嗎啡口服液最佳安定性之研究與開發改良生體可用率之處方

Studies of Morphine Oral Solution with Optimal Stability and Formulation of Improved Bioavailability

中文摘要

本研究之目的在於研究開發最佳安定性與改良生體可用率之嗎啡口服液處方，賦型劑以水溶性維生素 E (Tocopheryl polyethylene glycol 1000 succinate，TPGS) 爲主，其具有維生素 E 之抗氧化作用，同時又具有抑制腸道輸送蛋白 (P-glycoprotein，P-gp) 的效能，因此認爲是可以同時達到具有最佳安定性及改善生體可用率之添加物，並調配得到最佳化口服液處方，故本實驗欲探討 TPGS 添加於嗎啡口服液中，對嗎啡水溶液安定性改善之效果，同時評估 TPGS 於腸道抑制嗎啡受到 P-gp 排除（efflux）的效能，以增進嗎啡於腸道中之吸收情形。

嗎啡口服液之加速安定性試驗將探討以 TPGS 作爲嗎啡口服液抗氧化劑之效能，比較不同嗎啡濃度於不同酸鹼値、包裝量（半滿與全滿之充塡）、以及 TPGS 添加量對嗎啡口服液安定性所造成的影響，並將所配製成之口服液置於 40℃，相對溼度 75%之環境進行加速安定性試驗，於處方配製好後便採樣分析起始點濃度，另外分別於不同時間點也分別採樣分析嗎啡濃度的變化情形。體外試驗方面則是使用 Caco-2 cell 做爲人體腸道投與之體外模式，以探討 TPGS 對於抑制 P-gp 之最佳濃度，同時又採用 Pluronic F-68 作爲第二種 P-gp 抑制劑，以供 TPGS 作比較。

實驗結果顯示，嗎啡口服液於三個月的加速安定性試驗中，pH 値並無明顯變化，且各處方之嗎啡濃度也沒有明顯減少之情形，所配製之口服液處方均通過三個月之加速安定性測試。而在體外模擬腸道細胞的 Caco-2 細胞模式中，嗎啡被排除（efflux）的速度較吸收（influx）的速度快(3.68 × 106 cm/s vs 3.09 × 106 cm/s)，而當添加 TPGS 後，當其濃度達半致效濃度（EC50）0.887%時，嗎啡之輸送速率比起未添加的對照組速度快了一倍，且 TPGS 之 EC50 低於 pluronic F-68，顯示 TPGS 抑制 P-gp 的效果較 pluronic F-68 爲佳。

因此，嗎啡口服液中添加適量的水溶性維生素 E（TPGS），不僅可以作爲抗氧化劑，降低嗎啡水溶液氧化降解的情形，維持藥物的安定性，更可以抑制腸胃道中 P-gp，降低個體間 P-gp 的差異性，進而提高藥物的生體可用率，所以 TPGS 對於提高嗎啡的吸收情形以及影響個體間的生體可用率之差異性將需更進一步探討。

英文摘要

The object of this study was to develop the morphine oral solution with optimal stability and improve the formulation of bioavailability. Tocopheryl polyethylene glycol 1000 succinate (TPGS) was selected as an additive for the purpose of acting as an anti-oxidant and a P-gp inhibitor. The effects of TPGS on the improvement of morphine stability in the oral solution were investigated. The influence of TPGS on Pgp-mediated efflux in monolayers of Caco-2 cells to modify the morphine absorption in the intestine was also examined.

The accelerated stability of morphine in the oral solution was compared in the concentration of 2, 4, and 8 mg/mL with the addition of TPGS content at the various levels of 0.01%－0.5%. The pH values were controlled either at 3, 3.5, 4, or 4.5, respectively. All solutions were stored in high-density PE bottles either half-filled or full-filled. Samples were taken at the interval of immediately after preparation, after 1, 2 week, 1, 2 or 3 month of storage at 40°C / 75% RH (relative humidity). In vitro monolayer studies using caco-2 cells were employed to explore the optimal concentration of TPGS on the inhibition of P-gp mediated transport of morphine.

Results showed that in the accelerated stability studies of morphine solution, the pH of all formulations remained nearly unchanged over all of the periods. The concentrations of morphine also remained constant during the stability studies, indicating that morphine oral solutions were stable upto 3 months under all conditions tested. Transport of 10μM morphine in caco-2 cell model showed that the efflux to be higher than the influx (3.68×106 cm/s vs 3.09×106 cm/s). Morphine transport rates could be doubled when morphine administered with P-gp inhibitor of TPGS with EC50 (effective concentration 50%) of 0.887%. The EC50 value of TPGS was less than that of pluronic F-68 suggesting that TPGS had a stronger inhibitory potency than pluronic F-68.

In conclusion, when TPGS used as an antioxidants, which enable to prevent the degradation of morphine in the oral solution forms. Moreover, TPGS also played an important role of acting as a P-gp inhibitor to improve morphine absorption. The extent of its effects on the bioavailability of morphine absorption are needed for further exploration.