Supplementary Data

An integral evaluation method for the synchrony of drug release based on the mathematics set in guiding the preparation of a multi-component traditional Chinese medicine

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Running title: An integral evaluation method for the synchrony of drug release

Supplementary data 1: The introduction of FZHY and liver fibrosis

Liver fibrosis in chronic liver disease (such as chronic hepatitis B) is the inevitable pathological development process to cirrhosis. And its essence is liver tissue's extracellular matrix (extracellular matrix, ECM) hyperplasia and abnormal deposition, then causes pathological changes of liver structure or (and) dysfunction. Hyp is a non-essential amino acids, collagen-specific component. The content of Hyp is the important indicator to measure the body's collagen tissue metabolism, indirectly reflecting the status of the organization in collagen metabolism[1]. In the event of fibrosis tissues, Hyp content is much higher than normal, such as the content of Hyp in liver homogenate and the degree of liver fibrosis is proportional[2]. Liu Ping[3] had found that FZHY-C could effectively improve liver fibrosis of the chronic hepatitis B and liver fibrosis reversal rate up to 52%, and significantly could reduce the content of liver fibrosis serum markers, such as type IV collagen (IV-C), Hyaluronic Acid (HA), laminin (LN), and Type III procollagen peptide (P-III-P), which were from total 216 patients with chronic hepatitis B liver fibrosis in multicenter, randomized, double-blind and parallel control method. Liu Cheng[4] had found that FZHY-C drug serum could significantly inhibit the synthesis and secretion of collagen fiber cells. In this study, the weight of liver and the content of Hyp in liver tissue, as the main pharmacodynamic indicator could evaluated the reasonableness of the FZHY-P.

Supplementary data 2: The preparation of fat-soluble immediate release unit, water-soluble immediate release unit and water-soluble sustained release unit

The preparation technology of fat-soluble immediate release unit (pellets) was as followed. A S250E50 extrusion spheronization machine was purchased from Chongqing Enger Granulating & Coating Technology Co., Ltd. (Chongqing,China). Took a certain amount of effective components according to the prescription, mixed uniformly and then added PEG 6000 (Sinopharm Chemical Reagent Co., Ltd., Shanghai,China) , which dosage ratio was 3 : 2. The mixture was melt in 70 ^{o}C constant temperature water bath by stirring fully. Then transferred it rapidly to -20 ^{o}C refrigerator for curing 2 h. Cured samples were dried for 2 h in 45 ^{o}C blast drying box, took out and crushed over 80 mesh sieve. Then the solid dispersion was prepared. Took a certain amount of this solid dispersion and microcrystalline cellulose (Anhui Shanhe Excipients Co., Ltd., Anhui,China), mixed uniformly. Water as a wetting agent, the mixture was kneaded into soft material. It was squeezed into the same diameter, smooth and compact strip by extrusion machine sieve (aperture 0.6 mm). The strip material was put quickly into the high-speed rotation of the rolling machine to roll into balls in a certain rolling rate. Pellets were took out, dried at 60 ^{o}C for 2 h. Finally 40-60 mesh pellets were screened. The process parameters were as below: extrusion speed: 45 r · min^{-1} ; initial spheronization speed: 1000 r · min^{-1} ; spheronization time: 3 min ; spheronization speed reduced 200 r per minute.

The preparation technology of water-soluble immediate release unit (pellets) was as followed. Took a certain amount of effective components according to the prescription, mixed uniformly, added a certain amount of water in the mixture and stirred it to dissolve to make the liquid medicine of 10% solid content. Then added quantity for 0.3% silica gel as

antisticking agent to make suspension liquid. After that microcrystalline cellulose blank pellet cores (diameter: 0.3-0.425 mm, Hangzhou Gaocheng Biological Nutrition Technology Co., Ltd., Hangzhou, China) were loaded by drug with using fluidized bed spray equipment (Mini Glatt 3 fluidized bed, Germany) in suspension state. The process parameters were as below: inlet air temperature: 45^{o}C ; inlet pressure: 0.40-0.44 bar ; atomization pressure: 1.10-1.22 bar ; liquid intake rate: 1.0-1.2 mL · min^{-1}.

The preparation technology of water-soluble sustained release unit (pellets) was as followed. Took the above water-soluble immediate release unit (pellets), then adjusted the inlet temperature of 35^{o}C with other same preparation conditions, the coating was weighted of 2% with using fluidized bed spray equipment. Prescription and preparation method of coating solution: Eudragit RS 100 (Rohm, Germany) 10.0 g, talcum powder 2.0 g and polyethylene glycol 4000 (Sinopharm Chemical Reagent Co., Ltd., Shanghai, China) 1.0 g were dissolved in 200 mL 95% ethanol by ultrasound for 10 min. The coating liquid was maintained homogenized state by magnetically stirring in the coating process.

Table 1 S The dose of FZHY-P

the composition of FZHY-P	the high dose of FZHY-P group ($g \bullet Kg^{-1}$ weight)	the medium dose of FZHY-P group ($g \bullet Kg^{-1}$ weight)	the low dose of FZHY-P group ($g \bullet Kg^{-1}$ weight)
Water-soluble immediate release unit	37.8	18.9	9.45
Fat-soluble immediate release unit	1.42	0.709	0.355

Table 2S Preparation of standard curve

Reagents	Tube No.						
	0	1	2	3	4	5	6
Hyp standard (μL, 0.01μg•μL^{-1})	0	20	40	60	80	120	160
As the Hyp content (μg)	0	0.2	0.4	0.6	0.8	1.2	1.6
50% Iso-propanol (μL)	1200	1180	1160	1140	1120	1080	1040
Chloramine-T working fluid (μL)	200	200	200	200	200	200	200
Mixed with shaking， set at 25°C room for 10 min							
ER working fluid (μL)	1000	1000	1000	1000	1000	1000	1000

Table 3S Each group of weight, liver weight, spleen weight, Liver/weight, Spleen/weight and liver tissues Hyp content ($\bar{X} \pm SD$)

Group	N	Weight (g)	Liver weight (g)	Spleen weight (g)	Liver weight/weight	Spleen weight/weight	Hyp (μg • g^{-1} liver wet weight)
Normal group	10	471±46.48	17.13±2.21	1.12±0.26	0.04±0.0030	0.0024±0.0004	95.90±9.01
Model group	19	379±21.85 ##	11.95±2.24 ##	1.68±0.32 ##	0.03±0.0048 ##	0.0045±0.0010 ##	215.69±39.16 ##
Original formulation FZHY-C group	14	386±29.76	12.76±2.30	1.57±0.29	0.03±0.0050	0.0041±0.0010	167.38±52.14 *
High dose of FZHY-P	14	382±39.66	12.33±3.32	1.74±0.53	0.03±0.0070	0.0047±0.0018	177.50±102.96
Medium dose of FZHY-P	14	406±25.66 *	14.68±1.69 **	1.56±0.26	0.04±0.0029 **	0.0039±0.0005	161.95±18.59 *
Low dose of FZHY-P	14	371±44.80	10.79±3.09	1.81±0.24	0.03±0.0060	0.0050±0.0011	226.76±69.38

Compared with normal group, ## $P < 0.01$;

Compared with model group, * $P < 0.05$, ** $P < 0.01$

Reference

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