e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 14, Issue 3; 2026, 155-162

Formulation and Evaluation of Oral Thin Film of Simvastatin and Fenofibrate

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Received: 21-03-2026/ Revised: 09-04-2026/ Accepted: 10-04-2026

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Conflict of interest: No conflict of interest.

Abstract:

Cardiovascular disorders continue to represent a major global health burden, with elevated lipid levels recognized as one of the primary contributors to the development of atherosclerosis and related complications. Simvastatin and Fenofibrate are commonly utilized antihyperlipidemic agents for reducing cholesterol and triglyceride levels; however, their clinical performance is often restricted by poor water solubility, inadequate oral bioavailability, and the necessity for repeated administration. The present investigation focused on the development and evaluation of oral thin films (OTFs) incorporating Simvastatin and Fenofibrate through the solvent casting method using appropriate film-forming polymers and excipients. The prepared films were assessed for various physicochemical and mechanical parameters, including thickness uniformity, folding endurance, tensile strength, drug content, swelling behavior, disintegration time, and in-vitro drug release. The developed formulations exhibited smooth appearance, adequate flexibility, and rapid disintegration characteristics. Drug content uniformity was found within acceptable limits for both Simvastatin and Fenofibrate, indicating homogeneous distribution throughout the films. Dissolution studies demonstrated rapid and substantial release of both drugs within a short duration, suggesting improved dissolution behavior. Overall, the formulated oral thin films showed satisfactory mechanical properties, reproducible drug release, and formulation stability, indicating their suitability as an effective and patient-compliant alternative to conventional oral dosage forms for hyperlipidemia therapy.

Keywords: Simvastatin, Fenofibrate, Oral Thin Films, Hyperlipidemia, Solvent Casting, Fast-Dissolving Drug Delivery, Drug Release, Patient Compliance.

Introduction

Cardiovascular disorders continue to be one of the foremost causes of death and disability across the globe, and abnormal lipid metabolism is recognized as a major contributing factor to their progression. Hyperlipidemia, characterized by elevated plasma cholesterol, triglycerides, and low-density lipoproteins along with decreased

high-density lipoproteins, significantly increases the risk of atherosclerosis, myocardial infarction, and cerebrovascular diseases. Effective control of lipid abnormalities generally requires long-term pharmacological intervention in combination with dietary and lifestyle modifications.[1-3] Among the available antihyperlipidemic agents, Simvastatin is extensively used for lowering serum cholesterol levels through inhibition of HMG-CoA reductase, the rate-limiting enzyme involved in cholesterol synthesis. The drug is highly effective in reducing LDL cholesterol and preventing cardiovascular complications. Nevertheless, its therapeutic efficiency is restricted by poor aqueous solubility and extensive hepatic first-pass metabolism, resulting in limited oral bioavailability.[3-5]

Fenofibrate, another important lipid-lowering drug belonging to the fibrate category, is mainly employed for the treatment of hypertriglyceridemia and mixed dyslipidemia. It acts through activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), thereby promoting fatty acid oxidation and reducing triglyceride-rich lipoproteins. Despite its clinical usefulness, fenofibrate also exhibits poor dissolution characteristics and inconsistent gastrointestinal absorption, which may compromise therapeutic performance and patient adherence during long-term therapy.[6-7] The combined administration of Simvastatin and Fenofibrate offers an effective strategy for comprehensive lipid management by simultaneously controlling cholesterol and triglyceride levels. However, conventional oral dosage forms such as tablets and capsules are often associated with limitations including slow onset of action, variable absorption, swallowing difficulties, and reduced patient compliance, particularly among pediatric, geriatric, and dysphagic individuals.

To overcome these drawbacks, oral thin films (OTFs) have gained considerable attention as an advanced oral drug delivery platform. OTFs are ultra-thin polymeric strips intended to rapidly hydrate, disintegrate, or dissolve in the oral cavity without requiring water. These systems provide several advantages such as ease of administration, rapid drug release, improved convenience, enhanced patient acceptability, precise dosing, and the potential for improved bioavailability through faster dissolution and absorption.

The successful development of OTFs depends on the selection of suitable film-forming polymers, plasticizers, surfactants, and other excipients capable of producing films with adequate mechanical strength, flexibility, stability, and rapid disintegration properties. Comprehensive evaluation of the prepared films generally involves assessment of physical appearance, thickness, folding endurance, tensile strength, drug content uniformity, surface pH, swelling behavior, disintegration time, and in-vitro drug release characteristics.[8]

Considering the growing incidence of dyslipidemia and the challenges associated with conventional dosage forms, the formulation of oral thin films containing Simvastatin and Fenofibrate represents a promising and patient-friendly therapeutic alternative. Such a system may improve dissolution behavior, enhance drug absorption, increase treatment compliance, and ultimately provide better management of hyperlipidemia and associated cardiovascular disorders.[9]

The present investigation was therefore undertaken to develop and evaluate oral thin films of Simvastatin and Fenofibrate using suitable polymeric carriers and excipients, with emphasis on optimizing film characteristics, drug release behavior, and formulation stability for effective antihyperlipidemic therapy.

Materials and Methods

The study utilized a range of equipment including an analytical balance, digital pH meter, hot air oven, UV-visible spectrophotometer, FTIR spectrophotometer, magnetic stirrer, and centrifuge. The chemicals and reagents used in the study comprised Simvastatin and Fenofibrate as the active pharmaceutical ingredients (APIs), along with excipients such as Hypromellose, Polyvinyl Alcohol (PVA), Glycerin, Citric Acid, Sucralose, Clove powder, Croscarmellose Sodium, Crospovidone, and purified water.

Drug Evaluation [10]

Characterization and identification of Simvastatin and Fenofibrate were performed prior to formulation. Organoleptic properties, including color, odor, texture, and appearance, were recorded.

Identification was confirmed by infrared (IR) spectroscopy, where KBr powder was dried at 60°C and thoroughly mixed with the drug, and the spectra were recorded.

Melting points were determined using the capillary method, employing a Thiele tube with liquid paraffin.

Solubility studies were carried out in water, alcohol, acetonitrile, and buffer solutions (pH 1.2 and 6.8), and drug concentration was analyzed using a UV-Visible spectrophotometer after filtration and appropriate dilution.

Preparation of Oral Thin Films [11]

For the preparation of oral thin films, the solvent casting method was employed due to its simplicity, low cost, and reproducibility. Hypromellose, Carbomer, PVA, glycerin, and citric acid were dissolved in purified water at 1000 rpm and heated to 60°C (Solution A), while Croscarmellose Sodium and Sucralose were dissolved separately (Solution B). Both solutions were then mixed thoroughly, followed by incorporation of Simvastatin and Fenofibrate. Air bubbles were removed under vacuum, and the resulting solution was cast into thin films, which were dried and cut into 2.5 × 2.5 cm^2 pieces. Various formulations were prepared with different concentrations of polymers and other excipients to optimize film properties.

Evaluation of Oral Thin Films [12]

The formulated oral thin films were evaluated for their physical characteristics, including color, transparency, uniformity, texture, and odor, with particular attention to taste.

Thickness measurements were performed at multiple points on five films from each batch using a micrometer, and weight variation was assessed by individually weighing small films (1 × 1 cm^2).

Folding endurance was determined by repeatedly folding the films at 180° until breakage, and flexibility was considered acceptable if films withstood more than 300 folds.

Swelling studies were conducted by placing pre-weighed films in simulated physiological fluid, and the swelling index was calculated based on weight changes over time. Drug content uniformity was evaluated by dissolving films in a suitable solvent, filtering, and analyzing the solution using HPLC. In-vitro disintegration studies were conducted to determine the time required for films to disperse in contact with saliva or aqueous medium, with acceptable disintegration times ranging between 5–30 seconds. In-vitro dissolution studies were performed using USP Type II (paddle) apparatus in phosphate buffer (pH 6.8) at 37 ± 0.5°C, and drug release was quantified using HPLC. Stability studies of the formulated films were performed according to ICH guidelines by storing the films under accelerated conditions (40°C/75% RH) for three months. Periodic evaluations were

conducted to monitor changes in physical properties, drug content, and dissolution profiles to ensure formulation stability.

Results and Discussion: The analytical evaluation of Simvastatin and Fenofibrate confirmed their identity, purity, and suitability for formulation. Organoleptic assessment revealed that Simvastatin appeared as a white powder, while Fenofibrate was a fine white powder. Identification by IR spectroscopy demonstrated characteristic functional groups of both drugs.

For Simvastatin, prominent peaks were observed at 3550.96 cm^{-1} (O–H stretching), 3011.54 and 2955.26 cm^{-1} (C–H stretching), 1697.73 cm^{-1} (C=O aromatic stretching), and 1226 cm^{-1} (C–O stretching). Fenofibrate exhibited characteristic peaks at 2940.06 cm^{-1} (C–H aromatic stretching), 1710.01 cm^{-1} (C=O conjugation with aromatic ring), 1519.51 cm^{-1} (C–C aromatic stretching), and 710.29 cm^{-1} (C–Cl stretching).

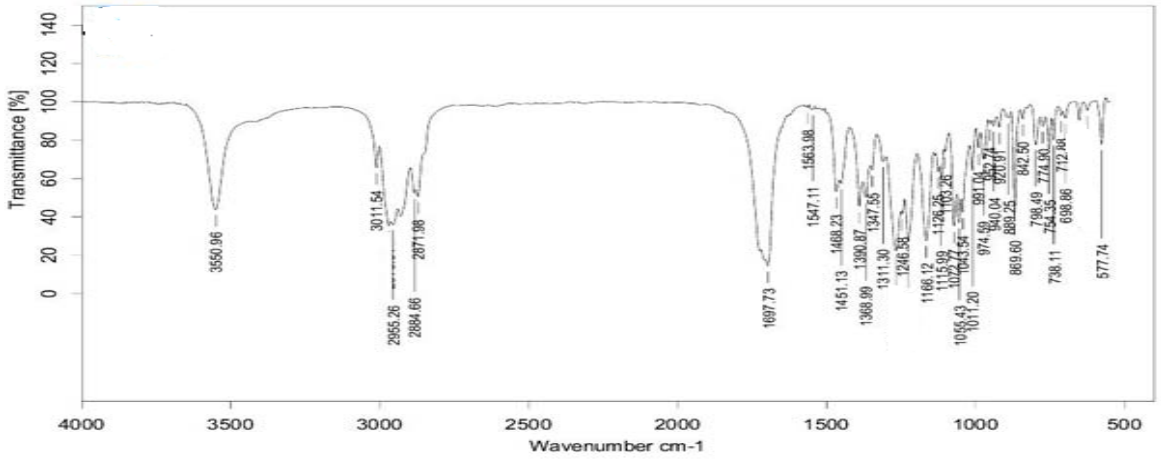

Figure 1: IR Spectra of Simvastatin

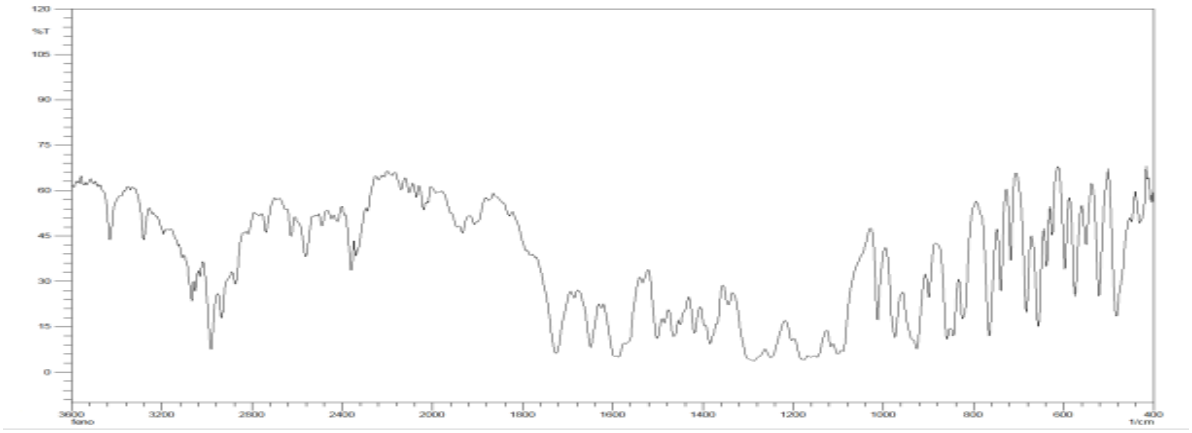

Figure 2: IR Spectra of Fenofibrate

UV spectroscopy showed absorption maxima at 241 nm for Simvastatin and 290 nm for Fenofibrate.

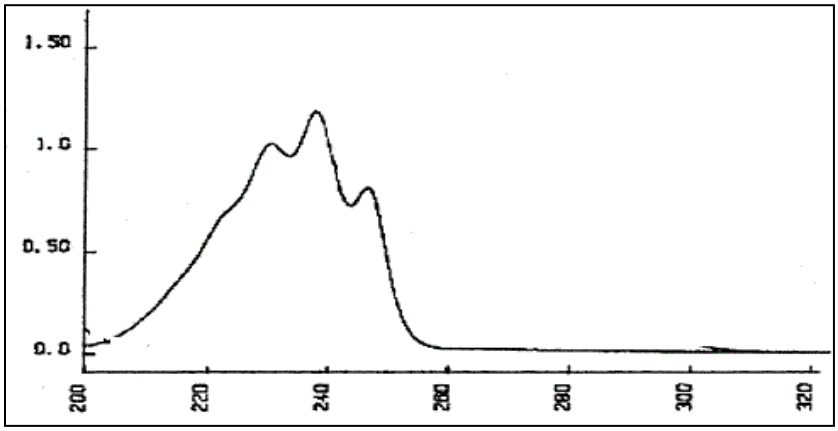

Figure 3: UV Spectra of Simvastatin

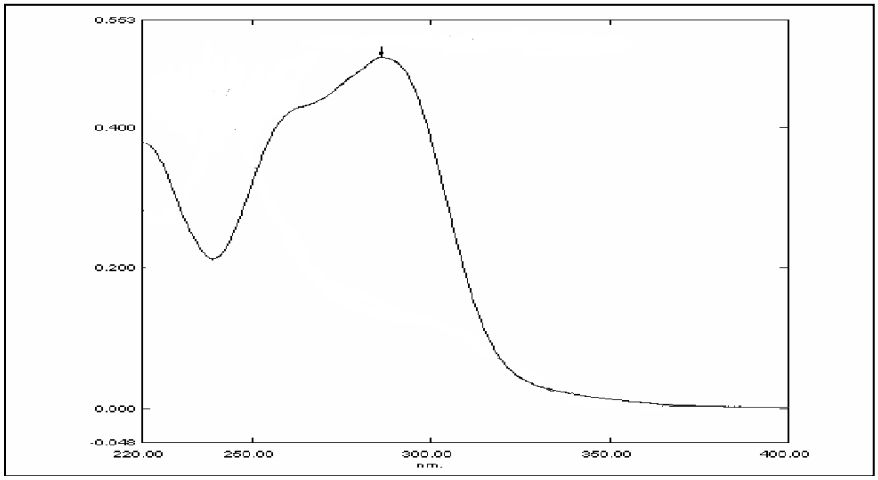

Figure 4: UV Spectra of Fenofibrate

Solubility studies indicated that Simvastatin was slightly soluble in water and pH 6.8 buffer, freely soluble in methanol, and soluble in pH 1.2 buffer, whereas Fenofibrate was insoluble in water, slightly soluble in methanol and pH 1.2 buffer, and soluble in pH 6.8 buffer. Melting point analysis confirmed the purity of both drugs, with observed values of 136.4°C for Simvastatin and 79.8°C for Fenofibrate, matching reported literature values. The formulated oral thin films exhibited uniform physical characteristics across all batches. Films were predominantly white to colorless, transparent or slightly opaque, odorless, and displayed uniform texture. Thickness measurements ranged from 1.1 ± 0.088 mm to 1.9 ± 0.048 mm, indicating controlled film casting and uniform polymer distribution. Weight variation analysis showed acceptable consistency, with values ranging from 31.75 ± 0.325 mg to 48.70 ± 0.569 mg, supporting reproducibility of the casting process. Folding endurance values ranged from 235 ± 2.497 to 294 ± 3.945, demonstrating adequate flexibility and mechanical strength suitable for handling and administration. Swelling studies revealed swelling indices between 48.48% and 71.26%, indicating effective water uptake, which is critical for rapid disintegration and drug release.

Table 1: Evaluation of OTF

Formulation	Thickness (mm)	Weight (mg)	Folding Endurance	Swelling Index (%)	Simvastatin Content (%)	Fenofibrate Content (%)	Disintegration Time (s)
F1	1.6 ± 0.034	36.38 ± 0.456	273 ± 1.223	67.77	94.36 ± 1.23	94.74 ± 1.57	27 ± 0.12
F2	1.4 ± 0.079	46.58 ± 0.128	235 ± 2.497	61.59	96.30 ± 0.88	94.57 ± 1.75	23 ± 0.25
F3	1.8 ± 0.043	42.82 ± 0.493	265 ± 2.465	60.78	97.49 ± 0.91	95.42 ± 0.86	29 ± 0.34
F4	1.7 ± 0.018	47.41 ± 0.458	274 ± 1.764	61.68	96.67 ± 0.89	96.12 ± 0.24	29 ± 0.13
F5	1.2 ± 0.043	32.69 ± 0.785	244 ± 3.864	58.91	98.58 ± 0.43	95.75 ± 1.45	24 ± 0.11
F6	1.9 ± 0.048	33.58 ± 0.453	285 ± 2.154	61.68	97.48 ± 1.01	96.88 ± 1.75	26 ± 0.15
F7	1.6 ± 0.043	31.75 ± 0.325	294 ± 3.945	58.91	96.11 ± 0.63	92.43 ± 0.85	28 ± 0.18
F8	1.1 ± 0.088	41.73 ± 0.148	261 ± 3.652	71.26	95.28 ± 0.79	97.72 ± 0.91	27 ± 0.12
F9	1.4 ± 0.046	48.70 ± 0.569	237 ± 3.102	48.48	97.46 ± 1.26	98.30 ± 1.77	29 ± 0.15
F10	1.3 ± 0.031	39.82 ± 0.783	249 ± 0.478	63.47	98.62 ± 1.09	95.91 ± 0.63	28 ± 0.19

Drug content analysis showed uniform distribution of Simvastatin and Fenofibrate across all film batches. Simvastatin content ranged from 94.36% to 98.62%, and Fenofibrate content ranged from 92.43% to 98.30%, with relative standard deviations below 2%, demonstrating excellent uniformity and reproducibility. In-vitro disintegration studies confirmed rapid disintegration of the films, with times ranging from 23 ± 0.25 to 29 ± 0.34 seconds, suitable for fast oral delivery and prompt onset of action. In-vitro dissolution studies indicated effective and controlled drug release from the OTFs. Simvastatin release ranged from approximately 28.4% to 95.9% within 25 minutes, while Fenofibrate release ranged from 23.2% to 98.6% in the same duration, with slight variations among formulations due to differences in polymer and excipient

concentrations. The dissolution profiles suggest that the films were capable of providing rapid and near-complete release of both drugs.

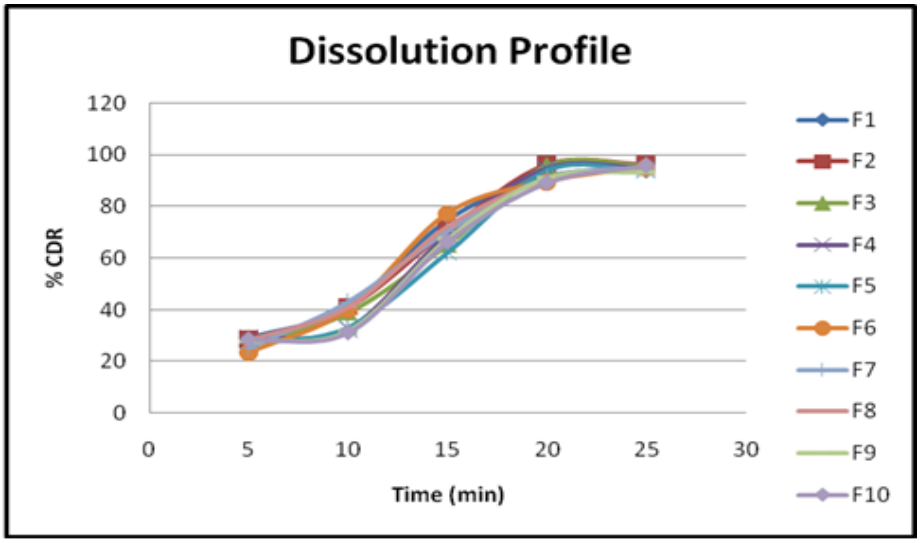

Figure 5: Dissolution Profile of Simvastatin (F1-F10)

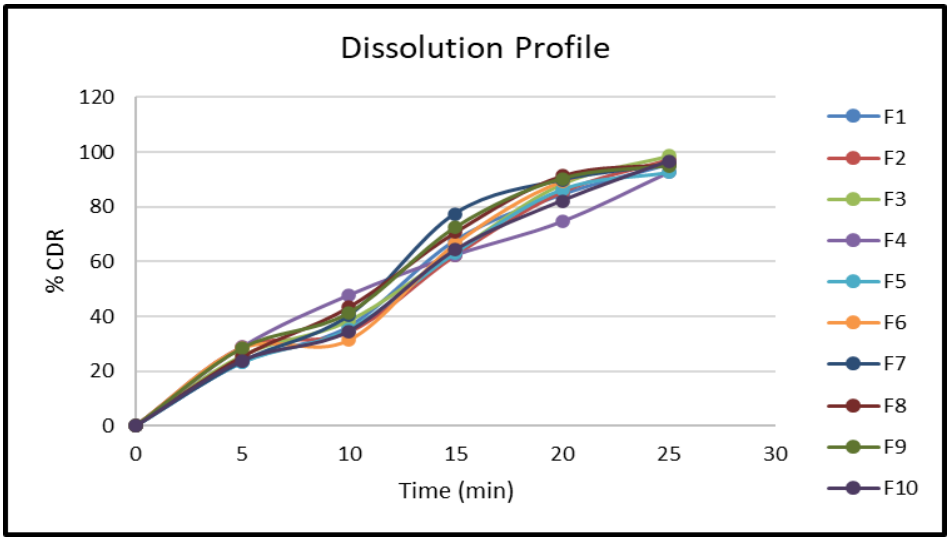

Figure 6: Dissolution Profile of Fenofibrate (F1-F10)

Overall, the results demonstrate that the solvent-cast oral thin films of Simvastatin and Fenofibrate were successfully formulated with uniform appearance, mechanical integrity, rapid disintegration, and consistent drug release. The compatibility studies, physicochemical evaluations, and dissolution data confirm the potential of these OTFs as an effective fast-dissolving dosage form for combination therapy, offering improved patient compliance and ease of administration.

Conclusion

The present study successfully formulated and evaluated oral thin films containing Simvastatin and Fenofibrate using the solvent casting method. The films demonstrated uniform appearance, appropriate thickness, acceptable weight variation, high folding

endurance, and optimal swelling characteristics. Drug content analysis confirmed uniform distribution of both APIs, while in-vitro disintegration and dissolution studies indicated rapid and effective drug release. Compatibility studies showed no significant interactions between drugs and excipients, confirming formulation stability. Overall, the developed OTFs offer a promising patient-friendly dosage form with enhanced bioavailability, rapid onset of action, and improved compliance, providing a potential alternative to conventional oral tablets and capsules for the management of mixed dyslipidemia.

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