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REVIEW

Curcumin Nanocrystals: Synthesis, Optimisation and Prospects of Anticancer Activity Against Primarily Female-Associated Cancers

Tanaka Ndongwe[1], Nathi Charmaine Skosana[1], Bwalya Angel Witika[1], Yohann Corvis[2], Xavier Siwe Noundou[1], Gauta Gold Matlou[3]

[1]Department of Pharmaceutical Sciences, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, Gauteng, South Africa; [2]CNRS, Inserm, Unit of Chemical and Biological Technologies for Health, University Paris Cité, Paris, France; [3]Electron Microscopy Unit, Sefako Makgatho Health Sciences University, Pretoria, Gauteng, South Africa

Correspondence: Bwalya Angel Witika, Department of Pharmaceutical Sciences, School of Pharmacy, Sefako Makgatho Health Sciences University, PO BOX 218, Pretoria, Gauteng, 0204, South Africa, Email Bwalya.witika@smu.ac.za; Gauta Gold Matlou, Electron Microscopy Unit, Sefako Makgatho Health Sciences University, Pretoria, Gauteng, South Africa, Tel +27785428849, Email Gold.matlou@smu.ac.za

Abstract: Curcumin is a polyphenol phytochemical that is extracted from the rhizomes of *Curcuma longa Linn*. (Zingiberaceae) in the Zingiberaceae family. In recent years, the investigation of curcumin has notably skyrocketed due to its broad pharmacological profile, as evidenced by its antimicrobial, antioxidant, anti-inflammatory, and antitumoral properties. While research and use of curcumin are significantly increasing, its apparent poor water solubility has notably limited its potential as a promising chemical entity. Consequently, efforts to enhance its apparent solubility without altering the chemical properties have been considered. Among the leading techniques is nanocrystasllisation which involves modifying its physicochemical properties, such as particle size, shape and electrical charge. Nanocrystallisation is a nanoscience technique that utilises the drug's crystalline properties to enhance its solubility, bioavailability, and overall pharmacological activity. To date, various nanocrystallisation techniques have been employed, including high-pressure homogenisation, sonoprecipitation, and the solvent-antisolvent precipitation technique. Curcumin nanocrystallisation has often been reported for the improvement of its loading capacity, as it requires fewer excipients and significantly enhances the minimal dose efficiency. Furthermore, the significant role of curcumin in primarily female-associated cancers has been highlighted in some in vitro studies. Therefore, this review will focus on the elaboration of nanocrystals and its promising role in breast and gynaecological cancers. Given the limited studies reported on the anticancer activity of breast and gynaecological cancers curcumin nanocrystals, this review also aims to highlight the research gaps concerning the anticancer activity of curcumin nanocrystals.

Keywords: curcumin, nanocrystals, biological activity, nanocrystal synthesis and cancer

Introduction

The global burden of breast and gynaecological cancers is gradually increasing due to the world's growing female population and fast social development and there is a noticeable trend towards women of childbearing age.[1] Breast cancer was ranked as the second most diagnosed cancer globally, with 2.3 million recorded cases worldwide and is predicted to increase to over 35 million new cases by 2050.[2,3] Gynaecological cancers are among the leading conditions globally with high incidence and mortality rates. In 2022, about1473427females were diagnosed globally with gynaecological cancers.[4] While cervical cancer continues to be a major cause of cancer-related mortality in several developing nations, breast cancer is one of the most prevalent cancers among women worldwide. Although ovarian cancer and uterine cancer have relatively lower incidence rates, they are nonetheless significant types of malignancies affecting the female reproductive system.[2]

The increasing cases of both breast and gynaecological cancers warrant the need for highly effective cancer therapy. Currently, chemotherapy remains one of the most widely employed and effective therapeutic modalities in the

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management of various malignancies.[3] These agents exert their cytotoxic effects primarily by targeting rapidly proliferating tumour cells, thereby interfering with DNA replication, mitotic processes, and cell cycle progression.[5,6] The United States food and drug administration (US FDA) has approved numerous cancer chemotherapy drugs such as docetaxel, trastuzumab, and paclitaxel and doxorubicin hydrochloride.[7,8] These drugs are mostly used in the ovarian, uterine, breast and cervical cancers.

However, the clinical utility of cancer drugs is limited by many factors that impact patient adherence and treatment outcomes.[9] For instance, the existence of multidrug resistance (MDR) is a primary limitation especially when there is an overexpression of efflux transporters like p-glycoprotein (P-gp), the active pharmaceutical ingredients (APIs) have low solubility, poor bioavailability, inconsistent absorption and elevated toxicity concerns.[10] Additionally, the severity of side effects necessitates dose reductions of the anticancer agent which eventually leads to inefficient therapeutic outcomes and potential metastasis. The lack of selectivity, chemotherapeutic drugs also damage normal cells with high mitotic activity, including those in the bone marrow, gastrointestinal mucosa, and hair follicles, leading to well-documented systemic toxicities.[11] A substantial proportion of these agents act as genotoxins, inducing DNA damage either directly or indirectly through the overproduction of reactive oxygen species (ROS).[12] While ROS-mediated genotoxicity contributes to the eradication of malignant cells by promoting apoptosis or necrosis, it simultaneously affects healthy cells, resulting in oxidative stress and cumulative tissue injury that limits therapeutic selectivity.[13,14] Consequently, more safe and effective chemical entities are under immense investigation for their potential use in cancer therapy.

Curcumin has been used since ancient times in Asian cuisine, and its utility has grown significantly over the years.[15] In scientific research, the pharmacological profile of curcumin has been extensively investigated.[16] The conditions in which curcumin has been recurrently cited to be potentially effective include cancer, rheumatism, skin diseases, and bacterial infections.[17] In this respect, the use of curcumin in many studies has demonstrated its broad pharmacological profile including anticancer, antioxidant, anti-inflammatory, antidiabetic, and anti-asthmatic properties.[18] Although promising, the pharmacological profile of curcumin has not been fully explored due, notably, to its poor water solubility (0.6 μg/mL).[19,20] Curcumin comprises two functional groups, namely polyphenol and enolizable β-diketone moieties, with 8 hydrogen bond acceptors and two hydrogen bond receptors that explain the low aqueous solubility of the compound.[21]

Consequently, methods have been devised to improve the solubility and, in some cases, biological activity of curcumin. Among some of the leading techniques the use of nanocrystals has garnered significant attention.[22] Nanocrystals refer to materials within the submicronic range (less than 1000 nm) that have a crystalline structure typically dispersed in an aqueous medium.[23] Nanocrystal formulations are reported to be cost-effective, to improve solubility, to increase specific area of the nanoparticles, to promote efficient loading capacity, to allow drug targeting, to enhance, and may require less excipients in their formulation.[23,24] Currently, several techniques as shown in Table 1 have been used to elaborate curcumin nanocrystals such as the high-pressure homogenisation, the solvent antisolvent technique, and the sonoprecipitation techniques.[23]

The Rationale for Nanocrystal-Based Delivery of Curcumin in Primarily Female-Associated Cancers

Curcumin (Figure 1) is a yellow polyphenol that is isolated from Curcuma longa Linn (turmeric). The compound has a molecular weight of 368.37 g.mol-1, chemical formula of C21H20O6 and falls under the Biopharmaceutics Classification System (BCS) class IV.[33] Curcumin has anticancer properties and offers a unique multi-target approach against carcinogenesis (Figure 2). Curcumin modulates key signaling pathways dysregulated in female-associated cancers, including the β-catenin protein, an essential part of the Wnt/β-catenin signalling pathway that controls stem cell differentiation, tissue regeneration and cell proliferation, is inhibited by curcumin. Additionally, curcumin promotes senescence by blocking the PI3K/Akt pathway, which stops angiogenesis, growth and cell proliferation.[33,34] Curcumin causes cancer cells to undergo autophagy and apoptosis.[34] Furthermore, curcumin inhibits the activation of the EGFR signalling pathway, which promotes tumour growth and cell proliferation.[35]

Table 1 Summary of the Reported Studies on the Synthesis of Curcumin Nanocrystals

Method	Stabilizers Used	Particle Size	PDI	Zeta Potential	Solubility	Reference
High-pressure homogenization	Polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), TPGS, SDS, carboxymethylcellulose sodium salt	500–700 nm	0.56 (SDS)	−37 - −2.3	Improved solubility	[25]
Precipitation and ultrasonication (sonoprecipitation)	Poloxamer 188 (Pluronic F-68), polysorbate80, poly (vinylpyrrolidone) (PVP) P188 and SLS	328.7 ± 16.87 260nm	0.361 ± 0.03 0.71–2,53	−36.7 ± 0.45 –49,8-9,0	Improved solubility –	[26] [27]
Bead milling Wet bead milling and HPH	(d-α-tocopherol polyethylene glycol 1000 succinate) Capryl glucoside, lauryl glucoside and decyl glucoside	290 nm 182nm	0.264 0.23	– 16 mV -30mV	Improved solubility Improved solubility	[24] [28]
Wet milling combined with the spray drying method.	Polysorbate80	1.5 μm - 924 nm			Improved solubility	[29]
Anti-solvent precipitation	PVP	60 - 480 nm	-	-	Improved solubilty	[30]
Wet ball-milling	Pluronic F127 (F127) and hexadecyl trimethyl ammonium bromide (CTAB)	150 nm		−16.7 to 36.5 mV	Improved solubility	[31]
Solvent evaporation and spray drying		128 nm,		–18.3 mV	Improved solubility	[32]

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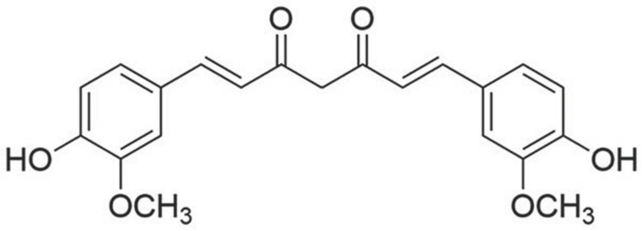

Figure 1 Curcumin chemical structure.

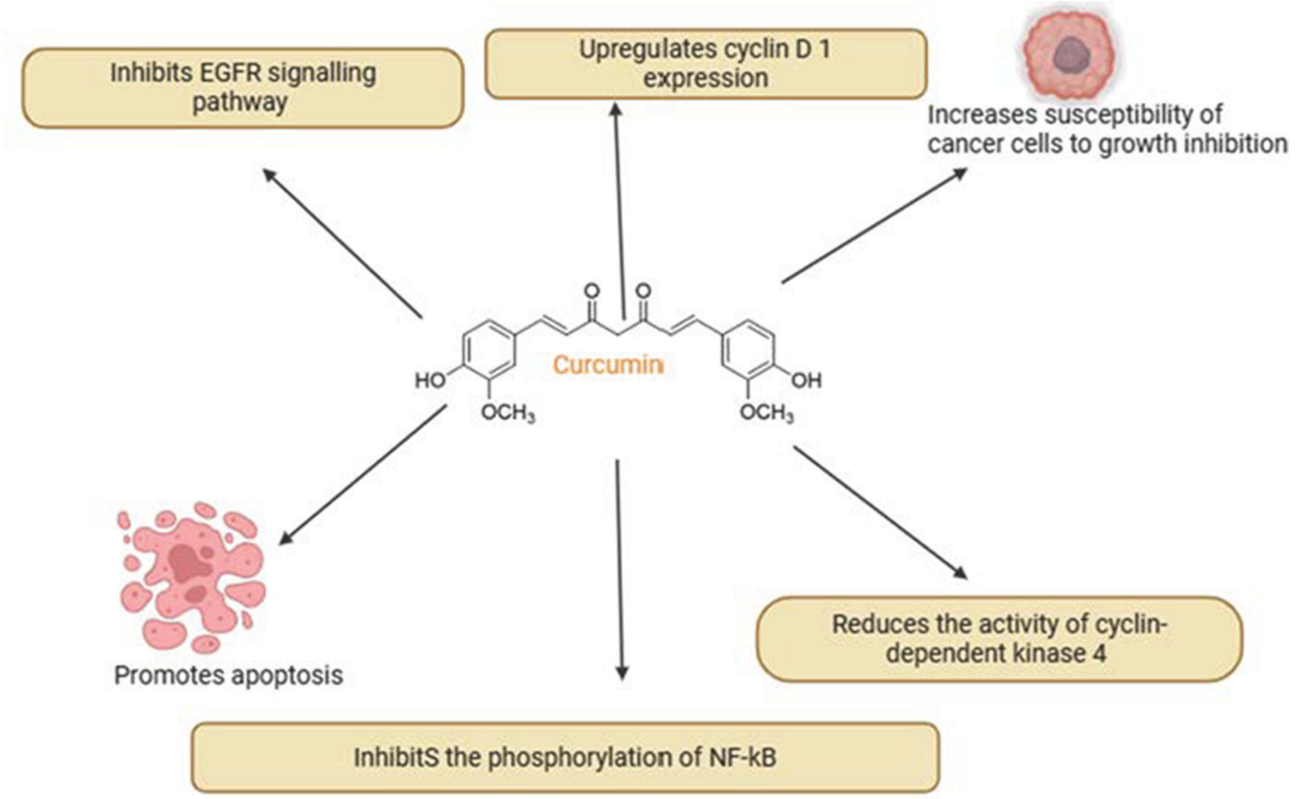

Figure 2 The multitarget mechanisms of action of curcumin in cancer.

Nuclear Factor kappa-light-chain-enhancer of activated B cells (Nf-kB) are important transcription of oncogenic genes and promote the growth of cancer cells. It is usually activated by TNF-αand other interleukins.[36,37] Curcumin efficiently suppresses these transcription processes and prevents proliferative pathways by inhibiting the phosphorylation of NF-kB. Furthermore, curcumin modifies the Bax-mediated apoptotic pathway in breast cancer and increases the generation of ROS.[38,39] In breast cells, curcumin affects cell cycle progression, migration and invasion in cell type-specific way via changing the network of interactions between microRNA (miRNA) and messenger RNA (mRNA).[40] Additionally, curcumin downregulates the expression of carcinogenic miR-19a and miR-19b in cancer cells while upregulating tumour-suppresive miR-181b, miR-34a, miR-16, miR-15a and miR-146b-5p. Curcumin reduces the activity of cyclin-dependent kinase 4 (CDK4) and stops cell division by preventing cyclin D1 from binding to CDK4, it also activates CDK inhibitors while promoting the degradation of cyclin E, a protein that is frequently overexpressed in breast cancer. Cell division is stopped by these effects in the G1 phase.[36–38,41]

Despite this promising pharmacodynamic profile, its clinical translation has been severely hampered by intrinsic biopharmaceutical limitations. As a Biopharmaceutics Classification System (BCS) Class IV compound, curcumin suffers from

Table 2 Anticancer Activity of Curcumin Nanoformulations in Breast and Gynecological Cancers

Type of Cancer	Curcumin Formulation Particle Size	Mechanism of Action	Authors
Ovarian Cancer	Gemini curcumin nanoparticles	Induction of apoptosis, inhibition of proliferation	[42]
Ovarian Cancer	Nanomicelles	Co-delivery with docetaxel to improve efficacy	[44]
Breast Cancer	Gemini surfactant nanoparticles	Enhanced therapeutic efficiency by overcoming poor bioavailability	[45]
Breast Cancer	Nanosuspension of curcumin and docetaxel	Inhibition of P-glycoprotein, increased oral bioavailability, decreased drug efflux	[46]

exceptionally poor aqueous solubility (≈0.6 μg/mL) and low permeability, leading to negligible oral bioavailability and rapid systemic metabolism and elimination.[19] In recent years nanotechnology-based formulations of curcum in (Table 2) have emerged as a promising strategy to overcome solubility, enhancing cellular uptake, and ultimately bioactivity. In this respect, the physiochemical properties of curcumin formulations play a crucial role in enhancing its pharmacokinetic profile and tissue distribution, thereby improving its anticancer efficacy.[42,43]

Nanocrystals: Advantages and Relevance to Curcumin Delivery

Nanocrystals have several advantages over other nanoparticle systems, making them a good choice for drug delivery. Unlike polymeric nanoparticles, liposomes, or micelles, which require complex formulation processes, nanocrystals achieve approximately 100% drug loading since they mostly consist of the pure drug.[47] Additionally, the nanoscale size of nanocrystals greatly increases the surface area of the drug, which improves the dissolution rates and bioavailability, especially for poorly water-soluble drugs.[48] Preparing nanocrystals can be done with simple and cost-effective methods, which facilitate large scale production and reproducibility.[49] Nanocrystals can be administered through various routes allowing for flexibility formulation. Altogether, these qualities make nanocrystals a promising option for improving the therapeutic performance and patient compliance of poorly soluble drugs.[50] As a result, formulation of curcumin nanocrystals is critical in cancer therapy.

The use of curcumin and its application in numerous conditions can be improved by increasing its solubility.[15,19,51–53] Recently, several drug delivery methods have been explored such as encapsulation and nanocrystallisation.[19] To date, a notable number of techniques have been reported to be effective in formulating nanocrystal (Figure 3),[54] leading to drug crystal nanoformulations that have been approved by the FDA such as Tricor®, Megace ES®, Invega Sustenna®, and Rapamune®.[22,55]

Nanocrystals are promising drug formulations with approximately 100% drug matrix, and these crystal formulations serve as intermediates between amorphous and crystalline states and therefore offer stability and improved solubility. To develop nanocrystals, different approaches either top-down, bottom-up, or in some cases the combination of the two approaches, are performed to engineer curcumin nanocrystals.[56] Among the leading techniques are High-pressure homogenisation (HPH), sonoprecipitation, bead and wet milling (Figure 3).[57] In addition, stabilisers such as polymers, lipids, and celluloses can be used to maintain curcumin crystals in the nano range and also improve the pharmacokinetic profile of the active pharmaceutical ingredient.[58]

Systematic Optimization of Curcumin Nanocrystals Using Quality by Design (QbD) and Design of Experiments (DoE)

The synthesis of curcumin nanocrystals is a highly intricate process, typically requires a lot of experiments to achieve optimisation and is often challenging where achieving optimal critical quality attributes (CQAs) such as particle size, polydispersity index (PDI), and zeta potential l.[22,59] Moreover, empirical optimising is tedious and time consuming as the desired critical quality attributes such as particle size, polydispersity index (PDI), zeta potential is often influenced by various independent variables. Therefore, systematic and reproducible methods such as Quality by Design (QbD) may be useful.[22,59,60] Accordingly, literature appraisal, careful selection of raw materials, identifying CQAs and Critical Process Parameters (CPPs), and defining additional input parameters are key steps to consider in the preparation of drug nanocrystals.[55] Identifying the design space is done using Design of Experiments (DoE) and greatly assists in method

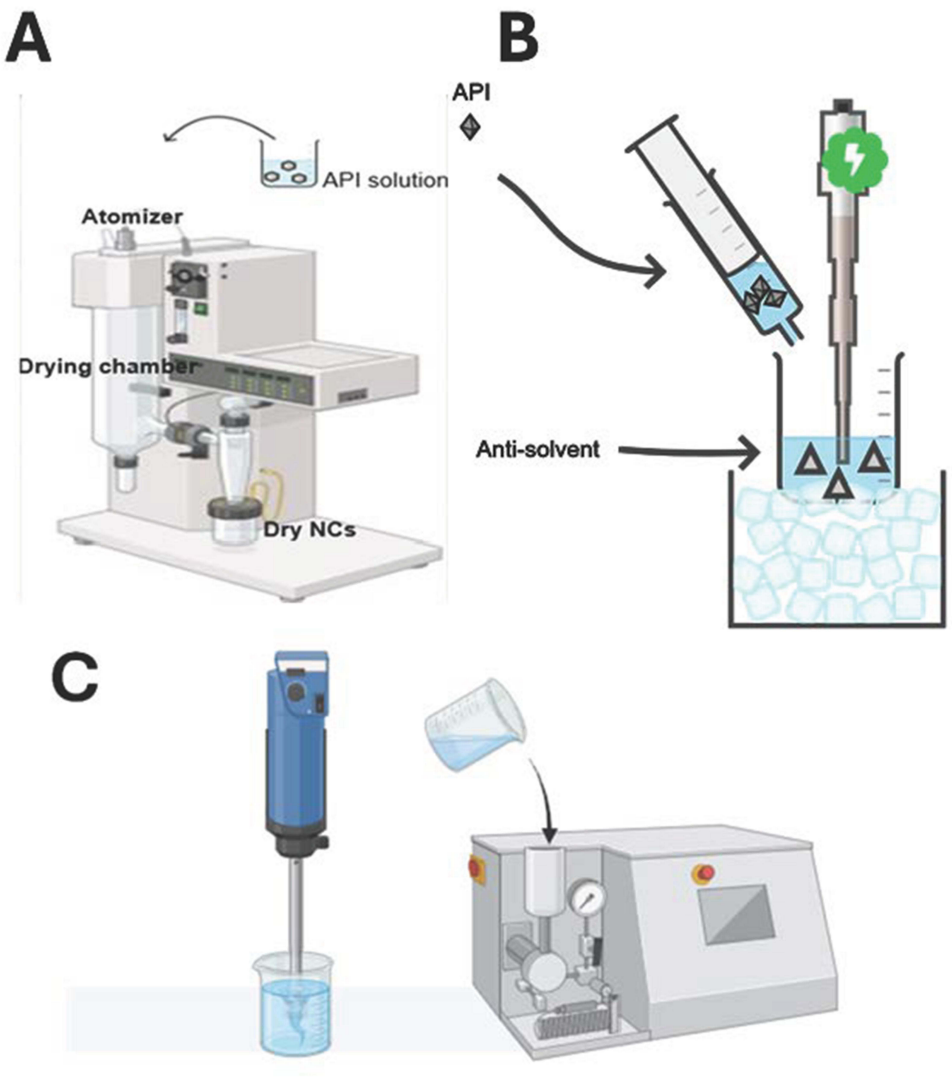

Figure 3 Examples of techniques of nanocrystallisation (**A**) Spray drying, (**B**) Nanoprecipitation (**C**) High shear homogenization and High pressure homogenisation.

optimisation through establishing the relationship between dependent and independent variables.[60] This approach operates by using statistical principles to evaluate factors and responses to give the least experiments while giving maximum information.[61] The integration of QbD and DoE is therefore not merely a procedural enhancement but a necessity for developing robust, reproducible, and scalable CUR-NC formulations. It ensures that the nanocrystals possess the consistent physicochemical properties required for reliable performance in subsequent in vitro and in vivo anticancer studies, ultimately accelerating the translational pathway for curcumin-based therapies against breast and gynecological cancers.[22]

Technique Synthesis of Curcumin Nanocrystals

High-pressure Homogenisation

The high-pressure homogenisation (HPH) technique has been employed in the preparation of numerous pharmaceutical products. HPH involves the use of a high-pressure mixer to produce a homogeneous product and, in some cases, reduce the overall size of the particles.[62,63] In the formation of curcumin nanocrystals, HPH technique is often used to modify surface morphology, reduce particle size, and improve the PDI of the nanosuspensions.[64] Parameters such as stirring, drug concentration, type and ratio of the solvents/anti-solvents, and nature of the stabiliser used should be carefully chosen and controlled to obtain convenient formulations.[55] If these parameters are not carefully selected, drawbacks may occur including inconsistent particle size, incomplete crystallisation, unstable nanocrystals and phase

separation which is the imbalances in solvent and anti-solvent ratios leading to improper precipitation, where drug molecules might not adequately disperse, leading to poor nanocrystal formation. HPH offers several advantages for producing nanocrystals, it is notably easy to scale up, allowing for industrial scale production and is highly reproducible ensuring consistency across batches.[65] HPH strengths lies in its ability to produce uniform particle sizes, enhancing product quality and stability.[66] Although the method is effective, it has limitations, such as high operational temperatures, significant energy input and potential degradation of components, which yield lower product quantities.[62]

Rachmawati et al investigated in 2013 the synthesis of curcumin nanocrystals using five stabilisers namely, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), sodium dodecyl sulfate (SDS), and carboxymethylcellulose sodium salt.[25,67] In this study HPH was used and formulations which contained 5% (w/w) curcumin and 1% (w/w) stabiliser with the exception of SDS which was 2% (w/w). The outcome of the study revealed that out of the five stabilisers, four (PVA, PVP, TPGS, and SDS) were found to be effective in the synthesis of curcumin nanocrystals within the size range of 500–700 nm and PVA, PVP, and TPGS demonstrated improved stability.

An oral formulation of curcumin nanocrystals was formulated by Ravichandran in 2013.[68] In this study, the researcher synthesised the NCs using 10% (w/w) curcumin, 2% (w/w) polyvinyl alcohol and 88% (w/w) water. HPH followed by spray drying was used. The results of the study showed that the thus-prepared NCs present improved dissolution properties.

Precipitation and Sonoprecipitation

The synthesis of nanocrystals has been enhanced using sonoprecipitation, a method that incorporates precipitation and ultrasonication. This approach relies on the use of different parameters such as temperature, the frequency of sonication, and the rate at which the solvent is added to the antisolvent medium.[69] The mixing process, nucleation, growth, and agglomeration are the primary changes brought about by ultrasound-assisted nanoparticle precipitation. The horn length, horn immersion depth, cavitation depth, and ultrasound treatment intensity all affect the size of the nanocrystals.[70,71] Additionally, ultrasonication does not require organic solvents or complex processing steps, making it economic friendly, relatively simple approach suitable for temperature-sensitive compounds due to the short, high-energy pulses applied intermittently.[70] Precipitation and ultrasonication have been used in the synthesis of Curcumin nanocrystals (CUR-NCs) with the broad aim of improving its solubility, permeability and ultimately bioavailability. However, a major limitation lies in maintaining the stability of nanocrystals after precipitation, as nanocrystals typically remain stable only for a limited duration.

Bonaccorso et al (2020b) and coworkers formulated CUR-NCs for intranasal use. The investigation was designed using Box Behnken design and the sonoprecipitation method was used to formulate 51 samples using three stabilisers (poloxamer 188, Tween® 80 [polysorbate 80] and PVP). After optimisation, the nanocrystal formulation was found to have an average particle size of 329 nm ± 17 nm, and the crystallinity of the sample was confirmed using a PXRD. The outcome of the study demonstrated that the use of the Box Behnken Design plays a significant role in optimising a formulation and was found to be reliable with a %error of 0.28.[26]

The solubility of curcumin was successfully improved by the use of nanoprecipitation.[27] The authors prepared the CUR-NCs using 100 mg of the active pharmaceutical ingredient and 20 mL of ethanol 60% (v/v), while 100 mg poloxamer 188/ SLS (20 mL distilled water) was used as a stabiliser. The prepared formulation was sonicated (40 kHz), resulting in the instant formation of NC. The findings of the study demonstrated that SLS resulted in a significant reduction of particle size and a narrow particle size distribution without aggregation.

enríquez and colleagues recently reported the step-by-step standard and reproducible synthesis of CUR-NCs using the bottom-up semi-automed approach.[22] The study followed a systematic approach as guided by Quality-by-Design (QbD) and Design of Experiments (DoE). In addition, the Central composite design was used in the optimisation. The outcome of the study revealed that the average particle size was 316 nm, while the PDI was observed to be 0.217. The study emphasised the significance of integrating systematic data collection for in-depth analysis with the standardisation of the nanocrystallisation process.

Bead Milling

The use of milling techniques has been frequently used in pharmaceutical settings. This method necessitates the use of milling media, dispersion media and stabilisers.[54] To improve the solubility of curcumin for use as a nanosuspension, bead milling and HPH were used by Vidlářová et al, (2016).[28] Stabilisers, namely capryl glucoside, lauryl glucoside and decyl glucoside were used in the synthesis of Cue-Ncs. The nanocrystal formulations were prepared using 5% w/w curcumin and 1% stabiliser was used in water, resulting in the particle size in the range of 200 nm.

In an attempt to improve the solubility of curcumin, small scale bead milling was used to prepare Cur-NCs.[24] The authors used 5.0% (w/w) curcumin, 1.0% (w/w) TPGS all dissolved in water up to 00% (w/w). Analyses of the results demonstrated the CUR-NCs had a particle size distribution of about 250 nm and PDI of 0.25.

Wet Milling

Wet ball milling is one of the leading methods used as a top-down approach in the synthesis of NCs. The technique relies on mechanical attrition, where particles are dispersed in an aqueous solution containing surfactants and then subjected to grinding by milling balls within a milling container. As a result, the particles size is substantially reduced, sometimes reaching a few hundred micrometres, though further modifications in conventional milling allow for the generation of nanosized crystals. Wet milling is also commonly preferred as it is a reproducible process.[72] However, drawbacks include potential contamination from metal erosion of milling balls, high energy consumption, lengthy operation times, and a decrease in crystallinity. Using polymeric beads as a substitute for metal milling balls may reduce contamination.[73]

This method on the other hand presents several advantages, making it a popular choice for nanocrystal production in the pharmaceutical industry. Its scalability is a significant benefit, allowing easy adaptation from laboratory to industrial production without extensive changes to the process. Additionally, the method is highly reproducible, enabling consistent particle quality across batches. It allows for the production of uniformly sized particles, which contributes to the stability and efficacy of the final product.[74] Through specific process modifications, the technique enables precise control over particle size, allowing customisation to achieve desired characteristics in the nanocrystal formation.

The pulmonary delivery of curcumin nanocrystals was reported by Hu et al, (2015).[29] In this research work, CUR-NCs were synthesised using wet milling combined with the spray drying method. The formulation was prepared using 20 g of curcumin, which was dispersed in 250 mL aqueous solution containing a stabiliser (6.25% polysorbate 80). Characterisation results from differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR) demonstrated that curcumin maintained its crystalline state throughout the process of reducing particle size (924–1,500 nm).

The variation of the size of CUR-NCs using a wet milling technique was investigated by He et al, reported in 2020.[75] The outcome of the study revealed that three distinct NC sizes were produced: small (NC-S, 246 ± 22 nm), medium (NC-M, 535 ± 50 nm), and large (NC-L, 1090 ± 194 nm). The investigation showed that nanocrystals with reduced size were absorbed more readily into the bloodstream due to increased dissolution rate.

A study by Lizoňová et al performed in 2022 evaluated the synthesis of curcumin nanocrystals.[76] The wet milling technique was employed to prepare these nanocrystals, utilizing a combination of polysorbate 80, sodium dodecyl sulfate, Poloxamer 188, hydroxypropyl methylcellulose, phospholipids (with and without polyethylene glycol). The study's outcomes unveiled a particle size distribution ranging from 40 to 90 nm.

Anticancer Activity of Curcumin Nanocrystals

Curcumin Nanocrystals in Breast Cancer

Seemingly, limited research has been reported on the use of curcumin nanocrystals in TNBC. Ji et al explored the use of hyaluronic acid (HA) through its incorporation onto the surface of NCs to achieve enhanced surface hydrophilicity in the form of reformed HA@Cur-NC for extended biodistribution. Evaluation of the findings indicated that HA@Cur-NC demonstrated increased cellular uptake in CD44 overexpressing MDA-MB-231 cells, which was diminished following pre-treatment with HA. Analysis of the mechanism of action revealed that the formulation specifically targets CD44 expressing cells. Also, prolonged enhanced permeability and internalisation via caveolae-mediated endocytic

mechanisms were also observed as CUR-NCs anticancer mechanisms in TNBC. Moreover, pharmacokinetic investigations conducted in vivo indicated a significant prolongation of curcumin in vivo.

Another recent study by Fuster et al (2024) reported on the formulation of folic acid-decorated curcumin nanocrystals (FA@Cur-NCs) to enhance the selective delivery of curcumin to folate receptor (FR)-overexpressing breast cancer cells.[43] The authors incorporated folic acid onto the surface of the nanocrystals with the broad aim to facilitate receptor-mediated endocytosis and minimize non-specific cellular uptake. Analysis of the results demonstrated that the formulation (FA@Cur-NCs) in MCF-7 breast cancer cells exhibited a significantly higher intracellular accumulation of FA@Cur-NCs compared to unmodified nanocrystals, confirming FR-specific uptake. Furthermore, cytotoxicity assays revealed that FA@Cur-NCs exhibited markedly enhanced anticancer efficacy while showing reduced macrophage uptake, suggesting improved circulation potential.

Curcumin Nanocrystals in Cervical Cancer

David et al (2020) formulated and evaluated curcumin-loaded liquid crystal (LC) systems as a novel vaginal drug delivery approach for cervical cancer therapy.[77] The LC systems were prepared using various surfactants (Tween 80, Cremophor EL, and Labrasol), with Tween 80 ultimately selected for its superior safety profile and physicochemical stability. The optimized formulation exhibited a pH between 3.9–4.4, suitable for vaginal application, and demonstrated high encapsulation efficiency (up to 93%) with vesicle sizes ranging from 6 to 12 nm. Structural characterization via ESEM confirmed spherical and hexagonal micellar morphology. In vitro release studies in vaginal simulated fluid showed sustained drug release (20–87% over 8 hours), while stability testing indicated optimal preservation at 5 °C. Cytotoxicity assays revealed that curcumin-loaded LCs significantly enhanced anticancer efficacy against HeLa cervical cancer cells compared to free curcumin, with negligible toxicity from blank formulations. Overall, the study highlights curcumin LC gels as promising, pH-compatible carriers for localized and sustained cervical cancer therapy.

Curcumin Nanocrystals in Uterine Cancer

Yan et al (2025) investigated co-crystals of curcumin (CUR) and berberine (BBR) encapsulated in a nanohydrogel formulation for endometrial carcinoma therapy.[78] The authors engineered the CUR/BBR co-crystals within a nanohydrogel matrix with the aim of improved stability, solubility and dual-drug synergetic delivery. The findings of the study indicated that the formulation (Nano-hydrogel@CUR/BBR) produced significantly enhanced apoptosis in endometrial cancer cell lines compared to either agent alone. Also, the mechanistic analysis revealed covalent and non-covalent inhibition of caspase-3 as well as amplified mitochondrial pathway activation. Furthermore, in vivo testing demonstrated superior tumour suppression and prolonged survival.

Taken together, the aforementioned curcumin drug delivery systems exemplify the diverse and complementary roles of nanocarrier design in advancing curcumin-based therapies for uterine cancer.

Conclusion and Future Prospects

The use of curcumin has significantly risen to prominence in recent years due to its broad pharmacological profile. Currently, Cur-NCs have been synthesised with distinct tunable nanomeric traits reported. Stabilisers including poloxamer P188, PVA, PVP, TPGS 1000, and SDS have been found to yield promising results in the synthesis of CUR-NCs. The synthesis of NC-NCs thus far has mostly used HPH, solvent evaporation and bead milling equipment. Nanocrystallization of curcumin emerges as a paramount formulation strategy to surmount the intrinsic biopharmaceutical limitations of this potent polyphenol. By engineering submicronic crystalline structures, this approach will not only improve dissolution kinetics but also bioavailability through increase in surface area, without molecular alteration of the phytochemical.

While reported studies show significant promise, particularly in breast cancer through mechanisms like targeted delivery and enhanced cellular uptake, research on their specific application in aggressive subtypes like triple-negative breast cancer remains limited. Few studies have explored the potential use of CUR-NCs in gynaecological cancers and in subtypes of breast cancer especially triple negative breast cancer (TNBC), both in vitro and in vivo. Furthermore, the functionalisation of CUR-NCs can also be explored to improve their targeted delivery and cell permeability in breast cancer. Moreover,

additional translational studies are warranted to evaluate the role of curcumin in such clinical settings, as few have been reported so far. There is also a need to introduce more efficient approaches to CUR-NCs synthesis and depiction of its mechanism of action. This can be improved using mechanochemistry techniques which are environmentally friendly and through bioimaging of CUR-NCs to fully depict its mechanism of action. Mechanochemistry utilises less solvents and incorporates environmentally friendly approaches which are not only safe but also economically friendly.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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