

Development of Ultra High-Dose Formulation of Traditional-Chinese-Medicine (TCM) Extract Tablets by Fluid Bed Granulation Process

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OBJECTIVE

To demonstrate the application of Starch 1500® as a binder in a formulation containing 94% w/w TCM full extract using a fluid-bed granulation process.

INTRODUCTION

In recent years, the global market of medicinal products has witnessed significant increases in demands especially in Asia and Europe. Significant efforts have been made to modernize the traditional medicinal products into typical westernized solid dosage forms. However, the conversion of medicinal plant extracts and powders into tablets presents many challenges to formulators. Most of the TCM products require extremely high doses to be effective and the high aqueous viscosity of the herbal full extracts and the poor compactibility of powders are not favorable for the manufacture of tablet dosage forms.

In this study, BarleyGreen extract was selected as a TCM for the development of a tablet formulation. Due to the high aqueous viscosity of the full extract, organic solvents were traditionally utilized in the manufacture of BarleyGreen tablets by wet granulation to ensure an acceptable quality of the granules. Due to the serious environmental issues associated with the use of organic solvents, a water-based system has become a system of choice in pharmaceutical industry. An aqueous-based granulation fluid with Starch 1500 dispersed in a slurry was then evaluated in a fluid-bed granulation process in comparison with an aqueous solution of polyvinyl pyrrolidone (PVP). The physical properties and *in-vitro* performance of the compressed tablets were tested and compared to formulas where a PVP/ superdisintegrant was utilized. The tablets compressed from the Starch 1500 formula were also film-coated with Opadry® II 85F19250, clear and tested against the acceptance criteria described in the Chinese Pharmacopeia. The clear coating of Opadry II 85F19250 allows the visualization of the natural appearance of the BarleyGreen tablets and also provides high gloss and moisture barrier properties.

MATERIALS & METHODS

Materials Used in the Study

BarleyGreen full extract	Haerbin Huatang, China
Partially Pregel. Starch NF	
[Starch 1500]	Colorcon, US

Polyvinyl Pyrrolidone NF	
[Plasdone® 30]	ISP, US
Croscarmellose Sodium NF	
[Vivasol®]	JRS, Germany
Sodium Starch Glycolate NF	
[Vivastar®]	JRS, Germany
Crospovidone NF	
[Polyplasdone® XL]	ISP, US
*L-HPC NF	Huzhou Zhanwang, China
Colloidal Silicon Dioxide NF	
[Aerosil® 200]	Degussa, Germany
Magnesium Stearate NF	Huzhou Zhanwang, China
Opadry II 85F19250, Clear	Colorcon, China

*Note: * L-HPC: Low-substituted hydroxypropylcellulose*

Formulation/Process - Study Design

Ingredient	Formula ID		
	1	2, 3 & 4	5
Fluid-Bed Granulation			
BarleyGreen Extract	94.0%	94.0%	94.0%
Starch 1500	4.0%	---	---
Plasdone 30 (PVP)	---	2.0%	2.0%
Dry Addition			
* Polyplasdone XL (Crospovidone) or Vivastar (SSG) or Vivasol (CCS)	---	2.0%	
L-HPC			2.0%
Aerosil 200 (CSD)	1.0%	1.0%	1.0%
Magnesium Stearate NF	1.0%	1.0%	1.0%
Total:	100.0%	100.0%	100.0%

*Note: * Crospovidone in Formula 2 – Sodium starch glycolate in Formula 3 – Croscarmellose sodium in Formula 4*

Fluid-Bed Granulation:

10% w/w Starch 1500 slurry or 5% w/w aqueous solution of PVP
 STREA-1 fluid-bed processor (Niro Aeromatic Inc.)
 Top-spray - nozzle size: 0.8mm
 Atomizing air pressure: 1.0 bar (14.5 psi)
 Inlet air temperature: 55°C
 Fluid delivery rate: 10g/min

Compression:

8-station instrumented Rimek MINI PRESS II, Karnavati, India
 Compression speed: 30rpm
 Tooling: triangular-shaped punch

Film-Coating:

8% solid w/w suspension & 3% weight gain using Opadry II 85F19250, clear
 Modified conventional pan 300, Jiangsu Taizhou, China

Inlet Air Temperature: 85°C
 Tablet Bed Temperature: 38°C
 Air Flow: 33m³/hr (19.4ft³/min)
 Spray Rate: 3-5g/min
 Nozzle Size: 1mm
 Atomization Air: 2 bar (29.0 psi)
 Pan Speed: 15-20rpm

Physical Tests

Final Blend:

Loss-On-Drying (Sartorius MA50 Moisture Tester at 105°C)
 Bulk/Tapped Density (Sotax TD2 Bulk Density Tester – USP Method I)
 Particle Size Analysis (Endecotts Octagon Digital Sieve Shaker)
 Flow Properties (Pharma Test PTG-1 Powder & Granulate Testing System)

Tablets:

Weight Variation (Erweka Multicheck Tablet Tester)
 Crushing Strength (Pharma Test PTB-411 Tablet Hardness Tester)
 Friability (Copley TAR10 Friability Tester)
 Disintegration Time (Pharma Test PTZ-E Disintegration Apparatus)

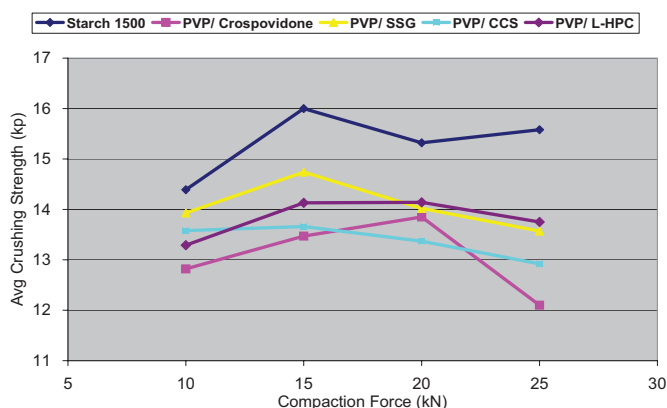
RESULTS & DISCUSSION

Properties of Final Blend

Test ID	Formula ID				
	Starch 1500	PVP/ Crospol.	PVP/ SSG	PVP/ CCS	PVP/ L-HPC
Bulk Density (g/cc)	0.35	0.30	0.31	0.30	0.30
Tapped Density (g/cc)	0.42	0.37	0.38	0.37	0.37
Carr's Index (%)	16	19	19	19	19
Angle of Repose (°)	33.2	34.8	34.0	34.5	35.1
*Flow Time (sec)	12.5	13.3	13.0	13.7	14.2
Geom. Mean Diam. (µm)	220	197	199	196	196

Note: * The time required for an amount of 100g of granulation to flow through a 10mm diameter aperture

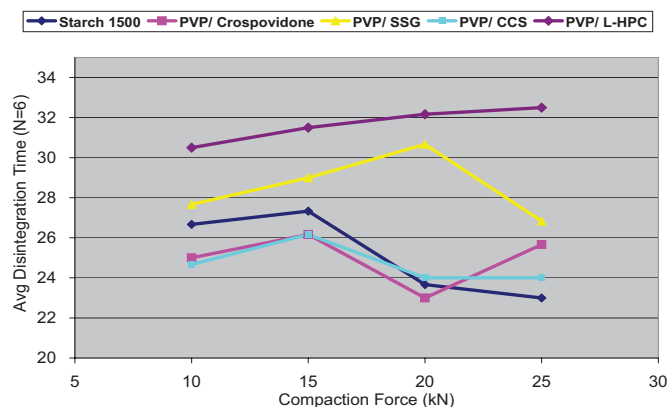
Comparative Compression Profiles of Uncoated Tablets



Granulations from all formulas had similar physical properties. Starch 1500-formula produced a slightly harder tablets than the PVP/superdisintegrant formulas.

The friability of all uncoated tablets was less than 0.1%.

Comparative Disintegration Profiles of Uncoated Tablets



Tablets from all formulas had similar disintegration time and within the specification limit of less than 60 minutes specified in the Chinese Pharmacopeia.

Properties of Starch 1500-Formula Tablets

Test ID/ Statistics	Test Results
Uncoated Tablets	
Avg Weight (N=20)	252.5mg
RSD%	2.15
Min. Weight	244.2mg
Max. Weight	260.4mg
Spread (% of the mean)	± 3.2
Avg Crushing Strength (N=10)	17kp
Friability (N=24)	0.05%
Disintegration Time (N=6)	24min. – 30min.
Avg Compression Force	15kN
Film-Coated Tablets with Opadry II 85F19250, Clear	
Disintegration Time (N=6)	30min. – 35min.

There was no significant effect of Opadry II 85F19250, clear coating on the disintegration time of the tablets.



BarleyGreen Full Extract



BarleyGreen FC Tablets

Formula Cost Estimation

Based on a general cost estimation analysis, the replacement of 2% PVP and 2% superdisintegrant with 4% Starch 1500 could reduce the excipient costs of the BarleyGreen tablet formula to 2.5 times lower than the PVP/SD formulas.

CONCLUSIONS

Tablets containing 94% w/w of BarleyGreen full extract have been successfully produced by fluid-bed granulation using an aqueous-base granulation fluid.

The commonly used PVP/superdisintegrant combination in wet granulation process can be substituted with Starch 1500 to produce tablets with good tablet hardness and disintegration properties.

The Starch 1500 tablets can be film-coated with Opadry II 85F19250, clear with no significant effect on the *in-vitro* performance of the tablets.

The use of Starch 1500 as a substitute for PVP and superdisintegrant minimizes the complexity of the formula and offers significant excipient cost reduction to the formula.

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