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An Overview On Targeted Drug Delivery System : Carriers For Targeting Drug

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ABSTRACT :

The main aim of this review article is to introduce the basic concepts of drug targeting as they have involved over previous decades. The most important chemical features and biological behavioural characteristics of the carrier molecules exploited for drug targeting purposes will be addressed. Targeted drug delivery is also known as smart drug delivery. This is self-contained, discrete dosage form which is applied to intact skin, at a controlled rate to the systemic circulation. In this system medicament given to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. System involves nanoparticles-mediated drug delivery in order to reduce drawback of conventional drug delivery. Active and passive targeting are two types of methods used for targeted drug delivery. Targeted drug delivery has some side advantages like reduces side effects, avoid hepatic first pass metabolism, enhance drug absorption, dose is less as compare to conventional drug delivery, reduced fluctuation in circulating drug levels etc. Brain targeted drug delivery system and tumour targeted drug delivery system is most widely used. Many drug carriers are used in this advanced drug delivery system are lipoprotein, liposome, micelles and immune micelles. The goal of targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with disease tissues.

Keywords: Carrier, targeting, nanoparticles, drug absorption, micelles.

INTRODUCTION: [3,5,8]

Targeted drug administration, sometimes known as smart drug delivery, is a method of administering medication to a patient in such a way that the medication concentration in specific places of the body is higher than in others. This method of delivery is mostly unknown in nanomedicine, which intends to use nanoparticle-mediated drug administration to overcome the drawbacks of traditional drug delivery. These nanoparticles would be loaded with medications and delivered to precise sections of the body where only diseased tissue exists, avoiding interactions with healthy tissue. A targeted drug delivery system's purpose is to prolong, localize, target, and have a safe medication interaction with the targeted tissue. The medication is absorbed through a biological membrane in the traditional drug delivery system, whereas the drug is released in a dose form in the targeted release system. To improve regenerative medicine, targeted medication delivery methods have been developed refers to the use of new technology and biological polymer materials technology to deliver genes or drugs to the designated body parts according to the clinical need time and dose. It can be designed to minimize drug degradation, increase bioavailability, allow targeting to specific cells and reduce the total amount of drug needed. It can be a controlled release of drugs to decrease toxicity and harmful side-effects. The idea of DDS drug research and development is to use new technology and new materials to improve curative effects, reduce the effects of patients with adverse reactions, and make them easier to use by changing the drug pharmacokinetic model and delivery channels. DDS is the application and development of modern science and technology in pharmacy. Targeted medication delivery is a type of smart drug delivery device that delivers a drug to a patient miraculously. The drug is absorbed across a biological membrane in the traditional drug delivery system, whereas the drug is released in a dose form in the targeted release system. A targeted medication delivery system is based on a method that delivers a specific amount of a therapeutic substance to a specific sick location within the body for an extended length of time. This aids in maintaining the required plasma and tissue drug levels in the body, preventing drug-induced harm to healthy tissue.

THEORY OF TARGETED DRUG DELIVERY SYSTEM: [2,5,]

What is drug targeting? The therapeutic response of a drug depends upon the interaction of drug molecules with cell-on-cell membrane related biological events at receptor sites in concentration dependent manner. Selective and effective localization of the pharmacologically-active moiety at pre-identified target(s) in therapeutic concentration, while restricting its access to non-target(s) normal cellular linings, thus minimizing toxic effects and maximizing the therapeutic index. Common Approaches of Targeted Drug Delivery

The basic approaches for targeting the drug to specific site based on different research outcomes may be categorized broadly in to followings, though there are number of effective and successful strategies used in drug targeting. I. Controlling the distribution of drug by incorporating it in a carrier

system II. Altering the structure of the drug at molecular level III. Controlling the input of the drug into bioenvironmental to ensure a programmed and desirable bio distribution Properties of ideal targeted drug delivery: I. It should be nontoxic, biodegradable, biocompatible and physicochemical stable in vivo and in-vitro II. It should be capable to deliver the drug to target cells or tissue or organ and should have uniform capillary distribution. III. It should release the dug in a controlled and predictable manner for a suitable period of time.

Strategies of Drug Targeting: [1,6]

1.Passive Targeting:

Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems. The ability of some colloid to be taken up by the Reticule Endothelial Systems (RES) especially in liver and spleen made them ideal substrate for passive hepatic targeting of drugs.

2.Inverse Targeting:

In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defence mechanism. This type of targeting is an effective approach to target drug(s) to non-RES organs.

3.Active targeting:

In this approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake by RES. Surface modification technique include coating of surface with either a bioadhesive, non-ionic surfactant or specific cell or tissue antibodies (i.e., monoclonal antibodies) or by albumin protein.

4. Ligand-mediated Targeting:

In his approach ligands are used as carrier surface group(s), which can selectively direct the carrier to the pre-specified site(s) housing the appropriate receptor units to serve as 'homing device' to the carrier/drug. Most of the carrier systems are colloidal in nature & can be specifically functionalized using various biologically-relevant molecular ligands including antibodies, polypeptides, oligosaccharides, viral proteins & mucogenic residues. The ligands confer recognition & specificity upon drug carrier & endow them with an ability to approach the respective target selectivity & deliver the drug

5.Physical Targeting:

This approach was found exceptional for tumour targeting as well as cytosolic delivery of entrapped drug or genetic material. Characteristics of environment changes like pH, temperature, light intensity, electric field, and ionic strength.

6. Dual Targeting:

In this targeting approach carrier molecule itself have their own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

7. Double Targeting:

When temporal and spatial methodologies are combined to target a carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs tissues, cells or even subs cellular compartment. whereas temporal delivery refers to controlling the rate of drug delivery to target site. H. Combination Targeting: These targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site.

Advantages of drug targeting: [

I. Drug administration protocols may be simplified.
II. Toxicity is reduced by delivering a drug to its target site, thereby reducing harmful systemic effects.
III. Drug can be administered in a smaller dose to produce the desire effect.
IV. Avoidance of hepatic first pass metabolism.

Disadvantages of drug targeting:

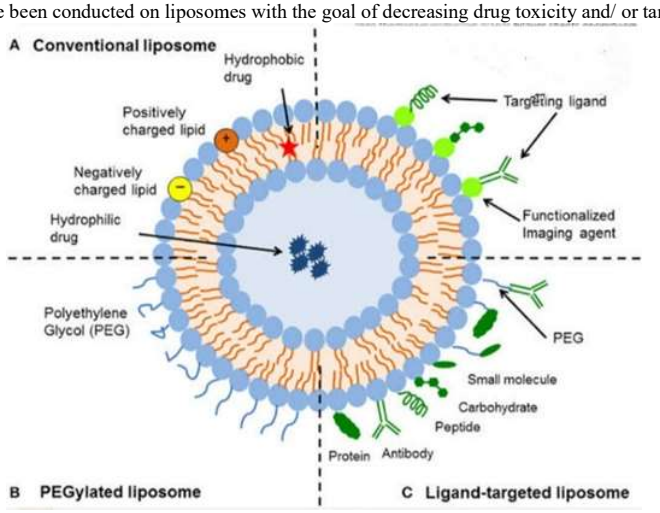
1)Rapid clearance of targeted systems.

2)Immune reactions against intravenous administered carrier systems.
3)Insufficient localization of targeted systems into tumour cells.
4)Diffusion and redistribution of released drugs.

CARRIERS FOR TARGETING DRUG [10,11]

LIPOSOMES [15,16]:

Liposome was first discovered in the early 1965 by Alec D. Bingham which is derived from the Greek word, where lip means "fatty" constitution and soma means "structure". Liposome are relatively small in size and it ranges from 50 nm to several micrometres in diameter. These are spherical vesicle in which aqueous core is entirely enclosed by one or more phospholipid bilayers. It having the unique ability to entrap both lipophilic and hydrophilic compounds. The hydrophobic or lipophilic molecules are inserted into the bilayer membrane, whereas hydrophilic molecules can be entrapped in the aqueous canter. Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs and simplify site-specific drug delivery to tumour tissues, liposomes have increased rate both as an investigational system and commercially as a drug delivery system. Many studies have been conducted on liposomes with the goal of decreasing drug toxicity and/ or targeting specific cells



ADVANTAGES

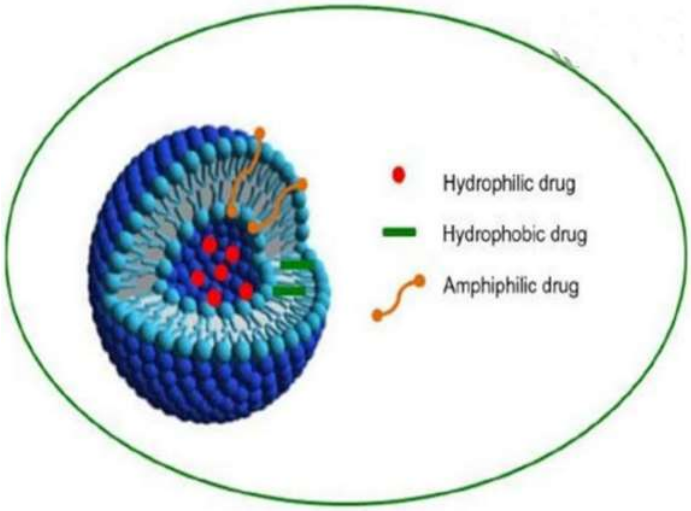
A. Suitable for delivery of hydrophobic (e.g., amphotericin B) hydrophilic (e.g., cytarabine) and amphipathic agents.
B. Liposome increases efficacy and therapeutic index of drug (actinomycin-D) Liposome increase stability via encapsulation
C. Suitable for targeted drug delivery
D. Suitable to give localized action in particular tissue

DISADVANTAGES:

A. Once administrated, liposome cannot be removed
B. Possibility of dumping, due to faulty administration.
C. Leakage of encapsulated drug during storage.
D. Low solubility

NIOSOMES: _ [3]

Noisome are one of the novel drug delivery systems of encapsulating the medicament in a vesicular system. The vesicle composed of a bilayer of non-ionic surfactants and hence the name noisome. The noisome are very small, and microscopic in size (in nanometric scale). Although being structurally similar to liposomes, they have several advantages over them.



ADVANTAGES OF NIOSOMES:

a. The vesicles may act as a depot, releasing the drug in a controlled manner.
b. They are osmotically active and stable, and also, they increase the stability of entrapped drug.
c. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. The surfactants used are biodegradable, biocompatible and nonimmunogenic.
d. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs and They can be made to reach the site of action by oral, parenteral as well as topical routes.

DISADVANTAGES OF NIOSOMES

A. The noisome vesicles are major disadvantage of the noisome drug delivery system.
B. The noisome vesicles can be another disadvantage to be considered. Fusion: Fusion of the noisome vesicles to form loose aggregates or to fuse into larger vesicles will affect the uniformity of the size of the noisome vesicles.
C. Leakage of the entrapped drugs from the polymer system will affect the intended properties of the noisome.

TYPES OF NIOSOMES:

The noisome are classified as a function of the number of bilayer (e.g., MLV, SUV) or as a function of size. (E.g., LUV, SUV) or as a function of the method of preparation.

1. Multilamellar vesicles (MLV): It consists of a number of bilayers surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used noisome. These vesicles are highly suited as drug carrier for lipophilic compounds.
2. Large uniflagellar vesicles (LUV): Noisome of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.
3. Small uniflagellar vesicles (SUV): These small uniflagellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of diacetyl phosphate in 5(6)-diacetyl (CF) loaded Span 60 based noisome.

APPLICATION [13,14]

Some of the applications of noisome in various diseases are either proven or research are still being carried out:

Drug targeting:

(RES) preferentially takes up noisome vesicles. The uptake of noisome is controlled by circulating serum factors called opsonin's. These opsonin's mark the noisome for clearance. Such localization of drugs is utilized to treat tumours in animals known to metastasize to the liver and spleen. This

localization of drugs can also be used for treating parasitic infections of the liver. Noisome can also be utilized for targeting drugs to organs other than the RES.

Anti-neoplastic

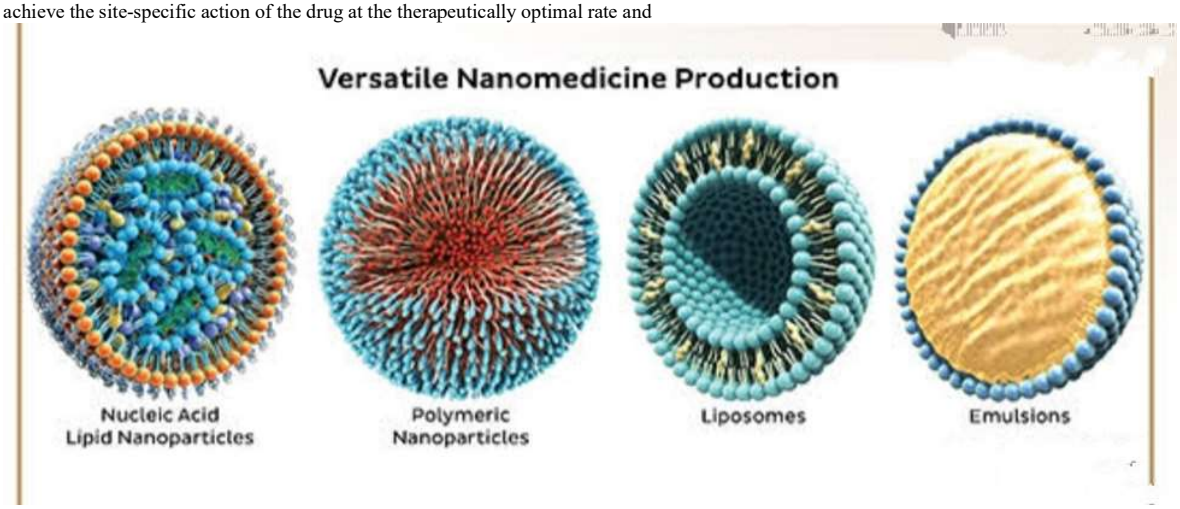
Treatment: Most antineoplastic drugs cause severe side effects. Noisome can alter the metabolism, prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Noisomely entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumour and higher plasma levels accompanied by slower elimination. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonial), which in higher concentrations can cause cardiac, liver and kidney damage. Use of noisome in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

Delivery of Peptide Drugs:

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of noisome to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study conducted by Yoshida et al, oral delivery of a vasopressin derivative entrapped in noisome showed that entrapment of the drug significantly increased the stability of the peptide. Use in Studying Immune Response: Due to their immunological selectivity, low toxicity and greater stability; noisome are being used to study the nature of the immune response provoked by antigens. Noisome as Carriers for Haemoglobin: Noisome can be used as carriers for haemoglobin within the blood. The noisome vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic Pati patient.

NANOPARTICLES _ [5, 6]

Rolland et. Al., (1989) designed a site-specific drug delivery system consisting of poly metacyclic nanoparticles. The main goal in designing nanoparticles as a delivery system is to control size of particle, surface characteristics and discharge of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and



ADVANTAGES:

1. Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
2. They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
3. Delivers a higher concentration of pharmaceutical agent to a desired location.

DISADVANTAGES:

1. Small size & large surface area can lead to particle aggregation.
2. Physical handling of nano particles is difficult in liquid and dry forms.
3. Limited drug loading.

4. Toxic metabolites may for form

[6] Nanoparticles: can be prepared from a variety of materials such as polysaccharides, proteins and Synthetic polymers. Selection of matrix materials depends on many factors including:

(a) Size of nanoparticles required
(b) Inherent properties of the drug, e.g., stability© Surface characteristics such as charge and permeability
(c) Degree of biodegradability, biocompatibility and toxicity

(d) Antigenicity of the final product.

Different methods And Techniques preparation Nanoparticles ☺

A) Nano precipitation
B) Emulsification/solvent diffusion
C) Salting out e) Dialysis

Techniques for Physicochemical Characterization of Nanoparticles [6]

Parameters Technique: Particle size and morphology Transmission electronic microscopy, scanning (electron, force, tunnelling) microscopy, freeze-fracture electron microscopy, photon correlation spectroscopy Drug content in vitro drug release Ultra centrifugation followed by quantitative analysis of in vitro release characteristics under physiologic and sink conditions. Molecular weight crystallinity Gel permeation chromatography, X-ray diffraction, differential scanning calorimetry Surface charge Surface hydrophobicity Zeta potential measurement, hydrophobic interaction chromatography, contact angle measurement Surface chemical analysis Secondary ion mass spectrometry, X-ray photoelectron spectroscopy, nuclear magnetic resonance, Fourier transform Infrared spectroscopy Protein adsorption Two- dimensional polyacrylamide gel electrophoresis

Application of Nano Particulate Drug Delivery Systems [6]:

- Vaccine adjuvant. DNA delivery. Ocular delivery. Internalization: Internalization within mammalian cells can be achieved by surface functionalized carbon nanotubes
- Vaccine delivery: Conjugation with peptides may be used as vaccine delivery structures
- Gene delivery: with the advancement in molecular dynamics simulations, the flow of water molecules through surface-functionalized carbon nanotubes has been modelled in such a So that they can be conveniently utilized as small molecule transporters in transporting DNA, indicating potential use as a gene delivery tool.
- Cancer therapy: This technology is being evaluated for cancer therapy. Nano shells are tuned to absorb infrared rays when exposed from a source outside the body and get heated and cause destruction of the tissue. This has been studied in both in vitro and in vivo experiments on various cell lines.
- Diagnostic purposes: They are useful for diagnostic purposes in whole blood immunoassays e.g., coupling of gold nano shells to antibodies to detect immunoglobulins in plasma and whole blood. Etc.

MONOCLONAL ANTIBODIES [7, 8]:

An antibody is a protein used by immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. The high specificity of antibodies makes them an excellent tool for detecting and quantifying a broad array of targets, from drugs to serum proteins to microorganisms. With in-vitro assays, antibodies can be used to precipitate soluble antigens, agglutinate (clump) cells, opsonize and kill bacteria.

- History and Development [7]
- Paul Enrich at the beginning of 20^{th} century coined the term “magic bullets” and postulated that, if a compound could be made that selectively targets a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity.
- In the 1970stB-cell cancer multiple myeloma was known. It was understood that these cancerous B-cells all produce a single type of antibody (a paraprotein).
- In 1975, Kohler and Milstein provided the most outstanding proof of the clonal selection

Advantage Monoclonal antibodies:

a) Though expensive, monoclonal antibodies are cheaper to develop than conventional drugs because it is based on tested technology.

B Side effects can be treated and reduced by using mice-human hybrid cells or by using fractions of antibodies.

b) They bind to specific diseased or damaged cells needing treatment. D) They treat a wide range of conditions.

DISADVANTAGES of Monoclonal Antibodies

A) Hybridoma culture may be subject to contamination.
B) Only well developed for limited animal and not for other animals.
C) More than 99% of the cells do not survive during the fusion process – reducing the range of useful antibodies that can be produced against an anti

Conclusion:

The rapid advancement of research into drug targeting mechanisms, the function of targeted medications will become increasingly important due to their curative impact and reduced adverse effects. Targeted medication applications are becoming more prevalent in a variety of fields. The delivery of a medication molecule to its target site is a tough task in and of itself. Finally, targeted medication delivery is on its way to become a cutting-edge technology for the treatment of deadly diseases. The goal of targeted medication delivery, as the name implies, is to help the drug molecule reach its desired location. Targeted drug delivery is an advanced method of delivering drugs to patients in such a targeted sequence that increases the concentration of delivered drug to the targeted body part of interest only (organs, tissues, and cells), thereby improving treatment efficacy by reducing drug administration side effects. The goal of targeted drug delivery is to help the medication molecule reach the desired spot as quickly as possible. The inherent benefit of this procedure is that it allows for the delivery of the required medicine at a lower dose and with fewer adverse effects. This inherent benefit of targeted drug delivery systems is being studied extensively in clinical and pharmaceutical research as the backbone of treatments and diagnostics. Soluble polymers are one type of drug carrier that can be used in this sophisticated delivery system. Neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes, micelles, and immune micelles are all biodegradable microsphere polymers (both synthetic and natural). The purpose of a targeted medicine is to achieve a specific result

REFERENCES:

1. Lachman L, Lieberman HA, König JL. The Theory and Practice of Industrial Pharmacy. Iron Khar, Vyas SP, Farhan A, Jain Gaurav, editors. Targeted Drug Delivery Systems, 3rd ed, Varghese Publishing House; 2014. P. 907-43
2. Bhargav E, Madhuri N, Ramesh K, Anand mane, Ravi V. Targeted Drug Delivery-A Review, World J. Pharm. Pharm. Sci. 2013;3(1):150 - 169
3. Lachman L, Lieberman HA, König JL. The Theory and Practice of Industrial Pharmacy. In Roopa Khar, Vyas SP, Farhan A, Jain Gaurav, editors. Novel Drug Delivery Systems, rd. ed, Varghese Publishing House; 2014. P. 872-906
4. Lasik DD, Applications of Liposomes. In Lipsky R, Spackman E, editors. Volume 1,2014. p. 493-94.
5. Jaya A, Shubin Sabha K. Targeting: New Potential Carriers for Targeted Drug Delivery System, Int. J. Pharm. Sci. Rev. Res. 2011;8(2):117-123
6. Gupta M, Sharma V. Targeted drug delivery system: A Review, Res. J. Chem. Sci. 2011;1(2):135 – 138.
7. Archana S, Jinju S, Suresh G, Alexander RV, Nagesh K, Omid CF. Nanoparticles for Targeted and Temporally Controlled Drug Delivery, Multifunctional Nanoparticles for Drug Delivery Applications: Imaging, Targeting, and Delivery, Nanostructured. Sci. Technol. 2012; 9 – 29.
8. Pascagoula R, Defy CS. Monoclonal Antibodies in Drug Targeting, J. Clin. Pharm. There. 1997; 22:7–19
9. Andrew MS, James PA, Jedd DW. Monoclonal Antibodies in Cancer Therapy, Cancer Immunity, 2012; 12:14 – 21
10. Nuri B, Itaú B. Antibody-Based Immunotoxins for the Treatment of Cancer, Antibodies, 2012; 1:39–69
11. Theresa M, Allen. Ligand-Targeted Therapeutics in Anticancer Therapy, Nature 2002; 2: 750 – 763
12. Bennett E. Smith, Paden B. Order, Yuezhi Yuezhi al. Nanoscale materials for hyperthermal theranostics. Nanoscale. 2015 , 7(16): 7115–7126. Wen S, Liu H, Cai H, et al. Targeted and pH-responsive delivery of doxorubicin to cancer cellusing multifunctional dendrimer-modified multi-walled carbon nanotubes. Adv healthc Mater. 2013; 2(9):1267–1276.
13. Aili, D., Mager, M., Roche, D. & Stevens, M. M. Hybrid nanoparticle-liposomedetection of phospholipase activity. Nano Lett .2011,11:1401–1405.
14. Ming Wang, John A. Zuris,Fantao Meng,et al. Efficient delivery of genome-editing proteins using bioreducible lipid nanoparticles PNAS .2016, 113(11) : 2868–2873
15. Cheng-Xiang Zhang, Wei-Yu Zhao, Lei Liu,et al.A nanostructure of functional targeting Epirubicin liposomes dually modified with aminophenyl glucose and cyclic pentapeptide Used for brain glioblastoma treatment. Oncotarget, 2015,6(32): 32681-32700
16. Wang ,Yufan Ma1, Hayssam Khalil. Fusion between fluid liposomes and intact bacteria: study of driving parameters and in vitro bactericidal efficacy. International Journal of Nanomedicine 2016,8: 4025–4036
17. Carolina Garrido, Carrie A Simpson, Noelle P Dahl,et al.Gold nanoparticles to improve HIV drug delivery. Future Med. Chem. 2015,7(9), 1097–1107
18. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. Nature Reviews Clinical Oncology. 2010; 7(11):653–664.
19. Zhang Z, Wang J, Chen C. Gold nanorods based platforms for light-mediated theranostics.Theranostics. 2013; 3(3):223–238.
20. Jing Zhang, Yingchong Chen , Xiang Li ,et al. The influence of different long-circulating Materials on the pharmacokinetics of liposomal vincristine sulfate. International Journal of Nanomedicine. 2016:11 :4187–4197

21. Gupta AK, Naregalkar RR, Vaidya VD,et al. Recent advances on surface engineering of Magnetic iron oxide nanoparticles and their biomedical applications. Nanomedicine2007; 2(1):23–39.
22. Ravi D. Vaishya, Varun Khurana, Sulabh Patel,et al.Controlled Ocular Drug Delivery with Nanomicelles. Wiley Interdiscip Rev Mahomed Nanobiotechnol. 2014 September ; 6(5): 422–437.
23. Mahdi Karimi, Navid Solati, Amir Ghasemi, et al. Carbon nanotubes part II: a remarkable carrier for drug and gene delivery. Expert Opin Drug Deliv. 2015 July ; 12(7): 1089–1105.
24. Cai D, Mataraza JM, Qin Z-H, et al. Highly efficient molecular delivery into mammalian cells using carbon nanotube spearing. Nat Methods. 2005; 2(6):449–454.
25. Pattinson SW, Ranganathan V, Murakami HK, et al. Nitrogen-induced catalyst restructuring for epitaxial growth of multiwalled carbon nanotubes. ACS Nano. 2012,6(9):7723-7730.
26. Tarn D, Ashley CE, Xue M,et al. Mesoporous Silica Nanoparticle Nanocarriers – Biofunctionality and Biocompatibility Acc Chem Res. 2013,19; 46(3): 792–801.
27. Lin Y-S, Haynes CL. Impacts of Mesoporous Silica Nanoparticle Size, Pore Ordering, and Pore Integrity on Hemolytic Activity. Journal of the American Chemical Society. 2010;
28. N. K. Jain Introduction to novel drug delivery systems Vallabh prakashan First edition e no 118- 134.
29. S.P.Vyas and R.K.Khar, Targeted and Controlled drug delivery, 07 Edition.
30. M. Gupta and V. Sharma, “Targeted drug delivery system: A review,” Research Journal of Chemical Sciences, vol. 1,2011.
31. A.M. Hillery and A.H. Lloyd, Drug delivery and targeting, London, Taylor & Francis e-Library, 2005
32. Y.H. Bae and K. Park, “Targeted drug delivery to tumors: Myths, reality and Possibility, “Journal of Controlled Release, vol. 153, 2011.
33. J. Agnihotri, S. Saraf, and A. Khale, “Targeting: new potential carriers for targeted drug Delivery system,” International Journal of Pharmaceutical Sciences Review and Research,Vol. 2012