SYSTEMATIC REVIEW

PHARMACEUTICAL ENGINEERING OF HERBAL EXTRACTS: FROM MULTICOMPONENT COMPLEXITY TO ROBUST DRUG DELIVERY SYSTEMS

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ABSTRACT

Herbal extracts are still among the widely used remedies, around the world. Turning them into medicines that work reliably and meet modern standards is tricky. There's no way to make sure they are absorbed well by the body give the same results every time or pass regulatory checks. The main problem is that an herbal extract is not a compound. It's a mix of substances that can change and interact in different ways. The benefits often come from how all those ingredients work not from just one active part. This makes it hard to control and standardize. The pharmaceutical engineering path from raw material to delivery system is followed in this overview.

First, we look at the causes and effects of multicomponent complexity, including the potential loss of pharmacokinetic synergy due to over-purification of extracts. Next, we go over characterization and standardization approaches that go beyond single-marker assays to include chemical fingerprints, multivariate analytical techniques, and lifecycle thinking under ICH Q14. Next, we go over green extraction technologies and the use of process analytical technology and Quality by Design (QbD) in extract manufacturing. We examine solid-state conditioning of extracts downstream, particularly spray drying, and the primary delivery platforms (phytosomes, self-emulsifying systems, lipid and polymeric nanocarriers, and related systems), focusing on the particular difficulty of simultaneously loading, protecting, and releasing numerous constituents with various physicochemical properties. The increasing roles of machine learning and network pharmacology are also discussed, along with the regulatory frameworks for botanical medications in the US and Europe, including the recent joint FDA/EMA negotiations. Finally, we suggest a research agenda for reliable, scalable, and therapeutically translable herbal drug delivery devices as well as a fingerprint-preserving design approach.

Keywords: herbal extracts; multicomponent systems; standardization; quality by design; phytosomes; self-emulsifying drug delivery systems; nanocarriers; botanical drugs; network pharmacology.

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1. INTRODUCTION

Many cultures have utilized medicinal plants and their preparations for millennia, and a significant portion of the world's population still relies on them as their main source of healthcare. Because of their traditional use and presumed therapeutic benefits, herbal medications are extensively utilized; yet, their efficacy and safety vary by product and necessitate thorough study **[1]**. The market for herbal medicines has grown quickly at the same time, and with it comes the expectation that herbal goods would be held to standards of quality that are comparable to those of conventional pharmaceuticals.

A structural mismatch is revealed by that expectation. Single, well-defined molecules—a medicinal ingredient with a known structure and purity, a dosage form designed to maximize its solubility, permeability, and stability, and analytical techniques that measure a single analyte against a reference standard—were the foundation of the contemporary

pharmaceutical paradigm. Nearly all of these presumptions are broken by a herbal extract. Alkaloids, flavonoids, glycosides, saponins, tannins, and terpenes are among the various chemical classes that make up its contents. These constituents are present in a wide range of quantities and polarity.

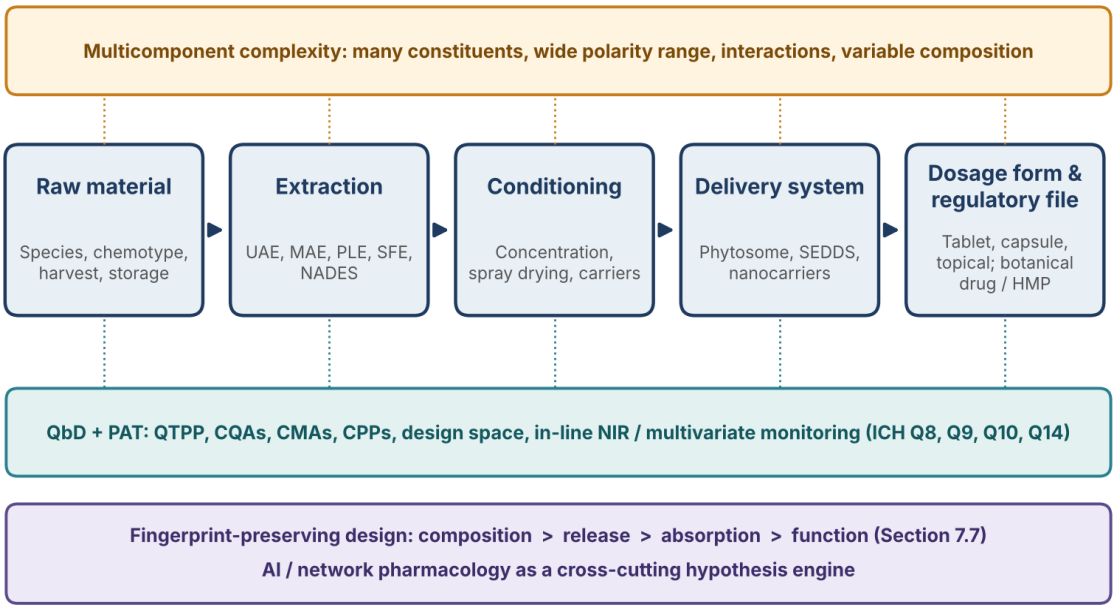
Single well-defined molecules an ingredient with a known structure and purity a dosage form that maximises solubility, permeability and stability and analytical methods that compare one analyte to a reference—were the basis of modern medicine. Almost all of these ideas are challenged by an extract. Alkaloids, flavonoids, glycosides, saponins, tannins and terpenes are some of the chemical types, in a herbal extract. These parts of an extract appear in many amounts and have different polarities. The species, chemotype grow conditions, harvest time post-harvest handling and the extraction method all change an extract's makeup. Its therapeutic action may result from several contents acting on multiple targets, or occasionally from inert constituents that alter the solubility, absorption, or metabolism of the active ingredients. **[1,10]**.

This problem has been addressed by pharmaceutical engineering in a number of essentially distinct ways. To characterize the entire chemical profile, analytical scientists have created chemometric and fingerprinting techniques **[1,2]**. Greener and more intense extraction technologies have been introduced by process engineers **[4–9]**. To increase the low oral bioavailability that restricts many herbal ingredients, formulation scientists have modified phospholipid complexes, lipid-based systems, and nanocarriers **[11,23–25]**. The Quality by Design framework of ICH Q8 has been applied to extracts and herbal products by quality scientists **[12–15]**. For their part, regulators have created separate paths for traditional herbal medicines and botanical medications **[33–35]**. More recently, data-driven solutions to multicomponent, multi-target complexity have been suggested using machine learning and network pharmacology **[38–42]**.

An integrated perspective that treats these streams as links in a single chain is currently missing, allowing decisions made at the extraction stage to be assessed for their effects at the delivery-system stage and vise versa. This review aims to provide such perspective. The core dilemma is simple: how can we keep the parts of a herbal extract, which give it both healing power and engineering difficulty, stable and reliable, in a dose form?

The review is organized to follow the material's course. The definition of multicomponent complexity and its implications for pharmaceuticals are given in Section 2. Characterization and standardization are covered in Section 3, while extraction engineering is covered in Section 4. While Section 6 deals with the transformation of extracts into solid and liquid intermediates, Section 5 uses QbD and process analytical techniques to generate extracts. Section 7 looks at delivery platforms and the special problems that come with loading combinations. Section 9 talks, about the role of intelligence and network pharmacology. Section 8 covers the challenges related to regulation and scaling up. Section 10 points out what we still don't know and where future research should go. Figure 1 gives a summary of the framework that guides the discussion.

Figure 1. Integrated framework for the pharmaceutical engineering of herbal extracts. Multicomponent complexity affects every stage; QbD and PAT provide the control layer, and fingerprint-preserving design links composition, release, absorption and function.



2. MULTICOMPONENT COMPLEXITY: THE CENTRAL ENGINEERING PROBLEM

2.1 Sources of Variability

Herbal extracts are variable long before they are extracted. The raw materials metabolite composition is influenced by a number of factors, including plant species and chemotype, geographic origin, climate, harvest season, drying, and storage. Batch-to-batch consistency is frequently cited by commercial producers as one of the most challenging quality issues for botanical products because the raw material is derived from nature and its quality is impacted by factors such as location of origin, weather, harvest season, and storage and processing conditions **[3]**. An additional layer is added by authentication: as adulteration and substitution of herbal components are known issues, official standardization methods incorporate chromatographic fingerprinting, chemical testing, macroscopic and microscopic identification, DNA profiling, quantification of markers, contaminant testing and physicochemical tests **[1]**.

Material variability is layered with process-induced variability. Which components are recovered and which are degraded depends on the extraction method itself, temperature, time, solid-to-liquid ratio, and solvent composition. Additional variability builds up at each unit activity since production is frequently done as a sequence of distinct batch activities **[20]**. As a result, two extracts with the same nominal marker content and botanical name may differ significantly in the remainder of their composition and, consequently, in their biological behavior.

2.2 Why the Mixture May Be the Drug

The intricacy of an extract is not just an annoyance that needs to be eliminated, which is an important consideration for formulation design. An increasing amount of research indicates that pharmacokinetic behavior may be influenced by non-active or weakly active components. Reduced intestinal absorption, which is connected to the loss of pharmacokinetic synergies among elements after the extract is purified, has been associated to a loss of pharmacological action when a purified constituent is given in place of the extract **[10]**. The literature has illustrative examples, such as daidzin, whose exposure following oral ingestion of a plant extract was documented. Examples compiled in the literature include hypericin and berberine, which exhibit significantly higher water solubility in the corresponding herbal extract than as isolated compounds, and daidzin, whose exposure following oral

administration of a herbal extract was reported to be approximately ten times higher than after the same dose of the pure compound **[10]**. The creation of naturally occurring nanoscale assemblies, interactions with transporters and metabolizing enzymes, and solubilization by co-occurring amphiphilic elements like saponins are some of the suggested methods. Herbal extracts have been described by certain authors as having their own natural, effective delivery methods **[10]**.

There are two real-world applications for this. First, engineering techniques that reduce an extract to a single marker chemical may eliminate the very qualities that make it beneficial because partial or complete loss of activity upon isolation or purification of constituents is recognized in the herbal literature **[11]**. Second, any delivery mechanism intended for an entire extract must cope with these internal interactions and, ideally, maintain or take advantage of them. A successful extract may become less effective if the carrier effectively encapsulates the marker but is unable to release or maintain the co-constituents in their natural proportions.

2.3 Pharmaceutical Consequences of Complexity

The key characteristics of multicomponent extracts are summarized in Table 1 as they relate to formulation and process issues. The lack of a single quality-critical trait is the most significant effect. The performance of the dosage form in a traditional product is determined by the drug substance's assay, content homogeneity, and dissolution. Each of these terms needs to be reinterpreted in an extract-based product: dissolving refers to the simultaneous release of constituents that may range in solubility by orders of magnitude; content uniformity refers to the distribution of a mixture; and assay may refer to a marker or a set of chemicals. The biopharmaceutical classification framework, which assumes one molecule, cannot be applied directly.

Table 1. Features of multicomponent herbal extracts, their pharmaceutical consequences and engineering responses.

Feature	Pharmaceutical consequence	Engineering response
Many constituents from several chemical classes	No single assay represents quality or content	Chemical fingerprints, multi-marker panels, chemometrics **[1,2]**
Wide polarity and solubility range	Unequal loading, release and stability in carriers; one solubilization mechanism is rarely enough	Constituent-resolved release testing; carriers able to host mixed polarity (SEDDS, phytosomes) **[28,29]**
Natural variability of raw material	Batch-to-batch differences despite equal marker content	Material specifications, feed-forward control, PAT **[13,16-19]**
Constituent interactions (pharmacokinetic synergy)	Purification or inappropriate encapsulation may reduce efficacy	Whole-extract formulation; fingerprint-preserving design **[10]**
Hygroscopic, sticky or thermolabile extracts	Poor flow and compressibility; physical and chemical instability	Carrier-assisted spray drying; moisture control **[21,22,31]**
Incompletely known active constituents	Critical quality attributes uncertain	Spectrum-effect and bioassay-linked CQAs; network pharmacology **[38-40]**

3. CHARACTERIZATION AND STANDARDIZATION: FROM MARKERS TO FINGERPRINTS

3.1 3.1 Limits of Marker-Based Control

The traditional approach to standardizing an extract is to quantify one or two marker compounds. This is simple and reproducible, but it captures only a small fraction of the chemical space of the extract, and it assumes that the marker is a valid proxy for efficacy. Fingerprinting methods were developed to address this limitation. Instead of focusing on one or two analytes, they evaluate the whole chemical profile and extract a common pattern that is then used as the criterion for assessing individual materials or formulations **[1]**. Reviews of hyphenated techniques coupled with chemometrics emphasise that chromatographic fingerprints are not always a perfect representation of all constituents, so that fingerprinting complements rather than replaces targeted

quantification and other forms of identification **[2]**.

3.2 The Analytical Toolbox

Table 2 summarises the analytical techniques most commonly used to characterize herbal extracts and formulations. High-performance thin-layer chromatography and liquid chromatography with diode-array detection remain the workhorses of fingerprinting in quality control laboratories, because they are inexpensive, robust and well understood. Mass spectrometry, particularly high-resolution LC-MS, provides structural information and allows untargeted profiling, which is valuable for discovering unexpected variation and for linking composition to activity. Spectroscopic methods such as near-infrared spectroscopy are fast and non-destructive and are increasingly used for process monitoring, as discussed in Section 5. DNA-based methods address botanical identity rather than chemistry and are useful for detecting substitution **[1]**.

The chemometric layer is as important as the instrument. Similarity measures, principal component analysis and related multivariate techniques turn high-dimensional chromatographic or spectral data into decision-ready statistics **[2]**. Their value has been demonstrated for batch release: combining multivariate statistical analysis with chromatographic fingerprints has been proposed as a way of evaluating batch-to-batch quality consistency of botanical drug products, with characteristic peaks weighted according to their variability across production batches **[16]**.

Table 2. Analytical techniques for characterizing herbal extracts and formulations. Compiled from [1,2,16-18] and general analytical practice.

Technique	Information provided	Typical role	Main limitation
HPTLC	Visual chemical profile; identity	Screening, routine QC	Limited resolution and quantitation
HPLC-DAD / UPLC	Quantitative fingerprint; marker content	Release testing; consistency	Needs chromophores and reference compounds
LC-MS / GC-MS	Structural information; untargeted profiling; volatiles	Discovery of variation; impurity and degradation profiling	Cost; matrix effects; complex data handling
NMR	Whole-extract metabolite profile	Reference and orthogonal method	Sensitivity; cost; throughput
NIR / Vis-NIR	Rapid chemical and physical attributes	Raw material screening; PAT	Indirect; requires calibration models
DNA-based methods	Species identity	Authentication; adulteration	No chemical quantitation; DNA degraded in processed extracts
Chemometrics (PCA, similarity, MSPC)	Pattern recognition; consistency statistics	Batch release; process monitoring	Model validation and lifecycle management (ICH Q14)

3.3 Analytical Procedures Under a Lifecycle Framework

ICH Q14 provides a useful frame for thinking about analytical procedures for complex products. It applies the systematic, risk-based logic of ICH Q8 and Q9 to analytical development, distinguishes minimal from enhanced approaches, introduces the analytical target profile, and includes dedicated considerations for multivariate analytical procedures and for procedures used in real-time release testing **[36]**. These features are directly relevant to herbal extracts. A fingerprint-based identity or consistency test is inherently multivariate, and its development, validation and lifecycle management benefit from the explicit treatment of model-based procedures that Q14 and Q2 (R2) now provide. Defining an analytical target profile for a fingerprint, for instance specifying the discrimination power required between acceptable and unacceptable batches, would make fingerprint methods more defensible than the informal similarity thresholds often used in practice.

3.4 Linking Chemistry to Function

Chemical fingerprints describe composition, not activity. Where a validated biological or pharmacokinetic readout exists, linking the two through bioactivity-guided or spectrum-effect approaches strengthens the argument that a fingerprint is quality-relevant. This is especially important when a formulation changes the biological behaviour of the extract, as delivery systems do. In such cases, comparison of in vitro release profiles of multiple constituents, together with a bioassay or pharmacokinetic study of marker constituents, provides a more meaningful equivalence criterion than total marker content alone. We return to this point in Section 7.7.

4. EXTRACTION ENGINEERING

4.1 From Solvent Maceration to Intensified, Greener Processes

Extraction is the first and arguably most consequential engineering step, because it defines the composition of the material on which all later steps depend. Conventional solvent-based methods are simple but consume large volumes of organic solvent and energy, and they may degrade thermolabile constituents. Greener alternatives, including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), supercritical fluid extraction (SFE) and extraction with natural deep eutectic solvents (NADES), have been developed to improve efficiency while reducing environmental impact **[4,9]**. Reviews of green extraction of botanicals emphasise combining these methods with GRAS solvents or unconventional solvents such as NADES **[4]**, and they place the discussion within the wider circular-bioeconomy context **[9]**.

Table 3 summarises the main technologies. Ultrasound intensifies mass transfer through cavitation, and its performance is governed by variables such as amplitude, sonication time, temperature, solid-to-solvent ratio and pressure, all of which must be optimised for maximum recovery of bioactive compounds **[6]**. Combining ultrasound with supercritical fluids or pressurized liquids has been explored as a route to process intensification, and the mechanisms, operating parameters and remaining obstacles to widespread use have been reviewed **[5]**. Supercritical carbon dioxide is attractive because it is non-toxic and leaves no solvent residue, but its intrinsically non-polar character limits the range of constituents that can be recovered without co-solvents, and the high pressures required raise capital and operating costs **[5]**.

Table 3. Extraction technologies used for botanicals.

Technology	Principle	Advantages	Limitations	Refs
Conventional (maceration, percolation, Soxhlet)	Solvent diffusion, often with heat	Simple, low-cost equipment	Large solvent and energy use; long times; thermal degradation	General
Ultrasound-assisted (UAE)	Cavitation enhances mass transfer	Efficient; moderate temperature; short times	Parameters must be optimized; probe wear; scale-up	**[4,6]**
Microwave-assisted (MAE)	Dielectric heating	Fast; reduced solvent	Local overheating; thermolabile constituents at risk	**[4,7]**
Pressurized liquid (PLE)	Liquid solvent at high temperature and pressure	Automated; reduced solvent	Equipment cost; thermal degradation risk	**[4,5]**
Supercritical CO2 (SFE)	Supercritical fluid solvent	Non-toxic; no solvent residue	Non-polar; high-pressure cost; co-solvents needed for polar constituents	**[4,5]**
Natural deep eutectic solvents (NADES)	Hydrogen-bond donor/acceptor eutectic mixtures	Biodegradable; high solvency; tunable	Viscosity; recovery of solutes; toxicological qualification	**[7,8]**

4.2 Natural Deep Eutectic Solvents

NADES are mixtures of hydrogen-bond donors and acceptors, such as choline chloride with sugars, organic acids or polyols, that are liquid at moderate temperature and have been described as a new frontier in green extraction because of their biodegradability, low volatility, high solvating capacity and, in many cases, biocompatibility **[7,8]**. Combined with UAE or MAE, they have been studied extensively for phenolic compounds **[7]**. From a pharmaceutical engineering perspective, NADES are interesting for a further reason. Because they can dissolve both polar and some less polar constituents, and because the NADES-extract system may itself behave as a delivery vehicle, they connect to the observation that natural nanoscale assemblies in herbal extracts contribute to absorption **[10]**.

The engineering difficulties are nevertheless real. Recovery of the target compounds from the viscous NADES after extraction remains a challenge, and the possible harmful effects of NADES have not been fully characterised **[7]**. If the NADES is retained in the product rather than removed, it becomes an excipient that requires toxicological qualification, compatibility studies and specification, a point that is rarely addressed in the extraction literature.

4.3 Selectivity Versus Compositional Fidelity

A conceptual tension runs through extraction design. Process development often aims at selectivity, for example maximising the yield of a marker or a class of constituents. Pharmaceutical development of whole extracts, in contrast, requires compositional fidelity, which we use here to mean how closely the constituent profile of each batch reproduces that of a defined reference extract, including minor constituents that may matter for activity. A process that is optimised for one marker may shift the profile in ways that the marker assay does not detect. We therefore recommend that extraction optimisation use a fingerprint-level response, such as a similarity index to a reference fingerprint or a small set of principal-component scores, alongside marker yield, so that the optimum reflects the profile rather than a single analyte.

4.4 Implications for Downstream Processing

The choice of solvent determines what the formulation scientist receives: a hydroalcoholic extract differs from an aqueous extract, a supercritical CO2 extract or a NADES extract in polarity, residual solvent, viscosity, hygroscopicity and stability. Extract properties such as lipophilicity are decisive for excipient selection; in a QbD preformulation study of a topical plant-extract product, characterising the lipophilicity of the extract guided the design of model lipid formulations **[12]**. Extraction and formulation should therefore be co-designed. Specifying the extraction solvent and drying method as part of the extract definition, and not only the botanical source, is a precondition for reproducible downstream performance.

5. QUALITY BY DESIGN AND PROCESS ANALYTICAL TECHNOLOGY

5.1 Applying the QbD Vocabulary to Extracts

QbD, as defined in ICH Q8(R2), is a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and control based on sound science and quality risk management **[37]**. Its vocabulary (quality target product profile, critical quality attributes, critical material attributes, critical process parameters, design space and control strategy) applies naturally to herbal products, but each term requires adaptation. Table 4 shows how these elements can be defined for an herbal extract. A systematic analysis of QbD for herbal extract development identified a set of critical material attributes and critical process parameters and mapped them through risk assessment to critical quality attributes of the extract. In that analysis, ten critical material attributes and six critical process parameters were judged to carry medium to high risk to

seven critical quality attributes **[14]**. Even if the specific numbers depend on the product, the exercise shows the value of making the causal chain from material and process to quality explicit, so that control strategies can proactively limit variability.

Table 4. QbD elements interpreted for herbal extracts and extract-based products.

QbD element	Interpretation for herbal extracts	Examples
QTPP	Target profile of extract or product: fingerprint, marker range, dosage form, release, stability	Defined for a polyherbal tablet **[15]**
Critical quality attributes	Marker content, fingerprint similarity, moisture, residual solvent, contaminants, release of a marker set, microbial limits	Seven CQAs for extracts **[14]**
Critical material attributes	Botanical identity and chemotype, marker content, raw material moisture and particle size	Ten CMAs rated medium to high risk **[14]**
Critical process parameters	Solvent composition, temperature, time, solid-liquid ratio, ultrasound amplitude, spray-drying inlet temperature	Ten parameters screened simultaneously **[13]**
Design space	Multivariate region in which CQAs are met, derived by DoE	Definitive screening design; central composite design **[13,15]**
Control strategy	Material specifications, feed-forward adjustment, PAT, real-time release testing	NIR with MSPC **[17-19]**
Lifecycle management	Continuous process verification; analytical procedure lifecycle	ICH Q8(R2), Q14 **[36,37]**

5.2 Examples of QbD in Herbal Development

Published case studies illustrate how the framework works in practice. In a study on *Panax notoginseng*, ten process parameters were studied simultaneously using a definitive screening design, and the resulting models were used to calculate a design space and to derive criteria for discriminating high-quality from low-quality raw material, leading to a quality control strategy for herbal materials that takes the matching between process characteristics and material attributes into account **[13]**. This is a significant conceptual step: most QbD work focuses on process parameters and treats the starting material as fixed, whereas in herbal manufacturing material attributes are among the largest sources of variation, and the control strategy must act on them, for example through incoming material specification or feed-forward adjustment of process parameters.

At the formulation stage, a QbD preformulation study of a topical plant-extract product evaluated extract-excipient compatibility at elevated temperature and humidity, characterised the extract's lipophilicity, and used experimental design to set a design space and rational excipient selection while confirming preservation of antimicrobial activity **[12]**. In a solid dosage form, a quality target product profile and critical quality attributes were defined for a polyherbal antioxidant tablet, and a central composite design was used to optimise disintegrant and diluent levels with respect to disintegration time and friability **[15]**. These examples are modest in scale, but together they show that QbD is feasible at each level, from the extract to the final product.

A recurring limitation of the herbal QbD literature is that the response variables are physical (hardness, disintegration, friability) or are limited to a marker, rather than reflecting the multicomponent profile. Extending the QbD response set to include fingerprint similarity or multi-constituent release would align the practice with the central scientific problem.

5.3 Process Analytical Technology and Batch Consistency

Process analytical technology (PAT) is the natural partner of QbD, because a design space is only useful if the process can be monitored and kept within it. Near-infrared spectroscopy has been the most widely used PAT tool in pharmaceutical process monitoring because it is fast, non-destructive

and inexpensive. In herbal manufacturing, it has been used to characterize tanshinone extract powder, determining several quality attributes simultaneously, including physical properties, although the relationship between spectra and physical attributes is partly nonlinear **[18]**. In-line Vis-NIR spectroscopy combined with multivariate statistical process control has been applied to the column chromatographic purification of *Ginkgo biloba* leaf extract for batch-to-batch consistency evaluation of the elution process **[17]**. For solid processing, an online NIR platform was used to control blend homogeneity across sixteen natural-product powders; the particle shape and flowability descriptors emerged as critical material attributes affecting blending end time **[19]**.

Multivariate statistical process control, with historical good batches used as a reference, allows deviations to be detected in real time, in contrast to the retrospective detection that end-product testing provides. For herbal extracts, where raw material variation is the dominant disturbance, such monitoring is likely to be more valuable than for synthetic APIs, because it can trigger compensation before the batch is lost. The broader regulatory context, including continuous manufacturing under ICH Q13, further supports the movement towards real-time control, although the application of continuous manufacturing to extract-based products remains largely unexplored.

6. CONDITIONING OF EXTRACTS: SOLID AND LIQUID INTERMEDIATES

6.1 Why Conditioning is a Formulation Problem

Most extracts leave the extraction plant as dilute liquids or viscous concentrates. These are unstable, prone to oxidation and microbial growth, and difficult to dose, store and standardize, so they are usually converted to dry powders, which are preferred over liquid presentations because of their higher stability **[21]**. This conversion is not a neutral operation. It determines moisture content, hygroscopicity, particle size, density, flowability and compressibility of the extract, all of which govern whether the material can be processed into tablets or capsules, loaded into a carrier, or dissolved reproducibly.

6.2 Spray Drying

Spray drying is the most widely employed technology for producing dried extracts from liquid plant extracts, and the quality of the powder depends on the operating conditions (inlet temperature, feed rate, atomization) and on the type and concentration of the carrier, or drying coadjuvant **[21]**. Extract powders are typically hygroscopic and show poor flow and compactability, which makes direct compression difficult, and operating conditions and feed composition are often reported to depend on the herb, so that new product development times are long **[22]**. An encouraging result is that a single set of operating conditions proved suitable for seven different medicinal plant extracts, giving powders with adequate flowability, stability and compactability whose properties were not a function of the type of herb **[22]**. If this finding generalises, platform conditions for spray-dried extracts, analogous to platform processes in biologics, could shorten development considerably.

Carrier selection remains empirical. For spray-dried Orthosiphon stamineus extract, addition of silicon dioxide at 30% w/w gave the best improvement in hygroscopicity, flowability and compressibility, whereas maltodextrin and lower silicon dioxide levels gave little benefit **[31]**. Hygroscopicity of individual extracts can also be a direct formulation constraint: in a polyherbal tablet containing amla extract, hygroscopicity of the extract had to be managed in the formulation **[15]**. Because carriers dilute the extract, they also reduce the drug load per unit mass, a trade-off that becomes critical when the dried extract is to be incorporated into a delivery system with limited loading capacity.

6.3 What Drying Does to the Profile

Thermal exposure, shear and interfacial stress during drying can alter the profile of an extract. Volatile constituents are lost,

thermolabile constituents degrade, and constituents that were solubilized by co-extracted amphiphiles may crystallise or precipitate on drying. Yet drying studies seldom report fingerprint-level outcomes, and recovery is typically assessed for a handful of markers. In keeping with the argument of Section 4.3, we suggest that spray drying and other conditioning steps be evaluated against the pre-drying fingerprint, with a pre-specified acceptance criterion for profile similarity, and that the hygroscopic behaviour of the dry extract be characterised as a critical material attribute for all downstream steps.

7. DELIVERY SYSTEMS FOR MULTICOMPONENT EXTRACTS

7.1 The Case for Advanced Delivery

Many herbal constituents are lipophilic or high-molecular-weight compounds with poor solubility and permeability, extensive presystemic metabolism, or instability in gastric fluid, and extracts that show excellent in vitro activity often disappoint in vivo **[11]**. Nanotechnology-based systems have been proposed to increase effectiveness of active components, to protect them from the acidic gastric environment, and even to reintroduce constituents that had been discarded earlier because they were not usable in conventional formulations **[11]**. Encapsulated extracts have been reported to outperform the free form in vitro; for example, nanoparticles prepared from a methanolic extract of Ocimum sanctum showed better antimicrobial activity than the free extract **[11]**. Yet the same review notes that such results depend on adequate characterization and that clinical confirmation is limited.

The distinctive problem for extracts is that most delivery-system design principles were established for single drugs. Loading capacity, encapsulation efficiency, release rate and stability are properties of a specific drug-carrier pair; for an extract with many constituents, they become vectors rather than scalars, and the carrier must be a compromise between the requirements of the most hydrophobic and the most hydrophilic components. Compositional heterogeneity makes the nanoformulation of botanical extracts intrinsically more difficult than that of single compounds **[44]**. Table 5 compares the main platforms in terms of their suitability for whole extracts.

Table 5. Delivery platforms and their suitability for whole herbal extracts. Evaluation of suitability reflects the authors' synthesis of the cited literature.

Platform	Mechanism	Suitability for whole extracts	Main limitations	Refs
Phytosomes (phyto-phospholipid complexes)	Complexation of polar functional groups with phosphatidylcholine	Good for polyphenol-rich extracts; class-based complexation of many constituents	Non-polar constituents may remain uncomplexed; metabolism not prevented	**[23-26]**
SEDDS / SMEDDS (liquid and solid)	Spontaneous emulsification and solubilization	Good for lipophilic constituents; can host a range of polarity	Constituent-dependent loading; high surfactant load; physical stability	**[28-30]**
Liposomes	Phospholipid bilayer vesicles	Hydrophilic and lipophilic constituents in principle	Unequal encapsulation; stability; cost	**[44]**
Solid lipid and nanostructured lipid carriers	Solid lipid matrix	Protects labile constituents; sustained release	Limited loading; polymorphic transitions	**[44]**
Polymeric nanoparticles	Polymer matrix or capsule	Controlled release; targeting possible	Organic solvents; scale-up; regulatory burden	**[11,32,44]**
Nanoemulsions	Surfactant-stabilised oil droplets	Lipophilic fraction	Hydrophilic fraction poorly served; stability	**[44]**
Solid dispersions, cyclodextrins, nanocrystals	Amorphization, inclusion, size reduction	Suited to one dominant constituent class	Selective for particular constituents	General

7.2 Phytosomes and Phyto-phospholipid Complexes

Phytosomes are complexes formed between herbal extracts or purified constituents and phospholipids, mainly phosphatidylcholine, and are among the most commercially advanced approaches to improving bioavailability of herbal actives **[23]**. The amphiphilic nature of the phospholipid provides a favourable hydrophilic-lipophilic balance, improving dissolution behaviour in the lipid-rich membranes of the gastrointestinal tract **[23]**. In the phospholipid complex the polar head of the lipid interacts with the polar functional groups of the phytoconstituent (typically phenolic hydroxyls), which is why the technology is best suited to polyphenol-rich extracts; the technology is protected by trademarks and patents, and its principles of formulation and characterization have been reviewed extensively **[25]**. Reviews also emphasise that the phospholipid protects constituents from degradation in the gastrointestinal tract and may extend shelf life, while stressing that more clinical trials are needed to confirm safety and therapeutic benefit **[24]**.

The most thoroughly documented example is the curcumin phytosome marketed as Meriva, a complex of curcuminoids with phosphatidylcholine standardised to a defined curcuminoid content that retains the three curcuminoids in the proportions found in the source extract **[26]**. Manufacturer-reported pharmacokinetic data indicate markedly higher plasma curcuminoid exposure than standard curcumin extracts; in one preliminary human study, plasma curcumin after 450 mg of the phytosome was reported to resemble that obtained from 4,000 mg of a standard extract, and the product is reported to be supported by dozens of human studies **[26]**. Fold-increases quoted in the commercial literature vary widely, and much of this evidence originates with the manufacturer, so independent replication and consistent pharmacokinetic reporting are desirable. Two further cautions apply. The phytosome does not prevent phase II metabolism, so most circulating curcuminoid after oral administration is conjugated, and higher blood levels do not automatically translate into higher tissue exposure or better clinical outcomes.

For multicomponent extracts, phytosomes offer an appealing feature: because complexation depends on a class property (polar functional groups) rather than on a specific structure, many constituents can be complexed simultaneously. Whether the complexation is quantitatively equal for all constituents, and whether non-phenolic constituents (terpenoids, alkaloids) are left outside the complex, are questions that are seldom answered, because most characterization focuses on the marker. Applications in topical delivery have also been reviewed, where phytosomes may enhance skin penetration of phytochemicals **[23]**.

7.3 Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant and cosurfactant, together with the drug or extract, that form fine emulsions spontaneously on contact with gastrointestinal fluids. They are attractive for poorly water-soluble herbal constituents because they promote solubilization and may reduce presystemic biotransformation **[30]**. A variety of herbal extracts and constituents, including silymarin, curcumin, berberine, puerarin, baicalein and zedoary turmeric oil, have been formulated in self-microemulsifying systems **[45]**.

SEDDS are probably the delivery platform for which the multicomponent issue has been addressed most directly. A solid self-microemulsifying system developed for Salvia miltiorrhiza extract was designed explicitly to load the various active constituents into a single system and improve the oral bioavailability of both hydrophilic and hydrophobic compounds, a challenge for which, according to its authors, success had been limited **[28]**. Selection of the cosurfactant was guided by extract solubility, which was markedly higher in Transcutol P

than in other cosurfactants tested **[28]**. In a mixture-design study of curcuminoids, a ternary system of Obleique CC497, Tween 20 and Transcutol P at a defined ratio gave droplets of about 250 nm and emulsification within about 70 seconds, and demonstrated simultaneous solubilization of the three curcuminoids **[29]**. The same study, however, illustrates the central issue: the maximum loading differed more than seventeen-fold between the least and the most soluble curcuminoid **[29]**. A single vehicle therefore loads each constituent to a different extent, and the ratio of constituents in a dose delivered by the system can differ from the ratio in the extract. Solid SEDDS prepared by adsorption onto carriers address the stability and handling limitations of liquid systems and have been explored for extracts such as Boswellia serrata, where ternary phase diagrams were used to define the self-emulsifying region and globule size and drug content were the key responses **[30]**.

7.4 Lipid and Polymeric Nanocarriers

Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and polymeric nanoparticles have all been applied to botanical extracts. They have been discussed in terms of their ability to improve physicochemical properties, protect against degradation and enhance delivery efficiency **[44]**, and have been reviewed for neurodegenerative disorders, where nanoformulations of curcumin, quercetin, resveratrol, piperine, Ginkgo biloba and Nigella sativa are reported to improve outcomes, although the underlying evidence is predominantly preclinical **[32]**. In practice, nanocarriers raise particular issues for whole extracts: differences in constituent polarity produce unequal encapsulation efficiency; surface-active constituents (saponins, for example) can destabilize or restructure the carrier; and the cost, scale-up and regulatory burden of the nanocarrier may exceed that of the simpler lipid-based systems described above.

Among the human data, the nanoparticle curcumin formulation Theracurmin is notable because it is described as the first nanoparticle curcumin shown to increase plasma levels in human volunteers, with a dose-dependent increase up to at least 210 mg in a single-dose study in healthy volunteers without saturation of absorption **[27]**. Systematic reviews of nanoparticle curcumin conclude that bioavailability is generally increased compared with conventional formulations **[27]**, but, as for phytosomes, evidence for clinical outcomes lags behind pharmacokinetic evidence.

7.5 Other Approaches

Solid dispersions and co-amorphous systems, cyclodextrin complexes, nanocrystals and mesoporous carriers are further routes to increasing dissolution of poorly soluble constituents. For extracts, each approach presents a version of the same difficulty: constituents with different physicochemical behaviour are unlikely to respond equally to a single solubilization mechanism. Hybrid designs, for example a phytosome incorporated into a self-emulsifying system, or a NADES-based extract combined with a lipid carrier, have been suggested but are still at an early stage. The observation that natural nanoscale assemblies in extracts contribute to absorption **[10]** points to a different, potentially simpler strategy, namely a formulation that preserves the native colloidal organization of the extract through gentle processing, rather than breaking it down and rebuilding it with synthetic carriers. This idea remains largely speculative and deserves systematic investigation.

7.6 Stability and Compatibility

Stability of delivery systems for extracts must be considered at two levels: physical stability of the carrier (particle size, phase separation, aggregation, drug leakage) and chemical stability of the constituents (oxidation, hydrolysis of glycosides, photodegradation). QbD-based compatibility studies, in which extract and excipients are stored under accelerated conditions and the extract's functional performance, such as antimicrobial activity, is monitored together

with composition, provide a model for how to address both **[12]**. For lipid-based systems, peroxide formation in unsaturated lipids is a particular risk when the extract contains pro-oxidant constituents such as polyphenols in the presence of trace metals, and compatibility studies should therefore include oxidative stress markers.

7.7 Defining Performance and Equivalence for Multicomponent Delivery Systems

The central gap in the field is the lack of agreed performance criteria for multicomponent delivery systems. We propose a tiered approach that we refer to as fingerprint-preserving design:

1. Composition tier: the fingerprint of the loaded system, after dissociation of the carrier, should be similar to that of the starting extract above a pre-specified similarity threshold, and the ratios of a defined set of marker constituents (not fewer than three, covering the range of polarity) should be within pre-specified limits.
2. Release tier: in vitro release of the marker set should be measured simultaneously in biorelevant media, and the release profiles should be compared with the extract using a suitable multivariate or model-independent comparison.
3. Absorption tier: pharmacokinetic comparison of the marker set against the unformulated extract, with attention to whether the carrier changes the relative exposure of constituents (the pharmacokinetic fingerprint).
4. Function tier: a mechanism-relevant bioassay or clinical endpoint, where one is validated, to confirm that the formulated extract retains the activity of the reference extract.

This tiered scheme links the analytical toolbox of Section 3 and the QbD logic of Section 5 to delivery-system development. It would allow a formulator to state explicitly what is being preserved, and to justify why changes in composition ratio are acceptable when they occur, for instance when a loss of a poorly absorbed constituent is offset by a gain in exposure of the main actives.

8. REGULATORY FRAMEWORKS, SCALE-UP AND TRANSLATION

8.1 Pathways for Botanical Drugs and Herbal Medicinal Products

Regulatory authorities regulate the quality and standard of herbal drugs in view of problems such as herb-drug interactions, adverse effects and toxicity, and the World Health Organization has issued guidelines for the evaluation and quality control of herbal drugs; reviewers argue that regulatory guidelines, standard operating procedures and GMP expectations still need to be improved **[43]**. Two distinct frameworks dominate the discussion of medicinal products. In the United States, botanical drug products can be developed through the investigational new drug and new drug application route, with guidance that dates from 2004, was revised in a 2015 draft and was issued in final form in December 2016, covering the regulatory requirements for phase 1 to 3 trials and for marketing applications **[33]**. Only a small number of botanical drugs have been approved through this route, sinecatechins and crofelemer being the best-known examples. In the European Union, a bottom-up approach relying on long-standing use and on safety information from products already on the market underpins the herbal medicinal product and traditional use registration systems under the Committee for Herbal Medicinal Products **[35]**.

A joint FDA/EMA workshop on regulatory perspectives for herbal medicinal and botanical drug product development, held on 25 September 2026, recognised that both agencies have existing guidance, that they share core principles, and that there are meaningful differences between their frameworks **[34]**. Press coverage of the meeting reported that a number of US submissions had failed because quality parameters could not be demonstrated to the agency's satisfaction, and described the central themes as safety, efficacy, quality,

pharmacovigilance, real-world evidence, appropriate regulatory pathways, education, transparency and collaboration **[35]**. Because this workshop took place only recently, authors citing it should consult the final agenda, presentations and recording published by the agencies. For delivery-system developers, the practical message is that quality, and especially demonstration of consistency of a complex mixture, remains the main reason for failure, which strengthens the case for the fingerprint-based and QbD approaches discussed above.

8.2 Quality Systems and Analytical Expectations

For extracts and their formulations, the relevant ICH framework comprises ICH Q8(R2) on pharmaceutical development, Q9 on quality risk management and Q10 on the pharmaceutical quality system **[37]**, supplemented by Q14 and Q2(R2) on analytical procedure development and validation **[36]**. ICH Q8(R2) accepts both minimal and enhanced approaches and states that continuous process verification can be an alternative to traditional process validation, and that end-product testing is not necessarily required when appropriately justified **[37]**. For herbal products, an enhanced approach that includes raw material attributes in the control strategy and uses multivariate analytical procedures would be consistent with these frameworks.

8.3 Scale-up

Scale-up of herbal delivery systems involves problems that are well known for conventional nanomedicines, such as reproducibility of particle size and encapsulation, together with problems specific to extracts. Feed variability changes the physical properties of the extract (viscosity, surfactant content, solids) and can therefore change the performance of a downstream carrier from one batch to another. Raw material variability has been shown to affect the end point of a blending operation across natural-product powders **[19]**. Strategies include (i) specification of the extract as an intermediate with defined fingerprint and physical attributes, (ii) use of PAT to monitor critical steps **[17-19]**, (iii) feed-forward adjustment of process parameters to compensate for material variation **[13]**, and (iv) adoption of platform processes where the unit operations are robust to extract identity **[22]**. Multivariate statistical process control with historical good batches as reference, as used in the manufacture of traditional Chinese medicines, provides a template **[16,17]**.

8.4 Clinical Translation

The gap between preclinical and clinical findings is a persistent feature of herbal pharmacology. Even for the best-studied examples, such as curcumin, human pharmacokinetic and clinical evidence for advanced formulations is far smaller than the volume of preclinical literature **[26,27]**. A shortage of controlled clinical trials with standardized, well-characterised formula-tions has been identified in reviews of phytosomes **[24]**. To strengthen translation, we recommend that clinical studies of herbal delivery systems (i) report the fingerprint of the test product, (ii) include the unformulated extract as comparator, (iii) measure more than one constituent in plasma, and (iv) use clinically meaningful endpoints alongside pharmacokinetic ones.

9. ARTIFICIAL INTELLIGENCE AND NETWORK PHARMACOLOGY

9.1 Network Pharmacology for Multicomponent Mechanisms

Network pharmacology treats a herbal formula as a network of constituents, targets, pathways and disease processes, which matches the multi-component, multi-target, multi-pathway nature of traditional Chinese medicine **[40]**. The typical workflow comprises identification of ingredients, construction of compound-target-pathway-disease networks, network analysis, and experimental validation **[40]**. Machine learning is increasingly used to select key features from these data. In one study, a machine learning-assisted approach combined serum metabolomics and network pharmacology to identify the key compound,

target and pathway underlying the efficacy of an herbal formula against alcoholic liver injury **[38]**. In another, machine learning was integrated with network pharmacology, molecular dynamics and in vitro validation to elucidate how a classical decoction acts on perimenopausal syndrome **[39]**. Deep learning and graph neural network methods are being developed for compound-target interaction prediction, including hypergraph representation learning designed for multi-compound, multi-target mechanisms **[41]**.

9.2 Data-driven Formulation and Process Design

Beyond mechanism, AI methods have been proposed to identify bioactive ingredients, anticipate synergistic interactions and screen formulations rapidly for safety, bioavailability and efficacy **[42]**. Table 6 summarises the principal uses and the associated limitations. For pharmaceutical engineering, the more immediate opportunities are probably more mundane than discovery of new targets. Multivariate models linking raw material fingerprints and extraction parameters to extract quality can support feed-forward control **[13]**; models linking extract physical descriptors to spray-drying outcome could reduce the number of experiments needed for platform processes **[21,22]**; and surrogate models for the phase behaviour of lipid-surfactant-extract systems could accelerate SEDDS design, which is currently done largely by ternary phase diagram **[30]**. Most published formulation optimisation still relies on classical response-surface or central composite designs **[15]**, and direct comparisons with machine learning approaches on herbal systems are rare.

Table 6. Applications of artificial intelligence and network pharmacology to multicomponent herbal products.

Application	Methods	Value	Limitations
Mechanism and target prediction **[38-41]**	Network pharmacology; machine learning; graph and hypergraph neural networks	Prioritises constituents, targets and pathways for validation	Database bias; bioavailability ignored; limited in vivo validation
Key compound identification **[38]**	Machine learning with serum metabolomics	Links exposure data to efficacy	Requires well-controlled datasets
Quality control **[16-18]**	Chemometrics; multivariate models of spectra	Batch consistency; real-time monitoring	Model validation and maintenance
Extraction and drying optimization (proposed) **[13,21,22]**	Multivariate and surrogate models	Feed-forward control; fewer experiments	Few herbal datasets published
Formulation design (proposed) **[30,42]**	ANN and machine learning on phase behaviour and release	Faster SEDDS and carrier screening	Rare comparison with classical DoE
Safety and interaction screening **[42]**	In silico ADMET; interaction prediction	Early hazard identification	Constituent coverage and quantitative exposure

9.3 Limitations and Cautions

There are a few restrictions that should be highlighted. Network pharmacology predictions are only as accurate as the underlying databases of compounds, targets, and interactions, which are biased toward well-studied elements and incomplete. Bioavailability is rarely taken into account in computational target predictions; a component that is expected to bind a target might never reach it, which is precisely where delivery-system engineering comes into play. Few studies go on to confirm predictions in vivo, and many only validate a small number of anticipated targets in vitro. For these reasons, rather than being a replacement for testing, AI outputs should be viewed as theories that direct it. Integration of network pharmacology, physiologically based pharmacokinetic modelling of multiple

constituents and formulation design, which could in principle predict how a carrier changes the exposure profile of each constituent, represents an attractive but largely unrealised goal.

10. KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Our analysis suggests six priority areas.

1. Fingerprint-level response variables in QbD. Extraction, drying and formulation studies should use composition-level, not only marker-level or physical, responses, and extend the design space concept to include fingerprint similarity.
2. Quantitative understanding of constituent-carrier interactions. For each delivery platform, constituent-resolved loading, release and stability data are needed, so that the "composition shift" caused by a carrier can be predicted and controlled.
3. Mechanisms of pharmacokinetic synergy. A better understanding of how natural assemblies and co-constituents modulate solubility, permeability and metabolism would allow rational design of simpler, more extract-compatible carriers **[10]**.
4. Regulatory science for complex mixtures. Agreed criteria for similarity, equivalence and change control of herbal intermediates and formulations, building on ICH Q14 for multivariate procedures [36], would reduce the uncertainty that currently limits botanical drug development **[34,35]**.
5. Excipient and solvent safety. Greener solvents such as NADES and novel carriers retained in the product need systematic toxicological qualification **[7]**.
6. Integration of AI with experimental pipelines. Open, well-annotated datasets of extract composition, processing and performance, and benchmarks that compare machine learning with classical design of experiments on herbal systems, are needed **[38-42]**.

CONCLUSIONS

Herbal extracts challenge pharmaceutical engineering because the multicomponent nature that underlies their therapeutic appeal also defeats single-analyte quality systems and single-drug delivery concepts. Progress in fingerprinting, green extraction, QbD and PAT now makes it possible to define and control extract quality with far greater rigour than a decade ago, while phytosomes, self-emulsifying systems and nanocarriers offer demonstrated routes to higher exposure of poorly bioavailable constituents. What is still missing is a design philosophy that treats the extract as a system to be preserved and delivered, rather than a source from which a marker is to be extracted and rescued. The fingerprint-preserving approach proposed here, which links composition, release, absorption and function, is one way of making that philosophy operational. Combined with regulatory clarity and data-driven tools, it could allow robust, scalable and clinically convincing herbal drug delivery systems to emerge from the current patchwork of promising but poorly connected advances.

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