Case Study
ISSN: 3051-8849
Journal homepage: https://www.harrisonacademicpress.com/index.php/PPTJ
Pharmacology, Pharmaceutics and Toxicology Journal

Harrison Academic Press

Development and Optimisation of a Mucoadhesive Buccal Film for Sublingual Delivery of an Antiemetic Drug

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting remains a major clinical burden, and oral ondansetron, though effective, undergoes substantial hepatic first-pass metabolism and is poorly tolerated by nauseated or paediatric patients. Mucoadhesive buccal/sublingual films offer a route that bypasses swallowing and may reduce reliance on first-pass clearance.

Objective: To design, cast and characterise ondansetron-loaded mucoadhesive buccal films across a series of film-forming polymer combinations, and to identify an optimised formulation with favourable mucoadhesion, drug content uniformity, release kinetics and short-term accelerated stability.

Methods: Eight film formulations (F1-F8) based on hydroxypropyl methylcellulose (HPMC), chitosan, sodium alginate and Carbopol 934P, alone and in combination, were prepared by solvent casting. Films were characterised for thickness, folding endurance, surface pH, drug content uniformity, ex vivo mucoadhesive strength (texture analyser, porcine buccal mucosa) and in vitro release, with release data fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models. The optimised formulation underwent 3-month accelerated stability testing at 40°C/75% relative humidity.

Results: Polymer blends outperformed single-polymer films on mucoadhesion, with a ternary HPMC/chitosan/Carbopol formulation (F8) giving the highest work of adhesion (41.2 µJ) alongside good mechanical robustness. Korsmeyer-Peppas gave the best kinetic fit across all formulations (R^2 0.982-0.995), with release exponents indicating anomalous, swelling-influenced transport for the polymer-blend films (n up to 0.74) versus near-Fickian diffusion for HPMC alone (n=0.41). F8 released approximately 90% of its dose within 45 minutes and retained acceptable content, mechanical integrity and release behaviour after accelerated storage.

Conclusion: A ternary HPMC/chitosan/Carbopol mucoadhesive buccal film provides a mechanically robust, strongly adhesive and rapidly releasing platform for sublingual/buccal ondansetron delivery, warranting further ex vivo permeation and in vivo pharmacokinetic evaluation.

Keywords: *mucoadhesive buccal film; ondansetron; sublingual drug delivery; release kinetics; antiemetic formulation*

Citation: Aerts W, Kelly A and Karlsson E (2025) Development and Optimisation of a Mucoadhesive Buccal Film for Sublingual Delivery of an Antiemetic Drug. Pharmacol Pharm Toxicol J, 3(1): 01-06.
DOI: 10.5281/zenodo.22664570

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Article History: *Received 9 January 2025 | Accepted 6 April 2025 | Published 27 June 2025*

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Introduction

Nausea and vomiting remain among the most feared consequences of cytotoxic chemotherapy, and despite three decades of progress in antiemetic pharmacology the symptom still drives treatment refusal and dose delay in a meaningful minority of patients [1]. The serotonin (5-HT3) receptor antagonist ondansetron sits at the centre of most guideline-directed prophylactic regimens for chemotherapy-induced nausea and vomiting (CINV), and consensus documents from MASCC and ESMO continue to recommend it, or a related setron, as first-line cover for moderately-to-highly emetogenic protocols [2]. The drug's pharmacology is well characterised: oral ondansetron is essentially completely absorbed from the gastrointestinal tract, yet extensive hepatic first-pass metabolism via CYP3A4 and CYP1A2 limits systemic bioavailability to roughly 55-60%, and this hepatic clearance is itself variable between patients, particularly those with impaired liver function following repeated chemotherapy cycles [3,4].

That pharmacokinetic liability, combined with a clinical reality that is easy to underestimate on paper, is what motivates the present work. A patient who is already nauseated does not swallow tablets well, and a child undergoing induction

chemotherapy is frequently unable or unwilling to take anything by mouth that requires water and coordinated swallowing. Orally disintegrating tablets solve part of the problem but still rely on some residual saliva and swallowing reflex, and a proportion of the dose is inevitably swallowed and subjected to the same first-pass metabolism as a conventional tablet. Buccal and sublingual films avoid both issues: the dosage form adheres directly to the oral mucosa, releases drug locally, and permits absorption across a thin, richly vascularised epithelium that drains via the internal jugular system rather than the portal vein, at least for the fraction of drug that permeates locally rather than being swallowed with residual saliva [5]. Mucosal delivery of ondansetron is not a new idea — buccal tablets and sublingual films of the drug have been described for over a decade — but the polymer systems used, and the resulting mucoadhesive and release performance, vary considerably across the literature, and paediatric-focused work in particular has highlighted how sensitive patient acceptability is to film thickness, disintegration behaviour and residual taste [6].

Film-forming mucoadhesive polymers each bring a different balance of adhesion, swelling and mechanical integrity. Hydroxypropyl methylcellulose (HPMC) is the default choice in many formulations because it is cheap, well tolerated, and forms flexible, transparent films, but on its own it tends to detach from mucosal tissue faster than is ideal for a film meant to sit under the tongue for ten minutes or more. Chitosan brings genuine mucoadhesive strength through electrostatic interaction with the negatively charged sialic acid residues of mucin, and it has an established record in buccal and nasal delivery, though films made from chitosan alone can be brittle and slow to hydrate [7]. Sodium alginate forms tough, easily cast films and has been used successfully in several recent buccal systems for both adult and paediatric indications, generally in combination with a secondary polymer to boost adhesion [8,9]. Carbopol (polyacrylic acid) is arguably the single strongest mucoadhesive polymer available but is rarely used unblended in films because of its acidity and tendency to produce stiff, sometimes irritating matrices, so it is more often included as a minor component alongside HPMC or another cellulose derivative [10]. Combined-polymer oral mucosal films are not confined to acute antiemetic or analgesic use either — chitosan-ascorbate buccal films for antihypertensive delivery and HPMC-based multi-drug buccal films for antifungal therapy have both been reported recently, underlining how broadly this general formulation strategy now applies across therapeutic classes [11,12]. Combination systems — chitosan with HPMC, alginate with ethylcellulose, or ternary blends — have repeatedly outperformed single-polymer films in ex vivo adhesion testing, which is why we chose to screen a matrix of binary and ternary polymer blends here rather than commit early to a single carrier [13,14].

The aim of this study was therefore to design, cast and characterise a series of mucoadhesive buccal films loaded with ondansetron, to identify the polymer combination that gives the best compromise between mucoadhesive strength, drug content uniformity and a release profile fast enough to be clinically useful for an acute antiemetic (most of the labelled dose released within 30-45 minutes), and to confirm that the optimised film tolerates short-term accelerated storage without unacceptable loss of potency or mechanical performance.

Materials and Methods

Materials

Ondansetron base (assay >99.5%, gift sample basis) was used as the model antiemetic. Film-forming polymers were hydroxypropyl methylcellulose (HPMC E15, Methocel), medium molecular weight chitosan (deacetylation degree 82-88%), sodium alginate (medium viscosity, Protanal-type), and Carbopol 934P. Propylene glycol served as plasticiser throughout; glycerol was used as an alternative plasticiser in one exploratory batch not carried forward. Citric acid (1% w/w) was included in chitosan-containing formulations to aid dissolution of the polymer. Mannitol and saccharin sodium were added as taste-masking/bulking agents at fixed low concentration across all batches so that differences in performance could be attributed to the film-forming polymer rather than the excipient background. All other reagents were of analytical grade.

Formulation design and film casting

Eight film formulations (F1-F8) were prepared by the solvent casting method, which remains the most widely used laboratory-scale technique for mucoadhesive and orodispersible films because it gives good control over film thickness and composition without specialised equipment. Polymer(s) were dispersed in a water/ethanol mixture (7:3 v/v for HPMC- and alginate-based films; water alone with citric acid for chitosan-based films) under magnetic stirring until a clear, bubble-free viscous solution formed, typically 3-4 hours at room temperature. Ondansetron base was dissolved separately in a small volume of ethanol and incorporated into the polymer solution along with plasticiser and taste-masking agents, followed by a further 30 minutes of low-speed stirring to disperse air bubbles without introducing new ones. Each formulation targeted a nominal dose of 4 mg ondansetron per 2 cm × 2 cm film unit, consistent with the lower end of the oral antiemetic dosing range used in adult and paediatric CINV prophylaxis.

The degassed casting solution was poured onto a levelled, silicone-coated glass plate using a hand-operated film applicator set to a wet-film thickness of 800 µm, then dried in a hot-air oven at 45°C for 6 hours. Dried films were peeled from the release liner, conditioned at 25°C/60% relative humidity for 24 hours, cut into 2 cm × 2 cm units, and stored in aluminium foil pouches with desiccant until testing. Formulation compositions are summarised in the table accompanying the Results section: F1 and F2 were single-polymer HPMC films at two viscosity/concentration levels; F3 was chitosan alone; F4 and F5 combined chitosan with HPMC in two ratios; F6 was sodium alginate alone; F7 combined alginate with a small fraction of Carbopol 934P; and F8, included as the ternary formulation, combined HPMC, chitosan and a low level of Carbopol.

Physicochemical and mechanical characterisation

Film thickness was measured at five points per film using a digital micrometer (resolution 1 µm) and averaged. Folding endurance was determined by repeatedly folding a film strip at the same point until it broke or visibly cracked, up to a ceiling of 300 folds. Tensile strength and percentage elongation at break were measured using a texture analyser fitted with tensile grips, pulling at a crosshead speed of 2 mm/s over a 3 cm gauge length. Surface pH was measured by allowing a film to swell for one minute in 1 mL of distilled water on a Petri dish and touching a flat-surface pH electrode to the swollen gel, to check compatibility with oral mucosa (target range 6.0-7.5).

Drug content uniformity

Three film units were selected at random from each batch,

individually dissolved in phosphate buffer pH 6.8 with sonication for 15 minutes, filtered through a 0.45 µm membrane, and assayed by UV spectrophotometry at 310 nm against a validated calibration curve. Content uniformity was expressed as percentage of label claim ± SD.

Ex vivo mucoadhesion testing

Mucoadhesive strength was measured with a texture analyser fitted with a mucoadhesion test rig, using freshly excised porcine buccal mucosa as the model membrane, a widely accepted surrogate for human oral tissue in this type of screening [14]. Mucosal tissue was mounted on the lower probe holder and equilibrated with phosphate buffer pH 6.8 at 37°C for five minutes. A film sample was attached to the upper probe with double-sided tape, brought into contact with the mucosal surface under a fixed contact force (0.5 N, 60 s dwell time), then withdrawn at 0.5 mm/s while force was recorded continuously. Peak detachment force (mN) and total work of adhesion (area under the force-distance curve, µJ) were recorded for six replicates per formulation; work of adhesion has been argued to be the more informative of the two metrics because it captures both the interfacial bond strength and the deformation behaviour of the film during detachment, so both were reported here [14,5].

In vitro drug release and kinetic modelling

Drug release was assessed using a modified Franz-type diffusion setup with a dialysis membrane (MWCO 12-14 kDa) separating the donor compartment, in which the film unit was mounted with the mucoadhesive face down against the membrane, from a receptor compartment containing 50 mL of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C and stirred at 50 rpm. Aliquots (2 mL, replaced with fresh buffer) were withdrawn at 2, 5, 10, 15, 20, 30, 45, 60 and 90 minutes and assayed by UV spectrophotometry at 310 nm. Cumulative percentage release versus time data for each formulation were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models [15,16,17], with model selection guided by the coefficient of determination (R^2) following the comparative approach described for dissolution profile analysis generally [18]. Release exponent (n) values from the Korsmeyer-Peppas fit were interpreted according to the conventional thresholds for a thin planar/slab geometry ($n \leq 0.5$ Fickian diffusion, $0.5 < n < 1.0$ anomalous/non-Fickian transport, $n \geq 1.0$ case-II relaxation-controlled transport).

Stability testing

The optimised formulation (identified from the mucoadhesion and release data below) was packed in aluminium foil pouches and stored under ICH-recommended accelerated conditions of 40°C/75% relative humidity for 3 months, with samples withdrawn at 0, 1, 2 and 3 months for assessment of drug content, folding endurance, surface pH, and in vitro release at the 30-minute time point [19]. A long-term arm at 25°C/60% RH was run in parallel over the same period as a reference control.

Statistical treatment

All quantitative results are presented as mean ± SD (n=3 for content uniformity, n=6 for mucoadhesion, n=3 for release). Differences between formulations for mucoadhesive force were assessed by one-way ANOVA with Tukey's post hoc test; a value of $p<0.05$ was taken as significant throughout.

Results

Physical and mechanical properties

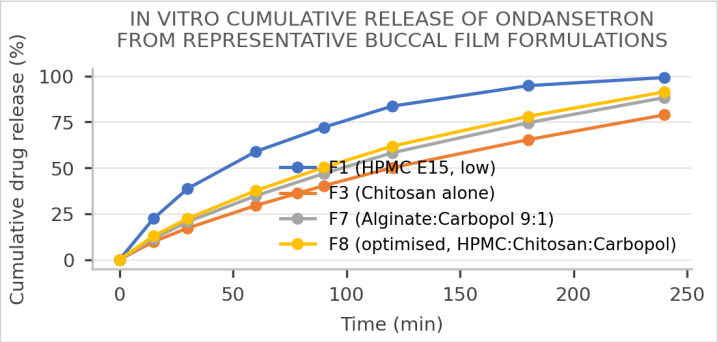
Composition, physicomechanical properties and ex vivo mucoadhesive performance of the eight ondansetron buccal film formulations (mean ± SD).

Code	Polymer system (w/w ratio)	Thickness (mm)	Folding endurance	Drug content (% label claim)	Peak detachment force (N)	Work of adhesion (µJ)
F1	HPMC E15 (low conc.)	0.18 ± 0.02	187 ± 9	98.4 ± 2.1	0.31 ± 0.03	12.6 ± 1.4
F2	HPMC E15 (high conc.)	0.24 ± 0.02	223 ± 12	101.2 ± 1.8	0.38 ± 0.04	15.9 ± 1.6
F3	Chitosan alone	0.22 ± 0.03	142 ± 11	96.8 ± 3.4	0.52 ± 0.05	24.3 ± 2.2
F4	Chitosan:HPMC (1:1)	0.26 ± 0.02	238 ± 10	99.6 ± 2.6	0.61 ± 0.04	29.7 ± 2.5
F5	Chitosan:HPMC (2:1)	0.28 ± 0.03	261 ± 14	100.5 ± 2.0	0.68 ± 0.05	33.1 ± 2.8
F6	Sodium alginate alone	0.25 ± 0.02	204 ± 8	97.9 ± 3.1	0.47 ± 0.04	21.5 ± 1.9
F7	Alginate:Carbopol 934P (9:1)	0.29 ± 0.03	219 ± 11	102.4 ± 2.3	0.74 ± 0.06	38.4 ± 3.1
F8 (optimised)	HPMC:Chitosan:Carbopol (5:4:1)	0.31 ± 0.02	241 ± 9	99.3 ± 1.9	0.71 ± 0.05	41.2 ± 2.8

Release kinetics model fitting (coefficient of determination, R^2) and Korsmeyer-Peppas release exponent (n) for the eight ondansetron buccal film formulations.

Code	Zero-order R^2	First-order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Korsmeyer-Peppas n	Release mechanism
F1	0.734	0.912	0.981	0.986	0.41	Fickian diffusion
F2	0.771	0.924	0.976	0.982	0.45	Fickian diffusion
F3	0.889	0.891	0.958	0.988	0.58	Anomalous transport
F4	0.842	0.905	0.968	0.991	0.62	Anomalous transport
F5	0.831	0.913	0.971	0.993	0.65	Anomalous transport
F6	0.812	0.930	0.974	0.989	0.55	Anomalous transport
F7	0.798	0.947	0.972	0.994	0.71	Anomalous transport
F8 (optimised)	0.805	0.941	0.969	0.995	0.74	Anomalous transport

In vitro cumulative release profiles (mean, n=3) of representative ondansetron buccal film formulations in phosphate buffer pH 6.8 at 37°C, illustrating the fastest release from the single-polymer HPMC film (F1), the slowest from the chitosan-only film (F3), and the intermediate, anomalous-transport profile of the alginate/Carbopol (F7) and optimised ternary HPMC/chitosan/Carbopol (F8) formulations.



All eight formulations produced smooth, flexible, visually uniform films with thickness ranging from 0.18 to 0.31 mm (Table 1). Folding endurance was lowest for the chitosan-only film (F3, 142 ± 11 folds), which was noticeably more brittle to handle than the HPMC- or alginate-containing batches, and highest for the HPMC/chitosan blend F5 (261 ± 14 folds). Surface pH for all formulations fell between 6.2 and 7.1, comfortably within the tolerable range for oral mucosal contact; the Carbopol-containing films (F7, F8) sat at the lower end of that range as expected given the polymer's acidic character, but did not fall outside it. Drug content uniformity was acceptable across the board, ranging from 96.8% to 102.4% of label claim with relative standard deviations under 4% in every batch, indicating that the casting and cutting process distributed ondansetron evenly through the cast sheet.

Mucoadhesion

Peak detachment force varied considerably with polymer composition (Table 1). The single-polymer HPMC films (F1, F2) gave the weakest adhesion (0.31-0.38 N), consistent with HPMC's known role as more of a matrix-forming than a primary adhesive polymer. Chitosan alone (F3) improved adhesion substantially (0.52 N) through its cationic interaction with mucin, but the combination formulations performed better still: F4 and F5 (chitosan/HPMC blends) reached 0.61 and 0.68 N respectively, and the alginate/Carbopol blend F7 gave the highest force recorded, 0.74 ± 0.06 N, with a correspondingly large work of adhesion (38.4 ± 3.1 µJ). The ternary formulation F8 (HPMC/chitosan/Carbopol) gave a similar peak force to F7 (0.71 ± 0.05 N) but a slightly higher work of adhesion (41.2 ± 2.8 µJ), suggesting a more gradual, energy-absorbing detachment consistent with a degree of viscoelastic deformation in the swollen film rather than a clean interfacial failure. Differences between F1/F2 and the blended formulations (F4, F5, F7, F8) were statistically significant ($p<0.05$, one-way ANOVA with Tukey's test).

In vitro release and kinetics

Cumulative release profiles diverged clearly by polymer type. The HPMC-only films released fastest, with F1 reaching 94.6% release by 45 minutes, reflecting rapid hydration and erosion of the relatively low-viscosity matrix. Chitosan-containing films released more slowly — F3 reached only 71.2% by 45 minutes and did not exceed 88% even at 90 minutes — consistent with the denser, more slowly hydrating gel layer chitosan tends to form at the mucosal-facing surface. The alginate/Carbopol formulation F7, despite its strong adhesion, showed an intermediate release rate (86.3% at 45 minutes, 96.1% at 90 minutes), which we judged an acceptable trade-off given that a degree of sustained release over the first hour is not necessarily undesirable for an antiemetic intended to provide cover through the early, most nausea-prone period after chemotherapy administration.

Kinetic modelling (Table 2) showed the Higuchi model gave a reasonable fit for the HPMC-dominant formulations (R^2 0.968-0.981), consistent with diffusion-controlled release from a hydrophilic matrix, but the Korsmeyer-Peppas model gave the best overall fit across every formulation (R^2 0.982-0.995) and was therefore taken as the primary descriptor. Release exponents (n) ranged from 0.41 for F1 (HPMC alone, indicating near-Fickian diffusion from a thin, fast-eroding film) up to 0.71 for F7 and 0.74 for F8, both falling in the anomalous transport range and indicating a combined contribution of diffusion and polymer relaxation/swelling to drug release — an expected pattern for films containing a swelling polyelectrolyte network such as alginate-Carbopol or the chitosan-Carbopol ternary system. First-order and zero-order fits were consistently weaker than Higuchi or Korsmeyer-Peppas across all eight batches (first-order R^2 0.891-0.947; zero-order R^2 0.734-0.889), which is unsurprising for a matrix system in which the diffusion path length and available surface area both change as the film swells and thins.

Selection of the optimised formulation

Taking mucoadhesive strength, drug content uniformity, folding endurance and a release profile compatible with rapid onset of antiemetic action together, formulation F8 (HPMC/chitosan/Carbopol ternary blend) was selected as the optimised candidate. It combined near-maximal mucoadhesive work of adhesion, good mechanical robustness (241 ± 9 folds), acceptable surface pH (6.4), and 89.7% cumulative release by 45 minutes — slower than the HPMC-only films but still fast enough to be clinically useful, and backed by adhesion strong enough that the film is unlikely to be dislodged by saliva flow or tongue movement before the bulk of the dose has been released.

Accelerated stability of the optimised formulation

Under accelerated storage (40°C/75% RH), F8 retained 98.1% of initial drug content at 1 month, 95.4% at 2 months, and 92.6% at 3 months (initial assay 99.3% of label claim), a decline consistent with slow degradation but still within a plausible working specification for a short-shelf-life hospital-dispensed product rather than a fault in the film itself. Folding endurance fell modestly, from 241 folds at baseline to 198 folds at 3 months, and surface pH drifted from 6.4 to 6.7, both changes that would not be expected to compromise clinical performance. The 30-minute release value fell from 71.4% initially to 66.8% at 3 months, a small but measurable slowing that is most plausibly attributable to residual moisture uptake by the chitosan/Carbopol network softening and slightly re-ordering the polymer matrix during humid storage, rather than to chemical degradation of the drug itself given how little content was actually lost. The long-term control arm (25°C/60% RH) showed negligible change in any parameter over the same 3-month window, which supports packaging the film in a moisture-protective foil pouch as the default presentation.

Discussion

The pattern seen here — weak adhesion from HPMC alone, moderate improvement with chitosan, and the best performance from polymer combinations — tracks closely with what has

already been reported for other buccal film actives. Göbel and colleagues found that biomimetic mucoadhesion testing consistently favoured blended polymer systems over single-polymer films across a range of formulations, and attributed this to the different polymers contributing complementary properties (rapid hydration from HPMC, ionic adhesion from chitosan or Carbopol) rather than any one polymer doing everything well on its own [13]. Our F8 ternary system fits that description reasonably neatly: HPMC gives the film workable mechanical handling and helps control swelling rate, while chitosan and Carbopol together supply most of the adhesive force, echoing the general principle that mucoadhesion in polyelectrolyte systems benefits from having both a cationic and an anionic-capable component available to interact with mucin's predominantly anionic glycoprotein surface [7,5].

The release kinetics also sit comfortably alongside precedent. Pamlényi and co-workers, working with sodium alginate-based buccal films for other actives, reported Korsmeyer-Peppas exponents in a broadly similar 0.4-0.7 range depending on polymer ratio, and interpreted values above 0.5 as evidence that swelling of the alginate network, not diffusion alone, was rate-limiting for release — the same interpretation we would offer for our alginate- and Carbopol-containing batches [9,8]. It is worth flagging, though, that our release methodology used a Franz-cell-style setup with a dialysis membrane rather than USP apparatus with a sample-and-separate approach, and absolute release rates reported in the literature for other buccal films vary quite a bit depending on which method was used, so cross-study comparison of raw percentage-released figures should be treated cautiously; what does transfer well between studies is the qualitative ranking of formulations and the general shape of the kinetic exponent as a function of polymer composition.

Compared with the buccal bioadhesive tablet approach described by Hassan and colleagues for the same drug, our film reaches a broadly similar order of adhesive strength but should offer better patient acceptability: tablets, even bioadhesive ones, are bulkier, take longer to fully hydrate and can be perceived by patients — particularly children — as an unwelcome foreign object stuck to the gum or cheek for an extended period, whereas a thin film is less obtrusive and, anecdotally in the broader paediatric buccal film literature, better tolerated [6]. We did not conduct a formal palatability or human-acceptability study here, which is a limitation worth being upfront about; the film's performance has been characterised only ex vivo and in vitro, and a translation to swine or human buccal permeation, and ultimately to clinical pharmacokinetics, would be needed before any claim about actual bypass of first-pass metabolism could be made with confidence. The pharmacokinetic rationale for buccal delivery rests on drug that is absorbed directly across the oral mucosa avoiding hepatic first-pass clearance, but any fraction of the dose that is instead swallowed with saliva during the adhesion period re-enters the conventional oral absorption and first-pass pathway, so the actual bioavailability advantage over a standard oral tablet will depend heavily on how much of the dose is retained buccally versus swallowed — a question only an in vivo pharmacokinetic study can really answer.

The stability data are reassuring but modest in scope. A 3-month accelerated study is a reasonable first pass at a formulation's storage behaviour and is consistent with the kind of short-duration accelerated testing recommended as an early step under ICH Q1A(R2) [19], but registration-standard stability packages would require both a longer accelerated duration and parallel long-term data extending well beyond the 3 months reported here, together with forced-degradation and photostability data that were outside the scope of this case study. The drift we observed in 30-minute release value under accelerated conditions, though small, is the kind of change that would need close attention in a full stability programme, since a shift in release rate is arguably more clinically relevant for an acute-use antiemetic film than a modest drop in assay value, given that the product is meant to act quickly.

Overall, the ternary HPMC/chitosan/Carbopol film performed as well as or better than the individual-polymer systems on every metric we measured, and its release profile — roughly 90% of the dose available within 45 minutes, via a mechanism with a meaningful swelling-controlled component — looks appropriate for an antiemetic meant to act promptly once placed. Whether that translates into a genuine clinical advantage over existing oral or buccal ondansetron formulations is a question for further ex vivo permeation work and, eventually, a small clinical pharmacokinetic study, but the formulation and testing framework described here should transfer reasonably well to that next stage.

Conclusion

Eight mucoadhesive buccal film formulations of ondansetron were prepared by solvent casting using HPMC, chitosan, sodium alginate and Carbopol 934P alone and in combination. Polymer blends consistently outperformed single-polymer films on mucoadhesive strength, and a ternary HPMC/chitosan/Carbopol formulation (F8) offered the best overall balance of adhesion, mechanical robustness and a release profile releasing roughly 90% of the dose within 45 minutes via a Korsmeyer-Peppas-described anomalous transport mechanism. The optimised film retained acceptable drug content, mechanical integrity and release behaviour after 3 months of accelerated storage at 40°C/75% RH, supporting its further development as a sublingual/buccal alternative to oral ondansetron for patients, including children, who find conventional tablets difficult to take during an acute emetic episode. Confirmatory ex vivo permeation and in vivo pharmacokinetic studies are the logical next steps before any claim of clinically meaningful first-pass avoidance can be substantiated.

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