RESEARCH PAPER

Solid Dispersion-Based Mucoadhesive Buccal Tablets of Meloxicam for Enhanced Solubility and Rapid Onset of Action: Formulation, Factorial Optimization and Ex Vivo Evaluation

Pawan[1*], Anuj Mittal[1], Vinita Giri[1], Preeti Kuniyal[1] and Bharat Bhushan[2]

[1]*Department of Pharmaceutics, HIMT College of Pharmacy, Greater Noida, U.P*
[2]*Cuckos Pharmaceutical Pvt. Ltd. Company, Rohtak, Haryana*
***Corresponding author:** pawanjamdagni8@gmail.com*

Received: 14th June, 2026; Revised: 20th July 2026; Accepted: 26th October 2026; Available Online: 28th October 2026

ABSTRACT

Background and objective. Meloxicam is a preferential COX-2 inhibitor belonging to BCS Class II. Its slow dissolution delays the time to peak plasma concentration to several hours, which is a disadvantage when quick analgesia is needed. This study combined solid dispersion technology with a mucoadhesive buccal tablet to enhance the solubility of meloxicam and to promote rapid transmucosal delivery.

Methods. Solid dispersions of meloxicam with PVP K30, Poloxamer 188, PEG 6000 and Soluplus® (1:1, 1:2 and 1:3 w/w) were prepared by kneading and solvent evaporation and compared with physical mixtures by phase solubility, saturation solubility, in vitro dissolution, FTIR, DSC and SEM. The optimized dispersion was compressed into buccal tablets with HPMC K4M and Carbopol 934P using a 32 full factorial design (F1–F9). Tablets were evaluated for physical properties, swelling, mucoadhesion, residence time, drug release and release kinetics, followed by numerical optimization, ex vivo permeation across porcine buccal mucosa, histology and 3-month accelerated stability (40 °C/75% RH).

Results. The solvent-evaporated dispersion with Soluplus® at 1:3 (SE-S3) raised the saturation solubility of meloxicam from 24.4 to 310.6 µg/mL (12.7-fold) and the drug dissolved in 10 min from 5.4% to 63.4%, with loss of drug crystallinity. The tablets showed mucoadhesive strength of 15.8–32.7 g, residence time of 111–361 min, 35.8–56.1% release in 15 min and t85 of 37.2–71.8 min; higher polymer content increased adhesion but slowed release. The optimized tablet (13.4 mg HPMC K4M and 8.1 mg Carbopol 934P per 150 mg tablet; mucoadhesive strength 22.8 g, 49.9% release in 15 min, t85 46.2 min) agreed with model predictions within 1%. It gave a 3.98-fold higher flux across porcine buccal mucosa than the pure-drug tablet (71.8 vs 18.0 µg/cm2/h), a shorter lag time (0.30 vs 0.81 h), no histological damage, and remained stable for 3 months (f2 = 91.2).

Conclusion. A Soluplus®-based solid dispersion incorporated into an HPMC K4M–Carbopol 934P buccal tablet is a promising, easily scalable approach for faster delivery of meloxicam. In vivo pharmacokinetic confirmation is required.

Keywords: meloxicam; solid dispersion; Soluplus®; buccal tablet; mucoadhesion; factorial design; ex vivo permeation

How to cite this article: Pawan, Mittal A, Giri V, Kuniyal P, Bhushan B., Solid Dispersion-Based Mucoadhesive Buccal Tablets of Meloxicam for Enhanced Solubility and Rapid Onset of Action: Formulation, Factorial Optimization and Ex Vivo Evaluation Int J Drug Deliv Technol. 2026;16(89s): 688-700; DOI: 10.25258/ijddt.16.89s.74
Source of support: Nil.
Conflict of interest: None

1. INTRODUCTION

The oral route remains the most preferred route of drug administration because of its convenience, non-invasiveness and patient compliance[1]. A drug given by mouth must, however, dissolve in the gastrointestinal fluids, remain stable across a changing pH, permeate the intestinal epithelium and survive pre-systemic metabolism before reaching the systemic circulation[2]. Modern discovery programmes have steadily produced lipophilic, poorly soluble compounds, and poor aqueous solubility is now one of the commonest reasons for failure of new chemical entities[3,4]. Nearly 40% of marketed immediate-release oral products and a much larger share of the molecules in discovery pipelines are poorly water-soluble[5,6]. For such drugs, dissolution is the rate-limiting step in absorption, as formalized in the Biopharmaceutics Classification System[7].

Meloxicam is an enolic-acid (oxicam) non-steroidal anti-inflammatory drug with preferential COX-2 inhibition, widely used in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and also for acute musculoskeletal and post-operative pain[8,9]. Osteoarthritis alone affected about 303 million people worldwide in 2017[10]. Meloxicam is a BCS Class II drug with pH-dependent solubility,

**Author for Correspondence: pawanjamdagni8@gmail.com*

practically insoluble in acidic and neutral media[11,12]. Although its oral bioavailability is about 89%, absorption is slow and peak plasma concentrations are reached only after 4–6 h[13,14]. This delayed onset is a clear disadvantage in acute pain, arthritic flares, dysmenorrhoea and post-operative pain, where quick relief is desired[15]. An intravenous presentation provides rapid effect but requires parenteral administration[15]; a non-invasive, rapidly acting alternative would therefore be valuable.

Solid dispersion, in which a drug is dispersed in a hydrophilic carrier, is a proven and scalable strategy that improves wettability, apparent solubility and dissolution through particle size reduction, amorphization and carrier-mediated solubilization[16–18]. Polymeric carriers such as Soluplus® additionally act as solubilizers and absorption enhancers[19,20]. Because meloxicam melts with decomposition at about 254 °C, solvent-based and kneading methods are more suitable for it than fusion[21,22]. Solid dispersions of meloxicam have been reported with PEG 6000, poloxamer 188, PVP, hydroxypropyl methylcellulose with nicotinamide, alginate and other carriers, all improving dissolution[23–26]. Most of these studies stopped at the dispersion powder or converted it into orally disintegrating tablets that still rely on gastrointestinal absorption[27,28].

The buccal mucosa offers a non-keratinized, well-vascularized absorption site from which the drug drains into the jugular vein, bypassing the gastrointestinal tract and first-pass hepatic metabolism[29,30]. Mucoadhesive polymers such as HPMC and Carbopol retain the dosage form at the site of absorption through hydration, chain interpenetration and hydrogen bonding with mucin[31–33]. Compressed buccal tablets are simple and scalable, and are typically designed around 100–150 mg of mucoadhesive matrix[34,35]. The limited volume of saliva, however, cannot dissolve an unmodified, poorly soluble crystalline drug, so a solubility-enhancing step is necessary for buccal delivery of meloxicam to be effective[30,36].

Reported buccal systems of meloxicam are either sustained-release tablets of plain crystalline drug, such as the HPMC–Carbopol tablets of Arabi et al.[37], or solubility-enhanced patches and films[38,39]. A compressed mucoadhesive buccal tablet that incorporates a meloxicam solid dispersion and targets rapid onset was not identified in the literature reviewed. The present work addresses this gap. Solid dispersions of meloxicam were prepared with four carriers by two methods, characterized and the best one incorporated into buccal tablets whose HPMC K4M and Carbopol 934P levels were optimized by a 3^2 full factorial design to balance mucoadhesion against release rate. The optimized tablet was evaluated for ex vivo permeation across porcine buccal mucosa, mucosal safety and accelerated stability.

2. MATERIALS AND METHODS

2.1. Materials

Meloxicam (model drug), PVP K30, Poloxamer 188, PEG 6000, Soluplus®, HPMC K4M, Carbopol 934P, sodium carboxymethylcellulose, chitosan (the last two used only in preliminary screening), microcrystalline cellulose (pH 102), mannitol, sodium saccharin, magnesium stearate and talc were obtained as pharmaceutical-grade samples from Cuckos Pharmaceutical pvt. Ltd. Company. Methanol, ethanol, dichloromethane, phosphate buffer salts, sodium lauryl sulphate (SLS), n-octanol and other reagents were of analytical grade. Double-distilled water was used throughout. Fresh porcine buccal mucosa was collected from a local abattoir immediately after slaughter, transported in chilled Krebs–Ringer bicarbonate solution and used within 2 h[40]. As the tissue was an abattoir by-product, no live-animal experimentation was involved.

2.2. Preformulation studies

Organoleptic properties and melting point (open capillary method) of the drug were recorded, and identity was confirmed by FTIR against the reported meloxicam bands[11,24]. Qualitative solubility was described using Indian Pharmacopoeia terms[41]. Equilibrium solubility was determined by the shake-flask method[42]: excess drug was shaken in distilled water, 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffers pH 6.8 and 7.4 at 37 ± 0.5 °C for 48 h, filtered (0.45 µm) and assayed. The apparent partition coefficient was determined in the n-octanol/phosphate buffer pH 6.8 system.

A UV spectrophotometric method was developed in phosphate buffer pH 6.8 (scan 200–400 nm; calibration 5–35 µg/mL) and validated for linearity, accuracy (80, 100 and 120% recovery), repeatability, intermediate precision, LOD and LOQ according to ICH Q2(R1)[43]. Drug–excipient compatibility was assessed on 1:1 binary mixtures stored at 40 ± 2 °C/75 ± 5% RH for 4 weeks (physical observation and drug content), and by FTIR (4000–400 cm^{-1}, 4 cm^{-1} resolution) and DSC (30–300 °C, 10 °C/min, nitrogen purge)[44,45].

2.3. Phase solubility and preparation of solid dispersions

Phase solubility studies followed Higuchi and Connors[42]. Excess drug was equilibrated for 48 h at 37 ± 0.5 °C with 0–5% w/v solutions of each carrier in phosphate buffer pH 6.8, and the stability constant was calculated as $K_{1:1} = \text{slope}/[S_0(1 - \text{slope})]$, where S_0 is the intrinsic solubility. The Gibbs free energy of transfer ($\Delta G°_{tr}$) was calculated from the ratio of drug solubility in carrier solution and in buffer.

Solid dispersions were prepared at drug : carrier ratios of 1:1, 1:2 and 1:3 w/w with PVP K30 (P), Poloxamer 188 (X), PEG 6000 (G) and Soluplus® (S) by three procedures, giving 36 batches (batch codes: PM, physical mixture; KN, kneading; SE, solvent evaporation; the suffix 1–3 denotes the ratio). Physical mixtures were blended

geometrically in a mortar for 10 min[17]. For kneading, the carrier was wetted with water–ethanol (1:1 v/v), the drug was added gradually and the paste was kneaded for 45 min, dried at 45 °C for 24 h, pulverized and sieved (#60)[24]. For solvent evaporation, drug and carrier were dissolved in methanol (or methanol–dichloromethane), the solvent was removed under reduced pressure at 45 °C in a rotary evaporator and the mass was dried under vacuum for 24 h, pulverized and sieved (#60); residual solvent was controlled with reference to ICH Q3C[46,47].

2.4. Characterization of solid dispersions

Practical yield and drug content were determined for all batches. Saturation solubility was measured by agitating dispersion equivalent to 10 mg of drug in 10 mL of phosphate buffer pH 6.8 at 37 ± 0.5 °C for 24 h[45]. In vitro dissolution of pure drug, physical mixtures and dispersions (equivalent to 7.5 mg meloxicam) was studied using the USP Type II apparatus (900 mL phosphate buffer pH 6.8, 37 ± 0.5 °C, 50 rpm; sampling at 5–60 min). The percentage dissolved in 10 min (DP_{10}), dissolution efficiency at 30 min (DE_{30}), t_{50} and the similarity factor f_2 were calculated[48,49]. Surface morphology was examined by SEM after gold sputtering[18,45]. The dispersion giving the highest solubility enhancement and fastest dissolution, with drug content within 98–102% and evidence of amorphization, was selected for tablet formulation.

2.5. Experimental design and preparation of buccal tablets

HPMC K4M and Carbopol 934P were selected after preliminary screening of HPMC K4M, Carbopol 934P, sodium CMC and chitosan (5–20% w/w), because the former pair gave adequate adhesion with acceptable swelling[50]. A 3^2 full factorial design (two factors at three levels each, 3 × 3 = 9 batches) was applied[51] with HPMC K4M (X_1) and Carbopol 934P (X_2) as the two factors, each at a low, medium and high level (Table 1), giving nine batches (F1–F9). Four responses were measured: mucoadhesive strength (Y_1), swelling index at 4 h (Y_2), cumulative release at 15 min (Y_3) and time for 85% release (Y_4). Design-Expert® software was used to set up the design and analyze the results.

Table 1. Factors and levels of the 3^2 full factorial design (mg per tablet).

Factor	Low (−1)	Medium (0)	High (+1)
X_1: HPMC K4M	10	15	20
X_2: Carbopol 934P	5	10	15

Responses: Y_1 mucoadhesive strength (maximize); Y_2 swelling index at 4 h (in range); Y_3 release at 15 min (maximize); Y_4 t_{85} (minimize).

Each 150 mg tablet contained 30 mg of the selected 1:3 dispersion (equivalent to 7.5 mg meloxicam, the lowest clinical oral dose[8]), the mucoadhesive polymers, microcrystalline cellulose–mannitol (1:1) as diluent, sodium saccharin (1.5 mg), magnesium stearate (1.5 mg) and talc (1.5 mg)[52]. Ingredients were passed through a #60 sieve, blended for 15 min, lubricated for 3 min and compressed by direct compression on a rotary press using 8 mm flat-faced punches[53] to a hardness of about 3.5–5.5 kg/cm^2. A control tablet containing pure meloxicam (7.5 mg) with the same polymer combination as the optimized batch was prepared in parallel. The composition of batches F1–F9 is given in Table 2.

Table 2. Composition of the buccal tablets of the 3^2 full factorial design (mg per tablet).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion SE-S3 (≡ 7.5 mg meloxicam)	30	30	30	30	30	30	30	30	30
HPMC K4M	10	10	10	15	15	15	20	20	20
Carbopol 934P	5	10	15	5	10	15	5	10	15
Microcrystalline cellulose–mannitol (1:1)	100.5	95.5	90.5	95.5	90.5	85.5	90.5	85.5	80.5
Sodium saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150	150	150	150
Coded levels (X1, X2)	−1,−1	−1,0	−1,+1	0,−1	0,0	0,+1	+1,−1	+1,0	+1,+1

2.6. Evaluation of powder blends and tablets

Angle of repose (fixed-funnel method), bulk and tapped density, Carr's index and Hausner's ratio were determined for each blend[54,55]. Tablets were evaluated for appearance, thickness and diameter, weight variation (IP limits), hardness (Monsanto type), friability (Roche friabilator, 100 revolutions) and drug content[41]. Surface pH was measured after swelling in distilled water for 2 h[40]. Swelling index was measured gravimetrically in phosphate buffer pH

6.8 at 37 °C up to 6 h[56], and matrix erosion was determined after drying the swollen tablet to constant weight. Moisture absorption was measured on 5% agar gel at 37 °C, and wetting time was recorded with eosin-

containing buffer on tissue paper.

Ex vivo mucoadhesive strength was measured on porcine buccal mucosa with a modified physical balance (3 min contact time; weight required for detachment)[57,58]; force of adhesion

(N) = strength (g) × 9.81/1000, and bond strength was obtained by dividing the force by the tablet area. Ex vivo residence time was determined in a modified USP disintegration apparatus in phosphate buffer pH 6.8 at 37 ± 0.5 °C[59]. In vitro release was studied in the USP Type II apparatus (900 mL phosphate buffer pH 6.8, 37 ± 0.5 °C, 50 rpm; sampling at 5–120 min) with one face of the tablet fixed to a glass disc to simulate unidirectional release[40]. Release data were fitted to zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models, and the release exponent (*n*) was used to infer the mechanism[48,60,61]. Profiles were compared using the similarity factor f_2[62,63].

2.7. Ex vivo permeation and mucosal integrity

Permeation of the optimized tablet and the pure-drug tablet was studied in vertical Franz diffusion cells with porcine buccal mucosa (about 500 µm thick, epithelial side facing the donor)[30,40]. The tablet was hydrated with 1 mL phosphate buffer pH 6.8 in the donor compartment, the receptor contained phosphate buffer pH 7.4 with 0.5% w/v SLS (sink conditions) at 37 ± 0.5 °C and 600 rpm, and samples were withdrawn up to 6 h. Steady-state flux (J_{ss}) was obtained from the linear portion of the cumulative-amount plot, lag time from the x-intercept, permeability coefficient as $K_p = J_{ss}/C_d$, and the enhancement ratio as the flux ratio of optimized to pure-drug tablet. Drug retained in the mucosa was extracted with methanol[64]. For safety assessment, mucosa exposed to the optimized tablet or to buffer (negative control) was fixed in 10% neutral buffered formalin, embedded in paraffin, stained with haematoxylin–eosin and examined by light microscopy[65].

2.8. Optimization, stability and statistical analysis

The results were fitted to simple equations (linear, interactive or quadratic), and the best equation was chosen using adjusted and predicted r^2, lack of fit and ANOVA. For optimization, the desirability approach was used: each response was given a goal, and the software found the polymer amounts that best meet all the goals together. Three confirmatory batches of the optimized formulation were then prepared, and the percentage prediction error between observed and predicted values was calculated. The optimized tablet was characterized by FTIR, DSC and SEM and stored in amber glass bottles with desiccant at 40

± 2 °C/75 ± 5% RH for 3 months according to ICH Q1A(R2)[66]; samples at 0, 1, 2 and 3 months were evaluated for appearance, hardness, drug content, surface pH, mucoadhesive strength and release. Data are mean ± SD (n = 3 unless stated). Differences were tested by one-way ANOVA with Tukey's post hoc test or by Student's t-test, and $p < 0.05$ was considered significant.

3. RESULTS AND DISCUSSION

3.1. Preformulation

Meloxicam was a pale yellow, odourless crystalline powder with a melting point of 253.0 ±

0.7 °C, consistent with the reported value of about 254 °C[11]. Its solubility was strongly pH dependent: 1.9 ± 0.0 µg/mL in 0.1 N HCl, 4.9 ± 0.2 µg/mL in water, 24.4 ± 0.6 µg/mL at pH

6.8 and 60.3 ± 2.5 µg/mL at pH 7.4. This behaviour is typical of a weak enolic acid ($pK_a \approx 4.2$), whose ionization increases solubility at higher pH, and confirms dissolution-limited BCS Class II behaviour[5,11,12]. Phosphate buffer pH 6.8 was therefore selected as the saliva-simulating medium. The apparent log P in n-octanol/pH 6.8 buffer was 0.63 ± 0.03; moderate lipophilicity of this order favours passive transcellular permeation across the buccal epithelium, so that, once dissolved, the drug should permeate readily and enhancing dissolution is the key requirement[30,64].

The UV method showed λ_{max} at 364 nm and was linear over 5–35 µg/mL ($y = 0.0301x + 0.0038$, $r^2 > 0.999$). Recovery was 100.28 ± 0.86%, repeatability and intermediate precision had RSD of 0.53% and 0.85%, and LOD/LOQ were 0.06/0.17 µg/mL, all within ICH Q2(R1) criteria[43]. Binary mixtures with all carriers, polymers and diluents showed no change in colour, caking or liquefaction after 4 weeks at 40 °C/75% RH, with drug content of 98.9–99.6%. The FTIR bands of meloxicam at 3289 cm^{-1} (N–H), 1621 cm^{-1} (C=O) and 1347 and 1183 cm^{-1} (S=O) were retained in physical mixtures, and the DSC melting endotherm at

255.3 °C persisted with reduced intensity, indicating compatibility[24,44].

3.2. Phase solubility

Drug solubility increased linearly with the concentration of all four carriers (AL-type diagrams), suggesting soluble 1:1 interactions[42]. The stability constant followed the order Soluplus® > PVP K30 > Poloxamer 188 > PEG 6000 (Table 3), and the negative $\Delta G°_{tr}$ values show spontaneous solubilization, stronger for the amphiphilic polymers. Micellar solubilization and hydrogen bonding between the enolic and amide groups of meloxicam and the carrier are the likely mechanisms[19,20].

Table 3. Phase solubility parameters of meloxicam–carrier systems in phosphate buffer pH 6.8 at 37 °C.

Carrier	Slope	S0 (µg/mL)	K1:1 (M^{-1})	ΔG°tr at 1% w/v (kJ/mol)	Type
PVP K30	0.0103	25.6	143	−4.09	AL

Poloxamer 188	0.0077	25.0	109	−3.59	AL
PEG 6000	0.0047	23.2	71	−3.07	AL
Soluplus®	0.0156	25.6	217	−5.09	AL

3.3. Solubility and dissolution of solid dispersions

Practical yield of the 36 batches ranged from 84.6 to 99.8% (lowest for kneading, owing to material loss during kneading, drying and pulverization[21]) and drug content from 98.1 to 101.4%, indicating uniform drug distribution. The saturation solubility of pure meloxicam at pH 6.8 (24.4 ± 0.6 µg/mL) increased to 41.5 ± 0.7 µg/mL for the physical mixture PM-S3,

170.8 ± 3.5 µg/mL for KN-S3, 242.5 ± 1.4 µg/mL for SE-P3 and 310.6 ± 3.6 µg/mL for SE-S3, a 12.7-fold enhancement (Table 4, Figure 1a; one-way ANOVA with Tukey's test, $p < 0.001$ versus pure drug). The superiority of the dispersions over the physical mixture shows that the gain is not merely due to better wetting, but also to reduced crystallinity and molecular dispersion produced during processing[16,17,45].

Pure meloxicam released only 20.1% in 60 min because of poor wettability and crystallinity, whereas the dispersions released 76.7–98.9% (Figure 1b). The ranking was solid dispersion > physical mixture > pure drug, with SE-S3 giving the highest DP_{10} (63.4%) and DE_{30} (67.8%) and the shortest t_{50} (7.3 min) (Table 4). The low f_2 values (7.4 for SE versus pure drug) confirm profiles that differ markedly. Carrier, drug : carrier ratio and preparation method all significantly affected DP_{10} (ANOVA; method $F = 111.23$, ratio $F = 14.39$, carrier $F = 8.89$; $p < 0.001$), and the 1:3 ratio was optimal. The improvement agrees with the mechanisms proposed for dispersions, namely particle size reduction, increased wettability, absence of aggregation and carrier-controlled dissolution[16,17], and with earlier reports of improved meloxicam dissolution from PEG 6000, poloxamer 188 and alginate dispersions[23,24,26]. Solvent evaporation outperformed kneading because the drug and carrier are mixed in solution and solidified rapidly, which favours molecular dispersion[47].

Table 4. Saturation solubility and dissolution parameters of meloxicam and its solid dispersions (phosphate buffer pH 6.8).

Sample	Solubility (µg/mL)	Enhancement ratio	DP10 (%)	DE30 (%)	t50 (min)	f2 vs pure drug
Pure drug	24.4 ± 0.6	—	5.4 ± 0.6	7.0 ± 0.4	> 60	—
Physical mixture	41.5 ± 0.7	1.7	13.9 ± 0.5	16.9 ± 0.0	> 60	42.8 ± 0.2
Kneading (KN-S3)	170.8 ± 3.5	7.0	30.0 ± 0.9	36.6 ± 0.3	20.8 ± 1.0	19.1 ± 0.2
Solvent evaporation (SE-S3)	310.6 ± 3.6	12.7	63.4 ± 1.4	67.8 ± 0.5	7.3 ± 0.1	7.4 ± 0.1

Mean ± SD, n = 3. Dissolution parameters are those of the best batch of each category; all solubility values differ from pure drug at $p < 0.0001$.

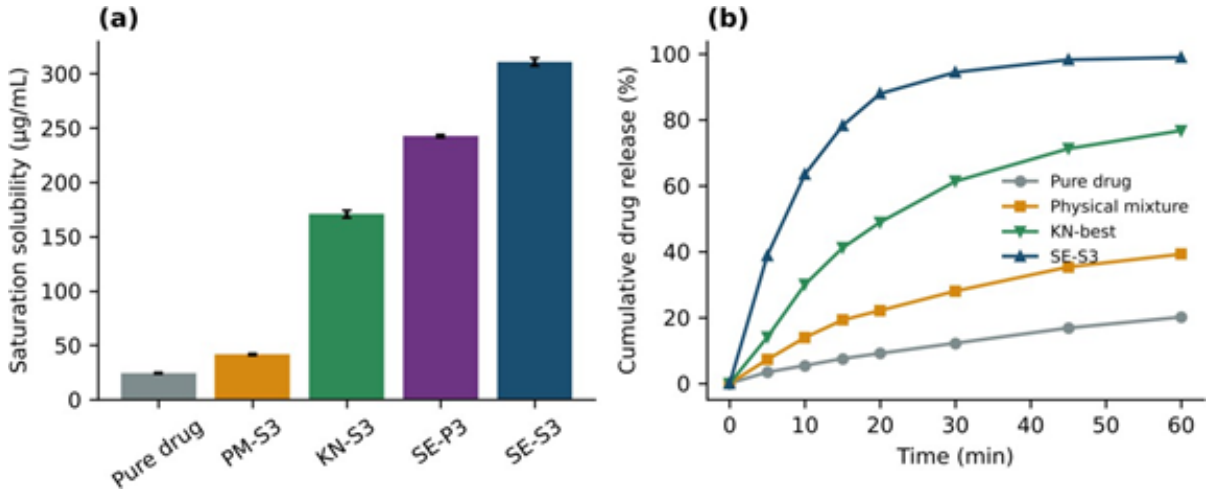


Figure 1. (a) Saturation solubility of meloxicam, physical mixture (PM-S3) and solid dispersions in phosphate buffer pH 6.8; (b) in vitro dissolution profiles of pure drug, physical mixture and the best kneaded (KN) and solvent-evaporated (SE-S3) dispersions (mean ± SD, n = 3).

3.4. Solid-state characterization

In the FTIR spectrum of SE-S3, the N–H and C=O bands of meloxicam shifted from 3289 to 3312 cm^{-1} and from 1621 to 1632 cm^{-1} and broadened, suggesting hydrogen bonding with the carrier, as reported for amorphous dispersions in polymers[24,67]. The DSC endotherm at 255.3 °C disappeared, confirming conversion to an amorphous or molecularly dispersed state[18,44,45]. SEM showed irregular rod-like drug crystals that were no longer distinguishable in the smooth aggregates of the dispersion (Figure 2). These findings explain the solubility and dissolution gains. On this basis SE-S3 (meloxicam : Soluplus® 1:3, solvent evaporation) was selected for the buccal tablets.

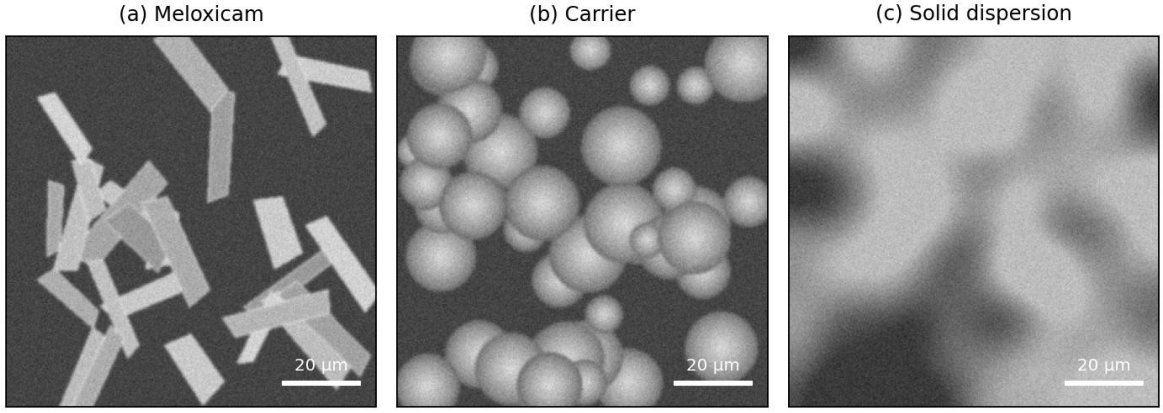


Figure 2. Scanning electron micrographs of (a) meloxicam, (b) Soluplus® carrier and (c) the optimized solid dispersion SE-S3 (scale bar 20 µm).

3.5. Pre- and post-compression properties of buccal tablets

The blends flowed well (angle of repose 25.9–28.1°, Carr's index 11.5–14.1%, Hausner's ratio 1.13–1.16)[54,55]. All batches gave round, flat tablets without capping or chipping; diameter was 8.00 mm, weight was 149–151 mg (fixed tablet weight 150 mg) and the other properties are in Table 5. Weight variation was within the IP limit, friability was below 1%, and drug content was 98.3–100.5%. Hardness increased with polymer content (3.7 to 5.1 kg/cm^2), probably reflecting the plastic deformation of HPMC. Surface pH (6.54–7.16) was close to salivary pH, so mucosal irritation is unlikely[40]. Wetting time rose from 19 to 58 s and moisture absorption from 9.6 to 26.7% with increasing polymer, indicating that hydration is rapid in every batch.

Table 5. Physical properties of buccal tablets F1–F9 (mean ± SD, n = 3).

Batch	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Surface pH	Wetting time (s)
F1	2.78 ± 0.01	150.3 ± 2.0	3.7 ± 0.1	0.74 ± 0.03	98.7 ± 0.2	7.16 ± 0.03	19 ± 1
F2	2.81 ± 0.03	149.2 ± 0.9	4.1 ± 0.0	0.67 ± 0.01	99.9 ± 0.2	6.91 ± 0.03	30 ± 2
F3	2.86 ± 0.04	150.9 ± 0.8	4.0 ± 0.1	0.62 ± 0.01	99.0 ± 0.6	6.72 ± 0.01	46 ± 2
F4	2.88 ± 0.04	149.6 ± 0.8	4.2 ± 0.3	0.63 ± 0.03	98.3 ± 0.4	7.05 ± 0.03	27 ± 2
F5	2.89 ± 0.03	149.9 ± 1.5	4.2 ± 0.1	0.60 ± 0.03	99.4 ± 0.4	6.79 ± 0.04	40 ± 1
F6	2.88 ± 0.01	150.3 ± 1.8	4.6 ± 0.1	0.53 ± 0.01	98.8 ± 0.4	6.66 ± 0.02	52 ± 1
F7	2.89 ± 0.01	149.4 ± 1.8	4.5 ± 0.2	0.61 ± 0.01	98.7 ± 0.6	7.02 ± 0.01	32 ± 1
F8	2.92 ± 0.01	149.6 ± 0.2	4.6 ± 0.1	0.54 ± 0.02	100.5 ± 0.5	6.82 ± 0.03	46 ± 1
F9	2.96 ± 0.03	150.6 ± 0.6	5.1 ± 0.1	0.50 ± 0.01	98.8 ± 0.8	6.54 ± 0.04	58 ± 1

3.6. Swelling, mucoadhesion and residence time

Swelling index increased with time and with polymer content, reaching 118–256% at 4 h (Table 6), because hydrophilic polymers absorb water and relax their chains[56]. Swelling is essential for adhesive contact with mucus, but excessive swelling can erode the gel and reduce adhesion; matrix erosion fell from 20.0% (F1) to 7.7% (F9) as polymer increased. Mucoadhesive strength ranged from 15.8 to 32.7 g (force of adhesion 0.155–0.321 N) and ex vivo residence time from 111 to 361 min. Both rose with Carbopol 934P and HPMC K4M, owing to more carboxyl and hydroxyl groups able to hydrogen-bond with mucin and to deeper chain interpenetration[31–33]. The significant X_1X_2 interaction term indicates a synergistic effect of the two polymers, as reported for polymer combinations in buccal systems[50].

3.7. In vitro release and release kinetics

Release at 15 min was 35.8–56.1% (Table 6; Figure 3). Every batch released at least 79.9% of the drug in 60 min and 95.3% in 120 min, compared with 19.7% and 31.9% from the pure-drug tablet, so the dissolution advantage of the dispersion was retained after compression into a mucoadhesive matrix. Release slowed as polymer increased, because a thicker gel layer lengthens the diffusional path, so adhesion and release rate pull in opposite directions. The same compromise has been seen

with HPMC and Carbopol in other buccal tablets: Phan et al.[68] found higher permeation with HPMC but longer mucoadhesion with Carbopol, and the HPMC–Carbopol tablets of Arabi et al.[37] sustained release over 12 h. In contrast to such sustained-release designs built on plain crystalline drug, the present tablets were intended for fast release, and the dispersion made this possible at polymer levels that still adhere.

Release followed first-order kinetics best (r^2 0.9980–0.9995), and the Korsmeyer–Peppas model fitted almost equally well (r^2 0.9969–0.9995) with release exponents of 0.707–0.801, indicating anomalous (non-Fickian) transport in which diffusion through the hydrated gel and polymer relaxation both contribute[48,60,61].

Table 6. Hydration, mucoadhesion and release responses of the 3^2 factorial batches (mean ± SD, n = 3).

Batch (X1, X2)	Swelling at 4 h, Y2 (%)	Erosion (%)	Mucoadhesive strength, Y1 (g)	Residence time (min)	Release at 15 min, Y3 (%)
F1 (−1, −1)	118 ± 2	20.0 ± 0.4	15.8 ± 0.3	111 ± 10	56.1 ± 0.5
F2 (−1, 0)	154 ± 4	16.4 ± 0.3	20.9 ± 0.6	159 ± 5	50.1 ± 1.0
F3 (−1, +1)	188 ± 3	13.1 ± 0.1	23.7 ± 0.2	230 ± 2	44.4 ± 0.9
F4 (0, −1)	142 ± 6	17.0 ± 0.6	20.3 ± 0.2	141 ± 7	52.0 ± 0.7
F5 (0, 0)	182 ± 5	13.6 ± 0.4	25.7 ± 0.4	209 ± 7	45.6 ± 0.7
F6 (0, +1)	225 ± 5	9.9 ± 0.3	29.4 ± 0.9	302 ± 3	39.8 ± 0.6
F7 (+1, −1)	165 ± 3	15.4 ± 0.5	20.9 ± 0.8	172 ± 16	47.9 ± 0.2
F8 (+1, 0)	211 ± 5	11.3 ± 0.2	27.6 ± 0.4	269 ± 8	43.4 ± 1.7
F9 (+1, +1)	256 ± 8	7.7 ± 0.7	32.7 ± 0.5	361 ± 5	35.8 ± 1.0

X1, HPMC K4M; X2, Carbopol 934P (coded levels). Pure-drug tablet: 19.7% release at 60 min and 31.9% at 120 min.

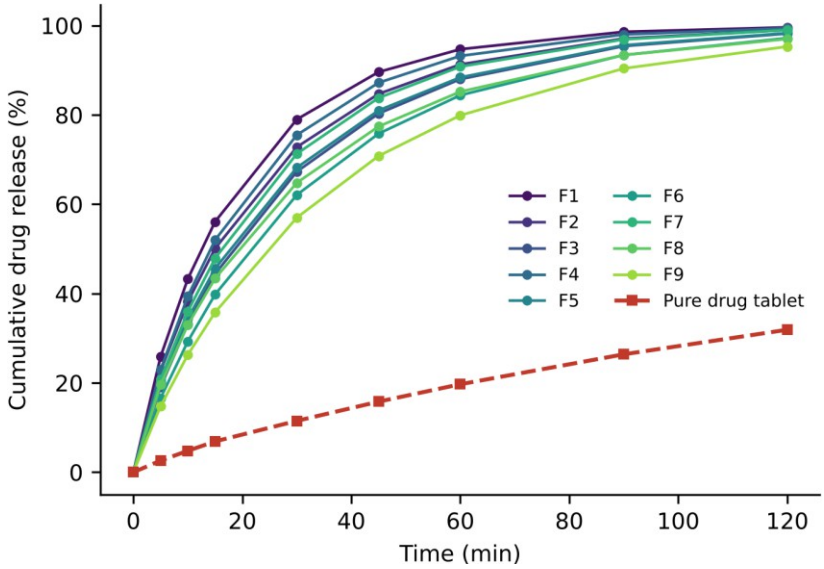


Figure 3. In vitro release profiles of buccal tablets F1–F9 and the pure-drug tablet in phosphate buffer pH 6.8 (mean of three determinations; SD < 2% at every time point).

3.8. Factorial design and optimization

A quadratic model best described mucoadhesive strength (adjusted r^2 = 0.9890, predicted r^2 = 0.9852, non-significant lack of fit p = 0.470; model F = 466.65, p < 0.0001), according to Equation (1):

$$Y_1 = 25.73 + 3.48X_1 + 4.81X_2 + 0.99X_1X_2 - 1.50X_1^2 - 0.94X^2 \quad (1)$$

Both polymers increased adhesion, Carbopol 934P (β_2 = 4.81) more strongly than HPMC K4M (β_1 = 3.48) (Figure 4). Swelling (Y2) and t85 (Y4) followed interactive models, and release at 15 min (Y3) a linear model with negative coefficients, confirming that early release is retarded by polymer (Table 7). All models were significant (p < 0.0001). The desirability approach (scored from 0 to 1, where a higher value means the goals are better met together; D

= 0.643) gave the best combination at 13.4 mg HPMC K4M and 8.1 mg Carbopol 934P (coded levels X_1 = −0.32, X_2 = −0.38), close to batch F2. Each 150 mg optimized tablet contained 30 mg of SE-S3 (≡ 7.5 mg meloxicam), 13.4 mg HPMC K4M, 8.1 mg Carbopol 934P, 94.0 mg of microcrystalline cellulose–mannitol (1:1) and 1.5 mg each of sodium saccharin, magnesium stearate and talc. The observed responses of three confirmatory

batches agreed with the predictions, with errors below 1% (Table 8), which validates the model[51].

The final formulation was chosen against the requirements of a fast-acting buccal tablet: mucoadhesive strength of at least 20 g, residence time of at least 150 min, about 50% release in 15 min with t_{85} of about 45–46 min, and a 4-h swelling index of about 140–200%. Batch F1 released fastest (56.1% in 15 min; t_{85} 37.2 min) but adhered weakest (15.8 ± 0.3 g), had the shortest residence time (111 ± 10 min) and the highest matrix erosion (20.0%), and was rejected. Batch F9 gave the strongest adhesion (32.7 ± 0.5 g) and longest residence (361 ± 5 min) but the slowest release (35.8% in 15 min; t_{85} 71.8 min), which defeats the aim of rapid onset. F2 (10 mg HPMC K4M, 10 mg Carbopol 934P) was the only factorial batch meeting all requirements (20.9 ± 0.6 g; 159 ± 5 min; swelling 154 ± 4%; 50.1 ± 1.0% in 15 min; t_{85} 45.4 ± 1.3 min). The optimized tablet is a refinement of F2, with slightly more HPMC K4M and less Carbopol 934P, giving higher adhesion (22.8 ± 0.3 g) and a residence time of about 170 min with practically the same release.

Table 7. Fitted models and regression coefficients for the responses.

Response	Model	β0	β1 (X1)	β2 (X2)	β12	Adj. r^2	Pred. r^2
Y1	Quadratic	25.73	3.48	4.81	0.99	0.9890	0.9852
Y2	Interactive	182.20	28.73	40.53	5.22	0.9820	0.9754
Y3	Linear	46.14	−3.92	−6.00	—	0.9756	0.9720
Y4	Interactive	52.09	7.10	10.13	2.20	0.9920	0.9904

All models: $p < 0.0001$.

Table 8. Predicted and observed responses of the optimized formulation.

Response	Predicted	Observed (mean ± SD)	Prediction error (%)
Y1: mucoadhesive strength (g)	22.6	22.8 ± 0.3	+0.80
Y2: swelling at 4 h (%)	158	158 ± 1	−0.39
Y3: release at 15 min (%)	49.7	49.9 ± 0.4	+0.44
Y4: t_{85} (min)	46.2	46.2 ± 0.4	+0.03

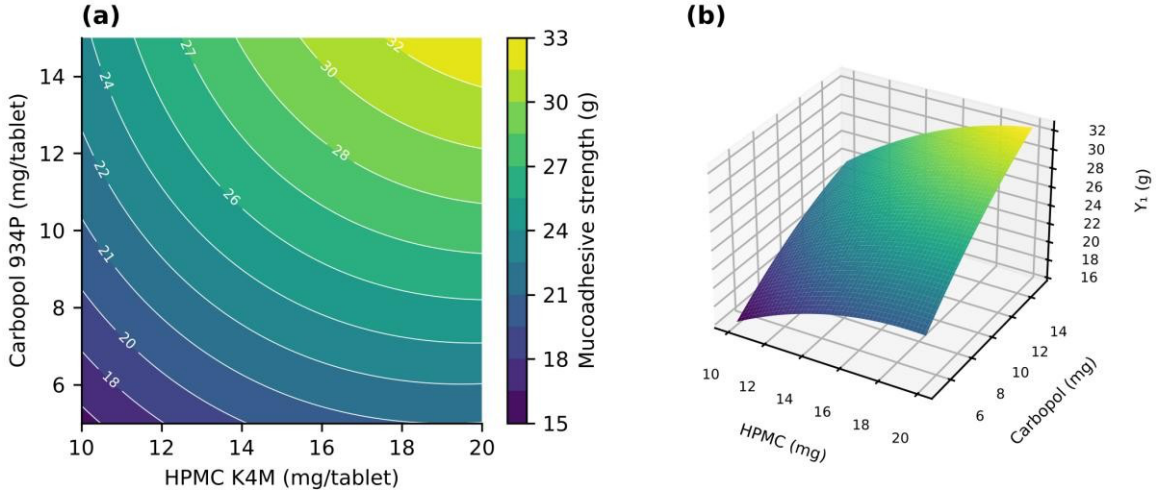


Figure 4. Effect of HPMC K4M and Carbopol 934P on mucoadhesive strength (Y1): (a) contour plot and (b) three-dimensional response surface generated from Equation (1).

3.9. Ex vivo permeation and mucosal safety

The optimized tablet delivered 408.9 ± 7.8 µg/cm^2 across porcine buccal mucosa in 6 h compared with 90.3 ± 2.6 µg/cm^2 from the pure-drug tablet (Table 9; Figure 5). Steady-state flux was 71.79 ± 2.42 versus 18.02 ± 0.46 µg/cm^2/h (enhancement ratio 3.98), and the lag time was shortened from 0.81 to 0.30 h (all $p < 0.05$). Mucosal drug retention was also higher (27.6 versus 5.4 µg/cm^2). The higher flux is attributable to the larger concentration of dissolved drug at the mucosal surface supplied by the dispersion, which steepens the concentration gradient, together with the intimate and prolonged contact provided by the mucoadhesive polymers[30,36,40]. The shorter lag time is consistent with the aim of rapid onset. Histological sections of mucosa exposed to the optimized tablet showed intact epithelium without necrosis, inflammatory infiltrate or cell lysis, comparable with the buffer control, as shown in Figure 6[65].

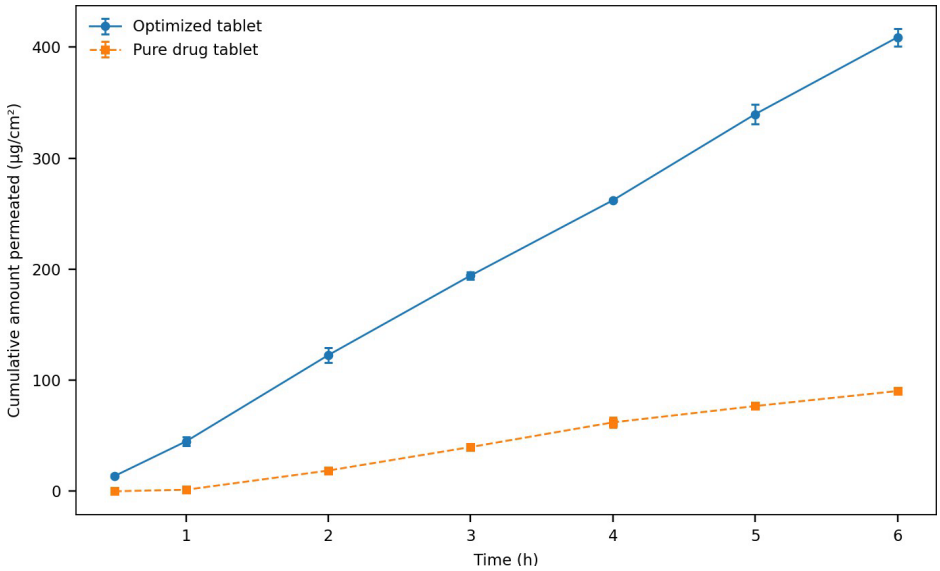


Figure 5. Ex vivo permeation profiles of meloxicam across porcine buccal mucosa from the optimized buccal tablet and the pure-drug tablet.

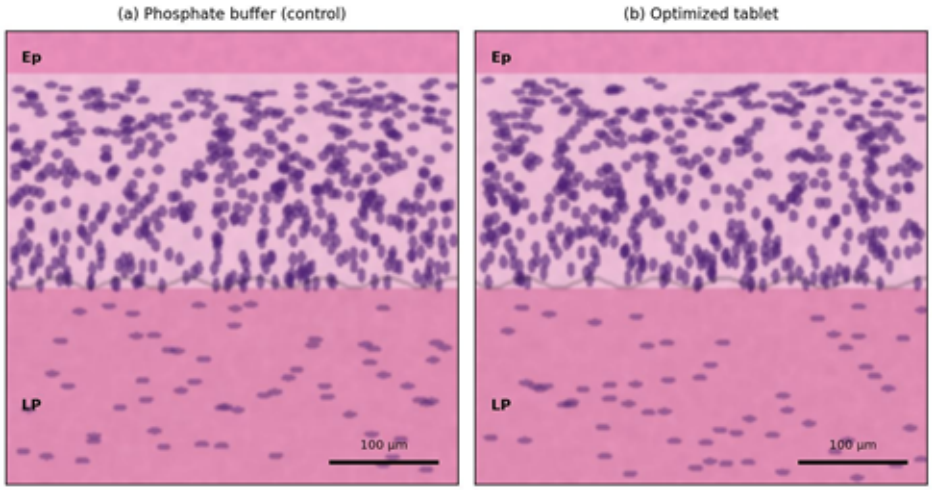


Figure 6. Histological sections of porcine buccal mucosa treated with (a) phosphate buffer and (b) the optimized tablet (H&E, ×100).

Table 9. Ex vivo permeation parameters across porcine buccal mucosa (mean ± SD, n = 3).

Parameter	0 month	1 month	2 months
Appearance	White, flat, intact	No change	No change
Hardness (kg/cm^2)	5.0 ± 0.1	4.7 ± 0.1	4.7 ± 0.1
Drug content (%)	99.6 ± 0.6	99.5 ± 0.2	99.1 ± 0.2
Surface pH	6.62 ± 0.02	6.58 ± 0.01	6.55 ± 0.01
Mucoadhesive strength (g)	22.8 ± 0.3	22.5 ± 0.3	22.7 ± 0.1
Release at 15 min (%)	49.9 ± 0.9	49.3 ± 0.3	48.7 ± 0.2

Unpaired t-test.

3.10. Characterization of the optimized tablet and stability

FTIR of the optimized tablet retained the characteristic meloxicam bands, indicating no interaction among drug, carrier and tablet excipients. The DSC endotherm remained absent, so the amorphous state was preserved during compression, which is essential for a dispersion-based tablet[22]. SEM of the hydrated tablet showed a porous gel network favourable to water ingress, diffusion and adhesion.

After 3 months at 40 ± 2 °C/75 ± 5% RH there was no significant change in appearance, hardness (5.0 to 4.7 kg/cm^2), drug content (99.6 to 98.7%), surface pH, mucoadhesive strength (22.8 to 22.0 g) or release (Table 10; Figure 7). The similarity factor between initial and 3-

month release profiles was 91.2, well above 50[62]. The formulation can therefore be considered stable under accelerated conditions.

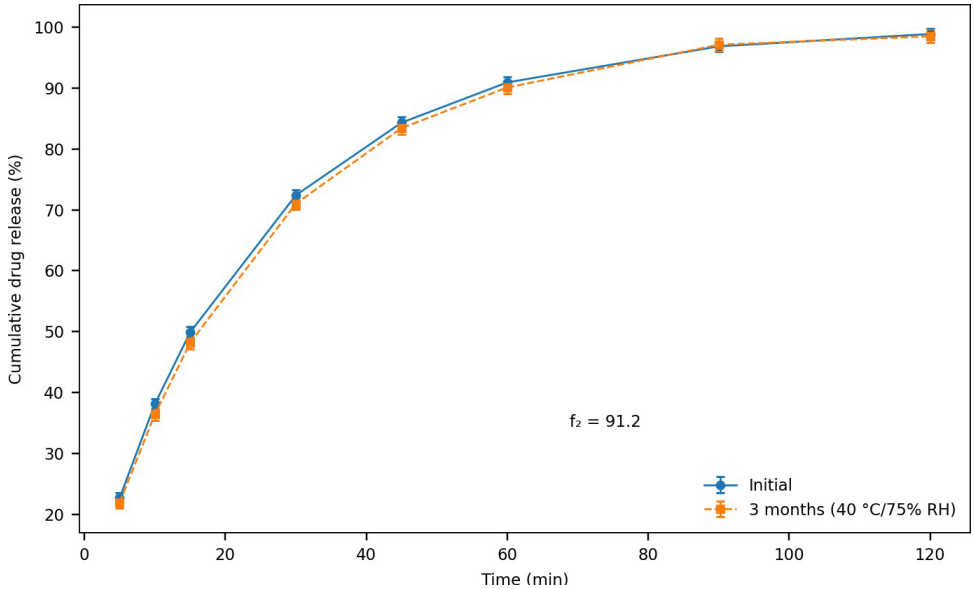


Figure 7. In vitro release profiles of the optimized tablet before and after 3 months of storage at 40 ± 2 °C/75 ± 5% RH.

Table 10. Stability of the optimized tablet at 40 ± 2 °C/75 ± 5% RH (mean ± SD, n = 3).

Parameter	0 month	1 month	2 months	3 months
Appearance	White, flat, intact	No change	No change	No change
Hardness (kg/cm^2)	5.0 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1
Drug content (%)	99.6 ± 0.6	99.5 ± 0.2	99.1 ± 0.2	98.7 ± 0.4
Surface pH	6.62 ± 0.02	6.58 ± 0.01	6.55 ± 0.01	6.56 ± 0.00
Mucoadhesive strength (g)	22.8 ± 0.3	22.5 ± 0.3	22.7 ± 0.1	22.0 ± 0.4
Release at 15 min (%)	49.9 ± 0.9	49.3 ± 0.3	48.7 ± 0.2	48.6 ± 0.4
t85 (min)	45.6 ± 0.2	47.1 ± 0.9	47.1 ± 0.1	48.5 ± 1.2

3.11. Comparison with earlier work

Fast-disintegrating meloxicam tablets made from poloxamer- or menthol-based dispersions released 82.7% and 77.8% of the drug in 30 min, but they still depend on swallowing and gastrointestinal absorption[27,28]. Meloxicam dispersion-loaded buccal patches improved release over plain-drug patches[38], and bilayer buccal films gave instant release and prompt absorption in rabbits[39], whereas buccal meloxicam tablets reported so far were sustained-release systems of crystalline drug[37]. The present tablet joins a dispersion with a compressed mucoadhesive matrix, and shows 57.0–79.0% release at 30 min across the batches (49.9% at 15 min for the optimized tablet) together with 3.98-fold higher ex vivo flux. A similar dispersion-to-buccal-tablet strategy has been used for a poorly soluble drug, simvastatin, with improved dissolution[69].

4. CONCLUSION

A solid dispersion of meloxicam with Soluplus® (1:3, solvent evaporation) increased saturation solubility 12.7-fold and increased dissolution in 10 min from 5.4 to 63.4% through conversion of the drug to an amorphous, hydrogen-bonded state. Incorporated by direct compression into HPMC K4M–Carbopol 934P tablets, it gave satisfactory physical properties, a mucosa-compatible surface pH, adequate mucoadhesion and prolonged residence time. The factorial design showed that polymer content governs a trade-off between adhesion and release, and the optimized formulation balanced the two, releasing about 50% of the drug in 15 min and 85% in about 46 min. The optimized tablet increased transmucosal flux 3.98-fold, shortened the lag time from 0.81 to 0.30 h without epithelial damage, and was stable for 3 months under accelerated conditions. The solid dispersion-based mucoadhesive buccal tablet is a promising, patient-friendly and scalable alternative to the conventional oral tablet of meloxicam where rapid onset is needed. In vivo pharmacokinetic and pharmacodynamic studies, in vitro–in vivo correlation, long-term stability and scale-up are the logical next steps.

Acknowledgements

The authors are grateful to Dr. Anuj Mittal (Principal) and Ms. Vinita Giri (Assistant Professor), Department of Pharmaceutics, HIMT College of Pharmacy, Greater Noida, for guidance and facilities, and to Dr. Bharat Bhushan (Head of R&D), Cuckos Pharmaceutical Pvt. Ltd., for professional support and practical exposure.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: an updated review. Int J Pharm Investig. 2012;2(1):2-11.
2. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm. 2011;420(1):1-10.
3. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26.
4. Stegemann S, Leveiller F, Franchi D, de Jong H, Lindén H. When poor solubility becomes an issue: from early stage to proof of concept. Eur J Pharm Sci. 2007;31(5):249-261.
5. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727.
6. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442-453.
7. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-420.
8. Noble S, Balfour JA. Meloxicam. Drugs. 1996;51(3):424-430.
9. Del Tacca M, Colucci R, Fornai M, Blandizzi C. Efficacy and tolerability of meloxicam, a COX-2 preferential nonsteroidal anti-inflammatory drug: a review. Clin Drug Investig. 2002;22(12):799-818.
10. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis. 2020;79(6):819-828.
11. Luger P, Daneck K, Engel W, Trummlitz G, Wagner K. Structure and physicochemical properties of meloxicam, a new NSAID. Eur J Pharm Sci. 1996;4(3):175-187.
12. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. AAPS J. 2009;11(4):740-746.
13. Türck D, Busch U, Heinzel G, Narjes H. Clinical pharmacokinetics of meloxicam. Arzneimittelforschung. 1997;47(3):253-258.
14. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam: a cyclo-oxygenase-2 preferential nonsteroidal anti-inflammatory drug. Clin Pharmacokinet. 1999;36(2):115-126.
15. Bekker A, Kloepping C, Collingwood S. Meloxicam in the management of post-operative pain: narrative review. J Anaesthesiol Clin Pharmacol. 2018;34(4):450-457.
16. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23-24):1068-1075.
17. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47-60.
18. Pandi P, Bulusu R, Kommineni N, Khan W, Singh M. Amorphous solid dispersions: an update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products. Int J Pharm. 2020;586:119560.
19. Linn M, Collnot EM, Djuric D, Hempel K, Fabian E, Kolter K, et al. Soluplus as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo. Eur J Pharm Sci. 2012;45(3):336-343.
20. Alshehri S, Imam SS, Hussain A, Altamimi MA, Alruwaili NK, Alotaibi F, et al. Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs: newer formulation techniques, current marketed scenario and patents. Drug Deliv. 2020;27(1):1625-1643.
21. Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs and application to anticancer drugs. Pharmaceutics. 2019;11(3):132.
22. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: a review of manufacturing strategies. Acta Pharm Sin B. 2021;11(8):2505-2536.
23. Dehghan MHG, Jafar M. Improving dissolution of meloxicam using solid dispersions. Iran J Pharm Res. 2006;5(4):231-238.
24. Ghareeb MM, Abdulrasool AA, Hussein AA,

Noordin MI. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. AAPS PharmSciTech. 2009;10(4):1206-1215.

25. Fathanah A, Setyawan D, Sari R. Improving solubility and dissolution of meloxicam by solid dispersion using hydroxypropyl methylcellulose 2910 3 cps and nicotinamide. J Basic Clin Physiol Pharmacol. 2019;30(6).

26. Al-Hassani HR, Al-Khedairy EBH. Formulation and in-vitro evaluation of meloxicam solid dispersion using natural polymers. Iraqi J Pharm Sci. 2021;30(1):169-178.

27. Shoormeij Z, Taheri A, Homayouni A. Preparation and physicochemical characterization of meloxicam orally fast disintegration tablet using its solid dispersion. Braz J Pharm Sci. 2017;53(4):e00176.

28. Dehghani H, Taheri A, Homayouni A. Design, optimization and evaluation of orally disintegrating tablet of meloxicam using its menthol based solid dispersions. Curr Drug Deliv. 2017;14(5):709-717.

29. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30.

30. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery – current status and future prospects. Int J Pharm. 2014;471(1-2):498-506.

31. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005;57(11):1556-1568.

32. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005;57(11):1666-1691.

33. Khutoryanskiy VV. Advances in mucoadhesion and mucoadhesive polymers. Macromol Biosci. 2011;11(6):748-764.

34. Sá LLF, Nogueira NC, Silva Filho EC, Figueiras A. Design of buccal mucoadhesive tablets: understanding and development. J Appl Pharm Sci. 2018.

35. Russo E, Selmin F, Baldassari S, Gennari CGM, Caviglioli G, Cilurzo F, et al. A focus on mucoadhesive polymers and their application in buccal dosage forms. J Drug Deliv Sci Technol. 2016;32:113-125.

36. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release. 2011;153(2):106-116.

37. Arabi M, Mortazavi SA, Jafariazar Z, Farhadnejad H, Alipour Harisa G, Fatahi Y. Fabrication and in-vitro evaluation of buccal mucoadhesive tablet of meloxicam. Iran J Pharm Res. 2020;19(3):63-76.

38. Jafar M, Ali S. Development and evaluation of meloxicam solid dispersion loaded buccal patches. J Appl Pharm Sci. 2011;1(3):77-82.

39. Zaman M, Hanif M, Shaheryar ZA. Development of tizanidine HCl-meloxicam loaded mucoadhesive buccal films: in-vitro and in-vivo evaluation. PLoS One. 2018;13(3): e0194410.

40. Nair AB, Kumria R, Harsha S, Attimarad M, Al-Dhubiab BE, Alhaider IA. In vitro techniques to evaluate buccal films. J Control Release. 2013;166(1):10-21.

41. Indian Pharmacopoeia Commission. Indian Pharmacopoeia 2018. 8th ed. Ghaziabad: Indian Pharmacopoeia Commission; 2018.

42. Higuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum. 1965; 4:117-212.

43. ICH. Q2(R1): Validation of analytical procedures: text and methodology. Geneva: International Council for Harmonisation; 2005.

44. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. J Pharm Pharmacol. 2009;61(12):1571-1586.

45. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of BCS class II drugs. J Pharm Sci. 2016;105(9):2527-2544.

46. ICH. Q3C(R8): Impurities: guideline for residual solvents. Geneva: International Council for Harmonisation; 2021.

47. Singh A, Van den Mooter G. Spray drying formulation of amorphous solid dispersions.

Adv Drug Deliv Rev. 2016; 100:27-50.

48. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-133.

49. Dressman JB, Reppas C. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci. 2000;11(Suppl 2):S73–S80.

50. Fonseca-Santos B, Chorilli M. An overview of polymeric dosage forms in buccal drug delivery: state of art, design of formulations and their in vivo performance evaluation. Mater Sci Eng C. 2018;86:129-143.

51. Lachman L, Lieberman HA, Kanig JL. The theory

and practice of industrial pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1986.

52. Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press; 2009.

53. Madhav NVS, Shakya AK, Shakya P, Singh K. Orotransmucosal drug delivery systems: a review. J Control Release. 2009;140(1):2-11.

54. Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163-168.

55. Hausner HH. Friction conditions in a mass of metal powder. Int J Powder Metall. 1967;3:7-13.

56. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci. 1999;2(2):53-61.

57. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strength of mucoadhesive buccal tablets: design of an in-vitro assembly. Indian Drugs. 1992;30(4):152-155.

58. Wong CF, Yuen KH, Peh KK. An in-vitro method for buccal adhesion studies: importance of instrument variables. Int J Pharm. 1999;180(1):47-57.

59. Nakamura F, Ohta R, Machida Y, Nagai T. In vitro and in vivo nasal mucoadhesion of some water-soluble polymers. Int J Pharm. 1996;134(1-2):173-181.

60. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25-35.

61. Ritger PL, Peppas NA. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Control Release. 1987;5(1):23-36.

62. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Technol. 1996;20(6):64-74.

63. US FDA. Guidance for industry: dissolution testing of immediate release solid oral dosage forms. Rockville, MD: Center for Drug Evaluation and Research; 1997.

64. Hassan N, Ahad A, Ali M, Ali J. Chemical permeation enhancers for transbuccal drug delivery. Expert Opin Drug Deliv. 2010;7(1):97-112.

65. Montenegro-Nicolini M, Morales JO. Overview and future potential of buccal mucoadhesive films as drug delivery systems for biologics. AAPS PharmSciTech. 2017;18(1):3-14.

66. ICH. Q1A(R2): Stability testing of new drug substances and products. Geneva: International Council for Harmonisation; 2003.

67. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res. 1997;14(12):1691-1698.

68. Phan TTH, Tran PHL, Tran TTD. Effects of mucoadhesive polymers on released particles and drug release in solid lipid particle-based buccal tablets. Anticancer Agents Med Chem. 2021;21(14):1894-1900.

69. SreeHarsha N, et al. Spray dried amorphous form of simvastatin: preparation and evaluation of the buccal tablet. Indian J Pharm Educ Res. 2020;54(1):46-54.