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COMPARATIVE EVALUATION OF TWO PHARMACEUTICAL BINDERS IN THE WET GRANULATION OF HYDROCHLOROTHIAZIDE LYCATAB™ DSH VERSUS KOLLIDON® 30

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ABSTRACT

LYCATAB™** DSH, a new pharmaceutical binder for the wet granulation process, was compared to KOLLIDON® K30, a frequently used povidone binder. Formulations containing 5% binder were prepared under the same processing conditions. Granule, compaction, ejection, and tablet properties, were evaluated to characterize differences between the two binders. Both binders produced end-products of similar quality. The LYCATAB™ however, produced a system which exhibited better granule friability, compaction profile, and ejection profile. This indicates that LYCATAB™ produced a more robust system when compared to KOLLIDON®.

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** LYCATAB™ is a trademark of Roquette Freres, 62136 Lestrem France.

INTRODUCTION

Drug substances are usually not compressible in their pure form.[1] Additives are included to increase their compressibility and flow, allowing for a more elegant and reproducible product. Quite often, formulators rely on experience with excipients rather than a controlled scientific evaluation in order to formulate a new product. In both instances, a prudent selection of excipients for any formulation is essential to assure a very high quality end-product.

Solid dosage formulations are a majority of all prescriptions dispensed. A labor intensive processes, wet granulation, is still frequently used in the production of these dosage forms. Wet granulation is commonly employed in solid dosage formulation to make powder mixtures more free-flowing, compressible, and homogenous.[2]

A most important excipient in the wet granulation process is the pharmaceutical binder. Adhesives or binders are used to increase particle size and flow, enhance granule quality, and aid in bonding during compression.[3] The choice of binder, as well as method of addition, have been shown to have a profound effect on granulation properties. Recent work by D'Alanzo et. al. explored two different types of binder addition and its effects on granular growth. The investigators found a good correlation between granular size and binder concentration when binders were dry mixed prior to wetting.[4] Dry binder addition would be the preferred method as it eliminates one step of an already lengthy process.

Over the years, povidone products and starch derivatives have been employed as binders in solid dosage formulations. This study was undertaken to evaluate a new binder, LYCATAB^{TM} DSH (LYC), in comparison with KOLLIDON^{R} K30 (K30). LYCATAB^{TM} DSH is a maltodextrin and is produced by the regulated hydrolysis of maize starch.[5,6] The povidone product (PVP, polyvinylpyrrolidone), KOLLIDON^{R} K30, was used as a benchmark in this study as its properties related to the wet-granulation process have been explored extensively.[7,8,9] This study is a practical evaluation of granule properties, events during compression, and tablet properties in an attempt to characterize what effects the two binders had on a hydrochlorothiazide formulation.

EXPERIMENTAL

MATERIALS

The source of the hydrochlorothiazide used in the formulation was from the Schering Corp (Kenilworth, NJ), while the hydrochlorothiazide used as an

analytical standard was obtained from the Sigma Chemicals Company (St. Louis, MO). Anhydrous lactose received from Sheffield Products (Norwich, NY) was used as a diluent. Binders employed in the granulation were KOLLIDON^{R} K30, supplied by the BASF Corporation (Parsippany, NJ), and LYCATAB^{TM} DSH, supplied by Roquette Corporation (Gurnee, IL). The lubricating agent used was magnesium stearate (Fisher Scientific Corp., Fairlawn, NJ), and the granulating media employed in the formulations was distilled water. Reagent grade hydrochloric acid manufactured by Fisher Scientific Corp. (Fairlawn, NJ) was also used to prepare the buffer employed in dissolution.

METHODS

The formulation used in the study consisted of 5% binder, 10% hydrochlorothiazide, 0.5% magnesium stearate, and 84.5% anhydrous lactose. Batch size was held to a laboratory scale of 2kg. The drug, binder and diluent, were mixed for 10 min. in and instrumented double planetary mixer manufactured by Charles Ross & Son[a]. The formulation was then granulated with water, at a flow rate of 60ml/min, using a peristaltic pump. Water was added for 1 minute then stopped for 30 seconds. This method of addition was repeated until endpoint was reached. Throughout the entire granulating process, power consumption was monitored as a function of time to provide an objective measure of the granulation endpoint. The Ross double planetary was useful in both drymixing and granulating the formulations used in this study. This equipment has the distinct advantage that it allows "one-pot" mixing and granulation of pharmaceutical systems. This gives it both labor saving and process validation attraction.

Granules were sieved through an 8 mesh screen and dried in a walk-in oven at 40 ° C to 0.1% loss on drying. The dried granulation was then passed through a 16 mesh screen and evaluated for granule friability[b], powder flow[c], and particle size and shape[d].

Prior to compaction granules, were mixed with 0.5% magnesium stearate in a Tuburla mixer[e] for 5 minutes. The final blends were compressed on a Stokes B-2[f] instrumented rotary tablet press equipped with 3/8" flat-face punches, to a tablet hardness of 6-8 kg and a weight of 315 mg. The lower punch force, ejection force, area under the compression time curve (AUC_{comp}), and area under the ejection time curve (AUC_{ej}) of 10 tablets were monitored and recorded during compression. Compression force was increased stepwise during the process. At each compression force interval, ejection force and tablet crushing strength were recorded and then plotted as a function of

compression force to develop the compaction and ejection profiles. Linear regression was used to estimate the profiles in the compression force range of 5-22 kN. After compression, tablets were evaluated for appearace tablet crushing strength[g], friability[b], weight uniformity, disintegration time[h], and dissolution[1](USP 1,900 ml of 0.1 N HCL).[10]

A spectrophotometric assay was used[j] to determine the concentration of hydrochlorothiazide in the dissolution media. At a wavelength of 270nm, aliquots of the dissolution media were compared with that of known concentrations of hydrochlorothiazide.

Mean data were compared using a two independent group t-test at a 95% confidence interval, to determine differences between the two formulations.[11] The software package X-stat (John Wiley & Sons, Inc.) was used to analyze the data for statistical significance.

RESULTS AND DISCUSSION

The formulations exhibited different granule properties (Table 1). Figures 1 & 2 are scanning electron micrographs of the formulations. Granules produced by both binders had a similar white and irregularly shaped appearance. The main difference in granule properties was seen in granule friability. A statistically significant difference was observed in granule friability with the LYCATAB^{TM} granules having a lower %loss and hence, better granule friability. Arithmetic mean particle size was determined by the method described by J.T. Carstensen[12]. As seen in Table 1, the LYCATAB^{TM} formulation consisted of particles with a higher arithmetic mean particle size than the K30 formulation. Flow properties of the granules, as measured by the flow rates for 25 gm of granules to pass through a I cm in diameter orifice, were similar.

Data observations made during compression are listed in Table 2. The LYCATAB^{TM} formulation had higher compaction and ejection forces. The AUC_{comp} and AUC_{ej} of the LYCATAB^{TM} formulation were notably higher than the K30 formulation. Differences in compression parameters between LYC and K30 were statisticaly significant at $p<0.001$.

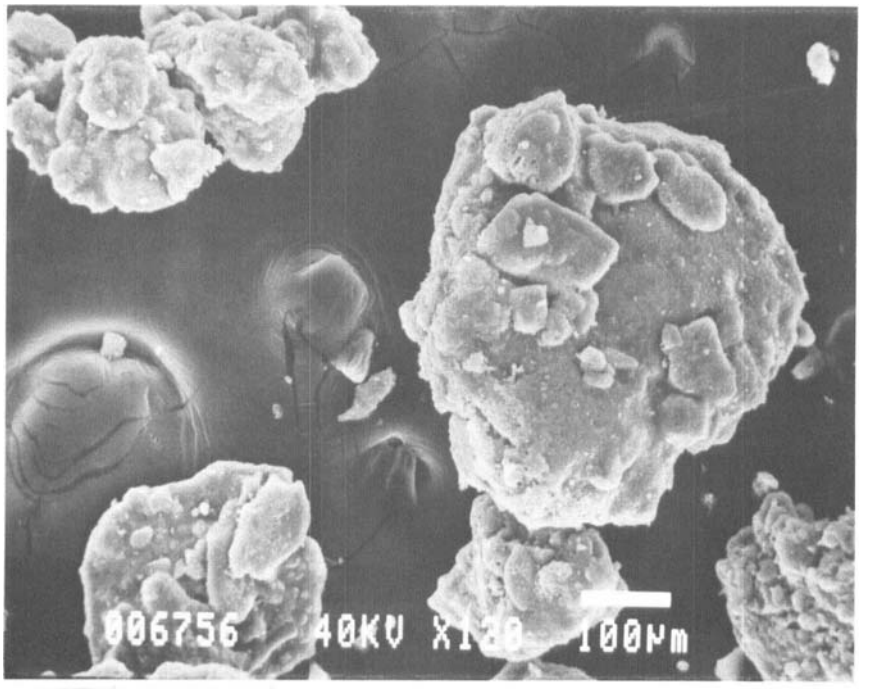
Figure 3 depicts the compression force as a function of tablet crushing strength profiles for both systems. The slope of the compaction profile is lower for the LYCATAB^{TM} formulation than the K30 formulation. These results indicate that small changes in compression force may have a greater effect on

TABLE 1
(Granule properties)

	LYCATAB™ DSH[a]	KOLLIDON® K30[a]
Flow Rate (g/sec)	4.39 (0.37)	4.51 (0.15)
Granule Friability[b] (% lost)	3.87 (0.15)	4.37 (0.23)
Particle size Arithmetic mean (um)	201.66	143.90

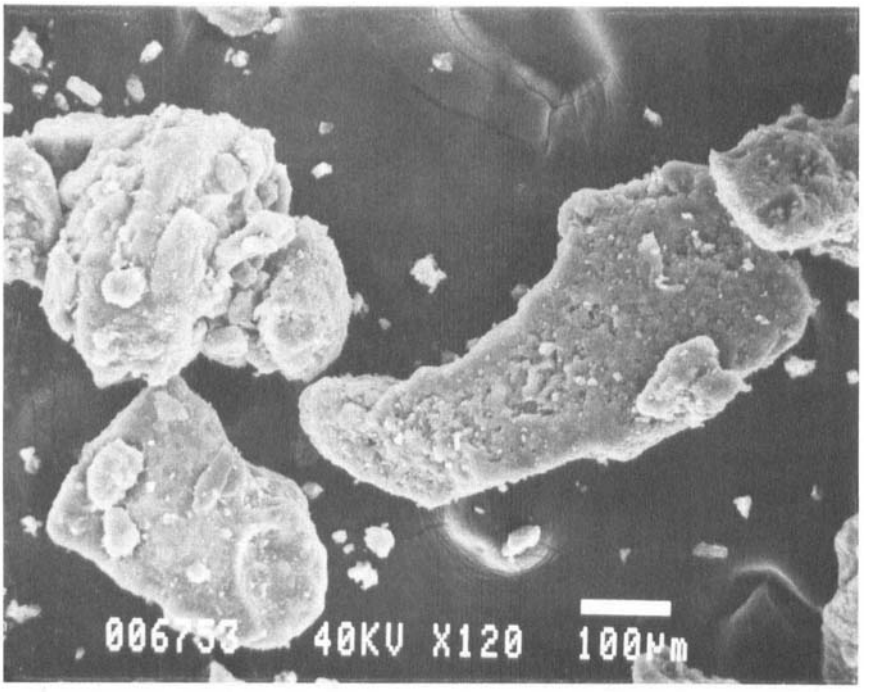
[a] mean (standard deviation)

[b] statistically significant difference $p<0.05$



LYCATAB™ DSH GRANULES 120X

FIGURE 1
Scanning Electron Photomicrographs of LYCATAB™ DSH Granules
120x magnification



KOLLIDON®30 GRANULES 120X

FIGURE 2
Scanning Electron Photomicrographs of KOLLIDON^{R} K30 Granules
120x magnification

TABLE 2
(Processing parameters)

	LYCATAB^{TM} DSH[a]	KOLLIDON^{R} K30[a]
Max Compression Force (kN)[b]	10.64 (0.09)	8.68 (0.23)
Max Ejection Force (N)[b]	748.39 (10.20)	686.01 (23.00)
AUC_{comp} (kN*msec)[b]	817.35 (8.38)	665.98 (22.60)
AUC_{ej} (kN*msec)[b]	55.03 (0.71)	52.38 (1.66)

[a] mean (standard deviation)

[b] statistically significant difference $p<0.001$

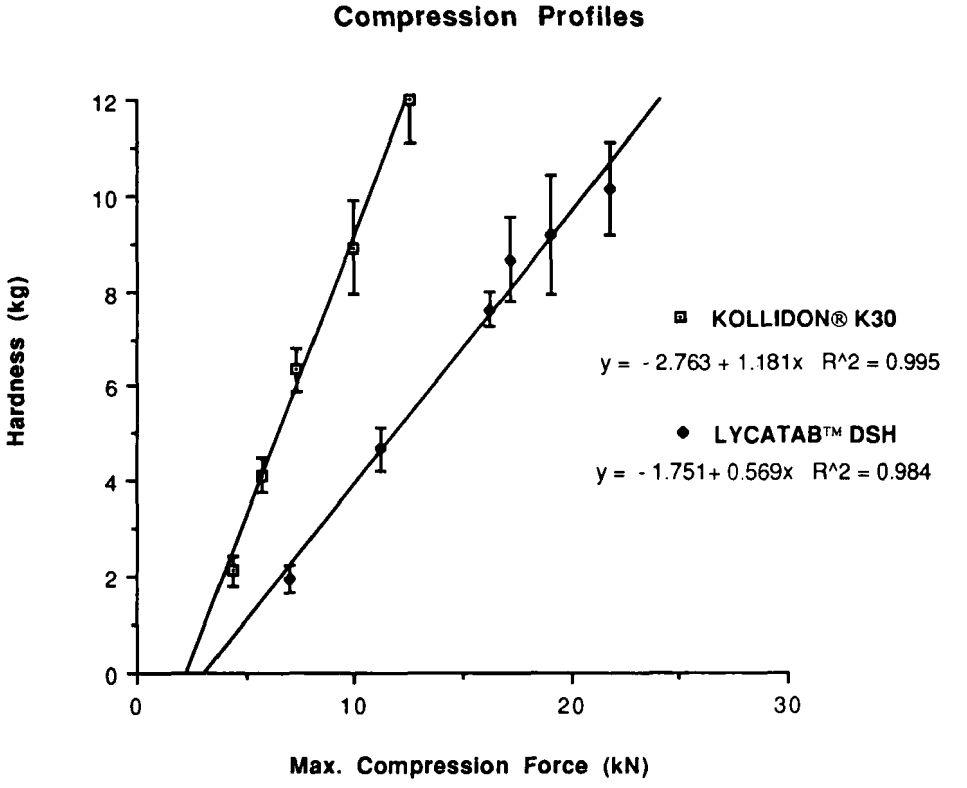


FIGURE 3
Compression Force vs. Tablet Hardness Profiles

tablet crushing strength for the K30 formulation as compared to the LYCATAB™ formulation.

Compression force / Ejection force profiles are presented in Figure 4. The slope of the profile for the LYCATAB™ formulation is lower than the slope of the profile of the K30 formulation. Small changes in compaction force may have a greater effect on ejection force for the K30 formulation as compared to the LYC formulation.

These profiles may perhaps be of significance in process validation as the LYCATAB™ formulation is shown to be a more robust system than the K30 formulation. The LYCATAB™ formulation may have the advantage of producing negligible changes in tablet hardness and ejection force, when small changes in compression force occur during the normal operation of rotary tablet presses.

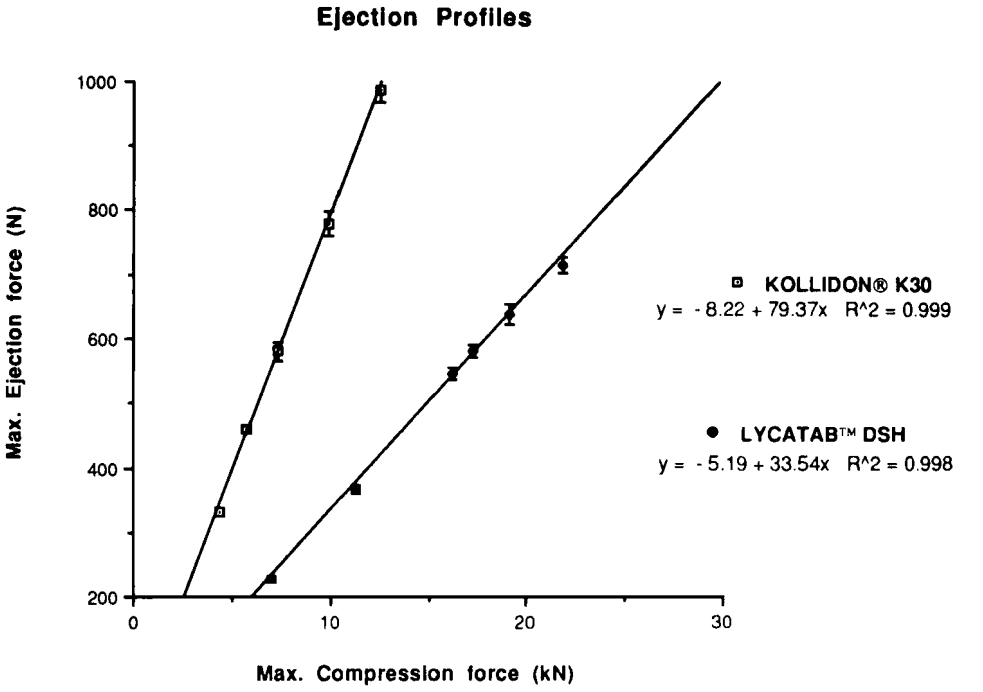


FIGURE 4
Compression Force vs. Ejection Force Profiles

TABLE 3
(Tablet Parameters)

	LYCATAB™ DSH[a]	KOLLIDON® K30[a]
Tablet wt. (mg)	315.5 (1.41)	313.1 (4.45)
Weight variation[b]	Within USP limits	Within USP limits
Friability (%)	0.38 (0.0)	0.51 (0.13)
Hardness (kg)	7.63 (0.36)	7.45 (0.61)
Disintegration time (min)	13.42 (0.94)	13.71[c] (1.24)

[a] mean (standard deviation)

[b] no tablets differed by ± 7.5%

[c] tablets adhered to apparatus

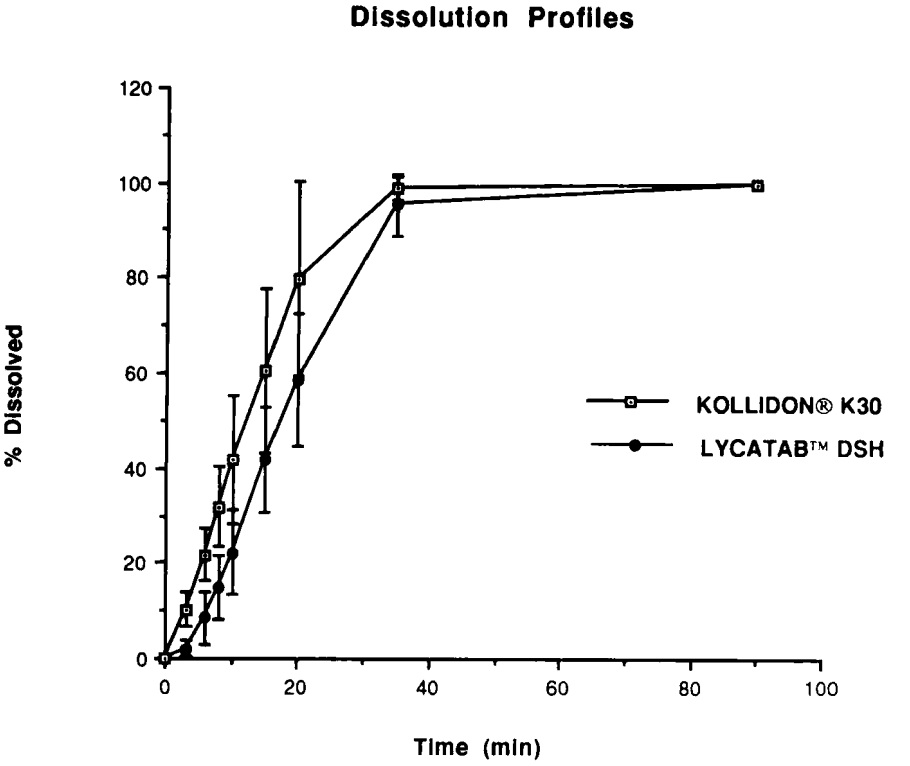


FIGURE 5
Dissolution Profiles

Table 3 compares the tablet properties exhibited by both formulations. No significant differences were seen in weight variation, friability, and hardness. Both formulations had similar disintegration times. However, the K30 formulation produced tablets which had a tendency to stick to the disintegration disks. Disintegration times for the K30 formulation are based on time for tablets, that did not adhere to disintegration disks, to disintegrate. As illustrated in Figure 5, both formulations had similar dissolution profiles.

CONCLUSION

This evaluation indicates that LYCATAB™ DSH is a suitable pharmaceutical binder in the wet granulation process when incorporated as a dry powder prior to granulation. The binders evaluated in this study produced

similar quality end-products. The main differences between the formulations were seen in the compression steps with the LYCATAB^{TM} system being shown to be a possibly more robust system for process validation. This study confirms that LYCATAB^{TM} DSH deserves serious consideration as a binder in solid dosage formulation prepared by wet granulation.

FOOTNOTES

a) Model LDM-2, Charles Ross & Son, Hauppauge, NY.
b) Model TA3 Roche Friabilator, Erweka Instrument Corp., Milford, CT.
c) Model PR1200 Top-loading Balance, Mettler Instrumentation, Hightstown, NJ in tandem with Cole-Parmer Chart Recorder, Chicago, IL.
d) Model 1200EX Scanning-transmission Electron Microscope, JEOL USA, Peabody, MA.
e) Model T2c, Wil A. Bachofen, Basel Switzerland.
f) Model B-2 sixteen station rotary tablet press, Stokes-Penwalt, Warminster, PA.
g) Model TBT Hardness Tester, Erweka Instrument Corp., Milford, CT.
h) Model 10-911-71B USP Disintegration Apparatus, VanKel Industries, Edison, NJ.
i) Model W-112A USP Dissolution Apparatus, VanKel Industries, Edison, NJ.
j) Model 8451A Diode Array UV Spectrophotometer, Hewlett Packard.

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