Ambroxol 緩釋錠之製造及其特性研究

PREPARATION AND CHARACTERIZATIONS OF AMBROXOL SR TABLET

中文摘要

本論文之研究目的乃在於發展以口服方式投與一天一次的緩釋型 Ambroxol 錠劑。藉由熱融造粒技術可以得到一最佳化的藥物釋出速率且具有 24 小時的持續性釋放藥物之錠片，商品名定為”安疏痰 緩釋錠片” （Amsolvon SR Tablet），同時評估其錠片之物化性質，包括重量差異試驗、含量均一度試驗、硬度試驗、粉碎度試驗及溶離度試驗等。

體外溶離試驗結果顯示熱融顆粒大小與壓錠速率並無明顯改變藥物的釋放速率與釋放總量，然而錠片的硬度卻有所不同。低壓錠速率與大顆粒所壓製得到的錠片錠片硬度較高，此乃因為錠片賦形劑具有塑性形變之特質。基於藥物溶離不受顆粒大小所影響與高產率的考量下，最後選擇顆粒規格在 420 mm （以 40 號篩網過篩）以下之 Ambroxol-Compritol 888 之熱融顆粒與其他錠片組成物質混合後，以 20 rpm 的壓錠速率製造”安疏痰 緩釋錠片”；此錠片進一步與國外市售 Ambroxol 緩釋膠囊（PR-ABX Capsules、Mucosolvan Capsules）進行體外溶離試驗比對。結果顯示”安疏痰 緩釋錠片”與 PR-ABX Capsules 有較佳的溶離相似度。而”安疏痰 緩釋錠片”的藥物釋放機制屬於 Higuchi 滲透模式，亦即藥物釋放速率與溶離時間的平方根成正比關係。長期與加速安定性試驗顯示”安疏痰 緩釋錠片”之有效期限至少可達 4 年。

選擇四位健康成年男性受試者進行”安疏痰 緩釋錠片”之先期性藥物動力學研究，採用多重劑量口服方式投與，結果顯示其具有持續釋放 ambroxol 達 24 小時之能力。於穩定血中濃度狀態之相關藥動學參數平均值與標準偏差值如下:AUC0-24 為 1559.6±149.4 ng/mL·hr、Cmax 為 104.63±6.34 ng/mL、Cmin 為 38.83±13.86 ng/mL、Cav 為 64.98±6.22 ng/mL、fluctuation 為 1.03±0.30、AUMC0-24 為 16246±1784 ng/mL·hr2、MRT0-24 為 10.41±0.46 hr、Tmax 為 7.50±1.29 hr、Kel 為 0.0673±0.0091 hr-1、T1/2 為 10.46±1.53 hr、CL/F 為 48.40±4.33 L/hr、Vd/F 為 735.45±162.44 L.

“安疏痰 緩釋錠片”已核准開始進行臨床藥效評估，預期此一製劑在未來將可提供更安全穩定的藥物療效，同時增加病患的依順性。

英文摘要

The purpose of this study was to develop a sustained release tablet of ambroxol that to be taken once daily. The optimized ambroxol sustained release tablet, Amsolvon SR tablet as trade name, was prepared via a melt-coating granulation technique and its functionality was characterized based on the following tests: weight variation, content uniformity, hardness, friability and dissolution tests.

In vitro dissolution studies show that the drug release rate and amount are not affected by particle size of ambroxol-Compritol 888 melted granules and tabletting speeds. But the hardness of ambroxol SR tablets is influenced by particle sizes and tabletting speeds. Low tabletting speed and large particle size may produce more compact tablets; this can be attributed to the plastic deformation characteristic of

the tablet excipients.

Finally the particle size of <420 mm of ambroxol-Compritol 888 melted particles were selected in terms of higher production yield. The selected melted particles were mixed thoroughly and tabletted at 20 rpm to obtain Amsolvon SR tablets. The dissolution profile of Amsolvon SR tablets was more similar with PR-ABX capsules than Mucosolvan capsules in all three dissolution media. The drug release mechanism of ambroxol from Amsolvon SR tablets can be described by Higuchi diffusion model. The long-term and accelerated stability tests both showed that Amsolvon SR tablet was stable and its tentative shelf life was 4 years at least. Pharmacokinetic pilot study in four healthy male human subject after oral administration with multiple doses of Amsolvon SR tablets show that the formulation was successful in providing slow release of ambroxol and has mean±SD AUC0-24 of 1559.6±149.4 ng/mL·hr, Cmax of 104.63±6.34 ng/mL, Cmin of 38.83±13.86 ng/mL, Cav of 64.98±6.22 ng/mL, fluctuation of 1.03±0.30, AUMC0-24 of 16246±1784 ng/mL·hr2, MRT0-24 of 10.41±0.46 hr, Tmax of 7.50±1.29 hr, Kel of 0.0673±0.0091 hr-1, T1/2 of 10.46±1.53 hr, CL/F of 48.40±4.33 L/hr, and Vd/F of 735.45±162.44 L.

The efficacy and safety of this ambroxol SR tablet (Amsolvon SR tablet) dosage form are currently being evaluated in clinical trials; it may be expected to provide optimum therapeutic efficacy and improve patient’s compliance in the future.