Journal of Medicine and Biological Studies
Volume 2 | Issue 1

Research Article Open Access

Study On the Preparation and Drug Release in Vitro of Nano-Sized Stilbene Glycoside Enteric Dropping Pills

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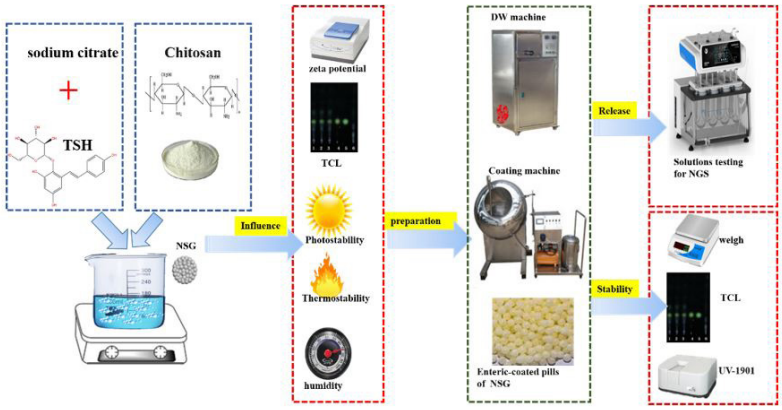
Citation: Wang yun, Xie Yongfang, Gao wenli, Gao chao (2019) Study On the Preparation and Drug Release in Vitro of Nano-Sized Stilbene Glycoside Enteric Dropping Pills. J Med Biol Sci 2(1): 102

Abstract

Extracting and purifying stilbene glycosides requires a large amount of the Chinese medicine raw materia Fallopia multiflora, which is not conducive to the conservation of wild Chinese medicine resources. We have solved this problem by using nanomaterials (nano-stilbene glycosides). The preparation used in this paper was developed by our group and is nanomaterial. While the general preparations containing stilbene glycosides cannot fully utilize the therapeutic effect of the scarce Chinese herbal medicine resources, there are no preparations made of nanomaterials related to Fallopia mul-ti-flora. The main reason lies in the safety, effectiveness and feasibility of the preparation, some of which are unstable or the production of the preparation is not feasible. In order to maximize the drug safety, effectiveness and feasibility of production of this preparation, the stability (high temperature, high humidity, high intensity light, etc.) of the nano-stilbene glucoside was extensively studied, which led to the selection of enteric drops, which are ba-sically insoluble in the stomach, solvent in the intestine, avoiding the effect of gastric acid, and then coating the enteric drops to ensure the maximum possible safety, rapid effectiveness and feasibility of the drug. Through the accelerated stability study of the developed enteric coated enteric drops of nano-stilbene glycoside enteric drops, characterization, thin layer identification, weight difference, loading difference, dissolution time limit, content determination and ex-amination of microorganisms, it was concluded that the nano-stilbene glycoside coated enteric drops formulation is qualified and feasible in produc-tion.

Graphical Abstract



Keywords: Nano-Distyrene Glycosides, Enteric-Coated Dropping Pills, Preparation Process, In Vitro Release,

Introduction

Stilbene glucoside is one of the main components of in Radix Polygonum multiflorum and can be extracted from Polygonum multiflorum readily [1,2]. It is a kind of polyhydroxy phenolic compound with a molecular weight of 406.39. It is a white amorphous powder with good water solubility and anti-oxidation and scavenging free radicals

Pharmacological and pharmacodynamic research: Stilbene glycoside can treat osteoporosis induced by oxidative injury and may be the main component leading to liver injury and 2,3,5,4'-tetrahydroxy-stilbene-2-O-β-D-glucoside attenuates methionineand choline-deficient diet-induced non-alcoholic fatty liver disease [3-5].In addition,it has biological activities such as regulating blood lipids, anti-oxidation, protecting nerve cells, and protecting vascular epithelial cells [6-8]. It is especially important in improving learning and memory,This highlights its important research and development value in today's aging society [9,10]

To seclect enteric dropping pills, because the dropping pill has the haracteristics fast absorption and onset, high bioavail ability, convenient administration, and the preparation process is mature and simple, the quality is easy to control, and it is suitable for clinical medication, and styrene glycosides are mainly absorbed in the stomach and less absorbed in the small intestinal segments. Stilbene Glucoside is unstable in gastric acid affects therapeutic efficacy [11,12]

In addition, dripping pills can also avoid the liver's first-pass effect and quickly enter the bloodstream to take effect. In this experiment, we study the optimal preparation process of nano-distyrene glycoside (NSG) dripping pills, as well as weight gain, coating liquid concentration, coating materials, and the number of coatings as the factors to determine the effect of intestinal drop pill coating [13].

Materials and Methods

Instruments and reagents

TU-1901 Ultraviolet-Visible Hydrolight Meter (Beijing Instruments Co., Ltd.), BSA2245-CW Analysis Balance (one in 100000), HH-1 electric thermostat water bath pot (Tianjin Test Instruments Co., Ltd.), SHB-B95 circulating water multi-use vacuum pump (Zhengzhou Great Wall Science and Trade Co., Ltd.), dw-1 drop pills (Taizhou City Jintai Pharmaceutical Co., Ltd.); BG-10 high-efficiency coating machine (Wenzhou Marriott Machinery Co., Ltd.).

Polyethyl glycol 4000 (PEG4000, Tianjin Damao Chemical Reagent Factory), liquid paraffin (Leiyang City Kant Chemical Co., Ltd.), petroleum ether (Tianjin Fuyu Fine Chemical Co., Ltd.), chromatography methanol (Shandong Weiwang Industrial Co., Ltd.), chromatography ethyl ether (Shandong Weiwang Industrial Co., Ltd.), the reagents used are pure analysis; distilled water; Nano-distyrene (NSG, homemade)(14, 15).

Nano-stilbene glycoside material influencing factors test

The so-called influencing factor test is to investigate the degradation of the API under the corresponding conditions by giving the matter more intense experimental conditions. For example, such as high temperature, high humidity, light, acid, alkali, oxidation, etc., It is important to understand the sensitivity of the test to light, humidity, heat, acid, alkali, oxidation, etc., Those can provide reference information for the selection of suitable packaging materials possible degradation routes and degradation products.

Zeta potentiometric determination

The test colloidal dispersion was perfused in a vial, filled with nitrogen and sealed, stored in a refrigerator at 4 °C for 5 days, and the Zeta potential (n=3) was determined at 0, 24, 48, 72, 96, 120h, and the average Zeta potential of nano styrene glycosides was -29.34±0.03mv, and the Zeta potential gradually became larger with time.

Nano-stilbene glycoside thin-layer chromatography

Preparation of styrene glycoside standard solution: precise weighing of 0.1 mg of stilbene glycoside standard, with a 1ml pipette gun plus 95% ethanol in a 1ml volumetric flask, to make a 0.1 mg/ml stilbene glycoside standard solution. Preparation of the sample solution: precisely weigh the nano-stilbene glycoside powder 0.25g, add 95% ethanol 50ml to heat the reflux for 1 hour, filter, the filtrate is concentrated to 3ml, as the test solution.

Effect of light on the stability of nano-stilbene glycosides

Three batches of nano-stilbene glycoside APIs were unpackaged, placed in a flat weighing bottle, irradiated with (4500±500) Lx for 30 days, sampled at 0 days, 5 days, 10 days, 30 days, extracted and measured the absorbance value at A295nm, calculated the content of stilbene glycosides, and the results were basically normal, indicating that the nano-stilbene glycosides were basically stable to the light (Figure 1).

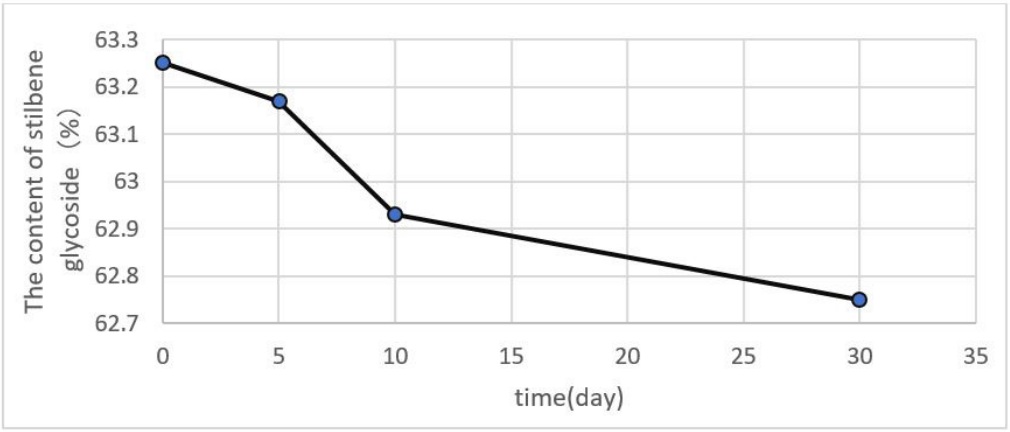


Figure 1: The Results of the effect of light on the stability of nanostilbene glycosides.4500±500) Lx

High temperature test

Three batches of nano-stilbene glycoside APIs were placed in a flat weighing bottle with a thickness of 2.5mm, placed in a 60 °C ±5 °C test incubator for 30 days, and the absorbance value at 295 nm was extracted and measured at 0 days, 5 days, 10 days and 30 days, respectively, and the stilbene glycoside content was calculated. After 30 days of high temperature, the investigation items were basically normal, indicating that nano-stilbene glycosides were relatively stable at high temperatures (Figure 2).

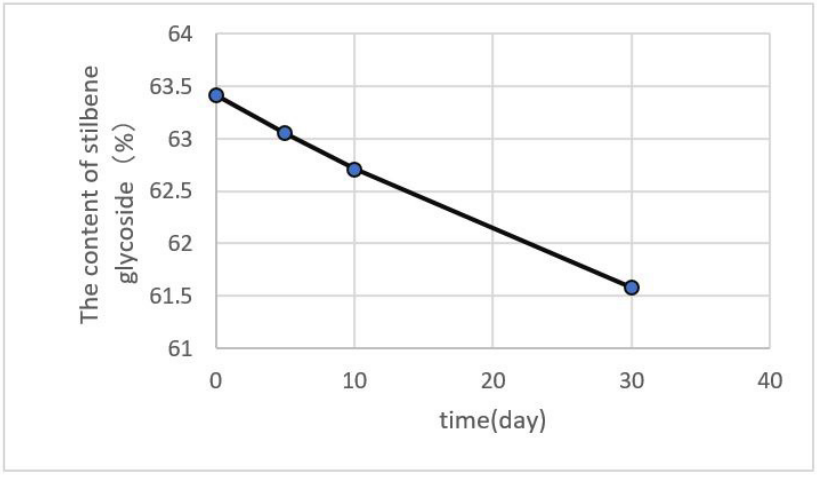


Figure 2: The effect of high temperature on the stability of nano-stilbene glycosides

High humidity test

Three batches of nano-stilbene glycoside APIs were placed in flat weighing flasks, placed in a dryer of NaCl (25 °C, relative humidity 75% ±1%) saturated solution, closed and placed in an incubator (25 °C), and tested at relative humidity of 75% ±5%. In 0 days, 5 days, 10 days, 30 days respectively, sampling to determine the absorbance value at A295 nm, after 30 days of high humidity experiments, the content decreased significantly, the traits changed, Zeta potential became larger, indicating that the nanodistyrene glycoside high humidity instability.

number	The content of stilbene glycoside (%) (n=3)	Thin layer chromatography	Zeta potential
20190312	63.25	Complies with standards	-29.18
	53.67	No new impurities were detected	-29.16
	48.38	No new impurities were detected	-28.16
	40.56	No new impurities were detected	-27.36
20190415	63.52	Complies with standards	-29.17
	52.36	No new impurities were detected	-29.15
	46.88	No new impurities were detected	-28.13
	38.76	No new impurities were detected	-27.53
20190708	64.81	Complies with standards	-29.16
	53.17	No new impurities were detected	-29.08
	47.53	No new impurities were detected	-28.13
	37.85	No new impurities were detected	-27.46

Table 1: 75%RH of on the stability of nano-stilbene glycosides

Substing selection

PEG has a large relative molecular mass. The molecules can form two parallel helical chains. The active ingredients can be inserted into the helical chains when they are melted and dispersed in a molecular state to form a filled solid solution, which can significantly improve the dissolution rate and biological utilization degree. As the solubility and permeability of stilbene glycosides are better. Therefore, PEG4000 or PEG6000 is selected for investigation. Taking the quality difference of dripping pills, dissolution time limit and appearance quality as indicators, PEG4000 is better.

Choice of drops of pill condensant

For water-soluble substrates, liquid paraffin, vegetable oil, methyl silicone oil, kerosene, etc. can be used as the condensing agent. Through the measurement of the sedimentation speed of the dropping pills, the liquid paraffin is 40-50 drops·min^{-1}, and the roundness and forming rate of the dropping pills are relatively high. There will be no sticking and agglomeration. Liquid paraffin is preferred as the condensing agent.

Choice of the ratio of dstyrene to substation

In the preparation of products, it is often hoped that the larger the drug loading of the dripping pills, the better, in order to improve the efficacy. However, with the increase in the drug loading of the dripping pills, they tend to become soft and irregular in shape. On the basis of fixed dripping pill matrix, coolant type and temperature, different ratios of stilbene glycoside to matrix (stilbene glycoside: matrix=1:1, 1:3, 1:5) were investigated.

Optimization of the Forming Process for Destyrene Glycoside Drop

According to the pre-experimental investigation, the best preparation process of stilbene glucoside dripping pills is: the ratio of drug (stilbene glucoside) and matrix is 1:5, the dripping temperature is 75 °C, the condensation temperature is 10 °C ~15 °C, and the drip distance is 7 cm. The factors and levels of the orthogonal experiment are shown in Table 1. The appearance quality, dissolution time, and the difference of the pill quality are comprehensively scored as the inspection indicators to determine the molding process of the stilbene glucoside dripping pill. The dissolution time is operated according to the method under the disintegration time limit check item. The experimental data is the average value of 6 dripping pills; the difference in pill quality is to take 20 dripping pills, measure the quality of the pills, and obtain the coefficient of variation; The appearance quality is scored as three indicators of roundness, color and hardness, and the results are recorded as 1 to 5 points according to the quality from good to bad. The results are directly added

Comprehensive score = (dissolution time/maximum dissolution time) + (variation coefficient of pill quality difference/maximum pill quality variation coefficient) + (appearance quality score /maximum appearance quality score). The lower the overall score, the better the quality of dripping pills, the higher the score, the worse the quality.

Factors levels	Drugs: Substrings A	Drip temperature (°C) B	Drop distance (cm) C	Condensation temperature (°C) D
1	1:1	65	8	5-10
2	1:3	75	7	10-15
3	1:5	85	6	15-20

Table 2: Orthogonal test factors and levels

	Factors				Index			
group	A	B	C	D	Pill weight difference (%)	dissolved time limit (min)	appearance quality	combined total
1	1	1	1	1	4.68	7.58	13	2.57
2	1	2	2	2	4.51	6.68	9	2.15
3	1	3	3	3	4.77	8.87	10	2.51
4	2	1	2	3	5.25	7.96	8	2.35
5	2	2	3	1	5.34	6.25	9	2.24
6	2	3	1	2	5.17	7.38	7	2.20
7	3	1	3	2	4.34	6.35	4	1.73
8	3	2	1	3	5.96	5.29	8	2.17
9	3	3	2	1	4.21	8.58	5	2.03
K1	2.410	2.217	2.313	2.280				
K2	2.263	2.187	2.177	2.027				
K3	1.977	2.247	2.160	2.343				
R	0.433	0.060	0.153	0.316				
S	**0.291**	**0.005**	**0.042**	**0.168**				

Table 3: Orthogonal experimental design

The source of the variation	SS	DF	F	P
A	0.291	2	58.200	P<0.05**
C	0.042	2	8.400	P>0.05
D	0.168	2	33.600	P<0.05*
Error (B)	0.005	2		

Table 4: Analysis of variance table

It can be seen from the above table 3 that the three factors of A, C and D have a certain influence. The primary and secondary order is A>D>C. Drugs: Substrings has a significant influence on the result. The best process conditions are $A_3B_2C_3D_2$. That is, the ratio of the drug to the matrix is 1:5, the temperature of the drug solution is 75 °C, the drip distance is 6cm, the liquid paraffin oil is used as the coolant, the coolant temperature is 10-15 °C, and the cooling column length is 80cm. The drip pill produced by dripping in this way has a smooth appearance, roundness and no tailing.

Verification of the Drip Process

According to the actual production and the requirements of clinical medication, the preparation process of stilbene glucoside dripping pills is adjusted as follows: polyethyl glycol 4000 as a substitin, the ratio of drugs to the substitin is 1:5, the liquid paraffin as a condensant, the drip temperature is 65 °C degrees, and the condensation temperature is 10 to 15 °C. Three batches of nano-distyrene glycoside drops were prepared, and the results were stable. Use a cotton cloth to absorb the condensation agent on the surface of the dripping pill, and then wash the remaining condensation agent on the surface of the dripping pill with petroleum ether. Dry the dripping pill at a low temperature of 45 °C for 3 to 4 hours.

Result

Preparation of NSG Intestinal-Soluble Clothing Drop

Since the aqueous solution of stilbene glycoside is unstable under high temperature conditions (80 °C) or acidic solution, it is easy to oxidize and unstable, so it needs to be coated.

Preparation of Clothing Liquid

Take the appropriate amount of pure water in the beaker, in stirring in a sub-sprinkled coating material, with the appropriate amount of NaOH solution as the pH adjuster, and continue stirring for 30 minutes to obtain an aqueous dispersion of the coating material. Take the appropriate amount of pure water, add a certain amount of PEG6000 and talcum powder under stirring, and then slowly add the coating material under the water dispersion, continue stirring 40 minutes, and pass through 80-mesh sieve to get the coating liquid.

Preparation of Artificial Intestinal Juice and Artificial Gastric Juice

Artificial intestinal juice: take 6.8 g KH2PO4 and add 500 ml of water to dissolve, adjust the pH to 6.8 with 1% NaOH, add 1g trypsin to per 100 ml liquid, mixed and filtered with 0.22 um microporous membrane; Artificial gastric juice: dilute hydrochloric acid with a concentration of $1mol{\cdot}ml^{-1}$, dilute with water, adjust the pH to 1.5, add 1g of pepsin to per 100 ml liquid, mixed and filtered with 0.22 um microporous membrane.

Coating Process Parameters

During the coating process, the coating liquid is continuously stirred. According to the pre-test results and references, the proposed coating process parameters are spraying speed 135-150 kg·h^{-1}, slurry temperature 22 °C, inlet air temperature 70-75 °C, The air outlet temperature is 35-45 °C, the speed is 8-9 r·min $^{-1}$, and the cooling time is 12 min. Prepare blank enteric-coated dripping pills without NSG in the same way.

Optimization of Coating Prescription and Process

According to the pre-test results, the weight gain of the coating (A), the concentration of coating materials (B), clothing materials (C) and the number of coats (D) were selected as the influencing factor. Each factor took three levels, and orthogonal tests were conducted with the dispersion time limit in artificial intestinal fluid as the evaluation index. The results are shown in Table 4, Table 5, and the variance analysis results are shown in Table 6.

From the visual analysis, it can be seen that the best condition is $A_1B_2C_3D_3$.That is, the coating material increases the weight of the coating by 2%, the coating liquid concentration is 20%, polyacrylic resin II, and the number of coats is 3 times. There are significant differences between the levels of the 4 factors (P <0.05).

Factors levels	the weight gain of the coating (A,%)	the concentration of coating materials (B,%)	clothing materials (C)	the number of coats (D)
1	2	10	HPMCP	1
2	4	20	CAP	2
3	6	30	Acrylic acid II	3

Table 5: Orthogonal test factors and levels

NO.	Factors				Index
	A	B	C	D	Dissolution time (min)
1	1	1	1	1	14.4
2	1	2	2	2	15.3
3	1	3	3	3	16.6
4	2	1	2	3	13.0
5	2	2	3	1	16.7
6	2	3	1	2	13.5
7	3	1	3	2	15.6
8	3	2	1	3	16.8
9	3	3	2	1	12.3
K1	15.433	14.333	14.900	14.467	
K2	14.400	16.267	13.533	14.800	
K3	14.900	14.133	16.300	15.467	
R	1.033	2.134	2.767	1.000	

Table 6: Orthogonal experimental design result

	df	F	F ratio	F critical value	p
A	1.602	2	1.015	6.944	P>0.05
B	8.329	2	5.275	6.944	P>0.05
C	11.482	2	7.272	6.944	P<0.05*
D	1.556	2	0.985	6.944	P>0.05
error (A.D)	3.16	4			

Table 7: Analysis of Variance Result

Verification Test

According to the actual production and clinical drug requirements, the preparation process of nano-distyrene drop pill coating is adjusted as follows: the coating material for the coating weight gain of 2%, the coating liquid concentration of 20%, polyacrylic resin II, the number of coatings 2 times. Parallel preparation of 3 batches of NSG intestinal drops, in artificial intestinal fluid for dissolution time measurement, the results of 3 batches of samples average dispersion time limit is (16.52±0.34) min, (15.45 ± 1.03) min and (15.38 ± 1.12 min), indicating that the package operation reproduction is good, the time limit for dissolution is in accordance with the regulations.

Release Test In Vitro Determination

According to the available literature(13), the standard curve equation of linear regression with absorbance (A) and corresponding concentration (C):A=0.07653 C+0.01861 for calculation, where the correlation coefficient (r) is 0.9998.

Release Investigation

Three batches of NSG enteric-coated dripping pills were taken(16), 900 ml of artificial gastric juice was used as the release medium, and the rotating basket method was used to investigate the release rate. The rotating basket speed was 100 r·min^{-1} and the temperature was (37 ± 0.5) °C, 2 hours later, the basket was lifted out of the liquid surface, 5 ml of the release medium was sucked, filtered with a 0.45 μm filter membrane, and the NSG content was detected. At the same time, the artificial gastric juice was discarded, replaced with 900 ml artificial intestinal juice preheated to (37 ± 0.5) °C, and the rotating basket was immersed at a rotation speed of 100 r·min^{-1} at 10, 20, 30, and 40, respectively. Take a sample of 5 ml in 50 min, filter through a 0.22 μm microporous membrane, detect the content of NSG, and calculate the release percentage Q (%). Immediately add the same amount of fresh artificial intestinal juice at the same temperature after each sampling. The results in the artificial intestinal fluid are shown in Figure 1. It can be seen that the NSG enteric-coated dripping pill releases more than 90% of the drug at 43 minutes (Figure 3).

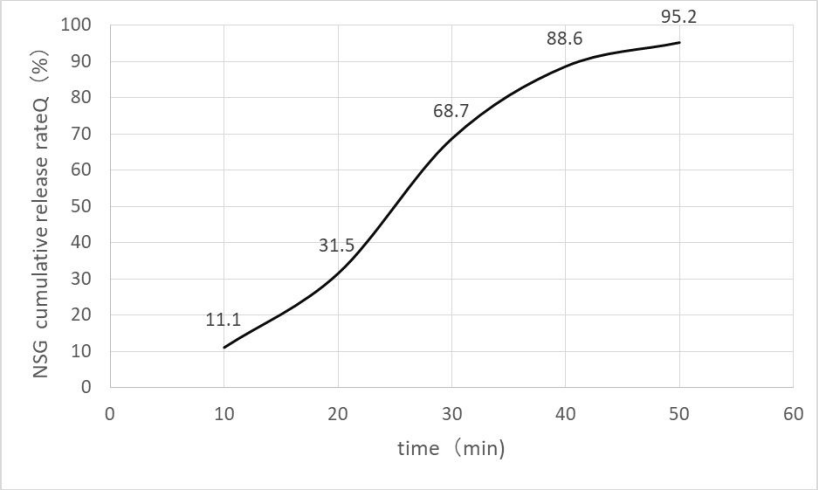


Figure 3: NSG in artificial intestinal fluid cumulative release chart

Discussion

The hot-melt liquid of polyethylene glycol 6000 has a high viscosity, and the hot-melt liquid of polyethylene glycol 4000 has a low viscosity, which is suitable for preparing dripping pills with dry powder of traditional Chinese medicine. For preliminary experiments, polyethylene glycol 4000 is the most suitable.

The study systematically compares the factors affecting the preparation of nano-stilbene glycoside solid dispersion droplets. From a production perspective, the faster the dropping speed of the dropping pill machine, the higher the production efficiency of the dropping pill, so the dropping speed is determined to be 40-50 drops/min. However, because the dripping speed is too fast, it will seriously affect the forming and roundness of the dripping pill.

This experiment optimizes the prescription of drop pills, because it is unstable in acid, its intestinal solute, examines the weight gain, dosage, coating material and the number of coatings, the results show that NSG drops in artificial intestinal fluid 8-9 min dissolved, intestinal solute, in artificial intestinal fluid dissolved around 17min, and in artificial gastric fluid almost unreleased medicine, for the NSG body release characteristics laid the foundation.

Conclusions

The preparation and enteric coating process of the optimized nano-stilbene dropping pills in this study showed that it owned higher drug release characteristics in vitro, the obtained enteric-coated dropping pills had good hardness and roundness, high forming rate, and (satisfied) were in line with enteric-coated dropping pills. Quality requirements for pills. In addition, it has obvious enteric effect and can be used to prepare stilbene glycoside intestinal drops. This work can provide a basis for further research and utilization of stilbene glycosides.

Author Contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.Y.F. and Y. W. formal analysis, G.W.L. investigation; X.Y.F. resources; G.W.L. data curation; writing—original draft preparation; Y. W,Yongfang Xie..writing—review and editin.; All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Data Availability Statement

In this section, All datas supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study.

Conflicts of Interest

The authors declare no conflict of interest.

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