Development of Controlled Release Bi-Layered Tablets Containing Oxycodone Hydrochloride

Kyung Hun Kim[1)], Kyung Soo Lee[1)], Cho Rok Shim[1)], Il Woo Jung[1)], Jin Seob Oh[1)], Seo Hyun Lim[1)], Sung-Hoon Lee[2)], Woo Heon Song[1)], Jun Sang Park*[1)]

[1)] R&D Center, GL Pharm Tech, Seongnam, Gyeonggi, South Korea

[2)] Pharmaceutical Engineering, Cheongju University, Cheongju, Chungbuk, South Korea

* Correspondence to jspark@glpt.co.kr

Introduction

- Oxycodone is a semi-synthetic opioid agonist that provides effective relief for moderate to severe pain in cancer[1,2] and post-operative patients.[3]
- Oxycodone oral bioavailability in humans is 60 % (range 50-87 %)[2,4,5] The terminal elimination half-life is independent of dose, with modest inter-individual differences.
- Controlled release oxycodone formulations have been studied to enhance the therapeutic effect by providing constant release over the whole dosing interval and improve patient`s convenience by reducing the frequency of administration as well.

Objectives

- Controlled release oral oxycodone systems offer the clinical advantage of less frequent dosing with an increase in quality of life for patients with chronic pain requiring repeated-dose opioid analgesia.
- So, the first objective of this study was to develop an oral controlled release oxycodone tablet using modulating release barrier in bi-layered tablet.
- The second objective of this study was to investigate the designed system to provide in vitro-in vivo correlation, using the three controlled release formulation containing different drug releasing profiles of oxycodone.

Methods

- A novel bi-layered tablet technology consisting of a release barrier layer and a diffusion controlled matrix layer with hydrophilic polymers as a once-a-day tablet formulation was established. The bi-layered tablet containing 20mg of oxycodone was produced by direct compression method.

Mixing (Mixer)

↓

Screening (30mesh, Oscillator)

↓

Post-mixing (Lubricant, Mixer)

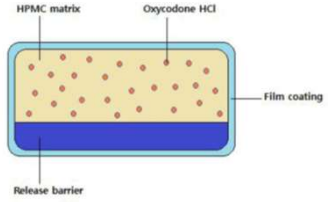
↓

Tableting (Tableting machine)

- Drug release tests were conducted according to USP Apparatus at 150rpm in pH6.8 media. Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC systems at a wavelength of 230nm.
- Three CR formulations having different drug releasing profiles (F1, F2, F3)were orally administrated to six subjects of beagle dogs.
- The plasma samples were analyzed by LC-MS/MS and calculated pharmacokinetic parameters. IVIVC was investigated using fraction dissolved and fraction absorbed data from three different formulations.

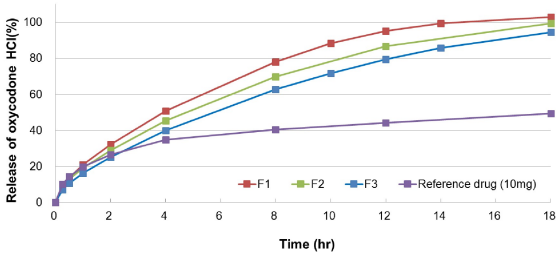
Results

Concept and Properties of bi-layered tablets

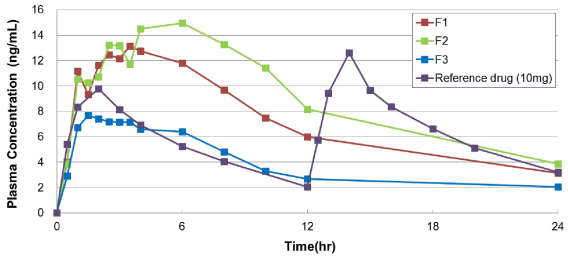


Properties	
Weight (mg)	404
Diameter (mm)	9.5
Thickness (mm)	5.4
Hardness (kp)	18
Friability (%)	0.1

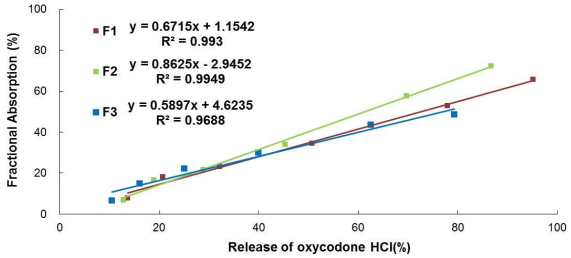
Dissolution and animal PK profile



Release profiles for Bi-layered tablets containing oxycodone hydrochloride



Average plasma concentration of oxycodone administration of reference drug and Bi-layered tablets containing oxycodone hydrochloride in beagle dog.



In vitro-in vivo correlation of Bi-layered tablets containing oxycodone hydrochloride

Conclusions

- Bi-layered controlled release formulations consisting of drug contained layer and barrier layer including hypromellose were established with respect to well controlled dissolution profiles and IVIVC in beagle dog model.
- The findings of the present study provide the potential of once-a-day controlled released oxycodone hydrochloride.

* Reference

1. Glare PA, Walsh TD. 1993. Dose-ranging study of oxycodone for chronic pain in advanced cancer. J Clin Oncol. 11, 973-978.
2. Kalso E, Vainio A, 1990. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Phamacol Ther. 47, 639-646.
3. Kalso E, Poyhia R, Onnela P, Linko K, Tigerstedt I, Tammisto T. 1991. Intravenous morphine and oxycodone for pain after abdominal surgery. Acta Anaesthesiol Scand. 35, 642-646.
4. Poyhia R, Vainio A, Kalso E. 1993. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. J Pain Sympton Manage. 8, 63-67.
5. Leow KP, Smith MT, Williams B, Cramond T. 1992. Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. Clin Pharmacol Ther. 52, 487-495.