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Polymers for biodegradable medical devices. IV. Hydroxybutyrate–valerate copolymers as non-disintegrating matrices for controlled-release oral dosage forms

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Summary

The release of a series of surrogate drugs from bioerodible polyhydroxybutyrate–polyhydroxyvalerate copolymer matrices has been investigated. Release was found to be dependent not only on drug loading but also on the porosity of the drug–polymer matrix. Release was affected significantly by the addition of porosigens, notably microcrystalline cellulose and lactose. At low porosigen levels release was matrix controlled and independent of solution hydrodynamics. Release from the matrices was independent of solution pH, except where the drug had different solubility in gastric and intestinal fluids. This is therefore a system which in its primary drug release function is not governed by the degradation or erosion of the polymer but which is ultimately biodegradable and bioabsorbable.

Introduction

Non-disintegrating matrices employing non-degradable materials such as polyvinylchloride have been used for controlled release oral dosage forms for some years. These systems release drugs in a controlled fashion either by diffusion through the matrix per se or via a pore network present in or generated in situ in the matrix. The depleted matrix does not disintegrate and then passes through the gastrointestinal tract and is excreted unchanged.

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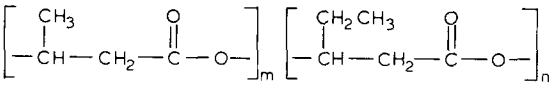
Recently a series of bioerodible polymers have become available that have potential for pharmaceutical and biomedical applications (Holmes, 1985; Uttley, 1985; Holmes et al. 1981). These polymers, poly-3-hydroxybutyrate (PHB) and its valerate copolymer (PHB-PHV; Scheme 1) have been discussed as systems for the controlled release of macromolecular drugs (Holland et al., 1986). The polymers are regarded as non-toxic, and the monomer is a normal constituent of human blood.

Biodegradation of the PHB-PHV copolymers, an essential requirement for a non-disintegrating controlled release system to prevent inadvertent intestinal retention on chronic dosing, is an important feature of these polymers. The polymers

Scheme 1. Structure of the polyhydroxybutyrate–valerate copolymer.



are known to break down to carbon dioxide by anaerobic bacteria and more slowly by aerobic bacteria and fungi (Holmes et al. 1981). The rate of biodegradation depends on many factors but notably those relating to the ease of microbial colonisation such as surface texture and high porosity are known to be important. However, little if any definitive information is currently available on the degradation in the gastrointestinal tract of man, but the degradation of polymers has been studied in the rumen of cattle (Rogers, 1985). The rate of degradation in moist air is negligible and therefore all solid dosage forms containing it should have an acceptable shelf-life.

Some work has been conducted by Korsatko et al. (1983) investigating the release of 7-hydroxyethyl theophylline from PHB matrices both in vitro and in vivo. Also, Brophy and Deasy have investigated the release of sulphamethiazole from PHB and PHB-PHV matrix microparticles (Brophy and Deasy, 1986). In both cases drug release was found to be exclusively by diffusion and to be related to drug loading.

We have now investigated the use of polyhydroxybutyrate–valerate copolymers for preparing by direct-compression non-disintegrating matrices for oral controlled release. A series of model drugs were chosen to span a molecular weight range of likely utility, incorporating the drug by dry blending. Dosage forms developed in this way not only have the benefit of simplified processing but, unlike those of polyvinylchloride, if they are retained inadvertently in the gut they will slowly erode by hydrolytic and enzymatic routes preventing retention and potential strictures on chronic dosing.

Materials and Methods

Materials

The PHB polymers used in these studies were polyhydroxybutyrate of 300,000 Da containing 20% valerate copolymer (PHB 300 K) and of 350,000 Da containing 12% valerate copolymer (PHB 350K). Both were obtained from ICI Biopolymers, Marlborough, U.K.

The drug surrogates employed were fluorescein (F) (mol. wt. 332) obtained as technical grade from BDH Chemicals, Poole, U.K. and fluorescein isothiocyanate labelled dextrans of 4057 and 41,000 Da mol. wt. (FITC4 and FITC40 respectively) obtained from the Sigma Chemicals Co. Both materials had 0.003 moles of FITC label per mole of dextran glucose residue.

The other materials used in the study were microcrystalline cellulose (MCC), grade Avicel PH102 (Honeywill and Stein); lactose; grade fast flo (Foremost McKessen); carboxyvinylpolymer (CVP); grades Carbopol 934 and 941 (B.F. Goodrich), hydroxypropylmethyl cellulose (HPMC); premium grades E4M and E15 (Colorcon, Orpington, U.K.).

Methods

Powder blends of PHB300K and PHB350K were prepared in various proportions with each of the diluents. Following sieving (150 μm) 7.5% w/w of a drug surrogate was then combined with these binary mixtures. Approximately 100 mg of the resultant blend was loaded by hand into the die of a single punch tablet press (Manesty F3) fitted with either 6 mm or 8.5mm normal concave tooling and compressed at a pressure of 130 MPa. The tooling was prelubricated with a 2% solution of stearic acid in chloroform. The hardness of tablets prepared was at least 13.4 kp (Schleuniger 2E) in all systems, but many tablets deformed plastically rather than by simple fracture under test. Indeed, one of the remarkable aspects of the preparation of the compacts of PHB by direct compression was the very high compressibility of the polymer particles.

Dissolution

Tablet dissolution was conducted using the USPXXI paddle method in a precalibrated dissolution bath (G.B. Caleva, Model 6ST) at 100 r.p.m. with 500 ml of dissolution fluid (pH = 7.4 phosphate buffer). The dissolution process was

followed automatically using a Uvikon 810 spectrophotometer (Kontron Instruments, St. Albans, U.K.), by analysis at the λ_{max} of the various drug surrogates; 490.1 nm, 493.7 nm and 491.9 nm for F, FITC4 and FITC40 respectively. The spectrophotometer was fitted with a programmable cell changer controlled externally by a Commodore PET 4032 microcomputer with an IEEE/RS232 interface. The dissolution medium, following passage through an in-line filter (sintered polypropylene) was circulated by a peristaltic pump (Watson Marlow, model S170) through flow cells in the spectrophotometer. Solution absorbances were read automatically and stored in the microcomputer during the dissolution test. Following completion of dissolution, profiles were generated by the microcomputer and a dissolution test report was generated.

'Static' dissolution tests were also conducted by placing the test compacts in a boiling tube containing 40 ml of a pH = 7.4 phosphate buffer. The tubes were inverted periodically and 5 ml samples then taken periodically for analysis up to 30 h after immersion (with concurrent replacement of buffer to maintain constant total volume).

Results and Discussion

Release of the various surrogate drugs from combination with PHB-PHV copolymers appears to be independent of polymer molecular weight, dependent on co-polymer composition and highly dependent on the molecular weight of the surrogate (Table 1). Release of F from both the 20% copolymer (PHB300K) and the 12% copolymer (PHB350K) is ca 6% after 6 h with the relatively more compressible, hydrophobic, 20% copolymer showing a somewhat lower release rate. FITC4 release reaches approximately 20% and FITC40 34% from the 20% co-polymer over the same period. The release from the 12% co-polymer is again somewhat greater but this difference is magnified as the release time is increased. Thus, release appears to be contrary to that expected from pure matrix diffusion of the surrogate (in which case FITC40 release would be less than that of FITC4) and suggests that release is controlled by

TABLE 1

Release rates of FITC4 and FITC40 from PHB300K, PHB350K matrices containing various amounts of MCC

Drug surrogate	Polymer	MCC loading	K (% h−0.5)	$t_{50\%}$ (h)	% Released at 6 h
F	PHB300K	0	2.60	> 24	5.6
	PHB350K	0	2.83	> 24	6.2
FITC4	PHB300K	0	7.00	> 24	18
		12.5	10.61	> 24	24
		50	28.2	2.8	73
	PHB350K	0	8.16	> 24	21
		7.5	4.18	> 24	14
FITC40	PHB300K	0	12.88	18	34
		7.5	12.04	19	29
		12.5	10.75	> 24	28
	PHB350K	0	13.18	16	34
		7.5	14.02	14	35
		12.5	14.64	13	38

the porosity of, and the rate of fluid influx into, the matrix. The soluble polymeric surrogates presumably yield a more porous hydrophilic matrix thereby facilitating drug release by diffusion through the pores. This hypothesis is supported by the fact that an increase in loading of FITC40 in the PHB matrix leads to an increase in the rate and extent of drug release (Table 2). This result is in line with the work of Korsatko et al. (1983) and the conclusions of Brophy and Deasy (1986) on microparticulate matrix PHB-PHV system. Thus, there appears to exist a potential to manipulate these systems by additives such as porosigens (Langer et al., 1980) in order to control drug release. This phenomenon was investigated by separately adding two excipients to the polymer matrix to assist porosity and/or pore generation. The

TABLE 2

Release data for FITC40 from PHB350K matrices containing no additives

% FITC40	K (% h−0.5)	$t_{50\%}$ (h)	$t_{90\%}$ (h)	% Released at 6 h
7.5	13.2	16	> 24	34
15	24.4	4.1	> 24	60

additive used to induce the former was microcrystalline cellulose (MCC) and the latter lactose.

The release of FITC4 and FITC40 when incorporated with varying levels of MCC into a matrix of the 20% copolymer PHB300K, is shown in Fig. 1. The MCC provides a compressible, insoluble, microporous (wicking) component to the PHB matrix and this would be expected to modify drug release by assisting fluid influx. As anticipated, release is greatest with both surrogates for higher levels of MCC in the matrix; the release being diffusion-controlled with drug release being a linear function of the square-root of time (Higuchi, 1963). Indeed, the release of FITC4 with a matrix containing 50% MCC and PHB300K is some 3 times that of a matrix composition with 12.5% MCC (Table 1). Decreasing the valerate level of the co-polymer by employing PHB350K leads to a more rapid release of both model drugs, presumably through the reduced compressibility and homogeneity of the polymer matrix and therefore more rapid fluid influx.

The release of FITC4 and FITC40 from matrices containing various amounts of lactose is shown in Fig. 2. As expected, the soluble lactose rapidly generates a porous matrix network with an increase in lactose loading leading to an increase in drug release. Indeed, the amount of FITC4 released at 6 h appears to be linearly related to lactose loading (Table 3). Perhaps surprisingly, release of FITC4, at the same lactose loading, is slower than that of FITC40. This reflects the decreasing surrogate matrix homogeneity and compatibility resulting from the much greater molecular weight of FITC40. This produces once again a difference in fluid influx that controls surrogate release. Similarly there is a small dependence on the grade of copolymer for reasons that have been previously discussed.

The release of FITC4 and FITC40 was also investigated from PHB matrices containing excipients that gel on immersion in water. Such systems provide another route to increasing the porosity of, and increase the fluid penetration into, the PHB matrix. The materials also assist the breakdown of the matrix because when fully hydrated they provide a physical weakening of the compact. However, it has been suggested that such systems may have the potential disadvantage (Ford et al.,

TABLE 3

Release rates of FITC4 from PHB300K, PHB350K matrices containing various amounts of lactose

Drug surrogate	Polymer	Lactose loading	Release rate % $h^{-0.5}$	% Released at 6 h
FITC4	PHB300K	12.5	10.91	27
		25	20.97	52
		50	31.83	71
	PHB350K	2.5	12.55	25
		7.5	13.11	31
FITC40	PHB300K	7.5	16.11	41
		12.5	19.50	51
		25	23.32	58
	PHB350K	7.5	19.39	48
		12.5	21.29	52

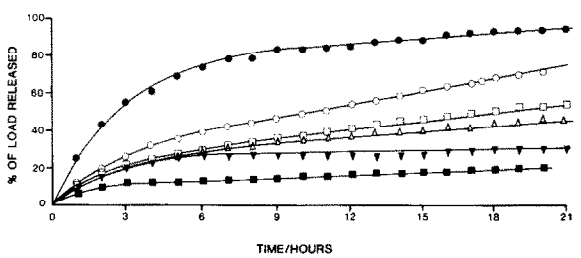


Fig. 1. Release of various surrogates (7.5% w/w) from PHB-PHV copolymers containing microcrystalline cellulose (MCC), 20% PHB, 300K unless otherwise states. ●, FITC4/50% MCC; ○, FITC40/12.5% MCC (12% PHV, 350K); □, FITC40/12.5% MCC; △, FITC40/7.5% MCC; ▼, FITC4/12.5% MCC; ■, FITC4/7.5% MCC.

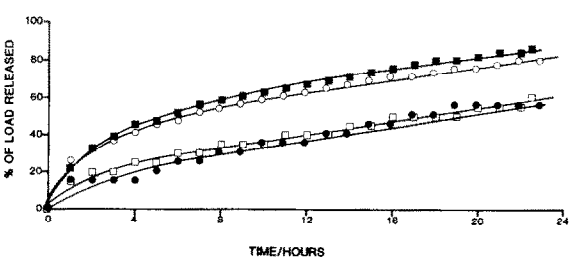


Fig. 2. Release of various surrogates (7.5% w/w) from PHB-PHV copolymer (12% PHB, 350K) containing lactose. □, 7.5% w/w lactose/FITC4; ●, 2.5% w/w lactose/FITC4; ■, 12.5% w/w lactose/FITC40; ○, 7.5% w/w lactose/FITC40.

1985) that their gelling could also further prolong the release of the drug. In the PHB-based matrices described here, however no such extension of drug release profile was observed. The results for the incorporation of 10% hydroxypropylmethyl cellulose (grades E4M and E15) in both PHB systems are shown in Table 4. The time for 50% release of FITC4 and FITC40 from the 20% co-polymer, PHB350K was of the same order with FITC40 being somewhat more rapidly released as in previous cases. Little difference was observed between systems based on the two grades of HPMC, where direct comparison was possible (FITC40–PHB350K).

Finally, the effects of in situ pH within the matrix, the pH off the dissolution fluid and the nature of the hydrodynamics to control drug release were investigated.

5% carboxyvinylpolymer (CVP; Carbopol 934) and 3% carbonate/bicarbonate buffer salts were incorporated into a PHB350K matrix to yield a low and high microenvironmental pH respectively. In practice, influence on the release mechanism by these pH adjusting additives were difficult or impossible to isolate. Release was significantly enhanced with the inclusion of bicarbonate/carbonate ions (Fig. 3); either through a beneficial pH/solubility effect on the drug surrogate or more probably by increasing matrix porosity by acting in a manner similar to lactose. The presence of the carboxyvinylpolymer also led to a significant increase in drug release; the rate for FITC40 increasing by a factor of some 150% and the percentage of FITC4 released at 6 h increasing from 21% to 34% in the presence of the additive. Given the pK_a of the fluorescein segment of the dextran surrogate this is unlikely to have been due

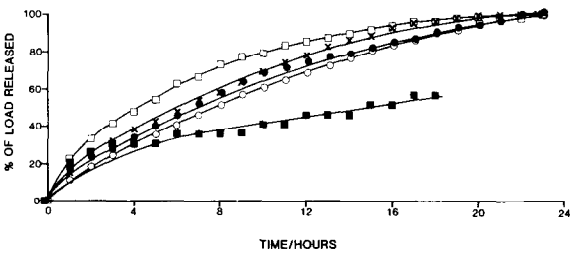


Fig. 3. Release of various surrogates (7.5% w/w) from PHB-PHV copolymers containing carboxyvinyl polymer (CVP) and buffer salts. ×, 3% w/w pH 10.6 buffer salts/FITC40/20% PHB 300K; □, 3% w/w pH 10.6 buffer salts/FITC40/12% PHB 350K; ○, 5% carbopol (CVP) 941/FITC40/12% PHB 350K; ●, 5% carbopol (CVP) 934/FITC40/12% PHB 350K; ■, 5% carbopol (CVP) 941/FITC4/12% PHB 350K.

to a solubility effect caused by a change in matrix pH but is probably due to an increase in matrix porosity/hydrophilicity caused by the inclusion of the CVP. The increased rate and extent of release in this case was partially due to matrix disintegration.

In contrast to the changes in release rate observed with additives causing in situ pH manipulation within the matrix, a change in the pH of the dissolution medium generally led to only minimal changes in the release of the dextran-based surrogates. Release of FITC4 and FITC40, from a variety of PHB-additive binary systems (Table 5) tended to be slower in simulated gastric fluid (pH = 1.3) than at pH (7.4). Release of fluorescein from PHB300K was significantly faster at pH 7.4, presumably because ionisation and high solubility of the drug occurs at that pH.

The influence of hydrodynamics on the release of surrogates was investigated by comparing the

TABLE 4

Release rates of FITC4 and FITC40 from PHB300K, PHB350K matrices containing various amounts of HPMC

Drug surrogate	Polymer	HPMC/loading	% Released at 6 h	$t_{50\%}$ (h)	$t_{90\%}$ (h)
FITC4	PHB350K	E15/10%	47	6.7	11.7
FITC40	PHB300K	E4M/10%	47	6.7	21.4
	PHB350K	E4M/10%	53	5.5	15.4
	PHB350K	E15/10%	53	5.6	14.5

TABLE 5

Release of drug surrogates from PHB-PHV copolymers containing additives into dissolution fluids at pH 1.3 and 7.4

Surrogate	Polymer	Additive	% Dissolution at 6 h	
			pH = 1.3	pH = 7.4
F	PHB300K	–	0.5	5.6
FITC4	PHB350K	7.5% Lactose	31	31
FITC40	PHB350K	7.5% Lactose	32	48
		12.5% MCC	30	37
		10% HPMC (E4M)	50	53
		5% CVP (934)	35	46

release profiles from static and rotating dissolution tests. Release of FITC40 from PHB300K matrices and those of PHB350K are largely unaffected by dissolution method (Table 6). Systems containing small amounts of MCC (7.5%) are less affected by matrix hydrodynamics in the early stages of dissolution (6 h), but are influenced significantly at extended times (12 h). The disparity in release profile was observed to increase as the amount of MCC in the PHB matrix is increased, producing a significant increase in the extent of the release in the more vigorous rotating test. Thus, release appears unaffected at early times or with small amounts of porosigen being present in the matrix. Hydrodynamics appears to affect drug release from both copolymer systems particularly with systems containing moderate amounts of a porosigen and at extended times. This suggests that fluid wicking into the matrix may be additive-controlled in the early stages but that solution hydrodynamics influences pore generation and fluid influx as the dissolution proceeds, leading to a faster release profile for the rotating system.

TABLE 6

Release rates of F, FITC4, FITC40 from PHB300K, PHB350K matrices under various dissolution conditions

Drug surrogate	Polymer	Additive	'Static' dissolution % released		USP dissolution % released	
			6 h	12 h	6 h	12 h
FITC40	PHB300K	–	28	36	34	46
		7.5% MCC	13	17	29	42
	PHB350K	7.5% MCC	34	46	35	50
FITC4	PHB300K	12.5% MCC	24	28	48	69
F	PHB350K	–	5.3	6.6	6.2	7.6

Conclusions

Polyhydroxybutyrate-valerate copolymers have potential as non-disintegrating, but biodegradable matrices for controlled-release oral dosage forms prepared by direct compression. Release can be controlled by manipulating drug and excipient loading. As a result, for a wide molecular weight range of drug candidates, release can be controlled by manipulating the porosity of the matrix; either by including a self-wicking additive such as microcrystalline cellulose or a porosigen such as lactose. Release from PHB-PHV matrices appears independent of solution pH since such effects on the matrices are small. Differences become apparent however with drugs that substantially change their degree of ionisation and solubility as the pH of the dissolution fluid is changed. The major controlling factors are those governing release from these systems i.e., the physical homogeneity and porosity of the drug-excipient-polymer matrix. There are 3 main ways in which this is influenced. *Firstly* the compressibility of the polymer: the greater compressibility of the 20% (high valerate) copolymer results from differences in crystallinity between the highly crystalline 12% valerate copolymer and the less crystalline 20% copolymer. *Secondly* is the homogeneity and uniformity of the excipient–polymer blends; thus lactose and microcrystalline cellulose PHB-PHV tablets demonstrate more consistent and slower release rates than do CVP or buffer salt tablets. *Finally*, molecular weight and the therefore compatibility of the drug itself — as exhibited by the decreasing uniformity of polymer-drug blends as the surrogate molecular weight increases from fluorescein to FITC4 and FITC40.

The rate of in vitro release is more rapid than that of matrix (PHB/PHV) bioerosion (Holland et al., 1987), these systems thus provide an oral controlled drug release with potential for ultimate bioabsorption rather than long term retention of the depleted matrix in the gut.

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