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REVIEW

Emerging Trends in the Application of Nanosuspension-Based Biomaterials for Anticancer Drug Delivery

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Abstract: The treatment of cancer remains a formidable challenge, largely due to the difficulty in achieving efficient co-delivery of chemotherapeutic and immunotherapeutic agents to specific tumor sites. Nanosuspension-based biomaterial drug delivery systems for anti-cancer (NBDDSC) have emerged as promising platforms for enhancing drug solubility, stability, and targeted delivery. These systems can be categorized into natural polymer-based, synthetic polymer-based, and hybrid nanosuspensions, each offering distinct advantages in biocompatibility, drug loading, and controlled release. However, the majority of existing NBDDSC rely on synthetic materials that function primarily as excipients, offering no intrinsic therapeutic value. These materials often require intricate manufacturing processes, which can result in issues with batch consistency, reduced stability, and diminished therapeutic efficacy. Additionally, the potential side effects associated with synthetic components further underscore the limitations of these systems. This review explores various preparation methods for nanosuspensions, including antisolvent precipitation, high pressure homogenization, and ultrasonication, highlighting their impact on particle size, drug encapsulation, and stability. Furthermore, the targeted applications of these nanosuspensions in treating of cancers such as glioma is discussed to emphasize their potential clinical relevance. By addressing current limitations, this review underscores the critical importance of simpler, safer, and clinically translatable NBDDSC in advancing cancer therapy.

Keywords: nanosuspension, cancer, biomaterials, tumor, NBDDSC

Introduction

Over the past two decades, the pharmaceutical industry has made significant strides in developing modern technologies to enhance drug discovery and delivery,[1] cancer treatment remains a significant challenge due to limitations in drug solubility, bioavailability, and targeted delivery.[2–4] Many potent chemotherapeutic and immunotherapeutic agents suffer from poor water solubility, leading to inadequate absorption, suboptimal therapeutic effects, and systemic toxicity. For instance, drugs such as paclitaxel, curcumin, and docetaxel exhibit low aqueous solubility, necessitating innovative delivery systems to enhance their clinical efficacy.

NBDDSC (Figure 1) have emerged as a promising strategy to address these challenges. By reducing drug particle size to the nanometer scale, these systems significantly improve solubility, dissolution rate, and bioavailability. Additionally, nanosuspensions offer enhanced stability and controlled release, making them suitable for both chemotherapeutic and immunotherapeutic applications. Unlike conventional drug carriers, such as liposomes and polymeric nanoparticles,

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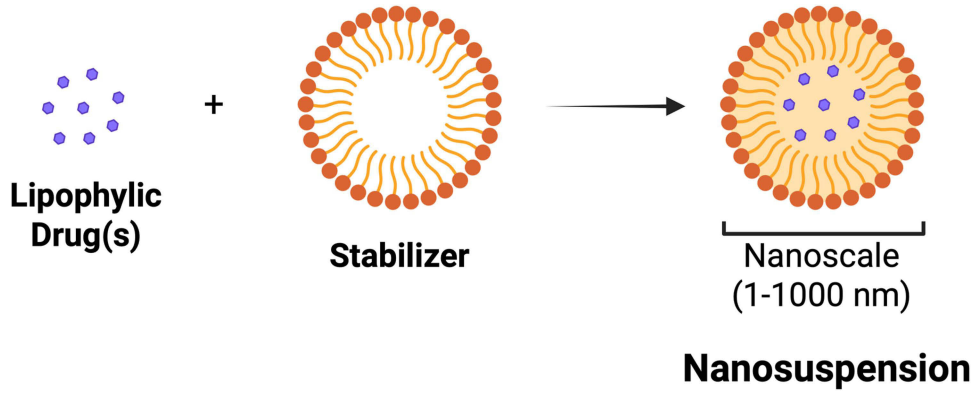

Figure 1 The concept of NBDDSs. Created in BioRender. Suliman, K. (2025) https://BioRender.com/ezu4wke.

nanosuspensions require fewer excipients and exhibit simpler formulation processes, improving cost-effectiveness and scalability.[5]

The issue of poor solubility not only impedes bioavailability but also affects the therapeutic efficacy of drugs, particularly in cancer treatment. To ensure therapeutic effectiveness, drugs must be bioavailable and easily absorbed, whether administered orally or intravenously.[6–8] Consequently, the pharmaceutical industry faces the ongoing challenge of for example, poorly soluble anticancer drugs such as sorafenib and etoposide often require alternative delivery methods to enhance their therapeutic impact. Consequently, the pharmaceutical industry faces the ongoing challenge of developing novel drug delivery systems that enhance the solubility and bioavailability of poorly soluble drugs.[9,10]

Immunotherapy has revolutionized cancer treatment, particularly in malignancies such as melanoma, lung cancer, and triple-negative breast cancer. However, its clinical success is often hindered by poor drug solubility, rapid degradation, and limited tumor penetration. Nanosuspensions provide a viable solution by enabling the co-delivery of chemotherapeutic agents with immune checkpoint inhibitors (eg, anti-PD-1/PD-L1 antibodies) or cytokines, enhancing immune activation and tumor targeting. Furthermore, nanosuspensions can be engineered to improve tumor accumulation via passive (enhanced permeability and retention effect) or active (ligand-mediated) targeting strategies.[11]

Among the various strategies developed to address these solubility issues, nanosuspension technology has emerged as one of the most promising. Nanosuspensions are colloidal dispersions of drug nanocrystals in liquid media, typically water.[5,12,13] They offer a versatile approach to delivering poorly soluble drugs by reducing particle size to the nanometer scale, thus increasing surface area and dissolution rate.[8,14,15] The ability to use nanosuspensions for both oral and intravenous administration further adds to their appeal, making them suitable for various therapeutic applications, including cancer treatment.[16–19]

Cancer therapy, in particular, presents unique challenges that can be addressed by NBDDSCs for cancer. Conventional chemotherapy and immunotherapy often suffer from suboptimal drug delivery to targeted tumor sites, leading to reduced efficacy and increased systemic toxicity.[20–22] Nanosuspensions, due to their nanoscale size and ability to be tailored for controlled and targeted release, offer a promising solution for co-delivering chemotherapeutic and immunotherapeutic agents. Moreover, their relatively simple formulation process and the use of minimal excipients make them cost-effective and easier to manufacture compared to more complex drug delivery systems.[20,22–26]

The preparation methods of nanosuspensions play a crucial role in optimizing drug encapsulation, stability, and therapeutic performance. Techniques such as high-pressure homogenization, antisolvent precipitation, and ultrasonication facilitate the formulation of stable nanosuspensions with uniform particle size. Additionally, co-delivery strategies, including hybrid nanosuspension systems combining natural and synthetic polymers, further enhance drug loading efficiency and controlled release kinetics.[27]

Despite these advantages, the clinical translation of NBDDSC faces several challenges, particularly in terms of reproducibility, scalability, and toxicity. These challenges are exacerbated by the complexity of synthetic polymers, which can lead to batch-to-batch variability, instability, and toxicity, necessitating the use of safer, biodegradable

alternatives.[16,19] Biodegradable biomaterials such as chitosan, alginate, and hyaluronic acid provide safer and more biocompatible options for nanosuspension formulations, reducing adverse effects and enhancing therapeutic outcomes.

Moreover, NBDDSs allow for the co-delivery of multiple therapeutic agents, such as chemotherapeutic drugs and Immunotherapeutics, in a single formulation. This co-delivery capability is essential in cancer therapy, as it enables the simultaneous targeting of multiple pathways involved in tumor growth and immune evasion. By enhancing drug penetration into solid tumors and reducing off-target toxicity, nanosuspension-based systems have shown great potential in improving patient outcomes in cancers such as pancreatic, colorectal, and breast cancer.[14]

This review aims to provide a detailed exploration of recent trends and challenges in the development of NBDDSC for cancer therapy. By examining the integration of biodegradable biomaterials, novel stabilization techniques, and scalable manufacturing methods, this discussion underscores the critical role of interdisciplinary research in advancing NBDDSC technology. The ultimate goal is to facilitate the clinical translation of these systems, enabling safer and more effective cancer treatments.

Preparation Methods of Nanosuspension

The preparation methods for NBDDSCs play a pivotal role in determining their stability, particle size, and therapeutic efficacy (Figure 2). These methods directly influence the physicochemical properties of the nanosuspensions, including their dissolution rate, bioavailability, and capacity for targeted drug delivery. Achieving consistent and scalable formulations requires precise control over particle size and surface characteristics to ensure batch-to-batch reproducibility and long-term stability.[28,29] Recent innovations have focused on refining preparation techniques to address challenges such as aggregation, high-energy input, and scalability.

Nanosuspensions are commonly generated by condensation/aggregation of particles from molecular dispersion to nanosized particles, as in the precipitation method (bottom-up technique), or reduction/dispersion of big particles to nanosized range, as in the milling process (Scale down technology).[1,18,29] The surface area of a nanosuspension significantly increases over its initial surface area owing to its smaller particle size. Thus, it can raise the saturation solubility, as determined by the Ostwald–Freundlich equation.[15,30] there are several methods to prepare nanosuspension including.

Precipitation Technology

Sub-colloidal materials combine to form particles within the colloidal size range. By creating a supersaturated drug solution in a water-miscible organic solvent at an optimal temperature, and then rapidly agitating it, a small amount of the drug is dispersed in water (a non-solvent), to quickly produce nuclei. This method is highly cost-effective and suitable for producing nanosuspensions with high purity.[31] The high level of supersaturation caused by a change in the solvent leads to quick nucleation while preventing supersaturation near the nucleating crystals. According to Ostwald law of nucleation, rapid nucleation and moderate growth rate are critical factors for successful thermodynamically stable crystal formation. The primary benefits of the precipitation method include the production of uniformly sized, finely distributed drugs, ease of scale-up, a straightforward and affordable procedure.[32]

Elevated levels of supersaturation can produce a needle- or acicular-like crystals, that are easily broken down to produce more nuclei at the expense of crystal development.[33] Furthermore, the absence of impurities may result in lattice flaws or faults that can be homogenized to reduce the particle size to the nanoscale. Challenges include controlling the rate of nucleation and growth to prevent aggregation, which can be addressed using surfactants and crystallization inhibitors. Innovations like Nanomorph™ technology have been developed to create stable amorphous nanoparticles, enhancing solubility.[34]

Homogenization Technology

Homogenization reduces the particle size by forcing the suspension through a valve with a tiny opening at high pressure (100–1000 pressures). The abrupt drop in the fluid velocity results in a loss of static pressure, which in turn creates implosion forces generated by cavitation. Shock waves within the liquid medium then break down the microparticles (less than 25 μm) into nano-sized particles.[35] Furthermore, particles with intrinsic crystal flaws can be fractured by the shear forces created by

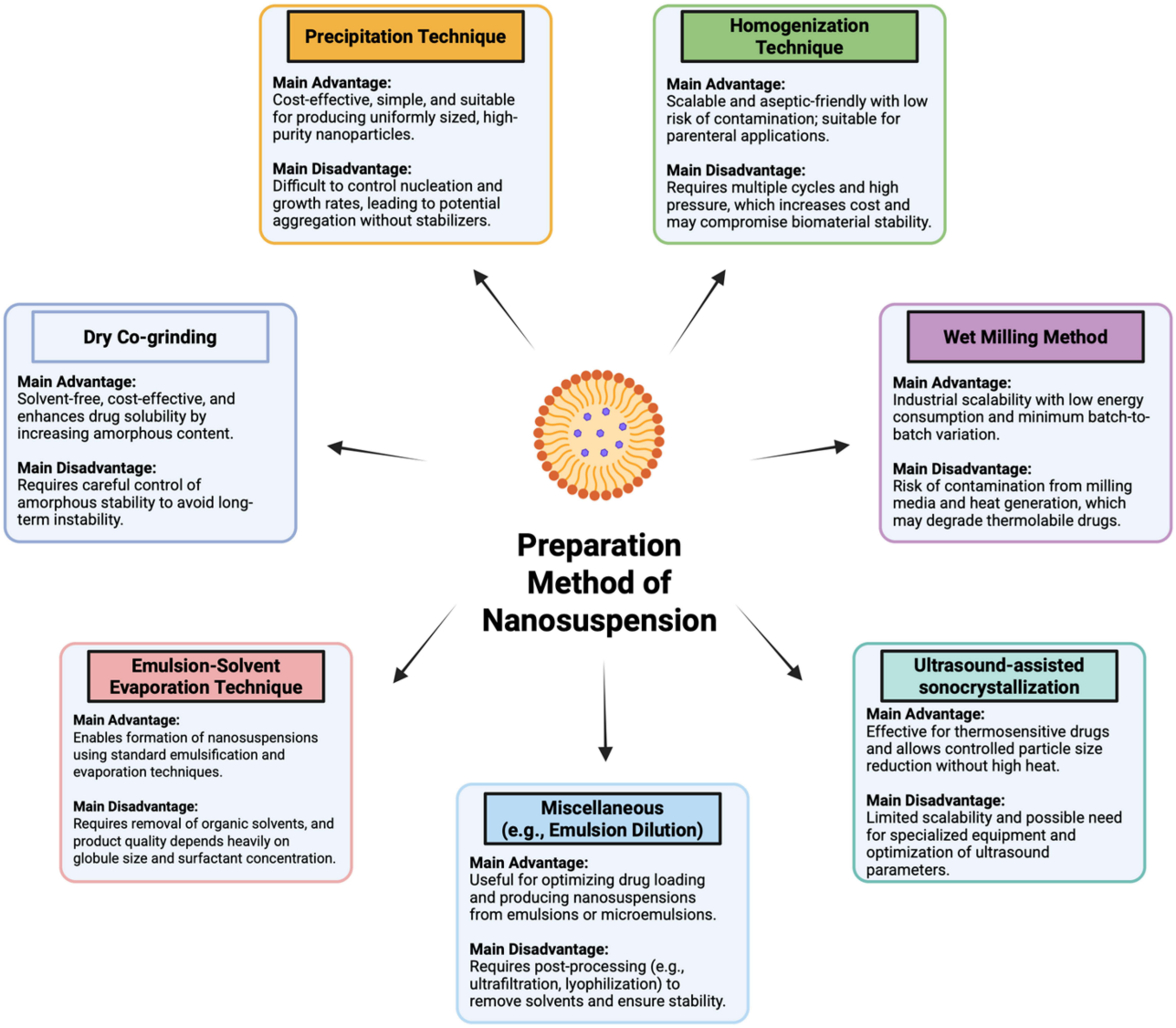

Figure 2 Common preparation methods of NBDDSs. Created in BioRender. Suliman, K. (2025) https://BioRender.com/3i9gma1.

particle collisions at high velocities. Viscosity enhancers can aid in the nanosizing process by increasing the particle density inside the dispersion area and inhibiting crystal formation. The metastable amorphous particles generated by the precipitation process can be transformed into stable crystal forms through homogenization.[36] High pressure homogenization is scalable and can be used for producing formulations suitable for parenteral applications.[37] Typically, several cycles are required to generate particles within the intended size range. The main advantages of this approach are its simplicity in scaling up, versatility in diluting or concentrating suspensions, low risk of contamination, and viability for aseptic manufacturing[38] Despite its benefits, high-pressure homogenization requires multiple cycles to achieve the desired particle size, which can increase production costs and processing time. Additionally, the high shear forces can compromise the stability of certain biomaterials. Recent innovations, such as combining homogenization with temperature-sensitive stabilizers like chitosan or vitamin E TPGS, have mitigated these issues, enabling more efficient and stable production of nanosuspensions.[7,22]

Wet Milling or Media Milling

This approach uses a media mill or high-shear ball mill to prepare nanosuspensions. Particle attrition and impact both contribute to the size reduction of the medication, stabilizers (s), and water in the chamber. This technique is more

appealing because of its low energy consumption, ease of scaling up, minimum batch-to-batch fluctuation, capacity to handle large quantities of materials, and the fact that it already led to four FDA-approved medications.[27] The amount of material in the mill is significant because too little feed results in inefficiency and abrasive wear on the mill parts, whereas too much feed has a cushioning effect. The remaining particles in the final product can occasionally be contaminated by deterioration of the milling[39] Nevertheless, this issue was reduced by employing a strongly crosslinked polystyrene resin milling medium. The increased amorphous fraction introduced into the materials by a longer milling process can cause instability.[40] Recent advancements in bead milling have improved the efficiency of the process, allowing for finer particle sizes and enhanced stability.[41] However, wet milling has limitations, including the potential for contamination from the milling media and the generation of heat, which can degrade thermolabile drugs. To address these challenges, researchers have developed modified milling systems that incorporate temperature control mechanisms and inert milling materials to minimize contamination. These advancements have made wet milling a robust option for scaling up nanosuspension production in industrial settings.[39]

Dry Co-Grinding

A stable nanosuspension was produced by dry co-grinding process using a variety of polymers and copolymers, including polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, sodium dodecyl sulfate, and cyclodextrin derivatives.[15,23] Dry grinding techniques are more cost-effective than wet grinding and do not require the use of hazardous solvents. The enhancement of surface polarity and conversion of a large amount of the drug's crystalline state to an amorphous form are the most notable effects of the method. For weakly soluble drug nanosuspensions, controlled stability of the amorphous phase can greatly increase the saturation solubility and, consequently, the rate of dissolution.[6,22,35]

Emulsion-Solvent Evaporation Technique

Drugs are first dissolved in organic solvents or cosolvents to generate an emulsion, which is then dispersed in an aqueous phase containing a surfactant that serves as a stabilizer.[25,42] Nanosuspensions are produced by the rapid evaporation of a solvent under low pressure. The size of the globules and stabilizer concentration are important variables to consider when using the emulsification process.[28]

Ultrasound Assisted Sonocrystallization Method

This is a cutting-edge method for creating stable nanosuspensions. Ultrasound between 20 and 100 kHz improves particle size reduction and regulates the size distribution of the active ingredient in pharmaceuticals. Additionally, This technique is particularly useful for thermosensitive drugs, as it reduces the need for high temperatures.[43]

Miscellaneous Methods

Another method for producing drug nanosuspensions is to dilute the emulsion, which will allow the dispersed phase to fully diffuse into the continuous phase and produce a nanosuspension. Similar procedures can be applied to produce nanosuspensions in microemulsions. To get the best possible drug loading, it is important to investigate the impact of globule size and surfactant quantity on internal phase drug uptake.[13,42] To make the nanosuspension produced by these techniques suitable for administration, clinging solvents and other components must be removed using ultrafiltration. To eliminate the incompatibilities between the different formulation components and increase the physical and chemical stability, lyophilization of the nanosuspensions is required.[44] Nanosuspensions can be sterilized by gamma irradiation, steam heat sterilization, or membrane filtration (<0.22 μm). According to published research, optimizing the bottom-up nanosuspension technique necessitates careful selection and calibration of the concentration of excipients, such as polymers and surfactants.[23,41]

Formulation Consideration of Nanosuspensions

The formulation of nanosuspensions for cancer treatments entails the preparation of colloidal dispersions consisting of drug nanocrystals in a liquid medium, typically water, aimed at improving the solubility and bioavailability of poorly

soluble pharmaceuticals (Figure 3). Within this framework, biomaterials defined as substances used in medical applications to support, enhance, or replace damaged tissues or biological functions are of paramount importance. These biomaterials can be classified as natural or synthetic and can be derived from diverse sources, including metals, ceramics, polymers, glass, and even living cells and tissues. Frequently utilized biomaterials in the formulation of nanosuspensions encompass stabilizers, polymers (natural and synthetic), surfactants, buffers, and complexing agents.[28,44] Table 1 presents a comprehensive overview of the different biomaterials utilized in this context, detailing their specific functions and contributions to improving the performance of nanosuspensions in cancer therapy.

According to published research, active pharmaceutical ingredients (APIs) with high log P and enthalpy values are more likely to stabilize nanosuspensions via both electrostatic and steric stabilization. Furthermore, physical characteristics, such as molecular weight, have not been shown to directly affect the stabilization stage or particle size.[22,29] However, because of the high surface energy of nanosuspensions, the stabilizer plays a crucial role in preventing agglomeration or aggregation. Various particle size analysis techniques can be used to investigate variations in the polydispersity index and particle size distribution at different stages of nanosuspension, including during manufacturing, storage, and stability testing.[28,44] Stabilizers also play an important role in preventing Ostwald ripening, wetting hydrophobic drug particles, and providing steric or ionic repulsion to create physically stable products. The in vivo stability of nanosuspensions and their physical stability are strongly influenced by the concentration of the stabilizer. Natural polymers like chitosan and alginate are favoured due to their biocompatibility, biodegradability, and controlled-release properties. These polymers have been used in formulations of paclitaxel and curcumin to enhance stability and bioavailability.[21,23,32]

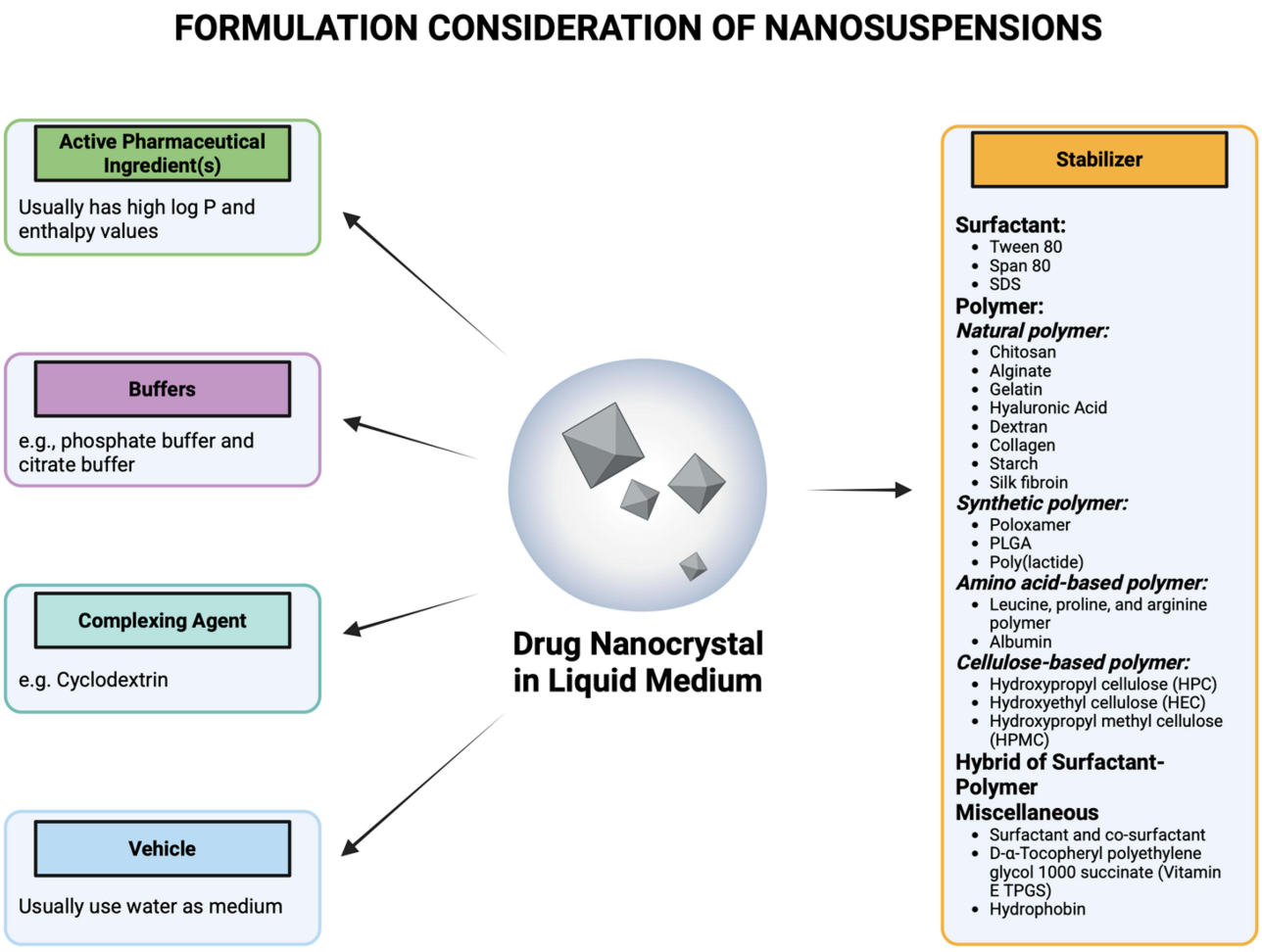

Figure 3 Formulation consideration of nanosuspensions. Created in BioRender. Suliman, K. (2025) https://BioRender.com/e55hkfu.

Table 1 Nanosuspension-Based Biomaterials for Cancer Therapy

Nanosuspension	Biomaterials	Applications	References
Natural Polymers	Chitosan	Sustained drug release (eg, Doxorubicin, Paclitaxel).	[45]
	Alginate	Drug stabilization (eg, Paclitaxel, Docetaxel).	[46]
	Gelatin	Tumor-specific targeting (eg, Cisplatin, Paclitaxel).	[47]
	Hyaluronic Acid	Drug targeting for tumors with high CD44 expression (eg, Doxorubicin).	[48]
	Dextran	Drug delivery for targeted immunotherapy and cancer treatments (eg, Methotrexate).	[49]
	Collagen	Drug carrier for anticancer agents and tissue engineering applications (eg, Curcumin).	[50]
	Starch	Controlled release for hydrophobic drugs (eg, 5-Fluorouracil).	[51]
	Silk Fibroin	Targeted and sustained drug delivery (eg, Paclitaxel).	[52]
Synthetic Polymers	Poloxamers	Poloxamers improve drug delivery, stability, and circulation for poorly water-soluble drugs.	[53]
	Poly lactic-co-glycolic acid nanosuspensions (PLGA NSs)	Biodegradable drug delivery systems for anticancer agents.	[54–56]
	Poly lactide nanosuspensions (PLA NSs)	Long-circulating drug delivery systems for anticancer therapy.	[57,58]
Amino Acid-Based Stabilizers	Leucine, Proline, Arginine	Enhanced cancer treatment and personalized therapy formulations (eg, Curcumin).	[59]
	Albumin	Targeted drug delivery for enhanced solubility (eg, Abraxane® - Paclitaxel).	[60]
Cellulose-Based Derivatives	HPMC, HPC, HEC	Stabilization in cancer therapy (eg, Docetaxel).	[61]
Hybrid Systems	Graphene oxide (GO) nanoplatelets	Targeted treatment and controlled delivery (eg, Methotrexate).	[62]
	Polymeric lipid hybrid nanosuspension	Controlled release formulations for enhanced efficacy (eg, Doxorubicin).	[63]
Miscellaneous Stabilizers	Surfactants (eg, Tweens, SDS)	Solubility enhancement for poorly soluble drugs (eg, Paclitaxel).	[64]
	Vitamin E TPGS	Vitamin E TPGS-based nanosuspensions enhance solubility and efficacy of anticancer drugs for targeted cancer therapy.	[65]
	Hydrophobin	Drug delivery optimization for sustained release (eg, Doxorubicin).	[66]

Notes: HPMC, (Hydroxypropyl Methylcellulose), HPC (Hydroxypropyl Cellulose), HEC (Hydroxyethyl Cellulose) are cellulose-based derivatives commonly used as stabilizers in nanosuspension formulations due to their ability to improve bioavailability and stability.[67]

The Table 2 summarizes the key differences between natural, synthetic, and hybrid nanosuspensions based on various properties. These properties highlight the advantages and limitations of each polymer type for drug delivery applications.

Natural Polymer-Stabilized Nanosuspensions

Chitosan Nanosuspensions

Chitosan is a biopolymer product produced from chitin, and it has drawn a considerable interest for its superior film-forming properties and its capacity to stabilize nanosuspensions. This multifunctional organic molecule is essential for

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Table 2 Comparison of Key Properties Across Natural, Synthetic, and Hybrid Nanosuspensions for Drug Delivery Applications

Property/Polymer Type	Natural Polymers (Chitosan, Alginate, Gelatin)	Synthetic Polymers (PLGA, PCL, PEG)	Hybrid Polymers (PLGA-PEG, Chitosan-PLGA)
Biocompatibility	High[68]	Moderate to High[69]	High[70]
Drug Release Control	Moderate[68]	High[69]	High[70]
Targeting Potential	Limited[68]	High[69]	Very High[70]
Stability in Aqueous Environment	Moderate[68]	High[69]	High[70]
Degradation Rate	Biodegradable[68]	Depends on polymer design[69]	Tailored degradation rates[70]

protecting the stability of nanosuspensions and guaranteeing their homogeneous dispersion. Likewise, alginate, a polysaccharide derived from brown algae, enhances the stability of nanosuspensions by creating a protective layer around them. The encapsulation of nanosuspensions serves the dual purpose of protecting them and improving their thermal stability, hence establishing alginate as a highly useful constituent in nanosuspension formulations. Furthermore, the efficacy of gelatin, derived from collagen, in stabilizing nanosuspensions has been thoroughly investigated. Its unique properties enable it to specifically interact with nanosuspensions, thereby providing a critical stabilizing effect that is essential for maintaining the integrity and functionality of the nanosuspension system.[1,6]

Several authors have successfully created chitosan-based porous nanofibers by combining chitosan with polyethylene oxide (PEO) followed by electrospinning and dehydration. They were observed using scanning electron microscopy to obtain porous morphological, Chitosan-based porous nanofibers in nanosuspension systems hold significant promise for cancer treatment, providing a targeted and controlled drug delivery platform. These systems are characterized by excellent biocompatibility and stability, with the added potential for intrinsic anticancer effects.[71–77] The nanofibers were immersed in a 0.1% w/w solution of paclitaxel to load the medication. For encapsulation, porous chitosan nanofibers were submerged in a 4% w/w solution of polyanion-type hyaluronic acid. Differential scanning calorimetry, or DSC, and Fourier transform infrared spectroscopy were used. The analysis of paclitaxel release from the encapsulated fibers in PBS was conducted using UV-visible spectroscopy.[76,78–80]

The in vitro activities against DU145 cancer cells treated with the loaded nanofibers were assessed using the MTT assay. This information provides compelling evidence that the chitosan/hyaluronic acid fibers influenced the pace at which paclitaxel was released and may have applications in postoperative treatment. For the intracellular delivery of anticancer drugs, **chitosan-Tripolyphosphate (TPP) nanosuspensions** have shown strong potential.[71,72,76,77,81] These nanosuspensions have garnered significant attention in the field of drug delivery due to their unique combination of biocompatibility, biodegradability, and mucoadhesive properties. The nanoparticles are commonly prepared via ionic gelation, wherein positively charged chitosan molecules interact with negatively charged sodium tripolyphosphate (TPP). This interaction leads to the spontaneous formation of stable nanoparticles that are well-suited for encapsulating a wide range of therapeutic agents.[82–85] One of the most valuable attributes of chitosan-TPP nanoparticles is their strong mucoadhesive property, which markedly enhances drug absorption across mucosal tissues. This adhesive interaction is most effective when the chitosan-to-TPP ratio is optimized. Studies have indicated that a ratio of 4:1 (chitosan:TPP) produces nanoparticles with favorable size and surface charge characteristics, facilitating prolonged retention at the absorption site and thereby improving therapeutic efficacy.[71,72,77,81,86]

Alginate-Based Nanosuspensions

Alginate-based nanosuspensions are colloidal systems formed from the biopolymer sodium alginate, widely used for stabilizing hydrophobic drugs like Paclitaxel and Docetaxel, which have poor water solubility and bioavailability. By encapsulating these drugs in alginate nanoparticles, their solubility is enhanced, and their stability is improved, preventing degradation and crystallization. These nanosuspensions are especially valuable in drug delivery systems, where they not only enhance solubility but also enable controlled or sustained drug release. Recent advancements have extended

their applications to multi-drug delivery systems, where they can co-deliver synergistic drug combinations, improving therapeutic outcomes by offering enhanced efficacy, reduced side effects, and more precise targeting of diseased tissues, such as cancer cells. The ability to combine multiple drugs in a single nanosuspension offers potential benefits like reduced dosage and toxicity. However, challenges remain, including scalability, high drug loading, and regulatory hurdles, which need to be addressed for broader clinical application. Despite these challenges, ongoing research continues to improve alginate-based nanosuspensions, making them a promising strategy for the future of drug delivery, particularly in the treatment of complex diseases like cancer.[46]

Gelatin-Based Nanosuspensions

Gelatin nanoparticles facilitate tumor-specific targeting of drugs such as Cisplatin and Paclitaxel. Current research has focused on the creation of gelatin-based nanosuspensions that enhance drug delivery efficacy and reduce toxicity in tumor tissues.[47]

Hyaluronic Acid-Based Nanosuspensions

Hyaluronic acid-based nanosuspensions are effective for targeting tumors with high CD44 expression. This polymer enhances the specificity of nanoparticles to CD44+ cancer cells, as seen with Doxorubicin-loaded systems, ensuring higher therapeutic efficiency and lower off-target effects.[48]

Dextran-Based Nanosuspensions

Dextran- based nanosuspensions are pivotal in cancer immunotherapy and targeted treatments. Methotrexate-loaded dextran systems have been refined for superior tumor targeting, with recent studies showing enhanced delivery precision and reduced systemic toxicity.[49]

Collagen - Based Nanosuspensions

Collagen nanosuspensions are increasingly used for carrying anticancer agents like Curcumin. Research has shown these carriers improve the therapeutic impact of drugs while providing sustained-release properties, making them useful in cancer treatment and tissue engineering.[50]

Starch Nanosuspensions

Starch nanosuspensions are employed for the controlled release of hydrophobic drugs like 5-Fluorouracil. Current advancements emphasize localized drug delivery systems, which provide sustained release at the tumor site, reducing systemic side effects.[51]

Silk Fibroin-Based Nanosuspensions

Silk fibroin-based nanosuspensions are being developed for sustained and targeted drug delivery, as demonstrated with Paclitaxel. These systems show improved therapeutic efficacy in tumor models, making them a valuable tool in modern oncological applications.[52]

Synthetic Polymer-Stabilized Nanosuspensions

Poloxamers, such as Poloxamer 188 and Poloxamer 407, are synthetic macromolecules commonly employed for the purpose of stabilizing nanosuspensions. The FDA has classified them as generally regarded as safe (GRAS) for pharmaceutical purposes, encompassing oral, parenteral, and topical usage.[6]

Poly (lactic-co-glycolic acid) (PLGA) is a novel substance employed in drug delivery systems based on nanoparticle engineering. Pharmacological bioavailability is improved and regulated release is facilitated by PLGA-based nanosuspensions.[28,42–44,87–91]

Poloxamers

The FDA has deemed these synthetic polymers to be generally recognized as safe (GRAS) for topical, parenteral, and oral pharmaceutical use. Poloxamers 188 and 407 are the most commonly used polymers with stabilizing effects in nanosuspensions. The primary determinants of the stability and formation of nanosuspension crystals include the hydrophilic-lipophilic ratio, shape, functional groups, and molecular weight. In cancer therapy, Poloxamers are

frequently employed to improve the delivery of poorly water-soluble drugs, enhance drug stability, and extend circulation duration. Nanosuspensions stabilized with Poloxamers facilitate targeted drug delivery, minimize adverse effects, and optimize therapeutic efficacy by regulating the release of anticancer compounds.[92]

Additionally, Poloxamers possess the ability to modify cell membrane permeability, which can further enhance drug absorption and promote cellular uptake, making them advantageous in the formulation of cancer treatments.[2,13,27,44]

PLGA Nanosuspensions

PLGA is a biodegradable copolymer frequently used in the formulation of nanosuspensions. It is hydrolyzed inside the body to produce water and CO_2, as well as the safe and non-toxic metabolites lactic acid and glycolic acid. These two primary metabolites have very little systemic toxicity because they can easily be eliminated.[36,54–56,78,93,94] Several techniques, including oil-in-water emulsion solvent evaporation, nanoprecipitation, and interfacial deposition, have been used to create PLGA nanosuspensions loaded with paclitaxel. Generally, the release of paclitaxel from the nanosuspension follows a biphasic pattern, with a rapid initial release rate occurring over a period of one–three days, followed by steady, persistent.[73–76,79,95,96] It has been demonstrated that these nanosuspensions have higher in vitro cytotoxicity than free paclitaxel in a variety of tumor cell lines, including HeLa, glioma C6, and human small-cell lung cancer. Paclitaxel-loaded nanosuspensions demonstrated significantly improved in vivo tumor-inhibitory effects in transplantable liver tumors. The modified surface of the nanosuspensions resulted in enhanced delivery of paclitaxel.[37,74,97,98]

Poly(Lactide) Nanosuspension (PLA NSs)

PLA is another popular matrix used to synthesize polymeric nanosuspension, because of its safe and biodegradable characteristics. To provide NSs with long-circulating qualities, a methoxy poly (ethylene glycol)-poly(lactide) copolymer (mPEG-PLA) was created and added, PLA nanosuspensions are a promising platform in nanomedicine for cancer therapy due to their biodegradability, biocompatibility, and ability to enhance the therapeutic efficacy of anticancer drugs while minimizing side effects.[57,58,99–102]

Amino Acid-Based Stabilizers

It has been shown that leucine copolymers can effectively form stable drug nanocrystals in aqueous media. Lecithin is the recommended stabilizing agent for sterile, steam-heat-sterilizable parenteral nanosuspensions. Albumin has been used in nanosuspensions at concentrations ranging from 0.003% to 5% as a surface-stabilizing and drug-targeting agent. Proline, transferrin, and arginine are other pharmaceutically acceptable amino acid copolymers utilized to stabilize the physical state of nanocrystals.[3,5,17,22,91]

Leucine, Proline, Arginine

These amino acid-based stabilizers enhance drug solubility and personalization of cancer treatments, especially with agents like Curcumin. Advancements in precision medicine have incorporated these stabilizers to improve nanosuspension stability and therapeutic outcomes.[59]

Albumin

Albumin-based systems, such as Abraxane® (Paclitaxel albumin-bound nanosuspension), have revolutionized controlled drug release and tumor targeting. Recent innovations focus on optimizing these formulations for enhanced drug solubility and tumor penetration.[60]

Cellulose Based Derivatives

Hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), and hydroxypropyl methyl cellulose (HPMC) are frequently used as stabilizing agents. The surface-adsorbed hydrophobic groups of these polymers constitute the fundamental mechanism for their steric stabilization.[12,14–19]

Hybrid Polymer-Stabilized Nanosuspensions

The aim of coupled hybrid nanosuspensions is to improve the stability of dispersion by combining different types of nanoparticle categories. Nanoparticle aggregation is hindered by the chemical bonding that occurs throughout the formulation process. Drug molecules or genetic material can be integrated into graphene oxide (GO) nanoplatelets to get highly specific and regulated administration. Polymeric lipid hybrid nanoparticles are formed by combining lipid vesicles with polymeric core components. The development of hybrid nanosuspensions covered with cell membranes involves the integration of lipid vesicles with polymeric core components, presenting a novel and sophisticated approach for drug delivery.[87–91,103–106]

Miscellaneous

Developed by BASF Industries, Soluplus® is a new excipient consisting of a copolymer of polyvinyl caprolactam, polyvinyl acetate, and PEG. Several nanosuspensions with improved stability, accelerated dissolution rate, and greater bioavailability have been utilized as stabilizers. It has been observed that the use of water-soluble polymers such as PVA, PEGylated chitosan, and polyvinyl pyrrolidone as stabilizers greatly increases the rate of dissolution and bioavailability of nanosuspensions.[88] A protein-based surfactant, hydrophobin, was used to create a functionalized surface coating for the low-solubility medication, beclomethasone dipropionate. Its adaptability to genetically engineered surface modification makes it appropriate for a variety of drug delivery applications.[88,90]

Nanosuspensions using polymers such as PTX is a unique approach that increases drug bioavailability and reduces the likelihood of side effects. A variety of synthetic and natural polymers, such as chitosan NSs, PLA NSs, and PLGA NSs, have been employed for PTX nanoencapsulation. The general characteristics of these polymers include regulated drug release, biodegradability, biocompatibility, and ease of manipulation of their physicochemical properties.[37,107–110]

Concurrent chemotherapy often fails due to the presence of cancer stem cells (CSCs) and the development of drug resistance, driven in part by altered microRNA expression within tumors One of the key contributors to this resistance is the dysregulation of signalling pathways, such as the hedgehog (Hh). To overcome this, combining paclitaxel with the Hh inhibitor cyclopamine (CYP) has been shown to effectively target drug-resistant cancer cells. Additionally, inhibition is a subset of cells called side populations, which are common in cancer stem cells. Researcher synthesized mPEG-b-PCC-g-PTX-g-DC (P-PTX) and mPEG-b-PCC-g-CYP-g-DC (P-CYP) PTX–polymer conjugates, forming micelles.[76,108,111] This combination prevented the growth of tumor colonies and helped fighting drug resistance to paclitaxel. Additionally, this combination inhibited Hh signaling and increased the expression of tumor suppressor miRNAs.[86,112–115]

Surfactant and Co-Surfactants

The choice of surfactant and co-surfactant is crucial for creating nanosuspensions, with microemulsions serving as the model. This may have an impact on drug loading in the internal phase, drug solubility, and phase behavior. For the stabilization and development of nanosuspensions, a variety of surfactants, including Tweens and sodium dodecyl sulfate, as well as co-surfactants, including bile salts, Transcutol, glycofurol, ethyl alcohol, and isopropyl alcohol, have been effectively employed, surfactants and co-surfactants are integral to nanosuspension systems, including those used for cancer therapy, as they improve stability, solubility, and delivery efficiency.[88]

D-α-Tocopheryl Polyethylene Glycol 1000 Succinate (Vitamin E TPGS)

An esterified, water-soluble derivative of vitamin E (tocopherol), vitamin E polyethylene glycol succinate, has been utilized as a stabilizing and solubilizing ingredient in several nanosuspension formulations. Because of its high physical stability and low toxicity profile, it is considered the best excipient for parenteral, ophthalmic, and oral use.[17,42,87]

Hydrophobin

Hydrophobin-modified nanocarriers are being explored for their ability to optimize drug delivery systems. These carriers have shown promise in sustained release applications for drugs such as Doxorubicin, improving cancer therapy outcomes.[66]

Nanosuspensions in Targeted Anticancer Treatment

Nanosuspension-based Biomaterial Drug Delivery Systems for Cancer (NBDDSC) represent an innovative approach to targeted cancer therapy, specifically designed to improve the delivery of poorly soluble anticancer drugs (Figure 4). By leveraging nanoscale technology, these systems enhance drug solubility, bioavailability, and precision, ensuring more effective delivery to tumor sites while minimizing adverse effects on healthy tissues. Integrating nanotechnology with biocompatible materials, NBDDSC provides a promising, patient-centered solution for developing safer and more effective cancer treatments. In terms of targeting strategies, nanosuspension-based biomaterials utilize the enhanced permeability and retention (EPR) effect for passive targeting, allowing nanoparticles to accumulate in tumor tissues due to leaky vasculature and impaired lymphatic drainage. Active targeting, in contrast, involves functionalizing nanoparticles with specific ligands that can recognize and bind to receptors overexpressed on cancer cells, thereby improving the precision of drug delivery. Combining passive and active targeting strategies can further enhance overall targeting efficiency, increasing therapeutic efficacy while reducing systemic side effects.[116]

Hybrid Membrane Coated Nanosuspensions for Anti-Glioma Therapy

With a median life span of less than 24 months and a 5-year survival rate of approximately 2–4%, glioma is one of the worst tumors that affects humans. In an effort to improve patient outcomes, doctors and scientists working on combinatorial therapies, particularly the combination of chemotherapy and immunotherapy, have expressed great interest in this short survival expectation.[117,118] While trials (on both female and male ICR mice) combining immunotherapy and chemotherapy have shown promise in treating other tumors, glioma remains uniformly fatal, with little improvement in overall survival. In contrast to other tumors, gliomas are characterized by their isolation behind the blood-brain tumor barrier (BBTB) and physiological barrier (BBB).[119] They also exhibit a higher mutational burden and heterogeneity while impairing the immune function due to both the tumor's own growth and the unique environment of the brain. Owing to these restrictions, relatively little chemotherapy and immune checkpoint blockade medication actually reach the glioma.[120] Therefore, in addition to the development of chemotherapeutic and immunotherapeutic drugs, the treatment of glioma has several challenges resulting from the lack of a potent platform that might deliver these therapeutic agents to the targeted areas.[121–123]

The co-distribution of these therapeutic agents has been the subject of numerous NBDDSC to date; yet, the US Food and Drug Administration has not approved any of these systems for the treatment of disorders affecting the central

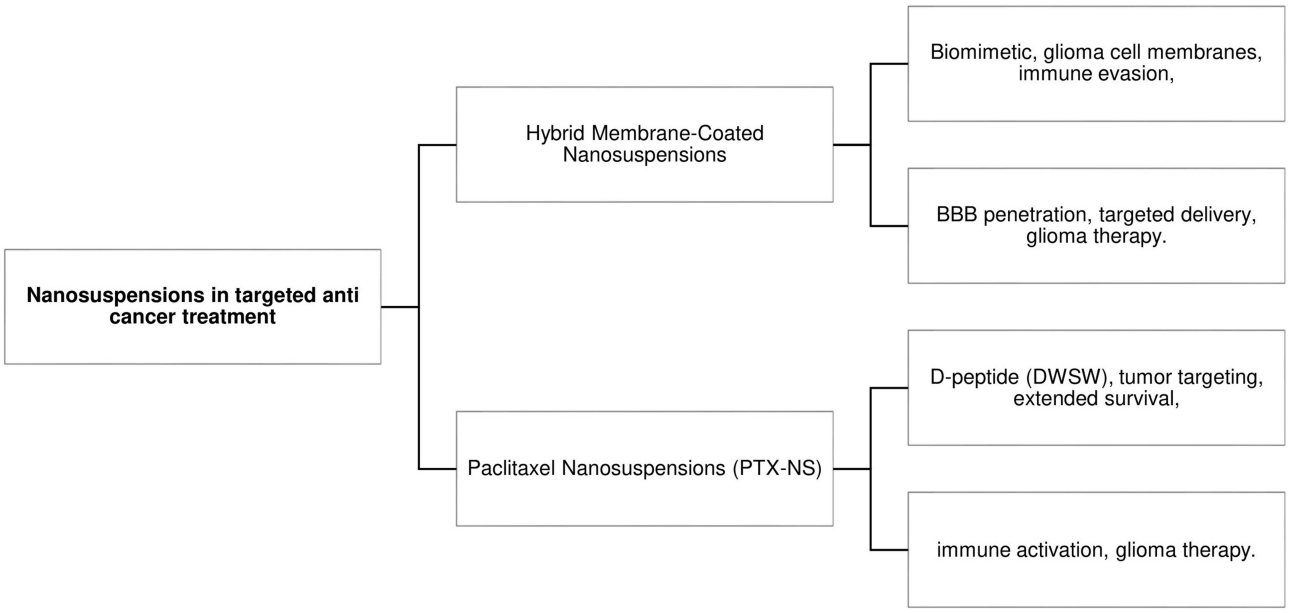

Figure 4 Nanosuspensions in targeted anti-cancer treatment.

nervous system (CNS).[124] Currently, practically all NBDDSC rely primarily on the properties of the materials they are composed of target tumors; nevertheless, these compounds have no inherent therapeutic activity and solely act as excipients. Customized materials and co-loading of many therapeutic agents sometimes entail intricate manufacturing procedures, which can lead to fluctuations in the reproducibility of batches and diminish the stability of non-digestible drug delivery systems, frequently culminating in inadequate therapeutic results. Furthermore, these systems are constrained by the inherent drawbacks of synthetic materials, including their possible negative side effects. Thus, the creation of a straightforward, safe, and effective delivery system is crucial for clinical translation.[125]

The study of biomimetic nanocarriers is being advanced by the new NBDDSC frontiers. Among these, cell membrane-coated nanosuspensions have been extensively studied for their potential to treat cancer. The potential uses range from improving the immunogenicity of cancer vaccines to improving the efficacy of cancer medicine delivery.[126] These types of biomimetic NSs for drug delivery display distinct roles from the source cells, offering a different approach to overcome biological barriers and increase the effectiveness of drug administration. Unfortunately, many synthetic materials are needed to create a scaffold for these biomimetic NSs, which frequently leads to low drug-loading rates.[125]

An enhanced tumor-inhibitory effect can be attained by increasing the drug concentration at the target site through high drug loading. In study, researchers applied a cell membrane coating to nanosuspensions. Like a "pure drug particle". Nanosuspensions are easily transferred to the clinical setting and have a high drug carrying capacity because they do not contain a carrier, which helps to increase drug concentration at the targeted areas[127] Cell membrane-bound tumor antigens are not only employed for drug administration; they are also used to teach the immune system how to identify and combat cancer. Previous studies have produced mimic particle carriers that have been altered to include these surface antigens, which has increased the effectiveness of vaccines.[128] Dendritic cells (DCs) are antigen-presenting cells that activate many immune resistance mechanisms. Tumor-associated antigens can stimulate mature DCs to increase their number and activate CD8+ and CD4+ T cells. T cells are selectively recognized by activated CD8+ T lymphocytes (CTLs), which then trigger tumor death.[127–134]

Additionally, major histocompatibility complex (MHC) molecules are expressed more often on the surface of tumor cells when CD4+ helper T lymphocytes are activated. This helps CTLs identify tumor cells and accelerate the death of cancer cells.[129,135] DC-based immunotherapy has recently attracted considerable interest. In patients with glioblastoma, melanoma, renal cell carcinoma, and prostate and ovarian malignancies, DC vaccinations have been shown to be both safe and efficacious.[49,136,137] Unfortunately, the effectiveness of these vaccinations still falls short of predictions based on basic science and evidence from clinical trials conducted over the past 20 years. Two primary factors were found responsible for this failure (1) the majority of tumor DC vaccines focus on a single antigen; however, tumor cells can quickly evade immune responses by mutating their antigen. (2) The body's proteolytic enzymes readily break down the extracted tumor proteins, making it difficult to obtain the optimal treatment outcome and produce immunological effects that are not long-lasting. This complicates the extraction procedure.[138–143] Consequently, enhanced stability and effective antigen loading are crucial for optimizing DC vaccines. Generally, a wide range of antigens, including tumor-associated and tumor-specific antigens, are present in cancer cells. High concentrations of tumor antigens in cancer vaccines are necessary to cross the threshold for T-cell recognition and end immunological tolerance.[119,123,127]

Nanosuspensions have shown promising therapeutic potential not only in glioma but also across various other cancer types. For instance, doxorubicin and methotrexate nanosuspensions have been effectively utilized in the treatment of breast and lung cancers, demonstrating improved drug solubility and extended circulation times. These nanosuspension formulations also contribute to reduced systemic toxicity by facilitating more targeted delivery to tumor sites. Furthermore, nanosuspensions hold promise in overcoming multidrug resistance (MDR) by enhancing drug delivery to cancer cells and increasing the intracellular accumulation of chemotherapeutic agents.[144]

Paclitaxel Nanosuspensions

Nanosuspensions are submicron colloidal dispersions containing nanosized drug particles stabilized by surfactants. These formulations suspend poorly water-soluble drugs directly in a liquid medium without incorporating a matrix material, enhancing their solubility in both lipid and aqueous environments.[6] Improved solubility allows the **API** to achieve peak plasma levels more rapidly due to an accelerated dissolution rate.[145] Nanosuspensions are particularly advantageous for

drugs with limited solubility, permeability, or both, and can be administered intravenously without blocking blood vessels because of the small particle size.[146]

In a recent study, Fan et al developed PTX nanosuspensions ((PTX)NS) coated with glioma C6 cancer cell membrane (CCM) and modified with a DWSW peptide (DS DY DP DG DW DS DW), which is a D-peptide with enhanced proteolytic stability and the ability to penetrate biological barriers. These nanosuspensions were fabricated using an ultrasonic precipitation technique and demonstrated capabilities to penetrate the blood-brain barrier (BBB) and target tumor sites. **This occurs through various mechanisms, such as receptor mediated endocytosis, enhanced permeation through tight junctions, and active targeting via surface modification with ligands**. Drugs like paclitaxel and curcumin, when delivered in nanosuspension form, have demonstrated enhanced brain bioavailability, which is crucial for treating central nervous system (CNS) diseases, including gliomas. However, **there remains a need for more extensive in vivo studies to fully understand the extent of BBB penetration and its clinical significance**[147] The cancer cell membrane coating camouflaged the nanosuspension, facilitating immune evasion and BBB crossing, leading to a preferential accumulation in glioma tissues. In glioma-bearing mice, DWSW-CCM-(PTX)NS significantly extended survival and inhibited tumor growth. This biomimetic approach conferred biological properties such as homologous adhesion and immune evasion to the nanosuspension, underscoring its potential in targeted tumor therapies and offering a comprehensive strategy to enhance nanosuspension targeting.[148]

Challenges and Limitations

Despite the promising potential of NBDDSC, several **significant challenges** hinder their clinical translation. These include toxicity concerns, solubility and bioavailability limitations, reproducibility and batch-to-batch variability, manufacturing scalability, and complex regulatory requirements Table 3.

Toxicity Concerns

Remain paramount, especially in oncology, where non-specific drug distribution can exacerbate systemic side effects. Commonly used synthetic excipients such as PLGA and PLA degrade into acidic byproducts, which may lead to localized inflammation and tissue damage.[57] Similarly, surfactants like SDS may induce hemolysis and cytotoxicity at higher concentrations. The mononuclear phagocyte system (MPS) uptake of nanosuspensions also leads to off-target accumulation in organs such as the liver and spleen, further increasing toxicity risks. Immunogenicity issues related to synthetic materials can additionally impair treatment efficacy upon repeated administration.[60]

Solubility and Bioavailability Challenges

Many anticancer agents suffer from poor aqueous solubility and low oral bioavailability, which hinders their therapeutic efficacy when formulated as nanosuspensions. Drugs with high lipophilicity often require solubilizing agents or surface modifiers, which can introduce toxicity or stability issues. Furthermore, limited mucosal permeability and first-pass metabolism in oral delivery systems restrict drug absorption. The physicochemical characteristics of nanosuspensions such as particle size, surface charge, and crystallinity significantly affect dissolution rate and membrane permeability, and hence must be carefully optimized for improved bioavailability.[43]

Table 3 Summary of Key Challenges and Potential Solutions

Challenge	Proposed Solution
Toxicity (synthetic excipients, MPS uptake)	Use of natural polymers (eg, chitosan, alginate); hybrid systems (eg, membrane-coated NPs).[149]
Solubility and bioavailability	Particle size optimization; use of lipid-polymer hybrids; surfactant alternatives.[150]
Reproducibility and batch consistency	Microfluidics, sonocrystallization, in-line monitoring systems.[43]
Manufacturing scalability	Process optimization; scalable methods (eg, high-shear mixing, freeze drying).[151]
Regulatory hurdles	Long-term preclinical studies; use of biocompatible materials; standardized testing.[60]

Strategies and Potential Solutions

To address toxicity, biodegradable and biocompatible materials like chitosan, alginate, gelatin, and silk fibroin have been explored. These natural polymers degrade into non-toxic byproducts and can exhibit additional therapeutic benefits such as anti-inflammatory and antimicrobial properties.[74] Hybrid nanosystems, such as cell membrane-coated nanoparticles, can mimic tumor cells to evade immune clearance and enhance target specificity, reducing off-target accumulation and systemic toxicity. Notably, paclitaxel-loaded cell membrane-coated nanosuspensions have demonstrated superior tumor selectivity in preclinical models.[149]

To improve reproducibility, technologies like microfluidics, microfluidization, and sonocrystallization offer precise control over particle synthesis and reduce batch variability. These methods enable uniform particle size distribution, stable drug encapsulation, and seamless scale-up[31] Integration of real-time quality monitoring systems (eg, in-line spectroscopy, particle size analyzers) also ensures critical attributes are maintained throughout production.[43]

To ensure regulatory compliance, developers must implement standardized protocols for toxicity testing and conduct robust long-term safety studies. Use of biodegradable materials and consistent production parameters helps meet FDA and EMA expectations for safety, efficacy, and environmental compatibility.[152]

Scale-Up Challenges

The transition from lab-scale to industrial production introduces unique scale-up challenges. Techniques like wet milling and freeze drying, though efficient in small-scale settings, often suffer from aggregation and poor energy efficiency when scaled. High-pressure homogenization requires multiple processing cycles, raising concerns around cost, yield, and processing time. Furthermore, achieving batch-to-batch uniformity is essential for regulatory approval, requiring the integration of automated systems and process analytical technologies to ensure reproducibility and quality at scale.[152]

Conclusion

Nanosuspensions represent a transformative approach in drug delivery, offering significant solutions to the longstanding challenges of poor solubility and bioavailability, particularly in cancer therapy. Literature has consistently shown that poorly water-soluble drugs often exhibit low bioavailability, limiting their therapeutic potential. Nanosuspensions effectively enhance solubility by reducing particle size, thus improving dissolution rates and bioavailability. By addressing toxicity concerns through biodegradable polymers and improving reproducibility with advanced manufacturing techniques, nanosuspensions have emerged as a promising tool to minimize systemic toxicity while delivering higher concentrations of drugs to the target site.

Additionally, the use of natural, synthetic, and hybrid polymers in nanosuspensions has shown great promise in tailoring release profiles and targeting specific cancer cells. Among these, hybrid polymer-based nanosuspensions, particularly those combining natural polymers like chitosan with synthetic ones like PLGA, have emerged as the most versatile and efficient for various cancer types. These systems not only enhance drug stability and bioavailability but also allow for improved targeting and controlled release, making them highly promising for personalized cancer therapy.

The best preparation methods for different cancer drug types vary, with techniques like high-pressure homogenization, microprecipitation, and solvent evaporation proving effective for both hydrophobic and hydrophilic drugs. For example, drugs like paclitaxel and doxorubicin, which are commonly used in cancer treatment, benefit from these methods as they enhance their solubility and ensure sustained release. Tailoring the preparation method based on the drug's physicochemical properties and targeting requirements is crucial for maximizing therapeutic efficacy.

Looking ahead, future research should focus on improving the targeting efficiency of nanosuspensions, particularly in overcoming the blood-brain barrier (BBB) for brain cancer therapies and enhancing drug delivery to multidrug-resistant cancer cells. Furthermore, exploring the combination of nanosuspensions with other novel drug delivery systems, such as immunotherapies and gene therapies, could pave the way for innovative treatments. As for future directions in the field of NBDDSs (Nanostructured Drug Delivery Systems), expanding their applications beyond cancer, including neurological disorders, infectious diseases, and regenerative medicine, holds immense promise. Advancements in scale-up production, long-term stability, and patient-specific formulations will be key to their successful clinical translation.

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Disclosure

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