Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: an overview

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ABSTRACT
Cisplatin cis-(diamine)dichloridoplatinum(II) (CDDP) is the first platinum-based complex approved by the food and drug administration (FDA) of the United States (US). Cisplatin is the first line chemotherapeutic agent used alone or combined with radiations or other anti-cancer agents for a broad range of cancers such as lung, head and neck. Aroplatin™, Lipoplatin™ and SPI-077 are PEGylated lipidosome-based nano-formulations that are still under clinical trials. They have many limitations, for example, poor aqueous solubility, drug resistance and toxicities, which can be overcome by encapsulating the cisplatin in Nemours nanocarriers. The extensive literature from different electronic databases covers the different nano-delivery systems that are developed for cisplatin. This review critically emphasizes on the recent advancement, development, innovations and updated literature reported for different carrier systems for CDDP.

Introduction
Nanomedicine is an emerging branch of nanotechnology that is mainly used for targeted delivery of anti-cancer drugs for numerous types of cancers [1]. Nanocarrier-based delivery of several anti-cancer drugs has gained more attention in the past decades because of its selective targeting, improved drug efficacy, lower systemic toxicity, cellular uptake and accumulation inside the tumour, particularly on the improvement of the enhanced permeability and retention (EPR) effect [2]. Meanwhile, nanotechnology is also used for cancer detection, biomedical imaging and disease monitoring [3]. The standardized definition of nanoparticles (NPs) is that it has a spherical shape whose size is considered one, two and three dimensions, having the diameter size of 1–100 nm [4]. Schematic illustration of various nanotechnology-based carriers is mentioned in Figure 1.

Michele Peyrone was the first person to discover the cisplatin, also known as the Peyrone’s salt, in 1845 [5]. Cisplatin, cis-(diamine)dichloridoplatinum (II) is the first platinum-based complex approved by the food and drug administration (FDA) US [6]. It is a simple inorganic molecule and a potent drug, which has a therapeutic effect against various types of tumours, for example, breast cancer, ovarian cancer, bladder cancer, cervix carcinoma, prostate carcinoma, endometrial cancer, head and neck cancer and lung cancer, including the non-small carcinoma of lung cancer (NSCLC) and small carcinoma of lung cancer (SCLC) carcinomas [7]. Cisplatin is also considered as an alternative therapy for the management of several solid tumors, including gastric, liver and brain carcinomas [8]. Several toxicities related to cisplatin were reported, including the sensory systems, ototoxicity, haematological and emetogenicity [9]. Some studies have also reported on the cisplatin-induced resistance to alter the drug transport, glutathione system, deoxyribonucleic acid (DNA) repair and apoptotic genes [10].

Current status of FDA-approved/under clinical trials CDDP nano-formulations
Many liposomal-based nano-formulations are at the stage of clinical trials. One of under clinical trials drugs, Lipoplatin (Regulon, Inc.), is liposome-based platinum formulation under Phase III clinical trials [11]. It contains a combination of cisplatin (9%) and lipids (91%(w/w)), including soy phosphatidylcholine (SPC-3), cholesterol, dipalmitoyl phosphatidyl glycerol (DPPG) and methoxy-PEG-distearoyl phosphatidyl
ethanolamine (mPEG2000-DSPE) [12]. Pre-clinical studies of Lipoplatin formulation have been performed on rats and mice, which showed less toxicity, particularly in view of the nephrotoxicity when in comparison to conventional cisplatin [13]. The European Medicines Agency (EMA) also declared the Lipoplatin as an orphan drug for the treatment of several cancers, such as pancreatic adenocarcinoma [14], NSCLC, HER2/neu negative metastatic breast cancer and advanced gastric cancer [15].

Another nanomedicine, SPI-77 (ALZA Pharmaceuticals, formerly known as the Sequus Pharmaceuticals) is under Phase II. This formulation contains stealth cisplatin-loaded liposomes and hydrogenated soy phosphatidylcholine, cholesterol and PEG-modified phosphatidylethanolamine. However, the safety result was reported under the Phase II trials for the treatment of non-small carcinoma of lung cancer (NSCLC) [16].

This formulation is at the final clinical stage, that is, Phase III, in Asia under the development name of NC-6004 (Nanoplatin; NanoCarrier Co., Ltd.; Japan). Phase I clinical studies demonstrated that the NC-6004 has significantly better tolerability, in contrast to cisplatin solution, without inducing significant nephrotoxicity [17]. Phase I study of these micelles started in 2012 for various solid tumours and applications for the Investigational New Drug (IND) that was submitted to the FDA in 2013, respectively [18]. Another nano-formulation Aroplatin™ (Aronex Pharmaceuticals) is registered under the orphan drug for the treatment of malignant mesothelioma from FDA US. Phase II had already been completed in 2002 for metastatic colorectal cancer and advanced solid tumours [19]. The summary of the nano-formulations of CDDP under these clinical trials is enlisted in Table 1.

**Nanocarrier-based approaches for CDDP**

**Polymeric CDDP based nanodrug delivery systems**

In recent decades, polymeric nanoparticles (PNPs) have attained considerable attention from scientists. The significant advantages of these biomaterials for drug delivery systems are their excellent biocompatibility, efficacy, bioavailability, most importantly, the simple elaboration, design and broad structural variety. Moreover, PNPs could be the ideal candidate for cancer therapy. One of the advantages of PNPs is their nanosize, which makes them able to penetrate and permit across the cell membrane, capillaries and barriers, while having the extended circulation in a different compartment of the body until they reach their targeting site [20]. The summary of cisplatin-loaded polymeric nanocarriers is given in Table 2.

**Polylactic-co-glycolic acid nanoparticles**

Poly (lactic-co-glycolic acid) (PLGA) is an emerging and potential biomaterial used as a nanocarrier in the drug delivery system and tissue engineering. Meanwhile, PLGA nanoparticles could be a great potential for imaging, drug
targeting and therapy. Moreover, PLGA undergoes complete biodegradation in an aqueous medium [21]. The PLGA nanoparticles have several advantages as compared with other nanocarriers in the drug delivery system. The PLGA is widely used in the preparation of PNP because of its properties such as biodegradability, biocompatibility, easy-to-functionalize, surface modification for improvement in the blood circulation and sustain the release effect. Most importantly, PLGA has already been approved by the FDA, as well as the European Medicine Agency for drug delivery systems such as the polymeric biomaterials [22].

Chunsha et al. have developed the cisplatin-loaded poly(L-glutamic acid)-g-methoxy poly(lactic-co-glycolic acid) nanoparticles (CDDP-NPs) for the management of non-small cell lung carcinoma (NSCLC). In vivo studies showed more suppression in the Lewis lung carcinoma (LLC) model. Anti-tumour efficacy and systemic toxicity were lower in cisplatin-loaded nanoparticles, in contrast to free cisplatin. The mechanism of releasing cisplatin from nanoparticles was typical manner of DNA crosslinking and reduced the toxicity of cisplatin by controlling the release of drug from nanocarrier [23]. Another research group has developed the multidrug resistance mutation 1 (MDR1), B-cell lymphoma 2 (BCL2) and small interfering RNA (siRNA) loaded PLGA-based nanoparticles. The CDDP encapsulated nanoparticles improved the apoptotic activity as compared free drug due to the maximum therapeutic effects achieved with folic acid (FA) conjugated around PLGA NPs [29]. Another study with the same method was reported to have up to 72% encapsulation efficiency. In vitro study was performed in mouse malignant cell line (EL4) and small carcinoma of lung cancer. The scanning electron microscopy (SEM), transmission electron microscopy (TEM) and drug release study were performed to characterize the nanoparticles. The CDDP encapsulated nanoparticles improved the apoptotic activity as compared free drug due to the maximum therapeutic effects achieved with folic acid (FA) conjugated around PLGA NPs [29]. Another study with the same method was reported to have up to 72% encapsulation efficiency. In vitro experiment results demonstrated a sustained release effect and dose-dependent efficacy against the IGROV1-CP cells. The releasing of the drug from PLGA nanoparticles reveals controlled release rate while maintaining the anti-cancer activity of CDDP [30].

**Polyethylene glycol (PEG) nanoparticles**

Polyethylene glycol (PEG) is a versatile polymer in the nano-drug delivery system. PEG has been accepted by the FDA-USA because of its unique characteristics and safety profile for human use [31].

Thermosensitive-based nanodrug delivery system was designed for the co-delivery of cisplatin and two photosensitizers (ICG and Ce6) as dual-targeting agents. Nanoparticles were synthesized by thin-film hydration method for the encapsulation of drug and photosensitizers. A synergistic effect against breast cancer cell lines was achieved. The results showed that the developed nanoparticles and co-encapsulated irradiation tempted apoptosis because of the

| Brand name       | Formulation type   | Administration route | Manufacturing company          | Therapeutic use               | Clinical trial phase | Ref.   |
|------------------|--------------------|----------------------|--------------------------------|-------------------------------|----------------------|--------|
| Lipointin        | PEGylated liposome | i.v.                 | Regulon Inc.                   | Various cancer                | III                  | [11,12]|
| SPI-077          | PEGylated liposome | i.v.                 | Alza Corporation               | Head, neck lung cancer        | II                   | [16]   |
| NC-6004 Nanoplatin™ | Polymeric Micelles | i.v.                 | Nano Carrier Co. Ltd. Japan    | Advance or metastatic pancreatic cancer | II                  | [18]   |
| L-NDDP Aroplatin™ | Liposomes          | i.v.                 | New York University School of Medicine, USA | Malignant pleural mesothelioma | II                  | [19]   |
| Serial no. | Fabrication technique | Drug used | Particle size (nm) | ZP (mV) | %EE – DL | Characterization | Betterment application | Ref. |
|------------|-----------------------|-----------|--------------------|---------|----------|-----------------|------------------------|------|
| 1          | PLGA                  | Cisplatin | 36.7 ± 8.1         | −8.5 ± 1.3 | 19.6     | In vivo and in vitro | Treatment with the CDDP-NPs improved the survival rates of tumour bearing mice | [23] |
| 2          | Double emulsion solvent evaporation method | Cisplatin/ Paclitaxel | 205.7 ± 2.5         | −2.51   | 71.5 ± 2.1 | In vitro | Overcome MDR and improved targeting | [24] |
| 3          | W/O/W double emulsion method | Cisplatin | 190.13 ± 5.17      | 1.94 ± 0.23 | 84.51 ± 3.11 | In vitro and in vivo | Improved antitumor efficacy | [25] |
| 4          | Electro hydrodynamic atomization | Cisplatin | 550 ± 80           | −70     | –         | In vitro and in vivo | Significantly improved anticancer efficacy of CDDP | [26] |
| 5          | Double emulsion solvent evaporation method | Cisplatin | 216.26 ± 4.64      | −10.38 ± 0.84 | –         | In vitro and in vivo | Targeted delivery to tumour tissue is successfully achieved | [27] |
| 6          | Nanoprecipitation method | Cisplatin/ Docetaxel | 125               | –       | 38.84 ± 0.31 | In vitro and in vivo | Enhanced the therapeutic efficacy | [28] |
| 7          | W/O/W double emulsion solvent evaporation method | Cisplatin | 235 ± 7.3          | −14.5   | 78       | In vitro and in vivo | Improved selective tumour targeting | [29] |
| 8          | W/O/W emulsion solvent evaporation | Cisplatin | 192 ± 12           | 9.5 ± 0.4 | 70.9 ± 62.6 | In vitro | Selective targeting to tumour cells | [30] |
| 9          | Thin film hydration method | Cisplatin | 102.6              | −47.7   | –         | In vitro | Synergistic treatment | [31] |
| 10         | Ring-opening Polymerization | Cisplatin | 63.2 ± 3.0         | −5.9 ± 3.1 | 47.5     | In vitro and in vivo | Showed dose and time dependent cell proliferation inhibition against human breast cancer cell line ZR-75-30 | [32] |
| 11         | Nanoprecipitation method | Cisplatin/ Docetaxel | 187.4 ± 2.4        | −25.7 ± 1.4 | 73.1 ± 5.8 | In vitro | Targeted co delivery of CDDP-DOX | [33] |
| 12         | Emulsification solvent evaporation | Cisplatin | 217 ± 13.54        | −29.5 ± 4.04 | 80       | In vitro | Achieved targeted delivery | [34] |
| 13         | Nanoprecipitation technique | Cisplatin | 350                | +30 mV  | 82       | In vitro | Increased sensitivity | [35] |
| 14         | Dialysis method | Cisplatin | 450                | −       | 57 ± 8   | In vitro and in vivo | Anti- tumour efficacy and reduced toxicity | [36] |
| 15         | Dialysis method | Cisplatin | 295.4 ± 32.9       | −19.7   | 31.8     | In vitro | Anti- tumour efficacy and reduced toxicity | [37] |
| 16         | Dialysis method | Cisplatin | 135                | −17.6 mV | 20.2     | In vitro | Enhanced cytotoxicity | [38] |
| 17         | Complexation method | Cisplatin | 52.4 ± 2.54        | −       | 63.4     | In vitro | Significant improvement in cytotoxicity | [39] |
| 18         | Dialysis Method | Cisplatin/ Paclitaxel | 84 ± 20            | 2.3 ± 1.0 | 50.4/95.8 | In vitro and in vivo | Enhanced chemotherapy efficacy and reduced side-effects. | [40] |
| 19         | Nanoprecipitation method | Cisplatin/ Docetaxel | 28 ± 9             | −8.1 ± 3.0 | –       | In vitro and in vivo | Enhanced anti-cancer efficacy | [41] |
| 20         | Ion complex method | Cisplatin | 102.5              | −20.86  | 75       | In vitro | Controlled release from nanoparticles | [42] |
| 21         | Precipitation and dialysis method | Cisplatin | 221 ± 9            | −11.1 ± 2.0 | 55.8 ± 1.2 | In vitro and in vivo | Enhanced antitumour efficacy | [43] |
| 22         | Ring-opening polymerization (ROP) | Cisplatin | 26                | −18.21  | –       | In vitro and in vivo | Enhanced the blood circulation time of CDDP | [44] |
| 23         | Synthetic method | Cisplatin | 30                | −20.6   | –       | In vitro and in vivo | Reduced the nephrotoxicity and neurotoxicity | [45] |
| 24         | Purified by ultrafiltration method | Cisplatin | 28                | −       | 39       | In vitro and in vivo | Enhanced antitumor activity against cell lines | [46] |
| 25         | Synthesis method | Cisplatin | 68.06              | 40.8    | –       | In vitro and in vivo | Targeted drug delivery | [47] |
| 26         | Synthesis method | Cisplatin/FU | 40                | −       | 26.64   | In vitro and in vivo | Reduced the drugs toxicity | [48] |
| 27         | Synthesis method | Cisplatin/ Paclitaxel | 16.9 ± 4.8        | 3.1     | 92       | In vitro and in vivo | Prolonged systemic circulation and reduced the renal toxicity of CDDP | [49] |
| 28         | Synthesis method | Cisplatin | 6.65              | 34      | –       | In vitro | Displayed better anticancer activity | [50] |
| 29         | Ring-opening polymerization | Cisplatin | 136.7 ± 14.2       | −20     | 90       | In vitro and in vivo | Enhanced safety and effective tumour inhibition | [51] |
| 30         | Synthesis method | Cisplatin | 107 ± 6.3         | −       | 65       | In vitro and in vivo | Sustained drug release | [52] |
| 31         | Double emulsion (W/O/W) method | Cisplatin/ Paclitaxel | 185.94 ± 7.43    | −24.68  | 51.24 ± 1.78 | In vitro and in vivo | Enhanced antitumour Efficacy | [53] |
| 32         | Complex formation | Cisplatin | 122              | –       | 64.7     | In vitro and in vivo | In vivo imaging and drug tracking | [54] |
| 33         | Poly butyl cyano acrylate nanoparticles | Cisplatin | 136.7 ± 14.2       | −20     | 90       | In vitro and in vivo | Overcome CDDP induced toxicity | [55] |
| 34         | Poly aspartic acid nanoparticles | Cisplatin | 140 ± 5          | −35 ± 2.0 | 40       | In vitro and in vivo | Overcome CDDP induced toxicity | [56] |
synergistic effect of therapy. Further, the possible mechanism based on cRGD and FA depicted the proactive targeted ability of transportation of NPs [32]. Another study was carried out, in which the cisplatin encapsulated nanoparticles were developed in a uniform size. In vitro drug release study of nanoparticles was observed at physiological and lysosomal pH, which released 30% and 39% drug, respectively. The possible mechanism behind the higher release of CDDP from nanoparticles was because of the greater number of carboxylic units conjugating with platinum of the cisplatin. The prolongation effect of nanoparticles was enhanced retention effects due to PEG coating around drug particle [33]. In this study, the co-delivery of cisplatin, docetaxel and Herceptin encapsulation in (HTCP NPs) was reported to overcome the overexpression of high human epidermal growth factor receptor 2 (HER2) against breast cancer [34].

**Chitosan nanoparticles**

Chitosan is a naturally occurring and linear polysaccharides obtained from chitin through partial deacetylation. Chitosan polymer possesses properties that make it biodegradable, biocompatible and non-toxic to other organs. Chitosan polymer can also be in the form of microparticles, nanoparticles and microspheres [35].

Emulsion solvent evaporation method was utilized to prepare the cisplatin-loaded chitosan nanoparticles with arginyl-glycyl-aspartic acid (RGD) peptide-modification. The chitosan nanoparticles displayed enhanced apoptosis and reduced toxicity against the cancer cell lines. The chitosan NPs modified with RGD showed enhanced cellular intake via integrin receptor-mediated endocytosis, improved apoptosis and enhanced cytotoxicity as compared with non-targeted nanoparticles in cancer cells [36]. Another attempt had been done to prepare multifunctional chitosan-coated cisplatin and siRNA/plasmid DNA chemosensitizers that have the reversal effect in the cisplatin resistance in human ovarian cancer cells. These multifunctional nanoparticles were spherical with a diameter of 350 nm, which showed entrapment efficiency up to 82%. The controlled release property of chitosan–cisplatin nanoparticles displayed its ability to slow release of CDDP over time, that is, more promising feature for cancer therapy. The efficient delivery of siRNA and plasmid DNA were observed due to the cationic surface charge of chitosan present on the surface of NPs [37]. Kim and co-workers had developed hydrophobically-modified glycol chitosan (HGCs) cisplatin-loaded nanoparticles via the dialysis method. The nanoparticles exhibited an enhanced anti-tumour efficacy and reduced toxicity, as compared with the cisplatin alone [38]. Polymeric chitosan-based nanocarrier was developed using three different deviates of chitosan N-benzyl-N, O-succinyl chitosan (BSCT), N-naphthyl-N, O-succinyl chitosan (NSCT) and N-octyl-N-O-succinyl chitosan (OSCT) for cisplatin encapsulation. Cytotoxicity investigations had been done against HN22 (head and neck) and human carcinoma cells. Most notably, cell accumulation, cellular uptake and toxicity studies have also been conducted against liver cancer cells. Among all nanocarriers, BSCT self-assembly nanocarrier has
Micelles were fabricated via the ring-opening polymerization method for passive targeting drug delivery system. Developed micelles were characterized in terms of particle size, zeta potential and fluorescence spectrosopy. The Micelles have shown a more sustained release effect over 50 h in phosphate buffer solution (PBS), and also demonstrated more anti-tumour activity against the KB cells. This slow release rate of CDDP from micelles showed decreased cytotoxicity in KB cell lines [41]. Shahin et al. had developed polymeric micelles and pharmacokinetics (PK) investigations were performed. In vitro studies exhibited slow release of CDDP from polymeric micelles at physiological pH. The intracellular uptake was remarkably improved in comparison to free cisplatin. These polymeric micelles are also reduced the toxicity of cisplatin because of slow release from developed micelles as compared to free drug solution [42]. Another strategy was used for the co-delivery of paclitaxel (PTX) and CDDP using micelles. These micelles were prepared by dialysis method to improve the synergistic effect against A549 human lung cancer cell lines. Micelles also exhibited tumour inhibiting effects with 83.1% tumour suppression rate (TSR %), which was more significant for that of free drug. These micelles improved the cellular cytotoxicity of PTX and CDDP based on prolong circulation and EPR effects of micelles systems that efficiently accumulated at the tumour site. The sustained release property of developed micelles also showed continuously tumour inhibition effects [43]. Another research reported that docetaxel and cisplatin-loaded, polypeptide-based micelles were developed and coated with an avb3 integrin-targeting peptide ([c]RGDK). Extended circulation of drug and anti-metastasis can be achieved by designing such nanodrug delivery system [44]. Saisyo and his team reported that the toxicity of developed micelles was fivefold higher, which was at pH 5.5, as compared to pH 7.4. However, the CDDP cytotoxicity is influenced by different pH conditions. It shows that the release of drug from micelles is higher at lower pH conditions. CDDP-loaded micelles observed higher anti-tumour efficacy and lower toxicity after the i.v. administration in mice. The drug release study showed rapid release in the acidic medium [45].

Recently, Chen et al. (2018) have developed novel poly-
\-l-glutamic acid, l-phenylalanine ethyl ester (PGA–PAE) based micelles for target delivery of anti-cancer drug cisplatin. The micelles were fabricated via dialysis method. In vitro drug release behaviour and toxicity studies were conducted against HCCC9810, A549 and HeLa cell lines. This showed that a delayed drug release behaviour from the micelles can significantly reduce the toxicity of drug-loaded micelles [46]. Another interesting experiment was designed by Song et al. to develop the cisplatin and iRGD-incorporated mPEG-b-PLG-loaded micelles in combination for the treatment of NSCLC chemotherapy. Thirty percent (30%) survival rate was noticed after the administration of micelles in mice. Toxicity was also reduced by loaded micelles in comparison to the free cisplatin [47]. In this study, the CDDP-loaded micelles were reported and PK studies revealed that the nephrotoxicity could be reduced with micelles. The reduced toxicity can be elaborated by various facts the micelles are less prone to filtration by nephrons because of the reduced nanoparticle size of about 30 nm, and the lower $C_{\text{max}}$ for CDDP in uriniferous tubules [48]. The CDDP-loaded micelles were highly accumulated and were 20-fold higher than the free cisplatin to achieve passive drug targeting. Reduced accumulation in other body organs and high penetration of drug on the tumour site were observed [49].

Dendrimers

Dendrimers are potential polymeric drug delivery system for the chemotherapeutic agent, as well as for cancer theranostics. Dendrimers are synthetic polymers having the monomer unit for branching. Hence, it is known as a polymer of the twenty-first century [50]. This novel nano-delivery system designed by Kesavan et al. is the diglycolamic acid (DGA) functionalized polyamido-40 doamine (PAMAM) dendrimers that were synthesized for potent anti-cancer drug cisplatin. Herceptin was used to evaluate drug targeting and in vitro studies that were conducted against the HER2+ve and HER2−ve human ovarian cancer cell lines. Enhanced cellular uptake, induced apoptosis and tumour accumulation were noticed to have been more effective in inducing the tumour regression, when compared with the cisplatin alone. This dendrimer-based formulation entered the nucleus and damaged nuclear fragmentation by inducing cell death via apoptosis. These nanoparticles are entered via receptor-mediated endocytosis [51]. This work reported a synthesis of pegylated polyamidoamine (PAMAM) dendrimer-loaded with cisplatin (CDDP) and fluorouracil (5-FU). Micelles exhibited more effective drug targeting and reduced toxicity based on the synergistic effect of both the anti-neoplastic agents. These dendrimers were characterized for their particle size, zeta potential and drug loading. In vivo experiment results showed a relative decrease in the tumour volume that is generated by MCF-7 cancer cells in xenograft mice model. These dendrimers may reduce the toxicity of CDDP due to their controlled release and also enhanced its accumulation in tumour site via EPR effect [52]. A low dose of CDDP and PTX can be used as a synergic regimen to enhance the anti-tumour efficacy and reduce the side effects. 1:2 ratio of CDDP-PTX has shown a stronger synergistic effect in contrast to other ratios against the SKOV-3 ovarian cancer in a xenograft mouse model [53]. Moreover, platinum-based drug-loaded dendrimers can be used for a reversal in the
cisplatin resistance in breast cell lines. Drug kinetics studies were performed at pH 5.5, as well as pH 7.7. The inductively coupled plasma mass spectrometry was used to measure the platinum content in MCF-7 cell lines. Meanwhile, cisplatin-loaded dendrimers displayed a more controlled release over 96 h and showed a 3–6-fold higher accumulation, compared to that of the free drug [54].

**Polymer–drug conjugates**

Drug polymeric nanoconjugates are water soluble and biocompatible, whereby they are bound to each other via biological linking and targeting moiety. The polymers in nanoconjugates are utilized to deliver drugs with improved solubility and to protect them from rapid elimination from the body. As the molecular weight of the polymer increases, it can increase the accumulation in the solid tumour due to its enhanced EPR effect. Advancement in drug conjugation is also based on its properties, such as high drug loading, excellent stability and controlled drug release; these are all considered for therapeutic effects [55]. Xiong et al. have developed cisplatin-stitched α-poly(glutamic acid) nanoconjugate for enhancing the safety and tumour inhibitions. In vitro conditions for toxicity and apoptosis assay were performed against the MCF-7 cells, which showed a significant improvement on the anti-tumour effect of the nanoconjugates, in comparison to the free cisplatin [56]. Another report on near infrared fluorescence (NIRF) demonstrated that drug-loaded nanoconjugates were gradually accumulating in tumour cells and had explored longer retention, compared to that of the unconjugated drug. The cisplatin released from nanoconjugates might be cross-linked with DNA interfering, thus locks the DNA down and loses its ability to replication. This mechanism of DNA with cisplatin make the sustained release of drug that is more promising for cancer treatment [57]. The FA-based polymeric conjugates were formulated by combining the cisplatin and paclitaxel through double-emulsion (W/O/W) method. Conjugates exhibited the synergistic effects against the A549 and M109 cell lines [58].

**Polybutyl cyanoacrylate (PBCA) based nanoparticles**

A polymeric nanocarrier (PBCA) is widely studied among all of the biomaterials. Poly(butyl cyanoacrylate) has indicated excellent biodegradability and non-toxicity. It has been extensively used in different clinical trials in Canada, Europe and USA [60]. Recently, Koohi et al. have developed PBCA nanoparticles via the mini-emulsion polymerization method. The methyl thiazolyl tetrazolium assay (MTT) was utilized to evaluate the toxicity and efficacy of nanoparticles against breast cancer cells. The inductively coupled plasma optical emission spectrometry (ICP-OES) and spectrophotometry techniques were used for the characterization of developed nanoparticles. These nanoparticles can successfully reduce the toxic effects as compared to what standard drugs can do [61].

**Poly aspartic acid (PAA) nanoparticles**

PAA nanoparticles have unique characteristics with regard to its biodegradability, biocompatibility and hydrophilicity in nature. Previously, PAA has been widely used in medicine, cosmetic and drug delivery system [62].

By utilizing PAA as carrier, nanoparticles were synthesized; the ultraviolet spectroscopy technique was utilized to measure the encapsulation of drug inside the nanoparticles. The cisplatin nanoparticles exhibited reduced local toxicity after intra-vesicle administration, as compared to the CDDP solution. In vivo results displayed a significantly reduced tumour proliferation, as compared to the control group [63].

**Polydopamine nanoparticles**

This interesting carrier based on polydopamine nanoparticles were reported with a hydrodynamic mean diameter of 148 nm and zeta potential −6.9 mV measured by dynamic light scattering (DLS) instrument. Additionally, the synergistic therapeutic effect was indited by nanoparticles, as compared with the single dose treatment [64].

**Glutathione-scavenging poly (disulfide amide) nanoparticles**

This group of scientists has designed the glutathione-scavenging nanoparticles loaded with cisplatin for efficient target delivery and reversing the resistance effect. The nanoprecipitation method was adopted for the formulation of the nanoparticle. These nanoparticles had remarkably improved the retention in blood circulation and enhanced the drug penetration and accumulation inside the tumour-bearing xenograft mice model [65].

**Albumin-based nano-formulations**

Albumin is a protein obtained from the oval albumin (OVA), bovine serum albumin (BSA) and human serum albumin (HAS). Commercially, albumins are obtained from white egg, bovine and human serum. Apart from these sources, they can be obtained from milk, soybean and grains. Albumin exhibits different properties, such as its non-toxicity, biodegradability, biocompatibility, high water solubility, non-immunogenicity and importantly, ease of purification [66].

Catanzaro et al. have developed CDDP-loaded BSA nanoparticles via the desolvation method for the treatment of medulla blastoma. The DLS and TEM were used to investigate the size of the nanoparticles. This formulation had significantly improved the safety and efficacy of selective targeting against pediatric brain tumour [67]. Another nano-delivery system albumin-loaded cisplatin mesospheres are developed by Lee et al. to reduce the toxicity by dissolving it in the dimethyl sulfoxide (DMSO). This developed mesosphere had attained a size of about 1–10 μm, with almost 100% encapsulation efficiency (EE). Meanwhile, in vitro kinetics explored the killing effects of lung cancer cells by developing
nanoparticles against the different cancers, including the non-small lung cancer (NCL-H23 and A549) mouse lung carcinoma cell lines [68].

**Gelatin NPs**

Gelatine is a natural biopolymer with versatile properties, such as biodegradability and biocompatibility. Gelatine is extensively used in food and pharmaceutical industries; gelatin-based nanoparticles and microparticles are promising tools for drug delivery system. Microparticles have its advantages over the nanoparticles due to their large surface area, which makes them excellent for metabolic and nutrient exchanges, and rapid cell development [69].

Cisplatin-loaded gelatin nanoparticle decorated with basic epidermal growth factor (bEGF) was synthesized by Tseng and co-workers to enhance the therapeutic efficacy. NPs that were administrated via the pulmonary route depicted higher antitumor effects and enhanced drug accumulation in the cancerous lung, compared to that of the free drug [70]. Gelatin–poly(acrylic acid) nanoparticles incorporated with cisplatin was synthesized with high drug payload. The resultant formulation displayed sustained release behavior, and the in vivo experiment indicated that NPs exhibited an anti-tumour effect when compared to the free CDDP in mice [71].

**Lipid-based nanocarriers for cisplatin**

Lipid-based smart nanocarriers were firstly reported in 1991 as an alternative of other nanocarriers, such as PNPs, emulsion and micro Particles. The lipid-based nanoparticles are colloidal nanocarriers that have a diameter between 50 and 1000 nm, prepared by the dispersion of lipids in water or an aqueous solution of surfactant. Lipids and surfactant are significant ingredients for developing lipid nanoparticles. These lipids are must biodegradable and biocompatible [72].

The summary of cisplatin-loaded lipid-based nanocarriers is given in Table 3.

In this work, redox-sensitive lipid-polymer nanoparticles were encapsulated with cisplatin and paclitaxel in combination to enhance the synergistic effect against the lung cancer cells. Pharmacokinetics studies in mice showed higher anti-tumour efficacy and toxicity, as compared with the model drug. The drug released from lipid-based nanocarriers based on the sustained release of cisplatin from the carrier and reduced its toxicity as compared to pure drug. The prolongation of the nanoparticle is observed in blood in the presence of PEG on the surface of nanoparticles, which provides stealth effect to nanoparticles [73]. The co-encapsulation of cisplatin with curcumin in lipid-based hybrid PNPs were characterized in terms of their particle size, zeta potential and drug release profile. Furthermore, anti-neoplastic activity was performed against the human cervix adenocarcinoma cell lines (HeLa cells). This lipid-based nanocarriers works based on delaying the release of drug from nanoparticles and improved the circulation of drug in blood and also increased the accumulation inside the tumour tissues [74]. Another study was reported for the reversal of cisplatin resistance, increase in the rapid release of drug in acidic conditions against the human ovarian cancer cells and also an enhancement in the cytotoxicity of A2780DDP cells [75]. Guo et al. reported that the lipid-coated cisplatin nanoparticles were prepared through a reverse microemulsion method to improve the poor solubility of cisplatin with maximum drug loading efficiency up to 80.8%. This nano-carrier based formulation enabled the accumulation of small size nanoparticles through the EPR effect [76]. The 5-FU-stearic acid-lipid surface modified hyaluronic acid (HA)-loaded cisplatin nanoparticles were designed to evaluate the in vitro cytotoxicity against the human gastric cancer cell line BGC823 [77]. The FA and cRGD dual-modified lipid-based nanoparticles carrying CDDP were developed by the film-ultrasonic dispersion method. The nanoparticles had increased the survival rate of MDA-MB 231 cell, as compared to that of the control group [78].

**Liposomes**

Liposomes were first approved in 1965 and considered as a main approach in the advanced drug delivery system. The importance of liposomes in terms of their various aspects are regarding the encapsulation of drugs depicted lower toxicity, biodegradability, targeting drug delivery and improved pharmacokinetics effect [79].

Zhang et al. have developed CDDP carrying cationic long circulating nanoliposomes via the esterification method. The surface morphology of these liposomes was investigated through SEM and TEM. These liposomes were quite stable over 28 days. These liposomes provide the sustained release and prolong circulation of CDDP in blood and reduced the nephrotoxicity. This feature suggested that it may be a potential carrier for cancer treatment [79]. Co-delivery of anticancer drugs and radiation therapy can improve the therapeutic outcome in various cancers. Cisplatin-loaded CAT nano-liposomal formulation was observed for the combined chemo-radiotherapy effect [80]. Stealth pH-sensitive liposomes were developed for the entrapment of cisplatin and characterized for various physiochemical properties, including physical stability, cytotoxicity and tumour accumulation that were noticed when against the human small-cell lung carcinoma cell line (GLC4) [81]. These nano-sized liposomes have improved the systemic extended circulation therapeutic efficacy of cisplatin owing to its fusogenic property. Additionally, the in vivo investigation is ongoing to evaluate the antitumor efficiency for the treatment of various cancers [82].

Kishimoto et al. had engineered a long, circulating and pH-sensitive CDDP-loaded nano-liposomes to improve the released kinetics near the target site and significantly reduce the systemic toxicity. The survival rate of mice was higher as a match free drug. Microscopic analysis confirmed the reduction in renal and bone marrow toxicities effectively. This formulation showed highly sustained release property and tumour accumulation for selective tumour targeting effects [83]. The CDDP-loaded sialyl Lewis X-modified liposomes (CDDP-SLX-LIP) were constructed and optimized. Liposomes had extended higher drug release and were gradually accumulated inside the tumour cell [84]. Vhora et al. reported
| Serial no. | Fabrication technique | Drug used | Particle size (nm) | ZP (mV) | %EE – DL | Characterization | Betterment application | Ref. |
|-----------|-----------------------|-----------|-------------------|---------|----------|-----------------|------------------------|------|
| 41        | Emulsification-sonication method | Cisplatin/Paclitaxel | 191.3 ± 5.3 | −37.2 ± 3.9 | 85.3 ± 3.3 | *In vitro and in vivo* | Increased the accumulation of the LPNs in tumour site | [73] |
| 42        | Nano-precipitation technology | Cisplatin | 118.5 ± 4.62 | 13.7 ± 1.36 | 81.5 ± 6.79 | *In vitro and in vivo* | LPNs prolong the release and circulation time | [74] |
| 43        | Acid and reduction sensitive method | Cisplatin/Oxaliplatin | 178 | −20 | – | *In vitro* | Overcoming cisplatin resistance | [75] |
| 44        | Water-in-oil reverse micro-emulsion | Cisplatin | 30 | – | 80 | *In vitro and in vivo* | Enhanced Anticancer Efficacy | [76] |
| 45        | Emulsification and low-temperature solidification method | Cisplatin/Fluorouracil | 181.6 ± 3.2 | +26.3 ± 2.4 | 89.8 ± 2.9 | *In vitro and in vivo* | Effective co delivery of 5-FU and CDDP | [77] |
| 46        | Film-ultrasonic dispersion method | Cisplatin/Polyaniline | 102.7 | −51.7 | 7.67, 5.88 | *In vitro* | Overcoming MDR and chemo-photo thermal cancer therapy | [78] |
| 47        | Thin film evaporation method | Cisplatin | 125.8 ± 0.5 | 5.61 ± 0.07 | 70 | *In vitro* | Reduced renal toxicity | [79] |
| 48        | Hydrating method | Cisplatin | 100 | – | – | *In vitro and in vivo* | Overcome tumour hypoxia for enhanced chemo-radiotherapy of cancer | [80] |
| 49        | Hydrating method | Cisplatin | 174 | – | 20.0 | *In vitro* | Overcome resistance | [81] |
| 50        | Extrusion method | Cisplatin | 126 ± 2 | 16.9 ± 6.3 | 18.75 ± 0.3 | *In vitro and in vivo* | Improve therapeutic efficacy | [82] |
| 51        | Reverse-Phase evaporation | Cisplatin | 178 ± 16 | 22.6 ± 1.0 | – | *In vitro and in vivo* | Improve the antitumor efficacy and decrease renal and bone marrow toxicity | [83] |
| 52        | Dialysis method | Cisplatin | 182 | – | 53 | *In vitro and in vivo* | Enhanced anti-tumour effect | [84] |
| 53        | Ethanol injection method | Cisplatin | 119 | – | 2.6 | – | *In vitro and in vivo* | Controlled release of CDDP | [85] |
| 54        | Emulsification solvent evaporation method | Cisplatin | 145.8 ± 8.9 | −3.99 ± 3.45 | 95.88 ± 0.41 | *In vitro and in vivo* | Increase the entrapment of cisplatin | [86] |
| 55        | Thin film by rotary evaporation | Cisplatin | 155.4 ± 16.1 | −50.92 ± 1.19 | 90 | *In vitro and in vivo* | Decreased side effects | [87] |
| 56        | Reverse phase evaporation (REV) | Cisplatin | 110.7 ± 3.1 | −30.1 | 94.2 ± 2.1 | *In vitro and in vivo* | Increased therapeutic efficacy | [88] |
| 57        | Reverse phase evaporation (REV) | Cisplatin | 127.6 ± 6.9 | – | 40.6 ± 5.9 | *In vitro* | Scaling-up of SpHl-CDDP | [89] |
| 58        | Reverse-phase evaporation | Cisplatin | 137 ± 12 | 2.00 ± 0.26 | 25.0 ± 3.20 | *In vitro and in vivo* | Improved safety | [90] |
| 59        | Ethanol injection method | Cisplatin | 130.4 ± 4.5 | −2.95 ± 1.30 | 23.4 ± 2.5 | *In vitro and in vivo* | Increased anti-tumour activity | [91] |
| 60        | Reverse-phase evaporation | Cisplatin | 135 | −2.8 | 23 ± 5 | *In vitro* | Improving the antitumor efficacy | [92] |
| 61        | Thin film hydration method | Cisplatin | 112.37 ± 0.52 | 23.83 ± 1.89 | 89.92 ± 4.28 | *In vitro and in vivo* | Increased antitumor activity | [93] |
| 62        | Emulsification technique. | Cisplatin/Metformin | 120 | −43 | – | *In vitro* | Exhibited strong antitumor activity | [94] |
| 63        | Chemical method | Cisplatin/Imiquimod | 429.5 | 68.1 | – | *In vitro and in vivo* | Optimal antitumor effects | [95] |

EE: entrapment efficiency; DL: drug loading; ZP: zeta potential.
that the sterol cisplatin-based liposome demonstrated the greater half-life as a match free drug. The X-ray fluorescence spectroscopy technique was used to determine the platinum content in the formulation [85]. Another research group reported that the liposomes formulation was designed to overcome the problem regarding poor solubility of cisplatin, improvement of the therapeutic index and safety profile [86]. The liposome-based formulation has a particle size of 155.4 ± 16.1 nm and zeta potential about −50.92 ± 1.19 mV. The PK studies of resultant liposomes exhibited prolonged circulation time, and improved anti-neoplastic activity and survival rate in A549-engrafted mice in comparison to free cisplatin [87]. The 3-octa decylcarbamoyl acrylic acid cisplatin-based liposome was prepared and investigated to evaluate the antitumor efficacy and safety profile as compared to free drug. The EE% of the formulation was up to 94.2 ± 2.1% [88]. In this work, long, circulating and pH-sensitive cisplatin-based liposomes were developed. In vivo parameters regarding the pharmacokinetics, antitumor efficacy and toxicity studies were carried out [89]. The pH-sensitive liposomes were synthesized to overcome the unwanted effects related to free cisplatin. The CDDP-loaded liposome can be a promising vesicle for clinical use [90]. Another study was carried out by Fernanda et al. by developing CDDP-loaded pH-sensitive liposomes and injected in the pancreatic tumour-bearing mice for 14 days. Toxicity studies were investigated based on the inflammation, a narcotic area in kidney, spleen and intestine. These experimental results revealed that CDDP-loaded liposomes have successfully improved the anti-tumour effect as free cisplatin [91]. The CDDP-incorporated, long-circulating liposomes that were developed by Wang et al. investigating the CDC-47 tumour cells. This formulation had significantly enhanced the antitumor activity, as compared to that of free cisplatin [92]. The EGF-modified cisplatin-loaded liposomes were prepared for target delivery for the treatment of the EGFR overexpression tumours, especially ovarian carcinoma. The in vivo results showed loaded liposomes had remarkably penetrated inside the tumour and enhanced the efficacy against EGFR-positive SKOV3 cells [93].

**Cubosomes**

Cubosomes are classified under lipid-based nanostructured carrier, having the size of between 100 and 300 nm; cubosomes displayed large surface area and low viscosity [94]. This strategy was utilized for the co-delivery of cisplatin with metformin via the emulsification technique. The developed cubosomes were characterized and optimized for further investigation. The enzyme-linked immunosorbent assay (ELISA) technique was utilized for AMPK/mTOR metabolic and the Akt/mTOR pathways. Meanwhile, cubosomes had enhanced their cytotoxicity based on the addition of metformin. This novel cubosomes-based formulation exaggerated different intracellular targets with efficient inhibition effect on tumour linked with different metabolic pathways leading to enhanced the apoptosis [94].

**Transfersomes**

Gregor Ceve introduced transfersomes in 1991; the word transfersome is derived from the Latin word “transferrerae”, which means “to carry across” and the Greek word “soma” means body [95].

Gupta et al. synthesized the cisplatin and imiquimod-loaded transfersomes with a particle size of 429.5 nm and zeta potential 68.1 mV. The drug-excipient interactions were confirmed by thin-layer chromatography (TLC), Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). The combinatorial drug delivery-based transfersomes can be ideal vesicles for the enhancement of anti-tumour activity and efficient targeting against skin that is related to carcinomas [95].

**Inorganic nanoparticle-based nanodelivery systems**

Inorganic nanoparticles have extended their importance in recent decades because of their distinctive materials and size regarding the physiochemical characteristics, which are not achieved with PNPs or other drug delivery systems. Most importantly, magnetic, optical, inertness, physical stability and easy to surface functionalization make them a promising tool, as compared to the organic nanoparticles for the biomedical imaging and cancer cells [96]. The summary of cisplatin-loaded inorganic nanoparticles is given in Table 4.

**Gold nanoparticles**

Gold nanoparticles have attained great importance by researchers in recent years. Physical and chemical surface modifications in the gold nanoparticles make them more attractive for several applications such as theranostic diagnosis, bioimaging and nanodrug delivery system [99,101].

Folate-conjugated hollow gold nanoparticles loaded with cisplatin were synthesized by standard solid-phase methodology. The release of drug from nanoparticle was quantified by using the inductively coupled plasma mass spectroscopy. The hollow gold nanoparticles could be used for combined photothermal therapy and NIR laser-triggered CDDP-based drug delivery system [97]. Erez et al. have developed gold nanoparticles that are coated with glucose and cisplatin, having a hydrodynamic mean diameter of about 30 nm. The cytotoxicity and cellular studies were performed against the A431 cells. These nanoparticles displayed multifunction’s as a drug carrier, radiosensitizer and tumour imaging for head and neck carcinoma against nude mice [98]. Recently, another research group reported gold nanoparticles carrying CDDP and 2 Gy, 6 MV (megavoltage) radiations prepared via the citrate reduction method. Monte-Carlo simulations were used to access the dosimetric differences in gold nanoparticles loaded CDDP and radiations. The results revealed a remarkable improvement on the therapeutic outcomes [99]. The dGTP templated luminescent gold nanocluster coated with PEG incorporated with anti-cancer agent cisplatin was synthesized. Also, PEG is utilized for improving the smoothness of nanoparticles and its nano-size was able to enhance the slow release of cisplatin. Gold nanoclusters were employed for the imaging and delivery of the drug in tumour
Table 4. Detailed description of CDDP loaded inorganic NPs based nano-formulation.

| Serial no. | Fabrication technique | Drug used | Particle size (nm) | ZP (mV) | %EE – DL | Characterization | Betterment application | Ref. |
|------------|-----------------------|-----------|--------------------|---------|----------|------------------|-----------------------|------|
| 64         | Standard solid-phase method | Cisplatin | 43.9 ± 1.2 | – | – | In vitro | Laser-triggered drug release | [97] |
| 65         | Synthesis method | Cisplatin | 20 | –24.3 ± 2.2 | – | In vitro and in vivo | Enhance tumour growth inhibition | [98] |
| 66         | Citrate reduction method. | Cisplatin/Radiaion | 10.04 ± 0.89 | – | – | In vitro and in vivo | Improves the therapeutic outcome | [99] |
| 67         | Synthesis method | Cisplatin | 145 ± 22 | –1.7 | 40 | In vitro | Employed for cellular imaging | [100] |
| 68         | Synthesis method | Cisplatin | 144.7 | –37.8 | 30 | In vitro and in vivo | Showed higher cytotoxicity | [101] |
| 69         | Distillation precipitation polymerization method | Cisplatin | 293 | –14.2 | 20.8 | In vitro | Synergistic and cytotoxicity | [102] |
| 70         | Synthesis method | Cisplatin/6-Mercaptopurine | 100 | –14.43 | 2 | In vitro and in vivo | Improve tumour-targeting | [103] |
| 71         | Hydrothermal treatment method | Cisplatin/ Doxorubicin | 290 | – | 56.2 | In vitro and in vivo | Efficient cellular uptake | [104] |
| 72         | Thermal decomposition method | Cisplatin/Turmerisinin | 141.4 | –37.6 | 7.7 | In vitro | Improved anti-cancer efficacy | [105] |
| 73         | Double emulsion method | Cisplatin | 145.9 ± 1.5 | 21.6 ± 1.24 | 25.03 ± 3.05 | In vitro | Improve inhibition effect | [106] |
| 74         | Co-precipitation method | Cisplatin | 205 ± 3.08 | 12.7 ± 1.7 | 32.4 ± 2.7 | In vitro | Simultaneous targeting imaging, drug delivery | [107] |
| 75         | Chemical method | Cisplatin | 34.6 | – | 83.56 | In vitro | Improve bioavailability & efficacy | [108] |
| 76         | Precipitation method | Cisplatin | 56.8 ± 6.5 | – | 1.7 ±0.09 | In vitro | Exhibited higher anti-cancer activity | [109] |
| 77         | Solvothermal method | Cisplatin/Doxorubicin | 100 | – | – | In vitro | Higher anti-tumour capacity and imaging | [110] |
| 78         | Europium(III)-doped yttrium vanadate nanoparticles | Cisplatin | 207 ± 23 | –29 ± 1 | 77.8 | In vitro | Reduced systemic toxicity | [111] |
| 79         | Aluminium NPs | Cisplatin | 88.9 | –29.9 | 78.67 | In vitro | Enhanced efficacy | [112] |
| 80         | Photo thermal conversion nanoparticles | Cisplatin /CJM-126 | 88.9 | –29.9 | 78.67 | In vitro | Enhanced synergistic antitumor efficacy | [113] |
| 81         | Melanin NPs | Cisplatin | 73.7 | – | 29.6 | In vitro and in vivo | Highly efficient photo thermal therapy and chemotherapy | [114] |
| 82         | Coordination polymer nanoparticles | Cisplatin | 03.3 ± 5.4 | –30 | – | In vitro and in vivo | Enhancing chemotherapeutic efficacy | [115] |

EE: entrapment efficiency; DL: drug loading; ZP: zeta potential.
cells [100]. Goto and his team had recently engineered hyaluronic acid decorated cisplatin-loaded gold nanoparticles for efficient tumour targeting and to improve the synergistic effect. Enhanced cytotoxicity with encapsulated cisplatin gold nanoparticle was noticed in comparison to free drug against MCF-7 cells, human primary glioblastoma U-87 cells and MCF-7 tumour-bearing mice. The gold nanoparticles work based on accumulation into the tumour site based on EPR because of leaky vasculature and lymphatic drainage of tumour [101].

Mesoporous silica nanoparticles
Mesoporous silica are emerging inorganic biomaterials used for the biomedical applications. Mobil corporation scientists had first reported MSNs with nanostructured pore size in 1992. Nanopore makes it an excellent candidate for sustained or controlled drug delivery system [102]. Poly(acrylic acid) modified mesoporous silica nanoparticles (PAA-MSNs) were prepared through distillation–precipitation polymerization method for the encapsulation of CDDP and Doxorubicin (DOX). The nanoparticles depicted controlled in vitro release behaviour within 144 h. The confocal fluorescence microscopy (CFM) had confirmed the efficient delivery of CDDP and DOX against human cervical carcinoma cells. The nanoparticles exhibited higher cytotoxicity and synergistic effect against HeLa and A357 cells [103]. Dual-cisplatin and 6-mercaptopurine had been successfully loaded in MSNs. The MSNs-6MP/CDDP showed higher anti-tumour activity in the S180 mouse model as compared with the cisplatin or 6-mercaptopurine alone. Myocardium and liver histological images displayed a complete elimination of toxicities related to CDDP or CCDDP-6MP that is used alone [104]. Hydrothermal treatment method was utilized for the simultaneous delivery of CDDP and DOX-loaded in mesoporous organosilica (MONs). The flow cytometry had confirmed the efficient cellular uptake of the encapsulated mesoporous nanoparticles against the human breast cancer MCF-7 cells [105].

Magnetic iron oxide NPs
Iron oxide nanoparticles were effectively used for magnetic imaging resonance (MRI). Still, the synthesis of super magnetic iron oxide nanoparticles is quite a challenge for scientists. Meanwhile, a recent innovation in nanotechnology makes them develop the desired sizes and shapes [106,108].

Super magnetic ferric oxide nanoparticles loaded with cisplatin and artemisinin were fabricated through a thermal decomposition method for improving the payload and achieving the excellent synergistic effect of simultaneous drugs. Further, flow cytometry results displayed increased reactive oxygen species (ROS) generation and cell apoptosis rate against the A549/R cells. The mechanism based on local hyperthermia was generated by magnetic nanoparticles by hysteresis loss. This generation of local heat increased the nanoparticles permeability and improved the drug release [106]. Cell-penetrating peptide decorated cisplatin-loaded magnetic nanoparticles that were synthesized for nasopharyngeal cancer treatment. Fluorescent tags were used for the determination of cell-penetrating and biocompatible ability [107]. In another approach by Ibarra et al., cisplatin-loaded iron oxide nanoparticles were encapsulated with biocompatible polymers, such as PLGA, PVA and chitosan matrix. The ICP-MS and UV spectroscopy were used to measure the drug content in nanoparticles. Chemotherapeutic effect of CDDP had been effectively enhanced against the cervical HeLa and breast MDA-MB-231 cells. The release mechanism of cisplatin from nanoparticles observed pH-dependent and layer around nanoparticles covered with PVA and chitosan acts as a physical barrier and inducing a slow and sustain release of drug from nanoparticles [108].

Calcium-based nanoparticles
Calcium carbonate nanoparticles have already been used in different fabrication techniques in the last decades. Recently, it gained a promising attention in the anti-cancer drug delivery system, owing to its bioavailability, less toxicity and slower biodegradability. Additionally, calcium phosphate-based nanoparticles have some drawbacks, such as low drug loading and initial burst of drug release [110]. Calcium carbonate particles have been widely used in pharmaceuticals, medicine and other healthcare. Dunuweera et al. had developed a porous calcium carbonate loaded with cisplatin by the chemical method to improve the bioavailability and efficacy. The drug release behaviour was observed to have slightly increased with a decrease in the pH in an acidic medium [109]. Another group had reported on the calcium phosphate nanocomposite prepared by precipitation method for the encapsulation of cisplatin, where the UV spectroscopy analysis had confirmed the cisplatin content in nanocomposites. These nanocomposites showed a more rapid burst of drug release, followed by a prolonged release. The anti-cancer activity studies were performed against the human osteosarcoma [110].

NaGdF4:Yb3+/Er3+ nanoparticles
NaGdF4:−Yb3+/Er3+ nanoparticles are hydrophilic in nature and suitable for biomedical and drug delivery systems. NaGdF4:−Yb3+/Er3+ coated with a carboxyl group and loaded with dual-drug CDDP–DOX were prepared by the modified solvothermal method. The TEM and FTIR were performed for the characterization of nanoparticles. These loaded NPs could be used for imaging, as well as for the co-delivery of cisplatin and doxorubicin to improve the efficacy and inhibition effect of the tumour [111].

Europium (III) doped yttrium vanadate nanoparticles
Carmona et al. synthesized Europium (III) doped yttrium vanadate incorporated cisplatin, which reduces the toxicity. A decrease in body weight and an increase in the serum creatinine level were observed in animals treated by the standard drug that functionalized as cisplatin nanodrug. Meanwhile, FA in inorganic nanoparticle had remarkably reduced the genotoxicity of cisplatin nanoparticles in bone marrow [112].
Aluminum-doped MCM-41 nanoparticles
Carmona and co-workers reported an innovative work about aluminum-doped MCM-41 NPs that were designed for the co-delivery of cationic carbon mono-oxide (CO) releasing molecules (CORM) [Mn(1,4,7triazacyclononane)(CO)3⁺ (ALF472⁺)], and cisplatin (CDDP). These results revealed that the incorporating of CO molecules with CDDP had enhanced the drug loading threefold, as compared with the unloaded drug. Meanwhile, the in vitro results showed a more controlled release of CO, compared to that of free CORM [113].

Photothermal conversion nanoparticles
In this work, CJM-126 2-(4-aminophenyl)benzothiazole molecule exhibited synergistic effect with anti-neoplastic agents. Conventional conjugate reaction method was utilized for the development of photothermal conversion nanoparticles loaded with cisplatin and indocyanine green (ICG) dye for increased synergetic anti-tumour efficacy. Under physiological conditions, nanoparticles were more stable, compared to that of free drug [114].

Melanin nanoparticles
Melanin is a potential photosensitizer that is strongly absorbed near the infrared region (NIR) and showed 40% photothermal conversion efficiency (PCE). The nanoparticles depicted low toxicity and biocompatibility. Melanin nanoparticles were developed via dopamine oxidation and self-polymerization method for highly efficient photothermal therapy and chemotherapy. No toxicity was noticed because of the biocompatibility of nanoparticles. The Pt (IV)-MeNPs can be considered as promising nanoparticles for future cancer treatment [115].

Coordination polymer nanoparticles
Coordination polymer nanoparticles (CPNs) are considered potential carriers in drug delivery system because of their versatile composition, particle size and shape. The CPNs have shown better stability in a physiological medium. Pharmacokinetics investigation displayed biodistribution of CDDP-loading CPNs that were in fourfold, delivered to the bone metastatic lesion as a compared control group. Besides, nanoparticles exhibited efficient tumour inhibition effect and had remarkably reduced the osteoclastic bone destruction [116].

Carbon-based nano-formulations for cisplatin
In the recent decade, there have been plenty of classes of carbon-based nanomaterials, for example, graphene quantum dots. Carbon nanotubes and fullerene nanocarriers are considered potential vehicles for biology and drug delivery system [117]. The summary of cisplatin-loaded carbon-based carriers is given in Table 5.

| Serial no | Fabrication technique         | Drug used     | Particle size (nm) | ZP (mV) | %EE / DL | Characterization      | Betterment application                                      | Ref. |
|-----------|-------------------------------|---------------|--------------------|---------|----------|----------------------|-------------------------------------------------------------|------|
| 83        | Chemical method                | Cisplatin     | 50                 | –       | 65.86    | In vitro             | Enhanced loading efficiency and improve release profile      | [118]|
| 84        | Electric-arc discharge method  | Cisplatin     | 50                 | –       | 95       | [In vitro and in vivo] | Enhance the in vivo efficacy                                | [119]|
| 85        | Chemical method                | Cisplatin     | 10                 | –25     | 58       | In vitro             | Cellular imaging and targeting                              | [120]|
| 86        | Modified hummers method        | Cisplatin     | 15.3 ± 3.7         | –       | –        | In vitro             | Enhanced apoptosis                                           | [121]|
| 87        | Synthesis method               | Cisplatin/C 60 fullerene | 122             | –23     | –        | In vivo and in vitro | Exhibited cytotoxic effects                                | [122]|

EE: entrapment efficiency; DL: drug loading; ZP: zeta potential.
Graphene

Graphene is an emerging nanocarrier in biomaterial science. Graphene-based nanocarrier is used in a drug delivery system because of its high aqueous solubility and surface functionalization [120]. Graphene quantum dots (GQDs) were utilized for dual-functioning drug targeting and biomedical cellular imaging. Western blot analysis with confocal imaging explored the targeting of epidermal growth factor receptor (EGFR) overexpression in breast cancer cells [120]. The modified graphene coated silver nanocomposite-loaded cisplatin was synthesized for the enhancement of the apoptosis and autophagy against the human cervical cancer cell. These quantum dots exhibited improved cellular uptake, cytotoxicity and apoptosis against the HeLa cells [121].

Fullerene

Pristine C 60 fullerenes exhibited anti-oxidant properties due to its high activity as free radical acceptors. At low physiological concentration, no toxicity was noticed in both in vitro and in vivo conditions. Nano-complexes were synthesized at about 122 nm in size. These nanoparticles were investigated using the computer simulation (CS), DLS and atomic force microscopy (AFM) techniques [122].

Other nano-formulations

Besides the PNPs, lipid-based nanocarriers, carbon-based nanoformulations, other nano-delivery systems have also been developed for CDDP. The description of these nano-delivery systems is enlisted in Table 6.

Nanocapsules

Nanocapsules are an ideal drug delivery system, which is used to improve the efficacy and reduce side effects. Magnetic nanocapsule was fabricated by double emulsion method for improving the drug efficacy and efficient targeting against A549-tumour-bearing mice in contrast to free cisplatin. Meanwhile, unwanted effects associated with free drugs like nephrotoxicity and hepatotoxicity had been drastically reduced [123]. The lipid-based nanocapsule was formulated via synthesis method around 71 ± 0.4 nm and zeta potential 20.50 ± 0.75 mV. The LNC incorporated cisplatin exhibited a sustained release of CDDP and improved the cellular uptake against HepG2 cells. Flow cytometry analysis also indicated enhanced apoptosis that was noticed with loaded nanocapsules, as compared with the free drug [124].

Nanogels

Nanogels are nanoparticles consisting of hydrogel with cross-linking hydrophilic polymers having a particle size of between 100 and 200 nm. Nanogels comprise 3D structures in which drug, polymers and dispersed phase of liquids are encapsulated [125]. Dual-drug cisplatin and lidocaine co-loaded nanogels were synthesized via the emulsion polymerization method for tumour targeting. Incorporating the lidocaine has also enhanced the apoptosis and metastasis...
against MDA-MB-231 breast cancer cells in the mouse model [125]. In this work, the pH, thermal dual-responsive nanogel incorporated with cisplatin was prepared to improve the prolonged circulation time and antitumor effect, as compared with the free CDDP and the drug released from formulation that was slower at 37 °C as compared 25 °C temperature. Further release behaviour indicated that CDDP released from the nanogel could decrease with increasing temperature [126].

**Silk fibroin nanoparticles**

Silk fibroin (SF) is a polymer that is usually obtained from natural sources and is widely used in skin, bone and cartilage due to its controllable biodegradability. In this interesting study, the electrospray method was employed for the preparation of CDDP-loaded SF nanoparticles without using an organic solvent. CDDP-loaded nanoparticles had successfully penetrated in the A549 lung cancer cells and triggered apoptosis. In vitro conditions drug can be sustainably released from the nanoparticles over 15 days [127].

**Casein NPs**

Casein is a naturally occurring ingredient obtained from milk proteins. It was widely used in the drug delivery system due to its properties of being non-toxic, inexpensive and biodegradable. Zhen et al. had designed and developed cisplatin-loaded casein nanoparticles in a spherical shape with 257 nm in size. The anti-neoplastic activity of nanoparticle loaded with cisplatin was conducted on a hepatic H22 mice model. These nanoparticles had significantly improved cell penetration, tumour targeting and inhibited the tumour progression [128].

**Fucoidan NPs**

Fucoidan NPs are considered as emerging nanocarriers due to its multifunctional properties, that is, possessed anti-inflammatory, anticoagulant and anti-cancer effects. In this work, cisplatin and fucoidan nanoparticles were synthesized for improving the immunotherapy and chemotherapy. The anti-tumour assay of nanoparticles showed higher cytotoxicity in HCT-8 cells as compared with those that are treated with cisplatin alone [129].

**Boldine NPs**

Boldine is obtained from alkaloid Peumus boldus, known chemically by (S)-2,9-dihydroxy-1,10-dimethoxy-aporphine. Boldine is plant-derived herbal therapeutic agent. It has been used as an antioxidant agent, as well as an indication for the inhabitation of cancer cell proliferation. The solvent displacement method was utilized for the development of cisplatin-loaded nanoparticles. Hydrodynamic mean diameter was approximately 115.5 ± 0.469 nm, with the encapsulation efficiency EE% of about 81.93 ± 0.915%. The oxygen reactive species (ROS) accumulations and mitochondrial functions were studied in both standard and cancer-induced mice. Sustained release from nanoparticles, site targeting and faster mobility were noticed as a free drug [130].

**Hydrogels**

Hydrogels are a network of hydrophilic polymer with numerous structures. These features make them the ideal candidate in drug delivery system, as nanoparticles or microparticles. Several hydrogel-based anti-cancer studies have been reported previously [134].

In this work, a novel injectable thermosensitive polypeptide-based CDDP with loaded hydrogel was formulated for enhancing the efficacy of the localized anti-cancerous. Enhanced antitumor activity of cisplatin-loaded thermal sensitive injectable hydrogel had been noticed, in contrast to the free drug with improved localized delivery to target sites. The mechanism behind to explain the improved anti-cancer efficacy of hydrogels based on depicting more sustained release of cisplatin from hydrogels. [131] Dual drug CDDP/PTX-loaded injectable hydrogel was developed for the treatment of ovarian cancer. The extended release of dual drug was observed for about two and a half months, with improved anti-cancerous effect against the SKOV-3 ovarian cancer xenograft mouse models [132]. Supramolecular alphacyclodextrin dual drug CDDP/PTX was prepared to overcome the acute toxicity. XRD and FTIR were performed to confirm the drug-polymer interactions. In vivo studies indicated higher tumour growth inhibition effect for the free drug [133]. This study reported that the injectable super molecular PEG-modified cisplatin-loaded hydrogel was developed to enhance the anti-tumour effect [134]. Thermosensitive polypeptide hydrogel was utilized for the combination of cisplatin and interleukin-15(IL-15) for localized drug delivery system. Dual drug loaded hydrogel can reduce the systemic toxicity and enhance the synergistic effect against the B16F0-RFP melanoma cells [135].

**Conclusion and future recommendations**

Cisplatin has proven its anti-tumour activity against the various types of cancers. Current review highlights the polymeric nanoformulations, inorganic carrier-based nano-formulations, carbon-based nanomedicine and other carrier-based advance drug delivery systems. Nanoplatin™, Aroplatin™, Lipoplatin™ and SPI-077 are under clinical trials; still, these formulations have yet to be marketed for the treatment of various cancers. Nano-drug delivery-based formulations have the potential to improve the physiochemical characteristics and efficient in the targeting of anti-cancer drugs. We believe that target DDs carrier can be developed for the effective delivery of CDDP. The significant findings of this review paper are the toxicities and drug resistance that can be reduced by combining cisplatin with other chemotherapeutic agents.

Moreover, the co-delivery of cisplatin with other anti-cancer agents has also enhanced the therapeutic profile, safety and efficacy. Future, nanomedicine-based drug delivery system still looks promising, where it can provide a better outcome in cancer therapy. Besides, more new attempts
must be designed for targeting moiety to reduce the toxicities, which are the major problem for cancer drugs.

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