

**Review Article**

# Discovery, Chemistry, Anticancer Action and Targeting of Cisplatin

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**Abstract:** Cisplatin is the first anticancer drug based on inorganic complexes which was discovered accidentally by Rosenberg in 1965. Cisplatin is now used to treat a wide range of cancers such as head and neck testicular, small-cell lung and non-small-cell lung, bladder, cervical and ovarian cancers. Cisplatin has become the premier in combination therapy for solid tumours such as gastric, bladder, cervical, ovarian, lung, breast, head and neck cancers and some malignant mesothelioma and some less common cancers. This review begins with an introduction to the accidental discovery of cisplatin highlighting the amazing fact of serendipity involved in drug discovery. This will follow a reviewing of chemistry of cisplatin, identification of cis and trans isomers of diamminedichloroplatinum(II). As for the most relevance to Pharmacy the action of cisplatin is reviewed next. Highlighted there are the reasons for cisplatin toxicity and hence ways and means of reducing cytotoxicity of cisplatin to healthy cells. Finally, the work on encapsulation of cisplatin in porous calcium carbonate nanoparticles for safe and targeted delivery to cancerous cells for more effective and selective action on cancer cells will be discussed.

**Keywords:** Anticancer Drug, Discovery of Cisplatin, Chemistry of Cisplatin, Action of Cisplatin, Ways of Reducing Cytotoxicity, Encapsulation, Targeted-Delivery, Slow-Release

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## 1. Introduction

Cisplatin is the first generation anticancer drug based on coordination complexes of platinum which was discovered through serendipity. It has astounding history in terms of drug discovery through serendipity as well as it has contributed to the advancement of knowledge in coordination chemistry also in terms of elucidating structures of organic compounds. As such, cisplatin has contributed to awarding a Nobel Prize for Inorganic Chemistry discipline. It is this cis configuration where two ammine ligands are one side while two chloro ligands are on the other side of the same square planar geometry around Pt(II) ion makes cisplatin to damage DNA in cancer cells. Transplatin where the two ligands are on both sides of the square plane is not effective against destroying cancer cells because transplatin cannot bind to the two strands of DNA. The chloro ligands are labile and hence cisplatin is supplied in saline solution with high chloride concentration.

When the chloride concentration is less cisplatin readily undergoes ligand exchange of chloride for aqua (H<sub>2</sub>O) ligand(s). The diamminediaquaPt(II) thus formed can react with N bases replacing aqua ligand(s) by N-based ligand(s). As such, cisplatin binds mainly to two guanine N atoms of DNA double strands and thereby induce programmed death. Since the trans configuration cannot do so, transplatin is not effective in destroying DNA. Cisplatin is effective against many cancers, particularly, in combination chemotherapy with other anticancer drugs, such as Taxol and/or vinblastine. However, cisplatin has severe cytotoxicities to healthy cells due to the fact that cisplatin has the ability to destroy DNA of healthy cells as well as those of cancerous cells. Besides Pt(II) has a great affinity for S containing ligands. As such, when cisplatin is administered intravenously to the blood stream it can react with S-containing proteins and thereby form toxic compounds. These reactions also reduce the amount of cisplatin bio-available thus requiring higher doses for its

anticancer activity. Minimizing these toxic effects is a prime need in safer chemotherapeutic treatments to cancers. In order to realize this synthesized porous nanoparticles of calcium carbonate can be used to encapsulate cisplatin in them. The encapsulation efficiency and release kinetics of cisplatin as a function of the pH of the released medium of well characterized cisplatin-encapsulated nanoparticles have to be studied. Studies have revealed that it is possible to very successfully encapsulate cisplatin in porous nanoparticles of vaterite to preserve its structure and can be released at low pH values. The release of cisplatin in the pH range from 7.0 to 8.0 was negligible and hence cisplatin exists exclusively within the nanoparticles when injected into blood. This prevents the reaction of cisplatin with thiol containing proteins present in blood and thereby the wastage of cisplatin. However, cisplatin releases very slowly over days when the pH of the medium is below 6.0. This means that at the acidic pH of around 5.5 that is maintained at cancer cells cisplatin is released slowly. As such, this strategy is successful in minimizing side effects of cisplatin and dosage requirements while enhancing the efficacy of cisplatin as an anticancer drug. Since cancer cells have an excellent affinity for folate there is a possibility of encapsulating both cisplatin and folic acid in vaterite for targeted delivery to cancer cells for slow-release only at the vicinity of them. By this way, it is possible to design and develop safe and highly effective chemotherapeutic treatment for various cancers. In this review we describe the discovery of cisplatin as an anticancer drug, chemistry of cisplatin, action of cisplatin, ways of reducing toxicity and increasing bioavailability of cisplatin and encapsulated cisplatin as a targeted drug towards cancerous cells for slow release only at the vicinity of the cancer cells.

## 2. Discovery of Cisplatin as an Anticancer Drug

It is indeed an astounding fact that the discovery of least 5.8% of all the drugs that are available on market involved serendipity, i.e., events occurred by chance in a happy and beneficial way. When taken together the drugs that were derived from those discovered through serendipity and laboratory accidents, this percentage covers nearly quarter, i.e., 24.1%, of the marketed drugs. In the case of anticancer drugs, an astonishing percentage of 35.2% of anticancer drugs that are available in the market were discovered through serendipity or by lucky chance clasped by an intelligent mind. Cisplatin is one such amazing anticancer drug; the fact of its anticancer activity revealed through serendipity [1-10].

In 1965, Rosenberg realized that microscopic images of dividing cells resembled the pattern shown by iron shavings subjected to a magnetic field [11-12]. This is the typical pattern observed when iron shavings are spilled over a sheet of paper placed on a magnet. The iron shavings then arrange in a particular order along the magnetic lines of the magnet, as is demonstrated in a famous high school experiment to give evidence for magnetic force lines created by a magnet. When

he was thinking about the similarity between these magnetic lines and mitotic spindles of a dividing cell, he wondered whether electrical currents also play any role in cellular divisions. To investigate this, he devised an experiment in which he placed two platinum wires in a beaker containing ammonium chloride/ammonium hydroxide buffer and *Escherichia coli* (*E. coli*) bacteria and passed an electric current through the solution. He used platinum metal since platinum is an inert metal, which he then thought, had no effect on cell divisions. He observed that the bacteria cells stopped dividing, as soon as current is turned on, but they kept on growing to up to about 300 times their normal length. The bacteria then resembled like spaghetti instead of their typical sausage-like shape [13]. When the power is turned off, the bacteria cells begin to divide again. Therefore, it appeared to Rosenberg that electrical current is perhaps affecting the cell division. As such, Rosenberg and his colleagues thought that they have discovered a way to control cell division since they thought electric current had such a profound effect on the cell division. They spent two more years trying to understand insight into the effect of electric current on cell division but to realize that electric currents had no effect on it. The profound effect on blocking the cell division was caused not by the electric current but by a platinum compound that was released into the solution from the platinum wires which were used to pass electric current [14]. Two years of further research enabled them to realize that cisplatin, whose IUPAC name is (SP-4-2)-diamminedichloroplatinum(II), is indeed the platinum compound that led to blocking cell division and expansion. They then thought that if cisplatin can block cell division in *E. coli* bacteria, it is possible to use cisplatin to prevent cell division in tumours also [14]. Rosenberg tested it with Sarcoma 180 tumours in Swiss white mice model to find out that tumours indeed responded to cisplatin and contracted [15]. The tumours of mice disappeared after six months and mice became healthy without recurring the tumour growth. However, high doses of cisplatin were found to be toxic to healthy cells also but mice could successfully tolerate to low doses of cisplatin [16-18].

Although, cisplatin did not go to human trials immediately, due to the general belief that heavy metals are toxic, it entered in clinical trials in 1971. Cisplatin showed over 90% cure rate for testicular cancers when used in combination with other chemotherapeutic drugs. [19, 20] The delay occurred is because, although cisplatin passed human trials producing positive results for anticancer activities, it had severe toxic side effects, such as nephrotoxicity (toxicity to kidneys), neurotoxicity (toxicity to nerves system), joint pain, ringing in the ears, problems associated with hearing, and weakness [19-23].

It was therefore necessary to give auxiliary drugs to control these side effects. However, in 1978, the US Food and Drug Administration (FDA) approved cisplatin for treatments of testicular and bladder cancers [24, 25]. Cisplatin, therefore, goes as another miracle compound with accidental discovery of its anticancer activity. Cisplatin is now used to treat a wide range of cancers such as head and neck [26] testicular [27],

small-cell lung [28] and non small-cell lung [29], bladder [30], cervical [31] and ovarian [32, 33] cancers. Cisplatin has become the premier in combination therapy for solid tumours such as gastric, bladder, cervical, ovarian, lung, breast, head and neck cancers and some malignant mesothelioma and some less common cancers. Since 1978 to-date, several millions of patients have been benefitted by cisplatin treatment.

### 3. Chemistry of Cisplatin

Cisplatin has very interesting historical milestones not only in pharmacology but also in chemistry. It was first synthesized in 1845 by Michel Peyrone and was then called Peyrone's chloride [34, 35]. Its structure was not elucidated until 1893 and it was finally done by the Father of Coordination Chemistry Alfred Werner who won Nobel Prize for Chemistry in 1913 for proposing and elucidating structures of coordination complexes, particularly, elucidating structures of square planar complexes such as cisplatin and transplatin [36]. In this way, cisplatin contributed to the first Nobel Prize awarded for Inorganic Chemistry also. Cisplatin is a square planar complex of diamminedichloroplatinum(II) where the ligands occupy cis positions. i.e. the two chloro ligands are on one side and two ammine ligands on the other side of the same plane as shown in its structure given below. If the chloro and ammine ligands occupy opposite sides the compound is then called transplatin. Structures of cisplatin and transplatin are given in Figure 1.

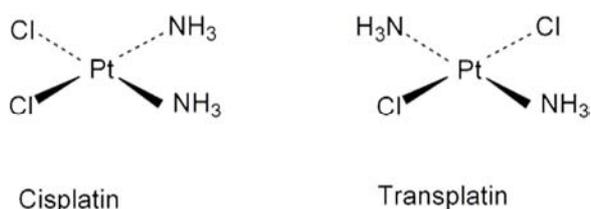


Figure 1. Chemicals structures of cisplatin and transplatin.

In order to distinguish between cisplatin and transplatin, the Korsakov test [37, 38] can be used. In this test, cisplatin or transplatin is heated with thiourea in the aqueous solution. Cisplatin reacts with thiourea in hot aqueous solution to result in deep yellow tetra bis(thiourea)platinum(II) which upon cooling crystallizes to give yellow needle-like crystals. Transplatin also reacts with thiourea in hot aqueous solution giving trans-bis(thiourea)diammineplatinum(II) which is colourless. Upon cooling snow white needles of trans-bis(thiourea)diammineplatinum(II) crystals separate [39, 40].

Although, Pt-NH<sub>3</sub> dative bonds are inert (NH<sub>3</sub> is a strong field ligand) in water Pt-Cl (Cl is a weak field ligand) bond is quite labile. Therefore, the latter can be replaced by a water molecule (aqua ligand) forming [PtCl(H<sub>2</sub>O)(NH<sub>3</sub>)<sub>2</sub>]<sup>+</sup> complex ion or with two water molecules forming Pt(H<sub>2</sub>O)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub><sup>2+</sup> complex ion. These ligand replacement reactions are concentration dependent and hence cisplatin is stable only in aqueous solutions containing high

concentrations of chloride ions. That is why cisplatin injection solution is supplied in saline water [41-43].

### 4. Action of Cisplatin

The anticancer activity of cisplatin is believed to be due to its interaction with DNA to result in programmed cell death by apoptosis; a sequences of events leading to cell death without releasing any harmful substances to the surrounding area [44]. Cisplatin injection solution is administered to a patient intravenously. The blood plasma has a relatively high chloride concentration of ~100 mmol.dm<sup>-3</sup> [45], and as such cisplatin exists exclusively as it is in blood without a chloride ligand being replaced by aqua ligand by the process known as aquation. However, platinum has a great affinity for thiol groups. Therefore, cisplatin can bind to proteins such as human serum albumin and amino acids such as cysteine [46, 47]. Therefore, part of the cisplatin present in blood plasma exists in protein bound form which contributes to the deactivation and the side effects of the drug. The unbound or intact cisplatin molecules can enter into cells by diffusing through cell membrane. Since the blood supply to cancer cells is much higher than that to normal cells, statistically, a higher fraction of the drug is supplied to cancer cells. Recent studies have shown that cisplatin enters cancer cells by actively transporting through the cell membrane by Cu(II)-transporting proteins [48].

The intracellular chloride concentration is ~ 4-20 mmol.dm<sup>-3</sup> [49] and hence it is quite low compared to that in blood plasma. Under these conditions, one chloro ligand is replaced by an aqua ligand forming highly reactive [PtCl(H<sub>2</sub>O)(NH<sub>3</sub>)<sub>2</sub>]<sup>+</sup> complex ion. This ion can react with N-sites of DNA by replacing aqua ligand by this N site [50-54]. As shown in Figure 2, there are several possibilities for cisplatin to bind to DNA. It can bind to guanine (G) N-7, or cytosine (C) N, or adenine (A) nitrogen. However, binding to guanine is more favoured due to higher nucleophilicity of G-N7 atom. Hence, cisplatin exclusively binds to guanine N-atom of the DNA strand forming a mono-functional adduct. The mono-functional adduct then can bind directly to another guanine or adenine N-7 by substituting for chloro ligand or it can undergo aquation replacing chloro ligand first by aqua ligand and then bind to 3guanine or adenine N-7 resulting in ring closure. This causes a significant distortion of DNA that can be recognized by one or more DNA binding proteins. Among other DNA repairing proteins, the distortion of DNA due to platinum binding is recognized by the high mobility group (HMG)-domain protein and it binds tightly to the complex and inserts a phenyl group into the groove created. This adduct formed de-stacks nucleotide bases making the DNA helix to be kinked [55-57]. This way, the DNA repair mechanism is blocked and hence the cell then undergoes its programmed death by signalling to endure apoptosis.

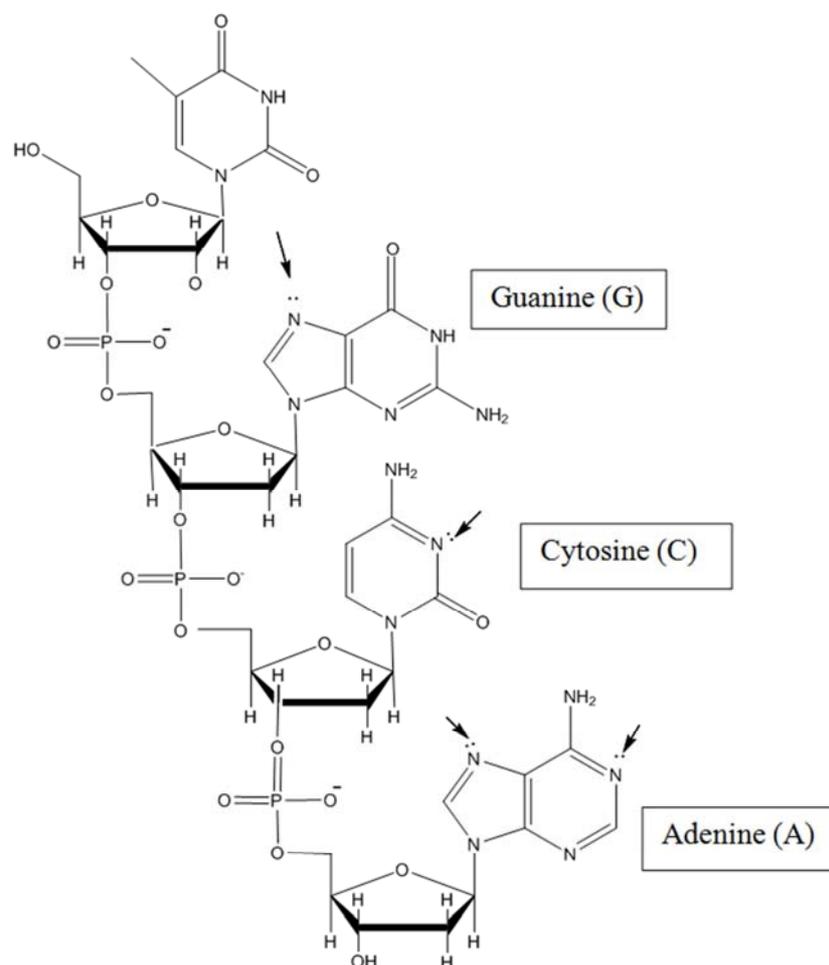


Figure 2. Possible binding sites for Pt(II) in  $[PtCl(H_2O)(NH_3)_2]^+$  and  $[Pt(H_2O)(NH_3)_2(G-N7)]^+$ .

## 5. Pharmacokinetics of Cisplatin

Since cisplatin readily reacts with thiol and S containing proteins present in blood, it is available in two forms; namely, unbound normal cisplatin and protein-bound cisplatin. Out of which the unbound cisplatin molecules are the important anticancer agents while those protein-bound cisplatin contribute to its toxicity. As such population pharmacokinetics of unbound and total (or bound) cisplatin in patients who receive cisplatin infusion is important and several studies have performed towards elucidating these factors [58-61]. In these studies, pharmacokinetic and demographic data have been obtained from adult patients treated with 30 min daily intravenous infusions of cisplatin for five consecutive days or twice a month with a dose per infusion varying from 15 to 80 mg. Following the drug administration blood samples were taken after 0.25, 0.45, 0.75, 1, 1.5, 2, 4, 6, 8, 12 and 24 h. Samples were then centrifuged immediately at each time and plasma was separated and subjected to ultrafiltration through an Amicon MPS I micropartition system and frozen at  $-20^\circ\text{C}$  until analysis. The concentrations of cisplatin in the samples were determined by measuring the Pt content using flameless atomic absorption spectroscopy. Urion et al. have used 43

patients for tis analysis and both unbound and total platinum concentration-time data were analysed using a nonlinear mixed effects model [58]. They had 483 plasma samples from the 43 patients which gave rise to 396 unbound and 477 total plasma concentrations. Their results matched well with previously reported results [59-61] for short-term infusions of  $< 3$  h where the total plasma platinum clearance between 0.5 to  $1.5 \text{ L}\cdot\text{h}^{-1}$ . Their results also tallied with previous values for the clearance of unbound plasma platinum also and fallen within the reported range of  $13\text{-}42 \text{ L}\cdot\text{h}^{-1}$ . The values obtained by Urion et al. are as follows. The mean population estimates for total and unbound cisplatin are 0.68 and  $35.5 \text{ L}\cdot\text{h}^{-1}$ , respectively, for the central distribution volume. They have found that the unbound cisplatin clearance depends upon the body surface area and creatinine clearance though the central distribution volume depends only upon the body surface area. As per metabolite formation, the elimination rate constant for plasma bound platinum is  $0.014 \text{ h}^{-1}$ . They have also found that the pharmacokinetic parameter,  $f_m/V_m$ , where  $f_m$  is the metabolite-to-parent clearance fraction and  $V_m$  is the metabolite volume, which is a measure of the clearance of unbound platinum due to irreversible plasma binding, is proportional directly to the serum protein concentration and inversely to the dose per  $\text{m}^2$ .

## 6. Reducing Toxicity and Increasing Bio-availability

One way to reduce toxicity of by-products formed by the binding of cisplatin to thiol containing proteins and amino

acids present in blood plasma and to decrease the rates of such ligand-exchange reactions taking place in the blood plasma is to search for other anticancer active coordination complexes of platinum(II) which are analogous to cisplatin [62, 63].

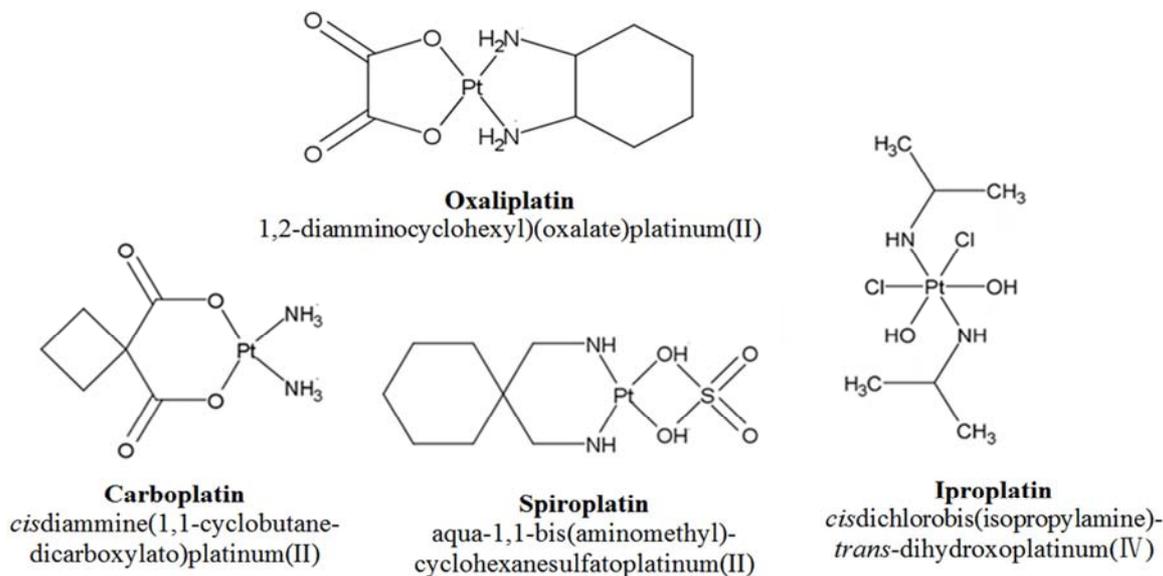


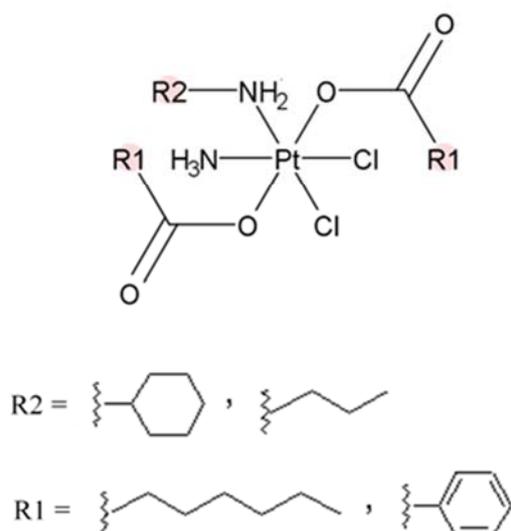
Figure 3. Chemical structures and chemical formulae of oxaliplatin, carboplatin, spiroplatin and iproplatin.

These compounds should satisfy several requirements: they should have two cis amino groups with at least one proton on N, two leaving groups should be in cis positions, leaving groups must be moderately easy to remove than chloro ligands and the compounds should be neutral so as to cross the cell membrane. Several such cisplatin analogues have been entered the clinical trials of which carboplatin; cis-diammine (1, 1-cyclobutanedicarboxylato)platinum (II) and oxaliplatin; 1, 2-diamminocyclohexyl(oxalate)platinum(II), have shown lower toxicities owing to slower rate of hydration of oxalate ligands than hydration of the chloro ligand in cisplatin. As such, both carboplatin and oxaliplatin have increased access to cells than cisplatin [64]. In parallel with the development of carboplatin, two such compounds known as spiroplatin, and iproplatin were developed [65]. Their structures and chemical formulae are given in Figure 3.

Out of these three drugs, carboplatin has been proven to be the most useful and hence its clinical use as an anticancer drug to treat ovarian cancer was approved by the FDA in 1989. Carboplatin is less toxic because the dicarboxylato ligand is not as labile as chloro ligand when bonded to Pt and hence the carboplatin will not undergo hydrolysis in aqueous solution as much as cisplatin does. As such, the wastage of the drug and consequent formation of toxic adducts in blood are less in carboplatin than that in cisplatin. Thus carboplatin has much higher retention half-life of about 30 h in blood when compared to much lower retention half-life of cisplatin in blood which is in the range 1.5 to 3.6 h. As such, the dosage requirement and toxicity to peripheral neurons and kidneys is less in carboplatin than that in cisplatin. There are reports that carboplatin has worked for cancers where cisplatin is inactive.

By 1993, nine platinum analogues were in clinical trials around the world. These include ormaplatin [tetraplatin], oxaliplatin, DWA2114R, enloplatin, lobaplatin, CI-973 [NK-121], 254-S, JM-216 and liposome-entrapped cis-bis-neodecanoato-trans-R, R-1, 2-diamminocyclohexane platinum (II) [L-NDDP] [57]. These cisplatin analogues were developed to overcome drawbacks associated with cisplatin such as toxicity and forced hydration due to labile Pt-Cl bond. However, a recent report of Gabriel Angel Gonzalez Esparza of University of Texas at El Paso, USA reveal that only cisplatin and carboplatin are in clinical use as of 2010 [66]. In this work, Esparza has claimed that they have prepared cisplatin analogues using heterocyclic compounds with N-containing ligands such as bipyridine and biquinoline and the compounds have shown very promising antitumor properties *in vitro* and *in vivo* in cisplatin-resistant model systems. Esparza has also shown that these heterocyclic compounds function as DNA intercalating agents and insert between the base pairs of the double helix, thus unwinding it and thereby disrupting the normal function of DNA leading to interference with gene transcriptions, gene expression, carcinogenesis, mutagenesis and finally cell death [66]. They have also focused on the design and synthesis of amphiphilic molecules having hydrophobic lipid hydrocarbon chains with ester functional groups and hydrophilic head groups containing platinum coordinated by N-heterocyclic compounds to make cisplatin analogues. These amphiphilic cisplatin analogues emulsify to make micelles which can be used as drug delivery systems that encapsulate anticancer drugs. The Pt-Cl groups will recede on the surface of the micelles. The micelles of platinum biquinoline and platinum

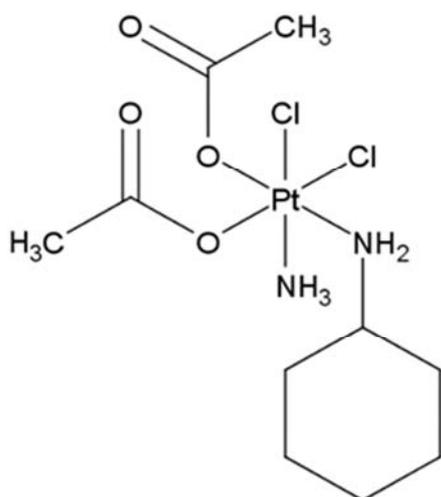
bipyridine will disassemble by the action of the esterases releasing the anticancer drugs. Then the Pt-Cl will bind to the DNA and the heterocyclic rings will intercalate in the DNA disrupting the DNA structure leading to cell death.



**Figure 4.** Cisplatin analogues with general structure shown where R1 and R2 are hydrocarbon moieties and two examples for each are shown in the right.

Of note is the development of cisplatin analogues that can be administered orally rather than intravenously. A broad range of compounds having general structure shown in Figure 4 have been synthesized. These drugs were proven to be capable of administering orally [65].

The first oral cisplatin analogue developed is called satraplatin; bis-(acetate)-ammine dichloro-(cyclohexylamine) platinum (IV) whose chemical structure is given in Figure 5 [67, 68]. It has been reported that satraplatin has similar antitumor activity to that of cisplatin and carboplatin as demonstrated in *in vitro* and *in vivo* studies. Satraplatin has also shown activity in some platinum resistant *in vitro* tumour models [69]. However, satraplatin has not been approved by the FDA to use as a drug.



**Figure 5.** Chemical structure of satraplatin.

## 7. Encapsulated Cisplatin

A better way to retain cisplatin with increased bio-availability and reduced toxicity is to encapsulate it in suitable hosts and to direct to cancer cells in a targeted manner so as to release slowly in minimum required constant doses. Our research is aiming at this targeted delivery and slow release of cisplatin to cancer cells.

Encapsulation of cisplatin in a suitable host material is expected to benefit in many ways. However, the host material should fulfil certain critical requirements for it be successful in hosting cisplatin to retain the anticancer activity while eliminating side effects associated with protein adducts that are formed in the blood plasma and thereby contributing to decreasing dosages. Therefore, the host material should encapsulate cisplatin without any structural changes, it should also encapsulate sufficient amount of chloride ions with minimal amount of water, the composite material should not release the drug cisplatin in blood plasma, the composite drug should cross the cell membrane and reach the nucleus of cells where cisplatin should release in constant minimum required dosage only at the nucleus of cancerous cells.

Reducing dosage and increasing efficacy and selectivity, while minimizing side effects of platinum-based anticancer drugs, are mandatory requirements for safe chemotherapeutic treatments to various cancers. Several attempts have been made to achieve these objectives and encapsulation of the drug in liposomes is one such way forward approach [70, 71]. Pt-based drugs such as cisplatin and carboplatin encapsulated in liposomes have shown to improve cytotoxicity of the drugs for several cancer cell lines possibly due to increased accumulation of liposome-encapsulated drugs in intracellular media. However, liposomes have some drawbacks also. They have very poor stability in blood plasma and as such they tend to break in blood plasma releasing the drugs [72].

In order to address the problem of poor stability of liposomes in blood plasma Sadhukha and Prabha studied the use of nanoparticles of the biodegradable polymer, poly(D, L-lactide-co-glycolide) to encapsulate carboplatin for targeted delivery and slow release at cancer cells. These nanoparticles had sustained release of carboplatin for 7 days. They have also demonstrated that the cellular uptake of carboplatin encapsulated in nanoparticles to be several fold higher than that with free carboplatin in A549 (lung) and MA148 (ovarian) tumour cells with up to 280 fold reduction in IC<sub>50</sub> values [73]. Vasir and Labhasetwar have reviewed Biodegradable Nanoparticles (NPs) for Cytosolic Delivery of Therapeutics [74]. In this review they have explained the use of various drug carriers which include liposomes, cell penetrating peptides, cationic polymer conjugates, and polymeric nanoparticles and so on that can be used for intracellular delivery of drugs. Figure 1 in their review [74] clearly shows the several barriers that are encountered in the cellular uptake of a drug encapsulated in a suitable carrier. They have identified seven processes when these systems reach a cell. These include (1) Cellular association of NPs, (2) Internalization of NPs into the cells by endocytosis, (3)

Endosomal escape of NPs, (4) Release of therapeutic in cytoplasm, (5) Cytosolic transport of therapeutic agent, (6) Degradation of drug either in lysosomes or in cytoplasm and (7) Exocytosis of NPs. As such the cytosolic delivery of therapeutics using polymeric nanoparticles (NPs) are associated with barriers in the processes such as the cellular uptake of NPs, endosomal escape of NPs, cytoplasmic transport of therapeutic/NPs and sustained therapeutic benefit [74]. The use of targeting ligands can help binding to specific receptors on cell membranes. One such example is the folate targeting. This is a method utilized in biotechnology for drug delivery purposes. In this method, a vitamin and folic acid are attached to a drug molecule to form a folate conjugate. Foliates have a very high natural affinity for the folate receptor protein that is commonly found on the surface of many human cancers. The folate-drug conjugates then bind to the folate receptor protein and trigger cellular uptake via endocytosis [75-83].

Among other materials being investigated by various scientists, our choice of porous microspheres of vaterite form of calcium carbonate formed from assembly of 30 nm sized nanoparticles of vaterite seems to fulfil all the above requirements. Our studies have shown that these microspheres can be readily synthesized through soft molecular template approach starting from readily available and mundane Sri Lankan mineral raw materials and that cisplatin in its right structural form can be encapsulated together with accompanying chloride ions, and the encapsulated drugs are stable in blood pH of 7.35 – 7.45. In vivo tests have revealed that cisplatin is slowly released in mildly acidic pH values of cancerous cells [84]. More studies are underway to study the crossing the cell membrane of drug-encapsulated vaterite microspheres to reach the nucleus of cells for programmed cell death by the apoptosis of DNA. If our approach will be successful a whole range of cancer therapeutic drugs can be developed which would have no cytotoxicity to healthy cells. Such a remarkable contribution to help fight against many cancers would be highly desirable.

## 8. Conclusions

In this review it has been revealed the serendipity in drug discovery particularly in the discovery of anticancer drugs 35.2% of those drugs have been discovered through serendipity. Cisplatin which was also discovered through serendipity has opened up a new Era of anticancer drugs based on transition metal complexes. It is effective against many cancers and is particularly used to treat testicular cancers. Cisplatin binds to DNA strands and leads to progressive damage of the DNA damage leading to cell death. When administered intravenously it can react with S-containing proteins thus reducing the bioavailability of the drug and increasing its toxicity. There are other alternatives of cisplatin such as oxaliplatin etc. which have strong ligands than chloro ligands thus making less susceptible for S-containing protein adduct formation. Encapsulation of cisplatin in porous nanoparticles leads to a targeted delivery and slow release of the drug only at the vicinity of the cancer cells. Folate

mediation may be used for targeting the drug and pH-responsive nanoparticles is yet another way of targeting the drug to cancer cells. Although there are many other ways of drug targeting this review focused only on the use of porous pH-sensitive nanoparticles of calcium carbonate for cisplatin encapsulation for targeted delivery and slow-release at the vicinity of cancer cells which is triggered by slight acidity of cancer cells.

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