固體分散相的製備與處方之探討

Studies on Formulation Preparation of Solid Dispersion Systems

中文摘要

對於難溶性的藥物而言，經由口服吸收的速率決定步驟在於它在胃腸道裡面的溶離，而不是穿越腸壁的步驟。因此增加難溶性藥物的溶解度而加快溶離速度，將有助於此類藥物的吸收速度。本研究試圖以 Gelucire 44/14 / PEG 600 與 PVP / PEG 6000 兩個系統作爲基劑，藉由熔融法與 Nifedipine(熔點 173oC)作成固體分散系統來增加 Nifedipine 的溶解度，進而增加溶離的速度。Gelucire 44/14 與 PEG 600 的系統分別以兩個方式製備，方式一是先將基劑融熔以後，再將 Nifedipine 均勻分散到裡面; 另一個方式則是將基劑與 Nifedipine 共同加熱到高溫融熔。首先利用 DSC 來測試各種基劑對 Nifedipine 的熔點與結晶抑制影響。結果顯示 : Gelucire 44/14 和 PEG 6000 分別在 50%及 60%的比例之上與 Nifedipine 經過高溫融熔以後可以抑制結晶的產生，形成非晶型的狀態，並且隨著基劑含量的不同，抑制結晶的程度也不同，而 PVP 則與 Nifedipine 在任何比例之下都有同樣的效果 ; 另外，PEG 6000 與 Nifedipine 以 3:1 的比例混合時，可以使 Nifedipine 的熔點降低到 110oC，這將有利於藥物的製備。經由溶離度測試的結果可以發現，經過處理的 Nifedipine 溶離速率都比未經處理的還快，加熱到高溫融熔的系列比低溫混合的快，溶離的速率也會隨著 Gelucire 44/14 含量的增加而加快。在 PEG 6000 / PVP 系列的系統中，結果顯示 : PEG 6000 / PVP 的量越多，Nifedipine 的溶離速率越快; 而 PVP 的分子量越高，溶離的速率則越慢。由於 Nifedipine 與 PEG 6000 / PVP 混合以後會增加粒子與粒子間的黏性，使得粉末在水中不易散開，因此進而將 Nifedipine : PEG 6000 : PVP K-12 = 1: 3 : 3 這一組與 Aerosil 200 : Tween 80 = 1 : 1 混合，提高其分散效果，結果顯示溶離速率變得更快。

英文摘要

It is well established that the rate-determining step in the absorption process for poorly water-soluble drugs is the dissolution rate for such drugs in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall. Thus, the increase of the dissolution rate by increasing the solubility of poorly water-soluble drugs will improve the absorption rate. In this study, solid dispersions of nifedipine (m.p. 173oC) prepared with two water-soluble carrier systems, Gelucire 44/14 / PEG 600 and PVP/PEG 6000, by fusion method was developed to increase the solubility of nifedipine, then increasing the dissolution rate. The system of Gelucire 44/14 and PEG 600 was made by two methods. The first one was to melt the carriers at its melting point before evenly distributing nifedipine into it. The other one was to mix the carriers and nifedipine before melting them together at a

higher temperature that both drug and carrier could melt. In the beginning, DSC analysis of the depression of melting point and the inhibition of crystallization of nifedipine by carriers was carried out. The results showed that Gelucire 44/14 and PEG 6000 inhibited the crystallization of nifedipine after melting them at a higher temperature over the ratio of 50% (w/w) and 60% (w/w), respectively. PVP could express the same effects at all ratios. The formation of amorphous state of nifedipine as a result of crystallization inhibition also increased with increasing ratio of carriers. Besides, mixing PEG 6000 with nifedipine at the ratio of 3:1, the melting point of nifedipine was decreased to approximately 110oC. This certainly would make the preparations of solid dispersion by fusion method more practically acceptable. Dissolution tests further demonstrated that nifedipine that fused with these carriers had a higher dissolution rate than that unmodified. For Gelucire 44/14 and PEG 600 system, the dissolution rate from those prepared at a higher temperature was faster than that prepared just at the melting point of Gelucire. The dissolution rate increased with increasing amount of Gelucire 44/14 as well. For the PEG 6000 and PVP series system, the results showed that the higher amount of PEG 6000 and PVP, the faster of the dissolution rate of nifedipine would become; The higher the molecular weight of PVP, the slower of the dissolution rate. Due to the viscous nature, the existence of PEG 6000 and PVP in the preparations would possibly increase the adhesion among particles, which makes them difficult to disperse into water minimizing the surface area available for dissolution. A set of formulation containing a higher amount of both additives (nifedipine : PEG 6000 : PVP K-12 = 1:3:3) was further mixed with Aerosil : Tween 80 = 1:1 to improve the dispersion. The results demonstrated that the dissolution rate became faster.