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ANTI CANCER THERAPY USING A MAGNETICALLY REGULATED MEDICATION DELIVERY SYSTEM

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ABSTRACT

Magnetic microcarriers are one of the novel drug delivery systems that have emerged, encompassing different routes of administration, to achieve controlled and targeted drug delivery. These microcarriers include magnetic erythrocytes, magnetic resealed erythrocytes, magnetic emulsion, magnetic microspheres, magnetic liposomes, and magnetic nanoparticles. Magnetic micro/nanoparticles and molecular magnetic labels have been used for great number of application in various areas of biosciences, targeted drug delivery, imaging and in bio separation technology. These projects will discuss about principle of magnetic targeting, mechanism of magnetic targeted drug delivery, benefits and drawbacks of magnetic targeting, magnetic microcarriers and application of magnetism in targeted drug delivery and some other field. Magnetically targeted drug delivery by particulate carriers is an efficient method of delivering drugs to localized disease sites such as tumours.

Keywords: Anticancer therapy, Conventional drug delivery, Magnetic, Particals, Diagnosis, Superparamagnetic, Microstructure.

INTRODUCTION:

Drug targeting refers to the distribution of medications to receptors, organs, or any other particular area of the body to which the medication is intended only.[1] From a commercial as well as a scientific perspective, drug delivery is crucial to the treatment of illnesses since the mode of delivery can greatly impact a medication's effectiveness.[2] It is quite difficult from a scientific standpoint to develop a medication delivery system that can both be site-specific and have regulated release.[3] By employing magnetic nanoparticles (ferrofluids) attached to chemotherapeutic medicines and a focused external magnetic field, magnetic drug targeting refers to the targeted delivery of these agents, such as cancers, to their intended targets. Target-directed medication injections of this kind aim to maximize the concentration of a pharmaceutical agent by maximizing its effectiveness and reducing any negative side effects.[4] Most anticancer medications are

injected intravenously and accumulate in tumors with a high concentration of blood vessels that are leaking.[5] In the last ten years, there has been a significant increase in interest in magnetic targeting due to the development of stronger magnets and more sophisticated magnetic probes with multiple functions, or theranostic probes (Nan et al., 2017; Sun, Q. et al., 2018; Tang et al., 2018). Magnetic drug delivery was first introduced in the 1980s (Widder et al., 1980; Kost and Langer, 1986). These probes enable a mix of therapies, such as drug release and hyperthermia, and diagnostics, such as magnetic resonance imaging (MRI) or magnetic particle imaging.[6] They also enable targeted medication delivery, such as when a magnetic field is applied.

Table 1: Conventional drug delivery and magnetic drug delivery difference

Sr no.	Conventional drug delivery System	Magnetic drug delivery System
1.	Slow onset of action	Fast onset of action
2.	Not target specific	Target Specific
3.	Accumulation of Drug may occur in healthy tissue hence show more adverse effects	No accumulation of drug in healthy tissue so have negligible side effect
4.	Diagnosis and treatment by single agent not possible	Diagnosis and treatment can be possible by single agent
5.	Cost is Low	Cost is high

Magnetic Nano/Microparticles

Reticuloendothelial system clearance and inadequate site specificity are two significant problems with non-magnetic microcarriers that were addressed with the development of magnetic microspheres (Kakar et al., 2013).[7] Making porous or hollow/porous microspheres out of magnetic spinel ferrites MxFe3−xO4 (where M = Fe, Zn) is one method.[8] Because of their strong magnetism, the microspheres may be easily moved around the vascular system by a magnet and, in particular, stay in the capillaries of the intended organ. In order to construct a larger cavity and a higher surface area where drugs can be encapsulated in both the mesopores and the cavities, Chen et al. used a hollow nanoparticle (NP) with a mesoporous shell (Chen et al., 2017).[9]

Combining a polymer with inorganic NPs is an additional method for creating microspheres. Fe3O4 NPs and the anti-cancer medication doxorubicin hydrochloride (DOX) were both encapsulated by Wang et al. using poly(ε-caprolactone) (PCL) (Wang, G. et al., 2018). The superparamagnetic composite microspheres exhibited rapid magnetic response and high drug loading. It was discovered that the drug's release was pH-sensitive, exhibiting a strong initial release and a prolonged release over several days.[10]

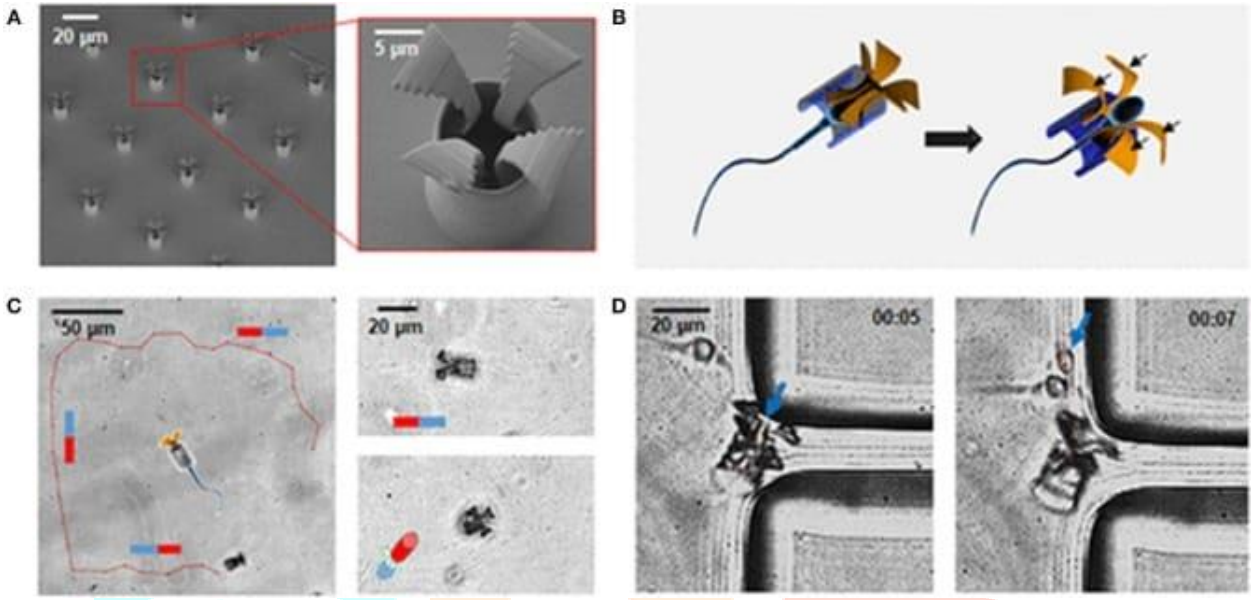

Fig:

SEM pictures of several printed tetrapod microstructures are shown in (A). (B) Diagram showing how the mechanical release mechanism works. (C) A sperm-hybrid motor's track (red line) in both the horizontal and vertical planes under magnetic guidance. (D) Picture sequence showing the release of sperm when the arms come into contact with a polydimethylsiloxane wall's corner. The sperm head is pointed at by blue arrows. Duration in minutes: (Xu and others, 2018). Reproduced with permission of American Chemical Society, the owner of the copyright.[11]

Nanoparticle Clustering/Assembly

The fact that individual superparamagnetic iron oxide nanoparticles (NPs) do not exhibit strong magnetism poses a significant problem for their internalization into the body (Kralj et al., 2017).[12] NPs can be clustered to improve their overall magnetic response as a solution to this issue. In order to create multifunctional micelles, Zheng et al. created copolymers of hyaluronic acid (HA) and C16 micelles by encasing docetaxel (DTX), an anti-cancer drug, and NPs after peptide synthesis (Zheng et al., 2018). In addition to its biocompatibility and biodegradability, HA is particularly appealing because it binds to the CD-44 receptor, which is overexpressed in a variety of cancer types (Lee et al., 2012).[13] Magnetic fields promoted cellular uptake, which was mediated by the CD-44 receptor through endocytosis.[14] By increasing the quantity of micelles in the tumor tissues relative to the normal tissues, this uptake technique produces a positive contrast in magnetic resonance imaging.[15] Moreover, NIR radiation caused the medication to leak. For in vivo cancer theranostics, the assembly of iron oxide NPs on polydopamine (PDA) NPs enabled an improved magnetic response and stimuli-controlled drug release (Ao et al., 2018). PEG chains enable in vivo cancer therapy, and the high responsiveness of the PDA surface provides a potential for reduction-responsive prodrugs.[16] Through a synergy of NIR photothermal ablation (due to PDA) and anticancer medication magnetic delivery, the successful tumor obliteration was achieved through a combination of controlled magnetic drug targeting and MRI/photoacoustic dual-modal tumor imaging.[17]

Magnetic Microbubbles

When magnetic medication delivery is employed with ultrasonography, magnetic microbubbles can be seen and are responsive to applied magnetic field changes.[18] Protamine-functionalized microbubble mix was recently formulated as a magnetic microbubble suspension using a heparinized NP41 suspension.[19] Ultrasonography is used to image tumors using magnetic microbubble guidance. The medication is delivered once the microbubble is collapsed using focused ultrasound37.

Magnetic Microcapsules

Using poly (allylamine hydrochloride) and poly (sodium 4-styrenesulfonate), magnetic microcapsules are utilized both in vivo and in vitro and are created by LbL deposition10.[20] The most promising medication delivery device uses a magnetic field to guide it remotely. iMushbots, or mesoporous mushrooms (Agaricus bisporous), are utilized to make microcapsules. Immushbots have better drug retention in alkaline pH conditions, such as in blood, while releasing drugs more easily in acidic environments, such as malignant cells 38.

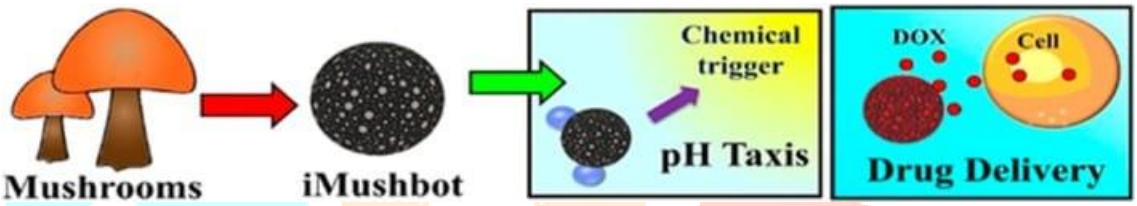

Fig:

Magnetic Fibers

Biocompatible magnetically triggered drug delivery vehicles were investigated using polyvinyl alcohol fibers loaded with magnetite nanoparticles, which were created by infusion gyration (Perera et al., 2018).[21] The authors showed that magnetic actuation can be used to controllably release acetaminophen, a model medication, that has been uploaded through impregnation. Furthermore, a 90% cumulative release was seen in 15 minutes after the creation of a magnetic field—much higher than in the absence of a magnetic field.[22] These findings point to the possibility of drug or other substance delivery via remote means.

Drug Uptake/Release

Similar to non-magnetic carriers, drugs are absorbed by conjugation (Chaudhary et al., 2015; Pourmanouchehri et al., 2018), hydrophobic interactions (Cho et al., 2018), aAccording to Wang et al. (2017), Wei et al. (2017), Wang, G. et al. (2018), Xu et al. (2018), Wang, Y. et al. (2018), Zheng et al. (2018), chemical reduction (Ao et al. 2018), HIFU (Moroz et al., 2001), and magnetic hyperthermia (Cho et al. 2018), the drug release can be initiated by changes in the microenvironment pH (Xu et al. 2018).bsorption within porous structures (Kakar et al., 2013), etc. in magnetic drug delivery vehicles.

Cytotoxicity

Numerous publications have addressed the cytotoxity of DOX bearing magnetic bioprobes for both healthy tissues and cancer cells (Lee et al., 2017; Ao et al., 2018; Sun, Q. et al., 2018). Because most systems are localized and made biocompatible, cytotoxicity toward healthy cells is minimized.[23] The effectiveness of magnetic bioprobes containing DOX is similar to that of free DOX, whereas it has been shown that bioprobes lacking DOX do not kill cancer cells (Ao et al., 2018). Moreover, cytotoxicity rises in response to NIR radiation and/or rising DOX concentrations (Sun, Q. et al., 2018).

Magnetically modulated microcarriers

Because magnetic microcarriers are site-specific, the issue of RES clearing them quickly is also resolved by localizing these microcarriers in the target area.[24] Since the linear blood velocity in capillaries is 300 times lower than that of arteries, or 0.05 cm/sec, a much smaller magnetic field—6–8 Koe—is enough to keep the blood vessels in the target area's capillary network10. Regarding composition, inactivation, or deformation, magnetic carrier technology seems to be a major substitute for bimolecular malformation.Among these microcarriers are:

A)Magnetic microsphere

B)Magnetic liposomes

C) Magnetic nanoparticals

D) Magnetic Resealed Erythrocytes

E) Magnetic Emulsion

F) Biomodulators

G) Magnetic neutrophils

A) Magnetic microspheres

Submolecular particles known as magnetic microspheres are small enough (less than 4 ʀ^m) to pass through capillaries without causing embolic occlusion, but they are also ferromagnetic enough to be drawn into microvessels and into neighboring tissues by magnetic fields ranging from 0.5 to 0.8 tesla (T). Two primary techniques were utilized to prepare magnetic microspheres: phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE).[25] By adjusting the size of the microspheres, the drug content, the magnetite content, the hydration state, and the drug release characteristic of the carrier, the amount and rate of drug delivery via magnetic responsive microspheres can be controlled.[26] Creating an effective therapeutic system requires carefully balancing the amount of drugwand magnetic content in the microsphere. Particle size analysis, including size distribution, surface topography, and texture, is one way that magnetic microspheres are characterized.[27] Other methods include drug entrapment efficiency, percent magnetite content, in vitro magnetic responsiveness, and drug releas.

One technique to physically direct these magnetic drug carriers to a desired site is by targeting them with magnetic microspheres, which involves incorporating magnetic particles into drug carriers (polymers) and applying an external magnetic field.[28] Widder was the first to report on the application of magnetic albumin microspheres.

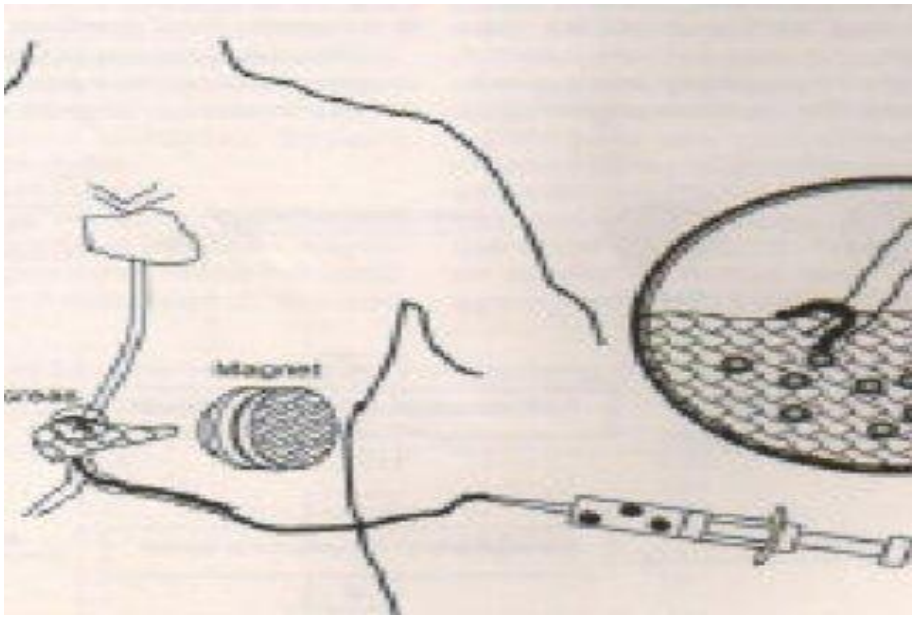

Fig: Magnetic targeting of Antitumour Microspheres to pancrease

B) Magnetic liposomes

Liposomes are a type of simple microscopic vesicles that contain lipid bilayer structures.[29] They have an aqueous volume that is completely surrounded by a membrane made of lipid molecules. A variety of components are found in liposomes; the primary ingredients are phospholipids and cholesterol; however, magnetite is one of the components in magneto liposomes. These are typically magnetic carriers that are made possible by trapping ferro fluid inside the liposome core.[30] Magneto liposomes can also be created by incorporating target lipids into the structural phospholipid matrix or by covalently attaching ligands to the vehicles' surfaces.Thirteen As an alternative, the phospholipid vesicle is used as a nanoreactor to prepare magnetoliposomes by precipitating magnetic nanoparticles in situ. As an alternative, the phospholipid vesicle is used as a nanoreactor to prepare magnetoliposomes by precipitating magnetic nanoparticles in situ.[31] Additionally, didodecyl methyl ammonium bromide-containing vesicles with an ionic magnetic fluid are made. These magnetoliposomes worked well as cell sorting tools, site-specific targeting tools, and magnetic resonance contrast enhancers.After selective heating brought on by electromagnetic fields, thermosensitive magnetoliposomes can release the drug that has been trapped. Immunofluorescence was made more sensitive by using magneto fluorescent liposomes.[32] The physical characteristics of the magneto liposomes are measured using P-NMR and freeze-fracture microscopy to determine their size, shape, and size distribution; surface charge; capture and magnetite content percentages; phase behavior drug release; quantitative measurement of phospholipids; and cholesterol analysis.

C) Magnetic nanoparticals

Due to their distinct magnetic characteristics and capacity to operate at the cellular and molecular level of biological interactions, magnetic nanoparticles (MNPs) are a desirable candidate for use as drug delivery vehicles and contrast agents in magnetic resonance imaging (MRI). Recent developments in nanotechnology have made it easier to precisely customize MNPs' characteristics and attributes for these biological uses. [33] MNPs with higher magnetic moments, non-fouling surfaces, and enhanced functionalities are currently being developed for applications in the diagnosis, treatment, and detection of neurological, cardiovascular, and malignant tumors in order to better meet specific clinical needs. The application and effectiveness of these MNPs have significantly increased with the addition of highly specific targeting agents and other functional ligands, such as fluorophores and permeation enhancers.[34] This review gives background information on the

uses of MNPs as drug delivery carriers and MR imaging contrast agents, as well as a summary of recent advancements in this field of study.15

For medical applications, magnetic particles' nontoxicity, biocompatibility, injectability, and high-level accumulation in the target tissue or organ are crucial characteristics. [35] Since an external magnetic field can be used to control the properties of the magnetic nanoparticles, their modification with organic molecules has found widespread application in biotechnological and biomedical fields16 Moreover, "magnetic force-based tissue engineering," a novel application of magnetic nanoparticles and magnetic forces for tissue engineering, has been proposed. The preparation techniques that enable the synthesis of particles with nearly uniform size and shape have received special attention.

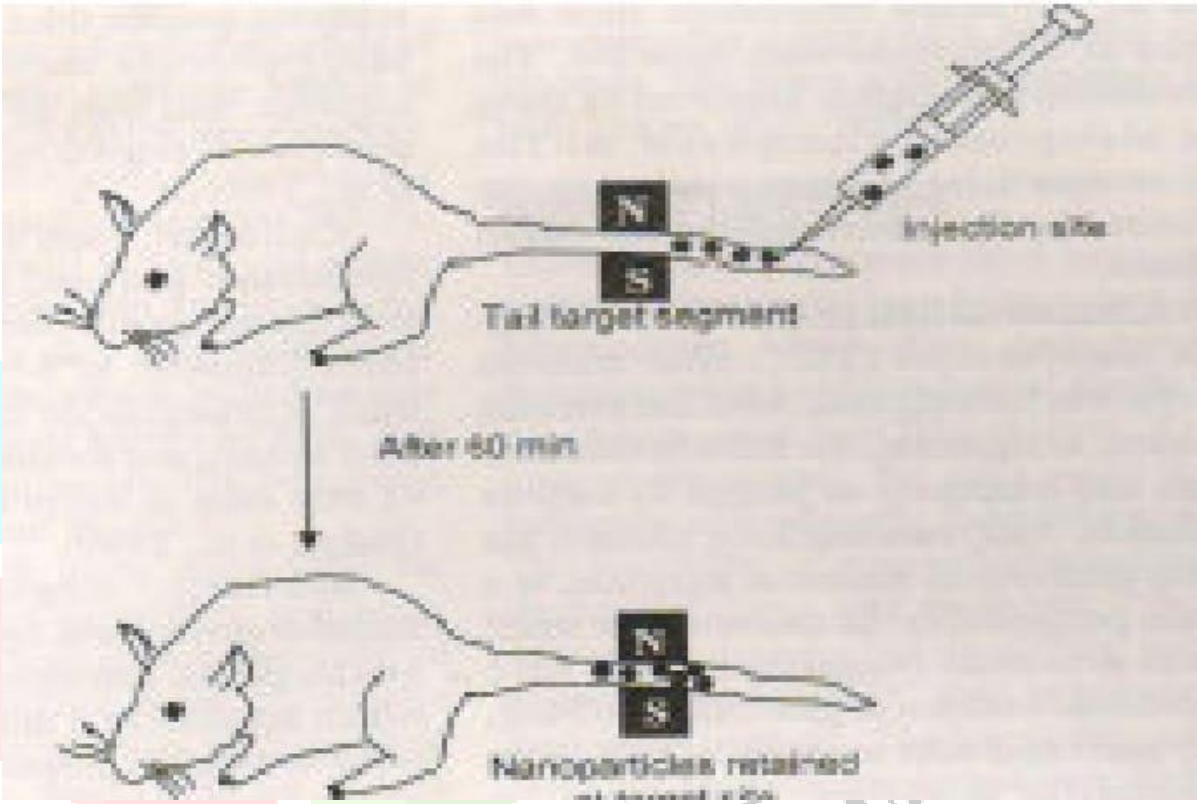

Fig: Schematic representation of retaining of Magnetic nanoparticles at Rat Tail target segment

D) Magnetic Resealed Erythrocytes

As drug carriers, resealed erythrocytes offer a number of benefits, including the ability to target specific organs, be biodegradable and biocompatible, and encapsulate a large variety of material in a small volume of cell.[36] These benefits of resealed erythrocytes led to the development of magnetic resealed erythrocytes, which include ferrofluides (magnetite) and drugs loaded within the cell. Ibuprofen-loaded magnetically responsive erythrocytes were created and examined in vitro. Using the preswell technique, the erythrocytes were loaded with ferrofluids (magnetite) and ibuprofen18. An external magnetic field was effectively sensed by the loaded cell. Numerous process variables that could impact the loading of drugs and magnetite were examined, such as drug concentration, magnetite concentration, and sonication of ferrofluids.[37] The hemoglobin release, morphology, osmotic fragility, in vitro magnetic responsiveness, and percentage of cell recovery of the loaded erythrocytes were all assessed. Erythrocytes containing diclofenac sodium were prepared using the preswell technique and characterized for a range of in vitro parameters as part of the ongoing study.19

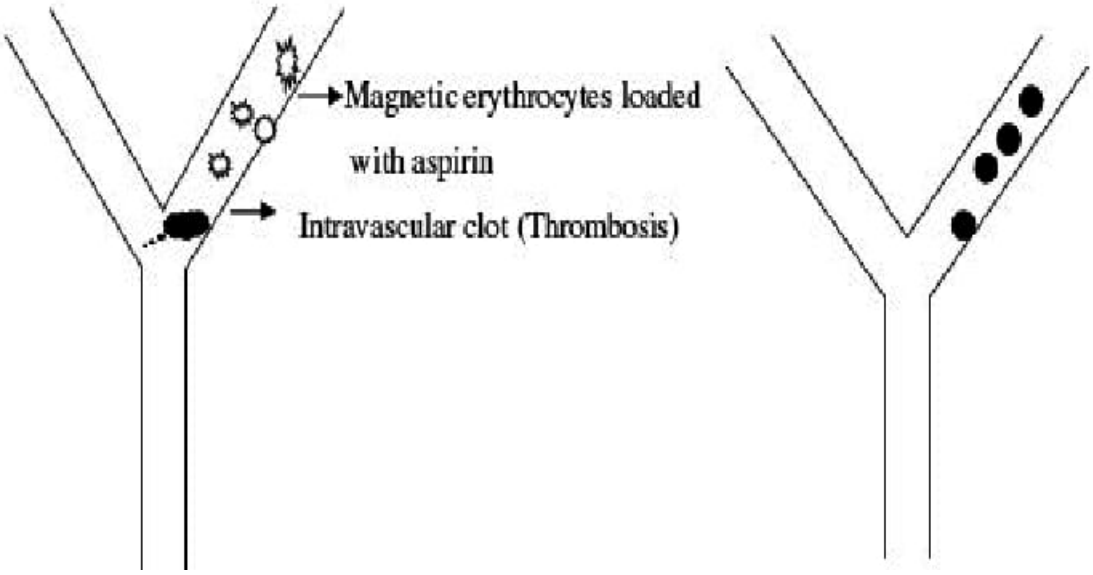

Fig: Prevention of Arterial Thrombosis by Aspirin loaded Magnetic Resealed Erythrocytes

E) Magnetic Emulsion

In addition to magnetically modulated systems, such as microspheres and microcapsules, Another attempt was made to use magnetic emulsion as a drug carrier for chemotherapy agents.[38] The emulsion, an oil in water type that is magnetically responsive and contains a chemotherapeutic agent, can be selectively localized by applying an external magnetic field to a particular target site.[39] By using casein solution as the continuous phase and anticancer agent, methyl CCNU trapped in the oily dispersed phase as an active chemotherapeutic agent, and ethyl oleate-based magnetic fluid as the dispersed phase, Akimoto and Morimoto created a magnetic emulsion. Certain chemotherapeutic agents may benefit from the site specificity that magnetic emulsion appears to offer.

F) Biomodulators

There are four ways in which biological response modifiers (BMRs) modify microbial, host, and tumor responses23.

1. Increasing host effector mechanisms that target microorganisms or tumor cells.

2.Redirecting the sites and duration of action of endogenous effector molecules or increasing their quantity can lead to a quantitative increase in endogenous effector resistance, which in turn reduces the host response that hinders tumor resistance.

3. Differentiating tumor cells increase the sensitivity of tumors to host cells.

4. A rise in the host's ability to tolerate traditional cancer treatment.

G) Magnetic Neutrophils

An indirect strategy of targeting white cells by chemoattraction fails in some clinical conditions where patient sera contains chemotactic factor in activators and neutrophils directed inhibitors of chemotaxis.[40] These illnesses include sarcoidosis, Hodgkin's disease, hemodialysate, Crohn's disease, alcoholic cirrhosis, and chronic lymphocytic leukemia.[41] These conditions are potentially fatal even though failure of chemotaxis is not seen in all patients. As a result, a method for getting neutrophils to consume magnetite bases should be created so that treatment can be delivered to infection sites only.[42]

CONCLUSION

The biggest benefit of magnetic drug delivery is that it makes drug targeting extremely simple. Magnetic delivery is particularly helpful in treating life-threatening diseases. The newest technology that gained attention in the 1990s is magnetic drug delivery. It has been discovered that magnetic vesicular systems are incredibly helpful carrier systems in a variety of scientific fields. Magnetic microcarriers have been studied for targeted drug delivery over the years, particularly for magnetic targeted chemotherapy because of their superior tumor targeting, therapeutic efficacy, reduced toxicity, and adaptability to be customized for a variety of desirable goals. Despite a few disadvantages, like the need for a strong magnetic field to dissolve ferrofluid and deposit magnetite, magnetic microcarriers are still crucial for the precise delivery of different medications and for selective targeting. Future drug targeting research in this difficult area will require more studies, long-term toxicity assessments, and characterization in order to guarantee the advancement of magnetic drug delivery systems.

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