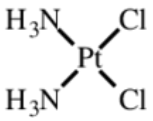
Nanocarriers for enhanced drug delivery of platinum anti-cancer complexes



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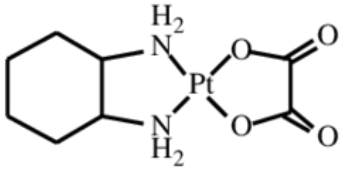

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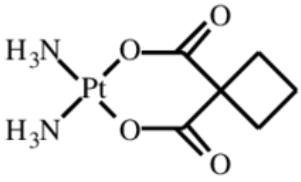

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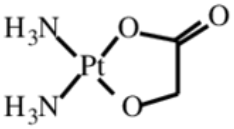

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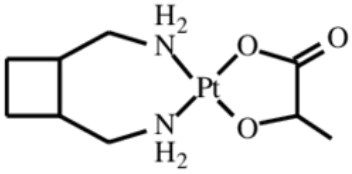

lobaplatin

Umar Sultan, Shahan Khan, Peter Comer, Kaysa Sekhavati and Charles Higgins

Contents

Introduction

Cancer remains a significant global health challenge, resulting in nearly 10 million deaths in 2020.[1] Platinum based complexes are among some of the most potent anti-cancer drugs and have made significant advances in the last few decades.[2]

From the introduction of cisplatin [3], which is effective against: leukaemia, lymphomas, breast, testicular, ovarian, and cervical cancers [4] to the use of recently synthesised alternative platinum complexes that have shown anti-cancer potency [5], it is apparent that there is still a need for additional research and advancements in the field to make these drugs as effective as possible.

Whilst platinum complexes are highly effective anti-cancer drugs, they also cause multiple side effects on noncancerous cells. These include nausea, neuropathy (nerve disease),

ototoxic effects (inner ear damage), myelosuppression (bone marrow suppression), and nephrotoxicity (kidney damage). Out of these, nephrotoxicity is the most harmful side effect and directly limits the dosage of platinum drugs during cancer therapy.[6]

Nanocarriers can reduce these side effects of platinum based anti-cancer drugs due to the EPR (Enhanced Permeability and Retention) effect which involves the passive accumulation of nano-sized particles in tumour tissues, thus reaching a high concentration. This effect is exploited by anticancer drugs, significantly improving their targeting and effectiveness while minimising side effects. Furthermore, the EPR effect prolongs the plasma half-life of nano-size drugs, allowing them to circulate in the bloodstream for an extended period, resulting in prolonged therapeutic effects.[7]

The aim for this project is to discuss and compare the modern nanocarrier formulations used for platinum based anti-cancer complexes to determine which nanocarriers have the potential to advance cancer therapeutics further. We will specifically discuss the drug delivery of several types of treatment, the mechanisms involved with each drug, and why they are effective or ineffective.

The article begins by highlighting the chemical mechanisms that underlies the effectiveness of platinum-based cancer medicines using cisplatin as a literature example. The discussion moves forward to look at organic nanocarriers ranging from liposomes to dendrimers and the effect of surface functionalisation on their effectiveness. Following this, inorganic nanocarriers are discussed and their role in drug delivery systems, using gold and iron oxide nanoparticles as examples, are evaluated. Subsequently, the articles transitions into a discussion regarding hybrid nanocarriers with a specific focus on carbon nanotubes and polysilsesquioxane (PSQ) nanoparticles.

The review concludes by providing a comprehensive analysis of each drug delivery system to determine which may have potential for further oncological research.

Mechanism of Platinum Drugs

Cisplatin

As this review will explore anti-cancer agents that are based on platinum. It is crucial to understand the mechanisms behind these complexes to appreciate and comprehend how nanocarriers can enhance their efficacy. To illustrate these concepts, we will focus on one of the pioneering anticancer drugs: cisplatin, as an example. However, many platinum-based anti-cancer drugs work by a similar mechanism (Fig.1).

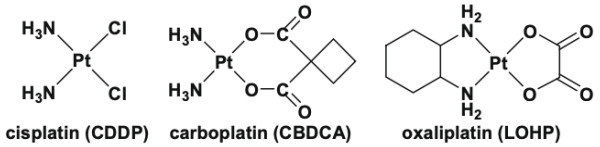

Fig. 1 – Diagram of different platinum based anti-cancer drugs.[8]

Cisplatin is a well-known platinum anticancer agent (cis-diamminedichloroplatinum (II)). This metal complex has undergone extensive research and is extremely effective, though it does have some side effects. Its therapeutic properties result from the formation of a macro chelate with two adjacent guanines in a (Deoxyribonucleic acid) DNA chain: [9] they form intra and inter-strand cross-links to N7 sites on purine base pairs of the DNA, unwinding the strands sufficiently to allow recognition by cellular proteins and leading to apoptosis, thus inhibiting cell replication. However, cisplatin must go through the activation process before any of these interactions could take place. The conformation of DNA bound to cisplatin is generated in low (chloride) Cl- intracellular space environments by replacing one Cl- ligand with a water ligand, which makes subsequent interactions with DNA simpler. Following this modification, cisplatin is ready to bind to DNA.[10,11]

Organic Nanocarriers

Liposomes

Liposomes are bi-layered vesicles made up of layers of amphiphilic molecules such as phospholipids. They have both inner and outer hydrophilic layers with a hydrophobic lipid layer in between. This structure allows liposomes to encapsulate both hydrophilic and hydrophobic drugs in the aqueous layer or lipid bilayer respectively. Liposomes were one of the first effective delivery systems for drugs.[12]

There are many liposomal carrier drugs that have been approved which show high potency against a variety of cancers such as Doxil™, Onivyde™, and Marqibo®.[13]

Regarding platinum liposome carriers, among the most popular is Lipoplatin (LIPO) which is a polyethylene glycol (PEG)-coated, liposomal cisplatin formulation held inside a unilamellar (single bi-layer) vesicle. LIPO has a nanoparticle size of 110 nm. A recent in vivo study on mice showed that LIPO treatment showed a significantly less lethal effect on healthy tissue and higher cytotoxicity against tumour tissue when compared to free cisplatin which confirms the effectiveness of the drug in reducing the inherent limitations of free cisplatin.[14]

Liposomes also increase efficacy in alternative platinum drugs. Q. Zhou et al. synthesised three alternative platinum anti-cancer complexes to cisplatin:

[PtCl(L2) (ACRAMTU)] $(NO_3)_2$ (where ACRAMTU = 1-[2-(acridin-9-ylamino) ethyl]-1,3-dimethylthiourea).

(**1**) PT-(en)-ACRAMTU, L2 = ethane-1,2-diamine (en)

(**2**) PT-(dach)-ACRAMTU, L2 = (1*R*,2*R*)-1,2-diaminocyclohexane (dach)

(**3**) PT-(pda-OH)-ACRAMTU, L2 = 2-hydroxy-1,3-propanediamine (pda-OH)

Out of these complexes, (**3**) showed the most anti-cancer potency. However, all three complexes were limited in their water solubility, which affects their delivery. Therefore, (**3**) was encapsulated into phosphatide liposomes and the surface was functionalized by addition of phospholipids which enhanced the stability of the liposomes (Fig.2).

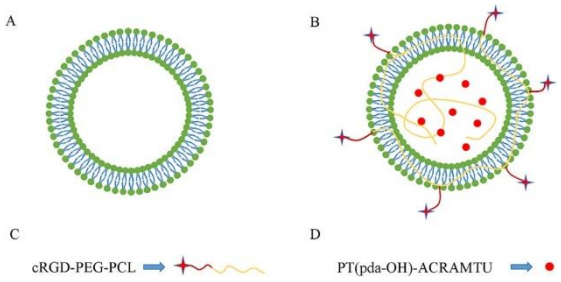

Fig. 2 – (A) Pure phosphatide liposomes; (B) Full nanoparticle formulation; (C) Added phospholipids; (D) Complex (**3**). Reused from reference [15].

The encapsulated complex (**3**) showed a size of 97nm and was stable for up to four weeks with only slight changes in nanoparticle size. The pH and temperature triggered, release of the liposomes showed that the release of the Pt

drug was steerable and that the release rate was fast under pH and temperature conditions for tumour tissue but slow for normal tissues.[15] This study therefore confirms the ability of phosphatide liposome carriers to improve drug release of platinum cancer complexes alternative to cisplatin and also gives evidence that surface functionalization of the liposome leads to further stabilisation of the nanoparticle formulation. However, it is important to note that the cancer potency of the drug is also dependent on the specific complex used and not the nature of the liposome.

As useful as liposomal platinum formulations are in drug delivery, they still have major limitations due to their low lipophilicity and low water solubility, this leads to inefficient encapsulation of the complex and therefore low drug/lipid ratio which causes a less potent drug and increases chances of resistance. On the other hand, if the liposomes affinity to the platinum complex is very favourable it can permanently deactivate the drug and prevent release of the platinum complex in the tumour environment.[16]

Liposomal drug delivery is an ever changing and progressing field. Very recent advances in liposome drug delivery use thermo-responsive liposomes (TLs). N. K. Sedky et al. synthesised TLs loaded with the platinum drug asplatin (Asp) and studied the effectiveness of the drug against the invasive triple-negative breast cancer cell line compared to free Asp. The Asp/TLs were prepared by the thin film approach using a blend of heat sensitive phospholipids:

(**1**) [1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC)

(**2**) 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*- [maleimide (polyethylene glycol)-2000] (ammonium salt) (DSPE-PEG-2000)]

The Asp/TLs were optimized using the Box-Behnken design. The synthesised formulations were characterised by UV-vis and transmission electron microscopy (TEM), and all showed nanoscale, spherical sizes, high entrapment efficiency and a low polydispersity index (PDI), meaning the formulations were all similar molecular weights. Mild local hyperthermia (38-42°C) caused the Asp/TLs to change state from solid gel to liquid causing the Asp to be released at the tumour cells. Optimal release of Asp was seen at 40°C and showed higher cytotoxicity against the tumour compared to free Asp.[17]

This study effectively improves liposomal drug delivery of platinum complexes by changing the properties of the phospholipids used to form the liposomes allowing for alternative techniques to improve targeting.

Overall, liposomal nanocarriers for platinum complexes are a promising field and show evidence of improved targeting, selectivity, release, and potency compared to the free drug. Drawbacks in these systems arise from low solubility however recent approaches have further stabilised and improved the effectiveness of these formulations using methods such as hyperthermia-induced targeting by use of TLs.

Micelles

Polymeric micelles are self-assembling structures formed from amphipathic block copolymers which traditionally form a hydrophobic core and hydrophilic shell which stabilises the micelle. They enhance drug delivery by encapsulating drugs in their core, or by coordinating the drug to their outer sphere.[18] Platinum micelle formulations will have hydrophilic cores and hydrophobic outer spheres because the ligands on platinum drugs are typically hydrophilic.

Platinum incorporated polymeric micelles improve the potency, targeting and selectivity of the drug compared to the free drug. H. Xiao et al. synthesised a platinum complex (Pt (IV)) consisting of a carboxylate functionalised axial ligand. This platinum complex coordinated to

the amino groups in the lysine residues of the amphipathic block copolymer (MPEG-b-PCL-b-PLL) and self-assembled into polymeric platinum pro-drug micelles (MPEG-b-PCL-b-PLL/Pt (IV)). Fluorescence tags (RhB) were also incorporated into the micelle for analysis (MPEG-b-PCL-b-PLL/RhB) (Fig.3).

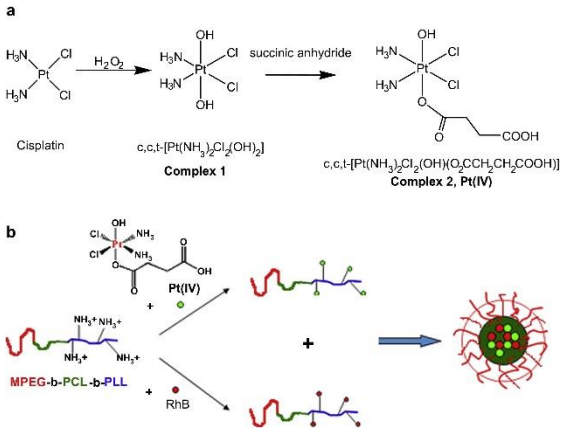

Fig. 3 – (a) Preparation of Pt (IV), (b) Schematic of micelle preparation of MPEG-b-PCL-b-PLL/Pt (IV) and MPEG-b-PCL-b-PLL/RhB. Reused from reference [19].

Using transmission electron microscopy (TEM), the micelles were shown to have spherical structures with an average diameter of 150-160 nm. Drug release experiments were carried out at a range of pH values and drug release was shown to be most efficient at pH = 5.0 which is the pH of the tumour environment. Based on drug release profiles and HPLC-MS measurements it was deduced that at the tumour environment, cisplatin was the predominantly released species. The same strategy of micelle synthesis was also applicable to carboplatin and oxaliplatin.[19] This study confirms the ability of polymeric micelles being used as an effective nanocarrier for a variety of platinum complexes. The self-assembled structures were stable and showed efficient encapsulation, transport and release of the pro-drug compared to the free platinum drug.

Current disadvantages in the use of micelles for drug delivery include the poor solubility of small-sized micelles, poor loading capacity, and poor physical stability in vivo; these limitations need to be overcome for micelle nanocarriers to be viable and approved drugs.[20]

Surface functionalisation of micelles can further improve targeting and selectivity of micelle platinum formulations. J Ahn et al. synthesised oxaliplatin containing polymeric micelles (DACHPt/m) and by tailoring the maleimide thiol surface density of the micelle, tissue factor (TF)-targeting Fab' antibodies were installed. The functionalised (anti-TF Fab'-DACHPt/m) and non-functionalised micelles anti-cancer behaviour was studies against pancreatic cancer cells in vitro/vivo.

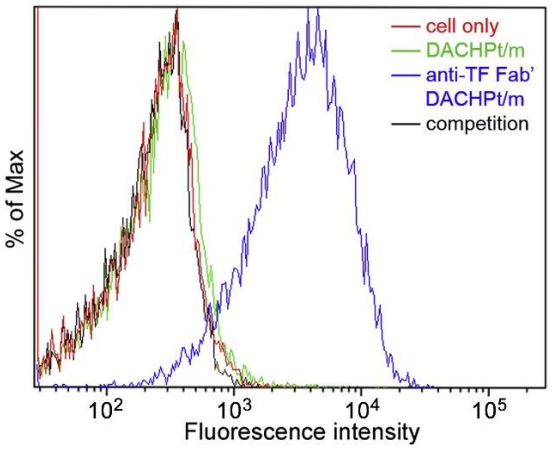

Fig. 4 – Binding of labelled DACHPt/m (green line) and anti-TF Fab'-DACHPt/m (blue line) against human pancreatic cancer BxPC3 cell. Competition experiments on BxPC3 cells (black line) were performed as well as a cell only control line (red line). Reused from reference [21].

In vitro fluorescence labelling experiments on BxPC3 pancreatic cells showed a 15-fold increase in tumour binding by anti-TF Fab'-DACHPt/m and a more rapid binding by anti-TF Fab'-DACHPt/m seen from shift in fluorescence intensities (Fig.4).

In vivo analysis of anti-TF Fab'-DACHPt/m in mice showed a supressed tumour growth deduced by the negligible weight loss in treated mice suggesting enhanced anti-tumour efficacy without damaging the parent micelle or causing substantial change in micellular size.[21]

This paper shows that surface functionalisation of micelles with antibodies can further improve the anti-tumour behaviour of platinum drugs and cause more favourable and rapid

interactions between the drug and tumour cells. Also, the integration of new chemistry into micelle formation suggests that improvements in the future are possible in this field.

Overall, micelle nanocarriers effectively improve the drug release of platinum drugs due to their pH dependent release. Surface functionalisation of micellular formulations can improve the cytotoxicity of the platinum complexes due to more favourable tumour binding when integrated with antibodies. Drawbacks in the use of micelle nanocarriers arise from poor physical stability, solubility (depending on size) and loading capacity.

Dendrimers

Dendrimers were originally created as a wonder molecule of chemistry due to their symmetry and tree-like image. Now the polymers are commonly used in drug delivery as they have many advantages such as increased solubility, more stability, better storage, more efficient transport, and greater permeability. There are two vital ways that dendrimers are employed, the formulation approach and the nano-construct approach. For the formulation approach, the desired drugs are locked inside a dendrimer using non-covalent interactions. The nano-construct approach uses covalent bonds to attach the dendrimers to the drugs.[22]

Dendrimers are uniform and well-defined of size and shape. They have 3 main sections: the core; the branches; the end groups. The core and the branches make up the physical structure of the molecule, whereas the end groups influence the dendrimers essential features such as solubility and toxicity. The size of the hyperbranched polymers also changes the configuration. Lower generation dendrimers tend to be open and not clearly defined, whereas their higher generation counterparts can form a spherical conformation, which can encapsulate the therapeutic agents.[23]

Dendrimers are radially symmetric, nanoscale molecules with a well-defined, homogenous, almost monodisperse branches or arms that resemble trees. They have space in their core to fit small molecules or drugs.[24]

Dendrimer platinum conjugates have been shown to increase the potency of platinum drugs meaning higher cytotoxicity towards certain tumour cells. N. S. Sommerfield et al. synthesised an unsymmetrically carboxylated platinum (Pt (IV)) analogue of oxaliplatin and coupled it to generation two (G-2) and four (G-4) polyamidoamine (PAMAM) dendrimers (Fig.5). The free Pt (IV) loaded dendrimers (Pt (IV)/G-2 and Pt (IV)/G-4) and unloaded dendrimers were characterised by NMR spectroscopy and HPLC-MS and in vitro cytotoxic experiments were undergone to analyse their anti-tumour activity against ovarian (CH1/PA-1), colon (SW480), and lung (A549) cell lines. The Pt (IV) free drug showed moderate anti-tumour activity however Pt (IV)/G-2 and Pt (IV)/G-4 showed significant increases in cytotoxicity with IC_{50} values in the nanomolar (nM) range. It is important to mention that G-2 and G-4 also showed moderate anti-tumour activity in absence of any Pt (IV) drug. Using ICP-MS it was determined that the loading of Pt (IV)/G-2 and Pt (IV)/G-4 were 38% and 34% respectively and attempts to increase these values were unsuccessful.[25]

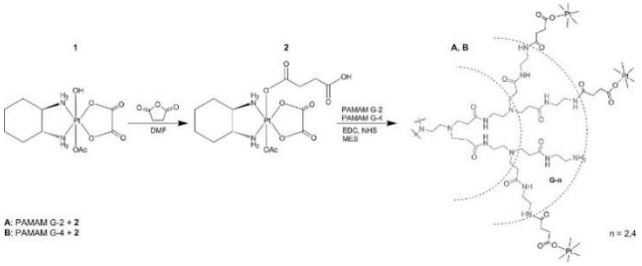

Fig. 5 – Synthesis of the platinum (IV) complexes **1** and **2** (Pt (IV)) and the dendrimer–platinum conjugates **A** and **B** (Pt (IV)/G-2 and Pt (IV)/G-4). Reused from reference [25].

This study confirms the advantageous effects in potency of platinum drugs by loading into dendrimer molecules. The dendrimer molecules having inherent anti-tumour activity also enhances the cytotoxic effect and points to

a promising future in the use of platinum dendrimer conjugates as anti-cancer drugs. However, room for improvement is paramount due to the low loading efficiency.

Inorganic Nanocarriers

Gold

Gold nanoparticles (GNPs) are small, ranging from 1 to 100 nanometres; they have become versatile tools with many applications over a wide range of fields over the last couple of decades. Many methods can be used to synthesise them; the most common method is the "Turkevich Frens" approach which involves the reduction of (tetrachloroaurate ions) $AuCl_4^-$ in an aqueous environment with a high concentration of citrate ions (sodium citrate).[26,27]

By leveraging their unique properties, GNPs have been found to serve as promising drug delivery carriers. Because of their chemical inertness, non-toxicity, and non-immunogenicity, they are ideal for drug release delivery platforms. They also come in a range of shapes such as: nanoparticles, nanorods, nanospheres and nanocages.[28] In addition to this, they are simple to synthesise and functionalise which further enhances their applicability.

A study in 2010 conducted by Sarah Brown et. al explored the efficacy of platinum-based anticancer drugs, specifically oxaliplatin, when tethered to GNPs (Fig.6). Lung epithelial and colon cancer cells were exposed to oxaliplatin-tethered GNPs at different concentrations for a prolonged period, after which the uptake of oxaliplatin-tethered gold nanoparticles by cells were evaluated through an in vitro assay.

The study revealed a significant increase in the cytotoxicity of oxaliplatin when tethered to a GNP than oxaliplatin alone in the cancer cells. In addition to this, they found it had the ability to penetrate lung cancer cells. The potential disadvantage discovered in this study was the unexpected 4.5-fold increase in the size of the GNPs when tethered with oxaliplatin which caused them to stick together/ aggregate; however, it was said that this issue could also think to be seen as an advantage as larger aggregated nanoparticles are more effective in targeting tumours, thus making them more selective. [29,30]

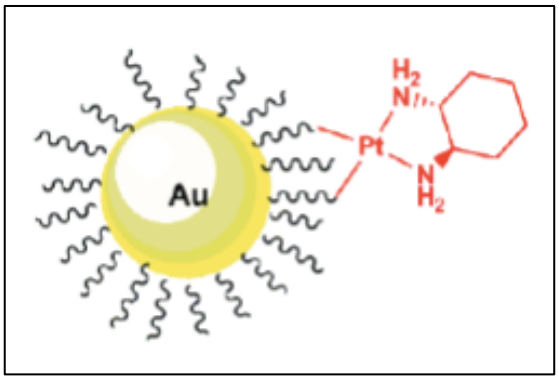

Fig. 6 – Platinum drug: oxaliplatin, bound to a gold nano particle, through coordination bonds to the platinum metal centre. Reused from reference [30]

This article displays the advantageous role of GNPs in enhancing delivery efficiency of platinum-based drugs by providing a pathway to minimise side effects (particularly their non-selectivity). It is important to note their size when tethered to platinum-based drugs; while at first was a challenge, its suggested that it can also be seen as an advantage in terms of improving their effectiveness in targeting tumours thus increasing selectivity and efficacy.

Photothermal therapy (PPT) is the use of electromagnetic radiation, usually near-infrared wavelengths (NIR), for the treatment of a variety of medical conditions.[31]

A recent study conducted by Shin-Yu et.al discovered that gold nanocarriers, in particular: gold nano-shells (GNSs) loaded with a platinum-based drug, were found to be well-suited in relation to chemo–PPT for the treatment of colorectal cancer. This is possible due to GNPs' unique tuneable optical properties which allow them to achieve strong absorption and scattering in the visible NIR region which ultimately leads to a localised temperature increase and the death of targeted cancerous cells in tumours

(hyperthermia and photothermal ablation upon NIR laser). As a result, they excel as photothermal therapy mediators.

Their findings supported that the GNSs exhibited controlled drug-releasing properties. GNSs on the micellar surface were also shown to have the ability to act as a diffusion barrier thus reducing premature drug release. The platinum-based drug was released only when under acidic conditions facilitated by the NIR laser.

Using platinum drug: Dichloro(1,2-Diaminocyclohexane) Platinum (II) (DACHPt), the study found that DACHPt-loaded GNSs (DACHPt@pGNSs) inhibited tumour growth significantly and more effectively than chemotherapy or photothermal therapy alone. This was because of the synergistic effects of platinum-based chemotherapy and photothermal therapy together. In addition to this, they were also found to have higher cytotoxicity in comparison to the free drug and PPT alone.

The researchers investigated DACHPt@pGNSs in a variety of experiments by looking at their photothermal properties, drug release properties, cellular uptake, and in vivo efficacy. Of particular interest is the in vivo efficacy, which was determined by monitoring treatment on tumour growth in mice; the results revealed high stability and intracellular accumulation as well as potent chemo-photothermal activity, all of which resulted in significant tumour suppression. The in vivo efficacy results best portray the effectiveness of the use of GNSs with platinum-based drugs to inhibit tumour growth and enhance their delivery (Fig.7).

From (Fig.7), it is observable that DACHPt@pGNS+NIR, pGNS+NIR, DACHPt@pGNS are more effective compared to free DACHPt. The tumour volumes treated with these three GNS complexes are consistently lower than those treated with DACHPt alone, especially with DACHPt@pGNS+NIR thus showing improved efficacy and delivery, further reinforcing the advantages of using GNPs. [32]

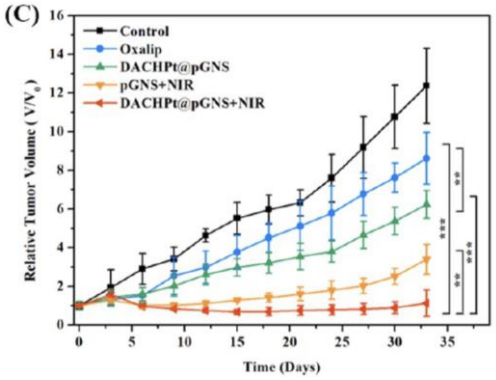

Fig. 7 – The in vivo Evaluation of Tumour Response Over Time: time-dependent changes in relative tumour volumes for different treatment groups. The graph compares the control group with those treated with Oxaliplatin, DACHPt@pGNS, pGNS+NIR, and DACHPt@pGNS+NIR. Each line represents the tumour response over the experimental period (approximately 36 days), providing a visual representation of the varying overall efficacies of the treatments. Reused from reference [32]

Overall, this study supports the critical role of GNPs in increasing the delivery effectiveness of platinum-based drugs. Incorporating GNPs in the form of GNSs was proven to not only reduce the concerns of non-selectivity but also double down on functionality by serving as mediators for photothermal therapy.

GNPs do face some challenges: they exhibit prolonged retention time which could impact optimal therapeutic application. Additionally, the cytotoxic nature could also pose a limitation in PTT as its effects may potentially extend beyond cancer cells.[33]

Despite these, the use of GNPs does show exciting and promising potential in advancing targeted cancer therapies.

Iron Oxide

Although there are multiple types of nanocarriers, a lot of them do not pose as many advantageous properties as iron oxide. Iron oxide has presented itself to be very versatile, biocompatible, and biodegradable it can also be used in combination therapy which is the coating of the surface for enhanced efficacy and delivery.[34]

In a study published in 2019 by A. Morovati et al. Iron oxide nanoparticles (IONPs) were coated with chitosan, which is a natural polymer derived from chitin, for use against breast cancer. These IONPs were synthesised via the use of eucalyptus leaf extracts as stabilising and reducing agents. Once coated with chitosan the IONPs were used against a line of breast cancer called MDA-MB-231. In this experiment the cell viability following administration of cisplatin-IONP-chitosan were compared with cisplatin-IONP and free cisplatin the findings of this experiment can be seen in (Fig.8).

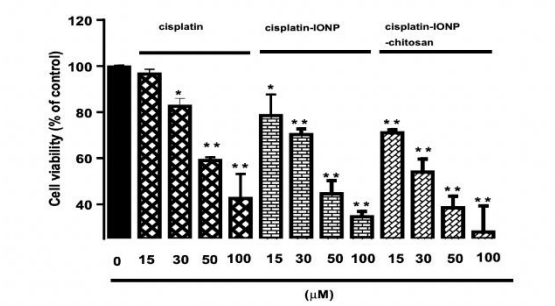

Fig. 8 – Cytotoxicity of free cisplatin, cisplatin-IONP and cisplatin IONP-chitosan in MDA-MB-231 cells treated with different concentrations of cisplatin, cisplatin-IONP and cisplatin IONPS-chitosan for 24h. Reused from reference [35].

This study is useful as it shows the effectiveness of cisplatin-IONPs as well as the effectiveness of cisplatin-IONP-chitosan. Cell viability refers to the ability of cells to stay alive and maintain their normal physiological functions, therefore low cell viability of cisplatin in MDA-MB-231 means that the drug was able to induce cytotoxic effects in the cancer cells. (Fig.8) shows that free cisplatin requires high doses to achieve low cell viability demonstrating the lack of potency of free cisplatin. Cisplatin-IONP increase the potency of cisplatin as shown in the graph however the surface coated IONP shows the most promise for further research as the study found it to have the lowest cell viability across doses.

Cisplatin can also induce apoptosis in cancer cells as it covalently binds with the DNA and creates crosslinks which disrupt the replication and transcription process. This leads to a series of events and this cellular stress which leads to apoptosis. This is useful as it aims to eliminate the cancer cells with minimal damage to healthy tissue. A. Morovati et al. repeated the experiment and measured the rate of apoptosis induced via the 3 cisplatin conjugates in MDA-MB-231. In this assay 30 μM of cisplatin, cisplatin-IONPs and cisplatin-IONPs-chitosan were applied to MDA-MB-231 cells for 24h. The results are given in (Fig. 9).

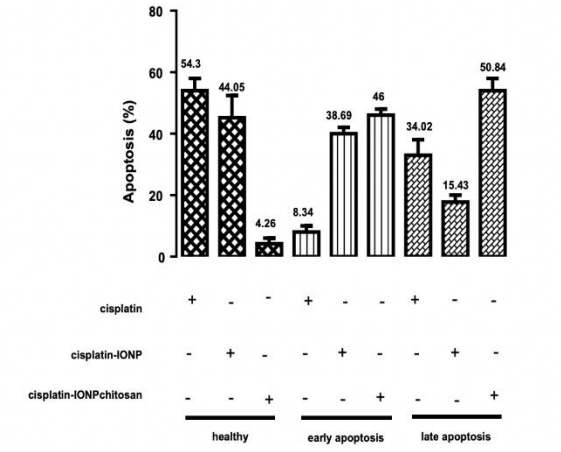

Fig. 9 – Rate of apoptosis induced via the cisplatin conjugates (cisplatin, cisplatin-IONP and cisplatin IONP-chitosan) Reused from reference [35].

Via flow cytometry analysis, the rate of apoptosis was 4.26% in the cells treated with cisplatin, 38.69% in the cells treated with cisplatin-IONPs and 46.33% in the cells treated with cisplatin-IONPs-chitosan after 24 h. This shows the significant impact of IONPs on cell apoptosis but also the increases efficacy of surface coated IONPs. [35,36]

This study is beneficial for this review article as it shows the success and high effectuality of cisplatin loaded IONPs on cancer cells. In addition to this the study highlights the lower doses required for optimal efficacy which would also reduce adverse side effects of high doses of cisplatin. Ultimately, composite systems such as cisplatin-IONPs-chitosan show a lot of potential for further research and further oncological research.

However, there are aspects which need further consideration such as the fact nanoparticles have shown greater deposition in the lung with inflammatory, oxidative, and cytotoxic effects.

There are also technological challenges too such as, scale-up synthesis, equal optimization, and performance predictions.[37]

Others

Cisplatin exposure has a significant fertility problem for childhood cancer and the presence of zinc oxide nanoparticles (ZnO-NPs) can moderate the negative effects of cisplatin associated with its exposure. In a very recent study in 2022, Eman T. Hamam et al. carried out an experiment to examine the effects of zinc oxide nanoparticles on cisplatin induced damage in the spermatogenesis initiation during puberty, this is the process of sperm cell development. In this experiment, 72 male rats aged 30-days, which are considered prepubertal at 37-days old, productive at 60 and fully adult at 90 days were examined after cisplatin induction. Groups treated with cisplatin induction showed increase in reactive oxygen species (ROS) which causes interreference with the blood-testis barrier (BTB). The study reports that following administration of ZnO-NPs to the cisplatin group the rats showed significant decrease in ROS and restoration of the BTB due to increase in mRNA and protein expression of Bcl-2, which is the protein responsible for regulation of apoptosis, in the 37-day old rats. In (Fig.10) we can see the significant increase in the protein expression of Bcl-2 when ZnO-NPs are applied across all ranges.[38] This highlights the effect of ZnO-NPs on the Bcl-2 expression and shows the potential ZnO-NPs have for oncology.

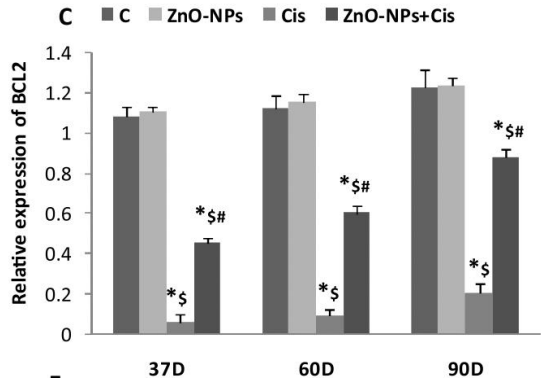

Fig. 10 – Relative expression of Bcl-2 protein following administration of ZnO-NPs + cis and control group. Reused from reference [38].

This study is beneficial as it shows the positive effects of ZnO-NPs on improving the treatment of childhood cancer. The data has shown that ZnO-NPs are able to increase Bcl-2 expression and thus better regulate the fertility problem that cisplatin induces during treatment of childhood malignancies.

Although this experiment reveals the anti-inflammatory effects of zinc oxide the study also refers to the need for further analysis to detect the presence of ZnO-NP in testicular tissue and a requirement to better understand the mechanism of how ZnO-NP restore spermatogenesis.

Ultimately, ZnO-NPs have potential and promise in paediatric and with appropriate research it can have a substantial impact on the fight against cancer.

The combination of magnetic nanoparticles with silica has shown potential in application for multifunctional thernostic systems. IONPs have been shown to have anti-cancer properties as previously explored and as previously mentioned the surface of these IONPs can be functionalised via various heteroatoms, here we explore the application of copper. Even though IONPs have been shown to be versatile and advantageous they still have variable oxidation states and result in dose dependent toxicity, silica supports are able to reduce such aggregation due to its known biocompatibility and abundance, silica is an exceptional candidate as a support. [39]

B. R. Jermy et al. synthesised $CuFe_2O_4$/monodispersed spherical hydrophilic silica (HYPS) and with the loading of cisplatin as an anti-cancer drug this was used in an experiment against a line of breast cancer, MCF-7. This was synthesised via the impregnation of $CuFe_2O_4$ into a matrix of HYPS through simple dry impregnation technique. Following this cisplatin was then loaded into the formulation via electrostatic adsorption over 24 h in a normal saline solution. The confirmation of the presence of $CuFe_2O_4$ on the HYPS was confirmed via powder X-ray diffraction. A schematic representation can be seen in (Fig.11).

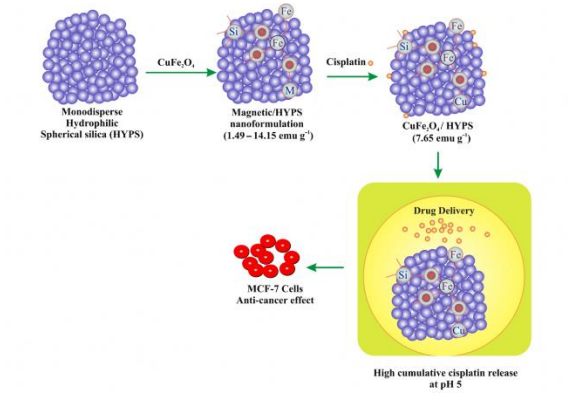

Fig. 11 – Representation of the synthesis of $CuFe_2O_4$/HYPS/Cisplatin. Reused from reference [40].

In vitro anti-cancer analysis carried out found that $CuFe_2O_4$ by itself as well as $CuFe_2O_4$/HYPS did not elicit a cytotoxic effect whereas $CuFe_2O_4$/HYPS/Cisplatin showed lower cell viability in a concentration dependent fashion, this can be seen in (Fig.12). The data shows that the highest dosage of $CuFe_2O_4$/HYPS/Cisplatin, 0.5mg/mL resulted in a 31.8% cell viability, whereas the lower dosage of free cisplatin, 0.0225mg/mL, produced a cell viability of 6%. [40]
This shows that the cytotoxic effects were due to the cisplatin being released from the nano-formulation. This also indicated the stronger potency of free cisplatin as compared to $CuFe_2O_4$/HYPS/Cisplatin synthesised.

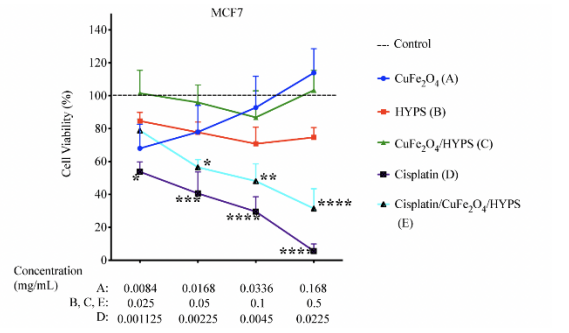

Fig. 12 – Percentage cell viability on MCF7 using different formulations: CuFe2O4 (A), HYPS (B), CuFe2O4/HYPS (C), cisplatin (D), and cisplatin/CuFe2O4/HYPS (E). Reused from reference [40].

This study is useful as it investigates and proves that cytotoxic effects can be induced via the use of these IONs coated with copper on a HYPS support and the inherent drawbacks of cisplatin can also be reduced via the HYPS support. Although the EC_{50}, may be lower for free cisplatin, meaning its more potent at lower concentrations, as compared to the $CuFe_2O_4$/HYPS/Cisplatin, the advantages of using $CuFe_2O_4$/HYPS/Cisplatin to prevent effects occurring in unintended areas outweighs this limitation. This is due to the $CuFe_2O_4$ providing a targeted delivery of these nanoparticles whereas the HYPS coating provides prevention of inadvertent effects that usually accompany free cisplatin administration.

Overall, this study shows a potential candidate for a multifunctional thernostic system for oncological applications using cisplatin as an anticancer agent.

Hybrids

Polysilsesquioxanes (PSQs)

PSQ platinum nanoparticles have a Pt (IV) metal centre which is used for a triggered delivery of cisplatin. PSQs are made of siloxane networks with organic or metal-organic bridging ligands (these bridging ligands carry the platinum cargo into the tumour cell). PSQs have only recently been prepared as nanomaterials for biomedical applications. The nanomaterials are synthesised using bis(tri-alkoxysilanes) ($(R'O)3\text{-}Si\text{-}R\text{-}Si\text{-}(OR')_3$) by sol-gel reactions.

During experimental research PSQ nanoparticles were found to have a Pt loading of 18-24% which gave an active agent loading of 35-47%. This is many a thousand times the drug loading of other known nanoparticle anti-cancer drugs formulation that delivers Pt (IV) drugs.

Release experiments have shown that PSQs are very stable in usual physiological conditions, only releasing 10% of its platinum cargo in 24 hours. With the addition of cysteine, an endogenous biomolecule, 30% of the platinum cargo was rapidly released followed by 80% over a prolonged period (2 days).

The effects of PSQs on tumour cells in female mice were compared with the effect of free oxaliplatin. The oxaliplatin had slightly inhibited the growth in the size of the tumours after 21 days. On the contrary, the PSQs tested, PEG-1 and APEG-1, showed a significantly large reduction in tumour growth. The tumour growth in the mice using the PSQs were 50% and 40% smaller than those of the untreated control mice.

The only stated negatives of using PSQ nanoparticles in anticancer treatment is that they are such a recent area of research we aren't truly sure of their true side effects or how efficacious they are. PSQs are showing a very high potential as being the next anti-cancer drug however they haven't even been tested on human cancer cells yet so there could be side effects that are unknown.[41]

Carbon Nanotubes (CNTs)

CNTs have great benefits in therapeutic agent delivery as they can undergo the EPR effect, and their needle-like shape allows them to penetrate the membranes of targeted cells effectively. Also, due to their high surface area to volume ratio, CNTs can have significantly large drug loading much like PSQs.

However, toxicity remains an issue in the biomedical applications of CNTs. Different studies have come out with varying results regarding their safety. Therefore, they are far from being used regularly in clinical settings. CNTs with non-functionalized hydrophobic surfaces and a high degree of residual heavy metal contamination from synthesis tend to cause toxicity. Heavy metal contamination can be fixed with purification and the surfaces of CNTs can be functionalised with organic molecules such as lipids to reduce these harmful effects.[42]

C. Tripisciano et al. synthesised an oxidised cisplatin Pt (IV) pro drug and contained it within single-walled CNTs (SWCNT). The SWCNT effectively coordinated and carried the prodrug to the tumour environment delivering a lethal dose to the cancerous environment causing an increase in potency compared to free cisplatin.[43] Therefore, this study provides evidence of the advantages in drug delivery of CNTs.

Conclusion

The purpose of this review was to collate and compare different nanocarrier (NC) methods for improving the delivery of platinum anti-cancer drugs. Throughout this review we have touched on organic NCs; liposomes, micelles, and dendrimers, which all show potential for effective drug delivery through their improvements in targeting and release. Liposomal formulations such as LIPO are already being used in a clinical setting. However, organic NCs have general solubility issues and dendrimer formulations possess poor loading issues. Inorganic NCs such as gold and iron oxide formulations introduce additional methods of improving targeting, using their inherent properties, such as photothermal therapy. Recent hybrid NCs show future potential for improving the drug delivery of platinum drugs. PSQs show the highest loading percentages of any NC. However, hybrid NCs are clinically untested, and ambiguity lies in their toxicity and side effects. Overall, inorganic NCs show the highest versatility and effectiveness of improving drug delivery of platinum drugs due to the depth of the field and the use of external techniques to further improve drug delivery. However, it is clear from the literature that advances in all fields are being regularly made by integrating new chemistry to further improve these methods.

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