EXCIPIENTS

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Optimizing Lubricant Usage in a Direct Compression Hydrochlorothiazide Formulation Containing a Plastically Deforming Excipient

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OBJECTIVES

Examine the effect of magnesium stearate on the properties of a direct compression hydrochlorothiazide formulation.

To develop a robust formulation which benefits from the addition of a plastically deforming excipient while avoiding potentially detrimental lubricant effects.

Assess the effects of the lubricants on powder flowability, tablet ejection forces, tablet hardness, dissolution, and coated tablet film adhesion.

Investigate the use of stearic acid as a potential alternative to magnesium stearate in this formulation.

Starch 1500® (partially pregelatinized corn starch), used in this formulation as a flow aid and disintegrant, is an example of a plastically deforming excipient which may exhibit sensitivity to high lubricant levels. Microcrystalline cellulose, another plastically deforming excipient, was also included in the study.

METHODOLOGY

Materials

- Hydrochlorothiazide USP (HCTZ)
  Abbott Laboratories
- Partially pregelatinized corn starch
  Starch 1500®, Colorcon
- Dicalcium phosphate dihydrate, unmilled
  Di-Tab®, Rhodia
- Lactose monohydrate spray dried
  Fast Flo®, Foremost
- Microcrystalline cellulose
  Emcocel® 50M, Penwest
- Magnesium stearate N.F.
  HyQual ®, Mallinckro
- Stearic acid N.F.
  Purified vegetable grade powder, Oleotec Ltd.

Formulations Tested

INGREDIENTS	PERCENTAGES						
HCTZ	25.000	25.000	25.000	25.000	25.000	25.000	25.000
Dicalcium phosphate	33.375	33.250	33.125	33.000	33.375	33.000	33.000
Lactose	33.375	33.250	33.125	33.000	33.375	33.000	33.000
MCC					8.00	8.00	
Starch 1500	8.00	8.00	8.00	8.00			8.00
Stearic acid							1.00
Mg stearate	0.25	0.50	0.75	1.00	0.25	1.00	
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

All ingredients except magnesium stearate were blended together in a "V"-blender for 15 minutes. The magnesium stearate was then added and blended for an additional 5 minutes.

Compaction

The tablets were compressed using a 10 station instrumented Piccola (*Riva*) rotary tablet press using size B, 5/16" flat-faced beveled edge tooling. Compaction and ejection force data were acquired using Director™ software (*SMI Inc.*). The target tablet weight was 200mg (50mg hydrochlorothiazide).

Tablet Hardness Testing

Tablet breaking force was determined using a Multicheck (*Erweka Instrument Inc.*) tablet tester.

Powder Flowability

Each of the powder blends was tested using an Erweka GDT funnel type flow testing apparatus. A constant amplitude vibratory device was employed for all tests.

Dissolution Methodology

USP method 219.990. Apparatus I (baskets)
Media: 0.1N HCL
Q (pass) = N.L.T. 60% dissolved in 60 minutes

Colorcon

Film Adhesion

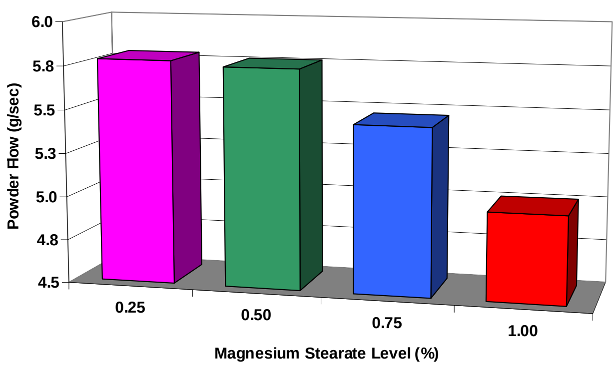
Tablets from four of the batches were coated to a 3.0% weight gain with Opadry® YS-1-10547A.

Film adhesion measurements were conducted using a Lloyds materials tester EZ L1000R (Lloyds Instruments Ltd.).

RESULTS

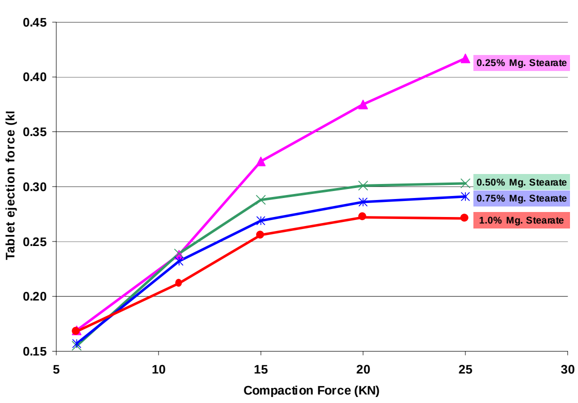
Starch 1500/Magnesium Stearate

Effect of Magnesium Stearate on Powder Flowability



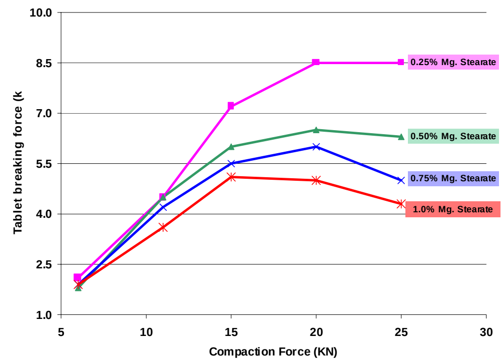
Contrary to the expectation that increasing lubricant levels would improve flowability, the opposite was observed. Under vibratory conditions, the increased lubricant level may have been responsible for a reduction in interparticulate friction. This resulted in closer particle packing and densification, thus impeding the flow of powder through the funnel orifice.

Effect of Magnesium Stearate on Ejection Forces



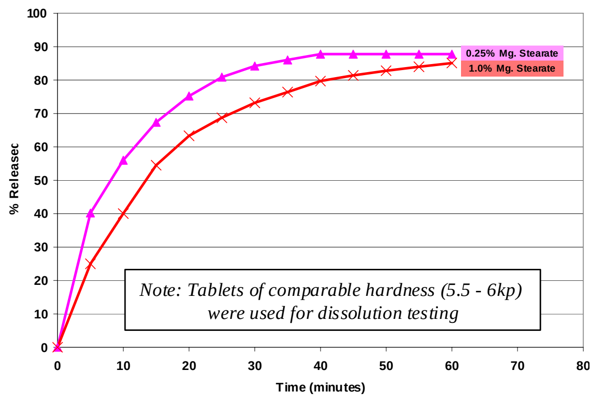
The primary function of a lubricant is to ensure that tablets will eject cleanly, with minimal stress, from the die at high speeds. The data show that in this formulation, increasing the magnesium stearate level past 0.5% had very little incremental effect in further reducing ejection forces.

Effect of Magnesium Stearate on Tablet Hardness



The effect of increasing magnesium stearate levels had a profound effect on tablet hardness. At levels over 0.25%, significant tablet softening occurred.

Effect of Magnesium Stearate on Dissolution

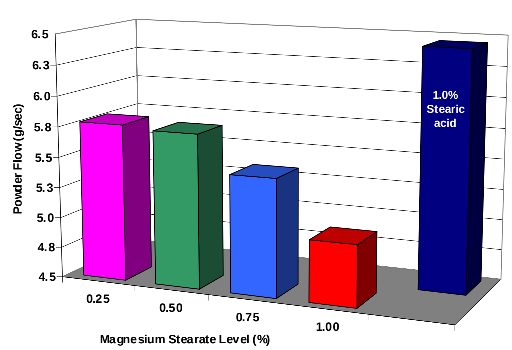


Comparison of the dissolution profiles shows a slight slowing of dissolution at the higher magnesium stearate level.

Starch 1500/Stearic Acid

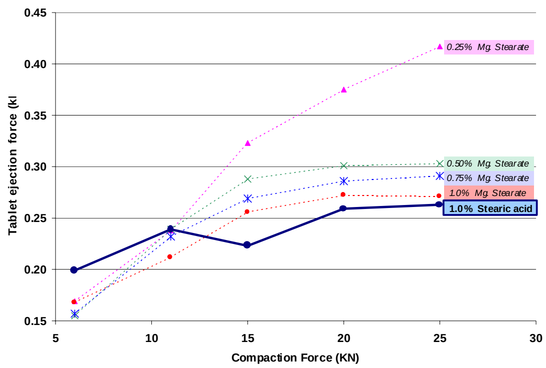
As an alternative to magnesium stearate, stearic acid was evaluated as a lubricant at a 1.0% usage level.

Effect of Stearic Acid on Powder Flowability



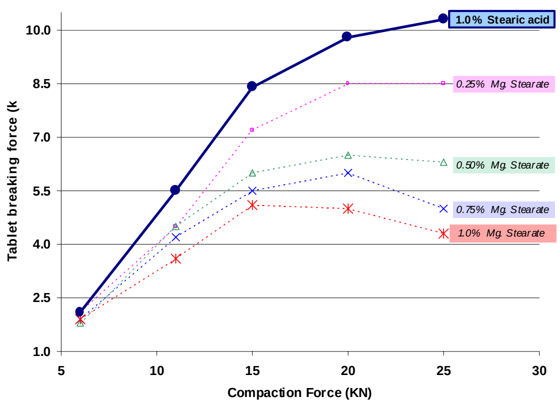
The flowability of the powder blend was improved compared to the previous batches containing magnesium stearate.

Effect of Stearic Acid on Tablet Ejection Forces



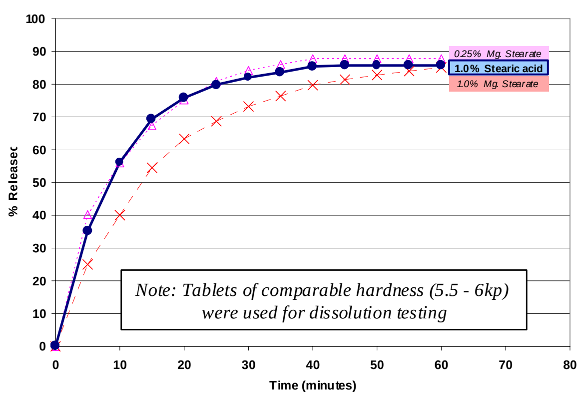
Overall, ejection force values were actually lower when 1.0% magnesium stearate was replaced with 1.0% stearic acid.

Effect of Stearic Acid on Tablet Hardness



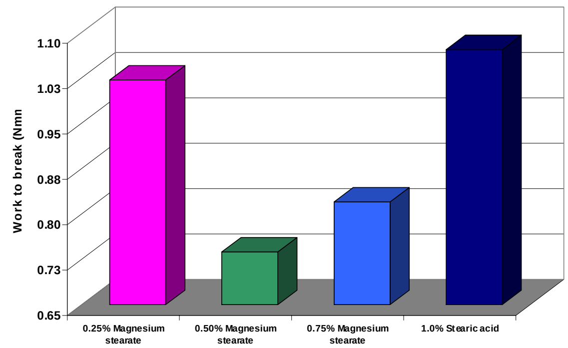
A significant improvement in tablet hardness was seen compared to any of the formulations containing magnesium stearate.

Effect of Stearic Acid on Dissolution



Dissolution was unaffected by the addition of stearic acid to the formulation.

Effect of Magnesium Stearate or Stearic Acid

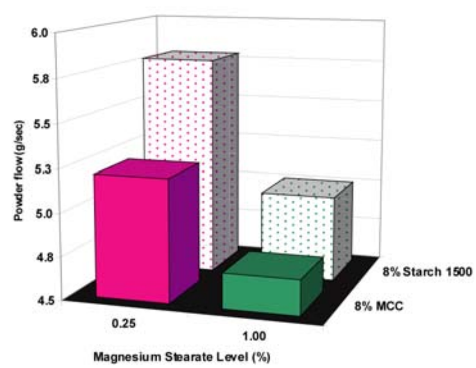


Film adhesion to the tablet surface was reduced at magnesium stearate levels greater than 0.25%. 1.0% Stearic acid in the formulation resulted in the highest measured adhesion values.

MCC / Magnesium Stearate

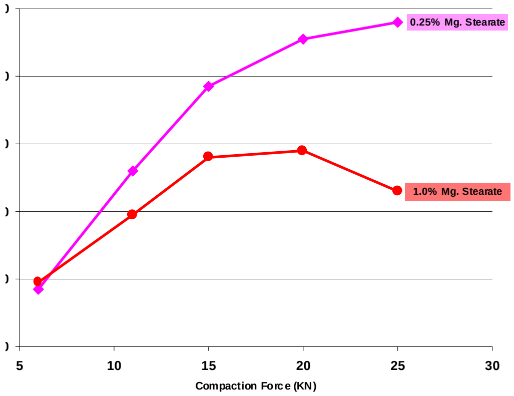
Microcrystalline cellulose was substituted for Starch 1500 in two of the formulations as an example of another type of plastically deforming excipient that may be adversely impacted by magnesium stearate.

Effect of Magnesium Stearate on Powder Flowability



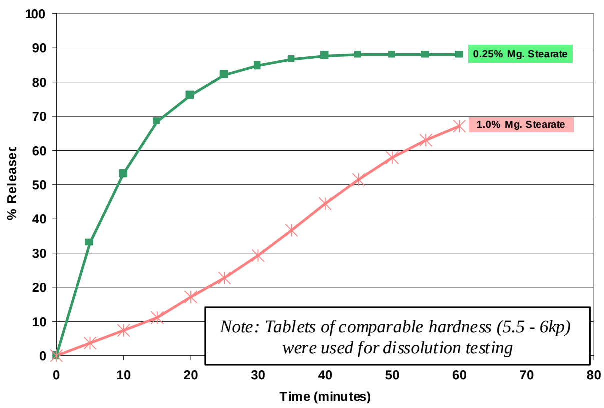
As with Starch 1500, the flow was decreased with an increasing magnesium stearate. The overall flowability was lower with MCC in the formulation.

Effect of Magnesium Stearate on Tablet Hardness



Tablet hardness was also severely impacted at the 1.0% magnesium stearate usage level.

Effect of Magnesium Stearate on Dissolution



Magnesium stearate in combination with MCC had a much greater impact on dissolution than in the formulations containing Starch 1500. The time to 60% released was reduced by 40 minutes at the 1.0% magnesium stearate usage level.

CONCLUSIONS

The multiple advantages of Starch 1500 as a flow aid, disintegrant, and dissolution aid may not be fully realized if proper lubricant types and levels are not identified.

Because of the tendency of magnesium stearate to “coat” the individual particles, detrimental effects of magnesium stearate can be exacerbated when using plastically deforming excipients.

Stearic acid has good lubricant properties and remains a discreet particle within the mixture without forming a waxy or hydrophobic coating on powder surfaces. Stearic acid can be used to reduce or eliminate magnesium stearate levels in formulations which exhibit lubricant sensitivity.

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