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Two-stage release of benzocaine from sunflower oil/gelatin emulsion films

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Summary

The release of benzocaine from thin emulsion-gel films is studied. It is shown that release of benzocaine from such films is complex possibly due to interaction between the drug and formaldehyde, the hardening agent. Reversible cross-linking of formaldehyde with gelatin may also be involved. With storage in a formaldehyde environment, a decrease in the apparent diffusion coefficient of benzocaine in the hardened films was observed. The release behaviour observed, with an initial burst, may be useful for designing systems with an immediate release dose. Stability of such systems will, however, need to be validated.

Introduction

Polymer films are now widely used for providing controlled drug release. Both matrix and reservoir systems are in clinical use. The release profiles will depend on the physical make-up of the system with planar matrices usually adhering to the square root of time profiles (Higuchi, 1961; Baker and Lonsdale, 1974; Broberg et al., 1982) and reservoir systems releasing drug according to zero order kinetics (Chien and Lambert, 1976; Cardinal et al., 1980) at least during a significant part of the release. In some cases, release dependent on polymer degradation have also been reported (Yolles et al., 1976; Heller, 1980).

Matrix systems based on dissolved drug have limited drug capacity while matrix systems containing suspended drug may suffer from dissolution-rate limitation. With reservoir systems, one containing suspended drug should theoretically maintain constant activity but even then problems still remain under in use conditions (Chien et al., 1975; Spilman et al., 1976). In this report, work is described on the design of an alternative film system, viz., one consisting of drug dissolved in an oil phase which is suspended in a gel matrix. This emulsion-gel system is suitable for highly water-insoluble compounds and has the advantage that drug-loading capacity is relative to other film systems high and flexible given that changes in oil-gel composition can be readily carried out.

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Materials and Methods

Materials

Gelatin (200 bloom, pKa 8.9) was kindly donated by Messrs. Alfred Adams of West Bromwich, U.K. All other chemicals were of analytical grade.

Preparation of formaldehyde-hardened emulsion films

A 20% w/w molten aqueous gelatin gel was stirred at 60 °C with benzocaine-containing sunflower oil at 2000 rpm using a Heidolph RZR 50 stirrer to produce an emulsion gel with 20% oil and a 0.5% w/w oil-content in the final emulsion. Thin films of the emulsion were cast between two stainless steel parallel plates. Circular discs of 1.8 cm diameter were cut and stored in a tank containing formaldehyde vapour at 95% relative humidity and 20 °C. The formaldehyde environment was created by wetting a piece of cotton wool with 2 ml of commercial formalin (38% w/w formaldehyde solution).

Monitoring release from hardened films

The films were first of all washed in a 50% aqueous methanol solution to remove any traces of benzocaine on the film surface. They were then placed in a USP dissolution basket and stirred at 40 rpm in 500 ml phosphate buffer (pH 7) at 37 °C. 5 ml aliquots were withdrawn for assay of benzocaine content.

Monitoring release from unhardened films

Unhardened films (diameter 7 cm) were clamped between a circular ring and plate of the same diameter. The ring ensured exposure of 6 cm diameter of one face of the film. Before clamping under the ring system, a membrane filter (Millipore SM 11307) and a stainless steel wire cloth (40 mesh) were placed on top of the film. Filter membranes were used to stop dissolution during the release experiments as previously described (Brodin and Nyquist-Mayer, 1982; Ayres and Lasker, 1974). The film assembly was then immersed in 500 ml of phosphate buffer (pH 7) at 37 °C and stirred at 75 rpm using a PTFE blade stirrer. 5-ml aliquots were withdrawn for assay of benzocaine.

Determination of the diffusion coefficient of benzocaine in a plain gelatin film

The diffusion coefficient of benzocaine across plain 20% gelatin films at 37 °C was determined using a diffusion cell. The diffusion of benzocaine across the membrane from a donor solution was monitored in the receptor phase and the results plotted on a graph of Q vs. t where Q is the amount released up to time t. The value of D was calculated from the time intercept (t_{lag}) using the formula:

$$t_{lag} = \frac{l^2}{6D} \qquad (1)$$

where l is the thickness of the film.

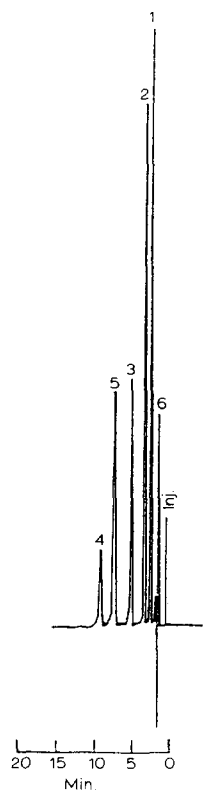

Fig. 1. Typical HPLC chromatogram of p-aminobenzoate esters: 1, methyl; 2, ethyl; 3, propyl; 4, butyl; 5, propyl-*p*-hydroxybenzoate (internal standard) and 6, *p*-aminobenzoic acid.

Assay of benzocaine

Benzocaine was assayed by HPLC using a 10 cm Shandon ODS Hypersil column. The mobile phase consisting of 6% phosphoric acid, 25% dilute ammonia solution, 50% methanol and 19% water was pumped at 1 ml min^{-1} (pressure 760 psi) using an Altex 100A double piston solvent metering pump. Detection was by UV spectroscopy at 285 nm using a Pye-Unicam LC UV detector. Methyl-*p*-aminobenzoic acid was used as the internal standard. A typical chromatogram is shown in Fig. 1.

Results and Discussion

Local anaesthetics, if formulated in thin flexible films, could prove useful in certain painful ulcerative conditions like mouth ulcers. This study was a continuation of previous efforts to obtain such formulations using other local anaesthetics in homogeneous and unhardened emulsion type films (Li Wan Po and Mhando, 1984; Li Wan Po and Mhando, in press). Unsatisfactory release rates were obtained in the earlier studies because either the polymer dissolved faster then required or release from the system was too fast. In this study a more lipophilic anaesthetic is used in a hardened gelatin matrix system which is insoluble in water.

Fig. 2 is a normal time release profile of benzocaine from the hardened emulsion films which were stored in formaldehyde vapour for 3 days followed by a further 3-day storage period in a formaldehyde-free environment. The release pattern consists of an initial burst phase of approx. 1 h followed by a steady release rate period of approx. 24 h before finally tapering off. The whole release process takes approx. 30 h and the percentage of drug released during the early stage is approx. 33%. On the other hand release of benzocaine from non-hardened emulsion films followed the square root of time model and is essentially complete within 9 h (Fig. 3). It appears therefore that mechanisms controlling release of benzocaine from these two systems are different. When the amount of benzocaine released from hardened films is plotted against $\sqrt{t}$, at least two distinct stages can still be observed (Fig. 4). This profile

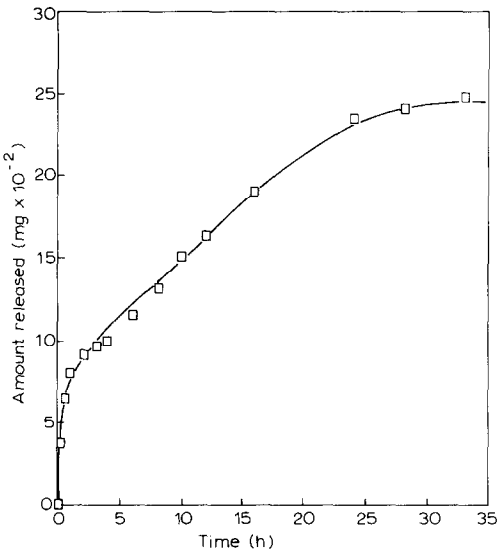

Fig. 2. Typical release profile of benzocaine from formaldehyde-treated emulsion films at 37 °C.

has been observed and studied in the case of diffusion of gases in polymers (Bagley and Long, 1955; Park, 1968). The behaviour has been explained as resulting from participation of two different sorption mechanisms. In the case of

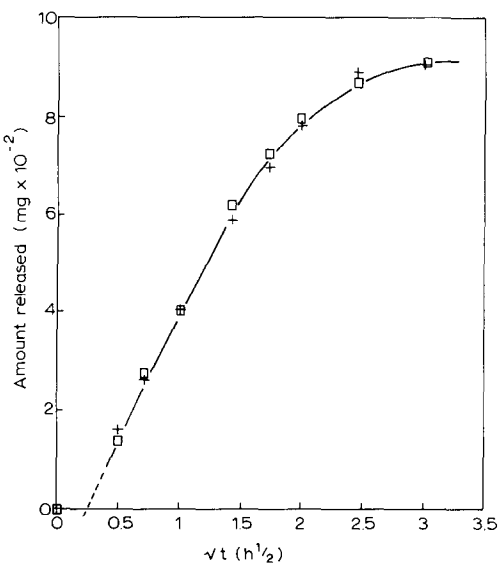

Fig. 3. Release of benzocaine from untreated sunflower oil emulsion gels at 37 °C. Films contained 20% w/w oil phase and 0.5% w/w benzocaine. (■, homogenised emulsion; +, stirred emulsion (at 2000 rpm).

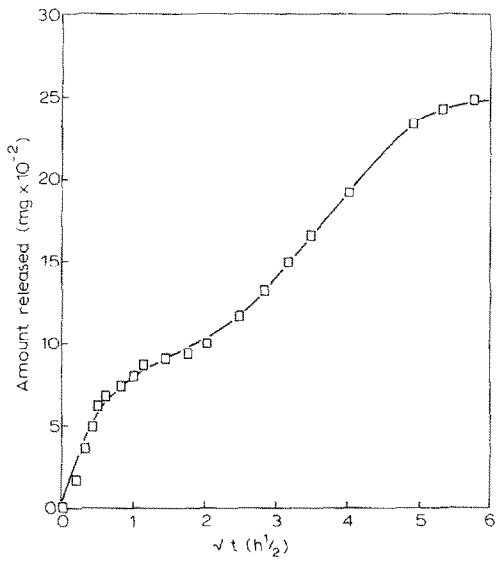

Fig. 4. Typical $\sqrt{t}$ profile of release of benzocaine from formaldehyde-treated sunflower oil emulsion films at 37 °C.

pharmaceutical systems, Ostrenga et al. (1971) have observed that release of fluocinonide from FAPG creams has an initial fast release phase, arising from the release of the unsolubilized fraction of the drug and a slower zero order release phase which represented release of the solubilized fraction of the drug in the formulation. That observation is very close to the current observation.

Two-stage release in pharmaceutical systems is interesting and desirable since it could form the basis for formulations containing both loading and maintenance doses. Attempts were therefore made to understand further the mechanisms involved in the release process.

The early stage

Fig. 5 is a schematic representation of the situation which may exist in the formaldehyde-treated films. In the most extreme case, the drug could exist as complexes in the oil phase or the polymer matrix. The possibility of complex formation is due to the highly active functional groups in formaldehyde and benzocaine. Furthermore, the amino, amido and guanidyl groups in the gelatin are susceptible to reaction with formaldehyde (Fraenkel-Conrat and Olcott, 1948); indeed, this is the cause of the hardening of the gel. The following complex situation may, therefore, exist in the film:

(i) Benzocaine + HCHO- - - - - -Benzocaine complex(es);
(ii) Gelatin + HCHO- - - - - -cross-linked gelatin;
(iii) Benzocaine + gelatin + HCHO- - - - - - matrix-bound benzocaine.

The $\sqrt{t}$ behaviour during the early phase suggests a predominantly diffusive process. Unbound benzocaine diffusing out (free or complexed) could most likely be responsible for this stage. The apparent diffusion coefficient calculated from the asymptote and slope of Fig. 4 gave a $D = 2.31 \times 10^{-10}$ m^2 s^{-1}. This is higher than the D obtained from benzocaine release from untreated films (3.33×10^{-9} m^2 s^{-1}) but lower than the diffusion coefficient of benzocaine in plain 20% gelatin films (2.94×10^{-10} m^2 s^{-1}).

Fig. 6 shows that the burst effect of the early stage decreases on continued storage outside the formaldehyde environment, a factor also reflected in the decreasing diffusion coefficients (Table 1). This behaviour indicated that the role played by

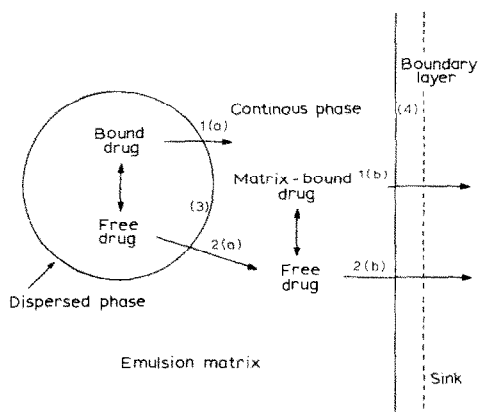

Fig. 5. Schematic presentation of processes determining release rate of a drug from a formaldehyde-treated emulsion gel.
(1) Release of bound drug with the rate being controlled by rate of release of gelatin or formaldehyde-bound drug:
  (a) drug bound in oil phase;
  (b) drug bound in matrix.
(2) Release of free drug where rate is controlled by diffusion:
  (a) drug in internal phase;
  (b) drug in continuous phase (matrix).
(3) Interfacially controlled release.
(4) Boundary layer diffusion-controlled release.

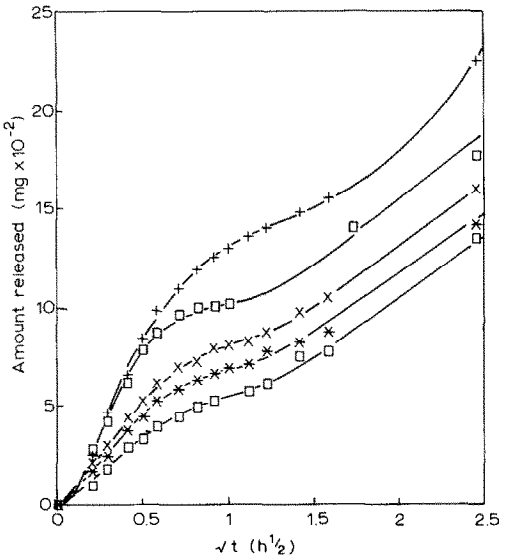

Fig. 6. Release of benzocaine from formaldehyde-treated films: decrease in amount released during early stage on removal from formaldehyde environment. Storage duration after removal from formaldehyde: +, 0 day; ■, 1 day; ×, 2 days; *, 3 days; □, 4 days.

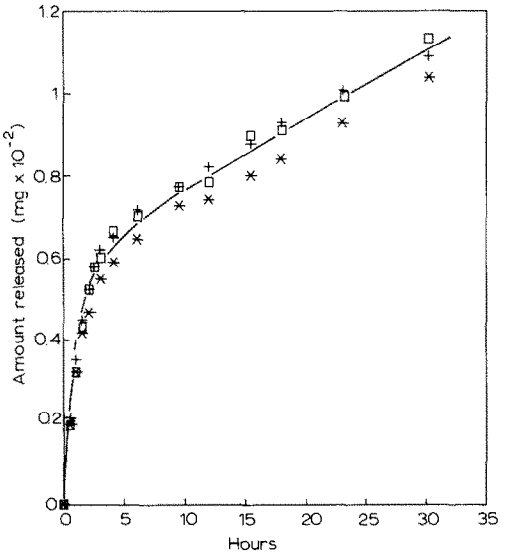

Fig. 7. Influence of emulsion particle size on late release of benzocaine from formaldhyde-treated sunflower oil emulsion films. *, homogenised emulsion; +, stirred emulsion (2000 rpm); ■, mixture of homogenised and stirred emulsions (1 : 1).

the internal phase of the emulsion decreases in the presence of higher levels of formaldehyde, i.e., formaldehyde causes the accumulation of benzocaine in the continuous phase (matrix).

The late stage

Fig. 2 shows that approx. 67% of the benzocaine in that study was released during the slower, late stage. Any of the following mechanisms could account for the behaviour observed during this stage: (i) release of benzocaine from the oil phase of the emulsion could result in first and zero order kinetics (Boddé and Joosten, 1985), (ii) interfacially controlled release from the oil could result in first or zero order release kinetics. The cross-linking of gelatin molecules at the oil/gel interface could increase resistance to interfacial transport and (iii) slow degradation of the matrix to release matrix-bound benzocaine could result in zero or first order kinetics.

It is unlikely that the first two alternatives were responsible for the observed behaviour because they should be affected by changes in particle size of the internal phase while release during the late stage has been shown to be independent of particle size variation (Fig. 7). This leaves constant release of matrix-bound benzocaine as the most possible mechanism responsible for the behaviour observed in the late stage.

TABLE 1

Variation of apparent diffusion coefficient of benzocaine in hardened films removed from formaldehyde after a 3-day initial curing period

Storage duration (days)	Reduced slope * (mg cm $h^{-1/2}$ $\times 10^{-2}$)	Graphical asymptote (mg$\times 10^{-2}$)	Apparent D ($m^2 s^{-1} \times 10^{10}$)
0	13.2	13.2	9.50×10^{-10}
1	10.6	10.2	6.13×10^{-10}
2	7.40	8.2	2.98
3	6.83	7.2	2.54
4	5.37	5.9	1.57

* Slope of Q vs. $\sqrt{t}/l$ plot.

Conclusion

The two-stage controlled release of benzocaine from sunflower oil/gelatin gel emulsion films pre-

sents an area of potential application in the field of controlled release delivery. If successful, devices with two stages of release may provide loading and maintance dose therapy on single administration. The behaviour observed in this particular study could most probably have arisen from fast release by diffusion of benzocaine accumulated in the continuous phase and a slower release of bound benzocaine on degradation of the crosslinked matrix. Formaldehyde plays a central role in release during both stages.

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