微晶纖維素的製程因子對其材質與機械性能及應用功能性的影響

Influence of manufacturing factors on the material properties, mechanical performances and functionalities of microcrystalline cellulose

中文摘要

微晶纖維素由於其良好的成錠性，爲目前直接打錠劑型最常使用的賦形劑之一。然而不同的製造商來源及批次間產品的差異，皆會影響其應用時的功能性。由於現代的製藥工業，普遍使用設計分子晶型及粉末顆粒的觀念，來調控賦形劑的機械性能與應用功能性。因此，推論微晶纖維素的分子結構特性及顆粒形態等材料性質，亦可能決定其於壓錠時的機械特性以及應用功能性。在粉末顆粒性質方面，已有許多文獻廣泛地探討其對微晶纖維素功能性的影響，然而，在分子結構特徵方面的影響性則研究不多，且未有任何研究對其整體材料性質與應用功能的相關性做定量評估；若藉由統計定量方法尋求掌控微晶纖維素機械性能與功能性的關鍵材料性質並加以規範，可改善製造商來源不同所造成的產品差異。另一方面，至目前爲止，未曾有研究詳細探討製程因子對微晶纖維素的整體影響性；就賦形劑製造商而言，產品的功能性可由製程的調配改良而予以最佳化，而控制關鍵製程因子則可降低批次間的產品差異。

本研究乃利用實驗設計法以了解酸水解製造條件的改變，如何影響微晶纖維素的材料物化特性、機械性能及功能性；進而探討材料性質 (尤其是分子結構) 對機械性能的影響及如何改變其應用功能。在了解製程因子對微晶纖維素的整體影響性後，進一步應用上述實驗設計法所得到的多項式方程式，製備具不同材料性質與功能性的微晶纖維素濕粒，利用此濕粒以共同乾燥法，修飾本身不具壓錠性的 acetaminophen，使之成爲直打藥物。

根據實驗設計法的結果顯示，利用適當的二次多項式方程式，可由酸水解製程因子的變化，預測微晶纖維素產品的材料性質及功能性，進而可將其功能性予以最佳化。主要影響材料性質及功能性的製程因子爲水解溫度；因此，嚴密地控制水解溫度可降低微晶纖維素產品的批次間差異。而機械性能的部份則無法由水解因子精確地預測之。不過，透過材料性質，微晶纖維素的各種機械性能及功能性仍可被定量地預測；而解析材料性質個別與其機械性能或應用功能性之間的相互關係，可提供處方設計者由基礎的分子結構分析或顆粒性質的變化，選擇適當的產品。再者，包括：分子質量、分子間吸引力 (CED)、結晶度、分子內氫鍵結合度，以及顆粒規則度、顆粒表面平滑度等皆爲主導微晶纖維素機械性能乃至於其錠片強度及各種應用功能的關鍵材料性質；規範這些關鍵材料性質，可使該賦形劑達到全球一致性的目的。

另一方面，經由與 10% w/w 微晶纖維素共同乾燥的方法，可以有效改善 acetaminophen 的粉體流動性及成錠性，成爲一可供直接打錠的藥物。而此共製

處方的功能性，明顯取決於所選用微晶纖維素的各種原有功能性。因此，此直打 acetaminophen 的各種應用功能性，可藉由選用具不同材料性質與功能性的微晶纖維素來加以調控。

英文摘要

Due to its excellent compactibility, microcrystalline cellulose (MCC) is one of the most preferred filler-binders in direct compression tablet formulations. However, source and batch variations affect the functionalities of MCC. In modern pharmaceutical industry, the concepts of crystal engineering and particle design are popular to manipulate the mechanical performances and functionalities of excipients. Accordingly, the material properties (molecular structure and the particle properties) may contribute to the mechanical performances and functionalities of MCC. The influences of particle properties rather than molecular features on the functionalities of MCC have been widely discussed in the literature. However, no work has quantitatively correlated material properties and functionalities of MCC. Meanwhile, it is desirable to find the key material properties that control the mechanical performances and functionalities of individual excipients. Only then, can reduction in source variations be made by the regulation of key material properties. Furthermore, the correlation constructed between manufacturing factors and overall qualities of MCC products is useful for manufacturers to optimize its functionalities. At the same time, the batch variations can be reduced by the control of key manufacturing factors. However, no work has been detail reported on these matters.

In this study, a statistical experimental design was used to evaluate the effects of manufacturing factors on the material properties, mechanical performances and functionalities of MCC products. How the material properties, especially for the molecular properties, dominate the mechanical performances and functionalities of MCC products were further explored. Based on the polynomial equations deduced from the experimental design, two MCC slurries with different material properties and functionalities can be prepared and co-dried with acetaminophen, which is inherently uncompressible, to produce direct compression formulations.

The results obtained from the experimental design demonstrate that the material properties and functionalities of MCC products can be predicted by the manufacturing factors using proper polynomial equations. Then, the functionalities can be optimized. Additionally, the key manufacturing factor is temperature. The careful control of temperature during the manufacture of MCC might minimize inter-batch variation. By contrast, the use of manufacturing factors to predict the mechanical performances was poor. Nevertheless, the mechanical performances as well as functionalities can be quantitatively predicted by material properties. The correlation of the material

properties of MCC products with their mechanical performances and functionalities might help the formulation designer rationally select proper MCC products. Meanwhile, the molecular mass, cohesive energy density (CED), degree of crystallinity, crystallinity index, roundness, and surface roughness may serve as important material properties for controlling the mechanical performances and functionalities of MCC. The universal harmonization of MCC products might be achieved by the regulation of these material properties.

On the other hand, the compactibility and powder flowability of acetaminophen can be modified by co-drying with 10% w/w MCC to prepare direct compression formulations. The functionalities of the coprocessed samples were dependent on the selected MCC. Thus, the functionalities of the direct compression formulation could be manipulated by selection of MCC.