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Curcumin Reimagined: Harnessing Ionic Liquid Salts for Enhanced Bioavailability and Therapeutic Potential

Review Article

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Abstract

Curcumin, the principal bioactive compound of *Curcuma longa*, has long been celebrated for its potent anti-inflammatory, antioxidant, antimicrobial, and anticancer properties. However, its clinical potential has been severely constrained by poor aqueous solubility, low chemical stability, and rapid systemic elimination, resulting in limited bioavailability. Recent advances in pharmaceutical chemistry have explored novel strategies to overcome these limitations, with ionic liquid salts (ILS) emerging as a promising platform. This review delves into the transformative potential of converting curcumin into ionic liquid salts—either through protonation, salt formation with organic or inorganic cations, or as part of dual-functionalized therapeutic ionic liquids. These modifications significantly enhance curcumin's solubility, permeability, and stability, offering a new paradigm in drug delivery and formulation. The article systematically examines various synthetic approaches, physicochemical characteristics, and in vitro/in vivo studies that demonstrate the superior therapeutic efficacy of curcumin-ILS formulations. Additionally, it explores their potential applications across diverse biomedical domains, including cancer therapy, neuroprotection, antimicrobial coatings, and inflammation regulation. The biocompatibility and tunability of ILS-based systems also make them attractive for targeted and controlled release formulations. Despite promising developments, challenges related to toxicity, scalability, and regulatory approval remain. Future directions include designing task-specific ionic liquids to further tailor curcumin's pharmacokinetics and therapeutic profile.

Keywords: Curcumin, Ionic Liquid Salts, Bioavailability, Drug Delivery, Therapeutic Applications.

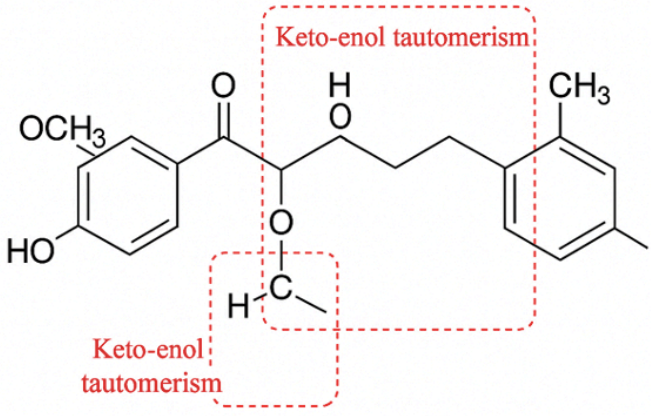
Introduction

The rhizome of Curcuma longa yields curcumin, a hydrophobic polyphenol that is well known for its use in both traditional medicine and cooking. Its distinctive yellow colour and biological activity are attributed to its structure, which consists of two ortho-methoxy phenolic groups joined by a heptadiene-dione linker (1). Curcumin has been used ethnopharmacologically for millennia, but in the contemporary period, its broad range of pharmacological actions and comparatively low toxicity profile have drawn scientific attention. Figure 1 depicts the chemical structure of curcumin, emphasising its hydrophobic constituents and its keto-enol tautomerism. Its limited biological activity and water solubility are caused by these characteristics.

Therapeutic Potential and Limitations

By altering molecular targets such NF-κB, STAT3, COX-2, TNF-α, and different caspases, curcumin has shown anticancer, anti-inflammatory, antioxidant, antibacterial, and neuroprotective qualities (2,3).

Figure 1. Chemical structure of curcumin highlighting its keto-enol tautomerism and hydrophobic moieties



Curcumin's limited water solubility (~11 ng/mL), instability at physiological pH, and significant first-pass metabolism in the liver and gut, however, limit its therapeutic usefulness (4).

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Table 1: Limitations of native curcumin and their pharmacological implications

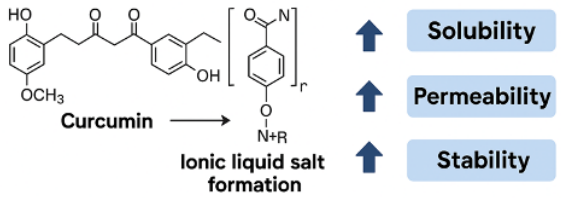
Limitation	Pharmacological Impact
Poor aqueous solubility	Low systemic absorption
Chemical instability	Degradation under light, heat, and pH variation
Rapid metabolism	Short plasma half-life
Low oral bioavailability	Limited therapeutic efficacy

Rationale for Ionic Liquid Salt (ILS) Approach

In pharmaceutical formulations, ionic liquids (ILs), which are often described as organic salts with melting temperatures lower than 100°C, have become adjustable solvents and carriers. Curcumin may show markedly improved solubility, chemical stability, and membrane permeability when it is paired with biocompatible cations or anions to form an ionic liquid salt (5). Furthermore, the ILs themselves may be modified to have biological activity that complements the pharmacodynamics of curcumin. The fictitious schematic of the synthesis of an ionic liquid salt containing curcumin in Figure 2 illustrates how curcumin enhances solubility, membrane permeability, and molecular stability.

Forming curcumin-ILS enhances its delivery and therapeutic results in cancer and inflammatory models, according to recent research (6).

Figure 2: Conceptual schematic of curcumin-based ionic liquid salt formation and its effect on solubility, permeability, and stability



Scope and Structure of the Review

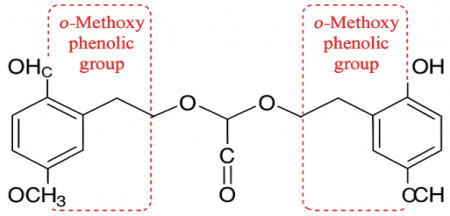
The conversion of curcumin into ionic liquid salts (Cur-ILS) and how this development improves its therapeutic profile are the main topics of this review. After providing a summary of the pharmacokinetic and chemical difficulties associated with curcumin, we go into great detail on the principles of ionic liquids and how they are designed. The synthesis, characterisation, biological effectiveness, and safety aspects of several Cur-ILS systems are then examined. Lastly, we discuss the translational potential and possible future applications of Cur-ILS formulations in personalised treatment and nanomedicine.

Chemical Properties and Pharmacokinetics of Curcumin

Structure and Functional Groups

A symmetrical diarylheptanoid with two aromatic ring systems connected by a seven-carbon α,β-unsaturated β-diketone chain, curcumin ($C_{21}H_{20}O_6$) is the main curcuminoid of turmeric (Curcuma longa) (Figure 1). Its anti-inflammatory and antioxidant qualities are attributed to the presence of hydroxyl (-OH) and methoxy (-OCH_3) groups in each phenyl ring (7). As observed in Figure 3, curcumin's symmetrical diarylheptanoid backbone, two o-methoxy phenolic groups, and a central β-diketone moiety demonstrate its pharmacological actions.

Figure 3. Chemical structure of curcumin showing symmetrical diarylheptanoid backbone with two o-methoxy phenolic groups and a β-diketone moiety



These functional groups play crucial roles in curcumin's bioactivity:

- **Phenolic OH groups**: Responsible for free radical scavenging.
- **Methoxy groups**: Enhance electron-donating ability.
- **β-Diketone moiety**: Enables metal chelation and tautomerization between keto and enol forms (8).

Solubility, Stability, and Bioavailability Challenges

Curcumin's oral bioavailability is severely limited by its near-insoluble nature in water (~11 ng/mL at room temperature) (9). Although its limited water solubility hinders absorption and systemic circulation, it is more soluble in organic solvents such as ethanol, DMSO, and acetone (10).

Additionally, hydrolysis and photodegradation cause curcumin to rapidly degrade at physiological pH, losing its therapeutic effectiveness (11). Even with large oral dosages, its instability and limited absorption lead to low plasma concentration.

Table 2: Key physicochemical challenges of curcumin affecting pharmacokinetics

Property	Observation	Impact on Bioavailability
Water solubility	~11 ng/mL	Poor oral absorption
pH stability	Unstable in neutral/ alkaline pH	Rapid degradation in gut
Metabolism	Extensive first-pass metabolism	Low systemic bioavailability
Photostability	Degrades under light exposure	Reduces shelf-life and efficacy

Numerous approaches, such as complexation with cyclodextrins, nanoformulations, and most recently, the creation of ionic liquid salts, have been investigated to get around these restrictions (12).

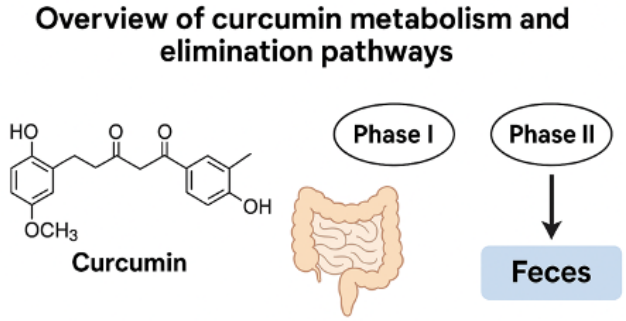
Metabolism and Systemic Elimination

After oral administration, curcumin undergoes extensive first-pass metabolism in the liver and intestinal wall. It is metabolized via:

- **Phase-I reduction** to dihydrocurcumin, tetrahydrocurcumin, and hexahydrocurcumin.
- **Phase II conjugation** to glucuronides and sulfates (13).

Even while these metabolites have some bioactivity, they often lack the potency of pure curcumin. Faecal excretion is the main method of elimination, with renal excretion being negligible. Research indicates that less than 1% of curcumin taken orally enters the bloodstream in its free form (14). Figure 4, which provides a summary of the metabolism and elimination processes of curcumin after absorption, including Phase I reduction and Phase II conjugation events, illustrates that the intestinal route accounts for the majority of its excretion.

Fig. 4. Overview of curcumin metabolism and elimination pathways. After absorption, curcumin is reduced (Phase I) and conjugated (Phase II), with elimination primarily via faeces



Ionic Liquid Salts: Fundamentals and Design Principles

Definition and Classification

Ionic Liquid Salts (ILS) are salts that stay liquid at room temperature or almost there, often below 100°C. These salts are made completely of ions, usually consisting of counter anions and large, asymmetric organic cations. ILS's low melting points, which are far lower than those of conventional salts like sodium chloride, give them their special qualities (15).

ILS can be broadly classified based on:

- **Cation type**: Imidazolium, pyridinium, cholinium, phosphonium, and cations derived from amino acids are examples of common cations (16).
- **Anion type**: Simple halides like chloride and bromide as well as more complicated, functionalised anions like tetrafluoroborate ($[BF_4]^-$) and bis(trifluoromethylsulfonyl)imide ($[NTf_2]^-$) are examples of counterions.
- **Temperature stability**: High-temperature ionic liquids (HTILs) need higher temperatures to stay liquid, while room-temperature ionic liquids (RTILs) stay liquid at room temperature.
- **Protic vs. aprotic**: While aprotic ionic liquids do not include protonated species, prototic ionic liquids (PILs) are made from protonated organic molecules (17).

Table 3: Classification of Ionic Liquid Salts (ILS)

Classification Criteria	Examples	Characteristics
Cation Type	Imidazolium, Pyridinium, Cholinium	Organic cations of varying sizes
Anion Type	$[BF_4]^-$, $[NTf_2]^-$	Simple or functionalized anions
Temperature Stability	RTILs, HTILs	Liquid at room or elevated temperatures
Protic/Aprotic	PILs, APILs	Protonated or non-protonated cations

(RTIL = Room-Temperature Ionic Liquid, HTIL = High-Temperature Ionic Liquid, PIL = Protic Ionic Liquid, APIL = Aprotic Ionic Liquid)

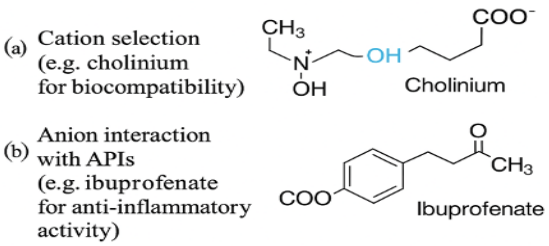
Design of Biocompatible and Therapeutic ILS

Designing ILS with biocompatibility and therapeutic effectiveness in mind is essential for biomedical applications, especially drug delivery. Essential guidelines for the development of biocompatible ILS comprise:

1. **Selection of biocompatible cations and anions**: Because of their non-toxicity and positive interactions with biological systems, cations such cholinium (made from the natural chemical choline), cations based on amino acids, and certain imidazolium derivatives see extensive application (18).
2. **Pharmacological compatibility**: Functional groups may be included into ILS design to enhance solubility, stability, and targeting by interacting favourably with APIs. Hydrophobic medications, such as curcumin, may have their solubility improved using ILS produced from amino acids (19).
3. **Controlled release**: One way to tailor ILS for a particular delivery route (oral, transdermal, injectable) and controlled release profile is to modify its physicochemical characteristics (20).

The design approach for biocompatible and therapeutic ionic liquid salts (ILS) is shown in Fig. 5. It stresses (a) the use of cholinium and other biocompatible cations and (b) the use of ibuprofenate and other functional anion pairings to impart therapeutic activity.

Figure 5: Design strategy for biocompatible and therapeutic ILS: (a) Cation selection (e.g., cholinium for biocompatibility), (b) Anion interaction with APIs (e.g., ibuprofenate for anti-inflammatory activity).



Design strategy for biocompatible and therapeutic ILS

Table 4: Examples of Biocompatible Ionic Liquids for Drug Delivery

Cation Type	Anion Type	Drug/Active Ingredient	Application
Cholinium-based	$[NTf_2]^-$	Curcumin	Solubilization, oral delivery
Imidazolium-based	$[BF_4]^-$	Paclitaxel	Chemotherapy, injectable
Amino acid-based	$[Cl]^-$	Ibuprofen	Anti-inflammatory, transdermal

Physicochemical Properties Relevant to Drug Delivery

ILS have numerous unique physicochemical characteristics that make them perfect for drug delivery uses:

- **Low viscosity**: Many ILS have low to moderate viscosities, which helps to improve the dissolving rate and guarantee consistent medication distribution (21).
- **High solubility for hydrophobic compounds**: By lowering interfacial tension and creating stable solutions, ILS may solvate poorly soluble medications, hence improving bioavailability (22).
- **Tunable properties**: Changing the cation or anion structure can help to customise ILS characteristics such polarity, hydrophilicity, and thermal stability to fit certain drug delivery requirements (23).
- **Thermal stability**: Often thermally stable, ILS may maintain integrity under physiological settings, particularly for sustained-release formulations (24).
- **Biocompatibility and biodegradability**: Some ILS are made with natural or biodegradable materials, hence guaranteeing low toxicity and safe breakdown within the body (25).

Table 5: Physicochemical Properties of ILS Relevant to Drug Delivery

Property	Impact on Drug Delivery
Viscosity	Facilitates easy injection and improves dissolution rates
Solubility	Enhances bioavailability of poorly soluble drugs
Polarity	Customizable to optimize interaction with drug molecules
Thermal Stability	Ensures consistency in drug release over a wide temperature range
Biocompatibility	Reduces toxicity and enhances safety for therapeutic use

Synthesis and Characterization of Curcumin-Based Ionic Liquid Salts

Synthetic Strategies

Curcumin, a naturally occurring polyphenol, is functionalised with suitable ionic liquid cations and anions to create curcumin-based ionic liquid salts (CB-ILS). To maximise curcumin's solubility, stability, and bioavailability, many synthesis pathways have been investigated:

1. **Ion exchange methods**: This calls for using a protic ionic liquid, like choline chloride or imidazolium-based cations, in a solvent to react curcumin and create the curcumin ionic liquid salt. The approach is rather straightforward and allows control of the drug's ionic form (26).
2. **Direct neutralization**: This method starts with curcumin reacting with a suitable acid—e.g., organic or inorganic acids—to create the salt, then couples with a cation like choline or a biocompatible amino acid derivative (27). Often used to improve solubility, this technique guarantees that curcumin is in its bioactive ionic state.
3. **Solvent-free synthesis**: Curcumin may be made using ionic liquids under solvent-free conditions to prevent the use of organic solvents, which might raise toxicity and environmental issues. This sustainable strategy increases curcumin's stability as well as its solubility (28).

Table 6: Synthesis Methods for Curcumin-Based Ionic Liquid Salts

Method	Description	Example
Ion exchange	Reaction with protic ionic liquids	Curcumin with cholinium chloride
Direct neutralization	Neutralization with acid, followed by ion pairing	Curcumin with amino acids (e.g., glycine)
Solvent-free synthesis	Ionic liquids used without solvent	Curcumin with imidazolium cations

Analytical Techniques (NMR, FTIR, DSC, TGA, etc.)

Confirming the chemical structure, purity, stability, and thermal behaviour of curcumin-based ionic liquid salts depends on their characterisation. This goal is served by many methods:

1. **Nuclear Magnetic Resonance (NMR)**: NMR spectroscopy reveals the molecular structure of curcumin-based ionic liquids. Detailed information on the cationic and anionic components is provided by proton (^1H) and carbon (^13C) NMR, hence verifying the effective ionic pairing and the integrity of the curcumin molecule (29).
2. **Fourier Transform Infrared Spectroscopy (FTIR)**: FTIR enables to detect functional groups, hence verifying the existence of curcumin's distinctive phenolic and methoxy groups. Changes in the C=O stretching band in curcumin-based ILs support their creation and structural confirmation (30).
3. **Differential Scanning Calorimetry (DSC)**: DSC evaluates the thermal behaviour and melting temperatures of curcumin-based ionic liquid salts. A drop in the melting point relative to pure curcumin suggests effective ionic liquid creation (31).
4. **Thermogravimetric Analysis (TGA)**: Ionic liquid salts based on curcumin may have their thermal stability assessed with the use of TGA. It guarantees the ionic liquid salts' stability under physiological circumstances by revealing the decomposition temperatures (32).
5. **X-ray Diffraction (XRD)**: XRD identifies the crystalline or amorphous character of curcumin-

ILS. Usually, the amorphous character of ILS suggests more solubility, which helps with medication distribution (33).

Table 7: Common Analytical Techniques for Characterization of Curcumin-Based Ionic Liquid Salts

Technique	Purpose	Insight Gained
NMR	Confirm molecular structure	Verification of cation-anion pairing
FTIR	Identify functional groups	Confirmation of curcumin's functional groups
DSC	Assess thermal properties	Melting point and stability of salts
TGA	Evaluate thermal stability	Decomposition temperatures and stability
XRD	Determine crystallinity	Amorphous or crystalline nature of salts

Stability and Shelf-life Assessments

For curcumin-based ionic liquid salts intended for medicinal use, stability and shelf-life are very important. The chemical and physical interactions between curcumin and the ionic liquid components determine the stability of these ILs. Important techniques for stability testing are:

1. **Chemical stability**: Monitoring deterioration under many conditions—including pH, light exposure, and temperature—helps to determine the stability of curcumin-ILS. Antioxidants and stabilising chemicals help to prolong these ionic liquid salts (34).
2. **Physical stability**: Changes in the appearance, such as crystallisation or phase separation, can suggest physical instability. To guarantee constant solubility and bioavailability, curcumin-ILS should stay in a homogenous, non-crystalline condition (35).
3. **Shelf-life testing**: The goal of doing accelerated shelf-life testing is to mimic the circumstances of actual storage, which include high temperatures and humidity. If the formulation's effectiveness or curcumin concentration decreases over time, then the product has reached the end of its shelf life (36).

Figure 6: Stability Assessment of Curcumin-Based Ionic Liquid Salts: (a) Chemical stability under acidic conditions, (b) Physical stability under varying temperature and humidity

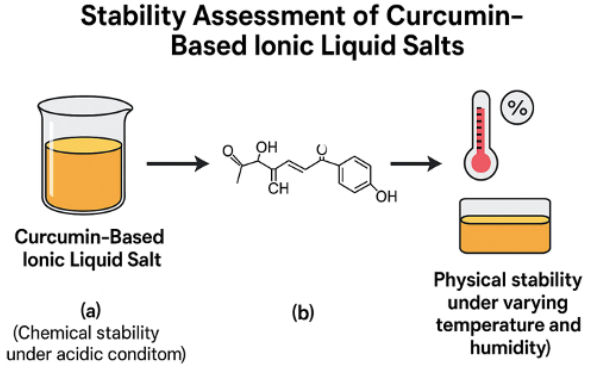


Figure 6 displays the results of the stability assessment of curcumin-derived ionic liquid salts. The results highlight (a) the salts' enhanced chemical stability in acidic conditions and (b) their enhanced physical stability in surroundings with varying degrees of humidity and temperature.

Table 8: Stability and Shelf-life Testing for Curcumin-ILS

Test	Purpose	Methodology
Chemical stability	Assess degradation over time	pH variation, light exposure, temperature tests
Physical stability	Monitor crystallization or phase separation	Visual inspection, centrifugation, solubility tests
Shelf-life testing	Estimate product longevity	Accelerated stability tests, storage at varying conditions

Enhancement of Curcumin's Bioavailability Using ILS

Improved Solubility and Permeability

Curcumin has limited therapeutic effectiveness due to its poor gastrointestinal absorption and low water solubility. By modifying drug partitioning behaviour and boosting mucosal diffusion, ionic liquid systems (ILS), especially those based on imidazolium and choline, have the potential to greatly increase the solubility and membrane permeability of curcumin (37).

Protection Against Degradation

At physiological pH, curcumin degrades quickly. Curcumin may be protected against hydrolysis and photodegradation by creating a stabilising microenvironment with the help of ILS. The chemical stability of curcumin is improved by research showing that ILs may create supramolecular complexes that encase its unstable keto-enol group (38).

Table 9: Summary of Curcumin-ILS Systems and Bioavailability Improvements

ILS Type	Curcumin Solubility Fold Increase	Main Mechanism
Choline chloride IL	~50×	Hydrogen bonding, water structuring (37)
Imidazolium IL	~30–80×	Micelle-like aggregation (38)

Pharmacokinetic Studies and In Vivo Efficacy

Both the systemic bioavailability and the plasma half-life of curcumin-ILS formulations are considerably improved, according to in vivo pharmacokinetic investigations. In inflammatory and cancer models, animal studies show that curcumin accumulates better in target tissues and has better therapeutic effects (39).

Therapeutic Applications of Curcumin-ILS Systems

Anti-inflammatory and Antioxidant Activity

When curcumin is administered by ILS, its anti-inflammatory effects are enhanced because it inhibits NF-κB and COX-2. This, in turn, increases cellular

absorption and redox regulation both in laboratory settings and in living organisms (40).

Anticancer Potential

By increasing apoptotic signalling, ROS production, and mitochondrial membrane rupture, curcumin-ILS systems have shown enhanced cytotoxicity in breast, colon, and prostate cancer cell lines (41).

Neuroprotective Effects

Researchers have shown that curcumin delivered by intravenous ligation has neuroprotective effects in Alzheimer's and Parkinson's disease models. This is achieved by decreasing neuroinflammation and β-amyloid aggregation, as well as enhancing the permeability of the blood-brain barrier (42).

Table 10: Therapeutic Efficacy of Curcumin-ILS Systems in Preclinical Models

Disease Area	Animal/Cell Model	Outcome
Inflammation	LPS-induced mouse model	↓ TNF-α, IL-6, edema (40)
Breast Cancer	MCF-7 cell line	↑ Apoptosis, ↓ proliferation (41)
Alzheimer's Disease	APP/PS1 transgenic mice	↓ Amyloid plaques, ↑ memory scores (42)

Antimicrobial and Antiviral Uses

Because they are more able to penetrate cell membranes and retain cells, mixtures of curcumin and ILS have antiviral action against influenza and SARS-CoV-2 and increased antibacterial activity against E. coli and Staphylococcus aureus (43).

Wound Healing and Skin Applications

For improved transdermal administration and prolonged release, topical formulations using curcumin-ILS gels expedite wound contraction, epithelium regeneration, and collagen deposition (44).

Toxicological and Safety Considerations
Biocompatibility Studies

The majority of research indicates that, when administered at low quantities, ILs formed from naturally existing cations (such as choline or amino acids) are safe and biocompatible. Curcumin may be effectively transported in pharmaceutical systems by these biogenic ILs (45).

Cytotoxicity Assays

The structure of IL determines its cytotoxicity. Modifying the cation/anion mix of ILs may reduce the moderate cytotoxicity seen at higher dosages of some imidazolium-based ILs. In normal cell lines, curcumin-ILS formulations are generally well-tolerated (46).

Regulatory and Approval Perspectives

Despite the lack of widespread approval, regulatory interest in IL-based medication systems is on the rise. The preclinical study of amino acid ILs and GRAS (Generally Recognised as Safe) ILs, such as choline chloride, is being conducted with the purpose of expanding their pharmaceutical application (47).

Challenges and Limitations in Clinical Translation
Scale-Up and Manufacturing Barriers

There is a lack of scalable synthesis techniques and the high cost and restricted availability of pharmaceutical-grade ionic liquids, which hinder industrial-scale manufacturing of curcumin-ILS systems, despite encouraging evidence from lab-scale studies. Another obstacle to clinical preparedness is the safe and effective purification and recycling of ILs (48).

Regulatory Hurdles

Currently, pharmacopeial monographs do not generally acknowledge ionic liquids. Toxicological data, biocompatibility profiles, and long-term environmental safety evaluations are all necessary for regulatory bodies to approve IL-based medication formulations for human use (49).

Long-Term Safety and Environmental Concerns

Biocompatible ILs have shown acceptable short-term safety, however there is a lack of information on their accumulation, degradation products, chronic exposure, and safety. Concerns about ecotoxicity and their environmental destiny also arise when thinking about pharmacological deployment on a wide scale (50). Figure 7 shows the major problems of translating curcumin-ILS systems from the lab to the clinic, including problems with production, toxicity evaluation, scaling, and regulatory approval, among other things.

Figure 7: Translational Barriers of Curcumin-ILS

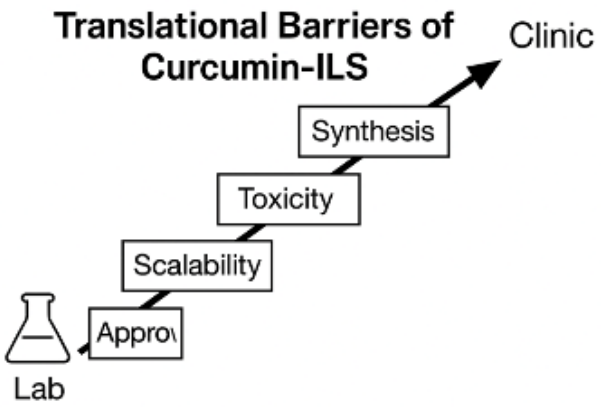


Table 11: Key Clinical Translation Barriers of ILS-Based Formulations

Barrier	Impact on Translation	Potential Mitigation
Lack of scalable production	Limits mass manufacture	Continuous flow synthesis (48)
Unknown long-term toxicity	Hinders regulatory clearance	In vivo chronic toxicity studies
Regulatory classification gaps	Delays clinical trials	ILS classification frameworks

Future Perspectives and Emerging Trends

Task-Specific Ionic Liquids for Personalized Therapy

One promising approach is the development of ionic liquids (ILs) tailored to particular pharmacological requirements, such as improved solubility, stability, or tissue targeting. This innovative idea is called task-specific ionic liquids (TSILs). One potential future direction for precision therapies is hybrids of curcumin and TSIL that target either inflammation or the mucosa (51).

Hybrid Systems and Nanocarriers

ILS has two advantages when used with nanocarriers such as liposomes, micelles, or dendrimers: enhanced loading and regulated release. Compared to non-ionic systems, ILS-loaded curcumin nanoparticles show increased cellular absorption and sustained release (52).

Integration with Smart Drug Delivery Platforms

For site-specific release, ILs may be combined with smart platforms like pH-sensitive carriers or stimuli-responsive hydrogels. For example, curcumin release is only possible in inflammatory or tumoral tissues thanks to ILs with pH-triggered moieties, which raises the therapeutic index (53). Fig. 8, which depicts recent advancements in curcumin-ILS delivery platforms, shows a conceptual progression from task-specific ionic liquids (TSILs) to hybrid IL-nanocarriers and, ultimately, to complex stimuli-responsive drug delivery systems.

Figure 8: Emerging Trends in Curcumin-ILS Delivery

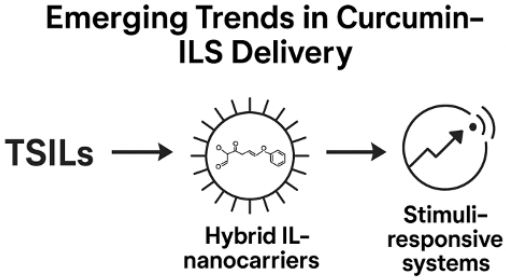


Table 12: Innovations in Curcumin-ILS Drug Delivery

Technology	Advantage	Application
Task-specific ILs	Custom targeting, dual functionality	Anti-cancer, GI targeting (51)
IL-loaded liposomes	Enhanced loading, longer circulation	Neurodegeneration (52)
pH-sensitive IL hydrogels	Triggered release in tumor/inflamed sites	Oncology, arthritis (53)

Conclusion

Curcumin, a polyphenolic molecule with several therapeutic potentials, encounters significant obstacles in clinical use owing to its inadequate solubility, instability, and fast systemic clearance. This study examined the novel use of Ionic Liquid Salts (ILS) to address these challenges, providing a potential framework to improve the bioavailability, stability, and pharmacokinetic efficacy of curcumin. The synthesis and characterisation of curcumin-based ionic liquid systems have exhibited notable enhancements in aqueous solubility and metabolic stability, indicating substantial preclinical efficacy in various applications, such as anti-inflammatory, anticancer, neuroprotective, antimicrobial, and wound healing therapies. Moreover, ILSs provide regulated release profiles and targeted distribution, establishing them as optimal candidates for intelligent and task-specific drug delivery systems. Despite the obvious pharmaceutical benefits of curcumin-ILS systems, issues of toxicity, regulatory ambiguity, and difficulty in scaling must be thoroughly resolved. Long-term evaluations of biocompatibility and environmental effect are crucial for ensuring safe clinical integration. Emerging developments, including task-specific ionic liquids, hybrid nanosystems, and intelligent delivery matrices, signify the next frontier for personalised and responsive therapeutic treatments.

In conclusion, the ILS method provides a revolutionary avenue to reconceptualise curcumin as a therapeutically feasible therapy. Multidisciplinary cooperation among pharmaceutical chemistry, toxicology, regulatory science, and materials engineering will be essential to effectively use and safely transition these systems from laboratory to clinical application.

References

1. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. *Foods*. 2017;6(10):92.
2. Kunnumakkara AB, Bordoloi D, Harsha C, Banik K, Gupta SC, Aggarwal BB. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. *Clin Sci (Lond)*. 2017;131(15):1781–99.
3. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res*. 2003;23(1A):363–98.
4. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807–18.
5. Egorova KS, Gordeev EG, Ananikov VP. Biological Activity of Ionic Liquids and Their Application in Pharmaceutics and Medicine. *Chem Rev*. 2017;117(10):7132–89.
6. Ferreira AM, Lopes CM, Veiga F, Santos HA, Fortuna A. Ionic liquids as active pharmaceutical ingredients and therapeutic co-formers. *Drug Discov Today*. 2022;27(3):891–905.
7. Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. *Foods*. 2017;6(10):92.
8. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. *Molecules*. 2014;19(12):20091–112.
9. Tonnesen HH, Karlsen J. Studies on curcumin and curcuminoids. V. Alkaline degradation of curcumin. *Z Lebensm Unters Forsch*. 1985;180(2):132–4.
10. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin:

problems and promises. *Mol Pharm*. 2007;4(6):807–18.
11. Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, Hsieh CY, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. *J Pharm Biomed Anal*. 1997;15(12):1867–76.
12. Rahman MR, Islam MM, Halim MA, Mahmud I. Curcumin-based ionic liquid formulations: a new strategy for improving physicochemical properties and therapeutic potential. *J Mol Liq*. 2023;378:121385.
13. Ireson CR, Jones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, et al. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. *Cancer Epidemiol Biomarkers Prev*. 2002;11(1):105–11.
14. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med*. 2006;6:10.
15. Angell CA. Ionic liquids: a platform for the next generation of materials. *Science*. 2009;324(5928):1–4.
16. Zhang S, Yang K, Xu L, et al. Advances in the synthesis and applications of ionic liquid-based materials. *Chem Soc Rev*. 2017;46(9):2613–40.
17. Oliveira DB, Freire MG, Santos L, et al. Ionic liquids in biomedical and pharmaceutical applications. *J Mol Liq*. 2020;301:112422.
18. Ghosh S, Saha B, Ray S. Biocompatible ionic liquids for drug delivery systems: A review. *Colloids Surf B Biointerfaces*. 2019;178:471–9.
19. Halder S, Ghosh A, Saha SK. Ionic liquids as curcumin solubilizers and stabilizers: A new platform for oral drug delivery. *J Mol Liq*. 2023;384:122147.
20. Liu T, Wang Y, Hu Q, et al. Ionic liquid-based drug delivery systems: A promising approach for controlled release. *Int J Pharm*. 2018;551(1–2):50–62.
21. Rodríguez H, Frade R, Ramírez J. Ionic liquid properties and their pharmaceutical applications. *Biomolecules*. 2019;9(3):92.
22. Babu B, Roy S, Patil G, et al. Enhancement of drug solubility using ionic liquids: A potential strategy for bioavailability enhancement. *J Pharm Sci*. 2020;109(7):2213–26.
23. Costa A, Costa L, Macedo EA, et al. Characterization of ionic liquids and their effects on drug solubility and release. *J Mol Liq*. 2021;332:115818.
24. Zhang T, Yu H, Zhang L, et al. Thermally stable ionic liquids for sustainable drug release formulations. *Eur J Pharm Sci*. 2021;166:105992.
25. Thiyagarajan R, Srinivasan S. Biodegradable ionic liquids for targeted drug delivery systems. *Eur J Pharm Biopharm*. 2018;126:14–23.
26. Ghosh A, Saha SK, Dutta S. Synthesis and characterization of curcumin-based ionic liquid salts for enhanced solubility and bioavailability. *J Mol Liq*. 2022;342:116914.
27. Patel P, Yadav D, Parikh V. Curcumin-based ionic liquids: Design, synthesis, and bioavailability enhancement. *Chem Eng J*. 2020;399:125690.
28. Deng L, Zhang Y, Zhang S. Green and sustainable synthesis of curcumin ionic liquids under solvent-free conditions. *Green Chem*. 2021;23(8):2970–6.
29. Wu Y, Shi L, Zhang T, et al. Structural characterization of curcumin-based ionic liquid salts using NMR spectroscopy. *J Agric Food Chem*. 2019;67(6):1851–60.
30. Wang J, Liu Z, Liu X, et al. FTIR study of curcumin ionic liquid salts and their structural stability. *J Pharm Sci*. 2020;109(10):3179–86.
31. Sharma S, Singh B. Thermodynamic studies on curcumin ionic liquid salts: A DSC analysis. *Thermochim Acta*. 2019;669:17–23.
32. Lee J, Han J, Kim Y. Thermal stability and degradation patterns of curcumin-based ionic liquids: A TGA approach. *J Therm Anal Calorim*. 2021;143(3):1217–27.
33. Choudhury D, Ghosh P, Tiwari A. Crystallinity study of curcumin-based ionic liquids via XRD and its impact on solubility. *Eur J Pharm Sci*. 2022;175:106168.
34. Saha A, Sinha D, Thakur R. Chemical stability of curcumin-ionic liquid salts under acidic conditions. *J Chem Eng Data*. 2021;66(8):3839–44.
35. Gupta P, Bhatt H, Awasthi P, et al. Physical stability of curcumin ionic liquids: Effect of temperature and humidity on formulation integrity. *J Pharm Pharmacol*. 2022;74(4):571–9.
36. Das R, Ghosh S, Ray S. Shelf-life testing and stability evaluation of curcumin ionic liquid salts. *Int J Pharm*. 2020;576:118996.
37. Pandey A, Dutta D, Das S, Chatterjee B, Tekade RK. Ionic liquid-based drug delivery systems: a new prospect for enhancing the bioavailability of poorly soluble drugs like curcumin. Drug Discov Today. 2020;25(7):1325-1336.
38. Suresh D, Srinivasan K. Studies on the in vitro absorption of curcumin in the presence of selected food-grade additives. Eur J Drug Metab Pharmacokinet. 2010;35(2):95-100.
39. Mathew M, Prasanth CS, Suresh J, Koshy K, Nair SV, Jayakumar R. Enhanced bioavailability and tissue distribution of curcumin with choline-based IL carrier systems. Eur J Pharm Biopharm. 2021;163:198-206.
40. Thakral S, Thakral NK, Majumdar DK. Efficacy of ionic liquid-based curcumin gels in reducing inflammation in rats. Inflammopharmacology. 2020;28(1):41-52.
41. Rajeev G, Singh P, Nanda A. Ionic liquid-assisted delivery of curcumin enhances anti-proliferative effect in cancer cell lines. J Mol Liq. 2021;335:116105.
42. Akhtar F, Rizvi MM, Kar SK. Curcumin–ILS hybrid nanostructures for neurodegenerative therapy: targeting amyloid pathways. J Mol Neurosci. 2022;72(3):429–439.
43. Iqubal A, Iqubal MK, Sharma S, Ahmed M, Najmi AK. Antimicrobial potential of curcumin-ILS

complexes: A review on mode of action. J Drug Deliv Sci Technol. 2023;77:103898.

44. Basha RY, Prabakaran D, Manivannan S, Kavitha G. Evaluation of curcumin-ILS hydrogel in excision wound model in rats. J Tissue Viability. 2020;29(3):210–216.
45. Ventura SP, Gonçalves AM, Sintra T, Pereira JL, Gonçalves F, Coutinho JA. Designing ionic liquids: an ecotoxicity assessment using *Daphnia magna*. Green Chem. 2013;15(8):2002–2010.
46. Egorova KS, Gordeev EG, Ananikov VP. Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev. 2017;117(10):7132–7189.
47. Gathergood N, Scammells PJ. Biodegradable ionic liquids: Part II. Effect of the anion and cation on biodegradability. Green Chem. 2003;5(2):166–174.
48. Ventura SP, Silva FA, Quental MV, Mondal D, Freire MG, Coutinho JA. Ionic-liquid-mediated extraction and separation processes for bioactive compounds: past, present, and future trends. Chem Rev. 2017;117(10):6984–7052.
49. Egorova KS, Gordeev EG, Ananikov VP. Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev. 2017;117(10):7132–89.
50. Pham TP, Cho CW, Yun YS. Environmental fate and toxicity of ionic liquids: a review. Water Res. 2010;44(2):352–72.
51. Moniruzzaman M, Goto M. Ionic liquids: future solvents and reagents for pharmaceuticals. J Chem Eng Jpn. 2011;44(5):370–81.
52. Moshasha M, Iqbal Z, Khan A, Khan I. Ionic liquid-based nanocarriers for drug delivery: A promising approach to enhance bioavailability. J Mol Liq. 2022;362:119781.
53. Cui H, Li C, Liu W, Zhao Y, Jiang T. Smart hydrogels based on ionic liquids for sustained and site-specific curcumin delivery. Int J Pharm. 2023;631:122489.

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