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Evaluation of a Partially Pregelatinized Starch in Comparison with Superdisintegrants in a Direct-Compression Hydrochlorothiazide Formulation

Charles R. Cunningham, Laura K. Scattergood
Colorcon, West Point, PA

Objectives

Corn starch has long been used as a disintegrant in oral solid dosage forms. Physical modifications of corn starch, through partial pregelatinization, have added functional benefits in terms of flowability and partial solubility, while retaining its disintegrant capability and moisture stability. The goal of this study was to compare the tablet disintegration and drug dissolution effectiveness of a partially pregelatinized starch (Starch 1500®) in comparison with various superdisintegrants in a poorly soluble, hydrochlorothiazide direct compaction applications.

Methods

Materials - Disintegrants

- Partially pregelatinized corn starch –Starch 1500®, Colorcon
- Sodium starch glycolate –Explotab®, Mendell
- Crospovidone –Polyplasdone® XL, ISP Technologies
- Crosslinked CMC –Ac-Di-Sol®, FMC

Materials - Primary Excipients

- Dicalcium phosphate dihydrate, unmille –Emcompress®, Mendell
- Lactose monohydrate spray drie –Fast Flo®, Foremost

Materials - Active

- Hydrochlorothiazide USP –Abbott Laboratories

Formulations

Six direct compression tablet formulations were prepared :

	1	2	3	4	5	6
INGREDIENT	%	%	%	%	%	%
HCTZ	25.000	25.000	25.000	25.000	25.000	25.000
Dicalcium phosphate	37.375	36.375	36.375	36.375	36.375	32.375
FF Lactose	37.375	36.375	36.375	36.375	36.375	32.375
Starch 1500		2.000				10.000
Crosslinked CMC			2.000			
Crospovidone				2.000		
Sodium starch glycolate					2.000	
Mg Stearate	0.250	0.250	0.250	0.250	0.250	0.250
Total %	100.0	100.0	100.0	100.0	100.0	100.0

For each batch, all ingredients except magnesium stearate were blended together in a twin-shell

Compaction

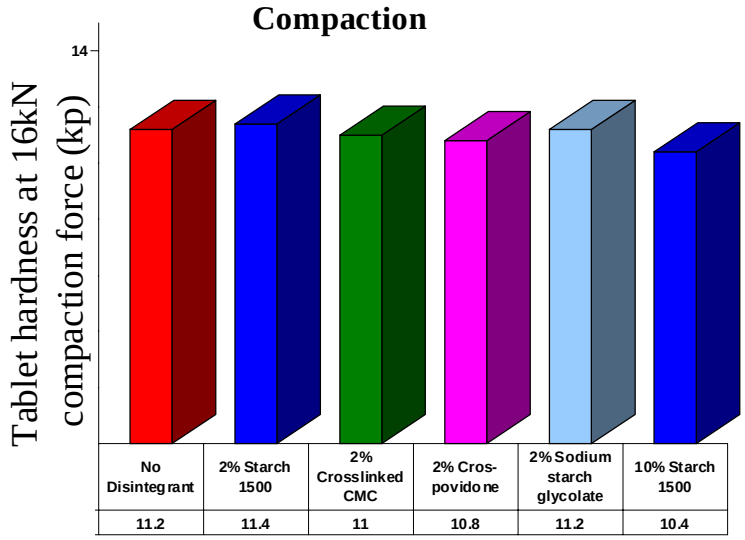
The tablets were compressed using a 10 station instrumented Piccola rotary tablet press using size B, 5/16" flat-faced beveled edge tooling.

The target tablet weight was 200mg (50mg hydrochlorothiazide).

Moisture-Uptake Isotherms

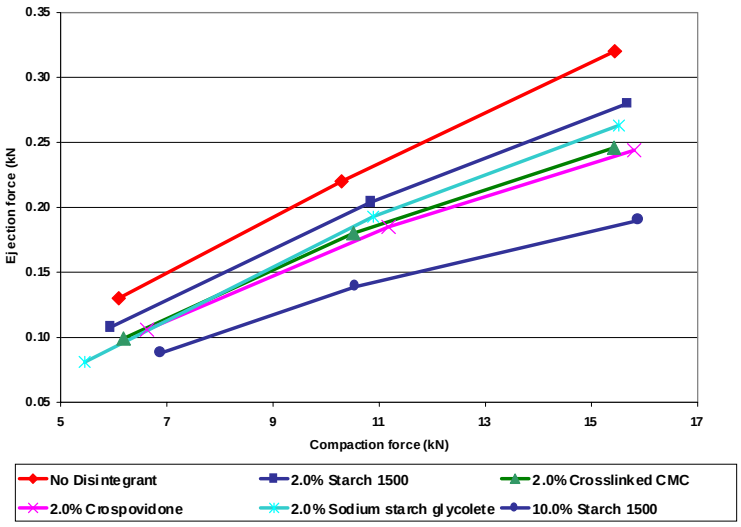
Moisture-uptake isotherms were conducted on each of the disintegrant powders using a VTI Corporation SGA-100 Symmetrical Gravimetric Analyzer. This is a continuous gas flow adsorption instrument for obtaining water vapor isotherms at temperatures ranging from 0° to 80° C at ambient pressure. The instrument temperature was controlled at 25°C for this study. In addition to the disintegrant powder testing, this instrument was used to test final tablet samples from each of the formulations with 2.0% disintegrant.

RESULTS



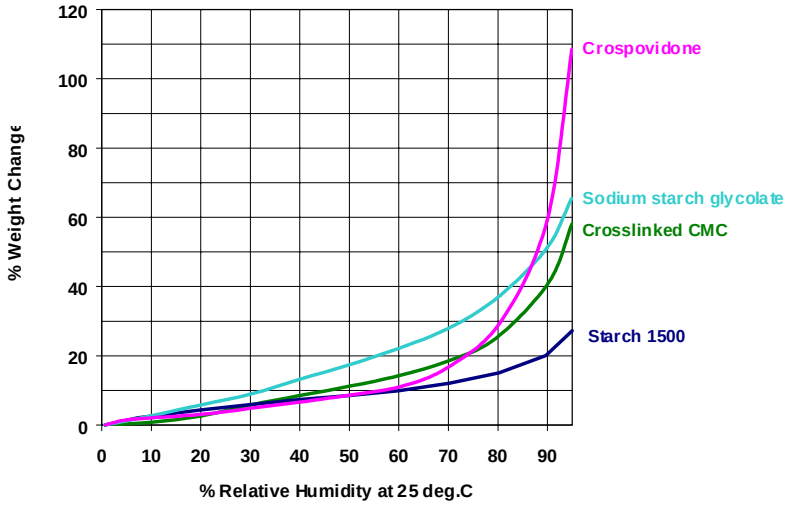
The tablet hardness at each compaction force was measured using a Schleuniger tablet hardness tester. No significant differences in the compactibility of the individual blends were seen.

Ejection Force Profiles



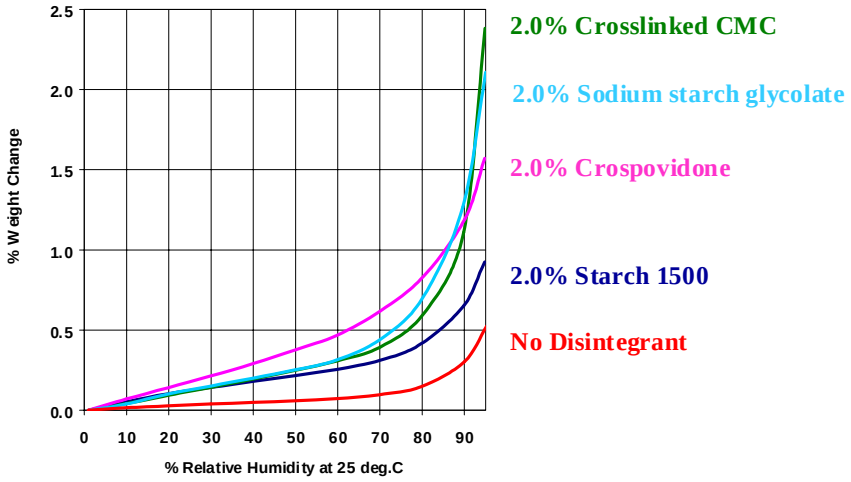
The control formulation with no disintegrant exhibited the highest ejection force profile. All other disintegrants at a 2.0% usage level provided a similar lowering of ejection force values while the batch containing 10.0% Starch 1500 provided a substantial decrease in ejection forces when compared to the control batch.

Moisture-Uptake Isotherms - Powders



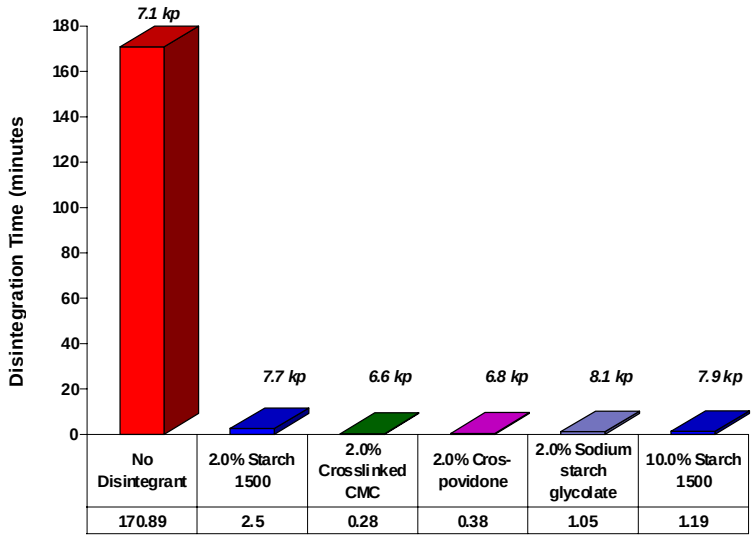
Moisture-uptake isotherm data showed significantly higher moisture uptake for the superdisintegrant powders in comparison with the Starch 1500.

Moisture-Uptake Isotherms - Tablets



Isotherm data for the individual tablets also show significant differences even though the disintegrants were only present at a 2.0% level. The tablet containing 2.0% crosslinked CMC showed 2.5 times the weight increase compared to the tablets with 2.0% Starch 1500.

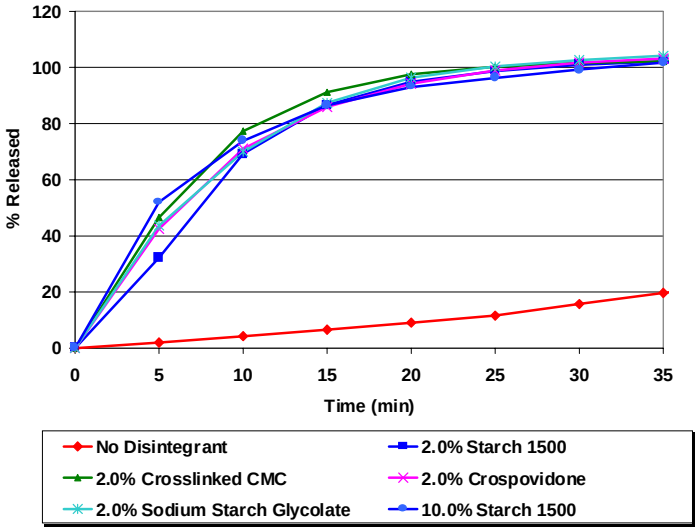
Disintegration Results



*Tablet hardness values

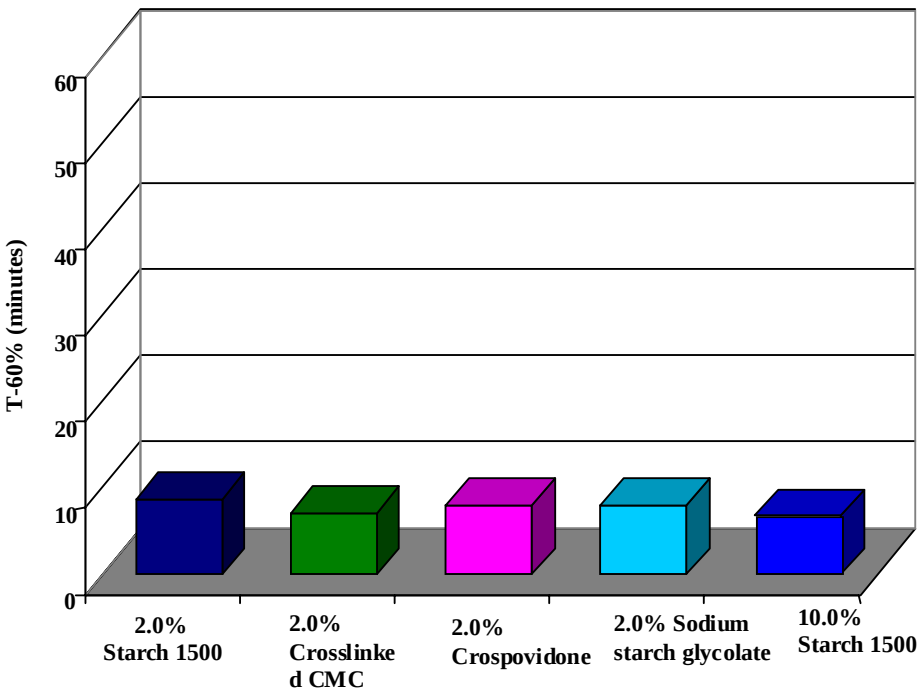
Tablets of comparable hardness (7-8 kp) were selected for disintegration testing. The effect of all the disintegrants was substantial. The disintegration time in 37°C DI water for the control batch with no disintegrant was 170.8 minutes compared to all other tablets disintegrating in 2.5 minutes or less.

Dissolution Results



Dissolution for the control batch with no disintegrant was very slow with only 20% drug released in 35 minutes. At the 5-minute time point, the tablets with 2.0% Starch 1500 released 30% of the drug compared with 40 to 50 % released for the tablets containing the other disintegrants. At 10 minutes, batches released between 70 and 78% including the batch with 2.0% Starch 1500.

Dissolution T-60% Released



The USP requirement for hydrochlorothiazide tablets is that not less than 60% drug be released in 60 minutes. All tablet samples with disintegrant met T-60% in less than 10 minutes. Dissolution was fastest for the batch with 10% Starch 1500 with a T-60% of 7.0 minutes. All other batches met a T-60% in under 10 minutes.

The control batch was not charted as it only released 30% drug in 60 minutes.

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