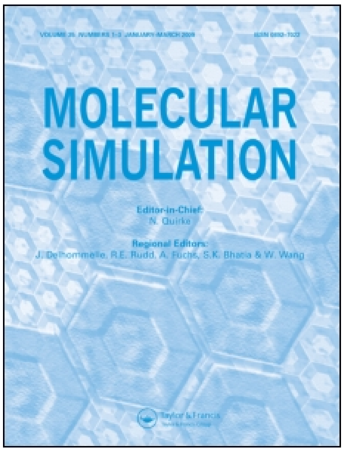

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Molecular Dynamics of Poly(Lactide-Co-Glycolide) Controlled Pharmaceutical Release Polymers: Preliminary Solid State NMR

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Preliminary Communication

MOLECULAR DYNAMICS OF POLY(LACTIDE-CO-GLYCOLIDE) CONTROLLED PHARMACEUTICAL RELEASE POLYMERS: PRELIMINARY SOLID STATE NMR

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Variable temperature ^{13}C cross polarization magic angle spinning (CP-MAS) and ^{1}H T_1 and $T_{1\rho}$ studies have been initiated on microspheres of the poly(lactide-co-glycolide) (PLGA) materials widely studied as controlled release pharmaceutical formulation excipients. Temperature dependence of lineshape and $T_{1\rho}$ suggest that around the broad glass transition at about 50°C slow polymer backbone motions (on the 10 to 100 μs time scale) become significant; modelling of these is in progress.

Keywords: Controlled release; poly(lactide-co-glycolide); PLGA; solid state NMR

Polyesters of lactic and glycolic acids – the so-called poly(lactide-co-glycolides) (PLGA's) – are used in controlled release formulations designed to limit the rate of release of medicinal compounds [1]. The physicochemical

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properties of such excipients determine manufacturing strategy, shelf stability, and kinetics of drug release. Additionally the incorporation of drugs themselves can profoundly alter polymer matrix properties, such as its susceptibility to solvent ingress, which are crucial to pharmaceutical performance [2]. It would be extremely valuable to be able to predict the properties of a formulation from a knowledge of its chemical constitution alone, but so far no attempts to simulate, for instance, thermal, mechanical and molecular dynamic properties [3 – 5], and solvent diffusion [6], in these systems have been reported.

Solid state NMR is an excellent technique for studying the molecular dynamics of polymers [7]. With a view to providing experimental molecular dynamical information against which to test theoretical simulations of PLGA backbone dynamics, a preliminary ^{13}C cross polarization magic angle spinning (CP-MAS) study of the temperature dependence of the spectrum, and spin-lattice (T_1) and rotating frame T_1 ($T_{1\rho}$) characteristics of 50 : 50 poly(glycolide-D,L-lactide) microspheres is reported here.

Microspheres were prepared by dissolving PLGA (Sigma) in dichloromethane, emulsifying in aqueous 2.5% polyvinyl alcohol, evaporating the organic phase by bubbling with nitrogen, filtering, washing with water, and drying under high vacuum [8]. NMR spectra were obtained using the following experimental parameters: Bruker AMX360, 4 mm zirconia rotor, MAS frequency 5.5 kHz, Hartmann-Hahn matched ^{1}H cross polarization field 50 kHz, contact time 1.6 ms, repetition time 5 s, ^{1}H decoupling field 80 kHz, chemical shifts externally referenced to TMS at 0 ppm. ^{1}H T_1 and $T_{1\rho}$ measurements were achieved by ^{1}H inversion followed by a variable recovery time, and by variable ^{1}H spin lock period, respectively, followed by cross polarization (1.6 ms) to ^{13}C.

Figure 1 shows ^{13}C spectra of PLGA microspheres at several temperatures below and above the broad glass transition temperature, T_g, centred at ca. 50°C. At room temperature all structurally distinct PLGA resonances are resolved, and assignments are shown. As the temperature increases through T_g resonances of the ester carbonyls, the lactide methine and, in particular, the glycolide methylene carbons, broaden, while the lactide methyl signal sharpens. We ascribe this to the assumption of significance of backbone motions at the same frequency as the proton decoupling, *i.e.*, ca. 80 kHz, which partially uncouples the proton resonances from the decoupling field; at the same time increased methyl group rotation reduces the linewidth of the lactide methyl through an increase in T_2 relaxation time. The introduction of new motions on the 10 – 100 kHz time scale as the T_g is attained is also attested to by the preliminary relaxation data, shown in

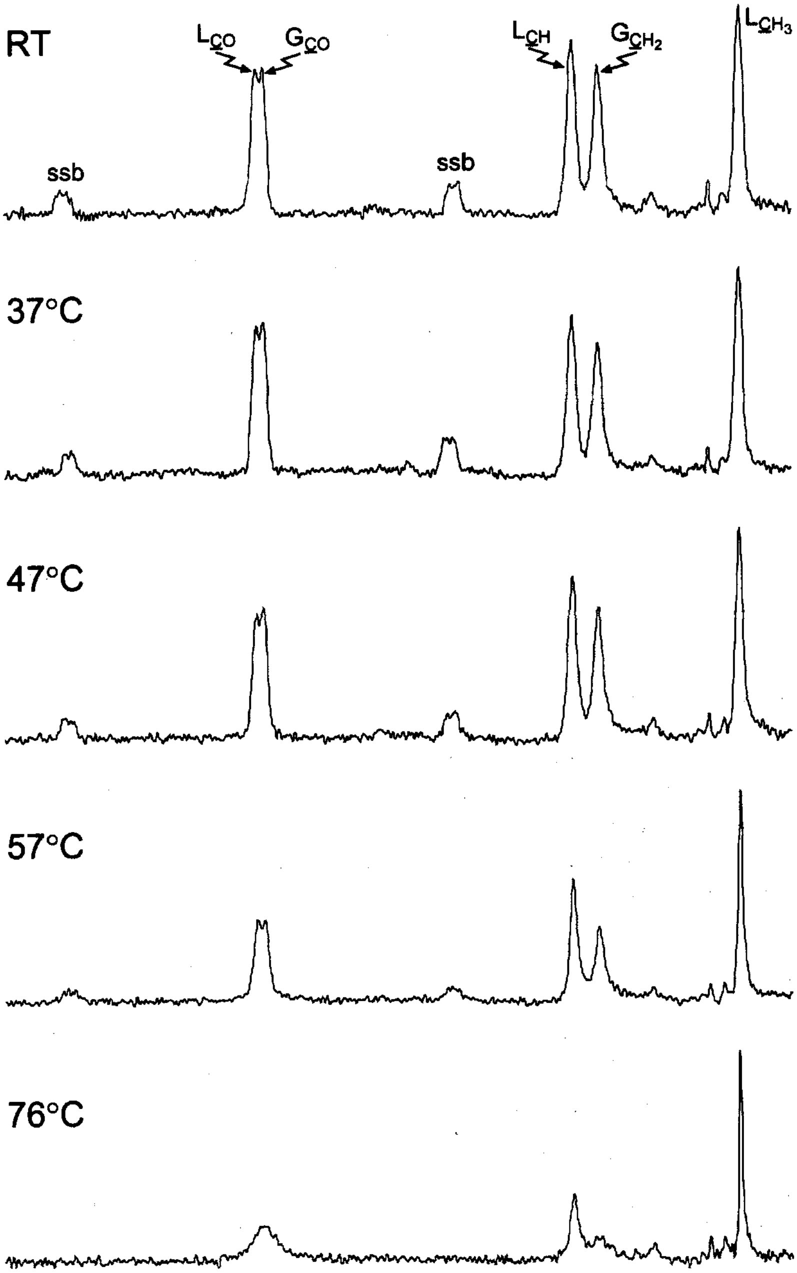

FIGURE 1 90.55 MHz ^{13}C CP-MAS spectra of 50 : 50 poly(glycolide-D,L-lactide) microspheres at several temperatures below and above T_g. (*RT* – Room temperature; ssb – spinning side band; L – lactide resonance; G – glycolide resonance).

TABLE I Temperature dependence of relaxation times

Temperature (°*C*)	T_1 (*ms*)	$T_{1\rho}$ (*ms*)
27	790	22
37	865	27
67	1,227	5.1

Table I. T_1 values show a modest steady increase through T_g while the $T_{1\rho}$ behaviour argues for new motions on the timescale of the spin lock field (50 kHz) becoming significant around T_g. More detailed relaxation and activation energy measurements, and modelling of the underlying motional dynamics, are in progress. These simulation will assess the underlying molecular motions at the atomic scale and, as such, will be on a relatively short time scale comparable to the experimental results reported here. Interestingly successful molecular dynamic studies, akin to those currently being undertaken, have been reported of the molecular dynamics of pristine and doped polyacetylene [9] whereby not only chain motions but also dopant diffusion could be investigated.

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