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Modified USP Assay for Simultaneous Determination of Aspirin and Nonaspirin Salicylates in Aspirin and Buffered Aspirin Tablets

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Abstract □ Modified USP procedures are described for the simultaneous determination of nonaspirin salicylates and aspirin in aspirin and buffered aspirin tablets. The existing USP procedures are not stability indicating for intact aspirin when significant levels of nonaspirin salicylates are present, as is often the case in short-term, high temperature stability programs. The modified procedures yield considerably shorter analysis times and stability-indicating assays for intact aspirin without the need for sophisticated equipment other than that presently required by USP XIX.

Keyphrases □ Aspirin—analysis, modified USP method, liquid chromatography, spectrophotometry, stability, buffered and unbuffered tablets □ Liquid chromatography—analysis, aspirin in buffered and unbuffered tablets, modified USP method, stability □ Analgesics—aspirin, analysis, buffered and unbuffered tablets, modified USP method, liquid chromatography, spectrophotometry, stability

The USP methods (1) for the quantitative determination of aspirin and nonaspirin salicylates in aspirin and buffered aspirin tablets are time consuming and nonspecific for evaluation of intact aspirin stability. The aspirin assay is based mainly on the work of Levine (2). A sample preparation in chloroform is passed through a sodium bicarbonate-treated, infusorial earth-packed column, which separates aspirin from tablet excipients. Following its elution, the aspirin is quantitated spectrophotometrically.

Although the method is reliable for production control, its accuracy as a stability-indicating assay is questionable because it does not isolate aspirin from its degradation product salicylic acid. Since the bicarbonate column concurrently traps both aspirin and salicylic acid, the result of their simultaneous elution is a positive interference in the aspirin UV absorption at 280 nm.

Another weakness in the USP method is that separate procedures are required for the aspirin and nonaspirin salicylates assays; hence, the complete analysis of aspirin tablets is quite lengthy. The USP nonaspirin salicylates assay is based on several studies (3–7). A sample is triturated in chloroform in the presence of citric acid monohydrate. Insoluble salts of aspirin or salicylic acid, if present, are converted to chloroform-extractable free acids by hydrochloric acid. Finally, the salicylic acid is separated from aspirin using an infusorial earth column treated with ferric chloride and urea, which complexes salicylic acid. The salicylic acid is eluted and quantitated spectrophotometrically.

This paper reports a modified USP method that simultaneously determined aspirin and nonaspirin salicylates in aspirin and buffered aspirin dosage forms. Complexing the nonaspirin salicylates on a ferric chloride–urea infusorial earth column and collecting the intact aspirin eluate achieved effective separation. Aspirin in the eluate was determined spectrophotometrically. The complexed nonaspirin salicylates were eluted and likewise determined spectrophotometrically. The results of this modification were a considerably shorter analysis time, a stability-indicating assay for aspirin, and a method that could be performed without sophisticated equipment other than that already required by the USP.

EXPERIMENTAL

Reagents and Chemicals—All chemicals and reagents were USP or ACS grade and were used without further purification.

Aspirin Tablet Assay—*Chromatographic Column*—A column was packed as described under the nonaspirin salicylates procedure in the USP. It was washed with a 25-ml portion of chloroform.

Aspirin Standard Preparation—About 50 mg of USP aspirin reference standard, accurately weighed, was dissolved in glacial acetic acid–chloroform (1:99) and diluted to 50 ml in a volumetric flask. A 5.0-ml portion was transferred to a 100-ml volumetric flask containing 2.0 ml of methanol, diluted to volume with glacial acetic acid–chloroform, and mixed.

Salicylic Acid Standard Preparation—A suitable, accurately weighed, quantity of salicylic acid was dissolved in chloroform to obtain a solution containing 30 μg of salicylic acid/ml. A 5.0-ml portion was transferred

Table I—Recovery of Added Aspirin (50.00 mg) by USP Procedure

Salicylic Acid Added, mg	Aspirin Recovered, mg	Recovery, %
0.00	50.00	100.0
0.75	50.35	100.7
1.50	50.95	101.9
2.25	51.50	103.0
3.00	52.10	104.2

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Table II—Statistical Evaluation

Determination	Aspirin Tablet Procedure: Recovered Aspirin, %	Aspirin Tablet Procedure: Recovered Nonaspirin Salicylates, %	Buffered Aspirin Tablet Procedure: Recovered Aspirin, %	Buffered Aspirin Tablet Procedure: Recovered Nonaspirin Salicylates, %
1	100.2	100.9	99.97	99.30
2	100.8	100.5	99.80	99.07
3	99.44	100.5	99.75	100.2
4	100.2	100.5	100.2	98.14
5	100.3	100.5	99.98	97.44
6	99.97	100.0	99.50	99.54
Mean	100.2	100.5	99.87	98.95
SD	±0.537	±0.356	±0.276	±1.090
Precision, %	±0.54	±0.35	±0.28	±1.10

to a 100-ml volumetric flask containing 20.0 ml of methanol, 5 drops of concentrated hydrochloric acid, and 20.0 ml of a 1:9 solution of glacial acetic acid in water-saturated ether. Chloroform was added to volume and mixed.

Assay Preparation—A quantity of finely ground tablets equivalent to 50 mg of aspirin was weighed accurately in a 50-ml beaker. Then 10 ml of chloroform was added, and the beaker was swirled for 3 min. The entire sample was transferred onto the chromatographic column.

Procedure—Without delay, the beaker and column were washed, in portions, with 90 ml of chloroform. The washings were collected in a 100-ml volumetric flask containing 1.0 ml of glacial acetic acid, diluted to volume with chloroform, and mixed. A 10.0-ml portion was transferred to a 100-ml volumetric flask containing 1.0 ml of glacial acetic acid and 2.0 ml of methanol. Chloroform was added to volume and mixed. The absorbances of the assay preparation and the aspirin standard preparation were determined at 278 nm in 1-cm cells *versus* chloroform as the blank.

To the column containing the ferric–salicylate complex was added 20.0 ml of a 1:9 solution of glacial acetic acid in water-saturated ether, followed by 60 ml of chloroform. The eluate was collected in a 100-ml volumetric flask containing 20.0 ml of methanol and 5 drops of concentrated hydrochloric acid. Chloroform was added to volume and mixed. The absorbances of the assay preparation and the salicylic acid standard preparation were determined at 306 nm in 5-cm cells *versus* a blank of the same solvent composition as that of the salicylic acid standard preparation.

Calculations—The quantity, in milligrams, of aspirin per tablet was calculated as follows:

$$\text{mg of aspirin/tablet} = \frac{C(A_u/A_s)(A.W.)}{W} \qquad \text{(Eq. 1)}$$

where C is the concentration, in micrograms of aspirin per milliliter, in the standard preparation; A_u and A_s are the absorbances of the assay preparation and the standard preparation at 278 nm, respectively; $A.W.$ is the average tablet weight; and W is the weight of sample in the assay preparation.

The quantity, in milligrams, of salicylic acid per tablet was calculated as follows:

$$\text{mg of salicylic acid/tablet} = \frac{C(A_u/A_s)(A.W.)}{W} \qquad \text{(Eq. 2)}$$

where C is the concentration, in milligrams of salicylic acid per 100 ml, in the standard preparation; A_u and A_s are the absorbances of the assay preparation and the standard preparation at 306 nm, respectively; $A.W.$ is the average tablet weight; and W is the weight of sample in the assay preparation.

Buffered Aspirin Tablet Assay—*Chromatographic Column*—The column was prepared as directed under *Aspirin Tablet Assay*.

Aspirin Standard Preparation and Salicylic Acid Standard Preparation—These standards were prepared as directed under *Aspirin Tablet Assay* except that the concentrations were doubled.

Table III—Effect of Methanol on Aspirin Assay

Methanol Added, ml	Wavelength Maximum, nm	Absorbance
0.0	279	0.802
2.0	278	0.740
6.0	277	0.702
10.0	276	0.690

Table IV—Assay Results on Commercial Aspirin Tablets

Product	Aspirin, %: Modified Method	Aspirin, %: USP Method	Nonaspirin Salicylates, %: Modified Method	Nonaspirin Salicylates, %: USP Method
A	99.2	99.4	0.09	0.05
B	99.9	99.5	0.10	0.09
C	100.2	99.6	0.07	0.07
D	98.1	98.6	0.04	0.06
E	100.1	100.7	0.04	0.04

Assay Preparation—A quantity of finely ground tablets equivalent to 100 mg of aspirin was weighed accurately in a 50-ml beaker. About 700 mg of citric acid monohydrate and 40 ml of chloroform were added, and the beaker was swirled for 1 min. The mixture was filtered through coarse filter paper into a 200-ml volumetric flask. The beaker and filter paper were rinsed with two 25-ml portions of chloroform, and the rinsings were collected in the volumetric flask.

The filter paper was allowed to dry, and the residue was transferred to a 125-ml separator containing 10 ml of 1 *N* HCl. It was then extracted with two 25-ml portions of chloroform and passed through nonabsorbent cotton into the 200-ml volumetric flask. Chloroform was added to volume and mixed.

Procedure—A 20.0-ml portion of the assay preparation was transferred onto the chromatographic column, and, without delay, the column was washed in portions with 90 ml of chloroform. The washings were collected in a 100-ml volumetric flask containing 1.0 ml of glacial acetic acid and 2.0 ml of methanol, diluted to volume with chloroform, and mixed. The absorbances of the assay preparation and the aspirin standard preparation were determined at 278 nm in 1-cm cells *versus* chloroform as the blank.

The ferric–salicylate complex was eluted from the column, and the absorbance was determined as described under *Aspirin Tablet Assay*.

Calculations—The quantity, in milligrams, of aspirin per tablet was calculated as follows:

$$\text{mg of aspirin/tablet} = \frac{C(A_u/A_s)(10)(A.W.)}{W} \qquad \text{(Eq. 3)}$$

where C is the concentration, in micrograms of aspirin per milliliter, in the standard preparation; A_u and A_s are the absorbances of the assay preparation and the standard preparation at 278 nm, respectively; $A.W.$ is the average tablet weight; and W is the weight of sample in the assay preparation.

The quantity, in milligrams, of salicylic acid per tablet was calculated as follows:

$$\text{mg of salicylic acid/tablet} = \frac{C(A_u/A_s)(10)(A.W.)}{W} \qquad \text{(Eq. 4)}$$

where C is the concentration, in milligrams of salicylic acid per 100 ml, in the standard preparation; A_u and A_s are the absorbances of the assay preparation and the standard preparation at 306 nm, respectively; $A.W.$ is the average tablet weight; and W is the weight of sample in the assay preparation.

RESULTS AND DISCUSSION

Aspirin Recovery by USP Procedure—The interference of salicylic acid with aspirin recovery was studied. Mixtures were prepared in chloroform containing 50.00 mg of aspirin and various amounts of salicylic acid. One milliliter of hydrochloric acid–methanol (1:49) was added to each mixture. The solution was diluted to 50.0 ml with chloroform.

The mixtures were assayed for aspirin content by the USP procedure. As shown in Table I, a positive interference was introduced in the USP aspirin assay, making it nonspecific for stability evaluation of aspirin products.

Table V—Assay Results on Commercial Buffered Aspirin Tablets

Product	Aspirin, %: Modified Method	Aspirin, %: USP Method	Nonaspirin Salicylates, %: Modified Method	Nonaspirin Salicylates, %: USP Method
A	99.4	100.9	0.65	0.64
B	97.1	97.6	0.32	0.37
C	96.6	97.4	0.84	0.82
D	99.2	100.4	0.73	0.73
E	97.3	96.5	0.82	0.82

Linearity of Modified USP Procedure—The linearity for the aspirin tablet and buffered aspirin tablet assays was examined. For the aspirin assay, mixtures of varying amounts of aspirin with 0.15 mg of salicylic acid for the aspirin tablet assay and 3.0 mg of salicylic acid for the buffered aspirin tablet assay were determined. The amounts of salicylic acid added were equivalent to the maximum amount allowed by the USP, assuming sample weights equivalent to 50 and 100 mg of aspirin, respectively. For the nonaspirin salicylates assay, mixtures of varying amounts of salicylic acid with 50 mg of aspirin for the aspirin tablet assay and 100 mg of aspirin for the buffered aspirin assay were determined. The amounts of aspirin added represented the quantity specified in the modified USP procedures.

The aspirin assay was linear in the 0–75- and 0–130-mg ranges for the aspirin tablet assay and the buffered aspirin tablet assay, respectively. The nonaspirin salicylates assay was linear in the 0–0.3- and 0–5.0-mg ranges for the aspirin tablet assay and the buffered aspirin tablet assay, respectively.

Precision of Modified USP Procedures—A statistical evaluation of the precision of the modified methods was performed on the assay results of two sets of six accurately weighed preparations. The sets used contained either ~0.15 mg of salicylic acid and 50 mg of aspirin or 0.30 mg of salicylic acid and 100 mg of aspirin (Table II).

Effects of Methanol on Aspirin Assay—Methanol was used in the modified USP aspirin assay to clarify the column eluate, which was often turbid due to the physical removal of water by chloroform from the chromatographic column. Methanol had to be added accurately to both the assay preparation and the standard preparation since the presence of methanol affected the magnitude of the absorbance and the wavelength maximum of the aspirin peak (Table III). Aspirin was stable in this solvent mixture for at least 6 hr. The absorbance of an aspirin solution at 278 nm after this time was 99.5% of the initial value. After 24 hr, however, the absorbance dropped to 75% of the initial value.

Comparison of Modified USP Assay and USP Assay—The results of studies on several commercially available aspirin and buffered aspirin tablets are summarized in Tables IV and V. The results indicate a good correlation between methods.

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Evaluation of Lanolin Alcohol Films and Kinetics of Triamcinolone Acetonide Release

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Abstract □ The film-forming potential of lanolin alcohol was evaluated. Inclusion of ethylcellulose in lanolin alcohol improved film integrity. The hardness and modulus of elasticity of these lanolin alcohol–ethylcellulose films were improved by incorporating propylene glycol or cetyl alcohol. *Triamcinolone acetonide release from selected film compositions was* investigated. The data were analyzed from the viewpoint of the first-order kinetic theory and the release from a planar system having a homogeneous or granular matrix. The results suggest that the drug release follows a diffusion-controlled matrix model and a square root of time release profile. The release rate constants were proportional to drug concentration. Drug release was maximal from a system containing the drug in a near-saturated solution.

Keyphrases □ Lanolin alcohol—films, kinetics of triamcinolone acetonide release, topical dosage forms □ Triamcinolone acetonide—release from lanolin alcohol films, kinetics, topical dosage forms, □ Dosage forms, topical—lanolin alcohol films, kinetics of triamcinolone acetonide release □ Glucocorticoids—triamcinolone acetonide, release from lanolin alcohol films, kinetics

Protective films containing therapeutically active agents have been used for dermatological and surgical applications (1–3). An inert polymeric matrix impregnated with pilocarpine has been utilized to achieve prolonged and steady release of the drug for ocular administration (4). In certain dermatological applications, polymeric films containing a drug could offer advantages over conventional dosage forms. These potential advantages include enhanced therapeutic effect, predictable control over rate and extent of absorption, occlusion of the skin surface, and improved patient acceptance.

Although several polymeric substances have been studied for their film-forming characteristics (5–7) and potential application in topical drug delivery systems, the nonpolymeric, high molecular weight substances apparently have not been investigated. Furthermore, the applicability of this concept to topical drug delivery system design has not been explored fully.

THEORETICAL

Drug release from a planar system having a drug dispersed in a homogeneous insoluble matrix was shown (8) to follow:

$$Q = \sqrt{Dt(2A - C_s)C_s} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit area at time t, D is the drug diffusion coefficient in the matrix, A is the total amount of drug present in the matrix per unit volume, and C_s is the drug solubility in the matrix. The relationship for release from a planar system having a granular matrix was shown to be (9) diffusion controlled and is given by:

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 2)}$$

where D and C_s refer to the diffusion coefficient and drug solubility in the permeating fluid, τ is the tortuosity of the matrix, and ϵ is the porosity of the matrix.

Both these equations describe drug release as being linear with the square root of time:

$$Q = kt^{1/2} \qquad \text{(Eq. 3)}$$

where k is the release rate constant. For a homogeneous matrix system:

$$k = \sqrt{D(2A - C_s)C_s} \qquad \text{(Eq. 4)}$$

and for a granular matrix system:

$$k = \sqrt{\frac{D\epsilon}{\tau}(2A - C_s)C_s} \qquad \text{(Eq. 5)}$$

These relationships were confirmed experimentally using plastic and wax matrixes (10–15).

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