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Magnetosome-Based Drug Delivery: Design, Development, Mechanism, and Applications

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Abstract: *Many current drug delivery technologies are precisely tailored to enhance drug distribution by minimising drug degradation or loss. Magnetosome (biological magnetic nanoparticles) drug delivery is one such promising method of delivering the drug cargo that can be realised when vehicle has a strong magnetic force. Magnetotactic bacteria strains can be used to create membrane-like structures known as magnetosomes. Its size is in the nanoscale (35–120 nm), and the magnetic iron crystals that are positioned around it in individual or cumulative chains allow the cell to passively align with the external magnetic field. Development of multi-functional magnetosomes by altering the biochemical composition present in the membrane of the magnetosome has immense potential for preclinical and clinical applications. Magnetosomes may also be used in biological procedures like magnetic resonance imaging (MRI), hyperthermia, magnetically assisted drug delivery system, and immunomagnetic assessment due to their great biocompatibility. The system for designing, developing, and mechanism of delivery of drugs using magnetosomes, as well as recent advancements gained in this domain to facilitate the treatment and diagnosis of numerous diseases, are summarised in this article. In this review, we aim to outline the current state of the science in magnetotactic bacteria research and its applications.*

Key Words: *Magnetosomes, drug delivery, magnetotactic bacteria, magnetic field, nanotechnology.*

1. INTRODUCTION:

One of the fundamentals of cancer treatment, and several other therapies, is targeted medication delivery, which may allow for improved treatment efficiency. The use of nanoparticles in clinical, biotechnological, and environmental domains has grown significantly in recent years. Focus on advances in nanoparticle research led to the invention of magnetic nanoparticles or magnetosomes [1]. These nano architectural motifs are encapsulated by lipid bilayer membrane and synthesized by magnetotactic bacteria (MTB). When MTBs are cultivated under low oxygen conditions (0.25 – 10 mbar), the magnetosomes self-assemble in the form of stable chains within the bacteria, thus forming non-aggregated nanostructures (~10 nm) with enhanced internalization within cells [2]. The magnetosome core is made up of magnetite (Fe3O4) which gets oxidized to maghemite (γFe2O3) and possesses a crystalline structure with exceptional purity. At physiological temperature, the magnetic moment inherent of these magnetosomes are thermally stable with greater heating capacities. Unlike other chemically synthesized nanoparticles, whose synthesis is cumbersome and form unstable dispersions, magnetosomes are covered with a layer of lipid and/or proteins which renders a negative charge on the surface and forms a stable dispersion in aqueous media. Further, their biocompatibility and low toxicity makes it an attractive carrier for drug delivery and diagnosis [3]. Incidentally, nanoparticles generated by magnetotactic bacteria having different properties would be an excellent alternative for clinical and biotechnological purposes [4,5]. This article

will concentrate on preparation and evaluation of magnetosomes as a potential drug delivery system to treat cancer, heart disease, and other disorders.

2. MAGNETOSOMES AS DRUG CARRIERS :

The process by which magnetosomes are biomineralized has drawn a lot of attention in research since the identification of MTB. Salvatore Bellini in the year 1963 was the first to study the behaviour of magnetite in freshwater. It was found that the existence of a magnet is what causes the bacteria to swim persistently in a north hemispheric direction [6,7]. Blakemore in the year 1975 discovered a variety of bacteria samples by looking at them using a transmission electron microscope (TEM), where it was discovered that the bacteria were swimming next to the geomagnetic field lines. The magnetic cell organelles that direct magnetically induced motility were called as magnetosomes, and these microorganisms were referred to as magnetotactic bacteria (MTB) by Blakemore [8,9]. According to reports, MTB are widely spread in extreme cold and hot spring environments, as well as aquatic environments like the sea depths, and the areas with high salt concentration like deserts.

In the current scenario, novel substitutes to fabricate magnetosomes have been identified in magnetotactic bacteria [10]. Magnetic-targeted drug carriers are made using a core of iron oxide with a biocompatible polymer coating for drug delivery. Numerous techniques, including coprecipitation, decomposition due to high-temperature, nano/microemulsions, bio nanoreactors, dendrimers, laser pyrolysis and spray have been widely used to create Fe3O4 nanoparticles [2,11,12]. However, particles generated in this method are frequently non-uniform, incompletely crystalline, compositionally non-homogeneous, and easily aggregated due to magnetic attraction [13]. The biological manufacture of magnetosomes offers a potential benefit in managing crystal size and its morphological features. Particles of magnetosome which are isolated have a high surface to volume ratio due to their tiny size (35-100 nm), making them effective as carriers for the immobilisation of various bioactive compounds. Magnetosomes are the ideal biotechnological materials because each one is enclosed within a highly stable lipid bilayer membrane that gives them superior handling and dispersion properties to artificial magnetic particle conjugates [5]. Additionally, magnetosomes are a viable material resource for the creation of early diagnostic methods and treatments for oncological and other severe ailments. Magnetosomes are particularly convincing as a therapeutic technique since they have no adverse effect on the recipient organism. Moreover, magnetosomes were suggested for use in a variety of practical applications, including computer memory chips, nanorobotics, and biosensors [14,15].

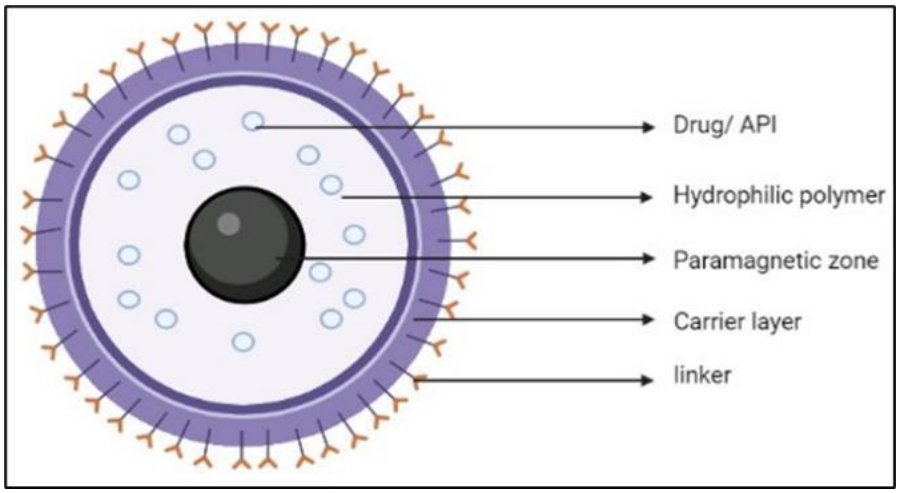

Figure 1. Structure of a magnetosome

In bacteria, since the bacterial cell wall is disrupted during magnetosome release, the chains-like arrangement of magnetosomes is strong enough to hold the structure together. Such configuration avoids aggregation and increases the rate of internalisation in human cells, that are typically desired properties in pharmaceutical and other clinical applications. The biological coating of magnetosomes, which is made up of lipids and trace amounts of proteins, causes the negatively charged magnetosomes to completely disperse in water [10]. Magnetotactic bacteria produce magnetosomes, which are iron oxide nanoparticles wrapped with biological material as shown in Figure 1. Due to their unique properties such as paramagnetism, nanotechnology, narrow-size distribution, and being confined to the membrane, bacterial magnetosomes (BMs) generated by magnetotactic bacteria aroused interest as choices for targeting drug carriers. The magnetosomes are used as a compass by these bacteria to navigate in the direction of the earth's magnetic field. The presence of a magnetosome chain within the MTB cell allows it to passively orient itself by the

geomagnetic field. This is known as the *"magnetotaxis"* phenomenon. Bacterial magnetosomes are enclosed by a lipoprotein membrane and made of magnetite (Fe3O4) and greigite (Fe3S4). MTB's magnetite crystals are 30-120 nm in length and give the cell a permanent magnetic dipole moment [10,14].

3. PREPARATION OF MAGNETOSOMES

Formation of magnetosome, extracellular intake of iron particles by cell, transport of iron into the magnetosomes, and physiologically regulated mineralization of magnetite within the magnetosomes are regarded as key steps in the mechanism of magnetosome formation from MTBs (Figure 2).

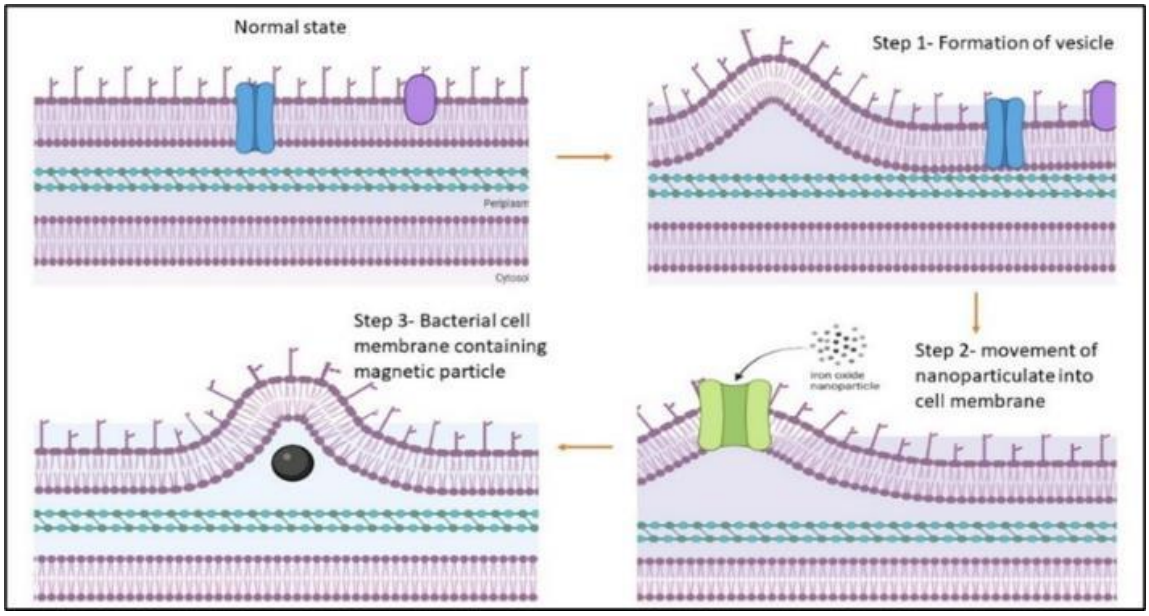

Figure 2. Steps involved in the development of magnetosomes

Magnetotactic bacteria and cultivation

For bacterial maintenance and culture, the anaerobic approach can be employed. According to Blakemore et al, *M. gryphiswaldense-1* (MSR-1) was cultivated micro-aerobically in regular Magnetospirillum growth medium (MSGM) [9]. To get rid of the dissolved oxygen, sterile nitrogen was flushed after 300 ml of medium had been dispensed into 500 ml serum bottles. Culture bottles were sealed with butyl rubber stoppers followed by autoclaving. About 10% (v/v) of the cells from the inoculum that were growing exponentially were added to the medium flasks as an inoculum. By setting the bottles of culture media on a magnetic stirrer and viewing the light scattering, the magnetic moment of the microbial culture was determined [16]. The generalized procedure involved in the extraction of magnetosome is shown in the Figure 3.

Magnetosome extraction and characterization

According to Alphande'ry et al. (2012), MTB cells were removed from growth medium by centrifuging for 20 min after being incubated in MSGM media for 48 h. The pellet was centrifuged for 20 minutes before being re-suspended in pH 7.0 Tris HCl buffer. The cells were then lysed by sonication of the suspension at 30 W for 2 h [3,16,17]. Cells were centrifuged at 2000 revolution per minute for about 10 minute to remove iron precipitates, further at the rate of 8000 revolution per minute for 10 minutes to condense the bacterial concentration after 90% of the ferrous ions had been oxidised. Finally, diluted sulfuric acid at pH 2.0 and 0.1 molar phosphate buffer saline were used to wash the cells (pH 7.2). The previously reported procedure was modified and used to isolate magnetosomes. In a brief, for 60 minutes at 37 °C, 5 g (wet weight) of *A. ferrooxidans* BY-3 cells were dispersed in 20 ml of 10 mM Tris-Hydrochloric acid buffer solution of pH 7.4 which contained DNase (50.0 g/ml), RNase (100 g/ml), magnesium chloride (5.0 mM), and 1.0 % (w/v) lysozyme [2]. The neodymium-iron-boron (Nd-Fe-B) magnet of 29/14/8 millimetres was used to generate an uneven magnetic field of 0.5 T on its surface, magnetosomes were extracted and collected from the supernatant. The supernatant was then discarded. Initially, 25 ml of 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) and 200 mM sodium chloride solution of pH 7.4 and then 10 mM HEPES (pH 7.4) were used to wash magnetosomes that were attached to the tube's bottom at least eight times. Phenylmethylsulfonyl fluoride, a protease inhibitor, was present in 0.1 mM concentration in each of the buffers used for magnetosome isolation. By suspending the magnetosome mixture in 1% SDS solution at 90 °C for 5 h, the mixture was further purified. By placing a bar magnet's south pole next

to the tubes, it was possible to distinguish between magnetosomes and leftover impurities. The magnetosomes were removed, freeze-dried, and preserved for further use [1,13].

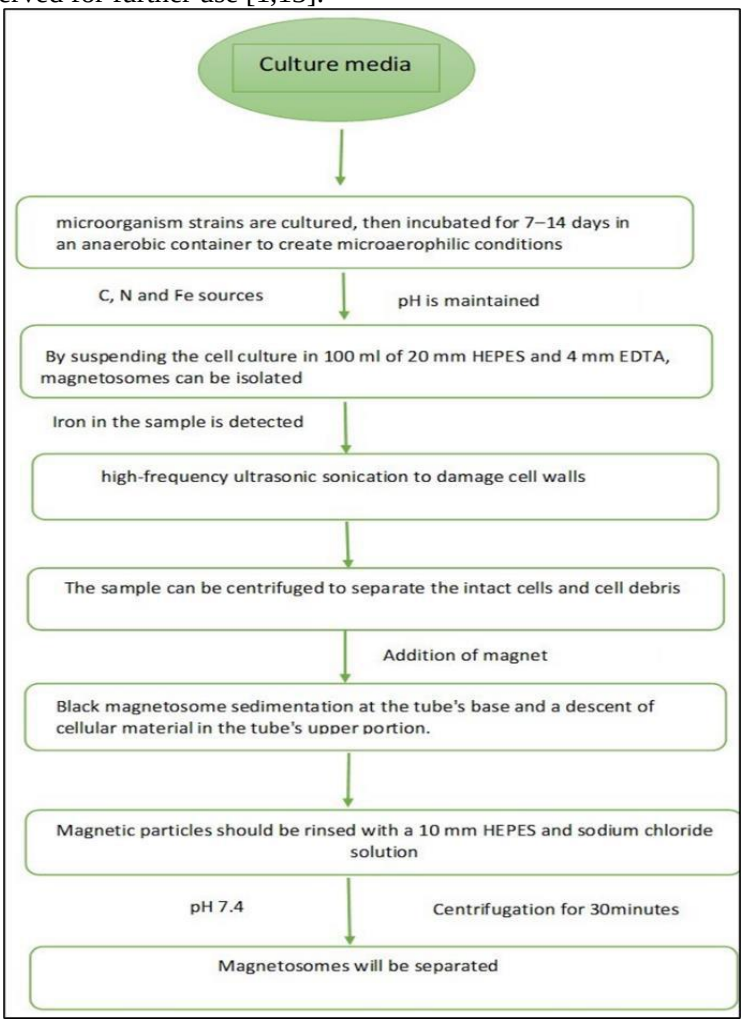

Figure 3. Schematic representation of cultivation and extraction of magnetosomes from MTBs

4. FACTORS INFLUENCING LARGE-SCALE SYNTHESIS OF MAGNETOSOMES

Research on the nutritional requirements and cultural settings related to magnetosome development is ongoing. The physiological characteristics of the MTB strain and strategies to enhance magnetosome production require further studies. The most crucial task at hand is still finding new magnetotactic bacterial strains and methods to increase yield with already used bacterial strains and few strategies has been listed below.

Nutrient balanced feeding

Amount of nutrients, namely carbon source, has a significant impact on the production of magnetotactic bacteria and consequently on magnetosome synthesis. Cell development is slowed down by the accumulation of excess nutrients and inhibitory substances in the media. A nutrient-balanced feeding strategy can lessen negative impact of an excess of nutrients in the medium. Substitution of carbon and nitrogen sources reduces the build-up of sodium and chloride ions in this approach. Lowering of osmotic potential is observed when there is accumulation of sodium and chloride ions in the fed-batch culture. This subsequently prevents cell development. Cell development slowed down even at low sodium chloride (NaCl) concentrations [1]. However, nutrient-balanced eating can significantly speed up growth. Magnetosome yield and cell development are effectively promoted by the chemostat culture approach with minimal time and energy expense. MSR-1 is grown utilising the "chemostat culture" method, which relies on pH-stat feeding to regulate the quantities of nitrogen, carbon, and iron. An increase in MSR-1 cell growth and magnetosome formation was reported when sodium lactate was employed as source of carbon. On the other hand, for quick cell development and the creation of magnetosomes, low sodium lactate concentration is required to regulate low dissolved oxygen (O2) content [18]. It has been demonstrated that ammonium chloride is a superior nitrogen source to Sodium nitrate.

Dissolved oxygen concentration

For effective magnetosome biosynthesis, microaerobic or anaerobic environments are quintessential. In order to produce an optimal yield, high dissolved O2 is required for high density culture. Low dissolved oxygen levels have a significant impact on cell development. Also, more dissolved O2 may result in an increase in MSR-1 density in the culture medium but a decrease in the creation of magnetosomes. By regulating dissolved oxygen to an ideal amount via adjusting cell growth rate, this conflict may be partly overcome. Nevertheless, lower levels of dissolved O2 (5-10 ppm) were found to result in increased iron intake rate and formation of magnetosomes, possibly due to sluggish bacterial growth [1,18].

Ferric ion uptake

Many enzymes, especially those engaged in important biological pathways, require iron as a cofactor. Cells' specific iron transport pathways deliver sufficient iron levels for optimum development. To absorb ferric iron (Fe3+), some bacteria synthesize ferric chelators (also known as siderophores). Ferric gallate and sulphate considerably increase the synthesis of magnetosomes [1]. While other iron sources (ferric quinate, ferric malate) have an impact as well.

ATP use in magnetosome production

The primary energy source needed for metabolic activity, molecular movement, signal transmission, and other essential physiological functions in cells is ATP. Energy-intensive processes like magnetosome production and iron absorption are both ATP-dependent. For ATP synthase to produce energy, NADH creates a proton gradient throughout the internal mitochondrial membrane [1,18].

Superoxide dismutase activity

In vitro hydrogen peroxide (H_2O_2) breakdown and defences against cell toxicity from H2O2 are both correlated with the production of magnetosomes. Superoxide dismutase, an enzyme found in microorganisms, degrades H2O2 and superoxide anion radical (O^{2-}), both of which are harmful to cell macromolecules. Superoxide dismutase also lessens oxidative stress in the magnetotactic bacteria during the production of the magnetosomes. When ferrous iron (Fe2+) donates an electron to H2O2, the resultant hydroxyl radical may be formed. The reactive oxygen species (ROS) called hydroxyl radicals can harm biomolecules. Therefore, the presence of diluted ROS may lead to a reduction in superoxide dismutase function. It is possible that diminished superoxide dismutase activity results from the scavenging of ROS by magnetosomes and artificial magnetic nanoparticles [1].

5. EVALUATION OF MAGNETOSOMES :

XRD and FTIR analysis

The magnetosomes can be subjected to X-ray diffractometer studies. The crystalline phase of the magnetosome is determined using the full width at half maximum (FWHM) of associated diffraction peaks. On an FTIR spectrophotometer, the magnetosome's FTIR spectrum was captured. The contents are completely combined with dry KBr before being formed into pellets. 500-4000 cm-1 is the acceptable wave number range when the environment is ambient [13].

Detection of drug incorporation on magnetosomes

The magnetosome-drug conjugates are dissolved in methanol, aggressively vortexed, and stored for an overnight period. The solution is centrifuged for 30 min at 15,000 rpm to extract the supernatant. HPLC is used to measure the processed supernatant [19]. The drug content is evaluated using below equation.

Drug content = amount of drug in nanoparticles/ amount of nanoparticles X 100

Surface characterization of drug-loaded magnetosomes

A drop of suspension is applied to the copper grid after the lyophilized drug loaded magnetosomes are sonicated to disseminate them. The grid is sputtered deposited after drying, and they are then examined using a field emission scanning electron microscope. Zeta potential was used to analyse the surface charge of magnetosomes [17,20,21].

Thermogravimetric analysis (TGA) and differential scanning colorimetry (DSC)

By using a heating rate of 10 °C/min in an air environment from room temperature to 1000 °C, TGA and DSC may be used to analyse both drug-covered and uncovered magnetosomes. Samples can be subjected to a DSC thermogram examination. Fifty ml/min of dry nitrogen is used to cleanse the DSC cell. With a heating rate of 20 °C/min,

correctly measured samples (3-5 mg). Then, it is heated to temperatures between 25 and 300 °C in a conventional aluminium pan. The thermogram can be used to measure the samples' melting points [20].

***In vitro* drug release**

Each magnetosome (5 mg) is dissolved in 10 ml of PBS (pH 7.4) before being incubated at 37 °C with a magnetic stirrer. The precipitate is taken and subjected to UV spectroscopic analysis at various time intervals [20].

Transmission electron microscopy analysis (TEM)

Unstained cells are adsorbed on carbon coated copper grids for standard TEM investigation. A bright-field TEM experiment is conducted at a 200 kV accelerating voltage. TEM micrographs are typically taken using an object pixel size of 1.672 nm/pixel. Generally, an 8 m defocus, and a 6,500x magnification is used. The photos can only have a 4.5 nm resolution [19,21].

Haemolytic assay

Once human blood has been collected, it is washed in 0.9% saline solution. After centrifuging the cells, the supernatant is discarded. In order to create the pellets, 0.9% saline is diluted. A phosphate-buffered saline solution containing calcium chloride and boric acid is then added to dilute the solution. In 96-well plates, the assay can be carried out. Magnetosomes are injected at various concentrations are added. Triton-X and water can serve as positive and negative controls, respectively. Erythrocytes are then added, and the mixture is incubated for 30 minutes. They are then examined under a light microscope to determine haemolysis due toxicity [16].

6. APPLICATIONS OF MAGNETOSOME :

Magnetosomes in treating diseases

Magnetic hyperthermia is induced using magnetosomes (using magnets to heat up cells that have taken up magnetosomes) as shown in the Figure 4. Staphylococcus aureus, a common cause of infections, is a harmful bacterium species that can be killed by magnetic heat and magnetosome infusion. Research on cancer is also looking into magnetic hyperthermia since it can find and kill tumour cells. These treatments may be especially helpful because they only target cells that have incorporated magnetosomes, leaving healthy surrounding cells unaffected. Additionally, the medicine's effectiveness can be increased by employing nanotechnology to reduce the size of the drug and eventually increase the loading dose, which might provide the patient with a continual release of biomolecules and aid in the healing of cardiac tissues [5,8,22]. It has been proven that magnetosomes can be targeted to macrophages and blood vessels in an infarcted heart through i.v. administration to the target organ's site.

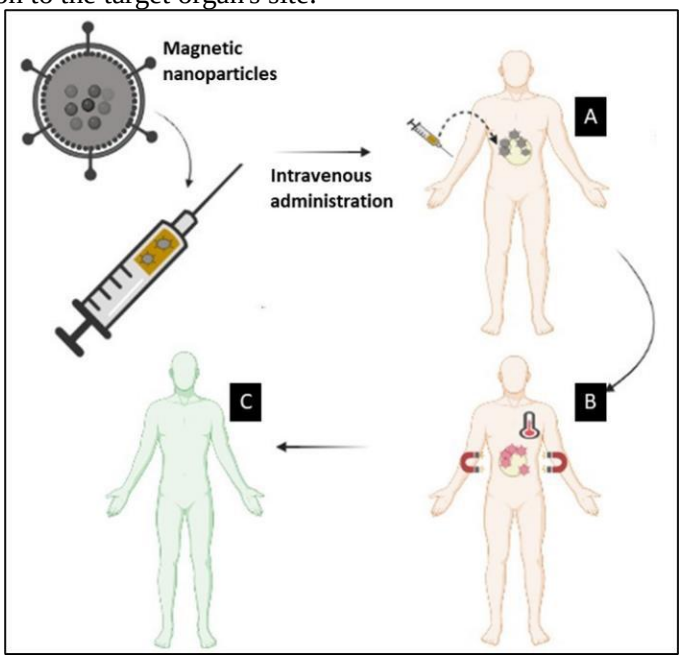

Figure 4. Schematic representation of theoretical cancer treatment with magnetic nanoparticles. A. Antibodies that can detect tumour cells are coated on magnetic nanoparticles. B. After being put into a patient, the nanoparticles bind to the tumour. C. Heating the nanoparticles and associated tumour cells with varying magnetic fields. D. Cancer cells die

Immunoassays

Magnetosomes have also been utilised in immunoassays to identify tiny toxic chemicals like hormones and detergents. The antibodies that are directly bound to magnetosomes help these tiny substances or molecules connect to their surface. Using layers of aminosilanes as a carrier, magnetosomes can now be utilised to extract DNA. The magnetosomes and DNA complex are then bound together before being eluted with phosphate buffer [23].

Targeted drug delivery

Recent investigations have shown that sterilised, purified *M. gryphiswaldense*-1 (MSR-1) magnetosomes are not harmful to tumour cells in vitro, indicating that they may be used as drug carriers in clinical cancer and other disease treatments [23]. Proteins and active groups which can be served as binding sites can be found in magnetosome membranes [1]. Because of their low/no toxicity and superior biocompatibility, magnetic nanoparticles have the potential to be used in biomedical applications. Chemotherapeutic chemicals in standard dose forms spread or circulated indiscriminately throughout the body, impacting both healthy, normal cells and cancer cells that were quickly multiplying [4]. On the other hand, a large dose is necessary to ensure that a significant amount of the medication has reached the affected area, which increases the likelihood of adverse effects. Magnetosomes present a desirable option as drug carriers because of these limitations [24]. Numerous recent studies have demonstrated the effectiveness of magnetosomes in multimodal imaging [15], targeted medication administration with fewer adverse effects, and controlled release of drug to the targeted organs or tissues of the body.

Enzyme immobilization

Recently, it has been revealed that magnetosomes are a popular technique for the immobilisation of enzymes because can be readily recovered by magnetic separation. Magnetosomes are excellent candidates that supports for immobilised enzymes due to their capacity to express catalytic units.

7. FUTURE PROSPECTS :

The chronological order of the iron intake, transport, and crystal biomineralization processes is well understood. However, it is unclear if magnetosome vesicle production takes place before or after crystal biomineralization, or if both processes take place at the same time. Numerous speculative models regarding the bacterial magnetosome's formation mechanism have been put forth considering the data provided by molecular genetics, physiology, and ultrastructural cytochemistry. Electron microscopic study revealed that iron starved cells of *M. magnetotacticum* and *M. gryphiswaldense* contained empty and partially full magnetosome vesicles. These showed that the magnetosome vesicles are evidently present before the mineral phase is biomineralized [13]. Due to their distinctive characteristics, including their restricted size distribution, consistent shape, excellent chemical purity, lower toxicity, including membrane envelope, magnetosomes are of major theoretical and practical significance. Magnetosomes' dispersion, ferrimagnetic characteristics, nanoscale size, membrane-bound structure, and capacity for dispersal all have applications [11,12]. However, due to labour-intensive culturing methods and limited yield, mass growth of magnetotactic bacteria in laboratories remains difficult.

Since there is potential for commercialization, these magnetosomes systems for drug delivery may be investigated in the future. It is urgently necessary to explore the many genes and proteins involved in magnetosome production in vivo and in vitro through systematic and coordinated efforts. Following the identification of the functions of specific magnetosome genes and proteins, the adoption of genetic engineering techniques may result in notably higher yields of magnetosome particulates with remarkable properties and a more dependable production process [19,20]. Immobilization of bioactive components like antibodies, enzymes, and biotin seems to be possible with them. Further research is necessary to comprehend the endocytotic mechanism of magnetosomes and regarding internal accumulation or recycling, as magnetosomes have the potential to be used in the delivery of genes and drugs. Although there have been significant advances in the fields of chemical, genetics, molecular, magnetic, and biochemical research areas, there is still a lack of knowledge about the risks associated with magnetosomes when administered to humans or animals.

8. CONCLUSION :

This paper explored magnetosome biodiversity and uses for successful targeted drug delivery. It has been reported previously that magnetosomes have a numerous of benefits over traditional drug delivery methods, due to the unique characteristics of magnetosomes are their nanoscale size, ferrimagnetism, membrane-bound structure, and higher biocompatibility. Also, they are potential carrier system for the treatment, diagnosis and involved in drug targeting that is more particularly for the cancer treatment and encountering diseases that are multidrug resistant. The development of high-yield magnetosomes from existing strains or the isolation of unique MTB-based large-scale magnetosome manufacturing would be key goals to overcome the difficulties.

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