MASTER'S THESIS

紫杉醇脂質體製備工藝和處方的改進

文詩泳

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摘要

目的：紫杉醇是從太平洋沿岸的短葉的紫杉屬紫杉中分離出來的天然產物。紫杉醇(paclitaxel)已成爲非常重要的一類廣譜化療藥物，治療腫瘤，尤其是卵巢癌、乳腺癌和非小細胞肺癌等[1、2]。在確定了它的理化性質、全身毒性反應、抗腫瘤作用的今天，有關它的藥物載體的構建已經成爲現今研究的重點，令其使在體內是有更合理分佈、更好的靶向作用、更少的毒副反應。紫杉醇在水中的溶解度很小，所以目前國內外上市的紫杉醇是聚氧乙基蓖麻油(CrEL)及無水乙醇的複合溶媒製成的粘稠性針劑[3]。紫杉醇注射液容易導致多種毒副反應，有溶劑的毒性、尤其是嚴重急性超敏反應和稀釋後的不穩定性，導致降低了使用的安全性，使其應用受到一定限制。此外，其在給藥時用生理鹽水或品質分數爲5 %的葡萄糖注射液稀釋後還會產生紫杉醇結晶，還需加用1個0.122 μm 微孔膜濾過裝置以除去沉澱保證用藥安全[3]。本研究的目的在於消除聚氧乙基蓖麻油引起的不良反應、增加紫杉醇的溶解度、穩定性、降低毒性、避免過敏反應而不影響抗腫瘤活性。

目前的製劑還可從聚氯乙烯輸液管路中溶出增塑劑，在塑膠容器中有非特異性吸附，故需採用特定材質的容器保存使用；藥物必須稀釋才能靜脈注射，但稀釋後又可出現紫杉醇原藥的沉澱[4]，因此臨床上迫切需要研製出一種新型的紫杉醇製劑。

脂質體是主要由磷脂和膽固醇構成的一種類似于細胞膜雙分子層的藥物載體，因磷脂具有雙親特性，故脂質體載藥範圍很廣。脂質體可以改善藥物的溶解度、改善藥代動力學、降低藥物的毒副反應且無毒、不產生免疫反應，目前已被廣泛應用於藥物載體的研究[5]。

大量的研究表明[6、7]，脂質體(liposomes，LP)作爲藥物載體可以提高藥物的治療指

數。降低或減少藥物的不良反應。因而，解決紫杉醇水溶性問題，增加臨床用藥的方便。脂質體是一種有前途的給藥載體，有許多其他載體不具備的優點，將紫杉醇製備成脂質體，可能是解決該問題的一條有效途徑[7]。按照紫杉醇的性質和實際的需要，普遍採用薄膜分散法[8、9]。

脂質體(liposomes，LP)作爲紫杉醇藥物載體可以提高其治療指數， 降低或減少藥物的不良反應[10、11]。 用卵磷脂和膽固醇製備紫杉醇脂質體(paclitaxel liposomes，LTAX) 可以拓寬其臨床應用[8]。因此本研究從文獻和實驗兩方面探討了紫杉醇脂質體的應用前景。

方法：檢索近十多年來國內公開發表的中藥類期刊、有關“紫杉醇”文獻共6402篇，再篩選出符合“脂質體“研究範圍的文章236篇，再以“制備“進一步檢索，結果出43篇，確定處方。在分析大量文獻上，本實驗研究對三方面的考察，對乙醇注入法和薄膜分散法進行了考察比較、考察膽固醇的加入對載藥量的影響（均採用薄膜分散法）、考查過膜對載藥量的影響。

結果：通過採用薄膜分散法和乙醇注入法製備工藝製備了紫杉醇脂質體，將制得的脂質體溶液進行單因素考察之後，使用薄膜分散工藝流程製備紫杉醇脂質體較佳；製備紫杉醇脂質體中，加入膽固醇對載藥量有增加影響；紫杉醇脂質體過膜對載藥量有增加影響。

結論：通過對現代相關醫學文獻的整理、統計、分析、歸納，總結出薄膜分散 爲最常見之製備紫杉醇脂質體方法；通過實驗研究，薄膜分散法是製備紫杉醇脂質體較佳方法、加入膽固醇對載藥量有增加影響；紫杉醇脂質體過膜對載藥量有增加的作用。

關鍵字：紫杉醇脂質體、薄膜分散法、膽固醇、微膜

Abstract

Aim :Paclitaxel is a natural product isolated from the pacific yew tree, Taxus brevifolia. Paclitaxel has effected as an important class of broad-spectrum antitumor drugs, and has been used as a front line treatment for aggressive cancer of the breast, lung, and ovary. After the Chemical nature, body toxicity, and so on were clearly stydied, its antitumor vehicles are becoming the research focus to build up reasonable distribution with well-targeted function for lower toxicity reaction. Paclitaxel is a water insolubile active pharmaceutical ingredient. so, it needs to solve in the Cremophor EL and ethanol(1:1) for the market and application onto injection. The injection of Paclitaxel (Taxol) cause adverse effect, solvent toxicity and hypersensitivity, unstability after deliquation. Besides, Use normal saline or 5%gluocose dilution cause Paclitaxel Crystallization, so use 0.122um mirco-filter to eliminate precipitation. for drug safety. The aim of this study is to eliminate the adverse effect of Cremophor EL ,increase the solubility, stability, lower toxicity and avoid the hypersensitivity of Paclitaxel, and keeping the antitumor activity.

Liposomes consist of phospholipids and cholesterol, which are double-layer of vehicles. Because of the double natures of lipids, liposome have a wide range of usage. Liposome may improve the solubility and features of pharmacokinetics, lower toxicity and immunoreaction , it is the vehicles widely applied on drug research.

Lots of articles prove that liposome can be a vehicle of drug for increasing therapy index, lower or reduce the adverse effect of drug. So, to solve the water soluble and increasing therapy index is the most popular in market. Liposome can be a vehicle, have a unique advantage. liposome may be the way to the solve problem Paclitaxel. By the nature of Paclitaxel , liposome can be the vehicle to improve the therapy index of paclitaxel, lower the

adverse effect. The objective of this study was a part of developing a good and stable taxol liposome and taxol modified liposome.

Method : In recent ten years, articles of paclitaxel published by China mainland at journals was about 6402, and there are 236 articles of liposome, 43 articles of preparation and lots of analysis articles. The experiment was designed in three steps--ethanol injection method, film dispersion method, test the amount of cholesterol and film affect the content.

Result : Use film dispersion method and ethanol injection methods to make liposome of Paclitaxel. After Consideration of single factor of liposome solvent, the film dispersion method is a better method. During preparation of Paclitaxel liposome, cholesterol was found to be a agent which may increase the content of paclitaxel.

Conclusion : Recent medical articles about palitaxel liposomes were sorted, analyzed, and sumed up. According to statistics and some experements, it may be concluded that use film dispersion method is the most common method to produce paclitaxel liposomes, in laboratory research, use film dispersion method is a better method. For preparation of Paclitaxel liposomes, cholesterol may increase the content of drug in liposomes.

KEY WORDS : Paclitaxel liposome ; Film dispersion method, cholesterol, film

目錄