Evaluation of Polymeric Materials II

Screening of Selected Vinyls and Acrylates as Prolonged-Action Coatings

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Acrylic and vinyl polymers, copolymers, and derivatives were evaluated as potential sustained-action coatings. Based on a screening of films of the polymeric materials for solubility characteristics, free film formation, and drug permeability, the *n*-butyl half ester of poly(methyl vinyl ether)/maleic anhydride offered the most *in vitro* promise of controlling drug release. The *n*-butyl half ester had no cumulative toxic effects based on a short-term feeding study.

IN THE SELECTION of polymeric films for application as protective, enteric, or sustained-release coatings to solid pharmaceutical dosage forms, the solubility, film formation, drug permeability, and toxicity of the coating materials must be considered.

In the past the usual method of evaluation entailed the application of the new coating agent directly to tablets, pills, etc., and the testing of disintegration rates. However this approach was very time consuming, especially when many substances were to be tested, and the method provided only limited information with which to interpret and analyze results. In 1953, Antonides (1) developed a test procedure for screening film-forming materials using microscope slides as a coating surface. Kanig and Goodman (2) and Munden, *et al.* (3), have evaluated several chemical and physical properties of polymers using the free polymer films as the test samples. These studies of film evaluation were not directed toward sustained-release products.

EXPERIMENTAL

Preparation of Polymer Derivatives.—In addition to the commercially available polymers studied in this project, several derivatives were prepared to produce polymeric materials with solubility properties more nearly approaching that desired in a prolonged-action coating (insoluble or slowly soluble in gastric media and slowly soluble in intestinal media). The polymers screened in this study are listed in Table I and were selected for investigation based on their reported low toxicity and solubility characteristics.

Of the polymers studied, poly(methyl vinyl ether)/maleic anhydride or PVM/MA was unique in the number of derivatives which were available or could be prepared from it. The derivatives commercially available or available as experimental chemicals were the methyl, ethyl, and 2-ethylhexyl half or partial esters of PVM/MA. In addition, the *n*-butyl and isobutyl half esters of PVM/MA were synthesized, which provided a series of derivatives that decreased in solubility with an increase in the degree of esterification or with an increase in the length of the substituted aliphatic group.

The *n*-butyl half ester was prepared by slurrying 100 Gm. of Gantrez AN119 in 500 ml. of *n*-butyl alcohol in a three-neck standard taper round-bottom flask, fitted with an air mixer, thermometer, and a reflux column. The mixture was heated between 107 and 115° with the aid of a heating mantle. After 23 hours of refluxing, the polymer was precipitated by pouring the alcoholic solution of the half ester into water, and allowing it to stand until the alcohol was substantially removed by diffusion into the water. The half ester was then filtered off, air-dried, cut into pieces, additionally air-dried, recut, and finally vacuum dried at 60° and 65 mm. Hg.

The isobutyl half ester was prepared by placing 200 Gm. of Gantrez AN139 in a three-neck flask, as previously described, with 860 Gm. of isobutyl alcohol. The resulting mixture was heated between 85 and 90° for 26 hours. Precipitation, filtration, and drying of the half ester were accomplished in the same manner described for the *n*-butyl ester.

The degree of esterification of the poly(methyl vinyl ether)/maleic acid esters was calculated by the modified acid value procedure of the manufacturer of the anhydride. The acid value determinations agreed within 5% of the theoretical values supplied by the manufacturer for the *n*-butyl and isobutyl half ester products. The two grades of anhydride (Gantrez AN119 and 139) used in the half ester syntheses differ only in molecular weight. The choice of the polymer anhydride grade used in the synthesis of the half esters is dependent on the viscosity of the formed half ester in its alcoholic solution. The highest molecular weight grade of PVM/MA did not lend itself to the synthesis method for the half esters defined above.

Film Preparation and Evaluation.—Film samples of the polymers listed in Table I were made by preparing solutions of the polymers in appropriate solvent systems (Table II), with the films then being cast from these solutions by the mercury substrate technique (3). According to this method, the polymer solution was poured on a layer of mercury contained in a Petri dish, after which the film was allowed to air-dry. Film thickness was controlled by diluting the stock polymer solutions (Table II) with acetone, as necessary, according to solution viscosity, to produce dry films having a thickness of 0.003 to 0.006 in.

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TABLE I.—TABULATION OF POLYMERS SCREENED

Commercial Name	Chemical Designation	Physical Form
Gantrez AN119 & 139[a,b]	Poly(methyl vinyl ether)/maleic anhydride	Powder
PVM/MA methyl half[b] ester	Poly(methyl vinyl ether)/maleic acid methyl half ester	Powder
PVM/MA ethyl half[b] ester	Poly(methyl vinyl ether)/maleic acid ethyl half ester	Powder
PVM/MA 2-ethylhexyl[b] half ester	Poly(methyl vinyl ether)/maleic acid 2-ethylhexyl partial ester	Powder
PVM/MA isobutyl half ester	Poly(methyl vinyl ether)/maleic acid isobutyl half ester	Powder
PVM/MA *n*-butyl half ester	Poly(methyl vinyl ether)/maleic acid *n*-butyl half ester	Powder
Butvar B-90[c]	Polyvinyl butyral	Powder
Lemac 541-20[d]	Vinyl acetate copolymer—1	Beads
Neovac V27N[e]	Vinyl acetate copolymer—2	Emulsion
Polectron 130[b]	Vinyl pyrrolidone/ethyl acrylate copolymer	Emulsion
Neocryl BT-4[e]	Acrylic copolymer	Emulsion
Acrysol ASE-75[f]	Acrylic/methacrylic copolymer	Emulsion
Carboset 511[g]	Acrylic resin	Solution
Pentalyn 255[h]	Polymeric resin	Solid

[a] Hereafter referred to as PVM/MA. [b] General Aniline and Film Corp., New York, N. Y. [c] Shawinigan Resins Corp., Springfield, Mass. [d] Borden Chemical Co., New York, N. Y. [e] Polyvinyl Chemicals Inc., Peabody, Mass. [f] Rohm and Haas Co., Philadelphia, Pa. [g] B. F. Goodrich Chemical Co., Cleveland, Ohio. [h] Hercules Powder Co., Wilmington, Del.

TABLE II.—POLYMER SOLUTIONS EMPLOYED IN PRELIMINARY SCREENING TESTS

Polymer, Chemical Designation	Polymer Wt., Gm.	Acetone, ml.	Ethyl Alcohol, ml.	Butyl Acetate, ml.	Butyl Alcohol, ml.
PVM/MA	10	50	50	..	..
PVM/MA esters	10	50	50	..	..
Polyvinyl butyral	10	50	..	25	25
Vinyl acetate copolymer 1	10	50	..	25	25
Vinyl acetate copolymer 2[a]	..	..	..	..	..
Vinyl pyrrolidone/ethyl acrylate copolymer[a]	..	..	..		
Acrylic copolymer[b]	10	50	50	..	..
Acrylic/methacrylic copolymer[b]	10	50	50	..	..
Acrylic resin[a]	..	..	..	..	..

[a] Films were cast from the polymer solution or emulsion as commercially supplied. [b] Polymer solids were recovered by dilution of the polymer emulsion with water, followed by the addition of 1*N* sodium hydroxide until solution of the polymer occurred. Precipitation of the polymer from solution was then accomplished by the addition of 1*N* sulfuric acid.

The removal of the unplasticized polymeric films as a complete sheet was the criterion for free film formation. Film strips were cut from the film disks using a microscope slide as a template Film solubility was evaluated by visual observation using two such film strips of each polymer. One sample was placed in 50 ml. of simulated gastric fluid at 38° and was agitated at low speed with a magnetic stirrer for a maximum of 2 hours or until dissolution of the film occurred. This procedure was repeated in intestinal fluid using the other film strip. The simulated gastric and intestinal fluids were prepared according to the following formulas (4):

GASTRIC FLUID	
Sodium chloride	2.0
Pepsin	3.2
Hydrochloric acid	2.5
Distilled water, *q.s.*	1000.0

INTESTINAL FLUID	
Pancreatin	10.0
Ox bile extract	4.0
Potassium biphosphate, 0.2*M*	250.0
Sodium hydroxide, 0.2*M*	205.0
Distilled water, *q.s.*	1000.0

Film Permeability and Drug Binding Studies.—To determine the permeability of the films to drug, a small dialysis cell (5) was employed with 26-mm. diameter samples of the polymer films being used as the dialyzing membrane. Four milliliters of a stock solution containing 20 mg./ml. of *d*-amphetamine sulfate was pipeted into one side of the cell through the side arm. Buffer solutions of pH 2.4 and 6.8 were prepared according to the U.S.P. XVI, and were used in addition to the simulated gastric and intestinal fluids previously described. Into the other side of the dialysis cell 4 ml. of gastric fluid was pipeted through the side arm. The side arms were then sealed, the dialysis cell was placed in a rocker device in a water bath at 37 ± 2° for 0.5 hour, and the amount of drug which had permeated the membrane at that time was determined. The cell was then refilled on the test solution side (opposite the drug solution side) with another 4 ml. of gastric fluid, dialyzed as previously described for 1.5 hours, and the dialyzate determined. Following this determination, pH 2.4 buffer, pH 6.8 buffer, and artificial intestinal fluid were placed in turn in the test solution side of the cell, and the dialyzate determined at the time intervals indicated in Table IV.

The same dialysis cell was used in the study of drug binding to the polymeric materials, but in this study the polymer film sample used in the earlier study was replaced with Visking Nojax casing[1] as the dialysis membrane. Four milliliters of water was placed on the fluid side or test solution side of the cell and 4.0 ml. of a solution of 20 mg./ml. of *d*-amphetamine sulfate plus polymer solution or dispersion resulting from the dissolution or dispersion of a 26-mm. film disk was placed on the drug side of the cell. The dialysis cell was rotated for 24 hours in the water bath, the amount of drug in solu-

[1] Visking Co., Chicago, Ill.

tion on both sides of the cell was determined, and the amount of polymer drug binding was calculated.

Short-Term Feeding Study of PVM/MA n-Butyl Half Ester.—In an effort to obtain the LD_{50} for the *n*-butyl half ester of PVM/MA, the most promising polymer studied based on preliminary screening, dosages of 5, 10, 15, and 20 Gm./Kg. of animal weight were selected for administration based on the reported LD_{50} of the parent polymer in rats of 8 Gm./Kg. (6). However, due to the low density of the polymer material and the large volume to be fed, these doses could not be successfully administered in any form. For this reason a short-term feeding study was undertaken.

Two groups of six female Holtzman rats were used in this study for preliminary determination of the short-term toxic feeding effects, if any, of the polymer half ester based on gross changes in animal well being and on liver weights. One group of six animals was observed as the test group and the other as the control group. The test animals received daily doses of 5 Gm. of polymer per kilogram of body weight mixed with 15 Gm. of ground food. The polymer was milled to 40-mesh to insure a uniform mixture. The control animals received a corresponding quantity of lactose mixed with their food. All animals were housed in individual cages and received water *ad libitum*. Prior to daily dosing, each animal was weighed and any change in general animal appearance was noted. This procedure was followed until the tenth day when the animals were sacrificed and the livers removed. The liver weights were determined on a wet and dry basis and were converted to grams of liver per 100 Gm. of rat weight. The average dry liver weight for each group of six animals was calculated and compared to ascertain whether any of the polymer had accumulated in the liver.

RESULTS AND DISCUSSION

Free Film Formation and Film Solubility.—Utilizing the 10% solutions described in Table II, unplasticized films were cast as previously described, and on drying were evaluated for free film formation and solubility. These results are shown in Table III. The polymeric resin and the acrylic resin were immediately eliminated from further study since free films could not be obtained. The vinyl pyrrolidone/ethyl acrylate, acrylic copolymer, and polyvinyl butyral did not appear to demonstrate adequate solubility and were eliminated. The vinyl acetate copolymers, PVM/MA, and the PVM/MA methyl and ethyl half esters showed good promise as enteric coatings, but doubtful direct application as prolonged-action coatings. On the basis of solubility in simulated gastric and intestinal fluids, the acrylic/methacrylic copolymer film and the PVM/MA butyl and ethylhexyl films demonstrated the most promise and were further investigated.

The solubilities of the PVM/MA half ester series varied considerably and ranged from the methyl and ethyl half esters, which were quite soluble at low pH values, to the ethyl-hexyl and butyl half esters, which were insoluble to slightly soluble, until the dissolution media became slightly alkaline. The heptyl half ester of PVM/MA is reported to be soluble only under very alkaline conditions, and half esters synthesized with alcohols containing more than seven straight chain carbon atoms are reported insoluble (7). Lappas and McKeehan (8) in a preliminary communication also report that variations in ester chain length affect the dissolution pH of PVM/MA esters. Film dissolution in gastric and intestinal media is one indicator of the potential of a polymer film as a sustained-release coating, but it is not the absolute or even necessarily an accurate measure of the polymer's potential in this regard should the polymer film prove to be permeable to drug molecules.

Film Plasticization.—The ultimate objective of this project was to produce a highly plasticized flexible film which would remain intact about a coated granule after compression in a tablet matrix. A high degree of film plasticization was therefore important. The four polymers showing the most promise as a result of the unplasticized film solubility study (the two butyl and the ethylhexyl esters of PVM/MA and the acrylic/methacrylic copolymer) were plasticized with a number of agents and were reappraised for solubility characteristics. The water insoluble plasticizers studied included ricinoleic and linoleic acids, castor oil, dibutyl and diethylphthalate, and sorbitan monooleate. Diethylphthalate and sorbitan monooleate were the most effective plasticizers of the PVM/MA ester films. The most flexible films, of the films which retained their integrity, resulted from the addition of 60% w/w of

TABLE III.—SOLUBILITY AND FILM FORMATION OF SELECTED POLYMERS

Polymer, Chemical Designation	Free Film Formation	Solubility	
		Gastric Fluid	Intestinal Fluid
PVM/MA 119 and 139	Yes	P. Sol.[a]	Sol.[b] (5 min.)
PVM/MA methyl half ester	Yes	P. Sol.	Sol. (15 min.)
PVM/MA ethyl half ester	Yes	P. Sol.	Sol. (30 min.)
PVM/MA 2-ethylhexyl half ester	Yes	Insol.	P. Sol.
PVM/MA isobutyl half ester	Yes	Sl. Sol.[c]	P. Sol.
PVM/MA *n*-butyl half ester	Yes	Sl. Sol.	P. Sol.
Polyvinyl butyral	Yes	Insol.	Insol.
Vinyl acetate copolymer 1	Yes	Insol.	Sol. (15 min.)
Vinyl acetate copolymer 2	Yes	Insol.	[d]
Vinyl pyrrolidone/ethyl acrylate copolymer	Yes	Insol.	Insol.
Acrylic copolymer	Yes	Insol.	[d]
Acrylic/methacrylic copolymer	Yes	Sl. Sol.	Sol. (1 hr.)
Acrylic resin	No	...	...
Polymeric resin	No	...	...

[a] Partially soluble—according to weight loss on a dry basis, after 2 hours in gastric or intestinal media, 10 to 50% of the polymer dissolved. [b] Soluble—50% or more of the polymer dissolved (dry weight basis). [c] Slightly soluble—less than 10% of the polymer dissolved (dry weight basis) after 2 hours. [d] No visible solubility, but the film fell apart on handling.

TABLE IV.—FILM PERMEABILITY AND DRUG BINDING AT DECREASING HYDROGEN ION CONCENTRATIONS

Time, hr.	Permeable, %	Bound, %	pH
	PVM/MA ISOBUTYL HALF ESTER		
0.5	0.00	0.00	1.2
1.5	0.00	0.00	1.2
2.5	0.00	0.00	2.4
4.5	0.00	0.00	6.8
6.0	Dissolved	10.8[a]	7.6
		20.5[b]	
	PVM/MA *n*-BUTYL HALF ESTER		
0.5	0.00	0.00	1.2
1.5	0.00	0.00	1.2
2.5	0.00	0.00	2.4
4.5	0.00	0.00	6.8
6.0	Dissolved	0.00[a]	7.6
		6.6[b]	
	ACRYLATE/METHACRYLATE COPOLYMER		
0.5	0.00	0.00	1.2
1.5	0.00	0.00	1.2
2.5	0.00	0.00	2.4
4.5	0.00	0.00	6.8
6.0	0.00	0.00	7.6

[a] Per cent of drug binding as indicated by equilibrium dialysis. [b] Per cent of drug binding based on filterable drug in solution after dissolution of the polymer film in the permeability study.

sorbitan monooleate and 30% w/w of diethylphthalate, based on polymer weight. This system necessitated a change in the solvent system, from the alcohol-acetone solvent previously used for the polymers alone, to a system of equal parts of acetone and ethyl acetate. The alcoholic solvent system did not adequately carry the phthalate plasticizer, which came out of solution before the polymer to form an oily or greasy film. The acetone-ethyl acetate solvent system containing 5% PVM/MA butyl or ethylhexyl ester, 3% sorbitan monooleate and 1.5% diethylphthalate, produced a series of films which were completely clear, very flexible, and only slightly greasy to nongreasy. The general solubility characteristics of the plasticized films were identical to the unplasticized films (Table III); insoluble to slightly soluble in gastric fluid and partially soluble in intestinal fluid.

The acrylic/methacrylic copolymer was plasticized with 40% w/w of sorbitan monooleate and was dissolved in a solvent system of 3 parts of acetone to 1 part of alcohol U.S.P.

Film Permeability to d-Amphetamine Sulfate.—Films ranging in dry thickness from 0.003 to 0.006 in. were cast from 5% solutions of the *n*-butyl and isobutyl half esters of PVM/MA and the acrylic/methacrylic copolymer in an acetone-ethanol (3:1) solvent system. One per cent by volume of sorbitan monooleate plasticizer was added to each solution. The results of this study (Table IV) indicated that all three films were impermeable to drug at all pH values studied.

Polymer-Drug Binding.—Drug binding to the polymers was determined by an equilibrium dialysis method which involved the dialysis of colloidal solutions or dispersions of polymer and drug across a semipermeable membrane that permitted the drug free passage while restricting the polymers. The concentration of drug which had permeated the membrane after 24 hours was compared to the theoretical concentration of drug which should have been present based on dialysis of the drug alone (about 8% of the *d*-amphetamine sulfate in the concentration studied was bound to the Nojax membrane). The per cent of bound drug was then calculated as

$$\% \text{ Bound} = \frac{\text{Theoretical drug concn. at equilibrium} - \text{drug concn. found}}{\text{Theoretical drug concn.}}.$$

According to this method only the isobutyl half ester bound the drug, and then at only one pH level and to an extent of only 10.8% (Table IV).

Drug binding was also calculated from analysis of the permeability data, by assaying total drug in solution in the cell after "dissolution" of the polymer film "membranes." According to this method 20.5% of drug was bound to the isobutyl half ester and 6.6% of drug to the *n*-butyl half ester colloidal polymer dispersion (Table IV).

At this point in the study, of the three polymers remaining, the *n*-butyl half ester of PVM/MA appeared to be the most promising. Its solubility characteristics were superior to the acrylic/methacrylic copolymer and were equal to the isobutyl half ester, while the *n*-butyl ester produced less drug binding than the isobutyl derivative. The acrylic/methacrylic copolymer, due to its extremely high molecular weight, produced solutions which were too viscous for spray application in concentrations above about 1.5%.

Short-Term Feeding Study of PVM/MA n-Butyl Half Ester.—The results of the feeding study are shown in Table V. From a comparison of the mean dry liver weight for each group of animals (variation in average group weights was less than 10 mg.), it can be concluded that the polymer did not accumulate in the liver. No gross physical changes were observed in the animals which were fed polymer.

SUMMARY

Fourteen acrylic and vinyl polymers and derivatives were systematically studied for their potential as sustained-action coatings based on their film forming characteristics, film solubility, flexibility, permeability, and drug binding properties. With-

TABLE V.—RAT LIVER WEIGHTS AFTER SUB-ACUTE DOSING WITH *n*-BUTYL HALF ESTER OF PVM/MA

Final Rat Wt., Gm.	Wet Liver, Gm.	Gm. Wet Wt./100 Gm. Rat	Dry Liver, Gm.	Gm. Dry Wt./100 Gm. Rat
	CONTROLS[a]			
212	7.095	3.347	2.105	0.993
218	7.715	3.535	2.300	1.055
204	7.460	3.657	2.300	1.128
226	8.615	3.812	2.565	1.135
236	8.295	3.515	2.419	1.025
$\bar{X}$	7.836	3.573	2.338	1.067
	POLYMER FED ANIMALS			
232	9.115	3.929	2.666	1.149
224	8.175	3.650	2.487	1.110
209	7.100	3.397	2.078	0.994
223	7.285	3.267	2.106	0.944
210	8.150	3.889	2.415	1.150
210	7.765	3.697	2.315	1.102
$\bar{X}$	7.931	3.637	2.345	1.075

[a] One animal died.

out exception, the carboxylic acid polymers (acrylic and maleic acids), demonstrated the most potential as prolonged-action coatings based on solubility in simulated gastric and intestinal fluids. Solubility of a maleic acid polymer varied in aqueous media at a range of pH levels with the degree of esterification of the polymer and with the ester chain length. Butyl half esters of the maleic acid polymer demonstrated good potential solubility properties for a prolonged-action coating. The intact films studied were impermeable to drug in solution. Polymer-drug binding was significant with only one of the three final polymers studied. Poly(methyl vinyl ether)/maleic anhydride *n*-butyl half ester demonstrated the best *in vitro* potential as a sustained-action coating. The polymer showed no toxic effects in a preliminary short-term feeding study.

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One-Phase Solvent Systems for Paper Chromatography

Mixtures of *n*-Butanol, Acetic Acid, and Water

By T. J. BETTS

Whenever possible, one-phase solvent systems, made up of the minimum number of constituents, should be used for paper chromatography. Two-phase systems should be replaced by their equivalent one-phase mixtures giving stability, accuracy, and simplicity. A "phase diagram" of the type shown is required for all commonly used three-component paper chromatographic solvent mixtures to facilitate the design of one-phase solvents for particular problems. Mixtures of *n*-butanol, glacial acetic acid, and water were studied with this concept in mind.

SOLVENT MIXTURES used for paper chromatography may consist of one or two phases. The two-phase mixtures have been traditionally used for paper chromatography, and may themselves be divided into *direct phase* mixtures (1) in which the phase flowing over the paper is an organic substance such as *n*-butanol or phenol which has been saturated with a more polar liquid such as water, and *reversed phase* mixtures (2) in which the mobile phase is the more polar of the two. *Zaffaroni type* paper chromatography is an example of the direct phase method in which the paper is impregnated with a relatively nonvolatile stationary phase such as formamide, the mobile phase being a less polar liquid such as benzene (3). The paper may also be impregnated for reversed-phase chromatography, being made hydrophobic with a grease.

With the Zaffaroni method, the results obtained obviously depend greatly on partition effects between the two phases. The term "partition" has been almost automatically associated with paper chromatography since the original paper of Consden *et al.* in 1944 (4), but some workers consider that in some cases other phenomena are involved such as adsorption (5,6) or ion exchange (7,8). Considering, for example, that tannins can be resolved with pure water as solvent (9), or hydroxyanthraquinones with pure toluene (10), the mechanism of partition is unlikely to be an explanation for all separations obtained by paper chromatography, even allowing for the formation of cellulose-water complexes (11).

The preoccupation with partition, however, has resulted in the use of many two-phase solvent systems; the conception apparently was that this would insure that partition takes place. The use of a two-phase system means that the composition of the mobile phase is not known, so that it cannot be varied in a controlled manner. In 1960, Smith (12) advocated the use of "monophasic" solvents in place of two-phase mixtures because "emulsions sometimes formed (during their preparation) and . . . a drop in

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