Swellable Three-layered Tablet for Sustained Release of Tamsulosin HCl

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Introduction

- The hydrophilic matrix tablets are widely used as oral controlled-release dosage forms but in vitro drug release behavior for once-a-day is not always reflected in in vivo performance.
- One of several reasons is the difference of amount of fluid around matrix under in vivo condition as it transits along the GI tract which compares with under in vitro test.
- Sako et al.[1)] elucidated the rapid gelation of matrix and abundant water in a tablet was useful in design of once-daily oral formulations to make drug release well in colon and allow continuous absorption.
- Tamsulosin OCAS® by Astellas Pharma[2)] is a gel matrix shows very rapid and nearly complete gelation/hydration in the upper part of the GI tract (stomach and small intestine). The gel matrix is then maintained in the hydrated state in the colon and therefore has sufficient strength to maintain drug release in the colon although water is poorly available there
- OCAS® formulation ensures continuous drug absorption throughout the entire GI tract which reduced several drawbacks of Harnal® capsule[2)].

Objective

The objective of this study is to develop a new desirable dosage form formulation for once-daily tamsulosin(TSN) tablets using GLARS system. And the characteristics of new dosage form, water-uptake capacity, the amount of it in a tablet comparing with OCAS and so on, were studied.

GLARS System

- GL Pharm Tech's **GLARS™**
  - Geometrically Long Absorption Regulated System
- **Three-layer tablet**
  - Swellable and slow release layer
  - **Water penetrating** layer
  - Swellable and slow release layer

- **Synergic advantages of GLARS**
  - Absorption improvement in the lower digestive tract for once-a-day
  - Variable release patterns independent of the drug solubility
    - Sigmoid or zero-order release

(PCT/KR08/794, KP 07-12944)

Methods

- The three-layered TSN tablets were prepared using a carver press. Granules containing TSN were compressed into tablets at the pressure of 6 MPa/cm^2.
- Comparison of water-uptake amount and swelling property of dosage forms, GLARS and OCAS and the possibility of breakage of GLARS tablet after oral administration were carried out under strong agitation force with magnetic stirrer or dissolution paddle at room temperature.
- Dissolution tests were performed to evaluate the *in vitro* drug release of the tablet and carried out using USP Dissolution Test Method II at a paddle speed of 100, 150 rpm in 900 ml of pH 6.8 buffer (2nd disintegration media, KP or JP).

Results

Photographs of the GLARS tablets during dissolution test

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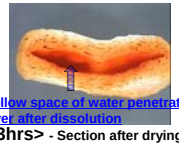
<1hrs>

<3hrs>

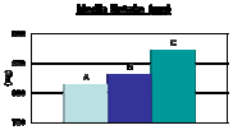


Hollow space of water penetrating layer after dissolution

<3hrs> - Section after drying

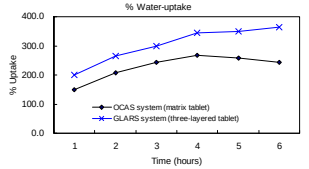
- During the dissolution test of GLARS, the tablet swelled rapidly and became much bigger about 4 times more.
- After 3 hours the tablet was vacuum-dried and sectioned. We can find a large hole in a tablet.
- It suggested that much of water was contained in this tablet before the tablet migrated into colon
- It could make a drug dissolved well and absorbed continuously in the lower digestive track.

Effect of water-soluble excipients in an intermediate layer



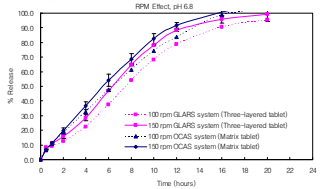
- Solubility of excipients
  - A < B < C
- The amount of water-uptake during dissolution
  - Initial : 270 mg (tablet)
  - 3 hrs : 875 mg (media) + 225 mg (tablet)

Comparison of the water-uptake behavior between GLARS and matrix tablet



- Water-uptake amount of GLARS was preferable to OCAS.
- A large hole in GLARS tablet contained much of water which could make drug released and absorbed sufficiently in colon.
- GLARS was not separated during water-uptake test over 500 rpm.

Release profiles of matrix tablet and GLARS tablet at different paddle speed



- In order to confirm robustness of GLARS, we evaluated the influence of paddle rotation speed in *in vitro* dissolution test.
- Similarity factor (f2) of different rotation speed (100 vs. 150 rpm) was over 50.
- But, a little change of release rate caused by paddle speed suggested that polymer layers played an important role in controlling the release rate of GLARS.

Conclusions

- GLARS was characterized that much of water was contained in a large hole of tablet during dissolution test at early stage of release
- The amount of water absorbed in GLARS tablet was dependant on the water-solubility of excipient in an intermediate layer and it could be more than in OCAS.
- It suggested that abundant water in dosage form could help drug dissolved and absorbed in lower intestinal tract.
- The less of an effect of paddle speed in dissolution but a little change was found. (f2 > 50)
- GLARS can be a useful tool for developing once-daily tamsulosin tablets which is comparable to tamsulosin OCAS.

* Reference

1. K. Sako, H. Nakashima, T. Sawada, and M. Fukui, "Relationship between gelation rate of controlled-release acetaminophen tablets containing polyethylene oxide and colonic drug release in dogs, *Pharmaceutical Research*, 13(4), 1996.
2. C. R. Chapple, "The development of the oral controlled absorption system (OCAS): a new improved formulation of tamsulosin, European Urology Supplements, 4(1), 2005.

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