Comparison of Availability of Ions from Sodium Salicylate and Salicylic Acid Tablets

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Abstract □ The *in vitro* release of the drug components from salicylic acid and sodium salicylate tablets was studied. Comparisons were made concerning the availability of sodium ions and salicylate ions from typically formulated tablets containing the salt of the drug. Similarly formulated salicylic acid tablets were also compared. The availability of sodium from the sodium salicylate tablets, while unaffected by pH, was substantially different from that of the salicylate ion and would represent the inherent disintegration-deaggregation-dissolution behavior due to the tablet formulation itself.

Keyphrases □ Sodium salicylate and salicylic acid tablets—*in vitro* drug release compared, pH effect □ Salicylic acid and sodium salicylate tablets—*in vitro* drug release compared, pH effect □ Dissolution, sodium salicylate and salicylic acid tablets—percentage of drug released *in vitro*, pH effect

The *in vitro* release of drug from the tablet dosage form has been studied in numerous ways to ascertain the efficacy of certain formulations, manufacturing techniques, and even the physical and chemical form of the drug to be used. Disintegration was adopted as the primary means of testing drug release but has been replaced by dissolution. Many different dissolution methods have been developed including the hanging pellet (1) and various beaker (2), basket (3), and flowing-stream apparatus (4).

Several of these dissolution methods have been used under special circumstances and with specially formulated tablets to elucidate some of the mechanisms involved in drug dissolution. Nelson (1) compared the dissolution of several weak acids and their sodium salts from pellets. These pellets, containing only the pure drug, were suspended from a balance and the dissolution was recorded as the loss of weight per unit time. For all drugs and at all hydrogen-ion concentrations tested, the rate of dissolution of the salt form of the drug far exceeded that of the acid form. Later, Higuchi *et al.* (5) developed the theoretical basis of dissolution from pure drug tablets. This work was expanded to include the theoretical and actual dissolution of several drugs from compressed disks (6, 7).

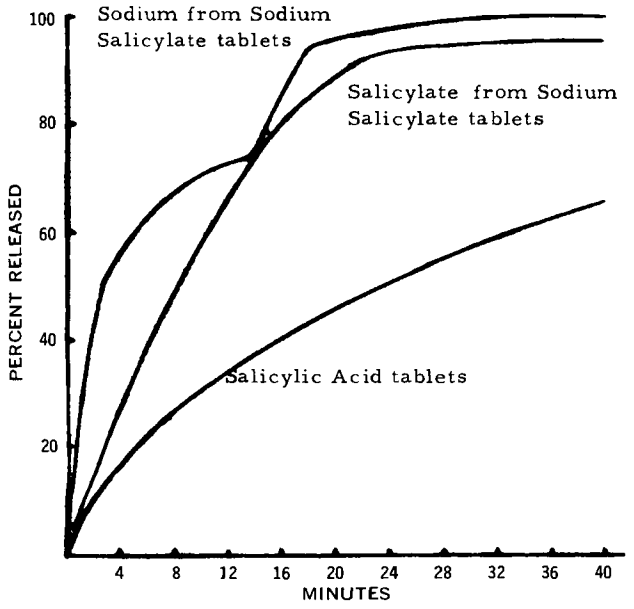

Figure 1—*Comparison of the dissolution rates of salicylic acid and sodium salicylate tablets at pH 2.0.*

Most reports have been concerned with dissolution from disks consisting of drug only. The purposes of this work were to follow the appearance of each drug component as it dissolved from more typical formulations of compressed tablets and to compare the dissolution of the sodium salt with that of the free acid at several hydrogen-ion concentrations.

EXPERIMENTAL

Materials—Salicylic acid[1], sodium salicylate[1], fast flow lactose[2], microcrystalline cellulose[3], starch[4], and stearic acid[5] were obtained from commercial sources. The dissolution medium at pH 2 consisted of a buffer mixture of hydrochloric acid and potassium chloride; at pH 8, it was made up of a 0.2 *M* buffering solution of monobasic potassium phosphate and potassium hydroxide (8).

Equipment—The magnetic basket (3) was used as the dissolution apparatus.

Tablets were compressed using a 16-station rotary tablet press[6] equipped with an induced die feeder. Standard concave punches, 0.95 cm (0.37 in.) diameter, were used. An electronic hardness tester[7] was employed to determine hardness.

Tablet Formulation—Tablets were compressed from the following formulations (in milligrams) to contain the same molar concentration of sodium salicylate and salicylic acid:

sodium salicylate	50.0	salicylic acid	43.13
stearic acid	3.6	stearic acid	3.6
lactose	203.3	lactose	228.27
starch	35.0	starch	35.0
microcrystalline cellulose	50.0	microcrystalline cellulose	50.0

All tablets were weighed, and 50% of those tablets meeting

[1] J. T. Baker Chemical Co., Phillipsburg, N.J.
[2] Foremost Dairy, San Francisco, Calif.
[3] Avicel, FMS Corp., Newark, Del.
[4] Ruger Chemical Co., Inc., Irving, N.J.
[5] Fisher Chemicals, Fairlawn, N.J.
[6] Model 216-RP Cherry Burrell.
[7] Erweka Electronic.

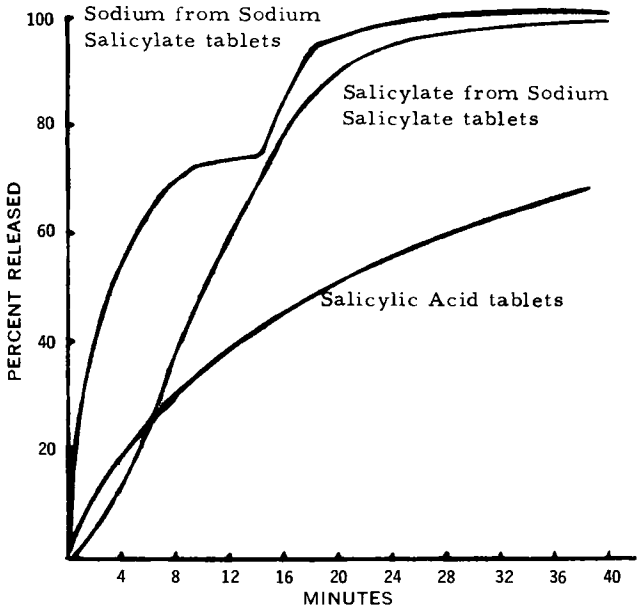

Figure 2—*Comparison of the dissolution rates of salicylic acid and sodium salicylate tablets at pH 8.0.*

specifications were examined for hardness. Although tablets of varying hardnesses were prepared, tablets of only one specific hardness for each formulation were used in this work. The salicylic acid tablets showed an average hardness of 0.8 unit with a range of 0.5–1.1, and the sodium salicylate tablets had an average hardness of 1.1 units with a range of 0.8–1.3.

Analysis of Tablets—The weight of each tablet was determined prior to dissolution. The amount dissolved at any time *t*, reported as a percent of the total active ingredient, was determined spectrophotometrically at 293 nm in the pH 8 buffer and at 301 nm in the pH 2 buffer using the appropriate blanks. The appearance of sodium was assayed using an atomic absorption spectrophotometer[8] on those samples previously assayed in the UV spectrum. All sodium concentrations reported have been corrected for the small amount of extraneous sodium present in the formulation. Samples were taken at 2-min intervals for the first 14 min, at 4-min intervals through 30 min, and then at 5-min intervals until dissolution was complete. Each dissolution profile is the average of at least five tablets determined separately in the magnetic basket dissolution apparatus (3) at 37 ± 1° with an impeller speed of 60 rpm.

RESULTS AND DISCUSSION

In this study the dissolution of three components of the tablet was followed at two different hydrogen-ion concentrations. The tablets were prepared to contain a lubricant, binder, disintegrant, and the drug to provide *in vitro* drug release patterns of typical compressed tablet formulations. Figure 1 illustrates the dissolution of the drug at pH 2 from identically formulated and manufactured tablets containing sodium salicylate and salicylic acid, respectively. Faster dissolution of the salicylate ion from the sodium salicylate tablets as compared to the dissolution of the salicylate ion from the salicylic acid tablets is evident, although the magnitude of difference is somewhat less than that reported for the dissolution of these two moieties from tablets containing only pure drug (1).

The release of the sodium ion from the sodium salicylate tablets at pH 2 provides an interesting contrast to that witnessed for the salicylate ion from the same tablets. As can be seen from Fig. 1, the concentration of sodium ion increases much more rapidly than that of the salicylate ion, but then its rate of dissolution decreases until a similar amount of release is found for both species at 14 min. After this point, the sodium ion again dissolves faster than the salicylate ion. This behavior of the sodium-ion concentration can be correlated to the visual observation of tablet dissolution. During the first phase, the tablet is disintegrating and falling from the basket to form a mound at the bottom of the beaker. Thereafter the release of sodium ions takes place from this mound. So in essence the dissolution profile formed by the sodium ions dissolving into the solution seems to represent the inherent disintegration–deaggregation–dissolution process due to the tablet formulation itself. The profile formed by following the salicylate ion should, therefore, represent the appearance of the drug from the tablet. This availability of the salicylate ion would be dependent on the dissolution media and the solubility of the drug. Two processes have been reported to occur which would affect the appearance of the salicylate ion during dissolution: (*a*) the initial formation of an acid coat around the tablet and its deaggregated particles (5) which, when combined with the diffusion coefficient of that species, will slow the dissolution of salicylate ion; and (*b*) the precipitation of the free acid into microsized particles (1) which, in turn, must dissolve before their concentration can be recorded (2). The sum total of these two processes shows (Figs. 1 and 2) a slower dissolution of the salicylate ion as compared to that of the sodium ion.

Figure 2 represents the dissolution of the same three species at pH 8. Although there seems to be little difference in the profiles as the pH is increased, Tables I and II present several interesting comparisons among the concentrations of sodium ions, salicylate ions, and the salicylate from the salicylic acid tablets. In comparing the appearance of salicylic acid at the two different hydrogen-ion concentrations, the expected slight increase in the rate of dissolution can be seen at pH 8. The salicylate ion at the higher pH lags slightly behind the amount dissolved at pH 2, while the availability of sodium ions at both pH's are almost identical.

Table I—Percentage of Drug Released from Salicylic Acid and Sodium Salicylate Tablets at pH 2.0

Minutes	Drug Released[a], %		
	Salicylic Acid Tablets	Sodium Salicylate Tablets	
		Sodium Ion	Salicylate Ion
2	9.6	46.8	12.2
4	15.0	53.9	25.3
6	21.4	62.0	38.3
8	24.8	66.7	50.0
10	31.6	66.9	57.6
12	34.4	72.4	66.1
14	35.8	72.2	73.1
18	42.0	96.2	88.5
22	47.3	96.9	92.1
26	55.3	100.0	93.8
30	57.0	100.0	94.1
35	60.8	100.0	94.6
40	65.9	100.0	95.1

[a] Each value is the average of five tablets.

Table II—Percentage of Drug Released from Salicylic Acid and Sodium Salicylate Tablets at pH 8.0

Minutes	Drug Released[a], %		
	Salicylic Acid Tablets	Sodium Salicylate Tablets	
		Sodium Ion	Salicylate Ion
2	12.2	48.9	5.7
4	19.8	51.2	12.1
6	23.6	65.1	26.2
8	28.7	70.2	44.9
10	33.0	73.1	61.8
12	37.6	72.9	59.7
14	40.3	74.3	71.2
18	47.9	94.8	87.2
22	53.2	96.7	93.7
26	55.8	100.0	96.5
30	58.1	100.0	97.5
35	64.7	100.0	98.5
40	69.5	100.0	98.9

[a] Each value is the average of five tablets.

[8] Perkin-Elmer 290 B.

This similarity witnessed for the appearance of sodium ions indicates that the inherent disintegration–deaggregation–dissolution process for the tablet formulation itself is not affected by pH.

In conclusion, tablets containing binders, lubricants, and disintegrants as well as drug itself dissolve in much the same manner as tablets containing only drug. The inclusion of these additional ingredients into the formulation may show changes in the dissolution profiles, but the overall relativity of behavior seems to remain the same. By following the appearance of sodium in the dissolution of a tablet containing the salt of a drug as well as the drug, two processes may be defined: (*a*) the disintegration–deaggregation–dissolution procedure, which is dependent on the tablet formulation; and (*b*) the solubility–dissolution behavior of the drug itself. Consequently, the inherent dissolution characteristics of the tablet formulation may be seen and changes in dissolution caused by various formulation ingredients may be adjusted. Furthermore, availability of the drug itself can be analyzed.

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Suspension Polymerization for Preparation of Timed-Release Dosage Forms

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Abstract □ An investigation was undertaken to develop a process, utilizing suspension polymerization, for the production of timed-release medicated dosage forms. The effects of production variables upon dissolution of acetaminophen from these dosage forms were studied. Nonexpanded spherical polystyrene beads produced in the presence of acetaminophen exhibited no timed release of medication. However, timed release of medicament was observed when spherical polystyrene beads produced in the absence of acetaminophen were expanded with the aid of a blowing agent and subsequently allowed to absorb medicament. In general, 64% of the available drug was released from the free expanded polystyrene beads within the 1st hr of dissolution, with an additional 29% being released by the conclusion of dissolution testing.

Keyphrases □ Suspension polymerization—formation of timed-release dosage forms, polystyrene beads containing acetaminophen □ Polymerization, suspension—formation of timed-release dosage forms, polystyrene beads containing acetaminophen □ Acetaminophen timed-release dosage forms—prepared by suspension polymerization of polystyrene □ Polystyrene beads—prepared by suspension polymerization for timed release of drugs (acetaminophen) □ Timed-release dosage forms—preparation, suspension polymerization

Although the technique of suspension polymerization has been in use for more than 40 years, its application to the production of a pharmaceutical dosage form had not been studied until very recently. One of the first pharmaceutical investigations involving suspension polymerization was undertaken by Khanna *et al.* (1). In their work, methyl methacrylate, vinyl acetate, and divinylbenzene were polymerized in suspension to produce spherical beads containing medicament. The variables studied included type of medicament, speed of agitation, length of polymerization, and concentration of suspension stabilizers added to the aqueous phase.

An investigation into the release of medicament from spherical beads produced by suspension polymerization has been undertaken. Styrene monomer, alone or in the presence of medicament, was polymerized to produce spherical beads. A portion of these beads was then expanded with the aid of a blowing agent, and dissolution studies were conducted on both the nonexpanded and expanded polystyrene beads.

Suspension polymerization is synonymous with bead or pearl polymerization. In this process, the monomer is dispersed by vigorous mechanical agitation into small droplets. These droplets are suspended in a second liquid phase in which both the monomer and polymer are insoluble. The droplets of monomer are polymerized with the aid of a catalyst and heat while dispersion is maintained. Agents that hinder the coalescence of these droplets during polymerization are added to the suspending liquid.

Depending upon the particular monomer treated, hard or soft spheres, beads, or, less often, irregularly shaped granules are formed. The intense heat of polymerization, common to most monomers, is dissipated rapidly; easily filtered products, which may then be dried, can be obtained from many types of monomers.