改善 TSB-9 口服生體可用率之劑型研究

Formulation Study for Improvement of Oral Bioavailability of TSB-9

中文摘要

在本研究中我們所使用的模式藥物爲 TSB-9，是一種萃取自藤黃(Gamboge)中的混合物，其成分之一，Gambogic acid (GA)在許多的藥理研究中被認爲對於癌細胞細胞週期中的 G2 期以及 M 期會產生不可逆的中止，所以有抑制腫瘤增生的功效。我們爲了增加服藥時的方便性，所以本研究希望能以藤黃其中所有的成分製成複方 TSB-9 來口服投予給藥。

根據我們的研究顯示出 TSB-9 口服吸收不好，口服生體可用率也極低，我們推測造成其口服吸收差可能的原因，應爲低水溶解度、以及抑制胃腸道的蠕動導致藥物的吸收不佳，因此 TSB-9 口服藥物劑型的設計上，利用親水性的賦型劑 PVP K-30、Kollidone VA-64、以及 PEG 6000 將 TSB-9 製備成固體分散相增加其溶解度，以及給藥前先口服投予 30 mg/kg 的 Metoclopramide 預先增加胃腸道的活性，以避免 TSB-9 對胃腸道過度的抑制，期望 TSB-9 能被良好的吸收，進而增加其口服生體可用率。

結果顯示 TSB-9 製備成固體分散相的劑型可以大幅的改善 TSB-9 溶解度，賦型劑所使用的比例越高則溶解度也越大。大白鼠口服以 PVP K-30 爲賦型劑，比例爲藥物比賦型劑爲 1:3，所製成之 TSB-9 固體分散相處方 A13 投予劑量 60 mg/kg 時，於動物體內可以產生較大的曲線下面積以及最佳的生體可用率，其口服生體可用率是 6.23% ，約爲同劑量的由 0.5% tween 80 所分散的 TSB-9 懸浮液 2.27% 之 2.74 倍。但是給藥前先口服投予 30 mg/kg 的 Metoclopramide 並不能有效的增加藥物的口服生體可用率。

所以將 TSB-9 製備成固體分散相之劑型可以有效改善其口服吸收差以及生體可用率低落的缺點，若將來製備成口服膠囊劑型可預期於癌症病患使用時，提高病患用藥的順服性。

英文摘要

In this study, the model drug, TSB-9, is a poorly water-soluble mixture extracted from Garcinia hanburyi Hook. f.. Gambogic acid (GA) is one compound which was proved potent cytotoxicities against various cancer cell lines by irreversible arrest in G2/M phase of the cell cycle in Gamgoge. However, the oral bioavailability (BA) of TSB-9 is so low that we tried to increase it.

We supposed the low oral BA of TSB-9 is because of its poor solubility and ability to inhibit the motility of gastrointestinal tract. Therefore, we formulated TSB-9 into solid dispersion (SD) by hydrophilic excipients, such as PVP K-30, Kollidone VA-64, and PEG 6000 to increase its solubility. Beside, we gave a pre-dose of metoclopramide 30 mg/kg prior to TSB-9 administration to prevent the excessive GI tract inhibition.

Base on the results of DSC, X-ray, and dissolution profile showed that TSB-9

formulated into SD could substantially increase its solubility. The more the proportion of excipients was added, the higher the solubility reached. Especially when the ratio of drug to PVP K-30 was 1:3, it obtained the highest area under curve (AUC) and the best oral BA about 6.23% , which is 2.74 times than that of TSB-9 suspension. But a pre-dose of metoclopramide 30 mg/kg prior to TSB-9 administration could not substantially increase its oral BA.

In summary, formulating TSB-9 into SD could effectively improve its bad oral absorption and low BA. It would be beneficial to make TSB-9 into oral capsule to raise the compliance of cancer patients.