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Full Length Research Paper

The effect of hydrophobicity/hydrophilicity balance of three kinds of adjuvants on pridinol mesylate orally disintegrating tablets and its quality assessment

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This study was aimed at investigating the effects of 3 kinds of adjuvants on the disintegrating ability of pridinol mesylate orally disintegrating tablets (PMODT), and evaluating the quality of PMODT. The hydrophobic balance of 3 adjuvants (polyvinylpolypyrrolidone (PVPP), microcrystalline cellulose (MCC) and Povidone K30 (PVPK30)) were detected using the L9(3^4) orthogonal test to determine their effects on the disintegrating ability of PMODT. The quality of PMODT was tested according to the requirements of the Chinese Pharmacopoeia (2010). Results indicated that the disintegrability of PMODT decreased with the increasing amount of PVPP from 4 to 8%. However, no significant influence on the disintegrability was found when the amount of MCC was increased from 10 to 15%. On the other hand, the disintegrability decreased with the increasing amount of MCC when the amount was 15 to 20%. Furthermore, the disintegrability was slightly affected when the amount of PVP K30 was 1 to 2%, while the disintegrability decreased when the amount of PVPK30 was at the range of 2 to 3%. The ratio of hydrophobic / hydrophilic adjuvants affected the disintegrability, which showed a "V" shape curve. The disintegrating tablets showed best property when the ratio of PVPP+MCC and PVPK30 (hydrophobicity / hydrophilicity) was 9.5. The results of hydrophobic balance test on the three kinds of adjuvants were consistent with the results of orthogonal test. In general, the quality of 3 batches of PMODT met the relevant requirements of the production of orally disintegrating tablets. This will provide new ideas and methods for the screening and dosage choice of variety of adjuvants in the study of pharmaceutical preparation.

Key words: Adjuvants, hydrophobicity, orally disintegrating tablets, orthogonal design, disintegration.

INTRODUCTION

The disintegration and dissolution process of tablet is caused by water, which touches the tablet and diffuses into the internal part. Therefore, moisture on the wettability and infiltration of the tablet in the disintegration process is the initial step of disintegration, which plays an important role on the tablet disintegration (Gao and Cui, 2000). The hydrophobicity of adjuvant is closely related to the infiltration rate of water into the internal part of tablet. Hydrophilic excipients can form temporary bonds with hydrogen bonding and water, which attracts the water molecules into the interior of the tablet; the tablets are more readily wet by water. Moreover, the interaction of hydrophobic excipients and water are weaker than the association of water molecules (Ren and Lu, 1999) so it is difficult for water to enter the interior. Therefore, the hydrophobic balance among adjuvants has great influence on the disintegrability of tablets.

Pridinol mesylate (PM) is one of the central anticholinergic drugs with skeletal muscle relaxant effects

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(Suzuki and Watanabe, 2005; Svensson et al., 2003), which is included only in "The Japanese Pharmaceutical Codex "(2002 Edition). The raw materials and preparations have not been documented in Chinese Pharmacopoeia. The report about pridinol mesylate orally disintegrating tablets (PMODT) can be found only in our study, which has been applied for a patent in China. PM is mainly used to treat muscle cramps and the pain or contractions of movement disorders, such as low back pain, shoulder carpal tunnel syndrome, arthritis of the shoulder and spine deformation (Pipino et al., 1991). PM also possesses a certain therapeutic effect on Parkinson syndrome, especially for the patients with serious symptoms such as autonomic swallowing difficulties, which make them difficult to accept traditional tablets (Prerna et al., 2010; Oertel and Dodel, 1995; Foley , 2009; Wang , 2002). Consequently, the applications of oral disintegrating tablet greatly improve the patient medication compliance (Wu et al., 2010; Sun et al., 2008).

Orally disintegrating tablet (ODT) is a new type of solid rapidly disintegrating dosage formed (Wen and , Dai, 2010; Cheng et al., 2011). The ODT can rapidly disintegrate in the oral cavity, dispersed or dissolved in saliva. No water or only a small amount of water is needed for patients to take ODT. Disintegrating tablet can be smoothly swallowed with fast absorption, while having small hepatic first-pass effect and so on. Disintegrating tablet is suitable for most patients, especially the elderly, children and dysphagia patients. In addition, ODT is convenient for geological workers, soldiers and earthquake disaster area people. Nevertheless, there is a very strict disintegrating time for ODT preparation. The provisions of the U.S. Food and Drug Administration (FDA) is 30 s (FDA, 2008), while for Saudi Food and Drug Authority (SFDA) is 60 s (SFDA, 2003). Microcrystalline cellulose (MCC), crospovidone (PVPP) and povidone K30 (PVPK30) are 3 kinds of different adjuvants. The present study investigated the effects of the 3 kinds of adjuvants on PMODT from the angle of hydrophobic balance. The quality assessment of PMODT was also discussed in this study.

MATERIALS AND METHODS

Apparatus

The following apparatus were used in the sample preparation: YPD-200C Tablet Hardness Tester (The Yellow Sea Medical Instrument Company, Shanghai, China); ZP-19 Rotary Tablet Press (Dawn Pharmaceutical Machinery Co Ltd, Taizhou, China); Mettler Toledo Classic Balance Line AB-S (Mettler Toledo instruments Co. Ltd, Switzerland); RCZ-6B2 Drug dissolution instrument (Huanghai Medicine Checking Instrument Co. Ltd, Shanghai, China).

Materials and reagents

The included: PM reference standard (SIGMA Company, American, 99.99% purity, Lot P4419); butyl-4-hydroxybenzoate (Kelong Chemical Reagent Factory, Chengdu, China, AR); pridinol mesylate (Modern Applications of Beibei Institute of Drug Synthesis, Chongqing, China, 99.56% purity, Lot 100703); pridinol mesylate ordinary tablets (Donlim Pharmaceutical Industries Ltd, Japan, specifications: 4 mg, Lot 21900AMX01432000); MCC (Shanhe Medicinal Materials Company, Anhui, China); PVPP (ISP, American); PVPK30 (South of Pharmaceutical Company, Hainan, China); Mannitol (Tian Guan Food Additive Company, Guangzhou, China); magnesium stearate (A Hua Pharmaceutical Company, Shandong, China).

Hydrophobic balance design test

According to Washburn equation $V^2 = (2*d*r*\cos\theta/k_0 G)t$ (Kanig and Rudnic, 1984), from the angle of hydrophobic balance of the excipients, we chose hydrophobic 4 to 8% PVPP and 10 to 20% MCC as disintegrating agent, hydrophilic 1 to 3% PVPK30 as binder, and the disintegration time limit as disintegrating indicator. In order to select the formulation of the PM orally disintegrating tablets, the effects of 3 kinds of accessories was investigated.

Orthogonal test

Disintegration time was used as index. Combined with the taste of the tablet, we used the four factors and three levels of $L9(3^4)$ orthogonal test to confirm the effects of the accessories hydrophobic balance on disintegration. The results are shown in Table 1.

Preparation of orally disintegrating tablets

According to "The Japanese Pharmaceutical Codex"(2002 Edition) (JP, 2002), each tablet contained PM 4 mg. The orally disintegrating tablet was prepared by wet granulation with filling agent, disintegrating agent, adhesive mixed together, and drought of powder materials at 45°C. With lubricant added, the tablet was prepared. Three batches (110901, 110902 and 110903) were prepared with the same method. The tablets were tested by the appearance, taste, rigidity, content, content uniformity, the disintegrating time and the dissolution as standard.

Appearance test

In accordance with the general requirements of the Chinese Pharmacopoeia (2010 Edition) for tablets, the present study investigated the color and smoothness of the orally disintegrating tablets.

Taste test

Six healthy volunteers were used in the present study. Their mouths were cleaned with water and the PMODT was placed in them with blind method. Good or bad taste, with or without gravel sense, easy to swallow or not, the extent and the stimulation on the oral mucosa were taken as indexes.

Hardness test

The hardness test of PMODT was done according to the requirements of the Chinese Pharmacopoeia (2010 Edition). Briefly,

3 batches of PMODT and 10 samples in each batch were selected randomly to investigate the hardness with tablet hardness tester.

Chromatographic determination

Content uniformity was tested according to Chinese Pharmacopoeia (2010 edition) XE (ChP, 2010). This was tested according to "The Japanese Pharmaceutical Codex" (2002 Edition). Chromatographic analysis was performed by a Shimadzu C18 column (4.6 mm × 150 mm, 5 μM, Shimadzu Corporation). The mobile phase consisted of methanol containing 0.05 mol·L^{-1} 1-octanesulfonic acid sodium salt solution 0.1 M: 0.1% phosphoric acid (60:40). Butyl p-hydroxybenzoate was used as internal standard. The flow rate was 1.0 ml/min and the injection volume was 3 μL. The column temperature was maintained at 30°C and the detection wavelength was 215 nm. A series of standard solutions at concentrations of 0.01, 0.02, 0.04, 0.08 and 0.16 mg/ml of PM were prepared by dissolving into PM standard substance with mobile phase. Then 3 μL of each solution was injected into high performance liquid chromatography (HPLC) for further analysis. A linear diagram was plotted by using the concentration of PM against the peak area.

Disintegration time determination

In accordance with the guidelines of State Food and Drug Administration (SFDA) published in September 2003 for the determination of the "Meeting minutes of type characteristics and quality control of orally disintegrating tablets" (Oertel and Dodel, 1995), after 6 pills were placed into 6 small beakers with 2 ml distilled water at 37 ± 0.5°C separately. The disintegration times were recorded immediately when they were fully destructible and got through the screen No. 2.

Dissolution test

Dissolution test was conducted at 50 rpm. PMODT and PM tablets were both used as the dissolution media at a volume of 500 ml at 37 ± 0.5°C. In brief, 5 ml aliquots of the dissolution media were collected and then quickly filtered through 0.45 μM membrane at 0.5, 1, 2, 4, 8, 15, 30 and 45 min. Then 20 μL of filtrate was injected into the column (as mentioned in the Chinese Pharmacopoeia (2010) (Vol II, Method 3, litter cup method) into the apparatus at a speed of 50 m/s.

RESULTS

The results of three kinds of adjuvants in hydrophobic balance test

A diagram was developed with the dosage of adjuvant as a vertical coordinate and the disintegration time as a horizontal coordinate (Figure 1I). When the amount of MCC was 10 to 15%, the influence of disintegration was slight, almost at the same levels (Figure 1Ic). However, when the dosage of MCC was more than 15% or the dosage of PVPP was 4 to 8%, the disintegration decreased with the increased dosage (Figure 1Ia and c). Moreover, when the amount of PVPK30 exceeded 2%, the disintegration time extended markedly and the disintegration decreased substantially (Figure 1Ib).

Another diagram was also developed with the ratio of (PVPP+MCC) / PVPK30 as a vertical coordinate, and the disintegration time as a horizontal coordinate. The effect of hydrophobic property on the disintegration showed a V shape. When the ratio of (PVPP+MCC)/PVPK30 was 6.5 to 9.5, the disintegration increased with the increased ratio. On the other hand, when it was 9.5 to 14.0, the disintegration decreased while the ratio increased. In addition, when the ratio was 14.0 to 23.0, its influence was slight, the trend was perfectly straight. These results showed that when the ratio of (4% PVPP + 15% MCC) / 2% PVPK30 was 9.5, there was a balance between these three accessories; other factors showed little effect and the disintegration was best.

Orthogonal test validation

The present results showed that the influence order was PVPP > PVPK30 > MCC > correction deodorant. The optimized program was $A_1B_2C_2D_3$, the amount of PVPP was 4%, the amount of MCC was 15%, the amount of PVPK30 was 2% and the amount of flavoring agent was 4%.The results of orthogonal test validation were shown in Table 2.

Quality evaluation

General quality indicators

The appearance, hardness, disintegration time, content uniformity and taste of the PMODT were in line with the relevant quality requirements for ODT. The results have been shown in Table 3.

Chromatographic determination

According to the above method, the obtained standard curve equation was y = 2.3721x+0.1002, r=0.9999, linear range was 0.01~0.16 mg·ml^{-1}. The recovery ratio of the method were 100.92 ± 0.79%, 101.22 ± 0.66% and 100.98 ± 1.12%, respectively, when the content were 0.02, 0.08 and 0.12 mg·ml^{-1}. The intra-day relative standard deviations (RSD) of large, moderate and small dosage were 1.01, 0.77 and 0.49%, respectively, while the day RSD were 1.32, 1.01 and 0.99%. With this method, the retention time of PM was 8.4 min as shown in Figure 2. The content of the three batches of PM orally disintegrating tablets were 97.96 ± 2.25, 98.69 ± 1.88 and 99.02 ± 2.12%, which were in line with the requirements of orally disintegrating tablets.

Dissolution test

The dissolution of PM orally disintegrating tablets at 1 min was 72.32 ± 1.27%; the accumulate dissolution at 4 min

Table 1. Factors and levels for orthogonal test.

Levels	Factors			
	PVPP (%)	MCC (%)	PVPK30 (%)	Correctant (%)
1	4	10	1	2
2	6	15	2	3
3	8	20	3	4

Table 2. The results of the experiments by orthogonal (n=6, $\bar{X}$ ±s).

Levels	Factors				
	A (PVPP (%))	B (MCC (%))	C (PVPK30 (%))	D (Correctant (%))	*Vitro* disintegration time (s)
1	1	1	1	1	21.3 ± 5.78
2	1	2	2	2	20.1 ± 6.23
3	1	3	3	3	28.1 ± 6.77
4	2	1	2	3	24.5 ± 5.89
5	2	2	3	1	29.2 ± 6.92
6	2	3	1	2	25.7 ± 7.23
7	3	1	3	2	34.1 ± 7.65
8	3	2	1	3	28.9 ± 6.24
9	3	3	2	1	31.1 ± 7.19
I	23.2	26.6	25.3	27.2	
II	26.5	26.1	25.2	26.6	
III	31.4	28.3	30.5	27.2	
R	8.2	2.2	5.3	0.6	

Table 3. The results of general quality examination of three batches of PMODT.

Batch number	Explore target				
	Appearance	Hardness(N)	Disintegration time(s)	Content uniformity	Mouth feel
110901	Smooth and clean	15.6	21.23 ± 1.5	7.86	Sweetness and no gritty feel
110902	Smooth and clean	16.0	22.56 ± 2.1	6.74	Sweetness and no gritty feel
110903	Smooth and clean	15.9	22.37 ± 1.8	8.23	Sweetness and no gritty feel

was 98.02 ± 0.92%. While the tablets at 1 min was 50.56 ± 1.13%, the accumulate dissolution at 4 min was 77.92 ± 0.88% and the accumulate dissolution was about 98% at 45 min. The results were shown in Figure 3.

DISCUSSION

The present study investigated the effects of dosage change of 3 adjuvants (PVPP, MCC and PVPK30) on the disintegrability of PMODT. PVPP is one of the most commonly used disintegrants; it neither dissolves in water, nor soluble in organic solvents. Prescription screening showed that PVPP-made PMODT produces better disintegration compared with other disintegrants. When MCC was used in PMODT as a disintegrating agent, it could increase the disintegration, thus enhancing the compressibility of PMODT with good acceptance due to its odorless and tasteless nature (Cui , 2008). Povidone (PVP) is one of the three pharmaceutical excipients advocated internationally, and K30 is the most commonly used model of PVP. PVPK30 (odorless and tasteless) is one of the most commonly used adhesives that can both dissolve in water and alcohol (Wang and Wang, 2010). PVPP and MCC are hydrophobic disintegrating agents, but adhesive PVPK30 is hydrophilic

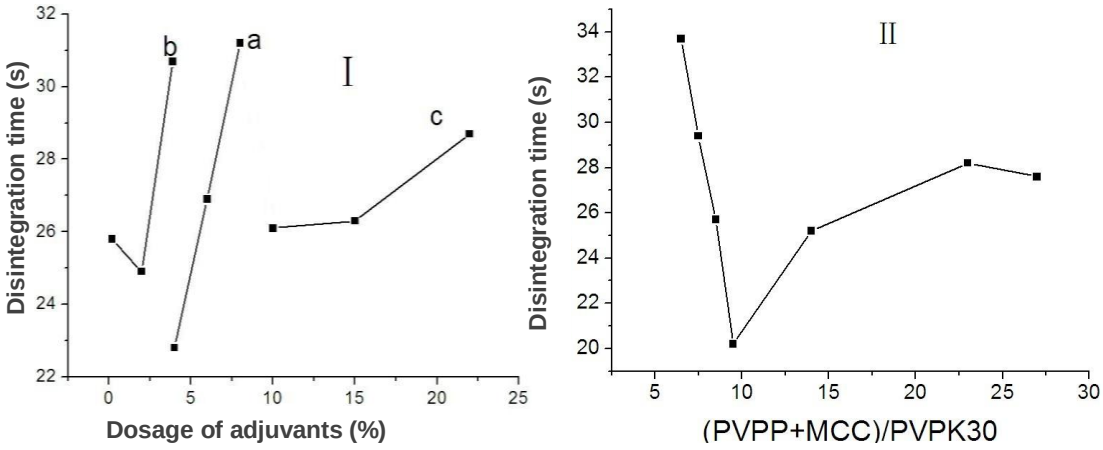

Figure 1. The relation of adjuvants and disintegration time: I, the relation of adjuvants dosage and disintegration time (a is PVPP; b is PVPK30; c is MCC) and II, the influence of discrepancy of adjuvants on disintegration time.

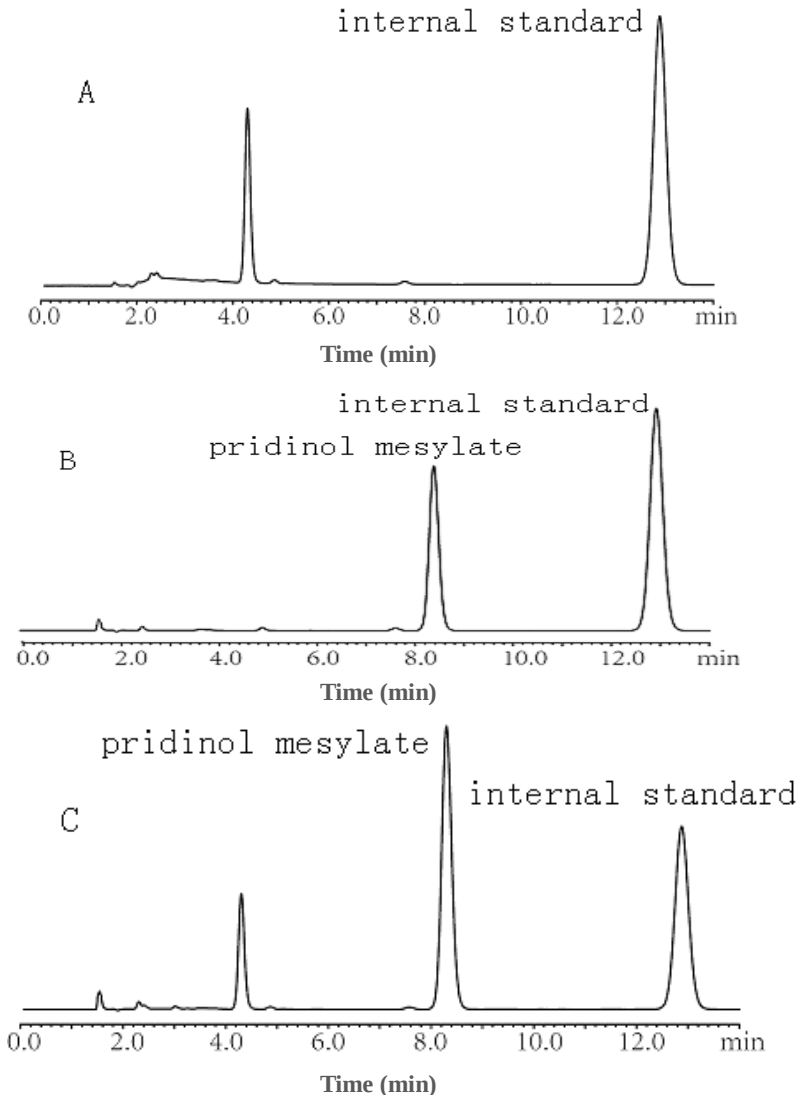

Figure 2. PM chromatogram: A , adjuvants and internal standard; B, PM reference substance and internal standard; C, PMODT and internal standard.

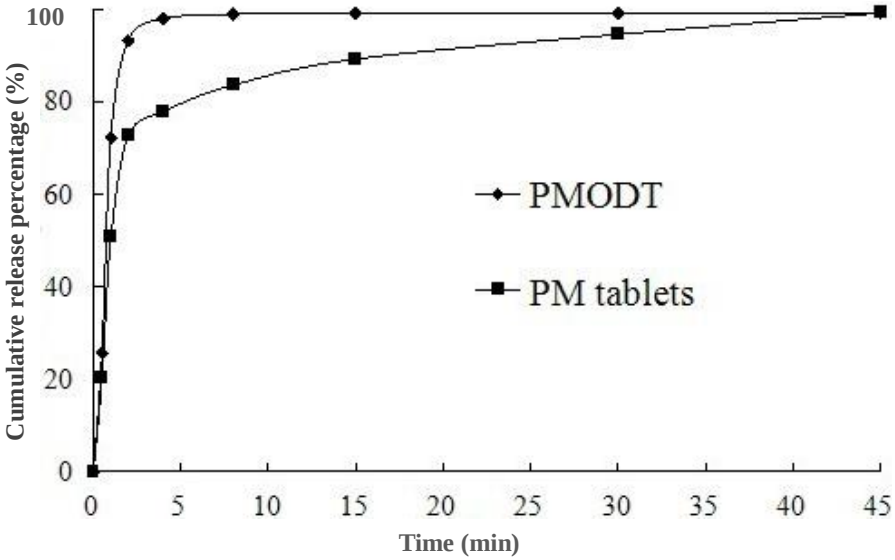

Figure 3. PMODT and PM tablets release curve.

polymers. When the dosage of (PVPP+MCC) / PVPK30 (hydrophobic/hydrophilic) achieved a certain proportion, the hydrophobicity of the three adjuvants attains a balance, and the disintegration of PMODT was best.

Besides the single adjuvant, the interaction between multiple adjuvants also has a greater impact on selecting formulation according to the Washburn equation: $V^2 = (2 * d * r * \cos\theta / k_0 G) t$ (Kanig and Rudnic, 1984), where "V" represents the amount of water penetration, "d" is the average pore size, r is the surface tension of liquid, "θ" is the contact angle of solid / liquid interface, "k_0" is the pore shape constant, "G" is the liquid viscosity, and "t" is the time. The larger the average pore (d) or the smaller the constant (k_0), the larger the amount of water penetration (V). On the other hand, the larger the surface tension of a liquid (r), the quicker the water infiltration. Moreover, the smaller the θ was, in other words the less the hydrophobic property was, the quicker the water infiltration. Additionally, the bigger the viscosity of the fluid was, the slower the water infiltration. It can be suggested that the permeation was determined by the pore, the distribution of the pore and the hydrophilic degrees of the adjuvants (Foley , 2009).

When the amount of MCC was 10 to 15%, the disintegration was less affected, almost at the same level. Within this context, the capillary action of the MCC played a dominant role; moisture was quickly induced to internal part of the tablet, which caused disintegration (Gao and Cui, 2000). Also, when the dosage of MCC was greater than 15% or the amount of PVPP was at the range of 4 to 8%, the disintegration of the tablet reduced when the dosage of MCC increased. The reason was that both PVPP and MCC are hydrophobic disintegrating agent. If the amount was more than the best critical point dosage, the water agglomerate phenomenon appears (Ren and Lu, 1999), which can block the water ingress and spread. This made the disintegration time significantly longer. In contrast, adhesive PVPK30 belonged to the hydrophilic polymers. The particle surface was more hydrophilic with the small amount. When it contacts with water molecules, it easily forms hydrogen bond that attracts water to the internal part, and thus speed up the disintegration process (Xiao et al., 2011; Wang et al., 2006). When the amount of PVPK30 was more than 2%, the tablet disintegration time was significantly prolonged, that is to say- the disintegration was significantly reduced. This was probably because the dosage of PVPK30 was beyond the best critical point; the particles bonded with each other closely. Hence, the small tablet internal pore size and the reduced porosity made the disintegration time longer (Wang and Wang, 2010; Rao et al., 2011).

In this study, we designed three formulations at the angle of hydrophobic balance. The disintegration time was (22.05±1.8) s, which was up to the requirements of FDA. The accumulate dissolution in 4 min was 98.02%, which showed more significant effect compared with the PM tablet, the dissolution of which in 30 min was required to be 80%. The other quality indicators were all in line with the relevant requirements of the orally disintegrating tablets. This was also consistent with orthogonal experiment results. Therefore, this study provides a new approach for the design and selection of a variety of materials and the pharmaceutical preparations.

Conclusion

From the perspective of the hydrophobic balance, the present study designed three kinds of excipients that possessed different hydrophobic property. When the ratio

of (PVPP+MCC) / PVPK30 (hydrophobic/hydrophilic) was 9.5, there was a hydrophobic balance; other factors showed a little effect. Therefore, the orally disintegrating tablets disintegration of our experiment was the best.

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