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Document heading doi: 10.21276/apjhs.2019.6.1.12 **Review Article**

Magnetic microspheres: An Overview

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Abstract

Magnetic microspheres are supramolecular particles that are small to circulate through the capillaries without producing embolic occlusion but are sufficiently susceptible to be encaptured in microvessels. Magnetic microspheres are particles that target the drug to the target site, RES Clearance is minimised. Now-a-days magnetic microspheres are being a trend of controlled and rapid drug release for better absorption, better penetration, rapid drug release, controlled drug release, improved bioavailability, improved physical stability, target drug delivery etc. The review article discusses its use in cancer therapies, applications,advantages,disadvantages etc.

Keywords: Magnetic, microspheres, target, drug.

Introduction

From many decades, scientists and researchers working hard to develop a novel drug delivery system with utmost better effectiveness, rapid drug release, controlled drug releases; so as to reach peak plasma concentration at right time and for the cure of acute and chronic diseases.Now-a-days magnetic microspheres are being a trend of controlled and rapid drug release for better absorption, better penetration, rapid drug release, controlled drug release, improved bioavailability, improved physical stability, target drug delivery etc. They are not only prolonged release drugs but also control release drugs. The magnetic properties of these particles add a new dimension where they can be manipulated upon application of an external magnetic field. This property opens up new applications where drugs that are attached to a magnetic particle to deliver the drug at a rate directed by the needs of the body during the period of treatment and target the activity entity to the site of action in the body using a magnetic field. Magnetic microspheres are freely flowing particles that are spherically encapsulated and with biodegradable and non-biodegradable components having size between 130p to 135p that is suspended within an aqueous vehicle or organic or inorganic vehicle.

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In magnetic microspheres, the one which is entrapped by a capsule wall is called microcapsule and the other entrapped substance entrapped through microsphere matrix is called micromatrices.

Advantages of magnetic microspheres

1. Increased bioavailability
2. Reduced toxicity
3. Targeted drug delivery
4. Controlled drug delivery
5. Reduced side effects
6. Minimized drug degradation
7. Biocompatibility
8. Controlled delivery of drugs
9. Ease of surface modification
10. Confers local effect
11. Duration of action is increased
12. Protein delivery is increased
13. Peptide delivery is also increased
14. Binding ability with receptor is high
15. Release of drug is high
16. Increased therapeutic value
17. Preparation method is easy
18. Better patient compliance
19. Site specific drug delivery
20. Increased efficacy
21. Bitter taste and smell can be masked
22. Physical stability can be improved.

Disadvantages of magnetic microspheres

1. Drug targeting is limited only to superficial tissues of skin like skin, superficial tumor and joints etc.
2. Toxicity of magnetic beads can occur.
3. In liver and RES regions , unknown localization of drug can seen
4. Dangerous effect of self flocculation of magnetic particles can be seen.
5. At the site of catheterization, thrombosis can occur
6. Magnetic targeting is very expensive.
7. It requires specialized technical approach.
8. It is only employed for severe diseases.
9. Removal is difficult, once injected.
10. During preparation, non-uniformity of drug can occur.
11. Due to intrinsic and extrinsic factors, sustained release can vary.
12. Rate of drug from one dosage form to that of another is different.
13. Failure of therapy can occur from dumping of dose.
14. Interaction and formation of complexes with blood components can occur due to parental delivery. This type of dosage form cannot be crushed or chewed.[1,2,3]

Applications of magnetic microspheres

1. The most popular applications of magnetic carrier technology are bioaffinity chromatography, wastewater treatment, immobilization of enzymes or other biomolecules and preparation of immunological assays.hormone replacement immunization and cancer chemotherapy. Magnetic
delivery of chemotherapeutic drugs to liver tumors. The first cancer clinical therapy trials using magnetic microspheres were carried out by Lubbe *et al.*,in Germany for the treatment of advanced solid cancer.

2. Magnetic targeting of radioactive compounds- magnetic targeting can be used to deliver the therapeutic radioisotopes. The advantage of this method over external beam therapy is that the dose can be increased resulting in improved tumour cell eradication without harm to adjacent normal tissues.

3. Treatment of tumors with magnetically induced hyperthermia development by Jordan and Chan lead to the current hyperthermia application of single domain dextran coated magnetite nanoparticles in tumors. The first clinical trials are going on in Germany. Magnetic hyperthermia is also possible with larger magnetic particles as shown by the group of *moroz et al*(2002).

4. Ongoing investigation in magnetic hyperthermia are focused on the development of magnetic particles that are able to self regulate the temperature they reach. The ideal temperature for hyperthermia is 43-45ºC.

5. Other magnetic targeting application -It can be used for encapsulation of peptide octreotide and protein tumour necrosis factor alpha. Advantages of this approach are target gene transfection at rapid speed and high efficiencies. It is also possible to use the mechanical physical properties ofmagnetic particles for therapy. One example is the embolization (clogging) of the capillaries under the influence of the magnetic field.In this way tumors could specifically starved of their blood supply. Another elegant example is the use of magnetic fields to prevent retinal detachment thus preventing the patients from going blind.

6. Magnetic control of pharmacokinetic parameters and drug release-*Langer et al*., embedded magnetite or iron beads into a drug filled polymer matrix and then showed that they could activate or increase the release of the drug from the polymer by moving the magnet over it or by applying an oscillating magnetic field.The microenvironment within the polymer seemed to have shaken the matrix or have produced micro cracks and thus have made the influx of liquid, dissolution and efflux of the drug possible. In this way it was possible to magnetically activate the release of drug from the depot underneath the skin. Done repeatedly this would allow for pulsatile drug delivery.

7. Magnetic system for the diagnosis of disease- The most important diagnostic application of magnetic particles is as contrast agent for magnetic resonance imaging (MRI). *Suini et al.*, tested 0.5-*in vivo* for the first time in 1987. Since then smaller supramagnetic iron oxides have been developed into unimodular nanometer sizes and have approved since 1994 and used for the imaging of liver metastasis or to distinguish loops of bowel from other abdominal structures.

8. Magnetic systems for magnetic cell separation- The era of using magnetic particles with surface markers against cell receptors started in 1978.Currently many different kits for the sample preparation, extraction,enrichment and analysis of entire cells based on surface receptors and sub cellular components such as proteins, m-RNA, DNA are available.[4]

Drug delivery system using magnetic microspheres

A drug delivery system (DDS) to deliver a drug when and where required is a powerful tool for reducing the doses of drugs administered and the side effects. Isolation of candidate materials and development of a new DDS using the materials should provide a more powerful tool in the medical field. Therefore, we are developing a new DDS using a combination of candidate magnetic microspheres and a magnetic field.

Surgical therapeutic, chemotherapeutic and radio therapeutic approaches alone or in combination have been used for treatment of cancer. However, each approach has side effects such as nausea,vomiting, anorexia, diarrhoea, alopecia and hepatic dysfunction. We have isolated novel magnetic microspheres to solve the problems of side effects of cancer chemotherapy and have studied a DDS using magnetic microspheres. Here, we introduce our study and other target-selective DDS. DDSs have been developed to enable drugs to safely elicit effects in target organs, tissues or cells.

DDSs can be classified into:

1) Target-selective drug delivery systems
2)Controlled-release drug delivery systems
3)Systems for drug delivery by absorption.

Target-selective drug delivery systems for delivering drugs to target organs, tissues and cells are expected to greatly reduce side effects in normal cells. The use of magnetic materials in the development of DDSs has been reported in the 1970s and accumulation of albumin microspheres containing doxorubicin and magnetite (Fe_3O_4,) in a sarcoma by a permanent magnet led to regression and disappearance of the sarcoma.

Drug Targeting

Drug targeting is a specific form of drug delivery where the drug is directed to its site action or absorption. This could be a particular organ structure, a cell, subset or even an intercellular region[4]

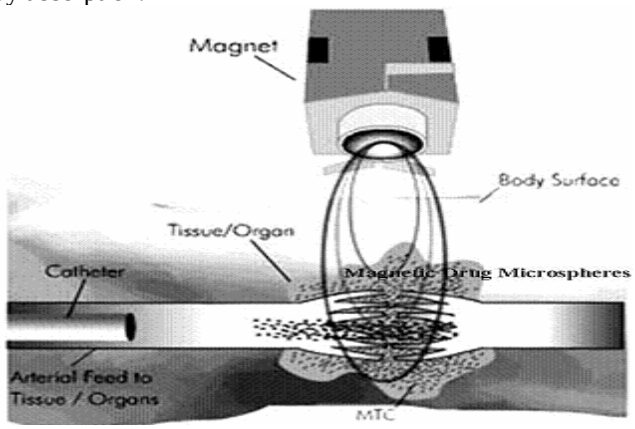
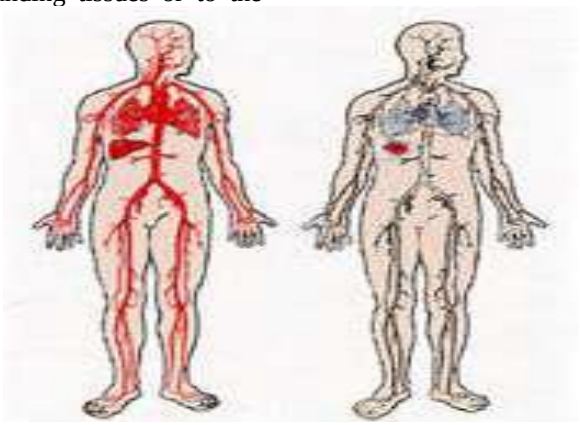


Fig 1: Magnetic drug targeting

Principle of magnetic drug targeting

Magnetic drug delivery by particulate carriers is efficient method of delivering a drug to a localized disease site. Very high concentration of the therapeutic agents can be achieved near the target site without any toxic effects to normal surrounding tissues or to the whole body. In magnetic targeting a drug is bound to a magnetic compound, magnetic field in the target area. Depending upon the type of drug it is then slowly released from the magnetic carriers and confers a local effect.



Systemic therapy **Magnetic targeting**

Fig 2: Representation of systemic drug delivery and Magnetic targeting

Evaluation parameters for magnetic microspheres

- **Percentage yield of microspheres**

Thoroughly dried microspheres are collected and weighed accurately. The percentage yield can be calculated using formula given below: Percentage Yield = mass of microsphere obtained/ total weight of drug & polymer*100

- **Particle size analysis and particle size distribution**
- **Density**
- **Flow properties**
- **Shape and surface characterization**
- **Determination of drug content**
- **Encapsulation efficiency**
- **Interaction study by TLC/IR**

IR spectroscopic studies

- **Surface topography by scanning electron microscopy (SEM)**
- **Zeta potential**
- **Stability studies[**6**,**7]

Review of literature

1. **Sahil Kataria *et al.*** Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm.This review gives information about conrolled release and therapeutice efficacy of magnetic microsopheres along with their characteristics, applications, advantages, limitations, methods of preaparation,their scope as various drug deliveries and important utilizations of chitosan polymer.[8]
2. **G. Poovi, S. Padmapriya, S.Lakshmi *et al*** Magnetic microsphere is prepared by various techniques and has various applications in diagnosis and treatment of various diseases. This review gives an overview of the benefits, drawbacks, limitations, preparation, characterization and biomedical applications of magnetic microsphere.[9]
3. **Amit Chandna, Deepa Batra, Satinder Kakar, Ramandeep Singh** This review is based on the history of magnetic targetting, ferrofluids and factors related to ferrofluids, classification of drug targetting, methods of preparation of magnetic microspheres, evaluation of magnetic microspheres etc.[10]
4. **Tarun P , Soni S , Thakar B , Pandya V, Bharadia P** This review includes magnrtic drug targetting, important characteristics of magnetic microspheres, drawbacks of using magnetic microspheres, therapeutic magnetic microspheres, target drug delivery for cancer and storage conditions.[5,11]
5. **Mukherjee *et al*** This review presents a broad treatment of magnetic microspheres discussing their advantages, limitations, and their possible remedies. Different production methods which are suitable for large scale production and applications of magnetic microspheres were discribed. Appropriate analytical techniques for characterization of magnetic microspheres like photon correlation spectroscopy, scanning electron microscopy,differential scanning calorimetry are highlited. Aspects of magnetic microspheres,routes of administration and their redistribution are also incorporated.[12]
6. **Yu Cao,Gang Bai,Jiaqi Chen,Wang Tian,Shenqi Wang ,Wenbo Yang** Magnetic agarose microspheres (MAMS), magnetic cellulose microspheres (MCMS), and magnetic poly(vinyl alcohol) microspheres(MPVAMS) were prepared by various different preparation methods. MCMS coupled with anti-IFN _-2b monoclonal antibodies (mAb) were selected for the purification of interferon _-2b (IFN _-2b) after performance characterization among microspheres.[13]
7. **Divya Rathore, Satinder kakar, Ramandeep singh** One such approach is using microspheres as carriers for drugs also known as microparticles. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. The nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines[14]**.**
8. **Pinaparolu Devarajulu,Arunkumar and Muniyandy Saravanan** Azathioprine loaded gelatin microspheres were formulated to control/target drug release in an arthritic joint by magnetic force or intra-articular injection. Glutaraldehyde cross linked microspheres were characterized for drug loading, entrapment efficiency, gas chromatography, magnetite content,particle size, scanning electron microscopy (SEM), Fourier-Infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and *in vitro* release studies. FT-IR revealed the absence of drug polymer interaction, and DSC suggested amorphous nature of entrapped drug in the microsphere[15].
9. **Yonghui Deng,Changchun Wang,Xizhong Shen, Wuli Yang,Lan Jin,Hong Gao, and Shoukuan Fu** Novel functional microspheres

with multistimuli-responsive properties have been prepared and characterized. The as-prepared microspheres respond to an external magnetic field, environmental temperature, and ultraviolet radiation. The in vitro drug-loading efficiency and drug-release behavior of these microspheres demonstrated that they could be used as drug carriers for drug controlled release.The results of in vivo distribution investigations of these microspheres showed that they exhibit a high magnetic- targeting effect, which holds promise for applications in various fields such as magnetic drug targeting and tissue labeling, among other[16].

10. **Chandrawanshi Pawan and Patidar Hemchand** Magnetic microspheres as an alternative to traditional radiation methods which use highly penetrating radiation that is absorbed throughout the body. Its use is limited by toxicity and side effects. The aim of the specific targeting is to enhance the efficiency of drug delivery & at the same time to reduce the toxicity & side effects. The present paper reviews the mechanism, preparation and applications of magnetic microspheres[17].
11. **Ramteke K.H, Jadhav V.B, Dhole S.N.** Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymerswhich are biodegradable in nature ideally having particle size less than 200µm.Various synthetic andnatural materials are used for the preparation of microspheres. These are prepared by methods like Single emulsion, Double emulsion, Polymerization, Phase separation coacervation, Emulsion solvent evaporation and solvent diffusion. Microspheres are having wide range of applications because of controlled and sustained release. Most important application is that it is used for targeting tumours using anticancer drugs. It is important carrier for safe and effective in vivo drug delivery[18] .
12. **Mohamed K. Nasra, Moustafa M. Mohamed, Mohamed A. Elblbesy, Bothaina A. Hefney** The present work we prepared chitosan magnetic microspheres (CMMS) with simple crosslinking method. The obtained CMMS were in size range of 1000 - 2600 nm with average particle size of 1800 nm. All the essential characterizations of prepared CMMS were done and the results were in a good agreement with other magnetic microspheres prepared with different method. To test the biocompatibility of CMMS with blood, the effect of them on erythrocytes aggregation and blood hemolysis were studied. results showed that CMMS work as good compatible materials with blood[19].
13. **Abdelrahman T Hereba, Mohamed A Elblbesy and Mamdouh M Shawki** Magnetic microspheres have many bio-medical applications, but they have contact with the blood before reaching to their target place in many cases, so the study of the effect of these microspheres on the blood can lead to optimization of the use of these microspheres. Five groups of normal blood samples were incubated with 10 mg magnetic chitosan microspheres for 1, 3, 6, 12, and 24 hours (h) respectively, then each group was compared to control group samples. The results showed that increase in hemoglobin conductivity with the time of incubation, no change in red blood cells osmotic fragility, no change in hemoglobin absorbance spectrum. Decrease in blood pH at 24 h, no change in neither hemoglobin electrophoretic patterns or in the blood components ultra structures. These results indicated no obvious toxicity of the magnetic microspheres on blood for incubation time up to 24 h, but on the other hand there are some changes especially at 24 h of incubation, so it is safer to avoid the remaining of the microspheres inside the body for more than 24h[20] .
14. **Kedar Prasad Meena, J.S. Dangi , P K Samal and K P Namdeo** Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm.A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body[21].
15. **Zuli Liu, Cuicui Liu, Kailun Yaoa, Pandong Liu, Qin Ning** Micron-sized magnetic microspheres with different functional groups were prepared by one-step suspension copolymerization of Styrene, Divinyl benzene and

methyl methacrylate (MMA) in the presence of oleic acid-coated magnetic nanoparticles. In the present work, we used Benzoyl peroxide (BPO) as an initiator and poly (vinyl alcohol) (PVA-1788, degree of polymerization 1700, degree of hydrolysis 88%) as a stabilizer. We also added acryamide (AM) monomer in the aqueous phase and methacrylic acid (MAA) in the oil phase. The morphology and properties of the resulting magnetic microspheres were examined by Optical micrographs (EM), Vibrating-sample magnetometer (VSM) and Fourier transform infrared spectrometer (FT-IR). The results showed the three products have uniform and spherical form with superparamagnetism and well dispersion. Moreover, we found that monomer AM had a little contribution to the copolymerization, and MAA could strikingly decrease the diameter of the final microspheres. The magnetic microsphereswith functional groups could be linked well with the IgG-FITC[22].

16. **Brandon H. McNaughton, Vladimir Stoica, Jeffrey N. Anker, Roy Clarke, and Raoul Kopelman** Magnetically Modulated Optical Nanoprobes (MagMOONs) are magnetic particles that indicate their angular orientation by emitting varying intensities oflight for different orientations and have shown promise for a variety of applications.In this letter we describe a new method to fabricate uniform magnetic half-shell particles that can be used as MagMOONs.Cobalt was deposited onto commercially made polystyrene nanospheres and microspheres,using ultrahigh vacuum vapor deposition, producing particles with uniform size, shape and magnetic content. Additionally, the coercivity of the cobalt deposited on the nanospheres was enhanced compared to its bulk value[23].
17. **Preeti Agrawal, Sarlesh Rajput, Ashish pathak, Nikhil Shrivastava, Satyendra Singh Baghel, Rajendra singh Baghel** Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. So the concept of targeted drugdelivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues.As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, *etc* which modulates the release and absorption characteristics of the drug. Among this drug delivery system we are selecting microspheres of various types which will be controlled release and which can be made specific site targeted by giving some specific characteristic to it like mucoadhesion character or by inserting any magnetic or radioactive material as a result of which it will show site specific action. So this article emphasis on different types of microspheres as a controlled and targeted drug delivery system[23].
18. **Amol Chaudhari, Mr. K.R.Jadhav, Dr. Mr. V.J.Kadam** All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere's matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations.The residence time in the cavity is considerably increased for microspheres compared to solutions.However, this is not the only factor to increase the absorption of large hydrophilic drugs.The dextran microsphere system was as effective as an absorption enhancer for insulin as degradable starch microspheres (DSM).The mode of action for improved absorption found for starch microspheres is also applicable to dextran micro spheres. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells[23].
19. **Kadam N.R. and Suvarna V** Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 μm consisting of proteins or synthetic polymers. The range of techniques for the preparation of microspheres provides multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience.

Such systems often use macromolecules as carriers for the drugs. The present review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction, Quassi emulsion solvent diffusion. Microspheres have wide range of applications because of controlled and sustained release[21,22].

Why magnetic microspheres are formulated

- To improve physical stability and gastric enzyme stability.
- To get better process ability (improved flowability, dispersability).
- To reduced dose size.
- To reduced dosing frequency therefore improves patient compliance.
- To reduced toxicity.
- To increase absorption window.
- To decrease gastric irritation problem.
- To avoid first pass metabolism.
- To enhance biological half-life.
- To improved bioavailability.
- Microsphere provides increased therapeutic efficacy and prolonged duration of action.
- Microsphere provides controlled, sustained and targeted drug delivery.
- Microsphere can be injected into body because of small size and spherical shape.[22,23]

Materials used in the preparation of Microsphere

Microspheres used usually are polymers. They are classified into two types:

1. Natural polymers
2. Synthetic Polymers

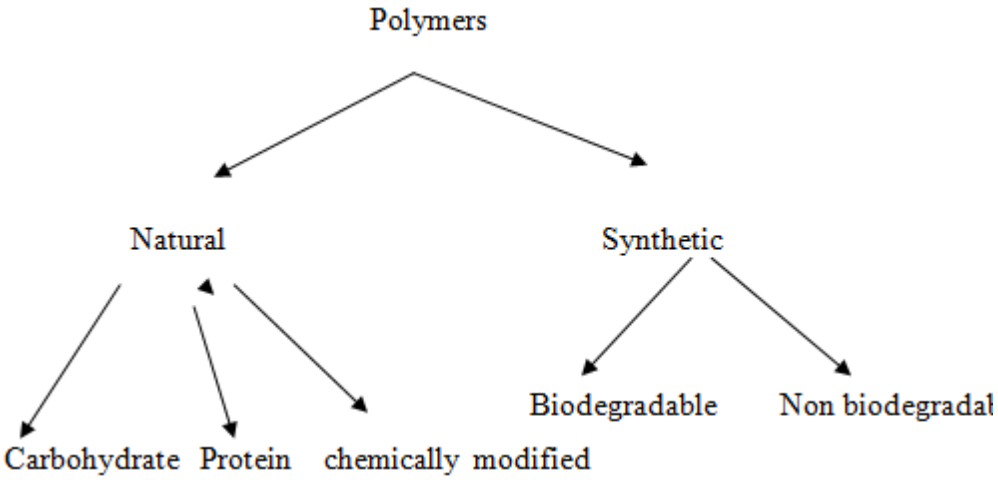


Fig.3 Materials for Preparatiom of Magnetic Microspheres

- Natural polymers obtained from different sources
- Carbohydrates: Agarose, Carrageenan, Chitosan,Starch
- Proteins: Albumin, Collagen and Gelatin
- Chemically modified carbohydrates: Poly dextran, Poly starch.
- Synthetic polymers are divided into two types.
- Biodegradable polymers
- E.g. Lactides, Glycolides & their co polymers,Poly anhydrides, Poly alkyl cyano acrylates Non biodegradable polymers
- E.g. Poly methyl methacrylate (PMMA),Glycidyl methacrylate, Acrolein, Epoxy polymers.

- **Synthetic polymers**
  Poly alkyl cyano acrylates is a potential drug carrier for ophthalmic, oral and parenteral preparations. Poly lactic acid is a proper carrier for sustained release of anti neoplastic agents such as cisplatin, cyclo phosphamide, and doxorubicin and narcotic antagonist. [23]

Method of Preparation

- **Solvent Evaporation**
- **Double emulsion technique**
- **Polymerization techniques**
  The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:
  I. Normal polymerization
  II. Interfacial polymerization. Both are carried out in liquid phase.
- **Phase separation coacervation technique**
  This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.[23]

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