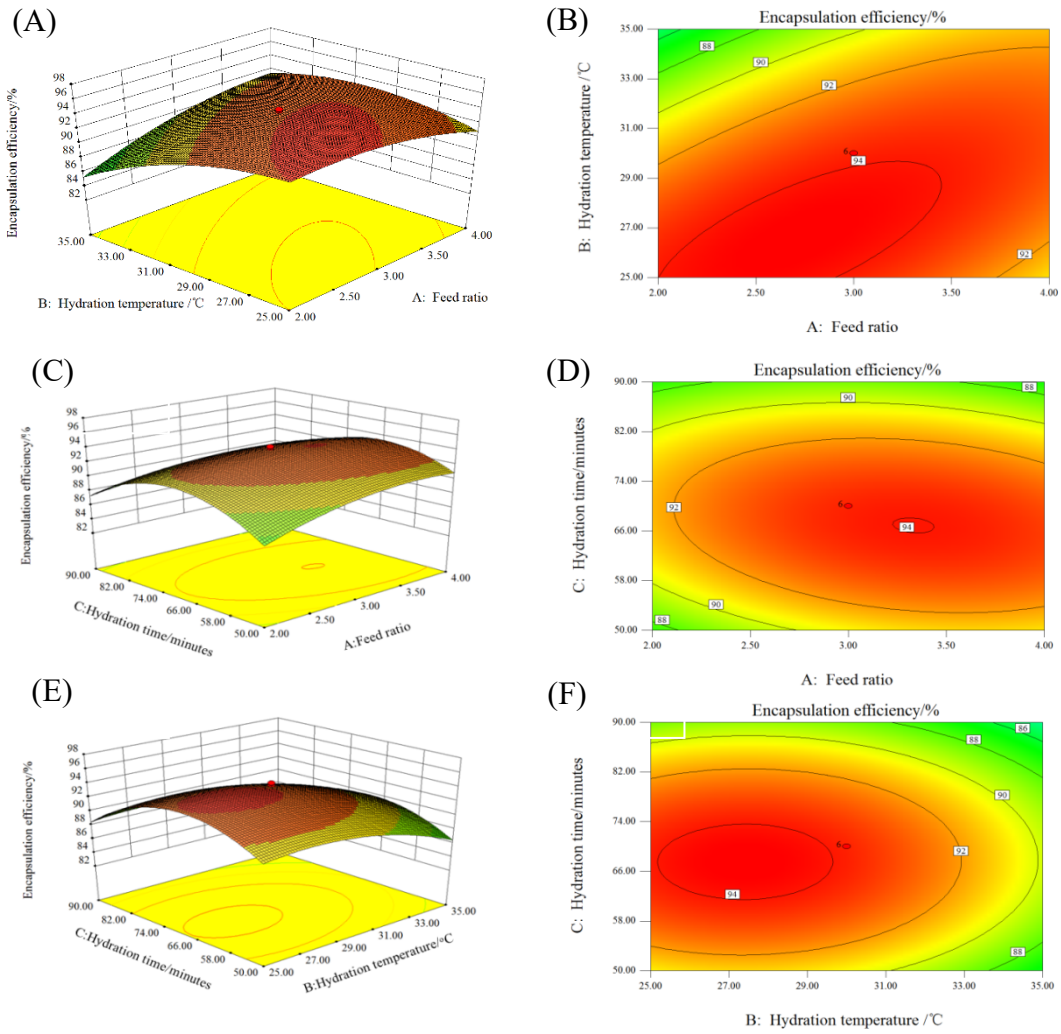

Figure 2. Contours and response surfaces of various influence factors on the encapsulation efficiency of the omeprazole vesicles.

From the central composite design-response surface method diagram, the optimal conditions can be obtained: the mass ratio of Tween-80 and cholesterol is 3:1, the hydration time is 65.40 min, and the hydration temperature is 30.35 ºC.

3.2.4 Verification of the test results

According to the analysis using the DesignExpert 8.05 software, the optimal conditions for preparing omeprazole vesicles are: the mass ratio of Tween-80 and cholesterol is 3:1, the hydration temperature at 30 ºC, and the hydration time is 65 mins. The experimental verification results are shown in Table 3. The average encapsulation efficiency is 92.40%, and the deviation from theoretical value is -1.03%. The experimental value is close to the theoretical value, indicating that this model is feasible and the optimization conditions are also feasible.

Table 3. Verification test results.

	Number of experiments			Average	Theoretical
	1	2	3	value	value
Y/%	92.61	91.41	93.18	92.40	93.43
Deviation /%	-0.84	-2.02	-0.25		

3.3 Representation of omeprazole vesicles

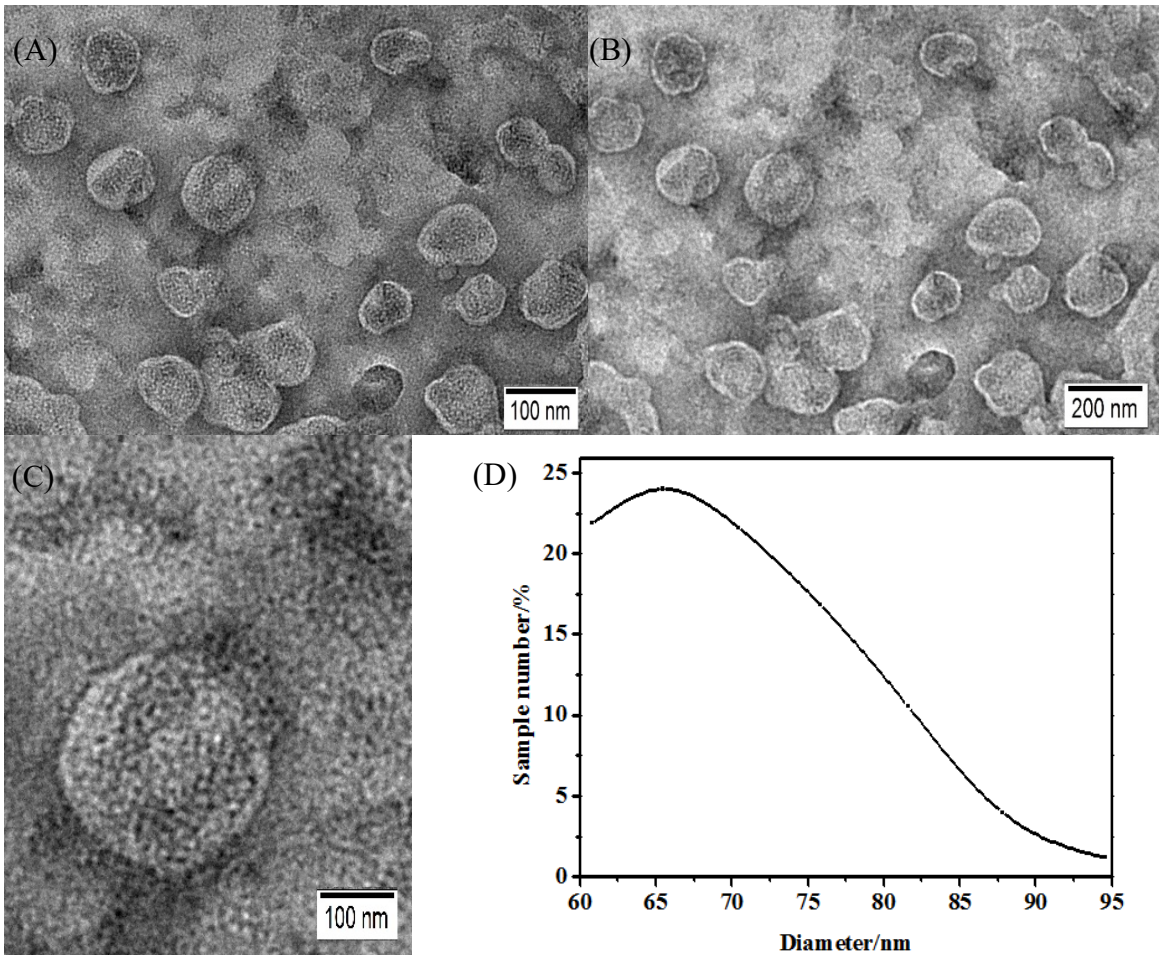

Figure 3. Transmission electron microscopy and particle diameter distribution of the omeprazole vesicles.

As shown in Figure 3, the transmission electron microscopy characterization of the omeprazole vesicles revealed that under the optimal preparation conditions, the prepared omeprazole vesicles exhibited a fully rounded or elliptical appearance, a uniform distribution, and a uniform size. It can be seen from the figure that because the vesicles are of nanometer diameter scale, some agglomeration occurs. According to the particle diameter distribution diagram, the diameter of the omeprazole vesicles was concentrated in the range of 60 nm~95 nm, and its average particle diameter was calculated to be 70 nm. The particle diameter obtained by transmission electron microscope was consistent with that measured by a dynamic light scatterometer.

3.4 Infrared spectroscopy and thermogravimetric analysis of the omeprazole vesicles.

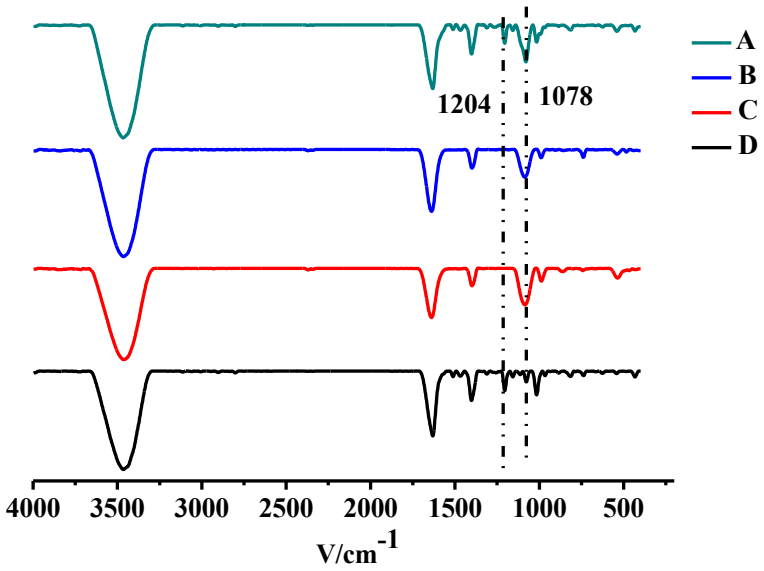

Figure 4. Infrared spectra of physical mixing (A), blank vesicles (B), omeprazole vesicles (C), and omeprazole (D).

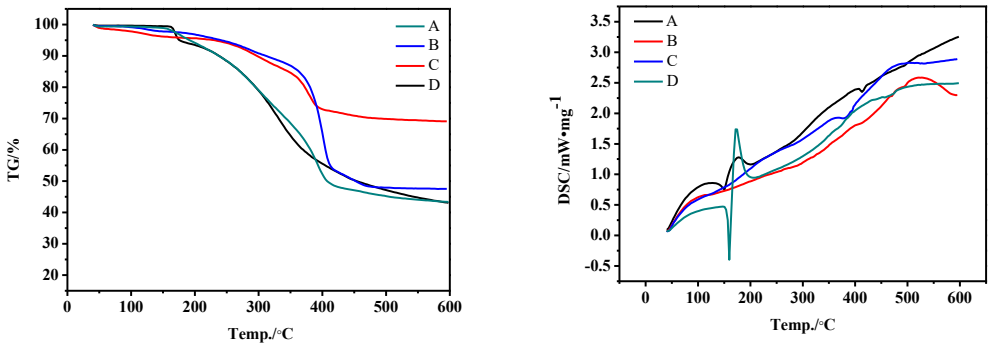

Figure 5. A Physical mixture (A), blank vesicles (B), non-ionic surfactant vesicles (C) and omeprazole (D) TG (left), DSC (right).

Figure 4 displays the infrared absorption spectra of the omeprazole vesicles, blank vesicles, omeprazole and following physical mixing. The omeprazole has an absorption peak at 1204 cm^{-1}, which is the absorption peak of the omeprazole υC-O [24]. Omeprazole vesicles are formed by Tween-80 and cholesterol. The characteristic peak of Tween-80 appears in the omeprazole vesicles, blank vesicles, physical mixing of blank vesicles and omeperazole drugs, which is the C-O-C stretching vibration peak at 1078 cm^{-1}. From the analysis of Figure 4, it can be seen that the absorption peaks that appear in the physical mixing are simply the superposition of the absorption peaks of blank vesicles and omeprazole. There is no C-O bond absorption peak for omeprazole in the IR spectrum of the omeprazole vesicles at 1024 cm^{-1}. By comparing the IR spectra of the omeprazole vesicles and the blank vesicles, it is evident that there is no difference between the absorption peaks in the omeprazole vesicles and blank vesicles spectra. In summary, it can be concluded that omeprazole is encapsulated by omeprazole vesicles and has no effect in the vesicles, indicating that omeprazole is simply encapsulated by vesicles and that the omeprazole is not deteriorated.

Figure 5 displays the TG and DSC charts for the omeprazole vesicles. From the TG chart on the left, the thermogravimetric curve of the omeprazole vesicles can be divided into three stages. The temperature range of the first stage is 191 °C ～332 °C, and the mass loss rate is

9%, which is mainly due to loss of moisture and surface bound moisture and the decomposition of some small hydrocarbons [21]. The temperature range of the second stage is 332 ºC～389 ºC, and the mass loss rate is 12%. This stage is mainly associated with the decomposition process of the omeprazole vesicles. The third stage is assigned to the complete decomposition of the intermediate product, and the corresponding temperature range is 389 ºC~468 ºC, and the loss rate is 5%. The average degradation rate and total mass loss in the first stage are lower than those in the second stage, and the thermal decomposition of the sample is basically completed after 500 ºC. At 600 ºC, the remainder is mainly ash, with 69.04% remaining in omeprazole vesicles, which is greater than the physical mixed ash 43.44%, blank vesicle ash 47.45% and omeprazole ash 42.93%. From the DSC chart on the right, it can be concluded that the endothermic peak for the omeprazole is at 159 ºC and the exothermic peak is at 173 ºC. Two peaks of the omeprazole appeared in the physical mixing, but no omeprazole appeared in the omeprazole vesicles. The absorption peak for the omeprazole indicates that omeprazole is encapsulated by the vesicles.

3.5 Sustained release of omeprazole vesicles in a simulated human environment.

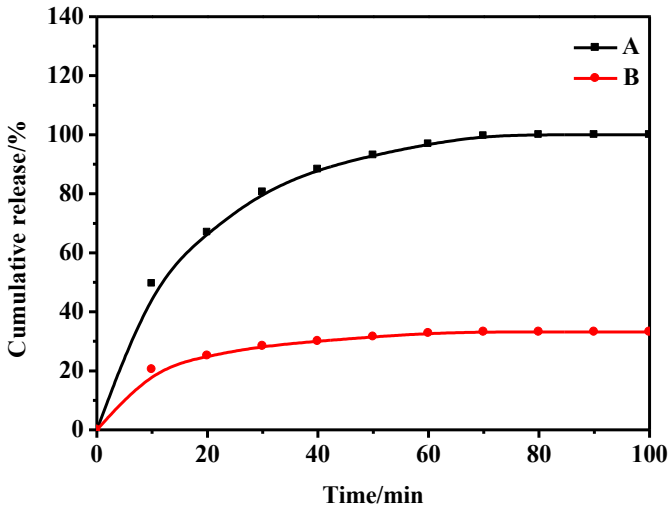

Figure 6. The release curve for the pure drug (A) and the omeprazole vesicles (B) in imitating intestinal juice (pH=6.8).

As shown in Figure 6, the release curve of the pure drug omeprazole reached the cumulative release balance over about 70 mins, whilst the release at the initial (20 mins) release rate of time of the pure drug omeprazole is faster. The drug release curve for the omeprazole vesicles reached the cumulative release balance over about 75 mins, which is not much different from the release time of the pure drug omeprazole, and the release rate when it reached the release balance is 33.19%. The initial (20 mins) release rate for the omeprazole vesicles is significantly lower than that of the pure drug omeprazole. Therefore, after converting omeprazole into omeprazole vesicles, the sustained release time, release rate and sudden release phenomenon of the drug have been improved.

Conclusions

By using a single factor experiment and a central composite design-response surface method optimization, the best preparation method and conditions for omeprazole vesicles can be obtained. These are a mass ratio of Tween-80 and cholesterol of 3:1, a hydration time of 65 mins, and a hydration temperature of 30 ^{o}C. Under these conditions, an encapsulation efficiency for the omeprazole vesicles to omeprazole of 92.40% can be achieved. The experimental value obtained is very similar to that predicted by the software. The order of influence between different factors is: feed ratio <hydration temperature <hydration time. This shows that the model optimized by a central composite design-response surface method is possible, and that it is a useful guide for the preparation process of omeprazole vesicles. From the IR spectra, TG and TEM analysis of the omeprazole vesicles, it is evident that the omeprazole forms spherical vesicles, and that the omeprazole is encapsulated by the vesicles. Omeprazole vesicles can improve the sustained release time, the release rate and sudden release phenomenon of drugs in the simulated intestinal fluid. Therefore, making omeprazole into vesicles provides a theoretical basis for making omeprazole into other preparations.

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