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Formulation and evaluation of Trelagliptin loaded fast-dissolving oral films

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Abstract

The present study focuses on the preformulation, characterization, and development of fast-dissolving oral films of Trelagliptin, aiming to enhance patient compliance and achieve rapid drug release for the effective management of type 2 diabetes mellitus. Preformulation studies confirmed the drug's identity, purity, and stability through organoleptic evaluation, solubility profiling, FTIR spectroscopy, loss on drying, and melting point analysis. Trelagliptin exhibited versatile solubility in both aqueous and organic solvents and showed excellent linearity (r^2 = 0.999) in UV spectrophotometric analysis at 276 nm.

Nine formulations (F1–F9) of oral films were prepared using different polymers and evaluated for physicochemical and mechanical properties. All formulations demonstrated uniform appearance, consistent thickness, and satisfactory film characteristics. Among them, formulation F6 was identified as the optimized batch, exhibiting the shortest disintegration time (55±7 sec), highest drug release (97.65% in 10 min), maximum folding endurance (185±5), and excellent assay value (99.12±0.18%). Drug release from F6 followed first-order kinetics with non-Fickian diffusion, indicating a combination of diffusion and polymer relaxation mechanisms. Stability studies under accelerated conditions over three months confirmed the formulation's robustness, with minimal changes in drug content and physical attributes.

In conclusion, the optimized Trelagliptin fast-dissolving film (F6) demonstrated promising attributes such as rapid onset of action, high drug release, and improved patient convenience, offering a stable and effective alternative dosage form for type 2 diabetes treatment.

Keywords:

Trelagliptin, Fast-dissolving oral films, Preformulation studies, Drug release kinetics, Non-Fickian diffusion, Type 2 diabetes mellitus

1. Introduction

The oral route is the most preferred method for drug administration due to its ease of use, non-invasiveness, and high patient compliance. Recent advancements have led to innovative oral drug delivery systems such as Fast Dissolving Oral Films (FDOFs), particularly useful for pediatrics, geriatrics, and patients with dysphagia.

2. Structure and Function of the Oral Mucosa in Drug Absorption

The oral mucosa is composed of stratified squamous epithelium, basement membrane, lamina propria, and submucosa. The buccal mucosa has 40–50 cell layers and is ideal for passive diffusion of non-ionized drug molecules. Compared to the simple epithelium of the GI tract, the stratified epithelium in the oral cavity provides protection while still enabling absorption through intercellular lipid pathways.

3. Fast Dissolving Oral Films (FDOFs): Definition and Benefits

FDOFs are thin polymeric films that dissolve quickly in the oral cavity without water.

FDOF can provide a convenient and effective vehicle for delivering active ingredients such as pharmaceutical compounds and breath freshening agents, to the mucosa of humans and animals.It allows the drug to be delivered to the blood stream either intragastrically, buc- cally or sublingually. As soon as FDOF are taken, rapid absorption of drug, through the sublingual route is possible, which finally leads to quick onset of drug action. The proper selection of incorporated excipients/ ingredients for formulating FDOF is very important as FDOF have to disintegrate and/or dissolve quickly into the oral cavity. Be-sides water- dissolving polymer, the formulation may include other components depending on its intended use, viz. pharmaceutical agents, antimicrobial agents, nutraceutical ingredients, plasticizers, surfactants, colorants, sweetening agents, saliva stimulating agents, flavors, flavor enhancers and other excipients

Advantages:

- Non-invasive and easy to administer
- No need for water
- Rapid drug onset
- Avoids hepatic first-pass metabolism
- High patient acceptability

4. Formulation Aspects of FDOFs

4.1 Key Components

- **Active Drug**: 1–25%
- **Polymers**: 40–50%
- **Plasticizers**: 0–20%
- **Other excipients**: sweeteners, flavors, saliva stimulants, surfactants

4.2 Ideal Properties

- Pleasant taste

- Mechanical strength and flexibility
- Quick disintegration and minimal residue
- Drug solubility in saliva
- Compatibility with excipients

5. Manufacturing Methods

5.1 Solvent Casting Method

Most common method; involves dissolving ingredients in water or alcohol, casting onto plates, and drying.

5.2 Hot Melt Extrusion

No solvents needed; uses heat and pressure to extrude the drug-polymer mixture.

5.3 Rolling Method

Drug solution is rolled onto a carrier and dried on rollers.

5.4 Semisolid Casting

Uses a gel-like mass of film-forming polymers and acid-insoluble polymers.

5.5 Solid Dispersion Extrusion

Drug is dispersed in a solid matrix (e.g., using cyclodextrins) and extruded into film form.

6. Challenges in FDOF Development

- **Dose uniformity**: Difficulty maintaining consistent dosing in each strip
- **Drug loading**: Max ~75 mg per 4cm² film
- **Hygroscopicity**: Moisture sensitivity requiring special packaging
- **Taste masking**: Bitter drugs require effective flavor/sweetener combinations
- **Mechanical issues**: Films must be strong but not brittle

7. Future Perspectives

7.1 Personalized Therapy

Use of 3D printing to tailor doses per patient.

7.2 Nanotechnology

Incorporation of nanoparticles for better solubility and bioavailability.

7.3 Expanded Applications

Potential use in treating CNS disorders, pain, allergies, and more.

8. Regulatory and Commercial Considerations

- Excipients must be GRAS-listed
- Packaging must ensure film stability (e.g., moisture-proof blister packs)

- FDOFs are widely used in OTC (e.g., breath fresheners) and are expanding into prescription drug markets.

Trelagliptin is a long-acting dipeptidyl peptidase-4 (DPP-4) inhibitor developed for the treatment of type 2 diabetes mellitus (T2DM). Currently under investigation in clinical trial **NCT03555591**, it has been approved for use in Japan and is notable for its **once-weekly oral dosing**, offering improved convenience over daily DPP-4 inhibitors.

Chemical Profile

- **Chemical Formula**: $C_{18}H_{20}FN_5O_2$
- **Molecular Weight**: 357.39 g/mol
- **IUPAC Name**:

2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl}methyl)-4-fluorobenzonitrile

- **Structure**: Refer to Figure 5.1

Pharmacology

- **Mechanism of Action**: Trelagliptin inhibits the DPP-4 enzyme, preventing the breakdown of incretin hormones (GLP-1 and GIP). This results in increased insulin secretion and reduced glucagon levels after meals, thereby enhancing glycemic control.
- **Protein Binding**: Approximately 22.1% to 27.6% in human plasma (in vitro).
- **Metabolism**: Primarily metabolized via **CYP2D6-mediated N-demethylation** to its active metabolite (MI); limited hepatic involvement.
- **Excretion**: Excreted **mostly unchanged via urine**, with ~76% of a single dose recovered renally.
- **Half-life**: Extended elimination half-life of approximately **54.3 hours**, supporting **once-weekly** dosing.

Therapeutic Use

- Indicated for **oral treatment of T2DM**, improving glycemic control, particularly postprandial glucose levels.
- Approved in **Japan** for weekly administration, offering a significant compliance advantage over daily DPP-4 inhibitors.

Common Side Effects

- **Gastrointestinal discomfort**, including nausea, abdominal pain, vomiting, and diarrhea—usually **mild and transient**.

Formulation Development of Oral Film of Trelagliptin

A **fast-dissolving oral film (FDOF)** of **Trelagliptin** was developed using the **solvent casting method**, ideal for lab-scale preparation. The formulation included HPMC K4 as the film-forming polymer, PEG-400 as plasticizer, citric acid as a saliva-stimulating agent, aspartame as sweetener, and superdisintegrants (SSG or CCS) to enhance disintegration.

Key Parameters Optimized:

- **Film size**: 2.5 × 2.5 cm, providing a unit dose of 50 mg Trelagliptin.
- **Casting reservoir**: 15 × 5 × 0.5 cm glass mould designed to yield 12 uniform strips.
- **Solution volume**: 30 mL for uniform film thickness (~200 µm).
- **Drying conditions**: 45 ± 1°C for 12–24 hours.
- **Mixing speed**: 200 ± 10 rpm for uniform dispersion.

Film Composition Optimization:

Nine formulations (F1–F9) were prepared by varying concentrations of:

- HPMC K4 (50–150 mg)
- Superdisintegrants (SSG and CCS)
- Trelagliptin (fixed at 600 mg for 12 strips)

Evaluation of Prepared Films

Several physicochemical parameters were evaluated to determine the quality and performance of the films:

- **Thickness**: Measured using a vernier caliper to ensure uniformity.
- **Weight Uniformity**: Ten films per batch were weighed individually to ensure dose consistency.
- **Folding Endurance**: Assessed by repeated folding until breakage to test flexibility.
- **Moisture Content**: Determined via desiccator storage and weighing.
- **Drug Content**: Analyzed using UV spectrophotometry at 276 nm.
- **Disintegration Time**: Films were tested for rapid disintegration using various superdisintegrants.
- **In Vitro Dissolution**: Conducted in phosphate buffer (pH 6.8) using USP paddle apparatus at 37 ± 0.5°C, with sampling over 10 minutes to determine drug release.

Stability Studies

Stability of the optimized formulation (F6) was tested under accelerated conditions (**40 ± 2°C, 75 ± 5% RH**) for **three months**. The **% drug assay** showed minimal reduction, and all physicochemical properties remained within acceptable limits, indicating **satisfactory stability** of the formulation.

Evaluation of Prepared Films

The Trelagliptin oral films (F1–F9) were assessed for general appearance, thickness, and weight. All formulations were transparent, smooth, and uniform, indicating excellent film-forming ability of the chosen polymers and excipients. No cracks, bubbles, or surface imperfections were observed, confirming satisfactory aesthetic and mechanical quality.

Film thickness ranged from **49 ± 4 µm (F4)** to **64 ± 4 µm (F9)**, increasing with polymer concentration due to higher solution viscosity. Film weights varied between **71.1 ± 0.2 mg (F4)** and **79.8 ± 0.4 mg (F6)**, correlating with polymer type and concentration. Low standard deviations across thickness and weight demonstrated good reproducibility and uniformity of the casting process, producing consistent films suitable for further analysis.

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	51±3	72.5±0.3
F2	Transparent	53±5	71.3±0.5
F3	Transparent	55±2	76.6±0.3
F4	Transparent	49±4	71.1±0.2
F5	Transparent	51±3	78.9±0.5
F6	Transparent	58±5	79.8±0.4
F7	Transparent	61±3	72.2±0.3
F8	Transparent	63±2	75.6±0.5
F9	Transparent	64±4	78.7±0.4

*Values represent mean ± SD (n=3).

Mechanical and Physicochemical Properties

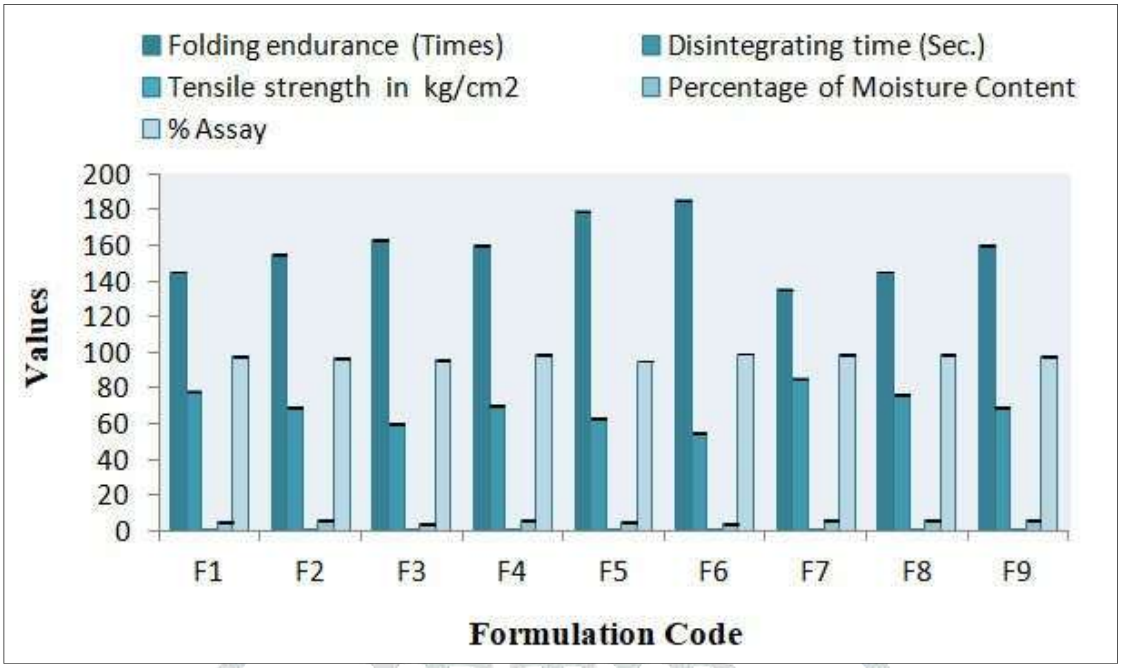
The films were evaluated for folding endurance, disintegration time, tensile strength, moisture content, and drug assay:

- **Folding endurance** ranged from **135 ± 3 (F7)** to **185 ± 5 (F6)**, showing sufficient flexibility and mechanical strength. Higher polymer content, especially HPMC K15 and sodium alginate, improved film elasticity.
- **Disintegration time** varied between **55 ± 7 sec (F6)** and **85 ± 6 sec (F7)**. Films with more hydrophilic polymers disintegrated faster, while sodium alginate slightly delayed disintegration due to gel formation. All films disintegrated within 1–2 minutes, suitable for fast-dissolving applications.
- **Tensile strength** ranged from **0.73 ± 0.14 kg/cm² (F5)** to **0.88 ± 0.33 kg/cm² (F9)**, indicating adequate mechanical resistance without brittleness.
- **Moisture content** varied from **4.12 ± 0.69% (F6)** to **6.33 ± 0.65% (F4)**, reflecting the hygroscopic nature of polymers but remaining within acceptable limits for stability.
- **Drug assay** results ranged from **95.12 ± 0.22% (F5)** to **99.12 ± 0.18% (F6)**, confirming uniform drug distribution and accurate formulation.

Among all, **F6** demonstrated optimal balance: highest folding endurance, shortest disintegration time, favorable tensile strength, lowest moisture content, and highest drug assay, making it the lead candidate.

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	145±8	78±5	0.85±0.15	4.85±0.15	97.85±0.36
F2	155±6	69±8	0.78±0.16	5.65±0.25	96.65±0.25

F3	163±4	60±6	0.75±0.32	4.32±0.35	95.45±0.48
F4	160±7	70±3	0.88±0.25	6.33±0.65	98.85±0.36
F5	179±6	63±4	0.73±0.14	4.96±0.74	95.12±0.22
F6	185±5	55±7	0.81±0.36	4.12±0.69	99.12±0.18
F7	135±3	85±6	0.78±0.35	5.65±0.85	98.65±0.30
F8	145±5	76±5	0.76±0.74	5.74±0.32	98.41±0.14
F9	160±2	69±3	0.88±0.33	5.69±0.45	97.45±0.33



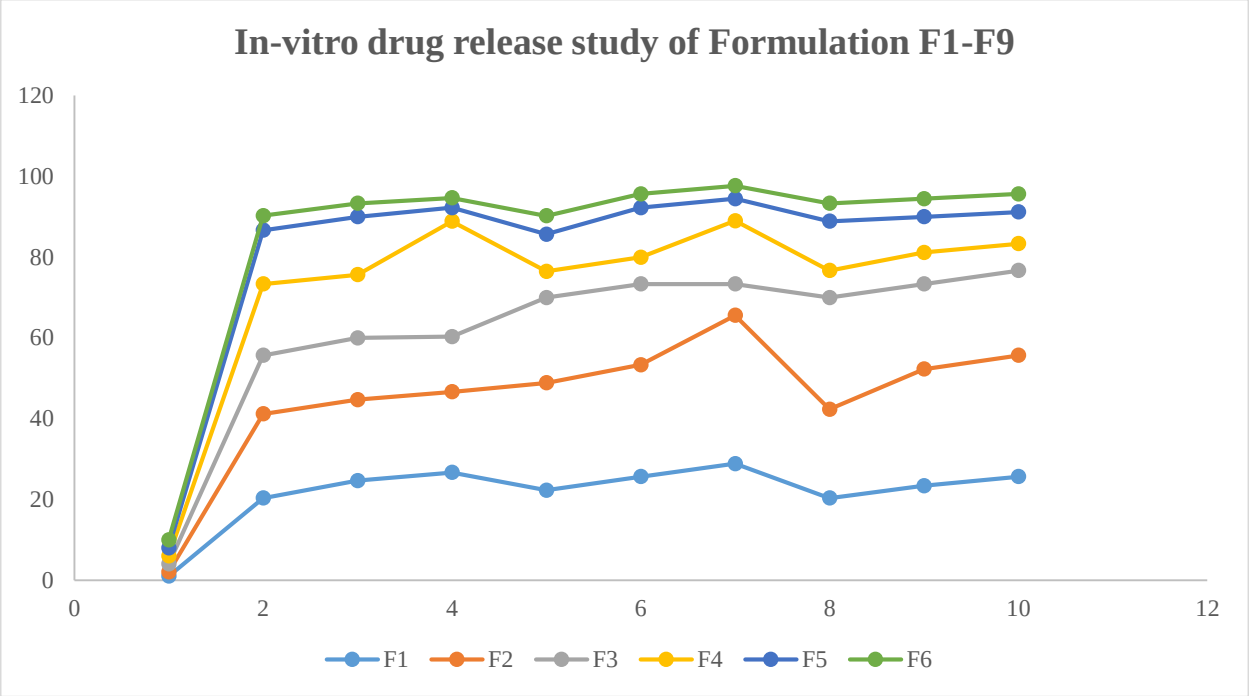
8.3 Optimized Formulation Composition (F6)

Ingredient	Amount per Strip (mg)
Trelagliptin	600
HPMC K4	25
HPMC K15	25
PEG-400	50
Sodium Alginate	20
Mannitol	20
Citric Acid	20
Distilled Water	qs to 30 mL

8.4 In Vitro Drug Release (F1–F9)

The cumulative drug release increased over 10 minutes for all formulations. F6 exhibited the fastest release, reaching **97.65%** at 10 minutes.

Time (Min.)	Cumulative % Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20.32	24.65	26.65	22.25	25.65	28.85	20.32	23.36	25.65
2	41.15	44.69	46.65	48.85	53.32	65.58	42.32	52.25	55.65
4	55.65	59.98	60.32	69.98	73.32	73.32	69.98	73.32	76.65
6	73.32	75.65	88.85	76.45	79.95	88.98	76.65	81.15	83.32
8	86.65	89.98	92.25	85.65	92.25	94.45	88.85	89.98	91.15
10	90.25	93.32	94.65	90.23	95.65	97.65	93.32	94.45	95.65



The preformulation and characterization studies of Trelagliptin were carried out to establish its physicochemical and analytical profile. The organoleptic evaluation revealed that the drug is a white to off-white, odorless, tasteless fine powder. Solubility analysis demonstrated that Trelagliptin is soluble in water, ethanol, methanol, chloroform, 0.1 N HCl, 0.1 N NaOH, and phosphate buffer (pH 6.8), indicating its versatile solubility in both aqueous and organic solvents.

The FTIR spectrum confirmed the presence of characteristic functional groups, including N–H/O–H stretching (3535.99 cm^{-1}), aliphatic C–H stretching (2924.45 cm^{-1}), C=O stretching of amide/succinate (1718.87 cm^{-1}), aromatic C=C/N–H bending (1693.07 cm^{-1}), CH_2 bending (1454.12 cm^{-1}), C–N/C–O stretching (1212.95 cm^{-1}), and aromatic C–H bending in the fingerprint region (966.57 cm^{-1}), confirming the structural integrity of the drug.

The loss on drying was found to be 0.241 ± 0.002%, indicating minimal moisture content and confirming stability against hydrolysis. The melting point of the sample (95–97°C) was consistent with the reported standard (95–100°C), further validating drug purity.

The calibration curve of Trelagliptin at λmax 276 nm exhibited linearity in the range of 2–10 µg/ml with the regression equation Y = 0.076x + 0.000 and a correlation coefficient (r^2) of 0.999, confirming excellent linearity and adherence to Beer–Lambert's law.

The present study was carried out to formulate and evaluate fast-dissolving oral films of Trelagliptin using different grades of polymers and excipients with the objective of improving patient compliance and achieving rapid drug release. Preformulation studies confirmed the identity, purity, and stability of the drug through organoleptic evaluation, solubility analysis, FTIR compatibility studies, loss on drying, and melting point determination. The calibration curve demonstrated excellent linearity with a correlation coefficient of 0.999, establishing suitability for further analytical work. All prepared formulations (F1–F9) were uniform, transparent, and smooth in appearance,

with consistent thickness and weight, confirming reproducible film formation. Mechanical and physicochemical evaluations revealed satisfactory folding endurance, tensile strength, disintegration time, moisture content, and drug assay, ensuring the films possessed desirable qualities for patient use.

Among the nine formulations, F6 was identified as the optimized batch as it exhibited superior properties including maximum folding endurance (185±5), shortest disintegration time (55±7 sec), high tensile strength (0.81±0.36 kg/cm²), lowest moisture content (4.12±0.69%), and maximum assay value (99.12±0.18%). In-vitro drug release studies revealed that F6 achieved the highest drug release (97.65% within 10 minutes), confirming its efficiency. Drug release kinetics indicated that F6 followed first-order kinetics with non- Fickian diffusion, suggesting concentration-dependent release influenced by both diffusion and polymer relaxation mechanisms. Stability studies conducted under accelerated conditions over three months demonstrated negligible reduction in assay values (99.12% to 98.10%) and no significant changes in physical or functional characteristics, establishing the stability of the optimized formulation.

In conclusion, the study successfully developed stable, fast-dissolving oral films of Trelagliptin with excellent mechanical strength, rapid disintegration, and high drug release. The optimized formulation (F6) offers a promising and patient-friendly alternative drug delivery system for the management of type 2 diabetes mellitus, ensuring rapid onset of action, improved compliance, and enhanced therapeutic effectiveness.

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