Drug Development and Industrial Pharmacy, 22(7), 645-651 (1996)

Studies on the In Vitro Release of Ibuprofen from Polyethylene Glycol–Polyvinyl Acetate Mixtures Liquid Filled into Hard Gelatin Capsules

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ABSTRACT

The release of ibuprofen from mixtures of polyethylene glycol (PEG) with polyvinyl acetate (PVAc) has been studied in vitro and complemented by x-ray diffraction measurements, differential scanning calorimetry (DSC), and melting point determinations via hot-stage microscopy (HSM). Results indicate that ibuprofen release can be affected markedly by alteration of the PVAc concentration. The molecular weight of the PEG and the pH of the dissolution medium are also shown to affect the release profile. Visual observation during the drug release process revealed a complex behavior which included emission of liquidlike droplets, formation of a crust around the releasing mass, and/or production of flakes of solid material. This behavior appeared to have a disadvantageous effect on the reproducibility of drug release. Construction of a phase diagram from results of thermal analysis using DSC and HSM indicated the formation of an eutectic mixture with a composition of 35% ibuprofen and 65% PEG 1500 and a melting point of 36°C. The complex behavior of the drug-releasing mass is discussed in terms of this phase diagram. Only the release data for systems containing 4% w/w or more of PVAc could be linearized by plotting against the square root of time whereas data for all of the systems studied could be linearized by first-order plots.

INTRODUCTION

The effects of various factors on the in vitro release of theophylline from mixtures of polyethylene glycol (PEG) with polyvinyl acetate (PVAc) liquid filled into hard gelatin capsules have been described previously (1). This paper extends the study to an investigation of the release of ibuprofen from the same mixtures. The short biological half-life of ibuprofen—i.e., 1.4–2.5 hr. (2)—renders it an appropriate candidate for presentation in a controlled-release dosage form. Other release studies on this drug appear in the literature (3,4) and controlled- or sustained-release preparations are available commercially.

MATERIALS

Materials were obtained from the following sources: Boots Pharmaceuticals, Nottingham, England, for ibuprofen [2-(4-isobutyl phenyl) propionic acid]; BDH Chemicals Ltd., Poole, England for PEGs 1500, 3000, 4000, and 6000 and PVAc with molecular weight of approximately 45,000; Davacaps, Monomouth, Gwent, Wales, for hard gelatin capsules.

METHODS

Preparation of Capsules

The general composition of the contents of the various liquid-filled capsules investigated in this study can be described by the following formula:

Ibuprofen: 200 mg
Base consisting of y% w/w PVAc in PEG of MW z: to 600 mg

In the specific formulas y = 0, 1, 2, 3, 4, 5, 6, or 10; and z = 1500, 3000, 4000, or 6000. (Note. In order to avoid considerable repetition henceforth in this report, the molecular weight of PEG is given only when the value differs from 1500.) The capsules were prepared using the method described previously for theophylline capsules (1).

Determination of the Uniformity of Weight and Contents of Active Ingredient

The methods described in the *British Pharmacopoeia* (5) were followed. The ibuprofen content of the capsules was determined by dissolving the contents of each capsule in 900 ml of phosphate buffer solution (6.805 g/dm^3 anhydrous potassium dihydrogen phosphate and 1.388 g/dm^3 sodium hydroxide) at pH 7.2 and assaying spectrophotometrically against the buffer solution using a Pye-Unicam SP8-400 uv/visible spectrophotometer at 264 nm.

Drug Release Studies

These were carried out using the flask-stirrer method described previously (1) and a dissolution medium of phosphate buffer solution at pH 7.2. Ibuprofen concentrations in the samples of dissolution medium removed from the apparatus at various times during the release process were assayed spectrophotometrically at 264 nm against a blank comprising phosphate buffer solution. Control experiments showed that interference with the assay from absorbing materials released from PEG or PEG/PVAc mixtures was low.

X-ray Diffraction Measurements

These were carried out on PEG, ibuprofen, and samples taken from the centers and edges of systems comprising either PEG alone or PEG plus 33% ibuprofen with or without 4% w/v PVAc. The measurements were carried out using the method described previously (1).

Differential Scanning Calorimetry (DSC)

This was carried out on PEG, ibuprofen, and various mixtures of both components using a Perkin–Elmer DSC-4. Dry nitrogen was used as the purge gas at a flow rate of 30 cm^3 min^{-1}. A temperature range of 20°–300°C was employed with a heating rate of 5°C min^{-1}. Ice/water mixture was used as the coolant and calibration was achieved using an indium standard.

Hot-Stage Microscopy (HMS)

The initial melting points (thaw points) of PEG, ibuprofen, and various compositions of these two components were determined using a Reichert–Koffler hot-stage microscope fitted with polarizers. The first appearance of liquid was taken to indicate the onset of melting.

RESULTS AND DISCUSSION

Uniformity of Capsule Fill Weight and Ibuprofen Content

The average fill weights ($\pm$ *SD*) of two series of 20 capsules containing a target dose of 200 mg of ibuprofen

and 400 mg of base comprising either PEG or PEG with 4% w/w PVAc were 606 mg (± 10 mg) and 607 mg (± 11 mg), respectively. In addition, the average ibuprofen content (± *SD*) of two further series of similar capsules were 199.6 mg (± 5.0 mg) and 199.5 mg (± 8.1 mg). The reproducibilities indicated by these results were considered to be satisfactory for the purposes of the present study.

X-ray Diffraction Studies

The diffraction patterns obtained using samples taken from the edges of solidified matrices removed from their enclosing gelatin capsules were the same as those obtained using samples taken from the centres of the same matrices. Analysis of the pattern given by PEG containing 33% ibuprofen shows that it contains several bands, which are characteristic of ibuprofen, particularly at d-spacings (i.e., distances between each set of atomic planes of a crystal lattice) of 14.2, 7.3, 6.4, 5.0, 4.4, and 4.0 Å. Thus, ibuprofen is obviously present in excess of its solubility in these systems. Most of the bands produced by PEG alone are either too weak to show up in the pattern produced by the mixture containing 33% ibuprofen or appear at d-spacings, which coincide with ibuprofen bands. Fortunately, the intense band at 3.8 Å provides a good indication of the presence of PEG in the PEG/ibuprofen mixture. The presence of the amorphous PVAc had no significant effect on the diffraction patterns.

Thermal Analysis Using DSC and HSM

PEG gave a single, uncomplicated endotherm. Incorporation of increasing concentrations (5–25% w/w) of ibuprofen into the PEG resulted initially in the broadening of the endotherm, lowering of the peak temperature and the appearance of an inflection on the leading edges of the endotherms. This inflection corresponded to the melting of a eutectic. Single, uncomplicated endotherms were obtained with mixtures containing 33% or 35% w/w of ibuprofen in PEG. Thermograms on the ibuprofen-rich side of this eutectic composition initially displayed offset temperatures apparent as small baseline drifts, which, with increasing ibuprofen concentrations, became more recognisable as endotherms corresponding to the melting of pure ibuprofen.

A phase diagram constructed using the peak temperatures of the thermograms obtained by DSC and the initial melting points obtained by HMS is shown in Fig. 1. This illustrates the formation of a eutectic mixture at a composition of 35% ibuprofen and 65% PEG. The

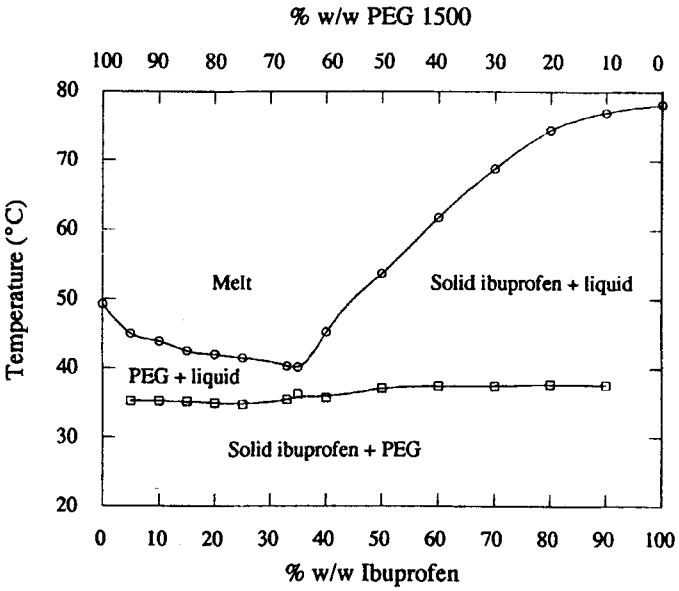

Figure 1. Temperature–composition diagram for ibuprofen/PEG system as determined using DSC (-○-) and HSM (-□-).

melting point of this mixture as determined by HSM is 36°C, which is the temperature noted when melting of the mixture first occurs. The higher melting point obtained using DSC arises because the temperature corresponding to the peak of the thermogram has been used rather than the less well-defined onset temperature. A similar affect was reported by Ford (6). Thus, at an experimental temperature of 37°C and a composition of 33% ibuprofen:67% PEG, the system will tend to consist of a liquid phase corresponding to the eutectic composition plus a small amount of solid PEG, provided that the experimental conditions remain unchanged. However, if the system is placed in water, as it is in the drug release study, it is likely that some PEG will be removed quite rapidly (after dissolution of the gelatin capsule) so that the composition of the ibuprofen:PEG mixture moves to the ibuprofen-rich side of the eutectic point. In this case the mixture would consist of a liquid phase with a composition corresponding to the eutectic mixture plus solid ibuprofen.

Effect of PVAc Concentration on Ibuprofen Release

The release rate curves of ibuprofen from encapsulated bases comprising PEG plus various concentrations of PVAc in the range of 0–10% w/v and containing 200 mg of ibuprofen are shown in Fig. 2. It can been seen that the rate of release decreases as the concentration of

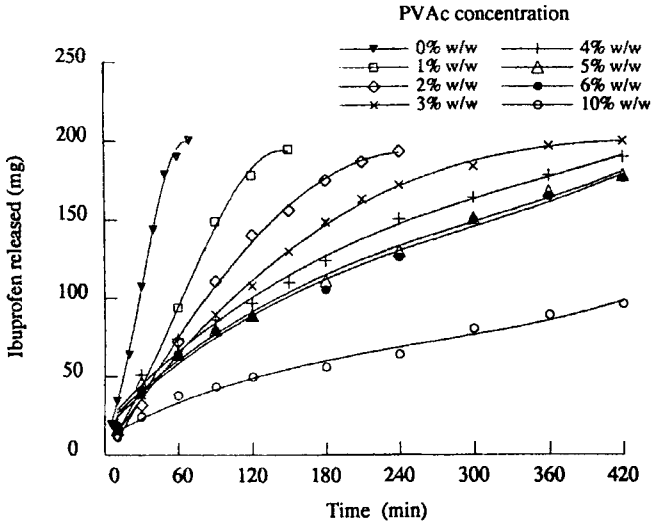

Figure 2. Effect of PVAc concentration on ibuprofen release from PEG/PVAc bases (drug load = 200 mg; dissolution medium = phosphate buffer at pH 7.2).

PVAc increases. This effect is similar to that obtained with theophylline capsules (1) except for the greater difference between the effects of 6% and 10% w/w PVAc exhibited by the ibuprofen capsules. The range of $t_{50\%}$ values shown in Table 1 illustrates the wide degree of control of ibuprofen release that can be achieved by the addition of 0–10% w/v PVAc.

The curves shown in Fig. 2 are based on the mean results of four separate determinations on each system. They are not so smooth as those obtained with theophylline-containing capsules (1). Reproducibility of results, as indicated by a comparison of coefficients of variation, is also less satisfactory for the ibuprofen capsules relative to the theophylline-containing ones. This more erratic behavior is probably due to the changes which occur in the ibuprofen capsules during the release experiments. Visual observations show that, after the gelatin capsules have dissolved, liquidlike droplets are emitted from the PEG and PEG/PVAc matrices, and remain at the bottom of the dissolution vessel until they dissolve in the dissolution medium. In addition, removal of matrices at various stages of the drug release process shows that the systems tend to form hollow cylinders with a relatively hard outer "crust," which dissolves gradually. The appearance of these cylinders, as formed by systems containing PEG and ibuprofen, is illustrated by Fig. 3(b). Figure 3(a) shows the initial appearance

Table 1

$t_{50\%}$ Values for Ibuprofen Release from PEG/PVAc Bases into Phosphate Buffer at pH 7.2

PVAc Conc. (% w/w)	Mean[a] (min)	$t_{50\%}$ SD (min)	Coeff. of Variation (%)
0	29.0	2.0	6.9
1	63.3	1.0	1.5
2	80.8	5.2	6.4
3	113.0	3.7	3.3
4	126.4	6.2	4.9
5	147.4	6.2	4.2
6	156.3	6.7	4.3
10	>420	—	—

[a]Mean of at least 4 replicates (except for 10% w/w PVAc system—single determination only).

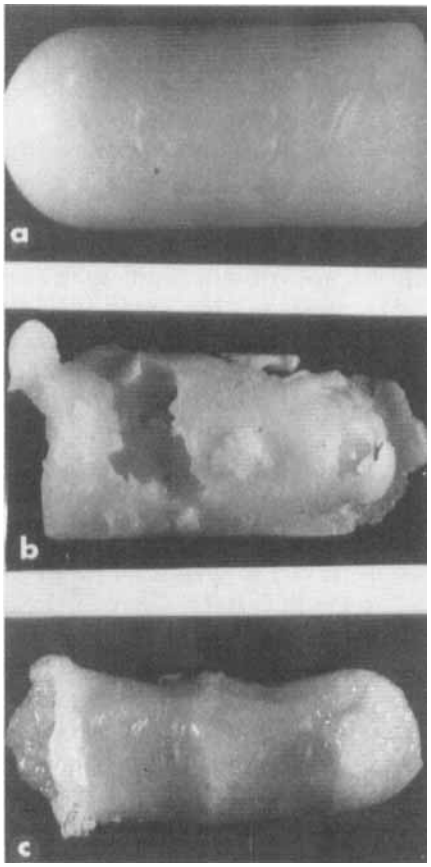

Figure 3. Photographs of systems before and after exposure to dissolution medium. (a) PEG/ibuprofen after removal from gelatin capsule. (b) Crust formed by PEG/ibuprofen after exposure to phosphate buffer (pH 7.2) for 20 min. (c) Crust formed by PEG/4% w/w PVAc/ibuprofen after exposure to phosphate buffer (pH 7.2) for 60 min.

for comparison purposes. The integrity of the crust is improved by the inclusion of 4% w/w PVAc in the formula, as illustrated by Fig. 3(c).

The melting point of material removed from the crust formed by PEG containing ibuprofen was 60°–65°C. From the phase diagram shown in Fig. 1, this temperature range indicates that the composition of the crust is approximately 60% ibuprofen plus 40% PEG; i.e., it is richer in drug than the initial formula which comprised 33% ibuprofen and 67% PEG. X-ray diffraction measurements confirm the presence of both components in the crust. The relative intensity of the band, which occurred at a d-spacing of 3.8 Å and which is characteristic of PEG, increased when 4% w/v PVAc was included in the formula.

The formation of drug-rich layers on the outsides of solid dispersions, corresponding to the crust observed in the present study, is referred to by Ford (7) in his composite scheme of the relation between dispersion composition and drug dissolution rate from constant area disks. However, explanation of the hollow nature of the cylindrical crusts is not obvious from Ford's scheme. An explanation may be proposed on the basis of the phase diagram, because the initial composition of the PEG/ibuprofen mixture is close to the eutectic composition and the latter has a melting point (36°C) which is just below the experimental temperature (37°C). Thus, liquefaction of the system will tend to occur. The release of liquidlike droplets from the PEG/ibuprofen matrices after dissolution of the gelatin capsules supports this suggestion. However, liquefaction of the whole matrix is unlikely if PEG is leached out of the matrix more quickly than ibuprofen because the remaining mixture will become richer in ibuprofen and its melting point will exceed the experimental temperature. This effect of change in composition caused by preferential removal of PEG will be most apparent on the outsides of the matrix.

Effect of Molecular Weight of PEG on Ibuprofen Release

The release profiles from systems containing 200 mg of ibuprofen in mixtures of PEG having molecular weights in the range of 1500–6000 with 4% w/w PVAc are shown in Fig. 4. As expected from the relative solubilities of the PEGs, the rate of drug release tends to decrease as the molecular weight of the PEG increases.

Visual inspection of the systems at various times during the drug release tests revealed a range of behaviors which included emission of liquid droplets, formation of a crust, and production of flakes of undissolved material. These visual observations are summarized in Table 2. The formation of crusts and flakes appears to agree with the scheme proposed by Ford (7). However, it would seem from the present results that other factors exert effects which are superimposed on those arising from composition. For example, the trend from crust formation to flake production as the molecular weight of PEG increases suggests that the relative solubilities of the two components are important. Furthermore, the appearance or nonappearance of liquid droplets suggests that the melting points of eutectic mixtures containing lower molecular weight PEGs relative to the experimental temperature should be considered.

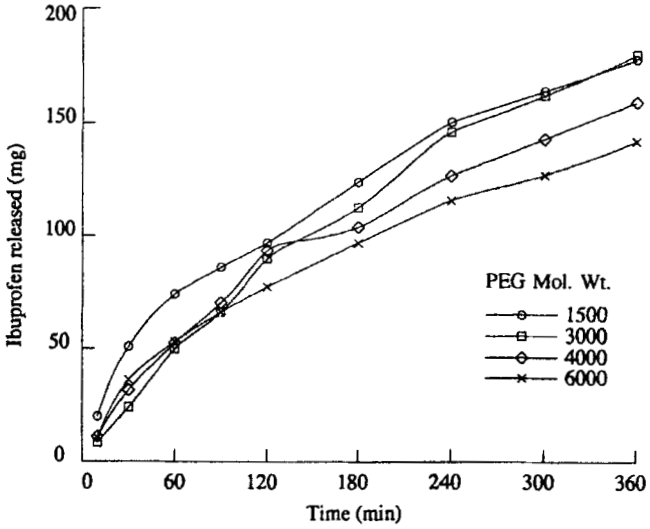

Figure 4. Effects of molecular weight of PEG on ibuprofen release from PEG/PVAc bases (drug load = 200 mg; dissolution medium = phosphate buffer solution at pH 7.2; PVAc concentration = 4% w/w).

Table 2

Visual Observations on Ibuprofen/PEG/PVAc Systems During Drug Release into Phosphate Buffer at pH 7.2 (drug load = 200 mg; PVAc concentration = 4% w/w)

Mol. Wt. of PEG	Droplet Emission	Crust Formation	Flake Production
1500	+	+	?
3000	+	+	+
4000	-	+	++
6000	-	-	+++

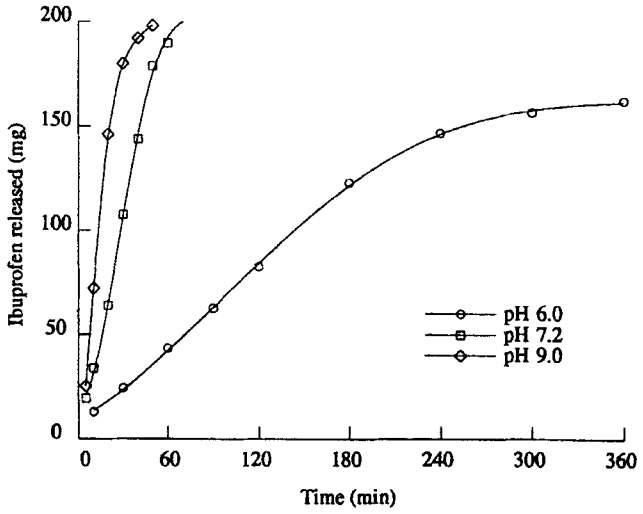

Figure 5. Effect of pH of dissolution medium (phosphate buffer) on ibuprofen release from PEG/PVAc bases (drug load = 200 mg; PVAc concn. = 4% w/w).

Effect of pH on Ibuprofen Release

The release profiles from systems comprising 200 mg ibuprofen in PEG at pHs of 6.0, 7.2, and 9.0 are shown in Fig. 5. The curve obtained at pH 6.0 illustrates the prolonged release which occurs when the solubility of the drug in the dissolution medium is decreased. It is interesting to note that crust formation was not apparent at pH 6.0 and was less pronounced at pH 9.0 than 7.2.

Kinetics of Ibuprofen Release

The release data for systems containing at least 4% w/w PVAc gave reasonably linear square root of time plots, as indicated by the correlation coefficients in Table 3. This is surprising in view of behaviors exhibited by the systems during drug release. It would seem reasonable to regard such plots merely as a means of linearizing the release data rather than as indicators of a diffusion-controlled release process.

A first-order type of plot also offered a means of linearizing the release data from a wider range of systems, which included those containing no or low concentrations of PVAc, as shown in Table 4.

CONCLUSIONS

The rate of release of ibuprofen from PEG bases can be prolonged by the inclusion of increasing amounts of PVAc in the formulation. Additional control over release rate can be effected by changing the molecular weight of the PEG. The pH of the dissolution medium must be taken into consideration. However, the complex behavior of ibuprofen/PEG mixtures during drug release may cause problems with regard to the reproducibility of release profiles.

X-ray diffraction is useful in determining whether or not ibuprofen is present in excess of its solubility in PEGs. The construction of phase diagrams for ibuprofen/PEG mixtures aids the understanding of the com-

Table 3

Slopes, Intercepts, and Correlation Coefficients of M_t vs. $t^{1/2}$ Plots (pH of dissolution Medium = 7.2)

Composition of Base		M_t vs. $t^{1/2}$ Plots		
PVAc Conc. (% w/w)	Mol. Wt. of PEG	Slope (mg $min^{-1/2}$)	Intercept (mg)	Correlation Coefficient
4	1500	9.49	-3.34	0.997
5	1500	8.80	-3.76	0.998
6	1500	8.80	-6.07	0.997
10	1500	4.52	0.09	0.995
4	3000	11.36	-35.20	0.997
4	4000	9.34	-20.52	0.999
4	6000	8.33	-14.09	0.997

Table 4

Slopes, Intercepts, and Correlation Coefficients of Log($M_\infty - M_t$) vs. $t^{1/2}$ Plots

Composition of Base			$\text{Log}(M_\infty - M_t)$ vs. $t^{1/2}$ plots		
PVAc Conc. (% w/w)	Mol. Wt. of PEG	pH of Dissolution Medium	Slope (min^{-1})	Intercept on Log Axis	Correlation Coefficient
0	1500	7.2	-0.0388	3.133	0.945
1	1500	7.2	-0.0110	2.649	0.983
2	1500	7.2	-0.0063	2.290	0.991
3	1500	7.2	-0.0046	2.472	0.974
4	1500	7.2	-0.0024	2.276	0.991
5	1500	7.2	-0.0019	2.255	0.991
6	1500	7.2	-0.0018	2.264	0.989
10	1500	7.2	-0.0006	2.256	0.993
4	3000	7.2	-0.0029	2.383	0.989
4	4000	7.2	-0.0017	2.284	0.997
4	6000	7.2	-0.0013	2.253	0.997
0	1500	6.0	-0.0021	2.309	0.993
0	1500	9.0	-0.0339	2.428	0.999

plex behavior exhibited by these mixtures during drug release studies.

The rate of ibuprofen release from PEG/PVAc mixtures can be linearized either by first-order plots or, in those systems containing 4% w/w or more of PVAc, by square root of time plots. In view of the complex behavior exhibited by the systems during drug release studies, the physical significance of such plots should be treated with caution.

ACKNOWLEDGMENT

The authors wish to thank Professor K. A. Khan, Pharmaceutical Formulation Department, Knoll Pharmaceuticals, Nottingham, for helpful discussions and advice.

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