Table III—Summary of Data Showing Concentration–Response Relationships for the Spasmolytic Effects of Compounds VII, VIII, and X and Atropine Sulfate Against Methacholine Chloride-Induced Spasm in Excised Rabbit Ileum

	Spasmolytic Agent			
	Compound X	Compound VIII	Compound VII	Atropine Sulfate
Ml. added to 10-ml. muscle bath	0.8 ml.	2.0 ml.	2.0 ml., 3.0 ml.	0.2 ml.
Concentration in muscle bath	1.15×10^{-4}	2.88×10^{-4}	2.88 and 4.32×10^{-4}	2.88×10^{-6}
Response: No. positive/No. tried	7/10	6/10	0/10 1/10	8/10
Relative potency	2.5	1.0	0	1×10^{2}

noting concentration in millimolar quantities as well as relative potency when compared to atropine sulfate.

Discussion of Results—Examination of Compound X reveals that it is about 2.5 times as active as Compound VIII. Compound VII was found to be inactive in the ability to reduce the spasms induced by mecholyl. While spasmolytic activity is present in Compounds X and VIII, the activity present is only about 1/40th and 1/100th, respectively, that of the standard spasmolytic agent, atropine sulfate.

REFERENCES

(1) M. S. Newman and B. J. Magerlein, in "Organic Reactions," Vol. V, Wiley, New York, N. Y., 1949, p. 413.

(2) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p. 240.

(3) G. Omodt and O. Gisvold, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 153(1960).

(4) A. J. Speciale and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961).

(5) L. H. Schlager, *Arch. Pharm.*, **296**, 217(1963).

(6) E. A. Zeller, *J. Biol. Chem.*, **234**, 389(1959).

(7) J. A. Carbon, W. P. Burkard, and E. A. Zeller, *Helv. Chim. Acta*, **41**, 1883(1958).

(8) J. H. Biel, in "Molecular Modification in Drug Design," American Chemical Society, Washington, D. C., 1964, p. 124.

(9) J. H. Biel, in "Psychopharmacological Agents," M. Gordon, Ed., Academic, New York, N. Y., 1964, p. 384.

(10) R. E. Taylor, *J. Pharmacol. Exp. Ther.*, **138**, 201(1962).

(11) S. Garrattini, A. Giachetti, A. Jori, L. Pieri, and L. Valzelli, *J. Pharm. Pharmacol.*, **14**, 509(1962).

(12) L. C. Miller, T. J. Becker, and M. L. Tainter, *J. Pharmacol. Exp. Ther.*, **92**, 260(1948).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 13, 1969, from the *College of Pharmacy, University of Texas at Austin, Austin, TX 78712*

Accepted for publication February 18, 1970.

* Present address: School of Pharmacy, Northeast Louisiana State College, Monroe, LA 71201

† Present address: College of Pharmacy, Idaho State University, Pocatello, ID 83201

Dissolution of Macromolecules II: Dissolution of an Ethylene–Maleic Acid Copolymer

ALLEN HEYD*, DANE O. KILDSIG, and GILBERT S. BANKER

Abstract □ Factors influencing the dissolution of an ethylene–maleic acid copolymer have been studied. Polymer swelling, hydrated layer thickness, and solvent pH were shown to influence the dissolution of the polymer. Linear dissolution rates were observed following an initial induction period. Hydrated layer thickness was found to be a controlling factor in the dissolution process. An immersion refractometry method was employed to measure aqueous polymer concentrations during dissolution.

Keyphrases □ Ethylene–maleic acid copolymer—dissolution □ Tablets, ethylene–maleic acid copolymer—dissolution study □ Dissolution test apparatus—diagram □ Refractometry, immersion—polymer determination

Polymeric materials are widely used in many pharmaceutical systems. In systems utilizing polymer films and particularly in dosage forms in which the polymer is compressed in tablets to produce controlled drug release, the dissolution of the polymer is an important parameter. Polymer systems are frequently sought which, based on their dissolution properties, will provide a particular type of drug release.

Previous investigators of polymer dissolution have studied the dissolution of polystyrene in organic solvents (1–3). However, a detailed investigation of the dissolution in aqueous solvents of polymers having reactive functional groups has not been reported. In an earlier report the surface phenomena associated with the dissolution of such polymers were described (4). The present investigation reports the dissolution of an ethylene–maleic acid (dicarboxylic acid) copolymer as affected by these surface parameters.

EXPERIMENTAL

The ethylene–maleic acid copolymer, referred to as EMA-22, and the polymer tablets used in this study were identical to those used in a previous investigation (4). The measurement of polymer swelling, solvent penetration, and hydrated layer thickness was also identical to that of the earlier study (4).

The dissolution apparatus employed for the study of polymer dissolution is shown in Figs. 1–3. Figure 1 describes the sample holder; Fig. 2 shows the dimensions of the Plexiglas dissolution cell. Figure 3 is a schematic representation of the dissolution unit and the component parts that made up the entire system. The lip of the

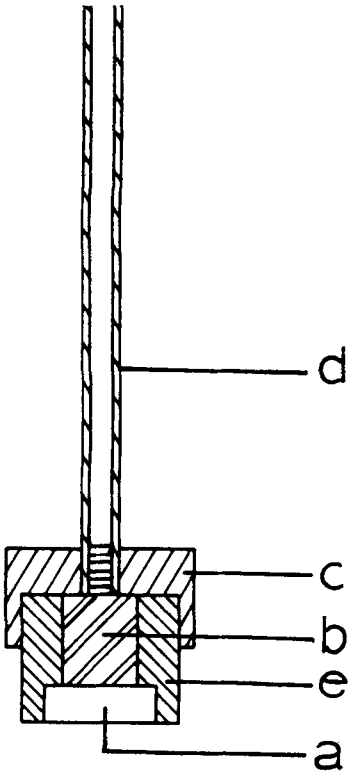

Figure 1—*Sample holder. Key: a, compressed disk cavity; b, plunger; c, die housing; d, steel shaft; and e, 1.12-cm. (0.44-in.) die.*

die housing of the sample holder (Fig. 1) was placed on the edge of the dissolution cell (Fig. 2), which provided constant sample geometry for each dissolution test. The plunger of the sample holder facilitated exact positioning of the compressed disk. The shaft of the sample holder, which permitted positioning of the holder in the dissolution apparatus, extended through the housing of the holder and was threaded into the plunger (Fig. 1).

A Bausch & Lomb immersion refractometer,[1] utilizing prism A, was used to follow the increase in polymer concentration with time. Standard curves of refractometer reading *versus* polymer concentration were linear over the concentration range used, 0 to 4 mg./ml. The precision of the refractometer method was excellent; identical

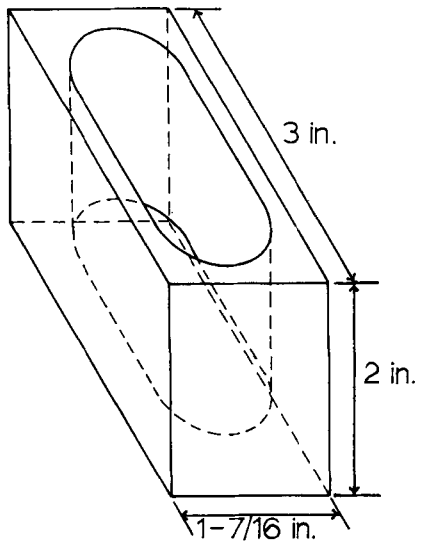

Figure 2—*Plexiglas dissolution cell. The external dimensions are indicated. The inside dimensions are 6.99-cm. (2.75-in.) total length, 2.87 cm. (1.13 in.) wide, and 3.66 cm. (1.44 in.) deep with the ends having a 1.42-cm. (0.56-in.) radius of curvature.*

[1] Bausch & Lomb Optical Co., model DB 502.

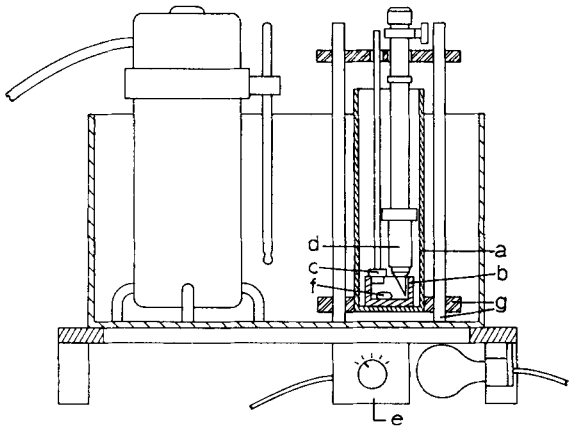

Figure 3—*Dissolution apparatus. Key: a, glass cylinder; b, dissolution cell; c, sample holder; d, immersion refractometer; e, magnetic stirrer; f, stirring bar; and g, support.*

readings on the refractometer scale were obtained for each replicate sample of each polymer solution.

In conducting the dissolution test, a 1-g. compressed tablet of EMA-22 free acid was positioned in the cavity of the sample holder so that 0.05 cm. of the tablet protruded. The dissolution cell was filled with 60 ml. of solvent, which was allowed to equilibrate to 30 ± 0.1°. This volume was sufficient to cover the exposed tablet after the sample holder and the refractometer were precisely positioned in the dissolution cell. A magnetic stirrer unit drove a 1.27-cm. (0.5-in.) stirring bar inside the dissolution cell at 130 r.p.m. Kolthoff's alkaline borate buffer (5) was used to prepare pH 7.4 and 9.4 buffers. The buffers from pH 1.2 to 6.2 were prepared from standard solutions as described by the USP (6). The immersion refractometry method and the technique and apparatus described permitted the dissolution process to be continuously followed without disturbing the system.

RESULTS AND DISCUSSION

The dissolution of EMA-22 in distilled water is shown in Fig. 4. The dissolution rate was linear following an initial induction period.

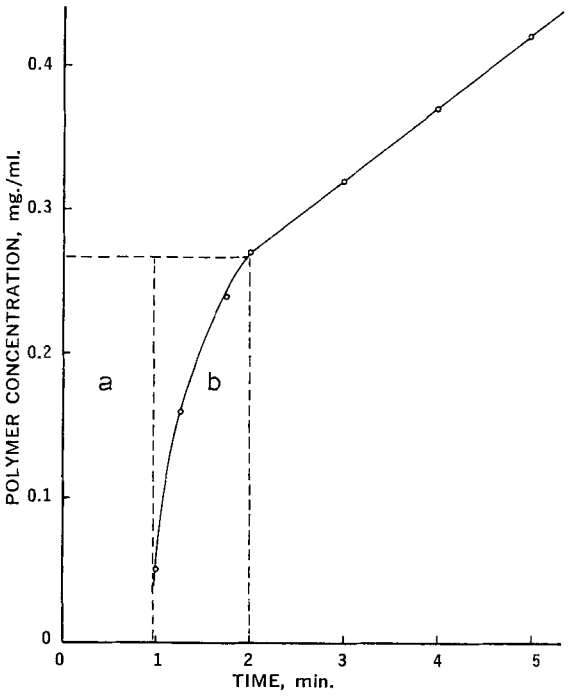

Figure 4—*Linear dissolution rate with initial induction period. Key: a, lag time; b, stabilization period; and a + b, induction period.*

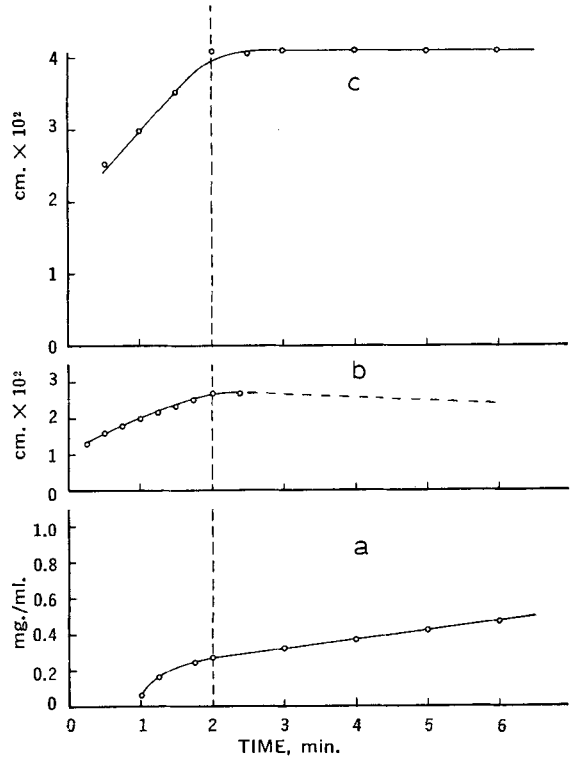

Figure 5—*Correlation between induction period, a, swelling time, b, and hydrated layer formation, c.*

The induction period consisted of a lag time and a stabilization period (Fig. 4). The lag time, or period before measurable concentration appears in solution, is attributed to the time required for initial solvent penetration and initial polymer swelling. During the initial swelling process (0–0.5 min.) in which the largest extent of swelling was achieved (4), little or no polymer dissolved. During the stabilization period, the dissolution rate continuously decreased as the polymer achieved maximum swelling. Also during the stabilization period, maximum hydrated layer thickness was achieved after which the dissolution rate was linear. The correlation between hydrated layer formation, swelling time, and the dissolution induction period is shown in Fig. 5. The establishment of both an equilibrium hydrated layer thickness and maximum swelling was found generally to correlate to the induction period required for achievement of a constant dissolution rate.

The polymer–solvent interaction is responsible for the expansion of the linear chain polymer and the subsequent formation of a gel structure. As the EMA-22 polymer is a dicarboxylic acid, the solvent pH would be expected to influence greatly the dissolution of the polymer (Fig. 6). Contrary to the dissolution of micromolecular weak acids, the equilibrium dissolution rate of the polymer weak acid decreases with increasing pH (Fig. 6). However, the dissolution rates reported in Fig. 6 are the equilibrium values obtained from the linear portion of the curve. The initial dissolution rates did increase with increasing pH but were quickly affected (within 0.5–2 min.) by the swelling phenomena and subsequent hydrated layer

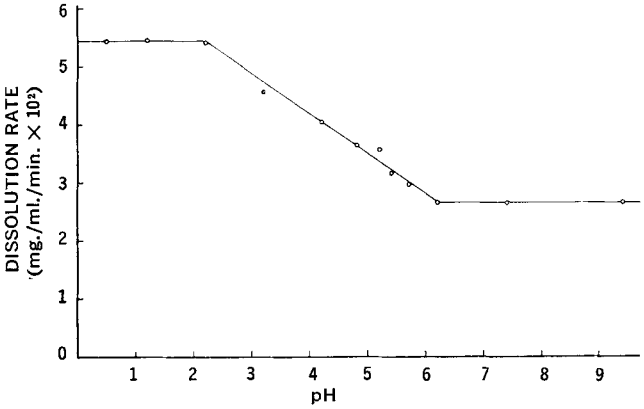

Figure 6—*Decrease in equilibrium dissolution rate with increasing pH.*

formation. Thus the swollen hydrated layer remains the determining factor in the dissolution of the EMA polymer following swelling equilibrium.

SUMMARY

The dissolution of an ethylene–maleic acid copolymer was investigated using an immersion refractometer for polymer analysis. An induction period was observed consisting of a lag time and a stabilization period, during which the dissolution rate was continuously decreasing until a constant rate was obtained. The solvent pH was found to influence the dissolution of the polymer through its effect on polymer swelling and hydrated layer thickness. These two parameters, swelling and hydrated layer thickness, were primarily responsible for the dissolution properties of the polymer. The refractometer method was adequately sensitive for following polymer dissolution and allowed a continuous determination of polymer concentration without sampling.

REFERENCES

(1) K. Ueberreiter and F. Asmussen, *J. Polym. Sci.*, **57**, 187 (1962).

(2) F. Asmussen and K. Ueberreiter, *ibid.*, **57**, 199(1962).

(3) K. Ueberreiter and F. Asmussen, *Makromol. Chem.*, **44–46**, 324(1961).

(4) A. Heyd, D. Kildsig, and G. Banker, *J. Pharm. Sci.*, **58**, 586(1969).

(5) I. M. Kolthoff, *J. Biol. Chem.*, **63**, 135(1965).

(6) "The United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 913.

ACKNOWLEDGMENTS AND ADDRESSES

Received October 28, 1969, from the *Industrial and Physical Pharmacy Department, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907*

Accepted for publication January 27, 1970.

* Fellow, American Foundation for Pharmaceutical Education. Present address, University of Connecticut, Storrs, Conn.