EXCIPIENTS

STARCH 1500®

PARTIALLY PREGELATINIZED MAIZE STARCH

Technical Data
Wet Granulation - Starch 1500®
Xiaochaihu Herbal Extract

Dual Functionality of Starch 1500® as a Binder and Disintegrant in XCH (Xiaochaihu) Herbal Extract/Powder Tablet Formula by High-Shear Wet Granulation

INTRODUCTION

XCH (Xiaochaihu) extract/powder is a medicinal herbal combination which contains radix bupleuri, rhizome pinelliae (processed with ginger), radix scutellariae, radix codonopsis, radix et rhizome glycyrrhizae, rhizome zingiberis recens and fructus jujubae. It is used for the affliction from external pathogenic factors, invasion of the Shaoyang by pathogenic factors with the symptoms of alternative chills and fever, fullness and discomfort in the chest and hypochondrium, anorexia, restlessness, proneness to vomiting, bitter taste in the mouth and dry throat.[1]

Herbal extract/powder combination has the typical property of a viscous plant extract and other properties associated with the powdered herbs and plants. Due to the high aqueous viscosity of the extract portion, preparation of XCH tablets by wet granulation using aqueous granulation fluid often results in an agglomeration of granules. Consequently, non-aqueous binder such as ethanol is more widely used in China. The powder portion of XCH compound has long fibers, poor compactibility and strong elastic recovery characteristic (Figure 1).

Figure 1 - Picture of XCH herbal extract/powder combination

OBJECTIVES

This study was aimed to demonstrate the feasibility and application of Starch 1500 in combination with MCC, in the preparation of a high dose XCH herbal extract/powder tablet (62.5% extract/powder combination content). Starch 1500 is a multi-functional excipient designed specifically for use in the formulation of pharmaceutical oral solid dosage forms. Manufactured exclusively for the global pharmaceutical market, Starch 1500 is a pharmaceutical grade of partially pregelatinized maize starch. Starch 1500 brings benefits to formulations through binding capability, improved disintegrant/dissolution properties, enhanced flow and lubricity, as well as moisture protection. The study was designed to compare the properties and performance of tablets that contain Starch 1500 and formulations that include a polymeric binder, polyvinyl pyrrolidone (PVP), in combination with a superdisintegrant. Three commonly used superdisintegrants were evaluated in the study, i.e., croscarmellose sodium (CCS), crospovidone and sodium starch glycolate (SSG). The tablets were manufactured from five different formulations using a high-shear wet granulation process. The compressed tablets were also film-coated with an Opadry® II film coating (85G 61282 - green), and tested for their performance in compliance with the Pharmacopeia of the People's Republic of China.

MATERIALS & METHODS

Materials used in the study were provided from different sources: XCH (Sichuan Jiuzhaigou Pharm, China), microcrystalline cellulose (Microcel® MC-101, Blanver, US), partially pregelatinized corn starch (Starch 1500®, Colorcon, US), polyvinyl pyrrolidone or povidone (Plasdone® 30, ISP, US), croscarmellose sodium (VIVASOL®, JRS, Germany), sodium starch glycolate (VIVASTAR®, JRS, Germany), crospovidone (Polyplasdone® XL, ISP), colloidal silicon dioxide (CSD) (Aerosil® 200, Degussa, Germany), and magnesium stearate (Huzhou Zhanwang, China). Opadry II 85G 61282 from Colorcon, China, was used as the film coating system in the study.

Colorcon®

Table 1 - Formulations of Tablets Investigated

	Formula 1		Formula 2		Formula 3		Formula 4		Formula 5	
Ingredient	**%**	**mg/tab**	**%**	**mg/tab**	**%**	**mg/tab**	**%**	**mg/tab**	**%**	**mg/tab**
XCH	62.50	250.00	62.5	235.00	62.50	250.00	62.5	250.00	62.50	250.00
MCC PH101	28.50	114.00	32.5	130.00	32.5	130.00	32.5	130.00	32.5	130.00
Starch 1500	8.00	32.00	4.0	16.00	-	-	-	-	-	-
SSG	-	-	-	-	1.00	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	1.00	-	-	-
CCS	-	-	-	-	-	-	-	-	1.00	-
Binder										
75% w/w alcohol	-	-	-	-	-	-	-	-	-	-
PVP K30 (5% solids)	-	-	-	-	1.00	4.00	1.00	4.00	1.00	4.00
Dry addition										
SSG	-	-	-	-	2.00	8.00	-	-	-	-
Crospovidone	-	-	-	-	-	-	2.00	8.00	-	-
CCS	-	-	-	-	-	-	-	-	2.00	8.00
Magnesium stearate	1.00	4.00	1.00	4.00	1.00	4.00	1.00	4.00	1.00	4.00
Total	100.00	400.00	100.00	400.00	100.00	400.00	100.00	400.00	100.00	400.00

Note: A 75% w/w hydro-alcoholic solution was used in Formula 1 & 2, while a 5% w/w of PVP in a 75% w/w hydro-alcoholic solution was used in Formula 3, 4 & 5.

Preparation of Granules and Tablets

The granulation process was carried out in a high shear granulator (HLSH2-6, BAMTRI, China). The batch size was maintained at 0.24kg for each trial. All the ingredients in the formula, except the magnesium stearate, were pre-blended for two minutes prior to the wet massing step with an impeller at a speed of 400 RPM and a chopper at a speed of 1500RPM. After the addition of the granulation fluid, the mixture was blended for additional 30 seconds. The moistened granules were sieved through a 16-mesh screen. The granulation was then dried to a target moisture content below 5%. The dried granulation was sieved through a 16-mesh screen, and further blended with the extragranular portion of superdisintegrants for one minute. The granulation was finally lubricated with magnesium stearate with one minute of blend time. The final granulation was compressed on an instrumented 8-station rotary tablet press (Rimek MINI PRESS-II, Karnavati, India) using a 10-mm shallow concave tooling. A compression profile was generated from 10 to 25 kN at a compression speed of 30 RPM.

Coating of Tablets

700 g of tablets were coated with a 20% solid contents of Opadry II 85G 61282 green dispersion on a modified conventional sugar-coating pan (300, Jiangsu Taizhou, China) with the process parameters summarized in Table 2. The tablets were coated to a theoretical weight gain of 4%.

Table 2 - Coating Process Parameters

Inlet Air Temperature	85°C
Tablet Bed Temperature	35-40°C
Spray Rate	2-3 g/min
Spray Nozzle Size	1 mm
Atomization Air Pressure	2.5 bar
Air Flow	33 m^3/hr
Pan Speed	15-20 rpm

Evaluation of Granules and Tablet Properties

Moisture content of the granulation was determined by a loss-on-drying test (LOD) using a Sartorius MA50 Moisture Tester at a temperature of 105°C. Each batch was dried to a target moisture content corresponding to the LOD value of the dry blend prior to the wet granulating step. Particle size analysis of the granules was determined by sieve analysis using an Endecotts Octagon Digital Variable Amplitude Test Sieve Shaker. The particle size of granules was determined by plotting the weight percentage above a given sieve size (on a probability scale) versus the logarithm of the sieve opening size. The geometric mean particle size and corresponding standard deviation were calculated from the linear regression curve. Bulk and tapped density was measured by a Sotax TD2 Bulk Density tester based on USP30 Method 1.

The tablet crushing strength was evaluated with a PHARMA TEST PTB-411 tablet hardness tester. The tablet friability was determined using a COPLEY TAR10 friability tester. Both uncoated and coated tablets were tested or disintegration time in distilled water and with disks according to the Chinese Pharmacopeia 2005 with a PHARMA TEST PTZ-E disintegration tester.

RESULTS & DISCUSSION

The processability of TCM tablet formulations was improved with the inclusion of binding agents. Certain degree of binding is desirable, since the binder provides enough cohesion to hold the ingredients together during compaction. However, due to the high aqueous viscosity of the plant extract portion, preparation of XCH tablet by wet granulation using aqueous granulation fluid often results in an agglomeration of granules. Consequently, non-aqueous binder such as ethanol is more widely used to avoid agglomeration in China. Povidone aqueous solution facilitates the nucleation process in the granulation step and produces granules with larger particle size than those prepared with alcohol or hydro-alcoholic solution. Nevertheless, the flow properties of all blends were similar and satisfactory with a compressibility Carr's index within a range of 16 – 19% (Table 3 and Table 4).

Table 3 - Density of Granules

Formula ID – Binder/ Disintegrant	Average Bulk Density	Average Tapped Density	Average Carr's index
	g/cc	g/cc	%
Formula 1 - Starch 1500	0.432	0.532	18.8
Formula 2 – Starch 1500	0.441	0.539	18.3
Formula 3 – PVP/SSG	0.489	0.583	16.1
Formula 4 – PVP/Crospovidone	0.475	0.569	16.5
Formula 5 – PVP/CCS	0.491	0.586	16.2

Note: A concentration of 8% Starch 1500 was used in Formula 1 and 4% in Formula 2.

Table 4 - Particle Size of Granules

Formula ID – Binder/ Disintegrant	Geometric Mean	Geometric Standard Deviation
	µm	N/A
Formula 1 - Starch 1500	250	1.61
Formula 2 – Starch 1500	244	1.66
Formula 3 – PVP/SSG	312	1.56
Formula 4 – PVP/Crospovidone	283	1.56
Formula 5 – PVP/CCS	291	1.65

Figure 2 shows comparative compression profiles of the five formulations. At all compression forces tested, PVP/superdisintegrant formulas produced tablets with similar crushing strength as Starch 1500 tablets. No significant differences were observed in the compactibility of individual formulas.

Figure 2 - Tablet Compression Profiles

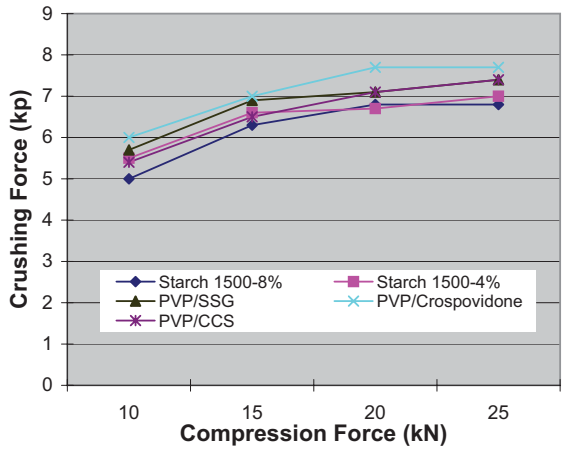


Figure 3 displays the tablet friability profiles of the products. All friability profiles of tablets were measured immediately after the compression operation was completed. While tablet samples were collected & tested, the tablet bulk from other formulations was stored in sealed containers. All tablets had similar and satisfactory friability results of less than 0.15%, and the tablets should be able to withstand the film coating and packaging operations.

Figure 3 - Tablet Friability Profiles

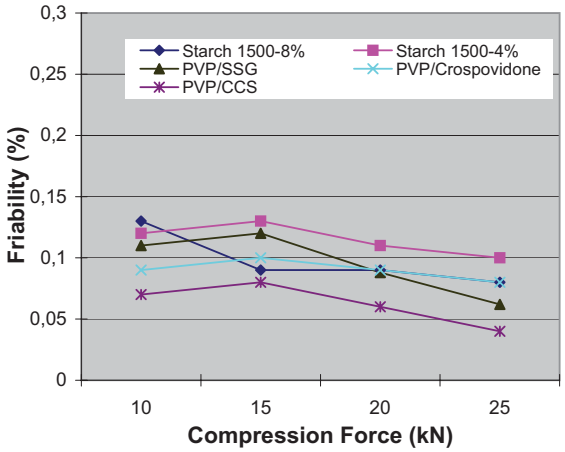


Figure 4 summarizes the disintegration properties of the five formulations. At a compression force of 10 kN, the 4% Starch 1500 formula had disintegration times that were slightly longer than the PVP/CCS and PVP/CROSPOVIDONE formula but similar to the PVP/SSG formula. At a higher compression force tested, the 4% Starch 1500 formula had a disintegration time that was slightly longer than the PVP/CCS formula, but shorter than the PVP/SSG and PVP/CROSPOVIDONE formulas. The 8% Starch 1500 formula had the shortest disintegration times among others and similar to the PVP/CCS formula. This result shows that the disintegration time could be shortened with a higher concentration of Starch 1500 in the formula. However, tablets compressed from either Formula 1 with 8% Starch 1500 or Formula 2 with 4% Starch 1500 still meet the Chinese Pharmacopeia requirement of less than 60 minutes of disintegration time.

Figure 4 - Disintegration Profiles of Uncoated Tablets

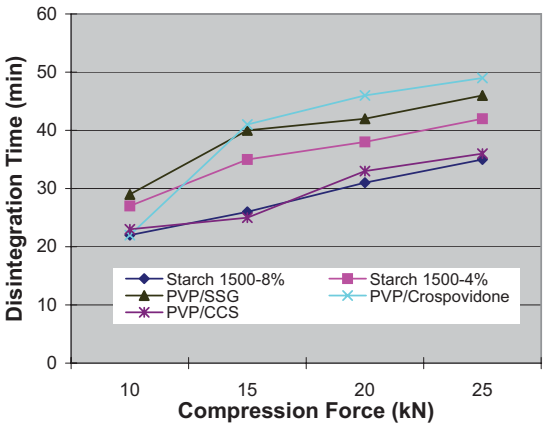


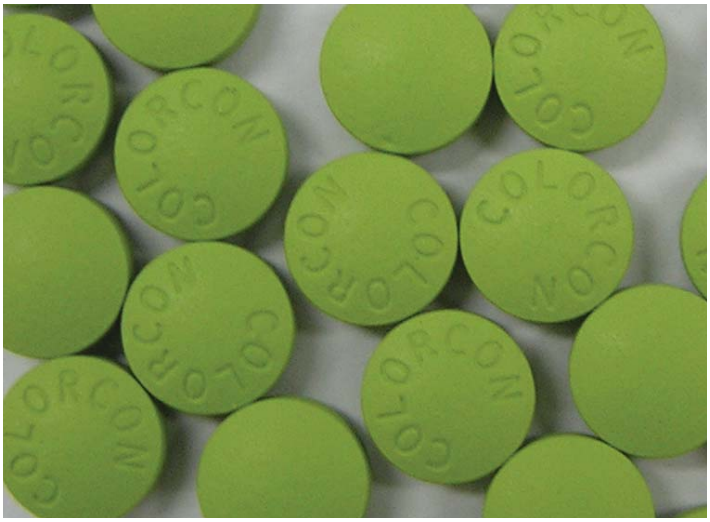
Table 5 - Tablet Properties of Formula 2 with 4% Starch 1500

Weight	400.0 mg
Thickness	5.0 mm
Hardness	6-7 kp
Friability	0.13% loss
Disintegration Time (uncoated)	35 min
Disintegration Time (coated)	38 min
Tooling: 10mm Shallow concave tooling Compression Force: 15 kN	

Starch 1500 formulas (Formula 1 and 2) used 75% w/w hydro-alcoholic solution as a granulation fluid, which could offer significant manufacturing time saving by eliminating an extra step for the preparation of polymeric binder solution. Furthermore, there was no dry addition step prior to lubrication which reduces blending time in the manufacturing process.

Starch 1500 has shown outstanding performance compared to other PVP/superdisintegrant blends investigated in this study. The use of Starch 1500 to replace the polymer/superdisintegrant combinations could significantly reduce formula costs, while ensuring excellent final product quality.

Figure 5 - Picture of XCH Film-Coated Tablets Formula 2 (4% Starch 1500) & Coated with Opadry II 85G 61282 Green



CONCLUSION

A high dose tablet formulation of XCH herbal extract/powder combination was developed and evaluated using Starch 1500/MCC in a high-shear wet granulation process. The properties and performance of the tablets were also compared to the formulas containing PVP and different commonly used superdisintegrants. The resulting tablets had similar crushing strength, friability values and disintegration time than the PVP/superdisintegrant systems. The use of Starch 1500 thus provides the advantages of reducing formula and process complexity and formula costs in comparison to the high costs of PVP/superdisintegrant systems. The disintegration time of the coated tablets has been proven similar to the uncoated tablets. The similarity between the coated and uncoated tablets indicates that the application of Opadry II 85G 61282 to the cores has no significant effect on the disintegration performance of the XCH tablets.

REFERENCE

1. Pharmacopeia of the People's Republic of China, Volume 1.

World Headquarters
Colorcon
415 Moyer Blvd., P.O. Box 24, West Point, PA 19486-0024
Tel: 215-699-7733 Fax: 215-661-2605 Website: www.colorcon.com

Locations	Telephone	Facsimile
United States		
Santa Ana, California	714-549-0631	714-549-4921
Indianapolis, Indiana	317-545-6211	317-545-6218
Humacao, Puerto Rico	787-852-3815	787-852-0030
Stoughton, Wisconsin	608-887-8970	608-887-8984
Canada		
St. Laurent, QC, Canada	514-337-8341	514-337-9159
Europe		
Dartford, Kent, England	44-1322-293000	44-1322-627200
Massy, France	33-1-6447-9750	33-1-6932-5983
Idstein, Germany	49-6126-9961-0	49-6126-9961-11
Gallarate, Italy	39-0331-776932	39-0331-776831
Budapest, Hungary	36-1-200-8000	36-1-200-8010
Istanbul, Turkey	90-216-465-0360	90-216-465-0361
Barcelona, Spain	34-9-3589-3756	34-9-3589-3792

Locations	Telephone	Facsimile
Asia/Pacific		
Singapore	65-6438-0318	65-6438-0178
Fuji-gun, Shizuoka, Japan	81-5-4465-2711	81-5-4465-2730
Shanghai, China	86-21-5442-2222	86-21-5442-2229
Goa, India	91-832-288-3434	91-832-288-3440
Gyeonggi-do, Korea	82-31-296-2173	82-31-296-2178
Latin America		
Buenos Aires, Argentina	54-11-4552-1565	54-11-4552-3997
Cotia, Brasil	55-11-4612-4262	55-11-4612-3307
Bogota, Colombia	571-418-1202	571-418-1257
Caracas, Venezuela	58-212-237-9842	58-212-238-2259
Mexico DF, Mexico	52-55-3000-5700	52-55-3000-5701 /02

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