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NANOBUBBLES DRUG DELIVERY SYSTEM

1st Mr. Sai Santosh Rathod
Department of Pharmaceutical Quality Assurance
Shree Santkrupa College of Pharmacy Ghogaon
sairathod767@gmail.com
2nd Dhanashri Chandrakant Chorage
choragedhanashri4522@gmail.com
3rd Shweta Annaso Gaikwad
Shwetagaikwad614@gmail.com
4th Swaraj Vijay Kadam
sawarjkadam0022@gmail.com
5th Rajwardhan Sampatrao Jagtap
rajjagtap0216@gmail.com
2, 3, 4, 5. B. Pharmacy Final Year, Shree Santkrupa College of Pharmacy Ghogaon

ABSTRACT

Because of their distinct physicochemical characteristics, small size, high stability, large surface area, and ultrasound responsiveness, nanobubbles (NBs) are becoming a promising nanocarrier in the field of novel drug delivery systems. They are composed of a gas-filled core encased in a stabilizing shell composed of lipids, polymers, proteins, or surfactants, and have drawn a lot of attention due to their potential to improve targeted drug delivery, enhance therapeutic efficacy, and reduce systemic toxicity. Mechanical stirring, agitation, emulsification, sonication, laser ablation, microfluidic techniques, hydrodynamic methods, acoustic cavitation, and membrane-based methods are some of the techniques used to prepare them. These systems are widely used in wound healing, cancer treatment, gene transfer, oxygen administration, biomedical imaging, and blood–brain barrier penetration. Additionally, therapeutic drugs can be delivered in a controlled and site-specific manner thanks to ultrasound-triggered drug release. Recent developments have concentrated on multifunctional and theranostic nanobubbles that integrate therapeutic and diagnostic imaging capabilities on a single platform. Physical instability, limited drug-loading capacity, manufacturing obstacles, safety concerns, and regulatory barriers persist despite their intriguing potential. Therefore, in order to improve their stability, safety, and clinical usefulness, more research and technology developments are needed. For the creation of sophisticated, targeted, and regulated medication delivery systems, nanobubbles offer a viable method.

Keywords: Nanobubbles, Novel drug delivery system, Targeted drug delivery, Ultrasound, Cancer therapy, Nanocarriers, Theranostics.

Introduction

To increase drug use and reduce adverse effects, drug delivery systems (DDSs) make it easier to deliver therapeutic substances in a targeted and regulated manner. Stimuli-responsive smart DDSs allow for precise and regulated medication delivery by reacting to either endogenous or external stimuli. While increasing therapeutic efficacy, these methods can lessen toxicity and variations in medication concentration. Because of their great ultrasonic responsiveness, gas systems, including microbubbles and nanobubbles, have emerged as attractive drug delivery systems in this external stimuli [1].

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DDS is committed to creating drug delivery systems and tools that can alter a drug's metabolism, potency, toxicity, immunogenicity, and biorecognition in order to improve the microenvironment in which it functions and make it easier for the body to absorb it [2]. Nanotechnology is one of numerous innovative DDS techniques. Unless we define "nanoscale" as a scale ranging from 1 to 100 nm, nanotechnology is just "technology on the nanoscale." Nanotechnology can be defined as "atomically precise technology" or "engineering with atomic precision" [3].

DDS has a number of significant advantages over traditional formulations.

1) Minimized degradation and increased medication stability.

2) More target concentration and less side effects due to improved medication distribution.

3) Accurate drug location, timing, and targeted release, including drug administration over the blood–brain barrier.

4) Higher therapeutic index, decreased toxicity, and decreased therapeutic dosage [4]. Nanobubbles (NBs) are spherical particles with a vapor-filled core composition and an outer shell that can display dynamic properties. They are concave spaces in an aqueous solution that convey gas and range in size from less than 1 nm [5].

Nanobubbles are gas-carrying concavities that range in size from less than 1μm in an aqueous solution. Bubbles are round, globular particles having a gas-filled core structure and a shell that allow them to have observable dynamic features [6].

The Latin root of the term "nano" means "dwarf." In this sense, a nanometer is one thousand millionth of a meter (i.e., 1 nm = 10−9 m), which is the perfect size range provided by nanotechnology.In 1950, Epstein-Plesset put up a theory to forecast how long a bubble would last. In 1959, American physicist Richard Feynman first proposed this idea [8].

NBs are tiny gas core nanocarriers that improve encapsulation efficiency, biocompatibility, and controlled release characteristics. They are supported by polymeric or surfactant shells. In order to make nanobubbles suitable for pharmaceutical and nutraceutical applications, recent developments in nanobubble design have concentrated on enhancing bio-degradability and lowering long-term toxicity risks [9,10].

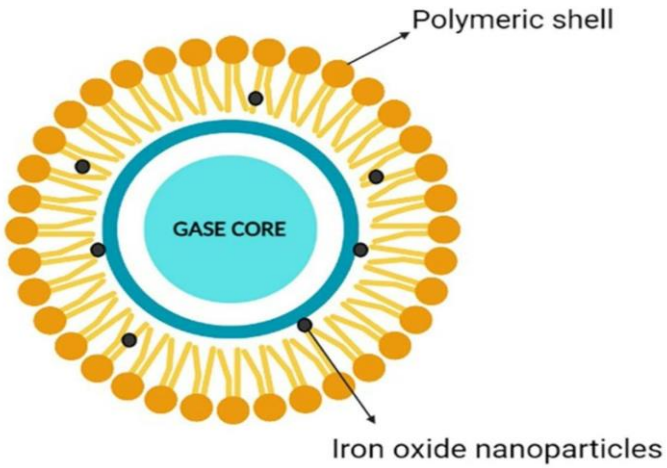


Fig 1:Basic structure of nanobubbles

Ideal properties of nanobubbles:

NBs are microscopic bubbles that range in size from 10–50 μm to 10–100 nm. They are nontoxic, nonbuoyant, and electrochemically active, resulting in a chemical-free system environment. Unlike

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regular bubbles, they typically float constantly in the system for a considerable amount of time. Over 20% of the oxygen in it can be retained above its saturation point [11].

They ought to be extremely stable and resistant to coalescence and early collapse. In addition to being biocompatible, nanobubbles shouldn't have any serious negative effects or toxicity. They ought to be biodegradable, and their constituent parts ought to be securely removed from the body. To transport a sufficient quantity of therapeutic medication, nanobubbles must have a high drug-loading capacity.

They ought to deliver continuous and regulated medication release at the intended location. To deliver the medication precisely to the damaged tissue, they should have superior targeting capabilities. Nanobubbles should exhibit triggered drug release and strong ultrasonic responsiveness for imaging. To travel to the intended location, they should have enough time to circulate. They should be stable in storage and retain their drug content, size, and structure .

NBs are highly stable and long-lasting, and they can readily attach to hydrophobic surfaces of many materials. These qualities can expand the variety of uses for NBs, including cleaning and surface coating, the removal of pollutants, medicine, and agriculture[12]

Characteristics of nanobubbles:

features of NBs in different methods. The investigation verified the demonstrated NBs' exceptional stability in the medium, which persisted for a long time despite breakdown. Because of these qualities, NBs can be used in a wider range of applications, including surface coating and cleaning, the removal of pollutants, medicine, and agriculture [13].

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Characteristics	**Nanobubbles**
Size	< 1 µm
US echo	weak
Half -life	Long
Drug loading capacity	High
Specific surface area	Small
Zeta potential	High
Physical stability	Stable
Gas dissolution rate	High
Appearance	Transparent
Internal pressure	High

Classification :

The primary distinction between bulk and surface NBs, according to recent developments, is that the former do not have a three-phase contact line, whereas the latter do [14]. Because of this, bulk NBs have a significantly smaller radius of curvature than surface NBs, and bulk NBs are movable whereas the surface is not. Furthermore, atomic force microscopy (AFM) has already demonstrated the existence of sNBs, whereas the existence of bNBs is suggestive but not confirmed. Dynamic light scattering (DLS), the primary experimental method for identifying bNBs, is unable to differentiate between bubbles, droplets, or particles, which is the reason for this uncertainty. However, the development of NB technologies and their applications depends critically on the search for novel methods for identifying both bulk and surface NBs [15].

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Nanobubble types	Size range (nm)	Stability	Constitution	Surface charge	Propertie
Plasma	1–200	Moderate	Plasma with gas	Mainly charged P	Made in plasma
Liquid	10-100	High	Liquid surrounding gas	Can be charged	Fixed and strong in liquids
Solid	100-200	Moderate to High	Gas in liquid	Mainly neutral	Float due to floatability
Gas	1-100	Very High	Solid in liquid	Normally charged	Strong in different environments
Bulk	100 to a few micrometer	Moderate	Gas in liquid	Normally neutral	Can affect the physical characteristics of liquids
Surface	50-500	High	Gas at the liquid-solid interface	Normally neutral	Invariable at interface

Stability of Nanobubbles:

The stability of nanobubbles is their capacity to endure in particular circumstances. The bubbles' surface charge, surface tension, and solution characteristics are some of the variables that affect their stability. Surface charge is the main factor that makes nanobubbles stable. High zeta potential nanobubbles are more stable. On the other hand, nanobubbles' zeta potential gradually drops. Research shows that the bubble size actually rises, despite the fact that gas diffusion predicts that it should decrease. This process is explained by the interaction of Brownian motion with zeta potential reduction, which results in bubble coalescence and the formation of larger bubbles [16].

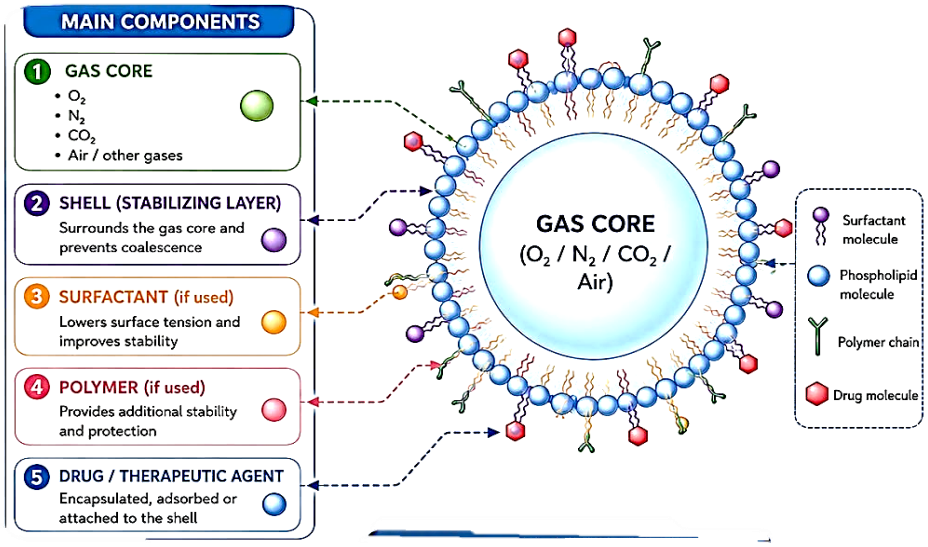
Technique of Nanobubbles Formation :

Numerous physical, chemical, and engineering aspects influence the intricate process of preparing NBs. Usually produced by gas dissolution, cavitation, and bubble nucleation, NBs' size, stability, and functioning are all impacted by these processes. There are two primary routes for NB formation: a) Gas dissolution method: This dissolving pathway calls for the gradual dissolution of gas into a liquid, followed by nucleation and oversaturation. Gas solubility pressure, temperature, and surfactant content all have an impact on this, which frequently happens at interfaces or bulk solutions.

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b) gigantic bubble collapse (cavitation method): Under strong shear stress or sonic cavitation, gigantic bubbles collapse to form smaller, more stable NBs. Microfluidic mixing, high-pressure shearing, and ultrasound all enhance this process [17].

Composition of Nanobubbles:



Most nanobubbles have comparable shell/core compositions, with a less soluble gas in the core and a unilaminar composition of proteins, polymers, or phospholipids in the shell. Nanobubbles can be used for gas distribution applications because they feature a monolayer shell with a less soluble gas core than bilayer liposomes of a similar size. Because of their smaller size, biodegradability, increased surface area, longer half-life, better cellular absorption, and echogenic qualities, nanobubbles are particularly interesting [10].

PEG/stealth agents, medicines, targeting ligands, and imaging agents are among the other components that make up nanobubbles, which are primarily composed of a gas core and a stabilizing shell.

Bubble size, stability, acoustic response, and medication delivery effectiveness are all influenced by the composition of the gas core and shell [18].

Composition of Nanobubbles

1. Central Gas

The inside part of a nanobubble that takes up the majority of its volume is the gas core. Air, nitrogen, oxygen, carbon dioxide, sulfur hexafluoride, and perfluorocarbons are often utilized gasses in the core [19, 20]. Simple, stable gasses like air and nitrogen are frequently employed as nanobubble cores. Oxygen-containing nanobubbles are helpful in cancer treatment because they can supply oxygen to hypoxic tissues. Strong ultrasonic contrast and acoustic responsiveness are provided by sulfur hexafluoride (SF_3). Due to their low water solubility, perfluorocarbon gasses like perfluoropropane and perfluorobutane enhance nanobubble stability [21].

2. Stabilizing Layer or Shell

The shell encloses the gas core, regulates medication loading and release, and stops bubble collapse. Biocompatibility, flexibility, and a strong drug-loading capability are provided by lipid or phospholipid

shells [22]. PLGA, PLA, chitosan, and dextran are examples of polymer shells that offer better mechanical stability and regulated drug release [23].

Protein shells, particularly albumin, offer functional groups for ligand or drug binding and are biocompatible [24].

Surfactants like Span, Tween, and Pluronic F-68 lower surface tension and stabilize the gas-liquid interface. Alternating positively and negatively charged polymers create polyelectrolyte multilayer shells, which enable regulated medication loading and release.Lipid–polymer or polymer–surfactant systems are examples of hybrid shells that can enhance stability and functionality [25].

3. Payload or Medicinal Substance

Small-molecule medications, proteins, genes, nucleic acids, and therapeutic gasses can all be transported by nanobubbles. Lipid bilayers and polymer matrices are frequently used to integrate hydrophobic medications.

Drugs that are hydrophilic can either combine with charged polymers or be adsorbed onto the shell. Electrostatic interactions can bind nucleic acids, such as plasmid DNA, siRNA, and mRNA, to cationic nanobubble shells. The nanobubble core can be filled with therapeutic gasses, particularly oxygen, for gas-based therapy [23].

To encourage targeted accumulation at sick cells, targeting ligands are affixed to the surface of the nanobubble.Antibodies, peptides, aptamers, folic acid, and sugars are often used targeted ligands.Antibodies enhance site-specific delivery by binding particular tumor or cell surface antigens.Cancer cells frequently overexpress folate receptors, which are the target of folic acid [22].

5. Stealth component or PEG

To increase colloidal stability and decrease nonspecific protein adsorption, PEG or other hydrophilic polymers are added to the shell.

PEGylation can enhance the systemic stability of nanobubbles and increase the duration of blood circulation [23].

6. The imaging or theranostic element

For medical and diagnostic purposes, nanobubbles can be functionalized with fluorophores, magnetic nanoparticles, or other imaging agents.

Nanobubbles' gas core enables them to support theranostic medication delivery systems and function as ultrasound contrast agents [26].

Methods Of Nanobubbles:

A.Mechanical /Energy based methods

1..Mechanical Stirring Method:

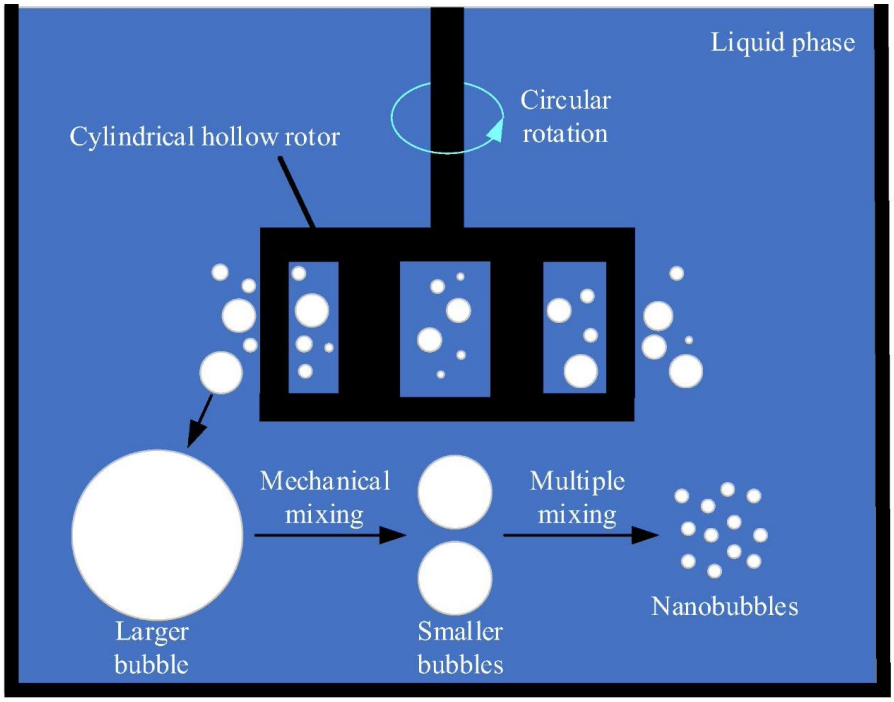
The mechanical stirring or mechanical shearing method generates strong turbulence and shear forces in a gas-liquid system using a high-speed stirrer, rotor-stator homogenizer, or high-shear mixer. Through repeated cycles of cavitation and shearing, the continual mixing retains gas in the liquid and splits bigger bubbles into smaller ones [27].

Although the size distribution may be wider and further stabilizing is frequently required, this technique is straightforward, affordable, and effective for creating bulk nanobubbles [28].

This technique involves adding gas to an aqueous solution that contains a polymer or surfactant while rapidly stirring the mixture. The liquid phase and the confined gas volume are completely combined, and mechanical cavitation encourages the creation of tiny bubbles. In the manufacture of nanobubbles and nanocarriers, mechanical agitation is also commonly employed as a post-treatment or auxiliary step [25].

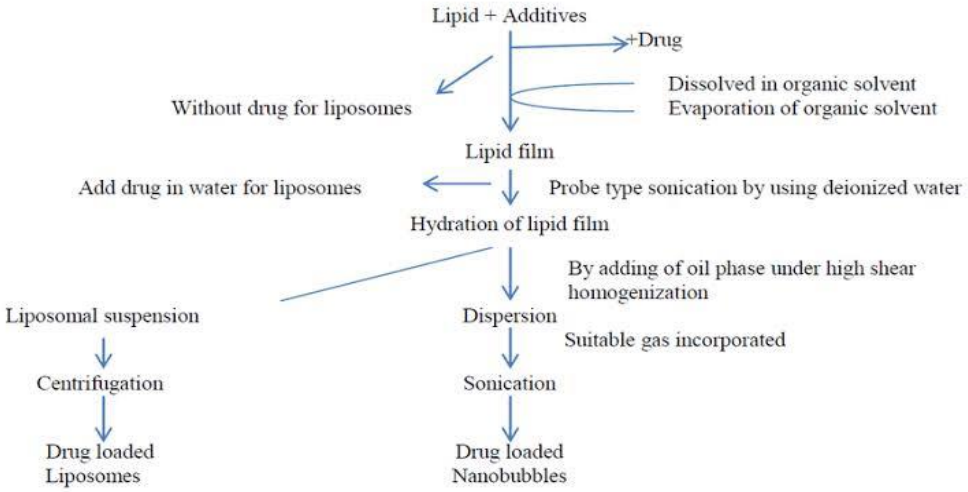
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2.Agitation:

By shaking the liquid solution at several thousand revolutions per minute in a shaker, MNBs—particularly those with lipid shells—can be created. This will result in bubbles that vary in size randomly. In order to encapsulate a specific gas in an MNB, the container is filled with the chosen coating material in the liquid phase, the gas is perfused from the top, and the container is then mechanically stirred until the required gas is encapsulated by the shell material. One promising approach for the industrial production of MNBs is mechanical agitation [29,10].



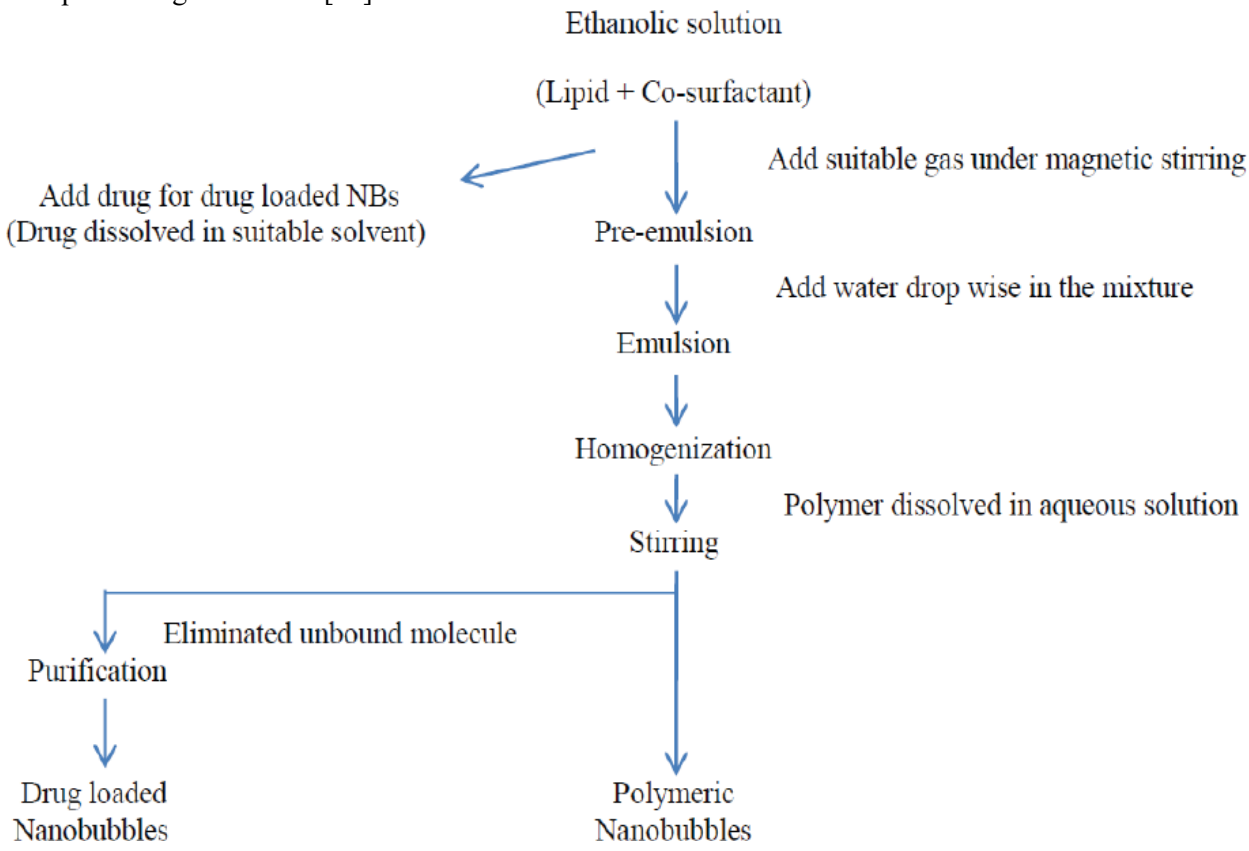
3.Emulsification:

When nanobubbles have a lipid, polymer, or other solid-like shell, the emulsification process is very helpful. The shell-forming polymer or lipid is typically dispersed using high-speed stirring in an organic solvent–water combination in a high-shear emulsification process. The resulting emulsion is treated to

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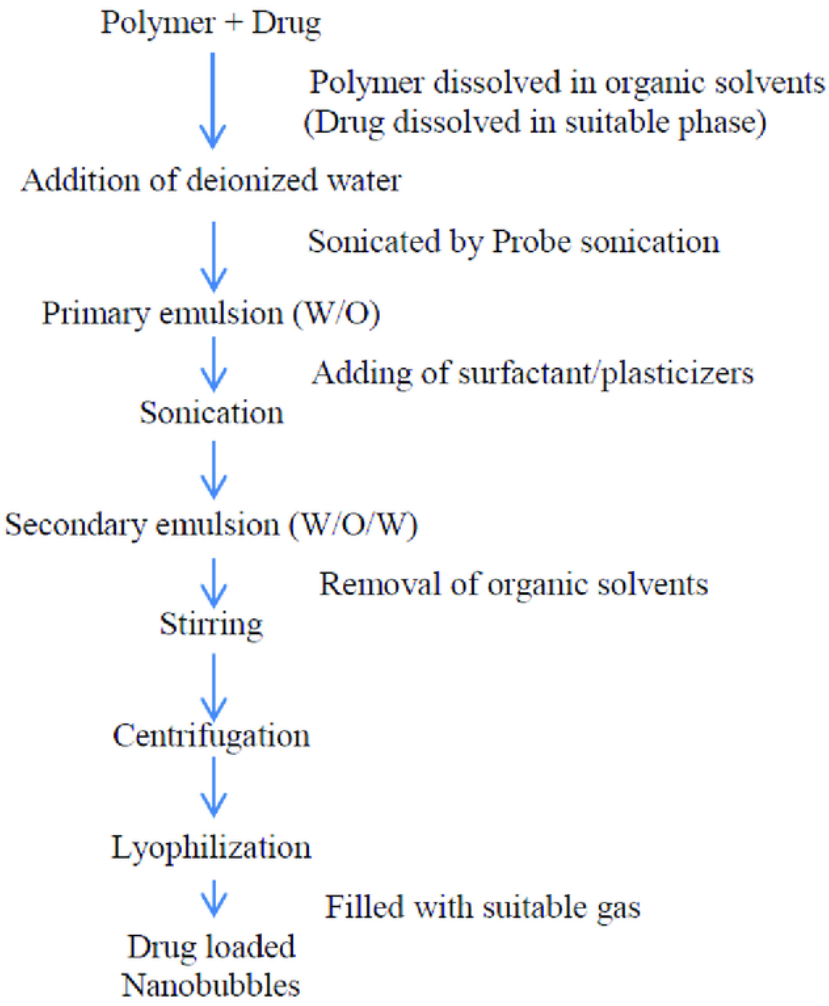
create nanoscale bubbles or bubble precursors after the addition of a second immiscible liquid phase as a stabilizer. High-pressure homogenization, ultrasonic emulsification, microfluidization, and rotor-stator stirring are examples of high-energy emulsification techniques [30].

These methods provide powerful mechanical energy that splits the distributed phase into tiny bubbles or droplets. Better control over shell formation and encapsulation can be achieved through emulsification, but it may necessitate the use of organic solvents, surfactants, purification procedures, and strict control over processing conditions [31].



4.Sonication:

Sonication, often known as ultrasonication, is one of the nanobubble preparation techniques that is most frequently described. Acoustic cavitation, or the creation, expansion, and sudden collapse of microbubbles in a liquid, is caused by high-intensity ultrasonic waves. Strong local shear, shock waves, and microjets are produced by these cavitation events, dispersing gas into the liquid and reducing bubble size to the nanoscale. Usually, either gas flow or headspace replacement is used to add gas to a suspension that contains a shell-forming substance, such as lipid, protein, surfactant, or polymer. The gas is then emulsified into a bubble suspension using high-power sonication, and the freshly created nanobubbles are stabilized by the shell material's adsorption at the gas–liquid interface. While sonication is useful for creating comparatively homogeneous nanobubbles, prolonged exposure to ultrasound might result in heating, shell deterioration, or gas loss [32].



5.Laser Ablation:

An excimer laser with the proper wavelength can target aluminum oxide particles in water that have oxidized into nanoparticles. Air bubbles are also created throughout the process at the solid-liquid contact. When a cluster of gold nanoparticles is subjected to a laser pulse with enough intensity, its temperature quickly increases, evaporating the surrounding water and creating plasmonic NB [33].

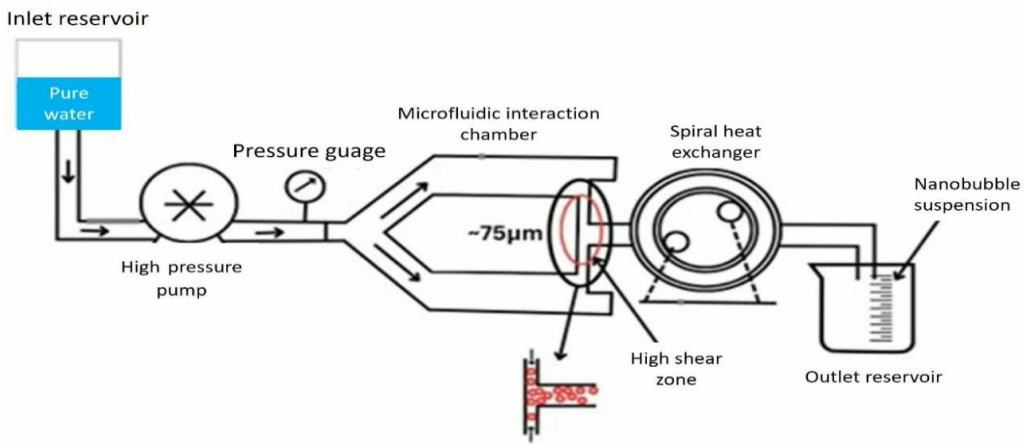
B.Microfluidic/Nozzle based methods

1.Microfluidic Method:

DPPC (1,2-dipalmitoyl-sn-glycero-3 phosphocholine) and DPSE-PEG2000 (1,2-distearoyl-sn-glycero-3 phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]) were mixed in a 95:5 molar ratio with a total lipid content of 2 mg/mL (Avanti Polar Lipids, AL, USA). Lipids were dissolved in a 1:1 solution of methanol and chloroform, dried under nitrogen to eliminate the solvent, and then resuspended in a phosphate-buffered saline (PBS) solution that contained 1% (v/v) glycerol. According to Peyman et al. [34], the lipid solution was then mixed with C4F10 (PFB) gas in a multiplexed microspray microfluidic system to create bubbles[34].

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2.Inkjet Method:

An ink-jet technique, which involves forcing a polymer solution through a piezo-driven ink-jet nozzle of a desired size depending on the application, has been used to create microbubbles. The bubbles that are created in the solution are extracted from the nozzle by the piezoelectric crystals. A similar technique that uses a high-pressure flow through the nozzle to create ultrafine oxygen nanobubbles from pure water and an oxygen supply has also been used [35].

C.Cavitation based methods:

NBs are formed by producing cavities inside the system that causes pressure reduction in that area below its critical value. Using this principle, numerous methods such as hydrodynamic, acoustic, particle, and optical cavitations are employed to generate NBs in solution[36].

1.Hydrodynamic Methods:

The hydrodynamic approach uses hydrodynamic compression of gas flow to dissolve gaseous molecules in liquid molecules. NBs have been produced at low pressure by releasing this mixture from the nano-sized nozzles. To generate a benign environment within the system, such a bubble persists for a week [37].

2.Acoustic Methods:

By using a high-speed propeller rotation or a negative pressure half-cycle produced by high-intensity sound waves, the acoustic cavitation method of BNB preparation aims to create localized negative pressure in the liquid, which eventually results in the formation of micro- and nano-scale bubbles close to tiny gas nuclei. BNB preparation experiments using the acoustic cavitation method were carried out using the experimental setup. The objective of BNB preparation using the acoustic cavitation method is to create local negative pressure in the liquid by means of a high-speed propeller rotation or negative pressure half-cycle generated via high-intensity sound waves, which ultimately leads to the formation of micro- and nano-scale bubbles near tiny gas nuclei.

According to the study, BNBs were present in pure water but not in organic solvents, and they vanished at a particular organic solvent to water ratio. This result is explained by the electrostatic charge on the BNBs' surface, which stabilizes them by adsorbing hydroxyl ions created by water's auto-ionization. Nevertheless, auto-ionization does not occur in pure organic solvents [38].

D.Membrane based method:

1.Nanoscale pore membrane method:

This technique uses pore-forming proteins, such as hemolysin alpha, aerolysin, and MspA porin, to create nanoscale pores that form a membrane over the skin's surface, allowing charged biological molecules to

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pass through and detect possible changes. It also aids in the biosensing of RNA, amino acids, and DNA sequencing [39].

Application of Nanobubbles:

1. Imaging for biomedical diagnosis

Because their gas core increases echogenicity and reflects ultrasonic waves, nanobubbles function as ultrasonic contrast agents. They can be used for monitoring the buildup of nanoparticles in diseased tissues, vascular imaging, tumor detection, and perfusion evaluation. Additionally, targeted NBs may bind to endothelial markers specific to a disease, allowing molecular ultrasound imaging of cancer, thrombosis, and inflammation [40].

2. Tumor detection

By accumulating in tumors through leaky tumor vasculature, NBs improve contrast and make tumors easier to see. Multiple scattering interface tumor-targeting NBs have demonstrated robust tumor binding, consistent size, high stability, and superior contrast-enhanced ultrasound imaging [41].

3. Molecular ultrasonography

By binding disease-specific indicators, aptamers, peptides, or antibodies can functionalize targeted NBs. This makes it possible to use molecular ultrasonography to image angiogenesis, inflammation, tumor vasculature, and other pathological indicators.

For instance, compared to non-targeted NBs or SonoVue, anti-VEGFR2 antibody-conjugated NBs demonstrated a greater and longer ultrasonic increase in the vasculature of hepatic tumors [42]. 4. Medicinal medication administration

Chemotherapeutic medicines, anti-inflammatory medications, proteins, and other therapeutic compounds can be transported via NBs. They undergo cavitation under ultrasound, releasing the payload locally and increasing medication absorption through sonoporation while lowering systemic toxicity.

The most sophisticated use of this technology is in cancer treatment, where NBs directly administer anticancer medications such as paclitaxel, doxorubicin, and docetaxel to tumor tissue [43].

5. Chemotherapy

Targeted delivery of anticancer medications to tumors is being studied using nanobubbles, with ultrasound-triggered release enhancing local drug concentration. Paclitaxel-loaded Fe3O4 NBs with pH/ultrasound-responsive release and docetaxel with immune-adjuvant NBs for chemoimmunotherapy are examples of modern systems [44].

6. Therapy with genes

Genes, siRNA, microRNA, mRNA, plasmid DNA, and oligonucleotides can be introduced into cells using NB-assisted ultrasound. Cavitation facilitates nonviral intracellular delivery by fostering endosomal escape and producing transient membrane pores.

Microfluidic NBs for ultrasound-guided gene delivery and polysaccharide-coated NBs for systemic microRNA delivery in triple-negative breast cancer are examples of modern systems [45].

7.Theranostics

Theranostic NBs combine diagnosis and therapy in one system. They provide ultrasound imaging contrast while simultaneously carrying drugs, genes, sonosensitizers, oxygen, or other therapeutic agents.

This enables image-guided treatment: NB accumulation can be visualized, drugs can be released by focused ultrasound, and therapeutic response can be monitored[46].

8.Hypoxia oxygen supply

By supplying oxygen to hypoxic tumors and tissues, oxygen-loaded NBs enhance the efficacy of sonodynamic, photodynamic, and radiation treatments.

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Oxygen NBs have also been investigated for use in tissue healing and mitochondrial dysfunction associated with hypoxia.

9.Photodynamic and sonodynamic treatments

NBs can administer photosensitizers or sonosensitizers for cancer treatment that is activated by light or ultrasound. These substances produce reactive oxygen species when activated, which kills tumor cells.

Modern NB systems create synergistic sonodynamic chemotherapy and immune activation by combining sonosensitizers like chlorin e6 (Ce6) with immunomodulators and chemotherapeutics [47].

10.Brain transport via the blood–brain barrier

Antibodies, chemotherapeutics, genes, and other big molecules can be delivered into the brain by temporarily opening the blood–brain barrier using NBs and focused ultrasound.

According to recent research, NB-actuated focused ultrasound can break the blood-brain barrier more precisely than traditional microbubbles, suggesting possible use in neurodegenerative illnesses, brain tumors, depression, and stroke.

11.Tissue restoration and wound healing

Oxygen NBs decrease inflammation, increase angiogenesis and tissue regeneration, and enhance oxygenation in hypoxic wounds. Hydrogels and wound dressing systems for diabetic and chronic wounds are being investigated.

In order to promote wound healing through prolonged oxygen release and regeneration signaling, a recent method paired oxygen NBs with exosomes in a hydrogel [48].

12.Treatment for fibrotic, cardiovascular, and renal diseases

Vasoactive gasses and medications, including nitric oxide, can be administered by NBs under ultrasound control. Thrombosis, inflammation, renal fibrosis, and vascular disorders may all benefit from this.

Recently, nitric-oxide-loaded NBs that combine localized NO release and ultrasound imaging have been created for ultrasound-activated therapy of renal fibrosis [49].

Recent advances to include:

1. Efficacy, responsiveness, and structure engineering

Cavitation, imaging signal, tissue penetration, drug release, and bubble size, shell composition, gas core, ligand density, and acoustic parameters all work together to determine NB performance, which is now treated as a design problem in recent reviews. You can use this "structure–response–efficacy" framework to organize your review.

2.Sonoporation and ultrasound-induced drug release

Under ultrasonic conditions, NBs function as cavitation nuclei, momentarily permeabilizing cell and vascular membranes. This reduces off-target toxicity, increases intratumoral drug accumulation, and permits spatially regulated release [50].

3.Cancer nanobubbles that are theranostic

Integrating drug delivery, therapy, and ultrasound imaging on a single platform is a significant trend. NBs can transport nucleic acids, oxygen, sonosensitizers, chemotherapeutics, or ultrasonic contrast agents.

4.Immune activation and chemotherapy

Chemotherapy is combined with immune adjuvants or sonodynamic therapy in new NB systems. For instance, following ultrasound-induced destruction, docetaxel with R837-loaded NBs increased antitumor immunity, immunogenic cell death, tumor cell damage, and dendritic cell maturation.

In a 4T1 breast cancer model, a distinct Ce6/paclitaxel NB system targeted by cyclic-RGD peptides demonstrated enhanced CD8+ T-cell infiltration, activation of the cGAS–STING pathway, and tumor growth reduction [51].

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5.Delivery of genes and nucleic acids

The usage of NBs for gene delivery, siRNA, and microRNA is growing. Lipid NBs coated with polysaccharides have been developed as systemic nucleic acid carriers for triple-negative breast cancer as well as ultrasound contrast agents.

Additionally, microfluidic NBs demonstrated strong monodispersity, enhanced brain-tissue distribution, ultrasound-guided gene delivery to irradiated areas, and enhanced ultrasound imaging.

6.Delivery of the brain across the blood-brain divide

NBs and focused ultrasound (FUS) can cause a localized, reversible opening of the blood-brain barrier. NBs for neuropsychiatric and neuro-oncology applications were supported by a 2025 study that found better brain antibody delivery precision compared to traditional microbubbles [52].

7.Multifunctional and stimuli-responsive formulations

In order to take advantage of the acidic tumor microenvironment and offer external spatial control, recent NBs are being developed to react to multiple stimuli, most frequently pH + ultrasound. Uniform particle size, high loading, and pH/ultrasound-responsive release were observed in a Fe3O4 NB system loaded with paclitaxel.

8.Hypoxia and oxygen regulation

Nowadays, oxygen-loaded nanobubbles are being employed to improve non-drug therapy and combat malignant hypoxia. Oxygen NBs used ultrasound-triggered oxygen release with anti-vascular treatment to reduce tumor perfusion, increase necrosis, and reduced hypoxia in pancreatic cancer.

By stabilizing ICG and upsetting the tumor redox equilibrium, oxygen NBs have also enhanced indocyanine green/Fe(III)-mediated treatment, causing ferroptosis in mice tumor models [53].

9.Immunotherapy using sonodynamics

Combining NBs with immune modulation and sonodynamic treatment (SDT) is a significant advancement. Necroptosis-inducing oxygen NBs were created for ultrasound-targeted nanobubble destruction (UTND), which combines immunogenic cell death, SDT, and oxygen delivery in breast cancer. Shikonin, an immunogenic cell-death inducer, was co-delivered with miR-497-5p on another liver cancer platform to boost antitumor immune responses.

10.Gene delivery systems

NBs are transitioning to ultrasound-triggered, nonviral gene delivery. Modern lipid-shelled NB platforms circumvent certain viral-vector safety and immunogenicity issues by using ultrasound to encourage intracellular uptake and release of nucleic acid cargo.

Progress in nucleic acid-loaded NBs, such as bubble liposomes and ultrasound-responsive gas-containing lipid nanoparticles for siRNA and gene delivery, is also summarized in a 2026 review [54].

11.Drug and gene delivery via ultrasound

As noninvasive, tailored, nonviral platforms for drug/gene administration, hypoxia modulation, drug-resistance reversal, immunological activation, and BBB penetration, recent studies highlight ultrasound-mediated targeted micro/nanobubbles.

12.Beyond cancer: cardiovascular treatment and fibrosis

Beyond cancer, NBs are becoming more prevalent. Phospholipid NBs loaded with nitric oxide were designed for simultaneous real-time ultrasound imaging and ultrasound-activated, spatiotemporally regulated nitric oxide administration in renal fibrosis.

13.Advances in mechanics and translation

The effects of NB design on cell internalization, acoustic behavior, and mechanical stress generation—important factors that determine safe and efficient delivery—are being described by more recent research.

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Gas-filled NBs with phospholipid shells are being tested as medication delivery vehicles and as ultrasound contrast agents [55].

Current challenges:

1.Instability, both colloidal and physical

During storage, gas diffusion, coalescence, Ostwald ripening, and shell degradation can alter the size, concentration, zeta potential, and acoustic sensitivity of nanobubbles. Therapeutic efficacy, shelf life, and repeatability are all impacted by this instability.

2.Low capacity for medication loading

Drug encapsulation space is restricted by the gas core. While nucleic acids often need surface complexation, hydrophobic medicines can be loaded into the shell; either method can lower loading efficiency or destabilize the nanobubble [56].

3.Inadequate repeatability and manufacturing expansion

Broad particle-size distributions and varying NB concentrations are frequently produced by bulk preparation techniques. Although high-throughput, hygienic, GMP-compliant manufacturing is still challenging, microfluidic techniques enhance monodispersity and process control.

4.Inadequate targeting and tumor accumulation

The increased permeability and retention (EPR) effect is frequently used in tumor delivery, however EPR varies between patients and tumor types. Rapid immune clearance, uneven vascularization, poor penetration through tumor stroma, and protein-corona formation can all restrict active targeting.

5. Control of ultrasound-triggered release is challenging

NB concentration, tissue depth, ultrasonic frequency, acoustic pressure, pulse length, duty cycle, and cavitation all affect drug release. While too much energy can result in vascular injury, bleeding, inflammation, or off-target delivery, insufficient energy might not cause release. Acoustic dosage regimens are still not standardized [57].

6. Issues with biodistribution, safety, and immunogenicity

Complement activation, inflammatory responses, endothelial damage brought on by cavitation, embolic effects, and buildup of nonbiodegradable shell or polymer materials are some possible hazards. Comprehensive long-term toxicity, biodistribution, and degradation data are lacking in many novel NB formulations

7.Dangers of blood–brain barrier delivery

For brain tumors and neurological disorders, careful control of the opened area, prevention of edema or hemorrhage, and safe repeated therapy remain key problems, even though targeted ultrasound with NBs can temporarily access the blood–brain barrier.

8.Obstacles to clinical and regulatory translation

NB systems are still mostly in the preclinical phase. Sterile injectable formulations, verified stability studies, scalable GMP production, repeatable ultrasonography dosimetry, and regulatory procedures for combination drug–device products are all necessary for translation.

9.Instability in the environment

NB stability is extremely sensitive to pH and temperature, according to recent experimental research. At 100°C, the concentration of oxyhydrogen NBs decreased and their particle size increased; freezing also resulted in moderate instability. While particle disintegration was increased at acidic pH 4 and alkaline pH 9, hydrogen NBs were most stable at neutral pH (6–7).

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Because NBs may come into contact with various pH values during storage, blood circulation, tumor microenvironments, endosomes, or the gastrointestinal tract, this is crucial for formulation development [58].

10.Cavitation-related risk to safety

When NB collapses under ultrasound, the nearby temperature and pressure can rise dramatically. A high-energy "water nanohammer" with a local temperature of about 1000 K and a pressure of about 25 GPa was created via NB collapse, according to a 2025 molecular-dynamics study.

While this action can improve medication release, if ultrasound parameters are not carefully regulated, it can also cause endothelial damage, vascular rupture, inflammation, hemolysis, and off-target tissue injury.

11.Response from patient to patient and biological variability

Patients vary significantly in terms of tumor vascularization, interstitial pressure, stromal density, immunological state, and ultrasonography penetration. As a result, an NB formulation that works well in one animal model might not work as well in another or in people.

12.The absence of uniform acoustic dosimetry

For ultrasonic frequency, mechanical index, acoustic pressure, pulse repetition frequency, exposure time, and NB concentration, there is no generally recognized standard. This makes it challenging to replicate cavitation effects, compare investigations, and convert preclinical acoustic environments into safe clinical procedures [59].

13.Safety and sustainability throughout time

For many sophisticated systems, the long-term biodistribution, degradation, clearance, immunogenicity, reproductive toxicity, and environmental impact of NB materials are not thoroughly defined. Another crucial translational necessity is the development of scalable and sustainable nanomanufacturing.

Future Perspective:

1.Computational formulation design with AI assistance

It is anticipated that future NB development would optimize bubble size, shell composition, gas type, drug loading, and ultrasound parameters using computer modeling, digital twins, and artificial intelligence. AI-assisted parameter tuning may help strike a balance between mechanical and thermal safety and cavitation for medication release.

2.Customized ultrasound-assisted treatment

Future methods may employ real-time ultrasound imaging to customize NB dosage, ultrasound intensity, and therapy timing because tumor perfusion, stromal density, and acoustic penetration differ among patients. This could make image-guided "see-treat" procedures possible, in which contrast, accumulation confirmation, and release are all provided by the same NB platform.

3.Multifunctional, intelligent nanobubbles

Drug or gene cargo, targeting ligands, oxygen or nitric oxide delivery, imaging contrast, and reaction to ultrasound, pH, enzymes, or redox conditions are all expected to be combined into next-generation NBs. These systems have the potential to offer concurrent diagnosis, therapy, and treatment monitoring [60].

4.Cancer treatment in combination

Combining NBs with immunotherapy, chemotherapy, radiation, sonodynamic therapy, and gene therapy is a significant potential path. Ultrasound-triggered NBs may increase immune-cell infiltration into tumors, correct hypoxia, encourage immunogenic cell death, and improve local medication release.

6.Neurological and brain applications

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For brain cancers, Alzheimer's illness, Parkinson's disease, depression, and stroke, focused ultrasound with NBs may make blood-brain barrier opening safer, more accurate, and reproducible. Future studies will require established safety endpoints, patient-specific acoustic design, and real-time monitoring [61].

7.Uses outside of cancer

Wound healing, fibrosis, cardiovascular disease, inflammation, obesity, and nutraceutical administration are among the areas where NBs are anticipated to grow. For instance, nitric-oxide NBs may be helpful in fibrotic and vascular conditions, while oxygen NBs may promote tissue repair in hypoxic wounds.

8. Eco-friendly and scalable manufacturing

Future translation will require lyophilized or ready-to-use formulations, sterile GMP production, microfluidic or continuous-flow manufacturing, and reliable quality-control techniques for size, gas content, concentration, sterility, and acoustic performance [62].

CONCLUSION

In the field of new medication delivery systems, nanobubbles have emerged as a promising and inventive platform. They are appropriate for the targeted and regulated delivery of therapeutic drugs due to their special structure, nanoscale size, gas-filled core, stabilizing shell, and ultrasound-responsive qualities. The development of nanobubbles with desired properties and enhanced performance is made possible by a variety of preparation processes, including mechanical, microfluidic, cavitation, and membrane-based procedures.

Their potential in contemporary pharmaceutical and biological research is highlighted by their applications in biomedical imaging, cancer treatment, gene transfer, oxygen transport, wound healing, and blood–brain barrier penetration.

Theranostic nanobubbles are even more significant in customized therapy when combined with diagnostic imaging and therapeutic delivery. Furthermore, new advancements in gene delivery, multifunctional formulations, and ultrasound-triggered release have increased their therapeutic potential. Physical stability, drug-loading capacity, reproducibility, large-scale production, long-term safety, and clinical translation are issues that must be resolved. Future studies should concentrate on creating stable, multifunctional, biocompatible, biodegradable nanobubbles with enhanced targeting effectiveness and regulated drug release. In summary, nanobubbles have the potential to significantly alter traditional drug delivery methods and may eventually lead to safer, more efficient, and patient-specific therapeutic techniques.

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