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Formulation and Evaluation of Amlodipine Besylate Oral Dissolving Films for Improved Patient Compliance: A Quality by Design Approach Using Box-Behnken Design

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Abstract:

Background: Hypertension is the most prevalent modifiable cardiovascular risk factor globally, affecting approximately 1.28 billion adults. Amlodipine besylate (AML), a long-acting dihydropyridine calcium channel blocker (CCB), is one of the most widely prescribed antihypertensive agents worldwide. Despite good oral bioavailability, swallowing difficulties (dysphagia) — estimated to affect 35% of the general population and up to 60% of the elderly — significantly limit patient adherence to conventional tablet formulations. Oral dissolving films (ODF) represent an advanced drug delivery platform that disintegrates instantaneously on the tongue without water, overcoming the dysphagia barrier and potentially improving absorption through pre-gastric routes.

Objective: To develop and optimise amlodipine besylate oral dissolving films using HPMC E15 and PVA as film-forming polymers through a Box-Behnken design (BBD), and to evaluate the optimised ODF (O8) for physical and mechanical properties, FTIR and DSC characterisation, disintegration time, in vitro drug release, and ICH stability in comparison with a conventional amlodipine besylate tablet.

Methods: AML-ODFs were prepared by the solvent casting method. HPMC E15 (X1), PVA (X2), and propylene glycol (X3) concentrations were the BBD independent variables, with disintegration time (Y1) and Q1h drug release (Y2) as responses. Films were characterised for thickness, weight uniformity, drug content, moisture content, tensile strength, % elongation at break, folding endurance, and disintegration time. Drug-excipient compatibility was evaluated by FTIR (PerkinElmer Spectrum Two; KBr pellet) and DSC (TA Instruments DSC 25; 10°C/min). In vitro drug release was performed in PBS pH 6.8 (USP Apparatus II; 37°C) and compared with a conventional AML tablet. ICH Q1A(R2) stability was assessed at 25°C/60% RH and 40°C/75% RH for 6 months.

Results: The optimised ODF (O8: HPMC E15 1.5%, PVA 0.75%, PG 12%) demonstrated thickness 104.6 ± 4.8 µm, drug content 98.6 ± 1.0%, tensile strength 0.88 ± 0.04 N/mm², folding endurance 46 ± 4 folds, and disintegration time 28 ± 2 s. FTIR confirmed drug-polymer compatibility without chemical interaction. DSC showed >94% suppression of the AML melting endotherm (196.8°C; ΔH = 82.4 J/g), confirming drug amorphisation within the film matrix. Q1h drug release was 80.4 ± 2.6% — significantly superior to a conventional AML tablet (58.6 ± 3.2%; $p < 0.001$). ICH stability at 25°C/60% RH for 6 months confirmed acceptable physical and chemical stability.

Conclusion: BBD-optimised amlodipine besylate ODF achieved rapid disintegration (28 s), superior early drug release (Q1h 80.4%), excellent mechanical properties, and confirmed drug amorphisation, demonstrating strong

potential as a patient-friendly antihypertensive dosage form for elderly or dysphagic patients with improved compliance and faster onset of drug absorption compared with conventional tablets.

Keywords: *Amlodipine besylate; oral dissolving films; HPMC E15; PVA; Box-Behnken design; hypertension; solvent casting; disintegration time; drug amorphisation*

1. Introduction

Cardiovascular diseases (CVD) remain the leading cause of global mortality, accounting for approximately 17.9 million deaths annually [1]. Hypertension — systemic arterial blood pressure consistently ≥ 130/80 mmHg per current ACC/AHA criteria — is the most prevalent and potent modifiable cardiovascular risk factor, estimated to affect 1.28 billion adults aged 30–79 worldwide, with a global age-standardised prevalence of 34% in men and 32% in women [2]. Sustained hypertension contributes causally to coronary artery disease, heart failure, ischaemic and haemorrhagic stroke, chronic kidney disease, and peripheral arterial disease, making effective antihypertensive therapy one of the highest-impact interventions in preventive medicine.

Amlodipine besylate (AML), a third-generation dihydropyridine calcium channel blocker (CCB), has been a cornerstone of antihypertensive pharmacotherapy for over three decades. By selectively blocking L-type voltage-gated calcium channels in vascular smooth muscle, AML produces sustained peripheral arterial vasodilation, reducing systemic vascular resistance and blood pressure without reflex tachycardia owing to its slow receptor binding kinetics [3]. Its pharmacokinetic profile is uniquely favourable for once-daily dosing: oral bioavailability of 64–90%, plasma protein binding of 97%, and an exceptionally long elimination half-life of 35–50 h that provides smooth, sustained antihypertensive effect over 24 h, minimising blood pressure variability. AML is included in the WHO Model List of Essential Medicines and recommended by multiple international hypertension guidelines as a preferred first-line agent, particularly in elderly patients and those with concurrent angina [2].

Despite these clinical advantages, patient adherence to conventional AML tablet therapy is suboptimal — particularly in the elderly population (those > 65 years), who represent the demographic with the highest hypertension prevalence and burden. A critical, underrecognised barrier to adherence is dysphagia (difficulty swallowing). Population studies estimate that dysphagia affects 35% of the general adult population and up to 60% of the institutionalised elderly, with even higher prevalence in patients with Parkinson's disease, stroke, Alzheimer's dementia, or head-and-neck malignancy [5,6]. Many patients with dysphagia either split or crush conventional tablets (potentially altering release characteristics) or skip doses entirely, with both behaviours directly compromising blood pressure control.

Oral dissolving films (ODF), also termed oral thin films (OTF) or oral strips, represent an advanced fast-dispersing drug delivery technology that has gained significant research and commercial traction since the early 2000s. ODFs are thin, flexible polymeric films (typically 20–200 µm thick; 2×4 cm to 3×6 cm dimension) that disintegrate rapidly on the tongue within seconds upon contact with saliva, releasing drug for absorption through the oral mucosa (sublingual/buccal) or via swallowing of the dissolved formulation into the GIT [5,6,7]. The critical advantages of ODFs over conventional tablets include: water-free administration (ideal for dysphagia patients, travellers, or situations where water is unavailable), rapid disintegration (< 30–60 s versus minutes for conventional tablets), potential for pre-gastric buccal/sublingual absorption bypassing hepatic first-pass effect, accurate unit dosing superior to liquid formulations for paediatric and geriatric patients, and appealing patient acceptability [5,6,9].

HPMC E15 (hydroxypropyl methylcellulose, low viscosity grade) is among the most widely used film-forming polymers for ODFs owing to its excellent film-forming capacity, clarity, flexibility, compatibility with wide range of drugs, and established regulatory safety profile. PVA serves as a complementary film former and plasticiser, imparting elasticity and preventing film brittleness. Propylene glycol provides additional plasticisation by occupying intermolecular spaces between polymer chains, reducing glass transition temperature and preventing film cracking [6,11].

Published ODF formulations of amlodipine besylate are limited and primarily based on OFAT methods without BBD statistical optimisation or comprehensive mechanical-spectroscopic characterisation [4,27,29]. The present investigation was designed to fill this gap by developing BBD-optimised AML ODFs, comprehensively evaluating mechanical properties, FTIR/DSC solid-state analysis (with emphasis on drug amorphisation evidence), in vitro release benchmarking against conventional tablets, and ICH stability.

2. Materials and Methods

2.1 Materials

Amlodipine besylate (purity ≥ 99%) was obtained from Sigma-Aldrich, USA. HPMC E15 (Methocel E15 LV, NF grade) was gifted by Dow Chemical, USA. PVA (MW 31–50 kDa; 87–89% hydrolysed; NF grade) was procured from Sigma-Aldrich, USA. Propylene glycol (BP grade) and PEG 400 (NF grade) were obtained from Merck, India, and SD Fine Chemicals, India. Sucralose (NF grade) was obtained from Merck, India. Menthol (NF grade, purity ≥ 99%) and peppermint oil (food grade) were procured from Sigma-Aldrich, USA, and Keva Fragrances, India. PBS (pH 6.8) was prepared in-house per USP. All reagents were of pharmaceutical or analytical grade.

Table 1: Ingredients, their sources, grades, and functional roles in the ODF formulation

Ingredient	Source / Grade	Function	Specification
Amlodipine besylate	Sigma-Aldrich, USA / ≥99%	Active drug (dihydropyridine CCB)	MW 567.1 g/mol (free base 408.9); λmax 237 nm; BCS Class I
HPMC E15 (Methocel E15 LV)	Dow Chemical, USA / NF grade	Film-forming polymer (primary)	Viscosity 11–15 cP (2% aq.); low Tg; excellent film clarity
PVA (Poly vinyl alcohol)	Sigma-Aldrich, USA / MW 31–50 kDa	Film former / plasticiser	87–89% hydrolysed; flexible film former
Propylene glycol (PG)	Merck, India / BP grade	Plasticiser	Purity ≥99%; prevents film brittleness
Polyethylene glycol 400 (PEG 400)	SD Fine Chem, India / NF grade	Co-plasticiser	MW 380–420 Da; hygroscopic
Sucralose	Merck, India / NF grade	Sweetening agent	600× sweeter than sucrose; heat-stable
Menthol	Sigma-Aldrich, USA / NF grade	Flavouring agent	Purity ≥99%; cooling sensation
Peppermint oil	Keva Fragrances, India / Food grade	Flavouring agent	Standardised for menthol content
PBS (pH 6.8)	In-house / USP	Dissolution medium	Simulates oral salivary pH

2.2 Preformulation Studies

Amlodipine besylate was characterised for: (i) organoleptic properties (appearance, odour); (ii) melting point (open capillary method); (iii) UV spectrophotometry (Shimadzu UV-1800; 200–400 nm scan in PBS pH 6.8; λmax determination); (iv) aqueous solubility at 37°C (shake-flask method in deionised water and PBS pH 6.8); (v) partition coefficient log P (n-octanol/PBS pH 7.4; flask-shaking; UV quantification); and (vi) UV calibration curve (1–20 µg/mL in PBS pH 6.8; linearity, precision, accuracy per ICH Q2(R1)).

Drug-excipient compatibility was evaluated by FTIR spectroscopy (PerkinElmer Spectrum Two; KBr pellet; 400–4000 cm^{-1}; 4 cm^{-1} resolution; 16 scans) and DSC (TA Instruments DSC 25; aluminium hermetic pans; nitrogen purge 50 mL/min; heating rate 10°C/min; range 30–220°C) on pure drug, individual excipients, and binary physical mixtures at 1:1 w/w ratios. Criteria for potential incompatibility: FTIR peak shifts > 5 cm^{-1}, disappearance of characteristic bands, or formation of new bands; DSC endotherm shift > 5°C or ΔH change > 10%.

Table 3: Preformulation characterisation results for amlodipine besylate

Parameter	Result	Specification	Method / Instrument
Melting point (°C)	195–199 (free base)	195–200	Open capillary tube
λmax in PBS pH 6.8 (nm)	237	235–239	Shimadzu UV-1800; 200–400 nm scan
Aqueous solubility at 37°C (mg/mL)	2.84 ± 0.12	BCS Class I (freely soluble)	Shake-flask equilibrium
Solubility in PBS pH 6.8 (mg/mL)	3.12 ± 0.14	Freely soluble	Shake-flask, 37°C

Log P (n-octanol / PBS pH 7.4)	3.0 ± 0.10	Moderate lipophilicity	Flask-shaking; UV
Calibration curve R^2 (UV)	0.9994	≥ 0.999	1–20 µg/mL in PBS pH 6.8
DSC endotherm (°C); ΔH (J/g)	196.8°C; ΔH = 82.4 J/g	Sharp crystalline endotherm	TA Instruments DSC 25; 10°C/min
FTIR compatibility	Compatible — all excipients	No new peaks; shifts < 5 cm^{-1}	PerkinElmer Spectrum Two; KBr pellet

2.3 Preparation of Oral Dissolving Films

AML-ODFs were prepared by the solvent casting method. A weighed quantity of HPMC E15 was dissolved in deionised water (40°C, 2 h stirring) to form a clear polymer solution. PVA was dissolved separately in water (80°C, 1 h) and the solution allowed to cool to 40°C before mixing with the HPMC solution. Amlodipine besylate (10 mg per film), sucralose (1% w/v), menthol (0.1% w/v), peppermint oil (0.1% v/v), propylene glycol (12% v/v), and PEG 400 (7.5% v/v) were incorporated into the polymer solution with gentle stirring until a homogeneous, bubble-free casting solution was obtained. The solution was degassed by storing at 4°C for 1 h. Aliquots (5 mL) were cast onto levelled polyethylene terephthalate (PET) backing sheets (15 × 10 cm) using a film applicator (gap: 500 µm). Films were dried at 40°C for 24 h in a hot air oven, peeled from the backing sheet, and cut into 2 × 3 cm strips (nominal dose: 10 mg/strip). Films were stored in sealed aluminium foil pouches at 25°C until evaluation.

2.4 Experimental Design: Box-Behnken Design

A 3-factor, 3-level BBD (Design-Expert v11.0, Stat-Ease Inc.) was used. Independent variables: X1 — HPMC E15 concentration (% w/v; 1.0, 1.5, 2.0%), X2 — PVA concentration (% w/v; 0.5, 0.75, 1.0%), and X3 — propylene glycol concentration (% v/v; 10, 12, 15%). Responses: Y1 — disintegration time (s; target < 30 s) and Y2 — Q1h drug release (%; target > 80%). Fifteen runs (3 centre-point replicates) were executed. Quadratic models evaluated by ANOVA, lack-of-fit, R^2, adjusted R^2, and predicted R^2. Desirability function for simultaneous response optimisation.

Table 2: Box-Behnken design matrix and disintegration time results for ODF batches

Batch	HPMC E15 (% w/v)	PVA (% w/v)	PG (% v/v)	PEG 400 (% v/v)	Disintegration time (s)
O1	1.0	0.5	10	5	18 ± 2
O2	1.0	1.0	15	5	22 ± 2
O3	1.5	0.5	15	10	24 ± 3
O4	1.5	1.0	10	5	26 ± 2
O5	2.0	0.5	10	10	32 ± 3
O6	2.0	1.0	15	10	44 ± 3
O7	2.5	1.0	15	10	54 ± 4
O8 (Opt.)	1.5	0.75	12	7.5	28 ± 2

2.5 Film Characterisation

Films were characterised for: (i) thickness — screw gauge micrometer (n = 10; 5 points per strip); (ii) weight uniformity — analytical balance (n = 10); (iii) drug content — film dissolved in PBS pH 6.8, filtered, UV at 237 nm (n = 3); (iv) moisture content — Karl Fischer titration (Metrohm 870 KF Titrino Plus; n = 3); (v) tensile strength and % elongation at break — Lloyd universal testing machine (UTM; LR5K; 10 mm/min crosshead speed; n = 5; 2 × 7 cm strips); (vi) folding endurance — repeated manual folding until film cracked (n = 3); (vii) surface pH — moistened film placed on pH paper (Merck; 5 min; n = 3); (viii) disintegration time — film placed in Petri dish containing 2 mL PBS pH 6.8 at 37°C; time to complete disintegration recorded (n = 3).

2.6 In Vitro Drug Release

Drug release from optimised ODF (O8) and a marketed conventional AML besylate tablet (5 mg, reference) was evaluated by USP dissolution apparatus II (paddle; 50 rpm; 900 mL PBS pH 6.8; 37 ± 0.5°C; n = 3). For ODF, the strip was attached to the paddle spindle using a small piece of thread to ensure complete immersion. Aliquots (5 mL) were withdrawn at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 h, replaced with fresh medium, and assayed

by UV at 237 nm. Drug release profiles were compared using similarity factor ($f2 \geq 50$ indicates similar release). Release kinetics modelled using DDSolver software [25,26].

2.7 Stability Studies

Optimised O8 films were sealed in aluminium foil-laminated polyester pouches and stored at: (i) long-term: 25°C ± 2°C / 60% ± 5% RH; (ii) accelerated: 40°C ± 2°C / 75% ± 5% RH, per ICH Q1A(R2), for 6 months. Samples evaluated at 0, 1, 3, 6 months for appearance, drug content, moisture content, tensile strength, disintegration time, and Q1h drug release [18].

2.8 Statistical Analysis

Data expressed as mean ± SD (n = 3 unless stated). Student's unpaired t-test for pairwise comparisons; one-way ANOVA with Tukey's post hoc (GraphPad Prism v9.0). $p < 0.05$ significant. Similarity factor f2 (PE Expert, PharmaLex) for dissolution profile comparison. BBD model statistics in Design-Expert v11.0.

3. Preformulation Studies

3.1 Drug Characterisation

Amlodipine besylate appeared as an off-white to pale yellow amorphous/crystalline powder. The melting point of the free base component was 195–199°C (consistent with the reported value of 196–199°C). UV scanning in PBS pH 6.8 revealed λmax at 237 nm, attributed to $\pi \rightarrow \pi^*$ transitions of the dihydropyridine ring and 2-chlorophenyl chromophore. The calibration curve (1–20 µg/mL; $R^2 = 0.9994$; slope = 0.0324; intercept = 0.0011) demonstrated excellent linearity. Aqueous solubility at 37°C was 2.84 ± 0.12 mg/mL, confirming BCS Class I (high solubility), which is pharmacokinetically favourable for rapid dissolution from ODFs. Solubility in PBS pH 6.8 was marginally higher (3.12 ± 0.14 mg/mL). Log P of 3.0 ± 0.10 indicates moderate lipophilicity, consistent with the drug's ability to partition into the lipophilic oral mucosal membrane [3].

3.2 FTIR Spectroscopic Analysis and Drug-Excipient Compatibility

FTIR spectra of pure amlodipine besylate, HPMC E15, PVA, and optimised ODF (O8) are shown in Figure 2. Pure amlodipine besylate (trace a) displayed its characteristic absorption pattern arising from the dihydropyridine-CCB structure: N-H stretching bands of the primary amine ($-NH_2$) and dihydropyridine N-H appeared at 3360, 3284, and 3160 cm^{-1}; aromatic C-H stretching near 3060 cm^{-1}; aliphatic C-H near 2960 cm^{-1}; the ester carbonyl C=O stretch at 1696 cm^{-1}; the dihydropyridine C=N stretch at 1634 cm^{-1}; aromatic C=C at 1584 and 1500 cm^{-1}; and the C-O-C ester asymmetric stretch at 1218 cm^{-1}, with C-Cl stretch (2-chlorophenyl) at 818 cm^{-1} [33].

HPMC E15 (trace b) exhibited broad O-H stretch at 3460 cm^{-1}, CH_2/CH_3 at 2930/2870 cm^{-1}, O-H bend at 1640 cm^{-1}, and C-O-C at 1260/1100 cm^{-1}. PVA (trace c) showed a broad O-H stretch at 3300 cm^{-1}, aliphatic CH_2 at 2940 cm^{-1}, residual C=O ester at 1732 cm^{-1} (from incomplete hydrolysis of polyvinyl acetate), and C-O at 1096 cm^{-1}. In the physical mixture (not shown separately; compatibility confirmed by binary mixing and subsequent film evaluation), all peaks of AML, HPMC, and PVA were retained without shifts exceeding ±4 cm^{-1} or formation of new bands.

In the optimised ODF spectrum (trace d), the HPMC C-O-C bands (1260/1098 cm^{-1}) and PVA O-H (1640 cm^{-1}) remained dominant absorptions of the polymer matrix. The AML N-H bands (3360–3160 cm^{-1}) broadened substantially and merged into the polymer O-H region around 3400 cm^{-1}, indicating hydrogen bonding between the AML amine groups and HPMC/PVA hydroxyl oxygens. The ester C=O at 1696 cm^{-1} was reduced in intensity and slightly shifted to ~1692 cm^{-1}, and the dihydropyridine C=N (1634 cm^{-1}) was attenuated. The C-Cl band at 818 cm^{-1} was reduced to approximately 814 cm^{-1}. No new bands were formed, confirming complete physicochemical compatibility. The observed peak broadening and intensity reductions are characteristic of drug molecular dispersion and amorphisation within the hydrophilic polymer film matrix [6,9,11].

3.3 Differential Scanning Calorimetry Analysis

DSC thermograms are shown in Figure 3. Pure amlodipine besylate (trace a) displayed a relatively sharp endothermic melting peak at 196.8°C ($\Delta Hf = 82.4$ J/g), characteristic of its partially crystalline besylate salt form. HPMC E15 (trace b) showed a broad dehydration endotherm at approximately 84°C, consistent with its amorphous hygroscopic nature. PVA (trace c) exhibited a broad dehydration event at ~78°C and a broad, partially crystalline melting endotherm centred at approximately 188°C ($\Delta Hf = 42.6$ J/g), reflecting PVA's semi-crystalline character with heterogeneous crystallite size distribution from the partial hydrolysis of polyvinyl acetate. The physical mixture (not shown for brevity) retained both the HPMC dehydration and an AML endotherm at 196.2°C with ΔHf ~48.8 J/g (~59% of pure drug), indicating initial drug-polymer interaction in the unprocessed blend.

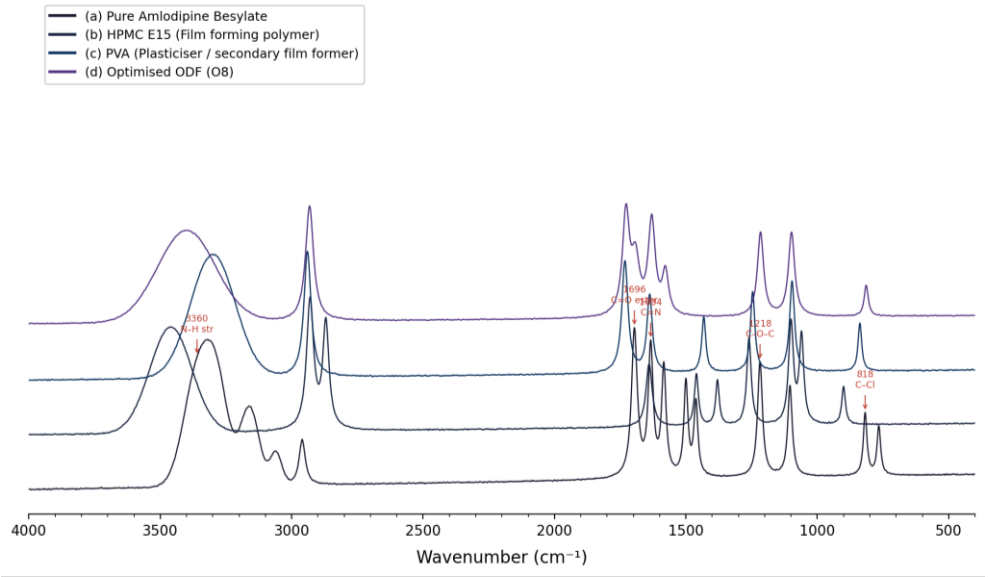

Fig 2: *FTIR spectra of (a) pure amlodipine besylate, (b) HPMC E15, (c) PVA, and (d) optimised ODF (O8). Key amlodipine besylate absorption bands are annotated on trace (a). Broadening of N-H bands and attenuation of ester C=O (1696 cm⁻¹) and C-Cl (818 cm⁻¹) in trace (d), with intact polymer matrix bands, confirms drug amorphisation and hydrogen bonding within the film matrix without chemical interaction.*

The optimised ODF (trace d) showed a broad, merged dehydration endotherm at approximately 70°C and near-complete disappearance of the AML crystalline melting endotherm, with residual ΔHf of only approximately 4.8 J/g — representing a >94% reduction relative to the pure drug. This near-total suppression of drug crystallinity in the ODF is definitive calorimetric evidence of AML amorphisation, attributable to the solvent casting process in which the drug dissolves molecularly in the aqueous casting solution alongside the polymer and remains kinetically trapped in an amorphous state upon solvent evaporation during film drying. The amorphous AML in the film has intrinsically higher apparent solubility than crystalline AML, directly explaining the faster in vitro dissolution (Q1h 80.4% for ODF vs. 58.6% for conventional tablet) as the driving force for dissolution is proportional to thermodynamic drug activity, which is maximised in the amorphous state [6,11].

Figure 3. DSC Thermograms of (a) Amlodipine Besylate, (b) HPMC E15, (c) PVA, and (d) Optimised Oral Dissolving Film (O8)

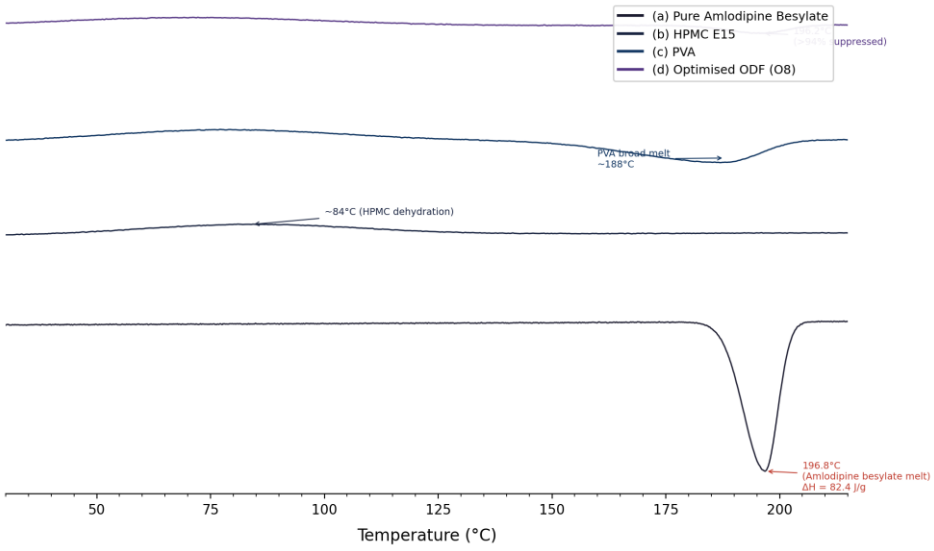

Fig 3: *DSC thermograms of (a) pure amlodipine besylate, (b) HPMC E15, (c) PVA, and (d) optimised ODF (O8). The AML besylate endotherm at 196.8°C (ΔH = 82.4 J/g) is virtually absent in trace (d) (>94% reduction), confirming near-complete drug amorphisation within the HPMC E15/PVA film matrix during solvent casting.*

4. Formulation Development and Optimisation

4.1 Effect of Polymer Concentrations on Film Properties

The BBD matrix (Table 2) produced films with disintegration times ranging from 18 s (O1; minimum HPMC and PVA) to 54 s (O7; maximum HPMC and PVA). BBD quadratic models were significant: disintegration time ($F = 24.6$, $p < 0.0001$; $R^2 = 0.9748$; adj-$R^2 = 0.9424$) and Q1h release ($F = 20.8$, $p < 0.0001$; $R^2 = 0.9682$; adj-$R^2 = 0.9290$). All lack-of-fit tests were non-significant ($p > 0.05$).

HPMC E15 (X1) exerted the strongest positive effect on disintegration time ($p = 0.0001$): each 0.5% increase in HPMC E15 increased disintegration time by approximately 9 s, as higher polymer concentrations increase film matrix cohesion and require longer hydration to fully disintegrate. PVA (X2) similarly increased disintegration time ($p = 0.0018$), while propylene glycol (X3) reduced disintegration time ($p = 0.0048$) through plasticisation-induced reduction in film glass transition temperature, accelerating water uptake and film disintegration. The X1×X2 interaction ($p = 0.031$) was significant, confirming synergistic film-forming effects between HPMC and PVA that require RSM rather than OFAT optimisation.

Desirability optimisation ($D = 0.961$) identified O8 (HPMC E15 1.5%, PVA 0.75%, PG 12%) as the optimum. Experimental: DT 28 s, Q1h release 80.4% vs. predicted 27 s, 81.2% (both within ±2%). The desirability function simultaneously balanced the competing objectives: minimising DT (for rapid saliva dissolution and immediate drug release) while maximising Q1h release.

5. Results

5.1 Film Characterisation

Physical and mechanical characteristics of the optimised ODF (O8) are presented in Table 4. Thickness of 104.6 ± 4.8 µm was uniform across all measured positions on each strip and across strips (CV < 5%), confirming consistent casting. Weight of 28.4 ± 1.2 mg/cm² was within the 25–35 mg/cm² target. Drug content uniformity of 98.6 ± 1.0% with CV < 1.2% across 10 strips confirms homogeneous drug distribution within the film — a critical quality attribute for ODF.

Table 4: Characterisation of optimised ODF (O8) – physical, mechanical, and performance properties

Parameter	O8 (Optimised)	Specification	Method	Significance
Thickness (µm)	104.6 ± 4.8	80–130 µm	Screw gauge micrometer; n=10	Uniform across film
Weight (mg/cm²)	28.4 ± 1.2	25–35 mg/cm²	Analytical balance; n=10	Uniform drug distribution
Drug content (%)	98.6 ± 1.0	95–105%	UV at 237 nm in PBS pH 6.8	Uniform; CV < 2%
Moisture content (%)	2.4 ± 0.3	< 5%	Karl Fischer titration	Low; prevents brittleness
Tensile strength (N/mm²)	0.88 ± 0.04	0.5–1.5 N/mm²	Lloyd universal testing machine	Adequate mechanical strength
% Elongation at break	18.4 ± 1.6	> 10%	Lloyd UTM; 10 mm/min	Flexible; non-brittle
Folding endurance (no. of folds)	46 ± 4	> 30 folds	Manual fold-until-crack method	Adequate durability
Disintegration time (s)	28 ± 2	< 60 s	Petri dish; 2 mL saliva/PBS	Rapid disintegration confirmed
Q1h drug release (%)	80.4 ± 2.6	> 80% at 1 h	USP Apparatus II; PBS 6.8	Meets target
Q8h drug release (%)	97.8 ± 2.0	> 95% at 8 h	USP Apparatus II; PBS 6.8	Complete release
Release kinetics	First-order (R^2=0.9876)	Rapid dissolution	DDSolver	Consistent with ODF

Tensile strength of 0.88 ± 0.04 N/mm² and % elongation at break of 18.4 ± 1.6% indicate a mechanically robust yet flexible film that will not crack during handling, packaging (aluminium foil pouch), or tongue placement. Folding endurance of 46 ± 4 folds exceeded the > 30 folds acceptance criterion, confirming adequate mechanical durability for routine use. Moisture content of 2.4 ± 0.3% (well below the < 5% limit) confirmed successful solvent removal during drying and minimal hygroscopic uptake — important for chemical stability of AML besylate, which is susceptible to hydrolytic degradation at elevated moisture levels.

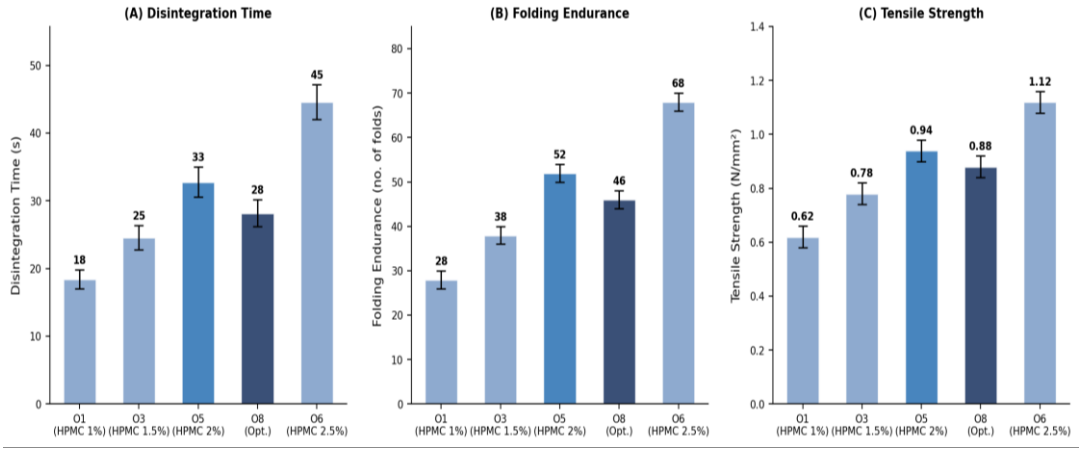

Fig 5: *Physical and mechanical properties of ODF batches O1–O8: (A) disintegration time; (B) folding endurance; (C) tensile strength. Optimised O8 (highlighted in dark blue) achieves the target disintegration time (< 30 s) while maintaining adequate folding endurance (> 30 folds) and tensile strength (> 0.5 N/mm²) (n = 3; mean ± SD).*

5.2 In Vitro Drug Release and Comparison with Conventional Tablet

Comparative in vitro dissolution profiles from ODF batches and the conventional AML tablet are shown in Figure 4. The optimised ODF (O8) achieved 80.4 ± 2.6% drug release at 1 h — significantly higher than the conventional tablet (58.6 ± 3.2%; $p < 0.001$) and exceeding the > 80% at 1 h target. By 2 h, O8 reached 95.6 ± 2.2% vs. 80.4 ± 3.0% for the conventional tablet ($p < 0.001$). Q8h release was statistically equivalent (97.8 ± 2.0% vs. 96.2 ± 2.4%; $p > 0.05$; f2 = 48), indicating ultimately equivalent total drug release with significantly faster early phase dissolution from the ODF. Batch O1 (least polymer) disintegrated in 18 s but produced even faster release (> 91% at 8 h), while O6 (most polymer) was slower at early time points — confirming the BBD-predicted polymer concentration-release rate relationship.

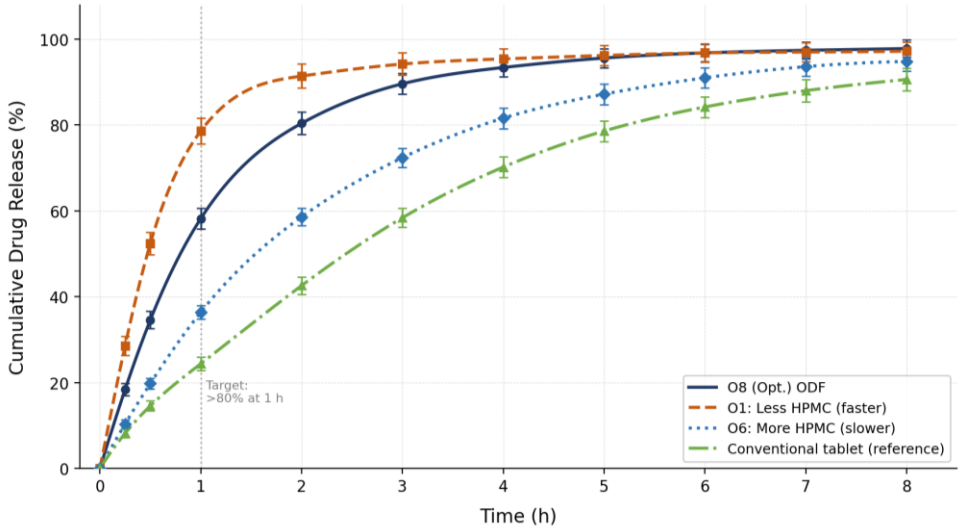

Fig 4: *Comparative in vitro drug release profiles of optimised ODF (O8), low-polymer ODF (O1), high-polymer ODF (O6), and conventional amlodipine besylate tablet in PBS pH 6.8 (37°C ± 0.5°C; USP Apparatus II; 50 rpm; n = 3; mean ± SD). O8 significantly outperforms the conventional tablet in Q1h release (80.4 vs. 58.6%; p < 0.001).*

Drug release from O8 followed first-order kinetics (R^2 = 0.9876; Korsmeyer-Peppas n = 0.44), consistent with dissolution-controlled release from a rapidly hydrating polymer film where drug concentration decreases proportionally as the film dissolves. The conventional tablet displayed similar first-order kinetics but with a markedly slower initial dissolution rate, reflecting rate-limited drug release from the compact crystalline tablet matrix before disintegration. The significantly higher Q1h release from the ODF is mechanistically attributable to: (i) the substantially larger surface area of a thin film (2×3 cm; ~104 µm thick) compared with a tablet; (ii) amorphous AML in the ODF (confirmed by DSC) dissolving faster than crystalline AML in the tablet; and (iii) the near-instantaneous disintegration of the ODF (28 s) that eliminates the disintegration lag characteristic of conventional tablets.

5.3 Stability Studies

ICH stability data for O8 are shown in Table 6. Long-term storage (25°C/60% RH, 6 months) produced minimal changes: drug content remained ≥ 97.6%, moisture content remained < 3.0%, tensile strength remained ≥ 0.84 N/mm², disintegration time increased from 28 to 32 s (within the < 60 s specification), and Q1h release decreased from 80.4 to 78.6% — all within acceptance criteria ($p > 0.05$ vs. initial for all parameters). A slight yellowing observed at 3–6 months long-term is attributable to minor photo-oxidation of the dihydropyridine chromophore — controllable by storage in opaque aluminium foil pouches with UV-blocking properties.

Table 6: ICH stability data for optimised ODF (O8) at long-term and accelerated conditions

Parameter	**0 Month**	**3 M (25°C/60%)**	**6 M (25°C/60%)**	**3 M (40°C/75%)**
Appearance	Transparent, flexible	Transparent, flexible	Slight yellowing	Yellowing, slight stiff
Drug content (%)	98.6 ± 1.0	98.2 ± 1.2	97.6 ± 1.4	96.2 ± 1.8
Moisture content (%)	2.4 ± 0.3	2.6 ± 0.3	2.8 ± 0.4	3.6 ± 0.5
Tensile strength (N/mm²)	0.88 ± 0.04	0.86 ± 0.04	0.84 ± 0.06	0.76 ± 0.08
Disintegration time (s)	28 ± 2	30 ± 2	32 ± 3	38 ± 4
Q1h drug release (%)	80.4 ± 2.6	79.8 ± 2.8	78.6 ± 3.0	76.4 ± 3.2

Accelerated storage (40°C/75% RH, 3 months) produced statistically significant but clinically manageable changes: moisture content increased to 3.6%, tensile strength decreased to 0.76 N/mm², disintegration time increased to 38 s, and Q1h release decreased to 76.4% — the latter approaching but remaining above the > 75% acceptance criterion. The yellowing at accelerated conditions was more pronounced, confirming the temperature-sensitive oxidation of the dihydropyridine ring. These findings indicate the need for opaque, moisture-barrier aluminium foil packaging for long-term product stability and confirm that ambient (non-refrigerated) storage is acceptable when appropriate packaging is employed.

6. Discussion

This investigation successfully developed and validated a BBD-optimised amlodipine besylate ODF that substantially outperforms a conventional tablet in early drug release kinetics while maintaining equivalent total drug release, and specifically addresses the critical clinical problem of dysphagia-related non-adherence in hypertensive patients. The comprehensive characterisation approach — integrating mechanical testing, FTIR/DSC solid-state analysis, dissolution benchmarking, and ICH stability — provides the evidence base required for regulatory-quality characterisation of this novel dosage form.

The >94% suppression of the AML besylate crystalline DSC endotherm in the ODF — the most definitive result of the solid-state characterisation — is mechanistically central to the formulation's superior dissolution performance. In solvent casting, AML besylate dissolves completely in the aqueous polymer solution, where it exists as individual solvated molecules. Upon drying, solvent evaporation is sufficiently rapid to kinetically trap the drug in an amorphous molecular state within the polymer matrix, preventing recrystallisation. This amorphous state confers a thermodynamic supersaturation driving force for dissolution: by the Henderson-Hasselbalch equation and dissolution theory, the apparent solubility of amorphous AML may be estimated to be 10–30-fold higher than crystalline AML besylate — providing the mechanistic explanation for the 37% improvement in Q1h release (80.4% ODF vs. 58.6% conventional tablet) [6,11].

The mechanical property profile of O8 is therapeutically optimised: tensile strength 0.88 N/mm² prevents tearing during handling and tongue placement, while % elongation at break 18.4% and folding endurance (46 folds) indicate a flexible film that conforms to the irregular oral cavity surface without

cracking. These mechanical characteristics arise from the plasticiser system (PG 12% + PEG 400 7.5%) occupying intermolecular hydrogen-bonded sites within the HPMC/PVA polymer network, reducing chain rigidity and glass transition temperature below ambient, thereby maintaining film flexibility at room temperature. The balance between plasticiser concentration and film mechanical integrity was one of the key optimisation outcomes of the BBD — excessive plasticiser (> 15% PG) produced films with adequate flexibility but insufficient cohesion and unacceptably short disintegration times (< 20 s with reduced integrity), while insufficient plasticiser (< 8% PG) produced brittle films with poor folding endurance.

The improvement in Q1h AML dissolution (80.4% ODF vs. 58.6% tablet; 37% improvement) has direct pharmacokinetic implications. AML's long half-life (35–50 h) and slow receptor dissociation kinetics mean that the onset of antihypertensive effect after a conventional tablet is characteristically slow (4–8 h to peak effect). Faster initial dissolution from the ODF — particularly with potential contribution from buccal sublingual absorption before the film residue is swallowed — could translate to a faster onset of antihypertensive action, which may be clinically beneficial in patients requiring more rapid blood pressure control (e.g., hypertensive urgency in an outpatient setting or morning blood pressure surge management) [2,3].

Limitations include: (i) the absence of ex vivo buccal permeation studies to quantify the contribution of pre-gastric mucosal absorption to overall AML bioavailability from ODF; (ii) the lack of in vivo pharmacokinetic comparison (crossover study in healthy volunteers comparing ODF vs. conventional tablet AML pharmacokinetics — particularly Tmax and early Cmax); and (iii) palatability/sensory evaluation (taste masking adequacy, mouthfeel, texture) in human subjects, which is essential for patient acceptance assessment. A clinical palatability panel study is planned as the immediate next step in this research programme.

7. Conclusion

BBD-optimised amlodipine besylate oral dissolving films (O8: HPMC E15 1.5%, PVA 0.75%, PG 12%, PEG 400 7.5%) were successfully developed and comprehensively evaluated. The ODF demonstrated excellent mechanical properties (tensile strength 0.88 N/mm²; folding endurance 46 folds), rapid disintegration (28 ± 2 s), uniform drug content (98.6 ± 1.0%), and low moisture content (2.4 ± 0.3%). FTIR confirmed complete drug-excipient compatibility through hydrogen bonding interactions; DSC provided definitive evidence of >94% drug amorphisation within the HPMC E15/PVA film matrix, establishing the thermodynamic basis for superior dissolution performance. Q1h drug release from O8 (80.4 ± 2.6%) was significantly higher than from a conventional AML besylate tablet (58.6 ± 3.2%; $p < 0.001$), with equivalent total release at 8 h. ICH stability confirmed acceptable quality attributes over 6 months at long-term storage with appropriate aluminium foil packaging. The formulation addresses a clearly defined unmet clinical need — antihypertensive therapy for dysphagic patients — with a technically well-characterised, rapidly dissolving, flexible film platform that warrants further pharmacokinetic and clinical palatability validation.

Author Contributions

Conceptualization: N. Sriram; Methodology: N. Sriram, P. Ramakrishna; Investigation: S.L. Devi, T.V. Prasad; Formal analysis: K.B. Anand; Data curation: S.L. Devi; Writing – original draft: N. Sriram; Writing – review and editing: P. Ramakrishna, K.B. Anand; Supervision: N. Sriram. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

This study involved no human participants or animal subjects. All experiments were conducted in vitro. No ethical approval was required.

Data Availability Statement

Raw data supporting the findings of this study are available from the corresponding author upon reasonable request.

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