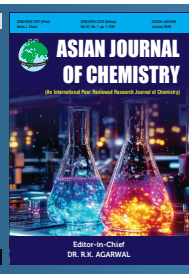
Asian Journal of Chemistry; Vol. 37, No. 8 (2025), 1813-1831

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.34015



REVIEW

Polysaccharide-Based Nanoemulsions for Enhanced Curcumin Delivery: A Multifunctional Strategy for Improving Solubility, Bioavailability and Therapeutic Efficacy

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Received: 8 May 2025; *Accepted*: 7 July 2025; *Published online*: 31 July 2025; AJC-22058

Curcumin, a polyphenolic compound derived from turmeric, holds significant promise for therapeutic applications due to its potent anti-inflammatory, antioxidant and anticancer properties. However, its clinical utility is hindered by poor aqueous solubility, low bioavailability and rapid degradation under physiological conditions. In this review, we explore polysaccharide-stabilized nanoemulsions as a versatile drug delivery platform for overcoming these limitations. Natural polysaccharides such as chitosan, pectin, alginate, starch, cellulose derivatives, hyaluronic acid and dextran offer unique functional properties, including mucoadhesion, biocompatibility and stabilization of nanoemulsion systems. These polysaccharide-based carriers enhance curcumin's solubility, stability and targeted delivery, improving its bioaccessibility and therapeutic potential in various applications such as cancer therapy, wound healing and gastrointestinal disease management. This article provides a comprehensive overview of formulation strategies, physico-chemical considerations and recent *in vitro* and *in vivo* findings that support the use of polysaccharide nanoemulsions as effective carriers for curcumin. The findings underscore the promise of these systems in developing advanced pharmaceutical formulations for enhanced therapeutic outcomes.

Keywords: Turmeric, Curcumin, Nanoemulsion, Polysaccharides, Chitosan, Drug delivery, Bioavailability, Therapeutic efficacy.

INTRODUCTION

The bioactive compound, curcumin obtained from *Curcuma longa* has antioxidant and antimicrobial activity. It exerts strong broad-spectrum antibacterial activity and it is active against a high number of bacteria. these bacteria comprise antibiotic-resistant strains, antifungal and antiviral activity [1]. Indeed, curcumin also offers effectiveness during the diseases induced by potentially fatal viruses. Thus, recent reports clearly indicate that curcumin exhibits greater potential due to its biological activity [2,3]. Hence, in combination therapy with other phyto-chemicals, curcumin can enhance the antimicrobial essence synergistically. Nanotechnologies, particularly nanocurcumin formulations, are increasingly being studied to overcome the low solubility of curcumin in water, poor bioavailability and fast degradation, thus augmenting its use in clinical cases, mainly in allograft and surgical procedures [4]. Curcumin has always been limitedly effective in treatment due to its poor water solubility, low bioavailability and exorbitant naturally rapid degradative process. These limitations prevent curcumin from being effectively cured [5]. Therefore, researchers have become determined to supplement the naturally and pharmacological activity of this natural compound by implementing nanoencapsulation technology. It can be concluded that nanocurcumin formulations provide a promising opportunity to substantially increase the benefits of curcumin, the scope of which has previously been limited. Ionic gelation and anti-solvent precipitation are two of the most common techniques

used to produce nanocurcumin [6,7]. These techniques have resulted in the development of significantly improved delivery systems that may potentially solve the problem of curcumin's poor solubility and bioavailability [8].

Nanoemulsions are the colloidal systems consisting of oil, water, surfactant and sometimes, co-surfactants. Small droplet size and a substantial interfacial area allow better solubilization of the hydrophobic [9]. Nanoemulsions also protect the drug from degradation in the physiological environment and improve its absorption and uptake into the cells. To develop nanoemulsions for curcumin transmission, oils, surfactants and co-surfactants are precisely chosen to increase particle stability and bioavailability [10]. Various methodologies are utilized, among which high-pressure homogenization, ultrasonication and microfluidization are only some of the methods used to produce lessened particles with a slim particle size distribution [11]. By encapsulating curcumin in nanoemulsions, its therapeutic potential is maximized, resulting in more effective treatment of cancer, neurodegenerative and inflammatory diseases. In addition, the broad features of formulations based on nanoemulsions can control the targeted drug administration and release, increasing the potency of curcumin and reducing its undesirable effects [12,13].

The incorporation of polysaccharides in nanoemulsion formulations contributes significantly to the stability, biocompatibility and therapeutic effectiveness of the method. Polysaccharides, which are biopolymers containing repetitive sugar units, have numerous benefits when formulated in nanoemulsions [14]. To begin with, polysaccharides, including chitosan, alginate and hyaluronic acid are characterized by mucoadhesive activity, promoting adhesion to mucosal surfaces, which reduces eliminate time in the body [15,16]. In addition, polysaccharides can serve as an emulsifying agent or stabilizer in nanoemulsion formulations due to which droplet coalescence and flocculation are decreased. Furthermore, by developing a barrier layer around the oil droplets, polysaccharides are reported to contribute to the physical strength of nanoemulsions, allowing them to remain consistently stable for a longer period during storage and following dilution by linear drug dispersion and storage on the shelf [17,18]. Due to their natural origin, polysaccharides are safe for use in various pharmaceutical and biomedical applications, which meet the needs of sustainable and environment consciousness. Moreover, they can be chemically functionalized to modify or improve their properties, such as increasing the hydrophobicity or their ability to be bound with other materials. Therefore, it is possible to modify, adjust and develop the unique properties of polysaccharides for different applications including the optimal performance in the nanoemulsion formulations [19].

Polysaccharide-based nanoemulsions: Formulation strategies

Overview of polysaccharide-based nanoemulsions: Polysaccharide-based nanoemulsions are one of the most promising classes of colloidal delivery systems that have combined the advantages of both natural polymers and nanoemulsions to improve drug delivery [20]. Due to their inherent characteristics including biocompatibility, biodegradability and mucoadhesiveness and multiple advantageous effects on nanoemulsions, they have improved the stability, bioavailability and targeting properties of emulsion [21]. Polysaccharide-based nanoemulsions are responsible for stabilizing nano-sized oil droplets in water. Because of possessing both hydrophobic and phosphorylated groups, polysaccharides were assumed to behave as an amorphous film over the oil-water interface, protecting the dispersed oil droplets [22]. Such a steric stabilization mechanism inhibits coalescence and the formation of an aggregate, maintains the uniform distribution of drug nanoparticles and enhances physical stability [23].

Nanodelivery systems loaded with polysaccharides can create mucoadhesive properties, facilitating binding to mucosa and extending the duration within the target mucosal tissues. It is especially useful for drug delivery to mucosal tissues, including the gastrointestinal tract and the respiratory system [24]. Mucosal adhesion increases drug uptake and bioavailability; therefore, polysaccharide-based nanoemulsions enhance therapeutic effects. Versatility in the encapsulation of a variety of hydrophobic and hydrophilic drugs is also an important characteristic of polysaccharide-based nanoemulsions [25]. While the diverse arrangement of molecules defines the emulsions' hydrophobic cores and stabilizes drug release and cell-internalization mechanisms, their complex bonds enable efficient encapsulation of relevant drugs. Additionally, the physico-chemical bonding for drug interaction and chemical modification facilitate controlled delivery of therapeutic agents [26]. Therefore, they are well-suited for encapsulating peptides, proteins and lipids as a whole, as well as poorly water-soluble drugs and nucleic acids as a whole. Moreover, the surface modification of nanoemulsion through functionalization of the polymer with targeting ligands allow the loaded drug or active agent to selectively target the cell or receptor of interest present in the TME [27]. The linkage of targeting moieties with polysaccharide can lead to high affinity and specific binding of the nanoemulsion to the receptors or biomarkers overexpressed on the targeted cancer cells, resulting in site-directed and improved therapeutic effects and reduced side effects [28].

Selection criteria for polysaccharides in nanoemulsion formulations: The preparation of nanoemulsion formulations using polysaccharides must be based on multiple selection criteria to guarantee optimal characteristics and functioning. Polysaccharide selection criteria fluctuate between their physicochemical existence and intended application and are closely tied to compatibility with the formulation and drug release needs [29]. In this respect, the scattered factor criterion on the selection of polysaccharides for nanoemulsion formulations involves the creation of stable nanoemulsions, dissolving, covering and defending sources of dielectric energy sources and their side consequences, biocompatibility [30]. Polysaccharides that present high emulsification efficiencies include octenyl succinic anhydride modified starch, chitosan and carboxymethylcellulose [25,31]. The most promising candidate for employment is OSA-MS due to its surfactant-like properties and thermal stability. Hence, it offers a high thermal stability against high temperatures and a wider pH and ionic strength while being combinable with other polysaccharides [32]. Chitosan is a non-toxic and biodegradable polymer with

cationic nature, which can combine other polysaccharides to increase the capacity to secure bioactive compounds [33]. Moreover, CMC is an anionic, biodegradable and food grade polyelectrolyte, which enables the construction of nano-systems through association with chitosan. The useful potential of the polysaccharides to safeguard the encapsulated bioactive compounds preserves its stability and bioavailability [34]. Polysaccharide with reasonable solubility and biocompatibility is more suitable for nanoemulsion. Finally, the choice of the type of polysaccharides should be made taking into account that they are capable of forming stable nanoemulsions, the droplet size and zeta potential of which will correspond to the desired values [35]. The conditions of nanoemulsion formulation can be selected based on the application area and the properties of the bioactive compounds encapsulated within the droplets. The factors to be optimized during the process are particle size, polydispersity index and zeta potential. Other aspects such as encapsulation efficiency, stability and the release profile of the bioactive compound should also be determined to confirm the required properties of the nanoemulsion [36].

Formulation techniques and considerations: Polysaccharide-based nanoemulsions are a potential drug delivery system that can enhance the stability and bioavailability of the bioactive compounds including curcumin. Nanoemulsions are thermodynamically stable colloidal dispersions of oil droplets in water and they are stabilized by polysaccharides which are natural, biocompatible and biodegradable biopolymers [37]. Different formulation methods used to formulate a polysaccharide-based nanoemulsion are summarized such as high energy methods like ultrasonication, microfluidization and high pressure homogenization play a major role in reducing the droplet size and improving the stability. The type and proportion of stabilizers, including surfactants or/and polymers, are the two vital aspects considered in nanoemulsion formulation. Stabilizers derived from polysaccharides, including alginate, chitosan and carboxymethyl cellulose, have been used in the nanoemulsion formulation [38]. The application of polysaccharides in emulsification, notably in nanoemulsification, acts as an emulsifier and nanoemulsifiers in nanoemulsion possess certain properties including large surface area, stability, emulsification, solubilization, number of molecules per surface arrangements, ionic strength, pH and temperature which significantly enhance the bioavailability and therapeutic efficacy of encapsulated compounds [17,39,40]. The nanoemulsions can be offered to patients in the liquid dosage forms or the above-mentioned post-production processes, including freeze drying, spray drying and spray freezing, can be used to convert the liquid state into the solid one for the preparation of various pellets, tablets, capsules, films or gels [41]. The development of nanoemulsions for the delivery of bioactive compounds implies the optimization of the components/amounts, preparation methods, process parameters/levels, administration routes and dosage forms to maximize the bioavailability, stability and efficacy of the encapsulated compounds and minimize the adverse side effects [42]. Table-1 summarizes the selection criteria based on the physico-chemical properties and compatibility of various polysaccharides in the nanoemulsion formulations.

Chitosan nanoemulsions for curcumin delivery

Utilization of chitosan in nanoemulsion formulations: Chitosan is another example of a polysaccharide used in the preparation of nanoemulsions because it has unique properties. It can typically increase potential biocidal, antibacterial or antifungal activity against various pathogens while increasing stability [43]. Chitosan-citral oil nanoemulsions have been manufactured and their rounds have been characterized. The droplet roundness is spherical with different chitosan: citral ratios. The viscosity of nanoemulsions was observed to be from 5.1 to 8.0 mPa.s, with the lowest viscosity in F5 occurring in the range 3.1 mPa.s [28,44]. In addition, this polysaccharide can be used in combinations with other polysaccharides that can stabilize relatively unstable nanoemulsions and acid. Hu & Luo [37] reported the alginate/sodium caseinate/γ-cyclodextrin nanoemulsion loaded with curcumin, which had a 30-day storage stability and increased acid stability. The nanoemulsions based on chitosan and essential oils have been proposed as antimicrobial agents to increase meat shelf life. Indeed, the use of chitosan in nanoemulsion formulations has gained a great interest for stabilization and delivery of bioactive compounds, including curcumin and it has shown stability, bioavail-

TABLE-1
SELECTION CRITERIA FOR POLYSACCHARIDES BASED ON PHYSICO-CHEMICAL PROPERTIES AND COMPATIBILITY IN NANOEMULSIONS

Polysaccharide	Emulsification capacity	Stability features	Biocompatibility	Application advantages	Additional insights
Octenyl succinic anhydride modified starch (OSA-MS)	High	Stable across wide pH and temperature ranges	High	Ideal for heat-sensitive bioactive compounds	Often combined with other polysaccharides
Chitosan	Moderate	Enhances mucoadhesiveness	High	Suitable for mucosal drug delivery	Cationic, improves bioactive compound protection
Carboxymethylcellulose (CMC)	Moderate	Forms stable nano-systems with chitosan	High	Used in oral and transdermal formulations	Anionic, food-grade, biodegradable
Alginate	Low to moderate	Gel-forming capabilities at low pH	High	Effective in gastro-resistant formulations	Used with divalent cations for gelation
Hyaluronic acid	Low	Highly biocompatible and bioadhesive	Very high	Targeted drug delivery, especially in ocular applications	Expensive, used for premium formulations

ability and antimicrobial activity [45]. Essential biofunctional characteristics like muco-adhesiveness, hemocompatibility and antibacterial efficacy of chitosan nanoemulsions indicating a wide range of tissue compatibility (Fig. 1).

Bioavailability enhancement of curcumin with chitosan nanoemulsions: The formulation of chitosan nanoemulsions has proven to enhance the bioavailability of curcumin by significant levels. This is through the shielding role that chitosan nanoemulsions play in ensuring environmental factors such as temperature and UV rays do not interfere with the compound [41,46]. Furthermore, they can enhance the load capacity of curcumin as well as release. The stability of curcumin nanoemulsion is enhanced by quaternized chitosan (QCS) due to the presence of a protective film surrounding the nanoemulsion system [47]. QCS has a positive charge that favours the stability of the nanoemulsion through the principle of electrostatic repulsion. Electrostatic repulsion reduces the extent of aggregation between nanoemulsion droplets as well as enhances the physical stability of the system [48]. To enhance the stability and bioavailability of curcumin, Zhu *et al.* [49] used the quaternized chitosan coated nanoemulsion, which enhanced all major indicators stability, *in vitro* gastric fluid stability and bioavailability in comparison with the control. In addition to superior emulsification activity, it also demonstrated better oxidative protection, which suggests that it can be widely used to increase bioavailability and therapeutic effects of curcumin. The developed curcumin loaded chitosan nanoemulsion gel may increase the stability and bioavailability of curcumin in comparison with other systems or products used for wound healing. The nanoemulsion gel may also exhibit more enhanced *in vitro* antibacterial and *in vivo* wound healing performance in comparison with other curcumin-loaded gels [50]. Thomas *et al.* [51] also developed a novel curcumin-loaded chitosan nanoemulsion gel intended for improving wound therapy. These drugs were prepared to study the skin disposition and investigate their physical qualities or this general approach. Owing to its distinct properties due to unique recipe for curcumin release, gel represented greater skin clinging and infiltration. Finally, it was shown that *in vivo* treatment could be done for skin regrowth, curcumin encapsulating nanoemulsion gel being a novel drug candidate for helping to regenerate skin for a potentially new treatment option.

Bioaccessibility, the biologically most relevant concept, reflects the fraction of a nutrient or bioactive compound released from the matrix which is available for absorption in the gastrointestinal tract. In case of curcumin, a main polyphenolic compound of turmeric, the poor bioavailability was the major disadvantage for the use in medications and health products [9,52].

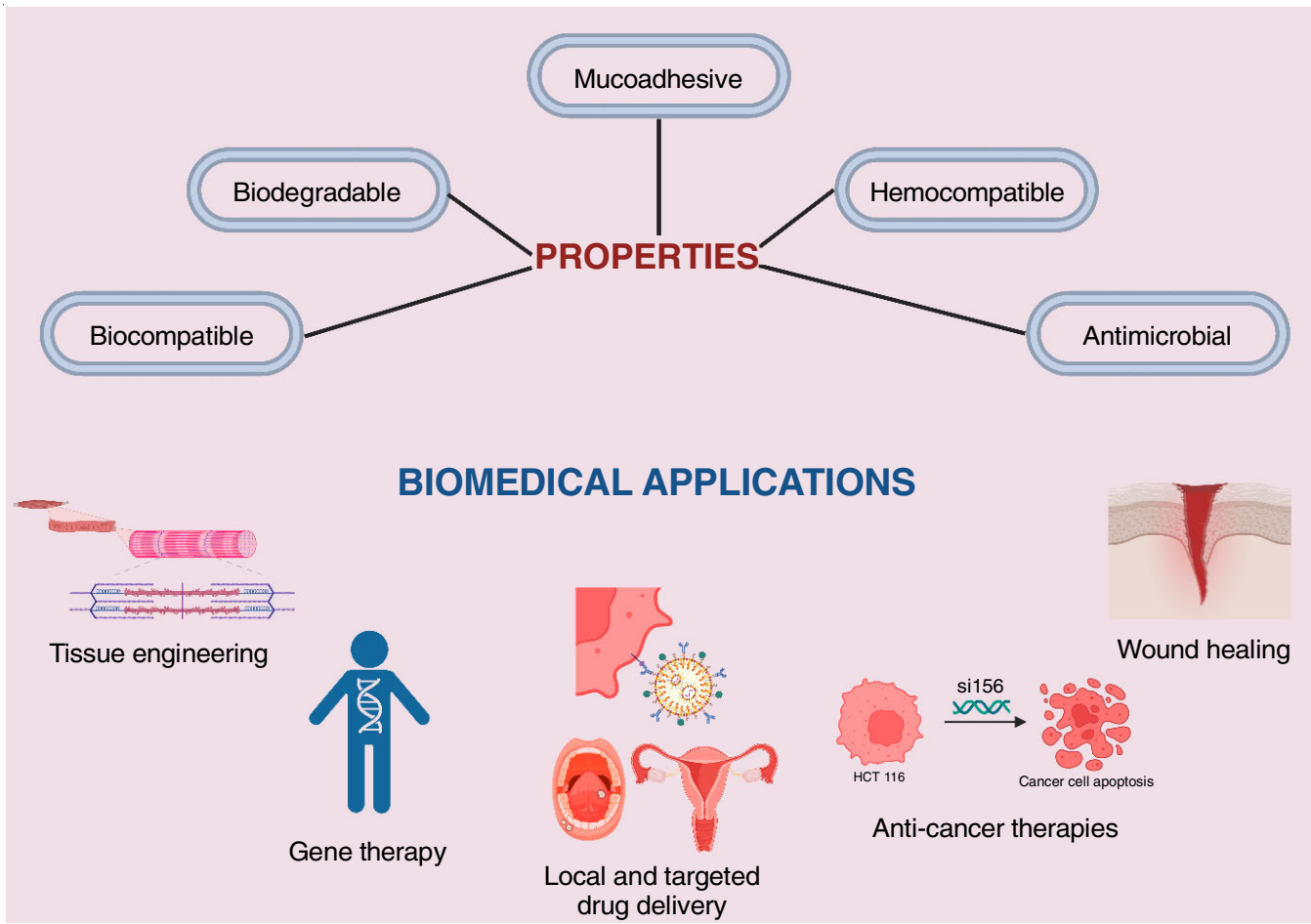

Fig. 1. A conceptual overview of chitosan nanoemulsions, highlighting their physico-chemical diversity and promise for various biological applications

Shah *et al.* [53] investigated the bioaccessibility and antioxidant activity of curcumin encapsulated in nano and pickering emulsions with chitosan-tripolyphosphate nanoparticles. In this work, prepared lipid-based formulations and then incorporated curcumin by an *in vitro* gastrointestinal model to examine their efficiency. The results demonstrated that encapsulated curcumin had higher bioaccessibility and antioxidant activity than free curcumin, with preferable outcomes for nanoemulsions compared to pickering ones. It means that the lipid-based nanoencapsulation has the potential to increase the dietary effects of curcumin, stability, bioaccessibility and antioxidant activity. The motivation for developing a pH-responsive nanoemulsion drug delivery platform was to provide target strategic response and controlled release of the drug only under the anticipated pH conditions in the body. It need arises where the drug becomes unstable or ineffective under certain pH conditions or the drug must target an organ or tissue with a specific pH environment [54]. Pourmadadi *et al.* [55] developed a pH-responsive Fe_3O_4/chitosan/agarose double nanoemulsion for curcumin targeting curcumin release into MCF-7 cell line treatment. The nanoemulsion exhibited 48.25% loading and 87.5% entrapment efficiency for curcumin. The nanocomposite material maintained its crystalline nature that supports functional groups confirmed by characterizations. Furthermore, the DLS and zeta potential analyses showed that the selected particle size and surface charge were stable suitable for EPR effect. The viability assays showed the biocompatibility of the nanocarrier and high cell death associated with apoptosis, representing MCF-7 cells' high efficacy. Thus, the nanoparticles can be used effectively with minimal toxicity in cancer management [55]. The coating with water-soluble chitosan is performed to improve the stability and masking effect of curcumin [37,56]. During the procedure, turmeric extract-loaded nanoemulsions are made through an ultrasonication method and afterwards coated with water-soluble chitosan, to increase the chemical stability of curcumin and reduce the strong scent of turmeric so that it can be used in many more applications including food and beverages [57]. Lee *et al.* [58] worked on improving the storage stability and scent of curcumin-enclosing nanoemulsions in order to dampen the natural scent of turmeric. The concentrate safflower mixture showed notably more steady stability at low or high pH balances and various concentrations of salt and temperate drastically lessened turmerone aroma, indicating that the water soluble-coated nanoemulsion might significantly broaden the applicability of curcumin in various food products [58]. The composition and structure of nanoemulsions are the crucial factors that may influence the interaction mechanisms with intestinal epithelial cells. Nanoemulsions are defined as colloidal dispersions of two immiscible substances, with oil and water and where one of them is dispersed in the other, using a surfactant or an emulsifier [59,60]. Langella *et al.* [61] carried out an *in vitro* investigation focusing on the interaction between the engineered oil in water nanoemulsions delivering curcumin and the intestinal epithelial surface. Specifically, the researchers examined the *in vitro* biocompatibility, efficiency and stability of the curcumin-loaded nanoemulsions' capacity of crossing the intestinal barrier as well as their *in situ* anti-inflammatory properties. Following the results, it was concluded that the nanoemulsions could be a promising drug delivery system for improving the therapy and management of intestinal inflammation and related pathologies. Similarly, Lei *et al.* [62] developed an oral hydrogel nanoemulsion co-delivery system to cure inflammatory bowel disease with anti-inflammatory efficacy and mucosa repair promotion. Macrophages in the colon were targeted and treated *via* pH-responsive sodium alginate hydrogels that encapsulated curcumin and emodin using this method. Therefore, it showed a remarkable impact and a decline in inflammation and oxidative stress, which supports mucosal repair. The study indicates that combining curcumin and emodin in a pH-sensitive tablet could be a novel and effective method to treat inflammatory bowel disease due to the synergistic effects.

γ-Alumina is a nanoporous material employed as a pH-responsive carrier for drug delivery. The drug is adsorbed on the gamma alumina surface due to the presence of hydrogen bonding and electrostatic forces and being porous in nature, it aids in loading and unbinding the drug. Moreover, the surface of γ-alumina coated with polymers, such as chitosan or polyvinylpyrrolidone (PVP) enhances the biocompatibility [63,64]. Karami *et al.* [65] developed a new chitosan/γ-alumina/carbon quantum dots hydrogel nanocarrier for the targeted curcumin delivery. The carrier could load the drug well and had high entrapment efficiency; in addition, a controlled pH-specific release was observed, which increased the cytotoxic impact of drug on the breast cancer cells (Fig. 2). The study demonstrates that the CS/γAl_2O_3/CQDs/CUR nano system is applicable to treat tumors. Therefore, this system delivers the drug effectively and gives hope to improve cancer therapy results. Another study by Abbas *et al.* [66] prepared polymeric nanocapsules using nanoemulsion templates loaded with curcumin through self-assembly with the help of food-grade polyelectrolytes. It was found that ultrasonicated nanoemulsion templates could be effectively used for the development of stable and prolonged release nanocapsules. Such a technique can be applied for the fabrication of formulations of food, dermal and oral application and cosmetic application with encapsulating hydrophobic ingredients. The developed and optimized curcumin nanoemulsion has vast potential in various therapeutic delivery systems. Sood *et al.* [67] intended to optimize a curcumin nanoemulsion for intranasal delivery using a design of experiments. It was utilized to determine the effect of oil and surfactant as well as cosurfactant concentrations on the globule size and zeta potential. The optimized nanoemulsion, using chitosan as a mucoadhesive polymer, did not show any cotyotoxicity and nasal ciliotoxicity, ensuring its safe intranasal delivery to the brain. This flexible and anticipated variant could be a useful tool of improving bioavailability and therapeutic outcomes of curcumin.

Therapeutic efficacy enhancement of curcumin with chitosan nanoemulsions: The therapeutic efficacy of curcumin can also be immeasurably increased by formulating it into chitosan nanoemulsions. Chitosan nanoemulsions, which improve the time-extended curcumin steadiness and shield wall from environmental contamination, allow for more efficient transportation of nanoemulsion [68]. Curcumin chitosan-based nanoemulsions protect the drug from temperature and UV rays

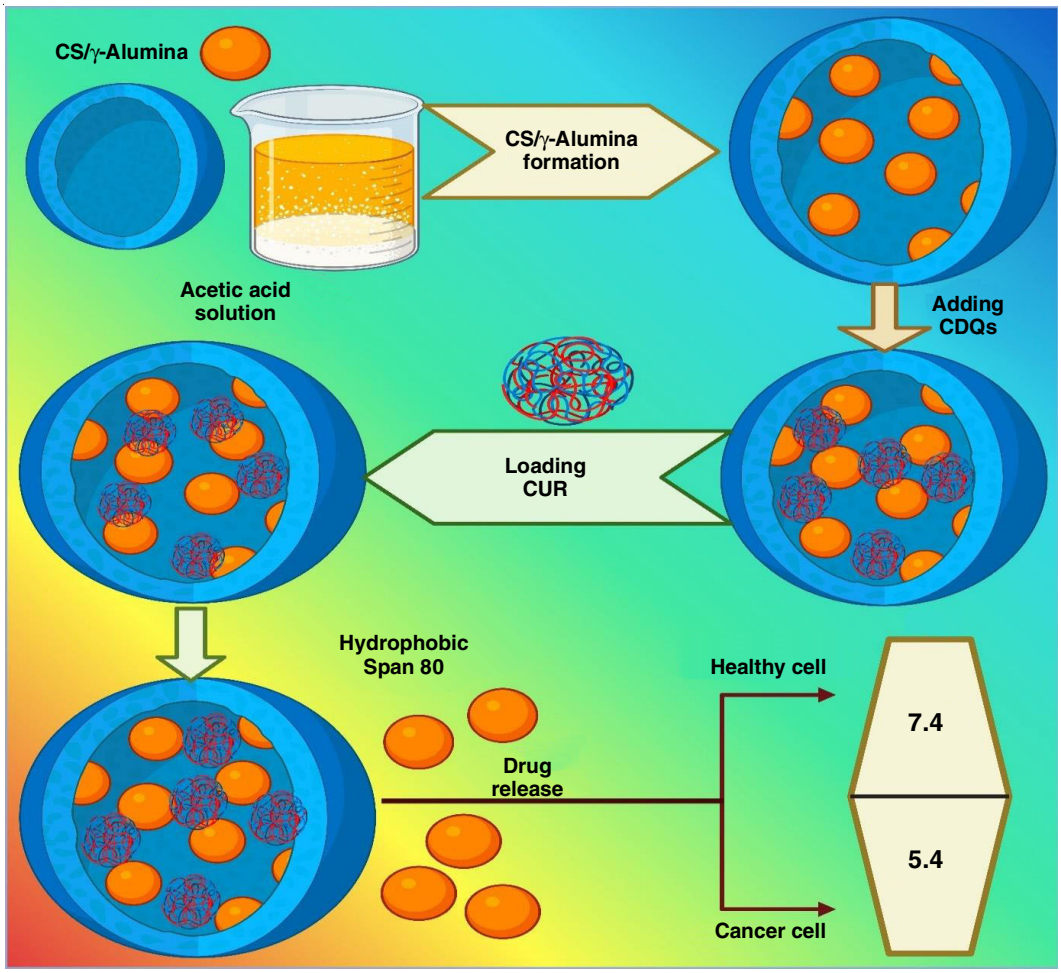

Fig. 2. Schematic representation of a chitosan nanoemulsion system integrated with γ-alumina and carbon quantum dots, designed to enhance the delivery and bioavailability of curcumin

and improve drug delivery to the goal cell by keeping it safe. Furthermore, the novel combination of factors such as solubilized forms and cellular uptake and active targeting, provides advantageous properties for curing other pathological conditions [69]. In this case, the increased antibacterial properties are caused by the utilization of oil-in-water nanoemulsions and chitosan nanocapsules. Oil-in-water nanoemulsions enhance the solubility and stabilization of curcumin, enabling dispersion in the structuring element and interaction with the slated surfaces of bacterial cells. Moreover, the nanoemulsion droplets work as curcumin carriers safeguarding it against degradation and enhancing its ingestion [70]. Hidalgo *et al.* [71] studied the effects of curcumin solubilized in nanoemulsions or chitosan nanocapsules on *Helicobacter pylori*. They indicated that both formulations can decrease growth, bacterial biofilm, adhesion to and internalization of the gastric cells by *H. pylori*, while chitosan nanocapsules have stronger activity and are safer for the gastric cells compared to nanoemulsions. Their findings implied that the curcumin nanoformulations can be considered as an approach of *H. pylori* infection treatment.

The stability and controlled release of nanoemulsions, especially those with hydrophobic or labile components, can be improved by using chitosan and alginate-based microbeads [72]. Chitosan is positively charged and can interact with the negatively charged nanoemulsion droplets. A stable complex is produced, which can shield the nanoemulsion from the surrounding environment and increase bioavailability by preventing degradation. The nanoemulsion can be encapsulated in a protective matrix using an alginate crosslinked network so that it is gradually released [73]. Hashim *et al.* [74] investigated ω-3 rich oils/curcumin nanoemulsions encapsulated in chitosan- and alginate-based microbeads with antioxidant and antibacterial activities. It became clear from this study that the addition of curcumin to the microbeads significantly improved their oxidative stability, loading capacity, encapsulation efficiency and antioxidant activity. Moreover, fish oil nanoemulsions exhibited better antibacterial activity than flaxseed oil; thus, they can be further added to various food and pharmaceutical products. The chitosan-gelatin composite films incorporated with curcumin nanoemulsions exhibit immense potential for a wide range of applications as a result of their shared and distinctive attributes and functionalities [75,76]. These films function by coupling the antimicrobial and antioxidative activities of curcumin with the film-forming qualities of chitosan and gelatin and by improving and stabilizing the bioavailability of the systems through nanoemulsion [77]. Luangapai *et al.* [78] investigated the impact of blending and layer-by-layer methodologies, specifically layer-by-layer assembly, on the

chitosan-gelatin composite films incorporated with curcumin nanoemulsion. The layer-by-layer films showed better water vapour barrier, tensile strength, solubility and antioxidant activity. The better physical and chemical properties as well as thermal stability of the layer-by-layer methodology suggest its superiority for obtaining composite films with improved functioning qualities [78]. The RGD-modified curcumin-loaded chitosan/perfluorohexane (PFH) nanocapsules is a positive approach in treating cancer. It paves great hope in cancer treatment, especially when it comes to the image-guided cancer, which has been a challenge for a long time. Hence, the conjugation of RGD peptide can significantly improve the antitumor efficacy of curcumin-loaded nanocapsules [79,80]. Wang *et al.* [81] have explored the anticancer potential of RGD-modified curcumin-loaded chitosan/perfluorohexane nanocapsules in the form of CS/PFH-Cur-NCs against MDA-MB-231 human breast cancer cells. The distinctive feature of both CS/PFH-Cur-NCs and RGD-CS/PFH-Cur-NCs is the option of forming spheres with smooth surface and uniformly distributed particles, whereas the RGD-modified nanoparticles demonstrated better targeting effects and killed cancer cells faster. These findings prove that nanocomposite encapsulation and RGD surface modification improve the antitumor activity of curcumin, therefore offering possibilities for cancer therapy guided by ultrasound imaging.

Curcumin, which is a natural polyphenol concentrated from turmeric, exhibits remarkable anticancer effects by regulating a variety of intracellular signaling pathways [82]. Unfortunately, its poor solubility, physico-chemical instability, low bioavailability and weak targeting effectiveness prevent its clinical usage. To combat these problems, various targeted drug delivery systems were developed such as passive targeting preparations, active targeting preparations or physico-chemical targeting preparations [83]. Perfluorohexane is a type of perfluorocarbon with several advantageous properties for use in nanodroplets integrated in drug delivery systems. As a class, PFCs have the capacity to dissolve numerous gases, including but not limited to oxygen. Hence, they are harnessed for oxygen delivery in various medical applications. PFH has a higher molecular weight than other PFCs like perfluoropentane hence, it exhibits several advantages when undertaking repeated therapeutic activation [84,85]. In another study, Baghbani *et al.* [86] formulated ultrasound-responsive chitosan/perfluorohexane nanodroplets for intelligent curcumin delivery, mediated contrast-ultrasound imaging and anchored cancer therapy. The recent results revealed that the optimized formulation exhibited excellent curcumin encapsulation efficiency and curcumin release profile, which was further promoted by exposure to ultrasound. Although the nanodroplets, triggered to bubble transition, yielded robust ultrasound contrast, transactivated with ultrasound, they significantly inhibited the growth of breast cancer cells. Therefore, the use of a nanodroplet is a unique approach to drug delivery, demonstrating the potential of ultrasound-responsive nanodroplets in image-guided cancer therapy.

Furthermore, nanoformulated curcumin has several advantages compared to its conventional form in the treatment of parasitic infections. Khedr *et al.* [87] evaluated the efficiency of curcumin-fommulation against *Trichinella spiralis* in mice. The comparative study of the effects of crude curcumin, curcumin nanoemulsion and curcumin-loaded chitosan nanoparticles was conducted using an acute and chronic trichinosis mice model. The results showed that crude curcumin and curcumin-loaded chitosan nanoparticles induced negative outcomes, while chitosan nanoparticles alone and especially in combination with albendazole reduced adult worm and muscle larvae burden and also decreased local pathology and MDA levels and CD31 expression, showing powerful antiparasitic and anti-inflammatory activities. Thus, curcumin may be a new therapeutic agent in trichinosis treatment and suppression [87]. Another common method of preparing nanosized emulsions is the high-pressure homogenization(HPH). HPH of curcumin-loaded glyceryl monooleate/chitosan (GMO /CS) was developed using a high-pressure homogenizer comprising a positive displacement pump and pressure valve linked to a homogenization chamber [88]. In another investigation by Mistry *et al.* [89], the effect of high-pressure homogenization and stabilizers on the curcumin-loaded GMO /CS nanostructures was studied. The results of the study demonstrated that HPH drastically decreased the particle size and zeta potential, surface morphology, release rate and cellular uptake varied depending on the stabilizer type; at low concentrations, poloxamer 407 was more effective in stabilizing nanoemulsions. Ultimately, this study illustrates that processing methods and stabilizer are critical issues that determine the physico-chemical properties of curcumin nanoformulations [89]. Significantly, the release kinetics of curcumin can be greatly influenced by the use of nanoemulsion loaded hybrid biopolymeric hydrogel beads. The biopolymeric hydrogel beads can provide a protective matrix for nanoemulsion and regulate curcumin release and stabilize it to provide more optimal release kinetics [90,91]. Kour *et al.* [92] studied the enhanced bioavailability and biological performance of curcumin-loaded nanoemulsion-encapsulated hybrid biopolymeric hydrogel beads. The novel formula demonstrated different release in simulated gastric and intestinal fluids. The diluted release in the gastric stretch could be due to the properties of the network of hydrogel. This technique of encapsulation showed considerable antioxidant and antibacterial activity and could be a promising solution for supplying hydrophobic active compounds in the functional and pharmaceutical foods. Table-2 presents a concise overview of significant research studies on chitosan nanoemulsions for curcumin delivery, detailing emulsion types, coatings, main findings, bioactivity focuses and references. It highlights the versatility and potential of nanoemulsions in enhancing drug efficacy and stability.

Alginate nanoemulsions for curcumin delivery

Properties and applications of alginate in nanoemulsions: Brown seaweed gives rise to a polysaccharide alginate that finds a place in a broad number of applications such as food, medicine, pharmaceuticals and biotechnology [93,94]. It consists of (1,4) linked β-d-mannuronic and α-l-guluronic acids that might be either MM or MG sequences. Alginate solutions exhibit greater viscosity than elasticity, demonstrating the behaviour of a fluid. Alginates are systems based on the range of

TABLE-2
SUMMARY OF CHITOSAN NANOEMULSIONS FOR CURCUMIN DELIVERY, HIGHLIGHTING EMULSION TYPES, COATINGS, BIOACTIVITY AND KEY FINDINGS

Emulsion type	Coating/substance	Main finding	Bioactivity focus	Ref.
Nanoemulsion	Quaternized chitosan	Enhanced stability and bioavailability	Stability, bioavailability	[49]
Nanoemulsion gel	Chitosan	Promoted wound healing	Wound healing	[51]
Nano and pickering emulsions	Chitosan-tripolyphosphate	Higher bioaccessibility and antioxidant activity	Antioxidant activity	[53]
Double nanoemulsion	Fe_3O_4/chitosan/agarose	pH-responsive, sustained release	Cancer therapy	[55]
Nanoemulsion	Water-soluble chitosan	Improved stability, masked turmeric scent	Food application	[58]
Oil in water nanoemulsion	N/A	Effective delivery across intestinal barriers	Intestinal health	[61]
Hydrogel nanoemulsion	Sodium alginate	Reduced inflammation, promoted mucosal repair	Inflammatory bowel disease	[62]
Hydrogel nanocarrier/ nanoemulsion	CS/γAl_2O_3/CQDs	Enhanced cytotoxic effect against breast cancer	Cancer therapy	[65]
Polymeric nanocapsules/ nanoemulsion	Food-grade polyelectrolytes	Controlled release, enhanced stability	Food, cosmetic, pharma	[66]
Nanoemulsion	Chitosan	Enhanced bioavailability and safety for intranasal delivery	Brain targeting	[67]
Nanocapsules/nanoemulsions	Chitosan	More effective against *H. pylori* than nanoemulsions	Gastric health	[71]
Nanoemulsion	Chitosan and alginate	Enhanced oxidative stability, antibacterial activity	Antioxidant, antibacterial	[74]
Composite films/nanoemulsion	Chitosan-gelatin	Improved physical properties for functional films	Packaging	[78]
Nanocapsules/nanoemulsion	RGD-modified chitosan/ perfluorohexane	Targeted anticancer properties	Cancer therapy	[81]
Nanodroplets/nanoemulsion	Chitosan/perfluorohexane	Ultrasound-responsive, targeted delivery	Image-guided cancer therapy	[86]
Nanoemulsion/nanoparticles	Chitosan	Enhanced anti-parasitic and anti-inflammatory effects	Parasitic infections	[87]
Nanostructures/nanoemulsion	Glycerol monooleate/ chitosan	Stabilizer type impacts nanoemulsion properties	Drug delivery	[89]
Hybrid biopolymeric beads	N/A	Enhanced bioavailability, biological activity	Functional foods, pharma	[92]

molecular weight, purity and composition [95,96]. In 2002, the Food Standards Agency approved the use of alginates as food additives, including alginic acid, potassium, ammonium, sodium and calcium salts of alginates (E400-E404) and alginic acid esters and propylene glycol alginates – E405. In the food industry, alginates are used due to their rheological properties such as thickening, water binding capacity, emulsion stabilization and film formation [97,98]. In the biotechnology industry, they are used as thickeners, gelling agents and colloidal stabilizers and as a matrix for the delivery of various molecules or particles. Due to their biocompatibility, low toxicity and biodegradability, negligible cost and simplicity, alginate gel particles are used in food, chemical and pharmaceutical sciences. Smart drug delivery systems are used to treat cancer, refine heavy metal ions and restore biological tissues [99,100].

Sodium alginate enhances physico-chemical characteristics of nanoemulsion in nanoemulsion formulations. The mixing method of sodium alginate has long-lasting impacts on the droplet size, polydispersity index and zeta potential of the prepared nanoemulsions, influencing their stability, rheology and self-life [101]. The mucoadhesive features can make a significant role along with alginate being used as specific polymer carrier for mucoadhesive for mucosal drug delivery into gastrointestinal (GI) tract and nasopharynx extending the drug retention time [102]. In addition, alginate has been employed in post-crosslinking to direct stimuli-responsive sodium alginate beads for dye and heavy metal removal. Alginate is a versatile polysaccharide with numerous applications in food, medicine and pharmaceuticals and biotechnology [103]. The physico-chemical properties make alginate an excellent candidate for nanoemulsion formulation, improving their stability, rheology and shelf life. The mucoadhesive model of a post-crosslinking substance also makes it a highly valuable material for drug release and environmental applications [104].

Evaluation of alginate nanoemulsions for enhanced curcumin delivery and therapeutic efficacy: Nanoemulsions of alginate have also been found to improve curcumin delivery and therapeutic efficacy. Efficacy was high when self-emulsifying curcumin was employed and low when ordinary curcumin powder was employed, demonstrating the potential of alginate microbeads as a novel form of sustained curcumin delivery [105]. Encapsulation of curcumin in alginate nanogels (alginate aldehyde-gelatin) with a ''core-shell'' design showed promising success in terms of stability and *in vitro* release behaviours when loaded with nanoemulsions, alginate hydrogel beads were investigated as a platform for curcumin release with controlled release patterns. Other studies also demonstrated an increase in water dispersion and bioavailability when water-insoluble drugs were formulated as alginate alginate aldehyde-gelatin nanogels [20,106].

Sodium alginate also plays a crucial role in enhancing the nanoemulsions' curcumin gastrointestinal stability by protecting curcumin from degradation during digestion and also in enhancing nanoemulsions structural stability [20,106]. Speci-

fically, several studies confirmed that the addition of sodium alginate, especially at a concentration of 1% or more, prevent curcumin from degradation by digestion, ultimately leading to a 23% improvement in stability [107]. The protective effect of sodium alginate against curcumin degradation helps maintain the integrity of curcumin and the emulsion structure of the nanoemulsions to ensure that curcumin maintains its bioactive activity and therapeutic property in the GI tract [108]. Teixé-Roig *et al.* [109] investigated the influence of alginate addition at different proportions on curcumin-loaded nanoemulsions produced from soybean lecithin or whey protein emulsifiers. Their results suggested that whey protein, as well as increasing amounts of alginate, adequately protected curcumin against digestion, preserved the nanoemulsion, but decreased lipid digestion and curcumin bioaccessibility. This work provides new opportunities for enhancing the gastrointestinal viability of curcumin nanoemulsions [109]. The encapsulation efficiency of curcumin in alginate hydrogels may depend on the concentration of alginate and crosslinking density, as well as on the presence of other components, including chitosan or PEG. The increase in alginate concentration and crosslinking density usually ensure the rise in the encapsulation efficiency, whereas chitosan or PEG may stabilize the hydrogel or enhance its compatibility with curcumin [110]. Afonso *et al.* [111] have proposed nanoemulsion-filled alginate hydrogel beads as vehicles to contain curcumin with the advantages of both emulsions and hydrogels. The nanoemulsions were around 24.26 nm, encapsulated within hydrogel beads with a 0.46 mm diameter, contained relatively high encapsulation efficacy of 99.15%, released in a way that depended on the pH and thus could be excellent candidates for hydrophobic compound-delivery propositions. Surfactant concentration is another significant factor affecting the stability of curcumin-loaded nanoemulsions. Nonetheless, an extremely high level of surfactant concentration could result in a rigid interfacial layer. This layer, in turn, may restrict the motion of the droplets and subsequently lower the stability of the system [112]. Artigas *et al.* [113] evaluated the nanoemulsion stability as affected by the surfactant type and concentration when loaded with curcumin. They concluded that compared to Tween 20, only lecithin at a concentration of 2.0% w/w confirmed the stability of nanoemulsions over 86 days, while similar effects could not be observed by using sodium milk protein at the same concentration levels. Therefore, this study might shed more light on the functions of various surfactants in curcumin encapsulation and nanoemulsion stabilization.

Microgels are anticipated to provide significant value as versatile materials for many biomedical applications, such as drug delivery, tissue engineering and cell imaging, among others [114]. As aqueous microgel particles that can be synthesized with any desired functionality and properties, microgels may be utilized in a variety of biomedical applications. Numerous microgels used in biomedical studies have been developed for simultaneous several applications [115-118]. Riquelme *et al.* [119] presented a novel preparation technique involved in the encapsulation of gold nanostructures and curcumin oil-in-water nanoemulsions into alginate microgels for potential biomedical purposes. The microgels tandem generated an alternative preferential toxicity against cancer cells, which was non-toxic to the non-cancerous cells. The use of on-demand photothermally induced microgels generated the gold nanostructures' photothermal outcomes in parallel to that achieved using curcumin nanocarriers. Thus, such studies could be helpful in preparing hydrogel formulations with biological applications [119]. Orally administering a co-delivery system for treating inflammatory bowel disease (IBD) has many advantages over other drug administration routes. It is the most convenient form of drug administration from the perspective of patient as it is the most self-administering and non-invasive. Furthermore, the formulation can be structured to deliver the drugs to different locations within the upper and lower areas of the gastrointestinal tract. This is essential because IBD affects various parts of the gastrointestinal tract [120]. Yerramathi *et al.* [121] constructed a pH-responsive sodium alginate hydrogel-coated nanoemulsion co-delivery system with a view to the curcumin and emodin co-delivery for a more effective treatment of inflammatory bowel disease through the colonic site-specific drug release and macrophage targeting. The results indicated the notable mitigation of the colon's inflammatory microenvironment, such as the decreased expression of TNF-α and IL-6 and increased IL-10. In addition, preparation contributed to the restoration of intestinal mucosal tight junction protein expression, hence offering promising prospects for combinatorial IBD therapy [119] Several factors that are dependent on the properties of the alginate-pectin microparticles as well as others related to the release media can affect the release kinetics of the loaded nanoemulsions. The composition, structure and crosslinking of the microparticles are rated among those properties. The same is relevant to the encapsulation efficiency, the interaction between the microparticles and the nanoemulsions and the degradation rate of the microparticles [121]. Amante *et al.* [122] developed an alginate-pectin microparticles encapsulated with curcumin for wound dressing. An optimized wound dressing with *in situ* gelling properties that showed curcumin release under simulated wound fluid analysis results and keratinocyte cell cytocompatibility was demonstrated in this work. Therefore, this methodology can serve as a promising means of treating wounds.

Starch nanoemulsions for curcumin delivery

Starch-based nanoemulsions as carriers for curcumin: Starch nanoemulsions have been employed as curcumin drug carriers to enhance its bioavailability and stability. Starch is an abundant polysaccharide and many kinds of it are cheap, biologically inert and biodegradable [123,124]. For the entrapment of curcumin, the octenyl succinic anhydride-modified starch (OSA-starch) and hydroxypropyl distarch phosphate (HDP) starch have been particularly adopted. The nanoemulsions were formulated using high-pressure homogenization and the impact of starch concentration and homogenization pressure on the size and stability of the nanoemulsions was tested [125]. Nanoemulsions formulated with OSA starch had smaller particle size and more stable formulations than those prepared with HDP starch. Nanoemulsions loaded with curcumin present improved solubility and stability than free curcumin

[126]. In the release study *in vitro* conduct, it was evident that the nanoemulsions released curcumin sustainably. For this reason, the nanoemulsions represent a good delivery system for curcumin. Starch-based nanoemulsions show promise as a nanocarrier of curcumin due to enhanced solubility, stability and release profile [127].

Starch-based nanoemulsions have several advantages in curcumin delivery related to the improvements in the soluble characteristics, stable characteristics and bioavailability [128]. Even nano-sized curcumin has more stringent surface charge and surface area and lubusanoicity and better optical characteristics and much better antioxidant activity in contrast to native curcumin [129]. The optical transparency and the curve indicate stability of the curcumin encapsulated nanoemulsion boosts and a silver versa. They also improve solubility and stability of curcumin, making it possible to incorporate starch-based nanoemulsions into bakery products to increase their nutritional value [130]. The presented nanoemulsion sample with curcumin exhibits activity against the growth of algae and suggests that the possibility of using an emulsion as an antioxidant agent. Moreover, starch-based nanoemulsions improve the colour properties of bread, characteristics porosity, elasticity, crumb colour, flavour and the resolubility of the clamped crumb of the mouth [131]. Therefore, natural plant-based emulsifiers like enzymatically modified quinoa starch can increase the stability and protection effect of curcumin N -emulsions. Starch nanoemulsions act as an efficient curcumin delivery system for improving its solubility, stability, bioavailability, antioxidant properties and modifying the sensory quality of food product [132].

***In vivo* studies and therapeutic outcomes:** *In vivo* studies carried out to assess the therapeutic efficacy of nanoemulsions of starch in delivering curcumin have had a positive outcome [133]. They established that the absorption of curcumin and biodistribution in the body are greatly improved, which addresses the problem of the extensive metabolism and conjugation of curcumin once it is delivered orally [134]. All these *in vivo* studies show that starch nanoemulsions can be used as an effective delivery system to improve the bioavailability and therapeutic efficacy of curcumin, generally offering a potential and safe means to enhance the delivery of this extraordinary bioactive compound [135]. As nanoemulsions form a protective layer around the biopolymers that form the edible film, such as chitosan, it may help stabilize the films and improve the shelf-life of films. When bioactive compounds are encapsulated, the formulation remains stable for long periods and the longer shelf-life of the product is observed [27,136]. Formulation with essential oils like oregano, clove, mandarin or lemon can be made and naturally, these oils have proven effects of antimicrobial activity, so the shelf-life is extended [137]. Sanchez *et al.* [138] developed active edible films by combining banana starch with curcumin-loaded orange oil nanoemulsions. The authors present this study with lower water vapour permeability and a higher elongation at break. In addition, the research discusses the diffusion-driven release profiles of curcumin into two dissipative media *viz*. various aqueous and non-aqueous food simulants, which have different release mechanisms in both types of simulants. Thus, the current development of active packaging for food products allows the usage of natural polymers to prolong food shelf life and enhance their safety. Enzymatic processes are essential in disintegrating starch gels and releasing curcumin into the gastrointestinal tract. Some of the enzymes used α-amylase, amyloglucosidase, pectinase, xylanase and cellulase, break down the starch granules in turmeric rhizomes and release curcumin. The addition of the enzymes to turmeric to help hydrolyze starch, pectin, xylans and cellulose enhances curcumin extraction yield and bioavailability [139]. Through a study by Qazi *et al.* [140], the gastrointestinal glycemic fate of curcumin-containing nanoemulsions under starch gels with different architectures was proven. The results suggest that the presence of the curcumin nanoemulsion loading alters the storage modulus and digestion features, resulting in substantial differences in curcumin bioaccessibility and release. This investigation exhibits the release of encapsulating compounds into the gastrointestinal glycemic digestion through the structure of a starch gel. This finding may facilitate the development of innovative approaches to nutrient delivery through the interaction of the food matrix with gastrointestinal disorders [140]. The influence of reduced graphene oxide on rGO has been shown to increase its mechanical properties, biocompatibility and drug loading capacity [22,141]. Geng *et al.* [142] developed carboxymethyl cellulose-starch-rGO composite hydrogels as novel pH-sensitive nanocarriers for curcumin release. The team confirmed the enhanced drug loading, encapsulation efficiency and pH-responsive release with higher toxicity towards MCF-7 cancer cells. Therefore, the conducted research suggested the possible terminal treatment of cancer with low side effects of hydrogels nanocomposites, proving the potential of nanotechnology in targeted delivery [142]. Encapsulation of curcumin and resveratrol in fish oil nanoemulsions promotes oxidative stability of these nanoemulsions. Since curcumin and resveratrol have antioxidant interact through nanoliposome coentrapment by providing their antioxidant preventing fish oil oxidation mechanism [143]. Most papers consider the antioxidant behaviour of curcumin and resveratrol. The features of these components have been examined *in vitro*, demonstrating their capacity to release radicals, whereas the adsorption of free radicals may prevent lipid peroxidation [144,145]. Shehzad *et al.* [146] improved the oxidative stability of fish oil nanoemulsions using curcumin, resveratrol, modified starches co-encapsulation. The findings indicated that the nanoemulsions had the antioxidant activity and stability, which was influenced by co-encapsulation and the type of starch used, thereby signifying the importance of both in the production of functional foods. This can enhance the application of omega-3 fatty acids in foods and pharmaceuticals to promote good health through the administration of appropriate carrier systems.

Cellulose nanoemulsions for curcumin delivery

Exploring cellulose derivatives in nanoemulsion formulations: A number of cellulose derivatives has garnered significant interest in the development of efficient drug delivery formulations, particularly for oral health, specifically in the design of novel nanoparticulate formulations [147]. Due to the numerous

beneficiate properties and ease of formulation development, cellulose derivatives such as hydroxyethyl methyl cellulose [131,132] and hydroxypropyl methylcellulose [133,134] arising from biomass have been used to prepare nanocomposite films [148]. The potential applications of films in drug delivery, particularly for curcumin, have been systematically explored through the investigation of nanoemulsions ranging from 50 to 200 nm. Pickering particle-stabilized nanoemulsions appear to be a suitable choice for the efficient delivery of curcumin [149]. Using cellulose derivatives and natural gums as gelling agents, emulgel-based preparations have been prepared. In drug delivery, these systems have potential applications and have exceptional properties like enhanced solubility, patient compliance and sustained drug release [150].

Less polydispersity in size and better morphology control have been obtained in cellulose nanocrystals (CNCs) stabilized nanoemulsions than other cellulose nanomaterials. The closely packed layer of the particles CNC-based nanoemulsions at the oil-water interphase is likely to affect the encapsulation of hydrophobic active ingredients (AIs), resulting in higher stability and degradation protection [151,152]. The incorporation of CNCs into nanoemulsions has demonstrated an improved resistance to creaming and coalescence, which extended the overall colloidal stability of the system. Cellulose derivatives and natural gums may find application as gelling agents in emulgel-based dosage formulations which are easily modifiable to achieve numerous preferences for diverse drug delivery usages [153,154]. Cellulose ether derivatives also possess viscosity raising points that make it very useful for enhancing drug bioavailability in ocular drug delivery systems, especially for class II medications with low aqueous solubility [155]. Cellulose derivatives are both biocompatible and biodegradable to be employed in pharmaceutical and biomedical applications. Derived cellulose offers several benefits in nanoemulsion formulation to include better stability, improve encapsulation, reduce coalescence and creaming, a second phase of application and improved bioavailability, biocompatibility and biodegradability [156,157].

Therapeutic potentials of cellulose nanoemulsions for curcumin delivery: The CNCs, especially CNC-CTAB, have potential as an efficient material for encapsulating curcumin [158]. These nanoemulsions can be expected to improve the curcumin delivery in terms of bioavailability and biological potential. The hydrophilic polymer has a significant impact on drug bioavailability as it leads to the solubility, stability and permeability of drug [159,160]. Moreover, the hydrophilic polymer fits in around the drug forming a defensive layer encircling the drug, which curbs liver metabolism as a result increases drug bioavailability. It can be easily harvested and purified in abundance therefore making it suitable for drug delivery [161]. Chen *et al.* [162] improved the bioavailability of curcumin by applying a supersaturable self-nanoemulsifying drug delivery system along with a hydrophilic polymer. Overall, the system enhanced curcumin's physical stability, as well as the solubility and absorption in the intestines, which resulted in an increase of the concentration levels in plasma, calculated at threefold. The experiment showed the significance of polymers for controlling curcumin supersaturation and increasing its absorption and bioavailability. The nanoencapsulated coumarin and curcumin have been reported to exhibit broad-spectrum biological and pharmacological activities, including environmental protection, microorganism growth and formation. Unlike the previous researches, these nanoparticles were based on nanocellulosic and were formulated using pickering emulsions. The nanoencapsulations demonstrated longer release, a more considerable cytotoxic effect on cancer cells and powerful antimicrobial action. This facture development is one of the approaches to drug delivery. Moreover, these nanosystems have shown potential applications in biomedicine [163,164]. The oily nature of nanoemulsions may affect wound healing. Using certain oils such as propolis oil, whose constituents, which include flavonoids and caffeic acid may actually increase the effectiveness of the same preparations [165]. The mechanism of action that enables the formulation to combat wound microorganisms involves the disruption of the cell wall. This property is paramount in reducing the wounds microbial or viral load [166]. Anjum *et al.* [167] sought for developing wound care systems comprising the synergistic action of wound nanosilver nanohydrogels in the presence of natural plant extracts alovera and curcumin to improve their antimicrobial characteristics and wound healing. The composite demonstrated composite material based wound care system formulated in nanosilver demonstrated effective silver release, dual-mechanism antimicrobial activity and the accelerated healing of wounds *in vivo*.

Hyaluronic acid nanoemulsions for curcumin delivery

Role of hyaluronic acid in nanoemulsion-based curcumin delivery: Hyaluronic acid is a key component of nanoemulsion based curcumin delivery systems that ensure optimum curcumin stability, bioavailability and targeted delivery [168]. It is a natural biopolymer with a recognized mucoadhesive activity, hence significantly enhancing bioaccessibility and retention of curcumin within a nanoemulsion system. Hyaluronic acid also functions as a stabilizer in nanoemulsions, which contributes to their physical stability and controlled release properties [169]. Moreover, hyaluronic acid might improve curcumin transdermal penetration, enhancing it as a skin delivery ingredient when incorporated into topical formulations [170,171]. In this case, hyaluronic acid mucoadhesive lipidic nanoemulsion has also yielded satisfactory outcomes; for example, when co-encasing curcumin with other polyphenols into the same compound for nose-to-brain delivery, it displayed stabilized the AUC and C_{max} values. Thus, hyaluronic acid may enhance the bioavailability and therapeutic efficacy of curcumin in these formulations [172].

The bioaccessibility of curcumin is significantly improved by the use of hyaluronic acid-based nanoemulsions. Hyaluronic acid is a well-established mucoadhesive agent used to increase the bioaccessibility of drugs delivered through nanoemulsions [173]. The incorporation of hyaluronic acid in the nanoemulsion shell increases the available curcumin for absorption. This improved bioaccessibility is essential to ensure that the curcumin is properly absorbed by the body, leading to proper utiliz-

ation and improved therapeutic results. Curcumin becomes more bioavailable when released and absorbed by hyaluronic acid found in the nanoemulsion shell, increasing its potential health effects [174].

Targeted delivery and therapeutic applications: Hyaluronic acid nanoemulsions have also been investigated to empower targeted delivery of curcumin for cancer immunotherapy [175]. Hyaluronic acid is a linear and naturally occurring polysaccharide comprising alternated residues of D-glucuronic acid and 2-deoxy-D-glucose, known for its strong affinity toward CD44, a cell surface receptor upregulated in numerous cancer, encompassing breast cancer 123 [176]. Hyaluronic acid and CD44 combining permit the receptor-specific intracellular cell signaling for drug deliver nanotechnology. The presence of hyaluronic acid can stabilize curcumin-loaded nanoemulsions in several ways [177]. First of all, hyaluronic acid can stabilize curcumin by forming a stable assembly with curcumin due to self-assembly thereby enhancing the solubility and stability of curcumin under certain conditions [178,179]. This is facilitated by the hydrophilic-hydrophobic properties of hyaluronic acid chains, forming a protective layer around the curcumin molecule and preventing degradation [180]. Garrido *et al.* [181] proposed curcumin-loaded liquid lipid nanocapsules supplemented with a bovine serum albumin and a layer of protective shell of hyaluronic acid. After the incorporation of hyaluronic acid, the percentage of curcumin left present within the lipid based liquid nanoparticles (LLNs) post-gastric digestion was highly enhanced, increasing it from 25% to approximately 85%. This is clearly due to the interaction of hyaluronic acid with bovine serum albumin (BSA) and with the latter's enhanced binding capacity at gastric conditions, which stresses the vital role of the interfacial composition in protecting curcumin-indent all over the LLNs for the enhanced bioassessment at the gut proportions [181]. Compared to the conventional treatment options for gingivitis, the proposed nanoemulgel solution of curcumin and hyaluronic acid has many benefits [182]. First, it ensures the stability and bioavailability of curcumin, which possesses anti-inflammatory and antimicrobial characteristics. Additionally, it includes hyaluronic acid, thus, it could even create a more favourable atmosphere for the therapeutic effect by supporting wound healing and tissue renewal [183].

Sindi *et al.* [184] address the idea of creating a hyaluronic acid-based nanoemulgel encapsulating a nanoemulsion of turmeric (Tur) and curry leaf oil (CrO) self-nanoemulsifying drug delivery system (SNEDDS). The target for the optimal formulation prepared using the response surface Box-Behnken design was to achieve efficient bacterial inhibition and anti-inflammatory properties. As a result, the CrO-Tur-SNEDDS with a 20 mm bacterial inhibition zone, a droplet size less than 140 nm and a high drug-loading rate were prepared. The emulgel with the CrO-Tur-SNEDDS showed improved transbuccal delivery and the controlled discharge of turmeric [184]. In addition to the internal delivery to brain, hyaluronic acid also helps external delivery to the brain by improving the permeability of blood–brain barrier (BBB) [185]. The BBB is a highly selective semipermeable membrane that separates the circulating blood from the brain extracellular fluid [186]. Hyaluronic acid has been shown to improve the transport of therapeutic agents across BBB by acting with CD44 receptors found on the surface of brain endothelial cells [187]. This interaction improves the coronal pathway of drugs or nanoparticles tagged with hyaluronic acid across BBB and into the brain, therefore, also improving drug delivery to the brain for different applications [188]. Nasr [189] examines a hyaluronic acid-based mucoadhesive lipidic nanoemulsion designed for nose-to-brain administration, co-encapsulating resveratrol and curcumin for neurodegenerative treatment. The designed nanoemulsion was optimized, which presented excellent mucoadhesive properties, spherical structure and programmed release of both polyphenols, maintaining the antioxidant properties and stability. The studied nanoemulsion was formulated with resveratrol and curcumin to enhance the cerebral concentrations of both polyphenols, serving as an effective composition for their solubility, stability, and brain-targeting in the management of neurodegenerative illnesses [189].

Pectin nanoemulsions for curcumin delivery

Potential of pectin as a carrier in nanoemulsion formulations: Pectin is a naturally occurring polymer that is extracted from the cell walls of plants. Pectin has demonstrated high affinity [190-195]. For stabilizing nanoemulsions, it is thought that pectin's capacity is high due to its hydrophobic moieties such as methyl ester groups, acetyl groups and amide groups, which allow for adsorption and spreading at the interface, as well as promoting the protection of newly formed droplets [196]. The viscosity of the aqueous phase, which promotes slowing the droplet motion, is enhanced. Thus, it stabilizes the system from phase separation [197].

Pectin allows reduction of the surface tension at the oil-water interfaces during the emulsification process and is good for stabilizing nanoemulsions with low and dispersed droplets [191]. Finally, pectin can affect the particle size of nanoemulsions by inducing depletion of flocculation deflocculation in turn, influencing the stability and performance of the formulations, as well [192]. In conclusion, this unique combination of pectin's attributes renders it an advantageous material for usage as a carrier in nanoemulsion formulations. Thus, it has the potential to help in enhancing the delivery and stability of various active ingre-dients including curcumin [193,194]. The stability of nanoemulsions may be affected by the pectin esterification degree and type and concentration, while the increase of the molecular weight and lowering the pH are beneficial [198]. However, the high pH or a drastic increase of pectin molecular weight may cause the destabilization of nanoemulsions. Therefore, pectin-based nanoemulsions were manufactured and loaded with itraconazole and used for pharmaceutical applications, proving the feasibility of pectin as a carrier in nanoemulsion formulation [199].

Recent developments and applications in curcumin delivery: Some of the recent advancements and uses of these pectin nanoemulsions in curcumin delivery have been nanoemulsion as a method to stabilize curcumin and increase its bioavailability in a food and pharmaceutical substances [200]. Apart from the application of pectin as a green emulsifier

material, it can also serve as a coating of nanoemulsion while improving curcumin stability under storage. It also has antimicrobial and antioxidant characteristics [201]. Due to the small size and large surface area of lipid droplets in nanoemulsion, digestion of the oil phase and release of curcumin is very fast, which can be incorporated into mixed micelles. Mixed micelles can penetrate through the mucus layer to the epithelium cells [202]. The nanoemulsion-based delivery system has been developed successfully and used for curcumin encapsulation and delivery into various food and beverages to increase curcumin bioavailability, followed by incorporation into mixed micelles, which will transport curcumin to the epithelium cells for absorption [203]. Furthermore, pectin as a coating material of nanoemulsions has been reported to provide improved storage stability, the effectiveness of curcumin as an antimicrobial agent and its antioxidant activity [204]. The release kinetics of the loaded nanoemulsions from the microparticles could be affected by a number of variables, including the arrangement and type of the microparticles, nanoparticle qualities, such as size, environmental issues and mechanical or thermal strain. The diffusion, erosion and lipolysis of the microparticles can all release the nanoemulsion droplets from the microparticles [205,206].

Amante *et al.* [122] combined natural polymers with nanoemulsions to produce the innovative dressing, alginate-pectin microparticles loaded with curcumin nanoemulsions. The developed nanocomposite has the following characteristics which are favourable for the wound healing process: quick gelation due to contact with the simulated wound fluid, good moist permeation rate and increased elasticity. In addition, the developed formulation enabled the release of curcumin over a long period of time, meaning severe bioavailability and was cytocompatible with keratinocyte cells. As a result of the higher viscosity, the pectin showed an increased physical stability of the nanoemulsions, which may be due to a higher content of pectin gel [207]. Fallah *et al.* [208] evaluated the potential of pectin-based nanocomposite coatings accompanied by the loading of curcumin nanoparticles and AEO mutNano, as well as low dose of γ-irradiation to protect the chilled lamb loins. Thus, the multifunctional treatments significantly enhanced the microbial, physico-chemical and sensory aspects, thereby extending the shelf life of lamb loins to approximately 25 days compared to 5 days in the control case. The study, which demonstrates a combined effect of the γ-irradiation (IR) exposure and coating on suppressing microbial accumulation and peroxide changes, showed the great potential of γ-irradiation processing combined with an active coating as an effective preservation tool to increase the safety and shelf life of a refrigerated chilled product such as lamb loins.

Dextran nanoemulsions for curcumin delivery

Dextran as a promising excipient for nanoemulsion-based curcumin delivery: Dextran is a potential excipient for dextran-encapsulated nanoemulsion formulations, which stabilize the nanoemulsions better and greatly improve curcumin protection and administration [209]. Nanoemulsions stabilized by casein-soy soluble polysaccharide complexes with dextran resulted in high curcumin incorporation efficiency, as high as 99.9%. Therefore, the high loading efficiency demonstrates the ability of dextran-stabilized nanoemulsions to encapsulate curcumin efficiently, thus protecting and delivering it to the target site [210-212]. Further, the usage of dextran in nanoemulsions implies that curcumin may have an increased performance in terms of bioavailability and bioaccessibililty, which will enhance its performance [213]. Conclusively, dextran is a desirable excipient in nanoemulsion formulation for the curcumin delivery, as it has desirable characteristics such as thermal and chemical stability, loading ability and optimal oral delivery performance [214]. The incorporation of dextran in nanoemulsions has significantly increased the bioavailability of curcumin. Nanoemulsions stabilized by dextran have a high curcumin loading efficiency of 99.9%, quantitatively demonstrating that dextran efficiently encapsulates curcumin, which in turn protects it and improves its efficacy to the target site [215,216]. The role of dextran in nanoemulsions is to protect curcumin from degradation and improve its solubility, increasing its absorption and bioaccessibility. Dextran in nanoemulsions is therefore an essential bioavailability enhancer due to its confirmation in improving the curcumin bioavailability [217,218].

Pharmacokinetics and biodistribution studies: Pharmacokinetics and biodistribution studies refer to the study of absorption, distribution, metabolism and excretion of nanoparticles within the body [219]. These studies are crucial as they provide insights into the interaction of nanoparticles with the biological systems, bioavailability and the person's health and safety [220]. Pharmacokinetic studies will investigate the effects of dextran-stabilized nanoemulsion on the metabolism, excretion, distribution and absorption of curcumin in the context of nanoemulsion based curcumin administration [221]. To reveal the localization of curcumin in various tissues and organs after injecting curcumin loaded dextran-based nanoemulsions, biodistribution studies might be performed. Such investigations are crucial to further developing the *in vivo* performance of nanoemulsions and their formulations to improve therapeutic performance while preventing safety issues as drug delivery systems [222, 223].

The Maillard reaction is a covalent bond formed by non-enzymatic reactions between the amino groups of proteins and the reducing ends of polysaccharides to obtain a suitable amphiphilic glycosylate-modified protein [224,225]. Its amphiphilicity provides steric hindrance, possibly preventing aggregation and disproportionation of the emulsion droplet and thus suitable for the stabilization and storage characteristics of the nanoemulsion [226]. Kim *et al.* [227] studied the applicability of pea protein isolate and dextran conjugates prepared by the Maillard reaction as strengthening agents in a curcumin-loaded pickering nanoemulsions. The study demonstrated that pea protein isolate–dextran (PPI-DX) conjugates enhance the physical properties of nanoemulsions containing curcumin and make them more stable and efficient, regardless of the environmental phase in which they are exposed. The study suggests that PPI-DX conjugates are a promising way for designing a stable and functional pickering nanoemulsions to be used in food fields, granting curcumin an increased solubilization, reduced surface hydrophobicity and enhanced bioaccessibility [227,228]. In

another study Menchicchi *et al.* [229] addressed *H. pylori* infection by developing low molecular weight dextran sulfate dextran sulfate nanocapsules. The authors hypothesized that the formulation would prevent the bacteria from adhering to the gastric cells. From their findings, DexS40-NC inhibits *H. pylori* adhesion dose-dependently and is cytotoxic, unlike the novel formulations. From this, DexS40-NC holds promise as a non-antibiotic intervention for *H. pylori* infection, which could potentially tackle the threat of antibiotic resistance for a novel intervention.

Conclusion and future perspective

Curcumin is a bioactive compound present in turmeric responsible for its medicinal properties such as antioxidant, anti-inflammatory and anticancer properties. However, the therapeutic potential of curcumin is limited due to its poor solubility and bioavailability. To enhance the therapeutic potential offered by curcumin and to increase its bioavailability, researchers have developed a polysaccharide nanoemulsion as a carrier to deliver curcumin. Nanoemulsion is a colloidal dispersion of oil droplets stabilized by a surfactant. When the nanoemulsion is stabilized by a polysaccharide, it is called a polysaccharide nanoemulsion. Such nanoemulsion can be prepared using different types of polysaccharides like chitosan, alginate, starch and hyaluronic acid, each having its unique characteristics that contribute to the stability and performance of the nanoemulsions used to deliver curcumin. Chitosan-based nanoemulsions have proven to increase the bioavailability of curcumin, rendering it well accessible to the body for therapeutic performance. Alginate-based nanoemulsions had superior stability and release controlling characteristics. Meanwhile, starch-based nanoemulsions were beneficial in improving the sensorial characteristics of food products. Hyaluronic acid h- and-l-based nanoemulsions were prospective for the potential of targeted delivery and transdermal penetration of curcumin. Dextran is the most valuable polysaccharide as an excipient in curcumin delivery employing nanoemulsions due to various functional advantages like the facilitation of better bioavailability, increased stability and release-controlling potential. Concerning cellulose derivatives, they have been exploited in the formulation nanoemulsions with encouraging results in stability, encapsulation and bioavailability enhancement. The above-mentioned polysaccharides render a multi-faceted strategy to enhance the therapeutic activity of curcumin. These nanoemulsions encourage the dissolution, preservation of of curcumin and allow it to open up its complete potential as a therapeutic agent. Researchers can improve the therapeutic capability of drug-loaded nanoemulsions composed of polysaccharide materials and help improve safer and more effective curcumin-based therapy for a variety of illnesses. Further research, design and development of novel and advanced drug-loaded nanoemulsions is an exciting area for the future. This will include developing new polysaccharide materials and their derivatives for use in nanoemulsions formulations. Development of more efficient and low-cost methods for the synthesis of polysaccharide-based nanoemulsions. This includes the use of green synthesis approaches as well as the optimization of the existing methods. Elaboration on the possibility of using polysaccharide-based nanoemulsions in combination with other therapeutic agents, including chemotherapeutic drugs, for an overall better therapeutic effect and diminished dose of the main therapeutic agent.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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