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Research paper

Sustained-release effect of codried excipients of microcrystalline cellulose and *Ganoderma* fiber

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Abstract

The sustained-release effects of codried excipient of modified *Ganoderma* (treated with alkaline solution) and microcrystalline cellulose at different ratios were examined using acetaminophen (ACT) as a model drug. Results demonstrate that the crushing strength of most ACT tablets made with codried powder at all ratios increased as compaction force increased; but a rapid decline was observed when compression force exceeded 2 tons. Drug release from tablets compressed at 0.5 ton increased as modified *Ganoderma* fiber content increased. But when the compression force exceeded 1 ton, the release rate was not influenced by the compaction force or the increasing content of *Ganoderma* fiber. However, the dissolution of ACT from these tablets could be sustained for longer than 24 h. The extent of drug release was shown to increase with increasing amounts of modified *Ganoderma* in the codried excipient. The addition of disintegrants could further accelerate the drug release from the tablet. Drug release was also dependent upon the amount and kind of disintegrant used. The influence was in the following order: primojel > crospovidone > starch 1500. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: *Ganoderma*; Sustained release; Microcrystalline cellulose; Acetaminophen

1. Introduction

Microcrystalline cellulose (MCC) is a popular pharmaceutical excipient in direct compression tablet formulations. In order to manipulate its tableting functionalities, some reports have examined the coprocessing of MCC with other excipients [1,2]. Recently, many fungal polysaccharides were explored and have been proposed for use as additives for various purposes in tablet dosage form [3–5]. The fiber obtained from the fruiting body of *Ganoderma* belongs to a fungal polysaccharide designated as β-glucan. In general, *Ganoderma* fibers are treated as useless waste after hot water extraction of their chemical ingredients. Waste *Ganoderma* fiber has been developed into wound dressings [6,7]. The enhancement of wound healing by *Ganoderma* fiber was comparable to that covered with crab chitin sheet, and was better than gauze. Applications have expanded into explorations for cosmetic uses.

Low toxicity of this fibrous material has been demonstrated, making it a suitable choice for a pharmaceutical excipient. Therefore, it is interesting to evaluate its sustained functionalities as a tableting excipient. In this study, a codrying process was employed, and acetaminophen was selected as a model drug. *Ganoderma* fiber was codried with acetaminophen in several ratios with or without the presence of MCC. The physical properties and the sustained-release profiles of tablets made with these codried samples were evaluated.

2. Materials and methods

2.1. Preparation of codried samples

Ganoderma fibers were crushed and sieved to reserve the fraction between 8 and 80 mesh in size. One hundred fifty grams of this fraction was immersed in 3 l of a 1 M NaOH solution and heated to 85°C for 3 h. The fiber was then bleached with 900 ml of Clorox (sodium hypochlorite 5.25%), which was diluted with distilled water to 3 l. The white fiber so obtained after washing was next homogenized to produce the hydrogel form of *Ganoderma* fiber. This hydrogel and acetaminophen were mixed in several ratios with or without the presence of the MCC slurry. These mixtures were individually transferred to a planetary mixer and granulated at a fixed speed for 10 min. The wet mass was dried at 50°C, then pulverized and sieved to reserve the frac-

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Table 1
Components of codried powder containing acetaminophen (ACT), modified *Ganoderma* fiber (m-GT), and microcrystalline cellulose (MCC)

Rx.	A	B	C	D	E
ACT	99[a]	95	95	95	95
m-GT	1	5	4	2.5	1
MCC	–	–	1	2.5	4

[a] % content.

tion between 60 and 150 mesh for further experiments. Table 1 lists the formulation design and its components. Three kinds of disintegrant (crospovidone, primojel, and starch 1500) were also mixed with the codried powders at either 2 or 5% before tablet compression to compare the sustained effect of codried excipient on the model drug.

2.2. Physical properties of codried powder and tablets

The angle of repose (°), bulk density, and tapped density for each codried powder and those mixed with three different percentages of Aerosil-200 were determined by an A.B.D. Fine Particle Characteristics Measuring instrument (Tsutsui Scientific Instruments, Japan). Compressibility of the powder was calculated using Carr's index. Tablets were compressed using a Carver laboratory press (Fred S. Carver, USA) utilizing standard 7.5-mm concave punches and die tooling at compression forces of 0.5, 1.0, 1.5, 2.0, and 3.0 ton. A raising speed of 0.5 cm/s and a zero contact time were used to form tablets. The punches and die wall were cleaned with facial papers and the tooling was lubricated with a thin film of magnesium stearate applied in an acetone solution. Then the die was filled with 200 mg of powder. Twenty replicate compactions were prepared at the same compression force. The tablet thickness and crushing strength were determined using a Pharma Test Model PTB-311 (Pharma GmbH, Germany). Friability of the compacts was evaluated from the weight loss of 10 tablets tumbled for 100 revolutions using a Roche type Friabilator (All-Trans Ent., Taiwan). The results of powder properties were listed in Table 2. The repose angles of all codried samples, including those mixed with three different percentages of Aerosil 200, were larger than 55°, and the compressibilities were higher than 35%, indicating that they all demonstrate poor flow ability. Although the flow ability gradually improved with the addition of increasing amounts of Aerosil-200 (0.2–1.0%), it was still inadequate for suitable scale-up production.

2.3. Scanning electron microscopy (SEM)

Powder morphologies were examined under a Hitachi model S-2400 SEM (at the Department of Pathology, Taipei Medical College). Samples were loaded on aluminum studs and coated with gold for 3 min at 8 mA under a pressure of 0.1 Torr. The samples were scanned and the micrographs were examined.

2.4. Drug dissolution

The USP paddle method (Jasco DT-610) was used to measure dissolution rates of acetaminophen. The dissolution medium was pH 5.8 phosphate buffer solution (50 mM) maintained at 37 ± 0.5°C with a stirring rate of 50 rev/min. The sample was automatically withdrawn at fixed time intervals and analyzed for the drug using a UV method

Table 2
Powder flow properties of codried powder of acetaminophen with different ratios of modified *Ganoderma* fiber and microcrystalline cellulose

Rx.	Respose angle (°)	Collapse angle (°)	Bulk density (g/100 ml)	Tapped density (g/100 ml)	Compressibility (%)
A	63.3 (2.1)[a]	46.0 (1.7)	17.70 (0.57)	31.67 (1.99)	43.92 (4.54)
A_1[b]	59.0 (0.0)	44.0 (6.9)	17.48 (0.79)	31.22 (0.69)	44.03 (1.81)
A_2	61.0 (3.5)	36.7 (7.6)	20.20 (0.88)	38.09 (0.51)	46.98 (1.65)
A_3	57.7 (0.6)	36.3 (1.5)	23.30 (0.34)	36.33 (0.77)	35.83 (2.23)
B	63.0 (0.0)	43.3 (1.5)	11.93 (0.74)	20.94 (2.06)	42.89 (2.99)
B_1	59.3 (1.5)	43.7 (0.6)	14.23 (0.24)	21.85 (0.60)	34.84 (2.71)
B_2	55.7 (0.6)	35.3 (3.8)	16.43 (1.30)	24.05 (1.01)	31.73 (2.83)
B_3	56.0 (1.0)	35.3 (2.1)	18.71 (0.32)	28.31 (0.37)	33.89 (1.96)
C	66.0 (2.0)	42.3 (1.2)	13.09 (0.15)	21.56 (1.07)	39.18 (2.51)
C_1	62.7 (1.5)	40.3 (2.5)	13.91 (0.66)	21.78 (0.35)	36.16 (2.63)
C_2	57.7 (2.3)	40.3 (5.5)	17.06 (0.05)	24.64 (0.81)	30.69 (2.38)
C_3	55.7 (2.1)	36.7 (1.5)	20.21 (0.22)	28.97 (0.68)	30.18 (2.30)
D	58.3 (1.5)	44.3 (2.3)	15.30 (0.70)	25.04 (1.68)	38.62 (6.67)
D_1	59.0 (0.0)	43.3 (4.5)	14.93 (0.82)	22.46 (1.05)	33.48 (3.78)
D_2	57.3 (0.6)	35.7 (1.5)	15.60 (0.25)	25.08 (1.03)	37.74 (2.50)
D_3	56.3 (1.5)	41.7 (1.5)	20.59 (1.09)	30.67 (0.58)	32.89 (2.64)
E	62.7 (0.6)	46.0 (3.0)	16.65 (0.39)	30.75 (1.18)	45.78 (2.62)
E_1	58.3 (0.6)	37.3 (2.5)	17.28 (0.20)	29.74 (0.76)	41.89 (0.86)
E_2	59.3 (1.2)	39.7 (4.7)	20.14 (0.41)	32.46 (0.32)	37.95 (0.78)
E_3	54.7 (3.1)	40.0 (4.4)	23.98 (0.31)	36.02 (0.49)	33.41 (1.41)

[a] Mean (SD); $n = 3$.
[b] Codried powder with $_1$, 0.2% Aerosil-200; $_2$, 0.5% Aerosil-200; $_3$, 1.0% Aerosil-200.

Table 3
Physical properties of tablets prepared with codried powder containing acetaminophen, modified *Ganoderma* fibers and microcrystalline cellulose

Rx.	Compaction force (ton)	Thickness (mm)	Diameter (mm)	Friability (%)	Crushing strength (kp)
B	0.5	4.32 (0.02)[a]	7.59 (0.01)	0.11	12.8 (0.9)
	1.0	4.10 (0.06)	7.58 (0.01)	0.12	16.2 (4.2)
	1.5	4.08 (0.01)	7.59 (0.01)	0.16	20.5 (2.7)
	2.0	4.05 (0.02)	7.59 (0.01)	0.15	19.6 (2.2)
	3.0	4.02 (0.01)	7.60 (0.01)	0.18	6.8 (0.7)
C	0.5	4.35 (0.03)	7.60 (0.02)	0.21	10.8 (1.9)
	1.0	4.16 (0.02)	7.59 (0.01)	0.25	14.8 (2.3)
	1.5	4.08 (0.02)	7.62 (0.03)	0.16	15.5 (3.0)
	2.0	4.04 (0.02)	7.59 (0.01)	0.16	16.5 (1.8)
	3.0	4.04 (0.03)	7.59 (0.00)	0.22	5.3 (2.0)
D	0.5	4.31 (0.02)	7.59 (0.01)	0.21	12.9 (1.5)
	1.0	4.17 (0.03)	7.60 (0.01)	0.24	14.4 (2.5)
	1.5	4.08 (0.04)	7.60 (0.00)	0.24	15.0 (3.5)
	2.0	4.03 (0.03)	7.60 (0.01)	0.14	14.5 (2.9)
	3.0	4.02 (0.02)	7.58 (0.01)	0.35[b]	6.3 (1.2)
E	0.5	4.27 (0.03)	7.59 (0.01)	0.25	11.1 (2.6)
	1.0	4.16 (0.03)	7.62 (0.03)	0.44[b]	12.7 (3.0)
	1.5	4.04 (0.03)	7.60 (0.02)	0.70[c]	17.1 (1.9)
	2.0	4.01 (0.03)	7.61 (0.01)	0.40[c]	9.4 (0.9)
	3.0	3.99 (0.01)	7.59 (0.01)	0.72[c]	3.4 (2.0)

[a] Mean (SD); $n = 6$.
[b] One tablet divided into two parts.
[c] Some tablets divided into several parts.

after an appropriate dilution. This UV method measured at a wavelength of 241 nm has been validated with an acceptable coefficient of variation for accuracy and precision (0.13–2.29% and 0.04–1.21% for inter-day and 0.03–3.70% and 0.14–2.29% for intra-day, respectively).

3. Results and discussion

Table 3 shows the tablet properties for all codried samples except formulation A. Tablet capping or lamination was observed for formulation A at all five compression forces. Nevertheless, the crushing strength of tablets increased and the friability decreased when the proportion of *Ganoderma* fiber increased and using the same compression force at a lower level. But the crushing strength of tablets decreased when the compression force further increased. No exception to the decreasing thickness of tablets with increasing compression forces was observed for all codried samples. Formulation D showed the highest friability at all compression forces among these four codried samples.

These results indicate that a minimal required amount (i.e. higher than 1% *Ganoderma* fiber in the codried excipients) seems to be necessary for successful tableting. The addition of MCC can improve the crushing strength of resulting tablets, but with a lower efficiency compared with that produced by increasing the proportion of *Ganoderma* fiber. During the codrying process, ACT and MCC are dispersed among the hydrogel forms of the *Ganoderma* fibers. Possibly, the linking effect of the *Ganoderma* fibers after codrying

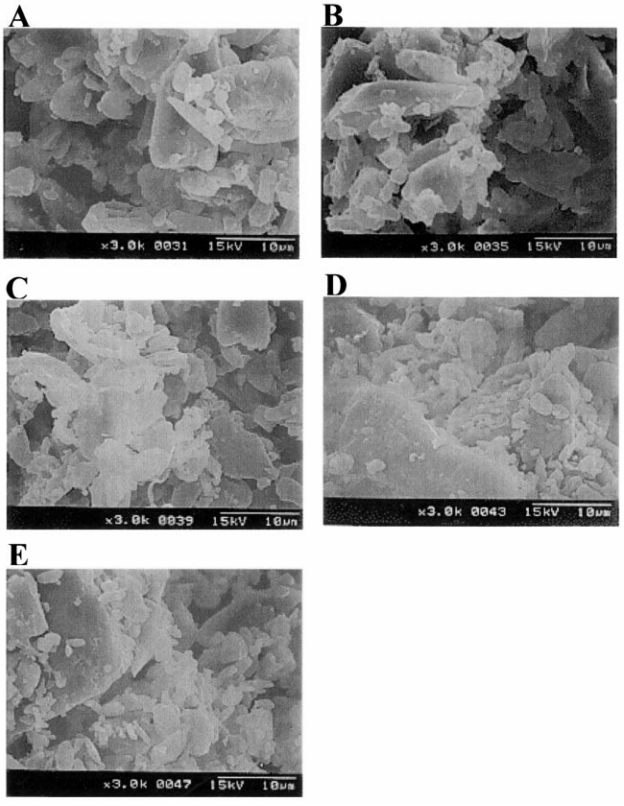

Fig. 1. SEM photographs of particles for formulations (A), (B), (C), (D), and (E). Bar: 50 μm.

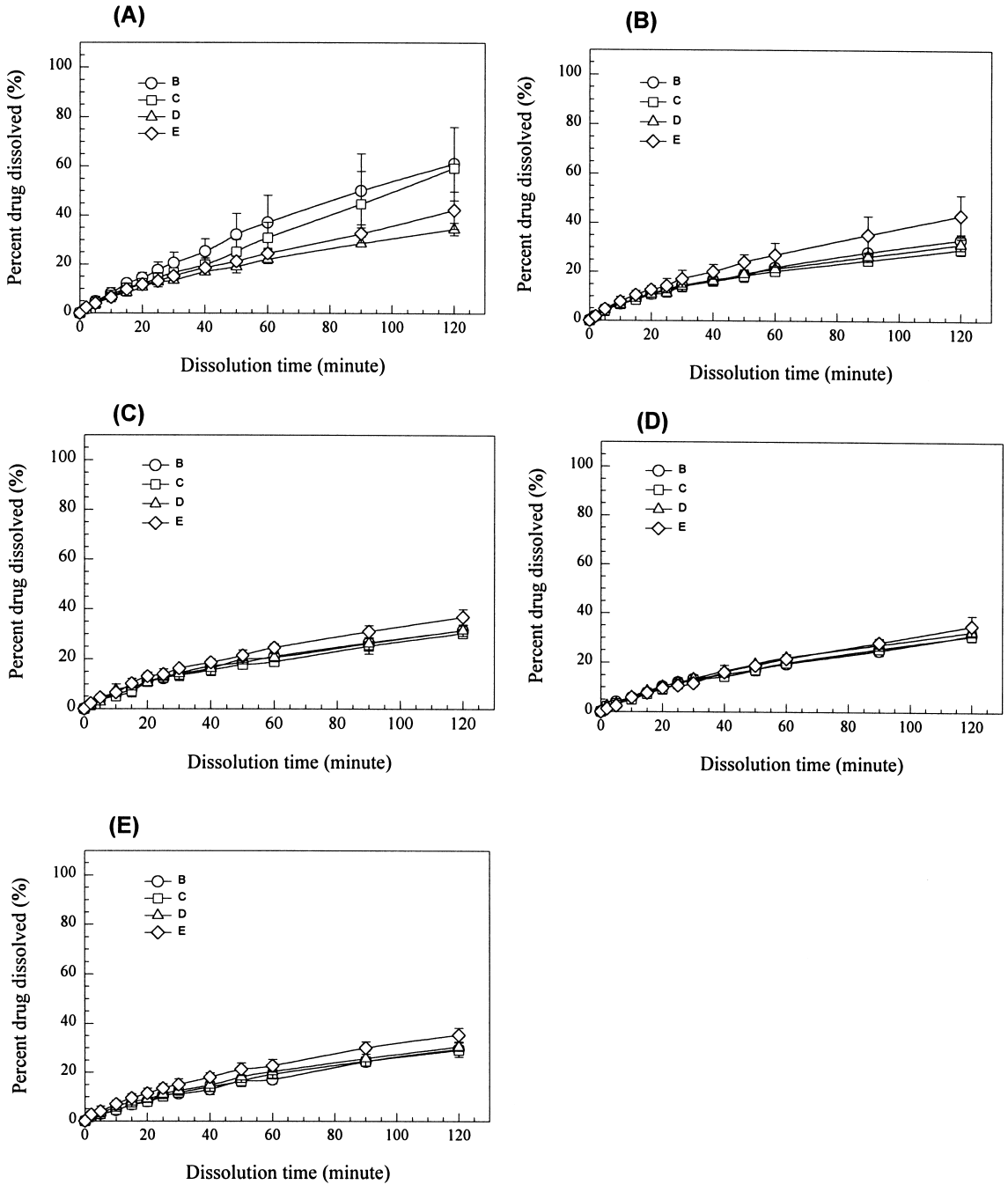

Fig. 2. Dissolution profiles of acetaminophen from tablets made with four different formulations compressed at 0.5 (A), 1.0 (B), 1.5 (C), 2.0 (D), and 3.0 (E) ton force.

strengthens the structure of the tablets, therefore increasing their crushing strengths. Obviously, the binding effect of MCC in this status was less efficient than that expressed by the hydrogel form of *Ganoderma* fiber. We also suspect that the difference in tablet strength is attributable to alterations in the fiber morphology of these codried powders. However, according to the SEM results, there were no obvious changes in these codried powders (Fig. 1).

On the other hand, acetaminophen is mainly compressed by fragmentation, by which an elastic deformation of fragmented granules would cause deterioration in tablet strength. This might play an important role in the determination of tablet strength. As expected, the extent of fragmentation increases with increasing compression force, in turn increasing the tendency for elastic deformation to deteriorate the tablet strength. This seems to conform with the results that tablet strength decreased when compression forces were higher.

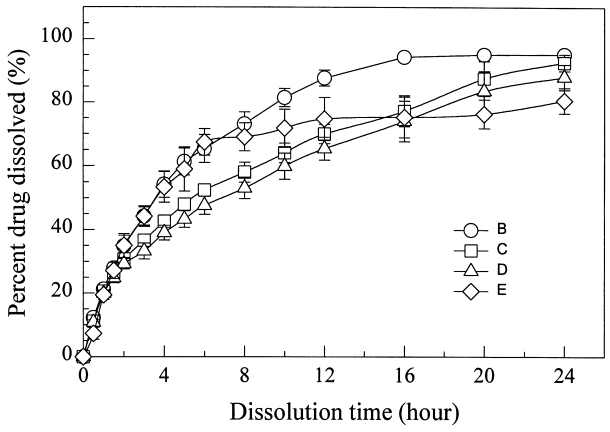

Fig. 3. Dissolution profiles of acetaminophen from tablets made with four different formulations compressed at 1 ton force.

The release profile of acetaminophen from tablets made with codried samples at all compression forces showed sustained-release characteristics as shown in Fig. 2. The influence of *Ganoderma* fiber proportions on the sustained-release effect of acetaminophen was obvious only for those tablets compressed at 0.5 ton. This indicates that increasing the proportion of *Ganoderma* fiber in the formulation moderately accelerates drug release. At higher compression forces, the amounts of drug released from these four formulations differ insignificantly. Since disintegration and swelling of those tablets were not observed, a wicking effect created by the hydrophilic nature of *Ganoderma* fiber might be responsible for inducing water penetration into the tablet. The diffusion of dissolved acetaminophen from this matrix type of tablet would then be activated by this mechanism. Accordingly, the increase of *Ganoderma* fiber proportion in the formulation facilitates drug release. Since the porosity of the tablet decreases with increasing compression force, the wicking effect of *Ganoderma* fiber seems to level off and then has an insignificant influence on drug release.

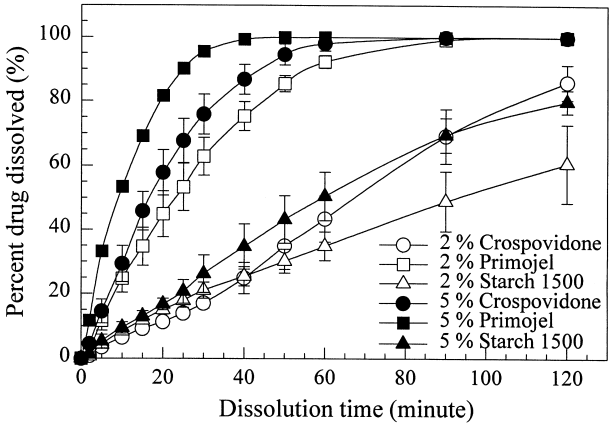

Fig. 4. Dissolution profiles of acetaminophen from tablets made with formulation B compressed with various disintegrants at 1 ton force.

A typical release profile is shown in Fig. 3 to demonstrate that an extended period of drug release for 24 h was achievable for these four codried formulations at a compression force of 1 ton. Since those tablets were non-disintegrated and non-swellable, a Higuchi model was applied to describe the dissolution relationship between the percentage released and the square root of time. A linear relationship was demonstrated, and the n values and rate constants for these four formulations were calculated. Results show that a Fickian diffusion release mechanism was preferable as indicated by the closeness of all n values to 0.5.

The inclusion of disintegrants in these codried formulations to manipulate drug release was examined. The release profiles of acetaminophen from tablets made from formulation B with the addition of three different disintegrants at two levels are shown in Fig. 4. As expected, drug release increases with increasing amounts of all three kinds of disintegrants, respectively. However, the effect of primojel on drug release was the most profound among these three disintegrants. Therefore, these codried samples might be potential material to formulate controlled-release tablet dosage forms by adjusting the addition of other suitable adjutants.

4. Conclusions

The codrying of *Ganoderma* fiber with MCC provided useful tableting excipients. The physical characteristics of granules and tablets proved to be suitable as matrix materials. All these codried samples showed a sustained effect on drug release. Including other suitable adjutants they may potentially be useful for the design of controlled-release tablet dosage forms. However, the sustained-release mechanisms of these codried samples are not so clear. A non-disintegration property of the resulting tablets and a wicking effect of *Ganoderma* fiber to induce drug release were suspected.

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