DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(15), 1633-1648 (1992)

PROPERTIES OF IMPLANTABLE PELLETS PREPARED FROM A BIODEGRADABLE POLYESTER

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ABSTRACT

Biodegradable pellets for implantation use were prepared from a naturally produced copolyester, poly(hydroxybutyrate-hydroxyvalerate) (PHBV), by a simple compression and melt technique. Progesterone was incorporated in the pellets. Differential scanning calorimetric (DSC) and scanning electron microscopic (SEM) examinations showed that the drug has limited solubility in the polymer and exists as crystals uniformly distributed in the matrix. However, the drug undergoes a polymorphic change during melting from α to β form. Ultraviolet and infrared spectrophotometric tests on melted drug and polymer samples detected no chemical

degradation. *In vitro* release of the drug was faster when the amount of drug in the pellet was increased. The drug release could be slowed by increasing the the size of pellet.

INTRODUCTION

Considerable progress has been made in the use of biodegradable polymers as carriers of drugs for parenteral delivery. Using these polymers, various dosage forms such as microspheres, nanoparticles, beads, rods, and films containing active ingredients have been prepared and evaluated. Biodegradable delivery systems can be either implanted in a body site or, if sufficiently small, injected into the blood stream.

Poly(hydroxybutyrate) (PHB) and its copolymers with hydroxyvalerate (HV) are biodegradable and biocompatible polyesters prepared from a bacterial source.[1] These polymers have been investigated for their potential as drug carriers in the form of microspheres and tablets.[2-8]

The homopolymer, PHB, is produced in nature by several Gram-negative and Gram-positive bacteria. The biodegradable copolymer, PHBV, is a copolyester produced naturally by bacteria grown under controlled conditions. A major source of these polymers is a Gram-negative bacteria - *Alcaligenes eutrophus* . An advantage of using this natural polymer is that it is free from harmful residues.

The objectives of this study were to prepare and evaluate pellets of a poly(hydroxybutyrate-hydroxyvalerate) (PHBV) copolyester. A hot-melt method was used to reduce the porosity of the pellet and to overcome the problem of poor compressibility of the polymer-drug mixture.

Progesterone was selected as a model drug to be incorporated into the pellets. Progesterone is not effective orally except in high doses and has a short elimination half-life in humans.[9] Physical properties and release characteristics of these pellets were investigated.

MATERIALS

The following chemicals were obtained from commercial supliers and used as received: poly(hydroxybutyrate-hydroxyvalerate) containing 24 mole% of hydroxyvalerate (ICI Chemical Ind., Wilmington, DE); chloroform (J. T. Baker, Inc., Phillipsburg, NJ); 2-propanol (Fisher Scientific Co., St. Louis, MO) and progesterone (Sigma Chemical Co., St. Louis, MO).

METHODS

Preparation of Pellets: The polymer and the drug were thoroughly triturated in a mortar and the mixture was passed through a 60-mesh sieve. The powder was compressed on a Carver press (Fred S. Carver, Inc., Summit, NJ) using a 1/4" round, flat-faced punch and die (F.J. Stokes Machine Co., Philadelphia, PA) under a pressure of 500 N/mm^2. One end of the die was closed by a removable metal insert. The punch-die set containing the compressed tablet was heated to 135°C (measured at the face of the upper punch with a thermocouple inserted into a hole drilled through the stem of the punch) on a temperature controlled hot plate (Fred S. Carver, Inc., Menomonee Falls, WI). After heating to the designated temperature, the die assembly was then cooled rapidly by dipping in water.

Drug Content Analysis: To determine the drug content, a pellet was placed in a 50 ml volumetric flask containing approximately 20 ml of chloroform. The flask was heated in a water bath at 50°C for 30 min. to dissolve the pellet. It was cooled to room temperature and filled to volume with chloroform. After appropriate dilution, the solution was assayed spectrophotometrically at 243.4 nm (Beckman spectrophotmeter, model du-7, Beckman Instruments Co., Irvine, CA). A solution of a drug-free pellet was used as a blank.

Drug Solubility: Excess progesterone was placed in contact with the dissolution medium. Triplicate samples were shaken for 72 hrs. at 37°C. The samples were filtered (0.8μm) and the solubility was determined by measuring the concentration of the drug spectrophotmetrically after suitable dilution.

Drug Release Studies: A USP XXI paddle type dissolution apparatus (Hanson Research Corp., Northridge, CA) was used for the *in vitro* release studies. A pellet was placed in the dissolution medium made of 60:40 v/v 2-propanol:water. The medium was stirred at 100 rpm and maintained at 37°C. Periodic samples were withdrawn and assayed spectrophotometrically at 242.4 nm. Graphical data points are an average of dissolution samples from three pellets.

Scanning Electron Microscopy: The freeze-fractured surfaces of the pellets were examined by a scanning electron microscope (SEM) (Philips, model 505, Mahwah, NJ). After fracturing, the pieces were dried overnight in a vacuum dryer. The dried pieces were mounted on metal stubs, coated under an argon atmosphere with 50 nm of gold-palladium (Hummer X coater, Anatech Ltd., Alexandria, VA) and then observed with the SEM.

Differential Scanning Calorimetry: Thermograms of the drug, the polymer, and the pellets were obtained with a Perkin-Elmer differential scanning calorimeter (DSC) (Model 1B, Perkin-Elmer Corp., Norwalk, Connecticut) that had been calibrated by

the melting transition of indium. Weighed samples were sealed in aluminum pans and scanned at a rate of 10°C/min.

Ultraviolet Absorption: An appropriate dilution of a chloroform solution of the drug and the polymer separately was used to record the ultraviolet (UV) spectra on a Beckman UV spectrophotmeter (model du-7).

Infrared Absorption: The infrared (IR) spectra of the drug (KBr pellet) and the polymer ($CHCl_3$ solution) were obtained on a Perkin-Elmer spectrophotometer (model 684, Perkin-Elmer Corp., Norwalk, Connecticut).

RESULTS AND DISCUSSION

DSC, UV, and IR spectrophotometric tests were done to observe any changes in the thermograms or spectra caused by the heat. Thermograms of the premelted and congealed progesterone showed a shift of the melting peak from 130°C to 121°C (Fig. 1). This is due to a change in polymorphic form of crystalline progesterone from α (m.p. 130°C) to β (m.p. 121°C).[10] Both of these polymorphic modifications of progesterone have equal physiologic activity. UV and IR spectra of drug samples heated up to 150°C showed no change (Progesterone solutions for injections can be sterilised by maintaining at 150°C for 1 hour).[11]

PHBV has a low glass transition temperature (Tg) between 0 to 5°C. It melts at 124°C as shown by a broad endothermic peak in its thermogram (Fig. 1). Melting causes irreversible breakage of bonds that hold the polymer chains in a particular three dimensional structure. In other words, the polymer passes into a higher energy state that is less crystalline and more rubbery. Therefore, when the melted and congealed polymer is scanned on the DSC, the melting endotherm is less

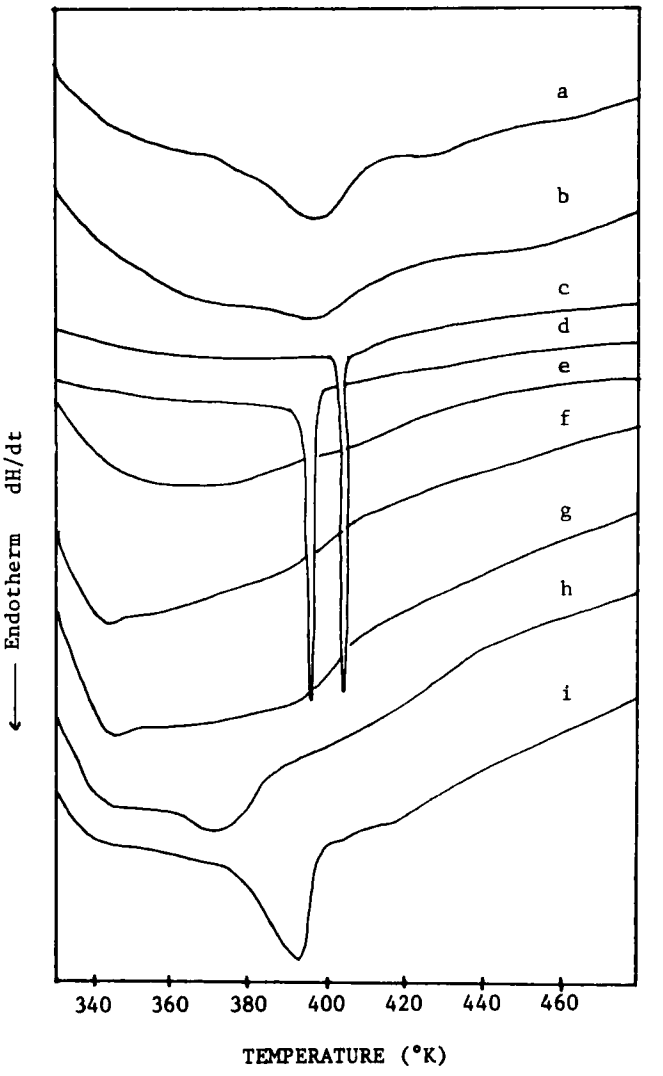

FIGURE 1

DSC Thermograms of a) PHBV, b) melted and congealed PHBV, c) progesterone, d) melted and congealed progesterone, e) drug-free pellet, f) pellet containing 5% w/w of progesterone, g) pellet containing 10% w/w of progesterone, h) pellet containing 30% w/w of progesterone, i) pellet containing 50% w/w of progesterone.

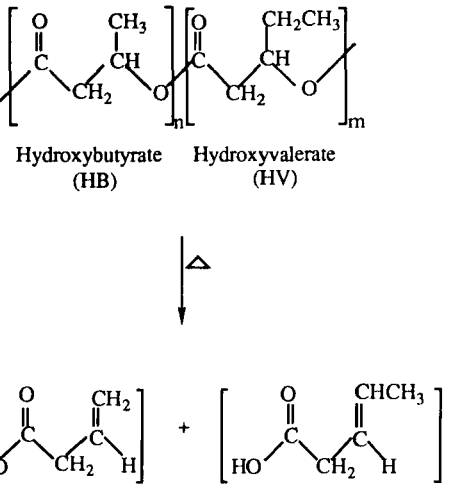

FIGURE 2
Scheme showing possible thermal degradation pathway of PHBV.

prominent. One of the reasons for choosing this PHBV copolymer for the pellets was its relatively lower melting point. The melting point of the polymer increases as the HV content in its composition is decreased. The PHB homopolymer melts at about 180°C.

A posssible scheme for thermal degradation of PHBV is shown in Fig. 2. According to this scheme, if the polymers breaks down, monomers and smaller fragments with carboxyl group (-COOH) and double bonds (C=C) will be formed. The IR spectra of PHBV24 samples that had been heated to 150°C and congealed, however, showed no new peaks corresponding to O-H (2500-3000 cm^{-1}) or C=C (900-1000 cm^{-1}). The UV spectrum of the melted polymer also remained unchanged.

Using the melt method, pellets weighing 70 and 140 mg containing different payloads were prepared. The compressed tablets before melting were soft and crumbled between fingertips upon application of a small pressure. After heating to

TABLE 1

Drug Contents of the Pellets Prepared in this Study

Batch	Theoretical Drug Content mg	Assayed Drug Content mg ± S.D.	Drug Released mg ± S.D.	Drug Remaining mg ± S.D.	Drug Released+ Drug Remaining mg
1	3.5	3.26 ± 0.07	1.65 ± 0.15	1.77 + 0.12	3.42
2	7.0	6.73 ± 0.35	3.62 ± 0.29	3.46 + 0.35	7.08
3	21.0	21.1 ± 0.29	17.0 ± 1.13	3.50 + 0.43	21.5
4	35.0	34.5 ± 1.27	29.0 ± 1.70	5.50 + 1.15	34.5

135°C to fuse the compressed polymer particles, the resulting pellets had a transparent appearance. The crushing strength of the pellets could not be measured because the pellets did not fracture but deformed plastically under pressure. Drug content analysis of the pellets showed that they contained more than 88% of the theoretical payloads. Pellets used for release studies were also analysed for the remaining drug-content. The amount of drug in original pellets matched within 6% of the total of released and remaining drug in the pellet used for release studies (Table 1).

SEM pictures of freeze-fractured pellets show that the drug has low solubility in the polymer. Even at 5% payloads, some of the drug crystallizes in the matrix (Fig. 3). Crystals of progesterone uniformly distributed and embedded in the polymer matrix can be seen in the electron micrograph of a pellet freeze fractured across its diameter (Fig. 4). Micrographs of pellets containing 10% and 30% progesterone are shown in Fig. 5 and 6 respectively. At 30% payloads, drug crystals are prevalent throughout the matrix. The polymer deposits as transparent granules

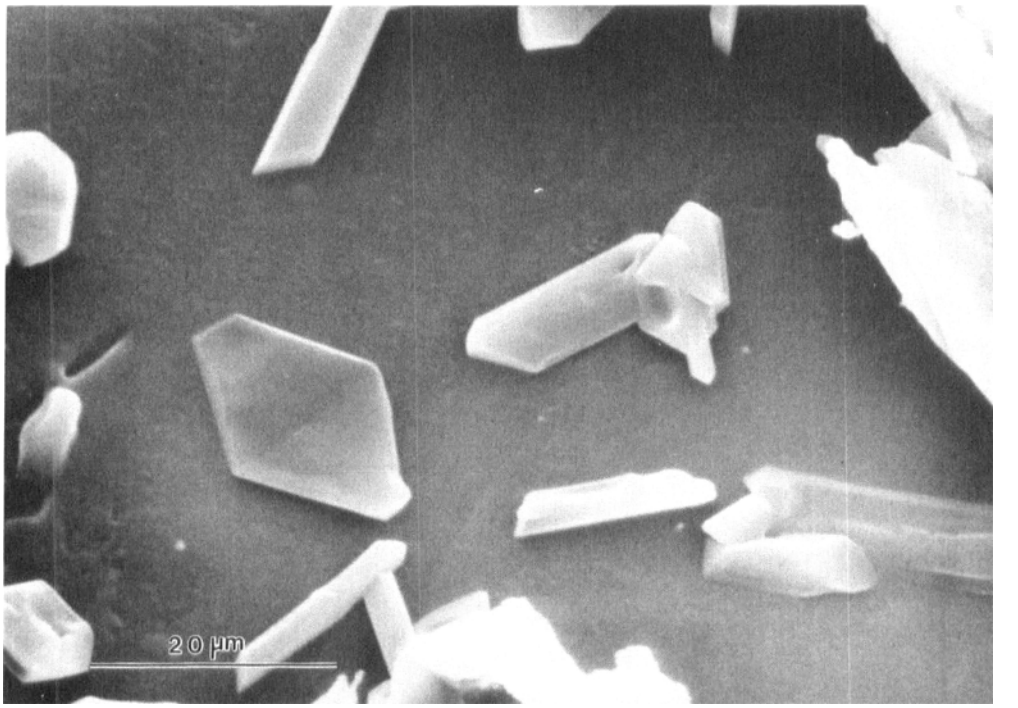

FIGURE 3
Scanning electron micrograph of a freeze-fractured pellet containing 5% w/w of progesterone.

between the drug crystals. A small amount of the drug, however, dissolves in the polymer matrix. This dissolved drug plasticizes the polymer, resulting in a lowering of melting point of the polymer (Fig. 1). Thermograms of pellets containing 5 to 50% w/w of progesterone are also shown in Fig. 1. At 5 and 10% levels, the melting peak of the drug can not be seen because the drug dissolves in the melted polymer. When the drug loading reaches more than the solubility of the drug in the melted polymer (30% level), a peak corresponding to the melting

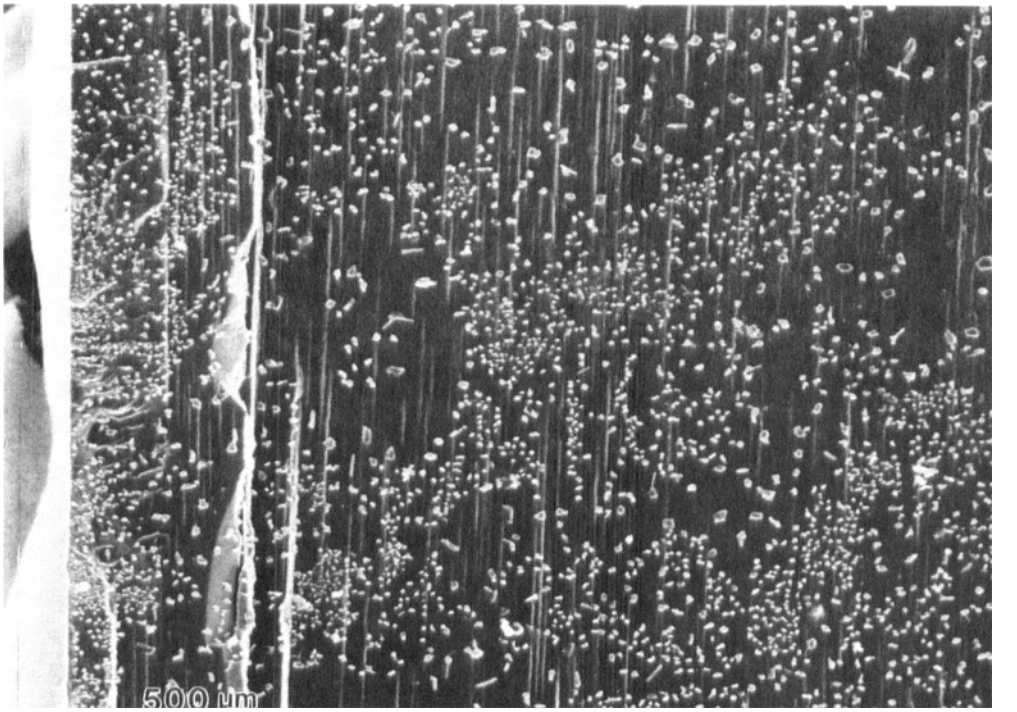

FIGURE 4
Full-view scanning electron micrograph of a freeze-fractured pellet containing 5% w/w of progesterone.

endotherm of the drug appears in the thermogram. This peak is even more evident in the thermogram of pellet containing 50% w/w of progesterone.

The mechanism of release of a drug dispersed in a polymeric matrix depends mainly on properties of polymer and drug such as their molecular weight, miscibility with each other and, in some cases, biodegradability of the polymer. Release of drug from a non-degradable matrix system takes place by diffusion or

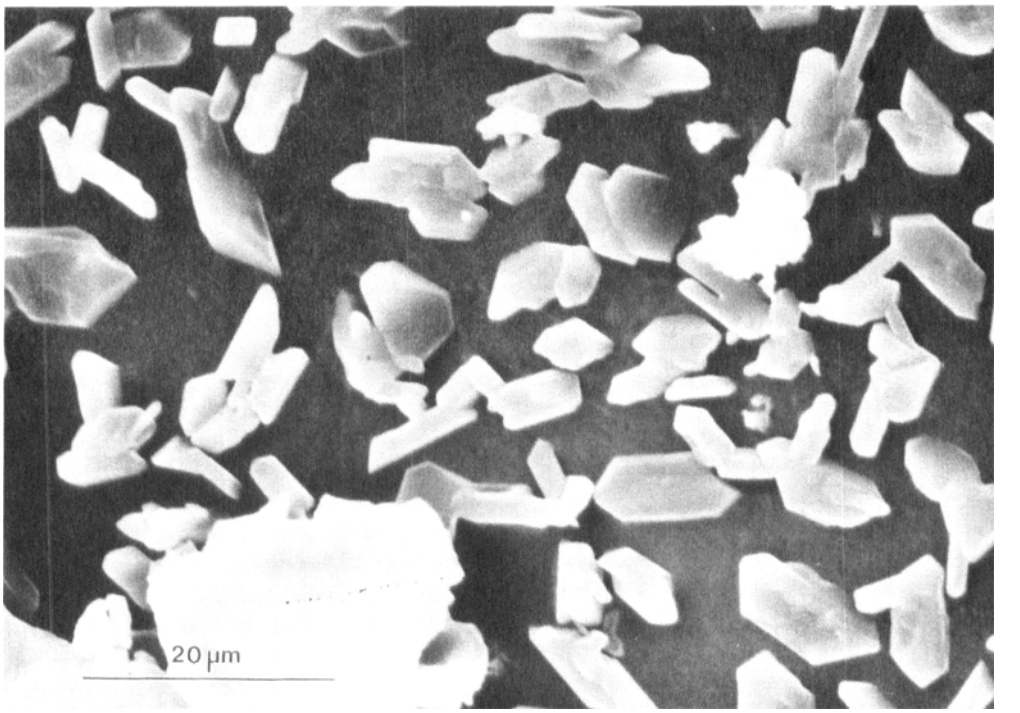

FIGURE 5
Scanning electron micrograph of a freeze-fractured pellet containing 10% w/w of progesterone.

leaching or a combination of both. In a nonporous system, diffusion is the primary mechanism of release of the drug at low drug loadings. At higher drug loadings, pores and channels are created by the dissolved drug particles and leaching contributes significantly to the release. In case of a biodegradable system, matrix erosion may add to the overall release of the drug.

The release of progesterone from pellets was faster with increased payloads of progesterone in the pellets (Fig 7). The t_{50} (time for 50% release) decreased from

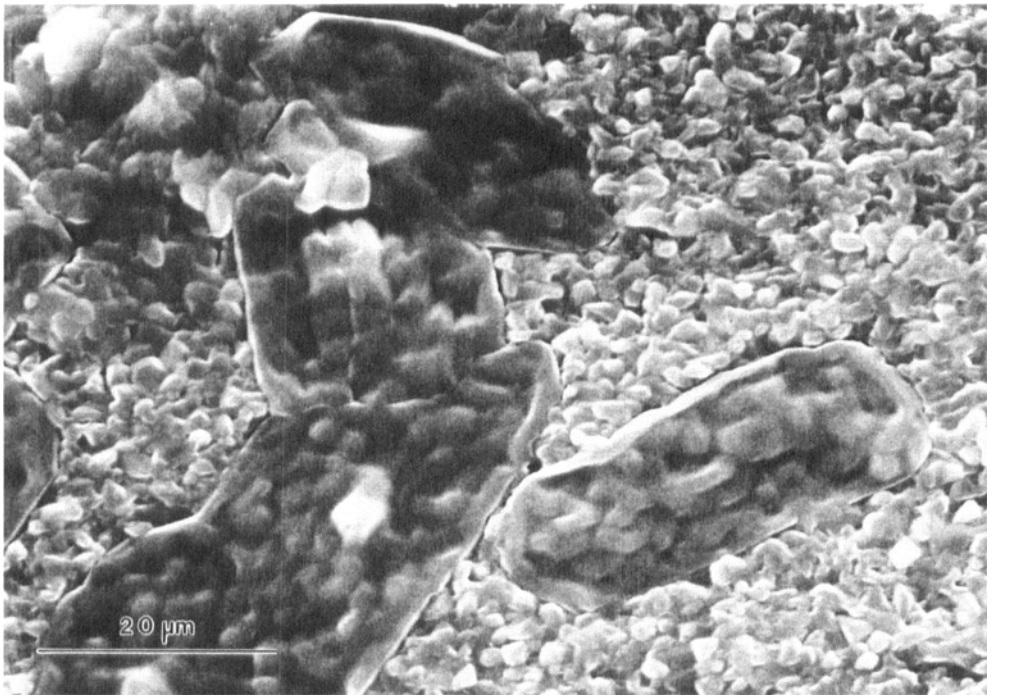

FIGURE 6

Scanning electron micrograph of a freeze-factured pellet containing 30% w/w progesterone.

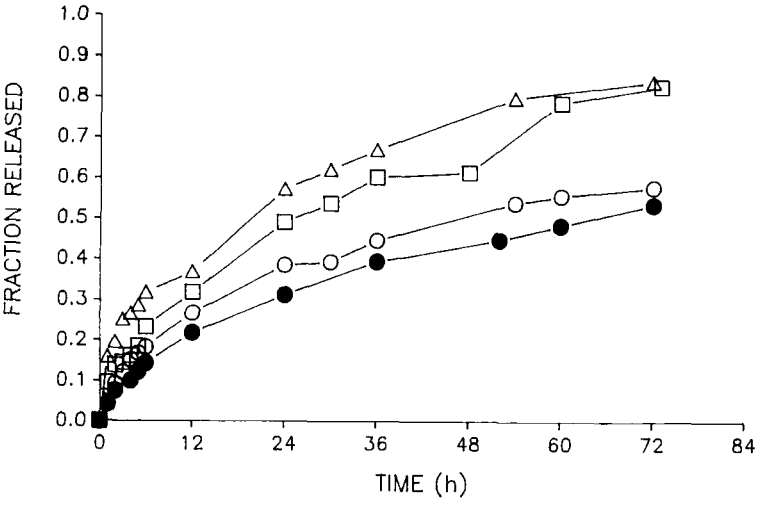

FIGURE 7

Effect of drug loading on the *in vitro* release profiles of 70 mg pellets. Key: Pellets containing 5% w/w (●), 10% w/w (○), 30% w/w (□), and 50% w/w (△) of progesterone.

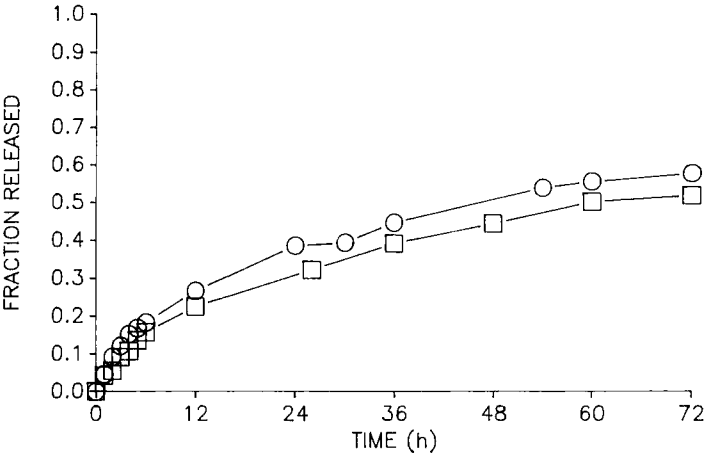

FIGURE 8

In vitro release profile of 70 mg pellet (○) and 140 mg pellet (□) each containing 7 mg of progesterone.

TABLE 2

Slopes, Intercepts, and Correlation Coefficients of Higuchi Plots of the Release Data

Pellet	Slope±S.D.	Intercept±S.D.	Correlation Coeff.
1	0.077±0.002	0.033±0.009	0.996
2	0.072±0.002	0.001±0.008	0.996
3	0.099±0.002	0.015±0.011	0.996
4	0.097±0.003	0.061±0.015	0.993

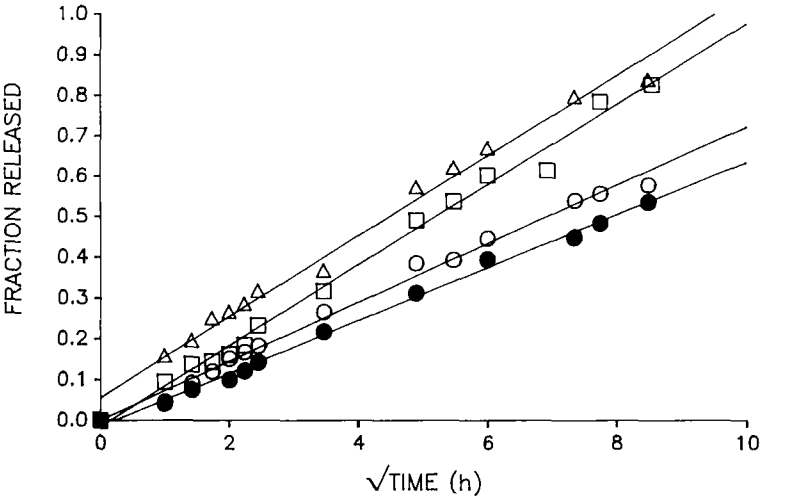

FIGURE 9
Higuchi plots of the *in vitro* release data of different pellets. Key: 70 mg pellets containing 5% w/w (●), 10% w/w (○), 30% w/w (□), and 50% w/w (△) of progesterone. 140 mg pellets containing 5% w/w of progesterone.

over 60 hours for pellet with 5% drug to about 20 hours for pellet with 50% drug. The release of the drug from pellets can also be controlled without changing the dose or the drug content by changing the polymer content. When the size of the pellet was doubled by increasing the amount of polymer but keeping the amount of drug (7mg) the same, the rate of release was slower (Fig. 8). This can be attributed to longer diffusion/leaching path length for the drug molecules in the polymer matrix. The release of a drug may be altered if the polymeric matrix swells in the dissolution medium. Measurment of thickness of pellets after the completion of release experiments showed that PHBV pellets did not swell in the dissolution medium.

Higuchi[12] proposed a mathematical model for the release of solid drug uniformly dispersed in a solid matrix. For a planar system, the amount of the drug

released at any time is directly proportional to the square root of time. For thin pellets (high diameter/thickness ratio), very little drug diffuses from the edges of the pellets. Therefore, the pellets behave as planar devices. Table 2 lists slopes, intercepts and correlation coefficients of Higuchi plots (Fig. 9) of the dissolution data obtained in this study. Values of correlation coefficient suggest that the release profiles of the pellets can be described adequately by the Higuchi model over a large fraction of their dissolution.

CONCLUSIONS

Biodegradable pellets of poly(hydroxybutyrate-hydroxyvalerate) containing progesterone were successfully prepared by a simple compression and melt technique. This technique has an advantage that organic solvents are not used in the preparation of the dosage form. These pellets can be used for parenteral administration of progesterone for contraceptive or therapeutic purposes.

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