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# PAMAM dendrimers as a potential oral drug delivery system: uptake by everted rat intestinal sacs in-vitro

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Dendrimers are hyperbranched macromolecules with a large number of reactive surface groups. They may be useful for carrying drugs covalently bound to their surface, complexed to the surface or entrapped within their internal cavity (Tomalia et. al., 1985). Previously we have described the biocompatibility of polyamidoamine (PAMAM) dendrimers (Duncan & Malik, 1996) and also other families of dendrimer (Wiwattanapatapee et. al., 1997). A PAMAM-platinate has been designed for parenteral use (Malik et al., 1998). In this study we sought to evaluate the potential of PAMAM dendrimers as an oral drug delivery system. The uptake of dendrimers was studied using the everted rat intestine as an *in vitro* model. The effect of incubation time, concentration of dendrimer and dendrimer size and surface charge on the uptake were determined.

PAMAM dendrimers (Dendritech), both cationic (Gen 3, 4) and anionic (Gen 2.5, 3.5, 5.5) of Mw in the range 6,011-50,865 Daltons were $^{125}$I-labelled using the chloramine T or Bolton and Hunter reagent. Using everted intestinal sacs from adult male Wistar rats (Naisbett & Woodley, 1994), the tissue uptake and serosal transport was determined over 2h. In initially a dendrimer concentration of 20μg/ml was selected (proven to be non toxic), but later the effect of concentration was also studied. Uptake and transport were expressed as an "Endocytic Index" (i.e. the amount of medium (μl) whose contained substrate is captured or transported per mg tissue protein per h (Williams et. al., 1975). The nature of the radioactivity in serosal fluid was confirmed by gel permeation chromatography.

All radiolabelled dendrimers were taken up by intestinal tissue and transferred to the serosal fluid in a time-dependent manner. The Endocytic Indices measured are shown in Table 1. For anionic dendrimers, the tissue uptake and transfer increased linearly with time, and also with concentration (results not shown). The small amount of substrate detected in tissue, indicated that anionic PAMAM dendrimers were transported rapidly across the tissue into the serosal fluid. Transfer rates were very high compared to those seen previously for other macromolecules such as $^{125}$I-labelled PVP and $^{125}$I-labelled tomato lectin (Naisbett & Woodley, 1994).

**Table 1 Uptake and Serosal Transfer of PAMAM Dendrimers ( initial rate)**

| Macromolecule | Endocytic index (μl/mg/h) | |
|---|---|---|
| | Tissue | Serosal |
| G2.5 | 0.76±0.07 | 4.04±0.99 |
| G3.5 | 0.65±0.09 | 3.39±0.51 |
| G5.5 | 2.48±0.51 | 4.40±0.67 |
| G3 | 3.33±0.86 | 2.34±0.28 |
| G4 | 3.46±0.65 | 2.45±0.37 |
| PVP | 0.6 | 0.7 |
| Tomato lectin | 13.0 | 0.85 |

In contrast, cationic dendrimers showed a higher rate of tissue uptake than usually seen for serosal transfer (Table 1). As concentration increased, the amount of substrate accumulating in tissue tended to increase. High levels of radioactivity in the tissue indicated that these dendrimers were transported across very slowly. As the cell membrane is negatively charged, it would be expected to interact strongly with these cationic molecules.

Dendrimers might provide an interesting new polymer system to aid oral drug delivery. Cationic PAMAM dendrimers showed bioadhesive properties and anionic PAMAM dendrimers had a particularly high transfer rate. *In vivo* experiments are ongoing to verify these observations.

Duncan R & Malik N (1996) Proceed. Intern. Sym. Control. Rel. Bioact. Mater. 23 : 105-106

Malik N & Duncan R (1998) Proceed. 3rd Intern. Sym. Polymer. Therap. p36

Naisbett B & Woodley J (1994) Int. J. Pharm. 107: 223-230

Tomalia D A et al (1985) Polymer J. 17: 117-132

Williams K E et al (1975) J. Cell. Biol. 64 : 113-122

Wiwattanapatapee R. et al (1997) J. Pharm. Pharmacol. 49, suppl 4: 28

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