

INTRODUCTION

Background

Amorphous Solid Dispersions (ASDs) prepared by hot melt extrusion (HME) are widely used to enhance dissolution of poorly water-soluble drugs. While ASDs primarily improve drug dissolution, lipid excipients such as Labrasol® can additionally enhance oral absorption through improved solubilization and intestinal permeation. Incorporating Labrasol® into an ASD therefore offers the potential to combine dissolution enhancement with permeation enhancement. However, incorporation of a liquid lipid excipients into a continuous HME processes can be challenging due to its impact on melt rheology, mixing behavior, strand formation, and process stability.

In-line liquid injection provides a potential approach for incorporating Labrasol® during continuous extrusion while maintaining process flexibility.

Model API: Fenofibrate, a BCS class II compound, log P 5.24 and molecular weight 360.83 g/mol.

Objective: To develop and optimize a continuous hot melt extrusion process for in-line incorporation of Labrasol® into fenofibrate-copovidone ASDs

MATERIALS & METHODS

Fenofibrate was selected as a model poorly water-soluble drug and polyvinylpyrrolidone-co-vinyl acetate (PVP VA 64) as the ASD carrier polymer. Fenofibrate and PVP VA 64 were obtained from Ambeed (IL, USA). Labrasol® (caprylocaproyl polyoxyl-8 glycerides was supplied by Gattefossé (Saint-Priest, France).

A physical blend containing 20% w/w fenofibrate and 80% w/w PVP VA 64 was prepared using a Turbula mixer. The blend was processed using a Leistritz ZSE 12-mm co-rotating twin-screw extruder equipped with 8-barrel zones to produce the binary ASD (77A). For the in-line liquid incorporation process, Labrasol® was injected into the extruder barrel using an auxiliary liquid feeding unit. The effects of liquid injection locations (zones 2, 3, or 4) and screw configuration on extrusion processability and strand quality were systematically evaluated.

Based on process optimization studies, two ternary ASDs were prepared:

- 78A - binary ASD blend with 10% neat Labrasol®

- 79A – binary ASD blend with 10% Labrasol® containing fenofibrate pre-dissolved at 80% saturation solubility.

The prepared ASDs were evaluated for:

- Extrusion processability and extrudate quality as a function of liquid injection location and screw configuration.
- Fenofibrate content uniformity throughout extrusion by UPLC assay of samples collected at multiple time points.
- Labrasol® stability by measuring acid value and peroxide value before and after extrusion.
- In vitro* dissolution performance using USP Apparatus II at 75 rpm in 1000 mL of 0.05M sodium lauryl sulphate (SLS) at 37°C. Samples were collected after 5, 10, 20, 30, 45, 60, 90 and 120 minutes and analyzed for solubilized fenofibrate content

RESULTS & DISCUSSION

Process Development and Optimization

Initial liquid injection trials demonstrated that extrusion performance was highly sensitive to both injection location and screw configurations. Incorporation of Labrasol® altered the melt rheology, resulting in liquid backflow and intermittent strand defects when highly distributive mixing configurations containing multiple 90° kneading elements were employed. Progressive optimizations identified zone 4 (Figure 1) as the optimal injection location, while 30°-30°, 60°-60°-90°, and 30°-60° kneading element sequences providing better extrusion processability and optimal strand quality (Table 1). Additionally, the downstream processing setup had a significant impact on the extrudate's physical quality (Figure 2).

Table 1. Screw configurations.

Configuration	Mixing Region 1 (Zone 1-2)	Mixing Region 2 (Zone 3-4)	Mixing Region 3 (Zone 5-6)	Observations
Initial	30-30	60-60-60	90-90-90	Too restrictive, high torque, backflow, strand defects.
Modifications	30-30	30s/60s/90s (Varied in trials)	30s/60s/90s (Varied in trials)	Improvement observed.
Optimized	30-30	60-60-90	30-60	Optimized.

Table 2. Acid & Peroxide Values

Sample	Acid Value (mg KOH/g) Spec. <2	Peroxide Value (mEq O ₂ /kg)
Labrasol®	0.56	3.13
Ternary ASD-78A	0.65	1.11
Ternary ASD-79A	0.69	1.07

Figure 1. HME barrel with liquid feeder

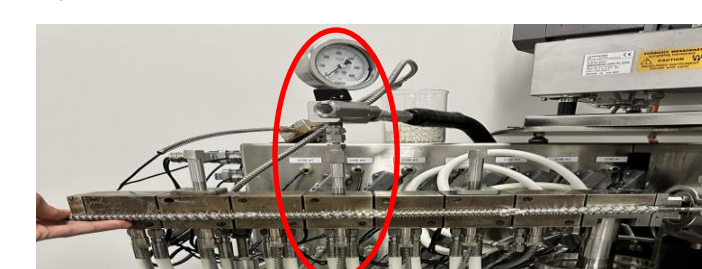
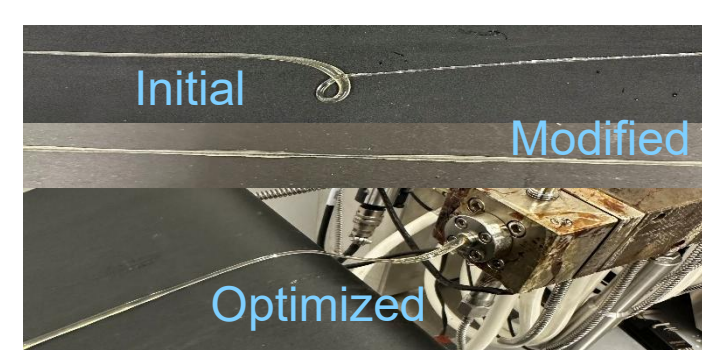


Figure 2. Extrudate appearance and HME barrel



Impact of Labrasol® on Extrusion Process

The incorporation of Labrasol® imparted a reduction in processing torque and temperatures during the extrusion process (Figure 3), indicating improved processability of the formulation due to the plasticizing effect. However, it did not significantly alter the thermal characteristics of the extrudates (Figure 4).

Solid-State Characterization (DSC)

DSC analysis displayed that the crystalline melting endotherm of fenofibrate observed in the physical blend was absent in all extruded ASD formulations, confirming successful drug amorphization. Despite incorporation of 10% Labrasol®, the glass transition temperatures of the ternary formulations remained comparable to the binary ASD, indicating that Labrasol® incorporation did not significantly alter the molecular mobility of the amorphous matrix at this concentration (Figure 4).

Labrasol® Stability in HME

Acid and Peroxide tests showed minimal changes before and after the extrusion, indicating that the HME processing conditions did not result in detectable chemical degradation or oxidation of Labrasol® (Table 2).

Content Uniformity throughout Extrusion

Fenofibrate assay values remained consistent throughout the extrusion run, demonstrating uniform drug distribution within the ASD matrix during continuous extrusion processing.

Dissolution Performance

All ASD formulations demonstrated significantly enhanced dissolution compared to the physical blend, confirming successful formation of amorphous dispersions from HME. Incorporation of neat Labrasol® enhanced dissolution performance while enabling successful lipid incorporation. However, the ternary ASD with Labrasol® containing pre-dissolved fenofibrate exhibited enhanced dissolution compared to the other ASDs (Fig 5). This improvement may be attributed to the enhanced molecular dispersion of fenofibrate within the ASD matrix and a potential synergistic effect of a pre-dissolved fenofibrate in Labrasol®.

Figure 3. Extrusion torque and process temperature profiles

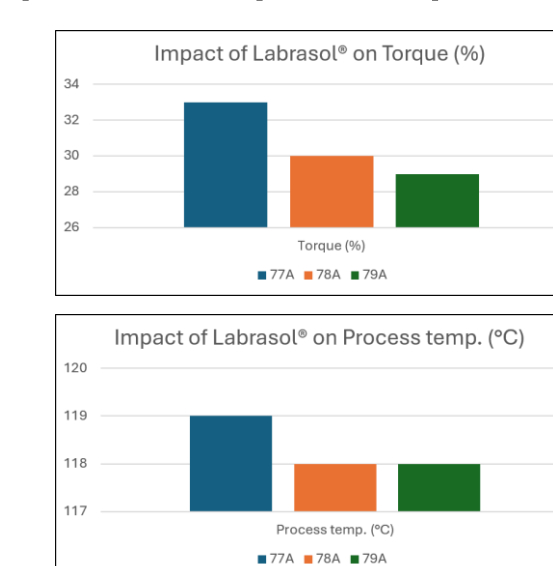


Figure 4. DSC thermogram of ASDs and physical blend.

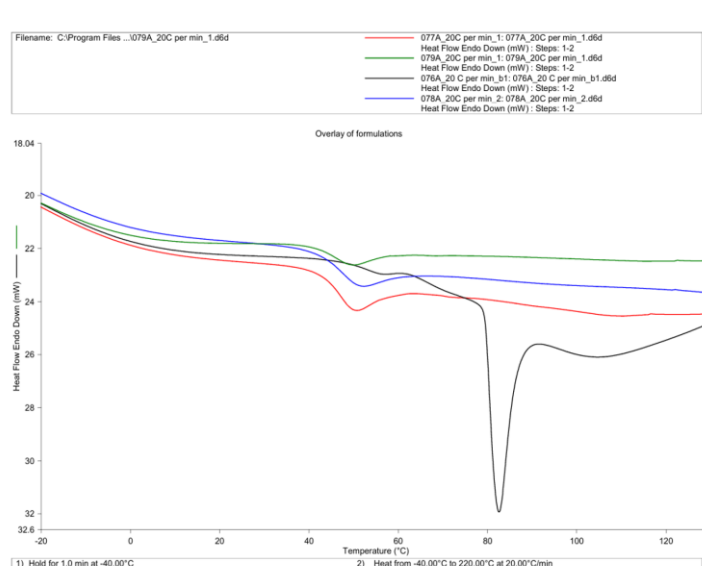
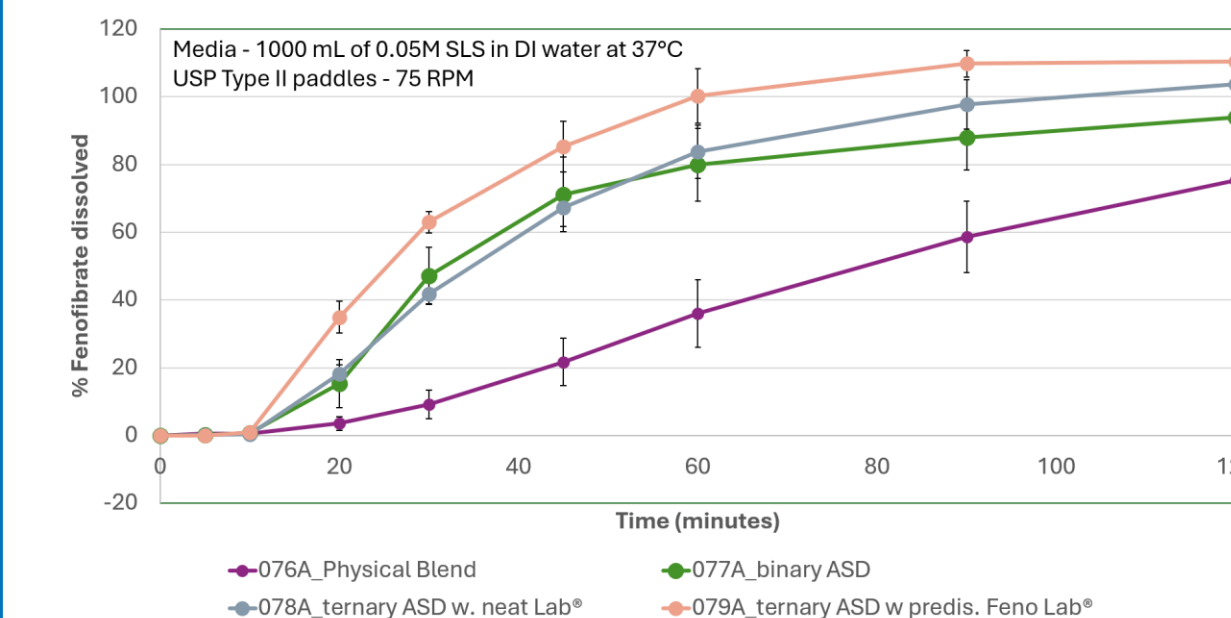


Figure 5. In vitro Dissolution profile for ASDs and physical blend



REFERENCES

- Wen et al. Fenofibrate Solid Dispersion Processed by Hot-Melt Extrusion: Elevated Bioavailability and Its Cell Transport Mechanism. Current Drug Delivery, 2019, 16, 538-547
- Zupancic et al. SEDEX—Self-Emulsifying Delivery Via Hot Melt Extrusion: A Continuous Pilot-Scale Feasibility Study. Pharmaceutics, 2022, 14, 2617.

CONCLUSION

This work introduces a robust and scalable strategy for in-line incorporation of liquid lipid excipients into ASD formulations using continuous hot melt extrusion, expanding the formulation toolbox for next-generation oral drug delivery systems.