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Chemical Modifications of Polymeric Film Systems in the Solid State I: Anhydride Acid Conversion

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Abstract □ Poly(methylvinyl ether/maleic anhydride) was employed as a pharmaceutical film coating employing new and unique film coating concepts. Films of this polymer, PVM/MA, have excellent gloss and clarity, are hard, demonstrate good abrasion resistance, and yet are flexible. Half esters of the polymer are reported to possess excellent enteric and prolonged-release properties. However the anhydride form of the polymer is soluble in organic solvents but is slowly soluble in water or gastric media, while the acid water-soluble form of the polymer is insoluble in common organic solvents. A method is described wherein the polymer is applied in the anhydride form from an organic solvent, after which the coated tablets are subjected to mild humidity conditioning treatment to partially convert the polymer to the more soluble acid form. Radiographic analysis in man indicated that the complete anhydride film disintegrated outside the stomach, in approximately 3–4 hr. after administration. Films partially converted to the poly-acid form disintegrated in the stomach or proximal jejunum in 30–45 min. compared to 10–30 min. for the uncoated tablets. The rate of water vapor transmission through the PVM/MA films was one-fourth that observed for a typical cellulosic film.

Keyphrases □ Poly(methylvinyl ether/maleic anhydride)—tablet film coating □ Polymer modification, solid state—anhydride to acid conversion □ Film solubilities, water vapor transmission rate—humidity pretreatment effects □ *In vitro* dissolution—film-coated tablets □ *In vivo* disintegration times, man—radiopaque, film-coated tablets

Film coating of solid dosage forms, as a means of promoting drug stability and esthetic appeal, is one of the more recent processes and dosage form modifications developed and employed by the pharmaceutical industry. Numerous advantages of film-coating techniques have been listed and contrasted to the time-honored technique or "art" of sugar coating (1, 2). There appears to be, however, one feature lacking related to film coating. Regardless of the application technique, polymer concentrations, and film additives used, coating by this method has been limited to a small group of polymer derivatives derived from cellulose.

Hydroxypropyl methyl cellulose, alone and in combination with ethyl cellulose, and cellulose acetate phthalate (CAP) with annealing agents, serve as the most widely, if not the only, systems used in the United States as soluble film-coating agents designed for substantially immediate drug release. Although systems of these types have been used for a number of years, they are not without disadvantages. The dissimilar solubilities of methyl and ethyl cellulose require that complex solvent systems be used to produce compatible film coating solutions which can be applied to tablets. These two polymers must be used in a balanced ratio to promote the desired film strength, coatability and yet retain the proper *in vivo* solubility characteristics.

Similarly, CAP, when used as a rapid-release coating, must be combined with high percentages of water soluble annealing agents for rapid film disintegration under gastric conditions (1). The soluble cellulosic films possess a low gloss index and therefore, are often combined with agents to produce gloss, or the final product must be polished to improve coat appearance and esthetic appeal. Yearly, the plastics industry produces numerous new and modified polymers, some of which may surpass the properties of cellulosic derivatives with regard to film coating. It would be advantageous, for example, to use a single polymer without the need for annealing agents and glossants, which could be prepared for coating using a single solvent. The applied film must comply with the intended film coating purposes, and serve to protect the drug against environmental conditions, yet be readily soluble at gastric conditions. This study was therefore undertaken to search for and develop simple, noncellulosic film-coating systems which would broaden the selection of materials currently available to the pharmaceutical industry. Of several classes of polymers investigated, poly(methylvinylether/maleic anhydride), co-polymer (PVM/MA), was shown to possess qualities which might meet the objectives.

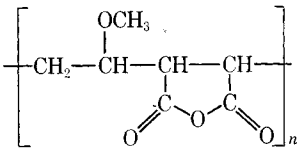
Heretofore, this co-polymer, modified by partial esterification, has been studied as an enteric or sustained-release coating for tablets and granules. Lappas and McKeehan (3), studied a series of partial esters of PVM/MA and found that the ester chain length and

degree of esterification were directly proportional to the *in vitro* dissolution pH. Their findings supported the objectives of controlling drug release by utilizing the pH gradient along the intestinal tract. Animal studies revealed that relatively high doses of the polymers were nontoxic over a 1-year feeding period. Nessel *et al.* (4) successfully employed the *n*-butyl half ester of PVM/MA to sustain the release of *d*-amphetamine SO_4 from coated granules. In another study, the isopropyl half ester, when applied to nonpariel sugar starters, was found to sustain the release of prednisolone (5).

In all previous studies reported, PVM/MA was modified by partial esterification. Apparently, PVM/MA has not been considered pharmaceutically useful by itself as a coating agent. This investigation therefore, concerns the potential applications of unesterified PVM/MA with regard to tablet film coating.

EXPERIMENTAL

Two molecular weight grades of poly(methylvinylether/maleic anhydride) were used throughout this study. Of the commercially available series, the lowest and highest molecular weight grades were selected for use, PVM/MA-119[1] and -169,[2] respectively. This copolymer is a true interpolymer having the following repeating structure:



The materials were used as received from the manufacturer.

Free Film Preparation and Conditioning—PVM/MA stock solutions were prepared by dissolving an accurately weighed amount of dry polymer in ethyl acetate or acetone to yield concentrations ranging from 4–10% w/v. The solutions were polished through cotton and allowed to solvate at least 24 hr. before film preparation. Triacetin was used to plasticize the PVM/MA films and was added to the stock solutions just prior to film preparation such that the dried films would contain polymer and plasticizer in a ratio of 8:5.

An aluminum foil substrate technique was developed for the preparation of free films. With this procedure, film solutions were cast on 17.78 × 20.54 cm. (7 × 10 in.) sheets of aluminum foil which were smoothly spread over glass plates and affixed by taping the foil perimeter to the glass. Film solutions were drawn over the leveled substrate using a variable gap doctor blade. The plates were covered to retard evaporation and to exclude dust. The films were allowed to form at ambient conditions for 6–8 hr. and then were separated from the substrate by peeling the foil from the films. Films were cut into 1.91-cm. (0.75-in.) or 2.54-cm. (1-in.) disks and placed *in vacuo* for 24 hr. to remove residual solvent. Dried films were then stored over anhydrous calcium sulfate until required.

Film samples were subjected to a variety of controlled temperature–humidity conditions and the effects of film conditioning with time were studied with regard to physical film properties. A humidity cabinet[3] was employed at constant conditions of 40° and 30, 40, or 50% R.H. Film exposure to these conditions ranged to 300 hr.

Evaluation of Free Films—Six film disks of PVM/MA-119–triacetin (8:5) and ten of PVM/MA-169 alone were studied for maximum anhydride to acid conversion at controlled temperature and humidity. Films were individually weighed as they existed in the full anhydride state and were then exposed to humidity treatment. Weight gain in each film was monitored until equilibrium was reached. At this point the films were cycled back to the original storage conditions of 0% R.H. and 25°. Moisture desorption was monitored by film weight loss until constant weight was obtained. The apparent anhydride to acid ratio was calculated on the basis of chemically bound water using the co-monomer unit molecular weight.

A semiquantitative procedure, based on a pH–polymer concentration relationship, was used to determine the dissolution characteristics of PVM/MA film systems. Standard aqueous solutions of PVM/MA-119 were prepared in concentrations of 20–1000 mcg./ml. and pH measurements were made to establish the pH-concentration relationship of the dissolved polyacidic material. Five pH observations were made on each solution over a period of 72 hr. using a pH meter.[4] The readings were repeated on separate solutions containing polymer and triacetin in an 8:5 ratio.

The dissolution rates of free films were determined in water using double-walled glass cells of 25–100-ml. capacity. Constant temperature water was circulated in the cells to maintain the dissolution medium at a temperature of 37 ± 0.1°. Individual film samples were placed in an accurately measured and preheated amount of water within the cells and the medium was agitated with a magnetic stirrer at 150 r.p.m. The pH electrodes were inserted through ports in a large rubber stopper used to seal the cell. The pH measurements were recorded with time and converted to concentration of dissolved polymer using the standard curve. The effects of polymer state (anhydride to acid ratio) on film dissolution patterns were assessed by this method.

Water vapor transmission properties of PVM/MA-169 films in the full anhydride form and in the partial polyacidic form were determined. In each study, five film disks were used to obtain the average transmission rate as milligrams of vapor crossing a film barrier of constant area (153.9 mm.^{2})/hr./0.1-mm. thickness. The transmission cells used were similar to those used by Gore *et al.* (6). The relative humidity at 30° within the cells was held at 91% R.H. using a saturated sodium tartrate solution. The distance from the solution to the film barrier was 4.75 cm. The external environment was held at 0% R.H., using anhydrous calcium sulfate at 30°. The assembled cells were allowed to equilibrate at these conditions for 12 hr. prior to initial weight readings. Subsequent cell weights were taken at 24-hr. intervals until 5–6 weighings had been made.

Applied Films—Tablet Coating—Standard convex 0.79 cm. (0.31 in.) and 1.12- and 0.65-cm. (0.44- and 0.25-in.) diameter modified ball tablets were prepared of the following composition:

Dicalcium phosphate dihydrate	500 g.
Cornstarch	50 g.
Amaranth (F.D. & C. No. 2 Red)	11 g.
Gelatin and acacia solution[5]	*q.s.*
Talc (5% of sized granule weight)	

A small scale immersion coating process was developed, whereby individual tablets could be identified after coating and the exact amount of material applied to each tablet could be measured. Tablets were individually weighed prior to coating. The amount of film which was applied was controlled by the viscosity of the coating solutions and by the number of immersions employed. Coated tablets were dried and stored in the same manner as described for the free-films.

To assess the value of PVM/MA film systems in more conventional usage, film coating was accomplished using a 38.10-cm. (15-in.) diameter pan loaded with approximately 3.5 kg. of tablets. Film-coating solutions were applied with airless spraying equipment[6] from a 0.25-cm. (0.011-in.) diameter tungsten-carbide nozzle at 1125 p.s.i. nozzle pressure, employing 3–5-sec. spraying times and forced warm air drying.

Evaluation of Film-Coated Tablets—The dissolution-release characteristics of the tracer dye from film-coated tablets was spectrally determined, with particular emphasis on PVM-MA-169–triacetin (8:5) films varying in anhydride–acid ratio. The use of a soluble dye permitted visual observation of the release pattern as well as an accurate quantification of dissolution rate, employing spectrophotometric analysis at 520 mμ.

Dissolution cells for determining release characteristics were the same as those used for studying free-film dissolution rates. Small monel wire baskets were used to suspend individual tablets in 100

[1] Gantrez-AN-119, Approx. No. Av. Mol. wt. = 56,000.
[2] Gantrez-AN-169, Approx. No. Av. Mol. wt. = 436,000, GAF Corp. New York, N. Y.
[3] Blue M Engineering Co., Blue Island, Ill.
[4] Beckman Zero-Matic, Beckman Instrument Co., Fullerton, Calif.
[5] USP gelatin, 12% w/v and 4% w/v USP powdered acacia.
[6] Binks Manufacturing Co., Chicago, Ill.

Table I—Analysis of Anhydride to Acid Conversion in PVM/MA-119–Triacetin Films (8:5)

Initial Film Wt., mg.	Storage Time, hr. (30% R.H. and 40°)	Moisture Sorption, mg.	Moisture Bound Following 0% R.H. and 25° Recycling, mg.	Theoretical Moisture Required, mg.[a]	Theoretical % Anhydride Converted to Acid
76.6	56	2.7	1.2	5.4	22
81.7	56	2.7	1.3	5.8	22
64.0	96	4.0	2.0	4.6	43
64.7	96	3.9	1.8	4.6	39
63.6	144	4.0	1.8	4.5	40
63.1	144	3.8	1.5	4.5	33

[a] Moisture required to hydrolyze all anhydride groups.

ml. of distilled water maintained at 37°. The distance of the tablets above the magnetic stirring bar was 1.91 cm. (0.75 in.), and the stirring speed was held at 150 r.p.m. The samples (1.0 ml.) removed periodically for analysis, were replaced with an equal volume of distilled water, and the necessary concentration corrections were made. Tablets tested in this manner included the 1.12- and 0.62-cm. (0.44- and 0.25-in.) tablets coated with PVM/MA-169–triacetin. (8:5), which were preconditioned for up to 144 hr. at 50% R.H. and 40°.

The *in vivo* disintegration characteristics of tablets coated with PVM/MA–169 triacetin (8:5) were determined using five male volunteers. Tablets were prepared in the three sizes previously described, substituting X-ray grade barium sulfate for dicalcium phosphate in the formula reported earlier. Three tablets of different sizes were administered to a given subject with 5 oz. of water at 1.5-hr. intervals starting at mid-morning. The different size tablets permitted their radiographic identification at selected examination times post administration. All subjects ate similar breakfasts and lunches at the same time of day and ingestion of other foods and liquids was prohibited.

Abdominal X-rays were taken throughout the day to determine tablet disintegration time and the location along the gastrointestinal tract. Control tablets of the same matrix formula but which were not coated, were administered to determine the *in vivo* disintegration times. All X-rays were interpreted by a radiologist.[7]

RESULTS

Anhydride-Acid Conversion—Moisture sorption-desorption studies on pure PVM/MA-169 films revealed that approximately 18% of the available anhydride groups were hydrolyzed to the dicarboxylic acid form at equilibrium by hydrolysis treatment conditions of 40% R.H. and 40°. In all of the eight films studied, film equilibrium moisture content was established within approximately 300 hr. at 40% R.H. and 40°. At this point, films had absorbed only about 50% of the water necessary to hydrolyze all anhydride groups. The time required for subsequent desorption of free water at 0% R.H. and 25° was 190 hr. Less than half the moisture absorbed was found to be chemically bound by the films, resulting in the 18% anhydride-acid conversion. Table I shows the results of a similar study using films of the low molecular weight grade PVM/MA plasticized with triacetin (glyceryl triacetate) in an 8:5 ratio. The equilibrium moisture content had been established by 96 hr. of exposure at 30% R.H. and 40°. Further treatment had little effect on moisture sorption. Based on initial film weights, an average of 6.15% moisture was absorbed at equilibrium and 2.78% of this moisture was found to be chemically bound. The apparent percentage of anhydride-acid conversion was 38.7% in these triacetin plasticized films (8:5 ratio), compared to 18% conversion of the 100% PVM/MA-169 films.

The measurement of the dissolution properties of free-films based on the pH-concentration relationship was found to be reliable and reproducible over the polymer concentration range employed. The standardization curve from which polymer concentration was determined by measurement of pH is shown in Fig. 1. The ordinate (mcg./ml.) was plotted on the log scale for ease in reading the graph. Each point represents the mean of 5 pH observations taken on two separate dilutions of the polymer. pH readings maintained consistency over a 3-day period with deviations from the means of approximately 0.02 pH units. Dilutions of polymer solutions containing triacetin (8:5 ratio) were shown to have identical pH values to those of the polymer alone.

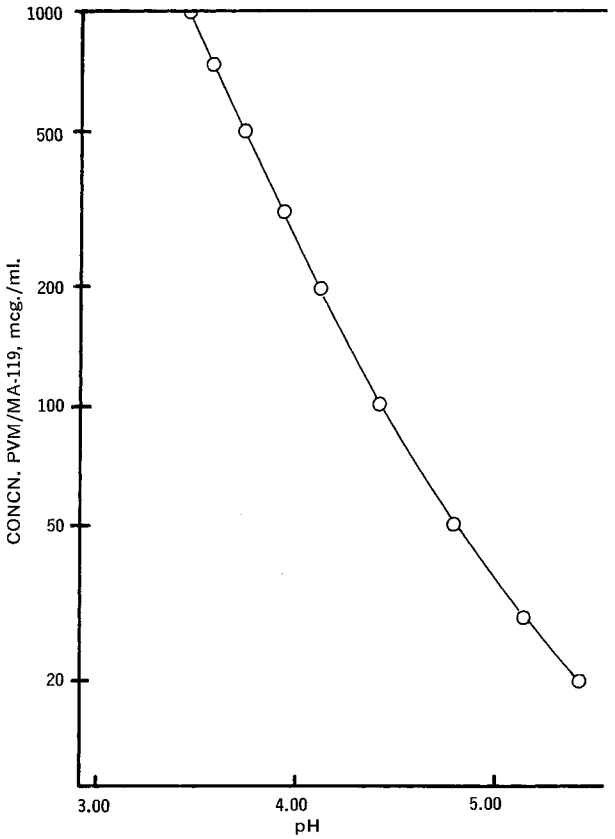


Figure 1—*pH standardization curve for PVM/MA-119 in distilled water.*

Ten replicate dissolution assays were made on the 8:5 films which had been stored at 0% R.H. and room temperature since preparation. Seven of the films were analyzed in cells containing 25 ml. of distilled water and three were analyzed in a cell designed to contain 100 ml. The results of these assays are listed in Table II. The reproducibility and accuracy of this method proved to be adequate. The increased time in the onset of dissolution for those films assayed in the 100-ml. cells was attributed to decreased fluid movement in that the same stirrer speed was used for both the 25- and 100-ml. volumes.

pH observations during the assays revealed that the PVM/MA-119–triacetin films remained unchanged for the first 1.5–2 hr. Film hydrolysis as reflected by visible swelling was noted at approximately 2–2.25 hr., with swelling continuing gradually until the films fragmented and dissolved. General visual observations of film swelling and dissolution corresponded to the pH decrease, with the final equilibrium pH coinciding with film disappearance and complete dissolution.

Dissolution rates of PVM/MA-119–triacetin films were markedly affected by the temperature-humidity conditioning at 30% R.H. and 40°. Dissolution patterns were determined for the six films shown in Table I which were used for the moisture sorption-desorption study. The effects of mild temperature-humidity conditioning on the dissolution rate are shown in Fig. 2. Following the 56-hr. treatment period, the time required for 50% of the film to dissolve was reduced by approximately 2.5 hr. as compared with nontreated films. Further treatment, *i.e.*, 96 and 144 hr. correspondingly increased the rate of film dissolution. However, these curves differed only slightly, indicating that equilibrium was being approached.

[7] Dr. Paul L. Webster, Purdue University, Lafayette, Ind.

Table II—Reproducibility of Dissolution Characteristics of PVM/MA-119–Triacetin Films as Determined by pH Measurement

Sample No.	Polymer Content mg.	pH at 3 hr.	Final pH with time	Coincidence Expt. *vs.* Calcd. pH	Slope[a] pH/hr.
1	15.67	4.42	3.37 4.25 hr.	Identical	−1.90
2	18.89	4.42	3.30 4.25 hr.	0.01 Deviation	−1.90
3	16.85	4.74	3.37 4.25 hr.	0.03 Deviation	−2.02
4	12.03	4.73	3.35 4.25 hr.	Identical	−2.02
5	17.96	4.64	3.33 4.25 hr.	Identical	−2.10
6	19.26	4.42	3.30 4 hr.	0.01 Deviation	−2.01
7	19.76	4.42	3.29 4.25 hr.	Identical	−2.07
8[b]	44.16	5.40	3.52 4.25 hr.	0.01 Deviation	−2.76
9[b]	40.44	5.30	3.54 4 hr.	Identical	−3.12
10[b]	54.62	5.40	3.43 4.25 hr.	0.01 Deviation	−2.77

[a] Measured at steepest part of the sigmoidal dissolution curve. [b] Film samples measured in 100-ml. cell.

These data describe a strong dependency of film dissolution rate on the polymer anhydride:acid ratio and show that only about 40% of the anhydride groups need to be prehydrolyzed to render the film essentially readily water soluble.

Water Vapor Transmission Analysis—PVM/MA-169 films which were maintained in the maximum anhydride state until being tested, showed a gradual increase in the water vapor transmission rate as the test proceeded. Figure 3 (Curve -●-) represents the mean of five film samples showing this phenomenon. The initial water vapor transmission rate, obtained by extrapolating to time zero, was found to be approximately 1.0 mg./hr./0.1 mm. film thickness. The increase in rate with time was due to the gradual hydrolysis of anhydride groups as water vapor transmitted the film barrier. As more acid groups were formed, the film became more polar, causing the water vapor transmission rate to increase. Figure 3 (Curve -○-) shows similar results but at a later state. In this case the five film samples had been preconditioned at 50% R.H. and 40° for 48 hr. before the start of the water vapor transmission test. Zero-order water vapor transmission rates were not established with PVM/MA-169 films until they had been preconditioned for 96 hr. at 50% R.H. and 40°. These data are also represented in Fig. 3 (curve -■-). The zero-order transmission rate was found to be 4.22 mg. of water/hr./0.1 mm. film thickness, representing about a 4-fold increase over that for the pure anhydride film.

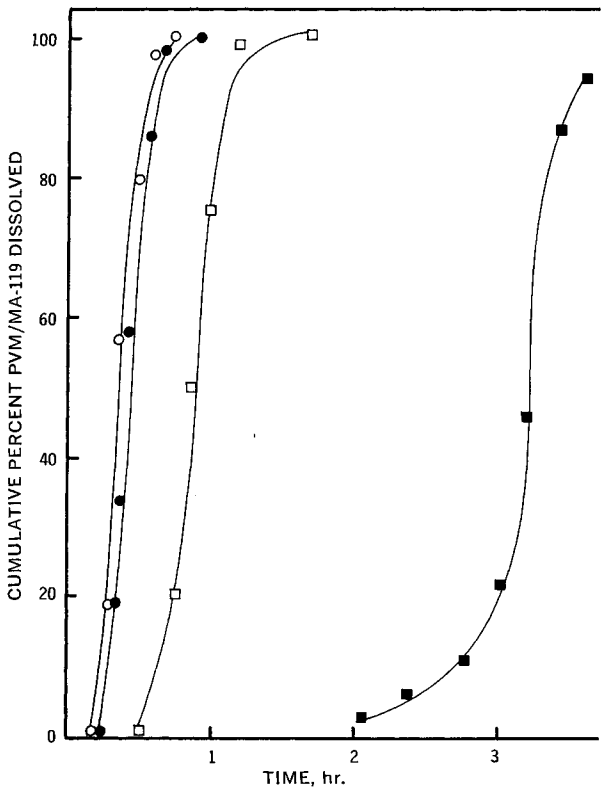


Figure 2—*Dissolution of PVM/MA-119 from free films as affected by temperature-humidity preconditioning at 30% R.H. and 40°. Key: ■, 0 hr.; □, 56 hr.; ●, 96 hr.; ○, 144 hr.*

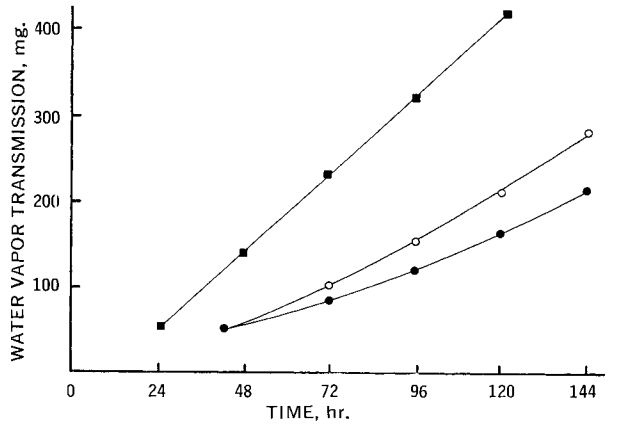


Figure 3—*Effects of anhydride to acid conversion on the water vapor transmission rate of unplasticized PVM/MA-169 films. Key: Time of preconditioning at 50% R.H. and 40°, ●, 0 hr.; ○, 48 hr.; ■, 96 hr.*

The addition of triacetin to the 169 films resulted in a 25% decrease in the zero-order water vapor transmission rate as compared with the unplasticized films using identical conditions. Methylcellulose 60 HG-50 cps. films were used for comparative purposes. The water vapor transmission rate for unplasticized films was found to be 4.51 mg. water/hr./0.1 mm. film thickness, or slightly higher than the fully hydrolyzed PVM/MA-169 unmodified films.

In Vitro Release From Coated Tablets—Applied films of PVM/MA-169–triacetin were found to exhibit solubility and release characteristics which were dependent on the anhydride:acid ratio of the polymer. Pretreatment storage time at controlled temperature and humidity conditions of 40° and 50% R.H. increased film solubility and the subsequent tracer dye release rates (Figs. 4 and 5). Standard convex 1.12-cm. (0.44-in.) tablets (Fig. 4) and 0.65-cm. (0.25-

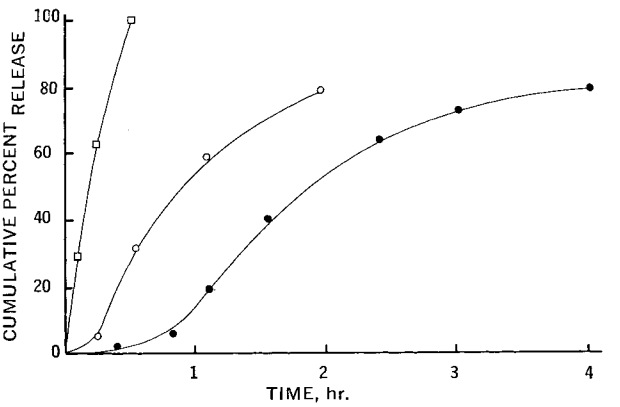


Figure 4—In vitro *release patterns of 1.12-cm. (0.44-in.) tablets coated with PVM/MA-169–triacetin (8:5), as influenced by preconditioning time at 50% R.H. and 40°. Key: ●, 48 hr.; ○, 96 hr.; □, noncoated tablets.*

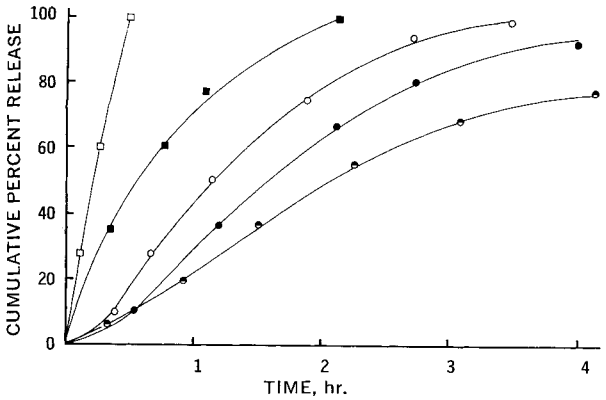


Figure 5—In vitro *release patterns of 0.62-cm. (0.25-in.) tablets coated with PVM/MA–169-triacetin (8:5), as influenced by preconditioning time at 50% R.H. and 40°. Key: ◓, 72 hr. (determination in pH 1.2 buffer); ●, 40 hr.; ○, 72 hr.; ■, 144 hr.; □, noncoated tablets.*

in.) modified ball tablets (Fig. 5) were film-coated with 45–50 mg. and 8–10 mg. of film, respectively. Release patterns approached that of noncoated tablets as the pretreatment time was increased. The delay in release of tablets tested in buffer at pH 1.2 as compared to the same systems tested in water, was attributed to a lower degree of hydrogen ion dissociation which effectively reduced the solubility rate of the partially converted films. The pK_1' of the polyacid form of PVM/MA is 4.85 (3). Other lag times in release patterns were apparently due to insufficient anhydride hydrolysis due to shorter pretreatment times. Lag times were reduced as the preconditioning time increased.

It was thus demonstrated that the hydrophobic polymer (PVM/MA-169) could be applied to tablets from organic solvents and transformed to water-soluble films by mild temperature-humidity pretreatment to product *in vitro* release characteristics approaching that of noncoated tablets.

In Vivo Tablet Disintegration—*In vivo* disintegration times of barium sulfate tablets coated with PVM/MA–169-triacetin systems were also observed to be strongly dependent on the chemical form of the polymer. Film-coated tablets which were not preconditioned but which were allowed to remain in the maximum anhydride state, disintegrated outside of the stomach within 3–4 hr. after administration. Disintegration occurred in the small intestines in each of the three subjects studied. A representative X-ray photograph is shown in Fig. 6. Though not yet fully substantiated by exhaustive testing, these results suggest a mechanism for enteric release based on the rate of *in vivo* hydrolysis and subsequent film solubilization.

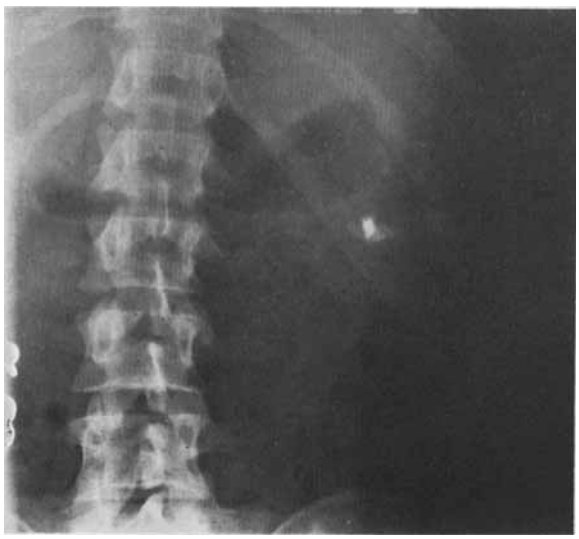


Figure 6—In vivo *radiographic illustration of the disintegration of a nonpreconditioned PVM/MA–169-triacetin-coated tablet. Location: jejunum; time: 3.5 hr. after administration.*

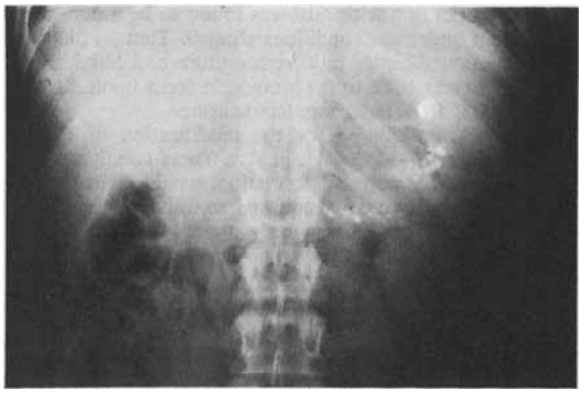


Figure 7—In vivo *radiographic illustration of the disintegration of noncoated control tablets. Location: stomach; time: 10 min. (upper tablet) and 30 min. (lower granules) after administration.*

Enteric effects of PVM/MA–169-triacetin films were eliminated after coated tablets had been preconditioned for 144 hr. at 50% and 40°. These tablets were shown to disintegrate in the stomach (jejunum in one case) within approximately 30–45 min. Noncoated control tablets disintegrated in 10–30 min. following ingestion; indicating that pretreated films impeded tablet disintegration for only 15–30 min. Figures 7 and 8 show the location of noncoated and coated tablet disintegration, respectively.

DISCUSSION

Chemical modification of PVM/MA in the solid state, as a result of controlled temperature and humidity treatment, produced marked effects on the physical film properties. As the duration of film treatment was increased, film solubility in aqueous media increased along with a rise in the rate of water vapor transmission. The polyanhydride form of PVM/MA is soluble in common organic solvents but is insoluble in aqueous media, while the polyacid form, insoluble in common organic solvents, is readily dissolved by aqueous media. Therefore, in order to produce PVM/MA film-coated drug products, designed for rapid release, it was necessary to modify the films by increasing their polarity after conventional deposition from an organic solvent. As was shown, only partial polyacid formation was needed to promote the desired film dissolution and drug release times. Chemical conversion of PVM/MA

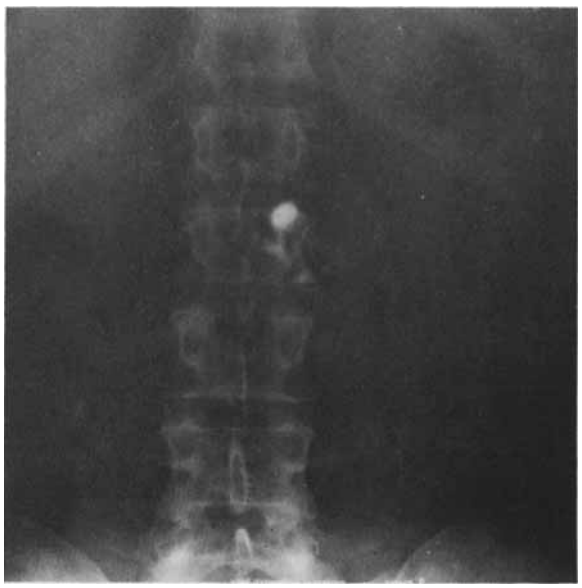


Figure 8—In vivo *radiographic illustration of the disintegration of a preconditioned PVM/MA–169-triacetin-coated tablet. Location: stomach; time: 30 min. after administration.*

films to the partial polyacid form was found to be a nonreversible transformation under the conditions studied. That is, films which were preconditioned under mild temperature and humidity treatment did not revert back to the anhydride form upon storage for 12 months at 0% R.H. and room temperature.

Pretreatment conditioning for the modification of PVM/MA films ranged from 30–50% R.H. at 40°. These conditions, during the time required for polyacid formation, would seem to be relatively mild with respect to moisture sensitive drugs. Free-film absorption studies showed that only about 4–6% moisture was absorbed based on initial film weights. As shown in studies on water vapor transmission, the rate of permeation would be lowest during the time when films are being chemically modified to produce water-soluble films. The time requirement for film modification would be expected to decrease as the temperature and humidity conditions are increased. Therefore, depending on the moisture sensitivity of the coated drug, chemical (film) conversion could be completed in short pretreatment storage times.

Complete conversion of the polyanhydride to acid was not demonstrated under the pretreatment conditions used in this study. Apparently, aqueous vapor tension was not adequate to complete this conversion in the solid state. It was hypothesized that films exposed to a given set of temperature and humidity conditions may undergo anhydride-acid conversion at the surface only to form a layer of the polyacid. This form would be readily capable of hydrogen bonding. Thus further moisture absorption would be preferentially bonded to the polyacid surface rather than penetrate this layer to cleave more of the polyanhydride. Imposing a water vapor gradient across polyanhydride films effectively allowed for moisture penetration resulting in chemical conversion to the polyacid. This conversion was reflected in a gradual increase in transmission rate until an apparent equilibrium was established and the water vapor transmission rate became constant. Unfortunately, films used in this study could not be accurately assessed for the percent anhydride to acid conversion at equilibrium due to the unexposed perimeter held between the cell gaskets. It was estimated that between 50–75% of the anhydride units were converted to the acid form during the water vapor transmission analysis due to the high aqueous tension and vapor pressure gradient.

In vitro and *in vivo* release studies from film-coated tablets as well as studies on free-film dissolution, illustrated that only partial polyanhydride preconversion was necessary to produce film dissolution and rapid release. Unmodified, free, and applied PVM/MA films which were maintained at the maximum anhydride content were shown to possess reliable enteric release in the human subjects studied. *In vivo*, enteric release would seem to be mainly a function of the exposure to gastrointestinal moisture for a time sufficient to cleave and convert the polyanhydride. However, film solubility is also affected by pH, but this effect would appear to be secondary in significance.

PVM/MA–triacetin systems offer notable advantages as new film-coating agents. Among these are the simplicity of solution preparation, the relative ease of application, and the hard, glossy mar-resistant films which are formed. Film conditioning to yield water-soluble films, did not affect physical appearance. With free-films however, it was noted that following the preconditioning, the increase in film polarity caused a slight increase in moist tack and slight decrease in plasticity. Spray coating with the two molecular weight grades of PVM/MA revealed that 4–8% w/v film solutions of either could be applied to tablets using the conditions described. Neither grade could be effectively applied in the absence of triacetin due to the inherent film brittleness resulting in coat peeling and chipping as a result of attrition and tablet-tablet adhesion. The inclusion of triacetin effectively reduced this tendency in the high molecular weight grade. Thus, film coating could be carried out with relative ease. The prominent, significant difference between the low and high molecular weight grades appeared to be the high wet tack associated with the low molecular weight grade which made coating with this polymer very difficult.

SUMMARY

PVM/MA film systems were chemically modified in the solid state by mild humidity conditioning to produce water-soluble films. *In vitro* tests on free and applied films illustrated solubility and release dependency on the polyanhydride–polyacid ratio, *i.e.*, the duration of moisture conditioning. *In vivo* studies indicated that such films can be classified as soluble when properly preconditioned. In the absence of the preconditioning procedure, film systems were shown to possess enteric properties which would be mainly dependent on film exposure time to body moisture.

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