Polymer–Drug Interacted Systems in the Physicochemical Design of Pharmaceutical Dosage Forms I

Drug Salts with PVM/MA and with a PVM/MA Hemi-Ester

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The applicability of a polymer-drug interacted system in the physicochemical design of pharmaceutical dosage forms has been investigated. Salts of poly(methyl vinyl ether/maleic anhydride) and methapyrilene base were prepared. *In vitro* release patterns were determined by an equilibrium dialysis procedure. Dialytic release rates of the polymer-drug salt in solution demonstrated no appreciable difference in drug availability with respect to the free drug or its hydrochloride salt. *In vitro* dissolution rates of the polymer-drug salt in solid form showed similar results. Polymer-drug salts formed with the 1,12-dihydroxyoctadecane hemi-ester of poly(methyl vinyl ether/maleic anhydride) exhibited prolongation of the release of the drug from granular and tableted forms *in vitro*.

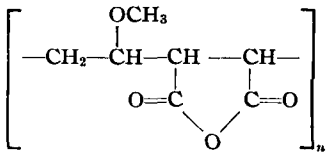
SOLUBILIZATION of various medicinal compounds by interaction with macromolecules has been extensively investigated. Such systems are usually produced by donor-acceptor mechanisms or hydrogen bonding. Unfortunately, few of these investigations have yielded products of practical value in the design of pharmaceutical dosage forms due to the low ratio of active ingredient incorporated in the system. In addition, recovery of these complexes from the reaction media is difficult or impossible in many instances.

Formation of polymer-drug salts provides a practical basis for the investigation of the physicochemical design of pharmaceutical dosage forms and subsequent biopharmaceutic evaluations (1). Such salts have been shown to alter the biologic distribution of the drug moiety as well as prolong release when administered parenterally (2). A recent patent (3), describes a method for preparing sustained-release dosage forms by the formation of polymer-drug salts. The product is based on the interaction of a therapeutically active amine with a crosslinked copolymer containing reactive carboxyl groups. Srinivas (4) studied the reaction between carboxyl-containing polymers and aliphatic and aromatic amines, and amine drug bases. Potentiometric and viscometric data indicated salt formation, with the polymer-drug salts exhibiting controlled release properties. The stability of thiamine is reported to have been enhanced by salt formation of the free base with carbonic and sulfonic acid derivatives of an unsaturated polymerizable material (5).

This investigation was undertaken to further study the application of polymer-drug mono- and di-salts of a dicarboxylic acid copolymer and of drug salts of a hemi-ester of the copolymer, in the physicochemical design of pharmaceutical dosage forms.

EXPERIMENTAL

Materials and Equipment—Poly (methyl vinyl ether/maleic anhydride),[1] (PVM/MA) (I) (6), is a free-flowing polymeric powder whose structural formula may be represented as shown below.



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PVM/MA is a linear polymeric anhydride which is soluble over a wide pH range. Good stability is exhibited in both acid and alkaline solutions. The pH of a 5% solution of the polymer is approximately 2.0. An aqueous solution of this concentration

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[1] Gantrez AN-169. Supplied through the courtesy of General Aniline & Film Corporation, New York, N. Y.

exhibits a Brookfield viscosity of 200 cps. The polymer is purported to be relatively nontoxic (6).

Methapyrilene, which was prepared from the commercially available hydrochloride salt[2] (USP), was selected as the model amine drug base for use in this investigation. The drug base has a molecular weight of 261.38 and occurs as a viscous oil, slightly yellow in color. The uncharged base has a pKb of 5.15, while the conjugate acid exhibits a pKa of 8.85 (7).

1,12-Dihydroxyoctadecane[3] (DOD) was used as the hydroxyl-containing moiety in the esterification of PVM/MA. This compound occurs as a white waxy solid which melts at 61 to 65°.[4]

Esterification reactions were carried out in the open-bottom portion of a 500-ml. split reaction flask[5] fitted with a heating mantle. The use of this apparatus permitted the easy retrieval of the esterified products which would be difficult to remove from conventional reaction flasks.

A Carver[6] laboratory press was used in the preparation of tablets employed in this investigation. All tablets were prepared with the use of 0.9-cm. (3/8-in.) standard cup punches. The tablets were compressed under a 5,000 lb. load, which was released immediately upon attaining that load.

Assay of Methapyrilene—Methapyrilene and its derivatives were assayed at 292.5 and 323.5 mμ[7] by a differential ultraviolet procedure. This assay employs the summation of absorbance maxima induced by a 3.2 unit pH differential, using buffer solutions of pH 7.4 and 10.6. The use of this assay procedure permitted the determination of unknown quantities of methapyrilene in the presence of other materials which would normally interfere with conventional ultraviolet spectrophotometric determinations.

Reactivity of PVM/MA—The reactivity of PVM/MA was evaluated by potentiometric titration in aqueous solution. Changes in the potential of the solution were monitored with the use of a research pH meter[8] equipped with standard glass indicator and calomel reference electrodes. PVM/MA was titrated with 0.1 *M* and 1 *M* sodium hydroxide and with methapyrilene base. Both the titration curves and their first derivative plots were constructed. End points were determined by evaluation of the first derivative plots.

Esterification of PVM/MA—Hemi-esters of PVM/MA and 1,12-dihydroxyoctadecane were prepared by melting the DOD in the open-bottom portion of the split reaction flask, and dispersing the PVM/MA powder in the melt. The temperature was then increased and the mixture was stirred. Esterification took place within 0.5 hr. as evidenced by solidification of the reaction mixture. The maximum temperature attained during the process was 120°. When the product had solidified, the heat was immediately removed. After cooling at room temperature, the ester was milled in a mortar and classified with the use of nested A.S.T.M. standard screens. All of the hemi-esters were prepared using excess quantities of DOD due to the fact that a stoichiometric amount of the DOD (1.33 g./g. of PVM/MA) proved to be an insufficient quantity in which to disperse the PVM/MA during the esterification reaction. The product was prepared in 2:1, 3:1, and 4:1 ratios.

Formation of Polymer-Drug Salts—Methapyrilene salts of PVM/MA were prepared in aqueous dispersions at 25° with agitation provided by a magnetic stirrer. Methapyrilene oil was weighed in a tared 250-ml. beaker and distilled water (100–150 ml.) added. The mixture was then stirred vigorously to disperse the oil (2–5 min.). PVM/MA was slowly added, by sprinkling it into the vortex created by the agitation. The solution was stirred at a moderate rate for 24–48 hr. to achieve salt formation (this length of time is necessary for complete hydrolysis of PVM/MA at room temperature). The amount of methapyrilene oil and PVM/MA employed for mono- or di-salt formation was calculated on a stoichiometric basis using the unit molecular weight (156) of PVM/MA. Salts remaining in solution (partial and mono-salts) were assayed directly, while the insoluble salts (di-salts) were filtered out and dried under vacuum at 25°. In the case of insoluble salts, the supernatant solution was also collected for assay.

Salts of methapyrilene with the PVM/MA-DOD hemi-esters were prepared as described above. Only mono-salts of PVM/MA could be prepared in the case of the hemi-esters since one of the carboxyl groups of PVM/MA was tied up by the ester group. Due to the low solubility in water of the hemi-esters, the salt formation reaction time of these systems was increased considerably. These systems were stirred in aqueous dispersion for 72–96 hr.

Dialysis Studies—Drug release patterns of methapyrilene in solution were determined by the use of an equilibrium dialysis procedure. Dialysis sacs[9] were prepared to contain 20 ml. of the drug or its salts in aqueous solution. The sacs were securely tied and checked for leaks before placing them in a 3-oz. powder jar containing 70 ml. of artificial gastric or intestinal fluid (without enzymes). The jar was then capped and sealed with a waterproof tape before placing it in a rotating water-bath apparatus maintained at 37 ± 1°. All samples evaluated in this manner were allowed to rotate for preselected time periods of 0.25, 0.5, 1, 2, 3, and 4 hr. The dialytic release patterns of base methapyrilene, methapyrilene hydrochloride, and a partial salt of methapyrilene with PVM/MA were determined by the use of this procedure.

Dissolution Rate Studies—Polymer-drug salts and drug salts of the PVM/MA-DOD hemi-ester which were prepared in solid form were evaluated for their release characteristics by a dissolution procedure. Samples of the salts were placed in previously tared 3-oz. powder jars and accurately weighed. Artificial gastrointestinal fluids were then pipeted into the jars which were subsequently capped and sealed in the manner employed in the dialysis procedure. Methapyrilene release by the dissolution method was studied for periods up to 3 hr. in artificial gastric fluid, and up to 8 hr. in artificial intestinal fluid (without enzymes). The release patterns of particulate materials were determined in

[2] Abbott Laboratories, North Chicago, Ill.
[3] K & K Laboratories, Inc., Plainview, N. Y.
[4] Determined on a hot plate melting point apparatus.
[5] Kontes Glass Company, Vineland, N. J.
[6] Fred S. Carver, Inc., Summit, N. J.
[7] Model DU spectrophotometer, Beckman Instrument Co., Fullerton, Calif.
Model 7403, Leeds and Northrup, Philadelphia, Pa.
[9] NoJax Casing, Size 30, Visking Company, Chicago, Ill.

50-ml. volumes of the gastrointestinal fluids and the release of tableted preparations in 70-ml. volumes. Assays were performed on the filtered fluids to determine drug concentrations following the various intervals in the water bath.

RESULTS AND DISCUSSION

Reactivity of PVM/MA—Titrations of PVM/MA in aqueous solution showed that the dicarboxylic acid hydrolysis product of the polymer exhibits both mono- and di-salt formation with sodium ions. Titrations of 100 and 150 mg. of PVM/MA in 150–200 ml. of distilled water were carried out using 0.1 *M* sodium hydroxide titrant. Analyses of the first derivative titration curves obtained showed that mono-salt formation occurred within 2.3% error relative to the calculated theoretical value based on the unit molecular weight of PVM/MA. Di-salt formation was not indicated with the use of the 0.1 *M* sodium hydroxide titrant, although the titrations were continued well beyond the theoretical di-salt end point. Titration of PVM/MA with 1 *M* sodium hydroxide titrant (Fig. 1) provided both mono- and di-salt formation. Analyses of the first derivative titration curves showed that the mono- and di-salt formation end points occurred within 0.6–4.8% error relative to the theoretical values. The ability of PVM/MA to react stoichiometrically in aqueous solution with sodium ions (Fig. 1), was taken as an indication of possible polymer–drug interaction capabilities with an amine drug base.

Esterification of PVM/MA—PVM/MA was shown to esterify within 0.5 hr. when dispersed in a melt of 1,12-dihydroxyoctadecane (DOD) and heated to 120°. The PVM/MA-DOD hemi-ester was found to be insoluble in artificial gastrointestinal fluids when prepared as described in the *Experimental* section. Swelling of the hemi-ester was observed in artificial intestinal fluid (without enzyme) at 25°, but was found to be negligible in distilled water and artificial gastric fluid (without enzyme). Increased DOD content of the product (*i.e.*, 3:1 and 4:1 ratios) reduced swelling dramatically in all three media. The 2:1 DOD-polymer material underwent a percent increase in volume due to swelling of about 15% in gastric fluid, 80% in intestinal fluid, and 25% in distilled water. The 3:1 DOD-polymer material underwent only a 10% swelling volume increase in water and intestinal fluid, and the 4:1 material did not swell appreciably in any of the three solvent media. The solid hemi-ester was observed to soften at 50–60° and begin to brown at 130°. The formation of the hemi-ester of PVM/MA with DOD was thought to be a method by which the solubility of the reactive PVM/MA could be reduced while retaining an anionic nucleophilic site potentially applicable to the formation of a polymer-drug salt with an amine drug base.

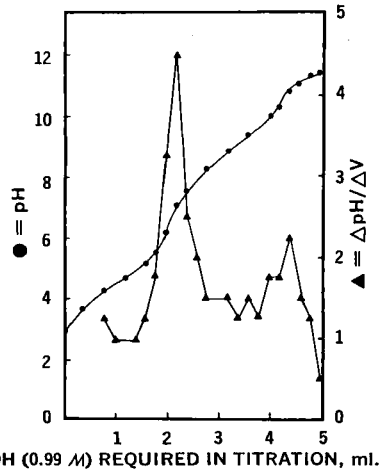

Fig. 1—Potentiometric titration of PVM/MA in aqueous solution.

Formation of Polymer-Drug Salts—The ability of PVM/MA to enter into the formation of a polymer–drug interacted system with an amine drug base was investigated using methapyrilene as the model drug. The formation of a PVM/MA-methapyrilene salt was shown by titrating the polymer in aqueous solution using methapyrilene base as the titrant. Solubilization of the base occurred in the aqueous PVM/MA solution as a result of mono-salt formation as indicated by the titration curve (Fig. 2). The titration of PVM/MA in aqueous solution produced mono-salt formation end points within 2.8% (Table I), of the stoichiometric value, indicating a constant w/w ratio of combination (Fig. 3). Methapyrilene titration of the polymer to the di-salt end point was not practical due to the low solubility of both the titrant and the titrate. While the titration curve (Fig. 2), did indicate a second end point, the first derivative peak was not considered valid in relation to the artifacts observed. A 1:1 mixture of dioxane and water was found to maintain the polymer-drug salt in solution but again the methapyrilene titration curve did not clearly discern the second end point.

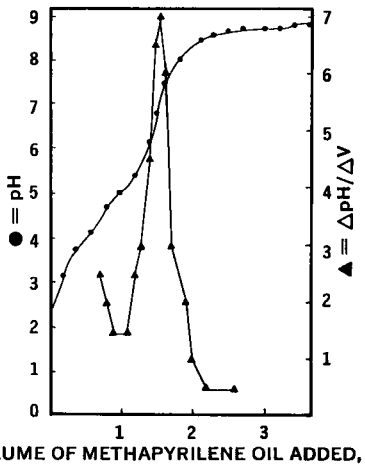

Fig. 2—Titration of PVM/MA in aqueous solution with methapyrilene base.

TABLE I—PVM/MA METHAPYRILENE BASE TITRATION DATA

Weight of Titrate, g.	ml. of Titrant	g. of Titrant	Calcd. Wt., g.	% Error
1.0019	1.530	1.6785	1.6780	0.03
0.7513	1.115	1.2233	1.2585	2.80
0.5010	0.775	0.8500	0.8390	1.31
0.2477	0.370	0.4060	0.4150	2.17

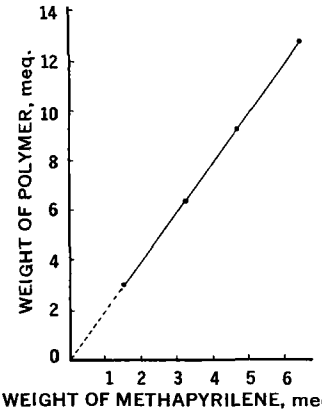

Fig. 3—Weight of PVM/MA versus *weight of methapyrilene base in formation of mono-salt.*

PVM/MA-methapyrilene salt formation was achieved by adding methapyrilene base to an aqueous solution of hydrolyzed PVM/MA in the titration procedure; however, it was found that salt formation was most conveniently accomplished by adding the PVM/MA powder to an aqueous dispersion of methapyrilene "oil." This procedure requires the gradual addition of the powdered polymer to the vortex of a vigorously agitated methapyrilene dispersion. By the use of this technique and with prolonged agitation of the system at 25°, stoichiometric quantities of the polymer were employed to produce partial, mono-, and di-salts of methapyrilene. Salts of methapyrilene and the PVM/MA-DOD hemi-ester were also produced in this manner as described in the *Experimental* section.

Evaluation of Polymer–Drug Interacted Systems—The availability of methapyrilene from the PVM/MA and PVM/MA-DOD hemi-ester salts was studied using the dissolution and dialysis procedures described previously.

A partial salt of PVM/MA and methapyrilene base was prepared by reacting 1 g. of the polymer with an equal weight of methapyrilene base. After stirring at 25° for 72 hr. the solution was filtered and diluted to 250 ml. in a volumetric flask. Assay of the solution indicated that the methapyrilene concentration was 3.9 mg./ml. This solution was dialyzed against the artificial gastrointestinal fluids and the availability of methapyrilene from the system was compared to the release patterns of the hydrochloride salt (Fig. 4) and the free base (Fig. 5), obtained in a like manner. The release pattern of the drug from the polymer salt did not differ substantially from that of the free base or the hydrochloride salt, but the precentage release rate of methapyrilene from the PVM/MA salt in both artificial intestinal and gastric fluids was more rapid than either the hydrochloride salt or the free base.

The di-salt of PVM/MA was prepared by reacting 3.35 g. of methapyrilene base with 1 g. of the polymer. Precipitation of the product from the aqueous system occurred within 6 hr., and after drying, the solid product was found to contain 3.15 g. of drug. Analysis of drug availability from the coarsely subdivided product by the dissolution method indicated that 98% methapyrilene release was attained within 15 min., in the gastrointestinal fluids.

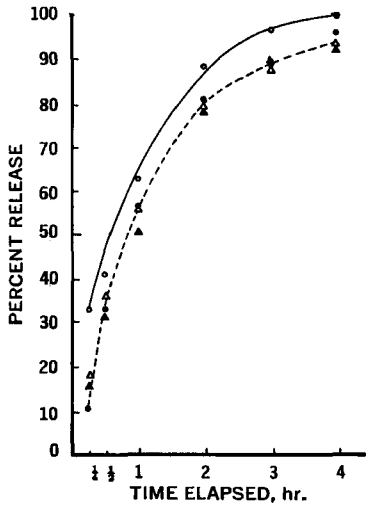

Fig. 4—Equilibrium dialysis release pattern of the PVM/MA-methapyrilene partial salt in comparison to methapyrilene hydrochloride in artificial gastric (●▲) and intestinal (○△) fluids at 37 ± 1°. Key: ▲△, methapyrilene hydrochloride; ●○, methapyrilene-PVM/MA partial salt.

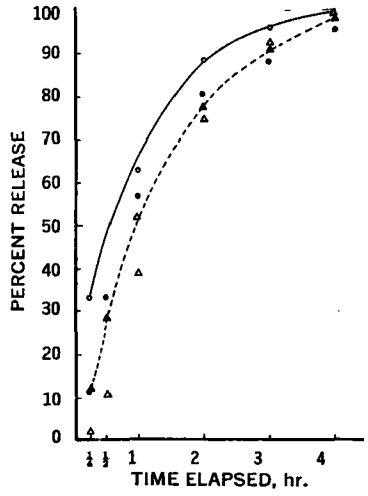

Fig. 5—Equilibrium dialysis release pattern of the PVM/MA-methapyrilene partial salt in comparison to methapyrilene base in artificial gastric (●▲) and intestinal (○△) fluids at 37 ± 1°. Key: ▲△, methapyrilene base; ●○, methapyrilene-PVM/MA partial salt.

Methapyrilene salts of the PVM/MA hemi-esters were prepared by reaction in aqueous dispersion as described in the *Experimental* section. These PVM/MA hemi-ester salts were prepared in granular form and evaluated for methapyrilene release by the dissolution method. The drug content of the hemi-esters ranged from 21 to 33% by weight, and was determined for each product by assaying the supernatant of the reaction dispersion for unreacted drug. The release of methapyrilene from granules of 20/40 mesh and smaller than 40 mesh was determined for each of the three hemi-esters described in the *Experimental* section. The release of metha-

pyrilene from the granules appeared to be dependent upon both the particulate dimensions and the amount of DOD incorporated. As was the case with the partial salt drug of PVM/MA, the release of methapyrilene was initially greater in artificial intestinal fluid (Fig. 6) than in artificial gastric fluid (Fig. 7). In both dissolution test fluids, for each granule particle size fraction studied, the order of drug release was most rapid from the 2:1 DOD-polymer ester, and least rapid from the 4:1 DOD-polymer ester. This finding corresponds with the swelling properties of the DOD-polymer esters, since the 4:1 ratio material evidenced the lowest extent of swelling. The coarser particle size fraction of each product in both test fluids exhibited the slower rate of release.

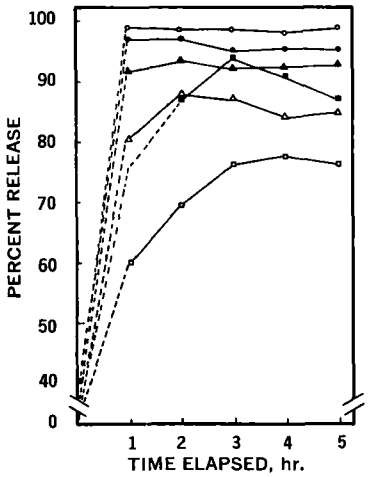

Fig. 6—Release of methapyrilene from granules of the hemi-ester salt in artificial intestinal fluid at 37 ± 1°. Key: ● 2:1 ester (> 40 mesh); ○, 2:1 ester (20/40 mesh); ▲, 3:1 ester (> 40 mesh); △, 3:1 ester (20/40 mesh); ■, 4:1 ester (> 40 mesh); □, 4:1 ester (20/40 mesh).

Samples of the granular hemi-ester salt were compressed into 0.9-cm. ($^3/_8$-in.) tablets weighing approximately 250 mg. The tablets were compressed under a load of 5,000 p.s.i. using a hand-operated hydraulic press as described in the *Experimental* section. The drug content of the tablets was determined on the basis of tablet weight and the drug content of the hemi-esters from which the tablets were compressed. Release-rate analyses of methapyrilene from the tablets prepared using both 20/40 mesh granules and granules smaller than 40 mesh, showed that drug release was substantially retarded by compression of the granules. As was apparently characteristic of the PVM/MA methapyrilene salts, the drug release from the tablets in artificial intestinal fluid (Fig. 8) was more rapid than in artificial gastric fluid (Fig. 9). The release of methapyrilene from the granular particles was dependent upon both particle size and the amount of DOD present in the system.

Drug release from the tablets in gastric fluid also indicated dependence on the amount of DOD in the systems, with the 4:1 hemi-ester salt again exhibiting the lowest rate of release. However, the 3:1 hemi-ester salt now demonstrated the most rapid rate of release (Fig. 9). The tablets prepared from the coarser particle-size fractions of a given ester product exhibited a more rapid release rate (Fig. 9), in the systems in which a particle size effect was noted, suggesting that the tablets prepared from the larger granules were more porous.

Drug release from the tablets in intestinal fluid followed that in gastric fluid, in that the 4:1 hemi-ester salt (>40 mesh) exhibited the slowest rate and the 3:1 hemi-ester salt (20/40 mesh) exhibited the most rapid initial release rate. The rates of release of the other systems were compressed between the rates of these two systems in an indeterminate order. The *in vitro* release pattern of the compressed

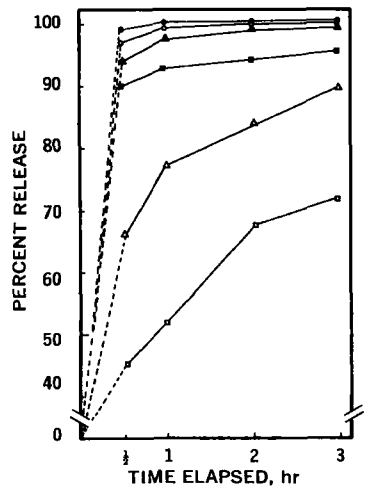

Fig. 7—Release of methapyrilene from granules of the hemi-ester salt in artificial gastric fluid at 37 ± 1°. Key: ●, 2:1 ester (> 40 mesh); ○, 2:1 ester (20/40 mesh); ▲, 3:1 ester (> 40 mesh); △, 3:1 ester (20/40 mesh); ■, 4:1 ester (> 40 mesh); □, 4:1 ester (20/40 mesh).

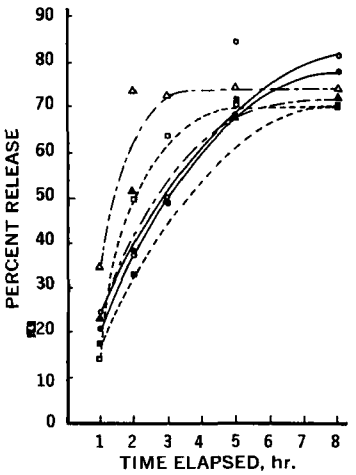

Fig. 8—Release of methapyrilene from tablets of the hemi-ester salt in artificial intestinal fluid at 37 ± 1°. Key: ●, 2:1 ester (> 40 mesh); ○, 2:1 ester (20/40 mesh); ▲, 3:1 ester (> 40 mesh); △, 3:1 ester (20/40 mesh); ■, 4:1 ester (> 40 mesh); □, 4:1 ester (20/40 mesh).

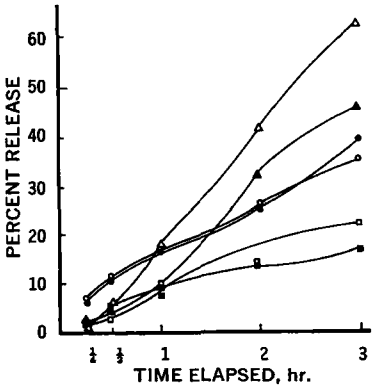

Fig. 9—Release of methapyrilene from tablets of the hemi-ester salt in artificial gastric fluid at 37 ± 1°. Key: ●, 2:1 ester (> 40 mesh); ○, 2:1 ester (20/40 mesh); ▲, 3:1 ester (> 40 mesh); △, 3:1 ester (20/40 mesh); ■, 4:1 ester (> 40 mesh); □, 4:1 ester (20/40 mesh).

tablet DOD-polymer ester drug salts were much more promising that that of the particulate materials. The tablets did not disintegrate under test, but gradually eroded.

SUMMARY

Polymer–drug interacted systems were prepared and evaluated as an approach to the physicochemical design of pharmaceutical dosage forms.

An amine drug base (methapyrilene) was found to form salts with the dicarboxylic acid hydrolysis product of poly (methyl vinyl ether/maleic anhydride) containing as much as 3.15 parts of drug per part of polymer. Release-rate analyses of the polymer drug salts indicated methapyrilene availability comparable to that from the free base or the hydrochloride salt. Increased initial drug release in artificial intestinal fluid was characteristic of the polymer-drug salt.

Hemi-esters of poly (methyl vinyl ether/maleic anhydride) with 1,12-dihydroxyoctadecane were prepared. The hemi-esters, containing excess DOD, were found to react with methapyrilene to form hemi-ester salts of the drug. Methapyrilene release rates from the hemi-ester salts were studied with the use of tablets and granules and found to be substantially reduced in comparison to the polymer salts or the hydrochloride salt and free base forms of the drug.

The potential application of a drug–polymer interacted system as an approach to the preparation of controlled and prolonged-release dosage forms was illustrated.

REFERENCES

(1) Wagner, J. G., *J. Pharm. Sci.*, **50**, 359(1961).
(2) Malek, P., Kolc, J., Herold, M., and Hoffman, J., *Antibiot. Ann.*, 1957–58, 546(1958).
(3) Tobin, L. C., and Weber, J. B., U. S. pat. 3,121,043 (Nov. 5, 1960).
(4) Srinivas, R., and Banker, G. S., Ph.D. Thesis, Purdue University, Lafayette, Indiana (1966).
(5) Utsumi, I., Ida, T., Kishi, S., and Takahashi, S., Jap. pat. 14038 (1961).
(6) Anon., *Tech Bull No. AP108-2*, General Aniline and Film Corp., New York, N. Y., 1961, pp. 1, 5–23.
(7) Marshall, P. B., *Brit. J. Pharmacol.*, **10**, 270(1955).

Keyphrases

Dosage forms–polymer-drug interacted system
Poly (methyl, vinyl ether/maleic anhydride) and hemi-ester—test polymers
Methapyriline—test drug
Salt formation—methapyriline, polymers
Dissolution rates—polymer-drug system
Dialysis rates—polymer-drug system
UV spectrophotometry—analysis
Potentiometric titration—reactivity analysis