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Polyamidoamine Starburst® dendrimers as solubility enhancers

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Abstract

The solubility of the hydrophobic drug ibuprofen has been compared in an aqueous solution of polyamidoamine (PAMAM) G4 dendrimer and sodium dodecyl sulphate (SDS). The PAMAM G4 dendrimer solution significantly enhanced the solubility of ibuprofen compared to 2% SDS solution. It was found that the solubility of ibuprofen in dendrimer solution was directly proportional to dendrimer concentration and inversely proportional to temperature. The influence of dendrimer solution pH on the solubility enhancement of ibuprofen suggests that it involves an electrostatic interaction between the carboxyl group of the ibuprofen molecule and the amine groups of the dendrimer molecule.

Keywords: Dendrimers; Solubility enhancement; PAMAM G4 dendrimer; Ibuprofen

Dendrimers are well defined macromolecules that have a specific size, shape and chemical functionality. Structurally they are highly branched macromolecules that can be subdivided into three architectural components: a central core branched cell, interior branch cells, and branch cells possessing surface groups. They are synthesised through a stepwise repetitive reaction sequence (Tomalia, 1995) which gives rise to different generations of the same molecule and determines the size and surface functionality of the macromolecule. It has been proposed that dendrimers may have potential applications in enhancing the solubility of low aqueous solubility drugs and as delivery systems for bioactive materials (Newkome et al., 1991). Indeed the ability of Starburst® dendrimers to function as potential drug carriers for the delivery of genetic material

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and anticancer agents has been demonstrated by Kukowska-Latallo et al. (1996) and Duncan and Malik (1996). It was suggested that the polycationic surface of the dendrimer macromolecule interacts electrostatically with biologically relevant anions, such as nucleic acids.

Starburst® polyamidoamine (PAMAM) dendrimers are a specific family of dendritic polymers, which are based on an ethylene diamine core and an amidoamine repeat branching structure (Tomalia et al., 1985). These dendrimers can be synthesised in a variety of well-defined molecular weights. Their size and surface functionality is defined by the number of controlled repetitive additions of monomer units giving rise to different generations. This study uses a fourth generation PAMAM dendrimer (G4) (Dendritech, USA) with a molecular weight of 14 215 and 64 surface amino groups per dendrimer molecule.

In the present study we investigated the potential of PAMAM dendrimers to increase the solubility of hydrophobic drugs as exemplified by the non-steroidal anti-inflammatory drug ibuprofen. The solubility of ibuprofen in G4 PAMAM dendrimer solutions in the range 2–4% w/v was determined and compared to that in a 2% w/v aqueous solution of sodium dodecyl sulphate (SDS) (as a model micellar system), 3×10^{-4} M NaOH and distilled water. The method used for sample preparation was similar for each system, i.e. excess ibuprofen was added to 20 ml vials containing 5 ml of each test solution. The vials were then incubated in a shaking water bath at 27°C for 24 h. After equilibration, the solutions were filtered through a 0.45 μm HA filter (Millipore) and the amount of ibuprofen in the filtrate determined by UV spectrophotometry at 265 nm. The effect of pH on solubility was examined over the range 2–14, which was achieved by dropwise addition of either 1 M NaOH or 0.1 M HCl. The effect of temperature was examined between 27 and 50°C.

Table 1 shows clearly the enhanced solubility of ibuprofen in dendrimer solution compared to that in water and SDS micelles. It could be hypothesised that the solubility enhancement was a consequence of the high pH of the dendrimer solutions (pH 10.5, 2% solution) rather than an interaction between dendrimer and drug, since ibuprofen being a weakly acidic drug ($pK_a = 5.2$) (Davis, 1975) will be fully ionised at pH 10.5. However, this is clearly not the case, as seen from its low solubility in 3×10^{-4} M NaOH (pH equal to that of dendrimer solution). It is proposed therefore, that the solubility enhancement is due to an electrostatic interaction between the surface amine groups of the dendrimer molecule and the carboxyl group of ibuprofen. Evidence for this is seen from the solubility of ibuprofen over a range of pH values (Table 2). At low pH there is no significant increase of solubility of ibuprofen in dendrimer solution compared to that at high pH. This is

Table 1
The influence of dendrimer concentration and temperature on the solubility (mg/ml) of ibuprofen

	Temperature (°C)				
	27	35	40	45	50
Dendrimer solution (%w/v)					
2.0	12.16	10.60	9.20	8.24	7.40
2.5	14.80	–	–	–	–
3.0	18.11	15.60	14.71	13.48	11.20
3.5	20.21	–	–	–	–
4.0	22.77	18.21	16.20	14.80	13.20
2% SDS	5.5				
3×10^{-4} M NaOH pH 10.5	0.76				
Water	0.086				

Table 2
Effect of pH on the solubility of ibuprofen in PAMAM G4 dendrimer solutions at 27°C

	2% G4 pH 10.5	3% G4 pH 10.5	Water pH 5.8	2% G4 pH 2	3% G4 pH 2
Solubility (mg/ml)	12.16	18.11	0.09	0.07	0.05

because the weakly acidic ibuprofen molecule is unionised at pH 2 and hence cannot interact electrostatically with the dendrimer molecule. Moreover, the solubility of ibuprofen increases linearly with an increase in dendrimer concentration (see Table 1) presumably due to the increase in the number of surface amines that are available to interact electrostatically with ibuprofen molecules. At each temperature, doubling the number of surface groups (an increase in concentration of 2–4%) approximately doubles the solubility of ibuprofen. Both observations are evidence of adsorption of ibuprofen molecules on the dendrimer surface.

The approximate number of ibuprofen molecules associated with each dendrimer is calculated to be 41. The primary amine groups on the surface of PAMAM dendrimers (64 surface amines/molecule) have a pK_a of 9.5 and will be insufficiently ionised at pH 10.5 to account for the observed solubility enhancement. Therefore, other processes may be involved in enhancing solubility, e.g. association of dendrimers. Table 1 shows that the amount of ibuprofen dissolved in G4 PAMAM dendrimers was inversely proportional to temperature. The cause of this effect is under further investigation.

In conclusion, PAMAM dendrimers enhance the solubility of ibuprofen to a much greater extent than SDS micelles. Evidence that the solubility increase involves electrostatic interaction between dendrimer and ibuprofen molecules is based on:

1. a proportional increase of solubility with increasing dendrimer concentration;
2. increased solubility only when the ibuprofen is in its ionised state.

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