包含水難溶性藥物之固態化自發性微乳化遞藥系統之處方開發與評估

Formulation Development and Evaluation of Solidified Self-Microemulsifying Drug Delivery Systems Containing a Poorly Water-Soluble Drug

中文摘要

自發性微乳化遞藥系統（SMEDDSs）在胃腸道中接觸水相並且靠著輕微的攪動或蠕動後，會自然乳化成爲澄清且均勻的微胞流體。自發性微乳化系統通常由油相、界面活性劑、助界面活性劑以及藥物所組成，相對於水難溶性化合物之傳統劑型是個具有發展潛力的替代劑型。在本研究中，fenofibrate 爲親脂性模式藥物，溶於正乳酸丁酯再以聚山梨酸酯（Tween 20 與 Tween 80）以及一些醇類（乙醇，正丙醇與聚乙二醇）混合後，以媒液（去離子水或醣類/固型劑水溶液）進行控速稀釋，再將溶液真空冷凍乾燥。初步目的爲利用擬三成分相圖建立處方，然後分析凍乾前後系統粒子的大小，期望重行分散於水相後還有良好的微小粒徑（奈米層級），之後再評估並調整製程參數。

很多的藥學乾燥技術皆可被應用於製備固態化微乳劑。在乾燥過程前會先加入上述的親水性固型劑（抗凍劑），因爲它能藉由立體障礙及斥力來防止粒子或微胞間的大量凝集，並且能維持原本液態自發性微乳化劑型的乳化效能。本實驗所用到的固型劑爲 lactose, mannitol, glucose, sucrose and trehalose。發展固態劑型主要的難度在於如何確保真空冷凍乾燥後粒子重行分散的安定性。因爲凍乾後粒子彼此凝集的關係，許多固化系統的粒徑皆大於 2 μm，而當以 0.5%(w/w) sodium lauryl sulfate（SLS）溶液進行分散，粒徑可以在凍乾後 30 分鐘到 90 分鐘維持穩定以及在許多實驗組中維持在 500nm~2 μm 的粒徑範圍內。這在 50%固型劑/Ethanol/Tween 80 組別中爲最明顯，平均從水相中的 4800nm 粒徑下降至 SLS 溶液中的 1700nm 粒徑左右，而該組中以 Lactose 當固型劑更能使各處方平均粒徑減至 900nm ~ 1000nm。

最後還進行處方晶型的研究。而從上述研究中建立固態化水難溶性藥物之自發性微乳化遞藥系統的最佳製備方式,可在往後將此可稀釋的遞藥系統以奈米級包覆材質包覆的技術提供試驗基礎與模式。

英文摘要

Self-microemulsifying drug delivery systems (SMEDDSs), which can be self-emulsified into a translucent and isotropic fluid in aqueous medium under gentle digestive motility in the gastrointestinal tract, usually consisting of a mixture of oils,

surfactants, cosurfactants and drugs, represent a promising alternative to traditional formulations of poorly water-soluble Compounds. In the present study, a model lipophilic drug, Fenofibrate, is formulated in n-butyl L-lactate, polysorbates (Tween 20 and Tween 80) and a number of alcohols (ethanol, 1-propanol and PEG 600) as well, then diluted with mediums (dH2O or solution of carbohydrates/solid carriers)at certain rate prior to the freeze drying process. Our initiative objective is to construct pseudo-ternary diagram phase for formulations and analyze the particle size of SMEDDS before/after lyophilization in hope of the smaller particle size (nanoscale) redispersed in aqueous phases following drying, then turn to evaluate the systems and adjust the procedural parameters.

A plenty of drying technology had been employed to prepare dry microemulsions by removing water from an ordinary microemulsions containing a water soluble solid carrier (or cryoprotectant) which could not only prevent particles or micelles from large aggregation by steric hindrance and repulsive force but preserve microemulsification performance the same as that of liquid self- microemulsifying drug delivery systems. On the study, solid carriers in use include lactose, mannitol, glucose, sucrose and trehalose. The main difficulties with a solidified formulation lied in the stability of particulate redispersibility after the drying step. As consequence of agglomeration, the particle size was much larger than 2μm though; when adding solution of 0.5%(w/w) SLS (sodium lauryl sulfate) to redisperse the solid systems, the particle could retain stable in size from 30mins to 90mins following drying and reach smaller size of 500nm~2 μ m in most experimental groups. In groups with 50% solid carrier/ethanol/Tween 80， it was most obvious that the range of size reduction could reach in average from 4800nm in water phase to about 1700nm in SLS solution；when it came to Lactose as a solid carrier, the system particles could even be reduced in mean size of 900nm ~ 1000nm in all formulas.
Furthermore, we proceed an observation of crystalline structures of formulations. Chances are that we can establish the most optimized preparation method of solidified self-microemulsifying drug delivery containing a poorly water-soluble compound from a set of the above evaluations. On the other hand, our study can provide a foundation and a model for pharmaceutical technology of the dilutable drug delivery systems combined with nanoparticulate polymers in the near future.