Boswellic Acid-Rich Boswellia serrata Extract Ethosomal Gel: A Quality-by-Design Review

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***Abstract*—Boswellia serrata gum resin is used for inflammatory joint disease, and its boswellic acids, especially 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), act on inflammatory enzymes and signalling pathways. Oral use is limited by poor solubility and low bioavailability, so a skin-directed product may suit local inflammation. Ethosomes are phospholipid vesicles that contain ethanol, and they have raised skin delivery of many drugs in ex vivo and animal studies. This review asks whether a standardised, boswellic acid-rich B. serrata extract can be placed in an ethosomal gel by Quality by Design (QbD). We read the abstracts of 47 papers on boswellic acids, ethosomes, ethosomal gels, Box-Behnken and central composite designs, HPTLC standardisation, skin deposition methods and anti-inflammatory models. Ethosomal gels of other drugs and plant actives are well described, and an AKBA nanostructured lipid carrier gel has been made by QbD. We found no published ethosome of a B. serrata extract. We outline a conceptual QbD pathway with a target profile, quality attributes, factors and tests. The design is conceptual, and the review reports no experimental data.**

***Index Terms*—Boswellia serrata; boswellic acids; AKBA; ethosomes; ethosomal gel; Quality by Design; Box-Behnken design; skin deposition; anti-inflammatory activity**

I. INTRODUCTION

Extracts of Boswellia serrata gum resin have been tested in animals and in pilot clinical trials for inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and asthma [1]. The resin contains pentacyclic triterpenes called boswellic acids, and reviews credit them with anti-inflammatory, anti-arthritic, antimicrobial and anticancer activities, among others [2]. The main weakness of the class is that boswellic acids dissolve poorly in water and are poorly absorbed, so oral bioavailability is low [3,4].
A topical product avoids the gut, where permeability studies suggested that AKBA is poorly absorbed [1]. The skin is a barrier of its own, however. Ethosomes were introduced as phospholipid vesicles that contain ethanol and water, and an early study showed that they delivered a fluorescent probe into the skin in greater amount and to greater depth than liposomes or a hydroalcoholic solution [5]. Since then many drugs, and some plant actives, have been put into ethosomal gels [6,7].

Quality by Design is a common way to build such a product in a controlled manner: a target profile is set, the factors that affect quality are ranked, and designed experiments model their effects. This review asks whether a standardised boswellic acid-rich B. serrata extract can be developed as an ethosomal gel in this way, for enhanced skin deposition and anti-inflammatory activity. We searched online sources for each element and read the abstracts of the papers cited, not the full texts. We report no experimental results of our own.

II. BOSWELLIA SERRATA AND ITS BOSWELLIC ACIDS

Mechanisms of action
An early study used rat peritoneal neutrophils, in which alpha- and beta-boswellic acids and their 11-

keto and acetyl derivatives reduced leukotriene B4 formation in a concentration-dependent way. Acetyl-11-keto-beta-boswellic acid was the most potent, with an IC50 of 1.5 µM. Up to 400 µM the acids did not impair cyclooxygenase or 12-lipoxygenase in isolated human platelets, and the authors concluded that they are specific, non-redox inhibitors of 5-lipoxygenase [8]. A structure study then showed that the pentacyclic ring system is needed for binding, and that the 11-keto group and a hydrophilic group at C4 are needed for inhibition. AKBA gave IC50 values of 1.5 µM in cells and 8 µM in a cell-free system, while beta-boswellic acid without the 11-keto group gave only partial inhibition [9].

The picture is not settled. A review of in vitro, preclinical, pharmacokinetic and clinical data noted that boswellic acids did not inhibit leukotriene formation in human whole blood, and that plasma AKBA and KBA levels were far below the concentrations active in vitro. Its authors suggested that beta-boswellic acid, with a plasma level about 100-fold higher, may act on microsomal prostaglandin E synthase-1 and cathepsin G instead [1]. Recent reviews name NF-kB, COX-2 and 5-lipoxygenase as targets [10], and add MAPK and the NLRP3 inflammasome [3]. Several targets are probably involved.

Preclinical, clinical and safety evidence

A Boswellia extract with at least 30% AKBA lowered TNF-alpha, IL-6, nitric oxide, COX-2 and phosphorylated NF-kB p65 in LPS-stimulated cells, and in rats with collagen-induced arthritis it reduced the arthritic index and paw volume in a way comparable to celecoxib [11]. A small crossover trial in knee osteoarthritis linked the extract to less pain and swelling, with only minor gastrointestinal adverse reactions [12], and a larger trial of 105 adults reported pain improvement from day 5 [13]. An extract standardised to 30% AKBA did not irritate rabbit skin and had an acute dermal LD50 above 2,000 mg/kg [14]. Several of these clinical and safety papers [11,13,14] are industry authored, so their positive findings need independent confirmation. Table 1 collects the main findings.

Table 1. Principal findings on boswellic acids and B. serrata extracts from the abstracts reviewed. Values are as reported by the authors.

Evidence type	Finding as reported	Ref.
Enzyme assay, rat neutrophils	Boswellic acids reduced leukotriene B4 formation; AKBA most potent (IC50 1.5 µM); no effect on cyclooxygenase or 12-lipoxygenase in human platelets up to 400 µM	[8]
Structure-activity study	AKBA IC50 1.5 µM (cells) and 8 µM (cell-free); 11-keto group and a hydrophilic C4 group needed for inhibition	[9]
Review of pharmacokinetics	Very low plasma AKBA and KBA; beta-boswellic acid proposed to act on mPGES-1 and cathepsin G	[1]
Human volunteers, oral extract	High-fat meal raised AUC and Cmax of three boswellic acids several-fold	[15]
Cells and rat arthritis (industry authored)	30% AKBA extract lowered TNF-alpha, IL-6, NO, COX-2; 40 and 80 mg/kg comparable to celecoxib	[11]
Safety (industry authored)	30% AKBA extract: oral LD50 above 5,000 mg/kg in rats; dermal LD50 above 2,000 mg/kg; non-irritating to rabbit skin	[14]
Crossover trial, knee osteoarthritis	30 patients; less pain, less frequent swelling, greater flexion; minor gastrointestinal effects	[12]
Parallel-group trial (industry authored)	105 adults; VAS pain -45.3% and -61.9% at day 90 on 150 and 300 mg twice daily	[13]

Solubility and bioavailability

A recent review lists poor water solubility, weak intestinal absorption and extensive metabolism as the reasons for low oral bioavailability, and compares phytosomes, micelles, self-emulsifying systems, solid lipid particles, polymeric nanoparticles, hydrogels and cyclodextrin complexes as remedies. It names extract standardisation, formulation stability and limited clinical evaluation as open problems [4]. Food also matters, since a high-fat meal raised the AUC and Cmax of three boswellic acids several-fold in volunteers [15]. For AKBA, a bioavailability under 10% and poor permeability have been reported [16].

III. ETHOSOMES AS SKIN CARRIERS

Composition and behaviour

Ethosomes are vesicles of phospholipid, ethanol and water. In the original characterisation study 2% soy phosphatidylcholine and 30% ethanol were examined, and electron microscopy and 31P-NMR showed multilamellar bilayer vesicles with flexible bilayers and a low transition temperature. Molecules of varying lipophilicity were entrapped [5]. Later reviews describe ethanol contents of up to 50%, with a fluid, soft vesicle membrane [6], and classify the systems as classical ethosomes, binary ethosomes and transethosomes [7]. A review notes strong permeation enhancement but limited commercialisation [17].

Comparison studies repeat the message. For trihexyphenidyl, flux through nude mouse skin was 0.21 mg/cm2/h from ethosomes, 87-fold higher than from liposomes and 4.5-fold higher than from a hydroethanolic solution [18]. For diclofenac sodium, ethosomes and transfersomes gave higher 24 h permeation, flux and skin-retained drug than conventional liposomes, a plain gel or a hydroethanolic solution [19].

How ethosomes are thought to work

Three mechanistic studies give a partly consistent account (Figure 1). In rabbit skin, ketotifen had to be entrapped inside ethosomes for the best delivery, because ethosomes did not improve delivery of non-entrapped drug [20]. With confocal microscopy in rat skin, ethosomes appeared to enter by hair follicles and the stratum corneum, the vesicles seemed to break down on the way, and the phospholipids stayed in the upper epidermis while the drug went deeper [21]. In a third study, spectroscopy showed that ethosomes moved the stratum corneum phospholipids from a steady to an unstable arrangement, and calorimetry on mini-pig skin showed a lower melting temperature and enthalpy. The stratum corneum ultrastructure was not damaged, the main route was intercellular, and only drug-loaded ethosomes raised the amount of drug that permeated [22]. The studies differ on the follicular and intercellular routes, and all used model drugs and not a multi-component extract.

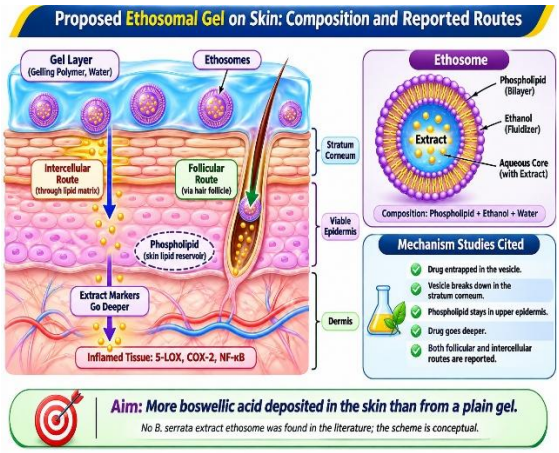


Figure 1. Conceptual scheme of the proposed ethosomal gel on skin, drawn from the mechanism studies cited in the text. The scheme is a reviewer's summary and not a result. 5-LOX, 5-lipoxygenase; SC, stratum corneum.

One result should temper expectations. Lipid vesicles with edge activator and ethanol, described in the paper as ethosomes, did not cross intact stratum corneum in vitro, although some cationic formulations improved penetration into tape-stripped skin [23]. That study concerned nucleic acids, but it shows that barrier state matters.

IV. ETHOSOMAL GELS AND PLANT-DERIVED ACTIVES

Gel bases and rheology

An ethosome suspension is a liquid, and reviews highlight gels, patches and creams as the dosage forms made from it [7]. The choice of gelling agent affects flow and permeation. In a study of Carbopol grades, the target was plastic flow with a yield stress of about 50 to 80 Pa and frequency-independent moduli. Grades C934, C971 and C974 were selected on screening, and ethosome-loaded C974 at 0.50 and 0.75% w/w kept plastic flow at 4, 25 and 32 °C [24]. Other gelling agents used with ethosomes include Carbopol 940 [25], hyaluronic acid [26], HPMC [27] and gelatin [28]. Tocopherol acetate ethosomes showed no significant change in rheology, conductivity or pH over three months [29].

Examples with drugs and phytoconstituents

Table 2 lists ethosomal gels that were designed by experiment or tested for anti-inflammatory activity. A pomegranate extract, with beta-sitosterol as the

measured marker, was made into an ethosomal gel by a central composite design, and the gel released more of the marker than the extract did [30]. A brucine gel reduced carrageenan oedema over 24 h [27], and an edge-activated curcumin and cyclosporine gel reduced arthritic symptoms in a 28-day rat model compared with a marketed product and a conventional gel [31]. A gelatin gel of curcumin ethosomes was active in carrageenan paw oedema [28]. A review covers ethosomes carrying natural actives for infection, inflammation, acne, arthritis and skin cancer [6].

Table 2. Selected ethosomal gels and related systems from the abstracts reviewed. Values are as reported by the authors; the studies differ in model drug and method, so the figures are not comparable between rows.

Active	Design and gel base	Reported result	Ref.
Naproxen sodium	Box-Behnken design; Carbopol 940 gel	105 nm, EE 84.59%; 24 h permeation above commercial products and ethanolic solution	[25]
Meloxicam	16-run Box-Behnken design; binary ethosomes in hyaluronic acid gel	169 nm, EE 83.1%; in vivo inhibition 53.2% vs 43% for classical ethosomes	[26]
Piperine	Box-Behnken design; binary ethosomes in Carbopol and HPMC-K100 gels	187.7 nm, EE 75.12%; 24 h release 86.81% vs 51.20% for plain gel	[32]
Pomegranate extract	Central composite design; ethosomal gel	516.4 nm; viscosity 32,158 cps; marker release 91.83% (gel)	[30]
Brucine	Central composite design; HPMC gel	Ethosome flux 0.548 µg/cm²/h; enhancement ratio 2.73; reduced rat paw oedema	[27]
Curcumin and cyclosporine	Edge-activated ethosomes; gel	About 93.3 nm; fewer arthritic symptoms in a 28-day rat model	[31]

Boswellia in topical carriers so far

The nearest work uses AKBA and not an extract, and it does not use ethosomes. AKBA nanostructured lipid carriers made by hot homogenisation under a three-factor Box-Behnken design (lipid, surfactant, sonication time) had a size of 173.700 nm and an entrapment efficiency of 82.349%, and the release was prolonged to 56 h. In a pseudoplastic gel the ex vivo permeation was 1.34 times that of a plain gel, and viscosity, size and assay were stable for one year [33]. The same group made AKBA lyotropic liquid crystalline nanoparticles coated with hyaluronic acid. Gels of this improved permeation 2.34- and 2.40-fold and retention in the viable dermal layers 4.98- and 6.73-fold against a free AKBA gel, and the coated system reduced paw oedema in a rat arthritis model [16]. A Boswellianano emulgel, made by combining a nanoemulsion of 141 nm with nanomicelles of 31.07 nm in a Carbopol 974 gel, gave a better anti-inflammatory and analgesic response in vivo than the other gels tested and a marketed Boswellia product. Its abstract does not state the plant part, the extract standardisation or the boswellic acid content [34].

V. QUALITY BY DESIGN FOR AN ETHOSOMAL GEL

Quality by Design starts from a quality target product profile (QTPP), from which the critical quality attributes (CQAs) are derived. The critical material attributes (CMAs) and process parameters (CPPs) that affect them are ranked by risk assessment and studied by design of experiments (DoE), and the results define a design space in which the product meets its limits. Box-Behnken design, which fits three factors at three levels without the extreme corner runs, and central composite design are the two

response-surface designs used in several of the ethosome papers we found (Figure 2).

The reported factors are consistent. A Box-Behnken design with yolk phospholipid, ethanol and ultrasonication time as variables and vesicle size as the response gave an optimum of 2.45% phospholipid, 30% ethanol and 67.55% water [21]. Naproxen ethosomes were optimised with phosphatidylcholine, cholesterol and ethanol as factors [25], and meloxicam ethosomes with soya lecithin, ethanol and propylene glycol in a 16-run design with four centre points [26]. Central composite designs used lecithin and ethanol for the pomegranate gel [30] and lecithin, cholesterol and ethanol for brucine [27]. A two-factor, three-level (3^2) factorial design for ketoconazole showed that vesicle size fell as phospholipid and ethanol rose, while entrapment rose with phospholipid and fell with ethanol [35]. Box-Behnken designs have also been used for a tioconazole transethosomal gel [36] and for piperine ethosomes in Carbopol and HPMC gels [32]. In the AKBA lipid carrier study, lipid and surfactant governed entrapment [33].

A Boswellia extract contains several boswellic acids, so entrapment has to be defined for chosen markers and not for the extract as a whole. We therefore propose AKBA, KBA and beta-boswellic acid as markers, measured by the HPTLC methods in the next section. Table 3 sets out the proposed plan, which is a proposal and not a result.

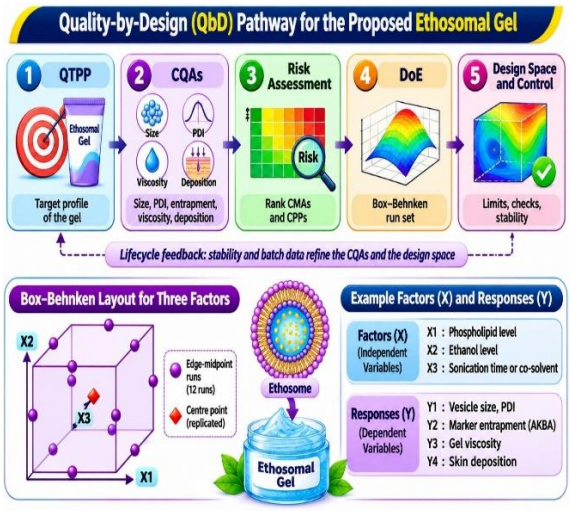


Figure 2. Conceptual QbD pathway for the proposed ethosomal gel (top) and a three-factor Box-Behnken layout (bottom). The factors and responses are examples drawn from the literature reviewed and are not experimental results. QTPP, quality target product profile; CQA, critical quality attribute; CMA, critical material attribute; CPP, critical process parameter; DoE, design of experiments.

Table 3. Proposed QbD plan for the boswellic acid-rich extract ethosomal gel. The entries are design proposals, based on the cited literature, and are not reported results.

Element	Proposed content	Basis	Ref.
QTPP	Gel for local skin use with a standardised boswellic acid-rich extract in ethosomes; non-irritating; stable on storage; anti-inflammatory in vivo	Targets set in ethosomal gel and AKBA carrier studies	[7,33]
CMAs	Content of AKBA, KBA and beta-boswellic acid in the extract; phospholipid and polymer grade	Variable content in commercial products	[37,38]
CPPs	Preparation method (hot, cold, injection), sonication time, neutralisation of the gel	Process variables in published designs	[21,31]
DoE factors	Phospholipid %, ethanol %, and a third factor such as propylene glycol, cholesterol or extract load	Box-Behnken and central composite studies	[25–27]

Element	Proposed content	Basis	Ref.
Responses	Size, PDI, zeta potential, marker entrapment; gel viscosity, yield stress, pH, spreadability	Common responses in ethosomal gels	[24,29,30]
Performance, safety and stability	Marker release; Franz-cell permeation; tape-stripping deposition; skin irritation; carrageenan oedema or arthritis model; stability for at least three months	Skin models, in vivo models, irritation and stability reports	[14,19,39–42]

VI. STANDARDISING THE EXTRACT

Standardisation comes before formulation, because the starting resin varies. KBA and AKBA are the markers in the European Pharmacopoeia 6.0 monograph for B. serrata [1]. A planar chromatography method with automated multiple development separated the four main boswellic acids, detecting KBA and AKBA at 254 nm and beta-boswellic acid and its acetate at 560 nm after derivatisation. The authors found significant variation in the content of these compounds in commercial products [37].

Two validated HPTLC methods are available for the markers. One quantified KBA and AKBA over 2 to 14 µg/band with RSD below 2% [38]. The other measured AKBA, beta-boswellic acid, 3-oxo-tirucallic acid and serratol, with a limit of quantification of 76 ng/band for AKBA and mass spectrometric confirmation [43]. Either could be used for the extract and the deposition samples once checked for the gel matrix. The extract would have to be characterised by the same method before the phrase boswellic acid-rich is given a number.

VII. EVALUATION OF SKIN DEPOSITION AND ANTI-INFLAMMATORY ACTIVITY

Permeation and deposition

Franz diffusion cells are the usual apparatus, but results can be poorly reproducible. A validation study with ibuprofen and synthetic membranes reduced the coefficient of variation of steady-state permeation from a gel from 25.7% to 5.3% (n=6) by refining cell dimensions, stirring, temperature control and sampling [39]. Deposition needs a skin model. Pig ear skin ex vivo reproduced the diffusion and partitioning parameters seen in human volunteers for four ibuprofen formulations after 30 min, which supports its use with tape stripping [40]. Skin handling still matters: by the fifth strip, frozen-thawed porcine skin had lost 80.6% of its stratum corneum against 33.5% for fresh skin [44]. Tape stripping and microdialysis are the main in vivo methods for local bioavailability [45].

Binary ethosomes of ketoconazole gave 5.3-fold epidermal and dermal deposition against a drug suspension [35], and tocopherol acetate ethosomes retained 51.20% in rat skin in a 24 h ex vivo study [29]. Release has been fitted to the Higuchi model [19,36] and, for the curcumin gel, to the Hixson-Crowell model [31]. A permeation study of the proposed gel should report both receptor-phase flux and skin content, using the same skin source for all groups.

Anti-inflammatory testing and irritation

Choice of the animal model is critical, and plant-derived agents need systematic screening [41]. Carrageenan paw oedema was the inflammation model in three of the ethosomal papers cited here [27,28,42], and it has also been used for a herbal emulgel, which was tested against a diclofenac emulgel in a second, arthritis model [46]. We do not quote the efficacy figures of that herbal emulgel study, because its abstract reports inhibition values that we could not reconcile. A curcumin nanoemulgel showed the lowest swelling at 12 h among three curcumin gels in that model [47]. Arthritis models, such as the Freund's complete adjuvant model, have been used for curcumin and AKBA carriers [16,31].

Assays in LPS-stimulated RAW 264.7 cells report cytokines and PGE2 [31]. Skin irritation was assessed by the Draize test for flurbiprofen ethosomes [42], and the curcumin and cyclosporine gel was non-irritating [31].

VIII. GAPS IN THE LITERATURE AND CONCLUSION

Several gaps limit what can be said today. First, we found no study of a B. serrata extract in ethosomes. The closest are the AKBA nanostructured lipid carrier gel made by QbD [33] and a Boswellianan oemulgel whose abstract does not give the plant part, the standardisation or the boswellic acid content [34]. Second, the AKBA carrier studies used the purified compound, so they do not show whether an extract with several boswellic acids behaves in the same way [16,33]. Third, the mechanism studies of ethosomes used model drugs, and they differ on the follicular and intercellular routes [21,22]. Fourth, ethanol-containing vesicles did not cross intact skin in one study [23], so results in damaged skin cannot be assumed to hold for intact skin. Fifth, the clinical and safety data for standardised extracts come largely from industry-authored papers [11,13,14]. Sixth, we read only abstracts, so methods and full results were not checked.

A standardised, boswellic acid-rich B. serrata extract in an ethosomal gel is a reasonable proposal. AKBA inhibits 5-lipoxygenase at micromolar concentrations in vitro [8,9], oral use is limited by bioavailability [4], ethosomal gels of plant actives have been built by Box-Behnken and central composite designs [27,30,32], and validated HPTLC methods exist for the markers [38,43]. The design in this review is conceptual. The next steps would be a specification for the extract, a screening study, a Box-Behnken optimisation with marker-based responses, deposition tests on a controlled skin model and an in vivo anti-inflammatory study.

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