# Sustained drug release profiles from three-layered tablets containing different excipients in the mid layer

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## Introduction

- A novel three-layered tablet technology consisting of an inner immediate release layer and two extended release barrier layers with swellable polymers as a once-a-day tablet formulation was established.
- Dissolution medium quickly permeates to the inner layer of water-soluble excipients, and the two barrier layers swell to surround the inner layer rapidly, controlling drug release from the inner layer.
- This rapid swelling property can suggest that the tablet, after oral administration, can go into full-hydrated state rapidly and arrives the colon where little water is available, which induce the continuous drug release there irrespective of the unfavorable environment.

• The objective of this study is to evaluate the feasibility for once-daily tablets using GLARS (Geomatrix Long Term Abosorption Release System) and to investigate an appropriate formulation for their feasibility the sustained release of Terazosin HCl.

• Various formulations of the tablets were investigated form their feasibility of sustained drug release.

## Materials and Methods

- Terazosin HCl dihydrate : Hanseo chemical (Seoul, Korea)
- The hydrophilic polymer, PEO : Polyox WSR N-1105, N-12K, WSR 301, WSR Coagulant and WSR 303 (Dow chemical, USA)
- The Dextrates, NF (Emdex®) and microcrystalline cellulose PH102 (MCC, Heweten 102) : JRS Pharma, USA
- FlowLac 100 (spray-dried alpha-lactose monohydrate) : Meggle, Germany
- The three-layered terazosin tablets were prepared using a carver press. Each tablet was compressed at the pressure of 6 MPa/cm$^2$.
- 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 50, 100 rpm in 900 ml of pH 6.8 buffer (2nd disintegration media, KP or JP).

• Table 1. Preparation of three-layered tablets : Different Filler

| Layers | Ingredients | Formulation number | | | |
|---|---|---|---|---|---|
| | | Dex-70 | Dex-30 | Lac-70 | Lac-30 |
| Upper and Lower | Polyox WSR Coagulant | 99.50 | 99.50 | 99.50 | 99.50 |
| | Mg.stearate | 0.50 | 0.50 | 0.50 | 0.50 |
| Mid | Terazosin HCl | 3.561 | 3.561 | 3.561 | 3.561 |
| | Filler | 62.94 | 24.94 | 59.44 | 23.44 |
| | Binder | 3.50 | 1.50 | 7.00 | 3.00 |

• Table 2. Grade of PEO polymers

| Grade | M.W | Viscosity |
|---|---|---|
| Polyox WSR N-12K | 1,000,000 | 430 |
| Polyox WSR 301 | 4,000,000 | 1,500-5,500 |
| Polyox WSR Coagulant | 5,000,000 | 5,500-7,500 |
| Polyox WSR 303 | 7,000,000 | 7,500-10,000 |

## Results

### I. Effect of central layer composition on media uptake and erosion

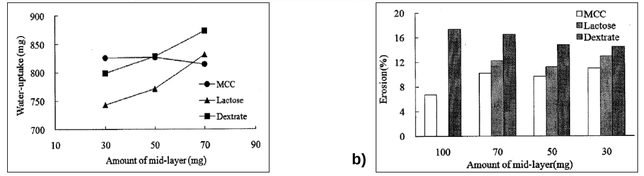


Figure 1. Influence of type and amounts of mid-layer on the degree of swelling and the erosion of three-layered tablets : MCC, Lactose, and Dextrate.
a) Water uptake (mg): MCC < Lactose < Dextrate, b) Erosion rate (%) : Dextrate < Lactose < MCC

### II. Drug release profiles from the matrix tablets containing various PEO polymer

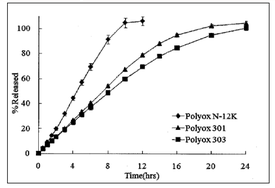


Figure 2. Drug release profiles from the matrix tablets.

i) Low molecular weight PEOs gave faster release rates than higher molecular weight PEOs.

ii) Drug release with different grades of PEO showed a good fit to the Korsmeyer-Peppas eqution.

• Table 3. The Korsmeyer-peppas equation fit using in vitro release data of the matrix tablet.

| Factors | Polyox WSR N-12K | | Polyox WSR 301 | | Polyox WSR 303 | |
|---|---|---|---|---|---|---|
| | 50 rpm | 100 rpm | 50 rpm | 100 rpm | 50 rpm | 100 rpm |
| n | 1.072 | 1.122 | 0.873 | 0.980 | 0.883 | 0.920 |
| k | 7.115 | 9.275 | 6.900 | 6.946 | 6.134 | 7.110 |
| $R^2$ | 0.998 | 1.000 | 0.998 | 1.000 | 0.999 | 1.000 |

### III. Effect of central layer loading amount on dissolution profiles [Dextrate , Lactose]

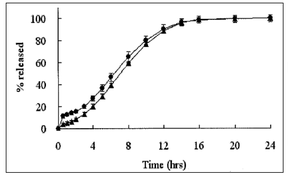


Figure 3. Drug release profiles from the three-layered tablets containing different amounts of soluble filler in the mid-layer ; Dextrate 70mg(●); Dextrate 30mg(▲).

i) The amount of dextrate in the mid-layer did not change the release profiles and rate except the initial time period.

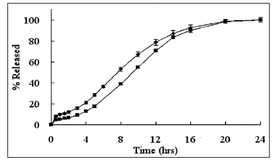


Figure 4. Drug release profiles from the three-layered tablets containing different solubility of filler in the mid-layer ; Dextrate 70mg(●); Lactose 70mg (▲).

i) The release of Dex-70 showed slightly faster release up to 14h compared to Lac-70.

### IV. Dissolution tolerance of three-layered tablet to agitaiton force

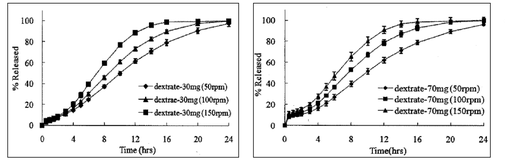


Figure 5. Drug release profiles from the three-layered tablets containing different amounts of dextrate in the mid-layer with various paddle speeds.

• Table 4. Dissolution tolerance of three-layered tablets to the agitation force, from 50 to 150rpm.

| f2 (vs.100 rpm) | Dex-30 | Dex-70 |
|---|---|---|
| 50 rpm | 50.5 | 58.5 |
| 150 rpm | 53.7 | 54.1 |

## Conclusions

1. The amount of water-soluble excipient in the mid-layer may affect the swelling properties.
2. However, the overall drug release rates of the three-layered tablets might be also dependent on the composition and properties of the barrier layers even though the mid layer may affect water penetration and diffusion properties.
3. It was also shown that dextrate and lactose induced the tablet more eroded rate of tablet was, which was related to the results of swelling poperty.
4. The three-layered tablets showed more consistent release kinetics than the matrix tablet. These findings can give good information for the development of sustained drug delivery system, especially once-a-day Terazosin HCl tablet.

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