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A Review On Nanostructure Drug Carriers for Treatment and Management of Neuroendocrine Cancer

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Abstract: Neuroendocrine (NE) cancer is a tumour that develops from neuroendocrine cells, which release hormones into the bloodstream and regulate body function. Neuroendocrine cancer can alter the normal function of neuroendocrine cells. Conventional therapies have limitations for treating Neuroendocrine cancer cells which arise the need for specific nanocarriers that can target and enable the drug release in a sustainable and controllable manner. Nanocarriers like dendrimers, carbon nanotubes, liposomes, gold nanoparticles, solid lipid nanoparticles, quantum dots, polymer nanoparticles, magnetic nanoparticles, and hybrid nanoparticles have spatial and temporal delivery ability. Nanomaterial used in nanocarriers plays a vital role in the release rate of the drug, specific targeting, diagnostic purpose, and prolongation time. Besides, the specific targeting potential of nanocarriers leads to diminished side effects. Additionally, surface-modified nanomaterials may offer better antitumour effects in neuroendocrine cancer therapy. Hence, nanocarriers can be effectively employed for the management of neuroendocrine cancer with specific targeting and minimal side effects compared to conventional therapy. Recently, there has been a lot of concern about the creation of cancer nanotherapeutics. Cancer nanotherapeutics have circumvented a number of the drawbacks of conventional medicines, including poor water solubility, nonspecific biodistribution, and restricted bioavailability. The main building blocks of nanotherapeutics are nanoparticles with tailored size and surface properties that are intended to either passively or actively transport anti-cancer medications to tumour cells. The present study overviews current developments in cancer therapeutics based on tumour-targeting delivery methodologies and nanoparticle drug delivery systems.

Keywords: Neuroendocrine Cancer, Nanomaterials, Gold Nanoparticles, Dendrimers, Liposomes.Tumour Targeting, Cancer Treatment, Nanoparticles.

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1. INTRODUCTION

Cancer has different types like major carcinoma, sarcoma, melanoma, lymphoma, and leukaemia. Neuroendocrine (ne) cancer falls in the category of carcinoma[1]. The term neuroendocrine is used when there is cancer-related to the nervous system and the endocrine system. In this system, the neural cells receive the signal via neurotransmitters and initiate the action by releasing hormones into the bloodstream[2]. Neuroendocrine cancers begin in these neuroendocrine cells only. The neuroendocrine cells have combined traits of hormone-producing cells and nerve cells[3]. These types of cancers are rare and found in any part of the body. The most affected organs are the small intestine, appendix, pulmonarysystem, rectum, and pancreas[4]. There are many types of ne tumours (figure 1).The study and use of materials with a nanometerscale enable the detection, eradication, and prevention of illness. Its uses include biological devices and nanometer-scaled electrical biosensors, as well as nanomaterials used in medicinal applications. Nanoparticles are the essential elements of nanomedicine and have drawn a lot of attention as prospective medicine delivery systems for the detection and treatment of cancer. 1-3 submicron-sized (100–1,000 nm) particles, systems, or devices, such as liposomes, viruses, and even inorganic materials, can be used to create nanoparticles that are used as drug delivery systems. For example polymers (such as polymeric nanoparticles, vesicles, micelles, or dendrimers), and even viruses. Nanoparticles can boost the concentration within cells of drugs in cancerous cells without causing harm to healthy cells by employing passive or active targeting TECHNIQUES. ALTHOUGH nanoparticles are potential drug delivery systems, there are still some issues with their practical implementation, including theirinstability in circulation, poor oral bioavailability, and toxicity[5]nanoparticle drug delivery systems continue to be a viable option for cancer treatment despite all the issues with nanomedicine. Systems with carefully regulated functionalities and material qualities have been developed with a lot of effort. For better cancer diagnosis and therapy, we will highlight recent developments in the creation of innovative nanoparticle systems with great sensitivity to tumour microenvironments in this review. We will also discuss combination nanoparticle-assisted cancer therapies[6].

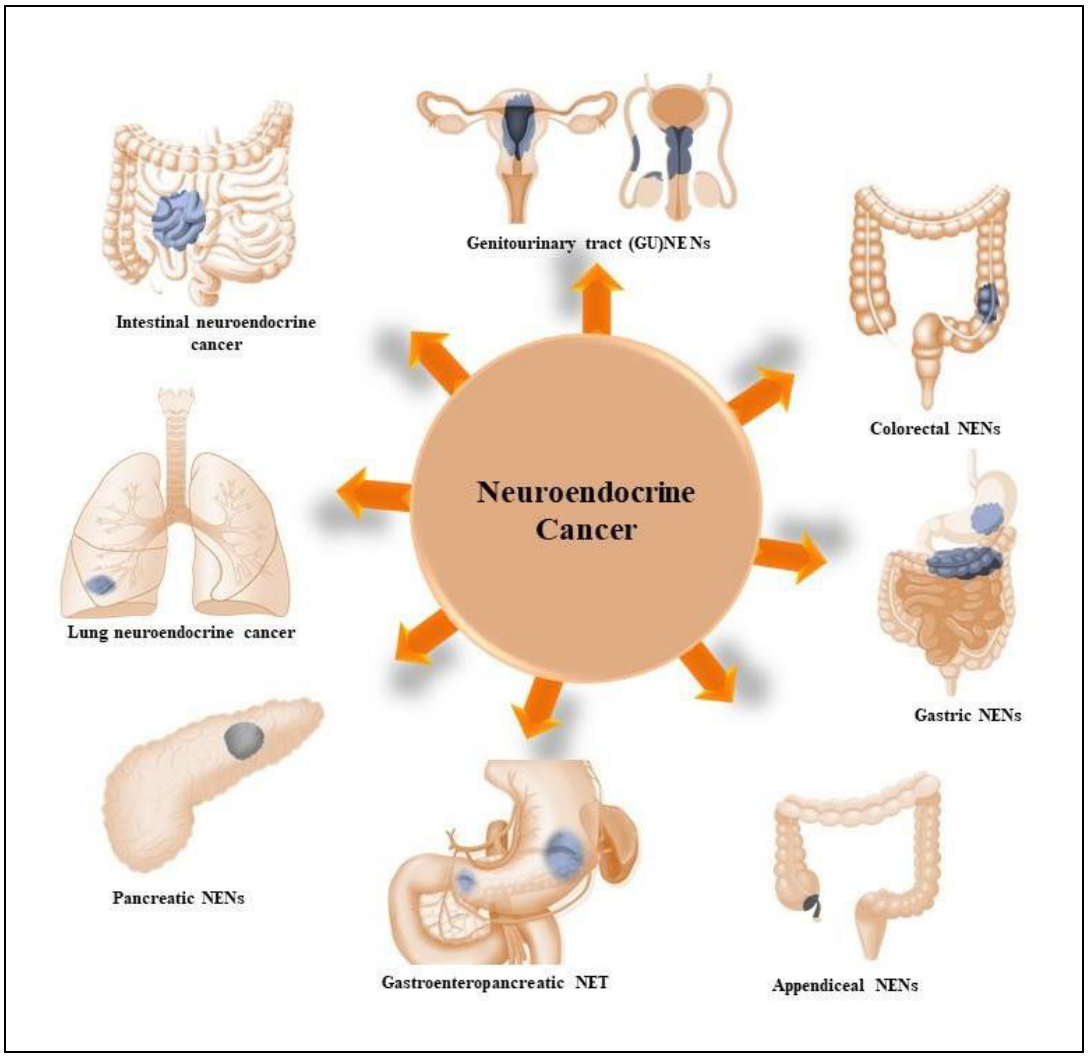

Fig: 1: various types of neuroendocrine tumors

1.1 NANOTECHNOLOGY IN MEDICINE

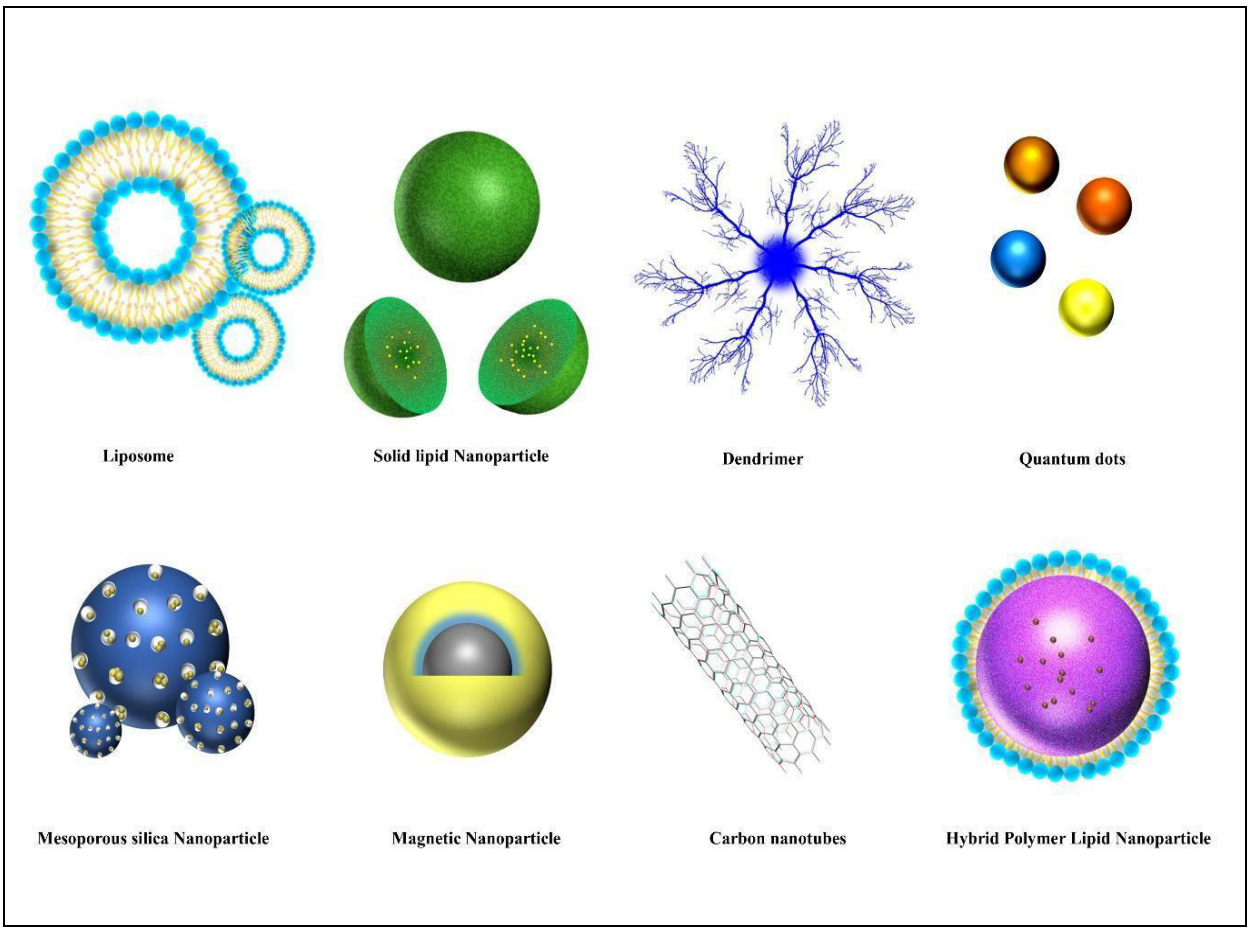

Fig 2: The general structure of different nanocarriers a) Liposomes b) Solid lipid nanoparticles c) Dendrimers d) Quantum dots e) Silica nanoparticles f) Magnetic nanoparticles g) Carbon nanotubes h) Hybrid nanoparticles

Nanoparticles have been the top priority for drug delivery in treating cancer. The main problem associated with conventional chemotherapy in the clinical management of any type of cancer is the development of multidrug resistance, poor bioavailability of drugs, high drug dose requirement, numerous side effects of the drug itself, low TI (Therapeutic indices), and no-specific targeting. To overcome these limitations of chemotherapy, Nanocarrier drug delivery has been developed by researchers. There are many added advantages of this modern technology like improved pharmacokinetics of the poorly soluble hydrophobic drugs, site-specific drug delivery, reduced dosage frequency, improved drug stability as well as biocompatibility, enhanced drug permeability, retention effect, and reduced side-effects. In addition, Nanocarrier formulations are capable of increasing the safety, the ADME profiles, the bioavailability and hence improving the efficacy of drugs. The nanocarriers are further classified into three main classes: Organic (Lipid, Polymer-based& Dendrimers), In-Organic (Gold NP, Carbon nanotubes, Silica Np, Magnetic NP, Quantum NPS), and hybrid (Lipid-polymer, Organic-inorganic, Cell membrane coated) nanocarriers[5].

1.2 DRUGS USED IN THE NEUROENDOCRINE CANCER

The innovative ADC (antibody-drug conjugate) has been effectively used to treat neuroendocrine tumours (NETs)[6]. The systemic treatment options for neuroendocrine tumours include biotherapy with somatostatin analogues and interferon-Ą as well as a targeted molecular therapy with Everolimus, and Sunitinib[7,8]. Lanreotide is a cyclic octapeptide auto gel (lanreotide ATG) (sustained-release (SR) aqueous formulation) that is administered subcutaneously and is a synthetic analogue of somatostatin approved by EMA & FDA regulatory bodies for well-to moderately differentiated, locally advanced, or metastatic gastro-enteric and pancreatic NETs [9,10]. Irinotecan and platinum agent[11] are indicated for neuroendocrine carcinomas, whereas Docetaxel and Cisplatin are used for Androgen Independent Prostate Cancer [12].

1.3 Nanocarriers in NEC

Nanocarriers act as transporters for therapeutically active drugs to the various parts of the body depending upon the properties of the material used in the formation of nanocarriers and the specific tissue of the body involved. Various nanocarriers with different properties have been explored for neuroendocrine cancers in figure2.

1.4 Liposomes and solid lipid nanoparticles (SLNP)

Liposomes are made up of naturally occurring phospholipid-based amphipathic nanocarriers[13]. Liposomes are made up of two layers viz lipid layer on the outer side and a core containing hydrophilic/ lipophilic drugs. Liposomes are further classified as multi-lamellar and unilamellar vesicles

based on the number of lipid layers 14,15. Different methods like Bangham, Reverse phase Evaporation, Solvent injection, Detergent dialysis, and conventional methods prepare liposomes. The size of liposomes ranges from 25 nm to 2.5 μ m and consists of 1 or more bi-layer membranes. The liposome has many disadvantages like high manufacturing cost, low drug loading capacity, low stability and rapid degradation [16]. The added advantage of lipid-based NPs is the easy uptake of drug-containing lipid molecules by the cells because of the outer lipid bilayer. SLNPs (Solid lipid nanoparticles) are colloidal particles prepared from biodegradable physiological lipids having the property of remaining in a solid state at body and room temperature and are thus harmless for usage. The SLNPs range from size 50 to 1000 nm based on the manufacturing method and the type of formulation required for it[17-22]. The disadvantage associated with SLNPs is the removal of the encapsulated drug during storage and the low capacity of drug loading [23]. The advantages of SLNPs are that they are manufactured without organic solvents, are biocompatible, are composed of biodegradable ingredients, and have decreased side effects on the GI tract. It acts by reaching normal and malignant cells using copper influx transporter control for its entry into the cytoplasm and releases Cytochrome C that induces the apoptosome formation and activation of procaspase-9, leading to apoptosis [24].

1.5 Dendrimer

Dendrimers are defined as perfectly monodispersed and enormously-branched three-dimensional (3D) macromolecules. Dendrimers are made up of the repetitive structure of monomers like poly-l-lysine, polyamidoamine (PAMAM) and poly-propylene imine (PPI)[25]. The high-density surface group are characteristic of dendrimers for their functions, and the internal spaces of dendrimers are used to encapsulate guest drug molecules. Some unique characteristics of dendrimers in clinical applications are site-specific targeting, enhanced drug solubility, and a reproducible pharmacokinetic (ADME) profile. The best example of a commercially available dendrimer is poly-amidoamine (PAMAM) which is widely used and studied for biological applications [23]. There are some disadvantages of dendrimers like their associated cytotoxic and hemolytic properties due to being non-degradable in the physiological environment. However, the cytotoxicity can be reduced with treatment with surfactants like PEG-2000[26]. The mechanism of action involves crossing the plasma membrane, entrapping by the endosome-like structures, the relocation into the mitochondria along with related overproduction of ROS, release of Cytochrome C and caspase activation, and apoptosis[24].

1.6 Carbon nanotubes

Carbon nanotubes(CNTs) are made up of materials like nanodiamonds, sheets of graphene, reduced graphene oxides, and graphene oxide in the form of a honeycomb structure. The CNTs are morphologically described as fixed geometry cylinders with different sizes ranging from nm to μm. They are classified as single− walled & multi-walled CNTs. The CNTs are produced using the arc discharge technique, laser ablation method, and chemical vapour deposition method. The single-walled CNTs measure around 0.4 nm to 2.0 nm and the multi-walled CNT measure greater than 100 nm. The main disadvantages of CNTs are their hydrophobic nature and limited aqueous solubility. Interestingly, CNTs allow maximum drug loading on the inner core or the surface, ligand conjugation, thermal ablation, and easy cellular uptake. The surface-modified CNTs are taken up inside the cells by different phenomena like phagocytosis and endocytosis. The various factors like surface functions, dimensions, and cell type determine the rate of uptake of CNTs into the cells[27]. The mechanism involves hyperthermia followed by MWCNTs-PEG laser treatment and NIR activation pathway, which leads to free radical flux generation within a cell resulting in cellular damage due to an oxidative state by mitochondrial depolarization in pancreatic cells leading to apoptosis[24].

1.7 Quantum dots

Quantum dots are made up of discrete materials like germanium and silicon and composite semiconductors like Lead selenide, cadmium selenide, and Cadmium telluride[28]. Semiconductor nanoparticles or QDs (Quantum dots) have attracted many researchers because of their unique magnetic, photophysical & optical properties, which are used in diagnosing and treating cancer. QDs have the advantages of being stable, water-soluble, non-bleaching, having good drug loading capacity, having controlled drug release features, better pharmacokinetic properties, and bio-distribution of the conjugated drug. However, many cancer drugs have limitations due to insolubility, poor absorption & aggregation, which can be conquered by conjugating the drug with QDs. The Optoelectronic properties of QDs depend on their size and shape. Larger-sized QDs with a radius ranging from 5–6 nm will emit red or orange colored light, while the smaller-sized QDs with a diameter of 4–6 nm will emit blue and green colored lights.QDs are widely used in cancer image sensing & other medicinal applications[11]. The notable disadvantages include inherent material toxicity and size-based toxicity [29,30]. The mechanism of Doxorubicin quantum dots preparation consists of using PEG or any Hyaluronic acid (HA). The hyaluronic acid molecule binds to NH2-ZnO quantum dots for specific target cells with HA receptor CD4. Doxorubicin covalently binds to Zn to form a Zn- DOX chelate. Doxorubicin acts by forming a complex with DNA by forming interactions between base pairs and inhibits Topoisomerases II activity by stabilizing the DNA-Topoisomerases II complex finally leading to apoptosis[30].

1.8 Gold nanoparticles

Gold nanocarrier is synthesized by reacting hydrogen tetrachloroaurate (HAuCl4) and citric acid in hot water. Citric acid is used as a reducing and stabilizing agent in the reaction[31]. AuNPs (Gold nanoparticles) are small 1-100 nm gold particles that can be dispersed and are called colloidal gold. The importance of AuNPs in biological sciences is increasing because of their low reactivity and toxicity, high biocompatibility, optoelectronic property, large surface-volume ratio, and susceptibility to modification[26]. AuNPs are used for advanced diagnostics, imaging, and biomedical therapeutics. The limitation of GNPs includes size and shape uniformity and complex biocompatibility. The mechanism of action of gold nanoparticles involves cellular uptake of the Au-NPs by Endocytosis into the cell, and their entry into mitochondria, thereby causing structural and functional damage that results in the disruption of the electron

transport chain. The damage caused to the mitochondria leads to respiratory chain damage, ROS generation, and induction of oxidative stress resulting in apoptosis [32,33]

1.9 Silica NPs (SNPs)

Silica nanoparticles are prepared from the condensation reaction of silane in which silicon and oxygen form an amorphous porous network-like structure[34]. SNPs have good pharmacokinetic properties, stability, and efficacy and are hence significant drug carriers. Various techniques synthesize SNPs whose size ranges from 10-500 nm each having different shape and surface properties. The Stober process is mainly used for the preparation of SNP[32]. They are a choice of material because of many properties like the appropriate size of silica particles, volume, surface area, morphology, and pore size in drug carriers. Their large internal volume enables them to carry large volumes of drugs, biomolecules, and probes in the core for diagnostic and therapeutic applications[35-37]. SNPs act by redox response mechanism mediated by generation of ROS species and cellular damage, for example, the surface-modified SNPs like disulfide bond peptide grafting in Doxorubicin. Due to the high level of Glutathione in the cancer cells, disulfide bonds get dissolved and drug molecules are released causing apoptosis[38].

1.10 Magnetic NPs

Magnetic nanocarriers are made up of materials like metal, metal oxide, and nanoalloys like iron, nickel, cobalt, etc. These materials are combined with other metals like zinc, barium, strontium, and copper[39]. These MNPs (Magnetic nanoparticles) are one of the effectively used classes of nanoparticles developed by magnetic field manipulation. MNPs are used for drug delivery of metal oxide or metal. The stability of MNPs is increased by surface modification technology, including their coating with fatty acids and different grades of polymers. MNPs are used for treating cancer, chemotherapy and gene therapy. NPs of Iron oxide have magnetic properties and thus have promising clinical, therapeutic, and diagnostic applications[40,41]. MNPs are prepared by thermal decomposition, co-precipitation, sonochemical, micro/nanoemulsion, solvothermal, microwave-assisted, and combustion methods. The MNPs work on the principle of super magnetic properties in the nano-size range. This makes it possible for MNPs to change their polarity a hundred thousand times per second, generating heat ranging from a temperature of 41°C to 47°C, leading to apoptosis of tumour cells[42].

1.11 Hybrid NPs

The hybrid nanocarriers comprise organic and inorganic materials such as metal oxide, graphene, silica, carbon nanotube material, and synthetic, natural biocompatible polymers. This material is blended with phospholipids, lipids, and proteins to get a final structure[43]. A concept of hybrid NPs arises, when the organic and inorganic NPs are developed together to get a hybrid species with multiple advantages[44]. One of the tested hybrid NP is a lipid-polymer consisting of a polymeric core inside and a lipid layer that has been effectively used for breast, pancreatic, and prostate cancers. To improve the therapeutic efficacy and other properties like biocompatibility of lipids and stability of polymer these hybrid concepts give the best results. By using this, both hydrophobic drugs and hydrophilic drugs can be effectively delivered at the site of action without degradation. Researchers developed the Liposome-silica hybrid nanoparticles utilizing the advantages of silica NPs core and lipid as a bilayer for their use in prostate and breast cancer[43]. The mechanism of action of Hybrid NPs involves the attachment of a lipid-coated polymer core to the cell membrane with a receptor on it. Degradation in the endolysosomes occurs due to these hybrid NPs causing membrane disruption by ROS that leads to apoptosis[45].

1.12 Nanoparticles used to target tumours (Cancerous Cells)

Nanoparticles' capacity to actively or passively accumulate in the targeted cells or tissues is the foundation for tumour-targeting medication delivery systems. When passive targeting is used, nanoparticles are built to go through leaking vessels and the distinct intra-organ pressures of tumors. Through the chemical identification of surface-bound ligands, active targeting uses nanoparticles to attach to specific cellular structures in malignancies. By avoiding nonspecific cell absorption and immunological clearance, the nanoparticles and medications they carry preferentially accumulate in the tissues and tumour cells that are being targeted. Some methods to target cancerous cells are discussed below

1.13 EPR effect (Enhanced Permeability and Retention)

The EPR effect is a feature that causes specific molecules, typically between 100 and 1,000 nm, to concentrate in tumour tissues as opposed to healthy tissues preferentially. The foundation of tumour medication delivery is EPR-passive targeting. We can increase the EPR effect of tumour-targeting by inducing tumour vasodilation, lowering lymphocytes, and prolonging circulation time[46]An illustration of this is Mundra et al.[47]covalently conjugated indocyanine green (ICG)-NH2 to the pendant carboxyl groups of poly (ethylene glycol)-block-poly(2-methyl-2-carboxyl-propylene carbonate) copolymer via coupling with a carbodiimide. The system self-assembles into micelles with high ICG loading and particle sizes between 30 and 50 nm. The NIR-irradiated ICG-conjugated micelles exhibit increased therapeutic efficacy with full tumour regression in an A375 human melanoma tumour model in athymic nude mice compared to the control ICG solution.

1.14 pH impact

The aberrant protein regulation and metabolism of tumour tissues create an acidic microenvironment to encourage the growth of tumour cells. In tumor-targeted administration, this pH anomaly is frequently used as an advantage[48]. An illustration of this is Doxorubicin (DOX) loaded P(Asp-g-Im)-PEG micelles (DPHAIM, Figure 3) were created by Lee et al.[49] for the weakly acidic tumour microenvironment. The copolymer P(Aspg-Im)-PEG may load up to 28% DOX using ethylene glycol as the hydrophilic group and aspartic acid imidazole as the hydrophobic group. The microspheres are protonated and disintegrated in the tumour microenvironment's acidic pH 7 conditions, releasing targeted DOX delivery with little harm.[50]

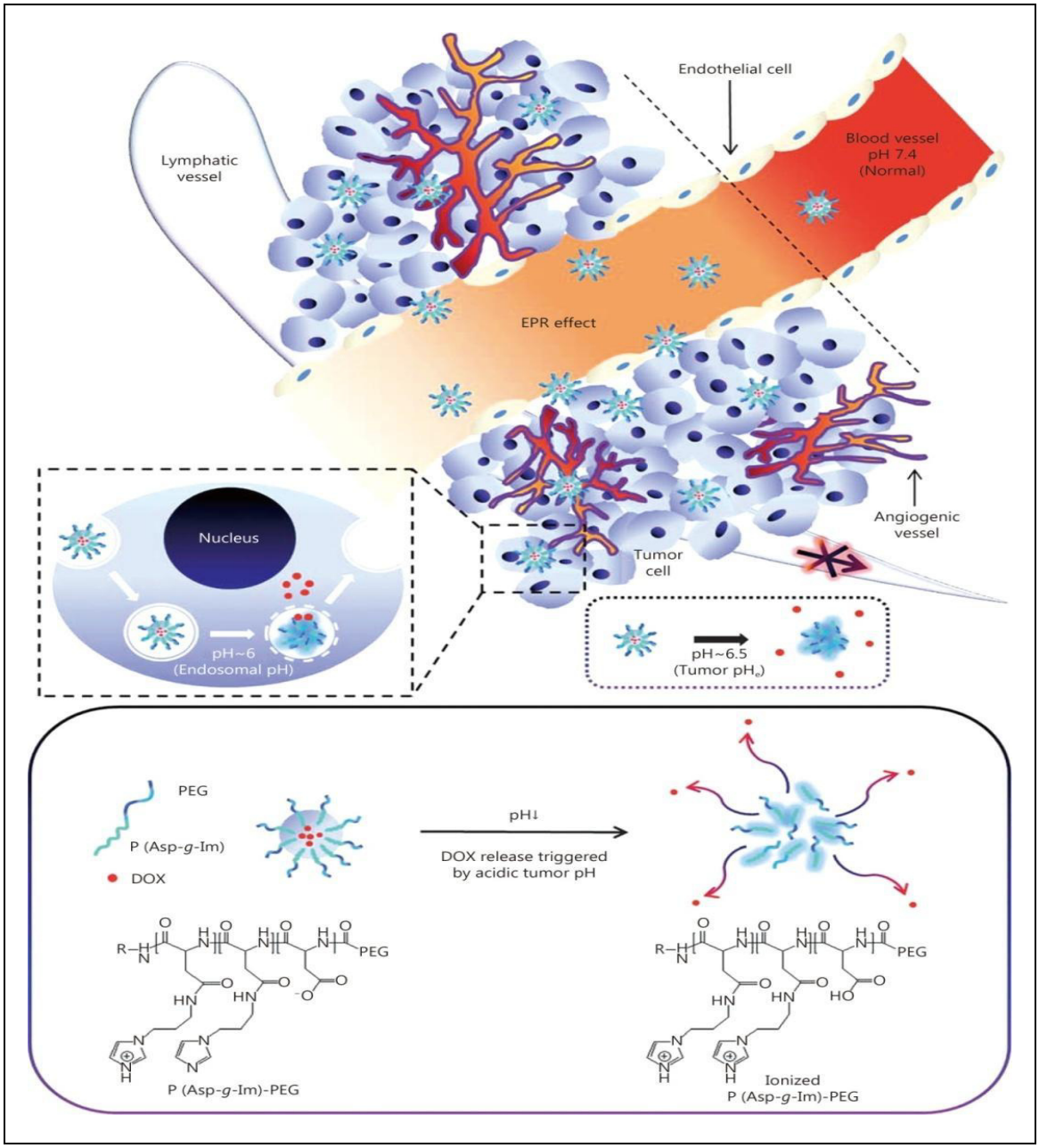

Fig 3: Schematic for the proposed *in vivo* behaviour of DPHAIM. [53]

1.15 Immune reaction

Similar to how enzymes are uniquely identified and related to one another, antigens and antibodies can be used to construct active targeted drug delivery. Ding et al.[51] achieved tailored medication delivery by using the precise interaction between a receptor and a ligand. To create the composite immune nanoparticle DTIC NP-DR5 mAb, the authors combined immune nanoparticles carrying kappa oxazine (DTIC) and the death receptor 5 monoclonal antibody (DR5 mAb). The monoclonal antibody's specificity and the body's DR5 recognition effect cause the drug-loading nanoparticles to aggregate in tumour cells. This system is also a nice illustration of combining immunotherapy with chemotherapy. Most importantly, DTIC-NP-DR5 mAb demonstrated considerably higher cytotoxicity and cell death in malignant melanoma cells that were DR5-positive compared to ordinary DTIC-NPs.To create drug delivery vehicles with superior targeting efficiency than linear RGD micelles, Saraf et al.[52] developed cyclic Arg-Gly-Asp (RGD) micelles. This increased targeting effectiveness is related to the micelles' kinetic stability and minimal drug solubilization. The study's findings demonstrated the value of self-assembling, low-molecular-weight RGD amphiphiles for the precise delivery of paclitaxel (PTX).

2. CONCLUSION

Nanomedicine, which combines medicine and nanotechnology to create drugs with increased safety and efficacy for human beings, is now one of the most important and sophisticated fields of cancer research. Many types of nanomaterials were used in the biomedical area in the previous decade, particularly for cancer diagnosis and treatment. Formulations of nanotechnology achieve good versatility and have the ability to target cancerous cells. The nanomaterial drug carriers can be structured and adjusted for site-specific chemotherapy, thermotherapy, photodynamic therapy, and radiation therapy. Despite the numerous advantages of metal-based nanoparticles, poisoning remains a major concern. Nanotoxicological concerns must also be addressed to produce more effective cancer therapy

techniques.The present review presented the neuroendocrine tumours, which are heterogeneously arising from various anatomical sites of the body. This incidence has increased in recent years, and limited research is available for therapy. The present review deals with neuroendocrine tumours, and their types, and mainly focuses on the nanocarriers used for the management and treatment of neuroendocrine tumours with their benefits as compared to conventional therapy. Future studies will aid in elucidating the cellular and molecular mechanisms which can distinguish healthy cells from sick cells, paving the way for the development of high performance.

3. AUTHORS CONTRIBUTION STATEMENT

Avhipsha Kar conceptualised and designed the study and Dr Gaurav Agarwal curated the data and prepared the original draft. Dr Shilpi Agarwal discussed the methodology and analyzed the data Avhipsha Kar and Dr Gaurav Agarwal provided valuable inputs towards designing the menu script. All authors read and approved the final version of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

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5. CONFLICT OF INTEREST

Conflict of interest declared none.

6. REFERENCES

1. Juliano R. Nanomedicine: is the wave cresting? Nat Rev Drug Discov. 2013;12(3):171-2. doi: 10.1038/nrd3958, PMID 23449291.
2. Bourzac K. Nanotechnology: carrying drugs. Nature. 2012;491(7425):S58-60. doi: 10.1038/491S58a, PMID 23320289.
3. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res. 2008;14(5):1310-6. doi: 10.1158/1078-0432.CCR-07-1441, PMID 18316549.
4. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3(2):133-49. doi: 10.2147/IJN.S596, PMID 18686775.
5. Ruponen M, Honkakoski P, Rönkkö S, Pelkonen J, Tammi M, Urtti A. Extracellular and intracellular barriers in non-viral gene delivery. J Control Release. 2003;93(2):213-7. doi: 10.1016/j.jconrel.2003.08.004, PMID 14636726.
6. Yang SY, Zheng Y, Chen JY, Zhang QY, Zhao D, Han DE, et al. Comprehensive study of cationic liposomes composed of DC-Chol and cholesterol with different mole ratios for gene transfection. Colloids Surf B Biointerfaces. 2013;101:6-13. doi: 10.1016/j.colsurfb.2012.05.032, PMID 22789783.
7. Ito I, Ji L, Tanaka F, Saito Y, Gopalan B, Branch CD, et al. Liposomal vector mediated delivery of the 3p FUS1 gene demonstrates potent antitumor activity against human lung cancer in vivo. Cancer Gene Ther. 2004;11(11):733-9. doi: 10.1038/sj.cgt.7700756, PMID 15486560.
8. Lu C, Stewart DJ, Lee JJ, Ji L, Ramesh R, Jayachandran G, et al. Phase I clinical trial of systemically administered TUSC2(FUS1)-nanoparticles mediating functional gene transfer in humans. PLOS ONE. 2012;7(4):e34833. doi: 10.1371/journal.pone.0034833, PMID 22558101.
9. Suzuki R, Namai E, Oda Y, Nishiie N, Otake S, Koshima R, et al. Cancer gene therapy by IL-12 gene delivery using liposomal bubbles and tumoral ultrasound exposure. J Control Release. 2010;142(2):245-50. doi: 10.1016/j.jconrel.2009.10.027, PMID 19883708.
10. Negishi Y, Hamano N, Tsunoda Y, Oda Y, Choijamts B, Endo-Takahashi Y, et al. AG73-modified bubble liposomes for targeted ultrasound imaging of tumor neovasculature. Biomaterials. 2013;34(2):501-7. doi: 10.1016/j.biomaterials.2012.09.056, PMID 23088840.
11. Liu J, Ma H, Wei T, Liang XJ. CO2 gas induced drug release from pH-sensitive liposome to circumvent doxorubicin resistant cells. Chem Commun (Camb). 2012;48(40):4869-71. doi: 10.1039/c2cc31697h, PMID 22498879.
12. Karanth H, Murthy RS. pH-sensitive liposomes—principle and application in cancer therapy. J Pharm Pharmacol. 2007;59(4):469-83. doi: 10.1211/jpp.59.4.0001, PMID 17430630.
13. Gao ZG, Lee DH, Kim DI, Bae YH. Doxorubicin loaded pH-sensitive micelle targeting acidic extracellular pH of human ovarian A2780 tumor in mice. J Drug Target. 2005;13(7):391-7. doi: 10.1080/10611860500376741, PMID 16308207.
14. Mo R, Sun Q, Li N, Zhang C. Intracellular delivery and antitumor effects of pH-sensitive liposomes based on zwitterionic oligopeptide lipids. Biomaterials. 2013;34(11):2773-86. doi: 10.1016/j.biomaterials.2013.01.030, PMID 23352118.
15. Banerjee S, Sen K, Pal TK, Guha SK. Poly(styrene-co-maleic acid)-based pH-sensitive liposomes mediate cytosolic delivery of drugs for enhanced cancer chemotherapy. Int J Pharm. 2012;436(1-2):786-97. doi: 10.1016/j.ijpharm.2012.07.059, PMID 22884831.
16. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013;12(11):991-1003. doi: 10.1038/nmat3776, PMID 24150417.
17. Parveen S, Sahoo SK. Polymeric nanoparticles for cancer therapy. J Drug Target. 2008;16(2):108-23. doi: 10.1080/10611860701794353, PMID 18274932.
18. Mora-Huertas CE, Fessi H, Elaissari A. Polymer-based nanocapsules for drug delivery. Int J Pharm. 2010;385(1-2):113-42. doi: 10.1016/j.ijpharm.2009.10.018, PMID 19825408.
19. Petros RA, DeSimone JM. Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov. 2010;9(8):615-27. doi: 10.1038/nrd2591, PMID 20616808.
20. Pridgen EM, Langer R, Farokhzad OC. Biodegradable, polymeric nanoparticle delivery systems for cancer

therapy. Nanomedicine (Lond). 2007;2(5):669-80. doi: 10.2217/17435889.2.5.669, PMID 17976029.
21. Stinchcombe TE. Nanoparticle albumin-bound paclitaxel: a novel Cremphor-EL-free formulation of paclitaxel. Nanomedicine (Lond). 2007;2(4):415-23. doi: 10.2217/17435889.2.4.415, PMID 17716129.
22. Dosio F, Arpicco S, Brusa P, Stella B, Cattel L. Poly(ethylene glycol)-human serum albumin-paclitaxel conjugates: preparation, characterization and pharmacokinetics. J Control Release. 2001;76(1-2):107-17. doi: 10.1016/S0168-3659(01)00420-5, PMID 11532317.
23. Schluep T, Hwang J, Cheng J, Heidel JD, Bartlett DW, Hollister B, et al. Preclinical efficacy of the camptothecin-polymer conjugate IT-101 in multiple cancer models. Clin Cancer Res. 2006;12(5):1606-14. doi: 10.1158/1078-0432.CCR-05-1566, PMID 16533788.
24. Gaur S, Chen L, Yen T, Wang Y, Zhou B, Davis M, et al. Preclinical study of the cyclodextrin-polymer conjugate of camptothecin CRLX101 for the treatment of gastric cancer. Nanomedicine. 2012;8(5):721-30. doi: 10.1016/j.nano.2011.09.007, PMID 22033079.
25. Ding HM, Ma YQ. Controlling cellular uptake of nanoparticles with pH-sensitive polymers. Sci Rep. 2013;3:2804. doi: 10.1038/srep02804, PMID 24076598.
26. Vivek R, Nipun Babu V, Thangam R, Subramanian KS, Kannan S. pH-responsive drug delivery of chitosan nanoparticles as tamoxifen carriers for effective anti-tumor activity in breast cancer cells. Colloids Surf B Biointerfaces. 2013;111:117-23. doi: 10.1016/j.colsurfb.2013.05.018, PMID 23787278.
27. Kemp MM, Linhardt RJ. Heparin-based nanoparticles. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2010;2(1):77-87. doi: 10.1002/wnan.68, PMID 20049832.
28. Wang Y, Xin D, Liu K, Zhu M, Xiang J. Heparin-paclitaxel conjugates as drug delivery system: synthesis, self-assembly property, drug release, and antitumor activity. Bioconjug Chem. 2009;20(12):2214-21. doi: 10.1021/bc8003809, PMID 19950889.
29. Wang Y, Wang Y, Xiang J, Yao K. Target-specific cellular uptake of Taxol-loaded heparin-PEG-folate nanoparticles. Biomacromolecules. 2010;11(12):3531-8. doi: 10.1021/bm101013s, PMID 21086982.
30. Tan Q, Tang H, Hu J, Hu Y, Zhou X, Tao Y, et al. Controlled release of chitosan/heparin nanoparticle-delivered VEGF enhances regeneration of decellularized tissue-engineered scaffolds. Int J Nanomedicine. 2011;6:929-42. doi: 10.2147/IJN.S18753, PMID 21720505.
31. Kemp MM, Kumar A, Mousa S, Dyskin E, Yalcin M, Ajayan P, et al. Gold and silver nanoparticles conjugated with heparin derivative possess anti-angiogenesis properties. Nanotechnology. 2009;20(45):455104. doi: 10.1088/0957-4484/20/45/455104, PMID 19822927.
32. Yuk SH, Oh KS, Cho SH, Lee BS, Kim SY, Kwak BK, et al. Glycol chitosan/heparin immobilized iron oxide nanoparticles with a tumor-targeting characteristic for magnetic resonance imaging. Biomacromolecules. 2011;12(6):2335-43. doi: 10.1021/bm200413a, PMID 21506550.
33. Li L, Huh KM, Lee Y, Kim SY. Biofunctional self-assembled nanoparticles of folate–PEG–heparin/PBLA copolymers for targeted delivery of doxorubicin. J Mater Chem. 2011;21(39):15288-97. doi: 10.1039/c1jm11944c.
34. Li L, Huh KM, Lee YK, Kim SY. Design of a multifunctional heparin-based nanoparticle system for anticancer drug delivery. Macromol Res. 2010;18(2):153-61. doi: 10.1007/s13233-009-0134-8.
35. She W, Li N, Luo K, Guo C, Wang G, Geng Y, et al. Dendronized heparin-doxorubicin conjugate based nanoparticle as pH-responsive drug delivery system for cancer therapy. Biomaterials. 2013;34(9):2252-64. doi: 10.1016/j.biomaterials.2012.12.017, PMID 23298778.
36. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. Nanomedicine (Lond). 2010;5(4):523-8. doi: 10.2217/nnm.10.23, PMID 20528447.
37. Chen Y, Lian G, Liao C, Wang W, Zeng L, Qian C et al. Characterization of polyethylene glycol-grafted polyethylenimine and superparamagnetic iron oxide nanoparticles (PEG-g-PEI-SPION) as an MRI-visible vector for siRNA delivery in gastric cancer in vitro and in vivo. J Gastroenterol. 2013;48(7):809-21. doi: 10.1007/s00535-012-0713-x, PMID 23179610.
38. Shen Y, Tang H, Zhan Y, Van Kirk EA, Murdoch WJ. Degradable poly(beta-amino ester) nanoparticles for cancer cytoplasmic drug delivery. Nanomedicine. 2009;5(2):192-201. doi: 10.1016/j.nano.2008.09.003, PMID 19223244.
39. Kaul G, Amiji M. Biodistribution and targeting potential of poly(ethylene glycol)-modified gelatin nanoparticles in subcutaneous murine tumor model. J Drug Target. 2004;12(9-10):585-91. doi: 10.1080/10611860400013451, PMID 15621684.
40. Van Vlerken LE, Vyas TK, Amiji MM. Poly(ethylene glycol)-modified nanocarriers for tumor-targeted and intracellular delivery. Pharm Res. 2007;24(8):1405-14. doi: 10.1007/s11095-007-9284-6, PMID 17393074.
41. Choi KY, Min KH, Yoon HY, Kim K, Park JH, Kwon IC, et al. Pegylation of hyaluronic acid nanoparticles improves tumor targetability in vivo. Biomaterials. 2011;32(7):1880-9. doi: 10.1016/j.biomaterials.2010.11.010, PMID 21159377.
42. Dubey N, Varshney R, Shukla J, Ganeshpurkar A, Hazari PP, Bandopadhaya GP, et al. Synthesis and evaluation of biodegradable PCL/PEG nanoparticles for neuroendocrine tumor targeted delivery of somatostatin analog. Drug Deliv. 2012;19(3):132-42. doi: 10.3109/10717544.2012.657718, PMID 22428685.
43. Kawano K, Maitani Y. Effects of polyethylene glycol spacer length and ligand density on folate receptor targeting of liposomal doxorubicin in vitro. J Drug Deliv. 2011;2011:160967. doi: 10.1155/2011/160967, PMID 21490746.
44. Chen J, Li S, Shen Q, He H, Zhang Y. Enhanced cellular uptake of folic acid-conjugated PLGA-PEG nanoparticles loaded with vincristine sulfate in human breast cancer. Drug Dev Ind Pharm. 2011;37(11):1339-46. doi: 10.3109/03639045.2011.575162, PMID 21524153.

45. Dixit V, Van den Bossche J, Sherman DM, Thompson DH, Andres RP. Synthesis and grafting of thioctic acid-PEG-folate conjugates onto Au nanoparticles for selective targeting of folate receptor-positive tumor cells. Bioconjug Chem. 2006;17(3):603-9. doi: 10.1021/bc050335b, PMID 16704197.
46. Park JH, Gu L, Von Maltzahn G, Ruoslahti E, Bhatia SN, Sailor MJ. Biodegradable luminescent porous silicon nanoparticles for in vivo applications. Nat Mater. 2009 Apr;8(4):331-6. doi: 10.1038/nmat2398, PMID 19234444.
47. Mundra V, Peng Y, Rana S, Natarajan A, Mahato RI. Micellar formulation of indocyanine green for phototherapy of melanoma. J Control Release. 2015 Dec 28;220(A):130-40. doi: 10.1016/j.jconrel.2015.10.029, PMID 26482083.
48. Yu P, Yu H, Guo C, Cui Z, Chen X, Yin Q et al. Reversal of doxorubicin resistance in breast cancer by mitochondria-targeted pH-responsive micelles. Acta Biomater. 2015 Mar 1;14:115-24. doi: 10.1016/j.actbio.2014.12.001, PMID 25498306.
49. Lee ES, Kim JH, Sim T, Youn YS, Lee BJ, Oh YT et al. A feasibility study of a pH sensitive nanomedicine using doxorubicin loaded poly (aspartic acid-graft-imidazole)-block-poly (ethylene glycol) micelles. J Mater Chem B. 2014;2(9):1152-9. doi: 10.1039/c3tb21379j, PMID 32261351.
50. Talelli M, Iman M, Varkouhi AK, Rijcken CJ, Schiffelers RM, Etrych T et al. Core-crosslinked polymeric micelles with controlled release of covalently entrapped doxorubicin. Biomaterials. 2010 Oct 1;31(30):7797-804. doi: 10.1016/j.biomaterials.2010.07.005, PMID 20673684.
51. Ding B, Zhang W, Wu X, Wang J, Xie C, Huang X et al. DR5 mAb-conjugated, DTIC-loaded immuno-nanoparticles effectively and specifically kill malignant melanoma cells in vivo. Oncotarget. 2016 Aug 8;7(35):57160-70. doi: 10.18632/oncotarget.11014, PMID 27494835.
52. Saraf P, Li X, Wrischnik L, Jasti B. In vitro and in vivo efficacy of self-assembling RGD peptide amphiphiles for targeted delivery of paclitaxel. Pharm Res. 2015 Sep;32(9):3087-101. doi: 10.1007/s11095-015-1689-z, PMID 26063045.
53. Cancer biology and medicine [Cited 2017 Aug 17]Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5570600