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A Review on Magnetic Microsphere as Magical Novel Drug Delivery System

Chaitalee G. Girde, Bilal Sufi, Pratiksha Budhbaware, Prajwal Wankhade
New Montfort Institute of Pharmacy, Ashti, Wardha, Maharashtra, India
chaitaligirde2020@gmail.com

Abstract: *Magnetic microspheres hold great promise for reaching the goal of controlled and site specific drug delivery. . A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery, magnetic micro carriers. Newer drug delivery systems are largely influencing the current medical practice. The application of Magnetic nanoparticles for drug targeting enables guiding the Magnetic microspheres to a target area, imaging the position of the Magnetic microspheres with magnetic particle imaging, and finally inducing drug release. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran. The concept of targeted drug delivery 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. The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the targeted therapy.*

Keywords: Magnette, Targeting Therapy, Magnetic Nanoparticles (MNP), Magnetic Microspheres (MNS), Radioimmunoassay.

I. INTRODUCTION

Microspheres are free flowing powders consisting of encapsulated (drugs) spherical particles of size ideally less than 125p that can be suspended in aqueous vehicle and injected by an 18 or 16 number needle. The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying (i) Size of microspheres; (ii) Drug content; (iii) Magnetite content; (iv) Hydration state; (v) Drug release characteristic of carrier.[1]Magnetic carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt[2] .The treatment of tumours with chemotherapy leads to severe side effects due to the systemic distribution of the anti-cancer drug and the resulting damage to healthy tissue. To deliver the therapeutic agent specifically to a desired area, so called drug delivery systems consisting of polymeric drug carriers are a promising approach[3]

By applying an external field, they can be moved inside the body while their current position can be determined by imaging via MPI or MRI. Additionally, MNP can generate heat by magnetic hyperthermia when they are exposed to an alternating magnetic field[4] There are a number carriers Microspheres, nanoparticles, liposomes and others for which optimized technologies are under development to enhance the performance of products that have already been delivered with some success via that route and modulates the release and absorption characteristics of the drugs particularly those drugs which have shorter biological half-life.[5] 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.[6]Nowadays several targeted treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and mechanical force are being used in many diseases treatments (e.g. cancer, nerve damage, heart and artery, anti-diabetic, eye, etc.).

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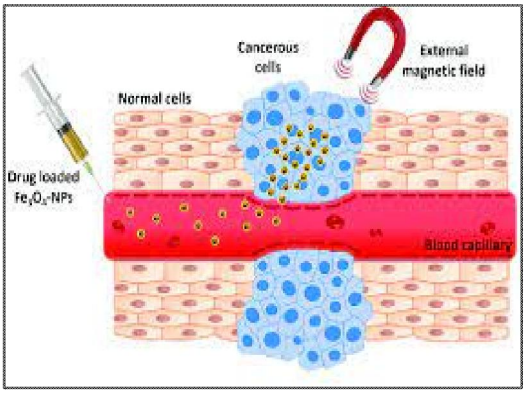

Mechanism of action of magnetic microsphere as targeted drug delivery system

In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration[7]. Nowadays several targeted treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and mechanical force are being used in many diseases treatments (e.g. cancer, nerve damage, heart and artery, anti-diabetic, eye, etc.). The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying the size of microspheres varying drug content, varying magnetite content, varying the hydration state and varying drug release characteristic of the carrier[8]. Up to 60% of an injected dose can be deposited and released in a controlled manner in selected non reticuloendothelial organs. Magnetism has application in numerous fields like diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay [9]

Using magnetic microsphere small amounts of drug targeted magnetically to localized sites can replace large doses of drug that, using traditional administration methods, freely circulate in the blood and hit the target site in a generalized way only. Also, drugs within the sphere are protected from breaking down during transport and, because they are targeted instead of distributed in blood, don't harm some sensitive organs such as bone marrow [10]

1.1 HISTORY

The earliest use of magnet for selective delivery of clinical agents involved treatment of arterial thrombosis by angiography and intravascular localization of carbonyl iron with guidance of catheters.[9] Turner and Rand combined then this radiofrequency heating method with embolization therapy[14] More defined spherical magnetic microspheres were made for the first time at the end of the 1970s by[15] Their magnetic albumin microspheres worked well in animal experiments for tumor therapy and as magnet resonance contrast agents, but were not explored in clinical trials.[16,17]

1.2 CONCEPT AND PRINCIPLE BEHIND MAGNETIC MICROSPHERE TARGETING DRUG DELIVERY SYSTEM

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected a patient's blood stream, and then localized with a powerful magnetic field in the target area [11]

$$F=M\Delta H$$

Where, F= force on particles

M= magnetic moment of particles

ΔH= magnetic field gradients

Magnetic microspheres is based on the force exerted by external magnetic field over the magnetically susceptible microspheres. The monitoring of the carrier localization is an important part of magnetic targeting that avoid the normal tissue injury.[9] These drug delivery systems contain magnetic responsiveness being integrated from different substances like magnetite, iron, cobalt, nickel, iron-boron or samarium-cobalt, The drug along with the magnetic compound is injected into the patient's blood circulation system and a magnetic field is applied at the target site to

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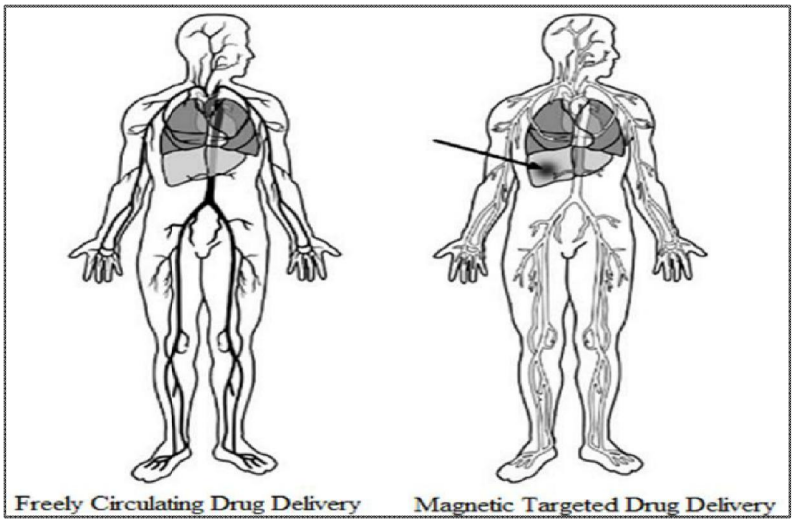
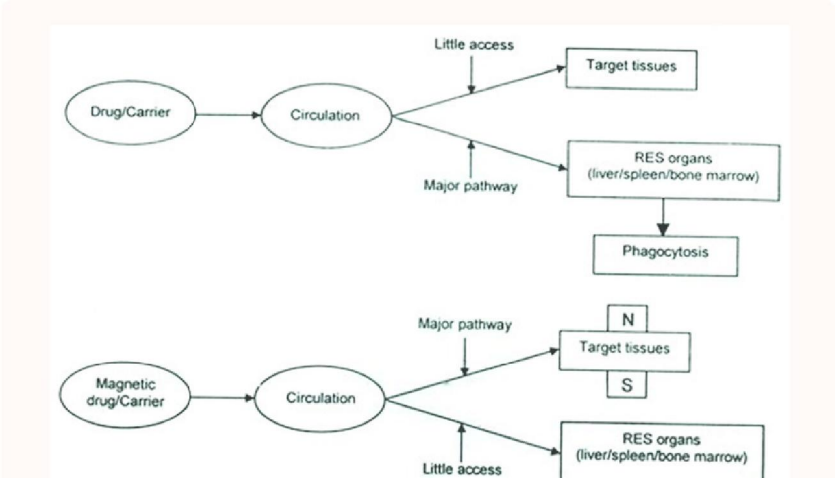
block it. Thus, considerable less amount of drug concentration can be achieved at specific site which minimizes the unwanted effects due to the high drug concentrations of freely circulating [10]



Representation of magnetic targeting



Principle of magnetic drug delivery system[15]

1.3 CLASSIFICATION OF TARGETING

Classification I	Classification II	Classification III	Classification IV	Classification V	Classification IV
1)First-order Targeting 2)Second-order Targeting 3) Third-order Targeting	1)Organ Targeting 2)Cellular Targeting 3)Subcellular Targeting	1)Passive Targeting 2) Active Targeting 3)Physiochemical Targeting	1)Site-directed Targeting 2)Site-avoidance Targeting	1)Biochemical Targeting 2)Biomechanical Targeting 3)Biophysical Targeting 4)Bio-Adhesive Targeting	1)Carrier-Dependent 2) Carrier Targeting

Whereas, first-order targeting is determined mainly by the shapes and sizes as well as the material properties of a carrier and by its route of administration.

Classification two, which categorizes drug targeting as organ, cellular, and subcellular processes, is analogue to the first-, second-,

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And third-order processes. According to classification three, passive drug targeting refers to the natural in vivo deposition of the drug carrier in the body.

In classification four, the approaches that involve a passive, active, or physical–chemical basis of drug delivery can be grouped under site-directed drug targeting. The application of liposome reduce the cardiotoxicity of doxorubicin is a good example of this type of delivery. Hence, according to classification five, biochemical targeting refers to extravascular transport by specific interaction between target cell ligands and drug carriers. Biomechanical targeting refers to extravascular drug delivery by the transient regional opening of endothelial junctions[13]

1.4 ADVANTAGES OF MAGNETIC MICROSPHERE [18,19,20]

Therapeutic responses in target organs can be achieved by only small fraction of the free drug dose.

- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effect
- They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue
- They provide protection for unstable drug before and after administration, prior to their availability at the site of action.
- They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug. They enable controlled release of drug. Examples: Narcotic, Antagonist, Steroid hormones.
- Difference occurs maximally in capillary network so efficient delivery of drug to diseased tissue is achieved.

1.5 DISADVANTAGES OF MAGNETIC MICROSPHERE [18, 19,21]

- It needs specialized magnet for targeting, for monitoring, and trained personnel to perform procedures.
- Magnets must have relatively constant gradients, in order to avoid focal over-dosing with toxic drugs.
- Thrombosis at the site of catheterization
- The unknown toxicity of magnetic beads.
- The possible unwanted localization of the product in the liver and the regions of RES and the dangerous effect of self-flocculation of the magnetic particles causing vascular

1.6 LIMITATION[22,23]

- The release pattern of the controlled release dosages form can be vary from a various factors like food and the rate of transit through gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity
- Dosage forms of this type should not be crushed or chewed to vital organs in the body

1.7 APPLICATION

- Magnetic microsphere carriers uses in the fields of biomedicine and bioengineering, biological and biomedical developments and trends such as enzyme immobilization, cell isolation, protein purification, and target drugs.[24,25]
- Magnetic microspheres are used in targeting drugs like mitoxantrone, paclitaxel and doxorubicin to tumor sites. Magnetic microsphere carriers labeled with radionuclide such as Rhenium-188 and Yttrium-90 have been also used in a preclinical study to treat liver and brain tumors solid cancer in 14 patients.[26,27]
- Their MMS were small, about 100 nm in diameter, and filled with 4`-epidoxorubicin. The phase I study clearly showed the low toxicity of the method and the accumulation of the MMS in the target area. However, MRI measurements indicated that more than 50% of the MMS had ended up in the liver.[28]
- Magnetic drug targeting: Tumor targeting The first clinical cancer therapy trial using treatment of advanced.[29]

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- Magnetic targeting can also be used to deliver therapeutic radioisotopes. The advantage of this method over external beam therapy is that the dose can be increased, resulting in improved tumor cell eradication, without harm to nearby normal tissue. Different radioisotopes can treat different treatment ranges depending on the radioisotope used—the β-emitters.[30]
- Magnetic polystyrene microspheres have been used as specific cell labelling.[31]
- Bioseparation is an important phenomenon for the success of several biological processes. Therefore, prospective bioseparation techniques are increasingly gaining importance. Amongst the different bioseparation techniques, magnetic separation is the most promising. The development of magnetically responsive microspheres has brought an additional driving force into play.[32]
- Supra-magnetic iron oxide microspheres have been used for detection of metastases in nonenlarged lymph nodes[33]

1.8 METHOD OF PREPARATION

1) Continuous solvent evaporation

In this method the drug and polymer are dissolved in appropriate volatile organic solvent and then magnetite (if magnetic microspheres) is added to this solution along with stirring in order to form a homogeneous suspension. This suspension is added to an immiscible auxiliary solution along with vigorous stirring. Now the volatile organic solvent is evaporated slowly at 22-30 °C to form microspheres. Microspheres are this centrifuged and freeze dried and stored at 4°C. Satinder Kakar et al. prepared magnetic microsphere by solvent evaporation technique. An attempt was made to target mesalamine to the colon. Eudragit S100, ethyl cellulose, chitosan were used in different drug polymer ratio. Chitosan microspheres were found to be best in terms of in vitro release characteristics.[34,35,36]

2) Phase separation emulsion polymerization

In this method, the aqueous solution of polymer, drug and magnetite are added to a vegetable oil which is then emulsified using a magnetic stirrer. The resultant emulsion is stabilized by heating at the temperature (100-150°C). The cross linking agent is then injected drop wise into the emulsion with continuous stirring. The formed magnetic microspheres are then separated from oil by washing procedures. The product is then freeze-dried & stored at 4°C.[37]

3) Emulsion solvent extraction method

The preparation involved the dispersion of an aqueous phase, containing magnetite nanoparticles and a water-soluble homo-polymer, into droplets in an organic medium using an amphiphilic block copolymer as the dispersant. This was followed by water distillation at a raised temperature from the aqueous droplets to yield polymer magnetite particles. The structure of the particles was then locked in by a reagent being added to cross-link the water soluble copolymer block and homo-polymer. Since the hydrophobic block of the copolymer consisted of a protected polyester, the removal of the protective moieties from the coronal chains yielded poly (acrylic acid) or other functional polymers to render water dispensability to the spheres and to enable biomolecule immobilization. Hong Zhao et al. formulated Magnetic microspheres (MMS) with the matrix material poly(lactide-co-glycolide) (PLGA) or PLA by the emulsion solvent extraction method with encapsulation efficiencies of 40%, 83% and 96% for oleate, PLA and oleate/sulfonate-coated magnetic particles, respectively. [38,39]

4) Sonochemical method

The microspheres composed of iron oxide-filled and coated globular bovine serum albumin (BSA). The magnetic microspheres were prepared from BSA and iron penta carbonyl, or from BSA and iron acetate. Protein microspheres have a wide range of biomedical application, i.e. use as echo contrast agents for sonography. The microsphere were formed by either heat denaturation at various temperatures, or by cross linking with carbonyl compounds in the ether phase. Cross linking was done as the microspheres are formed by chemically cross-linking cysteine residues of the protein with HO2 radical formed around a non-aqueous droplet. The chemical cross-linking is responsible for the formation of the microspheres and is a result of the chemical ejects of the ultrasound radiation on an aqueous medium. Two sonochemical methods for the fabrication of iron oxide nanoparticles were (i) Water as the solvent and (ii) Decalin

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as solvent. Decane and iron pentacarbonyl Fe (CO) 5 (7.43U1034M) were layered over a 5% w/v protein solution. The bottom of the high-intensity ultrasonic horn was positioned at the aqueous organic interface. The mixture was irradiated for 3 min, employing a power of W150 W/ 32cm with the initial temperature of 23 °C in the reaction cell. The pH was adjusted to 7.0 by adding HCl. This procedure was performed again with an aqueous solution of iron acetate, Fe (CH3CO2)2 95% (Sigma) (7.66U1033 M). After the synthesis, the products were separated from the unreacted protein and from the residues of iron acetate or iron penta carbonyl by centrifugation (1000 r/min for 5 min). The magnetic microspheres were washed a few times with sufficient volumes of water to remove the residues of the precursors.[40,41]

5) Microwave-assisted preparation of magnetic albumin microspheres

Microwave-assisted method was used to prepare magnetic bovine albumin microspheres. It produces smaller particles and is faster than traditional methods. The optimum conditions to prepare magnetic microspheres containing albumin were 4 minutes at 160°C that yielded smaller sized microspheres of 30 µm in diameter. This microwave process could become a preferred method for the synthesis of magnetized protein microspheres.[42]

6) Hot melt microencapsulation

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. poly anhydrides. Microspheres with diameter of 1-1000µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.[43]

7) Swelling and penetration method

For swelling of polymer micro particles, 0.25 g of PS (Micron-size polystyrene) particles was mixed with 35 mL of a NMP/water solution in a specific v/v NMP (N-methyl2-pyrrolidone)- to-water ratio. In later preparations of magnetic microspheres, SDS (Sodium dodecyl sulfate was added to the NMP/water solution. Whenever SDS was used, 0.025 g of SDS were added to each NMP/water solution. The NMP/water mixture with PS spheres was left soaking for 24 h at room temperature while stirring. 2.5 mL of the super paramagnetic nanoparticle dispersion (24 mg/mL or other specified concentration) was added to the mixture of PS sphere and NMP/water solution at 30°C while shaking (at 140 r/min) for 1-5 days to allow the magnetic nanoparticles to penetrate into the interior of the PS particles. Afterwards, the polymer particles were separated from the solution by centrifugation. Finally, particles were sequentially washed with methanol, deionized water, and vacuum dried at room temperature for 1-2 days to yield the magnetic polymer microspheres. [44]

1.9 SOME PROPERTIES OF MAGNETIC MICROSPHERE

Thermos-responsive magnetic microspheres have emerged as a great potential technology platform for targeted and controlled drug delivery. 4 First, magnetic components can guide microspheres to lesions directly by an external magnetic field and release drug at the right place. Second, the thermos-responsive polymer shell acts as a drug carrier and swells or shrinks in response to temperature changes, realizing enhanced controlled release at the right time [45-49]

Gastro-retentive drug delivery system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time[50]

Conventional cancer therapy using cytotoxic drugs and/or radiotherapy is dose-limited because of toxicity to bone marrow stem cells. An attempt to overcome this difficulty has been made by the use of high-dose chemotherapy and autologous bone marrow "rescue"[51-53]

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1.10 FUTURE ASPECT

Conceptually, magnetic targeting is a very promising approach. However, there are a number of physical, magnetism-related properties which require careful attention. The magnetic force, which is defined by its field and field gradient, needs to be large and carefully shaped to fit the target area. Furthermore, the pharmacokinetic characteristics must be optimized for the specific target organ, taking into account that the normal organ behaviour might differ from that of a diseased organ. . It might be possible in near future that magnetic particles would be used as detection probes for a variety of assays, replacing labelling techniques , The future holds lot of promises in magnetic microspheres and by further study this will improve delivery of different drugs by enhancing the site specificity.

1.11 TOXICITY OF MAGNETIC MICROSPHERE

The important factors, which determine the biocompatibility and toxicity of magnetic microspheres, are the magnetically responsive components such as magnetite, iron, nickel, cobalt, neodymium—iron—boron or samarium—cobalt, and the size of the particles, their matrix substance and the coatings used. Iron oxide particles seem to be generally well tolerated.[54] In the case of larger magnetic microspheres of diameters up to tens of l m, the matrix substance making up most of the sphere has a much larger influence on tissue reaction, both immediate and long-term. Large microspheres also can physically irritate the surrounding tissue or even embolize small blood vessels and capillaries, effects which must be taken into account for specific applications.[55] (Endoremt or Feridex I.V.t; Advanced Magnetics, Cambridge, , USA). With respect to size, in the case of nanospheres with a diameter generally less than about 100 nm, the coating is Massachusetts probably the most important factor and determines many of the particles' properties[56]

II. EVALUTION

A] Interaction study by TLC/ FTIR

I] IR Spectroscopic studies: The IR spectra of the free drug and the microspheres were recorded. The identical peaks corresponding to the functional groups and albumin (BSA, Egg albumin, Human serum albumin) features confirm that neither the polymer nor the method of preparation has affected the drug stability.

II] Thin layer chromatographic studies : The drug stability in the prepared microspheres can also be tested by the TLC method. The Rf values of the prepared microspheres can be compared with the Rf value of the pure drug. The values indicate the drug stability.[57]

B] Particle size analysis and particle size distribution

a) Sieving

b) Microscopy: This method is used to determine particle size by using optical microscope (Meizer OPTIK) The measurement is done under 450伊 (10伊 eye piece and 45伊 objective) and100 particles are calculated.

c) Coulter counter analysis.

d) Laser Diffraction analysis. Size distribution plays an important role in determining the release characteristics of the microspheres [58].

C] 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伊100[59]

D] Density

a) Bulk density: Bulk density (ρb) (g/cm3) = M/Vb; Where, M= mass of powder taken, Vb = bulk volume

b) Tapped density:

Tapped density (ρt) (g/ cm3) = M/Vt;

Where, M = weight of sample powder,

Vt = tapped volume.

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E] Flow properties

a) Angle of repose: θ = tan-1 h/r;

b) Hausner ratio = ρt/ρb;

Where, ρt =Tapped density,

ρb = bulk density

The angle of repose is calculated by using the following equation: tanθ = h/r;

Where θ - Angle of repose

h-height of pile, r - Radius of base[60]

F] Thermal analysis

Thermal analysis of microcapsule and its component can be done by using differential scanning calorimetry (DSC), thermo gravimetric analysis (TGA), differential thermometric analysis (DTA). Accurately the sample was weighed and heated on alumina pan at constant rate of 10oC/min under nitrogen flow of 40 ml/min. 3-Attenuated total reflectance Fourier Transform-Infrared Spectroscopy.

ATRFTIR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring attenuated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.[61,62]

G] Determination of solubility

The solubility of particular microspheres in specific solution as microspheres or microcapsules to be soluble in that particular environment (water or phosphate buffers of pH 7.4) can be determined by taking excess quantity of microspheres in 50 mL vials filled with water. Shaked the vials on a magnetic stirrer. Filtered the solution through Whatmann paper no.1 and drug concentration determined at particular λ max value for the particular drug.

H] Solid state by DSC/XRD

This test is done by an X-Ray diffractometer to find out the solid state of the drug, polymer and drug-polymer mixture and also to find out the solid state of the drug in the prepared albumin microspheres. The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier[63,64]

I] Particle size analysis and particle size distribution

a) Sieving;

b) Microscopy:

This method is used to determine particle size by using optical microscope (Meizer OPTIK) The measurement is done under 450伊 (10伊 eye piece and 45伊 objective) and100 particles are calculated; c) Coulter counter analysis; d) Laser Diffraction analysis. Size distribution plays an important role in determining the release characteristics of the microspheres[65]

J] Stability studies

Stability studies were carried out as per ICH Guidelines. The microspheres were stored at 40 degree c ±2ºC/75% RH ± 5% RH for 6 months. The formulations were analysed for appearance, entrapment efficiency and drug content.

K] Attenuated total reflectance Fourier

Transform-Infrared Spectroscopy FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material.[66,67]

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M] Drug release profiles

In vitro method

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production and product development. Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle and basket. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.[68-72]

III. CONCLUSION

To review magnetism has a function of opening a new vista of a multi-barrier of multi-steps drug delivery. Magnetic microspheres has been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting. The main application of this technique id the reduction in the dose and side effect of the drug. According to MAGNETIC BULET CONSEPTS- idea that drugs reach the right site in the body, at the right time , at the right concentration. Larger amount of freely circulating drug can be replace by smaller amount of magnetically targeted drug. Magnetic targeted has better tumor, and other drug targeting, therapeutic efficacy and lower toxicity. It is very challenging phased in future manner to study the various accommodation in magnetic microsphere as a targeted drug delivery system. From this review, we could conclude that characterization is mandatory.

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