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Protective Coatings XIII. Amphoteric Polyvinylpyridine Derivatives

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Polyampholites of vinylpyridine or its alkyl derivatives with acrylic or methacrylic acid and the copolymers of these compounds with other vinyl derivatives were synthesized and studied as protective coating agents for tablets. Results showed that the synthesized copolymers had adequate viscoelasticity, protective qualities, and disintegration characteristics to serve as protective coating agents.

POLYAMPHOLYTES of vinylpyridine or its derivatives with acrylic or methacrylic acid and copolymers of those with other vinyl compounds were experimentally synthesized. The purpose of synthesis was to obtain such protective-coating agents as to exhibit protective activity on drugs and solubility in both gastric and intestinal juice. Solubility, water vapor permeability through the film, and viscoelasticity were tested on each of copolymers.

The practical coatings on tablets were also carried out and disintegration time of the coated tablets, absorption of moisture and aging deterioration of the active ingredients were subsequently investigated. Most of the compounds have shown outstanding properties as protective-coating agents.

In the preceding reports, observations were made on the applicability of polyvinylpyridine derivatives and other compounds to protective-coating agents (1). All preparations coated with these compounds were easily dissolved in acid of gastric juice to release medicament. However, it is believed that there are marked differences in gastric acid secretion among individuals, particularly those patients with hypoacidity or anacidity. In this sense, it is feared that preparations coated with one of these compounds may be not disintegrated by gastric juice. In order to overcome this disadvantageous property of these compounds, preparations should be coated with such protective-coating agents as to be insoluble near the neutral pH but disintegrate favorably both in gastric juice of lower acidity and in intestinal juice.

Attempts to elucidate the properties of the polyampholytes obtained by the reaction of vinylpyridine or its alkyl derivatives with methacrylic or acrylic acid were made to examine their eligibilities for protective-coating agents.

Copolymerization of 2-vinylpyridine and methacrylic acid and physico chemical properties of the products have been reported by Alfrey (2) and Katchalsky (3), respectively. There have been other reports on the copolymerization of the main body of acrylonitrile with vinylpyridine, methacrylic acid or other vinyl compounds for textile-improving (4–6). On the other hand, no reported study has dealt with these products as coating agents for medicaments.

As starting monomers 4-vinylpyridine (4VP), 2-vinylpyridine (2VP), 2-methyl-5-vinylpyridine (MVP), and 2-vinyl-5-ethylpyridine (VEP) were used for basic components, whereas methacrylic acid (MAA) and acrylic acid (AA) were used for acidic components. Styrene (St), methylacrylate (MA), and acrylonitrile (AN) were used as other monomers.

Copolymers were synthesized from any two or three components using either a catalyst of benzoylperoxide (BPO) or α,α'-azo-bis-isobutyr-

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onitrile (AIBN) and their applicability to the protective-coating agents were studied.

EXPERIMENTAL

Materials.—Each monomer was rectified just before using. BPO and AIBN of pure grade in commerce were used without purification.

Synthesis of Copolymers.—A mixture of two or three monomers was dissolved in methanol and then polymerized at 50–60° and 60–70° in the presence of BPO and AIBN as catalyst, respectively, for 5 hr. To purify, each polymer thus obtained was dissolved in an adequate solvent, *e.g.*, methanol or acetone, and subsequently separated by pouring the solution into a large quantity of water. After repeating this reprecipitation, the polymer was dissolved in diluted hydrochloric acid and finally precipitated by adjusting the pH to isoelectric point with caustic alkali.

The copolymers with acrylic acid were synthesized by the presynthesis of the copolymers with MA followed by hydrolysis with an equimolecular amount of potassium hydroxide in acetone-methanol mixture for 5 hr. with heating.

Tables I, II, III, IV, and V show the yields of the copolymerizations and the analytical data of the copolymers.

Composition of Copolymers.—Vinylpyridine content in each copolymer was determined from nitrogen content (micro-Dumas method) and ultraviolet absorption (7, 8). Carboxyl content was determined by titration of copolymers with 0.1 *N* sodium methoxide solution in absolute pyridine using thymol blue as indicator (9).

TABLE I.—COPOLYMERIZATION OF 2-VINYL-5-ETHYL PYRIDINE

Monomer Ratio			Yield, %	Polymer Composition	
VEP Mol. %	Comonomer,	Mol. %		VEP Content, %	Acid Content, %
30	MAA	70	50.0	54.8	45.6
40		60	52.4	62.0	39.3
50		50	50.0	69.3	31.7
60		40	35.1	75.9	21.5
20	AA	80	47.0	45.1	54.1
40		60	70.7	49.6	45.8
60		40	49.2	69.5	36.2

TABLE II.—COPOLYMERIZATION OF 2-VINYL-5-ETHYL PYRIDINE

Monomer Ratio				Yield, %	Polymer Composition	
VEP Mol. %	MAA Mol. %	Comonomer,	Mol. %		VEP Content, %	Acid Content, %
20.0	50.0	St	30	35	56.1	29.3
30.0	40.0		30	61	54.8	19.9
35.0	35.0		30	75	46.1	17.1
40.0	30.0		30	68	37.3	11.8
50.0	20.0		30	57	76.0	8.6
60.0	10.0		30	53	75.5	3.1
28.6	21.4		50	55	37.0	20.0
34.3	25.7		40	56	56.1	11.2
45.7	31.3		20	55	63.5	19.5
51.4	38.6		10	58	65.5	16.1
28.6	21.4	AN	50	64	77.0	13.8
34.3	25.7		40	65	51.0	18.4
40.0	30.0		30	65	52.5	17.0
45.7	31.3		20	61	76.5	19.6
51.4	38.6		10	...	...	...
11.4	8.6	MA	80	70	16.6	47.4
17.2	12.8		70	54	20.4	43.0
22.9	17.1		60	56	41.5	14.0
28.6	21.4		50	61	66.7	13.7
34.3	25.7		40	60	64.6	16.5
40.0	30.0		30	47	72.0	18.0

TABLE III.—COPOLYMERIZATION OF 2-METHYL-5-VINYL PYRIDINE

Monomer Ratio				Yield, %	Polymer Composition	
MVP Mol. %	MAA Mol. %	Comonomer,	Mol. %		MVP Content, %	Acid Content, %
40.0	60.0	...		90.0	51.4	48.5
50.0	50.0	...		84.4	62.3	37.0
60.0	40.0	...		82.8	77.2	21.9
40.0	30.0	St	30	50.0	48.6	16.0
30.0	40.0		30	68.3	32.0	27.2
40.0	30.0	MA	30	72.0	42.0	15.35
28.6	21.4		50	65.3	55.2	18.96
22.6	17.1		60	72.4	59.8	17.10
17.2	12.8		70	50.0	62.4	16.00
40.0	30.0	AN	30	44.0	72.5	21.3
34.3	25.7		40	47.1	53.2	17.8
28.6	21.4		50	47.5	50.5	18.0
22.8	17.1		60	34.2	62.7	14.5
70.0	AA 30	St	30	37.7	68.8	23.4

TABLE IV.—COPOLYMERIZATION OF 2-VINYL PYRIDINE

Monomer Ratio				Yield, %	Polymer Composition	
2VP Mol. %	MAA Mol. %	Comonomer, Mol. %			2VP Content, %	Acid Content %
45.7	31.3	St	20	30.2	57.0	14.19
40.0	40.0		20	93.2	27.7	23.8
50.0	20.0		30	80.0	59.4	9.3
35.0	35.0		30	76.5	36.7	21.9
20.0	20.0		60	61.4	20.7	15.1
35.0	35.0	AN	30	28.3	45.5	22.0
34.7	25.7		40	20.3	81.3	15.7
34.3	25.7	MA	40	22.4	58.7	21.1
30.0	30.0		40	64.5	35.4	26.1
25.0	25.0		50	55.2	36.4	40.2
20.0	20.0		60	61.4	17.5	23.8
15.0	15.0		70	59.2	17.0	19.7
20.0	AA 20	St	60	63.8	21.4	13.9

TABLE V.—COPOLYMERIZATION OF 4-VINYL PYRIDINE

Monomer Ratio				Yield, %	Polymer Composition	
4VP Mol. %	MAA Mol. %	Comonomer, Mol. %			4VP Content, %	Acid Content, %
40.0	40.0	St	20	94.8	40.4	32.6
20.0	20.0		60	47.0	20.7	21.7
35.0	35.0	AN	30	86.5	45.5	26.8
40.0	30.0		30	21.4	54.5	23.40
34.3	25.7		40	45.0	91.0	10.28
15.0	15.0		70	33.3	17.0	45.6
40.0	30.0	MA	30	23.4	52.0	20.6
34.3	25.7		40	36.6	63.5	18.3
30.0	30.0		40	64.5	49.6	25.6
28.6	21.4		50	21.2	56.0	17.3
25.0	25.0		50	38.6	28.6	27.6
20.0	20.0		60	61.5	23.4	22.0
15.0	15.0		70	33.3	17.0	45.6

Isoelectric Zone.—A 100-mg. quantity of each copolymer was dissolved in 0.1% hydrochloric acid to make 100 ml. of the solution. A 50-ml. part of this solution was titrated with 0.1 *N* sodium hydroxide by using glass electrode pH meter (2). Isoelectric zone determined the pH value at which the solution began to get turbid and the pH value at which it became clear again.

Dynamic Viscoelasticity of Films.—Dynamic viscoelasticity of films was determined by "vibrating reed" method in a room at 20° and 60% R.H. The method of preparing the film of copolymers has been reported in a previous paper (10).

Water Vapor Permeability of Films.—The quantity of water permeated through the films per 24 hr. was examined by "cup method" specified in ASTM E-96-53T in a room at 25° and 92% R.H. (10).

Disintegration Test.—By the dipping method, the protective coating was applied on the starch-lactose tablets which were compressed in accordance with the method of a previous paper (10). Disintegration times of the coated tablets in distilled water, artificial gastric juice, artificial intestinal juice, and buffer solution from pH 2 to 9 were separately determined by the method specified in U.S.P. XVI. Acetic acid-sodium acetate system was used as the buffer solutions of pH 4 and 5, while Clark-Lubs system was employed as the buffer solutions with a pH other than pH 4 and 5.

The thickness of the coating film was calculated from the difference between the weight of coated and uncoated tablets. The composition of copolymers, solvents used in the coating process, and thickness of the films are shown in Table VI.

Aging Test.—Formulas of tablets used in the experiment for aging test were: (*a*) Carnitine chloride tablet containing 200 mg. of carnitine chloride was 9.6 mm. in diameter, 2.8 mm. of thickness and 260 mg. of total weight. (*b*) Acetylsalicylic acid tablet containing 115 mg. of acetylsalicylic acid had 8.0 mm. in diameter, 2.5 mm. of thickness and 150 mg. of total weight.

The dipping method was used to apply the protective coating to both tablets. Four copolymers selected from each series of VEP, MVP, 2VP, and 4VP were used as protective coating agents.

Coated carnitine chloride tablets were stored in a room at 25° and 90% R.H.; absorption of moisture was observed by measuring the change of tablet weight. Coated acetylsalicylic acid tablets were stored in a room at 37° and 85% R.H.; the amount of salicylic acid produced as a result of decomposition of acetylsalicylic acid was determined by means of its ultraviolet absorption (11).

Toxicity Test.—Each copolymer, suspended in water plus a small amount of sodium carboxymethylcellulose, was given to dd-strain male mice weighing 20 ± 1 Gm. by stomach tube. The mortality of mice 72 hr. after administration was observed to evaluate the toxicity of copolymers. The dose administered to the mice was the maximum which could be given.

RESULTS AND DISCUSSION

Solubility.—As shown in Table VII, two-component copolymers of vinylpyridine or its derivatives with MAA or AA were insoluble in water, soluble in

TABLE VI.—DATA FOR DISINTEGRATION TEST OF COATING

Tablet	Coating Agent: Basic Component, Mol. %		Acidic Component, Mol. %		Other Component, Mol. %		Coating Soln.[a] Concn., w/v %	Thickness of Film, μ
	VEP	40	MAA	30	St	30	10	108
		34		26	AN	40	10	108
		17		13	MA	70	5	150
		29		21		50	5	88
Starch-lactose	MVP	40	MAA	30	St	30	10	121
		40		30	AN	30	10	170
		17		13	MA	70	5	143
		23		17		60	5	111
	4VP	20	MAA	20	MA	60	10	308
	2VP	20	MAA	20	MA	60	10	230
	VEP	11	MAA	9	MA	80	10	41
Carnitine chloride	MVP	23	MAA	17	MA	60	10	31
	4VP	20	MAA	20	MA	60	10	48
	2VP	20	MAA	20	MA	60	10	42
Acetylsalicylic acid	VEP	11	MAA	9	MA	80	10	120
	MVP	23	MAA	17	MA	60	10	105

[a] Solvent utilized was chloroform and methyl alcohol (1:1).

TABLE VII.—SOLUBILITY OF COPOLYMER

Coating Agent: Vinyl Pyridine, Mol. %		Other Component, Mol. %		Solvent[a]: Methyl Alcohol	Ethyl Alcohol	Acetone	Benzene	Carbon Tetrachloride	Chloroform	Ethyl Acetate	Ether	Petroleum Ether	Artificial Gastric Juice	Artificial Intestinal Juice	Distilled Water	Isoelectric Zone
VEP	30	MAA	70	SS	I	I	I	I	I	I	I	I	S	S	I	3.8–7.2
	40		60	S	S	I	I	I	SS	I	I	I	S	S	I	4.1–7.6
	60		40	S	S	I	I	I	S	I	I	I	S	I	I	4.1–8.7
VEP	20	AA	80	SS	SS	I	I	I	I	I	I	I	S	S	I	3.8–7.2
	40		60	SS	SS	I	I	I	I	I	I	I	S	S	I	4.0–6.3
	60		40	SS	I	I	I	I	I	I	I	I	S	S	I	3.5–5.6
MVP	50	MAA	50	I	I	I	I	I	I	I	I	I	S	S	I	4.5–6.1
	60		40	SS	SS	I	G	SS	SS	SS	I	I	S	S	I	4.5–7.3
MVP	60	AA	40	S	S	SS	G	G	G	G	I	I	S	S	I	4.0–6.3
	70		30	S	S	SS	G	G	G	G	I	I	S	I	SS	4.5–9.0
2VP	60	MAA	40	G	G	SS	SS	G	G	I	I	I	S	I	SS	4.2–10.0
4VP	60	MAA	40	S	SS	I	I	S	I	I	I	I	S	S	I	3.9–6.5

[a] I = insoluble, S = soluble, SS = slightly soluble, and G = gelatinized or swollen.

weak acid and alkali, but very sparingly soluble in organic solvents, with a few exceptions, so that most of the compounds seemed to be unsuitable for protective coating agents.

On the other hand, three-component copolymers with St, AN or MA, as shown in Tables VIII, IX and X, were easily dissolved in organic solvents to form transparent films, were soluble in weak acid and alkali, but insoluble in near neutral. As seen in Table VIII, the copolymers composed of St in 30 mol. % content showed the highest solubility when the content ratio of VEP to MAA was 4:3 or 1:1. Therefore, various ratios of components for the synthesis of copolymers were later set up by maintaining the ratio of VEP to MAA; either 4:3 or 1:1.

Table XI represents the composition for synthesizing copolymers providing the most favorable solubility.

The copolymer films were strengthened with an increase of MA, St, or AN. Since copolymers containing up to 70 mol. % MA content were soluble, as indicated in Table XI, the films containing MA were considered the strongest.

As appended in Tables VIII, IX and X, each copolymer showed various ranges of the isoelectric zone according to the variation of composition. Therefore, a suitable copolymer could be selected freely depending on the property of medicament to be coated.

Water Vapor Permeability and Viscoelasticity of Films.—As indicated in Table XII, water vapor permeability of the film formed by these protective-coating agents was close to 10^{-4}–10^{-5} Gm. cm./cm.^{2}/24 hr. which were obtained by the protective-coating agents reported in a previous paper (10).

Less water vapor permeability of the films produced by three-component copolymers was noted as

compared with those produced by two-component copolymers in a same series of vinylpyridine derivatives. Furthermore, the copolymers with MA, St, or AN showed a decrease of water vapor permeability of the films with increasing the content of these components. Especially, the copolymers composed of MVP-MAA-MA and MVP-MAA-St showed the lowest water vapor permeability. It is believed that the lower water vapor permeability of films is desirable for a protective-coating agent.

Dynamic elasticity and dynamic viscosity of the films of copolymers, as indicated in Table XII, were approximately 10^{10} dynes/cm.^{2} and 10^6 poises, which are generally suitable for a protective-coating agent.

Disintegration of Protective Coated Tablets.—Disintegration tests of the tablets coated with a protective-coating agent were carried out in artificial gastric juice, intestinal juice, and also in the buffer solution to evaluate disintegration time and water resistance. The results of the disintegration tests are shown in Table XIII. All of the coated tablets showed a resistance to disintegration in distilled water for more than 3 hr. but disintegrated within 15 min. in artificial gastric juice and within 30 min. in artificial intestinal juice. The results of

TABLE VIII.—SOLUBILITY OF COPOLYMER

Coating Agent				Solvent[a]												
VEP, Mol. %	MAA, Mol. %	Other Comonomer,	Mol. %	Methyl Alcohol	Ethyl Alcohol	Acetone	Benzene	Carbon Tetrachloride	Chloroform	Ethyl Acetate	Ether	Petroleum Ether	Artificial Gastric Juice	Artificial Intestinal Juice	Distilled Water	Isoelectric Zone
20.0	50.0	St	30	G	I	I	I	I	G	I	I	I	I	I	I	...
30.0	40.0		30	S	S	I	SS	SS	S	S	I	I	S	I	I	4.4–9.2
35.0	35.0		30	S	S	I	SS	SS	S	S	I	I	S	S	I	4.3–7.2
40.0	30.0		30	S	S	SS	S	S	S	S	I	I	S	S	I	4.3–7.6
50.0	20.0		30	S	S	SS	S	S	S	S	I	I	S	G	G	4.3–8.2
60.0	10.0		30	S	S	I	I	I	S	I	I	I	S	G	G	4.3–8.1
28.6	21.4		50	G	G	I	G	I	G	I	I	I	S	I	I	4.4–9.8
34.3	25.7		40	S	S	SS	S	SS	S	S	SS	I	S	G	I	4.4–8.6
45.7	34.3		20	S	S	SS	S	SS	S	S	SS	I	S	G	I	4.6–8.7
51.4	38.6		10	S	S	I	S	I	S	S	I	I	S	I	I	4.3–10.0
28.6	21.4	AN	50	S	SS	SS	SS	I	S	S	I	I	S	I	I	4.9–9.0
34.3	25.7		40	S	S	SS	SS	I	S	S	I	I	S	SS	I	4.0–7.9
40.0	30.0		30	S	S	SS	SS	I	S	S	I	I	S	S	I	4.0–7.4
45.7	31.3		20	S	S	SS	SS	I	S	S	I	I	S	SS	I	4.3–8.0
51.4	38.6		10	S	S	SS	G	G	S	S	I	I	S	G	I	4.5–8.4
11.4	8.6	MA	80	S	S	S	SS	SS	S	S	SS	I	G	I	I	...
17.2	12.8		70	S	S	SS	SS	SS	SS	S	SS	I	S	S	I	3.7–6.0
22.9	17.1		60	S	S	SS	SS	SS	SS	S	SS	I	S	S	I	4.0–7.2
28.6	21.4		50	S	S	SS	SS	SS	S	S	SS	I	S	SS	I	3.9–7.9
34.3	25.7		40	S	S	SS	SS	I	S	S	SS	I	S	S	I	4.2–7.5
40.0	30.0		30	S	S	SS	SS	I	S	S	SS	I	S	G	I	4.7–8.3

[a] I = insoluble, S = soluble, SS = slightly soluble, and G = gelatinized or swollen.

TABLE IX.—SOLUBILITY OF COPOLYMER

Coating Agent				Solvent[a]												
MVP, Mol. %	MAA, Mol. %	Other Comonomer,	Mol. %	Methyl Alcohol	Ethyl Alcohol	Acetone	Benzene	Carbon Tetrachloride	Chloroform	Ethyl Acetate	Ether	Petroleum Ether	Artificial Gastric Juice	Artificial Intestinal Juice	Distilled Water	Isoelectric Zone
40	30	St	30	S	I	I	G	G	I	I	I	I	S	S	I	3.5–6.1
17.2	12.8	MA	70	S	I	I	S	G	I	I	I	I	S	S	I	3.5–6.1
22.8	17.1		60	S	I	I	G	I	I	I	I	I	S	S	I	4.3–6.4
28.6	21.4		50	S	I	I	G	I	I	I	I	I	S	S	I	4.5–6.4
34.3	25.7		40	S	I	I	G	I	I	I	I	I	S	S	I	4.3–6.3
40.0	30.0		30	I	I	I	G	I	I	I	I	I	S	S	I	3.8–5.8
22.8	17.1	AN	60	S	I	I	G	I	I	I	I	I	SS	S	I	...
34.3	25.7		40	G	I	I	G	I	I	I	I	I	S	S	I	4.3–6.3
40.0	30		30	I	I	I	G	I	I	I	I	I	S	S	I	4.4–6.4

I = insoluble, S = soluble, SS = slightly soluble, and G = gelatinized or swollen.

TABLE X.—SOLUBILITY OF COPOLYMER

Coating Agent					Solvent[a]											
4VP or 2VP, Mol. %		MAA, Mol. %	Other Comonomer, Mol. %		Methyl Alcohol	Ethyl Alcohol	Acetone	Benzene	Chloroform	Dioxane	Ether	Petroleum Ether	Artificial Gastric Juice	Artificial Intestinal Juice	Distilled Water	Isoelectric Zone
4VP	20	20	St	60	G	G	SS	G	S	S	I	I	S	SS	I	3.3–8.0
	40	40		20	SS	I	I	G	G	I	I	I	S	S	I	3.6–6.7
	35	35	AN	30	S	SS	I	G	G	I	I	I	S	S	I	3.8–6.1
	15	15	MA	70	S	SS	G	I	G	G	I	I	S	S	I	3.2–6.7
	25	25		50	S	S	I	S	G	I	I	I	S	S	I	3.5–6.4
	40	30		30	S	SS	I	G	G	I	I	I	S	S	I	3.9–6.5
2VP	20	20	St	60	S	SS	G	G	G	S	I	I	I	I	I	...
	35	35		30	S	SS	I	I	G	SS	I	I	S	SS	I	3.6–8.2
	35	35	AN	30	S	SS	I	I	G	SS	I	I	S	S	I	3.9–6.2
	15	15	MA	70	S	SS	G	I	G	G	I	I	S	S	I	3.5–6.5
	25	25		50	S	S	I	S	G	I	I	I	S	S	I	3.5–6.5
	30	30		40	S	SS	I	I	G	SS	I	I	S	S	I	3.6–6.4

[a] I = insoluble, S = soluble, SS = slightly soluble, and G = gelatinized or swollen.

TABLE XI.—BEST COMPOSITION OF COPOLYMER FOR SOLUBILITY

Mol. ratio of VP:MAA	Mol. % of other component	
VEP-MAA (4:3)	St	30
	AN	30
	MA	40–70
MVP-MAA (4:3)	St	30
	AN	30–40
	MA	40–70
2VP-MAA (1:1)	St	30
	AN	30
	MA	40–70
4VP-MAA (1:1)	St	20
	AN	30
	MA	30–70

disintegration tests in the buffer solutions showed generally same tendency within the pH range of the isoelectric zone determined previously.

Based on the foregoing, these copolymers seemed to be suitable protective-coating agents having an isoelectric zone around neutral and enough water resisting property suited for the purpose of this study. The tablets coated with these copolymers might be expected to disintegrate in a hypoacidic stomach or in the intestine even if it passed through the stomach without disintegration and subsequently exert therapeutic effect. This was noted in oral administration tests using vitamin B_2 tablets coated with these copolymers. These data will be disclosed in the near future.

Protective Effect on Active Ingredients.—Experiments to assess a protective effect of the copolymers against absorption of moisture were carried out by coating the carnitine chloride tablets, which are remarkably hygroscopic. Fig. 1 sets forth the results.

Hygroscopicity of the coated tablets was greatly reduced as compared with the uncoated control tablets. Both the appearance and hardness of the coated tablets remained unchanged while the uncoated tablets were softened, followed by change of form.

As described in Fig. 2, the results of aging test on the acetylsalicylic acid tablets coated with the copolymers revealed that the tablets were apparently stabilized when compared with stability of the uncoated tablets. The coated tablets disclosed a favorable result with reasonable disintegration time.

Toxicity.—The toxicity of polymers of vinylpyridine or vinylpyridine alkyl derivatives and copolymers of these monomers with VAc, AN, MA, or St has been reported in a previous paper (10). As summarized in Table XIV of this paper, no acute toxic

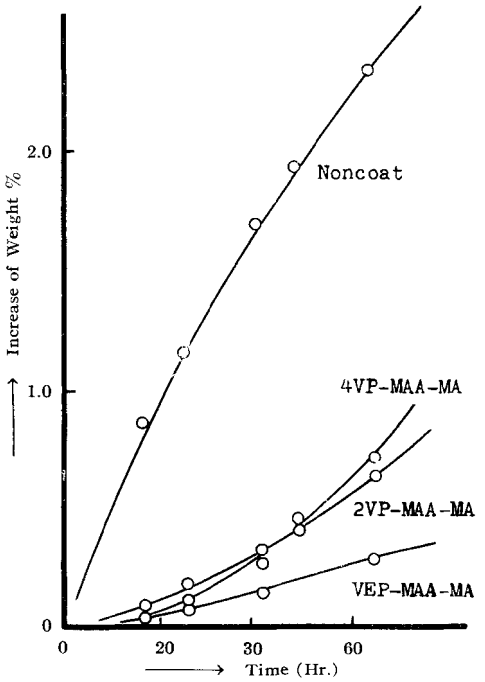

Fig. 1.—Hygroscopic curve of carnitine chloride tablet at 25°, 90% R.H.

TABLE XII.—WATER VAPOR PERMEABILITY AND VISCOELASTICITY OF FILMS

Composition of Coating Agent, Mol. %						Water Vapor Permeability, $\times 10^{-4}$ Gm. cm./cm.^{2}/24 hr.	Dynamic Modulus, $\times 10^{10}$ dyne/cm.^{2}	Dynamic Viscosity, $\times 10^6$ poise
VEP	17	MAA	13	MA	70	1.1	1.0	1.6
	25		13		60	1.0	1.0	6.5
	29		21		50	2.2	1.3	2.4
MVP	60	MAA	40			1.5	1.7	1.8
	40		30	St	30	0.1	1.2	0.6
	40		30	AN	30	0.9	1.8	5.6
	23		17	MA	60	0.3	2.3	1.1
	29		21		50	0.6	2.5	1.5
	34		26		40	0.2	5.5	1.5
4VP	20	MAA	20	MA	60	0.3	1.5	1.4
2VP	20	MAA	20	MA	60	0.3	1.2	1.3

TABLE XIII.—DISINTEGRATION TEST

Composition of Coating Agent, Mol. %						Disintegration Time		
						Distilled Water, hr.	Artificial Gastric Juice, min.	Artificial Intestinal Juice, min.
VEP	40	MAA	30	St	30	3	13	30
	34		26	AN	40	3	9	30
	17		13	MA	70	3	12	22
	29		21		50	3	7	30
MVP	40	MAA	30	St	30	3	9	30
	40		30	AN	30	3	13	30
	17		13	MA	70	3	13	22
	23		17		60	3	15	28
	29		21		50	3	10	28
	34		26		40	3	14	30
4VP	20	MAA	20	MA	60	3	12	28
2VP	20	MAA	20	MA	60	3	10	30

action upon mice was observed after the oral administration of four kinds of the typical copolymers with MAA and MA.

SUMMARY AND CONCLUSIONS

1. The polyampholites of vinylpyridine or its alkyl derivatives with acrylic or methacrylic acid and the copolymers of these compounds with other vinyl derivatives were synthesized to obtain new protective-coating agents.

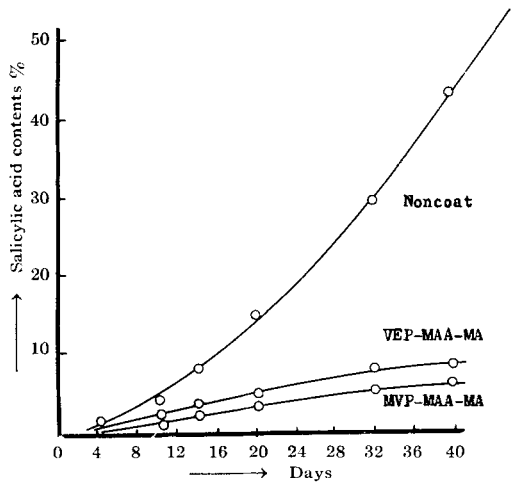

Fig. 2.—Aging of acetylsalicylic acid in acetylsalicylic acid tablets at 37°, 85% R.H.

TABLE XIV.—ACUTE TOXICITY TEST IN MICE[a]

No. of Animals	Protective-Coating Agent	Dose, mg./Kg.
5	VEP-MAA-MA	2000
5	MVP-MAA-MA	2000
5	2VP-MAA-MA	2000
5	4VP-MAA-MA	2000

[a] No deaths 72 hr. after administration.

2. These copolymers were dissolved in organic solvents to form transparent films which were soluble in both acidic and alkaline solutions but insoluble in an approximately neutral solution. Water vapor permeability through the copolymer films was found to be very low.

3. It was found that the copolymers synthesized had adequate viscoelasticity to serve as protective-coating agents.

4. Sufficient protection against absorption of moisture and aging deterioration of the active ingredients was provided by the copolymer coatings.

5. The tablet coatings were insoluble only in an approximately neutral solution, but seemed to be disintegrated in stomach with hypoacidity and in the intestine to produce the desired therapeutic effect.

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Tablets of Pyrilamine Resin Adsorbate with Aspirin and Vitamin C

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Marked changes in physical appearance manifested by dry formulations containing aspirin, an antihistamine, and vitamin C during an accelerated temperature stability study are discussed. The stabilization afforded by a resin adsorbate of a commonly used antihistamine, pyrilamine, is noted. Discrepancies in the results obtained from stability studies of these preparations have been traced to the efficiency of the closure utilized in the packaging of the product, as well as the methods employed in the pretreatment, sampling, and evaluation of test samples. The implications of these observations from a developmental standpoint are discussed.

THE AVAILABILITY of ion exchange resins suitable for oral administration has presented the formulator with a means of tailoring products in a way not heretofore possible. These materials are currently available in a wide range of types and mesh specifications and present a new means of complexation of an active ingredient which can lead to a significant enhancement in both the stability of the medicament and in the manipulation of its release pattern. It is with a variation of the former case, the reduction of an undesirable incompatibility of salts of pyrilamine in common formulations, that this paper concerns itself.

Tablet and capsule formulations for the symptomatic treatment of the common cold constitute a significant segment of the ethical and proprietary drug market. These products usually contain aspirin, an antihistamine, and vitamin C. The development of such products is complicated by interactions between the ingredients, resulting in marked changes in the physical appearance of the preparation after short storage intervals. Certain antihistamines have been shown to be incompatible in dry dosage forms containing aspirin and/or vitamin C (1, 2). This interaction is manifested by softening and darkening of tablets, surface crystal growth, and an acetous odor. Methods such as compression coating, multilayering, and pan coating, which overcome the existing problems by physical separation of the reactants, have been utilized to produce products having an acceptable shelf life. We have investigated resin adsorbates of pyrilamine for possible reduction in the degree of incompatibility in formulations of this type.

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EXPERIMENTAL

Analytical Methods

Pyrilamine Resin Adsorbate.—Accurately weigh a sample of finely ground tablets equivalent to 25 mg. of pyrilamine maleate. Disperse in 25 ml. of 2 *N* hydrochloric acid and shake vigorously for 30 minutes at room temperature. Extract with three 15-ml. portions of chloroform, discarding the chloroform layers. Add 5 ml. of 50% potassium hydroxide to the acid layer, shake well, and let stand at room temperature for 15 minutes. Extract with three 15-ml. portions of chloroform. Extract the combined chloroform extracts twice with 25 ml. of 1 *N* hydrochloric acid and measure the absorbance at 315 mμ in a suitable spectrophotometer. Use 1 *N* hydrochloric acid as the reference solution.

$$\frac{A \text{ of sample at } 315 \text{ m}\mu \times 10}{0.205 \times \text{No. of tablets}} = \text{mg. per tablet as pyrilamine maleate}$$

Ascorbic acid.—Ascorbic acid was assayed by the official U.S.P. XVI method.

Acetylsalicylic and Salicylic Acids.—A rapid spectrophotometric assay of acetylsalicylic and salicylic acids was utilized in this investigation (3). It is to be noted that the utilization of this assay procedure in preparations containing pyrilamine is somewhat inaccurate because of the interference exhibited by the absorbance of pyrilamine at the 308 mμ peak. To simplify the numerous assays involved, this interference was considered negligible; however, the values obtained should not be considered absolute.