The research of several natural edible materials as a disintegrant

Hung Chang Wu¹  Tsung Hsun Lee¹  Shu Yang Yen²  Chun Ren Chen²*

¹ Graduate Institute of Pharmaceutical Science,
² Department of Pharmacy,
Chia Nan University of Pharmacy and Science, Tainan, Taiwan, 71710, R.O.C.

Abstract

Starch is the only natural disintegrant which is still widely used today. Lentinula edodes (Berkeley) Pegler, Flammulina velutipes (Curt. Fr.) Sing, Auricularia polytricha, Tremella fuciformis, and Pleurotus eryngii are traditional Taiwanese food materials. They contain a lot of fiber and taste deliciously. They were investigated as a novel disintegrant in this study. The tablet contained hydrochlorothiazide, dibasic calcium phosphate, and each new material or starch respectively as the model drug, the bulking agent, and the disintegrant. The tablets were made by direct compression method. The disintegration time of these tablets in pH 1.2 or pH 6.8 medium was measured. The effect of disintegrant concentration on the disintegration time using Tremella fuciformis was studied. The swelling volume and hydration capacity of these materials in pH 1.2 or pH 6.8 medium were also studied to investigate the possible mechanisms of these materials to be used as a disintegrant. The result showed that the disintegration time of tablets containing each milled material (< 2 min in most materials) was much less than that of blank tablets (> 40 min). The disintegration time of tablets was further decreased if each material was cooked before milling. Especially, the tablets containing cooked Tremella fuciformis (3W) had the least disintegration time and it can be used from one to ten percents. The disintegrating activity of these materials is related to their swelling and water hydration abilities as shown in the swelling volume and hydration capacity studies. Generally speaking their swelling and hydration capacity are better in neutral environment than in acidic environment. The discrepancy between disintegration time and swelling and hydration capacity in pH 1.2 or pH 6.8 medium may be due to the effect of bulking agent.

Key words: Disintegrant; Auricularia polytricha; Tremella fuciformis

*Correspondence:Department of Pharmacy, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, 71710, R.O.C.
Tel: +886-6-3912082
Fax: +886-6-2667318
E-mail: hchunliw@gmail.com

I、Introduction

A disintegrant has been included in a solid formulation for a long time (Rudnic and Schwartz, 2005). Recently the orally disintegrating tablets (ODT) have gained more and more attention due to their popularity (Fukami et al., 2006; Kuno et al., 2008). One of the methods to make the orally disintegrating tablets is by direct compression of a tablet formulation with a large amount of a disintegrant inside (Solanki and Dahima, 2011).

Starch is the only traditional natural disintegrant still widely used today (Rudnic and Schwartz, 2005). However, it is not without drawbacks like low efficiency. Although efforts have been made to search a new disintegrant (Visavarungroj and Remon, 1990; Adebayo et al., 2008; Chang et al., 1998; Chebli and Cartilier, 1998), there is no new natural disintegrant to replace starch in the market yet. Therefore it is the goal of this study to investigate several natural materials of their potential to be a disintegrant.

Lentinula edodes (Berkeley) Pegler (LD), Flammulina velutipes (Curt. Fr.) Sing (FD), Auricularia polytricha (AD), Tremella fuciformis (2W), and Pleurotus eryngii (PED) are traditional Taiwanese food materials for a long time and taste deliciously. They grow abundantly in Taiwan, and are easy to purchase. The above substances swell in the aqueous medium, therefore they are chosen to evaluate their potential as disintegrants.

Hydrochlorothiazide and dicalcium phosphate,
The research of several natural edible materials as a disintegrant

Dihydrate are commonly used as a model drug and a direct compression excipient in disintegrant studies (Zhao and Augsburger, 2005a, 2005b). The investigated natural material will be combined with hydrochlorothiazide and dicalcium phosphate to evaluate its efficiency as a disintegrant and compared with starch. Finally, swelling volume and hydration test were conducted to understand their action mechanism. The above tests were conducted in a similar environment of which most traditional tablets and ODT disintegrate.

II. Materials and methods

1. Materials

LD, FD, AD, 2W, and PED were obtained from local market in Taiwan. Hydrochlorothiazide (Ipca, India) and dicalcium phosphate dihydrate (Di-tab, Rhodia, USA) were of US Pharmacopeia grade. The other chemical agents including monobasic potassium phosphate (Merck, Germany), hydrochloric acid (Merck, Germany), sodium chloride (Merck, Germany), potassium chloride (Merck, Germany) and sodium hydroxide (Katayama, Japan) were all analytic grade.

2. Methods

i. Preparation of natural material powder

LD, FD, AD, 2W, and PED from local market was respectively washed, sliced, and dried at 60°C till the moisture less than 5%. The dried material was respectively milled for 1 minute in a grinder (High Speed Grinder, KT-08, Taiwan). The powder whose size was under the 60-mesh was used for the following studies.

LD, FD, AD, 2W, and PED from local market was respectively washed, sliced, immersed in deionized water for 2 hours and cooked at 100°C for one hour. The material was respectively dried at 60°C till the moisture less than 5% and milled for 1 minute in the above grinder. The powder whose size was under the 60-mesh was obtained with the symbol of LWH, FWH, ADWH, WH and PEWH respectively.

The powder whose size was under the 60-mesh was obtained with the symbol of 3W if above Tremella fuciformis was prepared with the same procedure but cooked at 121°C for 10 minutes under 1.2 kg/cm² pressure instead of cooking at 100°C for one hour.

ii. Tablet preparation

Each tablet contains 20 mg hydrochlorothiazide, 274 mg Di-tab and 6 mg test material or starch. The blank tablet contains 20 mg hydrochlorothiazide and 280 mg Di-tab. Each ingredient was passed through an 80-mesh sieve, accurately weighed and well mixed with the other two ingredients. A mixture of about 300 mg was accurately weighed and compressed at 2000 lbs of force for 30 seconds by Carver press. The diameter and the thickness of the tablet were 8 mm and 3.3 mm respectively.

For the study of concentration effect of 3W, each tablet contains 20 mg hydrochlorothiazide, 1% (3mg), 2% (6 mg), 3% (9 mg), 5% (15 mg), or 10% (30 mg) 3W, and Di-tab q.s. to 300 mg with the same preparation procedure above.

iii. Disintegration study

The disintegration test followed the method in the USPXX described in the disintegrator (Shin kwang CT-2, Taiwan) with pH 1.2 HCl or pH 6.8 phosphate buffer at 37 ± 2°C as the medium. Each time six tablets were used.

iv. Swelling volume (Shangraw et al., 1980; Quadir and Kolter, 2006)

Material about two grams was accurately weighed and put into a 100-mL graduated cylinder. The pH1.2 HCl or pH 6.8 phosphate buffer was added into the cylinder till final volume of 80 ml and the cylinder was shaken thoroughly. The sediment volume was read after twenty four hours.

v. Hydration capacity (Patilet al., 2009; Iwuagwu and Onyekweli, 2002)

Material of one gram was put into a clean centrifuge tube and 40 ml deionized water, pH1.2 HCl buffer or pH 6.8 phosphate buffer was added and mixed well. The mixture stood still for 15 minute, and then was centrifuged at 2000 rpm for 15 minute. The supernatant was poured out, and the sediment weight was measured.

III. Results and Discussion

1. Disintegration studies

An ideal disintegrant could break the tablet rapidly when the tablet contacts water. The whole mechanism for the action of a disintegrant is still unclear until now. Studies have shown the mechanism of water wicking (capillary action), swelling, particle repulsion, deformation recovery, heat of wetting and their combinations (Kanig and Rudnic, 1984). The swelling of disintegrant particles is reportedly the most evident mechanism for disintegration (Kanig and Rudnic, 1984).

The result in Table 1 shows that tablets containing each material (2W, FD, LD, AD, or PED) had much shorter disintegration time than that of blank tablets. It indicates the material owns the inherent disintegration activity. However, the disintegration activity of most of them is well below starch.

Almost all materials have much better disintegration efficiency when precooked before milling as shown in Table 1. AD is the only exception that cooking doesn’t further improve the disintegration efficiency. This is probably because AD itself has excellent disintegration efficiency when
milled directly after drying.

The disintegration efficiency of 2W is improved by precooking at 100°C for 1 hour before milling or by 121 °C for 10 minutes under 1.2 kg/cm² pressure. This fact indicates that precooking by autoclave may be considered as a method to save the processing time.

The fact that precooking before milling improves the disintegration efficiency indicates these materials can also be used in wet granulation method of making tablets besides dry granulation method. The disintegrating activity of these materials is also heat-stable as they can stand 100°C for 1 hour without losing their disintegrating activity.

Among these materials AD, ADWH, WH, 3W, LWH, and FWH show more promising than PED as disintegrants. The disintegration time of tablets containing each of these materials after simple treatment is close to or less than that of starch tablet in pH 1.2 and pH 6.8 environments.

Table 1 Disintegration time of tablets containing a test material or starch

<table>
<thead>
<tr>
<th>Material</th>
<th>pH 1.2 buffer</th>
<th>pH 6.8 buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2W²</td>
<td>90 ± 13</td>
<td>280 ± 78</td>
</tr>
<tr>
<td>WH³</td>
<td>11 ± 2</td>
<td>25 ± 8</td>
</tr>
<tr>
<td>3W³</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>FD⁴</td>
<td>322 ± 63</td>
<td>587 ± 492</td>
</tr>
<tr>
<td>FWH⁵</td>
<td>21 ± 4</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>LD⁶</td>
<td>96 ± 8</td>
<td>119 ± 23</td>
</tr>
<tr>
<td>LWH⁷</td>
<td>25 ± 3</td>
<td>35 ± 10</td>
</tr>
<tr>
<td>AD⁸</td>
<td>18 ± 1</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>ADWH⁹</td>
<td>27 ± 4</td>
<td>38 ± 11</td>
</tr>
<tr>
<td>PED⁴</td>
<td>646 ± 57</td>
<td>815 ± 377</td>
</tr>
<tr>
<td>PEWH⁴</td>
<td>48 ± 5</td>
<td>105 ± 38</td>
</tr>
<tr>
<td>Starch</td>
<td>24 ± 7</td>
<td>60 ± 19</td>
</tr>
<tr>
<td>Blank</td>
<td>&gt; 40 minutes</td>
<td>&gt; 40 minutes</td>
</tr>
</tbody>
</table>

* All values are mean ± SD, n = 6

² Tremella fuciformis (2W), cooked Tremella fuciformis (WH), 121 °C cooked Tremella fuciformis (3W), Flammulina velutipes (Curt. Fr.) Sing (FD), cooked Flammulina velutipes (Curt. Fr.) Sing (FWH), Lentinula edodes (Berkeley) Pegler (LD), cooked Lentinula edodes (Berkeley) Pegler (LWH), Auricularia polytricha (AD), cooked Auricularia polytricha (ADWH), Pleurotus eryngii (PED), cooked Pleurotus eryngii (PEWH).

Disintegration time is related with the concentration of a disintegrant used. A disintegrant usually has its optimal concentration range. Sometimes a too high concentration will cause bad effect and prolong the disintegration time. Table 2 shows that 3W has a broad range which can be as low as 1% and as high as 10%. This is particularly useful in the ODT which may contain a high percentage of a disintegrant in a formulation.

Table 2 Disintegration time of tablets containing different concentration of 3W

<table>
<thead>
<tr>
<th>Concentration (%w/w)</th>
<th>Disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH 1.2</td>
</tr>
<tr>
<td>1</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>5</td>
<td>10 ± 1</td>
</tr>
</tbody>
</table>

* All values are mean ± SD, n = 6

2. Swelling volume

The activity of a disintegrant is usually attributed to its swelling and water sorption ability (Aulton, 2007). The swelling volume of various materials after treatment is shown in Table. 3. LWH and FWH have less swelling volume than that of 2W, 3W, WH, and ADWH.

Precooking before milling on the same material can result in higher swelling volume as WH and 3W have higher swelling volume than that of 2W. This may be related with the better disintegrating efficiency of WH and 3W than 2W.

Table 3 The swelling volume of test materials

<table>
<thead>
<tr>
<th>Material</th>
<th>Swelling volume (mL/g)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH 1.2</td>
</tr>
<tr>
<td>2W²</td>
<td>10.2 ± 0.3</td>
</tr>
<tr>
<td>WH³</td>
<td>12.8 ± 0.3</td>
</tr>
<tr>
<td>3W³</td>
<td>15.5 ± 0.1</td>
</tr>
<tr>
<td>ADWH⁴</td>
<td>13.7 ± 0.3</td>
</tr>
<tr>
<td>LWH⁴</td>
<td>6.8 ± 0.6</td>
</tr>
<tr>
<td>FWH⁵</td>
<td>7.5 ± 0.1</td>
</tr>
<tr>
<td>Starch</td>
<td>2.0 ± 0.1</td>
</tr>
</tbody>
</table>

* All values are mean ± SD, n = 3

² Tremella fuciformis (2W), cooked Tremella fuciformis (WH), 121 °C cooked Tremella fuciformis (3W), cooked Auricularia polytricha (ADWH), cooked Lentinula edodes (Berkeley) Pegler (LWH), cooked Flammulina velutipes (Curt. Fr.) Sing (FWH).
The research of several natural edible materials as a disintegrant

3 Hydration capacity

The hydration capacity indicates the ability of the material to absorb and hold the liquid. Therefore it should have some kind of relationship with the disintegrant activity. Table 4 shows that 2W, 3W, WH, and ADW have better hydration capacity and LWH and FWH have less hydration capacity. The hydration capacity of starch is the least among all the materials tested.

The hydration capacity of each material is also affected by the pH of the medium. 2W, 3W, WH, and ADW have less hydration capacity in acidic environment. The hydration capacity of LWH, FWH and starch is almost the same in the pH 1.2 and pH 6.8 environment.

The swelling volume and hydration capacity for 2W, WH, and 3W in the pH 6.8 buffer are better than those in pH 1.2 buffer. Therefore, it is expected that the disintegration time for tablets containing each of them should have less disintegration time. However, the tablets containing each of them have longer disintegration time in the pH 6.8 environment. This is because Dtab dissolves in acidic environment and results in a shorter disintegration time.

Table 4 The hydration capacity of test materials

<table>
<thead>
<tr>
<th>Material</th>
<th>pH 1.2 (g)</th>
<th>pH 6.8 (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2W</td>
<td>8.4 ± 0.1</td>
<td>12.3 ± 0.3</td>
</tr>
<tr>
<td>WH</td>
<td>9.6 ± 0.2</td>
<td>17.0 ± 0.5</td>
</tr>
<tr>
<td>3W</td>
<td>10.6 ± 0.1</td>
<td>20.6 ± 1.2</td>
</tr>
<tr>
<td>ADW</td>
<td>8.0 ± 0.6</td>
<td>10.0 ± 0.2</td>
</tr>
<tr>
<td>LWH</td>
<td>5.2 ± 0.2</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>FWH</td>
<td>6.2 ± 0.2</td>
<td>6.0 ± 0.2</td>
</tr>
<tr>
<td>Starch</td>
<td>2.2 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
</tbody>
</table>

* All values are mean ± SD, n = 3
§ Tremella fuciformis (2W), cooked Tremella fuciformis (WH), 121 °C cooked Tremella fuciformis (3W), cooked Auricularia polytricha (ADW), cooked Lentinula edodes (Berkeley) Pegler (LWH), cooked Flammulina velutipes (Curt. Fr.) Sing (FWH)

In fact, the shorter disintegration time in acidic environment is observed in all tablets containing each material. This indicates that the effect of excipient in a high percentage within a formulation exceeds that of a disintegrant (test material) in this study (Chen et al., 1997).

V. Conclusion

All these natural materials have the inherent ability to break up the tablets when they contact water. Precooking before milling significantly increases this ability. The disintegrating activity of these materials is related to their swelling and water sorption ability.

Generally speaking, the swelling volume and hydration capacity in acidic environment of these materials are close to or worse than those in the neutral environment. However, the disintegration time shows opposite result due to the dissolution of the excipient Dtab in this particular formulation.

3W has disintegrating activity in a wide range of 1 to 10%.

IV. Acknowledgement

The authors appreciate Chia Nan University of Pharmacy for the financial support.

V. Reference


利用天然食材作為崩散劑之研究

吳鴻璋1 李宗勳1 嚴淑揚2 陳俊仁2*

1嘉南藥理科技大學藥物科技研究所
2嘉南藥理科技大學藥學系

摘要

澱粉是目前唯一仍大量使用的天然崩散劑。香菇、金針菇、黑木耳、白木耳、杏鮑菇及珊瑚菇是台灣傳統食材且相當美味, 本研究將探討這些食材成為崩散劑的可能性。本研究所使用之實驗錠剤, 利用 hydrochlorothiazide 當做模型藥物, 用 dibasic calcium phosphate 作稀釋劑, 加入澱粉或上述食材當作崩散劑, 並以直接壓錠法製造。在酸鹼值 1.2 或 6.8 的溶媒中測定這些錠剤的崩散時間。崩散劑添加濃度對崩散時間的影響, 則以添加白木耳當崩散劑的錠剤做研究。酸鹼值 1.2 或 6.8 的環境中這些食材的膨脹體積及吸水能力也被研究, 希望藉這些研究結果了解這些食材可以當崩散劑的機轉。崩散試驗的結果顯示出這些含食材錠剤的崩散時間(大部份低於二分鐘)遠小於空白錠的崩散時間(超過四十分鐘)。當這些食材先烹煮後再進行研磨時效果更好, 尤其被烹煮處理過的白木耳, 其的崩散時間最少。因此本實驗進一步用添加白木耳的錠剤測試, 發現白木耳的添加濃度範圍很大, 可以從百分之三到百分之九, 從膨脹體積和吸水能力試驗中得知, 這些食材的崩散能力和其膨脹能力及吸水能力有關: 整體來說, 他們的膨脹能力及吸水能力在中性的環境中表現得比在酸性環境中好, 崩散時間和其在酸鹼值 1.2 或 6.8 溶媒中膨脹能力及吸水能力表現不一致, 應是受稀釋剤的影響。

關鍵字：崩散劑、黑木耳、白木耳

*通訊作者：嘉南藥理科技大學藥學系
Tel: +886-6-3912082
Fax: +886-6-2667318
E-mail: hchunliw@gmail.com