Polymeric Pharmaceutical Coating Materials II

In Vivo Evaluation as Enteric Coatings

By LEWIS C. LAPPAS and WAYNE MCKEEHAN

A series of polymeric films exhibited a gradient in dissolution pH within the pH range of the gastrointestinal tract. The *in vivo* release properties of these films were evaluated clinically as enteric coated tablets using acetylsalicylic acid as the marker. The absorption and excretion of these tablets were studied through plasma salicylate and urinary salicylurate measurements in normal, fasting subjects. A direct relationship was observed between the polymer dissolution pH and the onset and induction times of these enteric tablets in the plasma and urine, respectively. No significant difference in absorption rates existed between the stomach for the control and the upper intestine for two of the enteric products. A further increase in the dissolution pH of the polymers released the drug in the lower intestine effecting a progressive decrease in the absorption rate and total absorption. Variation in the upper intestine was significantly less than in the lower intestine.

THE INCREASING emphasis on the clinical efficacy of drug formulations has greatly stimulated the study of those physical and chemical properties which contribute directly to the release and subsequent absorption of orally administered pharmaceuticals. Many drugs are absorbed at various rates throughout the gastrointestinal tract due to their degree of dissociation and solubility (1). The pH gradient of the gastrointestinal tract may then be utilized to control and study the release and ultimate absorption of a drug in specific areas of the intestine. This factor is significant for those medicinals which are absorbed primarily in the intestine from enteric and sustained-release dosage forms. A series of films, half esters of poly(vinyl methyl ether maleate), was prepared to dissolve at various pH values within the pH range of the intestine (2). Earlier reports described the *in vivo* utility of some of these materials as enteric and sustained-release coatings (3–5).

The drug, acetylsalicylic acid, has been studied extensively relative to the effect of the gastrointestinal pH gradient on its rate of absorption. Proven analytical procedures are available for its detection as free salicylate in the blood plasma and as conjugated metabolites in the urine. In view of these considerations, this drug is suitable for use as a marker in this study.

Rapidly disintegrating tablet cores of acetylsalicylic acid were coated with the various films to produce a gradient in their disintegration pH. The effect of these products on the intestinal absorption was measured clinically in normal, fasting subjects through plasma salicylate and urinary salicylurate measurements.

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EXPERIMENTAL

Physiological Aspects—The essentially unionized form of acetylsalicylic acid and its hydrolysis product, salicylic acid, are passively and preferentially absorbed throughout the entire gastrointestinal tract (6). The pKa of acetylsalicylic acid is 3.49, and the pH of the gastrointestinal tract will determine its degree of dissociation at various absorption sites. Its rate of absorption is highest in the stomach (6, 7), decreases progressively in the intestine (8), and becomes minimal in the colon (9). At the fasting gastric pH range of 1.2–3.5, the ionic state of acetylsalicylic acid is highly favorable for absorption (10); the extent of its absorption is limited by the low solubility in this pH range and the emptying time of the stomach. The pH of the intestine varies from 4 to 7.5, increasing from the proximal to the distal end (11); therefore, the degree of unionized molecule is reduced to approximately 1%. The increased dissolution rate and greater mucosal surface in the upper intestine could effect an equivalent or more rapid absorption from this area than from the stomach (12–14). It is apparent that salicylic acid (pKa 3.0) might produce a similar absorption pattern in the gastrointestinal tract. Eriksen *et al.* demonstrated a similarity of absorption for salicylate in the stomach and 2–3 ft. past the pylorus (15). These investigators noted the rate and efficiency of absorption in the cecum were less than in the stomach and small intestine.

The absorption of acetylsalicylic acid from solid dosage forms is limited and controlled by the dissolution rate of the drug in the gastrointestinal fluids (16). Enteric coatings are designed to transfer the dosage form intact through the gastric fluid and render the drug available for dissolution in the intestinal fluid. Assuming the dissolution properties of a pharmaceutical dosage form are reproducible, it is evident that gastric emptying

time can become a source of significant variation in the intestinal absorption for enteric products. Those factors contributing greatly to this variation are the presence or absence of food (17) and position of the body during sleep (18). Another source of variation in intestinal absorption is the transit or resident time of the dosage form as it traverses the intestine. In general, transit time is minimal proximally and gradually increases distally. These potential variables make it essential to assess the dissolution rates of both the enteric coating and the drug from the solid dosage form.

Plasma and urinary salicylate measurements have been used frequently to study the relative absorption rates of various orally administered dosage forms. The majority of the plasma salicylate is present as protein bound salicylate or free salicylate ion in solution (19). Metabolism of acetylsalicylic acid occurs in the tissues, and elimination as conjugated salicylates is effected readily at 90% yield. Salicyluric acid is the chief metabolite excreted in a normal acid urine, and its rate of formation may become the limiting step in the excretion process. This metabolic lag is seen in the differences between peak times of the plasma and urinary salicylate levels indicating the metabolic rate is slower than the absorption rate from the gastrointestinal tract.

Cummings and Martin studied the kinetics of acetylsalicylic acid metabolism relative to dosage and noted the urinary excretion rates between doses of 325 mg. and 650 mg. were decreased with the higher dose (20). This change in half-life was attributed to the attainment of a saturation excretion level which was related to plasma concentration. Other investigators have studied the half-life of salicylate in the blood and observed a range from 4.7 to 19 hr. depending on the plasma concentration (21–23).

Preparation of Enteric Polymers—A series of half esters of the copolymer poly(vinyl methyl ether/maleic anhydride) (PVM/MA) was prepared, and the dissolution pH of these films was determined according to the procedures described by Lappas and McKeehan (2).[1] The dissolution pH of each enteric film, determined after 24 hr. at 25°, is listed in Table I.

Preparation of Tablet Core—A circular, biconvex tablet was formulated from a starch base and contained 0.325 Gm. of acetylsalicylic acid by the U.S.P. method of analysis (24). The disintegration property of this tablet was designed to rupture and disperse completely in 1–2 min. at pH 1.2, 6.0, and 7.5 using the U.S.P. disintegration apparatus, without disks, at 37° (25). The test fluids of designated pH were prepared by mixing solutions of enzymeless, U.S.P. simulated gastric and intestinal fluids (26). In order to promote the adhesion of these enteric polymers to this tablet, two types of subcoatings were used. In the film coating process, methylcellulose 10 cps. (Dow Chemical Co.) was applied at 3 mg./tablet, with a DeVilbiss sprayer, from a solution of equal volumes of methanol and methylene chloride. In the alternate process, approximately 15 mg./tablet of a powder subcoat was applied by ladling syrup on the tablets to produce tackiness and then dusting to dryness with talc–acacia (88:12). The disintegration times of these subcoated cores were the same as that of the uncoated tablet core.

[1] Polymer-grade used was Gantrez AN 139 for PVM/MA which is available from General Aniline and Film Corp.

TABLE I—DISSOLUTION pH OF ENTERIC FILM COATINGS

Half Ester of PVM/MA	Dissolution pH[a]
Ethyl	4.25
Isopropyl	5.25
n-Butyl	5.75
Cyclopentyl	6.25

[a] pH of complete solubility; the film is intact at 0.25 pH unit below this pH.

Preparation of Enteric Coated Tablets—The polymeric film coatings were applied to the subcoated tablets in batch sizes of 3000 in a conventional 16-in. diameter tablet coating pan. Solutions of 4% w/v polymer in a mixture of acetone–isopropanol (85:15) were applied from a DeVilbiss sprayer. The final weight of coating per tablet was determined as the amount required to withstand the disintegration test for 1 hr. in enzymeless gastric fluid without physical change. The maximum amount of acetylsalicylic acid extracted from any tablet under these conditions was 4.8 mg. The disintegration pH of the tablet was defined as a function of pH and time required to dissolve the enteric film coat and disperse the tablet contents. The apparatus and method of preparation for the pH-adjusted test solutions were described previously for the uncoated tablet core. The pH at which the tablet remained intact for a minimum period of 1 hr. demonstrated the small range in pH between solubility and insolubility. The presence of enzymes in the test solutions did not alter the disintegration times of the enteric tablets. The disintegration properties of the various enteric coated tablets are summarized in Table II. The rate of disintegration at pH 7.5 increased in direct relationship from a mean of 6 min. for the 1/2 ethyl PVM/MA coated tablet to 12 min. for the 1/2 cyclopentyl PVM/MA coated tablet. At the lower pH's, the differences in disintegration time between the various enteric tablets are more clearly defined than at pH 7.5.

Clinical Procedure—A total of 12 healthy male subjects, who were known to be absorbers of acetylsalicylic acid, were used throughout the study; however, not all members of this panel participated in all of the experiments. The subjects were selected at random for testing the various enteric coated tablets as follows: five subjects in a cross-over study with the uncoated control, the 1/2 ethyl PVM/MA and the 1/2 isopropyl PVM/MA; eight subjects were used to study the 1/2 *n*-butyl PVM/MA; and six subjects constituted the group for the 1/2 cyclopentyl PVM/MA. A total of 0.650 Gm. of acetylsalicylic acid, two tablets, was administered to overnight fasting subjects with 200 ml. of water. A light breakfast was permitted 1 hr. after the administration of this dose. Although liquids were taken freely after 1 hr., 100 ml. of water was administered after each urine void. Preliminary evaluation of these materials determined the optimal time for the withdrawal of blood and the collection of urine samples. Urinalysis was continued for 48 hr., the time of complete excretion for all products tested.

TABLE II—DISINTEGRATION PROPERTIES OF ENTERIC COATED TABLETS OF ACETYLSALICYLIC ACID 0.325 Gm.

Enteric Coating	Subcoat	Enteric Coat, mg./Tablet	Disintegration pH[a]	Disintegration min.	Insolubility pH[b]
1/2 Ethyl PVM/MA	Methyl-cellulose	28	5.75	25	5.0
1/2 Isopropyl PVM/MA	Methyl-cellulose	20	6.0	38	5.5
1/2 *n*-Butyl PVM/MA	Powder	16	6.2	38	6.0
1/2 Cyclopentyl PVM/MA	Powder	10	6.75	15	6.5

[a] pH of solutions was monitored constantly. [b] Tablet was physically unaltered for at least 1 hr.

Analytical Procedures—A modification of the procedure reported by Schachter and Manis was used to determine the plasma salicylate fluorimetrically (19). Freshly drawn blood samples were mixed with heparin, and the plasma was separated by centrifugation. An aliquot of this sample was acidified and extracted with chloroform to remove the free salicylate. This solution was alkalinized with sodium hydroxide and activated at a wavelength of 314 mμ. Its fluorescence was measured at an emission wavelength of 410 mμ using an Aminco-Bowman spectrophotofluorometer.

Generally, about 75% of the dose of acetylsalicylic acid is excreted as the metabolite, salicyluric acid; 10% is found as the free salicylate. In order to economize time and effort, the metabolite salicyluric acid was measured to evaluate the comparative absorption and total excretion of acetylsalicylic acid from the various preparations. Individual urine samples were pooled and collected at 4, 8, 12, 18, 24, 32, and 48 hr. These samples were refrigerated prior to analysis for pH and salicyluric acid content. Although the pH of the urine samples varied for the individuals, the range of pH 5.0 to 6.8 was considered normal for acid urine. The method of analysis for salicyluric acid was essentially that described by Schachter and Manis (14). An aliquot of the urine sample was acidified with hydrochloric acid and extracted with ether. This layer was subsequently extracted with sodium hydroxide solution, and its fluorescence was measured at an emission wavelength of 410 mμ after activation at 335 mμ.

RESULTS AND DISCUSSION

This investigation was undertaken to demonstrate the *in vivo* release properties of a series of polymeric

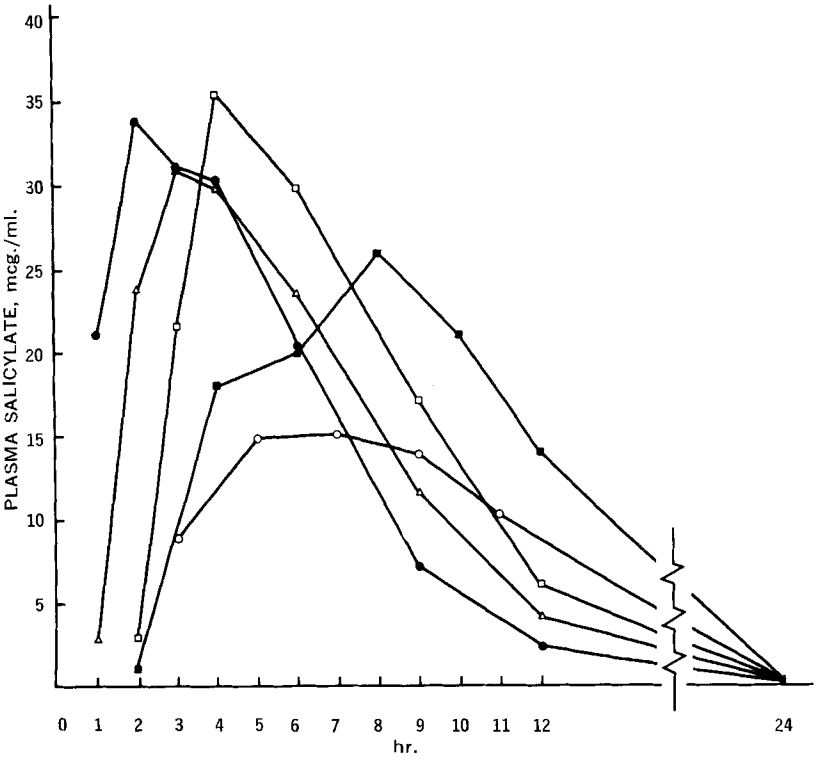

Fig. 1—Plasma salicylate concentration vs. *time: effect of polymer dissolution pH gradient. ASA blood levels; single dose, 650 mg. (two tablets). Key:* ●, *control uncoated;* △, *1/2 ethyl PVM/MA;* □, *1/2 isopropyl PVM/MA;* ■, *1/2* n-*butyl PVM/MA;* ○, *1/2 cyclopentyl PVM/MA.*

films having a dissolution pH gradient within the pH range of the intestinal tract. These films, applied over a rapidly disintegrating core of acetylsalicylic acid, exert a direct control over the release, dissolution, and subsequent absorption of this active ingredient. The significant physiological variables affecting its absorption are the pH of the intestine, the gastric emptying time of the stomach, and the transit time of the drug in the intestine. In consideration of these factors, the absorption aspects are revealed for areas of the intestine rather than exact locations.

The absorption-excretion data are expressed as average plasma salicylate and urinary salicylate levels as a function of time. These measurements illustrate the relative differences in the absorption of acetylsalicylic acid as it is presented to various pH values along the gastrointestinal tract. The frequency of the urine collection is a factor which limits the use of these data for quantitative kinetic study of the absorption-distribution-excretion properties of this drug.

The plasma salicylate levels plotted in Fig. 1 reveal similar peak levels for the control, the 1/2 ethyl PVM/MA and 1/2 isopropyl PVM/MA coated tablets at 2, 3, and 4 hr., respectively. The absorption slopes are steep and similar for the three products indicating equivalent absorption rates in the stomach for the control and two locations in the upper part of the small intestine for the enteric tablets. This observation is in accord with that of other investigators (6–14) and may be explained by the increased solubility of the drug in an area of vast intestinal mucosal surface which equalizes the optimal ionic conditions for absorption of this drug in the stomach. The 1/2 *n*-butyl PVM/MA coated tablet effected a decrease in the absorption slope and peak level; a salicylic acid concentration of 26 mcg./ml. was attained in 8 hr. Similarly, the 1/2 cyclopentyl PVM/MA coated product plateaued at 5–9 hr. reaching its peak salicylate value of 15.1 mcg./ml. after 7 hr. This gradient in the absorption rates of acetylsalicylic acid is attributed to the decreased efficiency in absorption from the lower parts of the intestine.

In Fig. 2, the average cumulative urinary excretion is expressed as mg. of salicylic acid and as the per cent released relative to the uncoated control. These data indicate the onset of absorption was progressively delayed with an increase in the disintegration pH of the enteric coated tablets. The cumulative excretions of the control, the 1/2 ethyl PVM/MA, and the 1/2 isopropyl PVM/MA coated tablets were equivalent after 12 hr. This level of

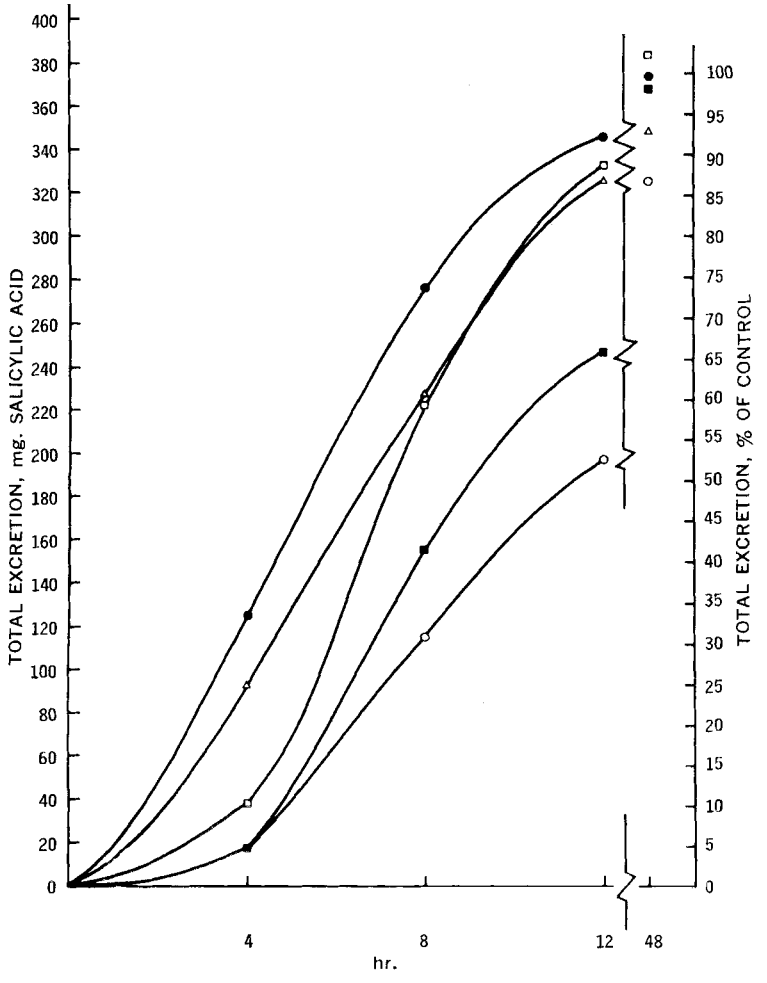

Fig. 2—Total urinary salicylate excretion vs. *time: effect of polymer dissolution pH gradient. ASA urinary excretion; single dose, 650 mg. (two tablets). Key: ●, control uncoated; △, 1/2 ethyl PVM/MA; □, 1/2 isopropyl PVM/MA; ■, 1/2 n-butyl PVM/MA; ○, 1/2 cyclopentyl PVM/MA.*

excretion was approached by the 1/2 *n*-butyl PVM/MA and the 1/2 cyclopentyl PVM/MA coated tablets in 18 and 24 hr., respectively. The excretion study was conducted through 48 hr. indicating complete availability for all enteric tablets except for the 1/2 cyclopentyl PVM/MA coated tablet which was 87% available. The deposition of an enteric tablet at a lower absorption site than the latter tablet would be expected to result in slower and less complete absorption with a lower plasma peak and lower degree of availability.

The variation of the tested products was considered by examination of the distribution of peak times for individuals. This parameter is a reflection of the combined variables of gastric emptying time, pH, and intestinal transit time. The distribution patterns for the control, the 1/2 ethyl PVM/MA, and the 1/2 isopropyl PVM/MA coated tablets were equivalent. The 1/2 *n*-butyl PVM/MA coated tablet indicated increased variation, and the 1/2 cyclopentyl PVM/MA coated tablet exhibited the greatest variation. In these fasting ambulatory subjects the absorption reproducibility of the enteric tablets was greatly dependent upon the absorption site of the intestine, *i.e.*, the upper part of the intestine exhibited significantly less variation in absorption than the lower part of the intestine.

These data reveal that the gradation in coating dissolution pH is significant in permitting some control over the absorption of acetylsalicylic acid. Many other drugs are absorbed at various rates throughout the intestinal tract. Therefore, each drug should be considered an individual problem in formulating enteric-release products to effect optimal absorption.

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Hydrolysis of Solubilized Aspirin

By A. G. MITCHELL* and J. F. BROADHEAD

The hydrolysis of aspirin in buffered solutions of the nonionic surfactant, cetomacrogol, has been studied at 37° over the pH range 1 through 7. Cetomacrogol reduces the hydrolysis rate of unionized aspirin but not that of ionized aspirin. The reaction occurs mainly in the aqueous phase but at low pH the contribution of a hydrogen ion catalyzed reaction within the micelles becomes significant. A kinetic expression has been derived to account for reaction both in the aqueous phase and in the micelles.

THE HYDROLYSIS of aspirin in aqueous solution has been investigated extensively by Edwards (1, 2) and Garrett (3, 4). They determined overall first-order rate constants as a function of pH and proposed various reaction mechanisms.

The effect of anionic, cationic, and nonionic surfactants on the stability of solubilized aspirin has been studied by Nogami *et al.* (5). It was shown that each surfactant suppressed the hydrolysis of unionized aspirin, while the hydrolysis of the anionic form of aspirin was suppressed only by cationic surfactants.

In this work, a detailed study has been made of the stability of aspirin at 37° in several concentrations of the nonionic surfactant, cetomacrogol, over the pH range 1 through 7. A kinetic expression has been derived to account for the hydrolysis of the solubilized drug.

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* Present address: Faculty of Pharmacy, University of British Columbia, Vancouver, B. C., Canada.

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Reagents and Solutions—Aspirin was recrystallized from acetone, m.p. 134–136°. Salicylic acid was recrystallized from alcohol and then water,