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Small Angle Neutron Scattering (SANS) from polymer-stabilised drug nanoparticles

D. J. Goodwin, S. Sepassi-Ashtiani, L. G. Martini[1], S. J. Holland[1], G. S. Leonard[1], S. M. King[2] and M. J. Lawrence

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An increasing number of new drugs exhibit extremely poor water-solubility, and hence, low and erratic oral bioavailability. One solution to this problem is to mill the drug in the presence of an aqueous solution of polymeric stabiliser, to produce crystalline drug nanoparticles of less than 400 nm. While this novel technology has been successful in producing stable nanoparticles of a wide range of hydrophobic drugs, the development process has thus far been largely empirical, with very little understanding gained into the fundamental interface science involved in the stabilisation. The aim of this study was to rectify this deficiency and in particular, to determine the amount and conformation of stabilising polymer adsorbed onto the drug nanoparticles with a view to understanding why some stabilisers are more effective than others. Nanoparticles of two poorly water soluble drugs, nabumetone and halofantrine were prepared by milling 4 g of nabumetone or 6 g of halofantrine in the presence of a 1.5% w/v solution of either hydroxypropyl cellulose (HPC) or hydroxypropylmethyl celluloses (HPMC) for nabumetone and HPMC or polyvinylpyrrolidone (PVP) for halofantrine. After removal of the excess polymer, the nanoparticles were re-suspended in either a 31.3 or 33.8 vol% D_2O/H_2O mixture (according to the experimentally determined 'contrast-match' point of nabumetone and halofantrine, respectively). Under these conditions only the scattering from the polymer stabiliser was detected. SANS experiments were performed at the Institute Laue Langevin, France, over the momentum transfer (Q) range 0.007–0.035 $Å^{-1}$. The neutron data were analysed using a "volume fraction profile independent surface Guinier model" (King et al 2000). This allowed , the mass of polymer adsorbed per unit area, also known as the adsorbed amount (in mg m^{-2}) to be determined, as well as s, the 'second moment' of the layer; the distance of the centre-of-mass of the adsorbed polymer layer from the interface (Table 1). There was little change in either the second moment of the polymer layer or the amount of polymer adsorbed onto the nabumetone nanoparticles with molecular weight of HPC and HPMC. Under the present experimental conditions, nabumetone nanoparticles could not be prepared using HPMC of molecular weight greater than 7 kg mol^{-1}. Compared with nabumetone, HPMC adsorbed to the halofantrine nanoparticles to a lesser extent, forming a thinner adsorbed layer and indicating that a different conformation is adopted at the drug nanoparticle surface. Similarly PVP only formed a relatively thin absorbed layer on the halofantrine nanoparticles. To our knowledge these SANS studies are the first that have been performed on polymer-coated drug nanoparticles.

Table 1 Characterisation (using SANS) of polymer layer on nabumetone and halofantrine nanoparticles as a function of polymer molecular weight

Nanoparticle composition	Polymer molecular weight (M_η kg mol^{-1})	σ (Å)	Γ (mg m^2)
Nab-HPC	110	80.4	11.4
	95	76.0	11.6
	80	78.9	11.6
	65	76.5	11.0
	55	78.3	11.0
	45	80.3	11.3
Nab-HPMC	7	76.8	10.5
	5	80.8	10.8
Halo-HPMC	7	42.3	6.9
	5	33.4	7.7
Halo-PVP	46	52.7	1.8
	3	51.6	1.9

Nab, nabumetone; Halo, halofantrine; σ second moment of the adsorbed polymer layer; Γ adsorbed amount of polymer.

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Poster Session 1 – Analytical Chemistry

001

A transdermal delivery system for aspirin as an antithrombotic drug

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More than 100 years after its introduction into therapy, aspirin may be the most widely used medication in the world. Aspirin has become the gold standard with which newer antiplatelet drugs are compared for reducing risks of cardiovascular diseases, while keeping low cost. Aspirin has been, and will be, the drug of choice for the long-term treatment of platelet hyperactivity. It imparts its primary antithrombotic effect through the irreversible inhibition of PGH-synthase/COX. The resultant decreased production of prostaglandins and TXA_2 accounts for the therapeutic effects, as well as the toxicity, of aspirin. Unfortunately, aspirin has a well-recognized repertoire of unwanted gastrointestinal side effects that can affect both the upper and lower gut and may occur even at very low oral doses. These can offset its clinical benefit by predisposing patients to gastrointestinal haemorrhage. Also, orally administered aspirin requires high frequent dosing because it undergoes extensive presystemic hydrolysis in the gut and the liver into salicylic acid, which is devoid of anti-platelet activity. Because of its extremely widespread, continuous and growing use, there is a need to minimize adverse effects of aspirin while maintaining its benefits. Transdermal delivery offers an alternative route for administering aspirin that bypasses the gut and may be a more convenient, safer and non-invasive means for aspirin delivery, especially for long-term use. This study comprised formulation of aspirin in different bases for topical application (Hydrophilic Ointment USP, Polyethylene Glycol Ointment NF, carboxymethyl cellulose gel, hydrocarbon gel (Plastibase) and vaseline bases). Release studies carried out according to the paddle method using the USP dissolution tester revealed that hydrocarbon gel base allowed the highest drug release. Ex-vivo permeation studies through full-thickness rat abdominal skin using Franz diffusion cell revealed the highest permeation of the drug from hydrocarbon gel. Several chemical penetration enhancers were surveyed for augmenting the permeation of aspirin from this base; these comprised oleic acid, methyl myristate, a combination of propylene glycol and alcohol, limonene, dimethyl sulfoxide, urea, β-cyclodextrin, hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The combination of propylene glycol and alcohol showed maximum enhancing effect and, hence, was selected for biological investigation. The biological performance of the selected formulation was assessed turbidometrically by measuring the inhibition of platelet aggregation in male Wistar rats relevant to different dosage regimens aiming to minimize, as far as possible, both the dose of the drug and its frequency of application. The results demonstrated the feasibility of successfully influencing platelet function by the selected formulation containing a low dose of aspirin and revealed that the therapeutic efficacy of the drug in a transdermal delivery system (TDS) is dose-independent, consistent with saturability of platelet COX-1 inhibition by aspirin at very low doses, which support the use of the lowest effective dose. Aiming to justify the goal of this study (i.e., designing a safe, stable and effective transdermal delivery system for aspirin), the biological performance of the selected formulation was re-assessed after storage at 37°C for 7 months. The results showed that the biological performance was not affected by storage, ensuring stability and persistent therapeutic efficacy.

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