

Development of A Self-Emulsifying Raloxifene HCl Liquid Formulation

Yunqi Wu and Atul Patel

SCOLR Pharma, Inc.
19204 North Creek Parkway
Suite #100
Bothell, WA 98011

Abstract

Purpose. To develop a self-emulsifying liquid formulation of raloxifene HCl with enhanced solubility and bioavailability. **Methods.** Two self-emulsifying formulations of raloxifene HCl were developed using polyoxyl 35 castor oil, PEG-8 caprylic/capric glycerides, dl-alpha-tocopherol, glycerol monocaprylate, ethanol and purified water. Raloxifene HCl was introduced into homogeneous mixtures of selected hydrophilic liquids for a higher hydrophilic-lipophilic balance (HLB) formulation and sonicated until a clear solution was formed. For a lower HLB formulation, tocopherol and glycerol monocaprylate were added into the solution and sonicated until a transparent solution was achieved. The prepared solutions were filled into hard shell gelatin capsules at various volumes and tested in a USP Type II dissolution apparatus at 50 rpm in 1000 ml of 0.1% polysorbate 80 at 37.0±0.5°C. The release of raloxifene HCl was detected at UV 285 nm. The prepared liquid formulations were also stored in closed containers under ambient and stressed conditions for stability observation. **Results.** The formulations rapidly dispersed in the dissolution media upon breakage of the gelatin capsule and complete release was achieved in 5-10 minutes; no remaining debris or particulate was observed. All the formulations displayed a faster release rate compared to the commercial tablet product, Evista® 60 mg. The developed formulations displayed UV absorbance greater than or equal to Evista across all dose levels. The formulation incorporating higher HLB emulsifiers showed excellent stability at both ambient and accelerated conditions, whereas the one with lower HLB was more stable under accelerated temperature than ambient condition for a retarded crystallization of drug. **Conclusion.** All raloxifene formulations presented good *in vitro* dissolution characteristics. The increased UV absorbance indicates that the developed formulations are capable of providing a better *in vitro* release performance at a reduced dose compared to the commercial product. A stable and cost-effective self-emulsifying raloxifene HCl liquid formulation was achieved and suitable encapsulation materials will be investigated in the future.

Introduction

Raloxifene HCl (Figure 1) is an off-white to pale-yellow solid that is very slightly soluble in water. It is a selective estrogen receptor modulator (SERM) used in the prevention of osteoporosis in post-menopausal women and is marketed as Evista® by Eli Lilly Pharmaceuticals, which supplied in a tablet dosage form for oral administration.

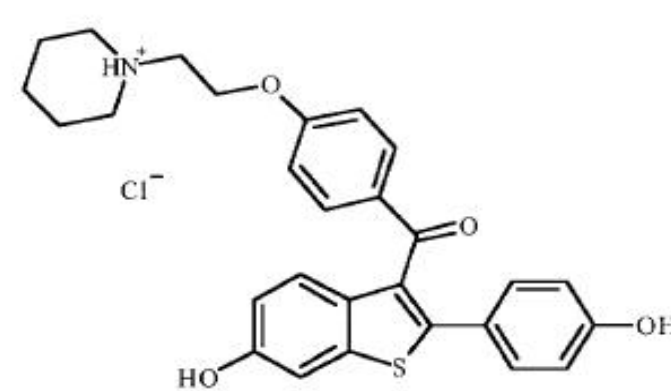


Figure 1. Chemical structure of raloxifene HCl.

It has been recognized that the self-emulsifying drug delivery system (SEDDS) shows the potentiality for enhancing the bioavailability of poorly soluble drugs. In this study, a self-emulsifying liquid formulation of raloxifene HCl was developed, which is expected to improve solubility and bioavailability of raloxifene HCl.

Methods

Materials and formulation

Raloxifene HCl, dl-alpha-Tocopherol, Polyoxyl 35 castor oil (Cremophor EL), PEG-8 caprylic/capric glycerides (Labrasol), glycerol monocaprylate (Capmul MCM L8), ethanol, and deionized water were used in formulating the raloxifene HCl self-emulsifying liquids.

Compositions of developed formulations are shown in Table 1.

Table 1. Compositions of Raloxifene HCl Self-Emulsifying Liquids

Ingredient (mg, ml)	Formulation A	Formulation B
Raloxifene HCl	+	+
Cremophor	+	-
Tocopherol	-	+
Labrasol	+	+
Capmul	-	+
Ethanol	+	+
Water	+	+

Liquid and capsule preparation

Based on the formulations (Table 1), all the liquid reagents in Formulation A and hydrophilic liquids in Formulation B were mixed separately. Powdered raloxifene HCl was then introduced into the homogeneous liquid. The mixture was stirred and sonicated until a clear solution was formed. For Formulation B, tocopherol and Capmul were added into the solution and sonicated until a transparent solution was achieved.

The prepared solutions filled into #00EL hard shell gelatin capsules at 1.0 ml. The target dose per capsule for Formulation A and B is 60 mg and 45 mg, respectively.

Dissolution test

Dissolution study was conducted in a USP Type II dissolution apparatus at 50 rpm in 1000 ml of 0.1% polysorbate (Tween) 80 at 37.0±0.5°C. The release of raloxifene HCl was detected at UV 285 nm.

Stability test

The prepared liquid formulations were also stored in closed containers under ambient and stressed conditions for stability observation.

Results and Discussion

The prepared liquids were light yellow and transparent in capsule. Typical pictures of the self-emulsifying liquid appearance in capsules and rapid dispersion in dissolution are shown in Figure 2.

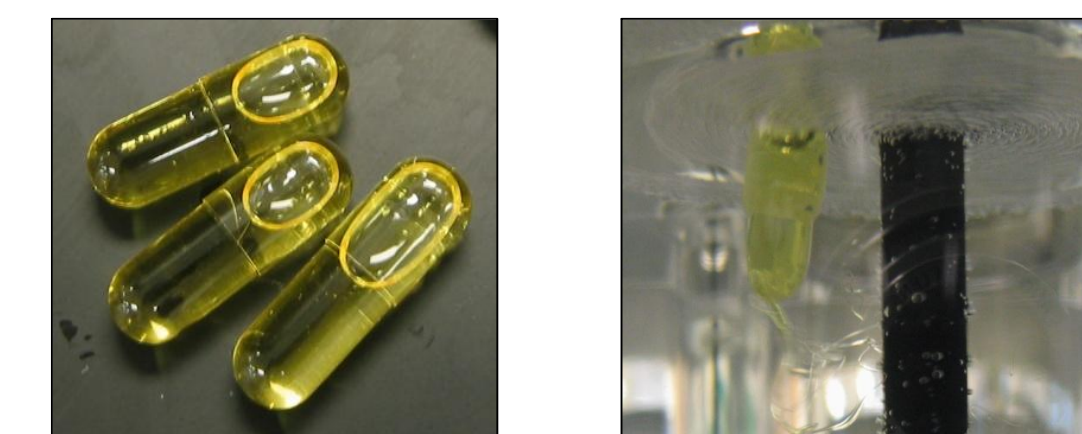


Figure 2. Formulation A in #00EL hard shell gelatin capsules (Left) and dispersion of liquid in dissolution at the first 1 min (Right).

Both formulated liquids showed higher absorbance than Evista®, especially Formulation B, which showed the highest potency with a lower dose (45 mg) (Figure 3).

The formulated liquids of raloxifene HCl rapidly dispersed in the dissolution media at the breakage of the capsule. The release completed in 5-10 minutes of dissolution with no debris or particulate observed. The derived solution of Formulation A from dissolution remained transparent, while the one of Formulation B was turbid but without precipitant even when kept overnight. The reference product Evista® 60 mg tablet, showed a slower release rate and the dissolution media was translucent with visible insoluble fine particles settled on the bottom of vessel when kept overnight.

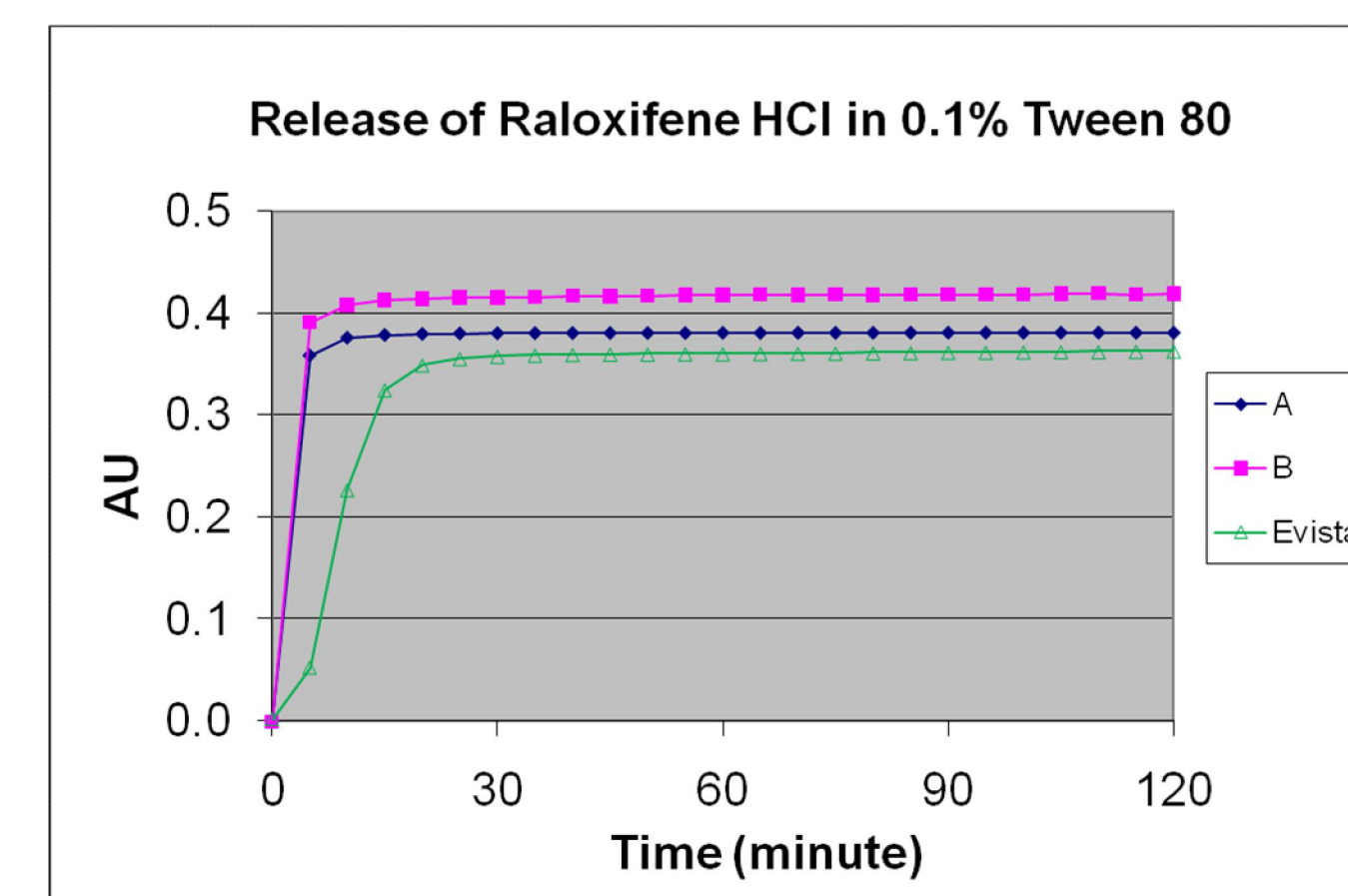


Figure 3. Raloxifene HCl released from developed formulations and reference product Evista 60 mg tablet.

After about 3 months observation, it was noted that the formulation incorporating higher HLB emulsifiers (Formulation A) showed excellent stability at both ambient and accelerated conditions, whereas the one with lower HLB emulsifiers (Formulation B) was less stable allowing crystallization of the drug under ambient storage conditions.

Conclusion

All raloxifene formulations presented faster *in vitro* dissolution characteristics when compared to the commercial product. The increased UV absorbance indicates that the developed formulations are capable of providing a better *in vitro* release performance at a reduced dose compared to the commercial product. A stable and cost-effective self-emulsifying raloxifene HCl liquid formulation was achieved and suitable encapsulation materials will be investigated in the future.

For additional information, come visit us at booth #708. *Licensing opportunities available, please contact info@scolor.com

