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A review on target drug delivery: Magnetic Microspheres

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ABSTRACT

Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the active entity to the site of action. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery, magnetic micro carriers being one of them.

Magnetic microsphere is newer approach in pharmaceutical field. 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. This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. magnetic microspheres can be prepared from a variety of carrier material. One of the most utilized is serum albumin from human or other appropriate species. Drug release from albumin microspheres can be sustained or controlled by various stabilization procedures generally involving heat or chemical cross-linking of the protein carrier matrix.

1. Introduction

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 μm) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged in to the adjacent tissues by magnetic fields of 0.5-0.8 tesla. 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 into a patient's blood stream, and then stopped with a powerful magnetic field in the target area. Magnetic carriers receive their magnetic responsiveness to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, neodymium-iron-boron or samarium-cobalt[1]. Magnetic microsphere were developed to minimize renal clearance and to increase target site specificity

2. History of magnetic targeting

History of Magnetic targeting is given in Table 1.

3. What is ferrofluid?

Ferrofluid (FF), is a colloidal suspension of single-domain magnetic particles, with dimensions of about 10 nm, dispersed in a liquid carrier[8]

4. Factors related to ferrofluid

Factors: 1. Size of the particles in ferrofluid. 2. Surface characteristics of particles. 3. Concentration of the ferrofluid. 4. Volume of the ferrofluid. 5. Reversibility and strength of drug/ferrofluid binding (desorption characteristics). 6. Access to the organism (infusion route). 7. Duration or rate of injection/infusion. 8. Geometry, strength and duration of the magnetic field application[10]. 9. Ferro fluids are optically isotropic but, in the presence of an external magnetic field, exhibit induced birefringence[11].

Wetting of particular substrates can also induce birefringence in thin FF layers. In order to avoid agglomeration magnetic

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Table 1.
History of Magnetic carriers.

S.No.	Scientist	Work in past
1	Gilchrist	published a seminar paper in 1956 on the selective inductive heating of lymph nodes after injection of 20.100 nm sized magnetite particles into the lymph nodes near surgically removed cancer[2]
2	Turner and rand	combined the radiofrequency heating method with embolization therapy[3]
3	Meyers	described how magnetic carriers were able to accumulate small iron particles intravenously injected into the leg veins of dogs, using a large, externally applied horse shoe Magnet. They imagined that it might be useful for lymph node targeting and as a contrast agent[4]
4	Hilal	Engineered catheters with magnetic ends, and described how they could be used to deposit and selectively embolize arterio-venous malformations with small magnets. The use of magnetic particles for the embolization therapy of liver cancer followed and has recently found renewed interest[5]
5	Widder	More defined spherical magnetic microspheres were made for the first time at the end of the 1970s. 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[6,7]

Table 2.
Characteristics of ferrofluids[9].

Ferrofluid characteristics	# (a) P6 iron uptake of malignant human glioma cells. (b)iron uptake by normal human cerebral cortical neuronal cells.	# (a) BU48 iron uptake of malignant human glioma cells. (b) iron uptake by normal human cerebral cortical neuronal cells
Average particle core diameter	3.3 nm	13.1 nm
Average hydrodynamic particle diameter	50-70 nm	17 nm
Type of nanoparticle coating	Dextran	Aminosilan
Suspension stability as sterilized fluid	Years	Months
Biocompatibility	High	High
Formation of intracellular particle aggregates	Yes	No
Magnetic susceptibility	117.2 emu/g	50-100 emu/g
Surface charge	Negative	Highly positive
Specific absorption rate	120 mW/mg Fe	146 mW/mg Fe
Super paramagnetic	Yes	Yes

Table 3.
Depiction of differences in surfacted ferrofluids and ionic ferrofluids[12,13].

S.No.	Surfacted ferrofluid	Ionic ferrofluid
1	Surfacted ferrofluid are formed by magnetic particles coated with surfactant agents (amphiphilic Molecules, as oleic acid in order to prevent their aggregation.	Magnetic particles (usually maghemite, $^{\circ}$-Fe_2O_3, and different ferrites, MFe_2O_4, where M = Mn, Co, Zn, Cu, Ni) are obtained through a chemical precipitation method, and an acid-alkaline reaction between particles and the bulk keeps the surface of them electrically charged
2	Steric repulsion between particles acts as a physical barrier that keeps grains in the solution and stabilizes the colloid.	Electrostatic interaction are for stability
3	In Surfacted ferrofluid, there are steric repulsion forces, of short range nature	In ionic ferrofluid, long-range electrostatic interactions between charged particles give rise to repulsive interactions, which guarantee colloidal stability

particles need coating. So they are classified in two ways: Classification of ferrofluids: 1. Surfacted ferrofluids: if the coating is a surfactant molecule. 2. Ionic ferrofluids: if it is an electric shell.

5. Classification of drug targeting

Classification I: First-order targeting, Second-order targeting, Third-order targeting. Classification II: Organ targeting, Cellular targeting, Sub cellular targeting. Classification III: Passive targeting, Active targeting, Physiochemical targeting. Classification IV: Site-directed targeting, Site-avoidance targeting. Classification V. Biochemical targeting, Biomechanical targeting, Biophysical targeting, Bioadhesive targeting. Classification VI: Carrier-dependent, Carrier-independent[26].

Considerable attention has been paid to the use of polymer microspheres for the sustained release of various drugs and the targeting of therapeutic agents to their site of action. Biodegradable poly-D, L-lactic acid (PDLLA) microspheres can be efficiently taken up by macrophages and M cells[27].

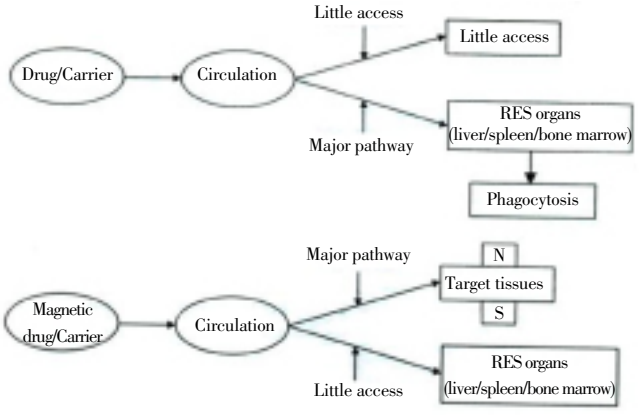

Figure 1. Principle of magnetic drug targeting.

Table 4.
Drugs and their polymers used in drug delivery.

s.no.	Drug	Polymer	Application	Method used	Reference
1	Diclofenac sodium	Gelatin	Reduced joint swelling	Emulsification and cross linking	14
2	Mitomycin C	Trimethylene carbonate (TMC) and 5,5-dimethyl trimethylene carbonate (DTC)	Potential hepatic carcinoma therapeutics	Solvent evaporation	15
3	Yttrium-90	Human serum albumin	Bimodal radionuclide-hyperthermia cancer therapy	Modified emulsification heat stabilization	16
4	alpha-chymotrypsin	Titanium oxide	Hydrolysis of N-acetyl-L-tyrosine ethyl ester	Immobilization	17
5	Doxorubicin	Albumin	Cancer therapy.	Solvent evaporation	18
6	Indomethacin	Methyl Methacrylate	Selective blood detoxification, tissue engineering and replacement, and magnetic resonance imaging contrast agents	Emulsion Solvent Evaporation Technique	19
7	Oxantrazole	Chitosan	Cancer therapy	Emulsion/polymer cross-linking/solvent evaporation	20
8	Amphotericin B	Albumin	Treatment of visceral leishmaniasis.	Spray drying.	21
9	5-Fluorouracil	Bovine serum albumin (BSA)	Tumor of hepatoma	Emulsion- ultrasound-heat stabilization technique.	22
10	Adriamycin	Albumin	Cytotoxic effect on tumor cells	Heat-stabilized protein methods	22
11	Vancomycin	Starch	Cytotoxic effect on tumor cells	Continuous solvent evaporation	23
12	Clindamycin	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	23
13	Azithromycin	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	23
14	Aclarubicin	Gelatin	Intravascular tumour targeting	Water in oil emulsion polymerization	24
15	Oxacyllin	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	24
16	Trimethoprim/ sulfamethoxazole	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	24
17	Rifampicin	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	24
18	Ofloxacin	Dextran	Potentiator effect on antimicrobial activity against *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 reference strains	Continuous solvent evaporation	24
19	Tetracycline	Dextran	Composite particles charged with antibiotics probably penetrate the bacterial cell wall and deliver the antibiotic in active forms to the intracellular targets.	Continuous solvent evaporation	24
20	Penicillin	Dextran	Potentiator effect on antimicrobial activity	Continuous solvent evaporation	24
21	Ciprofloxacin	Dextran	Potentiator effect on antimicrobial activity	Continuous solvent evaporation	24
22	Gentamycin	Dextran	Composite particles charged with antibiotics probably penetrate the bacterial cell wall and deliver the antibiotic in active forms to the intracellular targets.	Continuous solvent evaporation	24
23	Piperacillin/tazobactam	Dextran	Antimicrobial activity against *S. aureus*	Continuous solvent evaporation	24
24	Cefepime	Dextran	Potentiator effect on antimicrobial activity	Continuous solvent evaporation	24
25	Aztreonam	Dextran	Potentiator effect on antimicrobial activity	Continuous solvent evaporation	24
26	β -lactams antibiotics: Cefepime, Ceftriaxone,Cefuroxime and Cefoperazone	Chitosan	Inhibiting *Staphylococcus aureus* and *Escherichia coli* growth.	Chemical precipitation	25

Sandia model and metric are used to predict the detection platform's sensitivity and speed for several CONcepts of OPeration (CONOP): (1) agent detection (chemical or biological) in clinical samples, (2) botulinum toxin detection in milk, and (3) pathogen detection in airplane cabin air. Application of the model in these CONOPs indicates that the proposed platform can be optimized to reduce TTI, thereby minimizing the impact of Chem-bio events.

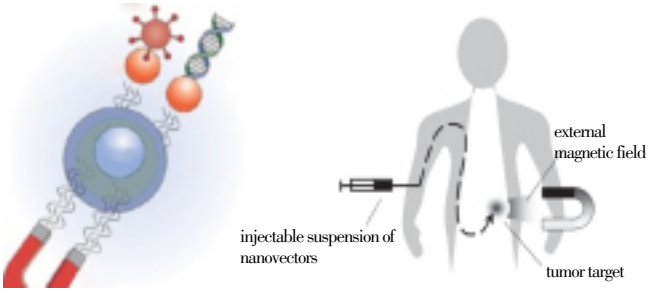

Figure 2. Magnetic targeting in drug and gene delivery.

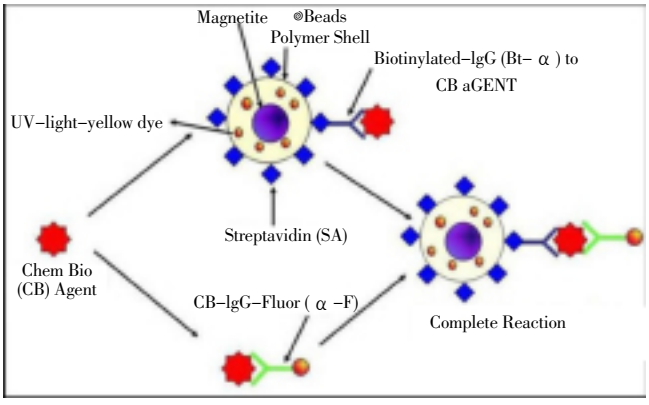

Figure 3. Chem-bio-threat agent detection using "sandwich" immunoassays.

Each bead contains a magnetic core to permit trapping for sample cleanup and concentration. Bead surfaces are modified with Analyte Specific Reagents (ASRs). ASRs may be antibodies or oligonucleotides for selective analyte capture, while an internal quantum dot (QD) or chromophore dye facilitates bar coding.

6.2. Solvents used for solvent evaporation method

Solvent used should meet the following criteria: (1) Being able to dissolve the chosen polymer; (2) Being poorly soluble in the continuous phase; (3) Having a high volatility and a low boiling point; (4) Having low toxicity[28]. Polymer encapsulated microspheres are synthesized on the basis of a continuous solvent evaporation technique. A solution of polymer, drug and magnetite should be added to the volatile organic solvent, which forms Auxiliary solution on stirring. The resulting solution should be homogenized at stirring temperature (22-30 ℃) (Figure 5 & 6). The magnetic microspheres will be formed in the suspension and should be separated by centrifugation. The product should be Freeze dried & stored at 4 ℃[29,30]

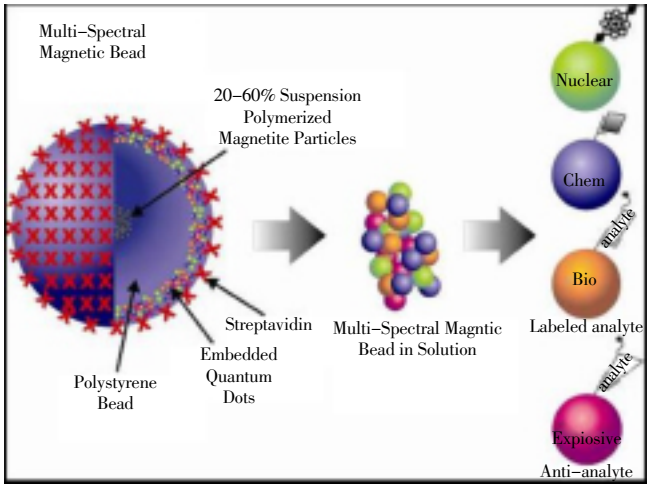

Figure 4. Microspheres for bio detection.

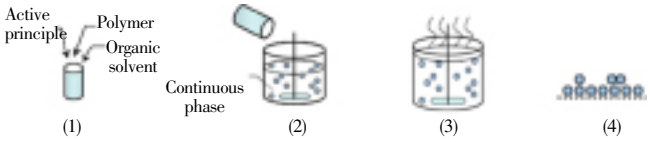

Figure 5. Continuous solvent evaporation method.

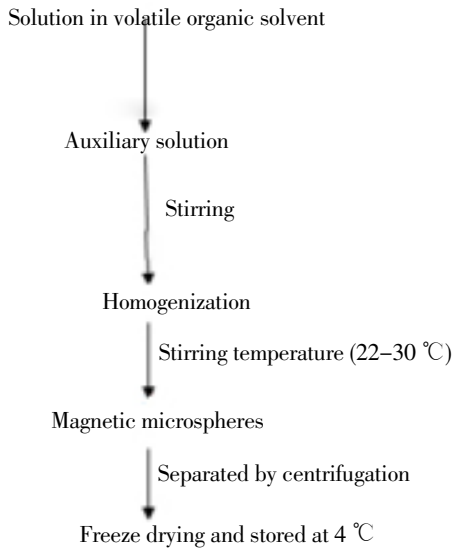

Figure 6. Schematic diagram of preparation of magnetic microspheres by solvent evaporation method.

Table 5
Solvents used for continuous solvent evaporation method.

Name of solvent	Vapour pressure (mbar) at 20 ℃; boiling point (℃); solubility in water (g/L) at 20 ℃	Advantages	Disadvantages
Chloroform	212; 61; 8	Low solubility in water	higher toxicity than dichloromethane
Dichloromethane	453; 39.7; 20	Dissolvation of most of the polymers; almost immiscible in water	high volatility and quite low boiling temperature; high toxicity
Ethyl acetate	100; 77; 90	Low toxicity	Very low vapour pressure partially soluble in water
Ethyl formate	259; 54; 105	Low toxicity	partially soluble in water

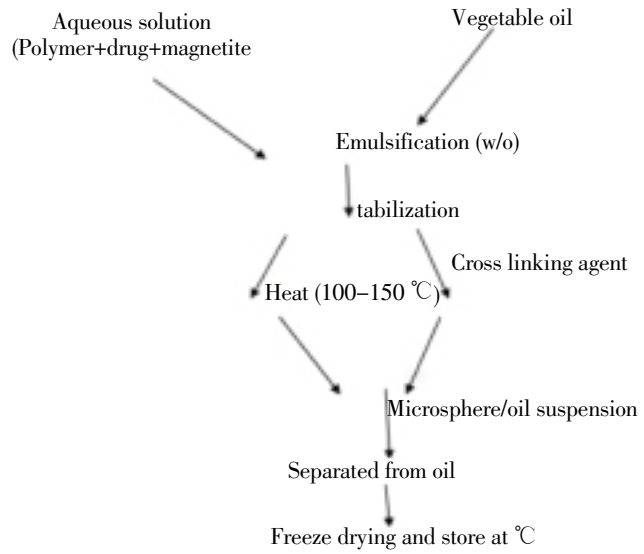

Figure 7. Schematic representation of phase separation emulsion polymerization.

6.3. Phase separation emulsion polymerization

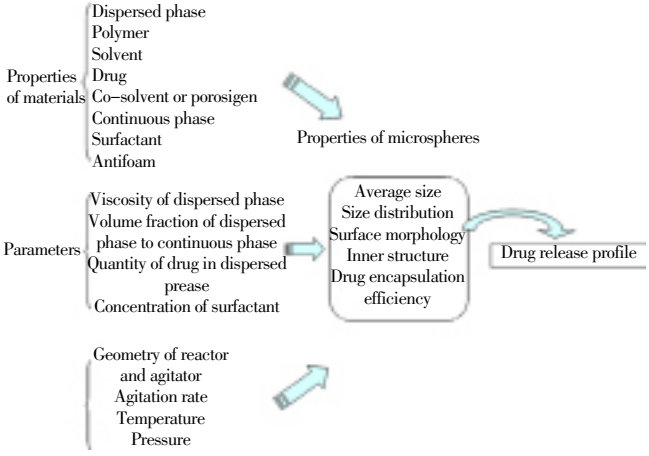

Figure 8. Factors affecting the properties of microspheres.

Polymer encapsulated microspheres are synthesized based on a modified phase separation emulsion polymerization technique. Briefly aqueous solution of polymer, drug and magnetite should be added to the vegetable oil and emulsified using a magnetic stirrer at 1 500 rpm for 2 min. The resultant should be stabilized by heating at the temperature (100–150 ℃). Then cross linking agent should be injected drop wise into the resultant emulsion under continuous stirring. (Figure 7). The magnetic microspheres will be formed in the oil suspension and then should be separated from oil by washing procedures. The product should be Freeze dried & stored at 4 ℃[31].

7. Evaluation parameters for magnetic microspheres

7.1. 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[32]

7.2. 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× (10× eye piece and 45× objective) and 100 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[33].

7.3. Density

a) Bulk density: Bulk density (ϱb) (g/cm^3) = M/Vb; Where, M = mass of powder taken, Vb = bulk volume; b) Tapped density: Tapped density (ϱt) (g/cm^3) = M/Vt; Where, M = weight of sample powder, Vt = tapped volume

7.4. Flow properties

Table 6
Depiction of flow properties.

Angle of Repose (θ)	Carr ' s Index(%)	Hausner Ratio	Flow Character
25–30	<10 %	1.00–1.11	Excellent
31–35	11–15	1.12–1.18	Good
36–40	16–20	1.19–1.25	Fair
41–45	21–25	1.26–1.34	Paasable
46–55	26–31	1.35–1.45	Poor
56–65	32–37	1.46–1.59	Very Poor
>66	38	>1.60	Very Very Poor

a) Angle of repose: θ = tan–1 h/r; b) Hausner ratio = ϱt/ϱb; Where, ϱt =Tapped density, ϱb = bulk density

Angle of repose is determined by using funnel method. The accurately weighed microspheres are taken in a funnel and then height of funnel is adjusted in such as way that the tip of funnel just touches the apex of heap of blends. The blends are allowed to flow through funnel freely on to surface. The diameter of powder cone is measured and angle of repose is calculated by using following equation: tanθ = h/r; Where θ – Angle of repose, h –height of pile, r – Radius of base.

7.5. Shape and surface characterization

The microspheres are mounted directly on the SEM sample stub, using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr) and photographed.

7.6. Determination of drug content

Accurately weighed 100 mg microspheres are crushed in glass mortar and pestle, powder microspheres are suspended in 100 mL of suitable solvent. After 12 h the solution was filtered and the filtrate was analyzed for the drug content using UV-Visible spectrophotometer.

7.7. Encapsulation efficiency

Encapsulation efficiency was calculated using the following formula: E =Qp / Qt × 100; Where, E = percentage

Table 7
Marketed products of magnetic microspheres.

Trade name	INCI name	Size (μ m)	Oil abs (g/g)	Refractive index	Density (g/in^3)
EA-209	Ethylene/acrylic acid copolymer	10.0	0.60	1.51	2.6
Flo-beads SE-3107A(soft beads A)	Ethylene/Methacrylate copolymer	11.0	0.62	1.49	3.12
Flo-beads SE-3207 B(Soft beads B)	Ethylene/Methacrylate copolymer	11.6	0.62	1.49	3.9
BPD-800	HDI/trimethylol hexyllactyl cross polymer (AND silica)	6.5	0.63	1.52	6.4
BPD-500	HDI/trimethylol hexyllactyl cross polymer(AND silica)	12.0	0.65	1.52	9.5
BPD-500T	HDI/PPG/Polycaprolactone cross polymer (AND silica)	13.5	0.58	1.52	8.2
BPA-500	Polymethyl Methacrylate	10.0	0.55	1.49	5.2
BPA-500X	Methyl Methacrylate cross polymer	7.0	0.58	1.49	6.7
MSP-822	Polymethyl Methacrylate	7.0	0.55	1.49	6.2
MSP-825	Methyl Methacrylate cross polymer	8.0	0.57	1.49	6.7
MSP-930	Methyl Methacrylate cross polymer	11.0	2.00	1.49	5.0
SUNPMMA-H	Methyl Methacrylate cross polymer	11.7	0.65	1.49	NA
TR-1	NYLON-6	13.0	1.12	1.53	4.0
TR-2	NYLON-6	20.0	1.41	1.53	3.5
POMP-605	NYLON-6	6.0	1.70	1.53	3.3
POMP-610	NYLON-6	11.0	1.80	1.53	2.8
SP-10	NYLON-12	10.0	0.60	1.53	6.2
SP-10L	NYLON-12	10.0	0.62	1.53	5.2
SP-500	NYLON-12	5.0	0.60	1.53	4.7
CL-2080	Polyethylene	12.0	0.60	1.51	4.0
TOSPEARL® 1110A	Polymethylsilsesquioxane	11.0	0.50	1.41	4.5
TOSPEARL® 120A	Polymethylsilsesquioxane	1.2	0.57	1.41	6.5
TOSPEARL® 145A	Polymethylsilsesquioxane	4.5	0.55	1.41	8.2
TOSPEARL® 2000B	Polymethylsilsesquioxane	5.0	0.54	1.41	8.5
TOSPEARL® 3000 A	Polymethylsilsesquioxane	5.0	0.54	1.41	7.0

of encapsulation of microspheres; Qp = quantity of drug encapsulated in microspheres; Qt = quantity of the drug added for encapsulation[34].]

7.8. Interaction study by TLC/IR

7.8.1. 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.

7.8.2. Thin layer chromatographic studies

The drug stability in the prepared microspheres can also be tested by the TLC method. The R_f values of the prepared microspheres can be compared with the R_f value of the pure drug. The values indicate the drug stability[35]

7.9. Surface topography by scanning electron microscopy (SEM)

SEM of the microspheres shows the surface morphology of the microspheres like their shape and size

7.10. Zeta potential

The polyelectrolyte shell is prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles are determined by zeta potential measurement

7.11. Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions: 1. Ambient humid condition; 2. Room temperature (27±2) ℃; 3. Oven temperature (40 ±2) ℃; 4. Refrigerator (50-80 ℃). It is carried out for 60 d and the drug content of the microsphere is analyzed.

8. Conclusion

Over the years, magnetic microspheres have been investigated for targeted drug delivery especially magnetic targeted chemotherapy due to their better tumor targeting. Targeted Drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. The main advantage of this technique is the reduction in the dose & side effects of the drug. It is a challenging area for future research in the drug targeting so more researches, long term toxicity study, and characterization will ensure the improvement of magnetic drug delivery system. The future holds lot of promises in magnetic microspheres and by further study this will be developed as novel and efficient approach for targeted drug delivery system

Conflict of interest

We declare that we have no conflict of interest.

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