DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(17), 1831-1851 (1992)

CHARACTERIZATION OF THE TABLETING PROPERTIES OF β-CYCLODEXTRIN AND THE EFFECTS OF PROCESSING VARIABLES ON INCLUSION COMPLEX FORMATION, COMPACTIBILITY AND DISSOLUTION

Ralph F. Shangraw[1], Girish S. Pande[1] and Pankaj Gala[2]

[1]University of Maryland, School of Pharmacy, 20 N. Pine Street, Baltimore, MD 21201

[2]Parke Davis, Division of Warner-Lambert Company, Morris Plains, NJ 07950

ABSTRACT

The tableting properties of a number of commercially available β-cyclodextrins were characterized. Fluidity was insufficient for routine direct compression. Compactibility varied by source but was excellent. Lubrication requirements were minimal. An inclusion complex of β-cyclodextrin/Progesterone was formed and the tableting properties of the complex were compared to those of a physical mixture in both directly compressed and wet granulated products. Inclusion complexes spontaneously formed during wet granulation processing. Substantial differences in tableting properties were found as processing variables were changed. β-cyclodextrin exhibits considerable promise as a standard filler binder in tableting.

INTRODUCTION

Cyclodextrins are cyclic oligosaccharides consisting of α-1,4 linked glucose units (1). The most common cyclodextrins are α, β and γ cyclodextrins, consisting of 6, 7 and 8 glucose units respectively (2). The cyclic structure of cyclodextrins resembles a donut, and is capable of accommodating a guest molecule within the 'donut' hole, thus forming an inclusion complex (1). The formation of inclusion complex between the cyclodextrins and a suitable drug molecule could result in improved rate and extent of dissolution and bioavailability (3-5), improved chemical and physical stability (6-8) and/or conversion of liquid substance into solid material (7).

Nakai et al. investigated the effect of changing crystallinity on the tableting properties of pure β- cyclodextrin (9). Even with the least compressible highly crystalline β-cyclodextrin, acceptable crushing strengths which increased with compression pressure were reported. Hegde and Rhodes studied the tableting properties of a wet granulated phenytoin/β-cyclodextrin complex on a single punch tablet press and found the properties to meet the USP standards for tablets (10). Lin and Kao were able to prepare tablets from a ground mixture and a physical mixture of warfarin and β-cyclodextrin (11). Similarly, Uekema et al. prepared tablets from the inclusion complex of isosorbide 5-mononitrate and β-cyclodextrin (12). Even though the compactibility of β-cyclodextrin and its usage as a tablet filler could be illustrated in all these studies and a few others (4,13-15), none of them investigated this property of cyclodextrin.

The objective of this study was to determine the feasibility of using β-cyclodextrin as a tablet filler and the effects of common processing variables on tablets made by both direct compression and wet granulation from complexes and/or physical mixtures with a model drug.

MATERIALS AND METHODS

The basic properties of a number of commercially available β-cyclodextrins were determined [1-4]. Analysis included particle size and shape, moisture, bulk and tap density and Carr's Index. Tablets were compressed on a single punch tablet press[5], instrumented with strain gauges and linear voltage transducers attached to the punches with both compression and ejection forces monitored. Tableting properties of the β-cyclodextrin were compared to spray dried lactose[6], unmilled dicalcium phosphate[7] and microcrystalline cellulose[8]. An inclusion complex of β-cyclodextrin/progesterone was formed and the tableting properties of the complex were compared to a physical mixture of the two ingredients in a formulation containing 87.2% β-cyclodextrin, 9.7% progesterone[9], 2% croscarmellose[10] and 0.1% fumed silicon dioxide[11]. Tablets were compressed on an instrumented rotary tablet machine[12]. The effects of mixer type on the degree of complexation occurring in the wet granulation of physical mixtures of progesterone and β-cyclodextrin were also determined using a Planetary mixer[13], V-blender[14] and a high shear mixer[15]. Dissolution studies were conducted on a multispindle dissolution system[16] using USP Method #2, a paddle speed of 50 R.P.M. and 900 ml of dissolution fluid (distilled water or 0.5% sodium lauryl sulfate in distilled water).

RESULTS AND DISCUSSION

Tableting Properties of Cyclodextrins

The basic properties of a number of commercially available β-cyclodextrin products were determined including particle size, moisture content, bulk density, tapped density and Carr's Index. As can be seen

TABLE 1

Properties of Various Commercial β-Cyclodextrins

Source	Moisture Content (%)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr Index (%)
Nihon	12.0	.51	.74	30
Amaizo	13.0	.40	.63	37
UR	12.5	.42	.75	44
Roquette	12.0	.70	.85	21

in Table 1 there were no significant differences in the equilibrium moisture content of the samples studied.

Roquette β-cyclodextrin possessed significantly higher bulk and tap densities than did the other products tested. As might be expected from their small particle size and irregular shape, it was not possible to measure the fluidity of any of the β-cyclodextrin samples using common flow measurement techniques. However, the Carr's Compressibility Index which is based on the loose and tap bulk densities gives a fair indication of fluidity (16). Values close to 20% (Roquette) indicates a fair to passable flow. However, higher values (30-44%) which were exhibited by the other products indicates poor flow. Particle size measurements were determined by dispersing the powder in silicon fluid and determining Martin's diameter of 400 particles using a calibrated optical microscope. As can be seen from Figure 1, the average particle size and particle size distribution of the three β-cyclodextrins are quite

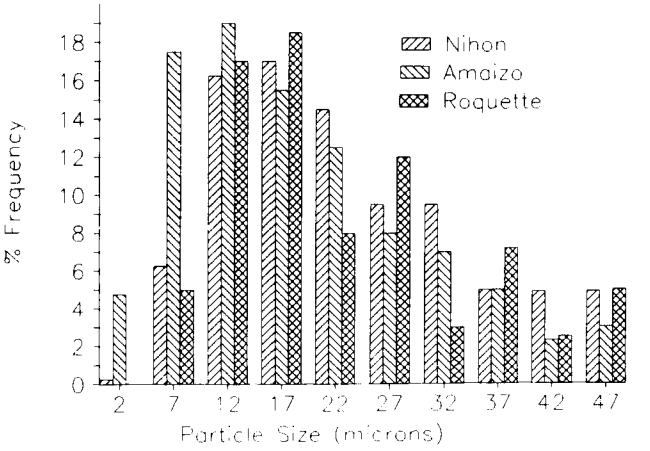

FIGURE 1
Particle size distribution of β-cyclodextrins.

similar. The average particle size of all samples was approximately 28 μm.

Tablets were compressed on an instrumented single punch machine. Because of flow problems, the dies were hand-filled with preweighed powder samples. The punch faces and die were prelubricated with a dispersion of magnesium stearate in acetone. Heckel plots based on the effect of compression pressure on relative density exhibited yield values of 68.4 MPa for in-die thickness measurements and 71.3 MPa for out-of-die thickness measurements (Figure 2). Such values have been associated with materials showing predominantly plastic deformation (similar to microcrystalline cellulose) but with minimal elastic recovery (17-19).

The relative compactibilities of the various β-cyclodextrins are shown in Figure 3. The compactibility varies significantly with the sample source in the following order Amaizo > Nihon > Roquette. All of the cyclodextrin samples were more compactible than either spray

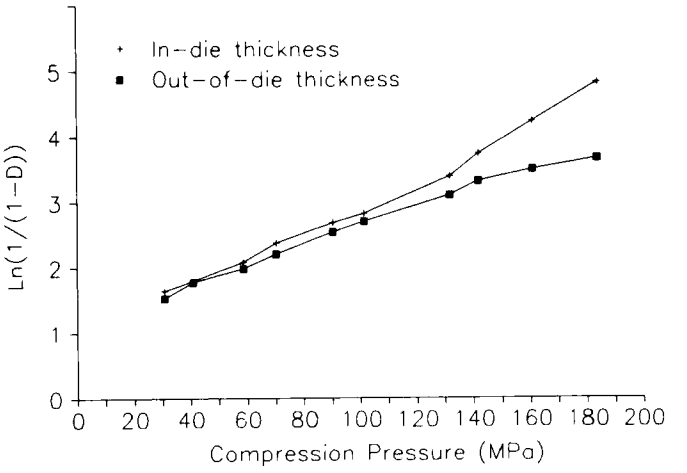

FIGURE 2
Heckel plots of β-cyclodextrin (Nihon).

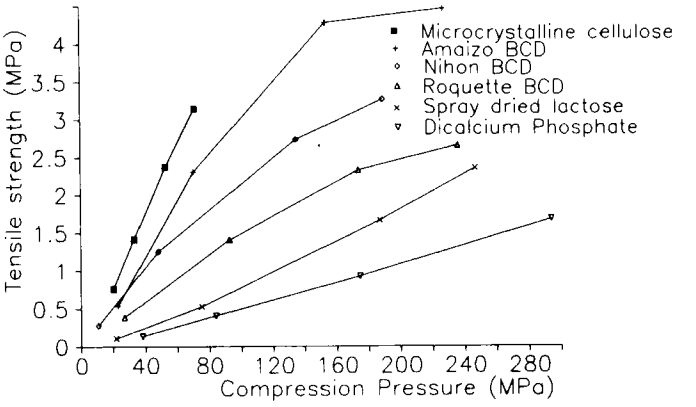

FIGURE 3
Tensile strength - compression profile. Comparison of commercial β-cyclodextrins with microcrystalline cellulose, spray dried lactose and dicalcium phosphate.

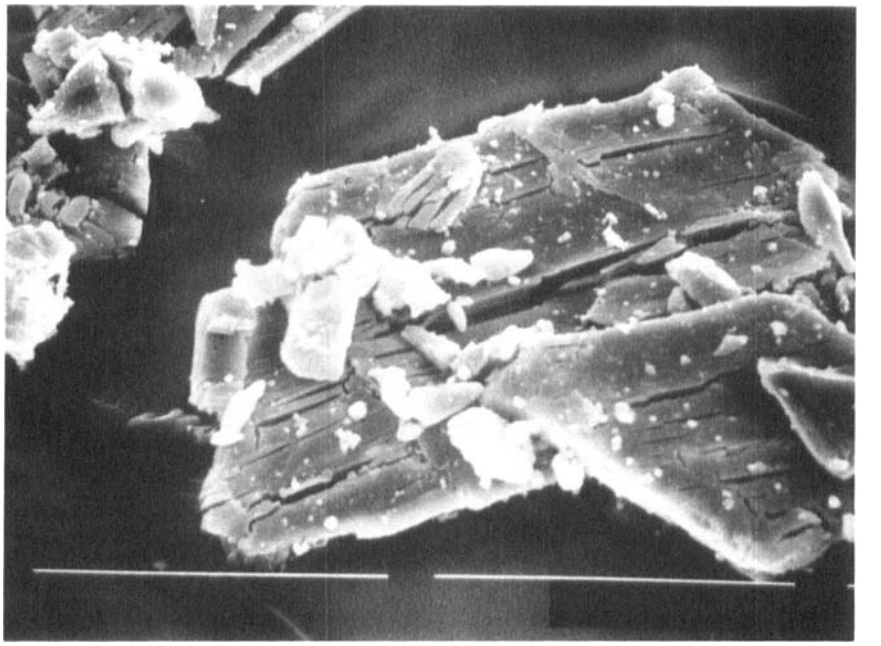

FIGURE 4
Scanning electron micrograph of Nihon β-cyclodextrin. Magnification: 500X

dried lactose or unmilled dicalcium phosphate, commonly used as direct compression fillers. However, even more interesting is the fact that some β-cyclodextrins have compactibilities approaching that of microcrystalline cellulose.

Some explanation of the differences between the commercial cyclodextrins can be observed by looking at scanning electron photomicrographs of the three different products (Figures 4, 5 and 6). Although, the particle sizes of the three materials are similar, the density and degree of lamination of individual particles does vary significantly. One would expect that the laminated crystals would exhibit more deformation under stress, thus creating more clean surfaces during compaction and producing stronger compacts. This appears to be the

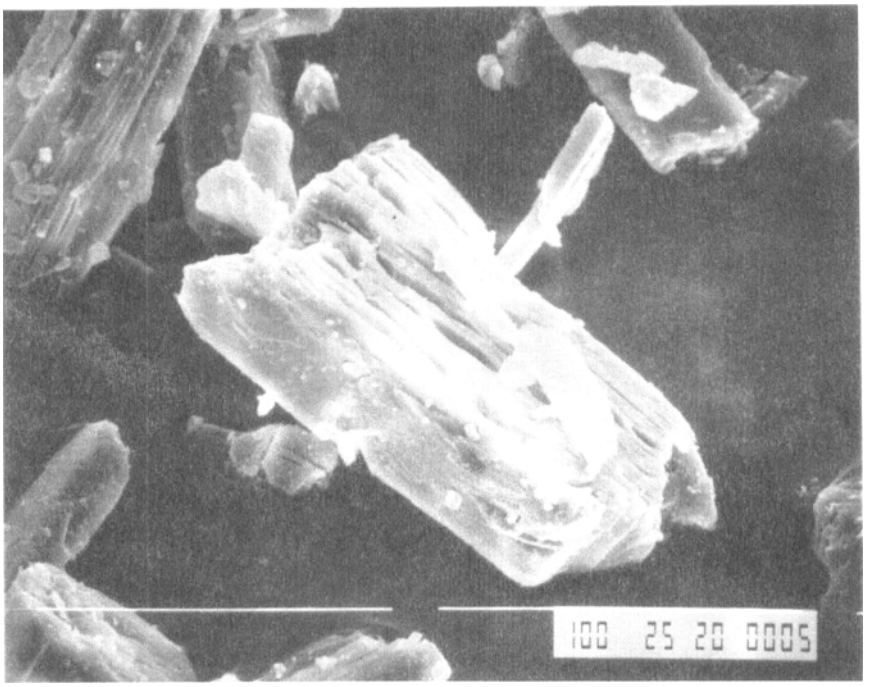

FIGURE 5
Scanning electron micrograph of Amaizo β-cyclodextrin. Magnification: 500X

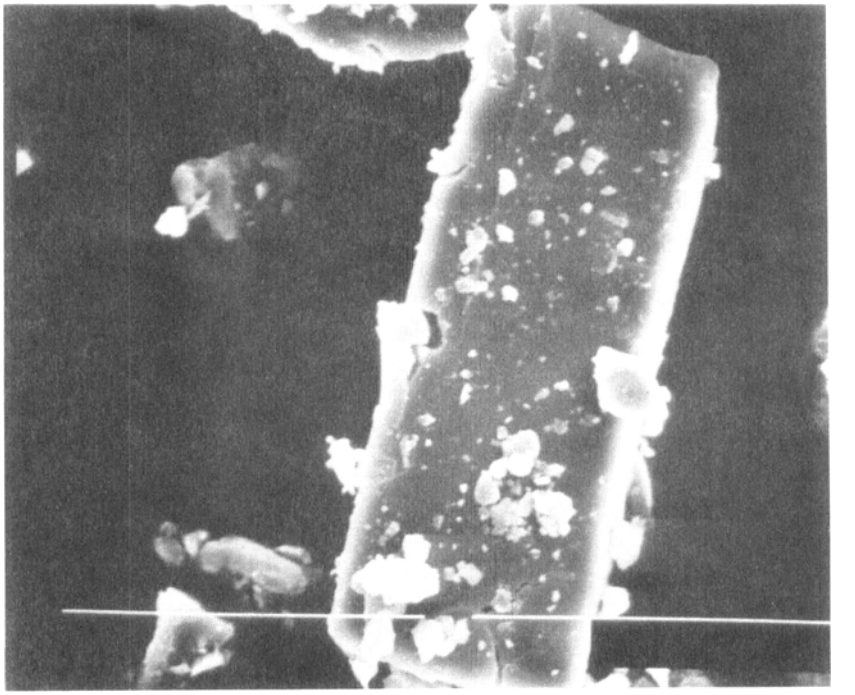

FIGURE 6
Scanning electron micrograph of Roquette β-cyclodextrin. Magnification: 500X

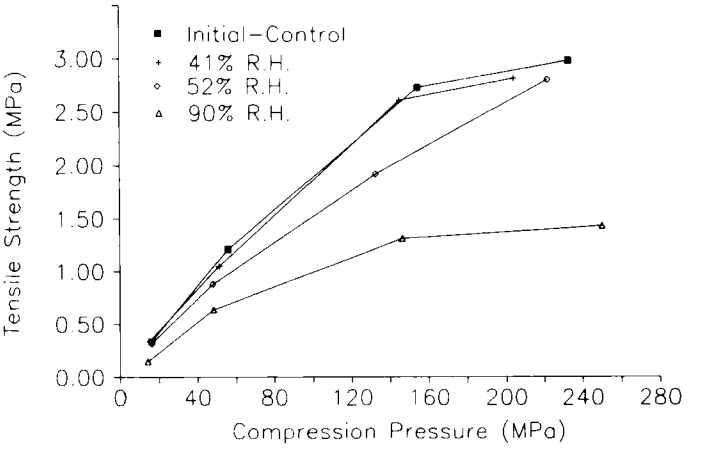

FIGURE 7
Effect of humidity and storage (15 days) on tablet tensile strength.

case with the Amaizo product having the greatest amount of compactibility and the Roquette product having the least amount. Due to the nature of the β-cyclodextrin and the level of moisture present, it would be anticipated that the strength of cyclodextrin compacts would depend to some degree on hydrogen bonding similar to what is seen in microcrystalline cellulose compacts (20). Compacts of β-cyclodextrin (Nihon) were stored at various relative humidities ranging from 21% to 90% for a period of 15 days. Tablets stored at 21 and 41% showed no change in crushing strength while tablets stored at 52% RH were slightly softer and those at 90% retained only one-third of their original crushing strength (Figure 7). It is obvious that high relative humidities are detrimental to tablets of plain cyclodextrin and would most likely have the same effect on tableted complexes.

Preliminary studies indicated that cyclodextrin tablets require a small amount of lubrication if long term problems in sticking and binding in the die are to be avoided. Figure 8 shows that as little as 0.1% magnesium stearate reduces the ejection force of cyclodextrin below

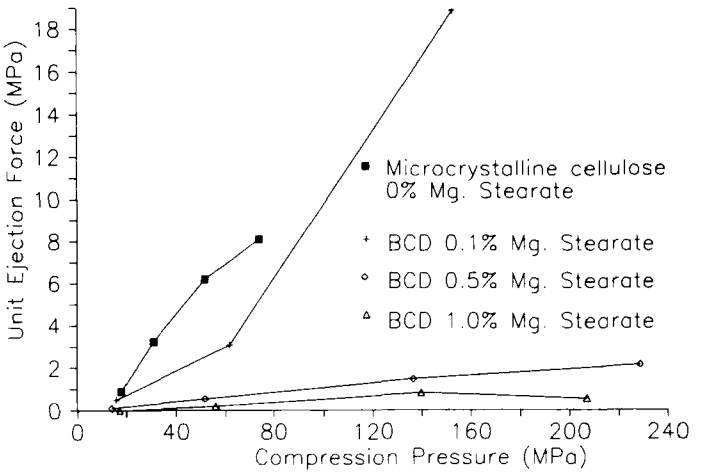

FIGURE 8
Effect of magnesium stearate on the ejection forces of β-cyclodextrin tablets.

that of Avicel[R] (which can be compressed without a lubricant) and an amount equal to 0.5% reduces the ejection force to an insignificant value. The addition of 1% magnesium stearate produces no advantages over the 0.5% level.

Tableting Properties of Physical Mixtures and Complexes of Progesterone and β-cyclodextrin

After determining the tablet properties of plain β-cyclodextrins, attention was turned towards the effects of pharmaceutical processing on physical mixtures of drug and cyclodextrin. A model drug progesterone was chosen because of its relatively low dose and the fact that the degree of complexation, which might occur during processing, could be determined using a combination of differential scanning calorimetry (21) to determine free progesterone and high pressure liquid chromatography (22) to determine total progesterone.

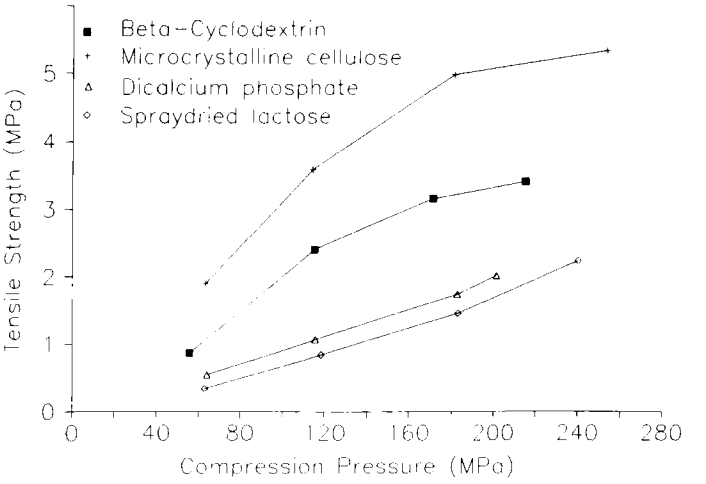

FIGURE 9
Effect of compression pressure and filler type on the tensile strength of progesterone tablets made by direct compression.

Although β-cyclodextrin has not been optimized for direct compression, it is possible to compress a mixture of 87.2% β-cyclodextrin, 9.2% progesterone, 2% sodium croscarmellose, 1% magnesium stearate and 0.1% colloidal silica on a rotary press. As can be seen in Figure 9, this combination was superior in compactibility to similar formulations containing spray dried lactose or unmilled dicalcium phosphate, but inferior to one containing microcrystalline cellulose. A similar but inverse effect is noted in ejection force, once again indicating that the lubricant requirements of β-cyclodextrin, even when a drug is present, is less than other common fillers except microcrystalline cellulose (Figure 10).

A 10% physical blend of progesterone and cyclodextrin was granulated using standard wet granulation techniques in three types of mixers: planetary, V-blender with dispersing bar, and a high shear

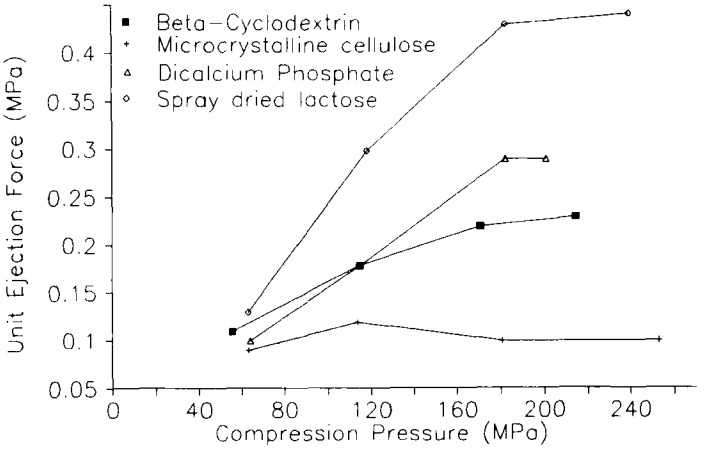

FIGURE 10
Effect of compression pressure and filler type on the unit ejection force of progesterone tablets made by direct compression.

blender. As one might expect, complexation of progesterone can occur during processing. In fact, the kneading process used for complex formation is not dissimilar to the wet granulation process for making tablets (23). In the kneading method of complex formation a semi-solid paste is aimed for, whereas in the wet granulation process for making a tablet, a drier dough-like consistency is employed. The degree of complexation varied according to the type and amount of solvent added and reached a level of almost 60% when 18% water was used as a granulating fluid in a planetary mixer. A mixture of water and alcohol as the binder solution gave a lower degree of complex formation than when water alone was used. While alcohol increased progesterone solubility, it decreased cyclodextrin solubility giving a net reduction in complex formation. Addition of a binding agent such as polyvinyl pyrrolidone (PVP) significantly reduced complex formation as PVP reduced solvent availability by increasing viscosity of the solvent (Figure 11). The mixer type also influenced the degree of complexation with a high shear

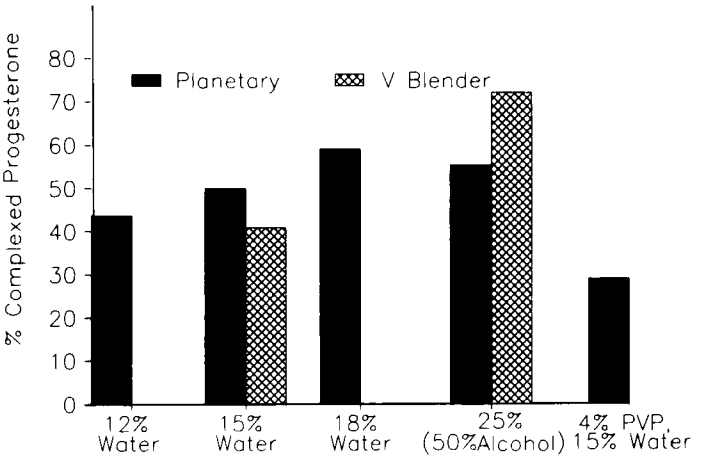

FIGURE 11
Effect of wet processing on formation of progesterone/β-cyclodextrin complex.

blender actually providing less complexation than a planetary mixer. This is probably due to a more efficient distribution of water over the cyclodextrin, thus reducing the chance of localized solvent formation in which co-solvation of progesterone and cyclodextrin can occur.

A large batch of totally complexed progesterone-cyclodextrin complex was formed and this preformed complex was then granulated using the same technique as the granulations made from the physical mixtures. It was not possible to form granules from the complex at a 15% water level, but a marginal granulation could be prepared with 18% water (Figure 12). The progesterone obviously reduces the ability of the cyclodextrin to serve as its own binder. However, the granulated complex formed a harder tablet than the granulated physical mixture which could be due to less interruption of cyclodextrin-cyclodextrin surfaces by the "hidden" progesterone. It is interesting to note also that although the tablets were harder, the ejection force was less - which again could be attributed to the hiding power of the cyclodextrin thus

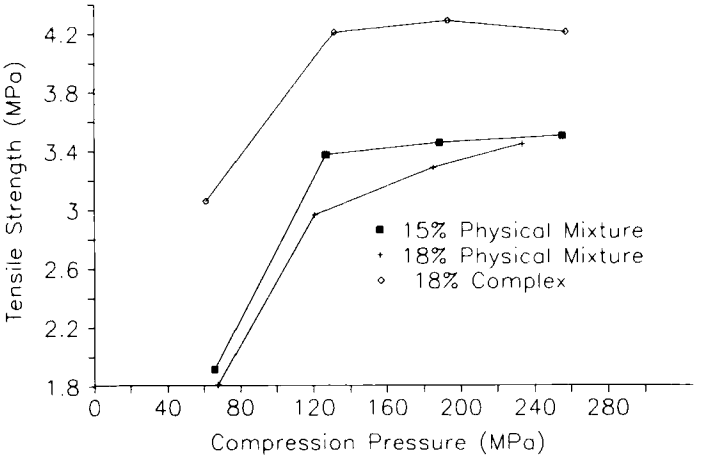

FIGURE 12
Effect of binder level on the compactibilty of granules made from physical mixtures or complexes of progesterone/β-cyclodextrin (1:9).

reducing the lubricant requirements of the progesterone (Figure 13). It should be noted that at no time during the processing of the complexed drug did the drug revert to its free form.

Dissolution studies were conducted on tablets made by wet granulation of both physical mixtures and complexes of progesterone and β-cyclodextrin. The rates of dissolution from the tablets were compared to a direct compression physical mixture of progesterone and β-cyclodextrin and a control physical mixture containing progesterone and microcrystalline cellulose. The results can be seen in Figure 14. All formulations containing β-cyclodextrin exhibited much faster dissolution than did the microcrystalline cellulose control. Surprisingly there was little difference between the tablets containing the wet granulated complex and the wet granulated physical mixture. Some of the similarity is obviously due to the complex formation which occurs during wet granulation. It is theorized that all of the remaining progesterone is

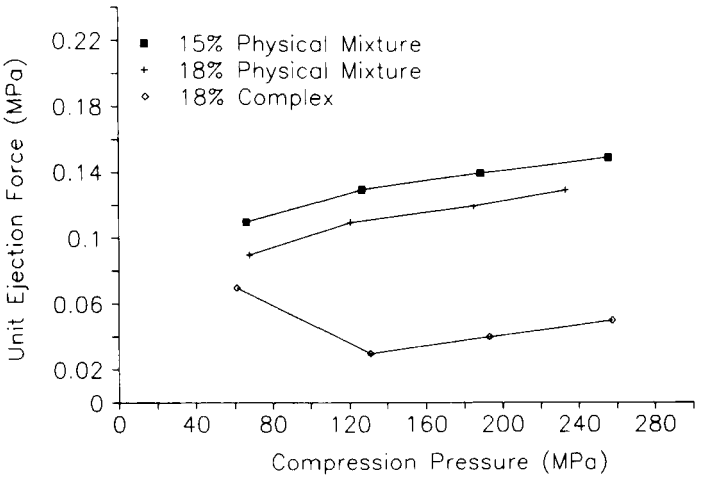

FIGURE 13

Effect of binder level (water) on the ejection of tablets made from granulations of physical mixtures or complexes of progesterone/β-cyclodextrin (1:9).

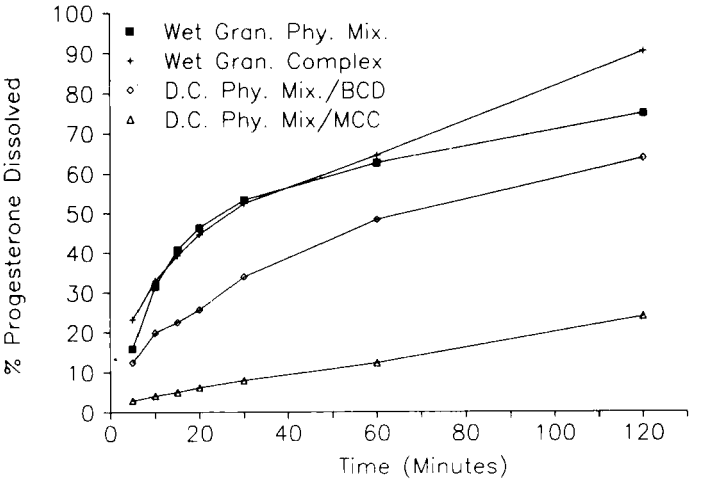

FIGURE 14

Dissolution of progesterone from formulations of progesterone/β-cyclodextrin (dissolution media : water).

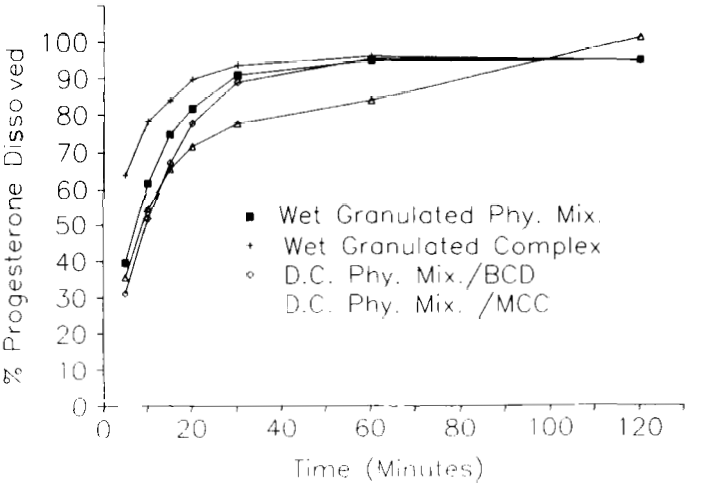

FIGURE 15
Dissolution of progesterone from formulations of progesterone/β-cyclodextrin (dissolution media : 0.5% sodium lauryl sulphate).

wetted in the granulation process and that when this progesterone dissolves it is quickly complexed with the free cyclodextrin in the dissolution media enhancing the dissolution process. Even in the case of the physical mixture, the cyclodextrin enhances the rate of solubility of the progesterone.

Even when a surfactant such as 0.5% sodium lauryl sulfate is added to the dissolution media to provide sink conditions, the dissolution of progesterone from the microcrystalline cellulose tablets is slower than from any formulation containing β-cyclodextrin (Figure 15).

CONCLUSIONS

It is clear from the results of this study that β-cyclodextrin shows considerable promise as a filler-binder in tablet manufacture. While it is more compactible than all other standard direct compression fillers

commonly in use except microcrystalline cellulose, the fluidity of presently available commercial products is not adequate for direct compression. In addition to high compactibility β-cyclodextrin alone requires very small amounts of lubricant and inclusion compounds reduce significantly the lubricant requirements of any complexed drug.

Formation of inclusion complexes of β-cyclodextrin and progesterone during common wet granulation processing procedures depends upon both binder solution and mixer type. While physical mixtures can be granulated with water alone, complexes may require an auxiliary binder such as PVP. The presence of β-cyclodextrin in a formulation will enhance dissolution of drugs of low water solubility even if the drug is not in the form of an inclusion compound. The use of β-cyclodextrin as a tablet and capsule filler shows considerable promise and needs to be explored further.

NOTES

[1]B. Celdrex, Lot #B-0416, Nihon Shokohin, Kako Co. Ltd. Tokyo, Japan

[2]β-cyclodextrin, Amaizo, American Maize Products Co., Hammond, Indiana 46320

[3]Kleptose, Lot #-129, Roquette Corporation, Gurnee, IL 60031

[4]β-cyclodextrin, Lot #8039, UR Industry Inc., Montville, NJ 07405

[5]Coltan Model 321-88 Single Punch Tablet Machine (Modified), Arthur Coltan Co., Detroit, Michigan 48226

[6]Hydrous Lactose NF (Fast Flo^{R}), Foremost Whey Products, Baraboo, Wisconsin 54913

[7]Dicalcium Phosphate Dihydrate USP, Unmilled (DiTab^{R}), Stauffer Chemical Company, Westport, Connecticut 06881

[8]Microcrystalline Cellulose NF (Avicel^{R} PH 102) FMC Corporation, Philadelphia, Pennsylvania 19103

[9]Progesterone, USP, Paddock Lab Inc., Minneapolis, Minnesota 55429

[10]Croscarmellose Sodium NF (Ac-Di-Sol[R]), FMC Corporation, Philadelphia, Pennsylvania 19103

[11]Silicon Dioxide, NF, Fumed (Cab-O-Sil[R]) Cabot Corporation, Boston, Massachusetts 02110

[12]Stokes RB-2 Rotary Tablet Press, Stokes Engineering, Philadelphia, Pennsylvania 19143

[13]Erweka Planetary Mixer, Erweka Apparatus, GMBH, Hausenstamm, Germany

[14]Patterson Kelly Twin Shell Blender, LB-5695, Patterson Kelly Company, Inc., East Stroudsburg, Pennsylvania 18301

[15]High Shear Mixer, Model W-10-B, Littleford Bros. Inc., Florence Kentucky 41042

[16]Distek Dissolution System, Model 2000, Distek Inc., Somerset, New Jersey 08873

ACKNOWLEDGMENTS

This work was supported in part by a Merck pre-doctoral fellowship award and financial assistance provided by Roquette Freres, France. Gifts of β-cyclodextrin from Nihon Shokuhin Kako Co., Japan and Roquette Freres, France are gratefully acknowledged.

REFERENCES

1. S. G. Frank, Inclusion compounds. J. Pharm. Sci.**64**:1585-1603 (1975).
2. M. Windholz. The Merck Index, Tenth edition, Merck and Co., Rahway, NY, 1983 pp 389.

3. O. I. Corrigan and C.T. Stanley. Dissolution properties of phenobarbitone-β-cyclodextrin systems. Pharm. Acta Helv. **56**:204-208 (1981).

4. K. Uekama, T. Fujinaga, F. Hirayama, M. Otagiri and M. Yamasaki. Inclusion complexations of steroid hormones with cyclodextrins in water and in solid phase. Int. J. Pharm. **10**:1-15 (1982).

5. N. Nambu, M. Shimoda, Y. Takahashi, H. Ueda and T. Nagai. Bioavailability of powdered inclusion compounds of nonsteroidal antiinflammatory drugs with β-cylodextrins in rabbits and dogs. Chem. Pharm. Bull. **26**:2952-2956 (1978).

6. K. Uekema, T. Fujinaga, F. Hirayama, M. Otagiri, Y. Kurono and K. Ikeda. Effects of cyclodextrins on the acid hydrolysis of digoxin. J. Pharm. Pharmacol. **34**:627-630 (1982).

7. M. Gal-Fuzy, L. Szente, J. Szejtli and J. Harangi. Cyclodextrin-stabilized volatile substances for inhalation therapy. Pharmazie. **39**:558-559 (1984).

8. K. Uekema, K. Oh, M. Otagiri, H. Seo and M. Tsuruoka. Improvement of some pharmaceutical properties of clofibrate by cyclodextrin complexation. Pharm. Acta Helv. **58**:338-342 (1983).

9. Y. Nakai, K. Yamamoto, K. Terada, and A. Kajiyama. Relationships between crystallinity of β-cyclodextrin and tablet charateristics. Chem. Pharm. Bull. **33**:5110-5112 (1985).

10. R. P. Hegde and C. T. Rhodes. Preparation of a phenytoin β-cyclodextrin complex and evaluation of a suspension and a tablet dosage form prepared from the complex. Pharm. Acta Helv. **60**:53-57 (1985).

11. S. Lin and Y. Kao. Physico-chemical stability of warfarin in ground mixtures with β-cyclodextrin or microcrystalline cellulose under storage conditions. J. Chinese Chem. Soc. **35**:173-178 (1988).

12. K. Uekama, K. Oh, T. Irie, M. Otagiri, Y. Nishimiya and T. Nara. Stabilization of isosorbide 5-mononitrate in solid state by β-cyclodextrin complexation. Int. J. Pharm. **25**:339-346 (1985).

13. F. M. Anderson and H. Bundgarrd. Inclusion complexation of disulfiram with cyclodextrins to enhance aqueous solubility. Arch. Pharm. Chem. Sci. Ed. **12**:17-25 (1984).

14. K. Uekama, T. Fujinaga, F. Hirayama, M. Otagiri, M. Yamasaki, H. Seo, T. Hashimoto and M. Tsuruoka. Improvement of the oral bioavailability of digitalis glycosides by cyclodextrin complexation. J. Pharm. Sci. **72**:1338-1341 (1983).

15. M. Otagiri, T. Imai, N. Matsuo and K. Uekama. Improvements to some pharmaceutical properties of flurbiprofen by β and γ cyclodextrin complexations. Acta Pharm. Suec. **20**:1-10 (1983).

16. R. L. Carr. Particle behaviour storage and flow. British Chem. Eng. **15**:1541-1549 (1970).

17. I. Krycer, D. G. Pope and J. A. Hersey. The interpretation of powder compaction data - A critical review. Drug Dev. Ind. Pharm. **8**:307-342 (1982).

18. M. Sheikh-Salem and J. T. Fell. The influence of initial packing on the compression of powders. J. Pharm. Pharmacol. **33**:491-494 (1980).

19. A. A. Al-Angart, J. W. Kennerly and J. M. Newton. The compaction properties of polyethylene glycols. J. Pharm. Pharmacol. **37**:151-153 (1984).

20. D. C. Fox, D. M. Richman, G. E. Reier and R. Shangraw. Microcrystalline cellulose in tableting. Drug Cos. Ind. **92**:1-6 (1963).

21. F. Theeuwes, A. Hussain and T. Higuchi. Quantitative analytical method for determination of drugs dispersed in polymers using differential scanning calorimetry. J. Pharm. Sci. **63**:427-428 (1974).

22. V. D. Gupta. Quantitation of hydroxyprogesterone caproate, medroxyprogesterone acetate and progesterone by reverse phase high-pressure liquid chromatography. J. Pharm. Sci. **71**:294-297 (1982).

23. N. Rajagopalan, S. C. Chen and W. Chow. A study of the inclusion compounds of amphotericin-B with γ-cyclodextrin Int. J. Pharm. **29**:161-168 (1986).