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ACKNOWLEDGMENTS AND ADDRESSES

Dissolution of Alkyl Vinyl Ether–Maleic Anhydride Copolymers and Ester Derivatives

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Abstract ☐ The dissolution properties of several alkyl vinyl ether–maleic anhydride copolymers and their ethyl, *n*-propyl, and *n*-butyl half- and quarter-ester derivatives were studied. An immersion refractometric method was employed to determine the polymer dissolution properties. Rates of polymer dissolution and lag times prior to the initiation of measurable dissolution rates were shown to be dependent upon several variables. The polymer variables studied included polymer molecular weight, degree of esterification, ester chain length, and ether substituent. Other factors studied were pH of the dissolution medium, type of sample (cast films or compressed disks), and inclusion of a plasticizing agent. Each factor was shown to influence the resulting polymer dissolution properties.

Keyphrases ☐ Dissolution rates, alkyl vinyl ethers–maleic anhydride copolymers and partial esters—determination, related to use as timed-release coatings ☐ Alkyl vinyl ether–maleic anhydride copolymers and partial esters—dissolution rates, related to use as timed-release coatings ☐ Maleic anhydride–alkyl vinyl ether copolymers and partial esters—dissolution rates, related to use as timed-release coatings ☐ Refractometry, immersion— determination of dissolution rates, alkyl vinyl ether–maleic anhydride copolymers

The existence of many commercial drug products containing similar amounts of identical active ingredients, but produced by different manufacturers and often having widely varying prices, has raised the question of generic equivalence of such products. Timed-release formulations command an expanding portion of the solid dosage form medications, but recent clinical evaluations have demonstrated vast differences in drug availability from competing products of the timed-release categories (1–5).

Recent experiments with copolymers containing maleic anhydride or maleic acid have indicated that polymers containing this chemical moiety may possess timed-release properties when used as coating materials. Nessel *et al.* (6, 7) demonstrated that the *n*-butyl half-ester of poly(methyl vinyl ether–maleic anhydride) copolymer was capable of producing a timed-release dosage form when coated on granules that were subsequently compressed into tablets. Wagner *et al.* (8) produced enteric disintegration properties from tablets coated with styrene–maleic acid copolymers. Lappas and McKeehan (9) found that partial esters of poly(methyl vinyl ether–maleic anhydride) might be suitable to control the release of drugs upon reaching a specific intestinal pH. Further studies (10) showed that some control of *in vivo* initial drug release could be obtained from such partial esters when applied as coatings to solid dosage forms.

Heyd *et al.* (11) recently reported fundamental studies concerning the surface phenomena associated with the dissolution of a model polymer series, ethylene–maleic acid, and reported in detail the use of immersion refractometry as a method of determining polymer dissolution parameters (12).

The investigations herein described were undertaken to elucidate the dissolution properties of the poly(alkyl vinyl ether–maleic anhydride) class of copolymers and their partial ester derivatives, with the ultimate objective of establishing the relationship between such properties and the usefulness of the various polymers as timed-release coating materials. The dissolution properties reported here were subsequently related to the *in vitro* and *in vivo* drug release characteristics from tablets coated with these polymers.

EXPERIMENTAL

Materials Studied—The polymers investigated were poly(alkyl vinyl ether–maleic anhydride) copolymers and selected partial ester derivatives synthesized in this laboratory. The general chemical structure of the anhydride copolymers is reproduced here, where R_1 was either a methyl or an isobutyl substituent. The copolymers were
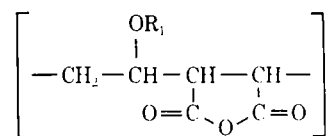
$$\left[\begin{array}{c} OR_1 \\ | \\ -CH_2-CH-CH-CH- \\ | \quad | \\ O=C_{\diagdown O\diagup}C=O \end{array} \right]_n$$

Table I—Anhydride Polymeric Materials Studied

Polymer	Polymer Number	Molecular Weight[a]	Relative Viscosity[b]
Poly(methyl vinyl ether–maleic anhydride)—119	II	250,000	1.41
Poly(methyl vinyl ether–maleic anhydride)—139	III	500,000	2.24
Poly(methyl vinyl ether–maleic anhydride)—149	IV	750,000	2.65
Poly(methyl vinyl ether–maleic anhydride)—169	V	1,125,000	3.12
Poly(isobutyl vinyl ether–maleic anhydride)	VI	Not available (low)	1.35

[a] Molecular weights were determined by light-scattering methods by GAF Corp. [b] Relative viscosity was determined in a 1% polymer concentration in methyl ethyl ketone solution by the manufacturer.

also modified by the formation of aliphatic half- and quarter-esters ranging from two to four carbon atoms in length.

The anhydride form of the methyl vinyl ether derivative is commercially available[1] in weight grades ranging from an average molecular weight of about 250,000 to 1,125,000, as determined by the light-scattering method. Molecular weights and relative viscosity data for the four weight grades included in this work are shown in Table I. Cellulose acetate phthalate[2] (I) was employed as a standard with which to compare the vinyl ether copolymers.

A plasticizing agent, triacetin[3], was included in selected film formulations used in the polymer dissolution studies.

Synthesis of Partial Esters—Partial ester derivatives, as half- or quarter-esters, were prepared from II and VI. The half-esters were prepared by reacting the anhydride copolymers with an excess of the selected reagent grade alcohol at the alcohol reflux temperature. The quarter-esters were prepared by refluxing the proper stoichiometric quantities of polymer and alcohol in a nonreactive auxiliary solvent, 2-butanone. The reflux solutions contained 10–20% (w/v) polymer anhydride, and reaction times ranged from 7 to 48 hr. All reactions were conducted with constant stirring in a 500-ml., three-necked, round-bottom reaction flask fitted with a mixer, thermometer, and reflux column. Products were partially dried on Teflon trays at 60–90° and then dried to constant weight under vacuum at the same temperatures.

Analysis of Polymers—Anhydride polymers were demonstrated to have at least 98% anhydride functionality (remaining monomer units in the polymer would be in the diacid form) by a two-part titration procedure (provided by the polymer manufacturer). This procedure was as follows.

Procedure Step A—Approximately 0.35 g. of polymer was accurately weighed into a 250-ml. beaker, and the sample was dissolved in 25 ml. of acetone and 5 ml. of aniline. After 1 hr. at room temperature, the sides of the beaker were rinsed with 50 ml. of acetone and 75 ml. of distilled water. The solution was titrated with 0.1 N NaOH, using a glass–calomel electrode system. The end-point occurred at an apparent pH of 9–12.

Procedure Step B—Approximately 0.32 g. of polymer was accurately weighed into a 250-ml. beaker, and the sample was dissolved in 10 ml. of acetone and 75 ml. of distilled water with the aid of gentle heat. The solution was cooled to room temperature, 75 ml. of methanol was added, and the solution was titrated as in *Procedure A*. The potential break was between an apparent pH of 7 and 8.

With *Procedure A*, in the presence of aniline, each mole of free diacid originally present in the sample consumes two equivalents of sodium hydroxide and each mole of anhydride originally present consumes one equivalent of sodium hydroxide. In *Procedure B*, both the free acid and the anhydride consume one equivalent of

sodium hydroxide per mole. Due to these relationships, the following equations can be used to calculate the percentage of copolymer originally present as free diacid and as anhydride:

% free diacid = [eq./g. from A = eq./g. from B] ×
diacid molecular weight × 100 (Eq. 1)

% anhydride = [2(eq./g. from B) − eq./g. from A] ×
anhydride molecular weight × 100 (Eq. 2)

The ester content of the synthesized half-esters was established by dissolving the polymer in ethyl alcohol and titrating the resulting solution to a phenolphthalein end-point. A 0.1 N aqueous sodium hydroxide solution was used as the titrant. The experimental results were compared to the amount of sodium hydroxide that should have reacted with a known amount of copolymer (half-ester of known average molecular weight). Agreement of theoretical and observed results confirmed half-esterification of the product.

With quarter-ester products, proof of quarter-esterification was established by using *Procedure Step A* and again comparing theoretical and experimental results.

Sample Preparation Techniques—This study required the preparation of polymer samples in the form of cast films and compressed polymer disks. Cast films were prepared by pouring organic solvent solutions of the polymer or polymer–plasticizer combination on an enclosed area of a smooth, level sheet of aluminum foil. Solvent evaporation rates during film formation were controlled by partially covering the organosols to allow drying to proceed at ambient room conditions over 10–12 hr. The dry films were left on the foil substrate and mounted in sample holders for dissolution studies. The sample mount consisted of a 5 × 5-cm. stainless steel backing plate on which the polymer-foil sample was placed; a second 5 × 5-cm. plate, containing a 3.33-cm. circular opening, was then placed over the polymer film. The four edges were sealed with electrical tape to hold the plates together with the film sandwiched between them. The mounted samples with a 3.33-cm. diameter exposed film surface were stored in a vacuum desiccator over anhydrous calcium sulfate until subjected to dissolution studies.

Compressed disks of the anhydride copolymers were prepared using a laboratory press[4]. The 1.59-cm. diameter flat disks were prepared under a compressional load of 4550 kg. held for 15 sec. Compressed polymer disks used in dissolution studies were mounted in paraffin so that only one flat surface was exposed. The compressed polymer disk in its holder was then mounted in the dissolution cell in the same geometric manner as the film samples (Fig. 1).

Dissolution Rate Determinations—The dissolution rates of polymer or polymer–plasticizer films and polymer compressed disks were determined in general at pH 2.3, 5.0, and 7.5.

An immersion refractometer[5], utilizing prism A, was used to determine the dissolution rates of the polymer samples; the entire apparatus, as set up for experiments, is schematically represented in Fig. 1. The essential components of the system were maintained at 37° by circulation of constant-temperature water from an external source through the 400-ml. jacketed beaker. The refractometer, magnetic stirrer, and jacketed beaker were fastened to a ring stand to maintain the reproducible geometry of the system. Mounted film samples were suspended into the dissolution medium by masking tape so that the bottom edge of the mount just touched the bottom of the beaker. Polymer disks in paraffin mounts were supported at the end of a metal holder and were placed in a position as nearly equivalent to that of the film samples as possible. The dissolution medium, 200 ml. of McIlvaine's citric acid-phosphate buffer (13), was stirred at 310 ± 1 r.p.m. by a 2.5-cm. stir bar. When experimental readings were taken, the stirrer was shut off and moved to the side, allowing the 60-w. light to be placed under the beaker. After each reading, the apparatus was returned to the original geometry. This experimental procedure was an improvement over that reported by Heyd *et al.* (12), because accuracy and precision were maintained while temperature equilibration and sample changeover times were greatly shortened.

The dissolution rates were determined by recording the change in refractometer reading with time and determining the change in

[1] Gantrez AN series, GAF Corp., New York, N. Y.
[2] CAP, DPI Division, Eastman Organic Chemical Products, Kingsport, Tenn.
[3] Eastman Organic Chemicals, Rochester, N. Y.

[4] Carver laboratory press model B, Fred S. Carver, Inc., Summit, N. J.
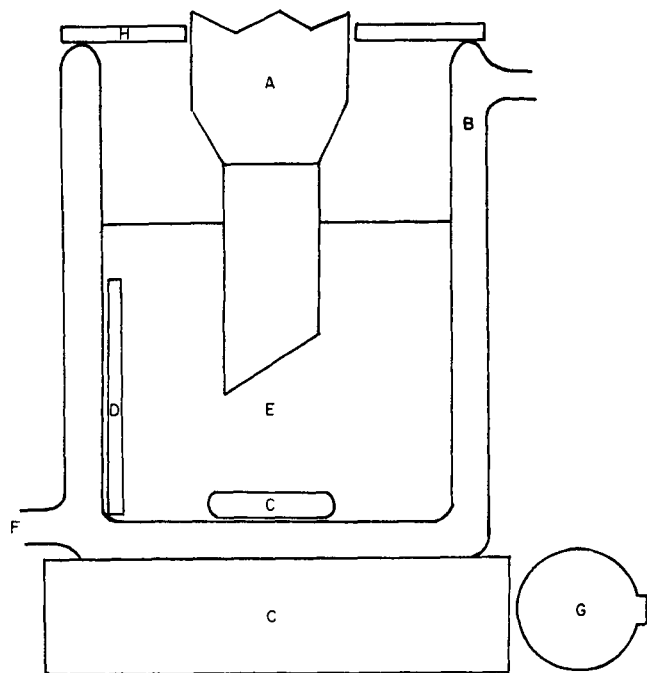[5] Model DB 502, Bausch & Lomb Optical Co.

Figure 1—*Apparatus used to study polymer dissolution properties from film or compressed disk polymer samples. Key: A, immersion refractometer using prism A; B, 400-ml. water-jacketed beaker; C, magnetic stirrer and 2.54-cm. (1-in.) stir bar; D, sample holder for film or disk (support not shown); E, 200 ml. of dissolution medium; F, constant-temperature water supply (37°); G, 60-w. lightbulb; and H, cover.*

Table II—Mean[a] Dissolution Data of Unesterified Copolymers in the Maximum Anhydride State as Influenced by pH

Polymer	pH	Lag Time, min.	Rate, mg. ml.$^{-1}$ hr.$^{-1}$
II	2.3	107	0.58
III		142	0.45
IV		150	0.48
V		148	0.47
II	5.0	65	0.93
IV		97	0.92
II	7.5	63	1.29
III		69	1.18
IV		65	1.06
V		68	0.82

[a] Average of three determinations.

sample. The contribution of the polymer and plasticizer to the refractometer readings could, therefore, be established separately. This allowed all results to be reported as polymer dissolution rates.

Polymer Dissolution pH—Polymers that were insoluble in pH 2.3 buffer during dissolution rate studies were subjected to further experiments to determine the pH at which they would be soluble within 24 hr. at an arbitrarily set level of 2 mg./ml., a parameter used previously (10). Polymer samples were placed in a large test tube along with the proper quantity of the desired buffer, and the tubes were agitated periodically over the 24-hr. experimental period. Determinations were performed to an accuracy of 0.1 pH unit, and the minimal pH of complete dissolution was regarded as the dissolution pH.

RESULTS AND DISCUSSION

Dissolution rates and lag times prior to initiation of the dissolution process were determined for each polymer studied. Using appropriate calibration constants, the dissolution rates were determined in units of mg. ml.$^{-1}$ hr.$^{-1}$. The lag time was determined by extrapolating the straight segment of the dissolution curve to zero change in the refractometer reading.

Dissolution as a Function of pH and Polymer Molecular Weight—Unesterified polymer films in the maximum anhydride form had dissolution rates and lag times dependent upon both the polymer molecular weight and the pH of the dissolution medium (Table II and Fig. 2). With each polymer, an increase in dissolution rate was observed with a corresponding increase in dissolution medium pH from one buffer medium to another. This would indicate that the polymers exhibited more rapid hydrolytic conversion from the water-insoluble anhydride to the water-soluble diacid as the me-

polymer concentration from refractometer scale reading–polymer concentration calibration plots. Calibration data, obtained for each polymer at each pH, demonstrated a linear relationship between polymer concentrations and refractometer readings. Repetitive studies showed the dissolution rates obtained to have standard deviations of 0.07–0.08 dissolution rate unit.

When triacetin was incorporated into the film systems, it contributed to the refractometer reading. By simultaneous use of a potentiometric analysis for polymer concentration, to which the triacetin caused no pH change, and a refractometric analysis for the total polymer–plasticizer concentration, to which both polymer and plasticizer contributed to the reading, the films were shown to dissolve uniformly since the experimental results demonstrated that the polymer–plasticizer ratio in solution was the same as in the film
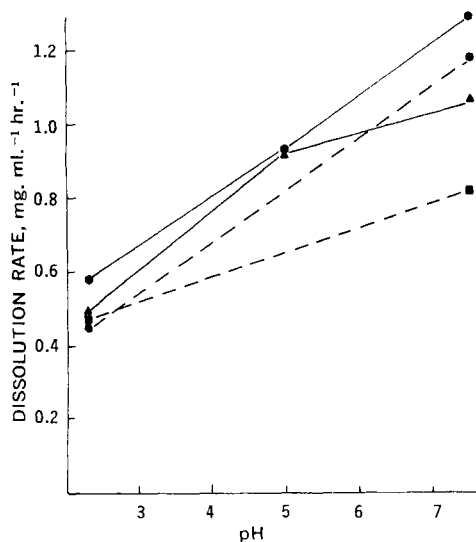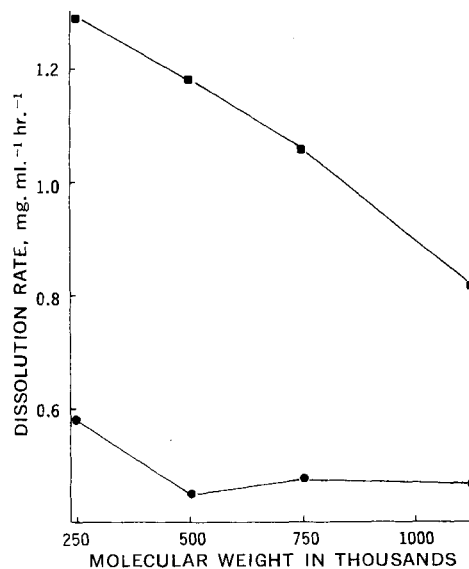

Figure 2—*Dissolution rates of poly(methyl vinyl ether–maleic anhydride) copolymers in the maximum anhydride state as affected by pH. Key: ■, II; ▲, III; ●, IV; and ◗, V.*

Figure 3—*Dissolution rates of poly(methyl vinyl ether–maleic anhydride) copolymers. Key: ■, pH 7.5; and ●, pH 2.3.*

Table III—Mean[a] Dissolution Data from Compressed Polymer Disks at pH 7.5

Polymer	Lag Time, min.	Rate from 1.59-cm. Diameter Disk, mg. ml.$^{-1}$ hr.$^{-1}$	Rate from 3.33-cm. Diameter Theoretical Disk, mg. ml.$^{-1}$ hr.$^{-1}$
II	30	0.56	2.48
III	38	0.65	2.88
IV	33	0.60	2.62
V	30	0.68	2.98

[a] Average of three determinations.

dium pH was increased. Lag time results (Table II) were consistent with this assumption and decreased accordingly as the medium pH was raised. The change of medium pH during dissolution rate studies was very slight but could be measured with a sensitive pH meter.

The molecular weight of the polymer also had an important influence on the dissolution properties of the polymers. Figure 3 shows that dissolution rates from cast film samples tended to decrease as the polymer molecular weight increased. The dissolution rate–molecular weight relationship was substantially linear at pH 7.5 but was basically constant at pH 2.3, where conversion of the polymer from the anhydride to the diacid form would be slower.

Dissolution from Compressed Samples—Molecular weight dependence was not demonstrated at pH 7.5 with the compressed disk samples. Table III shows both the observed rate of polymer dissolution from 1.59-cm. flat disks and the calculated rate from theoretical disks having a surface area equivalent to that of the film samples. The theoretical dissolution rates of disks and the observed rates from films having equivalent area differed extensively, with the disk values being 2–3 times greater than the film values. The disk samples also had lag times of about half those of corresponding polymer films.

Basic differences in polymer chain interactions could be expected to occur between cast film and compressed disk samples. Preparation of compressed samples involves particle–particle compaction and does not provide opportunity for the intertwining of polymer molecular segments to form a network structure. However, during the formation of a cast polymer film, a gel structure is formed and the dry film is an intertwined xerogel. This structure possesses interactions of polymer chain segments from various molecules and is more resistant to diffusion of molecules into solution than is a compressed disk.

These results demonstrated that the dissolution properties of cast films and corresponding composition compressed polymer disks

Table IV—Mean Dissolution Data of II and Its Partial Ester Derivatives from Film Samples

Polymer	pH	Lag Time, min.	Rate, mg. ml.$^{-1}$ hr.$^{-1}$
Unesterified II	2.3	107	0.58
n-Butyl half-ester of II		Insoluble	
n-Propyl half-ester of II		Insoluble	
Ethyl half-ester of II		Insoluble	
n-Butyl quarter-ester of II		Insoluble	
n-Propyl quarter-ester of II		110	1.32
Ethyl quarter-ester of II		58	1.27
Unesterified II	5.0	65	0.93
n-Butyl half-ester of II		77	0.49
Ethyl half-ester of II		0	1.88
n-Propyl quarter-ester of II		0	1.96
Unesterified II	7.5	63	1.29
n-Butyl half-ester of II		0	2.05
n-Propyl half-ester of II		0	2.17
Ethyl half-ester of II		0	2.04
n-Butyl quarter-ester of II		0	1.30
n-Propyl quarter-ester of II		0	2.33
Ethyl quarter-ester of II		0	1.96

Table V—Mean Dissolution Data of VI and Its Partial Ester Derivatives from Film Samples

Polymer	pH	Lag Time, min.	Rate, mg. ml.$^{-1}$ hr.$^{-1}$
Unesterified VI	2.3	Insoluble	
n-Butyl half-ester of VI		Insoluble	
n-Propyl half-ester of IV		Insoluble	
Ethyl half-ester of VI		Insoluble	
n-Butyl quarter-ester of VI		Insoluble	
n-Propyl quarter-ester of VI		Insoluble	
Ethyl quarter-ester of VI		Insoluble	
Unesterified VI	7.5	30	1.87
n-Butyl half-ester of VI		83	0.63
n-Propyl half-ester of VI		43	0.89
Ethyl half-ester of VI		0	2.18
n-Butyl quarter-ester of VI		10	2.03
n-Propyl quarter-ester of VI		17	2.13
Ethyl quarter-ester of VI		15	3.22

can be substantially different. If polymers are to be employed pharmaceutically as films, physical testing including dissolution analysis would be more relevant if conducted on structured (film) samples.

Dissolution as a Function of Esterification—The effects of the degree of esterification and of ester chain length on film dissolution properties were evaluated from cast films of polymer derivatives containing two, three, or four carbon atom straight-chain esters. The derivatives were half- or quarter-esters of II or VI. The dissolution data obtained are presented in Tables IV and V, and the dissolution rates obtained at pH 7.5 are plotted versus ester chain length in Figs. 4 and 5. These results demonstrate that the dissolution properties of the polymers were greatly altered by partial esterification. All of the half-esters of II had lag times of greater than 3 hr. in pH 2.3 media and were considered insoluble at that pH. These polymers were rapidly soluble at pH 7.5, having no lag time and rates of dissolution nearly twice that of the parent anhydride. No significant differences were noted in rates between the three half-esters at pH 7.5. At pH 5.0, the ethyl half-ester had no lag time and a rapid dissolution rate while the higher molecular weight n-butyl half-ester had greater than 1 hr. lag time and a relatively slower rate. This latter finding demonstrates a possible fallacy in evaluating enteric behavior at only two pH values, such as pH 1.2 and 7.5, the respective pH values of simulated gastric and intestinal fluids. Long lag periods or polymer insolubility at low pH's and very short lag times followed by rapid dissolution rates at higher, even though possibly still acidic, pH's would be desirable characteristics for potential enteric polymer coatings since rapid release of the medicament on leaving the stomach is usually desirable to take advantage of the better drug absorption character of the upper portions of the intestines.

The quarter-esters of II clearly demonstrate the effect of different alkyl ester chain lengths on polymer dissolution. At pH 2.3, the n-
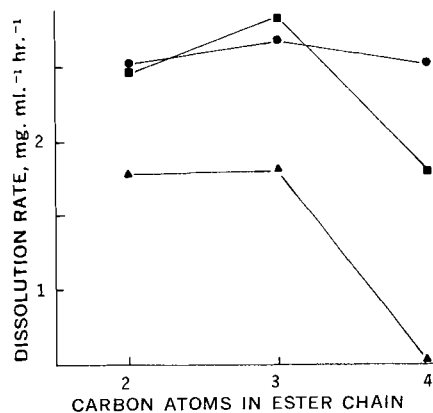

Figure 4—Dissolution rates from films of partial esters of II as a function of ester chain length. Key: ▲, quarter-esters, pH 2.3; ■, quarter-esters, pH 7.5; and ●, half-esters, pH 7.5.

Table VI—Comparison of Dissolution Data from Free Films with and without the Addition of Triacetin (4:1 Polymer–Plasticizer Ratio)[a]

Film	pH 2.3 Lag Time, min.	pH 2.3 Rate, mg. ml.$^{-1}$ hr.$^{-1}$	pH 5.0 Lag Time, min.	pH 5.0 Rate, mg. ml.$^{-1}$ hr.$^{-1}$	pH 7.5 Lag Time, min.	pH 7.5 Rate, mg. ml.$^{-1}$ hr.$^{-1}$
II	107	0.58	65	0.93	63	1.29
II + triacetin	48	0.76	10	1.78	0	1.85
IV	150	0.48	97	0.92	65	1.06
IV + triacetin	125	0.77	62	1.00	32	1.05
n-Butyl half-ester of II	Insoluble	—	77	0.49	0	2.05
n-Butyl half-ester of II + triacetin	Insoluble	—	67	0.81	0	1.92
n-Propyl quarter-ester of II	110	1.32	0	1.96	0	2.33
n-Propyl quarter-ester of II + triacetin	83	1.22	0	2.27	0	2.39
I	Insoluble	—	Insoluble	—	0	2.36
I + triacetin	Insoluble	—	Insoluble	—	0	2.28

[a] All results are reported on the basis of polymer dissolution. Corrections were made to account for the contribution of triacetin to the raw data.

butyl ester was insoluble while the n-propyl and ethyl esters dissolved at nearly identical rates. However, the longer ester chain, n-propyl ester, had almost twice the lag time of the ethyl derivative (110 versus 58 min.). None of the quarter-esters of II exhibited any lag time at pH 7.5, but dissolution rates again showed a dependence upon ester chain length, with the n-butyl ester dissolving less rapidly than the n-propyl or ethyl quarter-esters.

The VI partial esters (Table V) were all insoluble (lag times greater than 3 hr.) at pH 2.3. At pH 7.5, the half-esters and the quarter-esters showed definite trends toward more rapid polymer dissolution with shorter ester chains. Also, in each case, the half-esters had lower rates of dissolution than the corresponding quarter-esters. A comparison of the II and VI partial esters indicated that the half-esters of II would probably have the best enteric properties of any vinyl ether–maleic anhydride copolymer included in this study.

Dissolution as a Function of Alkyl Ether Substituent—The effect of the alkyl ether substituent on the polymer solubility may be seen by comparing the II and VI copolymers (Tables IV and V). In acidic media, II was slowly soluble after an initial lag period of nearly 2 hr., but VI was insoluble. This would be expected since the VI molecule is more hydrophobic than the II polymer. In the alkaline buffer, dissolution from VI started in about half the time required for II and continued at a more rapid rate. This anomalous result was probably due to the VI sample having a lower degree of polymerization than II. This hypothesis is substantiated by the relative viscosity measurements (Table I), although the difference in side chains makes direct comparison of the polymers impossible. Molecular weight data for VI were not available.

Dissolution as a Function of Film Plasticizer Content—Five polymers were selected, and films were cast from each polymer with

triacetin included in a 4:1 (w/w) polymer–plasticizer ratio. The results of dissolution experiments with these films are compared to the unplasticized systems in Table VI. The general effect caused by the addition of the plasticizing agent was to accelerate the overall dissolution process, that is, to increase the rate of dissolution and decrease the lag time prior to dissolution. This effect appeared to be most pronounced at the lower two pH values and with unmodified anhydride copolymers. The presence or absence of the plasticizer had a less substantial effect on the dissolution properties, lag time, or dissolution rate at any pH for the n-butyl half-and n-propyl quarter-esters of II. Likewise, I showed no solubility differences due to plasticization at these experimental pH's (insoluble films at pH 2.3 and 5.0). These results suggest that, with the anhydride films at the lower pH values, the addition of triacetin allows more rapid solvent penetration into the films, probably due to a decreased polymer–polymer segmental interaction and, therefore, less resistance to solute diffusion into the film or polymer diffusion from the film into the bulk of the solvent medium.

Polymer Dissolution pH—Polymers that were insoluble in the pH 2.3 dissolution rate tests were subjected to further experiments. These experiments established the lowest pH, within 0.1 pH unit, at which the polymers were soluble to the extent of 2 mg./ml., an arbitrarily set limit.

Alkyl ether chain length, degree of esterification, and ester substituent chain length were all shown to be factors influencing the polymer's minimum dissolution pH (Table VII). The results established that the higher degree of esterification produced polymers requiring higher pH's to attain the required polymer solution concentration corresponding to the dissolution pH. These two relationships are clearly evident in Fig. 6, in which the minimum dissolution pH of VI and its ester derivatives is shown. A comparison of the n-butyl vinyl ethers (Table VII) demonstrated higher minimum dissolution pH values required by the former ether at corresponding
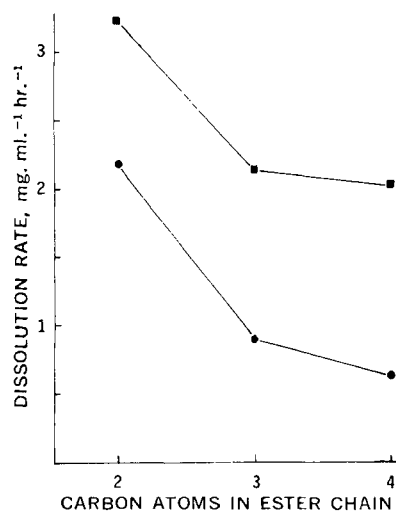

Figure 5—Dissolution rates from films of partial esters of VI as a function of ester chain length. Key: ■, quarter-esters, pH 7.5; and ●, half-esters, pH 7.5.
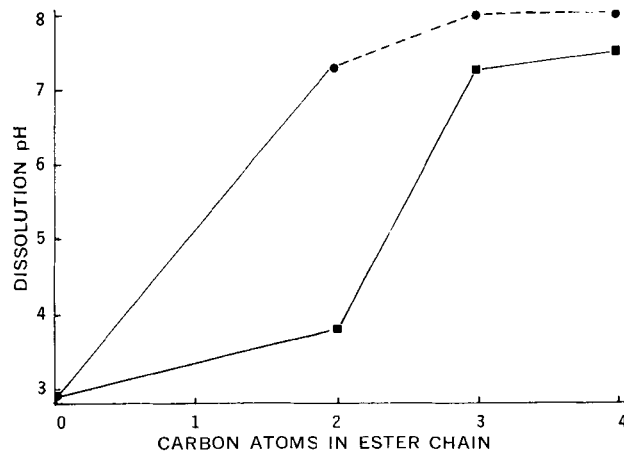

Figure 6—Minimum dissolution pH of IV and quarter- and half-ester derivatives. Key: ■, quarter-esters; ●, half-esters; and ●, IV.
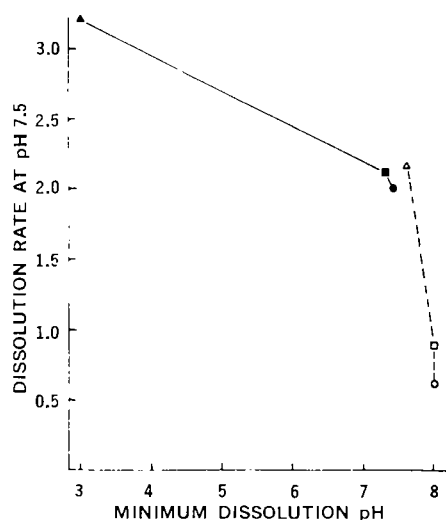
Figure 7—*Relation of dissolution pH to pH 7.5 dissolution rate of VI partial esters. Key:* ▲, *ethyl quarter-ester;* ■, *n-propyl quarter-ester;* ●, *n-butyl quarter-ester;* △, *ethyl half-ester;* □, *n-propyl half-ester;* and ○, *n-butyl half-ester.*

esterification levels. The relationship between ester chain length and minimum dissolution pH has previously been demonstrated with half-esters of ethyl, isopropyl, *n*-butyl, and cyclopentyl functions of III (10).

When using the partial esters of VI as examples, there appeared to be an inverse relation between the dissolution rate (pH 7.5) and the dissolution pH (Fig. 7). With these polymer films, the dissolution rate, in general, increases as the dissolution pH decreases. This inverse relation would be expected since the dissolution pH is a measure of the polymer's tendency to dissolve in aqueous systems, and a lower dissolution pH is indicative of a lower pKa value for the given polymer.

SUMMARY

1. The dissolution rates of the poly(methyl vinyl ether–maleic anhydride) copolymers were related to the molecular weights in apparently linear manner. Dissolution rates for all systems were found to be constant after the initial lag period. The general effect of an increase in buffer pH was to reduce the lag time and/or increase the rate of polymer dissolution. This effect was probably due to the increased dissociation of carboxyl functional groups at higher pH's, which would cause more rapid extension of the polymer molecules.

2. The effects of partial esterification and the use of different alkyl ether groups on the polymer dissolution properties were studied. Both longer ester chain lengths and a higher degree of esterification tended to decrease the dissolution rates. The longer alkyl ether chain of VI as compared to II caused the former to be a more hydrophobic polymer and, consequently, less rapidly soluble at low pH values. This effect was overshadowed at higher pH's by the apparent low degree of polymerization of the VI sample.

3. Addition of a plasticizer, triacetin, to the polymer films caused increased polymer dissolution rates and/or decreased lag times prior to initial dissolution. This effect was observed with anhydrides, a quarter-ester, and a half-ester but was most pronounced with unesterified, anhydride copolymers.

4. The rates of polymer dissolution from compressed polymer disks differed substantially from the rates of dissolution from cast films of identical composition, with the compressed, nonintertwined polymers having more rapid dissolution in all cases. Dissolution

Table VII—Minimum Dissolution pH Values of Polymers Insoluble at pH 2.3

Polymer	Lowest Soluble pH
II	
n-Butyl half-ester	5.0
n-Propyl half-ester	4.9
Ethyl half-ester	4.3
n-Butyl quarter-ester	2.6
VI	2.9
VI	
n-Butyl half-ester	>8.0
n-Propyl half-ester	>8.0
Ethyl half-ester	7.6
n-Butyl quarter-ester	7.4
n-Propyl quarter-ester	7.3
Ethyl quarter-ester	3.0
I	6.0

determination from cast film samples seems to be a more relevant method of illustrating differences between molecular weight fractions because it more closely corresponds to the condition encountered with film coatings.

5. The determination of minimum dissolution pH's clearly demonstrated that partial esterification changes the pKa values of the copolymers, and this change can be directly related to ester chain length, degree of esterification, and polymer dissolution rate for each homologous partial ester series.

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ACKNOWLEDGMENTS AND ADDRESSES