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Review Article

Magnetosomes: A Tool for Targeted Drug Delivery in the Management of Cancer

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The last two decades of developments in drug formulations and novel drug delivery systems have been seen as the beginning of a new era leading to increased patient adherence and pharmacological response to the therapeutic regimen. One of the most difficult tasks is efficiency and target-specific drug delivery or the extent of delivery at any given site of interest. Many currently designed drug delivery systems are precisely tailored to maximize the delivery of a particular form of drug by reducing the degradation or loss of the drug. In case of cancer treatment, the targeted drug delivery is of utmost importance as the anticancer agents are not having the ability to differentiate between healthy and tumor cells resulting in adverse effects and/or systemic toxicity. The targeted drug delivery is thus designed to focus on preventing side effects and encouraging the accumulation of the drug at the targeted site; one such promising drug delivery system is magnetosome drug delivery, i.e., drug delivery using magnetosomes (biological magnetic nanoparticles). In this article, we have summarized the system for design, development, and mode of drug delivery using magnetosomes along with the recent developments made in this field to facilitate the diagnosis and treatment of cancer.

1. Introduction

The last two decades have witnessed the developments in formulations and novel drug delivery systems as the beginning of a new era. The horizons for understanding the principles of drug transport and tissue-wide targeting have been expanded. These efforts have led to increased patient adherence and pharmacological response to the therapeutic regimen. One of the most difficult tasks is efficiency and target-specific drug delivery or the extent of delivery at any given site of interest [1]. Most of the current drug delivery systems are precisely tailored to maximize the delivery of a particular form of drug by reducing degradation or loss of the drug, to minimize the side effects, elicit the bioavailability, and promote and encourage the accumulation of the pharmaceutical drug at the necessary biozone (site) or other challenging issues associated with therapeutic delivery targeting or physical stability of the drug [2].

However, it is difficult to create a delivery system with optimized therapeutic action and reduced toxic adverse events specifically *in vivo*. Nanotechnology is fulfilling the gap amongst physical, chemical, and biological science by employing nanocarriers in the development of novel drug delivery systems [3]. Various nanocarriers being used in the effective drug delivery of pharmaceuticals are listed in Figure 1.

Conventional or Immediate release pharmaceutical dosage forms are unable to regulate the rate at which drugs are delivered to the target site. As a result, drug distribution in non-target tissue and body fluids necessitates therapeutic doses that are often much greater than those needed in target cells, resulting in significant side effects during the

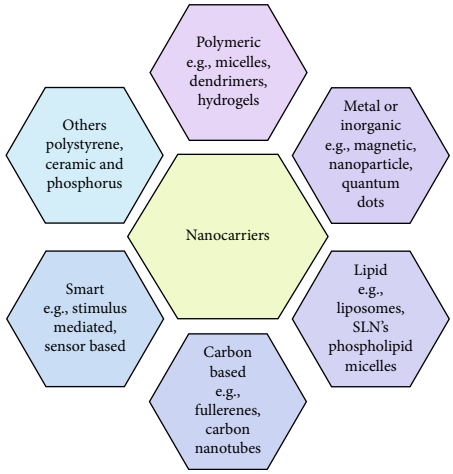

Figure 1: Types of nanocarriers.

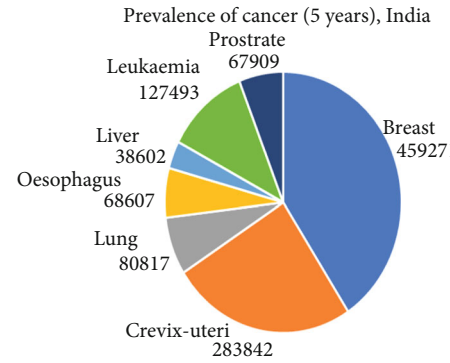

Figure 2: Prevalence of cancer cases in India (5 years) [6, 7].

treatment [4]. The targeted drug delivery is the key to provide effective delivery and better therapeutic response. Nanocarriers are the most promising way of targeted drug delivery and are the best choice to maintain the drug concentrations for a prolonged period of time either via lowering down the rate of degradation of the carrier or making it responsive to any given stimulus (e.g., pH or temperature, etc.), especially in cancer, cardiovascular diseases for treatment and to perform magnetic resonance imaging for the diagnosis of diseases [5].

One of the defining features of cancer is the rapid emergence of aberrant cells that grow beyond their normal bounds, allowing them to spread to the adjacent tissues and even to other organs at later stages (metastasis). World Health Organization has reported that cancer is the major leading cause of death globally, accounting for 10 million deaths in 2020. Most of the cases reported are of breast cancer (2.6 million), lung cancer (2.1 million), colon and rectum (1.93 million), prostrate (1.41 million), skin (1.21 million), and stomach (1.09 million). The total number of cases reported in India is 132413 with 851678 death cases in 2020 [6]. The prevalent types of cancer in India are represented in Figure 2:

Cancer develops when normal cells are transformed into tumor cells in a multistage process that usually evolves from a precancerous lesion to a malignant tumor as depicted in Figure 3. These changes are the result of a person's genetical factors interacting with external agents such as environmental pollutants; chemical agents, e.g., heavy metals and benzene; physical agents like ionizing and nonionizing radiations; and biological agents such as viruses [8].

One of the major factors to shift towards the targeted drug delivery in case of cancer is that most of the anticancer agents are not having the ability to differentiate between healthy and tumor cells resulting in adverse effects and systemic toxicity. Moreover, faster elimination and extensive distribution of conventional drugs to reach the targeted organs requires the dose in larger quantities, leading to undesirable toxicity and economic burden [10]. Nanocarriers are of much interest in cancer therapy with the aim of administration of drugs into the target tissue. Nanocarriers mainly follow the three pathways as illustrated in Figure 4, i.e., active, passive and stimuli-based targeting to show its biological action.

There are several novel carriers that have been developed and reported to be useful for the managed and targeted delivery of drugs [11]. Drug carriers such as polymers, magnetosomes, erythrocyte ghosts, microspheres, microparticles, nanoparticles, nanospheres, liposomes, and ethosomes are playing a significant role in the effective targeted delivery of pharmaceuticals. Magnetosomes have been observed to fulfill all necessities required for active drug delivery such as uniform size and narrow size distribution, morphological characteristics, and capability of magnetization [12].

This article will focus on magnetosomes as a novel carrier in the targeted drug delivery to treat cardiovascular and other diseases especially cancer.

2. Structure of Magnetosomes

Magnetosomes exist as intracellular structures, obtained using various strains of magnetotactic bacteria [13]. It is having the size in nanorange (35–120 nm), surrounded by crystals of magnetic iron arranged in an individual or cumulative chain arrangement which allows the cell alignment passively with the external magnetic field, referred to as the 'magnetotaxis' phenomenon. Magnetite (Fe_3O_4) and greigite (Fe_3S_4) are among the materials used successfully as magnetosome inorganic cores having varied morphological characteristics [14].

In case of the magnetotactic bacteria (MTB), the organic phase of the magnetosomes is formulated with the emergence of vesicles from the inner membrane. Magnetosomes organized as a single chain enhance the magnetic dipole moment of the microbial or bacterial (Magnetotactic bacteria) cells [15]. Depending on the bacterial strain, it is derived from, these magnetosomes may vary in their morphological characteristics. Cubooctahedral, bullet-shaped, elongated prismatic, and rectangular magnetosomes are some of the morphological dimensions reported till date [14, 15]. The typical structure of magnetosomes is illustrated in Figure 5. Research in the last decade has been emphasized two major compounds magnetite and maghemite due to their good biocompatibility and relatively high magnetic resistance

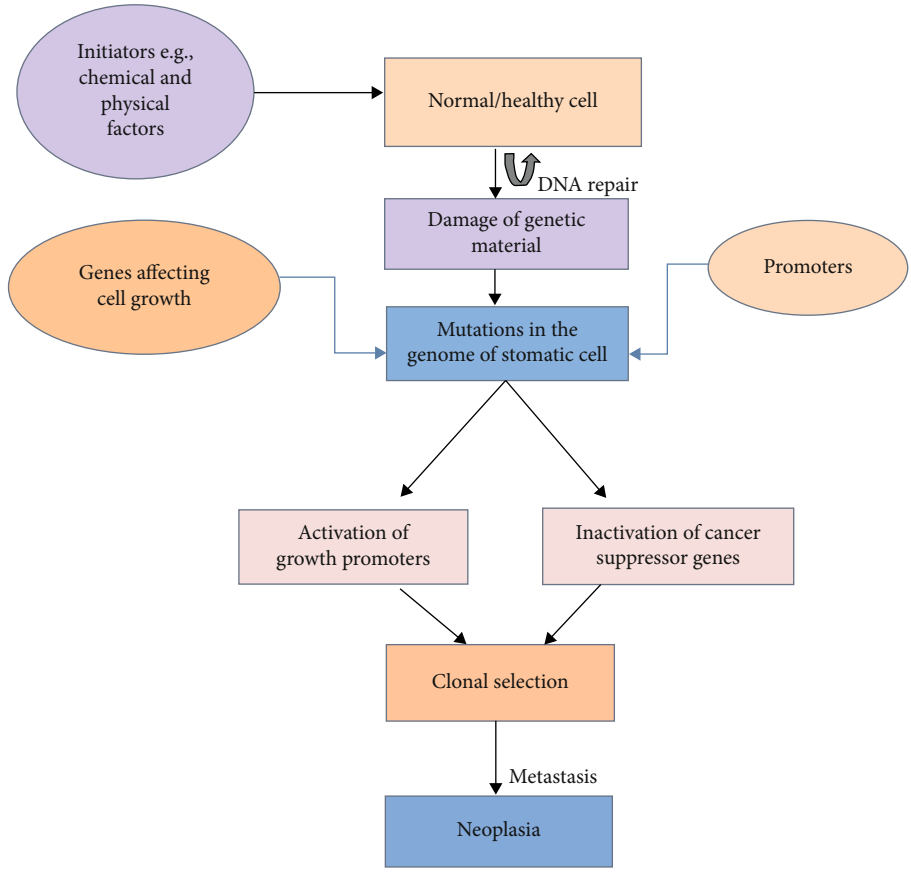

Figure 3: Pathogenesis of Cancer [9].

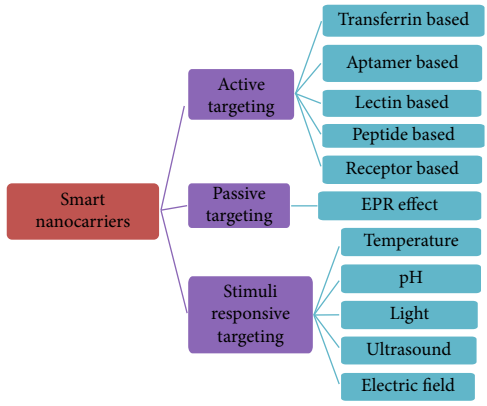

Figure 4: Classification of smart nanocarriers.

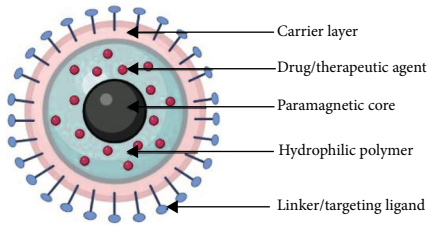

Figure 5: Structure of magnetosomes.

properties. Great efforts have been made in the recent time to formulate bacterial magnetic nanoparticles for addressing specific cancer diseases like magnetic hyperthermia, to achieve targeted delivery and detection of tumor cells.

3. Advantages of Magnetosomes

Magnetosomes reveal number of appealing properties; some of them as summarized below:

(I) Magnetosomes size and its distribution make it one of the most effective members in the nanoparticulate drug delivery. Its usual size ranges between 45 and 55 nm [16, 17], but it may be designed in the size range of 10-20 nm, if cultivated under optimum conditions of pH, minimal growth media, and concentration of dissolved oxygen (0.25-10 mbar) [18]

(II) Being single domain, magnetosomes exhibited thermal magnetic moment and larger values of coercivity as compared to the nanoparticles synthesized chemically that possess thermally unstable magnetic moment and act as superparamagnetic [19, 20]

(III) The magnetosomes are normally organized within the bacteria in chains. This structure is stable enough to be retained even after the release of

magnetosomes by disruption of the bacterial cell wall. Such type of arrangement prevents aggregation and results into high rate of internalization within human cell which are generally aspiring characteristics in pharmaceuticals and other biomedical applications [21, 22]

(IV) Magnetosomes exhibit a biological coating consisting of lipids and small quantities of proteins that result in the complete dispersion of magnetosomes in water, specifically the negatively charged magnetosomes. On the other hand, this biological coating is lacking in chemically synthesized nanoparticles and is thus devoid of stabilizing agents such as dextran or polyethylene glycol [23, 24]

4. Magnetotactic Bacteria and Its Biodiversity

Salvatore Bellini (1963) firstly observed the magnetite bahavior in freshwater and reported that the presence of magnet is responsible for the orientation of bacteria by observing their persistent north hemispherical swimming. After a decade, Blakemore (1975) invented numerous bacteria in the samples of marine sediment regions by observing them under the transmission electron microscope (TEM), where the bacteria were found to be swimming alongside the geomagnetic field lines. Blakemore referred to those bacteria as magnetotactic bacteria (MTB), and the magnetic cell organelles responsible for magnetically influenced movement as magnetosomes [25]. MTB are reported to be located extensively in aquatic environments like deep sea, areas with high concentration of salts such as deserts and extreme cold and hot spring regions [26–28].

It has been reported that being microaerophilic or anaerobic organisms, MTBs may occur at oxic-anoxic transition zones or interfaces in very high numbers (up to 10^4 cells/ml) [29, 30]. In the chemically stratified natural world, magnetotaxis, together with aerotaxis and chemotaxis, aids these species in locating a suitable microoxic state. The concentration of oxygen is reportedly a very significant ecological factor that not only affects the culturing of MTB by biomineralization process but also encourages the development of MTBs. Some MTBs are known to require molecular oxygen for magnetite formation. Iron is an important element in the formation of magnetosomes, although the relationship between the source of iron and the development of magnetosomes is not clearly known till date. MTBs entail higher amount of iron as compared to that of nonmagnetotactic bacteria, so as to perform biomineralization of magnetite to reach a level of about 4 percent of their cell dry weight [31].

Faivre et al. reported that ferric and ferrous ions are absorbed by most MTBs and may include siderophores (iron chelators of low molecular weight which helps in the binding and solubilization of ferric iron for absorption [32]. An extended component, i.e., source of nitrogen, is another important factor in the growth of MTBs and in the biomineralization process. Ammonium ions and nitrates are reported to be exclusive sources of nitrogen for the growth of magnetotactic bacterium like *Magnetospirillum gryphiswaldense*, a microaerophilic species of it. It has also been reported that the inclusion of nitrate greatly elevates the formation of magnetite at an appropriate 4 mM concentration [33]. Magnetite formation under the anaerobic conditions majorly depends on the concentration of nitrate, i.e., rise in nitrate concentration contributes to a decrease in the formation of magnetite magnetosome; implying that the synthesis of *Magnetospirillum Magneticum* is blocked with the conversion of NO_3 to N_2 by reduction. The components of the growth medium are also considered to be an important context of concern, as the growth of bacteria and formation of magnetosomes tend to be facilitated significantly in the presence of polypeptone and yeast extract [34].

Magnetotactic bacteria can be grown in mesophilic conditions, i.e., temperature should not be exceeded beyond 40°C [35]. Their morphological diversity includes various forms like cocci, bacilli, vibrio, ovoid, and spirilla, which can be visualized microscopically, specifically with electron microscopy. They have been classified as chemoorganoheterotrophs and chemolithoautotrophs in their mode of nutrition. MTB are classified in distinct classes as shown as tabulated in Table 1:

Magnetospirillum magntotactitum (MS-I) was the first laboratory strain isolated by Blakemore in 1975 [36], *M. gryphiswaldense* MSR-1 [37, 38], *M. magnetotacticum* AMB-I [39, 40], *M. magneticum* MG-T1 [41], and *Magnetovibrio* MV-1 [42] and MV-2 [43] and other closely related bacterial strain species were cultured and isolated subsequently. Prepared cultures of all the bacterial strains belonging to the class of alphaproteobacteria possess mesophilic conditions and formulate magnetite crystals intracellularly [10, 44–47].

5. Mechanism Involved in the Designing of Magnetosomes

The mechanism involved in the designing of magnetosomes is hypothecated as a complex process involving three discrete steps as shown in Figure 6. Step 1 includes the formation of magnetosome vesicles and step 2 involves iron uptake by the magnetosome cell extracellularly, and transport of iron to the vesicle via membrane channels followed by step 3, i.e., the process of biomineralization (formation of magnetite particle within the magnetosome cell vesicle).

6. Method of Preparation of Magnetosomes Using Magnetotactic Bacteria

Various strains of MTB have been studied till date which comprehensively involves *Magnetospirillium gryphiswalsense* (MSR-I), *Magnetospirillium magnetotactitum* (MS-I), *Magnetospirillum magneticum* (AMB-1), and *Magneto-ovoid* (MO-I). Generalized procedure to prepare magnetosomes is depicted in Figure 7. For the growth of magnetosomes, minimal growth media comprising of (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 1 M sodium nitrate, 0.74 M potassium dihydrogen phosphate, 0.1 M magnesium sulphate.7 hydrate, 10 mM ferric citrate monohydrate, soya bean peptone, yeast extract, and

Table 1: Magnetotactic bacteria strains and their characteristics.

Phylum	Class	Bacterial strain	Habitat/origin	Shape	Genomic structure	Reference
Proteobacteria	Alphaproteobacteria	*Magnetospirillum magnetotacticum* MS-1	Shallow fresh water and sediments/ woods hole, Massachusetts, USA	Spiral, polar flagella	36 contigs and 4,136 protein-coding genes	[48]
Proteobacteria	Alphaproteobacteria	*Magnetospirillum gryphiswaldense* strain MSR-1	Muddy areas/Ryck River, GreifswaldGermany	Spiral, polar flagella at each end	4,365,796 base pairs G + C content = 63.28%. Chromosome possess approximately 4261 coding sequences with average length of 954 base pairs [42]	[49]
Proteobacteria	Alphaproteobacteria	*Magnetospirillum magneticum* MG-T1	Stratified water columns/Tokyo, Japan	Spiral shaped	Circular chromosome with 4,967,148 base pairs and cryptic plasmid pMGT	[50]
Deltaproteobacteria	Deltaproteobacteria	*Desulfovibrio magneticus* strain RS-1	Oxic–anoxic interfacial region in medium lacking sulfate [42]	Irregular or bullet shaped crystals	Circular chromosome with 5,248,049 base pairs and also 2 circular plasmids, pDMC1 (58704 base pairs) and pDMC2 (8867 base pairs)[43]	[51]
Proteobacteria	Gammaproteobacteria	Strain SS-5	Freshwater pond sample/Qingyang, Gansu Province & Nanjing, China	Rod-shaped, forms octahedral magnetite crystals	Consists of 3,729,439 bp and G + C content = 61.6 %. It also comprises od 3223 coding DNA and 51 tRNAs.	[52, [52]
Proteobacteria	Alphaproteobacteria	*Magneto-ovoid bacterium* MO-1	Mediterranean Sea /Pionte Rouge Marseille,France,	Ovoid shape, seven filament flagella enveloped in a sheath	The chromosome of 5,043,095 base pairs G + C content = 55.2%. 44 TRNA genes covering all aminoacids	[53]
Nitrospirae	Nirospira	*Candidatus Magnetobacterium bremense*' (MHB-1)	Worldwide in aquatic environments	Bullet shaped magnetite crystals	Single circular chromosome possessing 4,869,843 bp and G + C content = 57.49 %.	[54]
Proteobacteria	Alphaproteobacteria	*Magnetospirillum magnetotacticum* AMB-1	Freshwater sludges and pond sediments/Koganei, Tokyo, Japan	Spiral, polar flagella at each end, cubohedral magnetite crystals	4,551,873 base pairs, G + C content = 65.63% and additional circular plasmid with 5,222-bp and G + C content = 60.67%	[55]

Table 1: Continued.

Phylum	Class	Bacterial strain	Habitat/origin	Shape	Genomic structure	Reference
Proteobacteria	Alphaproteobacteria	*Magnetovibrio blakemorei* MV-1	Marine water/ Boston, Massachusetts, USA	Vibrio shape, single polar flagella, truncated hexaoctahedrons	91 contigs 3638804 base pair and G + C content = 54.3% [41]	[56]

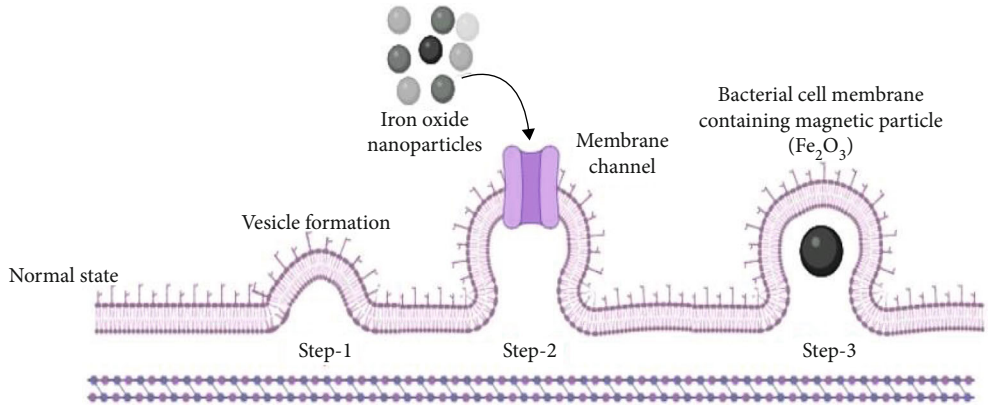

Figure 6: Mechanism involved in the designing of magnetosomes.

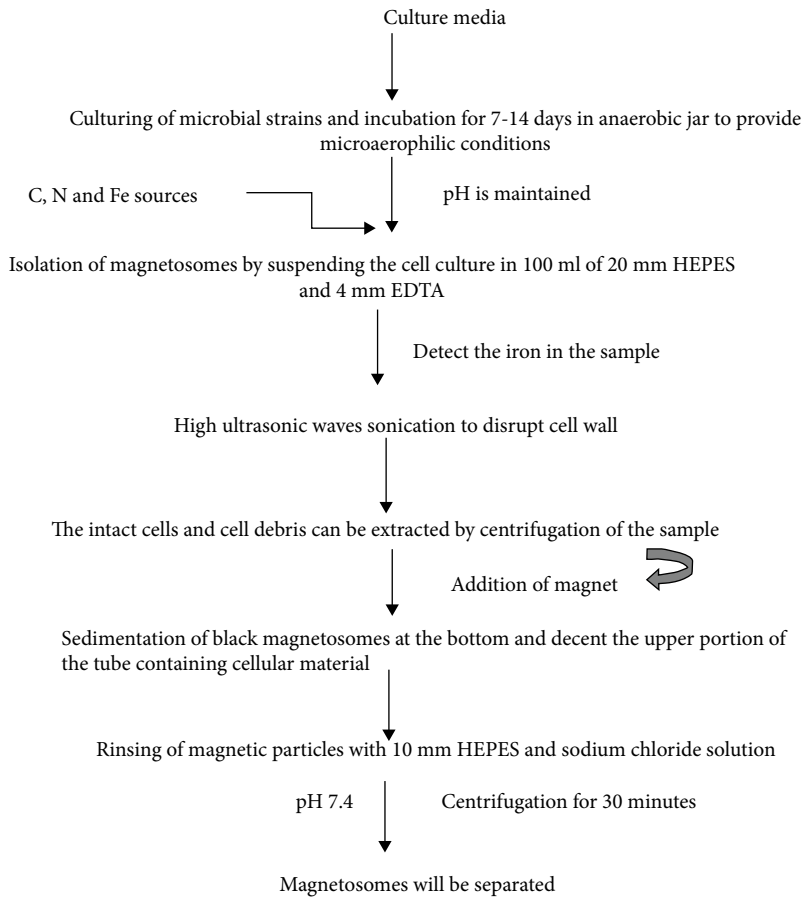

Figure 7: Flow chart representing generalized procedure to prepare magnetosomes.

Table 2: Effect of magnetic field strength on magnetosomes (loss per cycle).

Sr. no.	Magnetosome loss per cycle	Magnetic field strength	References
1	0.1 to 0.2 J/kg	6 mT	[86, 87]
2	0.5-1 J/kg	12 mT	[88–90]

50% w/v potassium lactate are required. Different strains of magnetotactic bacteria are cultured for 7-14 days in microaerophilic conditions using an anaerobic jar and pH is maintained using pH-stat feeding techniques [57–59]. The chemostat culture techniques are used to maintain a constant level of carbon, nitrogen, and iron sources. Nitrogen is subsequently dispersed in the culture tubes for a time duration of about 1 hour to provide microaerobic conditions. Moreover, to facilitate the cultivation compared to the standard culture media, ferric quinate and Wolfe vitamin solution could be added [60].

Grünberg et al. [61] reported that during isolation of magnetosomes from the body of bacterial strain the cell culture is suspended in 100 ml of 20 mM HEPES and 4 mM EDTA followed by sonication to disrupt bacterial cell wall. The intact cells and cell debris can be extracted by centrifugation of the sample, and then, magnet is to be introduced in the cell extract. The black magnetosomes will sediment at the bottom of the tube, and the residue of cellular material will be retained at the upper portion of the tube, which is then decanted-off. The rinsing of magnetic particles is performed with 10 mM HEPES and sodium chloride solution by maintaining the pH of 7.4, followed by centrifugation at 15000 rpm for a period of 30 minutes to separate out the magnetosomes [62, 63].

7. Applications of Magnetosomes

Magnetosomes have played a momentous role in biomedical, biotechnological, and industrial applications due to their excellent biocompatibility, low toxicity, ease of surface alteration, and most importantly exhibiting good magnetic properties [64–67]. Magnetosomes are being studied as next-generation drug carriers due to their unusual physicochemical properties [68, 69]. With a broad range of applications in the identification, evaluation, and treatment of life-threatening illnesses such as cancer [70], cardiovascular disorder [71], and neurological disease [72], it has a wide range of applications in the detection, diagnosis, and treatment of life-threatening ailments. As a result, it is reasonable to believe that magnetosomes can play a major role in meeting future healthcare needs [73].

7.1. In the Treatment of Diseases. Magnetosomes are found to be the effective carrier to deliver the drug due to its magnetic possessions [74–76]. In addition, the efficacy of the drug can be improved by decreasing the size of drug by using nanotechnology and eventually augment the loading dose which may offer the release of biomolecules at a constant rate to the patient and facilitate the repair of cardiac tissues [77].

Magnetosomes have been successfully tested to target macrophages and blood vessels of an infarcted heart via the intravenous route in the systemic circulation directly to the site of the target organ [78].

Another technique employing magnetosomes and used extensively is magnetic hyperthermia, which is utilized to promote cell necrosis [79, 80]. This emerging technology has been reported in the treatment of tumors in mouse to halt cancer cells through the process of magnetic hyperthermia [81–83]. The magnetosomes have stronger heating properties due to their size, ferromagnetic activity at euthermic temperature, crystal size distribution, and aspect ratio. Temperature attained by ferrimagnetic nanoparticles with the help of alternate magnetic fields is directly proportional to the area under the hysteresis loop that may increase with an increase in the size of nanoparticles. Magnetosomes are administered into the site of tumor and heated by an external alternating magnetic field resulting in elevation in the temperature around 4-6 degrees which emits highly dissipated energy finally leading to apoptosis of tumor cells without affecting healthy ones [84, 85].

The amount of heat released by magnetosomes is responsible for killing the tumor cell that can be calculated by measuring loss of magnetosomes with each heating cycle; expressed as ratio of specific absorption rate to oscillatory frequency of alternating magnetic field applied on the magnetosomes. It was observed that magnetosome loss per cycle is increased with increase in the strength of the magnetic field as tabulated in Table 2.

7.2. Immunoassays. In immunoassays, magnetosomes have also been used to detect minute particles of toxic chemicals such as detergents and hormonal substances. Such minute entities or molecules bind to the surface of magnetosomes with the help of antibodies which are directly bound to them. Magnetosomes have now been used to remove DNA using the layers of aminosilanes as a carrier, so as to bind magnetosomes and DNA complex followed by their elution with phosphate buffer [91].

7.3. Role of Magnetosome in Targeted Drug Delivery. The potential use of magnetic nanoparticles in biomedical applications is due to their low/no toxicity and better biocompatibility that have attracted the scientific community. In case of conventional dosage forms of chemotherapeutic agents were transported or circulated throughout the body in an indiscriminate manner, affecting both normal healthy cells and rapidly proliferating cancer cells. On the other hand, there is a requirement of a high dose to guarantee that a substantial number of drugs have reached the affected area which is very likely to produce side effects. Due to these drawbacks and lack in target specificity, Magnetosomes offer an attractive alternative as drug carriers. The number of recent studies reported have proved magnetosomes in targeted drug delivery with reduced side effects and controlled drug release to the specific organs or tissues of the body and in multi-modal imaging [92].

Table 3: Magnetosomes patent applications.

Sr. no.	Applicant	Inventor	Country name	Title	Reference
1	Natura Bisse international, S.A. 08290 Cerdanyola (ES)	Fisas Verges, Patricia M.08290 Cerdanyola del Valles (ES)	Spain	Cosmetic compositions comprising magnetosomes and uses thereof	[97]
2	Nanobacterie	Edouard Alphandery, S tephanie Faure, Imene Chebbi	France	Treatment of cancer or tumors induced by the release of heat generated by various chains of magnetosomes extracted from magnetotactic bacteria and submitted to an alternating magnetic field	[98]
3	Nanobacterie	Edouard Alphandery, Mickael Durand-Dubief	France	Non-pyrogenic preparation comprising nanoparticles synthesized by magnetotactic bacteria for medical or cosmetic applications	[99]

The wide applications of magnetosomes in targeted drug delivery are based on their unique properties, magnetism, and ease of being manipulated using an external magnetic field (EMF) that guides drug-carrying to the specific area directly [93]. Magnetosomes are being used extensively as investigated drug carriers. For example, chemotherapeutic agents are conjugated with biological MNPs through various interactions and the compounds can be specifically targeted to localized diseased areas under the force of an EMF. The EMF-guided system helps drugs to enhance localized therapeutic efficacy and decrease toxicity [94].

7.4. Magnetosomes in Enzyme Immobilization. Magnetosomes have recently been reported as a prevalent approach for the immobilization of enzymes, owing to the ease with which they may be recovered via magnetic separation [95]. Magnetosomes' protein display method can be used to express catalytic units, making them excellent candidates for supporting immobilised enzymes. Ginet and colleagues reported production of an organophosphohydrolase (immobilized protein) from opd gene of Flavobacterium sp. fused to mamC for the breakdown of paraoxon, observed as a deadly but widely used insecticide [96]. The paraoxon degradation activity rate of this protein complex was found to be similar to that of pure organophosphohydrolase. Some of the IPRs emphasizing upon the applications of magnetosomes are illustrated in the Table 3.

8. Future Prospects

Although magnetosomes exhibit several advantages such as magnetotaxis, optimum growth in the lower concentration of oxygen and flagella provide motility [100] and it has resulted into a promising technology as a nanocarrier in the field of medicines and disgnostics. Still, mass cultivation of magnetotactic bacteria in the laboratories is challenging due to time-consuming culturing techniques and low yield. The results on magnetosome functionalization are intriguing, but the majority of the investigations are still in the proof-of-concept stage. The enormous potential for preclinical and clinical applications of developing multifunctional magnetosomes by changing the biochemical content of the magnetosome membrane is established. Nutritional needs and culture conditions related to magnetosome formation are still being researched. More research should be focused on the physiological properties of the MTB strain and methods to improve the synthesis of magnetosomes. There is limited number of scientific studies in favor of this particular area mainly because of the fastidious nature of magnetotactic bacteria [101, 102]. There is an urgent need of coordinated efforts to do the research in a systematic manner for the various gene expressions involved in the formulation of magnetosomes. Methods to obtain high yield with existing bacterial strains and discovery of novel magnetotactic strains to get maximum outcome are yet the most important goal to be accomplished.

9. Conclusions

This review discussed the biodiversity and applications of magnetosomes to attain effective targeted drug delivery. It can be concluded that magnetosomes have number of advantages over conventional and other advanced drug delivery systems and offer a great potential for diagnosis, drug-targeting more specifically in cancer, and the ailments encountering multidrug resistance. Though, to overcome the challenges, a significant goal would be to develop for creating high-yield magnetosomes from current strains or to isolate novel large-scale production of magnetosomes using MTB. Therefore, these magnetosomes and magnetosome drug delivery systems may be explored in the future with scope for commercialization.

Data Availability

Data will be available on request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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