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## SOLID LIPID NANOPARTICLES OF CURCUMIN FOR ENHANCED ORAL BIOAVAILABILITY: PREPARATION AND IN VIVO EVALUATION

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### 1. INTRODUCTION

Curcumin, the main yellow pigment of turmeric (*Curcuma longa*), has been tested in more preclinical models than almost any other dietary polyphenol. Reported activities include anti-inflammatory, antioxidant and antiproliferative effects [1, 2], and a long history of culinary and traditional use gives it a reassuring safety image [3]. Yet the gap between laboratory promise and clinical delivery is wide. After oral dosing, plasma

### Abstract

Curcumin has wide pharmacological activity but is absorbed poorly after oral dosing, and solid lipid nanoparticles (SLN) are one of the most studied ways of improving this. This review summarises published work on how curcumin-loaded SLN are prepared, characterised and tested in animals, and it reports no new data. It covers the causes of low curcumin exposure, the choice of lipid and surfactant, common preparation routes, size, charge and stability measurements, and pharmacokinetic study design. Reported formulations generally raise plasma exposure several-fold over unformulated curcumin, although study designs differ widely. Direct comparisons, long-term stability data and human evidence remain scarce.

concentrations of free curcumin stay very low even when several grams are given, and most

of what is measured is conjugated metabolite rather than parent compound [4, 5]. Delivery has therefore attracted more effort than the pharmacology itself. This review draws on published reviews, formulation papers and animal studies to describe how solid lipid nanoparticles (SLN) have been prepared and evaluated for curcumin. It reports no new experimental data.

SLN were introduced in the early 1990s as an alternative to polymeric nanoparticles, emulsions and liposomes [6, 7]. The idea is simple. A lipid that is solid at room and body temperature is dispersed in water as particles of roughly 50 to 1000 nm, stabilised by surfactant, so that a lipophilic drug sits in a matrix which digestive enzymes attack only slowly. The appeal for oral use rests on three features: ingredients that are generally well tolerated, manufacturing methods already familiar from emulsion technology, and a particle size that can influence uptake across the intestine [7, 8]. Lipid-based systems are well established for poorly soluble drugs more broadly, and the physiology behind them has been set out in detail [9, 10]. Curcumin, with its high lipophilicity and very low aqueous solubility, is a textbook candidate.

Preparation and in vivo evaluation are treated together here because they cannot be judged apart. A particle that looks excellent by light scattering may release its payload too early in gastric fluid, or crystallise on storage and expel the drug. Equally, a favourable plasma curve means little if the batch is poorly described. The sections that follow therefore move from the reasons for poor curcumin exposure, through lipid and surfactant selection and the main production methods, to characterisation and animal pharmacokinetics. Published findings are gathered into a single comparison table, and the review closes with the gaps that limit confident translation. Where reports disagree, the disagreement is stated rather than smoothed over.

## 2. WHY CURCUMIN IS POORLY ABSORBED

Several separate problems stack on top of one another. Curcumin is practically insoluble in

water at the acidic pH of the stomach and dissolves only slowly in intestinal fluid, so dissolution is limiting before absorption even begins [4, 11]. It is also chemically fragile: at neutral to alkaline pH it degrades within minutes to hours, through hydrolysis and oxidation of its  $\beta$ -diketone and phenolic groups, giving products such as ferulic acid and vanillin [11]. Medicinal chemists have pointed out that the molecule is a frequent hitter in screening assays and shows poor stability in solution, which complicates interpretation of many in vitro results [11]. These properties set a low ceiling on what a simple powder or suspension can achieve.

Metabolism closes off most of what remains. Early work in rats found that a large share of an oral dose was excreted in the faeces unchanged, and that very little reached the blood as parent compound [12]. Later studies using chromatographic methods confirmed that the oral bioavailability of curcumin in rats is low, in the region of a percent or so, with glucuronide and sulphate conjugates dominating plasma [5, 13]. Reduction to tetrahydrocurcumin and related products also occurs in the gut and liver. Human volunteers show a similar pattern: even at doses of several grams, free curcumin is barely detectable in serum [2, 5]. Whatever formulation is chosen, it has to protect the molecule and deliver it in a form the intestinal wall can take up. Simply raising the dose is not an answer, since gram-level dosing is poorly tolerated by some patients and adds little to plasma exposure.

One celebrated rescue strategy uses piperine, an inhibitor of glucuronidation, taken alongside curcumin. In the study that popularised it, co-administration markedly raised curcumin exposure in rats and, to a larger relative extent, in healthy volunteers [14]. The result shows that metabolism, rather than dissolution alone, restricts exposure. It also suggests a design target for nanocarriers: if a lipid particle can carry curcumin through the enterocyte and divert some of it towards lymphatic transport, first-pass glucuronidation in the liver might be partly bypassed [8, 9]. Whether SLN truly achieve this for curcumin, as opposed to simply improving dissolution, is rarely tested directly

in the published studies, and most authors acknowledge the point only in the discussion.

Competing approaches give useful context for judging SLN. Phospholipid complexes of curcumin have raised plasma levels in rats [15], polymeric nanoparticles made from PLGA have been proposed for tumour delivery [16], and aqueous nanoparticulate dispersions have shown better stability than free drug in buffer and serum [17]. Reviews of curcumin nanoformulations also list micelles, liposomes, cyclodextrin complexes and nanoemulsions [16]. None of these has become a standard, and head-to-head comparisons are uncommon. A fair reading of the literature is that SLN occupy a middle position: simpler and cheaper to make than many polymer systems, but with less drug loading and a more demanding physical stability profile.

Dose and vehicle matter more than they are often given credit for. Rodent studies commonly suspend curcumin in carboxymethylcellulose or dissolve it in an oil, and the reference formulation can change the apparent benefit of a nanocarrier considerably [13, 18]. When the control is a poorly wetted aqueous suspension, almost any dispersed system will look good. An oil solution or a self-emulsifying mixture is a tougher comparator, and a few reports include one. Readers weighing claims of fold-increase in exposure should therefore look first at what the comparison arm actually was, then at the dose normalisation, before drawing any conclusion about the nanoparticle itself.

### 3. LIPIDS, SURFACTANTS AND LOADING

The solid lipid forms the core of the particle and sets drug loading, release and stability. Triglycerides such as tristearin and tripalmitin, partial glycerides such as glyceryl monostearate and behenate, fatty acids such as stearic acid, and waxes such as cetyl palmitate have all been used [6, 7, 19]. Curcuminoid-loaded SLN prepared with stearic acid were among the earliest reported for this compound and showed good entrapment together with sustained release in vitro [20]. Others have used glyceryl

monostearate or tripalmitin, often reporting that mixtures give better loading than a single pure lipid [18, 21]. The practical rule that emerges is to match lipid polarity to the drug, because curcumin dissolves best in lipids that are somewhat less crystalline.

Crystallinity is the central physical issue. Highly ordered lipids such as pure tristearin form a perfect lattice on cooling, leaving little room for drug and tending to expel it during storage as the particle moves from the  $\alpha$  to the more stable  $\beta$  polymorph [22, 23]. Mixtures of lipids, or the addition of a liquid oil to produce a nanostructured lipid carrier (NLC), create imperfections that hold more drug [24]. Wax-based and glyceride-based particles have also been compared directly, with differences in size and stability that depend on the surfactant used [19]. Many curcumin SLN papers do report differential scanning calorimetry (DSC) and X-ray diffraction (XRD) evidence of reduced crystallinity, which is consistent with molecular dispersion of the drug, though by itself it does not prove it.

Surfactants have two jobs: stabilising the hot emulsion during production and protecting the cooled particles from aggregation. Poloxamer 188, polysorbate 80, lecithin and bile salts are frequent choices, often in pairs, and the concentration used strongly affects particle size [6, 25]. Higher surfactant levels generally give smaller particles up to a point, beyond which micelles or excess surfactant start to affect toxicity and drug partitioning. For oral products, safety margins on polysorbates and the influence of surfactants on intestinal permeability need attention. A cationic surface, introduced for instance with N-trimethyl chitosan, has been used to prolong gut residence and promote uptake, with higher plasma and brain exposure in rats than with the uncoated carrier [26].

Digestion adds a layer that dissolution tests ignore. Once in the duodenum, glycerides in the particle core are substrates for pancreatic lipase, and bile salts and phospholipids convert the products into mixed micelles from which lipophilic drugs are absorbed [9, 10]. For SLN this means the matrix does not simply stay intact until it reaches the wall of the gut. Highly crystalline, long-chain

triglycerides are digested slowly and may release curcumin late, whereas partial glycerides break down faster. Surfactants such as polysorbate 80 can in turn slow lipolysis by competing for the interface. The balance between protection and timely release is therefore set partly by lipid chain length and partly by the surfactant, and it is best examined with in vitro lipolysis models rather than inferred from particle size alone.

Loading capacity deserves more honesty than it often gets. Because SLN are dispersions with a modest lipid content, typically a few percent by weight of the whole, the amount of curcumin carried per millilitre is small, and a human dose of hundreds of milligrams would require a large volume or a freeze-dried powder [6, 27]. Lyophilisation with a cryoprotectant such as trehalose is the usual solution, but it adds a processing step that can itself cause aggregation on reconstitution. Reports commonly give entrapment efficiency (the fraction of added drug found in the particles) in the range of most of the dose, yet drug loading as a percentage of particle mass is quoted less often, and the two are easily confused [7, 20].

#### 4. PREPARATION ROUTES

Hot high-pressure homogenisation is the reference method for SLN and the one most easily scaled. The lipid is melted above its melting point, the drug dissolved or dispersed in it, and the melt pre-emulsified in a hot surfactant solution before being passed through a homogeniser at several hundred bar; cooling then recrystallises the lipid droplets as particles [6, 7]. Cold homogenisation exists for heat-labile drugs, but curcumin is not especially heat-sensitive in the dry lipid, so the hot route suffices. The main drawbacks are exposure to elevated temperature and the heavy equipment, which makes the technique less suited to small laboratory studies than to pilot manufacturing.

Most academic curcumin papers use simpler laboratory methods. Hot emulsification followed by high-speed stirring and probe sonication is the commonest, because it needs no special equipment and gives particles in the range of roughly 100 to 300 nm [18, 20].

Solvent emulsification-diffusion uses a partially water-miscible solvent and avoids high temperatures, giving small particles with narrow size distribution, though residual solvent must then be measured and controlled [28]. Solvent injection offers another low-energy option in which lipid dissolved in a water-miscible solvent is injected into the aqueous phase [29]. Microemulsion dilution, originally developed by the Gasco group, has also been applied to curcumin [8, 25]. Each route leaves a different residue profile and a different batch-to-batch scatter.

Comparisons between methods are hard to make from the literature because each laboratory tends to use only one. Reviews that set the options side by side agree on a few broad points [7, 24]. High-pressure homogenisation gives narrow distributions and is the only route with a long record at industrial scale, including for parenteral lipid emulsions and SLN intended for injection [30]. Solvent-based and microemulsion routes give small particles with modest equipment but dilute the product and leave residues. Ultrasound is convenient but variable. For an oral curcumin product the choice will probably turn on cost, residual-solvent burden and the ability to dry the dispersion, not on particle size, since all the methods can reach the range of interest.

Process variables matter more than the choice of name might suggest. Homogenisation pressure and cycle number, sonication time and amplitude, lipid-to-drug ratio, surfactant level and cooling rate all influence size, polydispersity and entrapment. Over-processing can cause coalescence and even increase size, a point shown repeatedly in the lipid nanoparticle literature [24, 25]. Cooling rate decides which polymorph forms and how drug is distributed in the matrix. Experimental designs, such as factorial or Box-Behnken layouts, have been used to optimise curcumin SLN and do reduce the number of runs needed, but they optimise only the responses chosen, usually size and entrapment, and rarely stability or release in biorelevant media.

Scale-up and sterility are rarely addressed in curcumin work. For oral use, microbial limits rather than sterility apply, yet aqueous lipid

dispersions are good culture media and need preservation or drying. Residual solvents, where used, fall under ICH limits. Reproducibility between three batches is frequently the only evidence offered that the process is robust, and a single homogeniser or sonicator is rarely replaced with another to check that the method transfers [6, 24]. Anyone intending clinical supply would need to show consistent particle size distribution, assay and release across at least pilot-scale batches, which is a different undertaking from the published bench formulations.

Probe sonication deserves a brief caution. It is fast and effective for small volumes, but it heats the sample and can shed titanium particles from the tip, and the energy delivered depends strongly on vessel geometry and volume. Two papers that both state a sonication time of five minutes may have delivered quite different doses of energy, and neither would be at fault for the mismatch. Calorimetric calibration of the probe is possible but almost never reported. Ice baths and pulsed operation are commonly used to limit heating, which is sensible for a molecule as unstable as curcumin, though degradation during processing is seldom assayed directly. Reporting amplitude, probe diameter and sample volume would let others reproduce the step.

## 5. CHARACTERISATION AND STABILITY

Particle size and size distribution are measured almost universally by photon correlation spectroscopy (dynamic light scattering), which reports a mean hydrodynamic diameter and a polydispersity index (PDI). Oral SLN are normally in the range of about 100 to 300 nm, and a PDI below roughly 0.3 is usually taken as an acceptable, fairly homogeneous population, although what counts as acceptable depends on the intended use [31]. Light scattering is biased towards larger particles and cannot detect a small population of aggregates reliably, so it is good practice to confirm with electron microscopy or laser diffraction. Many papers quote both a number-weighted and an intensity-weighted size without saying which is which, which complicates comparison. Measuring after dilution can also

change the result, because dilution alters surfactant equilibrium at the particle surface.

Zeta potential indicates how strongly the particles repel one another. Values more negative than about  $-30$  mV or more positive than  $+30$  mV are conventionally associated with good electrostatic stability, but this rule of thumb applies to simple electrostatic stabilisation and not to systems stabilised sterically by poloxamers, which can remain stable at much lower charge [32, 33]. Light and temperature during storage influence zeta potential and aggregation, as demonstrated in early SLN studies [32]. In chitosan-coated particles the potential reverses to positive, which is a convenient check that the coating has attached [26]. Zeta potential also depends on pH and ionic strength, so measurements in water, which are the commonest, may mislead for behaviour in gastrointestinal fluid.

Morphology gives a visual check on what the scattering numbers imply. Transmission electron microscopy, often after negative staining, usually shows roughly spherical particles for lipid blends, whereas pure highly crystalline triglycerides may form platelets that look quite different from the spheres assumed in light-scattering models [22, 25]. Scanning electron microscopy of freeze-dried powder shows aggregates and cryoprotectant matrix, and atomic force microscopy has been used to confirm size on a dry surface. Drying and staining can distort soft particles, so image sizes are normally smaller than hydrodynamic sizes. A discrepancy between the two is therefore expected and not in itself a flaw, but a very large gap suggests aggregation in suspension or a poorly prepared grid.

Entrapment efficiency is usually measured indirectly, by separating free curcumin through ultrafiltration or centrifugation and assaying the supernatant by spectrophotometry or HPLC. The approach is quick, but it can overestimate entrapment if drug adheres to filters or if curcumin degrades in the aqueous phase during the procedure [11, 20]. A direct method, in which the particles are dissolved in solvent and total encapsulated drug assayed, is a useful cross-check. Reported entrapment for

curcumin SLN is generally high, which fits the compound's strong lipophilicity, but values near the top of the scale should invite a second look at the method. Stability-indicating HPLC is preferable to plain absorbance because degradation products also absorb in the visible range.

Release testing is where the field is least standardised. Dialysis-bag methods dominate, with curcumin released into buffer containing surfactant or alcohol to maintain sink conditions, and the profile is often biphasic: an initial burst from drug at or near the surface followed by slower diffusion from the core [20, 27]. The burst fraction depends on temperature, surfactant and whether the drug is enriched in the particle shell. Dialysis membranes themselves can limit the rate, so a plateau may reflect the apparatus rather than the particles. Testing in simulated gastric then intestinal fluid, with and without lipase, would better reflect what happens after swallowing, and stability under these conditions is a more informative measure than release in a fixed buffer.

Long-term physical stability needs careful attention because lipid nanoparticles can change on storage. Possible events include polymorphic transition, particle growth, gelation of the dispersion and loss of drug from the matrix [22, 23, 33]. Storage conditions in published work are often limited to refrigeration for a few weeks or months, while the stability of lipid particles can change slowly over a much longer period as the lipid recrystallises [34]. Freeze-dried powders usually fare better than liquids. Curcumin adds a further layer of vulnerability, since it is light-sensitive and discolours, so amber containers and protection from oxygen are sensible. A formulation that is not shown to be stable over a realistic shelf life has limited translational value, however good its first-week data look.

Drug-excipient interaction studies, mostly by Fourier-transform infrared spectroscopy, are included in many papers. They are useful for ruling out strong chemical interaction, but small shifts of broad bands are over-interpreted fairly often. Loss of the characteristic curcumin melting endotherm in

DSC is similarly read as proof of amorphous or molecularly dispersed drug, whereas it may simply reflect dissolution of the drug in the molten lipid during the heating scan. Combining DSC with XRD and, where possible, electron microscopy gives a firmer picture than any single technique, and cautious wording about what each result does and does not show is the best policy.

## 6. IN VIVO EVALUATION AND LIMITATIONS

Pharmacokinetic studies in rodents are the usual test of whether an SLN formulation delivers on its promise. Rats receive an oral dose by gavage, blood is taken at scheduled times up to 24 hours or so, and plasma curcumin is measured by HPLC or LC-MS/MS, preferably with and without enzymatic deconjugation so that parent and total curcumin can be distinguished [5, 13]. The standard outputs are C<sub>max</sub>, the time of C<sub>max</sub>, area under the plasma concentration-time curve (AUC) and relative bioavailability. Animal studies should follow national care guidance and report in line with the ARRIVE items, covering randomisation, blinding, housing and sample size, which many older papers did not do [35, 36].

The bioanalytical method deserves as much scrutiny as the formulation. Curcumin is unstable in plasma at neutral pH and sensitive to light, so samples need prompt acidification or protein precipitation, protection from light and storage at low temperature until analysis [11, 13]. Quantification by HPLC with ultraviolet or fluorescence detection suffices for high doses, while LC-MS/MS is needed for the low concentrations seen after modest dosing. Internal standards, calibration across the working range and stated limits of quantification should all be reported. Treating plasma with  $\beta$ -glucuronidase and sulphatase allows total curcumin to be measured, and comparison with untreated samples reveals how much is free [5]. Studies that skip this step may under- or over-state exposure considerably.

Published findings are summarised in table 1, and the spread of approaches is shown by the grouping of entries in fig. 1. The general picture is encouraging. In rats, curcuminoid

SLN given orally raised AUC several-fold over a curcumin suspension [18], and a formulation based on a solid lipid curcumin particle was reported to give higher exposure in a pharmacokinetic study that included healthy volunteers and patients [37]. A study using polymer-modified SLN recorded higher plasma and brain levels than unmodified particles [26], and another reported prolonged circulation together with greater cellular uptake and activity in tumour cells [21]. A food-grade SLN preparation has more recently been reported to improve oral exposure in rats [38].

Mechanistic explanations are varied and partly speculative. Improved dissolution and protection from degradation in the gut lumen are the least contentious: the lipid shields curcumin from hydrolysis at neutral pH, and the large surface area of the nanoparticles aids contact with the epithelium [9, 20]. Uptake of intact particles, including by M cells in Peyer's patches, and lymphatic transport have been shown for model SLN given into the duodenum of rats [8]. Inhibition of efflux transport or metabolism by excipients is plausible but seldom tested for curcumin. The more careful papers acknowledge that plasma curves alone cannot distinguish between these routes, and tracing of labelled lipid or drug would be needed to settle the question.

Several limits of the evidence should be stated plainly. Dosing, species, sampling schedules and analytical methods differ so much that fold-increases from different papers cannot be placed on one scale [13, 18, 38]. Few studies assay conjugated and free curcumin separately, so a rise in total curcumin may reflect more glucuronide rather than more active compound [2, 5]. Efficacy readouts, where included, are usually small and short, and human data are limited to a handful of small studies [2, 37]. Dosing of rats in fasted rather than fed state matters because food, and especially dietary fat, changes lipid digestion and absorption [9, 10]. Safety of chronic exposure to surfactants and lipid particles is largely unexamined, and no long-term toxicity study of an oral curcumin SLN product appears to have been reported. Even the short-term gastrointestinal tolerability of daily dosing with

polysorbate-containing dispersions is rarely described.

**Table 1: Published SLN approaches for curcumin and reported outcomes**

| Approach Feature                       | Reported finding                                                                    | Ref.         |
|----------------------------------------|-------------------------------------------------------------------------------------|--------------|
| Stearic acid SLN curcuminoids          | Good entrapment with sustained in vitro release from a fatty acid matrix.           | [20]         |
| Glyceride lipid SLN oral rat study     | Raised curcumin AUC several-fold over a suspension after gavage.                    | [18]         |
| Solid lipid curcumin particle clinical | Higher exposure than unformulated curcumin in patients and volunteers.              | [37]         |
| Chitosan-modified SLN surface coating  | Higher plasma and brain levels than uncoated particles in rats.                     | [26]         |
| Surfactant-stabilised SLN tumour cells | Prolonged activity, greater cellular uptake and improved bioavailability.           | [21]         |
| Food-grade SLN oral rat study          | Enhanced oral bioavailability using food-compatible ingredients.                    | [38]         |
| Emulsification-diffusion solvent route | Small particles with narrow size distribution; residual solvent must be controlled. | [28]         |
| Solvent injection low energy           | Lipid in water-miscible solvent injected into water; process variables set size.    | [29]         |
| Hot homogenisation reference method    | Established scalable route using melted lipid and surfactant solution.              | [6, 7]       |
| Lipid choice crystallinity             | Imperfect lipid mixtures hold more drug and limit expulsion on storage.             | [22, 23, 24] |

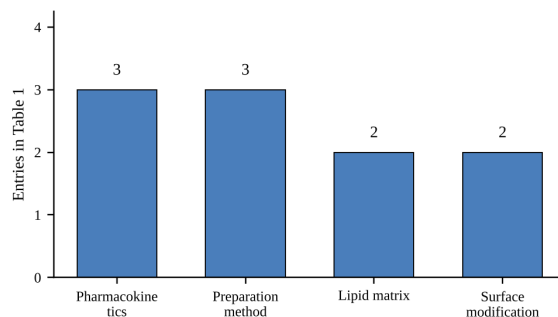


**Fig. 1: Number of entries in table 1 by approach category**

Future work could usefully focus on a few well-defined points. Direct comparison of

SLN with simpler lipid solutions and with other nanocarriers, in the same laboratory under matched dosing, would show whether the particle structure adds anything beyond the lipid. Biorelevant digestion and permeability models should become part of routine testing, as should long-term stability studies that follow lipid crystallinity [34]. Pharmacokinetic reports ought to give both free and conjugated curcumin, and efficacy studies should use disease models in which the plasma concentration achieved is known to matter [1, 2]. Reporting of animal methods to ARRIVE standards would improve confidence [36]. Finally, controlled trials of adequate size are needed before any claim of clinical benefit from lipid-based curcumin can be accepted.

Regulatory considerations are likely to shape which of the many published systems ever reach patients. A nanoparticle product intended as a medicine would be assessed for quality, consistency of particle attributes and excipient safety, and an oral food supplement faces a different but still demanding set of requirements. Excipients with a long record of use, such as glycerides and lecithin, are an advantage here. The need to justify every critical attribute, including particle size distribution and polymorphic state, argues for building characterisation into formulation work from the earliest stage instead of treating it as a final reporting exercise.

A word on the animal evidence is also warranted. Rats and mice differ from humans in gut transit, bile composition, lipase activity and glucuronidation capacity, so absolute bioavailability values from rodents cannot be transferred directly to people [5, 13]. Relative gains in exposure are more transferable than absolute levels, but even these can change across species, as the piperine example illustrates, where the improvement was far larger in volunteers than in rats [14]. Studies in a second species, ideally one with a gastrointestinal physiology closer to the human, would add useful information before proceeding to clinical work.

## 7. CONCLUSION

Solid lipid nanoparticles are a reasonable and technically accessible way to improve the oral

exposure of curcumin. The published work shows that careful choice of lipid, surfactant and production method yields particles of a few hundred nanometres or less with high entrapment, and that rats given such preparations usually reach higher plasma curcumin than animals given the plain compound [18, 20, 26]. The best-supported explanation is better dissolution plus protection from degradation, with lymphatic uptake and reduced first-pass metabolism as possible extra contributions [8, 9]. For a compound this unstable, protection inside a solid matrix is arguably as valuable as any change in solubility.

The weaknesses are as consistent as the gains. Control formulations, doses and assays vary, stability data are short, and almost nothing is known about long-term safety or clinical benefit [2, 34, 37]. Future studies should compare formulations head to head, separate free from conjugated curcumin, test stability under regulatory storage conditions and report animal work in line with ARRIVE [36]. Until then, claims about enhanced bioavailability should be read as promising preclinical observations and not as proof of therapeutic advantage. A well-controlled study in a second species, with full stability data, would be the most useful next step.

## 8. ABBREVIATIONS

ARRIVE-Animal Research: Reporting of In Vivo Experiments, AUC-Area under the plasma concentration-time curve, C<sub>max</sub>-Maximum plasma concentration, DSC-Differential scanning calorimetry, HPLC-High-performance liquid chromatography, ICH-International Council for Harmonisation, LC-MS/MS-Liquid chromatography-tandem mass spectrometry, NLC-Nanostructured lipid carrier, PDI-Polydispersity index, PLGA-Poly(lactic-co-glycolic acid), SLN-Solid lipid nanoparticles, XRD-X-ray diffraction

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## 10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## 11. CONFLICT OF INTERESTS

Declared none

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