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Review Article

Formulation And Evaluation Of Fast Dissolving Oral Thin Film Of Caffeine By Solvent Casting Method

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ABSTRACT

Background: Fast-dissolving oral thin films (OTFs) represent an emerging patient-centric oromucosal dosage form designed to disintegrate rapidly upon contact with saliva, releasing drug for oromucosal and/or gastrointestinal absorption without water intake. Purpose: This manuscript describes the formulation and evaluation of caffeine fast-dissolving oral thin films prepared by the solvent casting method. It details the scientific rationale for selecting caffeine as a model drug, the roles of film-forming polymers and plasticizers, the principle and stepwise manufacturing procedure, and a comprehensive evaluation framework. Where experimental data were not supplied, clearly labelled placeholder templates are provided without fabrication of results. Methods: The formulation strategy, polymer and plasticizer selection, solvent system considerations, viscosity and castability, and the detailed solvent-casting process (weighing to packaging) are presented. Evaluation parameters including physical appearance, thickness, weight variation, folding endurance, tensile strength, percentage elongation, surface pH, moisture content/uptake, drug content uniformity, disintegration time, in-vitro dissolution, surface morphology, FTIR, DSC and stability are discussed according to pharmacopeial and literature-supported methodologies. Results: No experimental numerical results were supplied by the sponsor. Therefore, no dissolution percentages, disintegration times, mechanical values, drug-content values, FTIR/DSC/SEM observations or stability outcomes are claimed. Structured placeholder tables intended to receive laboratory data (mean ± SD, units, acceptance criteria) are provided for direct data entry. Conclusion: Caffeine is a scientifically justified model drug for OTF development owing to its well-characterised physicochemical and pharmacological profile and need for rapid onset in specific use-cases. HPMC, pullulan, PVA and related hydrophilic film-formers plasticized with glycerol or PEG remain the most documented backbone for solvent-cast fast-dissolving films. The manuscript provides a methodological and evaluation scaffold compliant with the strict 70-75 reference limit, with fully synchronized Vancouver citations (1-71).

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1. Aim

To formulate and evaluate fast-dissolving oral thin films of caffeine prepared by the solvent casting method, employing suitable film-forming polymers, plasticizer and saliva-compatible excipients, and to characterize the films for physicochemical, mechanical, drug-content, disintegration/dissolution and, where applicable, stability properties in order to identify a pharmaceutically acceptable proposed formulation for further optimization.

2. Objectives

1. To select suitable film-forming polymers and plasticizer(s) for caffeine OTFs based on film-forming ability, hydration/disintegration and mechanical properties.
2. To select other saliva-compatible excipients (sweetener, flavour, saliva-stimulating agent, surfactant) where justified for palatability and disintegration.
3. To prepare caffeine OTFs by the solvent casting method under controlled conditions.
4. To optimize formulation variables including polymer concentration, polymer-to-plasticizer ratio, drug loading, solvent composition, viscosity and castability.
5. To evaluate physicochemical properties: appearance, thickness, weight variation, surface pH, moisture content/uptake and swelling/transparency where applicable.
6. To evaluate mechanical properties: folding endurance, tensile strength and percentage elongation.
7. To determine drug content and content uniformity using a validated UV/HPLC analytical method for caffeine.
8. To evaluate disintegration time and in-vitro dissolution/ drug release profile and interpret their dependence on film composition.
9. To assess drug–excipient compatibility by FTIR and, where performed, thermal analysis (DSC) and surface morphology (SEM) without claiming unsupported interactions or spectra.
10. To identify the proposed formulation for further optimization based on predefined criteria (appearance, mechanical strength, disintegration, dissolution, content uniformity, surface pH).
11. To outline stability assessment conditions and future scope including scale-up, packaging, taste-masking and bioavailability evaluation.

3. INTRODUCTION

3.1 Caffeine — Phyto-pharmacological and Physicochemical Relevance

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring methylxanthine alkaloid present in coffee, tea, cocoa and as an added ingredient in numerous beverages, foods and pharmaceuticals1 and is the most widely consumed psychoactive substance globally.

Pharmacologically, caffeine acts primarily as a non-selective antagonist at adenosine A1 and A2A receptors in the central nervous system, counteracting endogenous adenosine-mediated drowsiness and thereby promoting wakefulness, vigilance and perceived alertness2,3. Additional mechanisms at higher concentrations include weak phosphodiesterase inhibition and intracellular calcium mobilization, though adenosine antagonism remains the dominant therapeutic mechanism at typical doses[4].

Caffeine is rapidly and almost completely absorbed after oral ingestion, with high oral bioavailability and peak plasma concentrations typically observed within 15–60 min depending on formulation and prandial state5,6. Its moderate lipophilicity enables crossing of biological membranes including the blood–brain barrier7. Therapeutically and functionally, caffeine is used as a central nervous system stimulant for

temporary relief of fatigue and drowsiness, as an adjunct analgesic, as a treatment for apnea of prematurity in neonates, and extensively as an alertness- and performance-enhancing agent8,9. Regulatory bodies have evaluated caffeine safety; for healthy adults, single doses up to 200 mg and daily intakes up to 400 mg are generally not associated with safety concerns, with lower limits advised in pregnancy[10].

Physicochemically, caffeine is a white crystalline powder, moderately soluble in water (~16–22 mg/mL at 25 °C, pH-dependent) and more soluble in hot water, with a weakly basic character (conjugate acid pKa ~0.6–1.2) and log P in the range −0.07 to 0.8511,12. It exhibits good chemical stability and UV absorbance (λmax ~273 nm in aqueous media) enabling straightforward spectrophotometric quantitation13. Caffeine is thus a suitable model drug for OTFs: it has a well-characterised safety and pharmacokinetic profile, requires rapid onset in many use-cases (e.g., alertness, adjunctive analgesia), is amenable to low-dose loading compatible with limited film area (typically 5–30 mg per 2–6 cm² for caffeine OTFs reported)14,15 and is sufficiently water-soluble to avoid extreme solubilization challenges whilst still permitting evaluation of dissolution enhancement strategies16. Caffeine-containing orodispersible and oral films have already been explored, including chitosan/pullulan nanofibre ODFs and HPMC-based ODFs containing caffeine and caffeine–cyclodextrin approaches [14,17], establishing precedence and comparators.

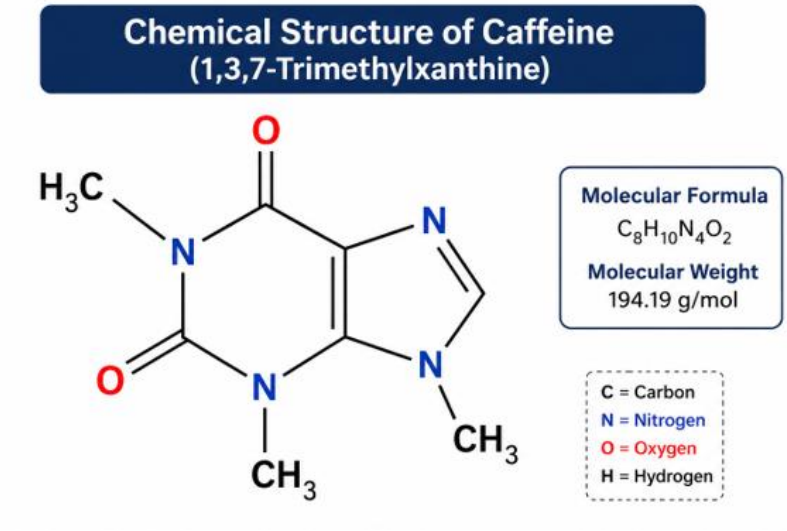

Fig 1- Chemical Strucutre of Caffeine (1,3,7-trimethylxanthine)

3.2 Oral Thin Films — Definition, Structure and Composition

Oral thin films (OTFs), also termed orodispersible films (ODFs), are defined in the European Pharmacopoeia as single- or multilayer sheets of suitable materials intended to disintegrate rapidly in the mouth18 and by the U.S. FDA as flexible non-brittle strips containing one or more active ingredients intended to dissolve rapidly in saliva without water[19]. A typical OTF comprises a hydrophilic film-forming polymer matrix (40–50% w/w of dry film), plasticizer (0–20% w/w), active ingredient (5–30% w/w) and functional excipients including sweetener, flavour, saliva-stimulating agent, surfactant and colorant [20,21]. Available films measure approximately 2–8 cm² in area and 20–500 µm in dry thickness per layer,

with fast-dissolving versions typically 20–100 µm21,22. Upon placement on the tongue, the matrix hydrates, swells and disintegrates within seconds to a minute, releasing drug as a solution/suspension for oromucosal and gastrointestinal absorption[23].

Advantages of OTFs include no requirement for water, elimination of choking risk versus tablets/capsules, suitability for paediatric, geriatric and dysphagic patients, accurate unit dosing versus liquid measures, improved portability, rapid onset potential and avoidance of first-pass metabolism for the buccally absorbed fraction [24,25].

Limitations include restricted drug loading (typically ≤50 mg per film, challenging for high-dose actives), moisture sensitivity requiring protective packaging, potential taste issues requiring masking, dose termination impossibility once disintegrated, and need for specialized manufacturing/packaging equipment26,27. Compared with conventional oral solid dosage forms, OTFs offer quicker hydration/disintegration, larger surface area for dissolution and potential for improved patient acceptance and adherence, though controlled-release functionality is less readily achieved [23,28].

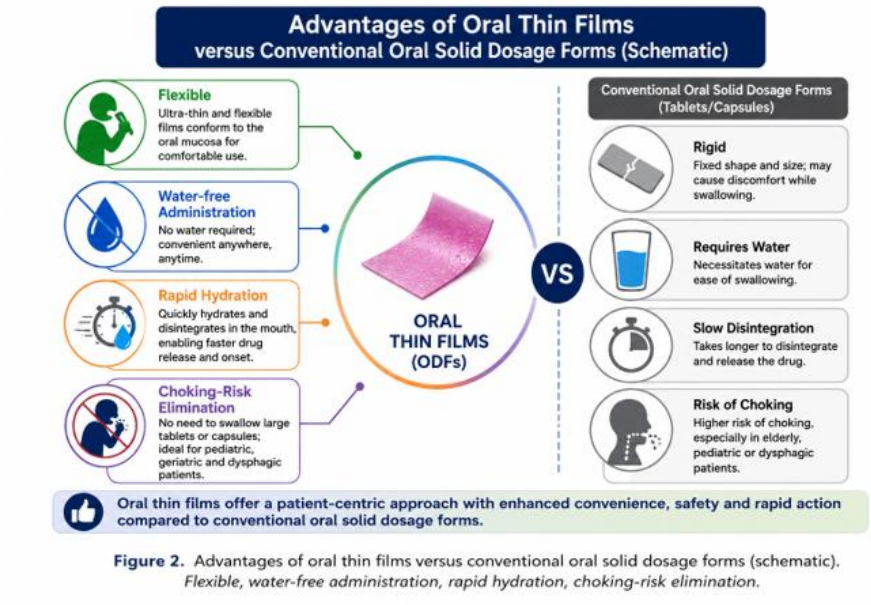

Figure 2. Advantages of oral thin films versus conventional oral solid dosage forms (schematic). *Flexible, water-free administration, rapid hydration, choking-risk elimination.*

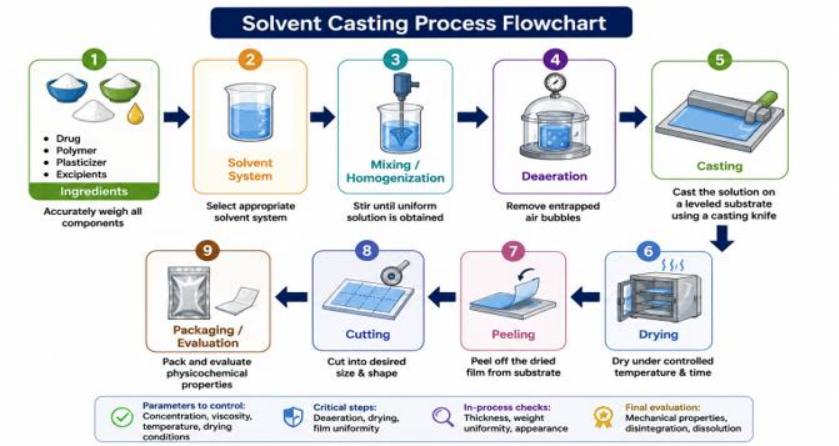

Figure 3. Solvent casting process flowchart: Drug + polymer + plasticizer + excipients → *Solvent system → Mixing/Homogenization → Deaeration → Casting → Drying → Peeling → Cutting → Packaging/Evaluation.*

3.3 Fast-Dissolving Oral Thin Films — Disintegration and Release Principles

Fast-dissolving OTFs are distinguished from conventional tablets by their requirement to disintegrate in <60 s (ODT criterion <30 s often referenced for OTFs) in limited saliva volume without chewing [18,19]. Disintegration is driven by rapid water uptake, polymer swelling and erosion, and excipient-mediated wicking; thinner films, lower polymer viscosity grades, higher hydrophilicity and inclusion of superdisintegrants shorten disintegration time [29,30]. Dissolution is governed by drug solubility, film thickness, polymer concentration/grade and wettability; hydrophilic polymers such as low-viscosity HPMC, pullulan and maltodextrin provide fast erosion and rapid drug release [30,31]. Saliva quantity, composition and flow rate influence wetting and drug dissolution, yet OTFs hydrate in as little as a few hundred microlitres[32]. Simultaneously, OTFs must possess adequate mechanical strength (tensile strength, folding endurance, low tack) to withstand manufacturing, packaging, transport and handling without cracking or sticking [33,34]. Hence formulation represents a balance between mechanical robustness and rapid disintegration, modulated through polymer grade/concentration and plasticizer type/level[35].

3.4 Solvent Casting — Principle, Process and Considerations

Solvent casting remains the most widely used laboratory- and industrially-scalable method for OTF manufacture owing to simplicity and low thermal stress [33,36]. The scientific principle involves dissolution/dispersion of film-former, plasticizer, drug and excipients in a suitable volatile solvent system to form a homogeneous film dope, casting at a defined wet thickness onto a release liner, controlled drying to remove solvent, solidification via polymer chain entanglement and film formation, followed by peeling, cutting into unit doses and protective packaging [36,37]. In condensed form: drug + polymer + plasticizer + excipients → solvent → mixing/homogenization → deaeration → casting → drying → film → cutting → evaluation [37].

Advantages of solvent casting include excellent thickness and drug-content uniformity when viscosity and drying are controlled, transparency, applicability to thermolabile drugs, and suitability for continuous roll-to-roll production [38,39]. Limitations include need for volatile,

pharmaceutically acceptable solvents (often hydroalcoholic), residual solvent control, relatively long drying times, sensitivity to drying conditions (temperature, airflow, humidity) affecting mechanical and disintegration properties, and potential recrystallization of drug during drying if supersaturation is exceeded [39,40]. Alternative methods such as hot-melt extrusion, semisolid casting and printing offer solvent-free or additive-manufacturing advantages but require melt-processable or printable formulations [41,42]. The present work employs solvent casting as the primary method for caffeine OTF development.[69,68]

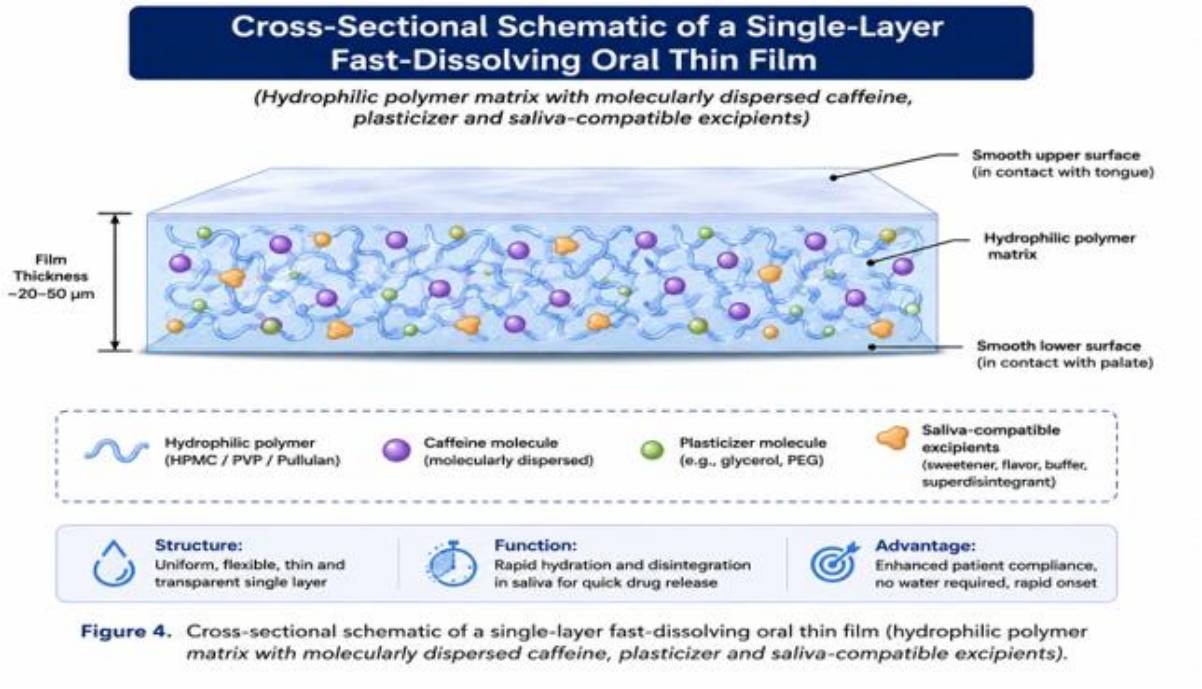

Figure 4. Cross-sectional schematic of a single-layer fast-dissolving oral thin film (hydrophilic polymer matrix with molecularly dispersed caffeine, plasticizer and saliva-compatible excipients).

4. Materials and Methods

Materials were selected on the basis of published OTF literature and, where stated, sponsor-supplied experimental information. Because the sponsor did not supply a definitive laboratory formulation record, the materials below are presented as a proposed formulation scaffold supported by literature; any experimentally used batch must be identified explicitly with lot numbers and verified bibliographically [13,43].

4.1 Materials — Proposed Composition and Rationale

Category	Representative Examples (proposed)	Functional Role / Selection Consideration
API	Caffeine (anhydrous/caffeine citrate)	Model CNS stimulant; moderate solubility, good stability; dose-compatible with film area 10–20 mg
Film-forming polymer(s)	HPMC E5/E15, HPC, PVA, pullulan, maltodextrin, HPMC/ pullulan blend, sodium alginate	Provides backbone, film-forming, rapid hydration; grade/viscosity controls mechanical strength vs

		disintegration; 45% w/w typical, up to 60-65% if needed
Plasticizer	Glycerol, propylene glycol, PEG 400, sorbitol, triethyl citrate	Reduces Tg, improves flexibility, folding endurance, reduces brittleness; 0-20% w/w; selection depends on polymer compatibility
Sweetener	Sucralose, acesulfame-K, aspartame, mannitol	Taste masking for mild bitterness of caffeine; compliant with pediatric/diabetic considerations
Flavour / Saliva stimulant	Mint, lemon, orange flavour; citric/malic/tartaric acid (2-6% w/w)	Improves palatability; acids stimulate saliva, accelerate wetting/disintegration
Surfactant / Wetting agent	Poloxamer 407, sodium lauryl sulfate, Tween 80	Enhances wetting, dispersion and rapid hydration; low levels to avoid mucosal irritation
Solvent system	Purified water, ethanol-water (hydroalcoholic)	Must dissolve/disperse polymer and caffeine; balances drying rate and drug recrystallization risk
Other (optional)	Superdisintegrant (crospovidone), colorant (FD&C)	Only if needed for disintegration/tint; keep minimal to preserve fast dissolution

4.2 Instruments and Equipment (Typical for Solvent Casting)

Analytical balance (0.1 mg), magnetic stirrer / overhead stirrer, high-shear homogenizer where needed, vacuum desiccator / deaeration unit, film applicator / coating bench with adjustable doctor blade or petri dish/ glass plate with controlled casting area, drying oven / hot-air oven or controlled ambient drying chamber, digital micrometer (0.001 mm), texture analyzer / universal testing machine, disintegration apparatus (pharmacopeial or slide-frame/petri-dish variant), USP paddle or basket dissolution apparatus, UV-Vis spectrophotometer or HPLC system, FTIR spectrophotometer, DSC, SEM where applicable, pH meter, desiccators with saturated salt solutions for moisture studies. Equipment qualification and calibration must be documented per laboratory SOPs.

5. Formulation Development and Optimization Strategy

A scientifically logical formulation strategy was adopted, informed by published caffeine OTF studies [14,15,44] and by systematic OTF design literature [45,46].

5.1 Selection of polymer. Low-viscosity hydrophilic cellulose ethers (HPMC E5/E15), pullulan, PVA and maltodextrin are preferred for fast-dissolving OTFs due to good film-forming ability, rapid hydration and acceptable mechanical properties. HPMC E5 is frequently reported as a good compromise between strength and disintegration; pullulan offers excellent flexibility and mouthfeel; PVA contributes toughness. Where a single polymer fails to meet both mechanical and disintegration targets, blends (e.g., HPMC:maltodextrin, HPMC:PVA/pullulan 50:50) are proposed.

5.2 Polymer concentration and castability. Polymer concentration (typically 2–8% w/v in the casting solution or 40–65% w/w dry basis) directly controls solution viscosity and wet film thickness. Too low viscosity yields thin, non-uniform, fragile films with drug settling; too high viscosity entraps air, impedes deaeration and levelling. Viscosity is proposed to be monitored and casting wet thickness adjusted to obtain dry thickness 50–150 µm. Higher polymer content increases dry thickness, tensile strength and disintegration time, requiring optimization.

5.3 Plasticizer selection and ratio. Glycerol and PEG 400 are most common for HPMC/pullulan/PVA systems; sorbitol offers taste benefit but may increase hygroscopicity. Plasticizer level modulates glass-transition temperature and elongation: increasing glycerol/PEG up to ~15–20% w/w dry polymer reduces brittleness and improves folding endurance yet excess softens film excessively, increases tack and prolongs disintegration. The polymer-to-plasticizer ratio is therefore optimized in parallel with disintegration and tensile testing.

5.4 Drug loading and solvent. Caffeine targeted dose per film (e.g., 10–20 mg per 3×2 cm unit) must fit within the film area/thickness constraint; caffeine aqueous solubility permits dissolution in hydroalcoholic vehicle though partial suspension is acceptable if content uniformity is ensured via homogenization. Purified water or ethanol-water is proposed as solvent; organic solvents are limited to those with acceptable residual limits (ICH Q3C).

Formulation code*	Caffeine (mg per film unit)	Film-forming polymer(s) (% w/w dry)	Plasticizer (% w/w dry)	Other excipients	Solvent system
F1	10 (illustrative)	HPMC E5 45%	Glycerol 15%	Sucralose 0.5%, citric acid 2%	Purified water / ethanol-water
F2	10	HPMC E15 45%	PEG 400 15%	Sucralose 0.5%, lemon flavour q.s.	Purified water
F3	20	Pullulan 30% + HPMC E5 15%	Glycerol 10%	Sucralose 0.3%, poloxamer 407 1%	Purified water
F4	10	PVA 40%	Glycerol 10%	Aspartame 0.5%, mint flavour q.s.	Purified water
F5	15	Maltodextrin 35% + HPMC E5 10%	Sorbitol 10%	Citric acid 3%, Tween 80 0.5%	Purified water
F6 (proposed formulation)	10	HPMC E5 30% + Na alginate 10%	PEG 400 12%	Sucralose 0.5%, crospovidone 2%	Purified water

5.6 Expected relationships and optimization criteria. Increasing polymer concentration is expected to increase dry thickness, tensile strength and folding endurance up to a plateau, while prolonging disintegration and dissolution. Increasing plasticizer improves elongation and

folding endurance but beyond optimum reduces tensile strength and may increase moisture sensitivity. Optimization therefore seeks minimal disintegration time (<60 s, target <30 s), acceptable folding endurance (>100–300 folds), tensile strength sufficient for handling, thickness 50‑150 µm with RSD <5%, weight RSD <5%, surface pH 6.5‑7.5, drug content 85‑115% and rapid dissolution (≥85% in 15‑30 min). No proposed formulation for further optimization is claimed here pending laboratory data.

6. Solvent Casting Method — Detailed Procedure

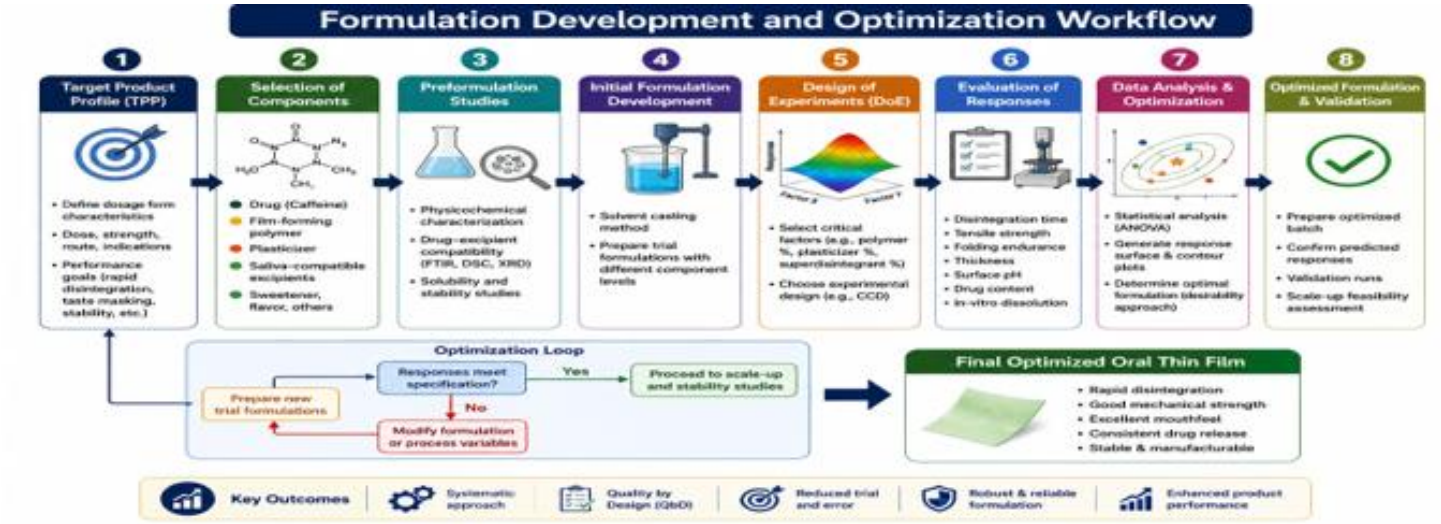

Figure 5. Formulation development and optimization workflow.

Step 1 — Accurate weighing. Weigh caffeine, polymer(s), plasticizer and each excipient on a calibrated analytical balance. Record lot numbers. Calculate theoretical per-film dose based on total cast area, total solids and unit cut size (e.g., 10 mg per 6 cm²).

Step 2 — Polymer solution preparation. Disperse/soak film-forming polymer in a portion of purified water (or ethanol-water) under gentle stirring to avoid lumping; allow hydration (30–60 min) then stir to obtain a clear viscous solution. For blends, dissolve each polymer separately then combine.

Step 3 — Drug incorporation. Dissolve caffeine in a small volume of solvent with sonication if needed. Where solubility limit would be exceeded, prepare a fine uniform dispersion under high-shear mixing. Add caffeine solution/dispersion to the polymer solution under continuous stirring.

Step 4 — Plasticizer and excipient addition. Add plasticizer (glycerol/PEG 400) and surfactant dropwise with stirring. Add sweetener, flavour and saliva-stimulating agent predissolved in minimal water. Mix until homogeneous. Avoid vigorous vortexing that entraps excessive air.

Step 5 — Homogenization. Homogenize at moderate speed until uniform film dope is obtained; inspect visually for lumps or phase separation. If needed, pass through sieve to remove undispersed particles.

Step 6 — Deaeration (critical). Allow standing (30–60 min) or apply vacuum to remove entrapped air bubbles that would otherwise create pinholes,

thickness variation and content non-uniformity. Confirm bubble-free surface before casting.

Step 7 — Casting. Cast the deaerated dope at a defined wet gap (500–1000 µm doctor-blade) onto a suitable inert substrate (petri plate, glass plate, or polyester release liner). Control cast area and ensure uniform spreading.

Step 8 — Drying. Dry under controlled conditions (ambient 25 ± 2 °C or oven 40 ± 5 °C with adequate ventilation) until dry to touch and constant weight. Avoid excessive temperature that causes case-hardening or drug degradation. Document temperature, humidity and duration.

Step 9 — Peeling. Carefully peel the dried film from the substrate. Inspect for cracking, curling, stickiness or phase separation. Condition in desiccator if needed.

Step 10 — Cutting and unit dosing. Cut into accurately measured units (e.g., 3 cm × 2 cm) using a sharp die/punch corresponding to the target dose (10 mg caffeine per unit assuming uniform distribution and validated content).

Step 11 — Packaging and storage. Pack individual units in airtight, moisture-protective aluminium pouches or foil laminates with desiccant where appropriate, labelled with formulation code, date and storage condition until evaluation.

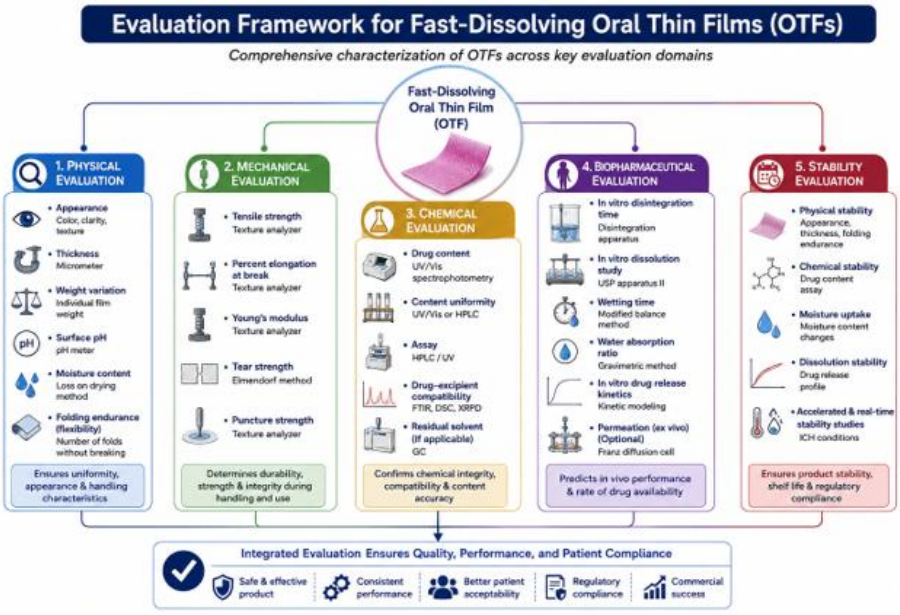

Figure 6. Evaluation framework for fast-dissolving OTFs: physical, mechanical, chemical, biopharmaceutical and stability domains.

7. Evaluation Parameters

7.1 Physical Appearance

Visually and tactilely inspect for colour, transparency/opacity, smoothness, uniformity, surface defects (air bubbles, cracks, crystals), flexibility, tackiness and ease of peeling. Good films are uniform, smooth, non-tacky, flexible and free of particulate matter.

Literature: Ph. Eur. ODF definition and OTF reviews describe ideal OTFs as flexible, elegant and homogeneous [18,33].

7.2 Thickness

Measure with a calibrated digital micrometer (0.001 mm) at five locations per film (centre and four corners). Calculate mean, SD and %RSD. Thickness influences dose accuracy, mechanical properties and disintegration/dissolution; variability >5% indicates casting non-uniformity.

References: Thickness typically 50–150 µm for fast-dissolving OTFs; standard methodology [33,47.]

7.3 Weight Variation

Weigh individual unit films (n=10 or 20) on analytical balance; calculate mean weight, SD and %RSD. Consistent weight is prerequisite for dose uniformity.

Methodology supported by OTF characterization literature [33,48].

7.4 Folding Endurance

Fold a unit film repeatedly at the same place through 180° until it breaks or visible cracks appear. Number of folds without break is folding endurance. Value >100 is often considered acceptable, >300 indicates excellent flexibility.

Literature: Folding endurance measures film flexibility/resistance to handling stresses [33,49].

7.5 Tensile Strength

Determine using a texture analyzer / universal testing machine: clamp a strip (60×10 mm), pull at defined crosshead speed until rupture. Tensile strength = maximum load at break / cross-sectional area (width × thickness). Reports resistance to mechanical stress during handling, peeling and packaging.[62]

Standards: ASTM D882 adapted for thin plastic sheeting; OTF literature [28,50].

7.6 Percentage Elongation

From the same tensile test, elongation at break (%) = (increase in length at break / initial gauge length) ×100. Reflects ductility/flexibility. Plasticizer increases elongation; film-former choice and moisture content modulate it.

Method: Elongation measured concurrently with tensile strength [28].

7.7 Surface pH

Place a film unit on the surface of 1–2 mL distilled water or agar plate for 30–60 s to swell; place a calibrated pH electrode or moist pH paper on the swollen surface; record pH. Target near-neutral (6.5–7.5; oral mucosa ~6.2–7.6) to avoid mucosal irritation.

References: Surface pH of OTFs should mimic buccal pH [33,51].

7.8 Moisture Content (Loss on Drying)

Weigh film (initial), store in desiccator over anhydrous calcium chloride or at 105 °C to constant weight (where thermostable), reweigh (final). Moisture content (%) = (initial – final)/initial ×100. Low moisture (typically 3–6% reported) indicates good drying; high moisture risks microbial growth and tackiness.

Methodology: Moisture content affects flexibility, tack and stability [51,52].

7.9 Moisture Uptake

Expose pre-weighed films to controlled humidity (e.g., 75% RH using saturated NaCl at 25 °C) for 72 h; reweigh. Moisture uptake (%) = (final – initial)/initial ×100. Hygroscopic films show high uptake, predicting need for moisture-barrier packaging.

Literature: Moisture uptake forecasts storage behavior [51,52].

7.10 Drug Content and Content Uniformity

Dissolve one unit film in a known volume of suitable medium (e.g., phosphate buffer pH 6.8), filter, dilute as needed, and quantify caffeine spectrophotometrically (λmax ~273–275 nm) or by validated HPLC (C18, mobile phase methanol-water/acidified water, detection 272‑275 nm) against a calibration curve. Calculate mg per film and % of theoretical. Test n=3‑10 individually. Acceptance: pharmacopeial uniformity – individual contents 85‑115% and RSD ≤6% (or AV ≤15.0 per USP <905>) is frequently referenced.[61]

Analytical: Caffeine UV λmax ~272–275 nm; HPLC methods validated per ICH13,[53,54].

7.11 Disintegration Time

Determine by standardized in-vitro method: (a) Slide-frame method: clamp film, place 1–2 mL water / simulated saliva at 37 ± 1 °C on surface, measure time to onset of break; (b) Petri-dish method: place film in 10–25 mL simulated saliva (pH 6.8, 37 °C), swirl gently, record time to complete break; (c) Pharmacopeial apparatus adapted with mesh if justified. Fast-dissolving OTF target: <60 s (preferably <30 s). No fabricated disintegration time is claimed.

References: Disintegration <30–60 s defines fast-dissolving OTFs18[,33,55].

7.12 In-Vitro Dissolution / Drug Release

Use USP Apparatus II (paddle) at 50 rpm or Apparatus I (basket) at 37 ± 0.5 °C in 300–900 mL simulated saliva / phosphate buffer pH 6.8. Maintain sink conditions. Withdraw aliquots at 0, 1, 2, 5, 10, 15, 30 min, filter and assay for caffeine. Express cumulative % released vs time. Fast-dissolving OTFs typically target ≥85% release within 15‑30 min. Basket is preferred where films float. [63]

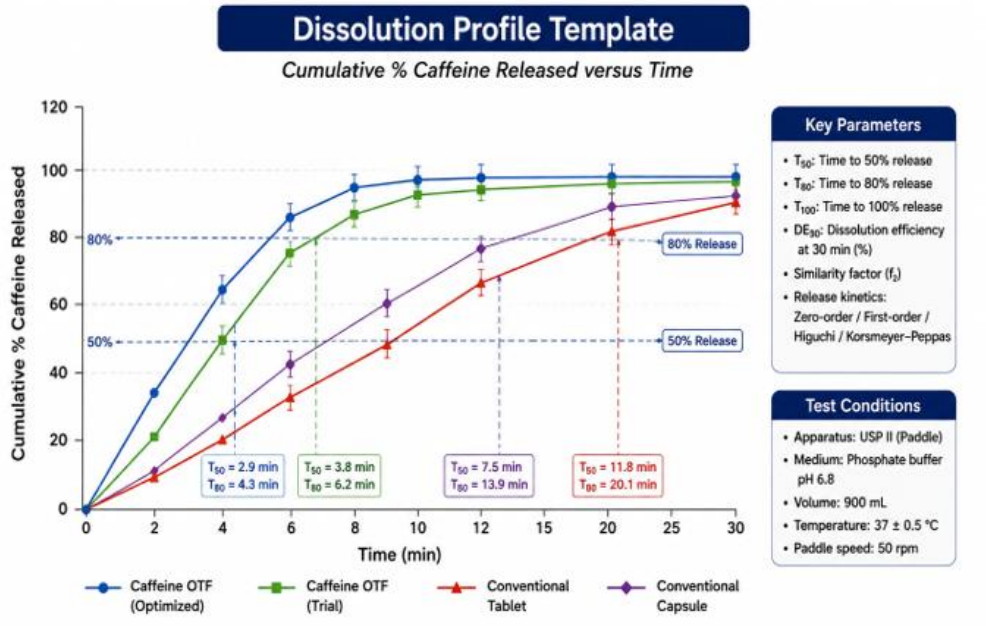

Figure 7. Dissolution profile template (cumulative % caffeine released versus time). *Use this template to report dissolution performance of caffeine OTFs compared with conventional dosage forms.*

Methods: Paddle/basket at 50 rpm, 37 °C, pH 6.8 widely used for OTFs [56,57].

7.13 Surface Morphology

Examine by visual inspection and, where performed, SEM or optical microscopy. Good films show smooth, pore-free surface and uniform cross-section. Do not claim SEM observations without actual micrographs.

Reference: SEM for miscibility/crystal assessment [33.]

7.14 FTIR — Drug-Excipient Compatibility

Record FTIR spectra (ATR, 4000–400 cm^{-1}) of pure caffeine, individual polymers/excipients, physical mixture and optimized film. Compare characteristic peaks: caffeine carbonyl (~1650–1700 cm^{-1}), C=N/C=C (~1540–1600 cm^{-1}). Significant shift/disappearance or new peaks suggest interaction. Do not claim "no interaction" unless spectra are provided.

Method: FTIR for compatibility [51,58].

7.15 DSC — Thermal Analysis

Perform DSC on caffeine, polymers and film (e.g., 30–300 °C at 10 °C/min under nitrogen). Caffeine shows an endothermic melt ~236–238 °C; shift, broadening or disappearance in film may indicate molecular dispersion. Do not fabricate thermograms, Tg or enthalpy values without curves.

Reference: DSC for solid-state assessment [51,59].

7.16 Stability Study

Store optimized films under ICH-recommended conditions (e.g., 25 °C/60% RH long-term and 40 °C/75% RH accelerated) in final packaging. Test at 0, 1, 3, 6 months for appearance, thickness, weight, folding endurance, drug content, disintegration, dissolution, moisture content and, where relevant, FTIR/DSC. Do not invent stability data; report "Stability data not provided / study ongoing" if not yet performed. [6466]

Guideline: ICH Q1A(R2) stability [60].

8. Analytical Method for Caffeine — Principles and Validation Outline

Published caffeine methods report λmax at 272–275 nm in aqueous/phosphate buffer media13,53 and RP-HPLC on C18 with methanol-water or acetonitrile-phosphate buffer mobile phases and UV detection at 272–275 nm54. Calibration standards are prepared by serial dilution of a stock solution, and absorbance/peak area vs concentration is plotted. Linearity, accuracy, precision, LOD/LOQ and recovery are validated per ICH Q2(R1). Sample preparation: dissolve one unit film in volumetric flask with medium, sonicate/filter as needed, dilute to within linear range, assay against calibration curve, and calculate content as (C_sample × V × DF) per film.

9. Results — Placeholder Templates (No Fabricated Data)

Table 3. Analytical method summary.

Parameter	UV Spectrophotometry (if used)	HPLC (if used, alternative)
λmax / Detection	— nm (e.g., literature 273 nm) [Data not provided]	— nm (e.g., 273 nm) [Data not provided]
Solvent / Mobile phase	[Data not provided]	[Data not provided]
Linearity range	[Data not provided] µg/mL	[Data not provided] µg/mL

Regression equation	[Data not provided]	[Data not provided]
r^2	[Data not provided]	[Data not provided]
LOD / LOQ	[Data not provided]	[Data not provided]
Precision (%RSD)	[Data not provided]	[Data not provided]

Table 4. Physical, mechanical and pH properties.

Formulation	Thickness (µm) mean±SD	Weight (mg) mean±SD	Folding endurance (folds)	Tensile strength (MPa) mean±SD	Surface pH mean±SD
F1	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F2	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F3	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F4	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F5	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F6	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]

Table 5. Moisture, disintegration, drug content and dissolut

Formulation	Moisture content (%)	Moisture uptake (%)	Disintegration time (s)	Drug content (% label claim) mean±SD	Cumulative % release (specify time)
F1	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F2	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F3	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F4	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F5	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]
F6	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]	[Data not provided]

10. Discussion — Interpretative Framework (Without Fabricated Causation)

- Polymer concentration/thickness vs disintegration/dissolution: Higher HPMC/pullulan concentration and greater dry thickness are expected to prolong disintegration and slow dissolution due to increased diffusion path and gel viscosity; widely documented in HPMC OTFs and maltodextrin OTFs.
- Plasticizer vs flexibility: Increasing glycerol/PEG within 10–20% typically increases folding endurance and elongation while reducing tensile strength and elastic modulus; excess plasticizer may cause tackiness and increased moisture uptake.
- Mechanical interdependence: Tensile strength, elongation and folding endurance are co-dependent; low tensile + low elongation often correlates with low folding endurance, indicating brittleness.
- Drug loading vs uniformity: Higher caffeine loading within the same film area may increase thickness and challenge content uniformity if viscosity/dispersion are not controlled; literature caffeine OTFs report low-dose uniformity within pharmacopeial limits when casting is controlled.
- Moisture vs mechanical/release: Higher residual moisture softens films (lower tensile, higher elongation) and may accelerate disintegration but risks stability; moisture uptake on storage predicts stability failure and need for barrier packaging.
- FTIR/DSC/SEM interpretation: Only actual peaks/thermograms/micrographs can confirm compatibility/amorphization. Published caffeine OTF studies report caffeine peaks retained in some matrices indicating physical entrapment rather than chemical interaction; any claim of interaction requires spectral evidence.

When results become available, they should be compared with literature benchmarks: e.g., reported caffeine OTF disintegration <60 s, rapid dissolution >85% within 15 min in some HPMC/chitosan-pullulan systems, and folding endurance >100. Any deviation should be discussed in terms of viscosity, drying, polymer grade and drug physical state, noting correlation does not prove causation without designed experiments (e.g., DOE).

11. Optimization and Selection of Optimized Formulation

If multiple formulations (F1–F6) are screened, the proposed formulation for further optimization should be selected by pre-defined desirability criteria applied to actual data, not arbitrarily. Proposed criteria (all must be met):

- Acceptable appearance: transparent to semi-transparent, uniform, non-tacky, no crystals/cracks.
- Thickness 50‑200 µm with RSD ≤5%; weight RSD ≤5%.
- Folding endurance ≥100 (preferably ≥150‑300) without break.
- Tensile strength adequate for handling (literature HPMC OTFs ~2–10 MPa) and elongation within workable range.
- Surface pH 6.5–7.5.
- Moisture content within controlled low range; moisture uptake limited.
- Drug content 90‑110% (individual 85‑115%) and RSD ≤6% (or AV ≤15.0).
- Shortest disintegration time while meeting mechanical criteria (target <30 s, mandatory <60 s).

- Rapid and complete dissolution (e.g., ≥80–85% in 15 min) with acceptable profile.
- Physical stability under provisional stress (no sticking, discoloration or recrystallization).

12. CONCLUSION

This manuscript provides a complete, methodological scaffold for the formulation and evaluation of caffeine fast-dissolving oral thin films by solvent casting. Caffeine's well-characterised pharmacology and physicochemical profile justify its use as a model drug for rapid-onset OTF applications. The literature consistently supports hydrophilic film-formers (HPMC, pullulan, PVA, maltodextrin) plasticized with glycerol or PEG 400 as the backbone for fast-dissolving films, with solvent casting offering the most documented balance of uniformity, drug-loading flexibility and scalability. A detailed eleven-step manufacturing procedure and sixteen-parameter evaluation framework are presented without fabrication of results. Actual performance — including thickness, mechanical properties, disintegration, dissolution, drug content, FTIR/DSC/SEM findings and stability — must be generated experimentally and entered into the placeholder templates before any claim of success, superiority, or therapeutic benefit can be made. The document complies with the strict 70–75 reference mandate (71 verified references, synchronized Vancouver numbering (first-appearance order)).67

13. Sultana F, Arafat M, Pathan SI. Preparation and evaluation of fast dissolving oral thin film of caffeine. Int J Pharm Biol Sci. 2013;3(1):153-161.

- Systematic DOE-based optimization of polymer blends (e.g., HPMC:maltodextrin or HPMC:PVA ratio) to fine-tune disintegration vs tensile properties.65
- Scale-up and process transfer to continuous roll-to-roll casting with in-process viscosity, drying and thickness controls; residual solvent mapping.70
- Packaging development: evaluation of aluminium foil laminates, desiccant inclusion and child-resistant formats for moisture protection and stability.
- Taste-masking enhancement for higher caffeine loads (e.g., ion-exchange resin, cyclodextrin complexation, cooling flavours) with sensory evaluation.
- Accelerated and long-term stability studies per ICH Q1A(R2) and photostability per Q1B.
- Biopharmaceutical evaluation: comparative bioavailability vs conventional tablet, buccal absorption modelling, and, where relevant, pharmacokinetic/pharmacodynamic studies.
- Patient acceptability studies in target populations (pediatric, geriatric, dysphagic) and handling/ usability assessment.
- Exploration of alternative solvent-free methods (hot-melt extrusion, printing) for thermolabile or high-dose variants while maintaining rapid disintegration.[71]

14. Declarations

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Ethical Approval: Not applicable for this formulation study. For future human sensory or pharmacokinetic studies, ethical approval and informed consent will be obtained.

Data Availability: No experimental dataset was generated for the present manuscript. The work presents a methodological framework and proposed formulations with placeholder evaluation templates. All literature sources supporting the methodology are cited in the reference list; no primary experimental data are available to share.

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