嘉南藥理科技大學專題研究計畫成果報告

含茄紅素之固體製劑研發（2）脂溶性藥品之處方與溶離

Investigation of solid products for lycopene (2) Formulation and Dissolution of hydrophobic drugs

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一、中文摘要

軟膠囊具有，對水難溶解性藥品高生體可用率之優點，同時內容均勻且安定，空氣及溼氣對膠囊之通透性皆低。

但是它也有動物來源之缺點，對素食者不適用。而且狂牛病之傳染，使得人們更有疑慮。

本計劃繼續研究半自動軟膠囊機製造軟膠囊之技術，也尋找開發軟膠囊之新原料。

關鍵詞： 軟膠囊

Abstract

Soft capsules as a pharmaceutical dosage form have the advantages of being: high bioavailability for nonpolar drug in oil solution, stable toward oxidation and hydrolysis, and content uniformity. However, it has also some limitations such as: the raw material is animal origin, it breaks up in the stomach fast. The purpose of this study is to optimize the technology to make the soft capsule by a semi-automatic soft capsule machine. Then, add the function of controlled release to this traditional dosage form of soft capsule. Finally, do a preliminary screening study on the replacement or modification of the raw material.

Keywords: *Soft capsule*

二、Introduction

Soft capsule dosage form is a very good dosage form for low water solubility drugs. By dissolving the drug in oil and put the oil solution into soft capsule, it will have very good bioavailability. Besides, the permeation of air and moisture through soft capsule shell is very limited, the drug inside the soft capsule should be very stable. Gelatin has been used for a long history to make hard and soft capsules. It is made from the skin and bone of animals. Although it is well accepted by the majority of people, it is not suitable for vegetarians. Recently, due to the infectious diseases by cows, people become worried about the use of gelatin.

To look for suitable materials, even from local, with proper formulations and less cost will be helpful to the vegetarians and industry of Taiwan.

三、Results and discussion

(A) Optimization study of soft-capsule making by a semi-automatic encapsulation machine:

1) the amount of fluid encapsulated is related to the thickness of the gelatin sheet. If the thickness of total gelatin sheets (upper sheet plus lower sheet) is too high, then it can only

accommodate a limited amount of liquid. If too much amount of liquid is to be encapsulated, it will burst out and won't make the two gelatin sheets stick together. On the contrary, if the total thickness of gelatin sheets (upper sheet plus lower sheet) is too thin, then it can accommodate more amount of liquid. If a little amount of liquid is to be encapsulated, the capsules will appear flat and not be beautiful. Generally speaking, the amount of liquid encapsulated is about 0.3ml. The weight of a soft capsule is about 1 Gm. for corn oil encapsulated.

2) Adjustment of the thickness of gelatin sheet by the machine. This machine has two ways to adjust the thickness of gelatin sheet. One is to adjust the height of the whole set of gelatin solution trough. The bigger the height, the less the resistance of back-flow. Then, the less the force to squeeze the gelatin solution forward. This height affects the rate of backflow of gelatin solution in the storage trough. The front height is the main control of the thickness of gelatin sheet. Of course, other variable as the moving speed of the stainless plates, viscosity of gelatin solution, room temperature, gelatin solution temperature, even the amount of gelatin solution in the trough may affect.

3) The gelatin solution tank should have great bottom area and low height. In this way it will make the degassing faster.

4) The place of the press that contacts the upper gelatin sheet should clean carefully. If it is not cleaned well, it will stick the whole mold up after pressing and drop down. In this way it will do damage to the mold.

5) Fungi easily contaminate the gelatin solution. 1 % (w/w) of methyl paraben is found not to inhibit the growth of fungi.

6) After the press, the capsules are to be dried by using hot air within a rotary basket. The purpose is to dry the outer shell immediately to prevent the capsules from sticking together. Then transfer them to a low humidity environment to dry the capsules.

7) Coloring of the soft capsule is tried by lakes and dyes. Tartrazine is not suitable as it is similar to the color of gelatin solution. Insoluble lake or soluble dye is being under study for the suitable use in the soft capsules.

<u>The search for a new material</u>:

1) 仙草 bag from the market. The bag contains 仙草, starch, and brown sugar. Dissolve the contents of the whole bag in the boiling water, Cool down to 52 ℃, and it starts to gel. At 39 ℃ it completely gels. Heat the gel again at 75 ℃ and it becomes solution again. This proves commercial 仙草 bag is thermoreversible. However, the gel is not strong enough and the viscosity in not enough either.

2) Put the dried 仙草 plant, add 20 times weight of water, and add sodium bicarbonate 0.04%(w/w) of water. Extract 3 hours by using reflux apparatus. There is not enough gelling property.

3) Add herb 白芨 into 12 times weight of water. Boiling them together, there is not enough gelling property.

4) Add 4.1 Gm of 石花菜 into 500ml water. Heat until the solution becomes viscous. It will gel. Heat them, it will dissolve again. Cool down, and it will

gel again. It has the thermoreversible property, but the viscosity is not enough.

5) Add 4.1 Gm of processed 石花菜 into 500ml water. Heat until the solution becomes viscous. It will gel. Heat it and it will dissolve. Cool down and it will gel. It has the thermoreversible property but the viscosity is not enough.
6) Combination of processed 石花菜 and herb 白芨 in various ratios. It was found that they all formed the gel and was thermoreversible. High percentage of herb 白芨 increased the viscosity, and high percentage of processed 石花菜 increased the hardness of the gel. However, the viscosity is apparently not enough to make soft capsule.
7) 洋菜 powder from 振芳. To dissolve 0.8% (w/w) of 洋菜 powder from 振芳 into water. Heat it until the solution becomes viscous. It will gel. Heat it, it will dissolve. Cool down it will gel. It has the thermoreversible property. However, there is not enough viscosity to make the soft capsule.
8) Add 0.8% (w/w) carageenan powder (grade WR-78G) into water. Heat until the solution becomes viscous. It will gel. Heat them, it will dissolve. Cool down and it will gel. It has the thermoreversible property. However, there is not enough viscosity to make the soft capsule.
9) Add 0.4% (w/w) Gm carageenan powder (grade RMD-102) into water. Heat until the solution becomes viscous. It will gel. Heat them, it will dissolve. Cool down and it will gel. It has the thermoreversible property. However, there is not enough viscosity to make the soft capsule.
10) Processed konjac powder from the market. It was found that konjac-containing powder dissolved in water upon heat and formed the gel at 70-80 ℃. Various ratio of processed konjac-containing powder with water were prepared. The 1:1 and 1:5 ratios were not suitable to prepare. When the 1:10 ratio was poured into the trough, it solidified and clogged the clearance, and made the sheet preparation impossible. The transition temperature is too high.
11) The mixture of processed 石花菜 with process konjac-containing powder in various ratio. When the water amount is fixed (200ml) , 1: 1 to 3:1 ratio of processed 石花菜 with process konjac-containing powder dissolved in water and formed the gel and is thermoreversible. The higher the percentage of processed 石花菜, the higher the congealing temperature. The viscosity is apparently too low for making the soft capsule.

The making of soft capsules is usually under the controlled temperature and humidity environment. At present, the making of soft capsule at biotechnology center is not very easy. As the temperature and humidity will affect the viscosity of gelatin solution, the congealing speed of gelatin solution in the ge

trough, the drying time of gelatin sheet, consequently, the thickness of gelatin sheet is influenced. The suitable time of pressing the mold is varied. The amount encapsulated is also varied. For drugs, it means the dose uniformity is varied.

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