World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Current prospective of magnetically triggered microsphere towards colonic disease: A review

Surender Verma*, Neha Khar, Lokesh Sadana

Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra (India) 136119

Received: 26-05-2015 / Revised: 30-06-2015 / Accepted: 01-07-2015

ABSTRACT

Magnetic microspheres hold great promise for reaching the goal of controlled and site specific drug delivery. Magnetic microspheres are traditional radiation methods which uses highly penetrating radiations that are absorbed throughout the body. These days targeted treatment system are used in many chronic diseases such as cancer, diabetes, nerve damage etc. Chronic Disease is a long lasting condition that can be controlled but not cured. Therefore, the *in-vivo* targeting of tumors with magnetic microspheres is currently realized through the application of external non-uniform magnetic fields generated by rare-earth permanent magnets or electromagnets. There has been keen interest in the development of a magnetically target drug delivery system. These drug delivery systems aims 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. 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 paper gives an overview of the mechanism, benefits, drawbacks, preparation and applications of magnetic microspheres.

Keywords: Magnetic microspheres, site specificity, magnetite, colon cancer.

INTRODUCTION

The oral route is considered to be most convenient form for the administration of drugs to patients. Oral administration with solid dosage form is a common route in the drug therapy and is widely used. The drug release by the disintegration process occurs in several gastrointestinal tract (GIT) regions [1]. Oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The problem associated with oral dosage form is first pass hepatic metabolism which has been overcome by novel drug delivery system like magnetic microsphere, liposomes, nanoparticles, niosomes, aquasomes, erythrosomes etc. There are various routes of administration of novel drug delivery system like oral, parenteral, transdermal and inhalation [2, 3]. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon such as colon cancer, Crohn's disease, inflammatory bowel disease, and ulcerative colitis where by high local concentration can be achieved while minimizing side effects and also used in treatment of Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which are absorbable in colon [3]. These conventional drug delivery systems for treating the colonic disorders fail, as the drug do not reach the site of action in appropriate concentration. Thus, an effective and safe therapy of these colonic disorders, using site specific drug delivery is a challenging task. Chemotherapy is also used to treat advanced colorectal cancer. Conventional chemotherapy is not as effective in colorectal cancer as it is in other types of cancers, as the drug does not reach the target site in effective concentrations [4]. There is a long-existing wish to treat local problems locally and systemic problems with systemic medical therapy. However, if the local disease problem is within an organism and inaccessible to conventional local treatment forms (surgery, radiation therapy, and topical application of antibiotics) systemic treatment is often used to treat local problems. This, in turn, requires administration of large amounts of drugs, most of which are metabolized by normal tissues. For drugs with a low therapeutic index, this causes a series of problems. Site directed drug targeting could

**Corresponding Author Address: Dr. Surender Verma, Assistant Prof. (Pharmaceutics), Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra (India) 136119*

circumvent this problem [5]. Magnetic microspheres form an important drug delivery strategy for controlled release and targeting prepared novel magnetic microsphere formulation which can be used for colon specific drug delivery for targeting even in diseased conditions such as IBD, Crohn's disease and Colon cancer.

NEED OF COLON TARGETING

- Targeted drug delivery to the colon to ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine.
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the Colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides [6].

MAGNETIC MICROSPHERE

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumor, without any toxic effects to normal surrounding tissue or to the whole body [7]. Magnetic microspheres are sometimes referred to as micro particles. According to FDA magnetic microsphere are supra-molecular particles that are small enough to circulate through capillaries without producing embolic occlusion. Their size ranges from 1 μm to 1000 μm [8]. Magnetic microsphere are sometimes referred to as micro particles. According to FDA magnetic microsphere are supra-molecular particles that are small enough to circulate through capillaries without producing embolic occlusion. Magnetic microspheres will be formulated with an intension to produce a depot near the target organ, by placing a suitable magnet near it. From the depot, drug will be released slowly & carried to the target organ through blood. By localizing the drug carrier near the target organ, unwanted distribution of drug to non-target organ can be avoided. This approach will localize the drug only at target site & minimize the drug-induced toxicity. Mainly Magnetite is added in microsphere for its magnetic property which helps in site specific targeting. Magnetic field applied to drag into tissues is 0.5-0.8 tesla (T) [7, 9].

Magnetite: Magnetite is also called as ferric ferrous oxide, tri iron tetra oxide, and black iron oxide. Magnetic iron oxide chemical formula Fe_3O_4 having a molecular weight of 231.55 with chemical composition of Fe=72.36%, O=27.64% [29]. To prepare magnetite, nitrogen gas flushed through 500 mL round bottom flask fitted with condenser. Charged the flask with 8.9 g (0.1mol) of goethite, 9.94g (0.05mol) of $FeCl_2.4H_2O$ along with 250 mL deionized water. Added 50 mL of 2M Sodium Hydroxide. Reaction mixture was heated to reflux for 12 h. Its pH fell from 14 (orange) in to 8-9 (black precipitates). Particles washed and air dried [23]. Magnetite is a type of magnetic particle that has been the target of important studies on biomedicine because of its non-toxicity, high level of accumulation in tissues [10].

Importance of Magnetite in Microspheres: It is possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels [7]

Advantages of Magnetic Microsphere: [11, 12]

1. Increased duration of action.
2. First pass effect can be avoided.
3. Patient compliance is good.
4. Improved protein and peptide drug delivery.
5. Reduce toxicity.
6. Method of preparation is simple.
7. Less side effects and release high concentration of drug.

Disadvantages of Magnetic Microsphere: [11, 12]

1. Removal once injected is difficult.
2. Needs specialized magnet for targeting.

Materials used in preparation of magnetic microspheres: Various polymers used in magnetic microspheres as shown in table 1.

Principle of Magnetic Targeting: Magnetic drug delivery by particulate carriers is an efficient method of drug delivery to a localized disease site. A drug or therapeutic radioisotope is encapsulated in a magnetic compound; injected into patient's blood stream & then stopped with a powerful magnetic field in the target area. Figure 1 shows representation of systemic drug delivery and magnetic targeting. Depending on the type of drug, it is then slowly released from magnetic carriers or confers a local effect, thus it reduces the loss of drug as freely circulating in body [4]. 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, sub-sector even an intercellular region. Fig1 shows magnetic drug targeting [13].

Principle of Magnetic Targeting in Cancer: After swallowing the capsule, the patient is positioned on a bed that resembles a magnetic resonance imaging scanner, with the upper abdomen at the center of an electromagnetically generated field. The magnet system generates varying magnetic fields that are controlled by a joystick to navigate the capsule as shown in fig 2.
Secondly Cora LA in 2014 took ten healthy volunteers were studied after an overnight fast. Each volunteer, in orthostatic position in the measurement system, ingested a magnetic dosage form (tablet or capsule) with 200 ml of water. The multi-sensor ACB system was positioned on the gastric region and the magnetic signals were acquired during 20 minutes. The lower tip of the sternum and the umbilicus were the anatomic references (Fig. 3a). A single-sensor ACB was used to monitoring the magnetic formulation between the measurements of the GI motility and to determine the Gastrointestinal Transit Time (GITT). An initial square matrix (9x9), corresponding to an area of 12x12 cm, was drawn in the colonic region of the volunteers (Fig. 3b). When the magnetic formulation reached the colonic region, the single-sensor ACB was used to scanning this delimited area. Scanning at least for 2 min and was performed at approximately 10 min intervals until 120 minutes post-colonic arrival [14].

Methods of Preparation of Magnetic Microspheres:

Ionic Gelation Method: Inotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as microspheres. Microspheres are spherical cross-linked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross-linked moiety. Biomolecules can also be loaded into these microspheres under mild conditions to retain their three dimensional structure. Alginate/chitosan particulate system for drug release was prepared using this technique. 25 % (w/v) of drug was added to 1.2 % (w/v) aqueous solution of sodium alginate and magnetite. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hour for internal jellification followed by filtration for separation [15-19] as shown in fig 4.

Other Method of Preparation:

I. Single emulsion technique:- There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods:
   - ❖ Cross linking by heat: By adding the dispersion into heated oil, but it is unsuitable for the Thermo labile drugs.
   - ❖ Chemical cross linking agents: - by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion5. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.[20,21]

II. Solvent evaporation:- For the formation of the emulsion between polymersolution and an immiscible continuous phase in aqueous (o/w) as well as non-aqueous phase (w/o) They prepared microsphere by using liquid paraffin/ acetone as the solvents by evaporation method. The drug solution (in acetone) was dispersed in chitosan solution and this mixture was emulsified in liquid paraffin and stirred. The suspension of microspheres was filtered, washed and dried. Magnesium stearate was also added for preventing

agglomeration as a Agglomeration preventing agent. The results showed that average particle size decreased with increasing amount of magnesium stearate used for microsphere preparation. They investigated the comparison of muco-adhesive microspheres of hyaluronic acid, chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation.[22-25]

III. Solvent extraction:- In this method preparation of micro-particles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be use as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer [26-28].

IV. Drying & Spray Congealing:- Evaporation is the basic mechanism in spray drying, where as in spray congealing it is that of a phase inversion from a liquid to a solid [29].

Three steps involved in spray drying:-

i. Atomization: of a liquid feed change into fine droplets.

ii. Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

Dry: Dried powder is separated from the gas stream and collected [30, 31].

Characterization properties of magnetic microsphere:-

- Particle size analysis: Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, To prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer.
- Scanning electron microscopy study: In this microcapsule were mounted directly on the SEM sample slub with the help of double sided sticking tape and coated with gold film under reduced pressure.
- Flow properties like
  - Bulk density

BD = M / Vo

Where, BD = Bulk density

M = Mass of sample in g

Vo = Bulk volume of powder in cc

- Tapped density

TD = M / Va

Where, TD = Tapped density

M = Mass of powder in g

Va = Tapped density of powder in cc

- Compressibility index or Carr's index

% Compressibility = (TD-BD) / TD x 100

Where, TD = Tapped density

BD = Bulk density

- Hausner's ratio

Hausner's ratio = TD / BD

Where, TD = Tapped density

BD = Bulk density

- Angle of repose

$\theta = \tan^{-1} h/r$

Where, θ = Angle of repose

h = height of cone

r = radius of cone base

- Swelling index**:** This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution(100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37˚C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper [35-37].

Evaluation of Magnetic Microspheres:

- Determination of percentage yield: The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100.
- Drug content: Drug loaded microspheres (100 mg) were powdered and suspended in 100 ml methanolic36: water (1:99 v/v) solvent. The resultant dispersion was kept for 20 min for complete mixing with continuous agitation and filtered through a 0.45 μm membrane filter. The drug content was determined spectrophotometrically (UV-1700, Shimadzu Japan) at 205.6 nm using a regression equation derived from the standard graph (r2=0.9954).
- Dissolution studies of microsphere: Drug release tests were performed according to USP XXIV paddle method for each size fraction separately. Accurately weighed amounts (100 mg) of microspheres were introduced into 900 mL of PBS (phosphate

buffer saline, pH 7.4) and stirred with 100 rpm at (37.0±0.5) ˚C . Five milliliters samples were withdrawn and filtered at selected time intervals. The concentration of drug was determined spectrophotometrically at different wavelength.

- *in vitro* drug release: The in vitro drug release data were fitted to various release kinetic models24 that can define mechanism of the release: Higuchi,25 Korsemeyer - Peppas,26 and Hopfenberg27 models employing the following set of equations:

  Higuchi model: Mt ¼ K _ t1=2

  Korsemeyer Peppas model: Mt=M1 ¼ k _ tn

  Hoffenberg: Mt=M1 ¼ 1 _ ½1 _ ðK1t=C0RÞ [37, 38]

- % Magnetite content:- Higher strength of HCl (1N) was used along with the definite stirring and ultra-sonication conditions. The stirring at 50 rpm and 40ºC during the dissolution ensured complete solubilization of magnetite. One hundred mg of magnetite-containing microspheres was added to a 100 mL volumetric flask containing 100 mL of 1N HCL and incubated for two days at 50 rpm, 40°C in a water bath shaker. The contents of the flasks were sonicated (Hielscher Ultrasound Technology, amplitude 80 for 2 min) thrice with a 5 min interval, and the incubation was continued for another eight days. Then the content was cooled, filtered and made up to 100 ml with distilled water. 10 ml of the resulting solution was diluted to 100 ml with distilled water; 5 ml of the diluted solution was transferred into a 25 mL volumetric flask containing 750 µL of 10% w/v sulfosalicylic acid (SAS) and stirred for 2 min. Then, 750 µL of 25% w/v ammonia solution was added before the flask was topped up to volume with distilled water. The absorbance of total iron complex was measured using a spectrophotometer at given nm against the reagent blank [39].

Application of magnetic microsphere:

1. Enzyme immobilization: Free enzymes were immobilized onto magnetic carriers' surface or porous wall by taking advantage of physical adsorption or covalence. Compared with other immobilized carriers, magnetic carriers have the following advantages:
   - ❖ Immobilized enzymes are easily separated from the products or reactants.
   - ❖ The manner of movement of immobilized enzymes can be controlled by external magnetic fields, which can greatly enhance the catalyzing efficiency of enzyme.
   - ❖ Enzyme catalytic reactions can be continuously carried out and controlled by a magnetic field in a bioreactor, which can reduce the consumption of enzyme.
   - ❖ The reutilization of immobilized enzyme will reduce cost.
   - ❖ The biocompatibility of enzyme will be improved etc.
2. Cell isolation: Magnetic carriers of cell isolation are based on affinity principles. An antibody was fixed on the surface of magnetic carriers and then immunomagnetic beads (IMBS) were formed. Under the external magnetism, cell isolation can be carried out by making these immunomagnetic beads combine with antigens on the surface of target cells. This method has many advantages: simple and swift operation, high purity and good activity of products etc. There are two methods to separate cells by IMBS: positive selection and depletion method. Positive selection means that the target cells were separated directly from the crude material; while depletion method means that irrelevant cells were depleted by IMBS and so the target cells were purified.
3. Protein purification: Magnetic carrier of protein purification is also based on the principle of affinity separation. Affinity ligands, which have special combinations with target proteins, are fixed on the surface of magnetic carriers. Target proteins are separated directly from the crude material through affinity adsorption, desorption and magnetic separation etc. Compared with traditional protein separation technologies such as salting out method, film separation technology and ion exchange chromatography, it is not necessary to adjust the pH values, temperature and ionic strength during the separation process. This can effectively avoid the loss of protein.
4. Target drugs: Target drugs refer to the drugs' oriented delivery to the pathological tissues by taking advantage of the pH sensitivity, thermal sensitivity and magnetism of drug carriers. The delivery method of target drugs can be divided into passive delivery of drug and active delivery of drug. Passive delivery of drug mainly depends on the changes of hydrophilic and hydrophobic characteristics on the surface of carriers and the size of carriers. Active

delivery transfers drugs to the expected pathological parts of the human body by making use of the guide function of external magnetic field and the special affinity of coupling ligands. This method not only reduces the possible toxic side-effects, but also reduces the quantity of drugs required.

5. Also used as a chemotherapeutic agent.
6. These can be used for stem cell.
7. These are used in the fields of biomedicine and bioengineering.
8. These can be targeted to specific locations in the body with magnetic field gradient.
9. They can be used for molecular targeting, DNA analysis, proteomics.
10. It is used in MRI, cell isolation, radiotherapy and protein purification.
11. Used in Bacteria Detection and magnetic bio separation [32-34].

Marketed products on magnetic microsphere with their INCI Names: Various marketed products are given in table 2.

Patent work done on magnetic microsphere: Various patent work on magnetic microspheres is depicted in table 3.

CONCLUSION

Magnetically triggered microspheres attracts considerable attention of researchers due to their enhanced efficacy along with reduced side effects due to targeted release properties. The magnetic microspheres have high magnetic susceptibility and high potency to an external magnetic field since they can be easily separated from other components of the mixture with the help of magnet externally. Therefore magnetic microspheres form an important drug delivery strategy for controlled release and targeting and it can be concluded that the prepared novel magnetic microsphere formulation can be used for colon specific drug delivery for targeting even in diseased conditions such as IBD, Crohn's disease and Colon cancer. So it can be proved to an important tool for targeted controlled release preparations.

ACKNOWLEDGEMENT

I want to say thank you to my Director of Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra who provide the opportunity to search the literature in the library online and offline.

Table 1: Materials used in preparation of magnetic microspheres:

Synthetic Polymers	PLGA, Poloxamer, Eudragit, Poly vinyl pyrrolidone, Ethyl cellulose, Sodium pyrrolidone carboxylate, Povidone, PLA PEG, HPMC, PVA.
Natural Polymers	Starch, Chitosan Hyaluronate, Human albumin, Gelatin Alginic acid, Collagen

Table 2: Marketed products on magnetic microsphere with their INCI Names

Sr. No.	Trade name	INCI name
1.	EA-209	Ethylene/acrylic acid copolymer
2.	Flo-beads SE-3207 B(Soft beads B)	Ethylene/Methacrylate copolymer
3.	Flo- beads SE-3107A(soft beads A)	Ethylene /Methacrylate copolymer
4.	BPD-800	HDl/trimethylol hexyllactyl cross polymer (AND silica)
5.	BPD-500	HDl/trimethylol hexyllactyl cross polymer (AND silica)
6.	BPD-500 T	HDl/trimethylol hexyllactyl cross polymer (AND silica)
7.	SUNPMMA-H	Methyl methacrylate crosspolymer
8.	BPA-500X	Methyl methacrylate crosspolymer
9.	MSP-822	Polymethyl methacrylate

10.	MSP-825	Methyl methacrylate crosspolymer
11.	TR-1	NYLON-6
12.	TR-2	NYLON-6
13.	POMP-610	NYLON-6
14.	TOSPEARL® 1110A	Polymethylsilsesqui oxane
15.	TOSPEARL® 120A	Polymethylsilsesqui oxane

Table 3: Patent work done on magnetic microsphere

Sr. no	Patent No.	Work Done
1.	US4285819 A	Functional magnetic microspheres
2.	US8568881 B2	Magnetic microspheres for use in fluorescence-based applications
3.	US7879625 B1	Preparation of SERS substrates on silica-coated magnetic microspheres
4.	CA2595292 C	Magnetic microspheres for use in fluorescence-based applications
5.	US7718262 B2	Magnetic microspheres for use in fluorescence-based applications

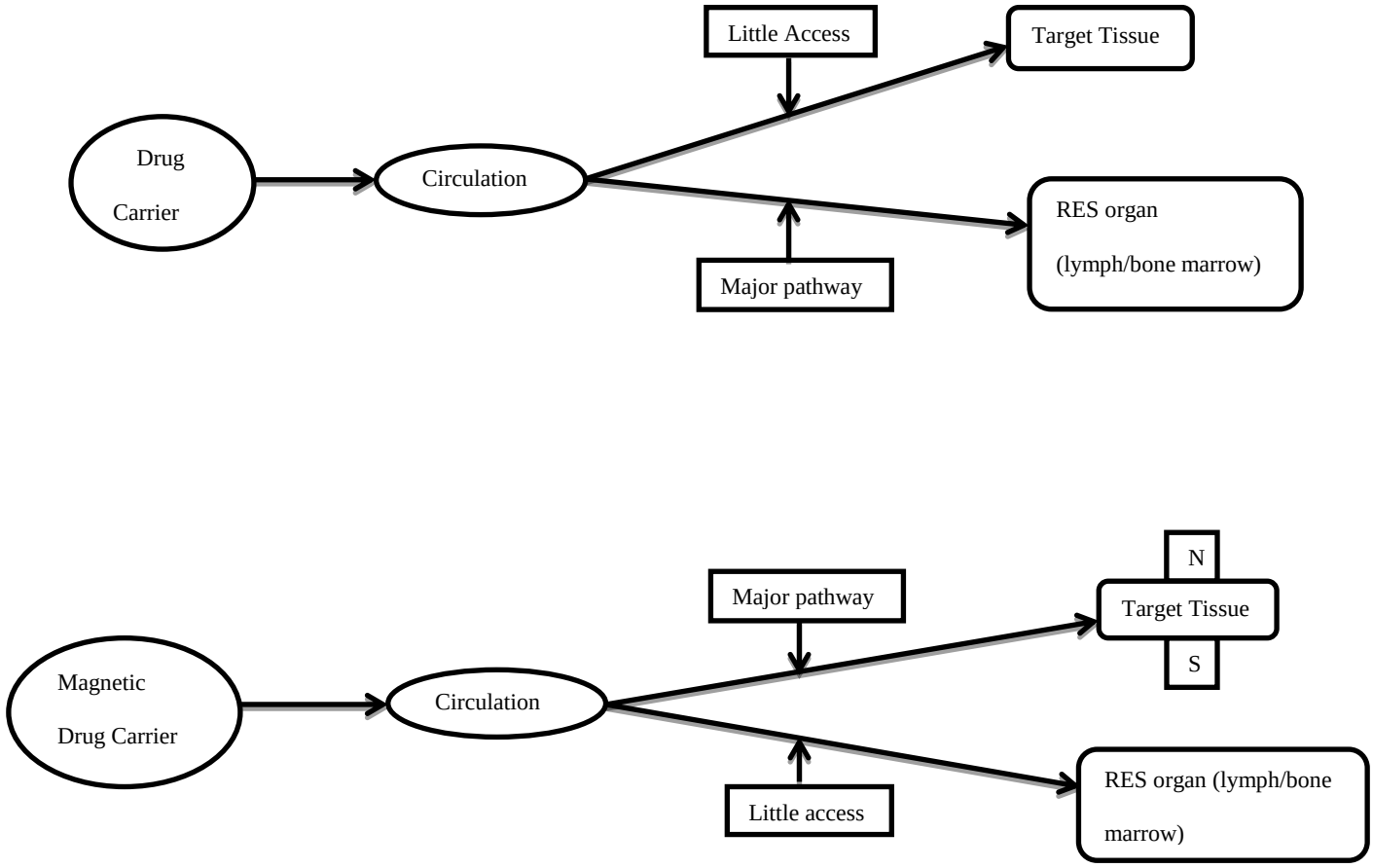

Fig1: RES: Reticulo-endothelial system

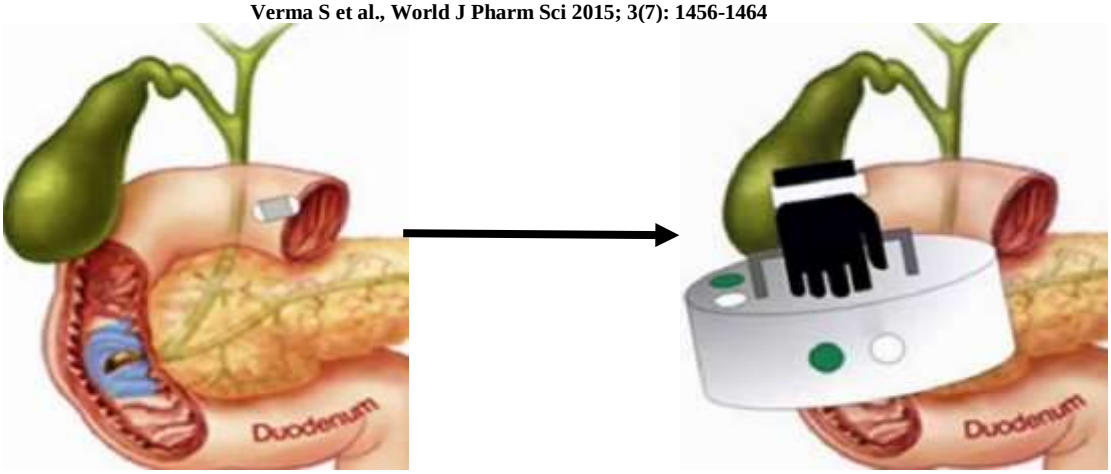

Fig 2: Principle of Magnetic Targeting in Cancer

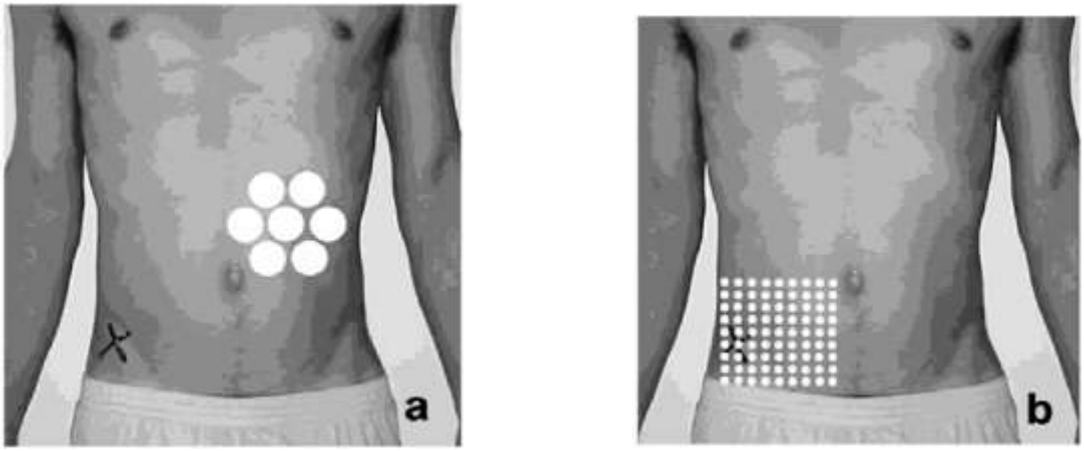

Fig 3: (a) Multi-sensor AC Biosusceptometer system positioned on the abdominal surface; (b) Square matrix (9x9) drawn on the colonic region.

Polyelectrolyte solution

[Sodium Alginate + polymer + Magnetite + Drug]

↓

Added drop wise under magnetic stirring by needle

↓

Counter ion solution

[Calcium chloride solution (+)/Sodium tripolyphosphate (-)]

↓

Microspheres

Fig 4 Preparation of Magnetic Microsphere

REFERENCE

1. Cora LA et al. Magnetic images with a biosusceptometer of pharmaceutical dosage forms in the human gastrointestinal tract. Res gate 2104; 10: 1-9.
2. https://en.wikipedia.org/wiki/Dosage_form 12 Feb 2015.
3. Hassan BAR. Overview on Drug Delivery System. Pharmaceut Anal Acta 2012; 3: 1.
4. Gowda DV et al. Development and Evaluation of Phosphated Cross-Linked Guar Gum Microspheres for Improved Delivery of Anticancer Drug to Colon. Polym-Plast Technol Eng 2012; 51: 1395–1402.
5. Lubbe AS et al. Predinical Experiences with Magnetic Drug Targeting: Tolerance and Efficacy. Cancer Res 1996; 56: 4694-4701.
6. Qureshi AM. Colon targeted drug delivery system: a review on current approaches. Indian J Pharm Biol Res 2013; 1: 130-147.
7. Häfeli UO. Magnetically modulated therapeutic systems. Int J of Pharmaceutics 2004; 277: 19–24.
8. Mukherjee S, Bandyopadhyay P. Magnetic Microsphere: A latest approach in novel drug delivery system. J Pharma Sci Innova 2012; 1: 21-25.
9. Kakar S, Batra D. Preparation and evaluation of magnetic microspheres of mesalamine (5-aminosalicylic acid) for colon drug delivery. J Acut Dis 2013; 226-231.
10. Silvaa EP et al. Covalent TiO2/pectin microspheres with Fe3O4nanoparticles formagnetic field-modulated drug delivery. Int J of Biological Macromolecules 2014; 67: 43–52.
11. Bansal H et al. Microsphere methods of preparation and applications; A Comparative Study 2011; 10: 1-8.
12. Hire NN, Derle DV. Microsphere as drug carrier: a review. Int J of Advanced Research 2014; 2(3): 901-913.
13. Kakar S et al. Magnetic microspheres as magical novel drug delivery system: A review. J Acut Dis 2013; 1-12.
14. Magnets in the GI tract: Report On Emerging Technology. Gastrointestinal Endoscopy: 2013; 78: 561-567.
15. Sun L et al. Preparation and characterization of porous biodegradable microspheres used for controlled protein delivery. Colloids and Surfaces A- Physicochem. Eng. Aspects 2009; 345: 173–181.
16. Priyadarshini MK et al. Formulation And Evaluation Of Microspheres Encapsulating Zidovudine By Ionic Gelation Techniques. Int J Res Pharma Nano Sci 2014; 3: 461-468.
17. Nayak BS et al. Preparation and characterization of famotidine microcapsule Employing muco-adhesive polymers in combination to enhance Gastro retention for oral delivery. Int J Pharm Pharm Sci 2009; 1: 112-20.
18. Shankar NB et al. Design and Evaluation of Controlled Release Bhara Gum Microcapsules of Famotidine for Oral Use. Research J. Pharm. and Tech 2008; 1: 433-37.
19. Patil P. A review on ionotropic gelation method: novel approach for controlled gastroretentive gelispheres. Int J Pharm Pharm Sci 2012; 4: 27-32.
20. Vyas SP, Khar RK. Target and controlled drug delivery. CBS Publishers and distributors 2002; 1: 458-01.
21. Manivannan R et al. In vivo Evaluation of Single Dose Tetanus Toxoid Vaccine Formulation with Chitosan Microspheres. Ind J of Pharm Sci 2008; 70: 23-8.
22. Shankar NB, Kumar NU. Lamivudine loaded microspheres for oral use: design, development and Establishment of in vivo-in vitro correlation. Asian J Pharm Clin Res 2009; 2: 55-60.
23. Anand KA. Formulation of Lamivudine Microspheres in Multiple Emulsion Form Using Osmogen And Different Polymers - Studying The Release Profiles. Int J Drug Develop Res 2011; 3: 277-284.
24. Behera BC et al. Characterization of glipizide-loaded polymethacrylate microspheres prepared by an emulsion solvent evaporation method. Trop J Pharm Res 2008; 7: 879-85.
25. Giunchedi P et al. Cellulose acetate butyrate and poly-caprolactone for keto proton spray-dried microsphere preparation. J Microencapsul 1994; 11: 381-93.
26. Ravivarapu HB et al. Polymer and microsphere blending to alter the release of a peptide from PLGA microspheres. Eur-J-Pharm-Biopharm 2000; 50: 263-270.
27. Parsant KR et al. Effect of method of preparation on physical properties and *in-vitro* release profile of Losarton microspheres. Int J Pharm Pharm Sci 2009; 1: 108-118.
28. Bodmeier R. Microencapsulation. J pharm. sci 1992; 9: 89–98.
29. Mansour HM, Materials for Pharmaceutical Dosage Forms: Molecular Pharmaceutics and Controlled Release Drug Delivery Aspects. Int J Mol Sci 2010; 11: 3298-3322.
30. Gohel MC, Parikh RK. A Spray drying a review. Pharma info 2009; 7: 5.
31. BJ Swarbrick. Spray drying and Spray Congealing of Pharmaceuticals. In: Encyclopedia of Pharmaceutical Technology. Marcel Dekker; 1992: 207-21.
32. Schutt W, Grüttner C, Häfeli U, Zborowski M, Teller J, H Putzar, Cschümichen. Applications of Magnetic Targeting in Diagnosis and Therapy—Possibilities and Limitations: A Mini-Review. Hybridoma 1997; 16: 109-117.
33. Zhang B et al. Preparation and application of magnetic microsphere carriers. Front. Chem. Eng. China 2007: 1: 96–101.
34. Xianqiao Liu et al. Immobilization of lipase onto micron-size magnetic beads. J Chromatogr Sci 2005; 822: 91–97.
35. Shah S et al. Formulation and evaluation of microsphere based oro dispersible tablets of itopride hcl. J Pharma Sci 2012; 20: 24.
36. Jagadeesh HG, Devi KV. Tamoxifen Loaded Poly (εCaprolactone) based injectable microsphere for breast cancer. Int. J. Pharm Pharm Sci 2010; 2: 189-195.
37. Fenandez A et al. Tamoxifen-Loaded Microspheres Based on Mixtures of Poly(D,L-lactide-co-glycolide) and Poly(D,L-lactide) Polymers: Effect of Polymeric Composition on Drug Release and In Vitro Antitumoral Activity. J Appl Polym Sci 2012; 124: 2987–2998.
38. Yadav N et al. Synthesis and Characterization of Sustained Release Atenolol Microspheres by Solvent Evaporation Technique. J *Pharm Sci Tech* 2011; 3: 559-562.
39. Philippova O et al. Magnetic polymer beads: Recent trends and developments in synthetic design and applications. Eur Polym J 2011; 47: 542–559.