Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.43.006969

A Systematic Review on Nanobubbles in Drug Delivery: Mechanism and Applications

Ashis Sutradhar Nitai, Rasel Mahmud, Ahsan Habib and Md. Ibrahim H Mondal*

Polymer and Textile Research Lab, Department of Applied Chemistry and Chemical Engineering, Rajshahi University, Bangladesh

***Corresponding author:** Md. Ibrahim H Mondal, Polymer and Textile Research Lab, Department of Applied Chemistry and Chemical Engineering, Rajshahi University, Rajshahi-6205, Bangladesh

ARTICLE INFO

Received: May 02, 2022

Published: May 17, 2022

Citation: Ashis Sutradhar Nitai, Rasel Mahmud, Ahsan Habib, Md. Ibrahim H Mondal. A Systematic Review on Nanobubbles in Drug Delivery: Mechanism and Applications. Biomed J Sci & Tech Res 43(5)-2022. BJSTR. MS.ID.006969.

ABSTRACT

The prosperity of nanoparticles delivers the tremendous potential for the formulation and advanced development of nanobubbles (NBs), such as an area of great interest in therapeutic ultrasound, diagnosis, detection and drug delivery system (DDs). Novel biocompatibility and nontoxicity are the vital reasons for use as reliable nanocarrier in DDs. This review compiles and gathers information for introducing NBs in a systematic way, where the importance, demand, mechanism and applications of NBs in DD are disclosed. After all, this review provides a small but informative overview including future approaches on NBs in DD purposes.

Keywords: Nanobubbles; Drug Delivery System; Target Triggering Mechanism

Introduction

In medical treatment, acquire an intended therapeutic effect in a specific target is the principal part of the DDs. Basically, DDs means utilized the engineered technologies to develop the directions, formulations, manufacturing techniques and transportation of pharmaceutical compounds in desired body site [1]. However, day by day these technologies are developed with newer approaches. Among these newer approaches, nanoscience and nanocarriers provide some better advantages than their basic or ancient micro technologies [2]. Nanocarrier in drugs represent some nanomaterials being used in safe transportation purpose of drug substances [3]. High stability and water solubility, excellent carrier capacity, being easily incorporation of both hydrophobic and hydrophilic substances, the feasibility of variable routes of administration, prolong the uptake rate of target cells or tissues and reduce enzyme degradation etc. properties and advantages of nanocarriers are the major reasons to promote and get special attention in DD technologies [4]. Several nanocarriers are developed include micelles, polymers and its derivatives, carbon-based materials, liposomes, NBs etc. are commonly used now-a-days in DD [5]. Among them, the NBs as nanocarriers has gained considerable attention during the last few decades because of their smaller size, higher surface area, relatively longer half-life, biodegradability, excellent cellular attachment, and echogenic properties especially include passive targeting and ease of transport of drug molecules [6]. NBs are nanometer-size bubbles (10–200 nm) and, structurally combined of one shell and core compositions (Figure 1) [7]. Where, shells consist of polymers, phospholipids or protein with unilaminar composition and core formed by a less soluble gas. However, because of their unique composition of NBs can be utilized for gas delivery applications [8]. More recently, they have also been studied in relation to drug and gene delivery also [9]. This study aims to summarize recent development knowledge on NBs application and its mechanism approach.

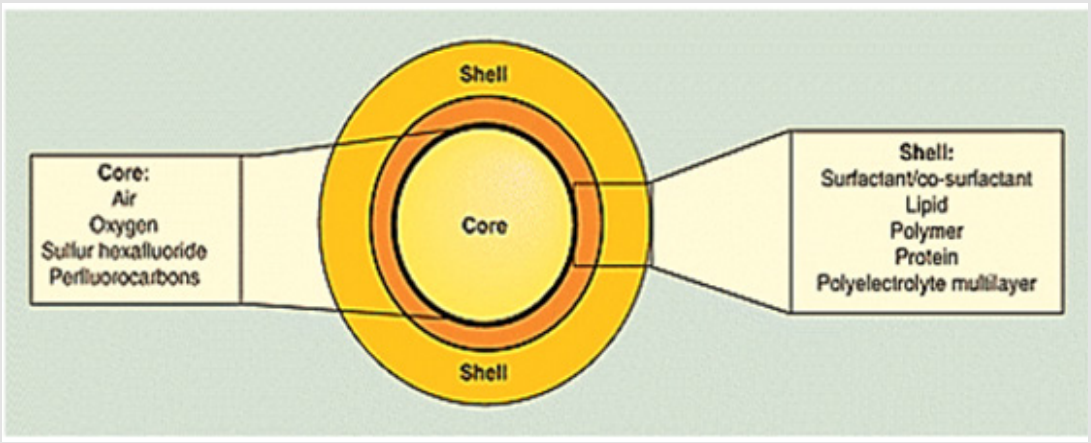

Figure 1: Construction of NBs [7].

Drug Delivery Systems (DDs)

Basically, two types of targeting drug delivery systems are used such as:

(I) Active targeted which is called smart drug delivery and based on ligands affiliation to receptors)

(II) Passive targeted that is based on the retention effect (EPR) and improved permeability [10].

Active System: In this drug delivery system, a fixed amount of a diagnostic or therapeutic drug or both is delivered to a targeted diseased area of the organ in the body. In traditional chemotherapy, it is impossible to distribute the drug in a specific area of the organ for some drawbacks. Modified Drug-loaded NBs by the addition of ligands or special chemical or physical structures are used for determination by specific receptors/antigens on target cells and distributed the drug in whole cells of the body and decreased cytotoxicity and the side effects of the drugs on healthy organs and cells. Smart nanoparticles vehicles have been accepted to treat human cancers [10]. An active targeted drug which loaded into nanoparticles/NBs enhances the ability to make the nanoparticles more specific for the targeting site. Active targeted drug is accomplished in several ways. One way is to know the receptor's nature on the cell [11]. By using transferrin as the cell-specific ligand this form was found successful. The transferrin was attached to the nanoparticle which possesses transferrin-receptor treated endocytosis mechanisms on cell membrane which increases uptake to target tumor cells. Active targeted drug delivery can be achieved by using magneto liposomes, which acts as a contrast agent in MRI (magnetic resonance imaging) [11]. Thus, magnetic positioning could help to deliver a specific drug to a desired region of the body by grafting liposomes with the drug. Another active triggering mechanism depends on the redox potential. active targeting can be found through a peptide-based targeting system [12].

Passive System: In passive targeting, the drug's success is directly related to circulation time [13]. This is accomplished by covering the NBs with some sort of coating. One of them is polyethylene glycol (PEG) which is added to the surface of the NBs and performs as hydrophilic. This allows water molecules to bind to the oxygen molecules on PEG through hydrogen bonding. Due to this bond, a hydration film is formed around the nanoparticle to make the substance antiphagocytic. By these hydrophobic interactions, the drug-loaded nanoparticles are able to circulate for a long time [14]. To perform in this mechanism of passive targeting, nanoparticles within the size of 10 and 100 nanometers have been found to circulate for longer periods of time in a systematic way [15]. By proper utilization of both active and passive targeting, a drug-loaded NBs has a vast advantage over the conventional drug. It has the ability to circulate throughout the body for a longer period of time until it is successfully attached to its target area through the use of cell-specific ligands, pH-responsive materials, or magnetic positioning. Thus, the drug-loaded NBs affecting only diseased tissue, side effects will be reduced much more than conventional drugs [16]. So, point of view, NBs have achieved this property and gained attention in DDs. For example, a peptide-based (part of NBs shell) drug targeting system can also be achieved active targeting [12].

Demand for Nanobubbles in Advanced Drug Delivery Systems

NBs play a great role in alternative treatments and as thrombolytic agents. In the treatment of peripheral arterial occlusions and acute stroke, their action is accelerated by ultrasound. NBs are a non-harmful technique to reduce tumor cell growth, shorten recurrence, and reduce severe drug side effects in combination therapy [17]. In comparison to bulk systems, NBs show

less surface tension. All these parameters depend on the presence of the substrate and nanobubble size, which ultimately affect stability [18]. Microbubbles have been mainly used in contrast-enhanced ultrasound for imaging of systemic circulation of blood, but they have limited application in tissue penetration. They cannot be visualized at a resolution of 50–100 mm but can be modified by activatable imaging probes inserted at protease cleavage sites. NBs explore the compressible surface and are found useful for ultrasound imaging. Using a combination of nanoparticles and NBs, tumors are imaged and stabilized using block copolymers. This has been considered a successful procedure for medical diagnostics. The small size, surface charge, and presence of nanobodies provide a guide to developing a new type of ultrasound-targeted NBs [19,20].

Effects of Nanobubbles in Target Trigering Mechanism

During proper delivery of drug carriers to their specific targets without sound effects on good cells, two things follow by the carrier are urgently needed. One of them, an additional mechanism that has the potential capability to detect the target site and, another crucial requirement is a triggering mechanism of the carrier, which maintains limited drug release into the target [21]. After all, based on these requirements, targeted NBs as nanocarriers gained considerable attention in efficient DDs caused by their capability in achieving the maximum accumulation of cytotoxic agents in a specific pathology [7]. This approach modifying drug biodistribution and pharmacokinetics. And can also improve the effectiveness of treatment with limit side effects. Targeted delivery may be achieved passively or actively [21] broadly discussed in Section II. However, during tumor selectivity, NBs are help to surface modifications that enhance their signal in the selection and reduce nonspecific toxicity. Targeting NBs through surface modifications is also considered an interesting theranostic approach [7]. In the last decade, (Jiang, et al. [22]) developed a novel Herceptin targeted nanobubble system as a promising carrier for diagnosing and evaluating the treatment feedback of Her-2-positive breast cancer. Which, provide efficiently penetrated tumor tissue *in vivo* and proper binding with tumor cells *in vitro* without toxic effects *in vitro* and *in vivo* (Figure 2) [22].

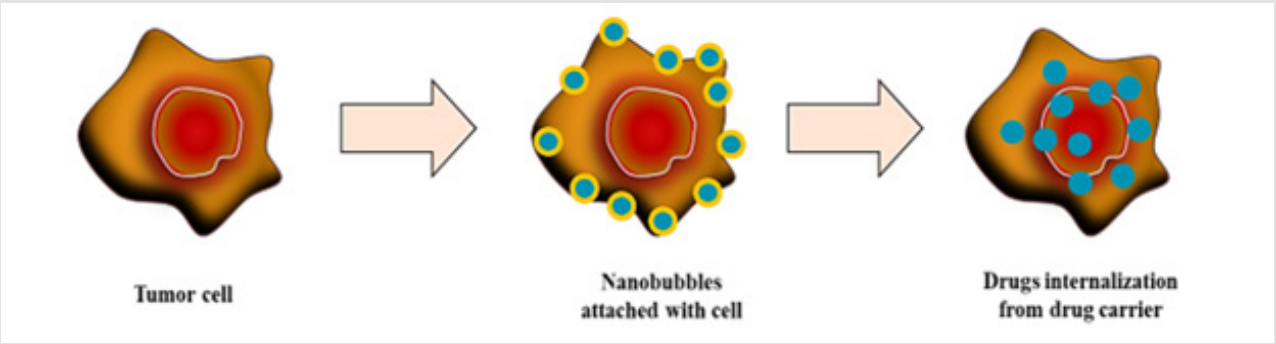

Figure 2: Penetration of drug via NBs in tumor cell.

On another side, a triggering mechanism is a vital method in DD, which controlling the span, rate, and compartment of drug release with proper adjustment. Generally, it is classified into two sections including an internal (enzymes, pH, etc.) and external trigger (temperature, laser, ultrasonic waves, alternating magnetic fields, etc.) [23]. In internal, the inherent pathological features of malignant tissues are utilized by enzyme triggering. During this process, increased specific enzyme activity in a tumor site, which soundly impacts the NBs (drug carriers) and its drug release property [24]. In addition, utilizes a class of carriers designed to be responsive to pH changes by used pH-triggering. In a pH-triggered release, nanocarriers are stable in light alkaline pH (pH 7.4) for normal tissue and stable in more (relatable) acidic pH (pH~6.5) for tumor tissue. So, they become destabilized and release their payloads, when crossing the limit [25]. In contrast, the rate of drug release can directly increase the result of external triggers and also stimulate internal triggers. For example, ultrasound (US) can enhance the rate of drug release from carriers directly (via its mechanical interactions) and indirectly (by warming the medium and due to its thermal interactions). In general, drug carriers for DD are usually designed to be operative at 37˚C. So, due to increasing the surface temperature of carriers with destabilizing and thereby facilitates in drug-releasing, external triggers (e.g., laser, US, microwaves, alternating magnetic field, etc.) can be used nowadays [26]. Both of them, NBs with external triggers especially include ultrasonic responsive mechanisms are broadly used nowadays in DDs. For example, recently Takahashi & Negishi [9] discussed broadly on NBs with ultrasound triggering for drug and gene delivery.

Application of Nanobubbles in Various Drug Delivery

NBs can be loaded with gases, small molecules and macromolecules, either hydrophilic or lipophilic ones. In the treatment of tumors, oxygen NBs are used by inducing heritable

changes in gene expression like global 5mC DNA methylation in hypoxic neoplasia cells [27]. NBs play an important role in alternative treatments and as thrombolytic agents [17]. In the treatment of acute stroke and peripheral arterial occlusions, their action is accelerated by ultrasound. Plasmonic NBs used in gene therapy directly act on cells for targeted gene transfection. Gene transfection methods employ heating, macro-bubbles, optical interruption, and shock wave origination [28]. NBs act as carriers alone and in combination with ultrasonic irradiation energy in the treatment of cancer. When exposed to a laser, NBs cause a short burst effect that adheres to cancer cells and release the drugs into the affected area. This is very useful in the treatment of multidrug-resistant breast cancer and drug-sensitive ovarian cancer. The treatment of Anaplastic thyroid cancer was studied using extracorporeal shock waves and NBs loaded with doxorubicin [29]. In bimodal therapy, novel sorafenib-loaded NBs are prepared to treat hepatocellular carcinoma under exposure to ultrasound [30]. NBs are useful in various neurodegenerative disorders. RNS60 containing charge-stabilized NBs in saline has been used to treat Parkinson's disease. The drug apomorphine in the form of perfluorocarbon NBs is delivered [31]. The applications of NBs in Drug Delivery is shown in (Figure 3).

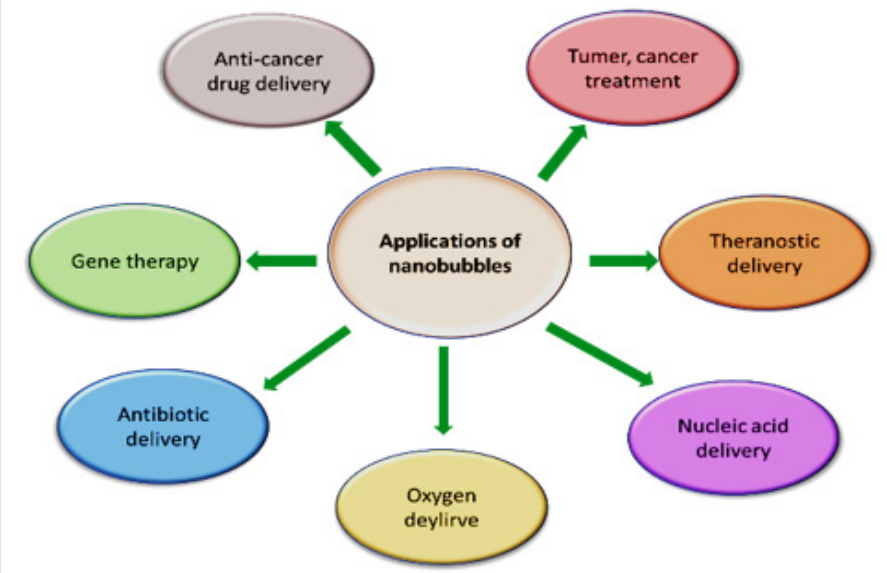

Figure 3: Application of NBs in DD.

Conclusion

NBs have many advantages; the most important is their target specificity, which means that they affect only tumor cells. The structural versatility of NBs allows efficient incorporation with a high payload of several active molecules, in other words, therapeutic gases, drugs, genes and biological molecules. This nanocarrier provides an innovative multifunctional DD platform that is suitable for a range of therapeutic applications and administration routes. However, in this review article, we summarize the overall thing systematically about NBs in DDs. Firstly, we introduce a small overview of DDs and correlates with NBs drug carriers. Then we are focused on the demands or advantages of NBs in DDs, where we comparatively discuss with other nanocarriers. In the last part, we summarize the mechanism of NBs (target identification and triggering process) and its recent and advanced applications in DD.

Future Prospects

Although many achievements have been attained, there are important challenges that need to be resolved to make more efficient nanobubbles as suitable nanocarriers for potential clinical application. Future studies are required to evaluate:

A. During the US responsive NBs in DD, fully avoided the damage of healthy tissue including DNA are the major challenges in recent development. So, in the future, required to solve this problem via using advanced and more effective technology in NBs.

B. Future studies should be focused on enhancing the therapeutic effect and the development of a nanobubble-based theranostic platform.

C. According to the recent challenges (i.e to detect pulmonary and pleural conditions and in the treatment of lung diseases such as coronavirus disease 2019 (COVID-19)), clinical systems need a reliable US responsive carrier to overcome these challenges. So, in the future studies are required to evaluate the impact of US responsive NBs in COVID-19 purpose.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.43.006969

Md. Ibrahim H Mondal. Biomed J Sci & Tech Res