Application of Solid Dispersion with Combined Carriers on the In-Vitro Release of Multi-Components from Danshen Extract and preparation of Fufang Danshen Tablets

by

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Institute of Chinese Medical Sciences
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UNIVERSIDADE DE MACAU
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碩士學位論文

辅料联用固体分散技术在丹参提取物多组分释放中的应用及複方丹參片的製備

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目　錄

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摘 要

辅料联用固体分散技术在丹参提取物多组分释放中的应用及複方丹參片的製備

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丹参为唇形科植物*Salvia miltiorrhiza Bge.*的干燥根及根茎[1]，收载于2005版《中国药典》。丹参具有祛瘀止痛、活血通经及清心除烦等功效，近年来多用于治疗冠心病、心絞痛等心脑血管系统疾病。

固体分散体是由药物与载体混合制成的高度分散的固体分散体系，可增加难溶性药物的溶解度和溶出速度，对 BCSII 类药物可提高其生物利用度。根据文献报道，载体单独应用存在一定的缺陷。如 PVP 在溶解时粘度增大，对药物的溶出反而起到阻滞作用[2]。而利用辅料联用技术制备的固体分散体具有可调节药物的释放速度，降低载体的吸湿性，和增加药物溶解及分散等优点[3-4]。本实验发现，加入 PVP10 制备成的固体分散体可以提高丹参中脂溶性成分的溶出，而 F127 对脂溶性成分有较好的润湿和分散作用，两者联用可以进一步提高脂溶性成分的溶出，为研制成新的复发丹参制剂提供前提。

本論文主要包括以下內容：

1. 丹參提取物 HPLC 測定方法的建立。選取水溶性成份丹參素、迷迭香酸和丹酚酸 B，脂溶性成份隱丹參酮和丹參酮ⅡA 五個成份作為指標成份，建立 HPLC 測定方法。排除輔料對指標成份吸收的干擾，建立了快速、高效的丹參提取物 2 類活性成份 5 大指標成份的 HPLC 測定方法，并進行了方法學考察。

2. 丹參藥材提取條件的優化。利用 HPLC 測定 5 個指標成份丹參素、迷迭香酸、丹酚酸 B、隱丹參酮和丹參酮ⅡA 作為測定成份。對提取方法、提取溶劑、提取溶劑的體積、提取時間進行了優化，優化過的提取效率明顯高於中國藥典里規定的迴流提取的提取效率。並且提取時間從藥典規定的 5 個小時縮短為超聲提取的 40 min。
3. 篩選適當的輔料，利用噴霧乾燥的技術製備丹參提取物固體分散體。利用 HPLC 測定 5 個指標成份丹參素、迷迭香酸、丹酚酸 B、隱丹參酮和丹參酮ⅡA 的溶出量，來評價固體分散體的體外溶出。並對丹參提取物固體分散體進行各項表徵，試圖解釋和闡明輔料對丹參提取物溶出行為影響的原因和機理。
4. 篩選不同的輔料和輔料的用量，利用單沖壓片機製備複方丹參片。利用超聲提取丹參藥材，繼而通過噴霧乾燥的方法製備出丹參固體分散體。添加三七藥材粉末和冰片。這三個處方藥材，加入適宜的填充劑、粘合劑、崩解劑以及潤滑劑來製備片劑。雖然口服分散片製片成功，但是指標成份丹酚酸 B 和丹參酮ⅡA 達不到含量要求。故而捨去。最後製備出傳統的口服片。通過片劑的常規檢查，從片劑的含量測定、片重和片重差異、硬度、脆碎度來評價製備的片劑質量，結果顯示製備的片劑符合藥典的要求。并且增加了一項片劑溶出度考察。
5. 選取兩個指標成份丹參中丹酚酸 B 和丹參酮ⅡA，三七中人參皂苷 Rg1 和人參皂苷 Rb1，冰片中龍腦這五個成份作為指標成份來評價製備出的複方丹參片質量，利用 HPLC 測定丹參和三七的指標成份，建立測定方法，并進行了方法學考察。利用 GC-MS 測定冰片的主要成份龍腦，建立測定方法，并進行了方法學考察。

關鍵詞：丹參；固體分散體；噴霧幹燥技術；輔料聯用；表徵；溶出度；複方丹參片

Abstract

Application of Solid Dispersion with Combined Carriers on the In-Vitro Release of Multi-Components from Danshen Extract and Preparation of Fufang Danshen Tablets

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Danshen (*Salvia miltiorrhiza*) is a commonly used traditional Chinese medicine for the treatment of cardiovascular and cerebrovascular diseases. It was included in the Chinese Pharmacopeia (2005).

Solid dispersions is made by drug and carrier ,it is highly dispersed mixture . On insoluble drugs can increase the solubility and dissolution rate; On BCSII drugs can increase their bioavailability . According to the reported, there are some defects in sole carrier. For instance, PVP10 as sole carrier, The drug played a retard dissolution with PVP in the solution viscosity increases. Combined utilizing of carriers to prepare solid dispersion for improving dissolution rate of drugs. The present study proclaimed that the combined use of carriers significantly increased the in-vitro release of lipophilic components in danshen extract, which may be attributed to the increased wettability of the powders. The simulating factor evaluation results suggest that the release profiles of either the lipophilic or the hydrophilic components in danshen extract was complete and similar, which could meet the requirements of the Chinese pharmacopoeia.

The following parts are included in this paper:

1. Determination of danshen extract by HPLC. Danshen extract were characterized by various methods. Three hydrophilic (danshensu, rosmarinic acid, salvianolic acid B) and two lipophilic components (cryptotanshinone and tanshinone IIA) of

danshen were determined as bioactive markers. HPLC method was developed for analysis of danshen extract.The validation results showed that the HPLC method established was simple, reliable and of good repeatability.

2. Comparison of different extraction method, extraction solvents, extraction quantities of solvents, extraction time on the extraction efficiency of danshensu, rosmarinic acid, salvianolic acid B, cryptotanshinone and tanshinone IIA. In the case of raised extraction efficiency, extraction time of 5 hours reduced from 40min.
3. Solid dispersions were prepared with carrier or their combinations by Spray Drying (SD) method. The prepared powders were characterized by various methods. The simulating factor (f_2) was inducted to evaluate similarities of dissolution profiles of hydrophilic and lipophilic components, respectively.
4. Screening of different amount of accessories and auxiliary materials. Evaluation Fufang Danshen Products.
5. Using a single punch tablet presser for the Preparation of Fufang Danshen Tablets. salvianolic acid B, tanshinone IIA of danshen were determined as bioactive markers. Ginsenoside Rg1 and Ginsenoside Rb1 of sanqi were determined as bioactive markers. Borneol of bingpian was determined as bioactive markers. HPLC method was developed for analysis of Fufang danshen tablets.The validation results showed that the HPLC method established was simple, reliable and of good repeatability.

Keywords: *Radix Salviae Miltiorrhizae*; Solid dispersion; Spray Drying (SD) Technology; Combined carriers; Characterization; Dissolution; Fufang Danshen tablets

缩略词对照表

HPLC	High Performance Liquid Chromatography	高效液相色譜
TanIIA	Tanshinone IIA	丹參酮 IIA
SD	Spray Drying	噴霧幹燥
F68	Flouric-68	泊洛沙姆 407
F127	Flouric-127	泊洛沙姆 188
PEG4000/8000	Polyethylene Glycol-4000/8000	聚乙二醇 4000/8000
PVP10/40/360	Polyvinylpyrrolidone-10/40/360	聚乙烯吡咯烷酮 10/40/360
PVPk30	Polyvinylpyrrolidone- k30	聚乙烯吡咯烷酮 k30
MS	Mass Spectrometry	質譜
GC	Gas Chromatography	氣相色譜
m/z	Mass to charge ratio	質荷比
PXRD	Powder X-ray Diffraction	粉末 X 射線衍射
SEM	Field Emission Scanning Electron Microscopy	場發射掃描電鏡
ASE	Accelerated solvent extraction	加速溶劑提取
1,L	Liter	升
BET	是三位科学家（Brunauer、Emmett 和 Teller）的首字母缩写	BET 比表面积检测法
SDS	Sodium dodecyl sulfate	十二烷基磺酸鈉