Journal of Molecular Science

Journal of Molecular Science
Volume 36 Issue 1, Year of Publication 2026, Page 297-303
DoI-10.004687/1000-9035.2026.038

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Development and Evaluation of Nano-Loaded Buccal Films of Amlodipine for Improved Bioavailability

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Article Information
Received: 06-03-2026
Revised: 28-03-2026
Accepted: 12-04-2026
Published: 25-05-2026

Keywords
Amlodipine; chitosan nanoparticles; mucoadhesive buccal film; ionic gelation; ex vivo permeation; bioavailability.

ABSTRACT

Amlodipine besylate, a dihydropyridine calcium-channel blocker, suffers from incomplete and variable oral bioavailability (≈60–65%) owing to extensive hepatic metabolism, while its slow oral absorption delays the onset of antihypertensive action. The present study aimed to develop amlodipine-loaded chitosan nanoparticles, embed them in mucoadhesive buccal films, and evaluate the system for enhanced transmucosal permeation and bioavailability. Nanoparticles were prepared by ionic gelation of chitosan with sodium tripolyphosphate and optimised for chitosan:tripolyphosphate ratio. The optimised batch (NP3) showed a particle size of 176 ± 8 nm, polydispersity index of 0.19, zeta potential of +35.1 mV and entrapment efficiency of 84.2 ± 2.1%. Nanoparticles were incorporated into hydroxypropyl methylcellulose/Carbopol 934P films by solvent casting. The optimised nano-loaded film (F3) exhibited a surface pH of 6.8, folding endurance >220, tensile strength of 1.86 N/mm², swelling index of 142%, drug content of 98.6% and mucoadhesive strength of 26.4 g. Compared with a plain drug film, F3 provided sustained release (93% over 8 h, Fickian–anomalous diffusion) and a 1.9-fold increase in ex vivo permeation. In rabbits, the buccal nano-film raised C_{max} from 4.2 to 7.6 ng/mL and increased $AUC_{0-\infty}$ by ≈1.86-fold relative to an oral suspension, confirming improved bioavailability. Nano-loaded mucoadhesive buccal films thus represent a promising platform for amlodipine delivery.

1. INTRODUCTION:

Hypertension remains one of the most prevalent chronic cardiovascular disorders worldwide and a leading modifiable risk factor for stroke, myocardial infarction and renal failure. Amlodipine besylate, a third-generation dihydropyridine calcium-channel blocker, is among the most widely prescribed agents for hypertension and chronic stable angina because of its long duration of action and once-daily dosing. [1]

Despite its clinical value, the oral performance of amlodipine is limited by pharmacokinetic constraints. Following oral administration its absolute bioavailability is only about 60–65%, attributable to extensive hepatic metabolism mediated mainly by cytochrome P450 3A4 [2,3], and peak plasma concentrations are reached slowly, between 6 and 12 h after dosing [2]. Although the besylate salt is reasonably water soluble, the parent base is poorly soluble and the molecule has been variously classified within the Biopharmaceutics Classification System, which contributes to inter-

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individual variability in absorption [4]. These limitations, together with reduced patient compliance among geriatric and dysphagic patients who struggle to swallow conventional tablets, justify the search for an alternative delivery route.

The buccal route offers an attractive alternative for drugs subject to presystemic hepatic loss. The buccal mucosa is highly vascularised and drains directly into the jugular vein, thereby bypassing hepatic first-pass metabolism, and it provides an accessible, well-tolerated surface that permits easy application and removal of a dosage form [5,6]. Nevertheless, the stratified squamous epithelium of the cheek represents a significant permeability barrier, and the continuous flushing action of saliva tends to remove non-adhesive formulations before absorption is complete [6,7]. Mucoadhesive buccal films have emerged as a patient-centric solid dosage form that overcomes these obstacles by adhering intimately to the mucosa, prolonging residence time and delivering the drug in a controlled manner from a thin, flexible and comfortable matrix [8,9].

A persistent challenge, however, is that simply dispersing a drug in a polymeric film does not by itself enhance transport across the epithelial barrier. Nanoparticulate carriers have therefore attracted growing interest for transmucosal delivery because their large surface area, intimate mucosal contact and capacity for controlled release can improve drug permeation and protect the payload [10,11]. Embedding pre-formed drug-loaded nanoparticles within a mucoadhesive film—a so-called nano-in-film strategy—combines the permeation- and residence-enhancing properties of nanoparticles with the convenience and dose precision of a film. This approach has been successfully demonstrated for propranolol-loaded nanoparticles in blend films [12], paliperidone-loaded nanostructured lipid carriers [13] and simvastatin-loaded carriers [14], each reporting enhanced permeation relative to conventional films.

Chitosan is an especially suitable carrier material for this purpose. It is biodegradable, biocompatible and cationic, which confers intrinsic mucoadhesion and a recognised ability to transiently open epithelial tight junctions, thereby acting as a permeation enhancer [7,15]. Chitosan nanoparticles can be produced under mild, aqueous, organic-solvent-free conditions by ionic gelation with the polyanion sodium tripolyphosphate, yielding spherical, positively charged particles with tunable size and high entrapment of suitable drugs [15,16]. Although amlodipine-loaded polymeric nanoparticles have been reported [4], their integration into a mucoadhesive buccal film for systemic delivery has received little attention.

The present work was therefore undertaken to develop and evaluate nano-loaded mucoadhesive buccal films of amlodipine. The specific objectives were to prepare and optimise amlodipine-loaded chitosan nanoparticles by ionic gelation, to incorporate the optimised nanoparticles into hydroxypropyl methylcellulose/Carbopol 934P films by solvent casting, to characterise the films for physicochemical, mechanical, mucoadhesive and release properties, and to assess ex vivo permeation and in vivo bioavailability relative to a conventional oral suspension.

2. MATERIALS AND METHODS:

2.1 Materials:

Amlodipine besylate was obtained as a gift sample from a pharmaceutical manufacturer. Low-molecular-weight chitosan (deacetylation degree ≈85%), sodium tripolyphosphate (TPP), hydroxypropyl methylcellulose (HPMC K4M) and Carbopol 934P were used as received. Glycerol and propylene glycol (plasticisers), glacial acetic acid and all other reagents were of analytical grade. Phosphate-buffered saline (PBS, pH 6.8) was used as the simulated salivary medium throughout.

2.2 Preparation of amlodipine-loaded chitosan nanoparticles

Nanoparticles were prepared by the ionic gelation technique [15,17]. Chitosan was dissolved in 1% v/v acetic acid (2 mg/mL) under magnetic stirring and the pH adjusted to ≈4.6. Amlodipine besylate (10 mg/mL stock) was added to the chitosan solution and stirred for 30 min. Sodium tripolyphosphate (1 mg/mL aqueous) was then added dropwise under continuous stirring (1000 rpm) at room temperature, producing an opalescent nanoparticle suspension by spontaneous electrostatic cross-linking. Four batches (NP1–NP4) were prepared by varying the chitosan:TPP mass ratio (3:1, 4:1, 5:1 and 6:1) to study its influence on particle characteristics. Nanoparticles were recovered by centrifugation (15,000 rpm, 30 min, 4 °C), washed and freeze-dried with mannitol (1% w/v) as cryoprotectant.

2.3 Characterisation of nanoparticles

Particle size, polydispersity index (PDI) and zeta potential were determined by dynamic light scattering and laser Doppler electrophoresis (n = 3). Particle morphology was examined by transmission electron microscopy. Entrapment efficiency (EE) was measured indirectly: the nanoparticle suspension was centrifuged and free amlodipine in the supernatant quantified by UV spectrophotometry at 360 nm. EE was calculated as the difference between total and free drug expressed as a percentage of total drug [16]:

$$EE\ (\%) = [(\text{Total drug} - \text{Free drug}) / \text{Total drug}] \times$$

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2.4 Preparation of buccal films

Mucoadhesive films were prepared by the solvent-casting method [8,12]. HPMC K4M and Carbopol 934P were dispersed in distilled water and allowed to hydrate overnight; glycerol and propylene glycol (30% w/w of polymer) were added as plasticisers. Four nano-loaded film batches (F1–F4) were cast with increasing HPMC:Carbopol ratios, each containing a freeze-dried nanoparticle quantity equivalent to 5 mg amlodipine per 2 cm² film. A plain drug film (FP) containing 5 mg of free amlodipine per 2 cm² and no nanoparticles was prepared identically as a comparator. The casting dispersions were sonicated to remove air bubbles, poured into glass moulds of defined area, and dried at 40 °C for 24 h. Dried films were cut into 2 cm² pieces, wrapped in aluminium foil and stored in a desiccator until use.

2.5 Evaluation of films

Films were evaluated for thickness (digital micrometer, five points), weight uniformity and drug content. Folding endurance was recorded as the number of folds at the same point before cracking. Surface pH was measured by placing a film in contact with 1 mL PBS for 1 h and reading with a flat-tipped electrode; values close to salivary pH (6.8) indicate mucosal compatibility [18]. Tensile strength and percentage elongation were measured with a texture analyser, and the swelling index was determined gravimetrically after hydration in PBS. Ex vivo mucoadhesive strength was assessed using a modified balance method against freshly excised buccal mucosa [19]. Drug–excipient compatibility was assessed by Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) [16,20].

2.6 In vitro drug release and kinetics

In vitro release was studied in PBS (pH 6.8, 37 ± 0.5 °C) under sink conditions. Films (2 cm²), an equivalent quantity of pure amlodipine and the plain film were placed in the medium with gentle agitation; samples were withdrawn at intervals, replaced with fresh medium and assayed spectrophotometrically. Release data were fitted to zero-order, first-order, Higuchi [21] and Korsmeyer–Peppas [22] models; the diffusional exponent (n) of the latter was used to interpret the release mechanism, where $n \leq 0.45$ denotes Fickian diffusion and $0.45 < n < 0.89$ denotes anomalous (non-Fickian) transport [23].

2.7 Ex vivo permeation

Permeation was studied in Franz diffusion cells using freshly excised porcine buccal mucosa mounted between the donor and receptor compartments [24]. The receptor was filled with PBS (pH 7.4) at 37 °C and stirred continuously. The optimised nano-loaded film (F3) and the plain film (FP) were applied to the mucosal surface; samples were withdrawn over 6 h and the cumulative amount of amlodipine permeated per unit area was determined. The steady-state flux and apparent permeability coefficient were calculated from the linear portion of the permeation profile.

2.8 In vivo pharmacokinetic study

The in vivo study was conducted in healthy New Zealand white rabbits after approval by the institutional animal ethics committee and in accordance with applicable guidelines for the care and use of laboratory animals [12,25]. Animals were randomised into two groups (n = 6). One group received the optimised buccal nano-film (F3) applied to the buccal mucosa, while the other received an equivalent dose of amlodipine as an oral suspension. Blood samples were collected at predetermined intervals up to 24 h, and plasma amlodipine was quantified by a validated reversed-phase high-performance liquid chromatography method [26]. Pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0-\infty}$ and elimination half-life) were derived by non-compartmental analysis, and the relative bioavailability of the buccal film versus the oral suspension was calculated.

2.9 Statistical analysis

All measurements were performed in triplicate (or n = 6 for the in vivo study) and expressed as mean ± standard deviation. Differences between groups were assessed by Student's t-test or one-way analysis of variance, with $P < 0.05$ considered statistically significant.

3. RESULTS

3.1 Formulation composition

The qualitative composition of the optimised nano-loaded buccal film is summarised in Table 1.

Table 1. Composition of the optimised amlodipine nano-loaded mucoadhesive buccal film (F3). Q.S. = quantity sufficient.

Ingredient	Function	Quantity (per 2 cm² film)
Amlodipine besylate	Active drug	5 mg (as nanoparticles)
Chitosan	Nanoparticle matrix / permeation enhancer	Q.S. (NP3, 5:1 with TPP)
Sodium tripolyphosphate	Ionic cross-linker	Q.S.
HPMC K4M	Film-forming / mucoadhesive polymer	60 mg
Carbopol 934P	Mucoadhesive polymer	20 mg
Glycerol + propylene glycol	Plasticiser	30% w/w of polymer
Distilled water	Casting solvent	Q.S.

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3.2 Optimisation of nanoparticles

All four batches formed nanoparticles in the colloidal range. As the chitosan:TPP ratio increased from 3:1 to 5:1, particle size decreased and zeta potential and entrapment efficiency increased, reaching optimal values at 5:1 (NP3); a further increase to 6:1 (NP4) enlarged the particles and broadened the size distribution (Table 2). NP3 was therefore selected as the optimised batch, showing a size of 176 ± 8 nm, a narrow PDI of 0.19, a strongly positive zeta potential of +35.1 mV indicative of good colloidal stability, and the highest entrapment efficiency (84.2%). The size distribution of NP3 was unimodal and narrow (Figure 1), and transmission electron microscopy confirmed discrete, near-spherical particles.

Table 2. Effect of chitosan:tripolyphosphate (CS:TPP) ratio on nanoparticle characteristics (mean ± SD, n = 3). PDI = polydispersity index; EE = entrapment efficiency.

Batch	CS:TPP ratio	Size (nm)	PDI	Zeta (mV)	EE (%)
NP1	3:1	245 ± 12	0.28	+28.4	71.3 ± 2.6
NP2	4:1	198 ± 9	0.22	+32.6	78.9 ± 1.9
NP3 (optimised)	5:1	176 ± 8	0.19	+35.1	84.2 ± 2.1
NP4	6:1	221 ± 14	0.31	+30.2	80.5 ± 2.4

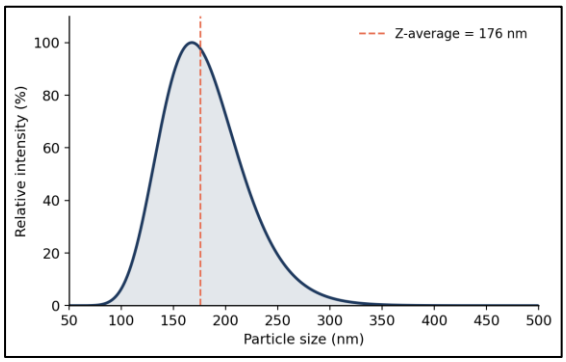

Figure 1. Particle size distribution of the optimised amlodipine-loaded chitosan nanoparticles (batch NP3) measured by dynamic light scattering.

3.3 Drug–excipient compatibility

FTIR spectra of the physical mixture and the nano-loaded film retained the principal characteristic absorption bands of amlodipine without the appearance of new peaks or significant shifts, indicating the absence of chemical interaction between the drug and the formulation excipients. In the DSC thermograms, the sharp melting endotherm of crystalline amlodipine was markedly broadened and reduced in the nanoparticle and film samples, consistent with molecular dispersion and partial amorphisation of the drug within the chitosan matrix [16,20]. Together these results confirmed that amlodipine was compatible with, and successfully entrapped in, the carrier system.

3.4 Physicochemical and mechanical properties of films

All films were thin, flexible, smooth and homogeneous. Increasing the HPMC:Carbopol ratio improved flexibility and swelling but, beyond an optimum, reduced mechanical strength. The optimised nano-loaded film (F3) balanced these attributes (Table 3): surface pH (6.8) was close to that of saliva, minimising the risk of mucosal irritation; folding endurance exceeded 220, indicating good flexibility; and mucoadhesive strength (26.4 g) was higher than that of the plain film. Drug content of all films was uniform (97–99%). Notably, nano-loaded films swelled more and adhered more strongly than the plain film, reflecting the additional hydrophilicity and cationic charge contributed by the chitosan nanoparticles.

Table 3. Physicochemical, mechanical and mucoadhesive properties of nano-loaded films (F1–F4) and the plain drug film (FP) (mean values, n = 3). opt. = optimised.

Parameter	F1	F2	F3 (opt.)	F4	FP (plain)
Thickness (mm)	0.21	0.23	0.24	0.26	0.22
Weight (mg)	62.4	65.1	66.8	69.2	61.0
Folding endurance	186	205	224	231	198
Surface pH	6.6	6.7	6.8	6.9	6.7
Tensile strength (N/mm²)	1.62	1.74	1.86	1.71	2.05
Elongation (%)	18.4	21.2	24.6	27.1	16.8
Swelling index (%)	118	131	142	158	104
Drug content (%)	97.4	98.1	98.6	98.0	97.9
Mucoadhesive strength (g)	21.0	23.6	26.4	25.1	19.2

3.5 In vitro drug release

Pure amlodipine dissolved rapidly, releasing almost completely within 3–4 h, and the plain film released ≈99% within 8 h with an initial burst. In contrast, the nano-loaded film (F3) displayed a markedly sustained profile, releasing 12% in the first 30 min and 93% over 8 h (Figure 2). The release from F3 best fitted the Korsmeyer–Peppas model ($R^2 > 0.99$) with a diffusional exponent of $n \approx 0.62$, indicating anomalous (non-Fickian) transport governed by both drug diffusion through the nanoparticle and polymer matrix and matrix swelling/erosion

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[21,22,23]. The slower, controlled release from F3 reflects the additional diffusional barrier imposed by encapsulation within the chitosan nanoparticles.

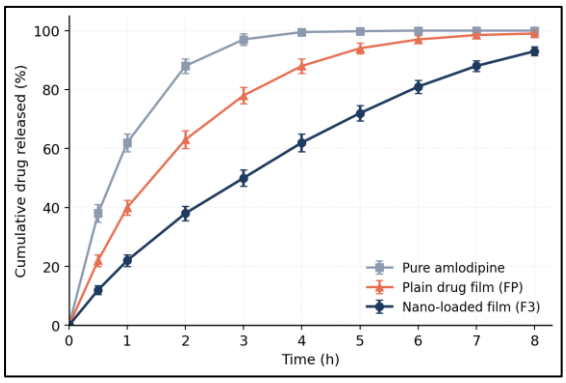

Figure 2. In vitro release profiles of pure amlodipine, the plain drug film (FP) and the optimised nano-loaded film (F3) in PBS pH 6.8 (mean ± SD, n = 3).

3.6 Ex vivo permeation

Permeation across porcine buccal mucosa was substantially greater from the nano-loaded film than from the plain film (Figure 3). At 6 h, the cumulative amount permeated was 540 µg/cm² for F3 versus 285 µg/cm² for FP, corresponding to a ≈1.9-fold enhancement and a proportionally higher steady-state flux. The improved permeation is attributable to the intimate mucosal contact and large surface area of the nanoparticles and to the tight-junction-modulating, permeation-enhancing action of chitosan [7,15].

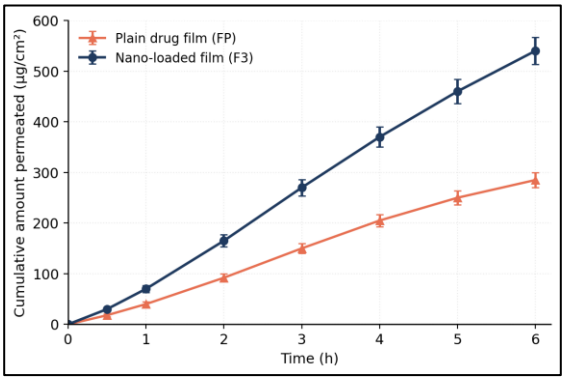

Figure 3. Ex vivo permeation of amlodipine across porcine buccal mucosa from the plain film (FP) and the optimised nano-loaded film (F3) (mean ± SD, n = 3).

3.7 In vivo pharmacokinetics

Plasma concentration–time profiles after buccal and oral administration are shown in Figure 4, and the derived pharmacokinetic parameters are listed in Table 4. The buccal nano-film produced a higher and earlier peak (C_{max} 7.6 ng/mL at T_{max} 3 h) than the oral suspension (4.2 ng/mL at 6 h), and a larger total exposure ($AUC_{0–\infty}$ 312 vs 168 ng·h/mL). The relative bioavailability of the buccal nano-film was approximately 186%, confirming a substantial improvement in systemic availability and a faster onset, while the elimination half-life remained essentially unchanged.

Table 4. Pharmacokinetic parameters of amlodipine in rabbits after buccal (F3) and oral administration (mean ± SD, n = 6).

Pharmacokinetic parameter	Oral suspension	Buccal nano-film (F3)
Cmax (ng/mL)	4.2 ± 0.4	7.6 ± 0.6
Tmax (h)	6.0	3.0
AUC0–∞ (ng·h/mL)	168 ± 15	312 ± 24
Elimination half-life (h)	35.1 ± 3.2	33.4 ± 2.9
Relative bioavailability (%)	100 (reference)	≈186

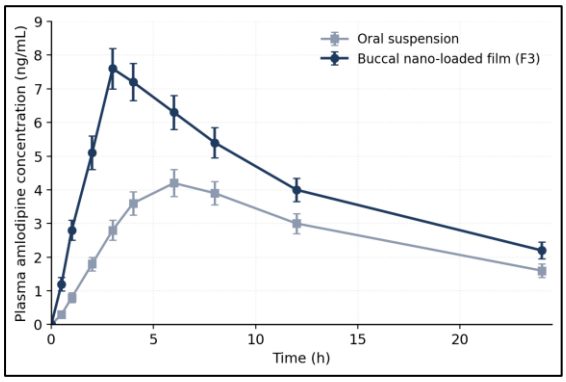

Figure 4. Mean plasma amlodipine concentration–time profiles after administration of the buccal nano-loaded film (F3) and an oral suspension in rabbits (mean ± SD, n = 6).

4. Discussion

The findings demonstrate that incorporating amlodipine-loaded chitosan nanoparticles into a mucoadhesive buccal film yields a delivery system that releases the drug in a controlled fashion, permeates the buccal mucosa efficiently and improves systemic bioavailability. The ionic gelation method produced nanoparticles in a desirable size range under mild conditions, consistent with established reports that the spontaneous electrostatic interaction between cationic chitosan and anionic tripolyphosphate generates small, spherical particles [15,17]. The dependence of particle properties on the chitosan:TPP ratio observed here mirrors previous work: an optimal ratio maximises cross-linking density and surface charge while keeping particles small, whereas excess chitosan promotes aggregation and size growth [16]. The high positive zeta potential of the optimised batch (+35.1 mV) explains both its colloidal stability and its strong interaction with the negatively charged mucin layer.

The sustained release achieved by the nano-loaded film is a central advantage of the nano-in-film design. Whereas the plain film released the drug

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rapidly, encapsulation within nanoparticles introduced an additional diffusional barrier, slowing release and fitting an anomalous transport mechanism. A comparable shift from burst to sustained release upon nanoparticle incorporation was reported for propranolol-loaded films, where the nanoparticle-bearing films also showed greater swelling and mucoadhesion [12]. Such controlled release is clinically desirable for an antihypertensive intended for prolonged, steady action.

The most important outcome is the marked enhancement of mucosal transport and bioavailability. The ≈1.9-fold increase in ex vivo permeation and the ≈1.86-fold increase in AUC over the oral suspension can be attributed to several complementary mechanisms. First, the buccal route circumvents the extensive hepatic metabolism responsible for amlodipine's incomplete oral bioavailability [2,3,5]. Second, chitosan is a recognised permeation enhancer that transiently loosens epithelial tight junctions and increases paracellular transport, while its mucoadhesion prolongs the contact time available for absorption [6,7,15]. Third, the nanoscale dimensions provide a large interfacial area and localise a high drug concentration at the mucosal surface, increasing the driving force for permeation [10,11]. These mechanisms are consistent with the bioavailability gains reported for other nanoparticle-loaded buccal systems [12,13,14].

The mechanical and surface properties of the optimised film support its practical use. The surface pH close to neutrality reduces the likelihood of mucosal irritation [18], adequate folding endurance and elongation indicate the flexibility needed to conform to and withstand movement of the cheek, and the enhanced mucoadhesive strength conferred by HPMC, Carbopol and the cationic nanoparticles favours prolonged residence [6,19]. The faster T_{max} relative to the oral route is a further benefit, as the slow oral absorption of amlodipine delays the onset of antihypertensive action [2].

Some limitations should be acknowledged. The pharmacokinetic evaluation was performed in a small group of rabbits, whose buccal mucosa differs from that of humans, so clinical extrapolation requires caution. Long-term physical and chemical stability, taste acceptability, and reproducibility on scale-up were not addressed here and warrant further study. Future work should include a robust design-of-experiments optimisation, in vitro–in vivo correlation, and stability assessment under storage conditions to advance the formulation toward translation [9,11].

5. CONCLUSION:

Amlodipine-loaded chitosan nanoparticles were successfully prepared by ionic gelation and incorporated into HPMC/Carbopol mucoadhesive buccal films. The optimised nanoparticles were small, positively charged and efficiently loaded, and the optimised nano-loaded film exhibited favourable mechanical properties, a mucosa-compatible surface pH, strong mucoadhesion, sustained drug release and significantly enhanced ex vivo permeation. In vivo, the buccal nano-film increased both the peak plasma concentration and the total systemic exposure of amlodipine relative to an oral suspension, improving relative bioavailability to approximately 186% while accelerating onset. Nano-loaded mucoadhesive buccal films therefore represent a promising, patient-friendly platform for improving the bioavailability of amlodipine and may be applicable to other drugs limited by hepatic first-pass metabolism. Further optimisation, stability and clinical studies are recommended to confirm these findings.

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