Towards Electrochemical Analgesia: Acetylsalicylate delivered from Polypyrrole by Electroreduction

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In a study of possible electrochemical control of epidermal patch medication, acetylsalicylate is now shown to be as readily released from polypyrrole as salicylate, by initially incorporating it in polymer of coarser appearance and possibly more open reticulation with hence wider exit channels.

Systems in the form of polymer implants have been studied for the delivery of medication which has been incorporated as redox-polymer counter-ion, then released on electrochemical oxidation or reduction of the polymer.[1–4] Apparent successes with glutamate[1,2] and protonated forms of l-dopamine,[3] together with a footnoted claim[1] regarding 'aspirin' have however provided no sequels. Thus only salicylate,[4] rather than acetylsalicylate, has hitherto been demonstrably liberated from redox polymer (apart from l-dopamine, glu$^-$ and nonmedicinal counter-ions). Furthermore, since the inception in 1982 of such studies, medication *via* epidermal patches has developed appreciably, thus offering wider scope to electro-release methods, which are much easier to use in this mode compared with implants. The lack of information regarding the obvious candidate, acetylsalicylate, prompted us to examine this species in such a role. The results are presented of a comparative study of salicylate (Sal$^-$) and acetylsalicylate (Acsal$^-$) in polypyrrole (PP), which now show how Acsal$^-$ can indeed be electrochemically delivered by redox-polymer patch technology. Polypyrrole is electropolymerised as a partly oxidised deposit of PP$^+$X$^-$ on, *e.g.* a Pt electrode, when X$^-$ is the electrolyte anion in solution.

We compared the PP$^+$Sal$^-$ system with[4] poly-3-methoxythiophene$^+$Sal$^-$, obtaining similar results. The former was prepared by electrooxidation of 0.05 mol dm^{-3} pyrrole in 0.1 mol dm^{-3} aqueous Na$^+$Sal$^-$ on a 1 cm^2 Pt flag electrode, at +1.0 V *vs.* SCE, at which potential polymer film of smoothest appearance ensues. The polymer, washed with water till Fe^{III} tests showed no Sal$^-$ leaching, then peeled off for *ex situ* IR study in KBr discs, showed three salicylate IR bands between 680 and 750 cm^{-1} which are absent in PP$^+$Cl$^-$ prepared from KCl solution (Fig. 1). Reduction at −1.0 V of washed PP$^+$Sal$^-$ polymer in fresh KCl solution resulted in the disappearance of the Sal$^-$ IR bands and the recovery in solution of 70–95% of the Sal$^-$, as determined by spectrophotometry on iron(III) salicylate.

Repetition of these experiments on PP formation now with Na$^+$Acsal$^-$ in solution also showed incorporation of Acsal$^-$ (three non-polymer IR bands between 660 and 800 cm^{-1}, Fig. 2). However, even prolonged electroreduction at −1.0 V liberated no Acsal$^-$ to solution; the IR bands persisted within the polymer, no cyclic voltammetry of Acsal$^-$ in the surrounding solution (transferred to a separate cell) was observed (current peak expected at +0.51 V), and no purple Fe^{III} complex formed on addition of Fe^{3+} following the attempted electroreduction. The clear inference is that Acsal$^-$ can be incorporated during electropolymerisation, but remains entrapped within the polymer.

Restraints[5] on ionic transport arising from counter-ion size and diffusion-channel diameters in redox polymers indicate that a more open reticulation in the PP$^+$Acsal$^-$ system is required in order to facilitate Acsal$^-$ egress. Open-structured polymer will result from more severe polymerisation condi-

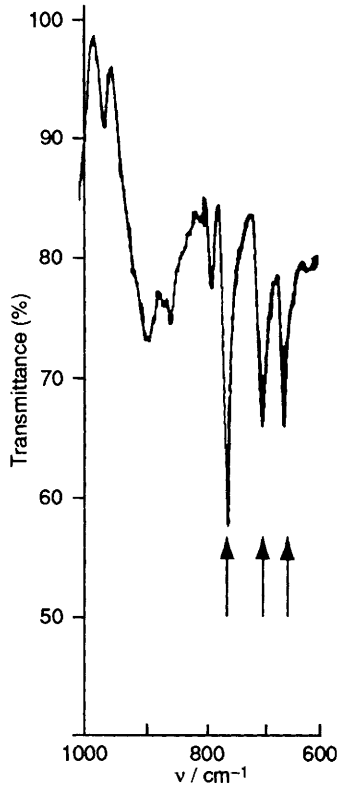

Fig. 1 IR spectrum of fragments of polymer in ground and compacted KBr disc showing (arrows) specific salicylate bands

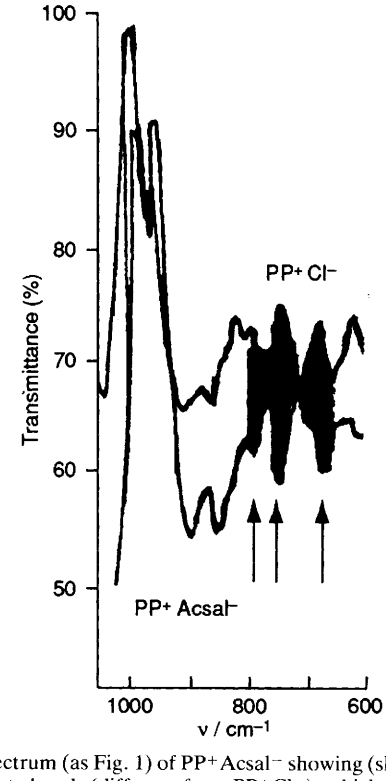

Fig. 2 IR spectrum (as Fig. 1) of PP$^+$Acsal$^-$ showing (shaded) specific acetylsalicylate bands (different from PP$^+$Cl$^-$), which remain despite attempted electroreduction of the polymer

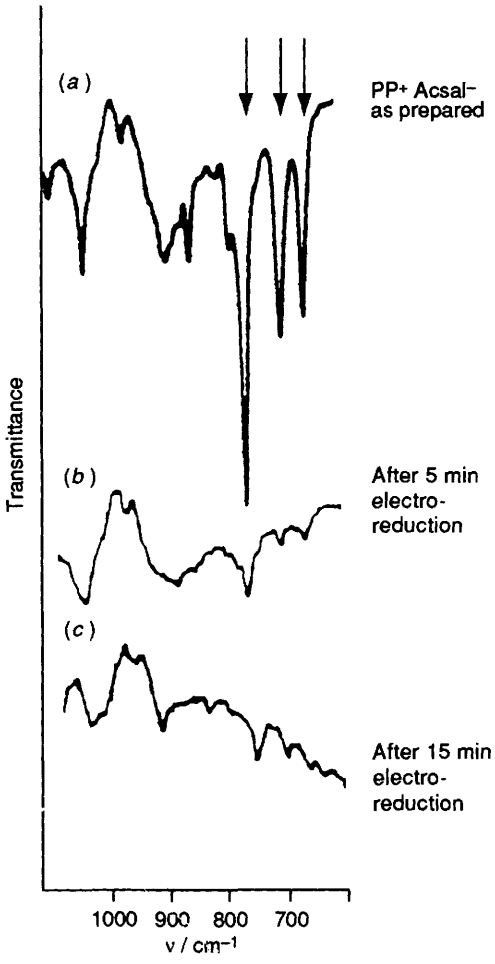

Fig. 3 IR spectrum as Fig. 2 of PP^+Acsal^- in open-channel polymer, showing decrease with time of $Acsal^-$ bands on electroreduction: (*a*) as prepared; (*b*) after 5 min electroreduction; (*c*) after 15 min electroreduction

tions engendering shorter chain lengths, or from chain breaking by the inclusion during electropolymerisation either of 2-substituted pyrroles[6] or of pyridine polymerisation inhibitors.[7] The first option proved successful: slightly alkaline (*ca.* 10^{-2} mol dm^{-3} OH^-) tetrabutylammonium acetylsalicylate (0.1 mol dm^{-3}) with nominally 0.43 mol dm^{-3} pyrrole were emulsified over 30 min by vigorous magnetic stirring, which was continued during the electropolymerisation. Somewhat coarser, lumpy, polymer resulted, of *ca.* 0.1 mm thickness. It was again washed, with Fe^{III} tests, then peeled off; IR spectroscopy again proved $Acsal^-$ incorporation (Fig. 3). In samples of polymer periodically removed after being subsequently electroreduced in KCl solution, the $Acsal^-$ IR bands diminished within seconds, and disappeared after 10 min (Fig. 3). When the electroreduction was performed in iron(III) perchlorate solution, an intense purple region of iron(III) acetylsalicylate complex grew at and diffused away from the derivatised electrode surface, but only on current flow, thus confirming the electrorelease mechanism.

Acetylsalicylate is thus liberated only from the probably more open-channelled electropolymerised polypyrrole, so pointing to a need for tailoring the polymer matrix to the size of the medicament moiety. By the means cited, even quite commodious channels should be achievable within such polymers, which, with suitable control circuitry, could then deliver epidermal-patch medication generally if the key species can be made ionic.

Dr B. Saville suggested the $Acsal^-$ experiments.

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