Squeezing Through the Skin: Deformable Vesicles for Boswellia serrata

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Abstract*—Osteoarthritis is among the most prevalent causes of disability worldwide, and its pharmacological management rests largely on non-steroidal anti-inflammatory drugs whose gastrointestinal and cardiovascular risks accumulate with the chronic use the disease demands. Current guidelines have responded by moving topical NSAIDs ahead of oral NSAIDs as first-line therapy for knee osteoarthritis — an endorsement of the principle that, for a superficial joint, local delivery is preferable to systemic exposure. Boswellia serrata gum resin offers a mechanistically distinct anti-inflammatory option: its boswellic acids, particularly 11-keto-β-boswellic acid and its 3-O-acetyl derivative, are non-redox inhibitors of 5-lipoxygenase, and standardised extracts have produced clinically and statistically significant improvements in pain and physical function in randomised placebo-controlled trials in knee osteoarthritis, with meta-analytic support. The limitation is pharmacokinetic. Oral absorption of the keto-boswellic acids is poor and highly variable, and permeability data have been poor enough to call the 5-lipoxygenase mechanism itself into question at achievable plasma concentrations. A topical route circumvents this entirely for a joint as superficial as the knee — but the boswellic acids are large, lipophilic pentacyclic triterpenoids, poorly suited to crossing the stratum corneum unaided. Deformable vesicles are the rational answer: phospholipid vesicles containing a single-chain surfactant edge activator that destabilises the bilayer, allowing the vesicle to deform and traverse intercellular channels several times narrower than itself. This review assembles the pharmacology and pharmacokinetics of boswellic acids, sets out the case for the topical route, examines deformable vesicle design with particular attention to the relationship between membrane elasticity and skin deposition, audits the Boswellia-specific vesicular literature, and argues that the elasticity–deposition correlation is the variable the field has most consistently failed to measure.

***Index Terms*—Boswellia serrata; boswellic acids; transfersomes; deformable vesicles; edge activator; skin deposition; osteoarthritis; Quality by Design**

I. INTRODUCTION

Osteoarthritis is a disease of chronic management rather than cure. The Global Burden of Disease analysis places it among the leading causes of disability worldwide, with projections to 2050 indicating continued growth driven by ageing and rising body mass index [1]. It is characterised by progressive cartilage degradation accompanied by subchondral bone change, synovial inflammation and persistent pain, and although its pathophysiology is now understood as involving the whole joint rather than cartilage alone, treatment remains predominantly symptomatic [2,3].

Symptomatic treatment means analgesia sustained over years, and that is precisely where conventional pharmacology struggles. Oral non-steroidal anti-inflammatory drugs are effective but carry gastrointestinal, renal and cardiovascular risks that scale with duration of exposure and with patient age — risks that fall most heavily on the population most likely to need them. Guideline bodies have responded by elevating the topical route. The 2019 American College of Rheumatology and Arthritis Foundation guideline strongly recommends topical NSAIDs for knee osteoarthritis and recommends them ahead of oral NSAIDs for that indication, and the 2019 Osteoarthritis Research Society International

recommendations likewise place topical NSAIDs among first-line therapies for knee osteoarthritis [4,5]. The evidence base for topical NSAIDs in chronic musculoskeletal pain has been reviewed systematically [6], and earlier guideline iterations had already identified the approach as appropriate for localised disease [7].

The endorsement is specific and instructive: it applies to the knee and hand, joints close enough to the skin surface for local delivery to reach the target, and it rests on the observation that comparable efficacy can be obtained with far lower systemic exposure. That logic is not specific to NSAIDs. It applies to any anti-inflammatory agent whose target tissue is superficial and whose systemic exposure is undesirable or unattainable.

Boswellia serrata is such an agent, and unusually so, because for boswellic acids systemic exposure is not merely undesirable but genuinely difficult to achieve. The gum resin of this Burseraceae tree has a long history in Ayurvedic practice and a substantial modern anti-inflammatory literature [8,9]. Its pentacyclic triterpene acids inhibit 5-lipoxygenase by a non-redox mechanism distinct from that of NSAIDs [10], and standardised extracts have shown significant benefit in randomised controlled trials in knee osteoarthritis [13,14], supported by meta-analysis [15]. Yet oral bioavailability of the most potent constituents is poor and variable enough that a careful pharmacokinetic review questioned whether the assumed 5-lipoxygenase mechanism can operate at clinically achievable plasma concentrations at all [11].

A delivery system that places boswellic acids in the skin and subcutaneous tissue overlying an affected joint therefore addresses a real and well-documented gap. The obstacle is the stratum corneum, and the most promising tool for crossing it is the deformable vesicle. This review examines that proposition: the chemistry and pharmacology of the boswellic acids, the pharmacokinetic evidence that motivates a change of route, the design principles of deformable vesicles, the specific and under-examined relationship between membrane elasticity and skin deposition, and what the existing Boswellia vesicular literature has and has not established.

II. BOSWELLIA SERRATA: CHEMISTRY, MECHANISM AND CLINICAL EVIDENCE

2.1 The resin and its acids

The gum resin of Boswellia serrata comprises approximately 10% volatile oils, 60% lipophilic resin and 30% hydrophilic gums. The anti-inflammatory activity is attributed principally to the boswellic acids: β-boswellic acid, α-boswellic acid, 11-keto-β-boswellic acid (KBA), 3-O-acetyl-11-keto-β-boswellic acid (AKBA), and the 3-O-acetyl derivatives of the α and β acids. KBA and AKBA are the markers adopted in the European Pharmacopoeia monograph for Indian frankincense, which makes them the reference points for standardisation as well as the presumed principal actives [11].

All are pentacyclic triterpene acids: large, rigid, strongly lipophilic molecules with a single ionisable carboxyl group. Those properties govern everything that follows. They explain the compounds' affinity for lipid membranes, their poor aqueous solubility, their erratic oral absorption, and — importantly for the present argument — their unsuitability for unaided transdermal delivery, since they sit at or beyond the practical molecular-weight ceiling for passive stratum corneum permeation [21].

Standardisation requires chromatographic quantification of the individual acids rather than a total-triterpene assay, since commercial extracts differ substantially in AKBA content: preparations standardised to 30% AKBA and to 20% AKBA have both been studied clinically and have not performed identically [14]. A simple high-performance liquid chromatographic method for estimation of boswellic acids in marketed formulations containing B. serrata extract provides a practical basis for this [12].

2.2 Mechanism: 5-lipoxygenase and the complications

The mechanistic foundation was laid by Safayhi and colleagues, who identified boswellic acids as novel, specific, non-redox inhibitors of 5-lipoxygenase [10]. This matters therapeutically because it places boswellic acids on the leukotriene arm of the arachidonic acid cascade rather than the prostaglandin arm targeted by NSAIDs, offering a mechanistically complementary anti-inflammatory action without cyclooxygenase-mediated gastric

toxicity. AKBA is the most potent of the series against the enzyme.

The picture has since become more complicated, and the complication is a pharmacokinetic one. The comprehensive assessment by Abdel-Tawab and colleagues noted that plasma concentrations of β-boswellic acid are roughly a hundred-fold higher than those of the keto acids, that β-boswellic acid inhibits microsomal prostaglandin E synthase-1 and the serine protease cathepsin G, and that permeability studies suggest poor absorption of AKBA after oral dosing. Their conclusion was explicit: on the available pharmacokinetic evidence, the previously assumed mode of action — 5-lipoxygenase inhibition — is questionable [11].

This is a genuinely important observation and it cuts both ways for the present argument. It weakens confidence that oral dosing engages the intended target. But it strengthens the case for a delivery route that can achieve local concentrations high enough to do so. If the obstacle to 5-lipoxygenase inhibition is that AKBA never reaches an adequate concentration at the site of inflammation, then delivering it directly to that site is not a convenience but the condition for the mechanism to operate.

Preclinical evidence in osteoarthritis models is consistent and multi-mechanistic. A standardised extract prevented joint pain and cartilage degeneration in a rat model through inhibition of inflammatory responses and restoration of matrix homeostasis [16]; an anti-inflammatory composition of resin extracts alleviated pain and protected cartilage in monoiodoacetate-induced osteoarthritis [17]; and a standardised gum resin extract alleviated knee joint pathology and inflammation in osteoarthritis-induced models [18]. Reported mechanisms extend beyond 5-lipoxygenase to suppression of matrix metalloproteinase-3 and of adhesion molecule expression — relevant because matrix metalloproteinase activity is a direct driver of cartilage degradation rather than of pain alone.

2.3 Clinical evidence in knee osteoarthritis

The clinical dataset is better than for most botanicals and is worth stating precisely.

A double-blind, randomised, placebo-controlled study of 5-Loxin, a B. serrata extract enriched to 30% AKBA, in patients with knee osteoarthritis found significant improvement in clinical signs and symptoms together with normalisation of elevated matrix metalloproteinase-3 in synovial fluid [13]. A subsequent 90-day double-blind, randomised, placebo-controlled study compared 100 mg daily of 5-Loxin with 100 mg daily of Aflapin — a composition combining AKBA-enriched extract with the non-volatile oil fraction of the gum resin — against placebo in 60 subjects, of whom 57 completed. Both conferred clinically and statistically significant improvements in pain and physical function. The Aflapin group improved by 47.3% in visual analogue scale score, 35.8% in Lequesne Functional Index, 61.7% in WOMAC pain, 60.1% in WOMAC stiffness and 49.4% in WOMAC functional ability, with significant improvement detectable as early as seven days; safety parameters were essentially unchanged relative to placebo [14]. These values are plotted in Figure 1.

A meta-analysis of nine randomised controlled trials in 712 adults with osteoarthritis, using products including 5-Loxin, Aflapin and combination preparations over intervention durations of one to six months, found that Boswellia-containing supplementation reduced pain on both visual analogue and WOMAC scales, reduced WOMAC stiffness, and improved physical function on both the WOMAC and Lequesne indices relative to control [15].

Two features are worth drawing out. The effect sizes are substantial and the onset is rapid. And the doses are small — 100 mg daily of an enriched extract — which makes the pharmacokinetic puzzle sharper rather than softer, and which also means that the total daily quantity of active that a topical formulation would need to deliver is not prohibitive.

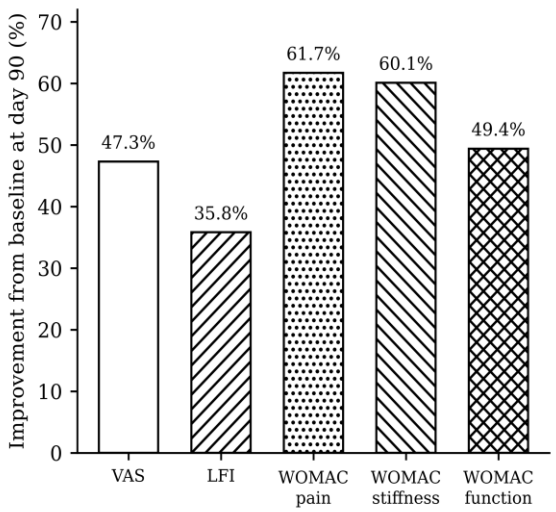


Fig. 1. Percentage improvement from baseline at day 90 with 100 mg daily of Aflapin, an AKBA-enriched Boswellia serrata composition, in a 90-day double-blind, randomised, placebo-controlled study in subjects with knee osteoarthritis [14]. VAS, visual analogue scale; LFI, Lequesne Functional Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Significant improvement was reported as early as day 7, and safety parameters were essentially unchanged relative to placebo.

Table 1. The principal boswellic acids of Boswellia serrata gum resin and their pharmacological and pharmacokinetic characteristics as reported.

Constituent	Reported pharmacology	Pharmacokinetic behaviour	Ref.
3-O-Acetyl-11-keto-β-boswellic acid (AKBA)	Most potent boswellic acid against 5-lipoxygenase; non-redox, specific inhibition; reported inhibition of MMP-3 and adhesion molecule expression	Poor oral absorption; permeability studies indicate limited intestinal uptake; plasma levels far below those of β-boswellic acid; t½ 6.8 ± 3.0 h from a solid lipid particle formulation	[10,11,20]
11-Keto-β-boswellic acid (KBA)	5-Lipoxygenase inhibitor; with AKBA, a European Pharmacopoeia marker for the gum resin	Poor and variable oral bioavailability; t½ 2.45 ± 0.3 h from a solid lipid particle formulation	[11,20]
β-Boswellic acid (βBA)	Inhibits microsomal prostaglandin E synthase-1 and the serine protease cathepsin G	Plasma concentrations approximately 100-fold higher than those of the keto acids — the observation that prompted re-examination of the assumed 5-LOX mechanism	[11]
α-Boswellic acid and the 3-O-acetyl α and β acids	Contribute to the overall anti-inflammatory profile of the resin	Present in standardised extracts at defined proportions; less extensively characterised pharmacokinetically	[11,12]
Whole standardised extract	Clinically significant reduction in pain and improvement in physical function in knee osteoarthritis; onset within 7 days reported	Efficacy at 100 mg daily of enriched extract despite low measured plasma levels of the keto acids — a persisting pharmacokinetic–pharmacodynamic discrepancy	[13,14,15]

III. THE PHARMACOKINETIC CASE FOR CHANGING ROUTE

Table 1 summarises the boswellic acids and their pharmacokinetic liabilities.

The central problem is that the compounds credited with the activity are the ones least present in plasma. Pharmacokinetic studies have repeatedly shown poor bioavailability of KBA and AKBA, the most potent boswellic acids, and metabolism studies in vitro and in vivo concluded that the efficacy of B. serrata extract might be enhanced specifically by increasing the bioavailability of AKBA [19]. Inter-individual variability is pronounced, as it tends to be for

lipophilic compounds whose absorption depends on bile-salt-mediated solubilisation and on co-administered food.

Formulation approaches to the oral problem have produced real but modest gains. Solid lipid particles of B. serrata extract were prepared to enhance boswellic acid bioavailability and evaluated in healthy subjects, with elimination half-lives of 6.8 ± 3.0 h for AKBA and 2.45 ± 0.3 h for KBA, and enhanced oral bioavailability relative to historically reported data for unformulated extract [20]. Lecithin-based and self-emulsifying approaches have likewise reported improvements of roughly two-fold. These are worthwhile but they start from a very low base, and a two-fold improvement on poor and variable absorption yields exposure that is still low and still variable.

The topical route sidesteps the problem rather than mitigating it. For knee osteoarthritis the target tissue lies a few millimetres below the skin surface, and the therapeutic objective is local concentration rather than plasma concentration. A formulation that deposits boswellic acids in the epidermis, dermis and underlying tissue achieves the pharmacologically relevant exposure while producing minimal systemic levels — the same trade that makes topical NSAIDs attractive, applied to a molecule whose oral performance is considerably worse than that of diclofenac.

The obstacle is the stratum corneum. The 500 Dalton rule — the empirical observation that compounds above approximately 500 Da rarely achieve useful passive skin permeation — is directly relevant, since the boswellic acids are pentacyclic triterpenoids well above that threshold [21]. Passive diffusion of such molecules through the intercellular lipid lamellae is negligible, and the history of transdermal delivery is in large part the history of attempts to overcome this constraint without damaging the barrier [22,23]. A simple ointment or cream containing Boswellia extract is therefore unlikely to deliver meaningful quantities to the target tissue, which is why a carrier capable of active barrier negotiation is required.

3.1 Does topical delivery actually reach the joint?

An obvious objection must be addressed before the strategy can be taken seriously. If the pathology of knee osteoarthritis involves cartilage, subchondral bone and synovium, can a drug applied to the skin reach those structures in meaningful quantity, or is any benefit simply a counter-irritant or placebo effect?

The guideline position is informative here precisely because it is differentiated. Topical NSAIDs are strongly recommended for knee and hand osteoarthritis but not for hip osteoarthritis, and the reason given is questionable joint penetration together with insufficient data for the deeper joint [4]. That distinction is not arbitrary: it reflects an accepted judgement that superficial joints are reachable and deep ones are not. The knee, with its anterior compartment lying a few millimetres beneath skin and a thin soft-tissue envelope, falls on the favourable side of that line, and the systematic evidence for topical NSAIDs in chronic musculoskeletal pain is concentrated in exactly these locations [6].

Three routes to the tissue are generally invoked. Direct diffusion through skin, subcutaneous fat and joint capsule provides the highest local concentrations in the most superficial structures and declines steeply with depth. Local vascular and lymphatic redistribution carries drug from the dermal plexus into underlying tissue before it is diluted into the systemic circulation. And a small systemic contribution returns some drug to the joint through the synovial circulation. The relative weighting of these is debated, but their combined effect is sufficient to produce the clinical efficacy that underpins the guideline recommendations.

For boswellic acids there is a particular argument in favour. Their lipophilicity, which makes oral absorption so unreliable, becomes an asset once the stratum corneum has been crossed: lipophilic molecules partition into and are retained by subcutaneous adipose and connective tissue rather than being cleared rapidly into the blood, which tends to favour local persistence over systemic redistribution. The same physicochemical property that frustrates the oral route therefore supports the topical one, provided the barrier problem is solved.

This is nonetheless an area where assumption has outrun measurement. Very few studies of topical botanical formulations quantify the active in deep tissue rather than in skin, and fewer still measure synovial concentrations. A study that reported boswellic acid levels in skin, subcutaneous tissue, muscle and joint tissue after topical application of a

deformable vesicular gel, alongside plasma levels, would settle for this compound a question that is currently answered by extrapolation from the NSAID literature.

IV. DEFORMABLE VESICLES: PRINCIPLE AND DESIGN

4.1 Origins and mechanism

Conventional liposomes are poor transdermal carriers. They accumulate in the uppermost layers of the stratum corneum, where they fuse or disintegrate, acting largely as a local reservoir rather than as a vehicle. The innovation that changed this came from Cevc and Blume, who showed that appropriately composed lipid vesicles could penetrate intact skin, driven by the transdermal osmotic gradient between the relatively dry surface and the hydrated viable epidermis, together with the hydration force [24]. The resulting carriers, which Cevc termed Transfersomes, were characterised in detail as permeation-enhancing vesicles capable of transdermal delivery [25].

The structural basis is the edge activator: a single-chain surfactant with a high radius of curvature which, incorporated into a phospholipid bilayer, destabilises it and dramatically increases its deformability. Common edge activators include sodium cholate, sodium deoxycholate, Span 80, Tween 20 and Tween 80 [27,31]. The practical consequence is remarkable: because the bilayer can deform without rupturing, such vesicles are reported to pass through constrictions five to ten times narrower than their own diameter, and this self-optimising deformability allows passage through the intercellular channels of the stratum corneum that would exclude a rigid vesicle of the same size [29,33].

The hydration gradient supplies the driving force. A vesicle applied under non-occlusive conditions at the dry skin surface tends to move toward the hydrated deeper layers in order to avoid dehydration; the deformable bilayer permits it to follow that gradient through narrow channels rather than being arrested at the surface. Occlusion abolishes the gradient, which is why deformable vesicle formulations are conventionally applied non-occlusively — a detail frequently omitted from experimental descriptions.

Related systems make different trade-offs. Ethosomes achieve flexibility through a high ethanol content rather than a surfactant, with ethanol acting both as a bilayer fluidiser and as a stratum corneum lipid disorganiser [26]. Niosomes and proniosomes substitute non-ionic surfactants for phospholipid, offering improved chemical stability at the cost of some deformability. Table 2 compares the principal vesicle classes.

One caveat deserves honest statement. Whether deformable vesicles traverse the stratum corneum as intact structures remains contested; critical reviews have noted that neither Transfersomes nor any other highly deformable vesicle has been unequivocally shown to penetrate beyond the stratum corneum intact, and that increasing bilayer deformability alone may be insufficient without a bilayer tailored to the specific drug and regimen [31]. For the formulator this is not disqualifying — the enhancement in delivery is well documented regardless of the mechanism — but it argues against over-interpreting mechanistic claims and in favour of measuring deposition directly.

Table 2. Vesicular carriers for skin delivery compared, with the considerations bearing on a lipophilic triterpenoid payload.

Carrier	Composition and basis of flexibility	Behaviour in skin	Relevance to boswellic acids
Conventional liposome	Phospholipid ± cholesterol; rigid bilayer	Accumulates in the upper stratum corneum; acts largely as a surface reservoir	Good lipophilic payload capacity but little barrier penetration; unlikely to reach the target depth
Transfersome (deformable vesicle)	Phospholipid plus a single-chain surfactant edge activator (sodium cholate, Span 80, Tween 80)	Deforms to pass constrictions reported as 5–10 times narrower than the vesicle; driven by the transdermal	Best-characterised option; elasticity is tunable, making it amenable to designed optimisation

Carrier	Composition and basis of flexibility	Behaviour in skin	Relevance to boswellic acids
		hydration gradient; applied non-occlusively	
Ethosome	Phospholipid with a high ethanol content	Ethanol fluidises the bilayer and disorganises stratum corneum lipids	Good for lipophilic actives, but high ethanol content raises irritation and stability concerns in a chronic-use product
Niosome / proniosome	Non-ionic surfactant (with cholesterol) in place of phospholipid; proniosome is a dry precursor hydrated before use	Moderate flexibility; the proniosome format improves chemical and storage stability	Attractive stability profile; reported for boswellic acid as an optimised proniosomal gel
Mixed micelle (over-activated vesicle)	Excess edge activator relative to phospholipid	Loses vesicular structure and entrapped payload	The failure mode that bounds edge activator concentration from above

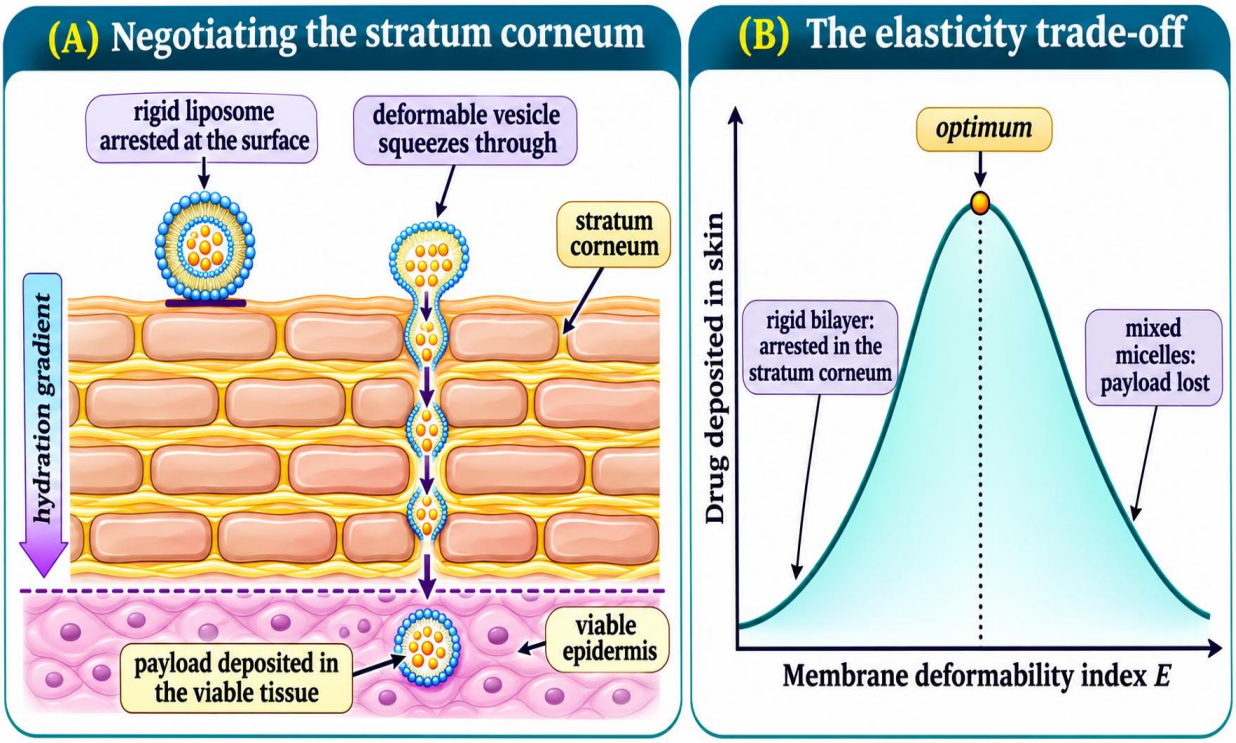


Fig. 2. (A) Why deformability matters. The intercellular lipid channels of the stratum corneum are far narrower than a typical vesicle. A rigid conventional liposome is arrested at the surface, whereas a vesicle whose bilayer has been destabilised by a single-chain edge activator deforms and follows the transdermal hydration gradient into the deeper layers. (B) The elasticity trade-off, shown schematically: too little edge activator leaves the bilayer rigid and deposition low, while excess edge activator converts the vesicle into a mixed micelle and the payload is lost. An interior optimum is expected, and locating it — rather than maximising elasticity — is the design objective. Panel B is illustrative and not drawn from a single dataset.

4.2 Edge activator selection and the elasticity trade-off

The edge activator is the formulation variable with the largest influence on performance, and its effect is not monotonic. El Zaafarany and colleagues examined the role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery and showed that both the identity and the concentration of the edge activator, together with the charge of the bilayer, determine the outcome [27]. Beyond conferring elasticity, edge activators influence vesicle size, entrapment efficiency, leakage during skin passage and the hydrophilic–lipophilic balance of the carrier.

The trade-off is straightforward once stated. Too little edge activator and the bilayer remains rigid: the vesicle behaves as a conventional liposome and is arrested in the upper stratum corneum. Too much and the bilayer is so destabilised that the vesicle becomes a mixed micelle, losing both its entrapped payload and the vesicular character that distinguishes it. Between these lies an optimum, and locating it is the central experimental task. Figure 2B represents this relationship schematically.

Elasticity is quantified by extrusion. The deformability index is calculated as $E = J (r_v / r_p)^2$, where J is the mass of vesicle suspension extruded through a membrane of defined pore radius r_p in a fixed time under constant pressure, and r_v is the vesicle radius after extrusion. The measurement combines flux and the extent of size change, and it is the only routine assay that reports the property the whole formulation strategy depends on.

Here lies the gap this review most wants to identify. Elasticity is frequently measured and reported. Skin deposition is frequently measured and reported. The two are rarely plotted against each other across a designed series of formulations, and so the relationship that would convert deformable vesicle formulation from empirical screening into rational design — does deposition rise linearly with elasticity, or plateau, or peak and fall? — remains largely uncharacterised for any given drug. Establishing it for boswellic acids would be a contribution independent of the formulation itself.

4.3 The gel vehicle: the step where vesicles are often lost

A vesicle dispersion is not a product. For application to a knee, the formulation must be a semisolid with acceptable spreadability, retention on the skin and patient acceptability, which in practice means incorporating the vesicles into a hydrogel — commonly a carbomer, a cellulose ether or a poloxamer base. This step receives far less attention than vesicle design and is where otherwise promising formulations frequently fail.

Three mechanisms of loss operate. Osmotic stress is the first: a gel base containing high concentrations of humectant or electrolyte can draw water across the vesicle bilayer, shrinking or rupturing vesicles whose membranes have deliberately been destabilised. The second is mechanical: the shear applied during dispersion of the vesicle suspension into a viscous base can fragment vesicles, and high-shear mixing of a deformable vesicle preparation is self-defeating. The third is chemical: carbomer gels require neutralisation to a pH at which they thicken, and a pH shift can alter the ionisation of an acidic payload such as a boswellic acid, changing its partitioning between bilayer and aqueous phase and so its leakage rate during storage.

There is also a direct conflict between the vehicle and the mechanism. The transdermal hydration gradient that drives deformable vesicles into the skin depends on the surface being drier than the viable epidermis. A highly occlusive vehicle hydrates the stratum corneum, flattens that gradient, and removes the driving force the carrier was engineered to exploit. The vehicle should therefore be chosen to be non-occlusive, and the formulation should be applied without an occlusive dressing — a point that follows directly from the mechanism but is often contradicted in practice.

The practical consequence for study design is that vesicle characterisation must be repeated after incorporation into the gel, not only on the parent dispersion. Size, polydispersity, entrapment efficiency and, where it can be measured, the deformability index should be determined on vesicles recovered from the finished semisolid. A formulation reported as having excellent elasticity in dispersion and excellent deposition from gel has not demonstrated that the two properties coexisted in the same material unless that measurement was made.

V. THE BOSWELLIA VESICULAR LITERATURE

Table 3 collects the reported systems. Several are directly relevant and together they establish feasibility without closing the question.

Ultradeformable vesicles loaded with boswellic acid have been developed and evaluated as a transdermal film, demonstrating that the actives can be entrapped in a deformable bilayer and delivered from a solid-state transdermal presentation [35]. A Boswellia serrata extract-loaded transferosomal gel has been formulated and evaluated in vitro specifically for the treatment of osteoarthritis, which is the closest published precedent to the proposition examined here [36]. Boswellic acid has also been formulated in a proniosomal gel, developed and optimised as a more chemically stable non-ionic surfactant alternative to phospholipid vesicles [37].

Two adjacent studies supply methodological templates. Proanthocyanidin-loaded transferosomes were optimised by a Box–Behnken design as a therapeutic approach for osteoarthritis, providing a directly transferable design-of-experiments framework for a polyphenolic natural product in the same indication [38]. Multidrug ultradeformable vesicles were developed and evaluated in vivo for the treatment of skin inflammation, demonstrating that the platform supports in vivo anti-inflammatory efficacy rather than in vitro permeation alone [39].

What is missing from this body of work is consistent. None of these studies systematically varies edge activator type and concentration across a designed series, measures the deformability index for each resulting formulation, measures skin deposition for each, and then correlates the two. Most report elasticity and permeation as parallel descriptive outcomes rather than as related variables. And few carry the work through to an in vivo osteoarthritis model with a conventional topical comparator, which is the test that would establish whether the deformability advantage translates into therapeutic benefit.

Table 3. Reported vesicular and related topical formulations of Boswellia serrata constituents and closely comparable systems.

System	Active and design	Reported outcome	Ref.
Ultradeformable vesicle transdermal film	Boswellic acid in deformable vesicles, formulated into a transdermal film	Demonstrated entrapment in a deformable bilayer and delivery from a solid-state transdermal presentation	[35]
Transferosomal gel	Boswellia serrata extract in transferosomes, gelled for topical application; developed specifically for osteoarthritis	In vitro evaluation supporting the transferosomal gel as a topical approach for osteoarthritis	[36]
Proniosomal gel	Boswellic acid in a non-ionic surfactant proniosome, developed and optimised	Optimised proniosomal gel offering improved storage stability relative to phospholipid vesicles	[37]
Transferosomes, Box–Behnken optimised	Proanthocyanidin (polyphenolic natural product) in transferosomes for osteoarthritis	Box–Behnken optimisation of a natural-product transferosome in the same indication; a directly transferable design template	[38]
Multidrug ultradeformable vesicles	Combination payload in ultradeformable vesicles for skin inflammation	In vivo evaluation demonstrating anti-inflammatory efficacy from the platform, not in vitro permeation alone	[39]
Oral solid lipid particles (comparator approach)	Boswellia serrata extract in solid lipid particles, healthy human subjects	AKBA t½ 6.8 ± 3.0 h, KBA t½ 2.45 ± 0.3 h; enhanced oral bioavailability versus historically reported unformulated extract	[20]

VI. QUALITY BY DESIGN AND STATISTICAL OPTIMISATION

A deformable vesicular gel has several interacting formulation variables and several competing responses, which is the situation response-surface methodology exists to address. The phospholipid-to-edge-activator ratio governs elasticity and entrapment in opposite directions. Edge activator identity changes the hydrophilic–lipophilic balance and therefore the partitioning of a lipophilic payload. Sonication time or extrusion cycle number controls vesicle size, which interacts with deformability in determining passage through intercellular channels. Cholesterol content, where used, rigidifies the bilayer and improves stability at the cost of the very flexibility being engineered.

The Quality by Design framework replaces one-factor-at-a-time screening with a defined quality target product profile, explicit critical quality attributes and critical process parameters, and a design space within which performance is robust [42,45]. For a Boswellia deformable vesicular gel the critical quality attributes are vesicle size, to be minimised or controlled within a defined window; entrapment efficiency for AKBA and KBA specifically, to be maximised; the deformability index, to be optimised rather than maximised, for the reasons given above; and skin deposition, which is the response that actually matters clinically.

The Box–Behnken design suits the problem well. Introduced as a family of three-level designs for quantitative variables [43], it estimates a full quadratic surface without extreme corner combinations — valuable here because extreme edge activator levels produce micellar rather than vesicular systems and would yield uninterpretable runs. Its advantages relative to other response-surface designs have been reviewed [44], and it has already been applied to transferosomes for osteoarthritis [38].

The analysis should not stop at a desirability-optimised composition. Because the elasticity–deposition relationship is the open scientific question, the designed series should be analysed as a dataset in its own right: deformability index plotted against skin deposition across all runs, with the form of the relationship reported. A design of experiments generates exactly the spread of elasticities needed to characterise it, and discarding that information in favour of a single optimised batch wastes the most interesting output of the study.

7. How such a system should be evaluated

A credible evaluation package has six components.

Extract standardisation and analytics. Quantification of KBA and AKBA in the input extract and in the finished formulation by a validated HPLC method [12], with validation to ICH Q2(R1) for linearity, accuracy, precision, specificity, detection and quantitation limits and robustness [46]. Entrapment efficiency should be reported per marker rather than for total extract, since the boswellic acids differ in lipophilicity and need not partition identically into the bilayer.

Vesicle characterisation. Size, polydispersity index and zeta potential by dynamic and electrophoretic light scattering; morphology by transmission electron microscopy; entrapment efficiency after separation of unentrapped drug by ultracentrifugation or dialysis; and the deformability index by extrusion through a membrane of defined pore size, with the pore radius, applied pressure and extrusion time all stated, since the index is meaningless without them.

Permeation and — more importantly — deposition. Franz diffusion cell studies on excised skin remain the standard in vitro method, and the relevance and limitations of such data have been discussed since the technique was established [40]. For a locally acting formulation, cumulative permeation into the receptor compartment is the wrong primary endpoint: it measures what passes through the skin and would enter the systemic circulation. The informative endpoint is deposition within the skin, measured by tissue extraction and by tape stripping to resolve stratum corneum from deeper layers. A formulation that maximises receptor-compartment flux may be a worse topical product than one that maximises dermal retention.

The correlation analysis. Deformability index against skin deposition across the full designed series, reported with the fitted relationship and its form. This is the step that distinguishes a formulation study from a contribution to the field.

In vivo efficacy. The monoiodoacetate-induced rat model is the established preparation, producing histological changes in subchondral bone and articular cartilage that reproduce key features of

osteoarthritis [41]. The comparison that matters includes a conventional, non-deformable topical preparation of the same extract at the same dose alongside the deformable vesicular gel; without that arm the study demonstrates the benefit of topical delivery rather than the benefit of deformability.

Stability. Accelerated and real-time testing to ICH Q1A(R2) [47], monitoring vesicle size, polydispersity, zeta potential, marker content and drug leakage. Deformable vesicles are thermodynamically fragile by design, and the gel matrix into which they are incorporated must be shown not to rigidify or rupture them during storage — a point at which otherwise promising formulations commonly fail.

VIII. GAPS AND OUTLOOK

Several gaps are worth naming directly.

The correlation gap. Membrane elasticity and skin deposition are both routinely measured and rarely related. Establishing the functional form of that relationship for boswellic acids — whether deposition increases monotonically with deformability or passes through an optimum — would give the field a design rule rather than another formulation.

The deposition gap. Much of the transdermal literature reports cumulative permeation across the skin as the primary outcome. For a locally acting anti-arthritic the relevant quantity is drug retained in the skin and underlying tissue, and tape-stripping or tissue-extraction data are reported far less often than flux.

The marker gap. Entrapment and release are commonly reported for total extract or for "boswellic acids" collectively. Given that AKBA and KBA differ in potency from the α and β acids, and that plasma data show them behaving very differently from one another [11], marker-resolved data are necessary.

The comparator gap. Few studies include a conventional topical preparation of the same extract as a control, so the contribution attributable to deformability is rarely isolated from the contribution of the topical route itself.

The translation gap. No deformable vesicular Boswellia preparation appears to have entered clinical evaluation, despite oral extracts having a respectable randomised trial record [13,14,15] and topical anti-inflammatory therapy having clear guideline support for knee osteoarthritis [4,5]. The modest daily doses used in the oral trials suggest that the quantity a topical formulation would need to deliver is within reach, which makes the absence of clinical work a gap of opportunity rather than of feasibility.

IX. CONCLUSION

Three things are well established. Boswellia serrata extracts produce significant, rapid and reproducible improvement in pain and physical function in knee osteoarthritis in randomised placebo-controlled trials, supported by meta-analysis. The oral bioavailability of the constituents credited with that activity is poor enough and variable enough that the assumed mechanism has been seriously questioned on pharmacokinetic grounds. And current guidelines endorse topical delivery ahead of oral delivery for anti-inflammatory therapy of the knee, on exactly the reasoning that favours local over systemic exposure for a superficial joint.

Taken together these point to a topical Boswellia formulation. The difficulty is that boswellic acids are large, rigid, lipophilic triterpenoids that will not cross the stratum corneum unaided, and deformable vesicles — phospholipid bilayers destabilised by a single-chain edge activator, driven by the transdermal hydration gradient — are the best-characterised carrier for exactly that problem. The Boswellia-specific literature establishes feasibility: ultradeformable transdermal films, transferosomal gels and proniosomal gels of boswellic acid have all been reported.

What has not been done is the piece of work that would make the field predictive. The elasticity of the vesicle membrane is the designed property of the entire platform, and skin deposition is the outcome it exists to produce, yet the two are almost never measured across a designed series and correlated. A Box–Behnken-optimised Boswellia deformable vesicular gel, characterised with marker-resolved entrapment, extrusion-based deformability indices, tape-stripping deposition data and an in vivo osteoarthritis model with a conventional topical comparator, would answer a formulation question

and a mechanistic one at the same time. On the evidence reviewed here, both are worth answering.

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