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THE STRENGTH OF MICROCRYSTALLINE CELLULOSE PELLETS: THE EFFECT OF GRANULATING WITH WATER/ETHANOL MIXTURES

G.P. Millili and J.B. Schwartz
Department of Pharmaceutics
Philadelphia College of Pharmacy & Science
Philadelphia, PA 19104

ABSTRACT

Pellets were prepared by wet granulating with various ethanol/water mixtures utilizing the extrusion/marumerization process. Binary mixtures of 10% active ingredient and 90% Microcrystalline Cellulose (Avicel PH-101) were found to form pellets when granulated with 95% ethanol but not with absolute alcohol. Differences in friability and dissolution were observed between water granulated and 95% ethanol granulated pellets. When mixtures were granulated with varying ethanol/water mixtures, pellets became stronger and harder as the mole fraction of water increased in the ethanol/water mixture used to granulate. Compaction experiments showed water granulated pellets were not very compressible whereas 95% ethanol granulated pellets exhibited excellent compressibility.

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Compaction of simple granulations that were water granulated, ethanol granulated and directly compressed showed similar trends, but the differences were not as great.

INTRODUCTION

Microcrystalline Cellulose (MCC) is an excellent and widely used excipient in the pharmaceutical industry. It has been extensively reported that this material produces very hard tablets upon compression.(1) It also has been demonstrated to be a very useful excipient in bead or pellet formulations.(2,3)

It was recently reported that when MCC is granulated with purified water, the resultant pellets are very strong and exhibit varying degrees of controlled release as shown by in-vitro dissolution testing by forming an inert matrix.(4) Little information is available in the literature pertaining to ethanol granulated (MCC) formulations.(5)

The purpose of this experimentation was to ascertain if MCC is amenable to the spheronization process when granulated with alcohol and to observe any differences in bonding strength between alcohol and water granulated products.

For these experiments, a formulation of 10% anhydrous theophylline, and 90% MCC was granulated with ethanol, with water, and with a range of ethanol/water mixtures and then extruded and spheronized. Physical properties were examined and further evaluation of compacted samples was carried out.

EXPERIMENTAL

Materials

The single excipient utilized in all formulations was Microcrystalline Cellulose NF (Avicel PH-101, FMC Corporation, Philadelphia, Pa.). The active ingredients used was Theophylline, Anhydrous USP (Knoll, New York, N.Y.) and Acetaminophen (Mallinckrodt, New York, N.Y.). The granulating solutions were purified water, absolute alcohol, alcohol USP (95% ethanol) and a range of ethanol/water mixtures.

Method

The spheronization method utilized for this work was extruder/marumerizer technology. The ingredients were both blended and granulated in a Hobart Model A-200T Planetary Mixer (Hobart Corp. Hobart, N.Y.). The batch size remained constant at 1.0 kg of dry solids. Following a 7 minute dry blend, granulating solutions were added until the desired consistency for extrusion was obtained.

The wet granulation was then passed through the Extruder, Model EXD-60 (Luwa Corp., Charlotte, N.C.) set to operate at 50 RPM and equipped with 1.5 mm screens. The resultant extrudate was immediately placed into the Marumerizer, Model Q-230 (Luwa Corp.) fitted with a 2 mm scored friction plate and was allowed to rotate at 1000 RPM for a one minute residence time. The wet pellets were spread on paper lined trays and dried to a constant moisture content in a Stokes Drying Oven, Model 38C (Pennwalt Corporation, Warminster, Pa.)

Compaction

Compacts of the granulations, pellets and a dry blend formula of 10% theophylline/90% MCC were made on a Laboratory Carver Press, Model 2462 (F. S. Carver Inc., Menomonee Falls, Wis.) equipped with 7/16 inch, round, flat face tooling. Each compact consisted of 600 mg of material that was held at the designated compaction pressure for a period of five seconds. Comparisons were based on samples prepared at constant pressure (3000 lbs) or at constant hardness (5.5 kg). Tablet hardness was measured via the Heberlein Hardness Tester.

Sieve Analysis and Density Testing

Particle size analysis and bed density determinations were obtained by conventional methods. A Cenco Sieve Shaker (Cenco Meinzer, Central Scientific, Chicago, Ill.) and a nest of U.S. Standard Sieves were used for sieve analysis; and a Vanderkamp Tap Density Tester Model 10700 (Van-Kel Industries Inc. Chatham, N.J.) was employed for bulk and tap density testing.

Friability Testing

A 10 g sample of 16/20 mesh cut pellets was placed into an Erweka Friabilator (Erweka Inc, Fairfield, Ct.) fitted with an abrasion wheel containing 200 (4mm) glass beads. After rotation for 10 minutes, the percent weight loss was determined. The material was placed on a nest of tared screens (Mesh Sizes: 8,20,Pan) and placed on the sieve shaker for 2 minutes. The % Friability (F) was determined and calculated by the following method based on initial weight (W_I) and weight retained (W_R):

$$\% F = \frac{W_I - W_R}{W_I} \times 100$$

Dissolution Testing

Dissolution testing was performed on specific mesh cuts of pellets and on compacts, where indicated. The USP/NF basket method was utilized at a rotational speed of 50 RPM with a solvent of 900 ml purified water at 37°C. Samples were collected over a 4 hour period and analyzed on a Beckman DU Spectrophotometer at a wavelength of 273 nm.

True Volume and Porosity Testing

True volume and porosity determinations were performed on pellets utilizing both a Micropycnometer Model MPY-1 (Quantachrome Corp., Syosset, N.Y.) which utilizes the principle of helium displacement, and a mercury intrusion porosimeter Quantachrome Autoscan, Model SP-33 (Quantachrome Corp., Syosset, N.Y.). Both methods are used to determine porosity of solid powders and dosage forms by forcing either helium or mercury into the dosage form void spaces under pressure.

RESULTS AND DISCUSSION

Processing

As expected and as shown previously (2), a formulation of 10% theophylline/90% MCC and a formulation of pure MCC, each granulated with purified water were processed successfully through all stages of spheronization and resulted in pellets that were hard and well formed (Table I). Batches of 10% theophylline/90% MCC would not process into pellets when granulated with absolute alcohol, but would when granulated with 95% ethanol. These pellets, however, were found to be friable during handling, smaller, and more irregular in shape as observed during sieve analysis testing. Upon physical testing, differences were seen between water and 95% ethanol granulated

TABLE 1
Physical Testing for 10% Theophylline/90% MCC Pellets
Formulated With Varying Ethanol/Water Mixtures

	Mole Fraction of Water in Ethanol/Water Mixture					
Sieve Analysis mesh #	1	.84	.73	.45	.14	0
	% retained					
8	0	0	0	1	3	*
12	0	1	0	4	3	-
16	23	21	3	26	6	-
20	62	35	34.3	29	14	-
30	13	23	21.2	32	23	-
40	2	13	15.2	7	25	-
PAN	0	7	26.3	1	26	-
Mean Particle Diameter (um)	900	760	570	790	490	-
Density(g/ml)						
Loose	.715	.641	.641	.454	.480	-
Tap	.735	.735	.676	.513	.543	-
% Friability	5	15	10	20	60	

*No Pellets Obtained

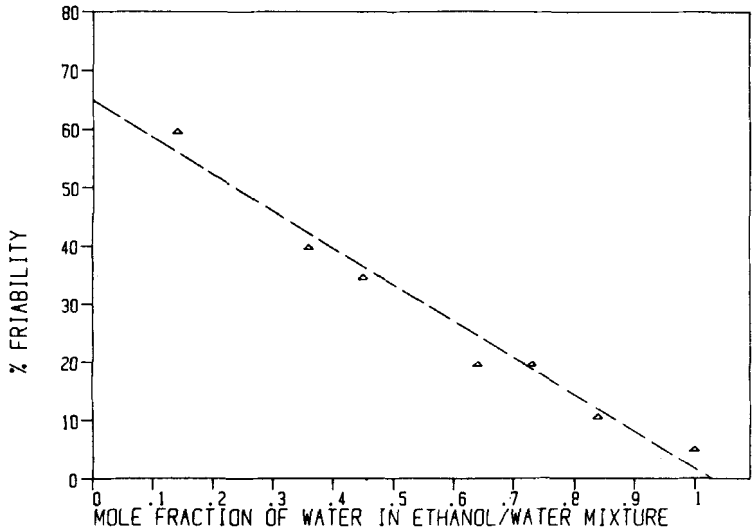

FIGURE 1

Effect of mole fraction of ethanol/water in the granulating liquid on the friability of pellets.

pellet systems (Table I). A formulation of pure MCC would not process into pellets when granulated with either absolute alcohol or with 95% ethanol.

Based on the above results, additional experiments were performed by granulating the formulation of 10% theophylline/90% MCC with varying ethanol/water mixtures. It was found that as the mole fraction of water in the mixture used to granulate increased, the resultant pellets generally increased in size, became more dense and less friable (see Fig. 1 and Table 1).

Porosity

The methods of mercury and helium displacement porosimetry gave similar results. The porosity of 95% ethanol formulated pellet systems was approximately 54% where as that of water formulated pellet systems was approximately 14% (see Fig. 2).

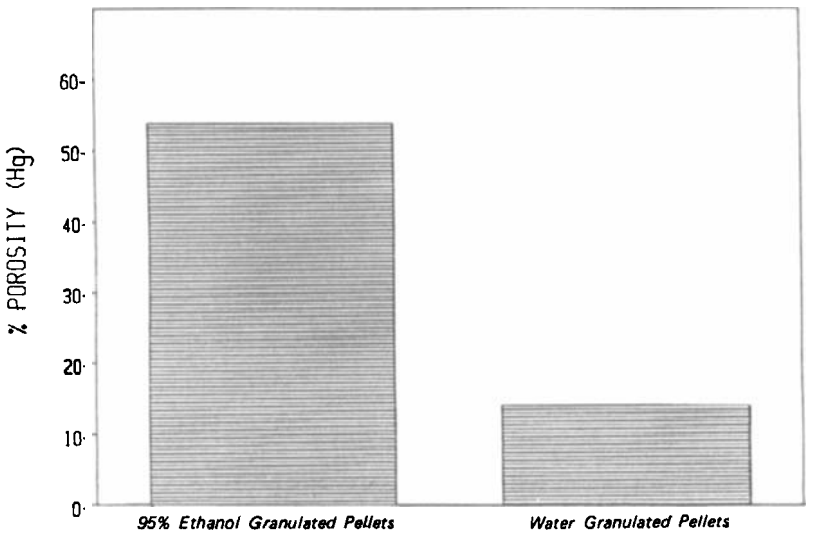

FIGURE 2

Percent porosity (Hg) for pellets containing 10% Theophylline/ Avicel PH-101.

Dissolution

The physical behavior of the two products was different during dissolution testing. The 95% ethanol formulated pellets immediately and completely disintegrated in the dissolution media resulting in almost complete release of the active ingredient at the first sample time point. The 100% water granulated pellet system remained intact during the entire dissolution test resulting in a slower drug release (Fig. 3). Other work in our laboratories indicates that pellets prepared by water granulation do remain intact during at least 12 hours of dissolution testing.(2)

Further differences between pellets prepared with the two solvents was observed when a dissolution mesh

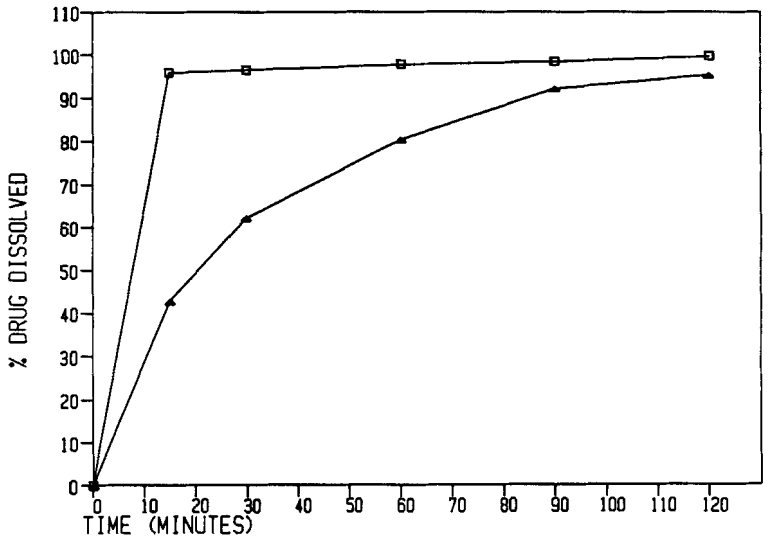

FIGURE 3

Dissolution profiles of 16/18 mesh 10% Theophylline/Avicel PH-101 pellets (Δ) water granulated; (□) 95% ethanol granulated.

cut comparison was performed. As expected, the strong water granulated pellet systems showed a difference in dissolution release rates with varying particle size (Fig. 4). The 95% ethanol granulated pellet formulations did not (Fig. 5). The intact pellets provide different surface areas based on bead size; the disintegrating beads provide a similar surface area.

Subsequent pellet batches of the same formulation were prepared by granulating with varying ethanol/water mixtures. A trend observed during dissolution testing was that, as the mole fraction of water in the ethanol/water mixture increased, the amount of drug released decreased (Fig. 6). When greater than 30% water is present in the ethanol/water mixture, pellets remained intact during the entire dissolution test. When less

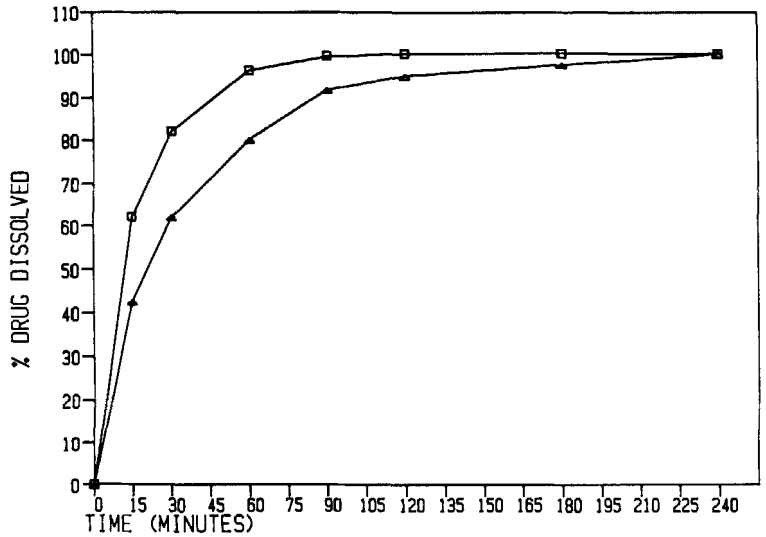

FIGURE 4

Dissolution profile (mesh cut comparison) of 10% Theophylline/ Avicel PH-101 water granulated pellets. (Δ) 16/18 Mesh; (□) 20/30 mesh.

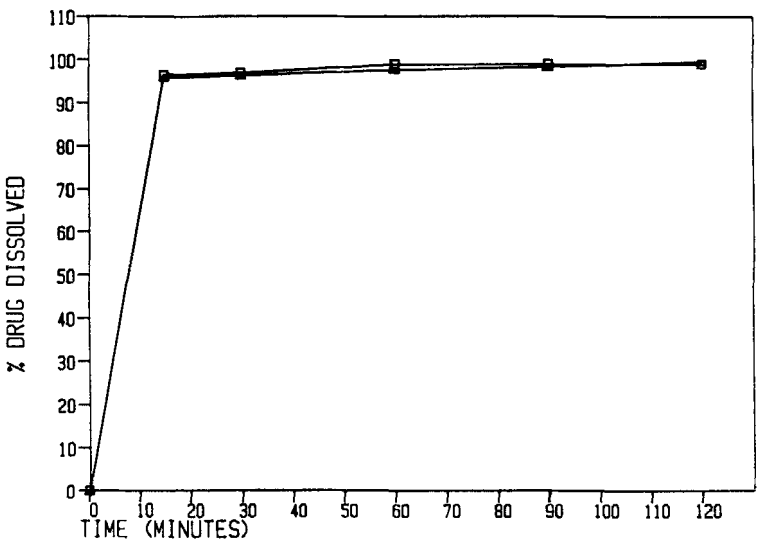

FIGURE 5

Dissolution Profile (Mesh Cut Comparison) of 10% Theophylline/ Avicel PH-101 95% ethanol granulated pellets. (Δ) 16/18 Mesh; (□) 20/30 mesh.

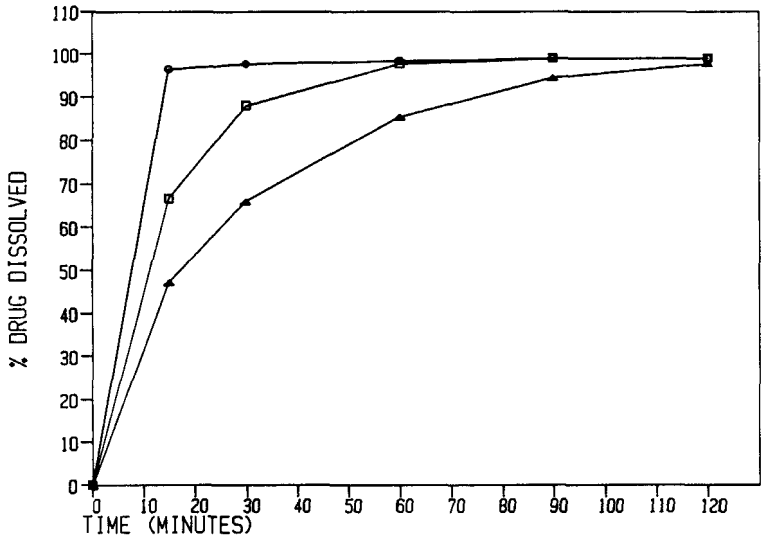

FIGURE 6

Dissolution profile of 16/30 mesh 10% Theophylline/Avicel PH-101 pellets (Δ) water granulated; (□) 50/50 ethanol/water granulated; (O) 95/5 ethanol/water granulated.

than 30% water is present in the mixture, pellets disintegrate.

All the data presented thus far seem to indicate that stronger bonding is present in water granulated pellet systems. Further evidence was obtained by subjecting the pellets to compaction.

Compaction

Compaction profiles of both the water and 95% ethanol granulated pellets are shown in Fig. 7. The results indicate that 95% ethanol granulated pellet systems are more sensitive to varying forces. The reason for this could be due to the weakly bonded 95%

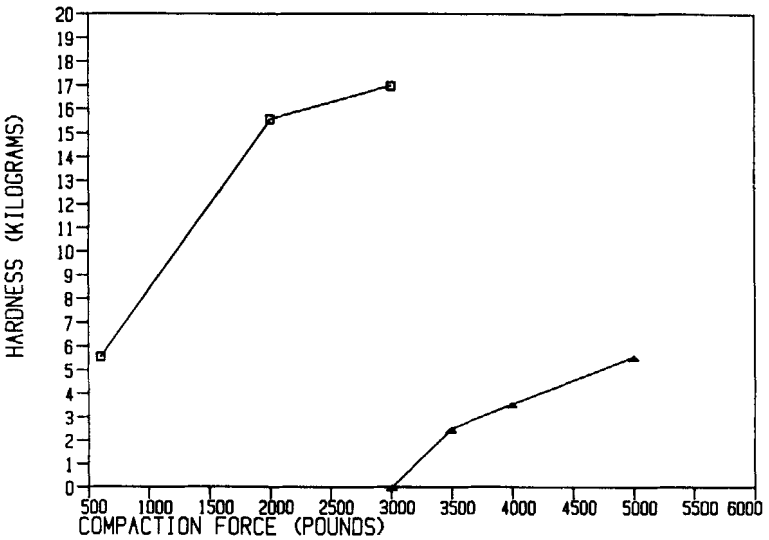

FIGURE 7

Effect of varying compressional force on hardness of compacted 16/30 mesh cut pellets of 10% Theophylline/Avicel PH-101. (Δ) pellets prepared by water granulation; (□) pellets prepared by 95% ethanol granulation.

ethanol granulated pellet systems rupturing upon compaction, exposing more smooth surface to surface contact for bonding. The water granulated pellet systems resist rupturing due to their strong bond strength and allow less surface to surface contact for bonding to occur. Photographs of the compacts show the outline of pellets in water granulated compacts and a smoother surface on the 95% ethanol granulated compacts (Figs. 8 & 9).

Compact hardness values were also different for the two systems. A constant 600 mg of 16/30 mesh cut pellets were compacted at a compressional force of 3000 pounds (or 13.3 kn). The compacted ethanol granulated

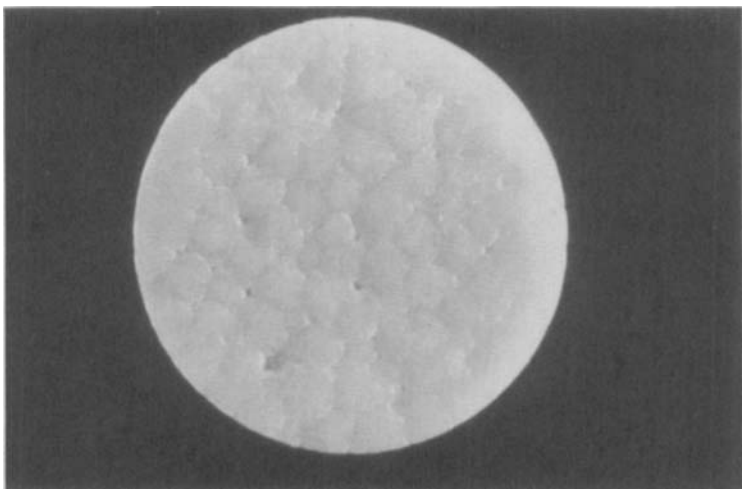

FIGURE 8

Photograph of 10% Theophylline/Avicel PH-101 pellets manufactured by water granulating and compacted at 5000 pounds force.

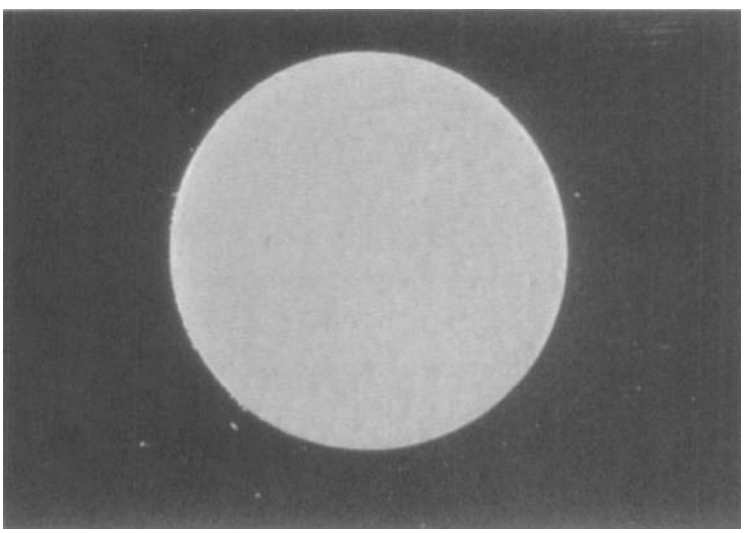

FIGURE 9

Photograph of 10% Theophylline/Avicel PH-101 pellets manufactured by 95% ethanol granulating and compacted at 5000 pounds force.

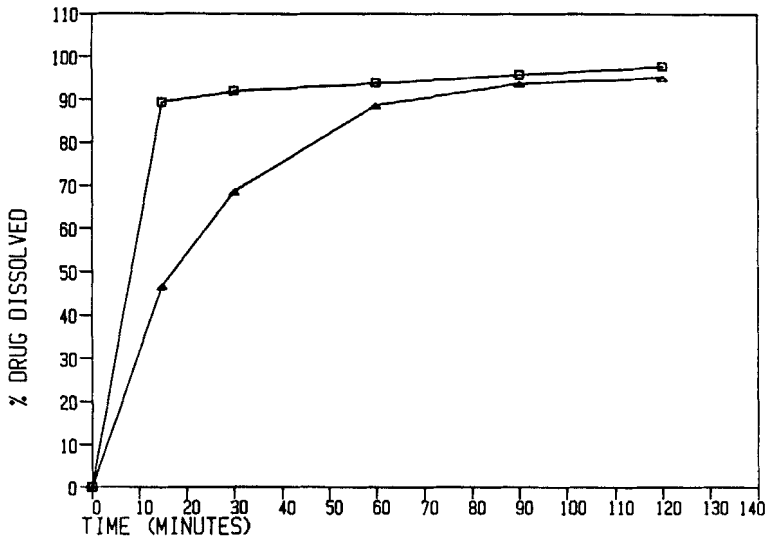

FIGURE 10

Effect of varying compressional force on percent drug release of 10% Theophylline/Avicel PH-101 pellets manufactured by 95% ethanol granulating. (□) 600 pounds compaction force; H = 5.5 kp (Δ) 3000 Pounds Compaction Force; H = 17 kp

pellets exhibit a breaking strength value greater than 16 kg, whereas the water granulated pellet compacts were too soft to give a reading greater than zero (Fig. 7). To obtain a compact of equivalent hardness (5.5 kg), 5000 pounds (22.2 kn) was required for the water pellets and only 600 pounds (2.7 kn) was required for the alcohol pellets (Fig.7).

The dissolution of the pellet compacts showed different trends than those observed in non-compacted pellets systems. The dissolution of the 95% ethanol granulated pellet compacts decreased with increased compressional force (Fig. 10), whereas water granulated pellet compacts had a dissolution profile nearly

identical to the non-compacted water granulated pellets. The latter phenomenon can be explained by physical observation; the compact with water granulated pellets disintegrates into its component pellets. The ethanol granulated pellet compacts did not; they erode as a conventional tablet.

Granulations were also prepared from the same formulations. These granulations (water granulated, 95% ethanol granulated) as well as a dry blend formula, as a control, were also compacted at a hardness of 5.5 kg. Similar trends in compaction and dissolution were observed, but the differences were not as dramatic as those seen with pellets. It is interesting to note that when MCC formulations were granulated with 95% ethanol, they do not lose compressibility and behave similarly to the dry blend formula.

SUMMARY AND CONCLUSIONS

The results indicate that the strength and physical properties of MCC containing pellets are affected by the granulating solvent, specifically mixtures of ethanol/water. Water granulated MCC containing formulas result in strongly bonded, hard pellets with good shape; but pellets with lower strength and less uniform shape do result as the level of ethanol in the ethanol/water granulating fluid increases.

A formulation of only MCC granulated with 95% ethanol could not be processed into pellets. However, the addition of a low concentration of active ingredient made the formulation amenable to the extrusion/marumerization process. Neither the same binary mixture nor a formulation of neat MCC could be

processed into pellets when granulated with absolute alcohol.

Pellets granulated with water exhibited poor compressibility, whereas the 95% ethanol granulated pellet formulations were reasonably compressible, again indicating a difference in bonding strength.

Further work is underway to explain differences in these pellets and to characterize the bonding behavior of these MCC systems.

ACKNOWLEDGEMENTS

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REFERENCES

1) G.E. Reier, R. Shangraw, J. Pharm. Sci., 55, 5, (1966).
2) R.E. O'Connor and J.B. Schwartz, Drug Dev. Ind. Pharm., 11, 1837 (1985).
3) FMC Corporation "Avicel Spheres" Technical Catalog.
4) R.E. O'Connor, Ph.D. Dissertation, Philadelphia College of Pharmacy and Science, 1987. "The Drug Release Mechanism and Optimization of a Microcrystalline Cellulose Pellet System."
5) S.R. Kalidindi, Ph.D. Dissertation, University of Maryland, 1983. "Study of the Various Techniques Utilized to Characterize Powder Compaction as Applied to Pharmaceutical Systems."