

Quality by Design-Based Development of a Herbal Ointment for Diabetic Neuropathic Pain: A Critical Review

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Abstract: Painful diabetic peripheral neuropathy affects a large share of people with long-standing diabetes, and the oral drugs used to treat it help only some patients while often causing dizziness, sedation and other adverse effects. Topical therapy, which keeps the drug near the painful skin and limits systemic exposure, is therefore an attractive option. Herbal ointments have a long traditional use for limb pain and numbness, yet they rarely reach clinical practice because their quality varies from batch to batch and their performance is seldom defined by measurable targets. Quality by Design (QbD), set out in ICH Q8(R2), Q9 and Q10, offers a way to build reproducibility into a product from the first day of development. This review brings together the pathophysiology of diabetic neuropathic pain, the clinical evidence for topical and herbal treatments, and published QbD work on semisolid and plant-based topical products. On that basis it lays out a practical roadmap for an herbal ointment: target product profile, critical quality attributes, risk ranking, a Box-Behnken optimization, design space, control strategy and analytical QbD. The review also points out where the evidence is thin, notably the absence of controlled clinical data for most plant extracts, and suggests what future studies need to show

Keywords: diabetic peripheral neuropathy, neuropathic pain, herbal ointment, Quality by Design, critical quality attributes, Box-Behnken design, design space, topical delivery.

I. INTRODUCTION

Diabetes is a lifelong condition in which blood glucose stays above the normal range, and its damage accumulates quietly in the eyes, kidneys, heart, blood vessels and nerves. Of these complications, nerve damage is the most frequent. Position statements and reviews put the lifetime figure at roughly half of all people with long-standing diabetes, although estimates vary with the definition used and the population examined. A subset of these patients develops pain: a burning or stabbing sensation in the feet and lower legs that is typically worse at night, sometimes so sensitive that a bedsheet feels unbearable. Sleep suffers first, then mood, walking and the ability to work. Because the same neuropathy dulls protective sensation, small injuries can pass unnoticed and progress to ulcers and infection, which remain a leading route to amputation.

Treatment is mostly symptomatic. Tight control of glucose, blood pressure and lipids may slow the disease but rarely removes established pain. The drugs that do help, namely gabapentinoids, serotonin–noradrenaline reuptake inhibitors and tricyclic antidepressants, bring a meaningful reduction in pain to only a minority of those who take them, and sedation, dizziness, dry mouth and weight gain frequently force a dose reduction or withdrawal. For older adults, who often already take several medicines for diabetes, hypertension and kidney disease, the burden of oral therapy and its interactions is a real concern.



Applying the drug to the painful skin is an obvious way around this problem. A topical product can act on the nerve endings where the symptoms arise while keeping blood levels low. Capsaicin and lidocaine are the best known examples, and both have a place in guidelines. Traditional systems of medicine such as Ayurveda, Siddha and Unani have used medicated oils and ointments for limb pain for centuries, and a handful of clinical studies suggest that herbal topical products may help. The difficulty is that a traditional preparation is only as consistent as its raw material and the person making it. Plant composition shifts with species, soil, season, harvest and drying, and a method that works one month may give a different product the next. Without defined specifications and process controls, it is hard to say what a patient actually received, or to compare one trial with another.

Quality by Design is a response to exactly this kind of problem. Instead of relying on end-product testing to catch failures, QbD starts from the intended clinical performance, identifies the material and process factors that can change it, studies those factors with planned experiments, and fixes an operating region in which quality is assured. It has been applied to creams, gels and plant-based topical systems, but we found little published work that follows the approach from beginning to end for an herbal ointment aimed at diabetic neuropathic pain. This review therefore has three aims: to summarise the disease and the evidence for current and herbal topical treatment; to examine how QbD has been used for semisolid and plant-derived topical products; and to propose a stepwise framework, with the assumptions made explicit, that a formulation scientist could follow.

Literature Search Approach

This is a narrative review. Sources were identified in PubMed, Google Scholar and ScienceDirect using combinations of the terms “diabetic peripheral neuropathy”, “painful diabetic neuropathy”, “topical capsaicin”, “herbal cream”, “polyherbal”, “quality by design”, “Box-Behnken”, “ointment” and “semisolid”. Regulatory documents were taken from the International Council for Harmonisation. English-language clinical studies, reviews, guidelines and formulation papers were considered, and priority was given to randomised or controlled human data, systematic reviews and peer-reviewed formulation studies that reported their design factors and responses. Conference abstracts, product brochures and papers that did not describe their methods were not used for evidence statements. Because no formal risk-of-bias scoring was done, the conclusions below should be read as an expert synthesis, not as a pooled estimate.

Diabetic Neuropathic Pain

Definition and Burden

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. In diabetes the lesion affects the small fibres that carry pain and temperature as well as the large fibres for touch and position sense. Several syndromes are grouped under diabetic neuropathy, including autonomic, focal and proximal forms, but the one most associated with pain is distal symmetric polyneuropathy. It starts in the toes, creeps upward, and eventually follows a “stocking-and-glove” distribution. Risk rises with the duration of diabetes, poor glycaemic control, age, hypertension, dyslipidaemia, obesity, smoking and alcohol use, and neuropathy can already be present when type 2 diabetes is first diagnosed because the preceding period of raised glucose often goes unnoticed.

Mechanisms

No single mechanism explains the pain; metabolic, vascular, inflammatory and neuronal changes feed into one another. Those most relevant to a topical product are summarised here, because they determine what a skin-applied treatment can realistically target.

Metabolic and Oxidative Injury:

Excess intracellular glucose is diverted into the polyol pathway, where aldose reductase converts it to sorbitol. The resulting osmotic and redox stress, together with the formation of advanced glycation end-products and increased



mitochondrial production of reactive oxygen species, damages axonal proteins, lipids and DNA. This is the main reason antioxidant plant constituents attract interest, though it should be remembered that most evidence for them comes from cell and animal work.

Microvascular and Inflammatory Change:

Endothelial dysfunction and reduced nitric oxide limit blood flow to the nerve, and the resulting hypoxia injures fibres further. Pro-inflammatory mediators such as TNF- α and interleukins 1 β and 6 sensitise nociceptors and activate glial cells in the spinal cord.

Peripheral and Central Sensitisation:

Injured fibres fire spontaneously, and the expression or behaviour of sodium channels and the capsaicin receptor TRPV1 changes. In the spinal cord, facilitating pathways strengthen while descending inhibition weakens, so the pain persists and spreads. Because the nociceptor endings and the inflammatory signals sit in the skin and superficial nerve layers, a rationale exists for acting there; whether a given topical product reaches those targets in diabetic skin is a separate and less certain question.

Clinical Features and Assessment

Patients describe burning, stabbing and electric-shock sensations, tingling, numbness, cramps and allodynia, meaning pain from a stimulus that is normally harmless. Symptoms are symmetrical and worse at night. On examination, vibration, light touch and temperature sensation are reduced, and ankle reflexes may be lost. The diagnosis is mainly clinical, supported by the 10-g monofilament and tuning-fork tests, with nerve conduction studies kept for unclear cases. Pain intensity is usually followed with the numeric rating scale or visual analogue scale, while questionnaires such as DN4 and the Diabetic Neuropathy Score help to characterise symptoms.

Treatment and the Case for Topical Therapy

Systemic Options and Their Limits

Current guidance recommends glycaemic and cardiovascular risk control, foot care, and drug therapy with pregabalin or gabapentin, duloxetine or venlafaxine, or amitriptyline, with opioids reserved because of the risk of dependence and other harm. A large meta-analysis found that the number of patients who need to be treated for one to obtain substantial pain relief is high for several of these drugs, and adverse effects are common. This is the practical space in which a well-tolerated local treatment could be useful, either alone in patients with a small painful area or as an addition to oral therapy.

Topical Agents

Capsaicin is the most thoroughly studied topical agent. It first activates TRPV1 on nociceptors and then desensitises them, with depletion of substance P. A review of clinical studies concluded that 0.075% capsaicin cream applied for about eight weeks can reduce pain in painful diabetic neuropathy, while a narrative systematic review noted that benefit from the cream was not consistent across comparative trials, with significance at weeks 2 and 6 but not at week 8, and that the lower 0.025% gel did not separate from placebo. The 8% patch has better support: a Cochrane review judged high-concentration capsaicin useful for some patients with chronic neuropathic pain, and a randomised study in painful diabetic neuropathy reported lower pain scores with the patch plus standard care than with standard care alone, along with changes in skin nerve fibre density. The recurring drawback is application-site burning and erythema, which can undermine adhere.



What Herbal Topical Studies Show

Human data on herbal topical products for diabetic neuropathic pain are limited and mostly small. In a randomised, placebo-controlled pilot of 50 patients with type 2 diabetes, a polyherbal cream applied twice daily produced a much larger fall in Diabetic Neuropathy Score at six months than placebo. A four-week placebo-controlled trial of a 10% *Trachyspermum ammi* cream in 92 patients with burning feet likewise reported reduced burning, numbness and tingling. The same group of investigators earlier tested a polyherbal cream against silver sulphadiazine in diabetic foot ulcers and found comparable healing. These results are encouraging, but the studies are small, short, and provide little information on how the creams were standardised, which makes them difficult to reproduce. Table I compares the main topical studies discussed.

TABLE I: Selected Clinical Evidence for Topical Treatment

Product	Design and population	Main finding
Capsaicin 0.075% cream	Review of clinical studies in painful diabetic neuropathy	Pain reduction after about 8 weeks of application
Capsaicin cream, gel and patch	Narrative systematic review	Patch effective; cream benefit not sustained at week 8 in comparative studies; local burning common
Capsaicin 8% patch	Randomised, 50 patients with painful neuropathy, plus 25 open-label non-painful	Lower pain scores than standard care alone; skin nerve fibre changes noted
Polyherbal cream	Randomised, placebo-controlled pilot, 50 patients, 6 months	Greater fall in neuropathy score than placebo
<i>T. ammi</i> 10% cream	Randomised, placebo-controlled, 92 patients, 4 weeks	Reduced burning, numbness, tingling and allodynia

Why an Ointment

An ointment is an oleaginous, occlusive semisolid that stays on the skin and softens it. Occlusion hydrates the stratum corneum and generally raises the uptake of lipophilic ingredients, which is helpful when the skin of the feet is dry and cracked, as it often is in diabetes. A wax-oil base also suits plant extracts rich in non-polar constituents. On the other hand, an ointment is greasy, can be difficult to spread over a large area, and releases water-soluble compounds poorly. These trade-offs make the choice of base, wax level and extract loading part of the design problem and not a detail to be settled by habit.

Quality by Design: Principles and Evidence

From Testing to Design

In conventional development a fixed process is validated and the product is tested at the end; a failed batch is rejected, and a change in process normally needs fresh approval. ICH Q8(R2) describes the alternative as development that begins with predefined objectives and stresses product and process understanding and control, based on sound science and quality risk management [8]. Quality is designed in, so that testing confirms rather than creates it [9, 18]. The vocabulary is compact. The Quality Target Product Profile (QTPP) states what the product must achieve. Critical Quality Attributes (CQAs) are the properties that must stay within limits to deliver that profile. Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) are the input and process variables that influence the CQAs. The design space is the demonstrated region of CMAs and CPPs in which quality is assured, and the control strategy is the set of controls that keeps production inside it [8].



Supporting Guidelines

Three ICH documents provide the framework. Q8(R2) covers pharmaceutical development, Q9 supplies the tools of quality risk management, and Q10 describes a pharmaceutical quality system that supports continual improvement throughout the product's life. A fourth, ICH Q14, extends similar thinking to analytical procedures, and Q1A(R2) specifies stability testing.

Why Herbal Products Need It Most

Synthetic drugs usually come from a controlled chemical process. Herbal ingredients do not. The marker content of a leaf extract can differ with variety, growing conditions, harvest time, drying method, extraction solvent and storage, and the extract itself is a mixture whose active components are often incompletely known. Fixing the process cannot solve a problem that begins in the field. QbD addresses it by identifying which attributes of the extract matter, setting ranges for them, and showing by experiment that the finished product remains within specification across those ranges.

Published QbD Work on Topical Product

Table II lists three formulation studies that applied QbD to semisolid or plant-based topical products. Simões and co-workers studied a 1% hydrocortisone cream with a three-factor, three-level Box-Behnken design, using a failure-mode analysis to pick glycerol monostearate, isopropyl myristate and homogenisation rate as the factors; their responses covered microstructure, drug release and permeation, assay and physical stability, and they ended with a design space. Oliveira and colleagues used the same type of design to optimise a topical formulation containing chestnut shell extract, arriving at a combination of surfactant, beeswax and macadamia oil, and then followed its stability over time. Lasprilla and colleagues applied QbD at the preformulation stage of a plant-extract product, testing extract–excipient compatibility, characterising extract lipophilicity and building model lipid formulations before defining a design space.

TABLE II: QbD Studies on Semisolid and Plant-Based Topical Products

Product	Design and factors	Key responses
1% hydrocortisone cream	Box-Behnken, 3 factors: glycerol monostearate, isopropyl myristate, homogenisation rate	Droplet size, rheology, drug release, permeation, assay, stability; design space established
Topical formulation with <i>Castanea sativa</i> shell extract	Box-Behnken, 3 factors, response surface analysis	Technological properties and stability of optimised formula
Plant-extract topical product (preformulation)	Compatibility screening, lipid model formulations, experimental design	Excipient choice, critical factors, design space

Two points stand out. First, the formulation-level logic transfers readily from cream to ointment, because the key factors are again the structuring agent, the oil phase and the process conditions. Second, none of these reports tied its quality targets to a clinical outcome in patients, so the link between a CQA and pain relief is still assumed and not demonstrated. For an herbal ointment this link matters even more, since the active constituents are not always known.

A QbD Roadmap for an Herbal Ointment

The sequence below is summarised in Fig. 1. The numerical targets and factor levels given are illustrations drawn from general pharmaceutical practice, not experimental results; each has to be confirmed in pre-formulation work for the specific plant material and base chosen.



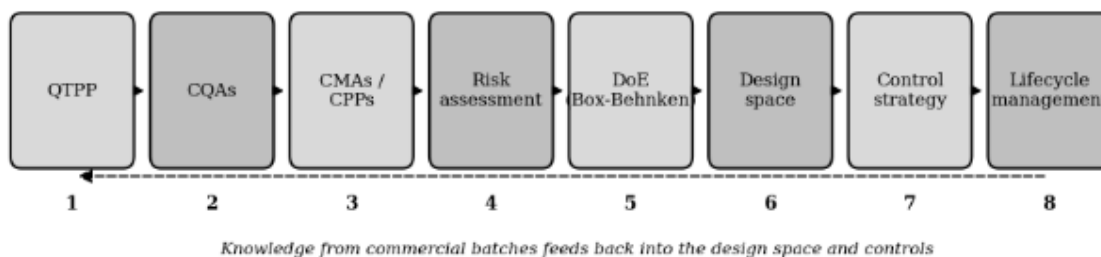


Fig. 1. Stepwise QbD workflow proposed for the herbal ointment

Defining the Target Profile and Critical Attributes

The QTPP should be written before any formulation work, because every later decision refers back to it. For a topical ointment against neuropathic pain, the profile covers the dosage form and route, patient acceptability, delivery of the marker compounds, local tolerance, microbial safety and shelf-life under the climate in which the product will be used. CQAs are then chosen by asking which attributes could most affect safety or efficacy if they drifted. Table III combines both steps.

TABLE III: Illustrative QTPP and Critical Quality Attributes

QTPP element	Target	Linked CQA	Critical?
Dose uniformity	Marker content 90–110% of label claim	Assay of marker compounds	Yes
Skin delivery	Reproducible release of markers	In-vitro release	Yes
Ease of application	Spreads with little force on painful skin	Spreadability, consistency	Yes
Skin compatibility	No more than mild irritation; skin-compatible pH	Irritation score, pH	Yes
Physical stability	No bleeding or phase change in warm climate	Softening point, viscosity	Yes
Microbial safety	Within pharmacopoeial limits	Microbial load	Yes
Stability	24 months at 30 °C/75% RH (zone IVb)	Assay and physical tests over time	Yes
Patient acceptance	Pleasant colour and odour	Appearance, odour	No (monitored)

Material Attributes and Process Parameters

For the extract, the critical material attributes are marker content, moisture, particle size or solubility in the base, and microbial and contaminant quality (heavy metals and pesticide residues). For the base, the ratio of wax to oil, oil acid and peroxide values, and the level of any cooling or penetration-enhancing agent matter. For a fusion-made ointment the critical process parameters include melting temperature, the temperature at which the extract and volatile components are added, stirring speed and time, cooling rate and filling temperature.

Risk Assessment

Following ICH Q9, an Ishikawa diagram is used to list every plausible source of variation under headings such as materials, method, equipment, people, measurement and environment, and a failure mode and effects analysis (FMEA) then scores each factor for severity, occurrence and detectability. The product of the three scores, the risk priority number, decides which factors justify experimentation and which can be fixed or controlled by specification. Table IV shows a plausible outcome.



TABLE IV: Illustrative Risk Ranking of Formulation and Process Factors

Factor	Severity	Occurrence	Detectability	Decision
Wax-to-oil ratio	High	High	Low	Study by DoE
Extract loading	High	Medium	Medium	Study by DoE
Cooling agent level	Medium	Medium	Medium	Study by DoE
Melting temperature	Medium	Medium	High	Control within a range
Stirring speed	Low	Low	High	Keep fixed
Extract moisture	Medium	Low	High	Control by specification

Design of Experiments

Changing one factor at a time is slow and cannot reveal interactions. Designed experiments vary several factors together in a planned pattern. Screening designs such as fractional factorial or Plackett-Burman layouts suit the early stage, when many factors are in play, and response surface designs are used to optimise the few that remain. The Box-Behnken design (BBD) is a common choice for semisolids. For three factors at three levels it needs only 15 runs, 12 edge midpoints plus three centre points, and it avoids the corner combinations in which every factor is at its extreme. That feature is useful here because the highest level of every ingredient together could be irritating or physically unstable. Studies on topical products have used this design successfully. A possible set of factors is given in Table V.

TABLE V: Illustrative Box-Behnken Factors and Levels

Code	Factor	Low (-1)	Middle (0)	High (+1)
X1	Beeswax, % w/w	8	12	16
X2	Standardised leaf extract, % w/w	2	4	6
X3	Menthol (cooling agent), % w/w	1	2	3

Responses might include spreadability (Y1), viscosity (Y2), cumulative release at six hours (Y3) and an irritation score (Y4). Each is fitted to a second-order polynomial:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X_1^2 + \beta_{22}X_2^2 + \beta_{33}X_3^2$$

where β_0 is the intercept, β_1 to β_3 are main-effect coefficients, β_{12} to β_{23} are interaction terms, and β_{11} to β_{33} are quadratic terms. Model adequacy is judged by analysis of variance, R^2 , adjusted and predicted R^2 , lack of fit and adequate precision. Numerical optimisation with desirability functions then selects the formula that best balances the responses, and confirmatory check-point batches test the prediction.

Design Space and Preparation

Overlaying the contour plots of all significant responses reveals the region where every CQA meets its limit at once; this overlap is the design space. Operating inside it is not treated as a change, whereas moving outside normally calls for regulatory notification. In practice the fusion method is typical. The authenticated, dried and powdered leaves are extracted and standardised against marker compounds; wax and oil are melted together, commonly in the range of 65–70 °C; the extract is incorporated with continuous stirring; the mass is cooled to around 40–45 °C before volatile ingredients are added to limit loss; and the ointment is stirred until set, then filled into tubes. A preservative is included if the water activity or extract justify it.

Evaluation of the Optimised Ointment

Evaluation should follow the CQAs in Table III. Physical testing covers appearance, homogeneity, pH, viscosity, spreadability, extrudability and softening point. A validated HPLC or HPTLC method determines marker content. Release and permeation are examined in Franz diffusion cells, using a synthetic membrane or excised skin. Safety testing includes skin irritation and sensitisation by an approved or validated alternative method, microbial limits, heavy metals and pesticide residues. Efficacy is explored in the streptozotocin-induced diabetic neuropathy rat, using von



Frey filament, hot-plate, tail-flick and cold allodynia tests, together with markers such as malondialdehyde, superoxide dismutase and TNF- α . Stability follows ICH Q1A(R2), with accelerated testing at 40 °C/75% RH for six months and long-term testing at conditions suited to the intended climate.

Control Strategy, Lifecycle and Analytical QbD

The control strategy combines specifications for the raw extract and excipients, in-process limits for temperature and mixing time, and release tests for the finished ointment. Batch and stability data are trended over the product's life, and under ICH Q10 this knowledge can be used to refine or widen the design space. The same logic applies to the analytical method used for marker assay. An analytical target profile defines what the method must achieve, critical method variables such as mobile-phase composition, flow rate and column temperature are optimised by experiment, and a method operable design region is established, as encouraged by ICH Q14.

Critical Discussion and Research Gaps

Several obstacles stand between this framework and a usable product. They are listed in order of how strongly we think they affect the outcome.

Evidence for the Active Ingredient:

For plant extracts other than capsaicin and a few polyherbal creams, most claims of benefit rest on cell and rodent experiments. A formulation can be perfectly consistent and still be ineffective. Dose-ranging studies in the neuropathy model should come before large optimisation campaigns, and human trials with validated pain scales, adequate sample size and a placebo base are needed.

Defining Markers for a Mixture:

QbD needs measurable CQAs. When the active constituents are not established, assay of one or two markers may not represent pharmacological activity. Chemical fingerprinting with more than one marker, linked to a bioassay where possible, is a more defensible approach.

Efficacy Versus Irritation:

Pungent or cooling agents can help pain but also sting. Capsaicin illustrates the point, as local burning limits adherence. Irritation therefore belongs among the measured responses of the design and not among the checks done afterwards.

Delivery Through Diabetic Skin:

Barrier function, hydration and blood flow in diabetic skin differ from those of healthy skin, so release data from healthy tissue or synthetic membranes may not predict performance. Nanocarriers such as nanoemulsions and lipid carriers might improve uniformity of delivery but add complexity and cost, and they should be considered only if a simple ointment falls short.

Regulatory Variation:

Herbal products are regulated differently in India (Drugs and Cosmetics Rules and the AYUSH framework), in Europe (traditional herbal medicinal products) and in the United States (botanical drug guidance). A QbD file built for one market will need adaptation for another.

Digital Tools:

Process analytical technology and machine-learning-assisted experimental design could shorten development and support real-time release, but they presuppose the basic product knowledge that this review has argued is still missing for herbal ointments.

II. CONCLUSION

Painful diabetic neuropathy remains difficult to treat, and a local, well-tolerated herbal ointment is a reasonable candidate to add to the options. What has held such products back is not a lack of tradition but a lack of defined quality. The studies reviewed show that QbD, with risk ranking and Box-Behnken optimisation, works well for creams and plant-based topical products, and the same logic can be extended to an ointment for neuropathic pain. Three things are still missing: controlled human evidence for most plant extracts, quality attributes that are demonstrably linked to



clinical effect, and an experimental study that carries an herbal ointment through the whole sequence from profile to design space. Closing these gaps is the next step, and the framework above is intended to make that work easier to plan and to compare.

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