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Magnetic nanoparticle-A review

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ABSTRACT

In the recent past, the targeted drug delivery has gained more attention for various advantages. Magnetic nanoparticles backed foremost attention offering local drug delivery, reduced side effect and controlled drug release for prolonged period of time addressing problems of healthy tissue damage, drug wastage. An approach is made herein to review the concepts and history of magnetic nanoparticle, magnetic property, methods of preparation, advancements, core and coating materials, protection of nano particles, applications explored in various field of drug delivery, nanoparticle in gene therapy.

Keywords: - magnetic nanoparticles, drug targeting, super paramagnetism, gene delivery.

1. INTRODUCTION

As of today oral route is still the most preferred route of administration as it is convenient and relatively easy to manufacture. But this route has several drawbacks primarily due to the incomplete absorption or degradation into the GI environment. Hence there is a continuous demand for exploring new methodologies to overcome these issues. Even topical route is widely used for some drugs which are meant for local action or are not stable in solution form or in GI mucosa [1]. Although skin is known to be hostile for most of the drugs because of its impermeable nature and complexity of skin anatomy. To some extent the absorption through the topical route has been successful using various techniques like using external stimuli and use of penetration enhancer.

This nanoparticle technique has emerged as a potential technology and has been explored for the last decade but still it has not been explored to its full potential [2,3]. The Nano particle technology basically works on the principle of

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reducing the particle size to submicron level where the drug has better chance of absorption with least side effects, this is primarily due to the large surface area. These nanoparticles include micro emulsion, nanoemulsion and other similar formulation and drug can be delivered using various mechanisms including use of external stimuli method. Magnetic nanoparticle is one of the promising approaches.

Magnetic nanotechnology is primarily used in the field of new therapeutic and diagnostic concepts in all areas of medicine including magnetic fluids, catalysis [2,3] biotechnology/biomedicine[4], magnetic resonance imaging[5,6] data storage[7] and environmental remediation[8,9].

In addition to the above mentioned uses, it can be used for drug delivery for local action, controlled drug delivery and above most the target drug delivery system with reduced side effects. The main idea of delivering drugs using magnetic nanoparticles is to the specific receptor site is to minimize the dose administered and avoid unnecessary exposure to human body to drug.

2. MAGNETIC PROPERTY

The classification of a material's magnetic properties is based on its magnetic susceptibility, which is given by the ratio of the induced magnetization (M) to the applied magnetic field which in turn depends on their temperature, external magnetic field H and atomic structures. At small sizes (in the order of tens of nanometer), ferri-or Ferro-magnetic materials, [10,11] such as magnetic Nanoparticles, become a single major domain and therefore maintain one large magnetic moment. However, at sufficiently high temperature (i.e., blocking temperature) thermal energy is sufficient to induce free rotation of the particle resulting in the loss of net magnetization in the absence of an external field [12, 13].

3. PREPARATION OF MAGNETIC NANOPARTICLES

Particles are usually prepared via using different method but homogeneous precipitation reactions is most widely used method of preparation, a process that involves the separation of the nucleation and growth of the nuclei.[14,15]

3.1. CO-PRECIPITATION

Co-precipitation method may be the most promising method because of its simplicity and productivity [18, 19]. It is a convenient way to synthesize iron oxides (either Fe_3O_4 or g-Fe_2O_3) from aqueousFe_2^+/Fe_3^+ salt solutions by the addition of a base under inert atmosphere at

room temperature or at elevated temperature. The size, shape, and composition of the magnetic nanoparticles depends on various parameters like type of salts used (e.g. chlorides, sulphates, nitrates), the Fe_2^+/Fe_3^+ ratio, the reaction temperature, the pH value and ionic strength of the media .The saturation values of magnetite nanoparticles is experimentally determined to be in the range of 30–50 emug. The stability of the nanoparticles is of concern especially when exposed to ambient conditions, if dissolved in an acidic medium. Degradation by oxidation is not a issue with these hence, magnetite particles can be subjected to deliberate oxidation to convert them into maghemite. This type of transformation is achieved by dispersing them in acidic medium, then add iron (III) nitrate. The magnetite particles obtained are then chemically stable in alkaline and acidic medium .However, even if the magnetite particles is converted into maghemite after their initial formation, the experimental challenge in the synthesis of Fe_3O_4 by co-precipitation depend upon the particle size and thus achieving a narrow particle size distribution. Since the blocking temperature depends on particle size, a wide particle size distribution has result in a wide range of blocking temperatures and therefore non-ideal magnetic behaviour for many applications. Particles are prepared by co-precipitation unfortunately tend to be rather polydisperse. It is well known that a short burst of nucleation and subsequent slow controlled growth is crucial to produce monodisperse particles. Controlling these processes is therefore the key in the production of monodisperse iron oxide magnetic nanoparticles. Recently, significant advances for preparation of monodisperse magnetite nanoparticles, of different sizes, have been made by the use of organic additives as stabilization and/or reducing agents. For example, magnetite nanoparticles with sizes of 4–10 nm are stabilized in an aqueous solution of 1 wt% polyvinlyalcohol (PVA). However, when PVA containing0.1 mol% carboxyl groups is used as the stabilizing agent, magnetite nanoparticles in the form of chain like clusters precipitate.[19] This result indicates that the selection of improper surfactant is an important issue for the stabilization of such particles. Size-tuneable maghemite nanoparticles is prepared by initial formation of magnetite in the presence of the trisodium salt of citric acid, using an alkaline medium, and subsequent oxidation at 908C° for 30 min by using iron(III) nitrate. The size particles is varied from 2 to 8 nm by adjusting the molar ratio of citrate ions and metal ions (Fe_2^+ and Fe^{3+}).[20] The effects of several organic anions, such as carboxylate and

hydroxyl carboxylate ions, on the formation of iron oxides or oxyhydroxides has been studied extensively.[20-24] The formation of surface complexes requires both deprotonated carboxy and deprotonated a-hydroxy groups.[24] Recent studies and advancement showed that oleic acid is best suited for the stabilization of Fe_3O_4.[25, 26] The effect of organic ions on the formation of metal oxides or oxyhydroxides can be rationalized by two competing mechanisms. Chelation of the metal ions can be prevented by nucleation and leads to formed larger particles because the number of nuclei formed is small and the system is dominated by particle growth. On the other hand, the adsorption of additives on the nuclei and the growing crystals may inhibit the growth of the particles, which favours the formation of small units

3.2. REVERSE MICELLE MECHANISM

The formation of micelles is a classic phenomenon of surfactant chemistry [27]. Surfactants are primarily surface acting agents and they have both hydrophilic head and a long, hydrophobic tail (shown in **Figure 1**). The formation of micelles occurs when the surfactant concentration reaches a critical micelle concentration CMC1, while CMC2 is the concentration triggering the self-assembly of liquid crystals which is not discussed here. Normal micelles forms in aqueous medium (such as using detergents in cleaning processes) but reverse micelles forms in oily medium (e.g., hexane). The center of the reverse micelles is hydrophilic and can accept inorganic components of the reaction mixture. For the synthesis of iron oxide-based magnetic nanoparticles, inorganic precursors such as iron(III) chloride are dissolved in an aqueous medium and added to the oily reaction mixture with the surfactants. This is followed by the addition of pH regulators like ammonia or NaOH and inorganic coating materials (.e.g., silica or gold).

By the use of micelles, the size of the particles can be easily controlled and consequently nanoparticles which are obtained are consistent size within a range of few nm to few hundred nm. Also, the inorganic coating materials can be added to the micelles during synthesis, so nanoparticles which is produced by this method can be coated with an inorganic protective layer during the process. This technique has limitation is that the synthetic organic coatings are not possible as the monomers will remain in the organic phase of the micelle solution which is usually outside the micelle structure and synthesis of particles outside this range are not possible using this method. Also, with such a large amount of organic solvent involved in making the micelles, the reverse micelle method is difficult to scale-up.

3.3. THERMAL DECOMPOSITION AND REDUCTION

This method is inspired with the synthesis of high-quality semiconductor nanocrystals and oxides in non-aqueous media by thermal decomposition,[30-32] similar methods for synthesis of magnetic particles having control over size and shape have been developed. Monodisperse magnetic nanocrystals with smaller size can be synthesized through the thermal decomposition of organometallic compounds in high-boiling organic solvents using surfactants as stabilizing agents [16, 33, 34].

When metal oxy-salts (such as nitrates, carbonates and acetates) are heated to a certain temperature, they decompose and form metal oxides. For example, iron (III) nitrate decomposes to iron (III) oxide according to the following equation:

$$4Fe(NO_3)_3(s) \rightarrow 2Fe_2O_3(s)+12NO_2(g)+3O_2(g) \quad (1)$$

These metal oxide nanoparticles can be further reduced to metal by heating the oxides to a certain temperature under a reducing gas, usually hydrogen gas or carbon monoxide (CO), following the equations:

$$MO+H_2 \rightarrow M+H_2O \quad (2)$$

$$MO+CO \rightarrow M+CO_2 \quad (3)$$

This reduction method applies to most metal oxides with a limitation that it can't be used on alkaline and alkaline earth metals [36]. With very little involvement of solvent, this thermal method is popular with industry. However, control of the particle size is difficult and the same problem as wet precipitation for particle coating hampers its use in some laboratories.

3.4. MICRO EMULSION

A microemulsion is a thermodynamically stable isotropic dispersion of two immiscible liquids, where the microdomain of either or both liquids is stabilized by use of surfactant [37]. In W/O microemulsions, the aqueous phase is dispersed as microdroplets (1– 50 nm in diameter) surrounded by a monolayer of surfactant molecules in the continuous hydrocarbon phase. The reverse micelle size is determined by the ratio of water to surfactant used [38-39]. By mixing two identical W/O microemulsions containing the desired reactants, the microdroplets is continuously collide, coalesce, and break again which results, the formation of precipitate in the micelles[40]. Extraction of precipitate is carried out by addition of solvent, such as acetone or ethanol, to the microemulsions, followed by filtration and centrifugation of the mixture. In this sense, a microemulsion is used as a nanoreactor for the formation of nanoparticles.

Using the microemulsion technique, synthesis of metallic cobalt, cobalt/platinum alloys, and gold-coated cobalt/platinum nanoparticles have been carried out by using reverse micelles of cetyltrimethlyammonium bromide and 1-butanol as the co-surfactant and octane as the oil phase.[41] MFe2O4 (M: Mn, Co, Ni, Cu, Zn, Mg, or Cd, etc.) are among the most important magnetic materials and have been widely used for electronic applications. Spinel ferrites can be synthesized in microemulsions and inverse micelles. For instance, MnFe2O4 nanoparticles having controllable sizes between 4–15 nm are synthesized through the formation of water-in-toluene inverse micelles with sodium dodecylbenzenesulfonate (NaDBS) as surfactant.[42] In the synthesis a clear aqueous solution consisting of $Mn(NO_3)_2$ and $Fe(NO_3)_3$. A NaDBS aqueous solution is added to the solution of metal salt, addition of a large volume of toluene results, the formation of reverse micelles. The volume ratio of water and toluene determines the size of the resulting $MnFe_2O_4$ nanoparticles. [43]. reported that iron oxide nanorods can be fabricated through a sol–gel reaction in reverse micelles which is formed from oleic acid and benzyl ether, using $FeCl_3 \cdot 6H_2O$ as a iron source and propylene oxide as a proton scavenger.[98] A cobalt ferrite fluid is prepared by using methylamine and in-situ formed cobalt and iron dodecyl sulphate which is formed by mixing an aqueous solution of sodium dodecyl sulphate either with iron chloride or with cobalt acetate solution.[44] The size of the cobalt ferrite particles decreases with decreasing the concentration of reactant and increasing the concentration of sodium dodecyl sulphate . The size of the particles can be varied from 2 to 5 nm. However, the polydispersity is rather high at 30–35%.

3.5. CHEMICAL VAPOUR CONDENSATION (CVC)

When volatile metal compounds are heated in a inert gas atmosphere, these compounds decompose and form metal nanoparticles. Metallic iron nanoparticles are prepared by using CVC mechanism [46]. In this process, iron carbonyl, $Fe(CO)_5$, is used as iron precursor and the average particle size is 5–13 nm. Oxidation of these metallic iron nanoparticles is possible. Magnetite nanoparticles of size 3 to 20 nm [53]and maghemite nanoparticles of size 4 to 16 nm [47]is prepared by oxidation of metallic iron nanoparticles. Although this technique produces high-quality nanoparticles but complex infrastructure is required. More important, some of the precursors such as $Fe(CO)_5$ are highly toxic (with CO as by-product) and unnecessary exposure is a point of

concern.

3.6. HYDROTHERMAL SYNTHESIS

Under hydrothermal conditions a broad range of nanostructured materials can be formed.[48]. A simple hydrothermal method for synthesis of a variety of different nanocrystals is by a liquid–solid–solution reaction. The system consists of metal linoleate (solid), an ethanol–linoleic acid liquid phase, and a water–ethanol solution under different reaction temperature and hydrothermal conditions.[49] Monodisperse, hydrophilic, single crystalline ferrite microspheres are also synthesized by hydrothermal reduction.[50] for example a mixture, consisting of FeCl3, ethylene glycol, sodium acetate, and polyethylene glycol, is stirred vigorously to form a clear solution, then enclosed in a Teflon-lined stainless-steel autoclave, and heated to a 200C° for extended time(8–72 hrs). In this way, monodisperse ferrite spheres are obtained with optimum sizes in the range of 200–800 nm. It is skilfully used the multicomponent reaction to direct the synthesis: Ethylene glycol is used as a high-boiling-point reducing agent, which is known from the polyol process to produce monodisperse metal or metal oxide nanoparticles; sodium acetate is primarily used as electrostatic stabilizer and thus prevent particle agglomeration, and polyethylene glycol can also be used as an surfactant to prevent particle agglomeration.

4. MAGNETIC CORE MATERIAL USED:

There are many magnetic materials with a wide range of magnetic properties. Certain materials due to their toxic potential like cobalt and chromium are not preferred as biomedical agents in vivo but if their use is absolutely necessary then they can be use with a non-toxic, protective coating with high mechanical strength. Iron oxide-based materials such as magnetite and maghemite, however, are relatively safe and are currently used in the clinic as MRI contrast agents. The following are some magnetic materials which can be used in biomedical applications.

4.1. Magnetite Fe_3O_4

Magnetite is a common mineral which exhibits Ferro-and ferri-magnetic properties. The structure of magnetite belongs to the spinel group, having a formula of AB2O4. Its ferromagnetic structures arise from alternating lattices of Fe(II) and Fe(III). This has an advantage as it gives very strong magnetization compared to naturally occurring antiferromagnetic compounds such as the ferrihydrite core of the ferritin protein.

4.2. Maghemite γ-Fe_2O_3

Maghemite, a top tactic by product of

magnetite and has the similar lattice structure as magnetite but all iron atoms are in Fe(III) oxidation state. It can be thermally transformed to other forms of iron(III) oxides such as hematite, which is antiferromagnetic.[51] The strong magnetization of maghemite is multifold stronger than hematite and ferrihydrite, is due to lattice vacancies which give rise to uncompensated electron spins within the structure. Maghemite is one of the most preferred materials for the core of magnetic nanoparticles because of its non- hazard characteristic. Iron (III) ions are normally found in human body so leaching of metal shouldn't cause significant untoward effects. As a result, maghemite is a popular choice for making magnetic nanoparticles, especially for biomedical applications.

4.3. Iron-based metal oxides

There are many iron-based metal oxides having strong magnetic properties and can be used as magnetic cores for preparation of magnetic nanoparticles. Process for preparation of mixed oxide nanoparticles such as $CoFe_2O_4$, $NiFe_2O_4$, and MnFe2O4 are common [52]. It doesn't matter that these materials have a remarkably similar spinel structure to magnetite Fe_3O_4. However, using these mixed oxide nanoparticles in biomedical research can be hampered by the inherited high toxicity of these transition metals (Co, Ni, Mn). Non-permeable coatings are for prevention of leaching of these metals. Other common examples of mixed oxides include alkaline earth metals such as barium (BaFe12O19) and strontium ($SrFe_{12}O_{19}$), which belong to the magnetoplumbite-system [54]. Again, leaching of these alkaline earth metals is a point of concern in biomedical applications.

4.4. Iron alloys

Although iron metal itself is a good material for magnetic applications, it is not commonly used as core material for the synthesis of magnetic nanoparticles unless they are coated with an inert, protective coating. Iron is susceptible to corrosion in presence of aqueous medium, i.e., rusting. Hence the use of iron alloys is restricted in nanoparticles. Also, characterizing the iron surface is very complex, hence iron alloys, such as FePt and FeAu, are more popular as core materials for magnetic nanoparticles.

Other possible core materials for magnetic nanoparticles include rare earth metal alloys and transition metal clusters. The use of these materials for magnetic nanoparticles core synthesis is still rare due to their potential toxic effects on the human body.

5. PROTECTION OF NANOPARTICLES:

5.1. Coating materials

Nanoparticles are more reactive than bulk materials primarily due to their high surface to volume ratio[55]. As a result, this magnetic core nonmaterial's required to be protected against corrosion. This coating also prevents the leaching of potentially toxic components into the body during in vivo applications. There are many choices of coating materials. One has to consider the nature of the coating and the ease of further functionalization to suit specific applications.

5.2. Surfactant and polymer coating

Surfactants or polymers are often employed to passivate the surface of the nanoparticles during or after the synthesis to avoid agglomeration. In general, electrostatic repulsion or steric repulsion both can be used to disperse nanoparticles and keep them in a stable colloidal state. The best example for such systems are the ferrofluids which were invented by Papell in 1965.[56] In the case of ferrofluids, for determination of collision stability of magnetic particles surface properties of magnetic particles is required . The main measures which are used to enhance the stability of ferrofluids are depend upon surface charge[57] and the use of specific surfactants.[58-60] For instance, magnetite nanoparticles synthesized through the co-precipitation of Fe_2^+ and Fe_3^+ in ammonia or NaOH solution are usually negatively charged, resulting in agglomeration. To achieve stable colloids, the magnetite nanoparticle precipitate can be peptized (to disperse a precipitate to form a colloid by adding of surfactant) with aqueous tetramethylammonium hydroxide or with aqueous perchloric acid. [57] The magnetite nanoparticles can be acidified with a solution of nitric acid and then further oxidized into maghemite by the help of iron nitrate. After centrifugation and redispersion in water, a ferrofluid based on positively charged g-Fe_2O_3 nanoparticles is obtained, since the surface hydroxy groups are protonated in the acidic medium.[61] Commercially, water- or oil based ferrofluids are available. They are stable when the pH value is below 5 (acidic ferrofluid) or over 8 (alkaline ferrofluid).

5.3. Polymers used:

5.3.1. Natural polymers

Coating magnetic nanoparticles with natural polymers such as carbohydrates and proteins is common [62- 69]. Many natural polymers are biocompatible and therefore suitable for coating nanoparticles for biomedical applications. Table 1 shows some examples of

magnetic nanoparticles with natural polymer coatings for biomedical applications

5.3.2. Synthetic natural polymer

Since many natural polymers have lack mechanical strength while others, such as cellulose, are too rigid to be manipulated to coat nanoparticles, synthetic polymers may help to get rid of this problem. Synthetic polymers such as polyethylene glycol (PEG 65), polyvinyl alcohol (PVA) [82-83] and poly-L-lactic acid (PLA) [84-85] are some examples or coatings for magnetic nanoparticles one interesting example is PVA coating, which has the structure shown in Figure 2. The hydroxyl groups (-OH) on the polymer skeleton ensure the hydrophobic property of the coating, which resembles the surface chemistry of carbohydrates such as dextran. The use of PVA-coated magnetic nanoparticles in biomedical applications has been reported [81]. This research group has demonstrated the internalization of PVA and PVA co-polymer-coated magnetic nanoparticles by synoviocytes and by cells of the synovial membrane in sheep [80] shown in figure 3.

5.4. Precious metal coating

It can be deposited on magnetic nanoparticles through reactions in microemulsion,[86, 87] redox transmetalation,[88–90] iterative hydroxylamine seeding,[91] or other methods, to protect the cores against oxidation. A synthesis of platinum-coated cobalt by refluxing cobalt nanoparticle colloids (ca. 6nm) and [Pt-$(hfac)_2$] (hfac=hexafluoroacetylacetonate) in a nonane solution which contain $C_{12}H_{25}NC$ as a stabilizer.[90] After 8 h reflux and add ethanol and then centrifugation carried out, the colloids in powder form are isolate from the dark red-black solution . The TEM images of the platinum-coated cobalt particles with sizes below 10 nm. The particles obtained are air stable and can be redispersed in typical organic solvents. The reaction by product was separated and analyzed as $[Co(hfac)_2]$, indicating that the formation of the core–shell structure was driven by redox transmetalation reactions between Co^0 and Pt^{2+}

5.4.1. Gold:

Gold is one of the most commonly used materials for bioscience interfaces [93-94]. It is not only very stable but can easily functionalized via thiol linkers (–SH) [95]. Figure 2 shows how gold-coated magnetic nanoparticles can be functionalized with thiol linkers. It is well-known that thiols, and many other sulphur compounds, have high affinity to the gold surface. Scientists have been using this phenomenon in biotechnology, such as binding

antigens for immunoassay [96-97].It's shown in figure 2.

5.5. Carbon coating

Right after the discovery of fullerenes, it was found that carbon-encapsulated metal or metal carbide nanocrystallites can be generated by the Kr Stschmer arc-discharge process.[98]Since then, many studies have shown that the graphitized carbon structures, such as carbon nanotubes and onions in the presence of metal nanoparticles (Co, Fe, Ni, Cr, Au, etc), are formed under arc-discharge, laser ablation, and electron irradiation.[99-103].Nanoparticles are well prevented against oxidation and acid erosion because of well developed graphitic carbon layers which provide an effective barrier . These facts indicate that synthesis of carbon-coated magnetic nanoparticles are possible, which have thermal stability and have high stability against oxidation and acid leaching, which is crucial for some applications.[104] Moreover, carbon-coated nanoparticles are usually in the metallic state, and thus have a higher magnetic moment than the corresponding oxides. Gedanken and co-workers reported a sonochemical procedure that leads to air-stable cobalt nanoparticles.[105] They claim that the high stability arises from the formation of a carbon shell on the nanoparticle surface. The particles obtained are rather polydisperse and not very uniform The cobalt nanoparticles were coated with furfuryl alcohol which was converted first into poly (furfuryl alcohol) and then carbonized to carbon during the pyrolysis, which result in a stable protection layer against air oxidation, and erosion by strong acids and bases. Interestingly, if CTAB is used as the carbon source, the carbon coating is not perfect and the cobalt core can be leached with acid. Since the imperfect graphite coating is not attacked, graphitic hollow shells were obtained, which may be interesting for use as electrodes. Similar graphitic- carbon -encapsulated cobalt nanoparticles were also prepared through pyrolysis of a composite of metallic cobalt nanoparticles (ca.8–10 nm) and poly(styrene-b-4-vinylphenoxyphthalonitrils).[107] These cobalt-graphitic particles are oxdatively stable and retain their high saturation magnetizations (ca. 95–100 emug_1) for at least one year under ambient conditions. Recent investigation suggested that the structure development of cobalt cations chemically adsorbed in an in-house synthesized ion-exchangeable polymer. During pyrolysis, the in-situ formed cobalt nanoparticles catalysis the decomposition of the polymer matrix which leads to the formation of mesoporous graphitic carbonand then Cobalt nanoparticles were embedded in graphitic carbon which were obtained as the final product. Magnetization measurements show

that the graphitic carbon/cobalt composites are ferromagnetic, and the cobalt nanoparticles are stable under air for more than 10 months without degradation of their magnetic properties.[108]

6. APPLICATION:

6.1. In catalysis and biotechnology:

Magnetic nanoparticles with good stability will be of great interest in catalysis and in biotechnology/biomedicine applications. Such magnetic nanoparticles can be very useful to assist an effective separation of catalysts, nuclear waste, biochemical products, and cells magnetically driven separations helps in making the recovery of catalysts in a liquid-phase reaction much easier than by crossflow filtration and centrifugation, especially when the catalysts are in the sub-micrometer size range. Such small and magnetically separable catalysts have advantages of high dispersion and reactivity with easy separation. In terms of recycling expensive catalyst or ligands, immobilization of these active species on magnetic nanoparticles leads to the easy separation of catalysts in a quasi-homogeneous system These magnetic nanoparticles coupled with chiral catalysts are more accessible to the reactants because of their small size, and are to some extent similar to homogeneous asymmetric catalysts. Magnetic nanoparticles with core–shell structure may be used for the development of a new type of catalyst. The shell consists of the catalytically active species, and the magnetic core can act as anchor for separation of and recycle the catalyst. As an example, core–shell-type cobalt–platinum nanoparticles have been prepared by a redox transmetalation reaction between cobalt nanoparticles and $[Pt(hfac)_2]$.[108-109] The platinum forms a shell around the cobalt core and the shell surface is stabilized by dodecyl isocyanides capping molecules. The core–shell structures are super paramagnetic at room temperature. Such a catalyst has the advantage of economically using the platinum atoms, because only the outer atoms are accessible for the reagents, and the magnetic cobalt core plays a critical role in the separation and recycling of the catalyst. This catalyst is effective for the hydrogenation of unsaturated organic molecules under mild conditions. If the magnetic species is intrinsically catalytically active for certain reactions, this magnetic catalyst will advantageously combine both the catalytic and the separation function. Thus, iron nanoparticles stabilized by 1,6-bis(diphenylphosphino)hexane or polyethylene glycol exhibit high activity for the cross coupling of aryl Grignard reagents with primary and secondary alkyl halides bearing b-hydrogen atoms. This catalyst has also proven

to be effective in a tandem ring-closing/cross coupling reaction.[110]

In biotechnology and biomedicine, magnetic separation can be used for the efficient and reliable capture of specific proteins or other biomolecules. Current use of most particles are super paramagnetic, means that they can be magnetized with an external magnetic field and immediately redispersed once the external magnetic field is removed. Magnetic iron oxide nanoparticles grafted with dopamine have been used for protein separation.[111] The dopamine molecule has bidentate enediol ligands which can convert the coordinatively unsaturated iron surface sites back into a bulk-like lattice structure with an octahedral geometry for the oxygen-coordinated iron centres, which results in tight binding of dopamine to iron oxide.[112] The obtained nanostructure can act as an anchor to further immobilize nitrilotriacetic acid molecules.

6.2. Magnetic nanoparticle for gene therapy:

In the first study to demonstrate targeted delivery of DNA using magnetic particles Cathryn Mah, Barry Byrne and colleagues [113] at the University of Florida, coated adeno-associated virus (AAV) encoding Green Fluorescent Protein (GFP) to the surface of magnetic particles using a cleavable heparin sulfate linker. In this study, AAV_2 conjugated to magnetic microspheres gave increased transduction efficiency in both C_{12}s cells cultured in vitro and in vivo following intramuscular injection to 129/svJ mice [114].

Although employing the target specific linkers undoubtedly provides an fair approach to the attachment of target molecules it is not always possible. An alternative approach for attaching DNA to the surface of particles is by using the electrostatic interactions between the negatively charged phosphate backbone of DNA and positively charged molecules linked to the particle surface. A popular choice for this approach is the cationic polymer Polyethyleneimine (PEI). This was among the first reported transfection agents and binds and condenses DNA due to the large number of secondary amine groups present along it's chain length [115]. In addition, PEI facilitates lysosomal release of the complex following internalisation by buffering the intralysosomal pH which causes the lysosome to rupture and release it's contents [116] Since it is now understood that particle DNA complexes typically enter the cell by endocytosis through clatharin-dependent pits [117], it is possible that this feature of PEI may remain beneficial for PEI-coated particles.

Polyethyleneimine-coated magnetic particles were first reported by Scherer et al in 2002 [118]and provided the first example of in vitro

magnetic nanoparticle-mediated non-viral gene delivery. In addition to facilitate the targeted gene delivery, the advantage of this approach is the rapid sedimentation of the gene-particle complex onto the target area which reduces both time and dose of vector to achieve efficient transfection. In their original study, Scherer et al demonstrated that association of DNA vectors with super paramagnetic nanoparticles increased the transfection efficiency of a number of commercial transfection reagents in vitro and enabled the duration of gene delivery to be reduced to as little as 10 minutes. Furthermore, conjugation of adenoviral vectors to the particles enabled transduction of a number of cells lines that expressed little or no Coxsackie and adenovirus receptor (CAR). This finding provides the further evidence to support the idea that associating viral vectors with nano- or microparticles may extend the host tropism to non-permissive cells. Since this original study, magnetofection has been used to transfect a number of cell types including primary lung epithelial cells [119] and blood vessel endothelial cells [121]. These particles have also been used to successfully deliver antisense oligonucleotides [120], and small interfering RNA (siRNA) to downregulate gene expression. In a recent study by Schilinger et al (2005) siRNA associated with magnetic particles significantly reduced retrovirally mediated expression of luciferase in Hela cells.

Recent studies reported an alternative approach for synthesizing PEI coated magnetic particles based upon covalently coupling PEI to the surface of composite iron oxide, dextran silica particles using glutardialdehyde linkers [122].

To date, much of the work based upon linking DNA vectors to magnetic particles has centered upon the ability of this approach to reduce the time needed for transfection, or minimize the dose of vector. Recent work by our group has focused on improving the overall transfection efficiency of this technique by using dynamic magnetic fields produced from oscillating arrays of permanent rare earth magnets. Preliminary data from these studies suggest that this approach can improve the level of transfection >10 fold compared to static magnetic fields. The oscillating fields introduce extra energy to the system which improves particle uptake. In addition, the non-linear motion of the particles as they move along the field gradient may aid tissue penetration for in vivo applications and help to overcome the extracellular barriers (such as mucus layers) to gene delivery that exist in some clinical targets for gene delivery such as the CF lung.

Another novel approach to nanoparticle mediated gene delivery has recently been reported by cai et al 2005[123] Termed as

nanotube spearing, it is based upon using nickel embedded carbon nanotubes coated in DNA. When the nanotubes are introduced to cells in the presence of a specifically orientated magnetic field, the nanotubes align with the magnetic flux lines as they are pulled towards the cells. Hence this enables the nanotubes to spear the cells, pass through the membrane and deliver the target DNA, and it is has been successfully used to transfect a number of different cell types including Bal17 B-lymphoma, ex vivo B cells and primary neurons, whilst maintaining a high rate of cell viability after transduction.

7. ADVANCEMENTS

Due to magnetic forces, generally they are short ranged and underwhelming compared to hydrodynamic forces in the body, the targeted collection of magnetic nanoparticles has met with the limited success. So, an attempt is made to overcome its shortcomings, the notion of using a ferromagnetic implant, in conjugation with the multi drug carrier particles(MDCPs) and an external magnetic field, has been receiving considerable attention termed as implant assisted magnetic drug targeting

8. CONCLUSION:

Magnetic nanoparticles offer to open new ways and possibilities in the area of drug delivery, and they promises as a prudent tactic to overcome the drug delivery related problems when the problems of toxicity, localization, cast are addressed.

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Table 1: Properties of natural and synthetic polymers for coating magnetic nanoparticles.

Polymer	Hydrophobicity	Applications	Reference
Natural polymers			
Carbohydrates:			
Dextran	Hydrophilic	Drug delivery	[70]
		Radioimmunoassay	[71]
		MR imaging	[72]
		Hyperthermia	
Starch	Hydrophilic	Tumour targeting, MR imaging, x-ray imaging	[73]
Proteins			
Albumin	Hydrophilic	MR imaging	[74]
Lipids	Hydrophobic	Immunoassay	[76]
Synthetic polymers			
Poly(ethyleneglycol) (PEG)	Hydrophilic	MR imaging	[77]
			[78]
			[77]
		Drug delivery	[79]
Polyvinylalcohol (PVA)	Hydrophilic	Drug delivery	[80]

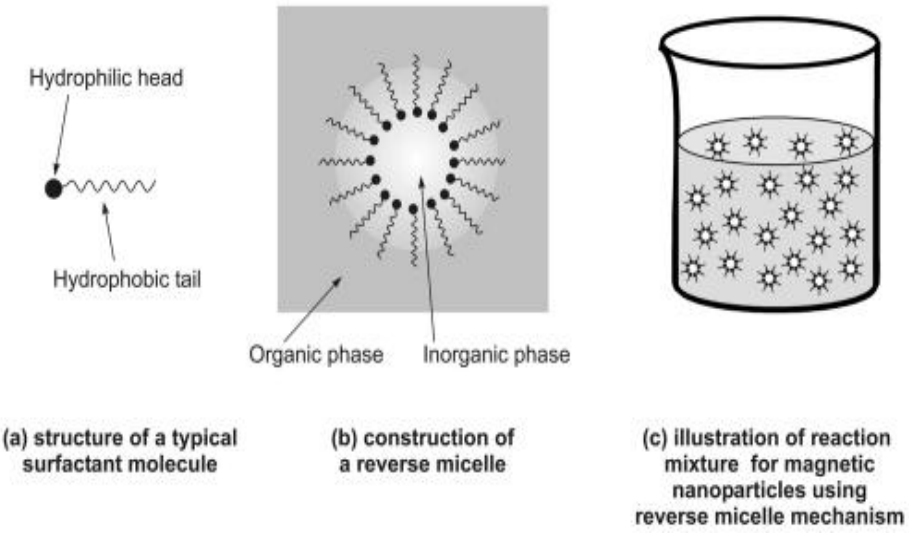

Figure 1: Schematic diagram of reverse micelle.

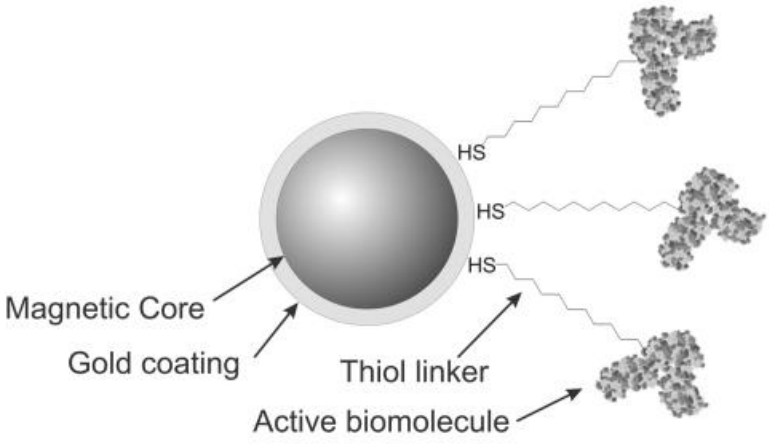

Figure 2: Gold coating

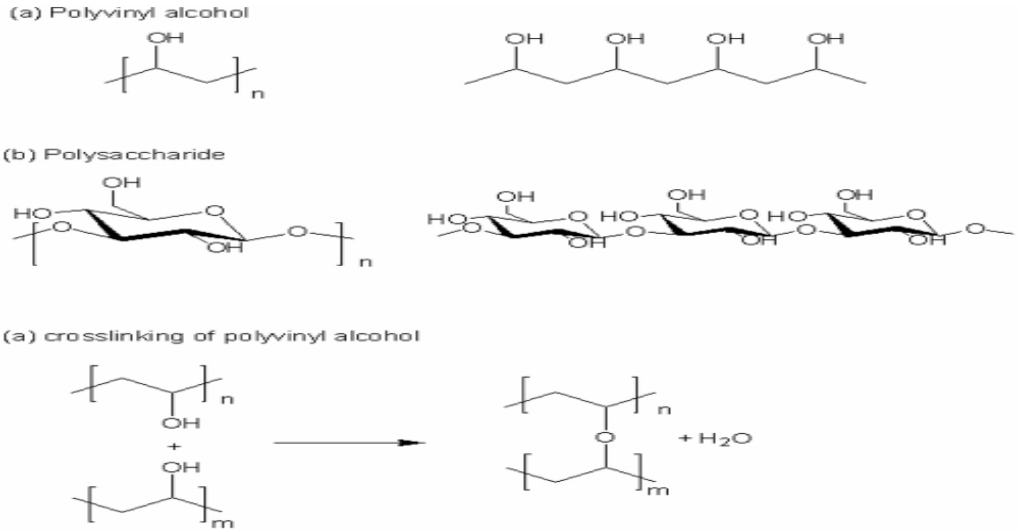

Figure 3: Reaction of poly vinyl alcohol and polysaccharide

The structure of PVA (a) which is compared with a polysaccharide (b) as both materials have abundant hydroxyl groups on surface. The cross linking reaction is shown in(a)