

Use of Starch 1500[®], Partially Pregelatinized Maize Starch, to Improve the Uniformity of a Low Dose Direct Compression Chlorpheniramine Formulation

OBJECTIVES

Wet granulation has typically been used when preparing low dose formulations to ensure homogeneity of the drug substance. Direct compression methods can offer a simplified and more economical process if drug uniformity can be assured. This study examines the effect of Starch 1500 as an agent for pre-blending a low dose active to ensure good uniformity in a direct compression chlorpheniramine maleate (4mg) formulation.

METHODOLOGY

Materials

Chlorpheniramine maleate U.S.P. (CPM)

Kongo Chemical Company Ltd.

Partially pregelatinized maize starch

Starch 1500, Colorcon

Lactose monohydrate spray dried

Fast Flo, Foremost

Microcrystalline Cellulose

Emcocel 50 M, Penwest

Magnesium stearate N.F.

HyQual, Mallinckrodt

Stearic acid N.F.

Purified vegetable grade powder, Oleotec Ltd.

Fumed silica

Cabosil, Cabot Corp.

Formulations

Chlorpheniramine was used at 2.7% (w/w) in all formulations. Starch 1500, lactose, and microcrystalline cellulose were used in combination as diluents at a 94.3% level in each of the formulations.

All formulations included 0.75% fumed silica as a glidant and 0.25% magnesium stearate and 2.0% stearic acid as the lubricants.

Table 1.

Ingredients	Percentages					
CPM	2.70	2.70	2.70	2.70	2.70	2.70
Lactose	47.15	47.15	47.15			47.15
MCC	47.15		47.15	47.15	47.15	
Starch 1500		47.15		47.15	47.15	47.15
Cabosil	0.75	0.75	0.75	0.75	0.75	0.75
Stearic Acid	2.00	2.00	2.00	2.00	2.00	2.00
Mg Stearate	0.25	0.25	0.25	0.25	0.25	0.25
Total	100.00	100.00	100.00	100.00	100.00	100.00

The excipient used to pre-blend the CPM for each batch is denoted in RED.

Blending:

Blending was carried out in a twin shell blender. Each of the primary excipients was used alone to preblend the chlorpheniramine for 5 minutes prior to the addition of the remaining excipients. Upon addition of the remaining excipients, blending continued for 10 minutes. Magnesium stearate was then added and blended with each batch for an additional 5 minutes.

Compaction:

The powder blends were tableted on a 10 station rotary tablet press using 5/16" flat-faced beveled edge tooling. The tablet weight was 150mg. Tablet samples were taken at the beginning, middle and end of each batch.

Assay and Content Uniformity:

Assay and content uniformity testing was conducted for Chlorpheniramine Maleate according to U.S.P. 23

RESULTS

Figure 1. Lactose as the Pre-Blend Excipient

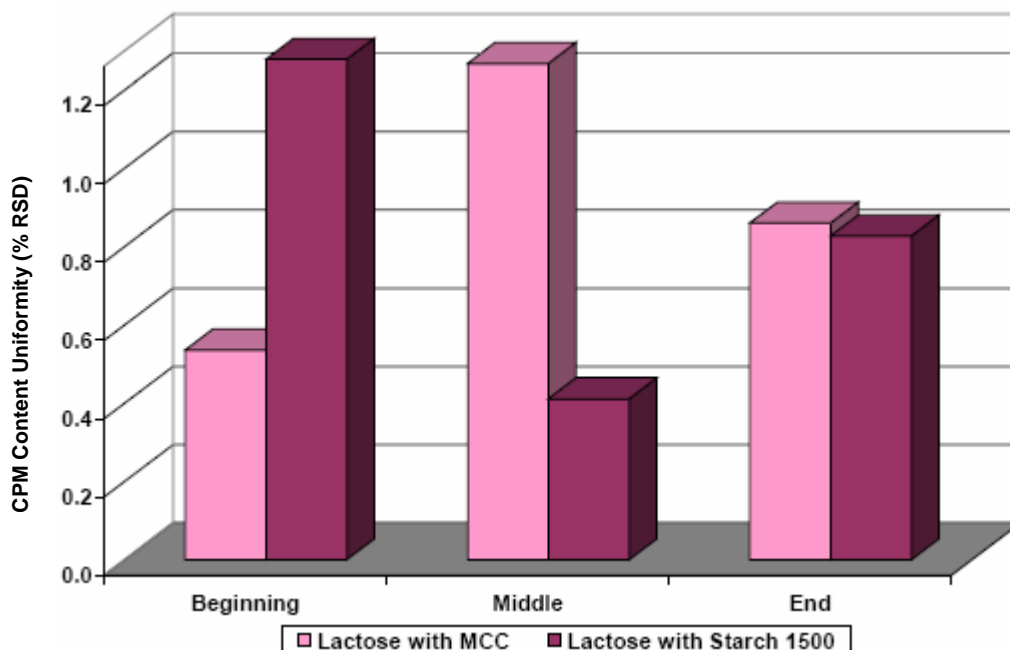


Figure 2. Microcrystalline Cellulose as the Pre-Blend Excipient

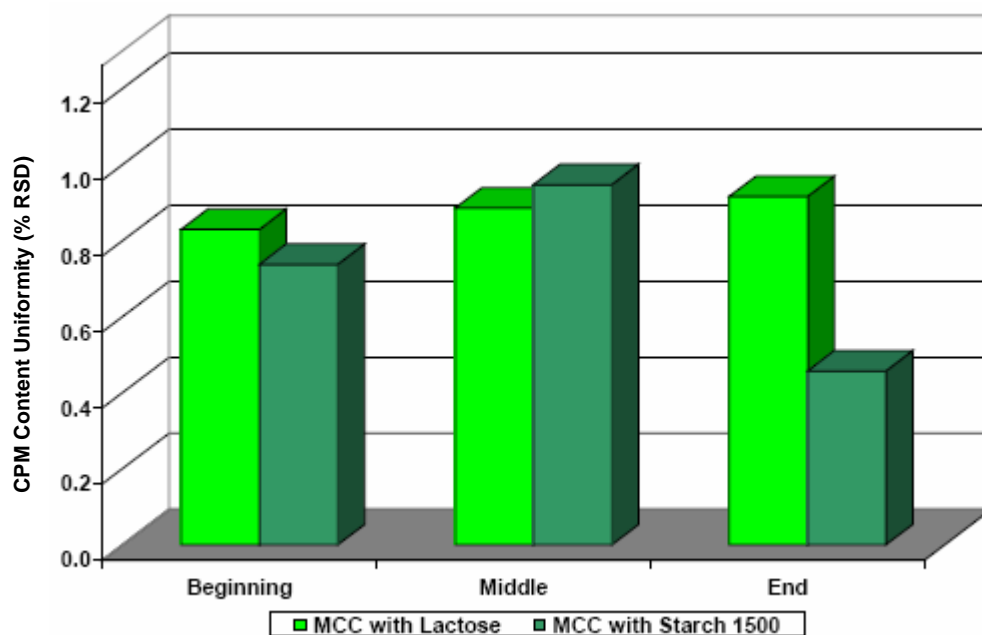
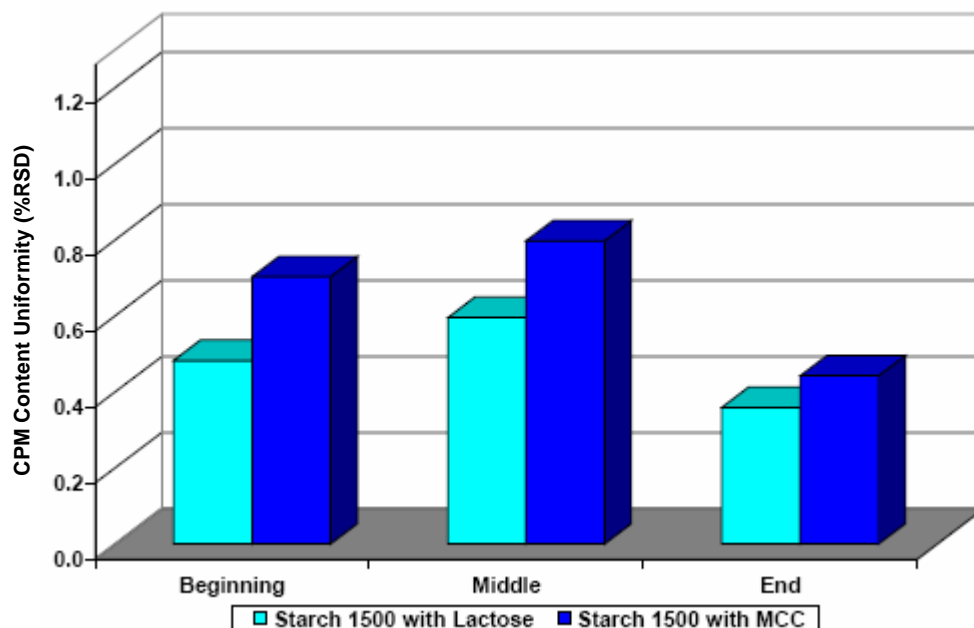


Figure 3. Starch 1500 as the Pre-Blend Excipient



Comparing the uniformity of CPM tablets collected from the beginning, middle, and end of the tableting run, the use of lactose as the excipient / drug pre-blend resulted in the highest overall relative standard deviations.

Batches with microcrystalline cellulose as the pre-blend had lower deviation both tablet to tablet or across the whole batch when compared to lactose.

Starch 1500, when used as the pre-blend excipient, showed the lowest relative standard deviations when compared to either lactose or MCC.

Confirmatory Trial:

A final formulation was developed with a slightly increased level of Starch 1500 to be used as the pre-blend along with MCC as the secondary filler.

Table 2. Final Formulation

Ingredients	Percent (w/w)
Chlorpheniramine maleate	2.70
Starch 1500	50.00
Microcrystalline cellulose	44.30
Stearic acid	2.00
Fumed silica	0.75
Magnesium stearate	0.25
Total	100.00

Figure 4. Chlorpheniramine Assay Results

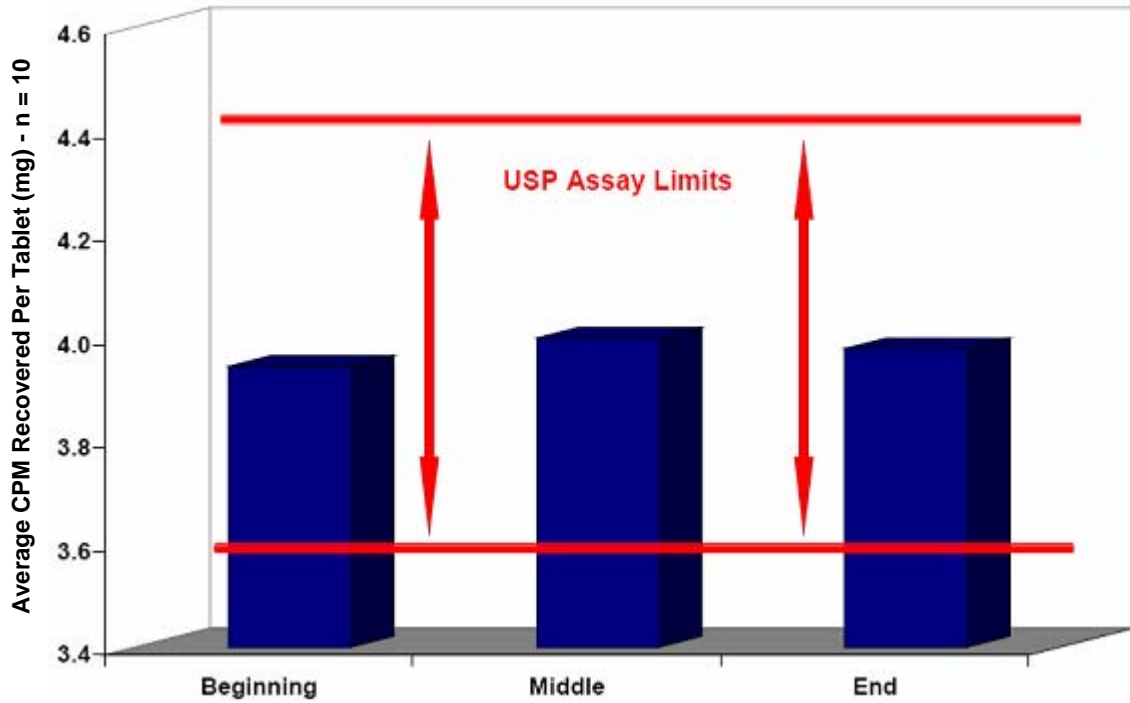
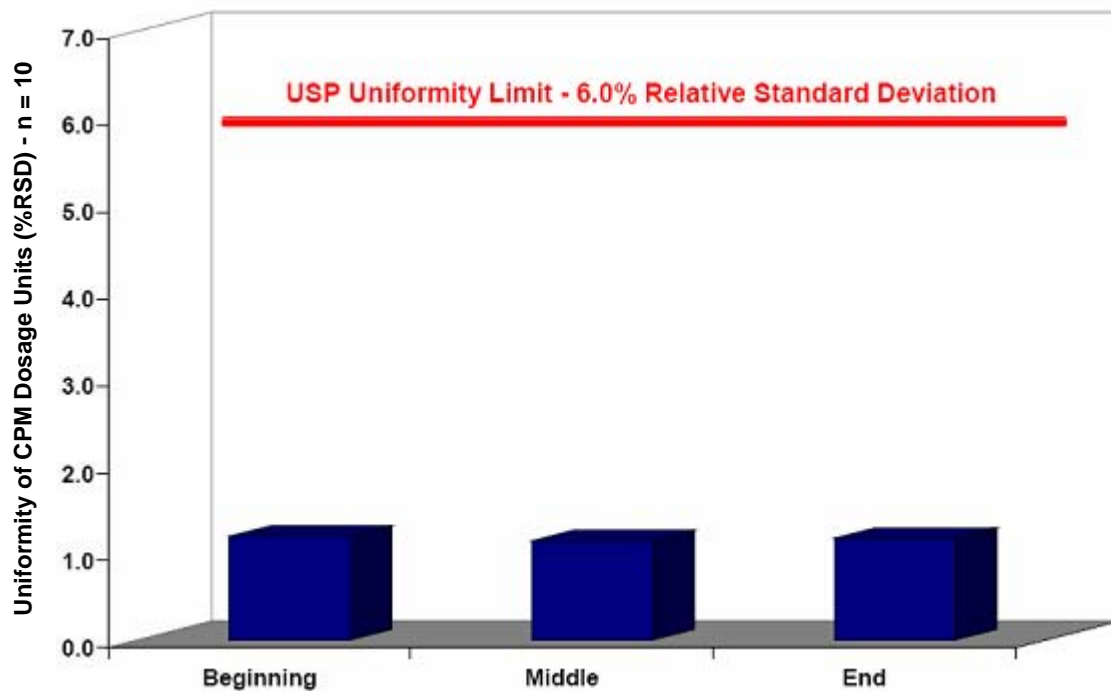


Figure 5. Chlorpheniramine Uniformity Results



Starch 1500, when used as the pre-blend excipient, and combined with microcrystalline cellulose provided for drug assay and uniformity results that were well below the USP limits and showed little or no variation throughout the course of the tableting run.

CONCLUSIONS

Starch 1500 was successfully used to uniformly disperse the chlorpheniramine and enable a switch to a more economical direct compression process from wet granulation.

The sphero-granular morphology of Starch 1500 may contribute to enhanced particle to particle homogeneity. Further studies will examine the specific properties of Starch 1500 and their contribution to enhancing the uniformity of low dose actives in direct compression formulations.

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