# SPHERULITIC MORPHOLOGY AND ITS INFLUENCE ON DRUG RELEASE FROM MELT-PROCESSED BIODEGRADABLE P(HB-HV) POLYESTERS

Saghir Akhtar, Colin W Pouton and Lidia J Notarianni
School of Pharmacy and Pharmacology, University of Bath, Bath BA27AY

Poly-D(-)-3-hydroxybutyrate (PHB) and its copolymers with poly-3-hydroxyvalerate (P(HB-HV)) are crystalline thermoplastics from the polyhydroxyalkanoate family of biopolymers which are produced by many microorganisms as energy reserve materials. The high purity and favourable biocompatibility of these copolymers have led to their investigation as matrices for drug delivery (Akhtar and Pouton, 1989). Drug release from P(HB-HV)s is dependent on HV content and thought to be influenced by the crystalline morphology (Akhtar et al, 1989). In this study we have examined the morphology and crystallization kinetics of melt-processed films containing a model drug, methyl red, and their influence on drug release kinetics.

PHB and P(HB-HV) copolymers containing 6, 12 and 16 mole% HV (PHV6, PHV12 and PHV16) were purchased from Marlborough Biopolymers Ltd. Films (30-50um) were cast from chloroform solution (4% w/w polymer). Dried films were heated to melt between two thin glass slides at 195°C for 30-60 seconds and isothermally crystallized at various temperatures using a Mettler FP82 hot stage. Growth of P(HB-HV) spherulites during crystallization was recorded in real time using polarized light video-microscopy. Crystalline morphology of spherulites was assessed in terms of the internal fine structure and size of crystallites. Release studies of methyl red from films crystallized at 90°C were carried out in vials (shaken at a frequency of 180 oscillations/min) containing 25ml phosphate buffer (pH 7.4) at 37°C. Release of methyl red was determined spectrophotometrically at 430nm.

The spherulite growth rate in pure polymer films is shown against temperature in Figure 1. (mean of 3 determinations are plotted). For a given polymer the growth rate (G) increased to a peak ($G_{max}$) as the crystallization temperature was lowered from 140°C. G then decreased at lower crystallization temperatures as the viscosity of the melt increased. G decreased with increasing HV content and there was a slight shift in the temperature at which $G_{max}$ occurred to lower temperatures with increasing HV content. The morphology of polymer spherulites was influenced by the crystallization temperature. At any given temperature the internal fine structure of spherulites (texture and banding) was also a function of HV content.

Figure 2 shows the release of methyl red (mean ± range is plotted; n=2) from films containing 4% w/w model drug which were isothermally crystallized at 90°C. The copolymers released drug more rapidly than PHB. This was explained by the progressively slower rates of crystallization of P(HB-HV)s. This produced morphologies in which drug was less well trapped. Polarized light microscopy confirmed that although some drug was entrapped intraspheruliti-cally (between chain-folded lamellae) progressively more drug was excluded to interspherulitic boundaries with increasing HV content.

FIGURE 1

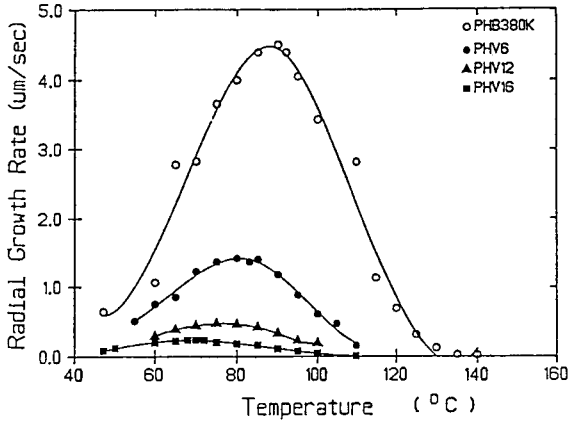
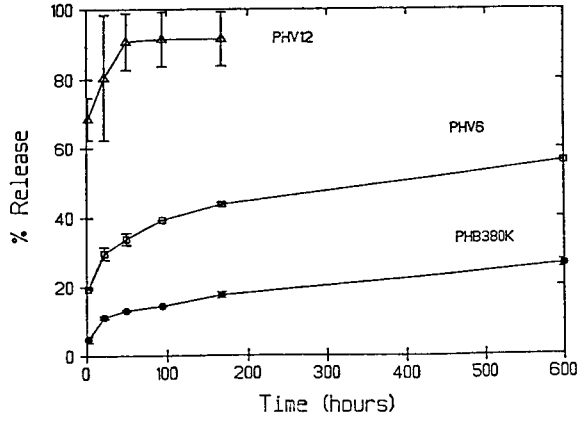



FIGURE 2




Our results showed that drug release from devices produced by melt-processing of P(HB-HV) was influenced considerably by the crystallization kinetics and morphology of the polymer.

Akhtar, S. and Pouton, C.W. (1989) Drug News and Perspectives, 2: 89-93
Akhtar, S. et al (1989) J. Pharm. Pharmac., 41: 5P