MAIZE STARCH AND SUPERDISINTEGRANTS IN A DIRECT-COMPRESSION FORMULATION

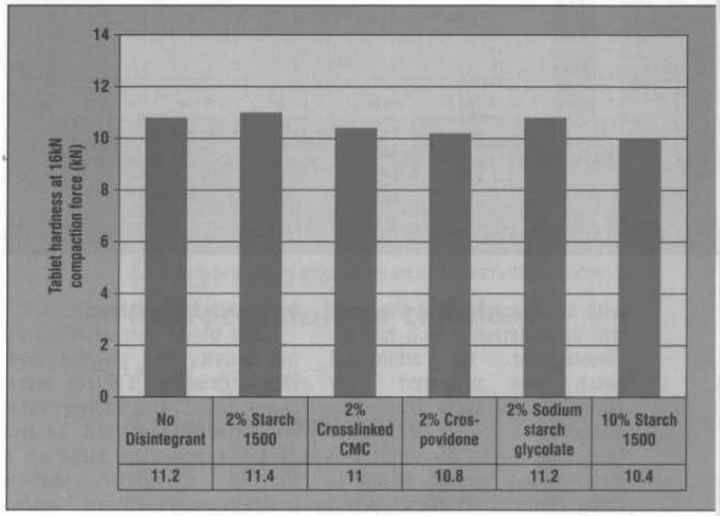
THIS ARTICLE DESCRIBES A STUDY OF THE DISINTEGRATION PROPERTIES OF A PARTIALLY PREGELATINISED MAIZE STARCH AND COMPARES ITS EFFECTIVENESS WITH VARIOUS SUPERDISINTEGRANTS IN A DIRECT COMPACTION HYDROCHLOROTHIAZIDE FORMULATION.

Maize starch has a long history of use as a disintegrant in oral solid dosage forms. Physical modifications of maize starch, through partial pregelatinisation, have increased the functional benefit of maize starch in terms of flowability and solubility, while retaining disintegrant capability and moisture stability.

While newer superdisintegrants have demonstrated improved disintegration and dissolution functionality over traditional starch disintegrants, they can also be associated with tablet stability problems related to moisture uptake. Superdisintegrants function primarily by drawing large amounts of water into the tablet and simultaneously swelling. It is this great affinity for water that can impact the stability of moisture-sensitive materials under accelerated storage conditions.

These materials have also been implicated in poor film coating quality when used at higher-than-recommended levels in the formulation. The rapid uptake of water by superdisintegrant particles on the surface of the tablet core can cause premature swelling of the particles during the aqueous film-coating process. These rapidly swelling particles result in the formation of craters in the tablet surface that impact the visual and mechanical quality of the applied film. In addition to core surface erosion, it was shown by Peck et al.,[1] that moisture penetration was not limited to the tablet surface alone but was drawn through the core by capillary forces and intra- and interparticulate wicking of the superdisintegrant particles.

Although a partially pregelatinised starch may have to be used at a higher level in a formulation to obtain the comparable disintegration time, additional benefits such as improvements in powder flow, compactibility, moisture stability and reduced formulation cost may be realised. It has also been reported by Shangraw et al.[2] that the disintegrant characteristics of partially pregelatinised maize starch are unaffected by pH, while the swelling characteristics of anionic crosslinked starches and celluloses may be altered in acidic media. It was further shown by Brzecko and Augsburger[3] that the disintegrant performance of partially pregelatinised maize starch in a hydrochlorothiazide tablet was generally unaffected at accelerated storage conditions up to 50 weeks.



△FIG 1. TABLET HARDNESS RESULTS.

PREGELATINISED STARCH COMPARED WITH SUPERDISINTEGRANTS

The aim of this work was to study the disintegration properties of a partially pregelatinised maize starch and compare its effectiveness with various superdisintegrants in a direct compaction hydrochlorothiazide formulation. Hydrochlorothiazide (from Abbott Laboratories) was chosen as the model drug due to its relative insolubility in water and its poor dissolution characteristics. It has also been cited in many publications on dissolution and disintegration. The propensity for moisture uptake of each of the disintegrants was examined, both as individual powders as well as their contribution to moisture uptake in the final tablet sample. Included in the study was the examination of other tablet quality attributes such as the effect of the disintegrants on tablet hardness, friability and dissolution. A further goal was to determine at what level in the formulation would the partially pregelatinised maize starch provide the equivalent disintegrant times as the other disintegrants.

TABLE 1. FORMULATIONS USED IN THE DISINTEGRATION COMPARISONS.

Formulation	1	2	3	4	5	6
Ingredient	%	%	%	%	%	%
HCTZ	25.0	25.0	25.0	25.0	25.0	25.0
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		2.0				10.0
Crosslinked CMC			2.0			
Crospovidone				2.0		
Sodium starch glycolate					2.0	
Magnesium stearate	0.25	0.25	0.25	0.25	0.25	0.25
Total %	100.0	100.0	100.0	100.0	100.0	100.0

EVALUATION METHODS FOR THE COMPARISON

Six direct-compression formulations were prepared for the study. The disintegrants evaluated were partially pregelatinised maize starch (Starch 1500®, Colorcon), sodium starch glycolate (Explotab®, Mendell), crospovidone (Polyplasdone® XL, ISP Technologies) and crosslinked CMC (Ac-Di-Sol®, FMC).

Hydrochlorothiazide was present at 25.0% (w/w) of all formulations. Each of the four disintegrants was added to a formulation at a 2.0% level

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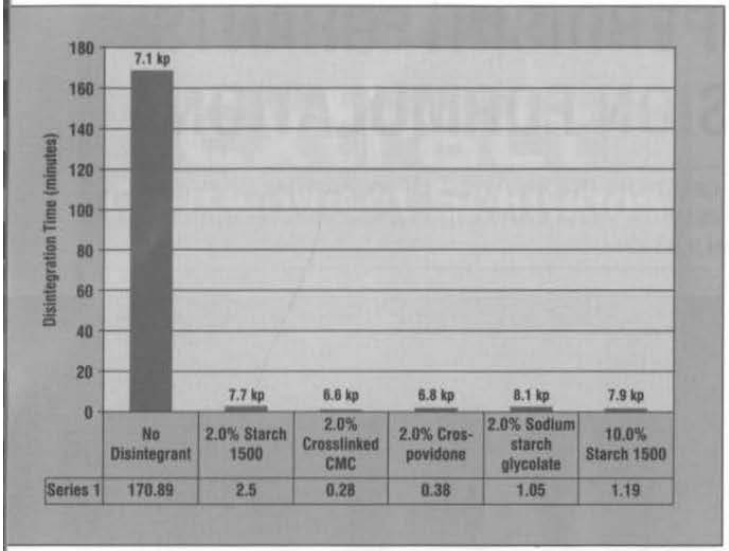

△ FIG 2. DISINTEGRATION RESULTS.

with the exception of the control formulation which had no disintegrant. An additional batch was prepared with 10.0% Starch 1500. Dicalcium phosphate dihydrate (Emcompress®, Mendell) and spray dried lactose monohydrate (Foremost) made up the remainder of the formulation at a 50:50 ratio (qs). Magnesium stearate at 0.25% was present in each formulation as the lubricant (Table 1).

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 vapour isotherms at temperatures ranging from 0 to 80°C at ambient pressure. The instrument was controlled at 25°C for this study. In addition to the disintegrant powder testing, this instrument was used to test the final tablet samples from each formulation.

Each blend was also tested for density and powder flow characteristics. Tablets were compressed to 200mg total weight at 6, 8, 10, 12, 14 and 16 kN compaction force on a Piccola (Riva)-10 station instrumented rotary tablet press. The tooling used was 5/16 inch flat-faced beveled edge. Tablet samples at each compaction force were tested for hardness, weight variation, thickness, disintegration time, and USP 23 dissolution for hydrochlorothiazide.

DISSOLUTION AND MOISTURE-UPTAKE TESTING

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. At 16kN of compaction force, the tablet hardness values ranged from 10.4 to 11.4kp. The formulation with 2.0% Starch 1500 produced the hardest tablets at 11.4kp (Fig 1).

Tablets of comparable hardness (7-8kp) were selected for disintegration, dissolution and moisture-uptake testing. The disintegration time in 37°C water for the control batch with no disintegrant was 170.8 minutes. The tablets containing 2.0% Starch 1500 disintegrated in 2.5 minutes, and the tablets containing crosslinked CMC and crospovidone had disintegration times of less than 1 minute. The tablets containing 2.0% sodium starch glycolate and 10% Starch 1500 disintegrated in about 1.0 minute (Fig 2).

Dissolution for the control batch with no disintegrant was very slow with only 20% 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 was fastest for the batch with 10% Starch 1500 with a T60% of 7.0 minutes. All other batches met a T60% in less than 10 minutes.

Moisture uptake isotherm data showed significantly higher moisture uptake for the superdisintegrant powders in comparison with the starch. Isotherms on the individual tablets also showed 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 batch with 2.0% Starch 1500.

PREGELATINIZED STARCH PERFORMED AS EFFECTIVELY AS THE SUPERDISINTEGRANTS

In this direct-compression hydrochlorothiazide formulation, the use of partially pregelatinised starch performed as effectively as the superdisintegrants, and due to its low propensity for moisture uptake may afford superior moisture stability to similar formulations. Although the use of superdisintegrants may be necessary in some formulations, the inclusion of Starch 1500 may allow for a reduction in superdisintegrant levels while avoiding potential stability problems. Additionally, the improved flow and tabletting characteristics of partially pregelatinised starch can impart further benefit to the formulation in terms of aqueous film-coating quality.

REFERENCES

1. Peck et al. *Pharmaceutical Production Tech Source*, October 1999.
2. Shangraw, R.F., Mitrevej, A. and Shah, M. *Pharmaceutical Technology*, **4(10)**, 49 (1980)
3. Brzecko and Augsburger, AAPS 2nd National Meeting, Boston, USA, June 1987.

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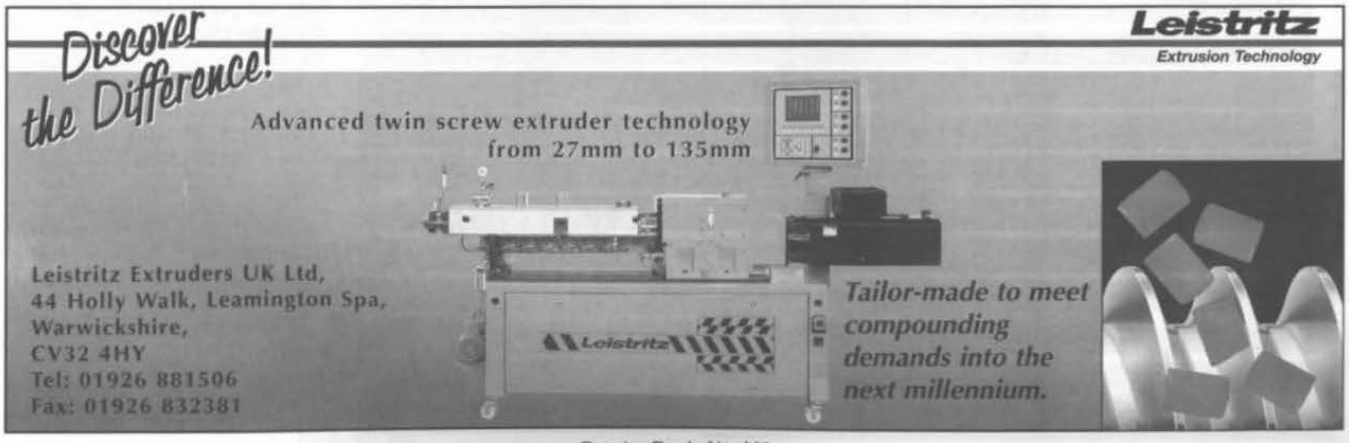

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