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Crospovidone: position in granulate and disintegration

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Three methods are generally employed for incorporating disintegrants into tablets, i.e. by positioning them intra-, extra- or intra/extragranularly [1]. Although it may theoretically be expected that this could lead to different effects the practical results are frequently marginal, probably due to encasement of the disintegrant in the binder and/or active. However, disintegrant positioning should be considered in tablet design as shown in the following example using a water soluble, high dose drug formulation with crospovidone, an excipient with powerful disintegrating properties [2, 3].

The drug used is soluble in water but very slightly soluble in ethanol. Granulations were carried out in an intensive mixer and tablet compression in a rotary tabletting machine.

Two 6 kg granulations, A and B, were prepared followed by drying, sizing, mixing with extragranular components (batch B), glidant and lubricant. The blends were compressed to a target tablet mass of 750 mg using 8×18 mm capsule shaped punches and similar compaction pressures. The compositions of the two batches are shown in Table 1.

The tablets were analyzed for hardness ($n = 20$), disintegration ($n = 6$, water, no disks) and dissolution ($n = 6$, water, 900 ml, 37 °C, paddle, 50 rpm). The results are enumerated in Table 2.

Table 1: Composition of batches A and B

Component	A (intragr.) mg/tablet	B (intra/extragr.) mg/tablet
Drug	583	583
Microcrystalline cellulose (intragranular)	97	61
Crospovidone (intragranular)	60 (8%)	30 (4%)
Ethanol	q.s.	q.s.
Microcrystalline cellulose (extragranular)	–	36
Crospovidone (extragranular)	–	30 (4%)
Colloidal silicon dioxide	5	5
Magnesium stearate	5	5

Table 2: Tablet properties

	A (intragranular)	B (intra/extragr.)
Hardness (kg)	27.8 (c.v. 4.1%)	27.3 (c.v. 3.9%)
Disintegration (min)	14.6	1.0
Time to 50% drug dissolved (min)	25	1.7

It is evident that positioning the disintegrant intra- and extragranularly makes a vital difference in this case, transforming the tablets from an unacceptable to a high quality product with almost flash disintegration.

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Pt(II) and Pd(II) complexes of 3-aminoflavone: *In vitro* and *in vivo* evaluation

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Since the discovery by Rosenberg et al. that *cis*-diamminedichloroplatinum(II) (cisplatin) exhibits antitumor activity [1], extensive studies of platinum amine analogues have been performed. Cisplatin was the first to be approved for clinical use in the treatment of genitourinary, head and neck tumors in humans. Unfortunately, cisplatin caused a number of negative side effects like nephrotoxicity, neurotoxicity and the development of resistance. Extensive effort has been devoted to the development of platinum compounds with a broader activity spectrum and lower toxicity [2]. Platinum complexes exhibiting antitumor activity should incorporate two *cis* nitrogen ligands each bearing at least one hydrogen (primary or secondary amines) together with two less strongly bound ligands (leaving groups) such as chlorides. The NH_2 moiety is believed to be essential because of the possibility of hydrogen bond formation between the amine and DNA fragments [3]. It is possible that amine release could play a role in the toxic side-effects of platinum anticancer agents. Our approach to design more effective anticancer drugs with less toxicity is based on the biological activity of flavanoids [4–8]. The observation that the flavanoide ligands themselves have anticancer activity [9, 10] prompted us to investigate novel platinum complexes, structurally related to cisplatin, containing a flavone ligand instead of amine with two *cis* bound labile chloride ligands. To minimize toxicity, 3-aminoflavone which possesses the desired NH_2 groups has been used as non leaving ligand. In the present preliminary study, we report on the antitumor activity of the complexes of the structure *cis*-$[Pt(AF)_2Cl_2]$ [11] and *trans*-$[Pd(AF)_2Cl_2]$, where AF = 3-aminoflavone. The alkylating ability of *cis*-platinum(II) and *trans*-palladium(II) complexes, containing 3-aminoflavone as ligands, has been also evaluated. The investigation is based on an *in vitro* test with 4-(4′-nitrobenzyl)pyridine (NBP) (Preussmann Test) [12].

The result of the NBP test show significant alkylating activities for the complexes (Table 1). The date are relative to those for cisplatin. The data revealed the markedly greater alkylating activity of *cis*-$[Pt(AF)_2Cl_2]$ than of *trans*-$[Pd(AF)_2Cl_2]$. In a previous study [12], a correlation between the alkylating activity *in vitro* and the *in vivo* cytostatic activity against a mice Sa180 sarcoma solid tumor was found for platinum(II) complexes. The antineoplastic activity of the *cis*-platinum(II) and *trans*-palladium(II) complexes of 3-aminoflavone were examined against the development leukemia L1210. In our experiments we implanted 3×10^5 L1210 cells intraperitoneally

Table 1: NBP test

Compd.	Concentration (M/l)	Absorbance* $\lambda_{max} = 545$ nm	ε	Relative alkylating activity (%)
cis-$[Pt(AF)_2Cl_2]$	1.25×10^{-4}	0.630	5040	2100
trans-$[Pd(AF)_2Cl_2]$	1.25×10^{-4}	0.100	800	333
Cisplatin	1.25×10^{-3}	0.300	240	100

* Means of 3 determination