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Research Article

Formulation And Evaluation Of Magnetic Microspheres Of Cytarabine Using Eudragit L-100 And Chitosan As Polymers

Rajeshwar Verma*[1], Ramandeep Singh[2]

[1]*School Of Pharmaceutical Sciences, MVN University, Palwal Haryana*
[2]*Department of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib, Himachal Pradesh*

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ABSTRACT

The ability to deliver extremely effective dosages to precise target areas within the human body has become the holy grail of medication delivery research. Drugs with established efficacy in in vitro research usually face a major obstacle in in vivo testing due to a lack of an effective delivery mechanism. Furthermore, many therapeutic conditions necessitate the delivery of entrepreneurs, which may be beneficial at the desired delivery location but are otherwise systemically hazardous. Magnetically responsive microspheres containing Cytarabine were prepared using the CSE technique and chitosan and Eudragit l-100 polymers, and they were assessed with regard to particle duration assessment via SEM, entrapment overall performance, magnetite content material fabric, and in vitro magnetic responsiveness in a 7000 Oe magnetic subject, in vitro drug release tests, in vivo drug targeted investigations, and stability experiments were conducted. Spherical particles with an average diameter of 3-12 m and an incorporation overall performance of 56.37% were achieved. The existence of magnetite in prepared Cytarabine magnetic microspheres is confirmed by X-ray diffractometry results. Using chemical analysis, it was determined that the average proportion of Fe2O3 within the microspheres was between 40.53% and 53.48%. For F-1-F-9, the cumulative percent drug release after 24 hours was 80.60%, 78.22%, 76.41%, 74.35%, 73.25%, 71.23%, 64.21%, 61.56%, and 58.45%, respectively. The results of in vitro magnetic responsiveness and in vivo focused on confirmed that the retention of microspheres in the presence of magnetic subject became significantly greater than those in the absence of magnetic subject become significantly greater than those without the magnetic subject. Stability investigations revealed that the samples maintained at 4 degrees Celsius had the highest drug content material fibre and the closest in vitro release to the initial records. Overall, this research reveals that magnetic microspheres may be kept at their target site in vivo, using magnetic subject software, and are capable of freeing their

***Corresponding Author:** Rajeshwar Verma
Address: *School Of Pharmaceutical Sciences, MVN University, Palwal, Haryana*
Email ✉: rajaerv8@gmail.com

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drug content material fibre for an extended period of time. This could lead to them being directed to a suitable depot for administering chemotherapeutic agent(s) in vivo.

INTRODUCTION

The oral path is the one, maximum often used for drug management. Oral dosage forms are usually indicated for systemic results due to drug absorption thru various epithelia and mucosa of the gastro intestinal tract. as compared with different routes, the oral route is the most effective, maximum handy and most secure means of drug management [1]. however oral administration of most of the medication in conventional dosage bureaucracy has brief-term limitations because of their incapability to restrain and localize the machine at gastro-intestinal tract. Microspheres represent a critical part of those particulate drug shipping structures by means of distinctive feature in their small size and green carrier ability. Microspheres are the carrier connected drug shipping gadget in which particle size is tiers from 1-one thousand μm variety in diameter having a core of drug and absolutely outer layers of polymers as coating material [2] A healing quantity of drug at right web page in the frame and its maintenance for a selected time frame are managed via a properly-designed drug device. some of drug transport systems keep great guarantees for achieving the goal of controlled and site precise drug shipping, one in every of them is magnetic microsphere, a unique drug delivery system. Currently, Novel drug delivery device ambitions to supply the drug at a charge directed by the desires of the body at some stage in the period of treatment, and target the lively entity to the site of movement. some of novel drug transport systems have emerged encompassing diverse routes of administration, to gain managed and targeted drug shipping, magnetic micro carriers being one of them. Magnetic microspheres are supra-molecular debris which can be small sufficient to flow into through capillaries without generating 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 (T). Magnetic microspheres were prepared by mainly two methods namely phase separation emulsion polymerization (PSEP) and continuous solvent evaporation (CSE). The amount and rate of drug delivery via magnetic responsive microspheres can be regulated by varying size of microspheres, drug content, magnetite content, hydration state and drug release characteristic of carrier, the amount of drug and magnetite content of microspheres needs to be delicately balanced in order to design an efficient therapeutic system. magnetic microspheres are characterized for different attributes such as particle size analysis including size distribution, surface topography, and texture etc. using scanning electron microscopy (SEM), drug entrapment efficiency, percent magnetite content, and in vitro magnetic responsiveness and drug release. Targeting by magnetic microspheres i.e. incorporation of magnetic particles in to drug carriers (polymers) and using an externally applied magnetic field is one way to physically direct this magnetic drug carriers to a desired site. 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 localizes the drug to the disease site. [3]

Advantages of Magnetic Microspheres:

1. Drug release rates can be tailored to the needs of a specific application; for example, providing a constant rate of delivery or pulsatile release.

2. Controlled release systems provide protection of drugs, especially proteins that are otherwise rapidly destroyed by the body.
3. Controlled release systems can increase patient comfort and compliance by replacing frequent (e.g., daily) doses with infrequent (once per month or less) injection. [4]
4. Magnetic microspheres are site specific and by localization of these microspheres in the target area, the problem of their rapid clearance by RES is also surmounted.
5. Linear blood velocity in capillaries is 300 times less as compared to arteries, so much smaller magnetic field is sufficient to retain them in the capillary network of the target area.
6. In case of tumour targeting, microsphere can internalize by tumour cells due to its much increased phagocytic activity as compared to normal cells
7. Problem of drug resistance due to inability of drugs to be transported across the cell membrane can be surmounted.

Disadvantages of Magnetic Microspheres

1. By the use of magnetic microspheres in the delivery system, the drug cannot be targeted to deep seated organs in the body.
2. Magnetic targeting is an expensive technical approach and requires specialized manufacturer and quality control system.
3. It needs specialized magnet for targeting, advanced technique for monitoring, and trained personnel to perform the procedure. [5]

Types of Microspheres:

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
   i) Biodegradable polymeric microspheres
   ii) Synthetic polymeric microspheres [6]

1. Bioadhesive / Mucoadhesive Microspheres:

Adhesion may be defined as sticking property of drug to the mucosal membrane by using water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged contact time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. Or Bioadhesion may be defined as the process by which a natural or synthetic polymer can adhere to a biological membrane. When the biological membrane is a mucosal layer then it is known as mucoadhesion. Mucoadhesion is a currently used in the design of new drug delivery system. Mucoadhesive microspheres provide a prolonged contact time at the site of application or absorption and helps in facilitating an intimate contact with the under lying surface at which absorption is suppose be occurred and there by improve or better to therapeutic performance of drug. Mucoadhesive polymer are used to improving drug delivery by promoting the residence time and contact time of the dosage form with the mucous membranes, it adhere the mucosal surface in the body and the drug absorption by mucosal cells may be enhanced or released at the site for an extended period of time and enhanced bio availability of the drug to high surface to volume ratio. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal, vaginal routes for either systemic or local effects [7].

Theories of Mucoadhesion:

The phenomenon of bioadhesion occurs by a complex mechanism. Many scientists have worked over bioadhesion; till date six the ories have been proposed which can improve our understanding for the phenomenon of adhesion and can also be extended to explain the mechanism of bio adhesion. The theories include

a The electronic proposes transfer of electrons among s the surface resulting in the formation of an electrical double layer there by giving attractive forces.
b The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.
c The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Vander waal's forces, for the adhesive interaction amongst the substrate surfaces.
d The diffusion theory assumes the diffusion of the polymer chains, present on the substrates Surfaces, across the adhesive interface there by forming worked structure.
e The mechanical theory explains the diffusion of the liquid adhesives into them cracks and irregularities present on the substrate surface there by forming anointer locked structure which gives rise to adhesion.
f The cohesive theory proposes that phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like molecules. [8]

The term "mucoadhesion" is adhesion of the polymers with the surface of the mucosal layer. The mucosal layer is made up of mucus which is secreted by the goblet cells columnar and is a viscoelastic fluid. The main components constituting the mucosa include >95% water and > 99 % mucin, the other issues include protein, lipids and mucopolysaccharides. The gel like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins at the side of the non-covalent interactions which ends in the formation of a hydrated gel like shape. [9]

2. Magnetic Microspheres:

on this larger quantity of unfastened circulated rug can be replaced via smaller amount of magnetically focused drug which get hold of magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. Magnetic microspheres preserve terrific promise for achieving the purpose of managed and location specific drug transport. Magnetic microspheres as an opportunity to conventional radiation techniques which uses highly penetrating radiation that is captivated during the frame. Its use is limited by means of toxicity and aspect outcomes. Now days, numerous embattled treatment systems which include magnetic field, electric field, ultrasound , temperature , UV light and involuntary force are getting used in many sickness remedies(e.g. cancer,nerve damage, coronary heart and artery, anti-diabetic, eye and other scientific remedies).amongst them, the magnetic focused drug shipping machine is one of the maximum attractive and promising strategy for handing over the drug to the desired web site. Magnetically managed drug focused on is one of the numerous feasible approaches of drug concentrated on. This technology is based on binding set up anti most cancers drug with ferro fluid that listen the drug in the region of hobby (tumor site) by way of magnetic fields. there was eager interest in the development of a magnetically goal drug shipping system. Those drug delivery structures intention to supply the drug at a charge directed with the aid of the needs of the body all through the length of remedy, and goal the interest entity to the web site of motion. [10]

The distinctive types of magnetic microspheres are as follows:

a Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. capsules like proteins and peptides can also be focused via this gadget.
b Diagnostic microspheres, used for imaging liver metastases and also may be used to distinguish bowel loops from other stomach

structures by way of forming nano length particles supra magnetic iron oxides.

3. Floating Microspheres:

Gastro retentive drug transport via floating types having benefits of bulk density is less than the gastric fluid and so remains buoyant in stomach with out have an effect on in gastric emptying rate. The drug is released slowly at the preferred fee, and the machine is determined to be floating on gastric content and will increase gastric house and increases fluctuation in plasma awareness. Furthermore, it additionally reduces possibilities of dose dumping. It produces extended healing effect and therefore reduces dosing frequencies. Few drugs like Famotidine can be given inside the shape of floating microspheres relying upon the pharmacokinetic homes.

4. Radioactive Microspheres:

Radio embolization remedy microspheres sized 10-30 nm are of large than the diameter of the capillaries and receives tapped in first capillary mattress once they come across. they're injected in the arteries that leads them to tumour of hobby so these kinds of situations radio lively microspheres deliver excessive radiation dose to the targeted areas without negative the ordinary surrounding tissues. It differs from drug shipping system, as radio pastime is not released from microspheres but acts from inside a radioisotope normal distance and the exclusive sorts of radio lively microspheres are αemitters, βemitters, γemitters. Microspheres as a drug transport gadget maintain exquisite promise in accomplishing the aim of managed drug shipping as well as website particular shipping. inside the last few a long time, medical and technological improvements had been made in their search and development of radio labelled microspheres. those are used successfully for the remedy of numerous styles of cancers and tumours. on account that response to chemotherapy and outside radiotherapy is not so effective and hazardous too, so an alternative to that is internal radiation remedy. this radio labelled microspheres are very strong and have a tested efficacy within the discipline of primary as well as metastatic cancers. Radio lively microspheres can be selectively focused to numerous tumours without beneath radiation to the non-tumorous tissues. The radioactive microspheres are injected to halt tumour boom thru the blood deliver, thereby allowing surgical removal as soon as the tumour size decreases. [11]

5. Polymeric Microspheres:

The distinctive forms of polymeric microspheres may be classified as follows and they're biodegradable polymeric microspheres and artificial polymeric microspheres.

I. Biodegradable Polymeric Microspheres:

Natural polymers including starch are used with the concept that they're biodegradable, bio well suited, and additionally bio adhesive in nature. Biodegradable polymers prolong the house time when touch with mucous membrane due to its high degree of swelling belongings with aqueous medium, results gel formation. The rate and volume of drug launch is managed via attention of polymer and the release sample in a sustained manner. the primary drawback is, in medical use drug loading performance of biodegradable microspheres is complicated and is hard to control the drug release. however, they offer wide variety of software in microsphere based totally remedy. [12]

II. Artificial Polymeric Microspheres:

synthetic polymeric microspheres are widely utilized in clinical application, extra over that also used as bulking agent, fillers, embolic particles, drug transport automobiles and many others. and proved to be secure and biocompatible however the major disadvantage of these form of microspheres, are have a tendency to migrate away from injection website and cause ability threat, embolism and in addition organ harm.

Drug Loading and Drug launch Kinetics:

The drug may be loaded over the microspheres basically using methods. –

1. In the course of the practice of the microspheres or
2. After the formation of the microspheres by incubating them with the drug/ protein.

The active factor may be loaded by using the bodily entrapment, chemical linkage and floor adsorption. The entrapment in large part relies upon at the technique of instruction and nature of the drug or polymer (monomer if used). most loading may be performed by incorporating the drug at some stage in the time of coaching but it tormented by many other technique variables inclusive of method of training, presence of additives (e.g. Pass linking agent, surfactant, stabilizers, etc.) heat of polymerization, agitation depth, and many others. release of the lively constituent is an crucial attention in case of microspheres. [13] the release profile from the microspheres depends on the character of the polymer used inside the coaching in addition to on the character of the active drug. the discharge of drug from both biodegradable in addition to non-biodegradable microspheres is influenced by way of structure or micro-morphology of the provider and the residences of the polymer itself. the drugs may be launched thru the microspheres by using any of the 3 methods, first is the osmotically driven burst mechanism, 2d through pore diffusion mechanism, and 1/3 by using erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the middle through biodegradable or non-biodegradable coating, growing enough pressure that ruptures the membrane. The burst impact is particularly managed by means of three elements the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. [14] The pore diffusion method is named so due to the fact as penetrating water the front hold to diffuse towards the center. The polymer erosion, i.e. lack of polymer is followed by means of accumulation of the monomer within the launch medium. The erosion of the polymer starts off evolved with the adjustments in the microstructure of the provider as water penetrates inside it leading to the plasticization of the matrix. Drug launch from the non-biodegradable type of polymers may be understood through considering the geometry of the carrier. The geometry of the service, i.e. whether it's miles reservoir kind in which the drug is gift as core, or matrix kind wherein drug is dispersed via out the service, governs normal release profile of the drug or energetic ingredients. [15]

Method of education

various techniques are followed for the instruction of microspheres relying upon the styles of drugs and polymers properties. Few examples of approach of preparation are as follows.

a. Solvent Evaporation and Solvent extraction.
b. Spray Drying/ Congealing method.
c. unmarried/Double emulsion technique.
d. segment separation coacervation approach.
e. Spray drying and spray congealing. [16]

a **Solvent Evaporation and Solvent Extraction:**

This approach is used for the practise of micro debris, entails the elimination of the natural phase with the aid of extraction of the organic solvent. The technique involves water miscible organic solvent and natural section is eliminated through extraction with water. The technique decreases the hardening time for the microspheres. One variant of the method entails direct addition of the drug. Solvent removal rate depends at the temperature of water, ratio of emulsion extent to the water and the solubility profile of the polymer.

b Spray Drying and Congealing:

these techniques are based on the drying of the mist of the polymer and drug within the air. On the basis of the cooling of the answer and removal of the solvent, those techniques are named

respectively. Atomization result in the formation of small droplets from which the solvent evaporates ends in formation of microspheres in a length range 1-one hundred. Microspheres are than separated from the new air by the cyclone separator and the solvent are eliminated by vacuum drying. [16, 17]

c single Emulsion/ Double Emulsion method: Microspheres of natural polymers

e.g. The ones of proteins and carbohydrates are organized via single Emulsion method. The natural polymers are dissolved or dispersed in aqueous medium accompanied by using dispersion in non-aqueous medium like oil. The go linking may be attain with the aid of go linkers. This technique involves the formation of the couple of emulsions or the double emulsion of type w/o/w and is most suitable to water soluble tablets, peptides, proteins and the vaccines. [17] each the natural as well as synthetic polymer experiment be used. The aqueous active constituent's solution is dispersed in a lipophilic organic non-stop phase. The non-stop phase is normally consisted of the polymer answer that in the end encapsulates of the active ingredients contained in dispersed aqueous segment. The number one emulsion is subjected then to the homogenization or the sonication earlier than addition to the aqueous answer. this will lead to the formation of a double emulsion.

d Section Separation and Coacervation:

This method is particularly designed for preparing the reservoir type of the machine like. to encapsulate water soluble pills. but, some of the preparations are of matrix kind, while the drug is hydro phobic in nature. The precept of technique is based totally on the lowering the solubility of the polymer. [18] The purpose of present work is to put together magnetic microspheres of Cytarabine the usage of Eudragit L-a hundred and Chitosan as polymer. Microsphere drug delivery device has won full-size interest due to its diverse programs that range from concentrated on the drug to precise site to imaging and helping the diagnostic functions. Novel drug transport machine pursuits to supply the drug at a fee directed with the aid of the needs of the frame throughout the period of treatment, and target the lively entity to the website online of movement. a number of novel drug delivery structures have emerged encompassing various routes of management, to reap managed and targeted drug shipping, magnetic micro providers being considered one of them. [19] Magnetic microsphere is more recent approach in pharmaceutical discipline. Magnetic microspheres as an alternative to traditional radiation techniques which makes use of especially penetrating radiation that is absorbed at some point of the body. Its use is restrained through toxicity and side effects. The goal of the specific concentrated on is to beautify the efficiency of drug transport & at the identical time to reduce the toxicity & facet outcomes. This type of shipping system is very a great deal crucial which localizes the drug to the disease web page. in this larger amount of freely circulating drug may be changed with the aid of smaller amount of magnetically cantered drug. Magnetic companies receive magnetic responses to a magnetic subject from included substances which might be used for magnetic microspheres are chitosan, eudragit, sodium alginate and many others. magnetic microspheres may be organized from an expansion of carrier material. one of the maximums utilized is serum albumin from human or different suitable species. Drug launch from albumin microspheres can be sustained or controlled through various stabilization tactics typically involving heat or chemical go-linking of the protein provider matrix. [20]

DRUG TARGETING

Drug transport structures (DDS) are divided into various subsystems. Any such, concentrated on DDS, recognizes goal cells and tissues of diseases including most cancers and sends drugs and genes

to the goal site. Cutting-edge research in this subject is focusing on the development of nanomaterials for passive targeting. Work is likewise being performed on so-called "missile tablets" for lively targeting DDS which could enhance the capability of targeting. Missile capsules are displaying promise because the "wonder pills" of the twenty first century. [21]

The concept of designing exact transport machine to achieve selective drug focused on has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a “magic bullet”. [22]

Reason Of Drug Targeting

The site-precise focused drug transport negotiates a different delivery to unique preidentified compartments with most intrinsic interest of drugs and concomitantly decreased access of drug to inappropriate non-target cells. The controlled fee & mode of drug shipping to pharmacological receptor and particular binding with target cells; as well as bioenvironmental safety of the drug en route to the web page of movement are particular capabilities of concentrated on. Continually, each event said contributes to better drug attention on the website of motion and resultant lowers concentration at non-goal tissue where toxicity might crop-up. The excessive drug attention at the target web page is a result of the relative cellular uptake of the drug vehicle, liberation of drug and efflux of loose drug from the target area site. [23, 24] Targeting is signified if the target compartment is prominent from the opposite cubicles, where toxicity might also occur and also if the lively drug will be placed predominantly within the proximity of target area site. The limited distribution of the determine drug to the non-target website online(s) with effective accessibility to the target area site(s) may want to maximize the blessings of centred drug shipping. [25]

Levels Of Drug Targeting [26]

The Multiple approaches of vectoring the drug to the target site can be broadly classified as:

1. Passive targeting.
2. Active targeting (Ligand mediated targeting and Physical targeting).
3. Inverse targeting.
4. Dual targeting.
5. Double targeting
6. Combination targeting

Magnetic Microspheres [27,28]

Excellent achievements were made in control of illnesses through invention of drugs during the last decade, that are pleasing the challenge of modern drug remedy i.e. optimization of the pharmacological action of the medicine coupled with the reduction in their toxic aspect outcomes in vivo. These days a whole lot of hobby has been proven in centred drug delivery system, magnetic microspheres being one in every of them.

Targeting by using magnetic microspheres i.e. incorporation of magnetic debris into drug carriers (polymers) and the usage of an externally implemented magnetic discipline is one manner to bodily direct this magnetic drug providers to a preferred site. Magnetic microspheres are supramolecular particles which can be small sufficient to circulate via capillaries without generating embolic occlusion (<m) but are sufficiently susceptible (ferromagnetic) to be captured in minor vessels and dragged into the adjoining tissue by using magnetic fields of 0.5-0.8 tesla (T).[29]

PRINCIPLE OF MAGETIC DRUG DELIVERY [30]

Magnetic drug delivery by means of particulate carriers is a totally green method of handing over a drug to localized disorder area site. Very high concentrations of chemotherapeutic or radiological retailers can be done close to the target website, which includes tumour, without any toxic results to ordinary surrounding tissue or to complete frame. Highlights, the idea of

magnetic targeting by using comparing systemic drug shipping with magnetic concentrated on. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into affected person's blood circulate, and then stopped with a effective magnetic field within the target location. relying at the form of drug, it's miles then slowly released from the magnetic companies (e.g. release of chemotherapeutic drugs from magnetic microspheres) or confers a nearby effect. it's far as a consequence viable to update massive amounts of drug focused magnetically to localized ailment websites, reaching effective and up to several –fold accelerated localized drug ranges.

Benefits supplied by Magnetically Responsive Microspheres [31, 32]

Magnetically responsive microspheres (MRM) are targeting site and through the localization of those microspheres inside the target place, the trouble in their speedy clearance by way of RES is also surmounted. Linear blood speed in capillaries is 300 instances less i.e. 0.05 cm/sec as compared to arteries, a lot smaller magnetic discipline, 6-8 Koe, is enough to hold them within the capillary community of the centred region. Furthermore, limiting microspheres to capillary bed of targeted region gives more blessings.

a. Diffusion occurs maximally in capillary community so green delivery of drug to diseased tissue is performed.
b. Microspheres can transit in to extravascular space thereby developing an extravascular drug depot for sustained launch of drug within the targeted vicinity.
c. Therapeutic responses in centered organs at best one tenth of the unfastened drug dose.
d. Managed launch with in goal tissue for durations of half-hour to30 hrs. as preferred.
e. Avoidance of acute drug toxicity directed in opposition to endothelium and regular parenchyma.
f. Adaptable to any a part of the body
g. This drug transport gadget reduces circulating concentration of loose drug by using a issue of one hundred or greater.
h. Magnetic service technology appears to be a enormous opportunity for the biomolecule malformations (i.e. composition, inactivation or deformation).

In case of tumour targeting, microspheres may be internalized via tumour cells due to its tons increased phagocytic interest in comparison to everyday cells. So the hassle of drug resistance due to lack of ability of drugs to be transported throughout the mobile membrane may be surmounted.

Limitations

But this novel technique suffers from positive hazards additionally as given
under:

- Drug(s) can't be focused to deep-seated organs within the frame. So this method is restrained to the focused on of medicine in superficial tissues handiest like pores and skin, superficial tumours or to joints and so forth.
- Magnetic focused on is a highly-priced, technical technique and calls for specialised manufacture and great manipulate gadget.
- It desires specialised magnet for targeting, advanced techniques for monitoring, and trained employees to perform manner.
- Magnets must have pretty consistent gradients, a good way to keep away from local over- dosing with poisonous drugs.
- A large fraction (40-60%) of the magnetite, that's entrapped in companies, is deposited completely in target tissue.

Idea of magnetic targeting of microspheres

ideally, magnetic microspheres are injected into an artery that substances a given website. as the microspheres might be selectively and

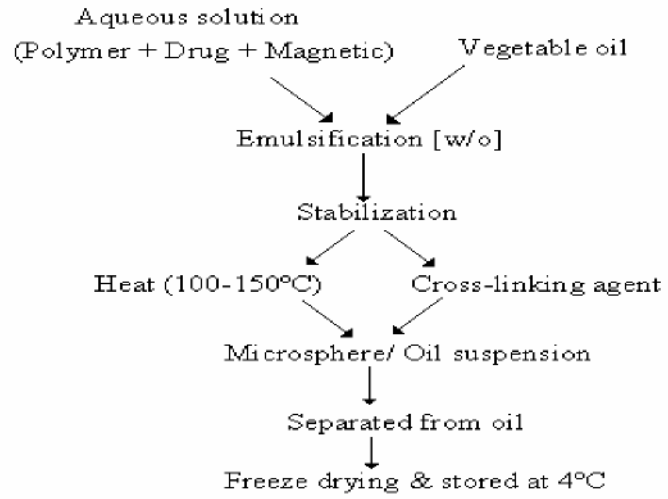
magnetically localized on the capillary degree, they might have loose waft get entry to through the large arteries. consequently, the microspheres could function time-launch capsule device sitting inside the preferred region. The selective capillary localization of the microspheres may be achieved by way of taking benefit of the physiological distinction inside the linear go with the flow pace of blood at the capillary degree (0.05 cm/sec). Glaringly, a miles lower magnetic field energy is important to restrict the microspheres at the slower moving glide velocities of blood in capillaries. After removal of the magnetic area, the microspheres still endured to inn at the goal website online, presumable because they had lodged inside the vascular endothelium, penetrated in to the interstitial area, resulting of their retention. [33] The intention of the particular concentrated on is to enhance the efficiency of drug shipping & on the equal time to reduce the toxicity & aspect consequences. Very excessive awareness of chemotherapeutic sellers may be achieved close to the goal website online without any poisonous effect to normal surrounding tissue or to complete frame. [34]

Methods Of Preparation [35,36]

There are basically two methods, which are commonly used for microspheres preparation: -

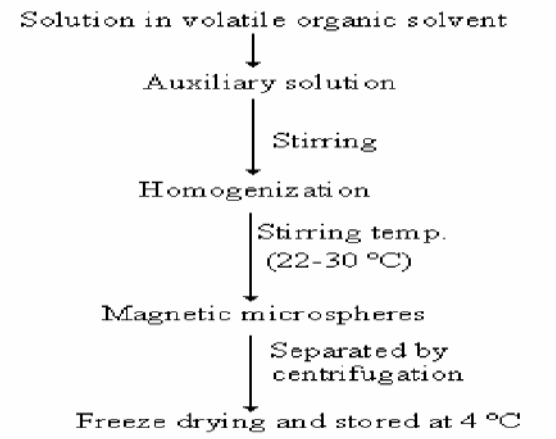
a. Phase separation emulsion polymerization (PSEP)
b. Continuous solvent evaporation (CSE).

Phase separation emulsion preparation



schematic representation for the preparation of magnetic microspheres by PSEP

Continuous Solvent evaporation



Schematic representation for the preparation of magnetic microspheres by CSE

MATERIALS AND METHOD

Table No 1: Materials used

Sr. No	MATERIALS	SUPPLIERS/MANUFACTURERS
1	Cytarabine	Avenscure life sciencesPvt ltd.
2	Chitosan	Sigma Aldrich pvt ltd.,
3	Eudragit l-100	HIP PG LAB, PAONTA SAHIB, HP
4	Magnetite	Manmohan International pvt. Ltd.
5	N hexane	Alpha chemical, Andheri, Mumbai, India
6	Liquid paraffin	Zeenish Pharma. Ahmedabad
7	Hydrochloric acid	Central drug house Ltd (CDH), New Delhi
8	Sodium hydroxide	Varun Enterprises, New Delhi
9	Sodium thiosulphate	Yogi Dye Chem Industries, Mumbai
10	Potassium iodide	Loba Chemical pvt ltd, Mumbai
11	Benzene	Loba Chemical pvt ltd, Mumbai
12	Starch	Loba Chemical pvt ltd, Mumbai
13	Potassium dihydrogen phosphate	SD Fine , Mumbai
14	Potassium ferrocyanide	SUV Chem, Mumbai

Table no 2: List of Instruments Used with Manufacturer

Sr. No.	Instruments	Manufacturer
1	Electronic Analytical balance	ACCULAB, Germany
2	UV-Visible spectrometer	ShimadzuUV-1800, Japan
3	FTIR	Perkin-Elmer , Panjab University.
4	Dissolution apparatus	Lab India, Mumbai, India
5	Magnetic stirrer	MLH Series, Microteknik, Ambala
6	pHmeter	Microteknik , Ambala
7	Scanning Electronic Microscopy (SEM)	ZEISS, WADIA IHG, D.DUN
8	Melting Point Apparatus	Microteknik , Ambala
9	Mechanical Stirrer	Microteknik, Ambala

PREFORMULATION STUDIES

Pre-Formulation method trying out is the first step inside the rational improvement of dosage styles of a drug. It is able to be defined as research of physical and chemical properties of drug substance, on my own and when combined with excipients. The overall objective of pre-formula checking out is to generate in formation beneficial to the formulator in growing stable and bioavailable dosage paperwork, which can be

produced at massive scale. A thorough know-how of physico-chemical houses may additionally in the end provide a motive for method design or support the need for molecular modification or merely confirm that there aren't any massive boundaries to the compound's development. The dreams of the program therefore are: [37,38]

1. To set up the vital physico-chemical traits of a brand-new drug substance.
2. To determine its kinetic launch price profile.
3. To set up its compatibility with specific excipients.
4. As a result, pre-formulation studies at the acquired pattern of drug consist of bodily tests and compatibility research.

DRUG-EXCIPIENT COMPATABILITY STUDIES

Discussion:

Drug excipient interactions play a vital role with respect to release of drug from formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. [39]

Table 3: Drug–Excipients Compatibility Study Results

Self-designed

Drug + Excipient	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + EUDRAGIT L-100	White powder	No change	No change	Yes
Drug + CHITOSAN	White powder	No change	No change	Yes
Physical Mixture	White powder	No change	No change	Yes

FTIR Spectroscopy

FTIR spectroscopy changed into done to check the compatibility among drug and excipients. Infrared spectroscopy was carried out using thermos Nicolet FTIR and the spectrum changed into recorded within the area of 4000 to 400 cm-1. The pattern (drug and drug-excipient combination in 1:1ratio) in KBR (two hundred-400mg) became compressed into discs by way of making use of a pressure of 5 lots for 5min in hydraulic press. The interaction between drug-excipients turned into found from IR-spectral research by means of gazing any shift in peaks of drug within the spectrum of bodily aggregate of drug-excipients. [40,41]

Solubility analysis

Pre-formulation solubility analysis became executed to pick an appropriate solvent system to dissolve the medication as well as numerous excipients used for components of microspheres.

Melting factor determination

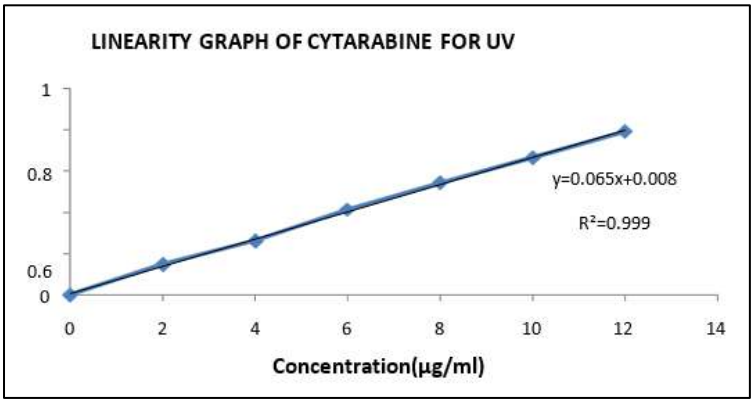
Melting point of Cytarabine was cited to be 208-213 through capillary fusion method. Melting factor willpower of the obtained drug sample was finished as it's far a first indication of purity of the pattern. The presence of enormously small amount of impurity can be detected by means of a lowering in addition to widening inside the melting factor range. The melting factor of Cytarabine turned into measured through capillary fusion technique. [42]

Determination of λ max

Cytarabine become dissolved in 0.1N HCL and phosphate buffer pH 6.8, in addition diluted with the same and scanned for max absorbance in UV double beam spectrophotometer (277.5 nm)in the range from200 to 400 nm, zero.1N HCL and phosphate buffer pH6.8as clean.

Preferred Calibration Curve of Cytarabine

Correctly weighed a 100 mg of Cytarabine changed into dissolved in one hundred ml of 0.1 N HCl (pH 1.2) (Conc. one thousand µg/ml) to prepare first stock answer. Take 10 vials of Cytarabine and degree the common weight and switch the sample equal to a hundred mg of Cytarabine into aa hundred ml volumetric flask and make up to the mark with the water. blend well and filter via 0.45 µm filter. The same old stock solution became scanned among 2 hundred-400 nm variety in opposition to the clean. From UV spectra, 277.5 nm was decided on as the absorption most for evaluation of Cytarabine. From the usual stock answer zero.2, 0.4, 0.6, 0.8, 1 and 1.2 ml changed into transferred into six 10 ml volumetric flask and make as much as the extent with water respectively. The absorbance of different awareness solutions changed into measured at 277.5 nm towards the clean. The calibration curve changed into plotted using attention as opposed to absorbance. The curve acquired turned into linear with the attention variety of two-12 µg/ml.



METHOD OF PREPARATION

Preparation of Cytarabine by Solvent evaporation technique

Cytarabine was obtained as a sample from Avans cure life sciences Private Ltd. Magnetite was obtained as a gift sample from Manmohan International Private Ltd. Chitosan were obtained from Sigma Aldrich Private Ltd. and Eudragit l-100 from HIP PG Lab, Paonta Sahib, HP. Liquid paraffin was obtained from Zeenish Pharma, Ahmedabad and n-hexane from Alpha Chemika, Andheri, Mumbai, India.

Magnetic Microspheres were prepared by using different ratios of drug: Polymer. Polymers (Eudragit l-100, Chitosan) were dissolved in 50 ml acetone. Weighed quantity of drug (Cytarabine)(100mg) was added to the above polymer solution. After that weighed quantity of Magnetite added to the above drug polymer solution. The organic phase was formed. Then poured the organic phase drop wise to the 25 ml of 1:1 mixture of heavy and light paraffin. 2o ml hexane were added to the stirred content to remove the adhering liquid paraffin. Filter it and dried, the Magnetic microspheres were formed.

Table 4: Formulation of Magnetic Microspheres at different RPM

Formulation (WITH CHITOSAN)	Formulation (WITH EUDRAGIT L-100)	Drug (mg)	Chitosan (mg)	Eudragit l-100	Formulation (WITH CHITOSAN)	Formulation (WITH EUDRAGIT L-100)
F1	F1	100	5	5	25	Low
F2	F2	100	10	10	25	Medium
F3	F3	100	15	15	25	High
F4	F4	100	5	5	25	Medium
F5	F5	100	10	10	25	High
F6	F6	100	15	15	25	Low
F7	F7	100	5	5	25	High
F8	F8	100	10	10	25	Low
F9	F9	100	15	15	25	Medium

RESULT AND DISCUSSION

PREFORMULATION STUDIES

Organoleptic properties

These tests were performed as procedure given as preformulation part. The results are illustrated in following table 5.

Table 5: Organoleptic properties

Test	Specifications/limits	Observations
Color	White to off white	Off White powder
Odour	Odorless	Odorless
Flow property	Free flowing powder	Free flowing Powder

The results comply as per specification

Table 6: Flow character of Magnetic Microsphere

Self-designed

Formulation code	Flow Character
F1	Good
F2	Good
F3	Excellent
F4	Passable
F5	Passable
F6	Poor
F7	Excellent
F8	Fair
F9	Fair

Table 7: Flow Character of Magnetic Microsphere

Self-designed

Formulation code	Carr's index	Hausner ratio	Angle of repose	Flow character
F1	16.67	1.20	32	Good
F2	13.47	1.10	30	Good
F3	10.0	1.1	26.5	Excellent
F4	25.8	1.38	38.29	Passable
F5	24.8	1.33	40.59	Passable
F6	29.1	1.42	43.36	Poor
F7	9.09	1.10	25.2	Excellent
F8	20	1.2	29.5	Fair

F9	20.1	1.2	30.1	Fair

Table 8: Mechanism of drug release from different Magnetic microspheres formulations Self-designed

Formulation Code	Zero order (R2)	First Order	Higuchi	Hixon Crowell	Kosemeyer peppas Model	
					R^2	N
F1	0.956	0.674	0.964	0.730	0.743	0.5887
F2	0.950	0.683	0.975	0.781	0.727	0.882
F3	0.957	0.674	0.780	0.780	0.623	0.6080
F4	0.964	0.680	0.768	0.768	0.818	0.6078
F5	0.948	0.676	0.950	0.762	0.796	0.7226
F6	0.949	0.683	0.955	0.745	0.791	0.4914
F7	0.963	0.708	0.922	0.697	0.782	0.4565
F8	0.961	0.703	0.956	0.780	0.808	0.621
F9	0.969	0.674	0.971	0.730	0.756	0.565

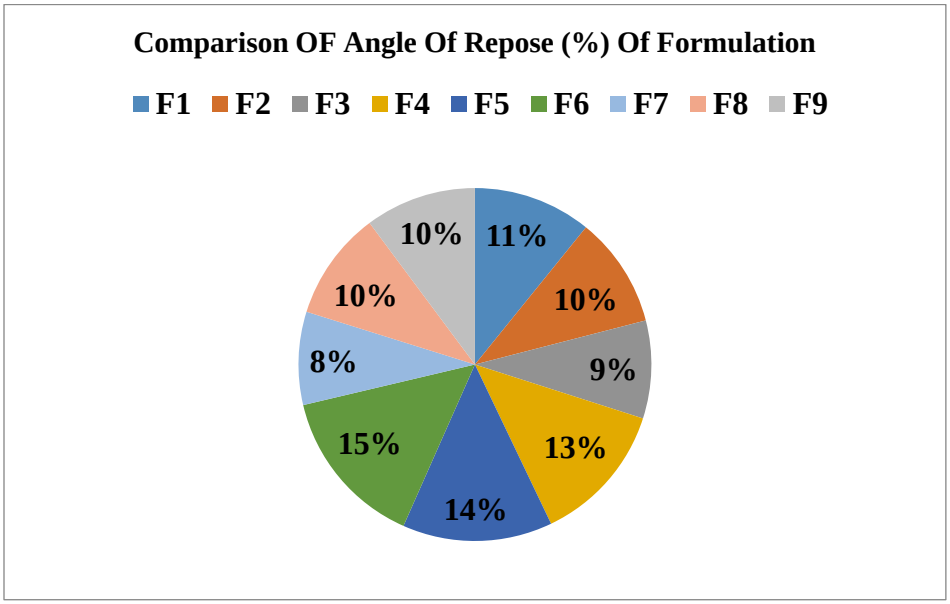


Fig. 9: Comparison of angle of repose (%) of Formulation

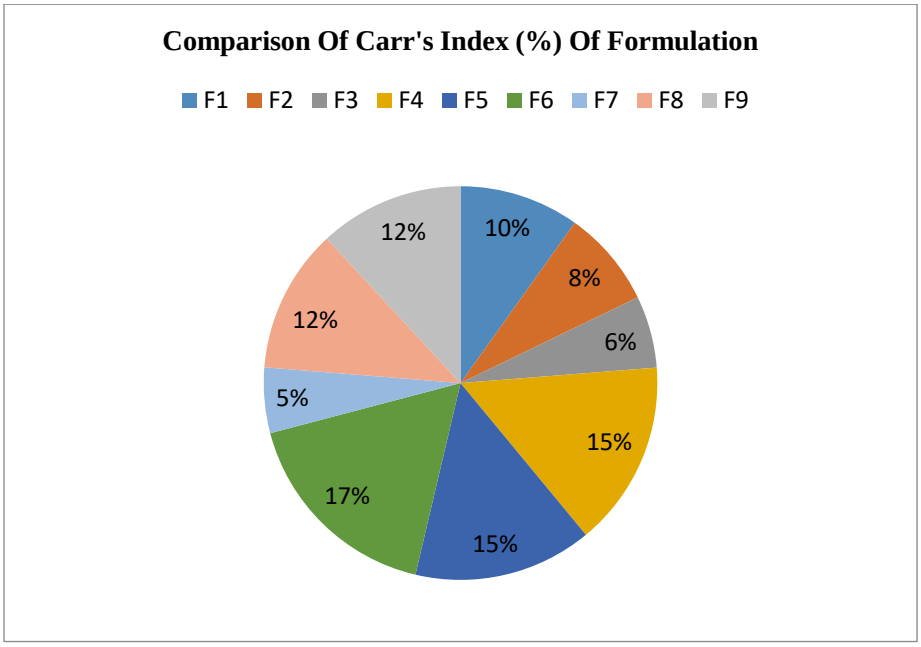


Fig. 10: comparison of Carr's Index (%) of formulation

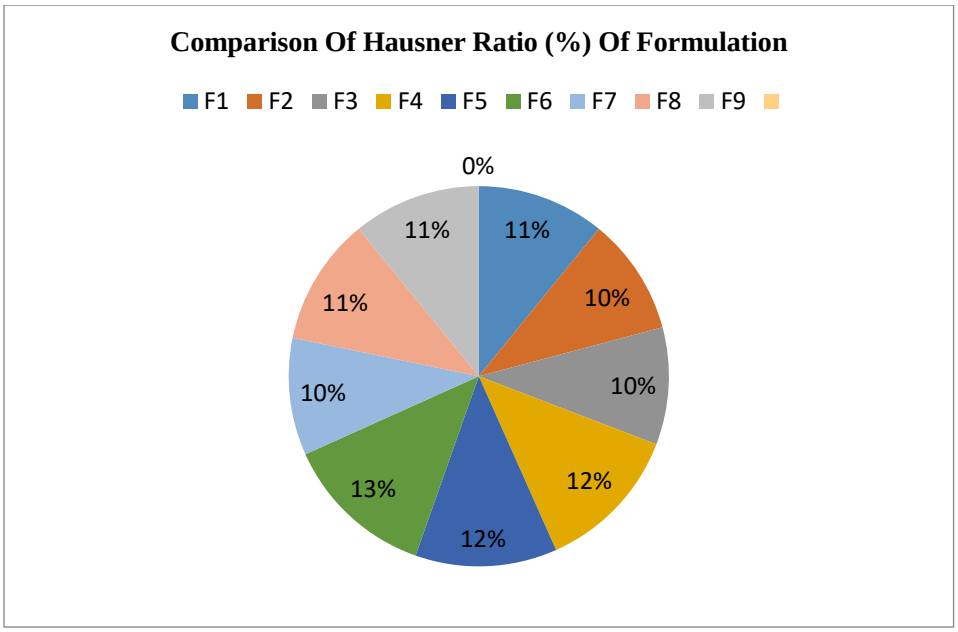


Fig. 11: comparison of Hausner Ratio (%) of Formulation

Melting point

It was determined as per procedure given in pre-formulation in material and method part. The results are illustrated in following table.

Table 9: Melting point

Material	Material point rang	Result
CYTARABINE	208-215°C	212 °C

The result complies as per specification.

SOLUTION PROPERTIES

pH of the solution

It was determined as per procedure given in pre-formulation in material and method part. The results are illustrated in following table.

Table 10: pH

Material	Test	Specification	Observation
CYTARABIE	pH	6	6

The result complies as per specification

Solubility

It was determined as per procedure given in pre-formulation in material and method part. The results are illustrated in following table.

Table 11: Solubility

Self -designed

Sr.no	Solvent	Solubility (observed)	Solubilty (standard)
1	Water	+ + + + +	+ + + + +
2	DMS0	+ + + +	+ + + +
3	Acetic acid	+ + +	+ + +
4	Ethanol	+	+
5	Methanal	+	+
6	Methylene chloride	+	+
7	Chloroform	+	+

temperature and humidity and 30ºC □ 2ºC/65% RH □ 5% RH in humidity control oven for sixty days. Two parameters namely residual percent drug content and in-vitro release studies were carried out. The results of drug content after 15,30 and 60 days are shown in Table 13shows the plots of % residual drug Vs. time for different formulations after 60 days storage. These studies reveal that there is a reduction in drug content after storage for sixty days at 4º C, ambient temperature and humidity and 30º C □ 2ºC/65% RH □ 5% RH. It was also revealed that out of the four formulated batches, the one stored at 4º C showed maximum residual drug followed by that stored at ambient

FTIR RESULT OF DIFFERENT SAMPLES

SAMPLE 1 (CYTARABINE)

Partition Coefficient

The P.C of cytarabine was estimated by using n-octanol/water system by shake flask method and was found to be -0.212. it shows its strong hydrophilic character.

Table 12: Partition coefficient values of cytarabine in n-octanol; water

Self -designed

Solvent system	Experimental value	Solvent system
n-octanol: water	-0.211	- 0.212
	-0.213	
	-0.212	

STABILITY STUDIES

Stability studies of the prepared microspheres were carried out, by storing all the formulations F-1 to F-9 (EACH) at 4ºC in refrigerator, Ambient temperature and humidity and30ºC □ 2ºC/65%RH□ 5%RH. In vitro release studies revealed that the formulation stored at 4ºC showed 80.56%release, the one which stored at ambient temperature and humidity showed 82.74 % and formulation stored at 30º C □ 2ºC/65% RH □ 5% RH showed 84.48 % release after24 hours. These results indicate that the drug release from the formulation stored at 30º C □2ºC/65%RH□5% RH was highest followed by formulation stored at ambient temperature and humidity and 4ºC. These results may be attributed to erosion of particles to some extent during storag

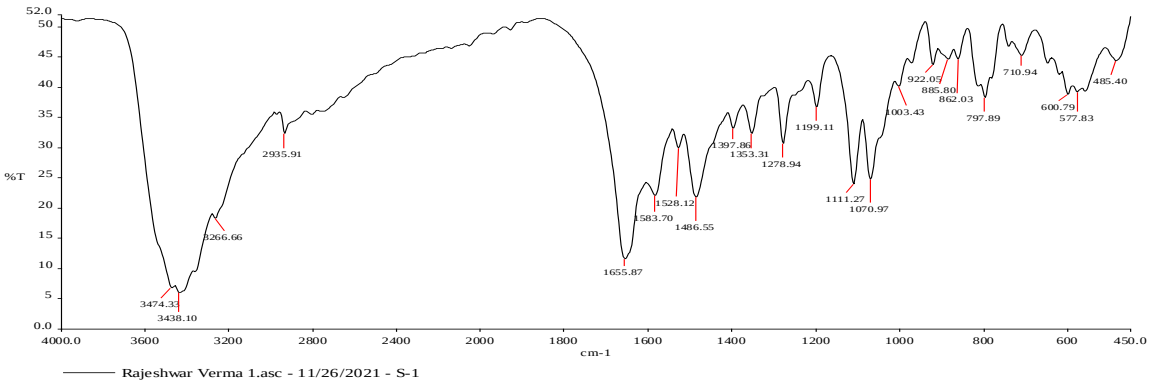


Fig. 12: FTIR Sample 1 (Cytarabine)

Table 12: Interpretation Of Ftir Spectrum Of Cytarabine

SELF DESIGNED

Infrared Spectrum Data Ir Absorption Band (Cm) (Experimental)	Functional Groups
3450, 3433, 3352, 3261	NH AND OH STRETCHING
2930, 2630	CH STRETCHING
1653	C1/4N STRETCHING
1573, 1536, 1432	C1/4N AND C1/4C STRETCHING
1275, 1113, 1063	C-O STRETCHING
795	C-H BONDING

SAMPLE 2 (MAGNETITE)

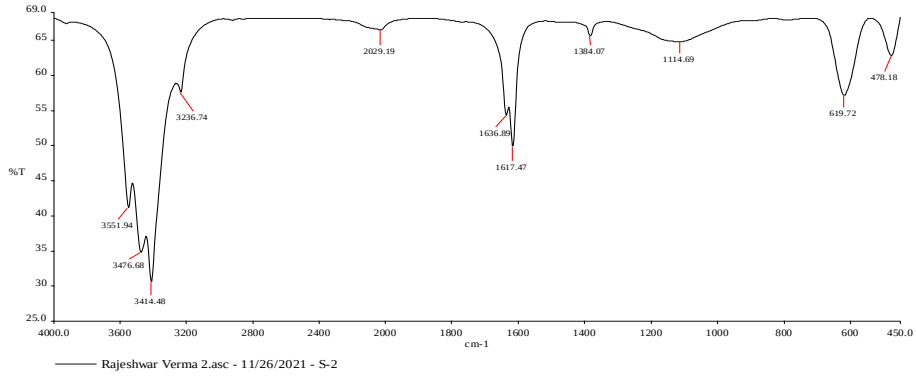


Fig. 13: FTIR Sample 2 (Magnetite)

SAMPLE 3 (CYTARABINE CHITOSAN)

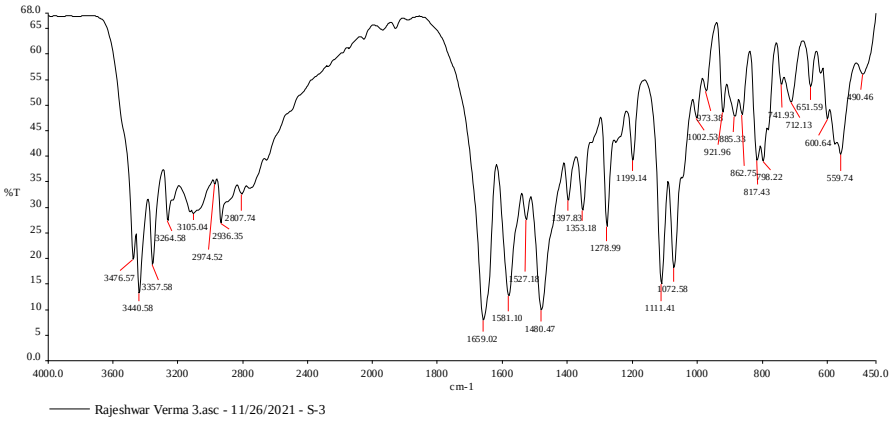


Fig. 14: FTIR Sample 3 (Cytarabine Chitosan)

SAMPLE 4 (CYTARABINE EUDRAGIT L-100)

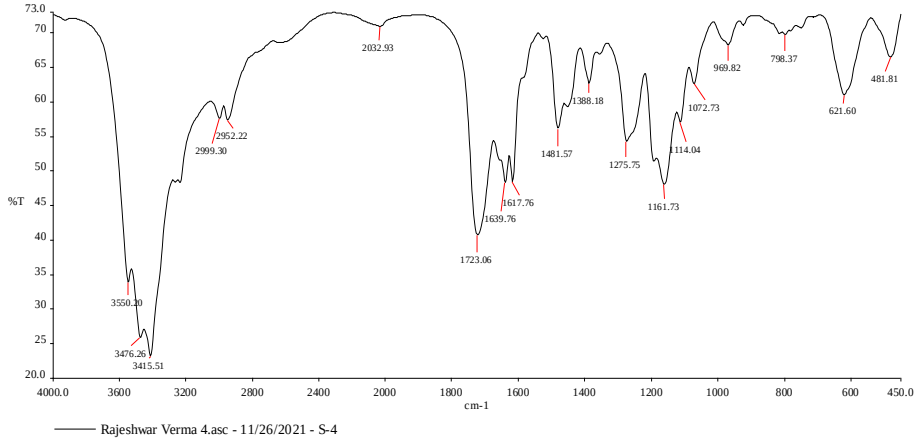


Fig. 15: FTIR Sample 4 (Cytarabine Eudragit l-100)

SEM RESULT OF SAMPLE WITH DIFFERENT EXCIPIENTS

SAMPLE A (CYTARABINE MAGNETITE CHITOSAN)

The following all figures from (fig. 16a to fig. 16g) to fig. are the result of SEM of sample containing formulation of Cytarabine Magnetite chtiosan microspheres.

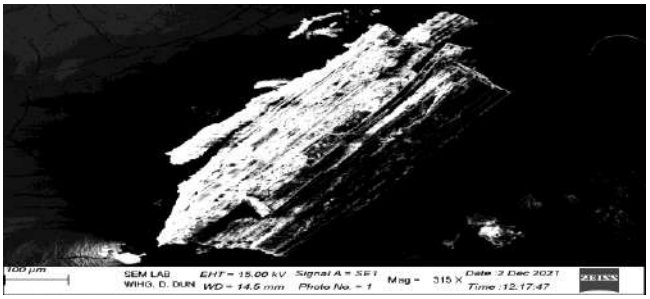


Fig. 16a: Cytarabine Magnetite Chitosan

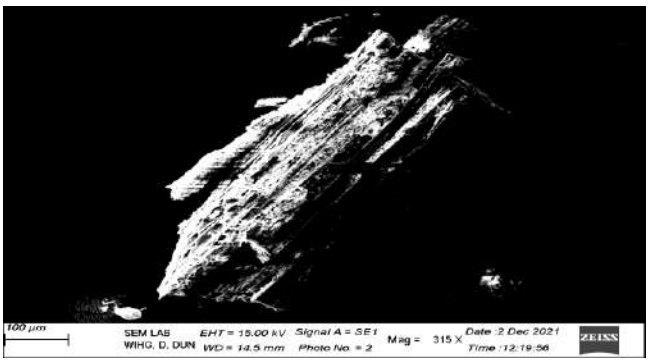


Fig. 16b: Cytarabine Magnetite Chitosan

Fig. 16c: Cytarabine Magnetite Chitosan

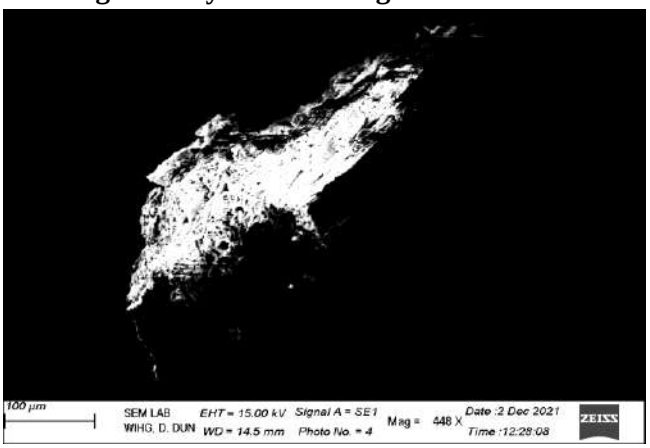


Fig. 16d: Cytarabine Magnetite Chitosan

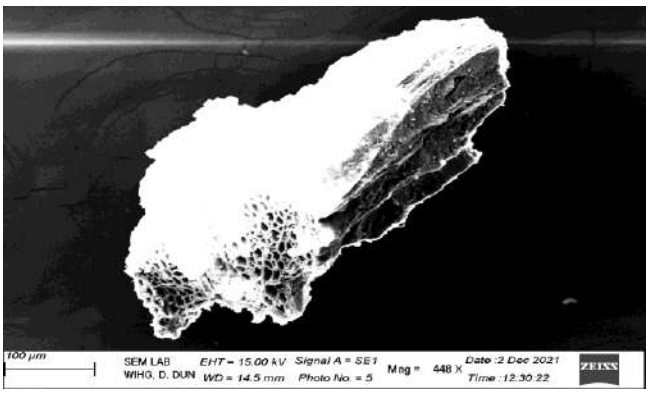


Fig. 16e: Cytarabine Magnetite Chitosan

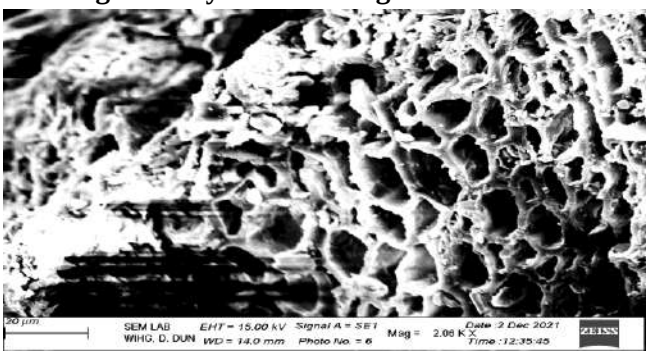


Fig. 16f: Cytarabine Magnetite Chitosan

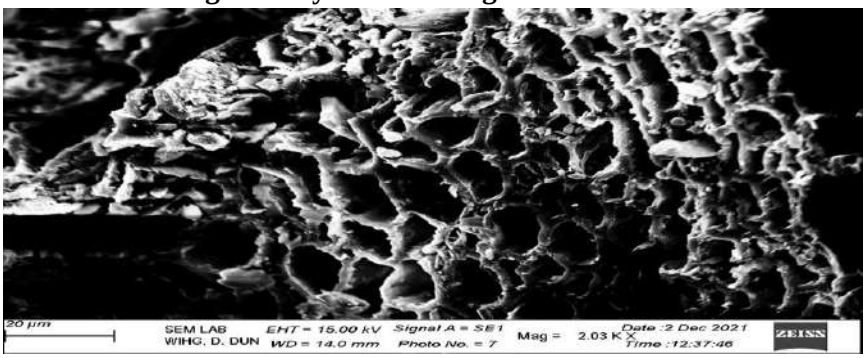


Fig. 16g: Cytarabine Magnetite Chitosan

SAMPLE B (CYTARABINE MAGNETITE EUDRAGIT L-100)

The following all figures from fig. 17a to fig. 17h are the result of SEM of sample containing formulation of Cytarabine Magnetite Eudragit l-100 microspheres

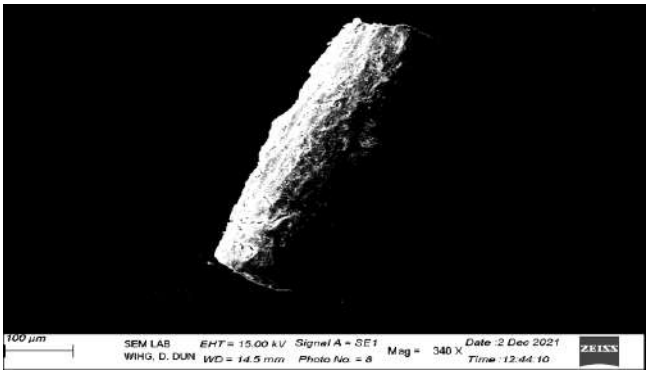


Fig. 17a: Cytarabine Magnetite Eudragit L-100

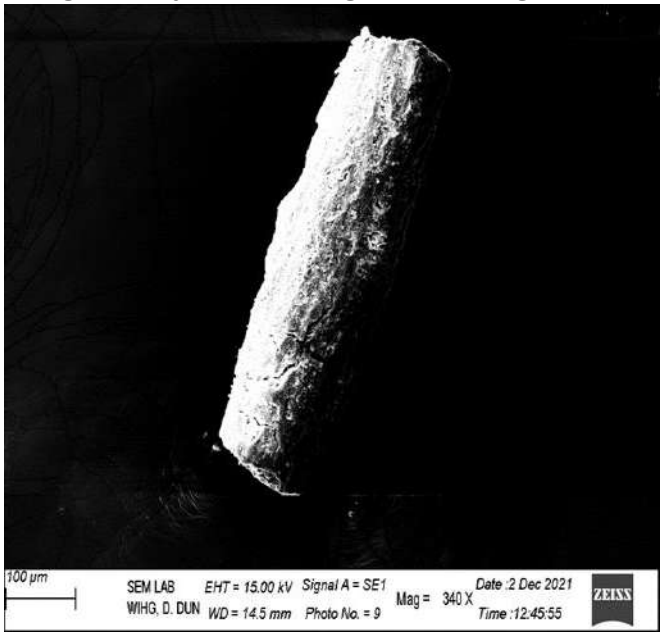


Fig. 17b: Cytarabine Magnetite Eudragit L-100

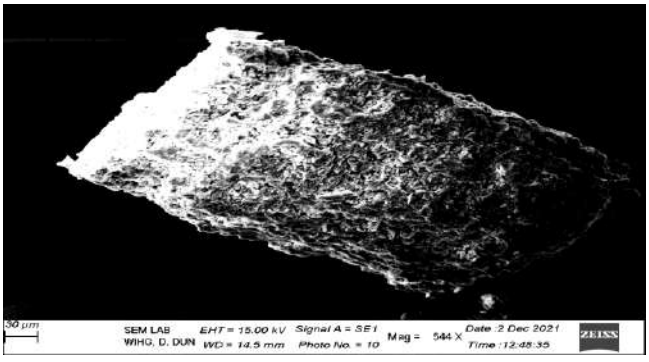


Fig. 17c: Cytarabine Magnetite Eudragit L-100

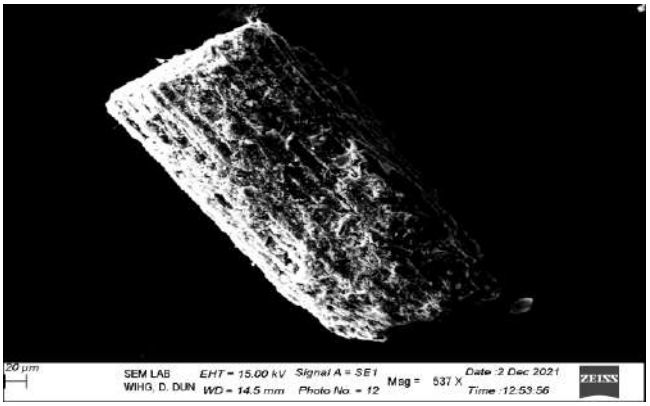


Fig. 17e: Cytarabine Magnetite Eudragit L-100

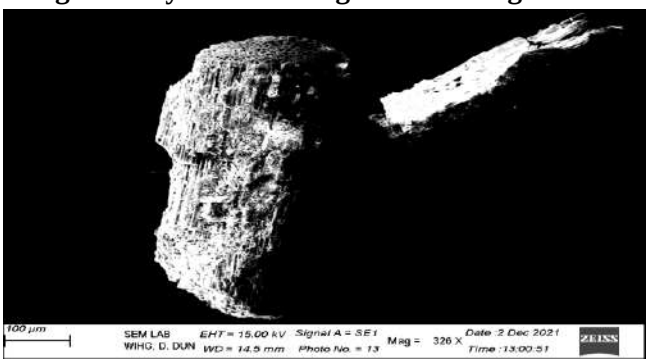


Fig. 17f: Cytarabine Magnetite Eudragit L-100

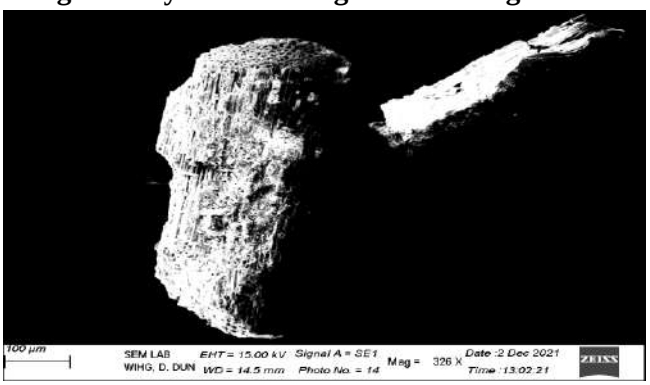
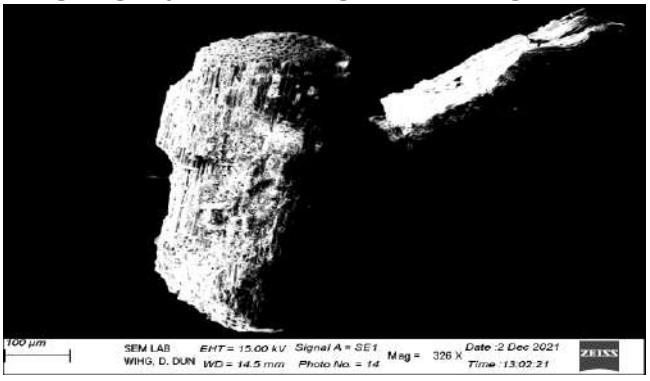


Fig. 17g: Cytarabine Magnetite Eudragit L-100



CONCLUSION

The ultimate goal for magnetic microspheres is to maximize therapeutic activity and targeted delivery of the drug while minimizing the negative side effects of the drug. In this regard, magnetic microspheres have emerged as a novel drug delivery system to treat cancer. It has been observed that magnetic microspheres are among the best novel drug delivery systems, as it has the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumors, detecting bio-molecular interaction etc. So in future by combining various other strategies, magnetic 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. Cytarabine is poorly absorbed from the GIT; it shows very good solubility in water. The half life elimination varies in patients depending on the age and it varies from 1-3 hours. As the bioavailability of orally administered Cytarabine is very low thus novel delivery system that is magnetic microspheres have been formulated. In each delivery system therapeutic amount of drug is needed at the needed site. Targeting is drug delivery to the chosen body part to which one wants to deliver the drug. The wanted drug distribution by targeted delivery would leave the rest of the body and thus lowers the overall toxicity while maintaining its therapeutic benefits. Many clinical schemes need delivery of agents that are therapeutic at the desired delivery point. An attempt was made to prepare Cytarabine magnetic microspheres in order to investigate targeting efficiency, enhance bioavailability, and reduce dose and thereby improving patient compliance. Targeting by means of magnetic fields seems to be a vital and most common function of opening a new vista of a multi-barrier of multi-step drug delivery. Their main advantage is the targeting of drug using an external magnet, which can be accomplished very easily thus Reticuloendothelial clearance can be minimized and target site specificity can be increased. Magnetic microspheres are novel drug delivery systems, having received attention from the early 1990s. Thus magnetic microspheres have the great potential for these objectives. This is an effective tool for the cancer patients. The future holds agreement in magnetic microspheres and by supplemental study this will be developed as novel and efficient approach for targeted drug delivery system.

REFERENCES

1. Bhalla. Neetika deep Arsh, Goswami Manish.“An Overview on various approaches to Oral controlled Drug Delivery System Via Gastroretentive Drug Delivery System”, RJP 2012;3 (4):1-6.
2. Harshad Parmar, Sunil Bakliwal, Nayan Gujarathi, Bhushan Rane, Sunil Pawar.“Different Methods of Formulation and Evaluation of Mucoadhesive Microsphere”. International Journal of Applied Biology and Pharmaceutical Technology 2010;1(3):1157-1166
3. Swarnimapandey, Sushantkama,(2011)“An overview on multifunctional nanomedicines for targeted drug delivery”. JPI’s Journal of Pharmaceutics and Cosmetology 2(1):120-128
4. Kyekyoon “Kevin” Kim and Daniel W. Pack University of Illinois at Urbana-Champaign, microspheres for drug delivery ,http://www.springer.com/978-0-387-25563-7
5. Tarun P, Soni S, Thakar B, Pandya V, Bharadia P (2012).“Magnetic Microspheres as a Targeted Drug Delivery System: A Review”. International Journal for Pharmaceutical Research Scholars (IJPRS);1(2):444-456

6. Prasanthv.v, Akash Chakraborthy Moy, Sam T Mathew, RinkuMathapan(2011). "Microspheres - An Overview". International Journal of Research in Pharmaceutical and Biomedical Sciences; 2 (2):332-338.
7. Johansen, L., Nustad, K., Berg Ørstavik, T., Ugelstad, J., Berge, A., and Ellingsen, T. (1983).Excess Ab immunoassay for rat glan-965 Mono-sized polymer particles as the prefered solid phase material. J. Immunological Methods; 59: 255-264
8. Noepel-DuennebackeS,ArnoldD,HertelJ,TannapfelA, HinkeA,Hegewisch-Becker S,Reinacher-Schick A, Impact of the Localization of the Primary Tumor and RAS/BRAF Mutational Status on Maintenance Strategies After First-line Oxaliplatin, Fluoropyrimidine, and Bevacizumab in Metastatic Colorectal Cancer: Results From the AIO 0207 Trial. Clinical colorectal cancer. 2018 Dec
9. GeoergerB,ChisholmJ,LeDeleyMC,GentetJC, ZwaanCM,DiasN,JaspanT,Mc Hugh K,CouanetD,HainS,DevosA,RiccardiR,Cesar eC,BoosJ,FrappazD,LeblondP,AertsI,Vassal G, Phase II study of gemcitabine combined with oxaliplatin in relapsed or refractory paediatric solid malignancies: An innovative therapy for children with Cancer European Consortium Study. European journal of cancer (Oxford, England : 1990). 2011 Jan;
10. Paswtto LM, D'Andrea MR, Rossi,E, Monfardini; Oxaliplatin-related neurotoxicity; How and Why? Crit Rev OncolHematol. 2006 Aug; 59(2):159-68. Epub 2006 jun 27
11. Graham J, Mushin M, Kirkpatrick P; Oxaliplatin. Nat Rev Drug Discovery 2004 Jan;3(1):11-2
12. Cripe LD, Hinton S (2000). "Acute myeloid leukemia in adults". Curr Treat Options Oncol.; 1: 9-17.
13. Schiffer CA (2001) "Acute myeloid leukemia in adults: where do we go from here?"CancerChemotherPharmacol; 48(Suppl 1): S45-S52.
14. Tallman MS, Gilliland DG, Rowe JM (2005). "Drug therapy of acute myeloid leukemia" Blood; 106: 1154-1163.
15. Cros E, Jordheim L, Dumontet C, Galmarini CM (2004) "Problems related to resistance to cytarabine in acute myeloid leukemia". LeukLymphoma; 45: 1123-1132.
16. Shaw Ranjana and Chakraborty Tamalkika, 'Magnetic Microsphere as novel drug delivery system' IJAR, ISSN NO. 2320-5407, APRIL 2020
17. Kakar satinder and singh et al, Magnetic Microsphere as magical novel drug delivery system, JAD, March 2013
18. Zhao H, Piwnica-Worms H. (2001) "ATR-mediated checkpoint pathways regulate phosphorylation and activation of human Chk1". Mol Cell Biol; 21: 4129-4139.
19. MorozP, jonesSK, Gray BN (2002) "Tumor response to arterials embolization hyperthermia and direct injection hyperthermia in a rabbit liver tumor model". J.surgoncol ;80:149-156
20. Muniyandy Saravanan, Kesavan Bhaskara, Gomathinayagam Maharajan, Kalathil Sadasivan Pillai. (2004) "Ultrasonically controlled release and targeted delivery of diclofenac sodium via gelatin magnetic microspheres", International Journal of Pharmaceutics ;283:71–82
21. Forbes Z. Magnetizable Implants for Targeted Drug Delivery. [online]. 2005 [Cited2005 May 17];
22. Chopra KS, Singla D. Drug targeting by magnetically responsive microspheres. The Eastern Pharmacist 1994 Aug;XXXVII(440):79-82.

23. Nanotechnology Research Institute (NRI). The World's First Successful In vivo Attempt to Produce Active Targeting DDS Nanoparticles for Missile Drugs- The development of treatment drugs for targeting the sites of various diseases with inflammatory symptoms is accelerating at a rapid pace. [online]. 2003 [Cited 2003Nov13]
24. Vyas SP, Khar RK. Targeted & Controlled drug delivery. New Delhi: CBS Publishers;2002.4,38-80,458-80.
25. Udupa N. Niosomes as drug carriers. In: Jain NK, editor. Controlled and Novel drug delivery. New Delhi: CBS Publishers;2002. 300-1.
26. Khar RK, Diwan M. Targeted delivery of drugs. In Jain NK, editor. Advances in controlled and Novel drug delivery. 1sted. New Delhi: CBS Published and Distributors;2001;452-62.
27. Jain NK. Controlled and Novel drug delivery. 1st ed. New Delhi : CBS Published andDistributors;2002.14.
28. Alexiou C, Arnold W, Hulin P, Klein RJ, Renz H, Parak FG, et. al. Magnetic mitoxantrone nanoparticle detection by histology, X-ray and MRI after magnetic tumor targeting. J Mage Magn Mater.2001;225(1-2):187-93.
29. Torchilin VP. Drug targeting. Eur JPharm Sci.2000;11(Suppl2) S81–S91.
30. Babincova M, Altanerova V ,Lampert M,Altaner C,Machova E,Sramka M, et.al.Site-specific In Vivo Targeting of Magneto liposomes Using Externally Applied Magnetic Field. Z Naturforsch (C.), 55 (2000), pp.278–281. [online]. 2004 [Cited 2004 May17]
31. Bogdansky S. Natural polymer as drug delivery systems In: Chasin M., Langer R.editor. Biodegradable polymers as drug delivery systems. New York: Marcel DekkerInc;1990p.231-59.(Drugs and the pharmaceutical sciences; Vol 45).
32. Ranney DF. Magnetically controlled devices and bio modulation. In: TyleP,editor.Drug delivery devices fundamentals and application. New York: Marcel Dekker Inc;1998.p.325-63.(Drugsand the pharmaceuticalsciences;Vol32).
33. Häfeli UO, Magnetically modulated therapeutic systems. Int J Pharm. 2004; 277:19–24.
34. Denkbas EB ,Kilicay E, Birlikseven C, Ozturk E. Magnetic chitosan microspheres: preparation and Characterization. Reactive & Functional Polymers.2002;50:225–32.
35. Ritter JA, Ebner AD, Daniel KD, Krystle L. Stewart Application of high gradientmagnetic separation principles to magnetic drug targeting. J Magnetism and MagneticMaterials.2004; 280(2-3):184-201.
36. Satinder kakar et al. Preparation of magnetic microsphere of mesalamine by phase separation emulsion polymerization technique. African Journal of Pharmacy and Pharmacology 2014;8 (9): 246-258.
37. Yadav N et al. Synthesis and characterization of sustained release atenolol microspheres by solvent evaporation technique. J Pharm Sci Tech 2011; 3: 559-562.
38. Schutt W et al. Applications of magnetic targeting in diagnosis and therapy possibilities and limitations: A Mini-Review. Hybridoma 1997; 16: 109-117.
39. Xianqiao Liu et al. Immobilization of lipase onto micron-size magnetic beads. J ChromatogrSci 2005; 822: 91–97.
40. Kenneth J. Widder et al. Tumor remission in Yoshida sarcoma-bearing rats by selective targeting of magnetic albumin microspheres containing doxorubicin. Proc Natl AcadSci 1981; 78(1): 579-581.
41. Shah S et al. Formulation and evaluation of microsphere based dispersible tablets of oroitopride HCl. J Pharma Sci 2012; 20: 24.

42. Satinder kakar et al. Preparation of magnetic microsphere of mesalamine by phase separation emulsion polymerization technique. African Journal of Pharmacy and Pharmacology 2014;8 (9): 246-258.

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