Atorvastatin-Loaded Mucoadhesive NLCs for Buccal Delivery: A Short Review

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***Abstract*—Atorvastatin calcium is one of the most widely prescribed lipid-lowering drugs, yet its absolute oral bioavailability is only about 14 % because of poor aqueous solubility, extensive presystemic metabolism by cytochrome P450 3A4 and intestinal efflux. The buccal mucosa offers a route that drains directly into the systemic circulation through the jugular venous system and therefore bypasses the hepatic first pass, but its usefulness is limited by short residence time and by the barrier properties of the non-keratinised epithelium. Nanostructured lipid carriers (NLCs), which are blends of solid and liquid lipids stabilised by surfactants, can increase the loading and apparent solubility of lipophilic drugs, and when dispersed in a mucoadhesive gel they may combine controlled release with prolonged mucosal contact. This short review summarises, from open online literature, the biopharmaceutical case for buccal delivery of atorvastatin, the anatomy and permeability of the buccal mucosa, the structure, composition and preparation of NLCs, the mechanisms and polymers of mucoadhesion, and the quantitative evidence available from NLC-based and statin-based buccal systems. Quality by design tools such as the Box-Behnken design and ex vivo permeation testing on porcine buccal mucosa are discussed as the practical route to a robust formulation. Current gaps, including the absence of in vivo pharmacokinetic data for an atorvastatin NLC buccal gel, are identified, and priorities for future work are proposed.**

***Index Terms*—Atorvastatin; nanostructured lipid carriers; buccal delivery; mucoadhesion; first-pass metabolism; Box-Behnken design; ex vivo permeation**

I. INTRODUCTION

Atorvastatin is a synthetic statin that lowers plasma cholesterol by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of hepatic cholesterol biosynthesis [1,2]. Inhibition of the enzyme reduces intracellular cholesterol in hepatocytes and increases the expression of low-density lipoprotein (LDL) receptors, so that circulating atherogenic lipoproteins fall. Atorvastatin is used for primary hypercholesterolaemia, mixed dyslipidaemia and for the primary and secondary prevention of cardiovascular events, and it is administered orally at doses of 10 to 80 mg once daily [2,3].

Despite this clinical position, the pharmacokinetics of oral atorvastatin are unfavourable. The approved prescribing information reports an absolute bioavailability of approximately 14 % for the parent drug, and the drug is extensively metabolised by CYP3A4 [3]. Reviews of its clinical pharmacokinetics attribute the low systemic exposure to a combination of presystemic gut-wall metabolism, hepatic first-pass extraction and limited dissolution of a poorly soluble compound [4,5]. High oral doses are therefore needed, and dose-related myopathy and transaminase elevation remain recognised adverse effects [2]. A recent review of non-oral statin systems lists limited bioavailability, statin-associated muscle symptoms and residual cardiovascular risk as the three main drivers for alternative routes, and specifically includes buccal and mucoadhesive delivery among the approaches under study [6].

The oral mucosa has been explored for systemic delivery for several decades. The buccal region has a rich vascular supply that drains into the internal jugular vein rather than the portal vein, so an absorbed drug reaches the systemic circulation without first passing through the liver [7,8]. Other attractions include ready accessibility, the possibility of removing

the dosage form to stop delivery, and lower enzymatic activity than the gastrointestinal tract [9,10]. The principal obstacles are the short residence of a dosage form under the continuous washing action of saliva and the modest permeability of the epithelium towards larger or lipophilic molecules [8,9].

Nanostructured lipid carriers (NLCs) are the second generation of lipid nanoparticles. By mixing a solid lipid with a liquid lipid, the particle matrix becomes deliberately imperfect, which allows higher drug loading and reduces the tendency of drug to be expelled during storage compared with solid lipid nanoparticles (SLNs) [11,12]. Incorporating an NLC dispersion into a mucoadhesive gel is an attractive way to combine the solubilising and release-controlling properties of the nanoparticle with the retentive properties of the polymer network [13,14].

This short review was prepared from open online resources, including publisher platforms, PubMed Central, drug-label repositories and monographs, and it brings together the information needed to judge whether a mucoadhesive NLC-based buccal gel is a rational strategy for atorvastatin. Sections 2 and 3 describe the drug and the buccal route; Sections 4 and 5 describe NLCs and mucoadhesive vehicles; Section 6 tabulates the quantitative evidence from related systems; Section 7 discusses formulation optimisation and ex vivo evaluation; and Sections 8 and 9 identify challenges and conclude.

II. ATORVASTATIN: PHARMACOLOGY, PHARMACOKINETICS AND THE CASE FOR A NON-ORAL ROUTE

2.1 Mechanism and clinical use

Atorvastatin is a competitive inhibitor of HMG-CoA reductase. Crystallographic work on the human enzyme in complex with statins has shown that the statin pharmacophore occupies the binding site of the substrate HMG-CoA and prevents its conversion to mevalonate, which explains both the potency and the selectivity of the class [1]. The liver is the main site of cholesterol synthesis and is therefore both the site of action and, through first-pass extraction, a major site of clearance. The therapeutic effect follows a once-daily regimen, in part because the pharmacologically active hydroxylated metabolites prolong the duration of HMG-CoA reductase inhibition well beyond the plasma half-life of the parent compound [2,3].

2.2 Pharmacokinetic profile

After oral administration, peak plasma concentrations are reached within one to two hours. The absolute bioavailability of the parent drug is approximately 14 %, while the systemic availability of HMG-CoA reductase inhibitory activity is around 30 %, reflecting the contribution of active metabolites [3]. Food lowers the rate and extent of absorption by about 25 % and 9 % respectively, although the LDL-cholesterol reduction is similar whether the drug is taken with or without food. Atorvastatin is more than 98 % bound to plasma proteins, is metabolised principally by CYP3A4 to ortho- and para-hydroxylated derivatives, and approximately 70 % of circulating inhibitory activity is attributed to these active metabolites. The plasma half-life of the parent drug is about 14 hours and that of the inhibitory activity is 20 to 30 hours [3]. These data are collected in Table 1.

Table 1. Biopharmaceutical characteristics of atorvastatin and their implications for buccal delivery

Parameter	Reported value or description	Relevance to buccal NLC gel design
Mechanism of action	Competitive inhibition of HMG-CoA reductase; increased hepatic LDL-receptor expression [1,2]	Pharmacological target is hepatic; systemic delivery must still reach the liver
Absolute oral bioavailability	Approximately 14 % (parent drug); about 30 % for HMG-CoA reductase inhibitory activity [3]	Principal justification for a route that bypasses hepatic first pass
Time to peak (oral)	1 to 2 hours [2,3]	Benchmark for the rate of buccal absorption
Food effect	Rate of absorption decreased by about 25 % and extent by about 9 % [3]	Buccal delivery is independent of gastric contents
Plasma protein binding	98 % or more [2,3]	Very lipophilic; suits lipid-matrix entrapment

Metabolism	CYP3A4/3A5; ortho- and para-hydroxylated active metabolites contribute about 70 % of circulating inhibitory activity [2,3]	Buccal absorption avoids intestinal and hepatic CYP3A4 on first passage
Elimination half-life	About 14 h (parent); 20 to 30 h (inhibitory activity) [3]	Supports once-daily buccal application if adequate flux is achieved
Usual oral dose range	10 to 80 mg once daily [2,3]	Limits the dose that a small buccal gel volume must deliver
Dose-related adverse effects	Myopathy; transaminase elevation greater than three times the upper limit of normal [2]	Lower effective dose is a potential benefit; hepatic exposure must be confirmed

2.3 Physicochemical limitations

Atorvastatin calcium is a lipophilic, poorly water-soluble compound with pH-dependent solubility, and it is usually classed in Biopharmaceutics Classification System (BCS) class II, in which dissolution rather than permeability limits absorption [4,5]. For this reason, solubilising lipid-based systems have been studied as a means of improving dissolution and biopharmaceutical performance. Ghanem and co-workers, for example, developed atorvastatin NLCs from Gelucire 43/01 as solid lipid and Labrasol as liquid lipid, stabilised with Tween 80 and lecithin, using a D-optimal screening design of 46 runs followed by a central composite design of 20 runs [5]. The optimised carrier had a particle size of 83.80 ± 1.13 nm, a polydispersity index of 0.38 ± 0.02, a zeta potential of −29.65 ± 0.65 mV and an entrapment efficiency of 93.1 ± 0.04 %; differential scanning calorimetry showed conversion of the drug from the crystalline to the amorphous state, and oral administration to rats significantly reduced serum total cholesterol, triglycerides and LDL ($p < 0.001$) with less hepatic steatosis than conventional suspensions [5]. These results confirm that atorvastatin is compatible with an NLC matrix and that lipid entrapment can be optimised systematically.

2.4 A note on hepatic targeting

The rationale for bypassing first-pass metabolism deserves one qualification. Because the liver is also the site of action of atorvastatin, first-pass extraction contributes to hepatic targeting as well as to clearance. Buccal delivery would alter the ratio of hepatic to systemic exposure, and the balance between improved bioavailability, a possibly lower dose and any change in extra-hepatic exposure can only be settled by pharmacokinetic and pharmacodynamic studies. The parenteral and alternative-route literature already cites statin-associated muscle symptoms as a reason for exploring other routes, which shows that the question is recognised in the field [6]. In the authors' view, the buccal proposition for atorvastatin should therefore be framed as a hypothesis to be tested rather than a demonstrated advantage.

III. THE BUCCAL MUCOSA AS A SITE FOR SYSTEMIC DRUG DELIVERY

3.1 Anatomy and histology

The oral mucosa is composed of an outer stratified squamous epithelium, an intermediate basement membrane and an inner connective tissue layer, the lamina propria, with a submucosa beneath it [15]. Regions differ in keratinisation: the gingiva and hard palate are keratinised, whereas the buccal and sublingual regions are non-keratinised and are consistently more permeable [15,16]. The buccal epithelium is described as non-keratinised, highly vascularised and of a surface area of about 50 cm^2, with a rapid rate of cellular turnover [17]. Membrane-coating granules extrude lipid material, including glycosylceramides, into the intercellular spaces of the upper epithelial layers, and this lipid domain is the principal restriction to paracellular passage of large hydrophilic molecules [16,17]. Isolated porcine buccal epithelial sheets prepared for permeation studies have been reported to be of the order of 500 μm thick [15,17].

3.2 Vascular drainage and avoidance of first pass

The submucosal venous plexus of the cheek drains through the facial and internal jugular veins into the superior vena cava, so that an absorbed molecule enters the general circulation without traversing the portal vein and liver [7,10]. Reviews of orotransmucosal delivery emphasise that the buccal, sublingual, gingival and palatal sites differ in surface area, permeability and residence potential, and

identify the buccal site as offering a favourable combination of accessibility, area and suitability for retentive dosage forms [8,10]. Drugs subject to extensive hepatic extraction, such as atorvastatin, are therefore natural candidates. Figure 1 contrasts the sequential barriers encountered by an oral tablet with the route followed by a mucoadhesive NLC gel applied to the cheek.

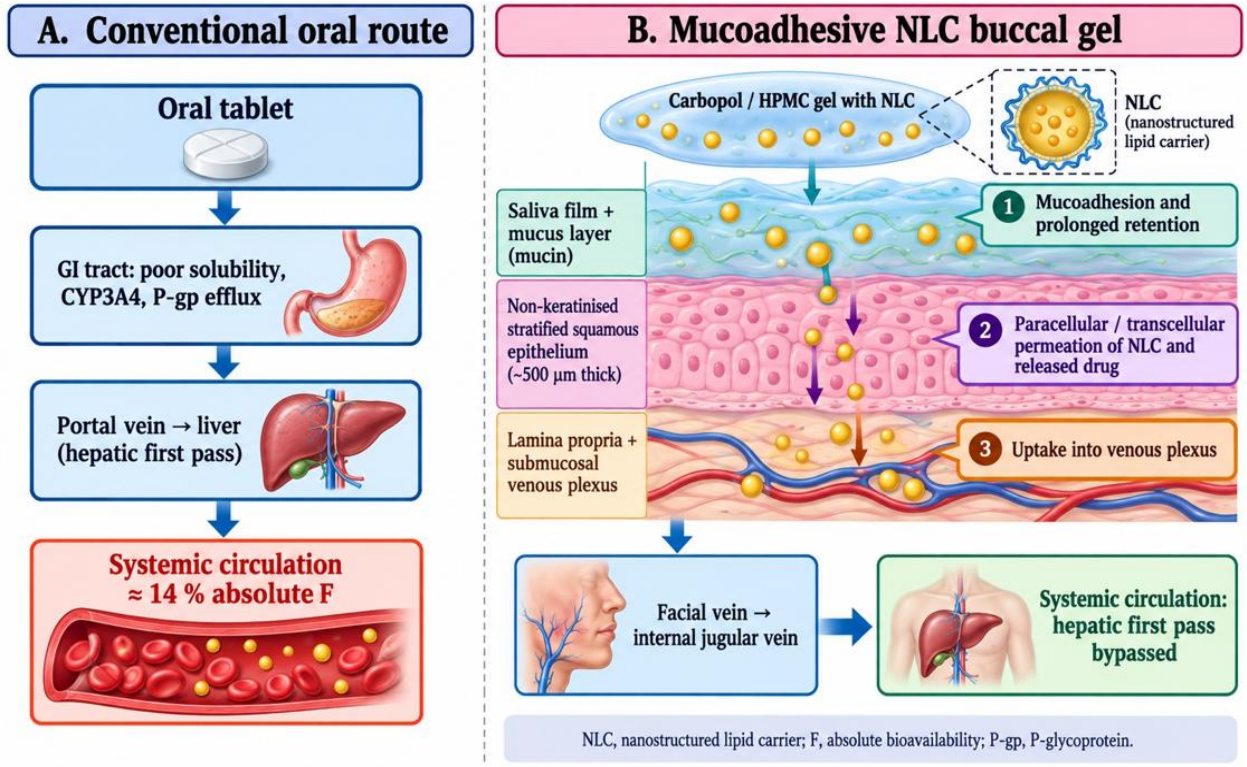


Figure 1. Conventional oral route (A) compared with the proposed route of a mucoadhesive NLC gel applied to the buccal mucosa (B). The absolute bioavailability of about 14 % is taken from the prescribing information [3]; the ~500 µm value refers to isolated ex vivo porcine epithelial sheets [15,17]. Schematic prepared by the authors.

3.3 Barriers to buccal absorption

Two categories of barrier limit buccal delivery. The first is physiological and concerns residence time. Continuous salivary secretion, tongue movement, swallowing and mastication tend to remove a dosage form from the site of application, and reviews of buccal bioadhesive delivery list the loss of the dosage form as a central design problem that mucoadhesive polymers are intended to address [8,9]. The second is anatomical and concerns the epithelial permeability barrier. The intercellular lipid domains restrict the paracellular route, and lipophilic molecules of low water solubility, such as atorvastatin, must also dissolve or be presented in molecular form at the mucosal surface before partitioning can occur [13,16]. Nanoparticle size and surface properties influence uptake into the epithelium, and Ortiz and Morales note that particle characteristics affect both epithelial uptake and the mechanism of transport [13].

Saliva also dilutes and can destabilise conventional aqueous vehicles. A gel with a rheology matched to the moist buccal environment, with adequate adhesion to the mucin layer, is therefore a logical vehicle for a nanoparticle dispersion. Compared with a film or tablet, a gel is easy to apply, can be adjusted in viscosity and spreadability, and holds the nanocarriers in intimate contact with the mucosa while allowing them to be released gradually [14,18].

3.4 Models used to study buccal permeability

A recent review of oral mucosa models notes that porcine buccal mucosa is the ex vivo tissue used most frequently, that rodent, rabbit, dog and human tissue have also been employed, and that carcinoma-derived

TR146 cells, although convenient, show barrier properties that differ from healthy epithelium: compounds such as mannitol and testosterone crossed the TR146 barrier faster than human mucosa [15]. Reconstructed oral mucosal equivalents composed of keratinocytes and fibroblasts show tight-junction formation and barrier properties closer to native tissue, but the authors conclude that no single standardised model is yet suitable for every purpose [15]. Kulkarni and co-workers examined porcine buccal mucosa in detail and showed that both the epithelium and the underlying connective tissue contribute to the overall barrier, the relative contribution depending on the properties of the permeant, which is why the way the tissue is prepared should be reported carefully in any permeation study [19].

IV. NANOSTRUCTURED LIPID CARRIERS

4.1 Concept and structural types

Solid lipid nanoparticles offered a biocompatible alternative to polymeric particles, but a highly ordered crystalline matrix tends to recrystallise on storage, which limits loading and can expel the drug. Müller and colleagues therefore proposed nanostructured lipid matrices in which spatially different lipid molecules are blended so that the crystal lattice is imperfect, providing space for drug and reducing expulsion [11]. Reviews describe three principal NLC models: the imperfect-crystal type, in which the disordered matrix contains many voids that accommodate drug molecules; the multiple type, an oil-in-solid-lipid-in-water system with oily nano-compartments that offers high entrapment and controlled release with minimal leakage; and the amorphous type, in which specific lipids give a non-crystalline particle that avoids polymorphic transitions [12,20]. The three types are illustrated together with a conventional SLN in Figure 2.

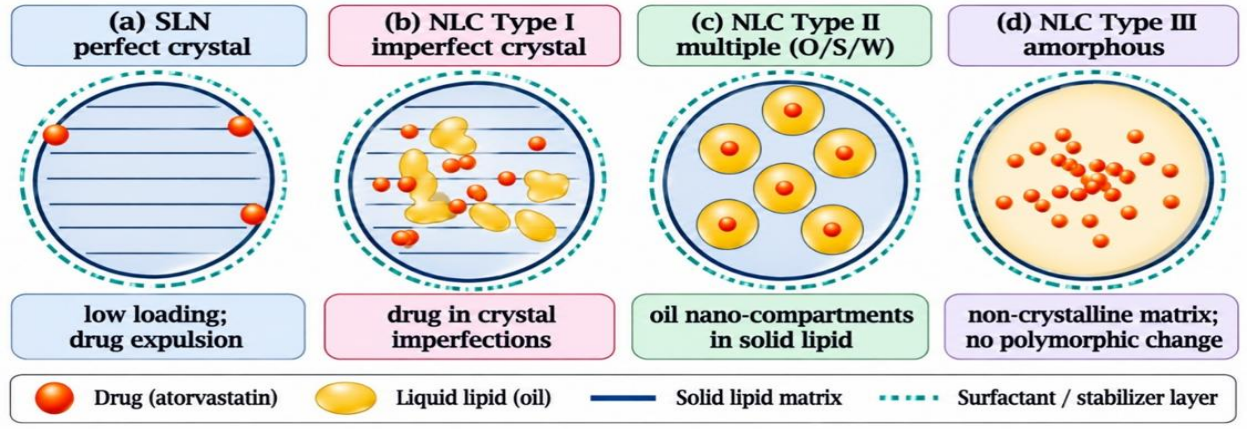


Figure 2. Structural models of lipid nanoparticles: (a) solid lipid nanoparticle with an ordered crystal lattice; (b) NLC Type I, imperfect crystal; (c) NLC Type II, multiple type; (d) NLC Type III, amorphous type [11,20]. Schematic prepared by the authors.

4.2 Composition

A typical NLC consists of a solid lipid, a liquid lipid, a surfactant or co-surfactant and an aqueous phase. Solid lipids reported for NLCs include beeswax, stearic acid, cetyl palmitate, Compritol 888 ATO, Precirol ATO 5 and tristearin; liquid lipids include Miglyol 812, oleic acid, castor oil, olive oil and coconut oil; and surfactants include Pluronic F68, Tween 80, polyvinyl alcohol, Solutol HS15 and soya or egg lecithin [20]. Many of these excipients have generally recognised as safe status or are already accepted for pharmaceutical or food use, which facilitates regulatory acceptance, and it is reported that more than thirty commercial NLC formulations are accessible in the market [20].

Excipient choice for the buccal route is guided by drug solubility in the lipid phase, lipid miscibility, and the effect of surfactants on the mucosa. In the buccal

permeation study of Vargas-Valderrama and Morales, the carrier was made from Gelucire 44/14 (600 mg), Miglyol 812 (150 mg) and Tween 80 (300 mg), and the authors attributed enhanced peptide transport partly to surfactant-induced perturbation of the epithelium and extraction of intercellular lipids, and partly to the lauric and caprylic acids released from Gelucire that disrupt lipid packing [17]. Marques and colleagues used Precirol ATO 5 as solid lipid, Miglyol 812 as liquid lipid and Tween 80 as surfactant for buccal ibuprofen NLCs [14], and Sodata and colleagues used spermaceti, soybean oil and polysorbate 80 for triamcinolone acetonide NLCs designed for a buccal film [21]. A number of different lipid systems have thus been used successfully for buccal NLCs, which suggests that the lipid combination for atorvastatin should be selected empirically on the basis of solubility and compatibility studies.

4.3 Methods of preparation

Reviews list high-pressure homogenisation (hot or cold), solvent emulsification–evaporation or diffusion, microemulsion, double emulsion, solvent injection, high-shear homogenisation with ultrasonication, phase inversion, microfluidisation and membrane contactor techniques as the principal preparative routes for NLCs [12,20]. Melt emulsification followed by high-shear mixing or probe ultrasonication is the most widely used laboratory method because it is scalable and avoids organic solvent: the drug is dissolved in the molten lipid blend, the hot aqueous surfactant phase is added, the coarse emulsion is reduced in size by homogenisation or ultrasound, and cooling causes the lipid to solidify into nanoparticles [12]. Vargas-Valderrama and Morales used a melt-emulsification process to prepare the NLCs studied on porcine buccal mucosa [17], and the method is therefore consistent with the buccal application.

4.4 Characterisation attributes

The critical physical attributes of an NLC dispersion are particle size, polydispersity index, zeta potential, entrapment efficiency and drug loading, morphology, physical state of the drug and lipid, and in vitro release. A zeta potential either below −30 mV or above +30 mV is generally regarded as favourable for electrostatic stabilisation [20]. Reported values for buccal NLCs illustrate that a lower absolute value need not preclude a useful system when steric stabilisation is provided: the NLCs of Vargas-Valderrama and Morales had a mean diameter of 83.73 ± 0.7 nm, a zeta potential of only −3.74 ± 0.40 mV and an association efficiency of 87.29 ± 0.34 % [17]. Thermal and diffraction methods are used to establish whether the drug is molecularly dispersed or crystalline, as in the calorimetric evidence of amorphisation reported for atorvastatin NLCs [5].

V. MUCOADHESION AND MUCOADHESIVE VEHICLES

5.1 Mechanisms

Mucoadhesion is the adhesion of a material to the mucus layer, a gel of glycoproteins that carries negative charge from sialic acid residues [22]. It is usually described as a two-stage process consisting of a contact stage, in which the mucoadhesive material spreads and wets the mucosal surface, and a consolidation stage, in which polymer chains interact with mucin through physical entanglement and chemical bonding [23]. Six theories are commonly quoted: wetting, mechanical interlocking, adsorption, electronic transfer, fracture and diffusion [22]. For the polymers used in buccal gels the diffusion or interpenetration theory, first developed for soft-tissue bioadhesion by Peppas and Buri, is the most widely applied, because it explains why chain flexibility, hydration and molecular weight determine the depth of interpenetration and the strength of the bond [24,25].

5.2 Polymer characteristics and choice

Reviews of mucoadhesive polymers for the buccal route describe hydrophilic macromolecules with hydrogen-bonding groups, such as polyacrylic acid derivatives (Carbopol, polycarbophil), cellulose ethers including HPMC and carboxymethylcellulose, and cationic chitosan, which adds electrostatic attraction to anionic mucin [22,25]. A review of bio-inspired mucoadhesive polymers reports that maximum adhesion is reached at a molecular weight of approximately 100 kDa and that concentrations of 1 to 2.5 % are typical for liquid formulations, and it identifies thiolated polymers as showing greater mucoadhesion through disulphide bonding with mucin cysteine residues [22]. More general reviews of mucoadhesive technology list chitosan (including

thiolated derivatives), carbomers, cellulose derivatives, gelatin, poloxamers and crosslinked poly (acrylic acid) among the polymers used, and note that mucoadhesive systems can enhance bioavailability, sustain release and lower the dose needed [23].

Carbomers are attractive for buccal gels because they have a high density of carboxyl groups that hydrogen-bond to mucin and they swell in a moist environment. In the simvastatin buccal film of Ahmed and colleagues, increasing the Carbopol 940 content raised the mucoadhesive response, and mucin-particle experiments showed that a film with 10 % Carbopol shifted the zeta potential from −9.2 to −19.3 mV, which the authors ascribed to hydrogen bonding between the polymer carboxyl groups and mucin hydroxyl groups [26]. In the atorvastatin buccoadhesive bilayer tablets of Ramani and co-workers, higher concentrations of Carbopol 934P relative to HPMC K15 increased swelling and matrix erosion and promoted sustained release, an ethylcellulose backing layer produced unidirectional release, and a combination with acacia gave superior mucoadhesive strength [27]. Both studies point to the importance of balancing swelling, erosion and adhesion when selecting a polymer system.

5.3 Mucoadhesive versus mucus-penetrating strategies

Mucoadhesion of the vehicle and penetration of the particle are different objectives. A gel that adheres firmly to the outer mucus layer prolongs residence, but a nanoparticle that is trapped in mucus far from the epithelium may not be absorbed. Ortiz and Morales discuss how nanoparticles interact with the glycoprotein-rich salivary film and how mucoadhesive polymers and particle properties can be combined to improve buccal retention and bioavailability [13]. In the NLC-in-gel concept the polymer network retains the vehicle on the mucosa, and the nanocarriers, which are small, lipidic and surfactant-coated, are released from the gel and are expected to approach the epithelium, where the lipid and surfactant components can act on the intercellular barrier [13,17]. The relative importance of these processes must be established experimentally for each formulation.

VI. EVIDENCE FROM NANOCARRIER-BASED AND STATIN BUCCAL SYSTEMS

No single report was found in the sources reviewed that describes an atorvastatin-loaded NLC dispersed in a mucoadhesive buccal gel with quantitative ex vivo permeation and pharmacokinetic data. The rationale must therefore be assembled from three groups of studies: atorvastatin NLCs designed for oral use, buccal delivery systems for atorvastatin and other statins, and NLC or lipid-nanocarrier buccal systems for other drugs. The main quantitative findings are collected in Table 2.

Table 2. Representative nanocarrier-based and statin buccal or NLC studies relevant to a mucoadhesive atorvastatin NLC gel

Drug	Carrier and vehicle	Principal quantitative or qualitative findings	Ref.
Atorvastatin	NLC (Gelucire 43/01, Labrasol, Tween 80, lecithin); oral	83.80 ± 1.13 nm; PDI 0.38; zeta potential −29.65 mV; entrapment 93.1 %; amorphous drug; lipid parameters lowered in rats ($p < 0.001$)	[5]
Atorvastatin	Buccoadhesive bilayer tablets (Carbopol 934P, HPMC K15, ethylcellulose backing)	Higher Carbopol 934P gave more swelling and erosion with sustained release; acacia combination gave best mucoadhesion; unidirectional release	[27]
Simvastatin	HP-β-cyclodextrin complex plus mixed micelles in HPMC/Carbopol 940 film; bovine buccal mucosa	Steady-state flux 1.704 vs 0.9324 μg/cm²·min (1.83-fold); micelles 16.48 nm, entrapment 54 %; 92.74 % release at 6 h; 11-fold and 430-fold solubility gain	[26]
Angiotensin II (peptide model)	NLC (Gelucire 44/14, Miglyol 812, Tween 80); porcine buccal mucosa	83.73 nm; zeta potential −3.74 mV; association 87.29 %; about 9 % permeated in 2 h; Papp 1.93×10^{-5} cm/s; free peptide not detected	[17]
Ibuprofen	NLC (Precirol ATO 5, Miglyol 812, Tween 80) in Carbopol 980 and polycarbophil gels	Nanometric size, low PDI; favourable rheology, firmness and adhesiveness; increased buccal residence; sustained release	[14]

Triamcinolone acetonide	NLC (spermaceti, soybean oil, polysorbate 80) in mucoadhesive film; Box-Behnken design	Optimised film showed mucoadhesion; release and permeation superior to pastes and emulsion-loaded films; Fickian release	[21]
Curcumin	Chitosan-coated lipid-core nanocapsules in HPMC/poloxamer 407 thermosensitive hydrogel	173 to 179 nm; hydrogel retained up to 8 h versus 90 min for suspension; no irritation in HET-CAM	[18]

6.1 Atorvastatin NLCs and atorvastatin buccal systems

The oral atorvastatin NLC of Ghanem and co-workers' shows that an NLC of pharmaceutically acceptable lipids can entrap atorvastatin at high efficiency in a size range appropriate for buccal application, and that the formulation retains pharmacological activity [5]. Although it was designed for oral use, its composition is useful as a starting point for lipid screening for a buccal system. On the buccal side, Ramani and colleagues designed atorvastatin calcium bilayer buccoadhesive devices explicitly to overcome its low bioavailability of about 14 % and studied swelling index, erosion, surface pH, adhesion time, adhesive strength and drug release [27]. Their work demonstrates the feasibility of retaining atorvastatin at the buccal mucosa with Carbopol-based polymers, but the abstract data available do not describe nanoparticulate enhancement or permeation across mucosa.

6.2 Simvastatin as a lipophilic statin comparator

Simvastatin is another lipophilic statin with low oral bioavailability, and the mucoadhesive buccal film of Ahmed and colleagues offers the closest permeation data for a statin. Using fresh bovine buccal mucosa in Franz diffusion cells with an area of 1.76 cm² and a receptor volume of 7 mL, the optimised film that combined a hydroxypropyl-β-cyclodextrin inclusion complex with sodium deoxycholate/phosphatidylcholine mixed micelles gave a steady-state flux of 1.704 μg/cm²·min against 0.9324 μg/cm²·min for the pure drug, an increase of about 1.83-fold [26]. The mixed micelles had a diameter of 16.48 ± 1.516 nm, a zeta potential of −30.81 ± 2.12 mV and an entrapment efficiency of 54 ± 0.88 %, and the film released 92.74 % of its drug in 6 hours with a dissolution time of 8.9 ± 2.5 min [26]. These data show that, for a lipophilic statin, carrier-assisted solubilisation combined with a mucoadhesive vehicle can produce a measurable improvement in buccal flux.

6.3 Lipid nanocarriers on buccal mucosa

The porcine buccal permeation study by Vargas-Valderrama and Morales is the most recent quantitative report on NLCs and buccal tissue. Their carrier was prepared by melt emulsification, and the loaded particles had a diameter of 83.73 ± 0.7 nm; after 2 hours in Franz cells at 37 °C the NLC formulation delivered about 9 % of the peptide to the receptor, corresponding to an apparent permeability coefficient of $1.93 \pm 0.11 \times 10^{-5}$ cm/s and a steady-state flux of $1.65 \pm 0.09 \times 10^{-2}$ μg/cm²·s, whereas free peptide was not detected in the receptor compartment [17]. The authors observed that the values were comparable to those reported for HPMC films combined with NLCs and for chitosan films combined with polymeric nanoparticles, so that the NLC was effective even without a mucoadhesive system in that experiment [17]. Because the model drug was a hydrophilic peptide, the result demonstrates the capacity of the NLC to open the epithelial barrier rather than the magnitude of any effect for a lipophilic statin.

Marques and colleagues incorporated ibuprofen NLCs into Carbopol 980 and polycarbophil gels, and reported desirable rheological behaviour, increased firmness and adhesiveness, sustained release and increased buccal residence, the closest precedent for the gel format proposed for atorvastatin [14]. Sodata and colleagues used a Box-Behnken design to optimise a triamcinolone acetonide NLC film, and found that the film gave superior release and permeation to pastes and to films loaded with emulsions, with Fickian drug release and rapid swelling [21]. Ortega and co-workers loaded curcumin lipid-core nanocapsules, coated with chitosan, into a hydrogel of HPMC and poloxamer 407; in their mucoadhesion assay the hydrogels remained adherent for up to 8 hours while suspensions were retained for only 90 minutes, and the HET-CAM test showed no irritation [18]. Together, these studies show that lipid nanocarriers in polymeric vehicles can be prepared with acceptable rheology, prolonged retention and sustained release for the buccal route.

6.4 Interpretation

Taken together, the evidence supports a stepwise argument. First, atorvastatin can be entrapped at high efficiency in an NLC [5]. Second, NLCs of nanometre size are able to enhance transport across porcine buccal mucosa in a suitable model [17]. Third, Carbopol-, HPMC-, polycarbophil- and poloxamer-based vehicles can retain lipid nanoparticles at the buccal mucosa for hours [14,18]. Fourth, a lipophilic statin has shown increased buccal flux when solubilised and presented in a mucoadhesive film [26]. What is missing is the integration of these findings for atorvastatin and, above all, in vivo evidence of systemic exposure after buccal application. The comparisons in Table 2 should also be treated with caution because tissue species, receptor conditions, time points and analytical methods differ between studies, and fluxes reported in different units cannot be compared directly.

VII. FORMULATION DESIGN, OPTIMISATION AND EVALUATION

7.1 Quality by design and the Box-Behnken design

The International Council for Harmonisation guideline on pharmaceutical development (Q8(R2)) describes a science- and risk-based approach in which a quality target product profile is defined, critical quality attributes are identified, and the effect of material attributes and process parameters on those attributes is studied systematically to define a design space [28]. For an NLC buccal gel, the quality target product profile would include a particle size in the nanometre range, a high entrapment efficiency, sustained release, adequate mucoadhesion, a pH compatible with the mouth, acceptable viscosity and spreadability, and enhanced ex vivo permeation.

Response surface designs are the usual tools for exploring the relationships between formulation variables and these attributes. The Box-Behnken design is a three-level design for quantitative variables that avoids the extreme corner combinations of a full factorial design and requires fewer runs than a central composite design; for three factors, it needs 15 runs including three centre points [29]. It has been applied to NLC development in several of the studies discussed above: Sodata and colleagues varied spermaceti, soybean oil and polysorbate 80, and modelled film weight, thickness, tensile strength, elongation at break, contact angle and surface free energy [21]. Ghanem and colleagues used a two-stage combination of a D-optimal screening design and a central composite optimisation design for atorvastatin NLCs [5]. For a mucoadhesive atorvastatin gel, plausible factors are the ratio of solid to liquid lipid, the surfactant concentration and the homogenisation or sonication time, with particle size, entrapment efficiency and cumulative release as responses; a second design can then be used to tune the gelling polymer and mucoadhesion.

7.2 Evaluation of the gel

The NLC dispersion is incorporated into a gel prepared by dispersing the mucoadhesive polymer and neutralising where necessary. Characterisation of the gel should include pH, viscosity and rheological profile, spreadability, drug content and homogeneity, and mucoadhesive strength. Marques and colleagues characterised rheology, firmness and adhesiveness of their NLC-containing gels and used these parameters to argue for enhanced buccal residence [14], while Ortega and co-workers measured the quantity of curcumin removed over time by washing to assess retention [18]. Tensile detachment, texture analysis, mucin-particle zeta-potential shifts and residence measurements on excised tissue provide complementary information about mucoadhesion; Ahmed and colleagues, for instance, reported a tensile mucoadhesive strength of 523.41 ± 29.68 N for their optimised film together with a mucin-particle assay [26].

7.3 Release and ex vivo permeation

In vitro release is generally studied by dialysis or Franz cell methods with a membrane and a receptor medium that ensures sink conditions for a poorly soluble drug, and the data are fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. Ex vivo permeation is measured on freshly excised porcine or bovine buccal mucosa mounted between the donor and receptor chambers of a Franz cell at 37 °C. Vargas-Valderrama and Morales used porcine tissue over 2 hours [17], and Ahmed and colleagues used bovine tissue with a 1.76 cm² diffusion area and 7 mL receptor volume [26]. The permeation profile provides the steady-state flux (Jss), the permeability coefficient and the lag time. The tissue should be used soon after

slaughter, and the way in which epithelium and connective tissue are separated should be recorded because it affects the barrier [15,19].

For atorvastatin the analytical method must be sensitive enough to quantify the low concentrations of drug that reach the receptor, and should be validated in line with ICH Q2 principles. Because lipophilic drugs may bind to tissue, mass balance and the amount retained in the mucosa should be determined at the end of the experiment, as retained drug can provide a local depot but is not systemically available. A cytocompatibility or histological evaluation on the buccal tissue or a buccal cell line should accompany the permeation study to exclude damage from surfactants and permeation-enhancing excipients [17,18].

7.4 Stability

Physical stability of the NLC dispersion, including changes in particle size, polydispersity and zeta potential, and the chemical stability of the drug should be examined under the conditions recommended by international guidelines. Lipid nanoparticles may undergo aggregation, gelation or lipid polymorphic transitions, and the imperfect matrix of an NLC is designed to reduce these events relative to SLNs [11,12]. The gel matrix adds further parameters such as viscosity drift, pH change and preservative efficacy.

VIII. CHALLENGES AND FUTURE PERSPECTIVES

Several challenges remain before a mucoadhesive NLC buccal gel of atorvastatin can be considered for clinical study. The first is dose. Atorvastatin is prescribed at 10 to 80 mg per day [3], whereas the volume of gel that can be retained comfortably in the cheek is small, so that drug loading in the NLC, in the gel and the flux across the mucosa must all be high enough to deliver a useful fraction of the dose. A lower buccal dose is plausible only if first-pass loss is truly avoided, and this must be demonstrated by pharmacokinetic studies. The second is taste and patient acceptability, since repeated daily application to the cheek requires a palatable formulation, and sweeteners or flavours are commonly considered for oromucosal products.

The third challenge is the selection of predictive models. A review of oral mucosa models concluded that no single model is suitable for all purposes and that each has advantages and limitations [15]. Porcine buccal tissue is a pragmatic first choice, but confirmatory studies in reconstructed human mucosa or in vivo animal models are needed before quantitative predictions are made for humans. The fourth is the balance between mucoadhesion and penetration. An excessively strong or thick gel might slow the release of NLCs, whereas a weak gel would not remain in place [13,23]. Combining mucoadhesive polymers with carefully chosen surfactants, or coating NLCs with mucoadhesive materials such as chitosan, are options that have been explored with lipid-core nanocapsules and merit examination for atorvastatin [18].

The fifth challenge concerns safety. Surfactants such as polysorbate 80 and lipids such as Gelucire fluidise or extract lipids of the epithelium, which is the mechanism of permeation enhancement but also a potential source of irritation [17]. Cytocompatibility on buccal cells or histology, as well as an irritation test such as HET-CAM used by Ortega and co-workers, should therefore be included at an early stage [18]. Finally, scale-up and quality control of the two-stage process of NLC manufacture followed by gel incorporation must be justified in a quality by design framework [28].

Future work should aim to close the evidence gap with a complete data set for the atorvastatin system: a Box-Behnken optimised NLC, its incorporation into a Carbopol/HPMC gel, comparative ex vivo permeation and mucoadhesion against a plain gel and a free-drug gel, cytocompatibility testing and accelerated stability, followed by an in vivo pharmacokinetic study that measures parent drug and active metabolites in plasma. It would also be valuable to compare the buccal exposure profile of the parent drug and its active hydroxylated metabolites with those of the oral tablet, since the metabolite profile is expected to change when CYP3A4-mediated first-pass metabolism is avoided [3]. Physiologically based pharmacokinetic modelling could then be used to explore dose requirements.

IX. CONCLUSION

Atorvastatin is an effective and widely used statin whose oral bioavailability of about 14 % is limited by poor solubility and extensive CYP3A4-mediated first-

pass metabolism. The buccal route avoids the portal circulation and offers a sound pharmacokinetic rationale, provided that residence time and epithelial permeability are addressed. Nanostructured lipid carriers can be prepared by simple, scalable methods, can entrap atorvastatin at high efficiency, and have been shown to cross porcine buccal mucosa, and mucoadhesive gels based on Carbopol, polycarbophil, HPMC or poloxamer have retained lipid nanocarriers on the mucosa for hours in published studies. The convergence of these findings supports a mucoadhesive NLC-based buccal gel as a rational strategy for atorvastatin. The strategy remains a hypothesis until quality by design optimisation, ex vivo permeation and mucoadhesion testing, safety assessment and, most importantly, in vivo pharmacokinetic data are obtained for the specific formulation.

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