Polymeric Drug Delivery of Platinum-Based Anticancer Agents

KATHERINE J. HAXTON,[1,2] HELEN M. BURT[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

[2]School of Physical and Geographical Sciences, Keele University, Keele, Staffordshire ST5 5BG, United Kingdom

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ABSTRACT: Platinum-based anticancer agents such as cisplatin and carboplatin are in widespread clinical use but associated with many side effects. Improving the delivery of cytotoxic platinum compounds may lead to reduced side effects and achieve greater efficacy at lower doses. Polymer-based therapeutics have been investigated as potential drug delivery vehicles for platinum-based drugs. Against a background of the chemistry and pharmacology of cytotoxic platinum compounds, this review discusses the formation and properties of platinum–polymer complexes, dendrimers, micelles, and microparticulates. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:2299–2316, 2009

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INTRODUCTION

Platinum anticancer drugs are in widespread use despite dose limiting toxicity.[1–5] Much research has been focused on methods of reducing side effects and increasing efficacy in humans. One extensive area of research is concerned with improving the delivery of platinum anticancer drugs by polymer drug delivery.[6,7] These may be micelles, micro- or nano-spheres, implants or simply polymer–drug conjugates.[8–10] Polymer drug delivery systems have been successfully used to deliver hydrophobic drugs.[11–13] Improving the delivery of platinum-based drugs may lead to reduced side effects, greater efficacy at lower doses of drug, and a means to target drugs directly to the tumor site.[14,15] For a drug delivery system to be effective, it must have high plasma stability,[7] low toxicity and immunogenicity, and protect drugs against premature metabolism.[15,16] This review provides a background to the chemistry and pharmacology of platinum compounds and then discusses the formation and properties of platinum–polymer complexes, dendrimers, micelles, and microparticulates.

PHYSICOCHEMICAL PROPERTIES OF PLATINUM DRUGS

Physical Properties of Platinum Drugs

Classical anticancer platinum complexes in clinical use consist of neutral, square planar, platinum(II)

Correspondence to: Helen M. Burt (Telephone: 604-822-2440; Fax: 604-822-3035;
E-mail: burt@interchange.ubc.ca)

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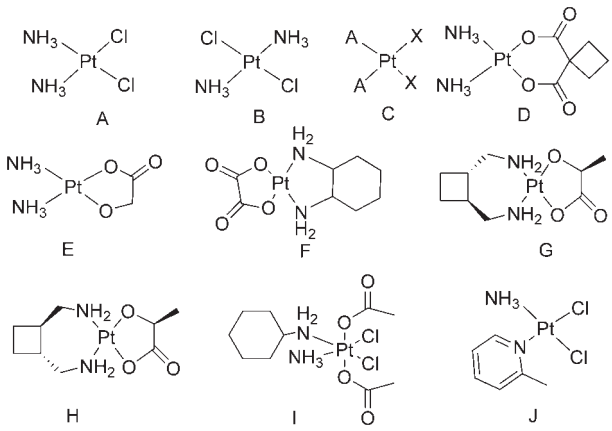

Figure 1. Platinum drugs: (A) cisplatin, (B) transplatin, (C) generic structure, (D) carboplatin, (E) nedaplatin, (F) oxaliplatin, (G) Lobaplatin SSS diasteriomer, (H) Lobaplatin RRS diasteriomer, (I) satraplatin, (J) picoplatin.

complexes with no overall charge, and a *cis* configuration at the metal centre (Fig. 1A and C–I).[5] They can be described by the general formula *cis*-[PtA_2X_2] (Fig. 1C). A_2 represents two monodentate or one bidentate ligand with nitrogen donor atoms. X_2 represents two monodentate or one bidentate anionic ligand(s) that are labile leaving groups during reactions.[17] The substituent A may be ammonia (ammine), 1,2-diaminocyclohexane (DACH) or another amine group. The substituent X may be chloride ions, oxalic acid or 1,1-cyclobutanedicarboxylic acid, or another organic acid. Some octahedral platinum(IV) complexes have also been found to be active against tumors, and are considered non classical (Fig. 1J).[2,4] Cisplatin (*cis*-diamminedichloroplatinum(II)) was the first of this class of drug, and its structural isomer, transplatin, shows no anticancer activity (Fig. 1A and B).[18,19] Importantly, cisplatin and transplatin do not isomerise under biological conditions.[17]

Modifying the leaving group, X on the complex will alter the biodistribution and the nature of the side effects.[2,20] Modifying the non-leaving groups, A_2 will alter the anticancer properties and lead to structurally different DNA adducts being formed.[20]

Chemical Properties of Platinum Drugs

The chemistry of any organometallic drug will be influenced by the oxidation state of the metal, the strength of bonds between the metal ion and surrounding ligands, and the ability of the complex to participate in ligand exchange. Ligand exchanges are reactions in which one or more of the ligand groups at the metal centre are replaced by new ligands. The ligand group that is replaced is referred to as a leaving group, and the incoming ligand allows for the formation of a more stable complex under the conditions of the reaction.

Platinum has two principal oxidation states, Pt(II) and Pt(IV). Platinum(II) is diamagnetic and has a preference for nitrogen and heavy donor atoms such as phosphorus, arsenic, sulfur and selenium, but has low affinity for oxygen and fluorine atoms. Bonds between platinum and sulfur are strong due to the formation of metal–ligand π bonds caused by overlap of the d π orbitals on the metal with the empty d π orbitals in the valence shell of the sulfur. This is important because the platinum drugs will bind strongly to sulfur containing biomacromolecules and will be discussed later. Platinum(II) is typically square planar with four coordinated ligands (Fig. 1A–I), while platinum(IV) is usually octahedral with six coordinated ligands (Fig. 1J). Square planar platinum(II) is subject to the trans effect, where a ligand trans to a leaving group, can influence the rate of substitution of that leaving group.[17] If the ligand is a strong σ donor or π acceptor, it accelerates the substitution of the trans ligand, due to greater overlap of the ligand orbitals with the σ or π Pt 6p orbitals. The greater the orbital overlap, the stronger the trans effect. Platinum nitrogen bonds are stable while platinum chlorine and platinum oxygen bonds are labile.[17]

Aquation of cisplatin is the ligand exchange process where chloride ligands in cisplatin are replaced by water molecules.[4,21] In general terms, rate of exchange of the X_2 ligands with water will affect the toxicity of the platinum complexes. Aquation may be called hydrolytic activation or hydrolysis of platinum drugs (Fig. 2). In biological fluids, the rate of hydrolysis is dependent on the concentration of chloride ions present in the solution. Where the chloride ion concentration is high, hydrolysis is unlikely and cisplatin remains intact,[17] for example in blood. Aquation is essential for binding to proteins, DNA or

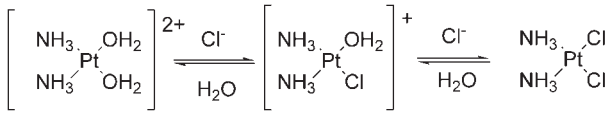

Figure 2. Initial equilibria of cisplatin in water.

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