NANOMATERIALS FOR DRUG DELIVERY

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Abstract

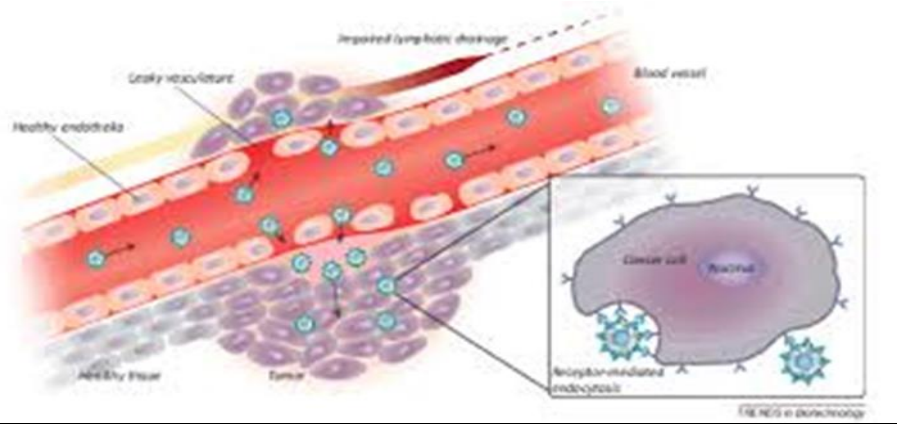
Nanomaterials have gained immense attention in medicinal field due to their small size and large surface area.They act as drug carriers and have the ability to deliver them to a specific target site.With the increase in respiratory diseases the number of deaths are also increasing but combining nanotechnology with existing drugs new treatments are being made available with least side effects.such technology can also be used for targeting cancerous and tumour cells.Four important characteristics og nanoparticles considered are size,encapsulation efficiency zeta potential that takes into consideration the surface charge and some releasing features.

INTRODUCTION

The nanoparticles carrying the drug can be injected into the body which travels through the blood vessels and thud targeted drug delivery can be achieved[1].This paper emphasises on the different kinds of integrated nanotechnology used to treat variety of diseases.

USE OF NANOTECHNOLOGY AT TARGET SITES

Delivery of drugs to the tumorous sites is a major issue due to low accumulation of therapeutic substances and this accumulation can be improvised by the EPR(enhanced permeability and retention) effect which is a result of the leaky vasculature of tumour cells.



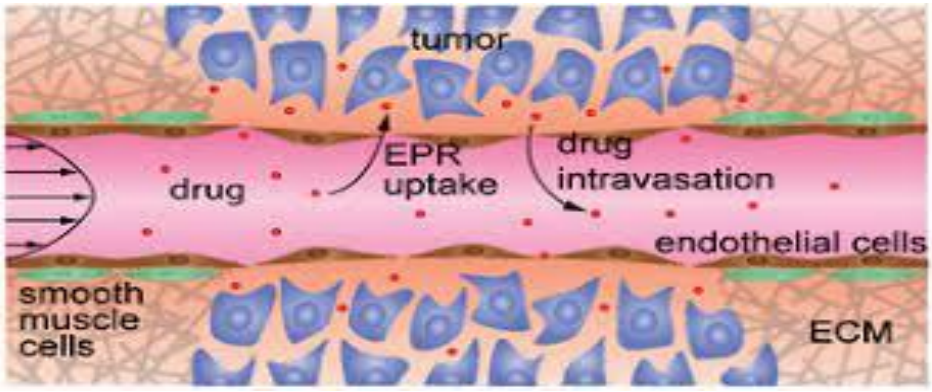


Fig A:EPR effect

Exposing GEP-C-poly(OEGMA) conjugate to blood for longer time in association with EPR effect causes higher accumulation of GEP-C-poly(OEGMA) conjugate. Once the nanomaterial carrying the protein drug is injected into the body, it travels through the interstitium of the tissue without any hindrance due to smaller size(sub 100-nm) and are transported to draining lymphatics[1],[2].Nanocarriers on close contact with the cell membrane gets engulfed by it.For it to be delivered to the nucleus It is necessary to transport it from the endosome organelle to the cytoplasmic content.siRNA carried by a complex nanostructure is administered in the blood stream by injection.This nanoparticle functionalised with transferrin,using PEG as a linker releases siRNA in the cytoplasm from endolysosome.Graphene is two dimensional,sp2 hybridised and a commendable drug carrier due to its pi-pi stacking and can be loaded with weakly soluble substances.Liu et al synthesised graphene oxide functionalised with PEG (NGO) sheets carrying camptothecin analog SN38 which exhibited water solubility and showed toxicity towards HCT-116 cells[1],[3].Carbon nanomaterials like graphene oxide generates heat on exposure to NIR radiation and the reduced form has a good photothermal property.Graphene oxide acts as a good drug carrier due to its high surface area and high drug loading efficiency. PEG-BPEI-rGO under photothermal effect, acidic pH and high concentration of glutathione causes endosomal rupture and releases anticancerous drug DOX into cytoplasmic matrix[4].

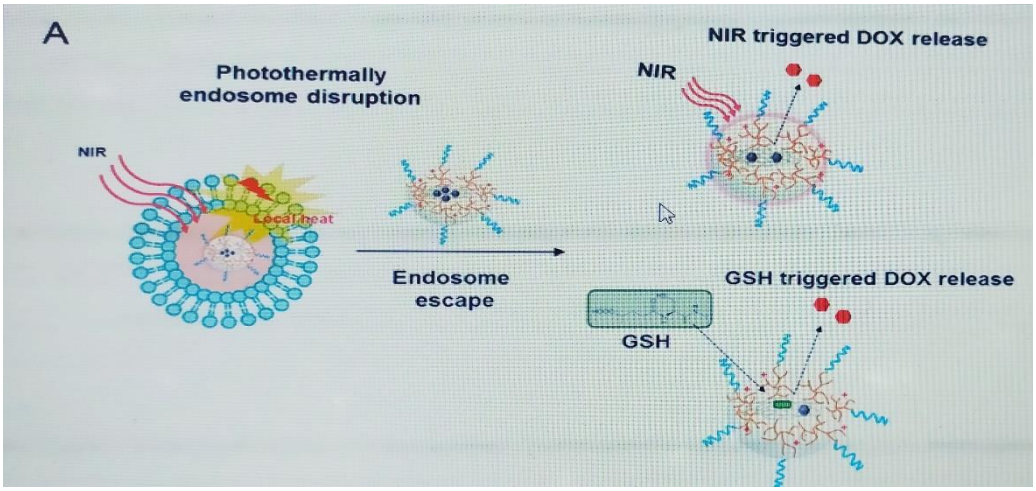


Fig B:Photothermal disruption of endosome to release DOX drug in cytoplasm

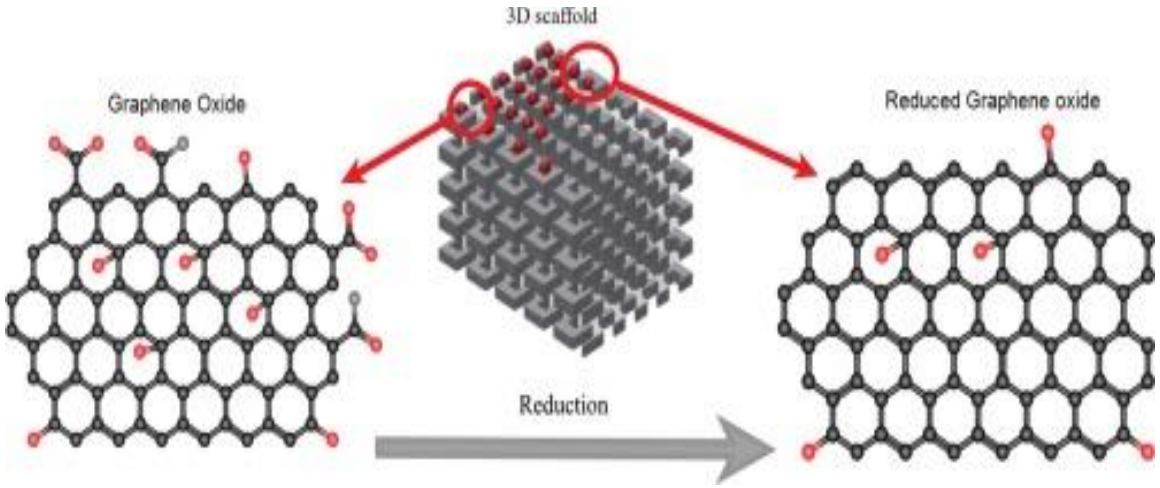
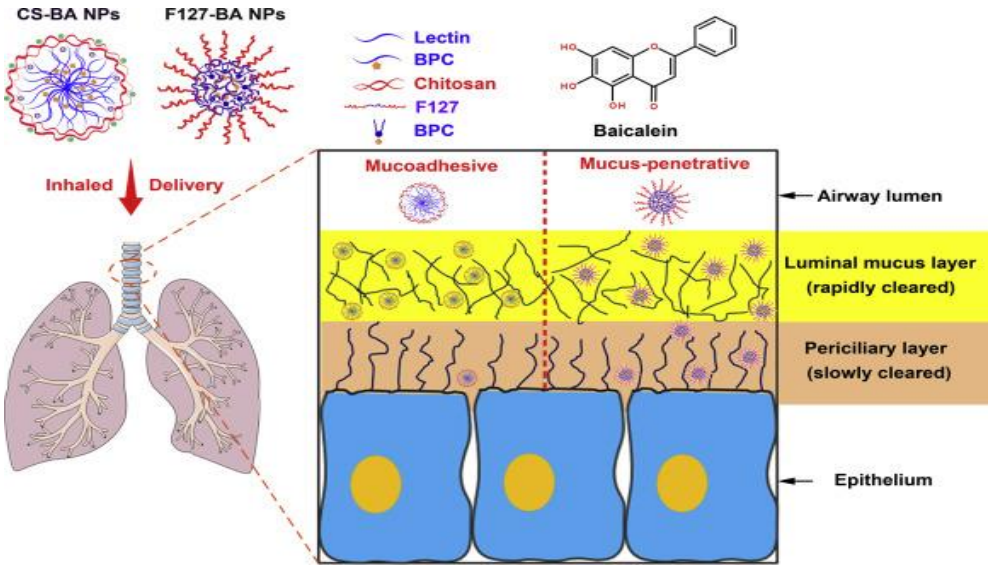


Fig C:Graphene and its reduced form

When it comes to respiratory diseases,the inhalation route is the most common way to treat pulmonary diseases as it directly reaches the site of action.the respiratory diseases include lung cancer,asthma,other viral and bacterial infections.Drugs sent via blood vessels are excreted via renal pathway but this can have side effects such as formation of blood clots therefore lung based drug delivery has gained importance.Polymeric nanoparticles showing two types of structures,nanospheres and nanocapsules are used to deliver drugs as it can hold large amount of drugs and can deliver large molecules.some of the polymers used are polyethylene glycol,polylactic acid,polyglycolic acid.Lipid based nanoparticles are also

investigated as drug carriers. Lipids are organic compounds made up of fats and oils and are nonpolar.LBNPs include solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). Ref. tested lumacaftor and ivacaftor-loaded NLCs through inhalation to treat cystic fibrosis.NLCs and SLNs loaded with sildenafil can treat lung hypertension[5].Although inhalation route to deliver drugs is efficient,it still has drawbacks such as poor accumulation in bronchioles,inefficient penetration through mucosal lining due to which nanostructures acting as encapsules can be used.



FigD:Mucoadhesive and mucous penetration concept

Some examples include polylactic-co-glycolic,chitosan,polylactic acid.chitosan is mucoadhesive and thus can spend longer time in the respiratory tract but they were found on the inner mucous layer which were then swept away.Nanoparticles should be designed such that they do not possess mucoadhesive property.Baicalein is a compound having antimicrobial properties but is hydrophobic and has less affinity for lipid environment.Baicalein-phospholipid complex can be easily associated with nanocarriers .Chitosan modified nanoparticles (CS-BA NPS) is prepared by solvent injection method and pluronic F127 modified nanoparticles(F127-BA NPs) is prepared by by pressure homonization.Both have similar mean size approximately 200 nm.Zeta potential defining the stability of nanocarriers was highly positive for chitosan based NPs compared to F127-BA NPs which depicted that it has high surface charge.When transmission electron spectroscopy was conducted it was observed that both had spherical shape and can act as encapsules.Both these structures were sent into the respiratory tract and it was revealed that CS-BA-NPs were

stationary due to their mucoadhesive behaviour whereas F127-BA NPs having no net charge travelled longer distances[6].

Diving into the catergory of biodegradable class of delivers,liposomes are a classic example of the same.But they are weak encapsules and also leak hydrophilic drugs.Nanoparicles that can undergo biodegradation given a new direction for research.Calvo and co-workers devised a method to prepare hydrophilic chitosan nanoparticles.Ingredients include ionic gelation,two aqueous phases,one containing chitosan and other diblock copolymer of ethylene oxide(EO) and the other is aqueous solution of TPP. Positive amino group of interacts with TPP containing negative charge.These nanparticles can associate with proteins ,bovine serum albumin.Mao and coworkers prepared DNA-gelatine NPs but chitosan NPs were seen to be better carrier.According to Calvo et al drug release takes place depending on the affinity of drugs for water but the prime factor to be considered is the concentration of medium used.Diluted medium shows better release of drug but according to Lu et al release of bovine serum albumin from PLA nano capsule does not occur by drug partitioning but instead depends on the mass.Drugs to target brain has been challenging because they have to cross blood brain barrier.Some drug are prepared that can pass through this barrier and target CNS.

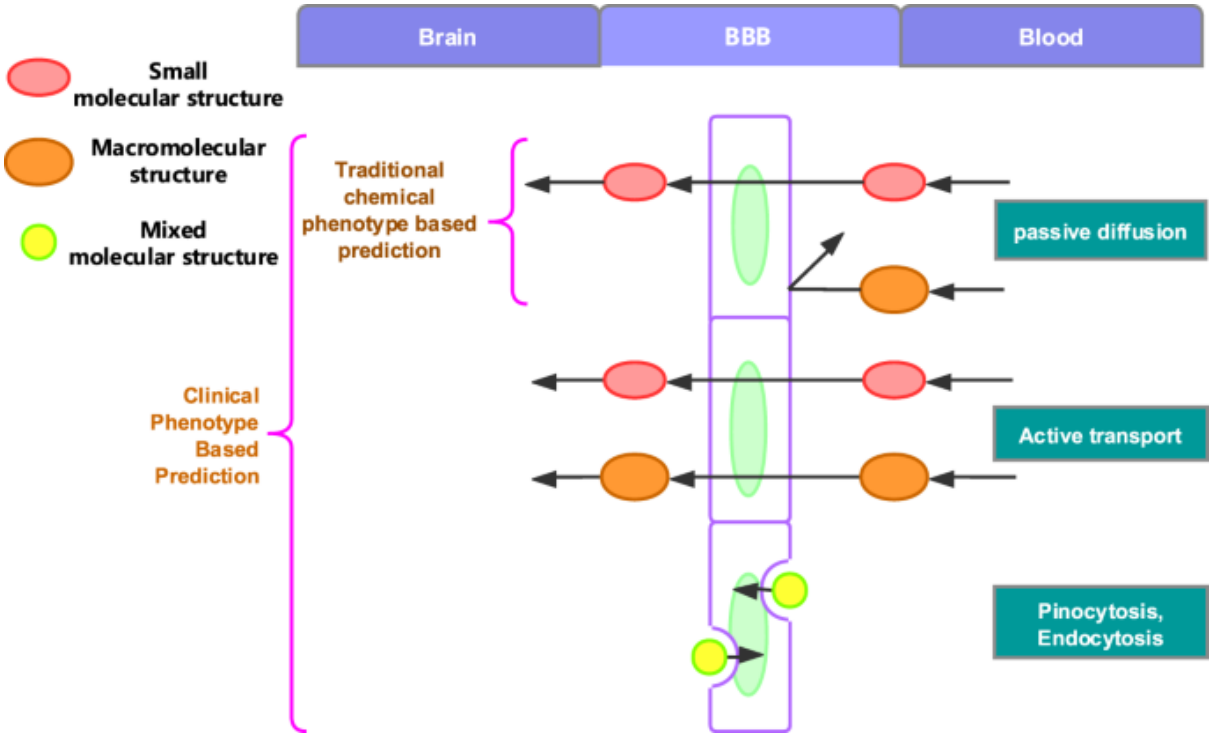


Fig E:Drugs crossing blood brain barrier

Borchardt et al studied an increased uptake of polysorbate-80 PMMA poly(methyl methacrylate) NPs.Troster et al showed high radioactivity in the brain after using polysorbate-80 coated C-14 PMMA NPs.According to Steiniger et al,polysorbate-80 coated poly(alkyl cyano acrylate)NPs are finest for transportation of drugs across blood brain barrier. While Encapsulating hydrophilic molecule like a protein,the main problem faced is quick diffusion in outer medium while emulsification.This decreases the nanocarriers capacity to load drugs therefore it is necessary for the polymer to be quickly deposited.Song et al achieved this by using high concentration of PLGA in oil phase containing DCM and acetone solution.Insulin can be encapsulated by a method wherein Zn-insuline is made to dissolve in tris-HCl and to small quantity of it,10% ZnSO4 is added.The precipitate formed is added to PLGA solution in methylene chloride and emulsification is done.The solvents used are chlorinated and thus can destabilize the drug.The stability of the drug can be increased by emulsification-diffusion method where acetone and propylene carbonate is used as solvents [7],[8].Lungs show high permeability and absorbtivity.Drug targeted may lead to systemic drug exposure and thus alveoli should be targeted.Some other barriers include mechanical barriers like excess of mucous secretion or may be lost in large airways.Chemical barriers are proteolytic enzymes degrading the drug or due to presence of surfactants.The particle may be destroyed by alveolar macrophage. Inhalers prescribed by doctors may not be correctly use that is failure to inhale deeply.

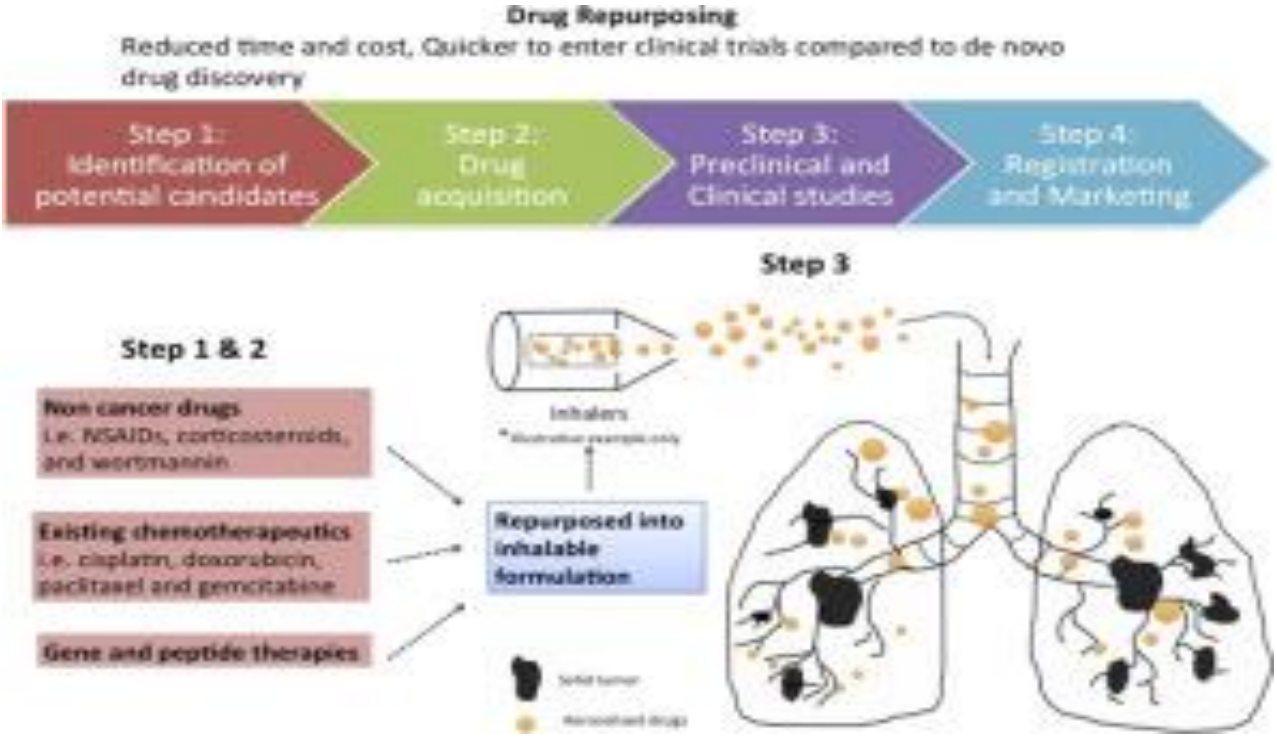


Fig F:Inhalers to target lung tumorous cells

Due to a ban on the use of CFCs pressurised metered dose inhalers (pMDIs) were reformulated using hydrofluoroalkane(HFA)-134a but the implications for pMDIs are not very clear. By nebulization technique drug solutions can be transported as aerosol droplets. CFCs in the form of aerosol droplets were used but since it affected ozone layer alternatives were brought up.One such alternative is dry powder inhaler. Yama moto et al produced chitosan nanoparticles and elcatonin peptide was packed into it. Vaughn et al studied delivery of itraconazole(ITZ) to treat fungal infection which can be eliminated via lymph system. Modifying ITZ with polysorbate-80 and potoxamer407 and delivering it via respiratory tract showed high concentration in the lungs. Corticosteroids can be used for treatment of chronic obstructive pulmonary disease(COPD).Emphysema, asthma and chronic bronchitis are most common conditions. Symtoms include chronic cough, falling short on breath, fatigue, wheezing. Budesonide (BUD) is used control asthma.[9],[10],[11].

Around 1.04 milion cases of lung cancer are recorded worldwide.It is categorised a small cell lung cancer(SCLC) and non small cell lung cancer(NSCLC).The most common cause of lung cancer is smoking. Traditional ways used for therapeutic drug delivery are unable to deliver small amounts and thus focuses on the use of nanocarriers. Phosphatidylethanolamine and phosphatidylcholine are common examples of phospholipids used.[12]

Hydrogel technology has evolved in the pharmaceutical and biomedical area.These are 3-D polymeric networks that can hold large quantity of water and their absorbtivity towards fluids is very high due to –OH,CO-NH,-SO3H groups and these groups are responsible for formation of hydrogel structures. Chitosan,alpha(1-4)-2-amino-2-deoxy beta-D-glucan is deacetylated form of chitin found abundantly in crustacean shells(chitosan based hydrogel nanoparticles).Chitosan is hydrosoluble and positively charged and this leads to interaction of polymers with negatively charged polymers. Chitosan NPs loaded with insulin were prepares which increased the loading efficiency.Patients body not accepting multidrug exposures led to failure of anti-tubercular chemotherapy but the modified drug delivery systems have proven to be ideal for treatment. Using PVA as cross linker Guowie et al synthesised PVP [poly(vinyl pyrrolidone)] as magnetic molecular delivery system[13].

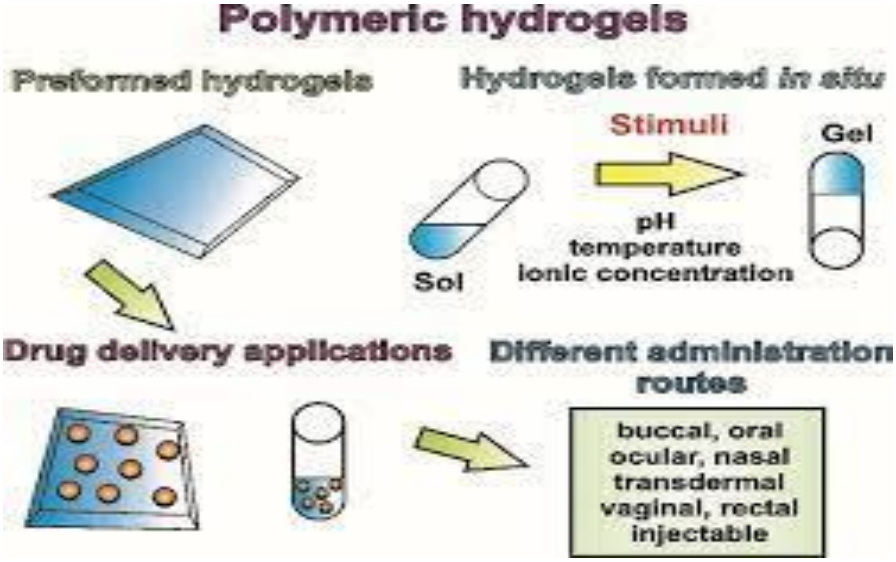


Fig G:Hydrogel drug delivery

Magnetic NPs are applicative in biomedical world and one of its most important application is in magnetic resonance imaging (MRI).Applied external magnetic field leads the magnetic nanocarriers to the target. The particles have the core made up of magnetite(Fe_3O_4) and maghemite and the shell is of polymer of silica or metals like gold having functional groups. Gold/cobalt NPs are better than magnetite or maghemite. Magnetic gradient is a necessary factor. At times the particles do not respond to the external magnetic field and these may also lead to blockage and prevent blood flow. Small size of these nanoparticles can lead to agglomeration after removing the external magnetic field[14].Applications of magnetic nanoparticles are MRI,as hyperthermia agents,magnetic vectors.In blood nanoparticles coated with silica possess a negative charge and therefore do not form aggregates which is beneficial. Polyethylene glycol is used as a coating on NP surface. Magnetic nanoparticles are injected into the patients body and a permanent magnet is placed on the tumour region where the particles get attracted and the release of drug takes place.

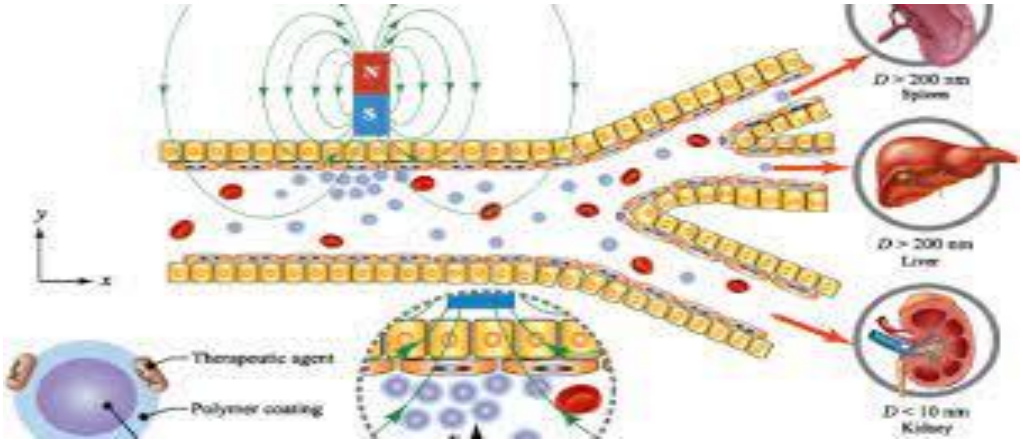


Fig H:Magnetic nanoparticle drug delivery

Alexiou et al prepared MNPs by coating it with starch and modified using phosphate groups and than loaded the drug but the drug dissociated. Delivering water insoluble drugs was problematic. A water insoluble drug could be loaded into oleic acid (OA)–pluronic-coated iron oxide magnetic particles. Magnetic cationic (MAG-C) liposomes can be effectively used for targeting small tumour .

Seo et al reported magnetic NPs of magnetite entrapped into poly(hexadecylcyanoacrylate) coated with poly(ethyleneimine) loaded with DOX hydrochloride drug was applicable for cancer treatment and also diagnosis[15],[16].

Biopolymers from proteins and polysaccharides are beneficial because they are biodegradable,not toxic,antibacterial.Desolvation method to produce bio-nanoparticle based drug delivery system using acetone and ethanol as solvents is one of the easiest methods.Silk fibroin shows brilliant properties such as mechanical hardness,is biocompatible and is used to deliver biomolecules like bovine serum albumin (BSA), adenosine, curcumin, rhodamine B. Li et al. prepared curcumin and DOX loaded nanofibers and was able to achieve dual release of drugs. Gelatin hydrogels,due to larger surface area can easily diffuse in blood during delivery of drug [17].

Parkinson's disease is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination.Rasagiline-encapsulated-chitosan-coated-PLGA-Nanoparticles (RSG-CS-PLGA-NPs) were used to study their capability to target brain cells and could enhance bioavailability in brain.

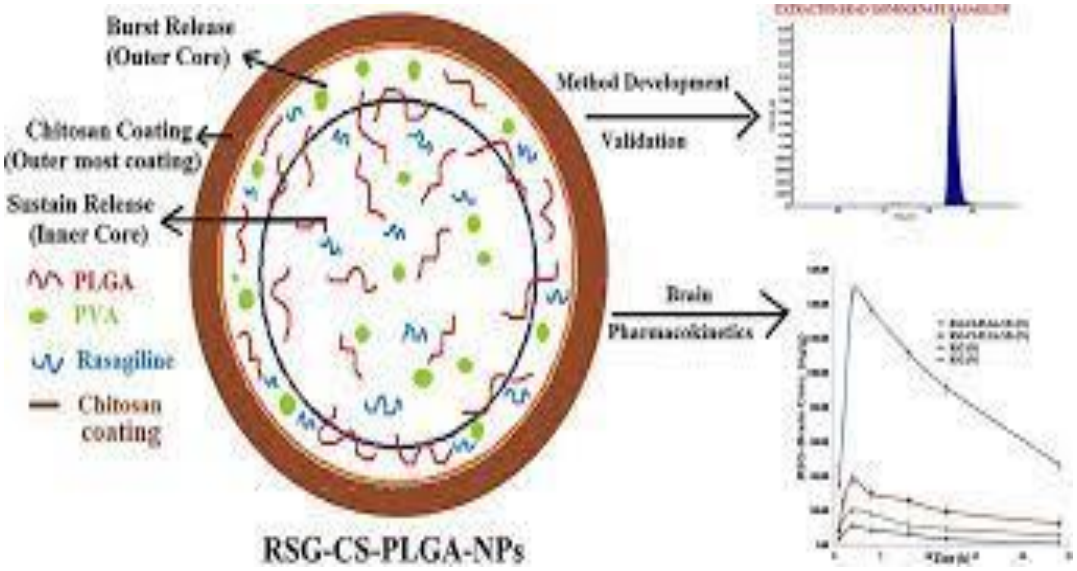


Fig J: RSG-CS-PLGA-NPs to target brain cells

Dopamine production is decreased which is responsible in movement coordination and this decrease is caused by Monoamine Oxidase Type B (MAO-B) enzyme in our body that breaks down several chemicals in the brain, including dopamine.Rasagiline (RSG) acts as an inhibitor for this enzyme.

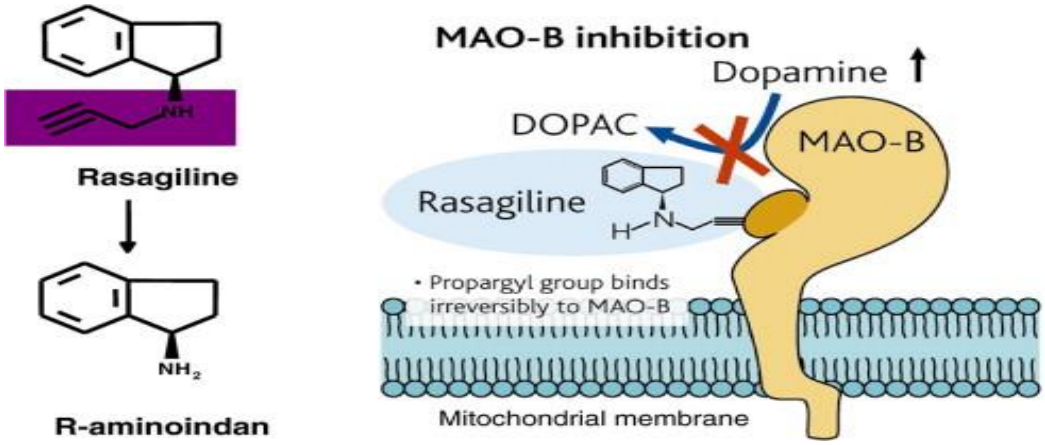


Fig K:Rasagiline inhibiting degradation of dopamine

RSG is highly water soluble but do not pass BBB and to avoid this issue researches have attempted Nose-to-brain drug delivery.But the residence time of this inhibitor in nasal pathway is low due to which PLGA-NPs with optimum shape, size are used for intranasal drug

brain targeting. CS-coated-PLGA-NPs were formulated due to mucoadhesive nature of chitosan and delayed drug release.RSG-loaded-CS-coated-PLGA-NPs thus helps achieving high therapeutic levels in the brain[18].To transport hexapeptide dalargin across BBB P80 coated PBCA NPs were investigated and was onserved that it relieved pain. Other surfactants such as

poloxamers 184, 188, 338, 407, poloxamine 908 were inactive.The drugs that otherwise do not penetrate BBB were easily able to cross it when associated with P-80 coated NPs.Brain of mice was targeted by Poloxamer 188 stabilized stearic acid camptothecin-loaded solid lipid nanoparticle(SLN).High concentration of this drug was observed in its brain[19]. Alzheimer's disease is a progressive neurologic disorder that causes the brain to shrink (atrophy) and brain cells to die. Alzheimer's disease is the most common cause of dementia — a continuous decline in thinking, behavioral and social skills that affects a person's ability to function independently.Degradation of BBB causes the malicious agents to reach the cerebrum." Kabanov and Batrakova gave an interesting review of maximizing drug trans- port through the BBB by inhibiting efflux transporters by block copolymers, by using artificial hydro- phobitization of peptides and proteins by fatty acids, and by using receptor-mediated drug encapsulated nanoparticles". Kreuter et al. gave the suggestion that transfer of polyalkylcyanoacrylates (PACA) across the BBB occurs by engulfment by the single cell layer that lines all blood vessels[20].Magnetic nanoparticles trapped in the polystyrene nanostructures were able to cross intact BBB of mice. 3'Azido-3'deoxythymidine5'-triphosphate (AZTTP) bound to magnetic particles and loaded in the liposomes could cross BBB in the presence of external magnetic field and showed excellent results than the free AZTTP[21].

Multidrug resistant phenomena is due to P-glycoprotein (P-gp).This transport protein is involved in the extrusion of anticancer drugs. Tsuruo et al could identify the first inhibitor of P-gp that is verapamil[22]. STEALTH particles are able to deliver high concentration of drug overcoming Reversal of multidrug resistance (MDR).Among the two drugs, pegylated liposomal doxo- rubicin (PD) and doxorubicin (D) given to the women having breast cancer,PD caused skin irritation and D led to vomiting. Paclitaxel loaded in the nanoparticle and conjugated by transferrin on the surface was able to deliver large amounts of the drug to the tumour[23].Core of the gold nanoparticles is inert and when functionalised has proven to accumulate drugs at the tumour cells.Synthesis of Au NPs include reducing agent, a metal precursor, and a stabilizer.Turkevich method of synthesis of Au NPs includes $AuCl_4(+3)$ salt,citrate as the reducing agent.Au NPs have higher cellular uptake. Au NPs with triangle shapes are more efficient than the rod shape in RAW264.7 whereas the star shaped has the least efficiency.Smaller particles(4-5 nm) are toxic.Uptake of Polyethylene Glycol-coated Au NPs in the cells is higher and has low toxicity.Doxorubicin attached to the surface of Au NP

With PEG could overcome P-gp mediated drug resistance. Carboxymethyl chitosan Au NPs treated by plasma(to reduce the size) kills breast cancer cells.

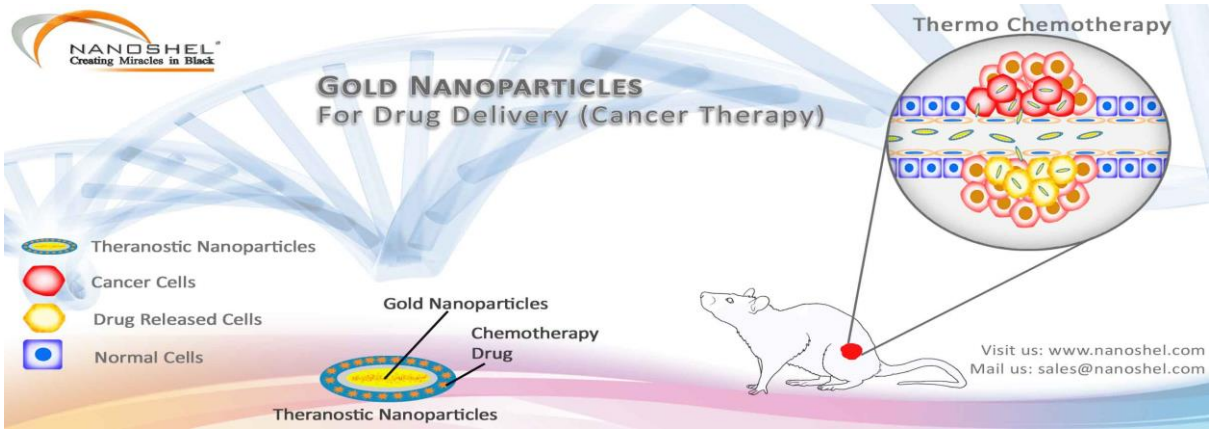


Fig L: Gold NPs targeting cancer cells

Mesoporous silica nanoparticles,due to large pore volume are able to hold large amount of drugs.Liposome-silica hybrid (LSH) NP kill prostate and breast cancer cells.Two types of mechanisms for drug delivery are active and passive transport.In active transport there is direct interaction between ligands and receptors while passive targeting is based on the EPR effect[24],[25].Dendrimers are synthetic branched structures. Polyamidoamine dendrimers have excellent properties like water solubility,can be easily conjugated to drugs and are not toxic to the cells.In vivo delivery of dendrimer– methotrexate reduces the size of the tumour to large extent in comparison to the free methotrexate.Dendrimers are expensive and producing them on a large scale is a challenge as some of the steps require repetition[26].

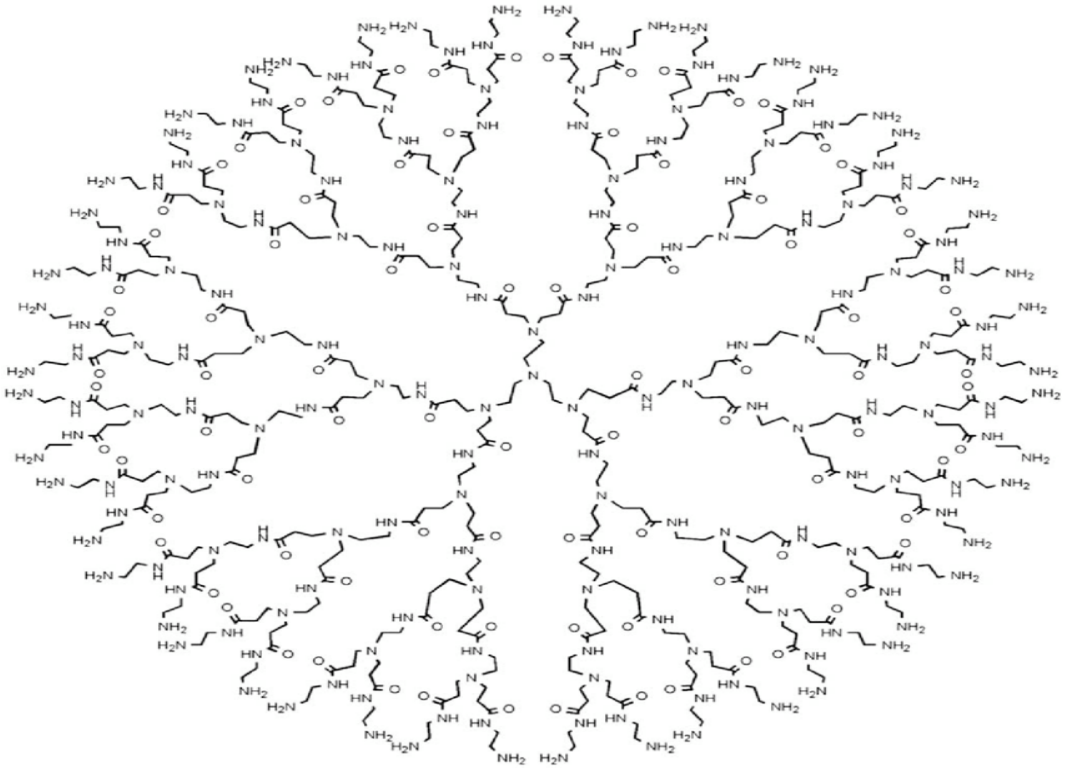


Fig I: Polyamidoamine dendrimer

[1] G. Wunner, H. Herold, F. Geyer, W. Schweizer, H. Wintgen, L.S. Cederbaum, M.A. Liberman, Certain Critical Fi Eld Strength, the 3 Σ, 337 (2012) 303–305.

[2] W. Gao, W. Liu, T. Christensen, M.R. Zalutsky, A. Chilkoti, In situ growth of a PEG-like polymer from the C terminus of an intein fusion protein improves pharmacokinetics and tumor accumulation, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 16432–16437. https://doi.org/10.1073/pnas.1006044107.

[3] S. Goenka, V. Sant, S. Sant, Graphene-based nanomaterials for drug delivery and tissue engineering, J. Control. Release. 173 (2014) 75–88. https://doi.org/10.1016/j.jconrel.2013.10.017.

[4] K. Hyunwoo, L. Duhwan, K. Jinhwan, K. Tae-Il, K. Won Jong, Photothermally triggered cytosolic drug delivery via endosome disruption using a functionalized reduced graphene oxide, ACS Nano. 7 (2013) 6735–6746.

[5] L.Á. Ibarra-Sánchez, A. Gámez-Méndez, M. Martínez-Ruiz, E.F. Nájera-Martínez, B.A. Morales-Flores, E.M. Melchor-Martínez, J.E. Sosa-Hernández, R. Parra-Saldívar, H.M.N. Iqbal, Nanostructures for drug delivery in respiratory diseases therapeutics: Revision of current trends and its comparative analysis, J. Drug Deliv. Sci. Technol. 70 (2022). https://doi.org/10.1016/j.jddst.2022.103219.

[6] W. Dong, J. Ye, J. Zhou, W. Wang, H. Wang, X. Zheng, Y. Yang, X. Xia, Y. Liu, Comparative study of mucoadhesive and mucus-penetrative nanoparticles based on phospholipid complex to overcome the mucus barrier for inhaled delivery of baicalein, Acta Pharm. Sin. B. 10 (2020) 1576–1585. https://doi.org/10.1016/j.apsb.2019.10.002.

[7] M.L. Hans, A.M. Lowman, B iodegradable nanoparticles for drug delivery and targeting, 6 (2002) 319–327.

[8] M.T. Chevalier, J. Gonzalez, V. Alvarez, Biodegradable polymeric microparticles as drug delivery devices, IFMBE Proc. 49 (2015) 187–190. https://doi.org/10.1007/978-3-319-13117-7_49.

[9] J.C. Sung, B.L. Pulliam, D.A. Edwards, Nanoparticles for drug delivery to the lungs, Trends Biotechnol. 25 (2007) 563–570. https://doi.org/10.1016/j.tibtech.2007.09.005.

[10] N. Ahmad, R. Ahmad, M.Z. Almakhamel, K. Ansari, M. Amir, W. Ahmad, A. Ali, F.J. Ahmad, A comparative pulmonary pharmacokinetic study of budesonide using polymeric nanoparticles targeted to the lungs in treatment of asthma, Artif. Cells, Nanomedicine Biotechnol. 48 (2020) 749–762. https://doi.org/10.1080/21691401.2020.1748640.

[11] S.P. Newman, Drug delivery to the lungs: Challenges and opportunities, Ther. Deliv. 8 (2017) 647–661. https://doi.org/10.4155/tde-2017-0037.

[12] P. Sharma, M. Mehta, D.S. Dhanjal, S. Kaur, G. Gupta, H. Singh, L. Thangavelu, S. Rajeshkumar, M. Tambuwala, H.A. Bakshi, D.K. Chellappan, K. Dua, S. Satija, Emerging trends in the novel drug delivery approaches for the treatment of lung cancer, Chem. Biol. Interact. 309 (2019). https://doi.org/10.1016/j.cbi.2019.06.033.

[13] M. Hamidi, A. Azadi, P. Rafiei, Hydrogel nanoparticles in drug delivery, Adv. Drug Deliv. Rev. 60 (2008) 1638–1649. https://doi.org/10.1016/j.addr.2008.08.002.

[14] J.D. Ã, The Role of GABA, 494 (2006) 477–494. https://doi.org/10.1002/ddr.

[15] M. Arruebo, R. Fernández-pacheco, M.R. Ibarra, J. Santamaría, Magnetic nanoparticles Controlled release of drugs from nanostructured functional materials , 2 (2007) 22–32.

[16] M. Namdeo, S. Saxena, R. Tankhiwale, M. Bajpai, Y.M. Mohan, S.K. Bajpai, Magnetic nanoparticles for drug delivery applications, J. Nanosci. Nanotechnol. 8 (2008) 3247–3271. https://doi.org/10.1166/jnn.2008.399.

[17] J. Jacob, J.T. Haponiuk, S. Thomas, S. Gopi, Biopolymer based nanomaterials in drug delivery systems: A review, Mater. Today Chem. 9 (2018) 43–55. https://doi.org/10.1016/j.mtchem.2018.05.002.

[18] N. Ahmad, Rasagiline-encapsulated chitosan-coated PLGA nanoparticles targeted to the brain in the treatment of parkinson's disease, J. Liq. Chromatogr. Relat. Technol. 40 (2017) 677–690. https://doi.org/10.1080/10826076.2017.1343735.

[19] P. Blasi, S. Giovagnoli, A. Schoubben, M. Ricci, C. Rossi, Solid lipid nanoparticles for targeted brain drug delivery, Adv. Drug Deliv. Rev. 59 (2007) 454–477. https://doi.org/10.1016/j.addr.2007.04.011.

[20] C. Roney, P. Kulkarni, V. Arora, P. Antich, F. Bonte, A. Wu, N.N. Mallikarjuana, S. Manohar, H.F. Liang, A.R. Kulkarni, H.W. Sung, M. Sairam, T.M. Aminabhavi, Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease, J. Control. Release. 108 (2005) 193–214. https://doi.org/10.1016/j.jconrel.2005.07.024.

[21] V. Agrahari, A.K. Mitra, Therapeutic Delivery, Ther. Deliv. 7 (2016) 117–138.

[22] R. Callaghan, F. Luk, M. Bebawy, Special Section on Transporters in Toxicity and Disease — Commentary The Role of Transporters in Toxicity and Disease, Drug Metab Dispos. 42 (2014) 623–631.

[23] B. Haley, E. Frenkel, Nanoparticles for drug delivery in cancer treatment, 26 (2008) 57–64. https://doi.org/10.1016/j.urolonc.2007.03.015.

[24] Y. Yao, Y. Zhou, L. Liu, Y. Xu, Q. Chen, Y. Wang, S. Wu, Y. Deng, J. Zhang, A. Shao, Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance, 7 (2020) 1–14. https://doi.org/10.3389/fmolb.2020.00193.

[25] S. Siddique, J.C.L. Chow, applied sciences Gold Nanoparticles for Drug Delivery and Cancer Therapy, (2020).

[26] D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, 84 Nat nanotech 2007 R Langer Nanocarriers as an emerging platform for cancer therapy.pdf, Nat. Nanotechnol. 2 (2007) 751–760. https://doi.org/10.1038/nnano.2007.387.