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## Abstract

**Purpose.** To develop fenofibrate immediate-release formulations using hot-melt technology that facilitates enhanced drug solubility with faster release rate. **Methods.** Three fenofibrate formulations were developed. Physical mixtures of fenofibrate and polyethylene glycol 1500 were heated to liquid at 78°C. After solidification, the mixtures were pulverized and sieved through 30 mesh screens. The hot-melt product was granulated with amino acid(s) and guar gum or with guar gum alone. The granulated hot melt product was then blended with microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulfate. The blends of powders were compressed into tablets using a Carver press. Dissolution studies were conducted by Type II USP apparatus at 75 rpm in 900 ml 50 mM sodium lauryl sulfate at 37.0±0.5°C. The release of fenofibrate was detected at UV 290 nm. **Results.** All tablet formulations disintegrated within 10 minutes and complete drug release was achieved within 1.5 hours. Formulations incorporating amino acid(s) presented more rapid release rates in comparison to the formulation without any amino acid and their dissolution behavior was comparable to the commercial product Tricor® 48 mg tablet. **Conclusion.** Hot-melt technology, especially when combined with specific amino acid(s) used as solubility enhancers, significantly increased the release rate of fenofibrate. The results suggest that solid dispersion incorporated with amino acids may significantly improve the dissolution behavior of poorly soluble drugs.

## Introduction

Fenofibrate is 1-methylethyl-2-[4-(4-chloro-benzoyl) phenoxy]-2-methyl-propanoate (Figure 1). The empirical formula is C<sub>20</sub>H<sub>21</sub>ClO<sub>4</sub> and the molecular weight is 360.83. Fenofibrate is a white solid which is stable under ordinary conditions. It is insoluble in water. The melting point is 79-82°C.

Fenofibrate is an oral antilipemic agent, which helps lower triglycerides and cholesterol

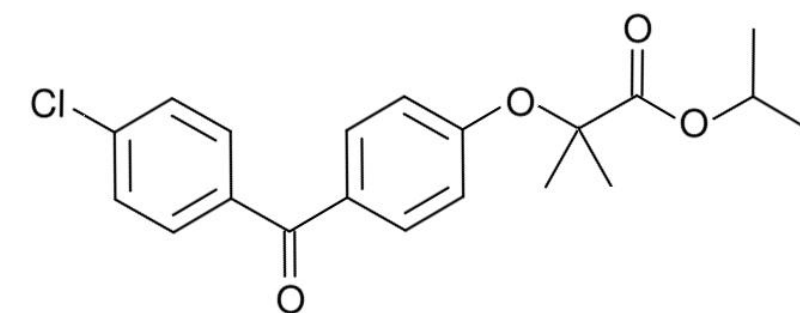


Figure 1. Chemical structure of fenofibrate.

in blood. Tricor® is the reference listed drug (RLD) for oral administration available in doses of 48 mg or 148 mg. By utilizing nano-particle technology to enhance the solubility of fenofibrate, Tricor® presents a significant improvement in oral bioavailability, compared to previous formulations.

The SCOLR patented amino acid CDT® platform offers the advantage of altering the physicochemical characteristics of the BCS II drug through improvements in solubility. This feature has been demonstrated by many successfully developed formulations of various BCS II/III drugs. In this study, three fenofibrate immediate-release formulations were developed. By combining traditional hot-melt technology with the SCOLR amino acid CDT® platform, we expect to improve drug solubility and enhance the *in vitro* dissolution of the developed formulations.

## Methods

### Materials and formulation

Fenofibrate, polyethylene glycol 1500 (PEG), guar gum 8/22A, isoleucine, arginine, microcrystalline cellulose (MCC, Avicel PH102), sodium lauryl sulfate (SLS), and croscarmellose sodium (Ac-Di-Sol) were used in this study.

Compositions of developed formulations are shown in Table 1.

Table 1. Compositions of Developed Fenofibrate Immediate-Release Tablets

Ingredient (mg)	Formulation A	Formulation B	Formulation C
Fenofibrate	+	+	+
PEG	+	+	+
Guar Gum	+	+	+
Amino acid 1	-	+	+
Amino acid 2	-	-	+
MCC	+	+	+
SLS	+	+	+
Ac-Di-Sol	+	+	+

### Manufacture of Tablet

Fenofibrate and PEG 1500 were physically mixed and heated in a water bath at 78°C until the mixture was completely melted to clear liquid. After gentle stirring for an additional 1 minute, the hot-melt liquid was removed from the heated water bath and allowed to cool at room temperature. When completely solidified, the mixture was pulverized and sieved through a #30 mesh sieve (US standard mesh).

Sieved powders of the hot-melt product were granulated with amino acid(s) and guar gum or with guar gum alone in a glass mortar with pestle, and then blended with microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulfate.

The final blends were compressed into tablets with a Carver press using Natoli HOB #67146 modified oval tooling. The compaction force was 4000 pounds.

### Dissolution study

Dissolution study was conducted by USP apparatus II at 75 rpm in 900 ml of 50 mM sodium

lauryl sulfate (SLS) at 37.0±0.5°C. The release of fenofibrate was detected at UV 290 nm.

Tricor® 48 mg tablets were evaluated as the reference for the SCOLR developed formulations.

## Results and Discussion

The developed fenofibrate immediate release tablets, Formulations A, B, and C, presented good dissolution behavior (see Figure 2). All the tablets disintegrated within 10 minutes, and Formulations B and C provided complete drug release within 1 hour, while Formulation A provided complete drug release within 2 hours.

It has been demonstrated that amino acids can be used as solubility enhancers and mobilizing excipients for a poorly soluble drug in a previous study (Wu and Brunelle, Amino acid dependant enhancement of solubility in a fenofibrate tablet,

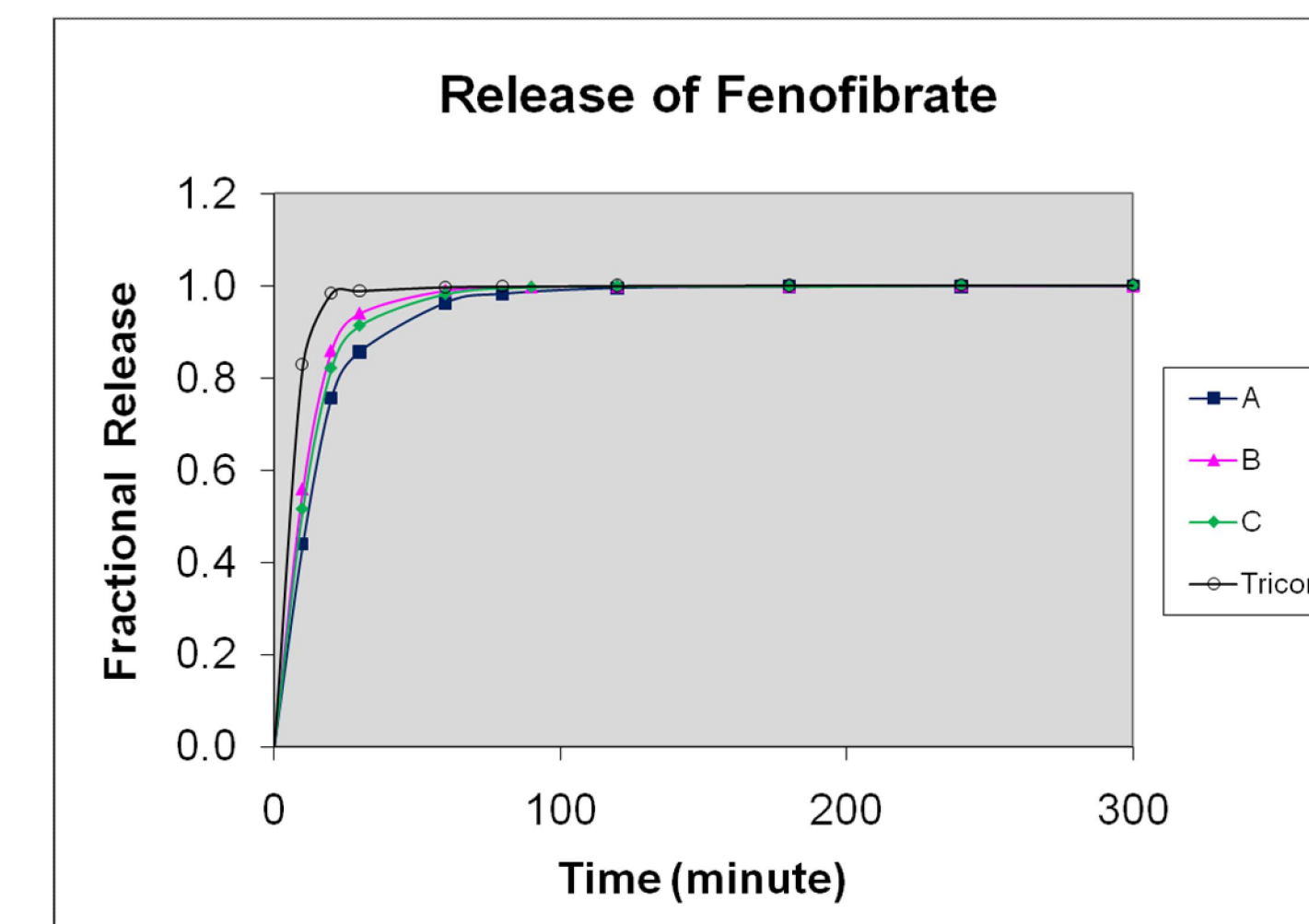


Figure 2. Fenofibrate released from developed formulations and Tricor® 48 mg tablets.

AAPS 2007). In this study, when using hot melt powders of fenofibrate, a faster release rate was achieved when amino acid(s) were incorporated into the formulation. This may be explained by a synergistic or combined effect of the hot-melt process and the interactions of the amino acids on solubility.

In comparison to the Tricor® tablet, the developed formulations using both the hot-melt process and the CDT® amino acid platform showed a slower initial burst in *in vitro* dissolution tests. This indicates that the increased surface area from nano-particles of fenofibrate used in Tricor® formulation play a dominant role in drug solubility, drug release rate and consequently bioavailability. However, the combination of hot-melt technology and the CDT® amino acid platform provides a more simplified processing stream and a commercially viable alternative to the nano-particle technology utilized in the RLD.

## Conclusion

Three formulations of fenofibrate immediate-release tablets using hot-melt technology were developed. Hot-melt technology, especially when combined with specific amino acid(s) used as solubility enhancers, significantly increased the release rate of fenofibrate. The results suggest that solid dispersion combined with amino acids may significantly improve the dissolution behavior of poorly soluble drugs.

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