Studies on preparation of matrine solid dispersion sustained-release tablets

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Abstract: **Objective**: Matrine was made into solid dispersion sustained-release tablets. **Methods**: Ingredients are screened by single factor test and orthogonal ,forming ingredient of sustained-release tablets was determined by appearance,formability, dissolution and d hardness of tablets. **Results**: The result showed that the optimum formulation was composed of HPMC 12g ,lactose 9.5,3%PVP 8ml,magnesium stearate 0.5g. **Conclusion**: Matrine solid dispersion sustained-release tablets meets the requirement of meets the requirements of suspension preparation with pharmacopoeia with stable quality.

Sophora flavescens which contains a variety of alkaloids is the dry roots of legumes, whose main component is matrine extracted with ethanol organic solvent. Preventing liver injury,anti-hepatic fibrosis,antitumor,cardiovascular are the main pharmacological effects of matrine.the traditional oral dosage form of matrine absorption effect is relatively poor. preparation of matrine solid dispersion sustained-release tablets can improve drug stability,increase the solubility and reduce the number of medication to a stable plasma concentration and treatment effect which avoid the phenomenon of peak and valley because of timing positioning drug release.. [1-5]

1 Instruments and materials

PEG6000,HPMC,MC,EC,PVP,CMC-Na,MCC,dextrin,lactose,magnesium stearate ,talc（Tianjin Damao Chemical Reagent Factory）;Other drugs and reagents are of analytical grade. YPD-300D tablet hardness tester, CJY-300D tablet friability tester, RCZ-8 drug dissolution tester, TDP-1.5 single punch tablet machine (Ohaus); GZX-914MB electric thermostat oven (Changsha City in the South Pharmaceutical Machinery Factory)

2 Experimental method

2.1 Preparation of matrine solid dispersion and standard curve

Matrine monomer is dissolved in the proper amount of anhydrous ethanol. PEG6000 water bath heat and melt in constant temperature(80 ℃).A mixture of matrine monomer and PEG6000(1:9) magnetic stirring (100 r / min) 3 min to achieve uniformity and continue stirring to solvent evaporated. Cooled at -20 ° C for a predetermined time, the finished product are stored in the dryer for 24h , porphyrize and sieve(80 meshes).

Preparation of standard curve: the standard curve equation with the absorbance A and matrine standard concentration C (ug / mL) is the ordinate and abscissa in the linear range of 5 ~ 25 ug • mL-1.

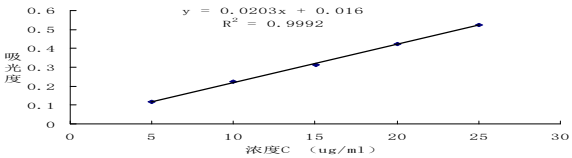

Figure 1: standard curve

2.2 Screening for the specie and dosage of Skeleton material[6]

The recipe that are the matrine solid dispersion(30g),lactose(9.5g),3%PVP(7ml), magnesium stearate(0.5g), HPMC(12g) or MC(12g) or EC(12g) are respectively made. HPMC is the skeleton material by release rate as evaluation indicator.

The recipe that are matrine solid dispersion(30g), lactose(9.5g), 3%PVP(7ml), magnesium stearate(0.5g), HPMC(12g or13g or14g or15g or16g) are respectively made. The dosage of HPMC is 12g by release rate as evaluation indicator.

Table 1: screening for the specie skeleton materials

skeleton materials	(12h) release rateQ（%）
HPMC	89.4
MC	82.2
EC	84.6

Table 2: screening the dosage of skeleton materials

evaluation indicator	12g	13g	14g	15g	16g
12h release rate（%）	93.40	86.20	82.10	81.50	89.80

2.3 Screening for the specie and dosage of lubricant[7]

The recipe that are the matrine solid dispersion(30g), lactose(9.5g),HPMC (12g),3%PVP(7ml), magnesium stearate(0.5g) o rtalc (0.5g) or micro-silica (0.5g) are respectively made. Magnesium stearate is lubricant by appearance and formability as evaluation indicator.

The recipe that are matrine solid dispersion(30g), lactose(9.5g), HPMC (12g),3%PVP(7ml), magnesium stearate(0.4g or 0.5g or 0.6g) are respectively made. The dosage of magnesium stearate is 0.5g by appearance and formability as evaluation indicator.

2.4 Screening for the specie and dosage of filler[8]

The recipe that are the matrine solid dispersion(30g),HPMC(12g),3%PVP(7ml), lactose(9.5g),MCC(9.5g) or dextrin(9.5g) or magnesium stearate(0.5g) are respectivey made. Lactoseis filler by release rate as evaluation indicator.

The recipe that are matrine solid dispersion(30g), lactose(9g or 9.5g or 10g), HPMC(12g),3%PVP(7ml), magnesium stearate(0.5g) are respectively made. The

dosage of lactose is 9.5g by release rate as evaluation indicator.

Table 3: screening for the specie of filler

the specie of filler	12h release rateQ（%）	hardness（kg/cm^2）
MCC	91.6	4.5
dextrin	83.5	5.2
lactose	94.5	5.7

Table 4: screening for the dosage of filler

the specie of filler	9g	9.5g	10g
12h release rate(%）	84.50	92.50	85.40
hardness（kg·cm^{-2}）	4.2	5.7	4.5

2.5 Screening for the specie and dosage of adhesive[8,9]

The recipe that are the matrine solid dispersion(30g), HPMC (12g),lactose (9.5g) ,3%PVP (8ml)or 10% starch slurry(8ml) or CMC-Na(8ml),magnesium stearate(0.5g) are respectively made. 3%PVP is adhesive by formability and hardness as evaluation indicator.

The recipe that are matrine solid dispersion(30g),lactose(9.5g),HPMC (12g) ,3% PVP(7ml or 8ml or 9ml), magnesium stearate(0.5g) are respectively made. The dosage of 3%PVP is 8ml by formability and hardness as evaluation indicator

.**Table 5: screening for the specie of adhesive**

the specie of adhesive	formability	hardness（kg·cm^{-2}）
10% Starch pulp	lobe	4.37
CMC-Na	the shape is complete ,the number of spotted spots<5 %, few serious spots and special foreign bodies	4.10
3%PVP	surface gloss，the colour is the same，the shape is complete ,the number of spotted spots<5 %, no spots and special foreign bodies	5.16

Table 6: screening for the dosage of adhesive

the dosage of adhesive	formability	hardness（kg·cm^{-2}）
7ml	lobe, surface gloss	4.67
8ml	the shape is complete, no spots and special foreign bodies	4.51
9ml	sticking and picking	5.25

2.6 Screening for the proportion of drugs and excipient

The recipe that the proportion of the matrine solid dispersion and excipient is 1:1or 2:3 or 1:2 or 1:3 are respectively made. The proportion of the matrine solid dispersion and excipient is 1:1 by release rate as evaluation indicator.

Table 7: the proportion of drugs and excipient

The proportion of drugs and excipient	1:1	2:3	1:2	1:3
12h release rate（%）	94.62	86.47	82.36	82.17

2.7 Orthogonal test method

After single factor study, the factors and levels of orthogonal test are determined. Through the orthogonal design scheme of $L_9(3^4)$, screen the optimum dosage of the skeleton material, the lubricant, the filler and the adhesive by 12h release rate as evaluation indicator.

Preparation of standard curve: the standard curve equation with the absorbance A and matrine standard concentration C (ug / mL) is the ordinate and abscissa in the linear range of 5 ~ 25 ug • mL-1.

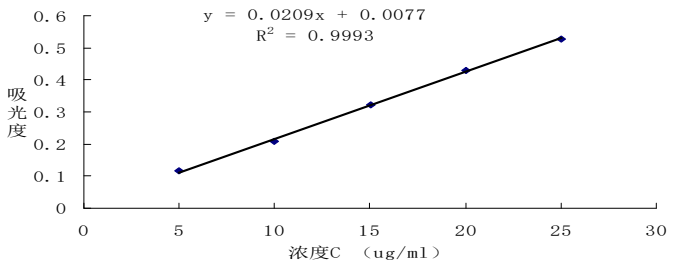

Figure 2: standard curve of orthogonal test

Table 8: factor level charts

level	factor			
	A HPMC(g)	**B** lactose（g)	**C** 3%PVP(ml)	**D** magnesium stearate（g)
1	12	9	6	0.4
2	14	9.5	7	0.5
3	16	10	8	0.6

Table 9: orthogonal test results

Test number	A （HPMC/mg）	B (lactose/mg)	C (3%PVP/ml)	D (magnesium stearate /mg)	Q(%)
1	1	1	1	1	86.46
2	1	2	2	2	94.03
3	1	3	3	3	93.35
4	2	1	2	3	79.35
5	2	2	3	1	83.36
6	2	3	1	2	75.85
7	3	1	3	2	84.11
8	3	2	1	3	76.32
9	3	3	2	1	78.31
Ⅰ	91.28	83.31	79.54	82.71	
Ⅱ	79.52	84.57	83.90	84.66	
Ⅲ	79.58	82.50	86.94	83.01	
R	11.76	2.07	7.40	1.95	

Based on the orthogonal test results ,the order of influence is A＞C＞B＞D. The best combination of factors is $A_1B_2C_3D_2$ in which the dosage of HPMC, lactose, 3%PVP and magnesium stearate are respectively 12g,9.5g,8ml,0.5g.

Table 10: analysis of varia-nee

The source of cariance	square of deviance	degree of freedom	F ratio	F value	significant
HPMC	275.191	2	42.259	19.000	*
lactose	6.512	2	1.000	19.000	
3%PVP	82.924	2	12.734	19.000	
magnesium stearate	6.648	2	1.021	19.000	
error	6.51	2			

The results of variance analysis show that the HPMC have significant effect on experimental results. The 3% PVP, the lactose and the magnesium stearate have no significant effect .

2.8 Verification test

Accoding to results obtained by orthogonal test, three batches of matrine solid dispersion sustained release tablets are made and measure the release rate of this sustained release tablet to verify whether the excipient and preparation process is optimal.

Table11: verification test(n=3)

number	（12h）release rate（%）
1	94.46
2	94.23
3	94.37

2.9 Quality inspection [10,11,12]

2.9.1 Visual inspection

Inspecting twenty pieces of matrine solid dispersion sustained release tablets showed surface gloss,complete, no spots and special foreign bodies which conform to the Chinese Pharmacopoeia.

2.9.2 Determination of tablet weight difference

According to 2015 ChP, weigh twenty pieces of matrine solid dispersion sustained release tablets and determine each weight and average weight.The result shows sample piece of weight differences are within limits.

2.9.3 Hardness determination

According to 2015 ChP,inspect the hardness of matrine solid dispersion sustained release tablets. The consequence showed average hardness of sustained release tablet is 5.16kg/cm^2.

Table12:the results of hardness test

number	1	2	3	4	5	6
hardness（$kg.cm^{-2}$）	5.72	5.35	4.79	4.82	5.33	4.94
Average hardness（kg.cm-2）			5.16			

2.10.4 Drug release determination

Matrine standard substances (10mg) is set in 100 mL with anhydrous ethanol and amount 0.5mL、1.0mL、1.5mL、2.0mL、2.5mL to 100mL. Matrine standard substances at concentration of 5.0ug/mL、10.0ug/mL、15.0ug/mL、20.0ug/mL、25.0ug/mL determine absorbance at wave length of 620nm.The standard curve equation with the absorbance A and matrine standard concentration C (ug / mL) is the ordinate.

The release behavior of sustained-release tabletis studied by cylindrical basket method. The release medium is pH6.8 KH_2PO_4-NaOH,and temperature is 37±1 ℃ , samples were obtained 4,6,8,10,12h and quantitated at 620nm by Ultraviolet spectrophotometer.

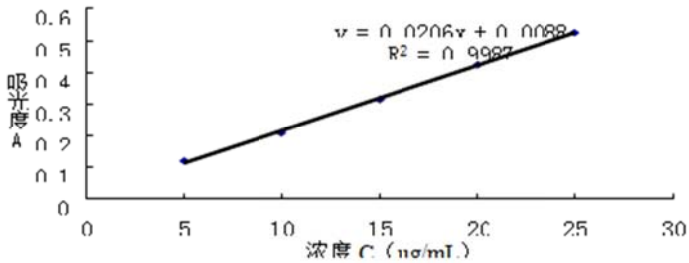

Figure 3: standard curve of quality inspection

Table13: Cumulative release (%) Test results

number	4h release rate Q（%）	6h release rate Q（%）	8h release rate Q（%）	10hrelease rate Q（%）	12hrelease rate Q（%）
1	29.37	48.81	74.86	82.84	94.86
2	28.95	49.24	75.42	88.62	95.42
3	28.87	48.88	74.44	84.43	94.44

2.10.5 Fragileness determination

According to 2015 ChP, inspect the fragileness of matrine solid dispersion sustained release tablets. The result shows every sample weight loss is<1%.

Table 14: Fragile checklist

number	1	2	3
Total weight of sustained release tablets before testing（g）	6.5834	6.5953	6.5446
Total weight of sustained release tablets after testing（g）	6.5512	6.5559	6.5234
loss of weight（g）	0.0322	0.0394	0.0212
percentage of weight loss （%）	<0.49%	<0.6%	<0.32%

3 Summary

From this study, the excipients and the best formula of the sustained-release tablets and other conditions were optimal selection by the single factor test, orthogonal test, validation test, and quality inspection.Matrine common tablets contain low total alkalinity, and is not easy to disperse and dissolution ,low bioavailability, poor compliance to patients .Compared with the conventional preparation, the sustained-release preparation is easy to use, the frequency of drugs is small, plasma concentration is stable, no the "peak and valley" phenomenon and timing and positioning release. Adverse reactions are relatively reduced, and its great advantage is to meet the need for long-term use of drugs .

References

[1]Liu mei, Liu xueying &Cheng Jianfeng. Progress in Pharmacology of Matrine [J]. Chinese Journal of Chinese Materia Medica, 2003,09: 11-14.
[2]Chen weiguang. Study on Progress of Matrine Pharmacological[J].Occupation And Health, 20 02 , 02:14-15.
[3]Gong fengge. Research Progress of Controlled Release Tablets[J].TianJin Pharmacy,2010 (05):8-10.
[4]Lin hui. Development of Traditional Chinese Medicine Sustained - release Preparations [J].Strait Pharmaceutical Journal, 2002,05:114-117.
[5]Zhang xiudan, Li xianqing &Liu lin. New Advances in Matrine Pharmacology and Preparations [J]. Archives of Traditional Chinese Medicine, 2006,11:2011-2013.
[6]Yao hui,Deng hongzhu &Zhang jiping. Preparation of Ginkgo biloba sustained release tablets[J], Pharmacy Today,2009,(04):52-54.
[7]Shi lei,Fan Changchun. Preparation and in vitro release of simvastatin gelssu stained release tablets, China Medical Herald,2011.8(26):76-78.
[8]Jing qiufang,Ren fuzheng&Shen yongjia. The preparation and preparation of puerarin composite skeleton sustained - release tablets, Journal of East China University of Science and Technology, 2011.2.(22):25.

[9]Zhang fang, Study on Preparation Technology of Nimergoline Sustained Release Tablets, China Pharmaceuticals, 2010.19(15):41-42.
[10]Peng zhiping. Study on the preparation technology and in vivo release of Panax notoginseng saponins sustained - release tablets, Hubei University of Traditional Chinese Medicine, 2012.
[11]Huang haowu,Luo yuhong &Liang feihua. Effect of preparation process of theophylline sustained - release tablets on release, China Medical Herald, 2010,7(7):42-44.
[12] National Pharmacopoeia Commission edits. Pharmacopoeia of the People 's Republic of China [M].China Medical Science Press, 2015:226.