Development of enteric-coated extended release paroxetine hydrochloride tablets

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INTRODUCTION

Properties of paroxetine

Paroxetine, a phenylpiperidine derivative, is a potent and selective serotonin reuptake inhibitor (SSRI) with currently approved indications for the treatment of depression, obsessive-compulsive disorder, panic disorder and social phobia.

It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl$. The molecular weight is 365.8 (329.4 as free base).

Rationale for development of enteric-coated extended-release dosage formulation

One important benefit of extended-release (ER) formulation is that the time during which plasma drug concentrations exceed some minimum threshold for causing an adverse event may be decreased, which may translate into marked improvement in tolerability. ⇨ **extended-release formulation**

The other is a possibility for minimizing SSRI-associated nausea. Nausea is the most frequently reported adverse event associated with SSRI. Its occurrence is thought to be partially mediated by 5-HT_3 and other 5-HT receptor subtypes located in the upper gastrointestinal tract, in addition to a centrally mediated effect.
⇨ **enteric-coated formulation**

- Improvement tolerability (Delay and diminishes the C_{max})
- Reduction adverse events (Reduce the SSRI-associated nausea)

Pharmaceutical interaction between paroxetine extended-release core and enteric coating materials

When an enteric coating material is directly coated on extended-release tablets core containing paroxetine, the release behavior of the tablets changes significantly after the tablets passed through the acid stage because of the interaction between paroxetine and the enteric coating polymer.

OBJECTIVES

- **To investigate the influence of intermediate coating layer between core matrix and enteric coating layer on the *in vitro* release of paroxetine hydrochloride**

- **To develop enteric-coated extended release paroxetine hydrochloride tablets that can minimize adverse events and offer constant drug release rate regardless of the residence of the tablet in the acid stage.**

METHODOLOGY

Preparation of enteric-coated ER tablets

Single layer matrix tablets containing hydroxypropylmethylcellulose (HPMC) as a release-controlling agent were prepared by wet granulation, posterior mixing and compressing. The tablets were enteric-coated directly or intermediate coating layer was applied between the core matrix and enteric coating layer. For the intermediate coating layer, HPMC was used individually or in combination with ethylcellulose (EC) based aqueous latex (Surelease®, Aquacoat®).

Formulations

- Control is a formulation that was enteric-coated directly on the core matrix.

- F1, F2, F3 are formulations that intermediate coating layer was applied between the core matrix and the enteric coating layer.

Composition	Formulations			
	Control	F1	F2	F3
Core	HPMC matrix core	HPMC matrix core	HPMC matrix core	HPMC matrix core
Intermediate coating	none	3% coating (HPMC base)	8.5% (HPMC base)	8.5% (HPMC+EC base)
Enteric coating	8% coating (Acryl-Eze)	8% coating (Acryl-Eze)	8% coating (Acryl-Eze)	8% coating (Acryl-Eze)

In vitro dissolution testing conditions

- **Dissolution tester**
  - VK7000 dissolution tester (Vankel. Inc.)
- **Method**
  - USP Apparatus 2
- **Dissolution media**
  - 0.1N HCl (acid stage), pH7.5 tris buffer (buffer stage)
- **Rotation speed**
  - 150rpm
- **Temperature**
  - 37±0.5℃

In vitro dissolution testing methods

- **DT02 :** *In vitro* dissolution testing of the delayed and extended release tablets was performed using USP Apparatus II for 2 hours in 0.1N HCl followed by 8 hours in pH 7.5 tris buffer.

- **DT01 :** Also *in vitro* dissolution testing in pH7.5 tris buffer without an acid stage was performed.

RESULTS

Control formulations

It was found that the release rate of directly enteric-coated tablets was decreased significantly after an acid stage in 0.1N HCl for 2 hours (Figure 1).

The following two release profiles was not similar comparing the profiles by using the FDA recommended f2 factor (similarity factor).

It was assumed that the interaction between cationic paroxetine and anionic enteric polymer inhibited the release of drug from the matrix.

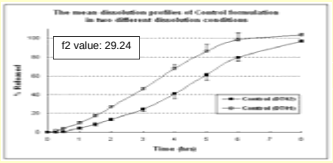

Figure 1. The dissolution profiles of Control formulation

**(DT01: Drug release rate of drug in pH7.5 tris buffer,
DT02: Drug release rate of drug after transition in pH7.5 tris buffer from 0.1N HCl)**

F1 formulations

It was found that the significant gap between two dissolution profiles by applying an intermediate coating layer was decreased (Figure 2).

The following two release profiles was not similar comparing the profiles by using the FDA recommended f2 factor (similarity factor).

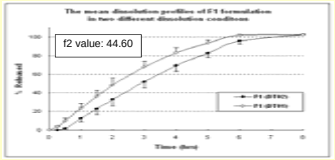

Figure 2. The dissolution profiles of F1 formulation

F2 formulations

It was found that the gap between two dissolution profiles by applying proper HPMC based intermediate coating layer was remarkably decreased (Figure 3).

The following two release profiles was similar comparing the profiles by using the FDA recommended f2 factor (similarity factor).

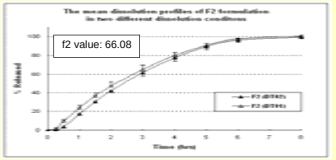

Figure 3. The dissolution profiles of F2 formulation

F3 formulations

It was found that there is no significant change between two dissolution profiles by applying proper HPMC+EC based intermediate coating layer (Figure 4).

The following two release profiles was similar comparing the profiles by using the FDA recommended f2 factor (similarity factor).

The addition of EC based latex in intermediate coating composition was helpful to prevent the interaction between drug and enteric polymer.

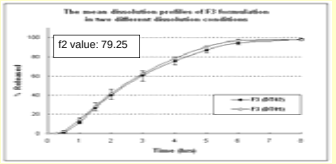

Figure 4. The dissolution profiles of F3 formulation

CONCLUSIONS

- **The proper intermediate coating layer should be applied in order to minimizing the change of in vitro release profiles of enteric-coated ER paroxetine hydrochloride tablets.**

- **The new enteric-coated ER paroxetine hydrochloride tablets that offer constant drug release rate regardless of the residence of the tablet in the acid stage was developed.**

● **This research is a part of patent KP 10-0591142**