Controlled Drug Release through Polymeric Films

A. L. FITES, G. S. BANKER, and V. F. SMOLEN

Abstract □ The drug-permeability properties of several water-insoluble films were studied with respect to their potential application for the control of drug release from solid pharmaceutical dosage forms. Films composed of poly(methylvinylether)-maleic anhydride copolymer, crosslinked with polysorbate 20 (Tween 20), appeared as the most promising of the systems studied for the film-controlled drug-release applications. The permeability of the films can be controlled by appropriate adjustment of their polysorbate 20 content, molecular weight of the polymer, and humidity pretreatment. The permeability of the films was, however, found to be affected also by the pH of the diffusion medium.

Keyphrases □ Drug release, controlled—through polymeric films □ Polysorbate 20 effect—polymeric film formation □ Polymeric films—drug permeability □ Permeability coefficients—polymeric films □ Diagram—permeation cell □ UV spectrophotometry—analysis

The importance and pharmaceutical applicability of polymer films are well established in providing protective coatings and controlling drug release from oral dosage forms. In general, two basic factors may be involved in the film-controlled release of medicaments; *i.e.*, the dissolution of the film in the gastrointestinal fluids and its permeability (1, 2). With insoluble films, which maintain their integrity in traversing the gastrointestinal tract, only the latter need be considered. Therefore, the application of an insoluble film coat of desired permeability characteristics to an ordinary compressed tablet could conceivably be utilized to control drug release. This method would be advantageous in its economy and simplicity, provided predictable and controllable release rates are attainable.

In the present study, several synthetic polymeric films were investigated with respect to their drug-permeability properties for the purpose of determining their feasibility for controlled drug-release applications. One film which appeared promising was further investigated with respect to the factors influencing its permeability.

MATERIALS AND METHODS

Polymers, Drugs, and Diffusion Media—Table I describes the polymer systems used in this study. These systems were selected primarily on the basis of the insolubility of the resulting films in gastric and intestinal fluids. The cellulose acid phthalate (CAP) film system contains the maximum amount of plasticizer, PEG 400, consistent with insolubility of the film and absence of tackiness. The proportion of ethylcellulose (EC) to the methylcellulose (MC) was chosen, on the basis of preliminary studies, to produce a maximum permeability and insolubility. The observation in this laboratory that the addition of polysorbate 20 (Tween 20) renders the otherwise soluble poly(methylvinylether)-maleic anhydride (PVM-MA) films insoluble was the basis for its inclusion in this study.

Caffeine was chosen for these studies due to its relatively nonionogenic nature, stability, and ease of assay. Nicotinic acid was also used as a model drug in some of the preliminary experiments.

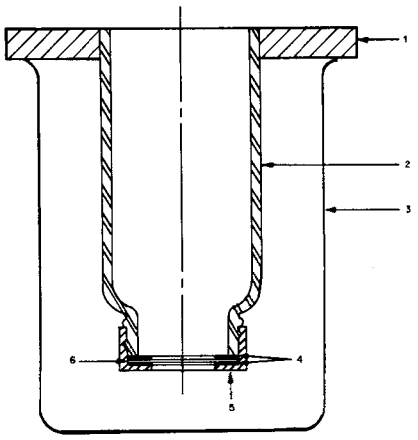

Figure 1—*Permeation apparatus employed in the study of drug permeation through free films. Key: 1, adjustable cell clamp; 2, 120-ml. amber bottle; 3, 600-ml. beaker; 4, polyethylene gaskets; 5, screw cap; and 6, film sample.*

The media in which the drugs were allowed to diffuse consisted of distilled water and buffer solutions of the following composition:

pH	Composition (mmole/l.)	
1.30	HCl, 1.4	NaCl, 34.2
5.83	KH_2PO_4, 25	NaOH, 1.8
7.20	KH_2PO_4, 25	NaOH, 17.4

The pH values of the solutions approximate that of gastric and intestinal fluids.

Permeation Cells—Figures 1 and 2 illustrate the permeation cells and the experimental arrangement. The cells consisted of approximately 120-ml. glass screw-capped chambers. The polymer films were placed between two polyethylene gaskets and were held in place by the plastic screw caps which were drilled to contain a 1.91-cm. (0.75-in.) diameter opening. These cells were inverted into their respective 600-ml. beakers, which contained the receiving medium for the diffusing drugs, where they were held by lucite clamps which allowed adjustment of their depth in the beakers. The medium in each beaker was maintained at 37° and was agitated with a magnetic stirrer employing the setup described in Fig. 2. The magnetic stirrers were connected to a central control; each was synchronized to 325 r.p.m. with a strobe timing light and was rechecked periodically. Fluctuation was minimized during operation by use of a voltage stabilizer and by allowing a warm-up period before proceeding with an experiment.

Preparation and Treatment of the Film—The films of composition listed in Table I were prepared by a casting technique employing a glass substrate. A fixed area on the smooth glass surface was marked off with masking tape. In each case the polymer was evenly spread into the area with a brass film-casting knife as described by Munden (3). The resulting film possessed a uniform thickness, which was controlled by adjustment of the blade level in the film-casting knife and by the number of tape layers. The average thickness of completed films was determined with a micrometer.[1]

Prior to testing, all films were stored over anhydrous calcium sulfate[2] under vacuum at 25° for a minimum of 48 hr. In addition, the PVM-MA films were stored for precisely 48 hr. at a humidity of 52.4%, maintained by a saturated solution of sodium bromide at 41°.

[1] Lufkin Rule Corp., Saginaw, Mich.
[2] Drierite, W. A. Hammond Drierite Co., Xenia, Ohio.

Table I—Film Systems Selected for Permeation Studies

Polymer	Polymer Concn., % w/v of Solution	Plasticizer Concn., % w/v of Solution	Composition of Solvent Systems, ml.
Cellulose acetate hydrogen phthalate (CAP)[a]	7	Polyethylene glycol 400 (PEG 400),[b] 0 & 3	Methylene chloride—50 Acetone *q.s.*—100
Ethyl cellulose (EC)[c]	6	Propylene glycol, 2.8	Methyl chloride—50 Methanol *q.s.*—100
Methyl hydroxypropyl cellulose (MC)[d]	3.5		
Poly(methylvinylether) maleic anhydride 139 & 169 (PVM–MA)[e]	8	Glyceryl triacetate,[f] 5	
		Polyoxyethylene sorbitan monolaurate,[g] 2, 4, and 8	Acetone *q.s.*—100

[a] Cellulose acetate phthalate; Eastman Organic Chemicals, Rochester, N. Y. [b] Carbowax 400; Union Carbide Chemicals, New York, N. Y. [c] Ethocel; Dow Chemical Company, Midland, Mich. [d] Methocel; Dow Chemical Company, Midland, Mich. [e] Gantrez A N; G.A.F. Corp., New York, N. Y. [f] Triacetin; Eastman Organic Chemicals, Rochester, N. Y. [g] Tween 20; Atlas Chemical Company, Chicago, Ill.

Procedures—The pretreated polymer film was secured in the cell which was immersed into the beaker containing 400–500 ml. of the receiving medium, either distilled water or buffer solution, previously equilibrated to 37°. The upper chamber of the cell was filled with drug solution, usually 25 ml., and covered; the level of the fluids was adjusted to the same height to prevent a hydrostatic pressure difference between the two compartments. Four units of this type were set up in the same thermostated water bath and agitated as described previously.

At selected time intervals over an 8- to 10-hr. period, samples of the receiving media were removed and assayed spectrophotometrically for transferred drug. The samples were read on a Beckman DU spectrophotometer at 273 and 262 mμ for caffeine and nicotinic acid, respectively. The blank consisted of fluid taken from a cell containing only the diffusion medium. The volume of sample removed from the receiving chamber was, in each case, replaced by an equal volume of diffusion medium. Six to eight replications were performed on each run. When linear relationships were expected, the data were treated by the method of least squares and the lines of best fit were reported.

RESULTS AND DISCUSSION

Preliminary Screening of Film Systems—The selection of films for further study of their permeability properties was primarily based upon a preliminary study of selected film formulations. The results are presented in Table II and Fig. 3.

The permeability of the cellulose acetate phthalate films studied was severely limited, as is apparent from the relatively small quantities of the drug that traversed the films over the 8-hr. period. Although plasticization of the CAP films by the inclusion of polyethylene glycol 400 (43% w/w polymer) produced approximately a tenfold difference in drug permeability relative to the unplasticized film, total drug permeability in the plasticized film was still less than 3%. The increase in permeability was likely a consequence of the unbound water-soluble plasticizer being leached from the membrane. The practical upper limit of polyethylene glycol content in the films was 43%. Higher concentrations imparted tackiness to the film.

Ethycellulose produced films which were quite brittle and showed negligible drug permeability. The addition of methyl(hydroxypropyl)cellulose to the ethylcellulose film enhanced film clarity, decreased brittleness, and increased drug permeability.

The addition of methyl(hydroxypropyl)cellulose improved the overall properties of the ethylcellulose films, particularly with regard to brittleness. However, the films were observed to lose their integrity at methyl(hydroxypropyl)cellulose contents greater than that contained in the tested film (58% w/w polymer). This was quite apparent from the rapid passage of the drug across the disintegrating films.

Prior to the 2-hr. period, a relatively small quantity of drug was found to permeate the untreated PVM–MA film (Table II and Fig. 3). The rate of drug passage became greatly accelerated between

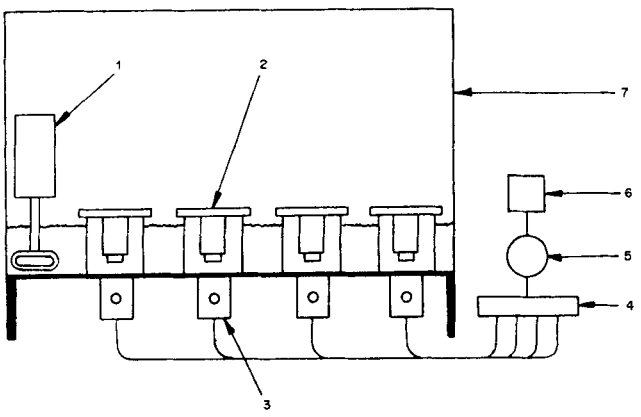

Figure 2—*Diagram of experimental arrangement for permeability studies. Key: 1, constant-temperature bath (stirrer constant-temperature regulator); 2, cell apparatus (Fig. 1); 3, magnetic stirrers; 4, control box; 5, variac; 6, line voltage regulator; and 7, water bath.*

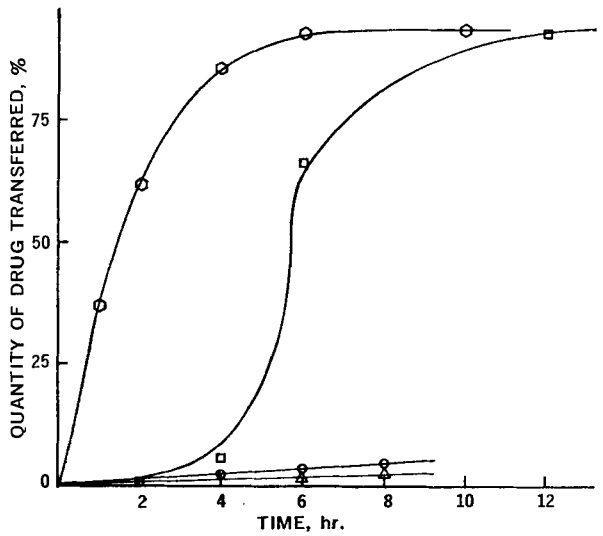

Figure 3—*Drug permeability properties of polymeric film membranes included in preliminary studies. The films studied included PVM–MA (4:1) pretreated, —○—; PVM–MA (4:1) untreated, —□—; EC–MC, —○—; and CAP + propylene glycol, —▽—.*

Table II—Results of Preliminary Investigations of Permeability Properties of Polymeric Films in Distilled Water

Film System[a]	Thickness, mm.	Time, hr.	Cumulative Percent of Drug Transferred across Membrane at Given Time
CAP[b]	0.030	8	0.2
CAP + PEG 400[b]	0.040	2	0.8
		4	1.6
		6	2.2
		8	2.7
EC–MC[c]	0.040	2	0.8
		4	1.8
		6	3.0
		8	4.1
PVM–MA 169[d]	0.045	2	0.9
(4:1)[e]	0.045	2	0.9
		4	5.3
		6	64.9
		12	92.5

[a] Film systems as designated in Table I. [b] Initial concentration of drug 0.25% nicotinic acid. [c] Initial concentration of drug 2% caffeine. [d] Initial concentration of drug 1.5% caffeine. [e] Refers to four parts polymer and one part polysorbate 20.

2 and 4 hr. The increase in permeability is attributed to the observed swelling of the film resulting from the hydration of acid anhydride groups on the polymer. In addition to a Donnan-type swelling effect (4), a polymer chain expansion likely arises from the mutual electrostatic repulsion of the resulting ionized carboxyl groups (5). The effect serves to diminish further the consolidation of the membrane and thereby increases its permeability. The apparent acidic pK's of the carboxyl groups have been reported (5, 6) as having values of 4.85 and 8.95. The swelling of the films may therefore be expected to become increasingly pronounced with an increase in pH of the diffusion media.

It was found that the initial delay in the enhanced permeability of PVM–MA films could be essentially abolished through pretreatment of the films by storage in a humidity chamber, for 48 hr., at 25° and 52.4% relative humidity, to allow film hydration prior to testing. Figure 3 presents a comparison of results obtained with caffeine using treated and untreated films.

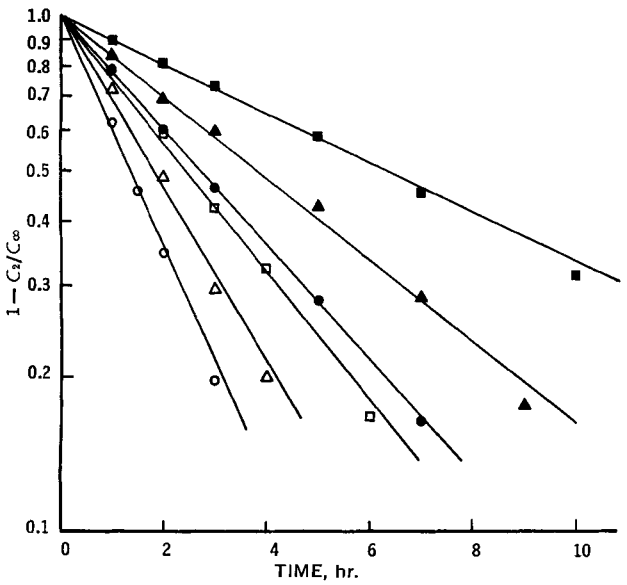

Figure 4—*Permeation of caffeine through PVM–MA 169 polymer films in distilled water and pH 1.30 buffer solution as influenced by the polysorbate 20 content and thickness of the films. At pH 1.30 the films studied included polymer: polysorbate 20 weight of 9:1 (—●—), 2:1 (—▲—), and 1:1 (—■—), with corresponding thicknesses of 0.069, 0.071, and 0.066 mm., respectively. In distilled water the films included were 4:1 (—○—), 2:1 (—△—), and 1:1 (—□—) with corresponding thicknesses of 0.068, 0.068, and 0.066 mm., respectively.*

Table III—Permeation (P) and Correlation (r) Coefficients for PVM–MA Films of Varying Weight Ratio of Polymer to Polysorbate 20 (R)

	PVM–MA 169 Films					
	1.30		5.83		7.20	
R/pH	P[a]	r	P	r	P	r
4:1	0.0024	−1.00	0.0066	−0.99	—	—
2:1	0.0017	−1.00	0.0085	−1.00	0.022	−0.83[b]
1:1	0.0012	−1.00	0.0059	−0.98	—	—

	PVM–MA Films in Distilled Water		PVM–MA Films in pH 1.30 Buffer	
R	P	r	P	r
4:1	0.0060	−1.00	—	—
2:1	0.0037	−0.99	0.0018	−1.00
1:1	0.0030	−1.00	0.0089	−1.00

[a] P is defined by Eq. 3 and has units of hr.$^{-1}$. [b] This relatively low value of the correlation coefficient is attributable to the considerable swelling of the films observed at this pH, with accompanying changes in thickness and area, which vitiates the vigorous applicability of Eq. 1.

Among the films included in the preliminary study, the PVM–MA films appeared most promising with respect to their potential applicability for controlled drug release. Films formed from the PVM–MA and polysorbate 20 were therefore selected for further study with respect to the influence of various factors anticipated to affect their permeability properties. Only caffeine at an initial concentration of 2% w/v and humidity-chamber pretreated films were employed in this further work.

Effect of Polysorbate 20 Content on the Permeability of PVM–MA Films—The PVM–MA polymer itself is water dispersible to a considerable extent. The presence of polysorbate 20 in films formed from the polymer renders them insoluble in water. However, they are still subject to appreciable swelling. Powell (7) has shown that the insolubilization of PVM–MA films by polysorbate 20 results from crosslinking of polymer chains by the polysorbate 20. The crosslinking occurs through esterification of acid anhydride groups on the polymer and hydroxyl groups of the sorbitan ester. Figure 4 illustrates the influence of polysorbate 20 content on the permeability of the PVM–MA films. The results correspond to films prepared from weight ratios of polymer to polysorbate 20 of 9:1, 2:1, and 1:1, having thicknesses from 0.066 to 0.071 mm. Films studied in distilled water (pH 6.70) were found more permeable to caffeine as compared to results obtained with a solution buffered at pH 1.30 with hydrochloric acid. As expected, less swelling of the films was noted for the films immersed in the diffusion medium of lower pH. Table III summarizes these results. Assuming that the permeability constants of the films are directly related to the reciprocal of the film thicknesses for the small range of differences involved allows their normalization to a constant standard thickness. The values for the permeability constants listed in Table III have been corrected to a constant film thickness of 0.071 mm. to allow the relative magnitude of the effects studied to be more readily discerned.

The permeability coefficients, P, listed in Table III are defined by the following equations where V_1, V_2, and C_1, C_2 refer to the volumes and drug concentration within the compartments of the permeation cell at any time, t. The subscript 2 refers to the receiving cell that was devoid of drug at zero time. The final concentration ultimately approached in the receiving compartment, designated with the subscript 2, is symbolized by C_∞ and is defined by Eq. 2 where C_0 refers to the initial concentration of drug in Compartment 1.

$$\log\left(1-\frac{C_2}{C_\infty}\right) = -\frac{V_2+V_1}{V_1}\,2.303\,Pt \qquad \text{(Eq. 1)}$$

$$C_\infty = \frac{C_0V_1}{V_2+V_1} \qquad \text{(Eq. 2)}$$

$$P = -\frac{0.071V_1\,(\text{slope})}{h\,(V_2+V_1)\,2.303} \qquad \text{(Eq. 3)}$$

Values of P obtained from Eq. 3 are normalized to a thickness of 0.071 mm.; the symbol h in the equation denotes the actual mea-

sured thickness of a film. The slope referred to in Eq. 3 is a least-squares regression value obtained from plots of C_2 as a function of time in accordance with Eq. 1. Such plots were always observed to be reasonably linear as indicated by the values of the corresponding correlation coefficients listed in Table II. This indicates that sufficient agitation was maintained in the diffusion cell to allow its description in terms of two compartments.

Greater extents of crosslinking in the films are likely responsible for the observed reduction of swelling and permeability of the films observed to accompany an increased polysorbate 20 content.

Effect of PVM–MA Polymer Molecular Weight—Films were prepared with a ratio of polymer to polysorbate 20 of 2:1 and 1:1 using higher (169) and lower (139) molecular weight grades of the PVM–MA polymer. Using pH 1.30 diffusion medium, the film composed of the lower molecular grade polymer was more permeable to the drug. The permeability coefficients, corrected to constant film thickness, are listed in Table III. The greater permeability of the lower weight grade polymer film is not surprising, considering their greater solubility and potential for being leached from the film. The effectiveness of polysorbate 20 crosslinking in maintaining the integrity of the film may be expected to be diminished as a consequence of the relative reduction in the size of the interacted components.

Effect of pH on PVM–MA Film Properties—As could be predicted from the theoretical considerations previously mentioned, the swelling of PVM–MA 169 (2:1 and 4:1) films was considerably retarded in the pH 1.30 buffered diffusion medium as compared to its immersion in buffers of pH 5.83 and 7.20. The pH of the latter medium exceeds the first acidic pK of the polymeric fixed carboxyl groups and allows the establishment of a fixed anionic charge density within the film. The fixed charge is undoubtedly responsible for the observed swelling and the marked increase in the permeability of the films at higher pH values. The permeability constants are listed in Table III. Although it is not readily apparent from these values, the effect of pH might be expected to be retarded by a further increase in polysorbate 20 crosslinking within the films.

SUMMARY AND CONCLUSIONS

The application of insoluble films to the coating of tablets or for the manufacture or coating of capsules must be accompanied by an ability to predict and to control the permeability properties of the films. The present study is a first exploratory step toward this goal. The study revealed that the PVM–MA films possess promise with regard to their application to the control of drug release. The permeability properties of the PVM–MA films can be controlled through adjustment of the polysorbate 20 content, molecular weight of the polymer, and the initial extent of hydration of the film. However, the influence of pH on the permeability of the films precludes a film-controlled uniform drug-release rate in all regions of the gastrointestinal tract. In cases where it may be desirable to delay drug release until the dosage form reaches the intestinal tract, the increased permeability of the film observed at higher pH could prove to be advantageous. It is conceivable, however, that when a uniform drug-release rate is desired, the expected changes in permeability of the film in response to variation of pH in the gastrointestinal tract may in part be circumvented by the inclusion of buffering agents in the drug formulation contained within the film envelope. The continual presence of a constant pH in at least one side of the film could function to reduce the change in film swelling and allow the permeability of the film to approximate more closely the relatively uniform rates obtained in either acidic or alkaline media. In this manner, the effects of the variations in the external environment could be ameliorated. The PVM–MA films do possess sufficient potential for eventual practical application and thereby warrant further studies into the influence of environment (particularly *in vivo*), film formulation, and the effect of the drug and other components of the dosage form on the controlled drug release imposed by the insoluble PVM–MA films. However, in any practical application, the elastic properties of the films and their ability to resist rupture due to mechanical abuse and osmotic pressure gradients are considerations of fundamental importance to the safety of any proposed product. These factors must be considered in future work.

REFERENCES

(1) E. Stempel, *Drug Cosmet. Ind.*, **98,** 44(1966).

(2) *Ibid.*, **98,** 36(1966).

(3) B. J. Munden, H. G. DeKay, and G. S. Banker, *J. Pharm. Sci.*, **53,** 395(1964).

(4) F. Helferich, "Ion Exchange," McGraw-Hill, New York, N. Y., 1962, pp. 100–123.

(5) H. Eisenberg and R. M. Fuoss, in "Modern Aspects of Electrochemistry," J. M. Bockris, Ed., Plenum Press, New York, N. Y., 1968, p. 1.

(6) L. C. Lappas and W. McKeehan, *J. Pharm. Sci.*, **54,** 176 (1965).

(7) D. R. Powell, "Polyalkylvinyl Ether Copolymers as Protective and Controlled Release Pharmaceutical Film Coatings," Ph.D. thesis, Purdue University, 1967.

ACKNOWLEDGMENTS AND ADDRESSES

Received August 20, 1969, from the *Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907*

Accepted for publication December 9, 1969.

Abstracted in part from a thesis presented to the Graduate School, Purdue University, by Alan L. Fites in partial fulfillment of the Master of Science degree requirements.