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Evaluation of the solution impregnation method for loading drugs into suspension-type polymer matrices: a study of factors determining the patterns of solid drug distribution in matrix and drug release from matrix

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Summary

Several implications of using the solution impregnation method for loading drugs into suspension-type polymer matrices are discussed. The effects of impregnation solvent volatility, drug physicochemical nature and polymer composition gradients on the ultimate solid drug distribution in the dried matrix and the drug release pattern generated by such a distribution are investigated. Polydimethylsiloxane (PDS) elastomer is used as the basic matrix material. In some instances a hydrophilic layer is created at the surface of the PDS matrix by means of a gradient interpenetrating network (IPN) of poly(2-hydroxyethyl methacrylate) (p-HEMA). Progesterone (PGT) and benzocaine (BZC) are used as model drugs. When a volatile solvent and a highly soluble drug in solvent are used to load the unmodified PDS polymer, drug accumulation in matrix core and a surface layer free of solid drug result from matrix drying. Such a distribution pattern reduces the time dependence of the drug release rate with respect to the uniform distribution. A similar drug distribution is also obtained with the IPN-modified matrix when it is loaded by a PGT-chloroform impregnation solution. The drug release pattern in this case is nearly of zero order as the hydrophilic layer comprises a rate-limiting barrier to PGT escape. On the other hand BZC distributes mainly in the IPN-modified surface layer, owing to its high affinity for p-HEMA, and therefore, the drug release pattern in this case is characterized by a strong burst effect.

Introduction

The procedure usually adopted to load drugs into polymer networks that cannot be cross-linked in the presence of the drug is known to consist in soaking the pre-cross-linked polymer in a solution of the drug in a solvent able to swell the polymer network and then drying the drug-impregnated system. This loading procedure poses some questions as to what the ultimate drug distribution in matrix will be like. While a homogeneous distribution is expected where the whole drug load is free to diffuse and equilibrate in the dried polymer, such as with solution-type matrices, this is not the case when suspension systems result. In these cases, indeed, solid drug distribution gradients may be

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found in matrix after attainment of thermodynamic equilibrium. The factors determining the ultimate drug distribution in matrix should be kept under control since such a distribution can influence the pattern of drug release. In fact, several researchers have resorted to immobilized drug distribution gradients to obtain fairly constant release rates from monolithic matrices. Such gradients were realized through either partial extraction of drug-loaded polymers (Lee, 1984; Mueller, 1987) or modification of substrate polymer composition by gradient interpenetrating polymer networks (IPN) (Mueller and Heiber, 1982). With the latter approach the drug concentration gradients in matrix after drying were thought to be determined by the compositional gradients of the IPN.

In the present work we have investigated several implications of loading a drug into a suspension-type polymer matrix by solution impregnation, such as the effects of impregnation solvent volatility, drug physicochemical nature and polymer composition gradients on the ultimate solid drug distribution in matrix and the drug release pattern generated by such a distribution. Polydimethylsiloxane (PDS) elastomer was used as the basic matrix material. Hydrophilicity gradients were introduced into the PDS network by allowing 2-hydroxyethyl methacrylate to diffuse and simultaneously polymerize into PDS, thus forming a gradient IPN (Predecki, 1974; Vale and Greer, 1982). Chloroform and xylene were used as impregnation solvents with markedly different evaporation rates. Progesterone and benzocaine were chosen as model drugs.

Materials and Methods

Materials

Medical grade polydimethylsiloxane (PDS) elastomer 382 (fillerless), silica filler Celite Superfloss, stannous octoate (Catalyst M) (all gifts from Dow Corning, Midland, MI, U.S.A.), progesterone (PGT) (Merck, Darmstadt, F.R.G.), benzocaine (BZC), chloroform RP and xylene RP (Carlo Erba, Milano, Italy), 2-hydroxyethyl methacrylate (HEMA) (Sigma, St. Louis, MO, U.S.A.), α,α'-azoisobutyronitrile (AIBN) (Fluka AG, Buchs, Switzerland) were used as received. For some experiments the commercial PGT or BZC powders were micronized by a vibration ball mill (Fritsch GMBH, Idar-Oberstein, F.R.G.).

Preparation of PDS substrate

Two percent filler was uniformly dispersed into the PDS prepolymer by repeatedly spreading a film of the mix on a glass plate and recollecting with a spatula with care to avoid air entrapment. The mix, after addition of 0.2% stannous octoate catalyst by the same mixing technique was carefully filled into 2.5 cm lengths of a polyethylene tube of 0.4 cm internal diameter. The filled tube pieces were joined in twos by sticking the ends together and were left to cure 4 days at room temperature, after which clear, non-tacky, rubbery sticks were extracted by pulling the tube pieces apart. The sticks were washed 7 h in boiling xylene and then dried. Cylinders of the desired length were cut from the polymer sticks.

Synthesis of a poly(2-hydroxyethyl methacrylate) (p-HEMA) IPN in PDS cylinders

A typical batch of gradient IPN-modified PDS cylinders was prepared as follows. Eight PDS cylinders of ~2.5 cm length (310–320 mg weight range) prepared as described in the preceding section were swollen in boiling xylene, then simultaneously added to a 500 ml conic flask containing a mixture of 117 ml xylene, 3 ml ethanol and 30 ml HEMA pre-heated to incipient boiling. A small amount (~70 mg) of AIBN initiator was quickly added, a condenser applied to the flask, and the mixture refluxed 8 h. Contact of cylinders with the overheated walls of the flask was prevented by a nest of glass wool. After completion of polymerization the IPN-modified cylinders were recovered from the spongy mass of p-HEMA entrapping them after softening such a mass with excess ethanol. The cylinder surfaces were then mechanically cleared of clinging p-HEMA, and the cylinders washed in ethanol and next chloroform. Their weights after drying were in the 425–465 mg range, corresponding to an average p-HEMA content of 29% w/w.

IPN hydration kinetics

The hydration kinetics of the IPN was followed either in water or iso-osmotic NaCl at 37 °C, by determining the time increase of weight per unit length of cylinders, the IPN-modified ends of which had been cut off.

Polymer loading

Either IPN-modified or -unmodified PDS cylinders were loaded by soaking 3 days in chloroform or xylene solutions of PGT or BZC. Then they were dried to constant weight in a controlled air circulation drier at 37 °C. With a given solvent the drying times with the IPN-modified systems were much longer than with the unmodified ones. Drug migration and crystallization outside the polymer during drying occurred to different degrees with the different systems. Where the amount of drug crystals clinging to the cylinder surface after drying was significant crystals were collected and weighed. The drug load in polymer was determined gravimetrically after drying. The physical state of the drugs in the matrices was checked by differential scanning calorimetry (DSC). BZC was in its crystalline form (melting peak at 92 °C) in all of the systems prepared, while PGT was in its stable polymorphic form (melting peak at 129 °C) only in 22 out of 30 IPN-modified matrices analyzed. In the remaining 8 of these matrices and in all the unmodified ones PGT crystallized as a mixture of polymorphs (melting peaks at 105 °C, 109 °C, 122 °C and 129 °C) (Bernabei et al., 1982; Theeuwes et al., 1974) either from chloroform or xylene. The drug distribution in such systems was unstable as the less stable polymorphs would gradually dissolve and the stable morph crystals grew erratically either inside the matrix, as was verified by visually examining cross-sections taken at successive times, or on the matrix surface. Only the IPN-modified systems containing the only stable morph were retained for the release studies. Unmodified PDS cylinders uniformly loaded with 10% micronized PGT or BZC were prepared by dispersing the drug powder in the PDS prepolymer together with 2% filler and 0.2% catalyst, and then shaping and curing as described earlier. These matrices will be referred to henceforth as PGT-Disp and BZC-Disp, respectively.

Differential scanning calorimetry (DSC) measurements

A 1-mm-thick layer was cut away from each end of cylinders after drug loading, next a slice of 15–20 mg weight was cut from each end and analyzed by the Mettler TA 3000 Thermal Analysis System, consisting of a TC-10 TA processor, DSC20 measuring cell and printer–plotter. Samples were scanned in sealed aluminum pans at a heating rate of 10 °C/min.

Drug release measurements

Matrices were eluted in water at 37 °C under controlled hydrodynamics. Each drug loaded cylinder was trimmed to a length of 2 cm, its end surfaces covered with thin polytetrafluoroethylene sheeting impermeable to the drug by means of a silicone adhesive (355 Medical Adhesive, Dow Corning, Midland, MI, U.S.A.), then stuck axially to a propeller (5 cm diameter) by means of a needle, and rotated at 300 rpm by a synchronous motor in 1 liter of water. At intervals the elution medium was analyzed spectrophotometrically for PGT at 249 nm or BZC at 286 nm. Such a medium was renewed before the drug concentration in it could exceed 10% of saturation. Each experiment was run in quadruplicate.

Results

Properties of IPN-modified cylinders

Preliminary work had shown that IPNs obtained from fillerless PDS as the substrate polymer could not withstand deswelling from chloroform without cracking and/or peeling. Addition to PDS of as little as 2% filler was sufficient to grant the IPN-modified cylinders the wanted resistance to sharp differences in swelling between core and modified surface, at the same time preserving the clearness of the unmodified regions. Such a clearness made these regions visually distinguishable from the opaque IPN-modified ones. Indeed, the gradient IPN is clearly apparent in Fig. 1a, where a representative cross-section of an IPN-modified cylinder is viewed against a black screen. The hydration kinetics of IPN-modified cylinders either in water or normal saline is shown in Fig. 2.

TABLE 1

Data on polymer loading by solution impregnation

PDS cylinder	Drug	Impregnation solution		Matrix label	Dp (Range) [b] (%)	DLOD [a] (Range) [b] (%)
		Solvent	Ci (%)			
IPN-modified	PGT	chloroform	9.0	IPN-Mod/PGT/CF	10.3 (9.9–11.4)	nd [c]
		xylene	14.0	IPN-Mod/PGT/XL	4.4 (3.8–5.0)	17.0 (28.3–2.0)
	BZC	chloroform	3.0	IPN-Mod/BZC/CF	7.3 (5.5–8.2)	20.1 (38.3–8.9)
		xylene	5.0	IPN-Mod/BZC/XL	1.0 (0.7–1.6)	68.2 (76.7–54.3)
unmodified		chloroform	3.0	Un-Mod/BZC/CF	10.9 (10.5–11.2)	12.2 (14.8–9.0)
		xylene	5.0	Un-Mod/BZC/XL	3.1 (2.5–3.6)	59.6 (65.3–52.0)

Concentration of impregnation solution (Ci), drug load in polymer (Dp), and dose loss on drying (DLOD) for IPN-modified or unmodified PDS cylinders.

[a] Drug fraction crystallized outside matrix, on a total inside plus outside weights basis.

[b] Mean and variation range for 10 cylinders.

[c] Not determined (negligible).

The equilibrium hydration, which was little different in the two cases, was practically attained in a day.

Drug distribution in matrices loaded by solution impregnation

Data on matrix loading are found in Table 1, together with labels of the different matrix systems. The drug concentration in the chloroform impregnation solutions was tentatively adjusted to give loads around 10% w/w. Such high loads could not be realized with the xylene solutions because of a lower polymer equilibrium swelling, a higher loss of drug load on matrix drying (DLOD) due to outside crystallization, and a lower drug solubility in solvent limiting the impregnation solution concentration. As pointed out earlier in this report, unmodified PDS loading with PGT by solution impregnation was immaterial due to an erratic distribution of drug polymorphs in matrices of this type. With a given impregnation solution the BZC load in the IPN-modified matrix was lower than in the unmodified one because the hydrophilic IPN limited the swelling degree of the

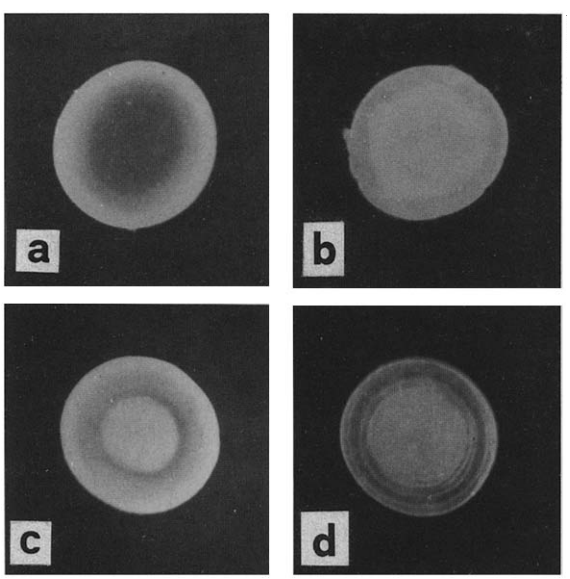

Fig. 1. Cross-sectional views of unloaded IPN-modified PDS cylinder (a), IPN-Mod/PGT/CF matrix (b), IPN-Mod/BZC/CF matrix (c), and Un-Mod/BZC/CF matrix (d).

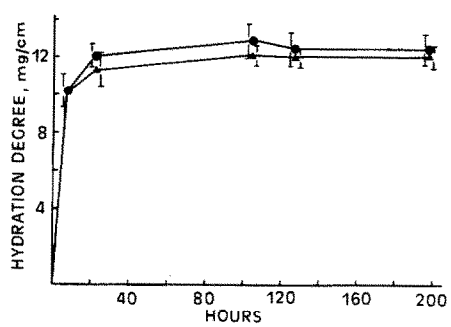

Fig. 2. Hydration kinetics of IPN-modified PDS cylinders in water (●) or iso-osmotic NaCl (▲). Weight increase per unit cylinder length plotted against time. Each data point represents the mean of 5 cylinders. Vertical bars represent the S.D. Where not shown they fall within the drawn symbol.

former matrix in the lipophilic medium. Information on the drug distribution in matrices was gathered from inspection of cross-sections. A sharply defined outer layer of virtually drug-free IPN could be seen in the cross-section of the IPN-Mod/PGT/CF cylinder. Such a layer can be distinguished in the photograph of the matrix cross-section presented in Fig. 1b. The compositional gradients in polymer and a higher affinity of the lipophilic PGT for the lypophilic PDS core than for the hydrophilic IPN layer seemed an easy explanation of such a drug distribution. In contrast with this hypothesis, however, the cross-section of the IPN-Mod/PGT/XL cylinder (photograph not reported, as it was similar to that of the unloaded polymer seen in Fig. 1a) showed no solid drug in the core. These findings suggested that the particular impregnation solvent might be of a major importance in determining the ultimate drug distribution in matrix. In fact, matrices impregnated with chloroform solutions always exhibited a distinct region of solid drug in the core, as the representative examples c and d of Fig. 1 show, even when the drug was BZC, which is much less lipophilic than PGT, or the polymer was the unmodified PDS, which contained no compositional gradients at all. A drug distribution similar to that seen in Fig. 1d for the Un-Mod/BZC/CF system was also shown by the cross-section of an unmodified PDS cylinder loaded with a PGT-chloroform solution, before the erratic changes in such a distribution caused by the physical instability of polymorphs were manifest. With xylene as the impregnation solvent BZC showed a tendency to crystallize outside rather than inside either the IPN-modified or the unmodified matrices, as appears from the relevant Dp and DLOD values found in Table 1. The small drug amounts remaining entrapped in polymer could not be detected visually in the case of the IPN-Mod/BZC/XL system, or were seen as rare crystal clusters distributed at random along the cylinder length with the Un-Mod/BZC/XL one.

Drug release studies

Although the present matrix types are intended to release drugs to a physiological environment pure water was used as the elution medium in that its effects on the releasing systems in terms of a hydration of the IPN layer were virtually the same as with physiological saline, as Fig. 2 clearly shows. All the patterns of drug distribution in matrix that showed a potential to improve the drug release pattern over that typical of a uniform distribution were obtained with chloroform as the impregnation solvent. Systems loaded by this solvent were compared with each other and with the reference systems PGT-Disp and BZC-Disp on the basis of the curvature of the respective release profiles. This was determined by fitting the release data points up to a 70% released fraction to the following equation:

$$Q = a + bt^n \quad (1)$$

to obtain the regression parameters for each case. In all cases but that of the IPN-Mod/BZC/CF system the fit was very good ($r \geqslant 0.999$). The exponent of time in Eqn. 1 gauges the curvature of the release plot. The n values for the different systems are compared in Table 2. Typical release profiles are presented in Figs. 3 and 4. Note that the n values for the reference systems PGT-Disp and BZC-Disp are equal, in accord with an equal release mechanism. This finding rules out any significant influence of the hydrodynamic diffusion boundary layer on release in the present hydrodynamic conditions. Any such influence, indeed, should have been much stronger and hence, the n value significantly higher with PGT than BZC, since it is estimated from literature data that the PDS-water distribution coefficient of the former is about 20 times as high as that of the latter (Bottari et al., 1978; Roseman, 1972). Then it is understood that comparing n values means

TABLE 2

Values of parameter n, as calculated through fit of Eqn. 1 to release data

Matrix	n [a]
IPN-Mod/PGT/CF	0.76 (0.06)
Un-Mod/BZC/CF	0.56 (0.01)
PGT-Disp	0.39 (0.00)
BZC-Disp	0.39 (0.01)

[a] Mean (S.D.) for 4 runs.

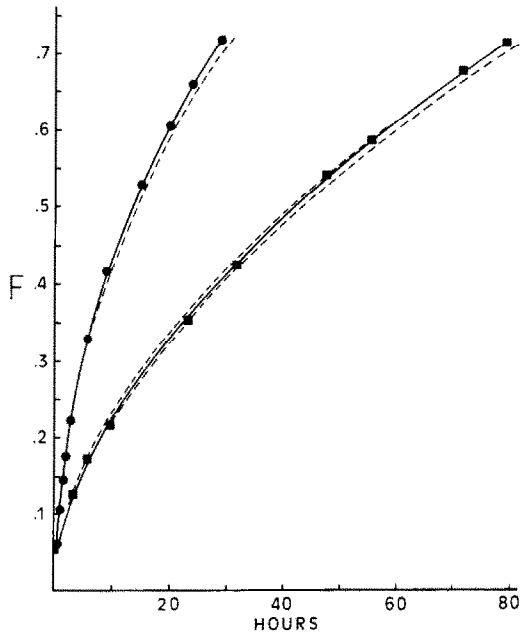

Fig. 3. Comparison between BZC release profiles (F, fraction released) for the Un-Mod/BZC/CF matrix (■) and the BZC-Disp matrix (●). Symbols represent experimental data points. Full lines represent regression curves as calculated with Eqn. 1. Dotted lines represent the regression curves for the extremes of the variation range for each system. One is omitted for clarity.

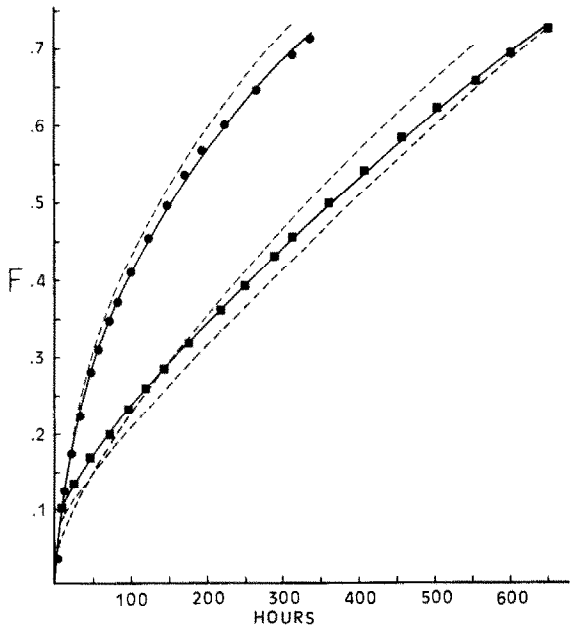

Fig. 4. Comparison between PGT release profiles (F, fraction released) for the IPN-Mod/PGT/CF matrix (■) and the PGT-Disp matrix (●). Symbols represent experimental data points. Full lines represent regression curves as calculated with Eqn. 1. Dotted lines represent the regression curves for the extremes of the variation range for each system. One is omitted for clarity.

comparing intrinsic release properties of matrices. As expected, the outer virtually drug-free layers seen in the cross-sections of the IPN-Mod/PGT/CF and Un-Mod/BZC/CF systems, represented in Fig. 1b and d, respectively, were in both cases responsible for a much longer duration of release and a lesser decline in time of release rate compared to the respective reference systems PGT-Disp and BZC-Disp. With the Un-Mod/BZC/CF cylinder the exponent of time was brought to surpass 0.5, whereas with the IPN-Mod/PGT/CF system the effect was markedly stronger as a zero-order pattern was approached. The release data points for the IPN-Mod/BZC/CF system did not fit Eqn. 1. In fact, the release profile with this system as appears in Fig. 5 was biphasic, with 65% of drug load being bursted off within the first 5 h and a further 30% being released at nearly zero-order over the following 75 h. The second phase reasonably corresponded to the release of the drug portion distributed in the matrix core, seen in Fig. 1c, whereas the initial burst revealed a distribution of a major portion of load in the IPN layer. The release profiles yielded

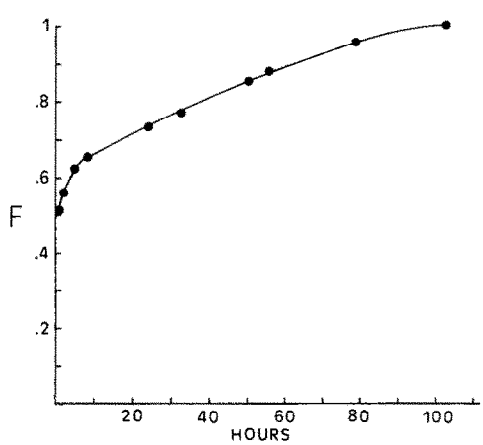

Fig. 5. Typical profile of BZC release (F, fraction released) from the IPN-Mod/BZC/CF matrix.

by the drug loads and distributions generated by the xylene impregnation solutions were not reported, as they were uninteresting.

Discussion

On the basis of the reported results the following mechanisms regulating drug distribution in matrix are suggested. With chloroform as the impregnation solvent, matrix swelling degrees sharply decreasing in the direction from core to surface developed in the matrix drying course, as a result of a high solvent evaporation rate. As a consequence, drug thermodynamic activity gradients developed in the opposite direction causing drug molecules to diffuse toward the matrix core. This process lasted almost the entire drying time as drug saturation of matrix regions was attained at rather low swelling degrees, owing to a high chloroform solubility of either BZC or PGT. Crystals first formed at the surface while the inner regions of the near-dry matrix went through a supersaturated state. Then further crystallization centres formed in the inner regions of higher supersaturated concentration. The subsequent crystal growth was "sucking" drug molecules in excess of saturation from the neighboring regions which remained devoid of crystals when thermodynamic equilibrium was finally attained. Such drug-free regions were indeed visible in the cross-section of all the matrices loaded with chloroform as the impregnation solvent (see Fig. 1b–d). With the IPN-modified systems a non-uniform drug distribution in matrix was not only caused by polymer swelling gradients but also by polymer composition gradients. Where the drug affinity was higher for the hydrophobic core than the hydrophilic IPN layer, as in the case of PGT, both swelling and compositional effects were in one direction, so virtually the whole load accumulated in the core. Conversely with BZC, which can form hydrogen bonds with p-HEMA, such effects were opposite to each other, therefore the solid drug divided in two distinct portions of which the major was in the IPN layer, the minor in the core, as co-operatively indicated by the view of the matrix cross-section and the release profile shown in Figs. 1c and 5, respectively.

When xylene solutions were used for matrix impregnation in no case could solid drug accumulate in the matrix core, probably because the driving force, namely, the drug thermodynamic activity gradient was inadequate in these instances. Apparently in these cases the solvent evaporation rate was not high enough to produce pronounced swelling gradients in matrix. Also, the development of effective drug activity gradients could have been limited by a higher saturation degree of the impregnation solutions, due to a lower solubility of the drugs in xylene compared to chloroform. As a result no drug crystal seeds could form in the matrix core but rather, crystals developed on the surface and from surface they grew to only a limited distance inside the matrix.

As already illustrated, the effect of the outer drug-free layers in the IPN-Mod/PGT/CF and Un-Mod/BZC/CF cylinders to decrease the time dependence of the drug release rate with respect to the respective references PGT-Disp and BZC-Disp was markedly stronger with the IPN-modified than with the unmodified system, even if, as the sections b and d of Fig. 1 show, the thickness of the former layer was somewhat smaller. However, it must be considered that the IPN-modified layer became fully hydrated at the very beginning of the PGT release course, as Fig. 2 shows, and therefore it soon grew both thicker and less permeable to the sparingly water-soluble PGT. Still, such a stronger effect of the hydrated IPN layer on the release pattern must be reconciled with a weaker effect of this layer on the release rate. Indeed, the decrease of release rate for the IPN-Mod/PGT/CF system with respect to the reference PGT-Disp seen in Fig. 3, was less than that seen in Fig. 4 for the Un-Mod/BZC/CF relative to the BZC-Disp system. Such an apparent contradiction might be solved by hypothesizing a higher solubility of PGT in the IPN-Mod/PGT/CF than in the PGT-Disp matrix. This hypothesis was checked by analyzing the systems in question by DSC. As Fig. 6 shows, the melting peak of PGT in the IPN-modified matrix was broader than that for the PGT-Disp matrix. Such a broadened peak can reasonably be ascribed to a

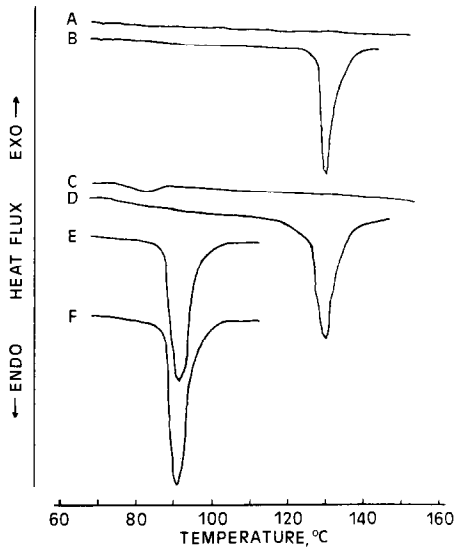

Fig. 6. DSC thermograms for drug-free unmodified PDS (trace A), PGT-Disp matrix (trace B), drug-free IPN-modified PDS (trace C), IPN-Mod/PGT/CF matrix (trace D), BZC-Disp matrix (trace E), and Un-Mod/BZC/CF matrix (trace F).

higher energy of the PGT particles formed by crystallization in the former matrix, possibly because these particles had more defects than the PGT powder used in the PGT-Disp matrix (Van Dooren and Muller, 1984). An increased PGT solubility in the IPN-modified matrix could well be a consequence of such a higher energy level of crystals. On the other hand, no appreciable differences in melting peak between absorbed and dispersed BZC are seen in Fig. 6, which suggests that the crystal energy and, hence, the drug solubility was the same in the Un-Mod/BZC/CF as in the BZC-Disp system.

Conclusions

The distribution of solid drug in the present suspension-type matrices loaded by the solution impregnation technique has been shown to be non-uniform with either one of the drugs and solvents tested in this study, even though the distribution pattern was strictly dependent on the physicochemical nature of solvents and drugs. The polymer swelling gradients which developed in the matrix drying course generated drug thermodynamic activity gradients whereby the drug molecules were driven toward the matrix core. The intensity of this phenomenon was higher as the solvent was more volatile and the drug solubility in solvent was higher. In fact, when chloroform solutions were used to load the unmodified PDS cylinders, drug accumulation in core and a surface layer virtually free of solid drug particles were observed. Such a drug distribution pattern improved the drug release pattern over that relative to the uniform distribution in that it reduced the time dependence of release rate. With the IPN-modified systems drug distribution gradients in matrix were not only determined by polymer swelling gradients but also by polymer composition gradients. The contribution of the latter was in a direction depending on the drug affinity for the IPN-modified layer relative to the unmodified PDS core. With PGT as the drug and chloroform as the solvent the IPN-modified layer remained devoid of solid drug after matrix drying so that, once hydrated by the elution medium, it exerted a function to control drug release to nearly zero order. On the other hand BZC distributed mainly in the IPN-modified region, owing to its comparatively high affinity for p-HEMA, and therefore, the drug release pattern in this case was characterized by a strong burst effect. With xylene as the impregnation solvent no activity gradients adequate to produce drug accumulation in core ever developed because of comparatively low evaporation rate and drug solubility for this solvent. In fact, the matrix core was found devoid of solid drug at all as drug distribution in this instance was determined by crystal growth which always started from the matrix surface. Finally it must be stressed that using the solution impregnation loading technique may bring about problems with drug polymorphism. With the unmodified PDS, PGT crystallized in matrix as a mixture of morphs which made the drug distribution unstable. Modification of the matrix surface layer by the IPN relieved the problem as far as the single stable morph was found in matrix in 22 out of 30 cases.

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