1970

Differential spectrophotometric analysis of intravenous admixtures containing metaraminol with selected corticosteroids

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DIFFERENTIAL SPECTROPHOTOMETRIC ANALYSIS OF INTRAVENOUS ADMIXTURES CONTAINING METARAMINOL WITH SELECTED CORTICOSTEROIDS

A Thesis

Presented to

the Faculty of the School of Pharmacy

the University of the Pacific

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

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May, 1970

This thesis, written and submitted by

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Dated May 15, 1970

ACKNOWLEDGEMENTS

The author wishes to express his deep appreciation to Dr. James C. King, who acted as research director and chairman of the thesis committee. At his suggestion, this research project was initiated and with his guidance, it was successfully completed.

Sincere appreciation is extended to Dr. Donald Y. Barker, Dr. Madhukar G. Chaubal, and Dean Ivan W. Rowland for their careful reading of this thesis.

Special acknowledgement is also extended to three fellow graduate students, Patrick Catania, Donald Floriddia, and Timothy Haidlen. Their encouragement and assistance eased the difficult transition of returning to school after an absence of many years.

Also, sincere appreciation is extended to those manufacturers noted in this thesis for their generous cooperation in furnishing the drugs used in this study.

To my wife, Nancy, I dedicate this thesis. Her confidence in me has never wavered, for this and more, I give her my thanks.

F. E. T.

University of the Pacific
Stockton, California
May 3, 1970

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CHAPTER I

INTRODUCTION

The environment of the active ingredient in a parenteral drug formulation is carefully controlled. By a manufacturer's judicious use of antioxidants, stabilizers, buffers, and preservatives, a predictable duration of stability can be expected for the active ingredient.

When this same drug formulation is diluted in a large volume of intravenous infusion solution, the controlled environment is lost, and the duration of stability of the active ingredient can be altered markedly. The presence of other drug formulations in admixture could further complicate stability. Chemical interactions between the multiple components of this mixture could result in a partial or complete inactivitation of the active drug entity.

Intravenous admixtures consisting of one or more drug formulations, diluted in a large volume of intravenous solution, are used extensively in current medical practice. Development of reliable methods to predict the compatibility of the admixture components is essential as a guide for their selection.

Because the majority of the reports published, to date, have used a visible change as the criterion for judging compatibility, it was the purpose of this study to demonstrate

the use of spectrophotmetric analysis to detect the occurrence of chemical interactions between two components of an intravenous admixture.

Incompatability Studies

Myers (1), in a paper reviewing the problems confronting the physician and pharmacist in handling parenteral admixture, emphasized the need for a comprehensive study of incompatibilities. He stated:

> It is generally acknowledged that formulations of manufactured products are complex and their compatibility characteristics are not the same as those of the active components alone. Predictions as to how these components will react when used as a combined form, have many times been deficient in light of actual trial. Any changes in pH, particle size, light exposure, solvents, oxidation - reduction conditions, can easily upset the drug system, causing loss of activity, inertness or toxicity.

Surveys concerning the extent of multicomponent admixtures prescribed and administered in various American hospitals have supported Myers's concern.

Meisler and Skolaut (2) reported that over 50% of the intravenous solutions administered at the Clinical Center of the National Institute of Health at Bethesda, Maryland, contained additives. Of their admixtures, 42% contained one or more drugs. Francke (3) reported that, in a 14 day period at the University of Illinois Hospital, over 60% of the I.V. solutions contained additives. A considerably higher percentage was reported by Patterson and Nordstrom (4). Their one month survey at the Veterans' Administration Hospital in Louisville, Kentucky, indicated that 86% of the I.V. solutions

contained one or more additives. Holysho and Ravin (5) reported that an average of 2.1 additives were mixed in each I.V. solution dispensed from the centralized I.V. additive service at St. Joseph's Hospital in Ann Arbor, Michigan.

To emphasize the enormity of possible admixture combination, Plein (6) stated that, for 500 given drugs, 124,755 different mixtures of two drugs are possible. If these drugs are mixed in combinations of more than two, then the number of possibilities becomes astronomical. Considering the number of multicomponent admixtures administered yearly, the potential for the occurrence of incompatibility must be recognized.

Since 1955, numerous incompatibility studies have been reported. In some of the studies, the authors have dealt with specific areas such as pH and stability problems of drug additives. Other authors have attempted to determine the compatibility of a specific drug or combination of drugs in selected I.V. fluids. Still others have attempted to incorporate information obtained from various articles into a single guide.

It is interesting to note that the methodology of study, brand and concentration of the drug additives, and especially the criteria for determining incompatibility have been varied. As a result, there have been conflicting reports as to the compatibility of certain admixtures.

The initial studies utilized observable visual changes in the admixture for incompatibility determination; such as precipitation, evolution of a gas, color change, or haze. Later studies have demonstrated that the chemical interaction

which can affect the effectiveness of one or more of the admixture components need not be manifest by a visual change. Changes in pH, oxygen concentration, drug additive concentration, light exposure, and storage temperature can induce chemical interactions resulting in a decreased stability of one or more admixture components. It has been suggested that the lack of visible changes after a chemical interaction might be attributed to the solubility of the end product of the reaction (6).

One of the first compatibility charts published was prepared by Bogash (7) in 1955. Admixtures consisting of two parenteral drug formulations were prepared and observed for the appearance of particulate matter immediately after admixture and again after four hours. The criterion for incompatibility was the presence of readily visible amounts of particulate matter within a four hour period.

Kirkland and co-workers (8) conducted an incompatibility study by adding 137 parenteral drugs, either as single or multiple components, to 60 Abbo-Liter[a] parenteral solutions. Maintaining both drug additive concentration and the order of mixing constant, admixtures were prepared and observed for visible changes at definite time intervals of 1, 6, and 24 hours.

Admixtures which were clear after 24 hours were classified as compatible. Admixtures in which a haze or precipitate

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a - Abbott Laboratories, North Chicago, Illinois.

occurred within one hour were incompatible. For those admixtures in which visual changes occurred in less than six hours but in more than one hour, the authors suggested their use be tempered with caution because of obvious hazards that might exist.

After an initial survey of I.V. admixtures used in their hospital, Dunworth and Kenna (9) selected 24 of the most commonly used parenteral drug formulations for an incompatibility study. With both concentration and brand remaining constant, two drug additives were admixed in 5% Dextrose Injection. To approximate a random order of mixing, admixture pairs were selected in alphabetical order by generic name. The resulting 270 admixtures were observed visually for particulate matter, immediately after admixture and at intervals of 3, 8, and 24 hours. Twenty-three admixtures exhibited particulate matter at various time intervals and were classified as incompatible.

Using a different method of admixture, Misgen (10) reported an incompatibility study for 34 parenteral drugs in a two-component system. After reconstitution, when necessary, 1 ml. of solution was withdrawn from each drug formulation and added to vials containing 5 ml. of sterile distilled water and the pH was recorded. To each of the vials, 1 ml. of solution from a different drug was then added. The admixtures were observed for particulate matter, immediately after admixture and two hours later. Admixtures containing particulate matter were classified as incompatible and the pH of these

admixtures was determined. The author noted that the pH of the incompatible admixture roughly paralleled the average pH of the two combining drugs.

Patel and Phillips (11) tabulated a two-component incompatibility chart for parenteral drugs based on a still different method of study. Preliminary work was done by mixing a drop of each of the two different solutions of the drug additives on a slide, and examining the mixture under a microscope. If a precipitate was observed, different dilutions of the drugs were prepared and observed. Finally, two component admixtures of unstated concentration were prepared and observed for particulate matter for a 24 hour period. The results of their work were presented as an incompatibility chart.

Studies demonstrating the occurrence of a chemical interaction between one or more components of an I.V. admixture have been reported. Although visible changes did not occur in the admixtures studied, the extent of chemical degradation detected in the components was sufficient to classify the admixtures as incompatible.

Dony-Crotteaux (12) reported that tetracycline, oxytetracycline, and chlortetracycline were found to lose biological potency in the presence of vitamin B complex. Riboflavin was identified as the cause of the inactivation of the antibiotics through a photo-oxidation process. It was also noted that fluorescein, eosin, and methylene blue can cause oxidative degradation of the tetracyclines. An important factor

demonstrated in this early study was the absence of visual change in the solutions, even though tetracycline degradation was sufficient to classify the admixture as incompatible.

After a survey of the available data from chemical incompatibility studies, Carlin and Perkins (13) presented a method for estimating the reaction rates of different drug additives. This method involved calculating the time required for a 10% reduction in the potency of the drug additive at various pH ranges. The authors suggested that the same drug, as an admixture component in the same pH range, would react in a similar manner. Carlin and Perkins stated that this method could be used as a guide to predict potential admixture incompatibilities for the drugs tested, e.g., the penicillins, tetracyclines, B-complex vitamins, hydrocortisone, and aminophylline.

Two factors relative to drug reactivity were emphasized in this study: a) The acidic or basic character of a drug can definitely influence its reactivity, and b) The majority of reactions take place by an apparent first order process, so that the time required for a given fraction of a drug to react is independent of the original drug concentration.

In a detailed study involving admixtures of specified formulations of penicillins and tetracyclines in 5% Dextrose Injection, Im and Latiolais (14) reported an inactivation of potassium penicillin G by tetracycline hydrochloride. The degradation of the penicillin was the result of its instability in an acid medium. The acidic pH of the admixture was

attributed to the tetracycline hydrochloride and to a greater extent to the ascorbic acid present in the formulation. The method used to detect drug degradation was based on a spectrophotometric assay of the individual drug components. After the determination of the wavelength of maximum absorption, the absorbance of each drug was determined before and after admixture. The decrease in absorbance of the penicillin component reflected a 69% loss of activity within a four hour period.

Stability Studies for Parenteral Drugs

The stability of a pharmaceutical drug has been defined as the period of time from completion of the preparation until it no longer fulfills the specifications given in the compendia, or until the potency has been reduced by not more than 10% (15). From this statement, it is evident that knowledge of the factors which influence drug stability is of the utmost importance if they are to be used properly. To use a drug beyond its stability period is dangerous, as its therapeutic effectiveness will have diminished and the expected patient response may not be evidenced. Also the decomposition of some drug formulations results in the formulation of chemical by-products which may cause untoward or toxic manifestations in the patient.

Whittet (16) reported several factors which produce a chemical degradation without altering the physical appearance of a drug formulation. Changes in pH, oxygen concentration, light exposure, storage temperature are included in the factors responsible for such degradation.

Lin and Lackman (17) have presented examples of the effect of photo-chemical degradation in parenteral drug formulations and their influence on stability. Oxygen in the presence of sunlight produce loss of stability in solutions of sulfonamides, reserpine, and sympathomimetic amines such as epinephrine.

Several stability studies for parenteral drug formulations have been conducted, and in general, have concentrated in three areas:

(1) Stability of a drug after reconstitution.

(2) Stability of a drug after dilution in a large volume of intravenous infusion solution. (single component admixture)

(3) Stability of a drug after dilution in a large volume of intravenous solution in the presence of one or more other drug additives. (multiple component admixtures)

Latiolais and co-workers (18) have compiled a tabulation of over 300 drug products which require reconstitution prior to administration. The tabulation contains the recommended diluent, the quantity to be used and the resultant concentration of the drug in solution. The stability of the drug after dilution with the diluent when kept under specified conditions of storage is also given. One factor, readily apparent from this study, was that different brands of the same drug entity may have different durations of stability. The manufacturer's choice of buffers, stabilizers, preservatives, and final

product pH can alter the stability of parenteral drug formulations.

Many parenteral products have specific reconstitution procedures which must be followed to assure their stability. Shoup (19) has given examples of parenteral drug formulations in which stability can be altered if one or more of several factors are not controlled. These factors include the diluent used, its temperature and pH, the presence of bacteriostats, exposure to light, and the method of mixing.

He also reported that stability after reconstitution of certain antibiotics could be prolonged by storage in the frozen state. After reconstitution, potassium penicillin G is stable for only seven days under refrigeration. However, when kept frozen below -18°, in a concentration of one million units per ml., the stability is increased to at least 12 weeks. Reconstituted cephalothin sodium is stable for 48 hours under refrigeration. Storage at -20°, at a concentration of 230 mg./ml. will increase stability to six weeks.

Bair and Carew (20) investigated the stability of antibiotics after single component admixture. Ten antibiotics in their usual therapeutic concentrations, were diluted in four different parenteral solutions. The 24 hour stability of these admixtures was tested by physical and microbiological assay. It was reported that six of the antibiotic admixtures were stable, i.e., less than 10% loss of the initial potency, in all four of the I.V. infusion solutions. Certain admixtures containing erythromycin, nafcillin sodium, novobiocin sodium,

oxacillin sodium and oxytetracycline hydrochloride were found to have lost greater than 10% of their initial potency over a 24 hour period and were classified as subpotent. Because they demonstrated that the stability of certain antibiotics after admixture could be reduced markedly, it is suggested that all antibiotic admixtures be administered as soon as possible after admixture.

Gallelli (21) conducted studies on the stability and duration of activity of six drugs of different pharmacological categories after reconstitution and dilution in I.V. infusion solutions. The drugs included were prednisolone sodium succinate, mercaptopurine sodium, cyclophosphamide, methicillin sodium, ampicillin sodium, and amphotericin-B. The study was limited to single component admixtures of the drug at therapeutic concentration after dilution in both Sodium Chloride Injection and 5% Dextrose Injection. Sample solutions were inspected visually for particulate matter, assayed either spectrophotometrically or microbiologically, and the pH recorded over a period of one to four weeks. During this period, the duplicate admixtures were stored at 25° (room temperature) and at 5° (refrigeration). The results were then compared to official statements concerning the administration and stability of the drugs in I.V. solutions. It was shown that the stability of drugs in a single component admixture could be quite different from the stability of reconstituted solutions reported in the official statements and in pharmaceutical manufacture's brochures. He suggested that

drug stability after dilution was a function of the change in concentration, change in pH, storage temperature, and light exposure.

In a continuation of his earlier work, Gallelli and co-workers (22) evaluated the stability of 16 parenteral formulations of antibiotics. The specific purpose of the study was to determine the duration that the selected antibiotics would retain their antimicrobial potency after single component admixtures. The drugs used in the study were admixed at therapeutic concentration in both Sodium Chloride Injection and 5% Dextrose Injection. Each of the sample solutions was inspected visually for physical compatibility, the pH recorded, and assayed microbiologically. This was done at specified intervals up to two months. The admixtures were stored in darkness at constant temperatures of 25° and 5°.

All antibiotics tested, except ampicillin sodium, retained their initial antimicrobial potency for a minimum of one month at 5° in both Sodium Chloride Injection and 5% Dextrose Injection. The antimicrobial activity of five antibiotics (ampicillin sodium, penicillin G potassium, buffered, cephalothin sodium, nafcillin sodium, and tetracycline hydrochloride) at 25° varied considerably depending upon which vehicle was used.

Three conclusions were reached, based on the experience of this study:

(1) The storage temperature after admixture can have a marked influence on the duration of

stability of the antibiotic; storage under refrigeration (5°) is preferred to room temperature storage (25°).

(2) Physical changes (color changes) which may occur were not an index of drug stability. All of the admixtures which exhibited such changes retained their initial potency.

(3) With the exception of a change of pH of three units in methcillin sodium, it was impossible to correlate minor changes in pH with decrease in drug activity.

Parker's (23) interim report on the stability of eight parenteral drug formulations, after single component admixtures in various I.V. solutions, utilized both chemical and biological assays. The stability of each drug (90% of the initial concentration remaining) was determined for intervals up to 72 hours. Again, the pH of each admixture was noted. Although several admixtures exhibited a significant decomposition of the active ingredient with the exception of one, all were free of any visible change during the duration of the study. Once again, the admixture pH, drug concentration, and brand variation in formulation appeared to be dominant factors in the degradation observed.

In a continuation of his earlier work, Parker (24, 25, 26, 27) presented a series of detailed stability studies for seven parenteral drug formulations, both in single and double component admixtures. Single component admixtures at

therapeutic concentrations were adjusted to varying pH values by the addition of acid or base. Using either spectrophotometric or microbiological assay, the 24 hour stability of the drug admixture at different pH values was obtained. The results of this study were then compared to stability data obtained for the same drug after admixture in various I.V. solutions.

To obtain further data, two of the parenteral drugs tested were admixed, individually, with other drug additives to form double components. The stability data obtained from this study were also compared to the previous tests. This study demonstrated a striking correlation between the final pH of the admixture and the duration of stability.

Dancey and Carew (28) investigated the therapeutic availability of various concentrations of antibiotics along with other intravenous additives after admixture in various I.V. solutions. Each of the 68 multicomponent admixtures were assayed microbiologically four times over a 24 hour period. In addition, the pH was recorded before each assay and visual examinations of the admixtures were made. With the exception of admixtures of oxytetracycline and penicillin G, all of the admixtures investigated were found to maintain their antibiotic potency for a 24 hour period after preparation. (The authors also stated that there appeared to be no correlation between a loss of activity and a change in admixture pH.)

It is interesting to note that the authors of three different stability studies (22, 23, 28) have made somewhat

different remarks concerning the effect of pH and the stability of the drugs tested. Potassium penicillin G, in a concentration of 1-2 million units/liter, was used in all three studies. Both Gallelli and Dancey reported a pH change in admixture and storage but observed no decrease in activity. However, Parker reported that the activity of the drug was pH dependent.

An explanation to this apparent discrepancy lies with the pH stability range of 5.5 to 7 for potassium penicillin G. When the admixtures pH changes fall within this range, as in the first two instances, no loss of activity was observed. When the range is exceeded, as in Parker's study, the activity of the drug will be pH dependent.

pH Studies Relative to Intravenous Admixtures

As already indicated, the pH of an admixture may have a profound influence on the solubility and chemical stability of the drug components. An alteration in pH is probably the chief cause of incompatibility in I.V. admixtures (29). A number of other investigators have expressed similar views and have presented several studies to demonstrate the relationship between pH and incompatibility.

To explore the apparent relationship of pH to incompatibility, Webb (30) rearranged an I.V. compatibility chart compiled by Patel and Phillips (11) so that the organic salts (I.V. additives) were listed in terms of increasing pH, and were at right angles to the same salts listed in terms of decreasing pH. A pattern of incompatible admixtures was shown

to cluster mainly in the upper left and lower right portions of the chart. These results indicated that, generally, solutions of high pH are mutually incompatible with solutions of low pH.

Edward (31) conducted an investigation to determine the pH change in an intravenous vehicle when a drug, or combination of drugs at definite concentrations were added. This information was then compared to the published pH range of stability of each drug component. The results of the comparison were used subsequently to predict the possible acid-base stability of a drug or drug combination in a vehicle. Admixtures were classified as incompatible when the pH of the solution was outside the accepted stability range of one or more of the drug components.

Many factors relative to the pH of admixtures were apparent from this study:

(1) The order of mixing may influence final pH due to a possible buffering action of the drug additives.

(2) Increasing the concentration of the drug additive may produce only minor changes in pH.

(3) The wide official pH range of the I.V. infusion solutions may affect final pH.

(4) The change in pH, per quantity of drug added to a given volume of solution, varied little from one unbuffered vehicle to the other.

The effect of pH on the solubility of ampicillin sodium was reported by Miyake and Keyofuzi (32). Solutions of ampicillin sodium in distilled water at concentrations of 250 mg./ml. and 50 mg./ml. were prepared and the pH recorded. The pH range for these solutions was 8.4 - 8.8. By reduction of the solution pH with the addition of an acid, the authors determined the pH (4.2) at which separation of the free ampicillin acid occurred. This separation of the ampicillin was manifest by a visible change (cloudiness) in the solution. Double component admixtures of the two concentrations of ampicillin sodium were then prepared with 120 different parenteral drug formulations. Cloudiness occurred in 26 admixtures with a pH range of 4.2 or below. However, the authors reported that the separation of ampicillin could be prevented by the use of a buffer system which would retard pH change.

Buffer capacity is defined as the ability of a system to resist a change in pH by the addition of an acid or base. Parker (33) suggested that the buffer capacity of either intravenous solutions or drug additives may greatly influence the admixture pH. In general, intravenous solutions containing organic anions such as lactates and acetates present in Ringers Injection, U.S.P., and Lactated Ringers Injection, U.S.P., have a relatively high buffer capacity. Intravenous solutions containing electrolytes and monosaccharides such as Sodium Chloride Injection, U.S.P., Dextrose Injection, U.S.P., have a low buffering capacity. As an example, an acid sensitive drug may precipitate from an intravenous solution

containing organic anions at pH of 5.5, and not from a dextrose solution having a pH of 4.5. In the latter case, the acid sensitive drug may have enough alkalinity to raise the pH of the admixture beyond that of precipitation.

In spite of the contributions made by those investigators, whose work has been reviewed here, one might be curious to find other instances of incompatibility which may not be made apparent by development of a precipitate or other visual signs of change. Because of the widespread use of corticosteroids in combination with pressor agents for the treatment of cardiogenic shock, this study will examine the possible interactions of one such pressor amine, metaraminol bitartrate, with a group of corticosteroid preparations. The admixtures will be examined spectrophotometrically to assess the advisability of these combinations.

CHAPTER II

EXPERIMENTAL

The purpose of the experimental work was to demonstrate the use of differential spectrophotometric analysis in detecting the occurrence of chemical interactions between two components of an intravenous admixture.

The admixtures used in this study were prepared in both Sodium Chloride Injection, U.S.P., and 5% Dextrose Injection, U.S.P., by the combination of metaraminol bitartrate (Aramine[a]) with each of the following corticosteriods: prednisolone sodium phosphate (Hydeltrasol[a]), dexamethasone sodium phosphate (Decadron[a]) methylprednisolone sodium succinate (Solu Medrol[b]), hydrocortisone (Cortef[b]), hydrocortisone-21-phosphate (Hydrocortone[a]), and hydrocortisone sodium succinate (Solu Cortef[b]).

Preliminary Investigation

The purpose of the preliminary investigation was to determine the spectrophotometric activity of each drug formulation after dilution in both Sodium Chloride Injection and 5% Dextrose Injection. The resultant spectra were considered to be the theoretical or standard activity of the drug formulation

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a - Merck, Sharp and Dohme, West Point, Pennsylvania.

b - Upjohn Comp., Kalamazoo, Michigan.

tested.

Using pipets and volumetric flasks, admixtures for each drug formulation in the two infusion fluids were prepared in varying concentrations. The resulting solutions were stored at room temperature, with normal light exposure.

A Bausch and Lomb Spectronic 600[a] Double Beam Spectrophotometer, providing an incident beam wavelength range of 220 to 320 millimicrons, was used to measure the absorbance of a sample from each admixture. The reference solution was determined by the diluent of the admixture sample. An attached Linear/Log Varicord 43[b] Recorder provided continuous recording of the ultraviolet spectrum showing the wavelength of maximum absorption (λmax).

The optimum spectrophotometric concentration for each drug formulation was determined from the concentration of those admixtures which demonstrated an absorbance range of between 0.2 and 0.9. At 4 and 8 hours after initial admixture, the absorption spectra for these solutions were redetermined. The optimum spectrophotometric concentration for the drug formulations was considerably less than the usual therapeutic concentration of the components of the admixture used in clinical practice.

The absorbance values obtained were used to plot Beer's-Law curves for each drug formulation in both Sodium Chloride

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a - Bausch and Lomb Optical Co., Rochester, New York.

b - Photovolt Corp., New York, New York.

Injection and 5% Dextrose Injection at 1, 4, and 8 hour intervals. At the same time intervals, the pH of a therapeutic concentration of each drug in both Sodium Chloride Injection and 5% Dextrose Injection was measured using a Corning Model 7[a] pH Meter.

Admixture Analysis

Two component admixtures were prepared in Sodium Chloride Injection and 5% Dextrose Injection containing metaraminol bitartrate in combination with each of six corticosteriods; prednisolone sodium phosphate, dexamethasone sodium phosphate, methylprednisolone sodium succinate, hydrocortisone, hydrocortisone-21-phosphate, and hydrocortisone sodium succinate.

Maintaining the same order of mixing, metaraminol bitartrate was added, using graduated pipets, to volumetric flasks containing Sodium Chloride Injection. The flasks were stoppered and shaken thoroughly. To each of these solutions, one of the corticosteriods mentioned previously was added, the flask stoppered and again shaken. The same admixture sequence was followed when the dextrose solution served as the diluent. The resulting admixtures were colorless and were stored at room temperature with normal light exposure. At 1, 4, and 8 hours after initial admixture, the pH of these admixtures was recorded.

After inspection for any visible changes (precipitation,

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a - Corning Scientific Instruments, Corning, New York.

color change, gas evolution), aliquots from each admixture were withdrawn and diluted in volumetric flasks to produce the optimum spectrophotometric concentration for each of the admixture components. This procedure was followed at each of the specified time intervals.

Solutions to be used in the reference beam of the spectrophotometer were prepared for each admixture component. The composition of the reference solution was identical to that of an individual component within the diluted admixture. By alternating the reference solutions, a differential spectrophotometric analysis was performed on each of the diluted admixtures obtaining the ultraviolet absorption spectrum for each drug component at 1, 4, and 8 hours after therapeutic admixture. Variations from the standard spectrum, either as an appreciable change in absorbance or in the development of secondary peaks, were considered to suggest the occurrence of a chemical interaction.

The absorption spectrum obtained for each drug formulation after admixture is shown in the figures which follow. The spectrum represents the average value of three replicates for each admixture combination. To provide a visual comparison, the standard or reference spectrum of the same drug in the same concentration and diluent is also provided. Included in the legends which accompany the ultraviolet spectrum are the λmax, admixture concentration, reference solution used in spectrophotometric analysis and the time interval which the spectrum was obtained after admixture.

The standard spectrum for each drug formulation was determined from the Beer's-Law curves obtained in the preliminary work. The graphs that follow contain the plotted Beer's-Law curve for each drug formulation in both Sodium Chloride Injection and 5% Dextrose Injection.

pH values obtained for the therapeutic admixture and the individual components are recorded in the tables that follow. A summary of the results of the admixture analysis is also presented.

CHAPTER III

RESULTS

In each of the admixtures described in this section, the medicinal agents were combined with the two infusion fluids, 5% Dextrose Injection and Sodium Chloride Injection, in concentrations resembling those employed in clinical application. Because the resulting admixtures were too dense, optically, for examination in the spectrophotometer, it was necessary to dilute aliquot samples to concentrations which would produce clear spectra throughout the U.V. range. The final dilutions were made at 1, 4, and 8 hours after initial admixture, immediately prior to scanning, so as to provide the maximum opportunity for a reaction to occur. In this way both physical and chemical changes could be observed.

Measurements of the pH of the original admixtures were also made at the 1, 4, and 8 hour intervals. The results of these observations are summarized in the tables accompanying the description of each admixture.

Metaraminol Bitartrate and Prednisolone Sodium Phosphate in Sodium Chloride Injection

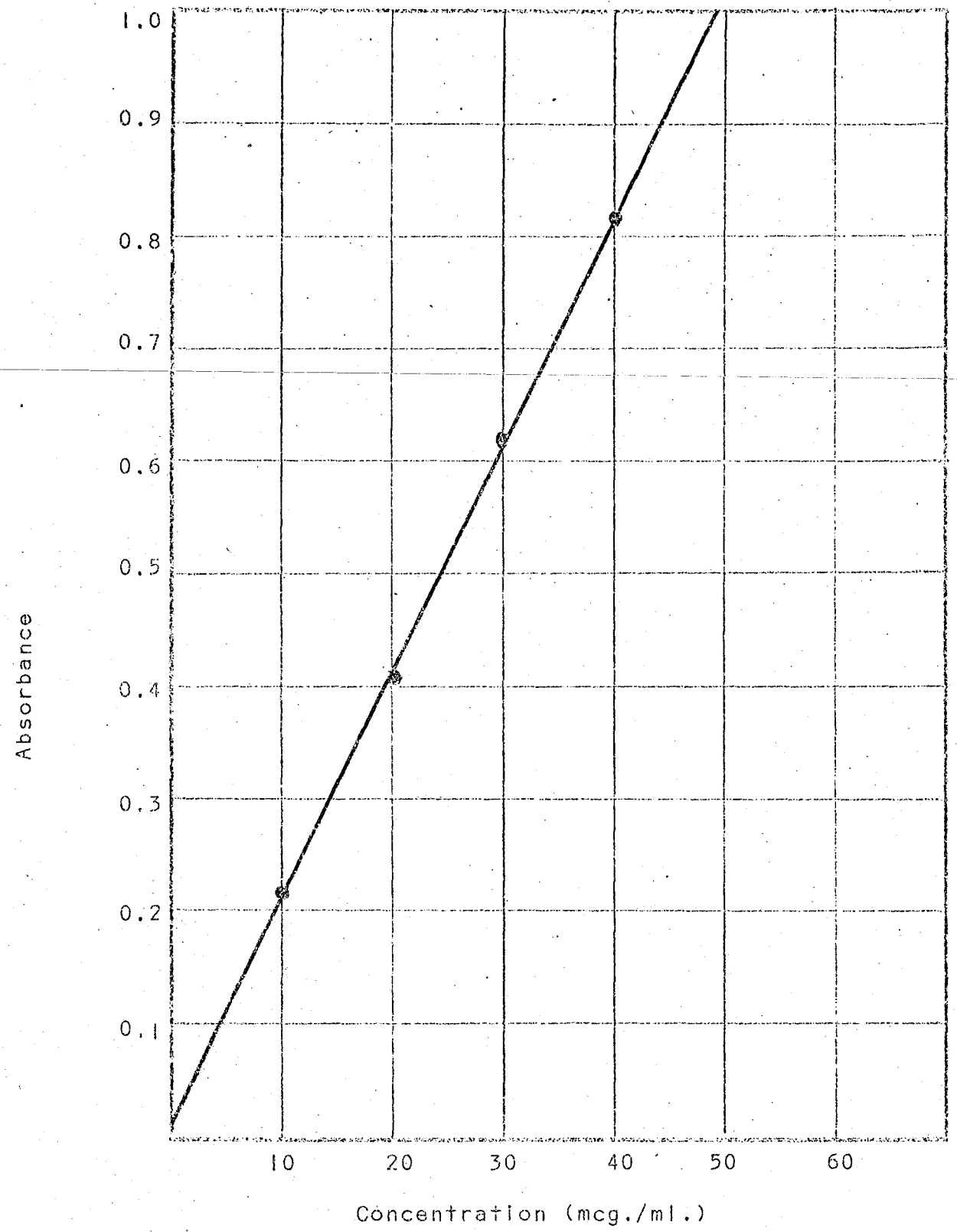
Metaraminol bitartrate, 500 mcg./ml., and prednisolone sodium phosphate, 100 mcg./ml., were mixed in Sodium Chloride Injection. Dilutions of the admixture were made to provide a concentration of 40 mcg./ml. for metaraminol bitartrate and 8 mcg./ml. for prednisolone sodium phosphate.

The absorption spectrum of the admixture was compared with the standard spectrum and demonstrated the development of a secondary peak for prednisolone sodium phosphate. This altered absorption spectrum would be suggestive of a change in this component. The absorption spectrum for metaraminol bitartrate was not altered appreciably throughout the eight hours of study (Figures 1, 2, 3).

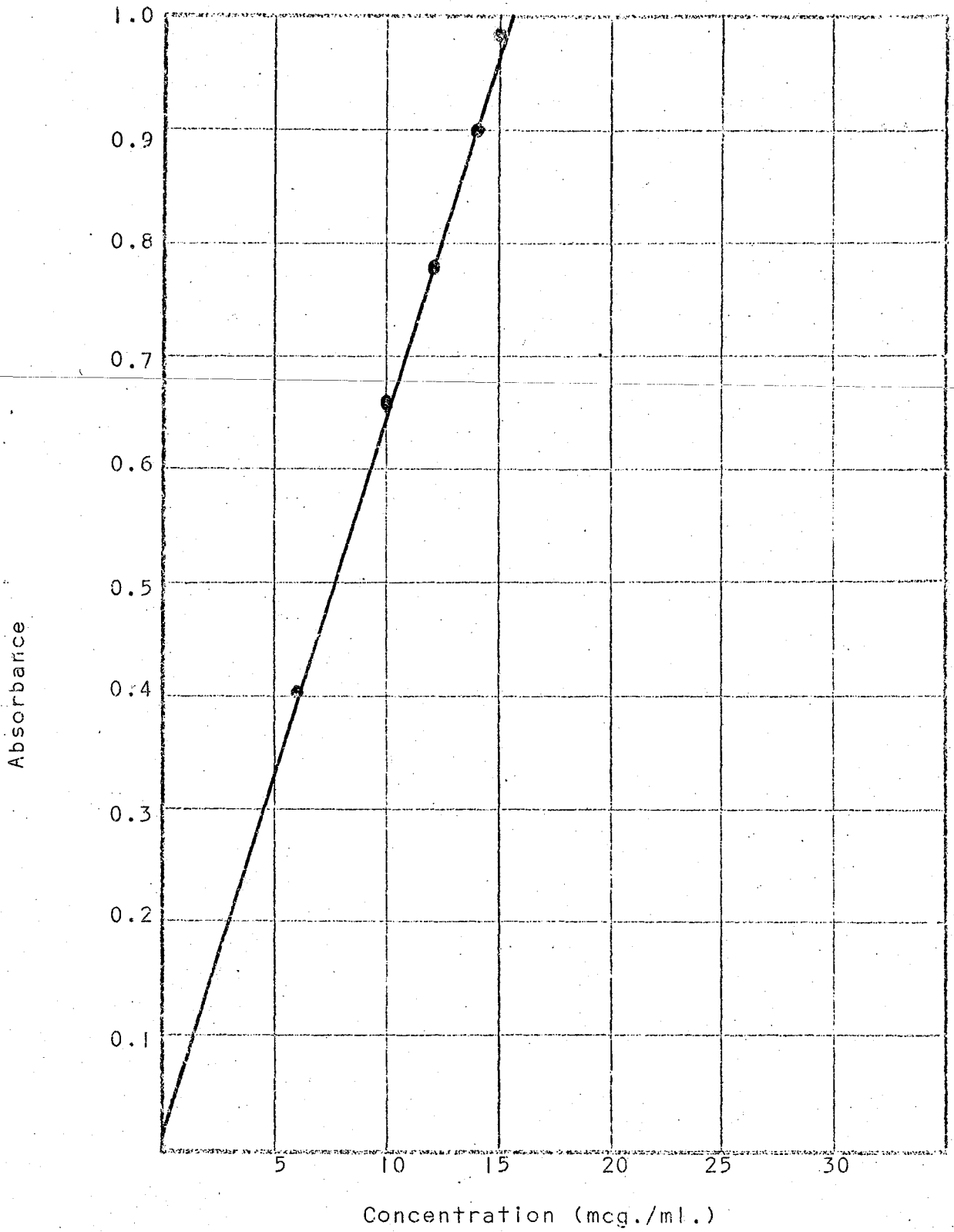
Measurements of the pH revealed only minor changes in the admixture during the period of study. The pH of the admixture was quite acidic, approximating that of metaraminol bitartrate without the presence of the corticosteroid (Table 1).

Table 1: pH Change of Metaraminol Bitartrate and Prednisolone Sodium Phosphate in Sodium Chloride Injection.

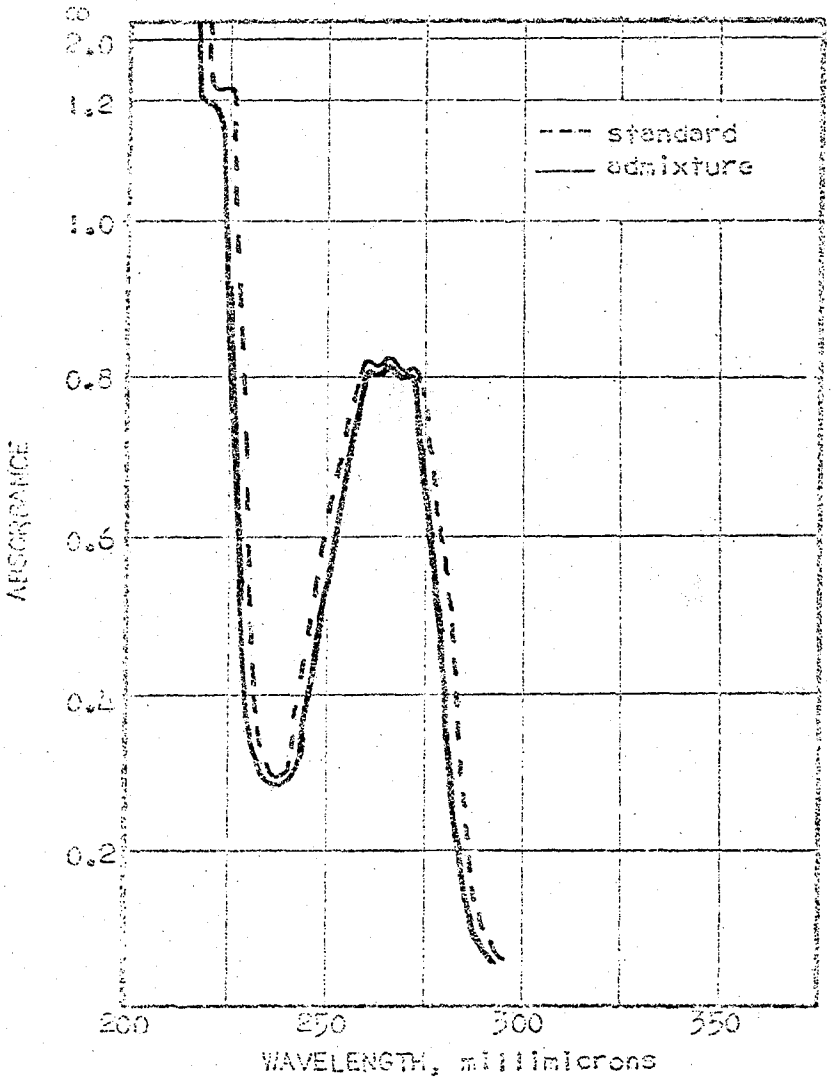
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Prednisolone Sodium Phosphate	500 100	3.8	3.7	3.7
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	500	3.7	3.7	3.6
Prednisolone Sodium Phosphate	100	6.9	6.8	6.8



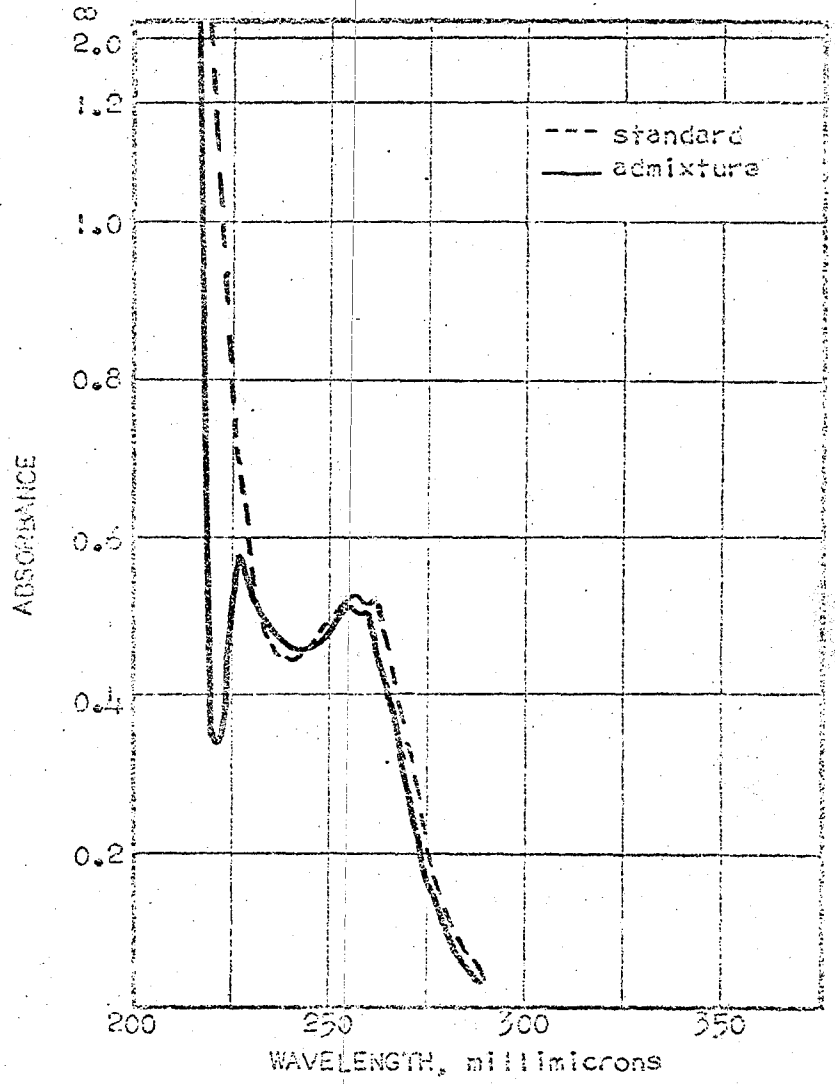
Graph 1. Beer plot for Metaraminol Bitartrate in Sodium Chloride Injection.



Graph 2. Beer plot for Prednisolone Sodium Phosphate in Sodium Chloride Injection.

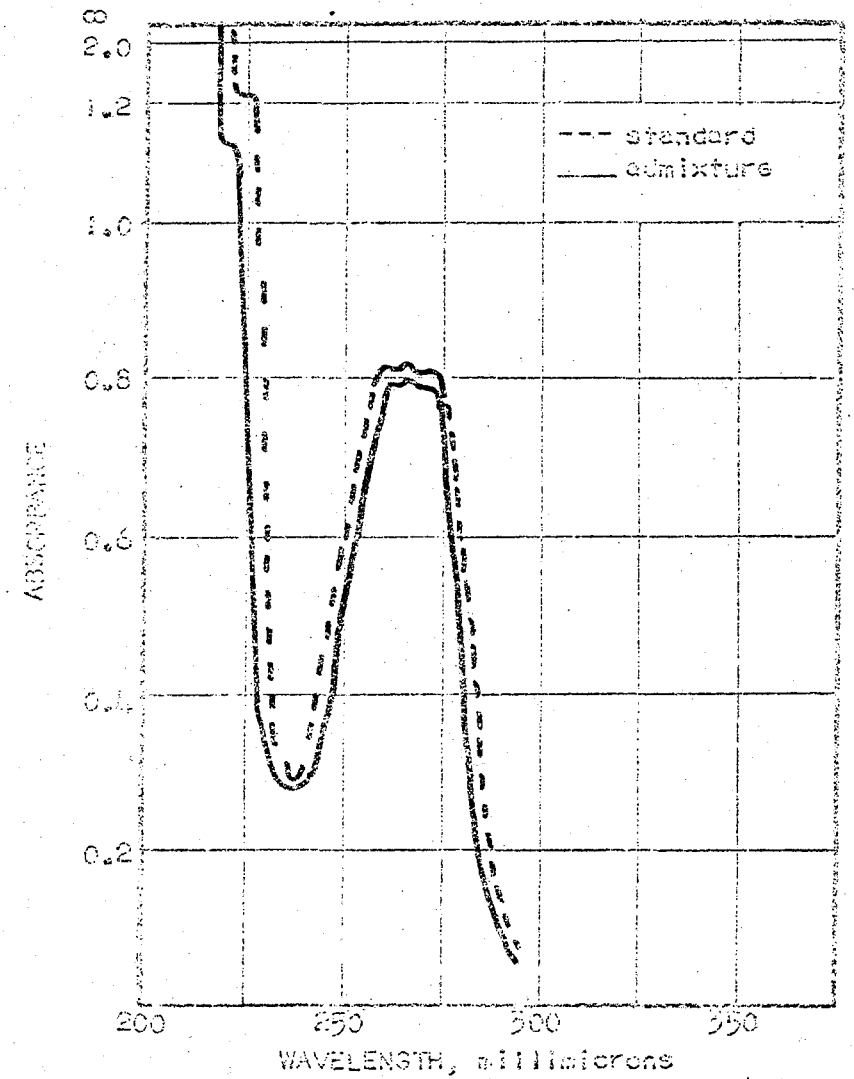


Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.

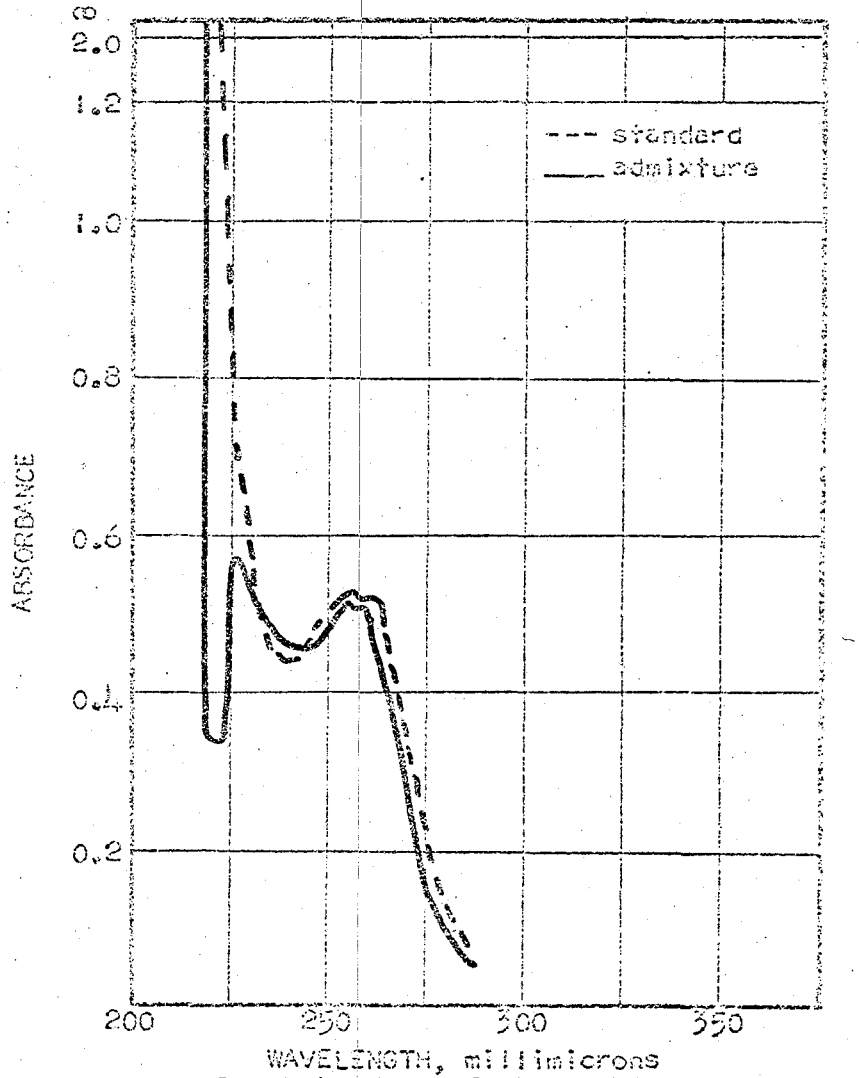


Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 1. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in Sodium Chloride Injection at one hour.

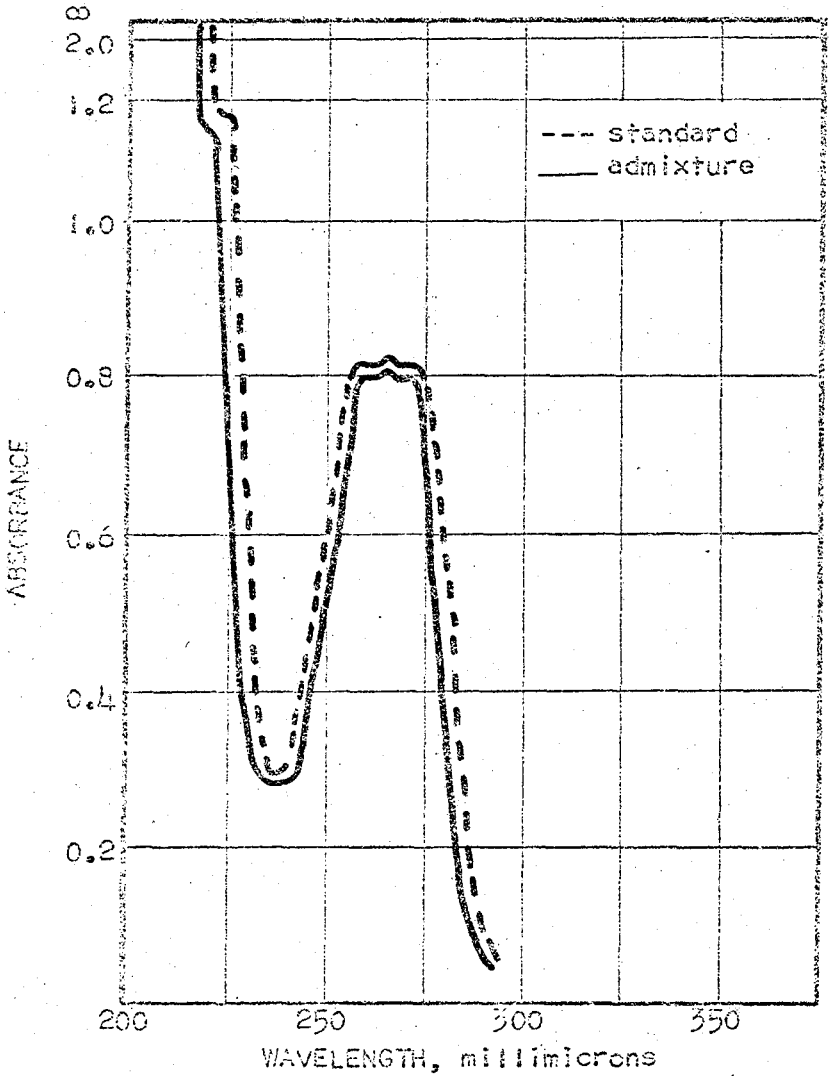


Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.

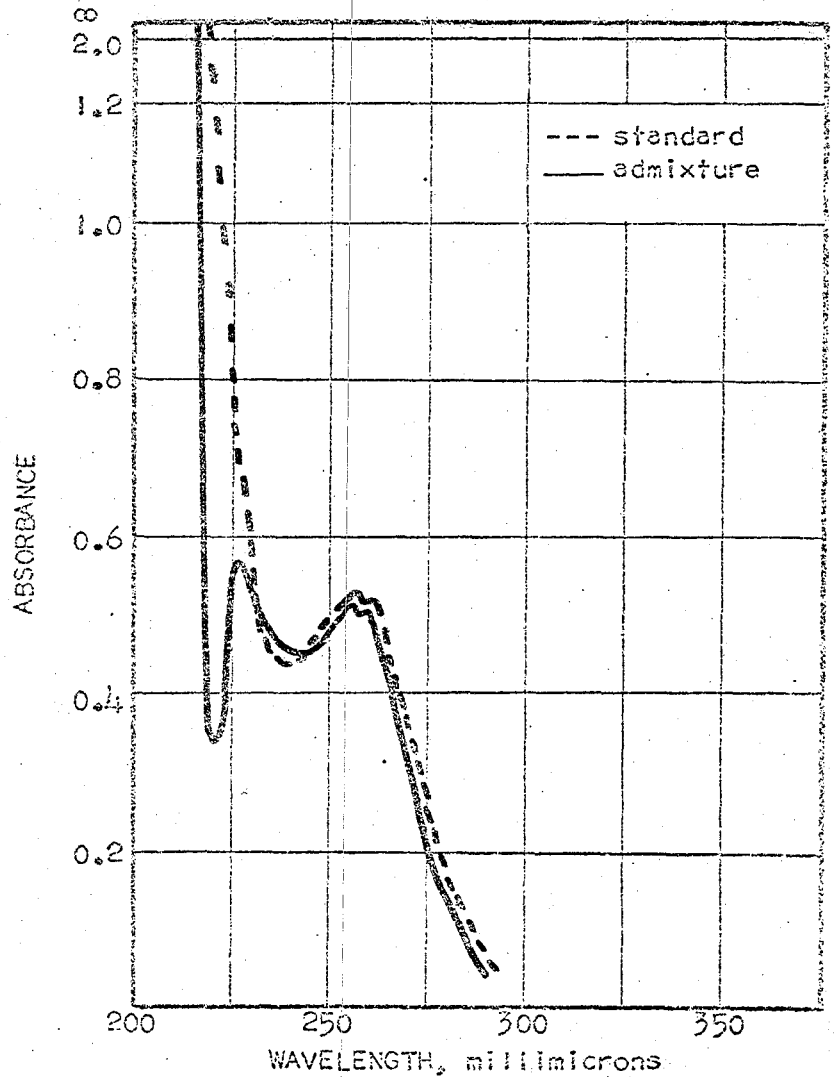


Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 2. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.



Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 3. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in Sodium Chloride Injection at eight hours.

Metaraminol Bitartrate and Prednisolone Sodium Phosphate in 5% Dextrose Injection

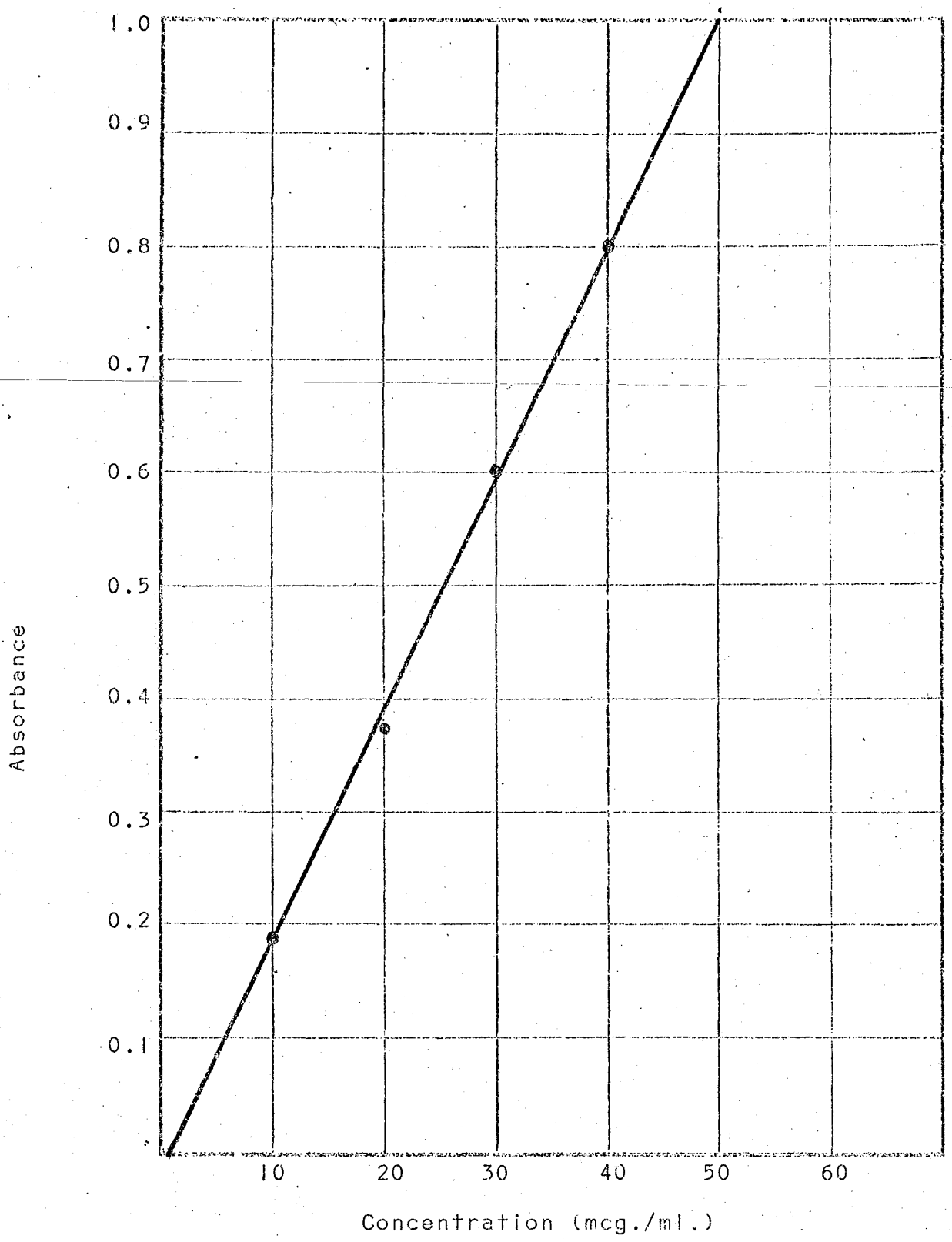
Using 5% Dextrose Injection as the diluent, metaraminol bitartrate and prednisolone sodium phosphate were mixed at a concentration of 500 mcg./ml. and 100 mcg./ml. respectively. As with the previous sodium chloride admixtures, dilution of aliquot samples was necessary to provide the optimum spectrophotometric concentration of 40 mcg./ml. for metaraminol bitartrate and 8 mcg./ml. for prednisolone sodium phosphate.

The absorption spectrum for the components of this admixture compared quite favorably with the results of the admixture analysis for the saline admixtures. Prednisolone sodium phosphate demonstrated a remarkably similar secondary peak, while the absorption spectrum for metaraminol bitartrate remained unaltered. It would appear that the influence of the diluting solutions selected was minimal (Figures 4, 5, 6).

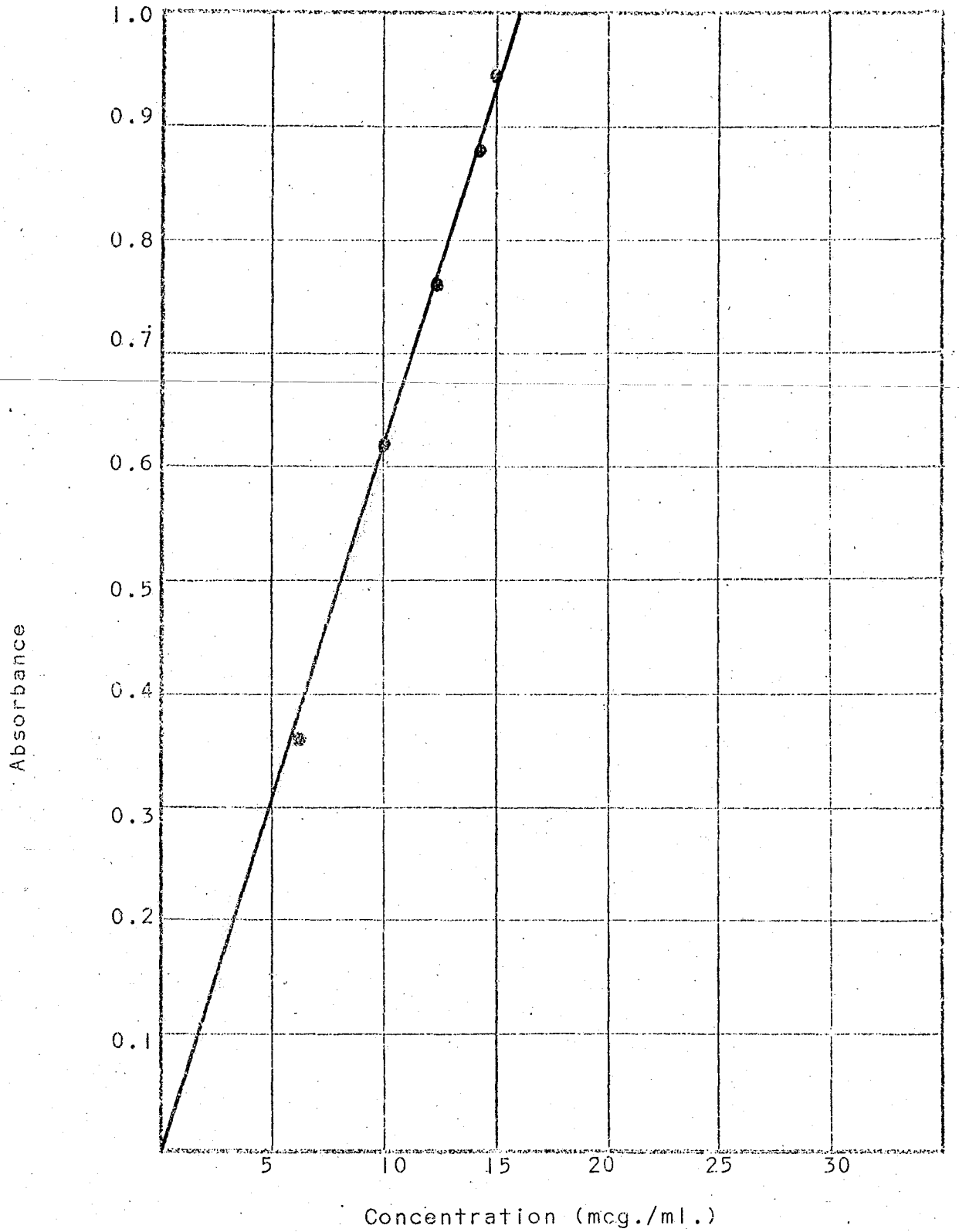
The pH values recorded for the therapeutic admixture and the individual components closely paralleled the values obtained for the saline admixtures (Table II).

Table II: pH Change of Metaraminol Bitartrate and Prednisolone Sodium Phosphate in 5% Dextrose Injection.

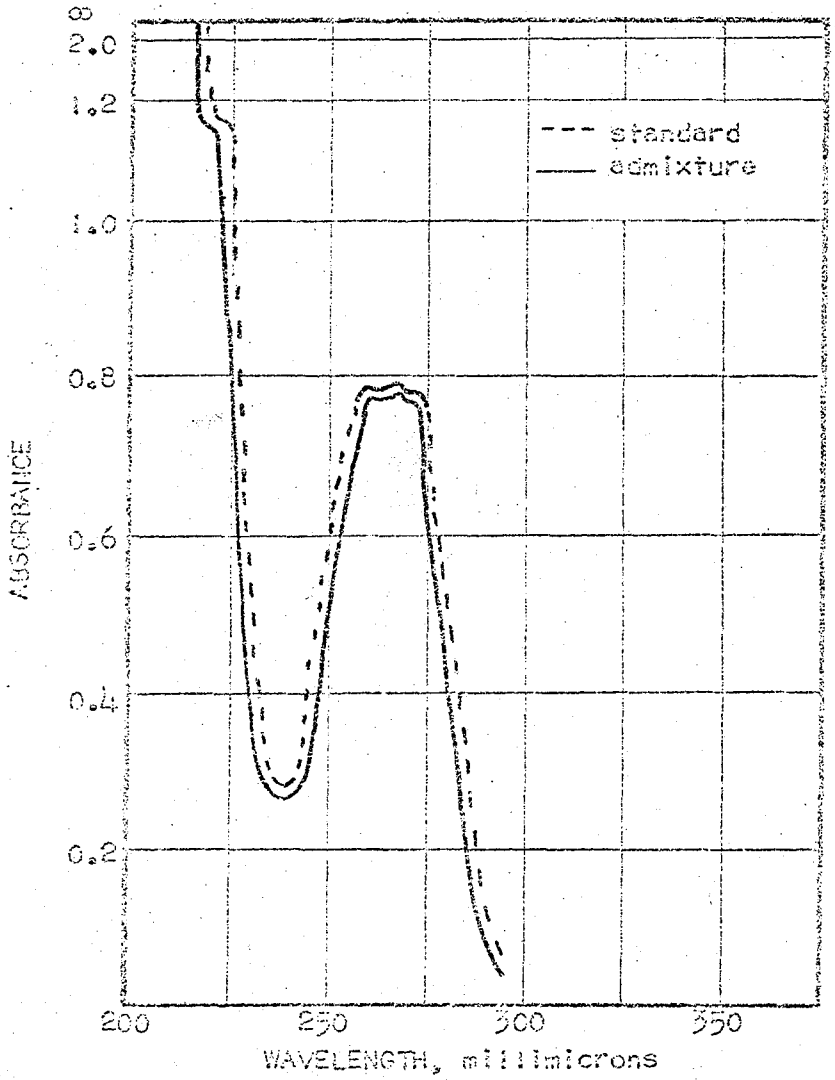
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Prednisolone Sodium Phosphate	500 100	3.8	3.9	3.9
5% Dextrose Injection		4.9	4.9	4.9
Metaraminol Bitartrate	500	3.6	3.6	3.6
Prednisolone Sodium Phosphate	100	6.5	6.5	6.5



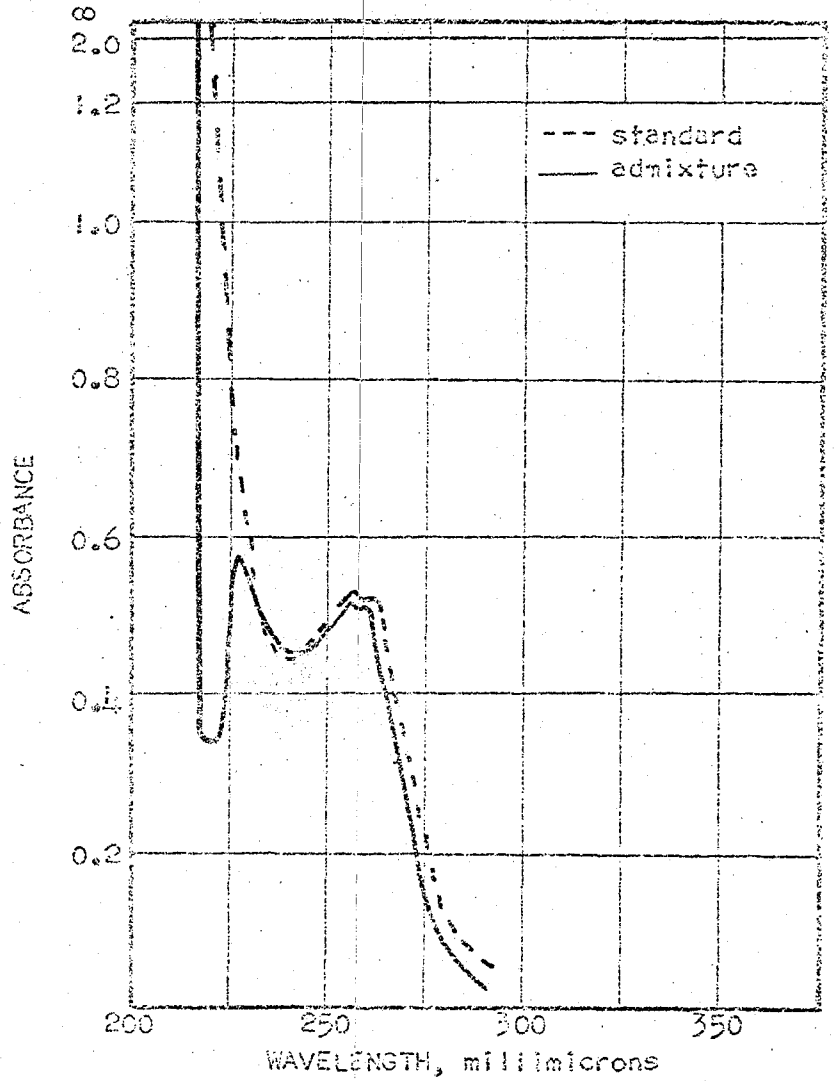
Graph 3. Beer plot for Metaraminol Bitartrate in 5% Dextrose Injection.



Graph 4. Beer plot for Prednisolone Sodium Phosphate in 5% Dextrose Injection.

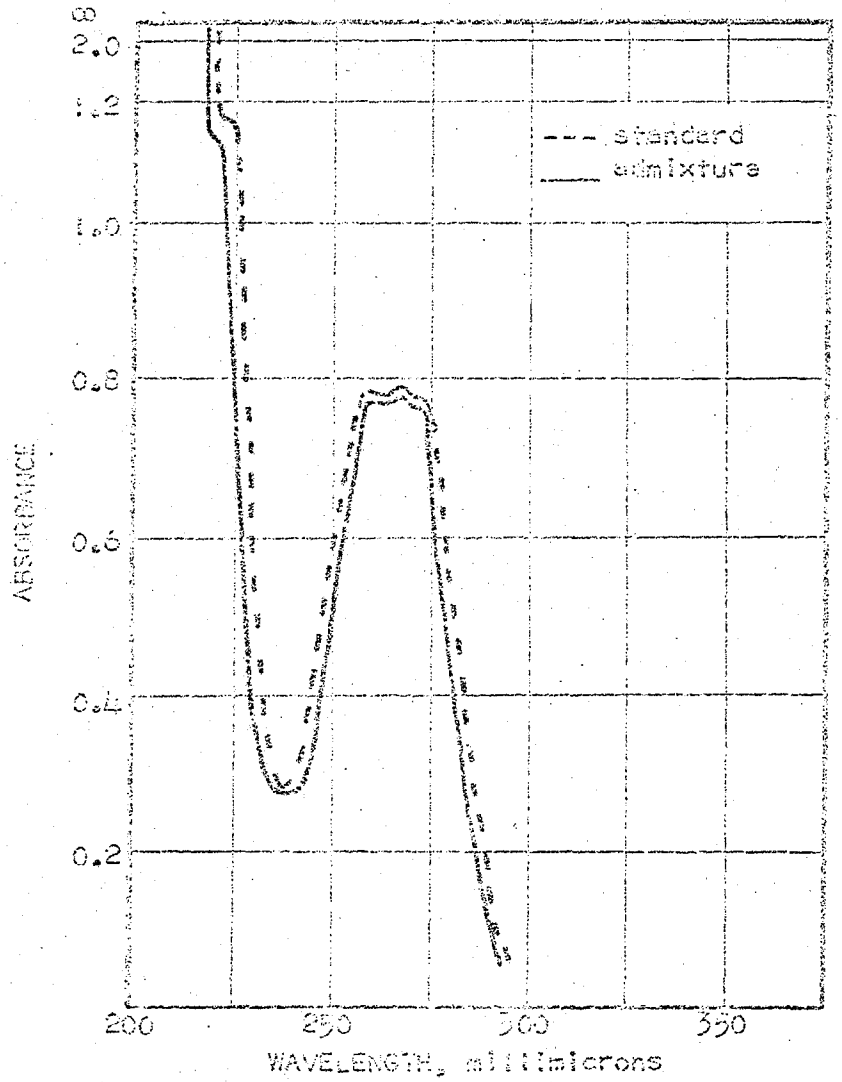


Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.

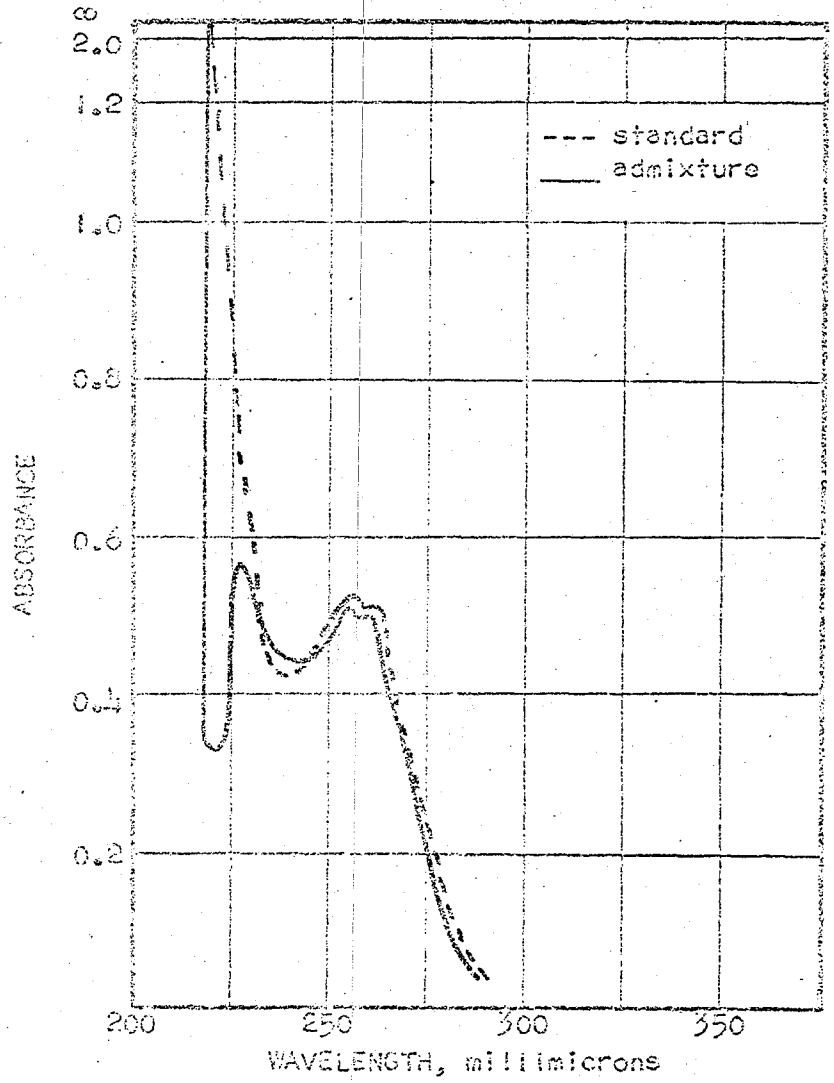


Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 4. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in 5% Dextrose Injection at one hour.

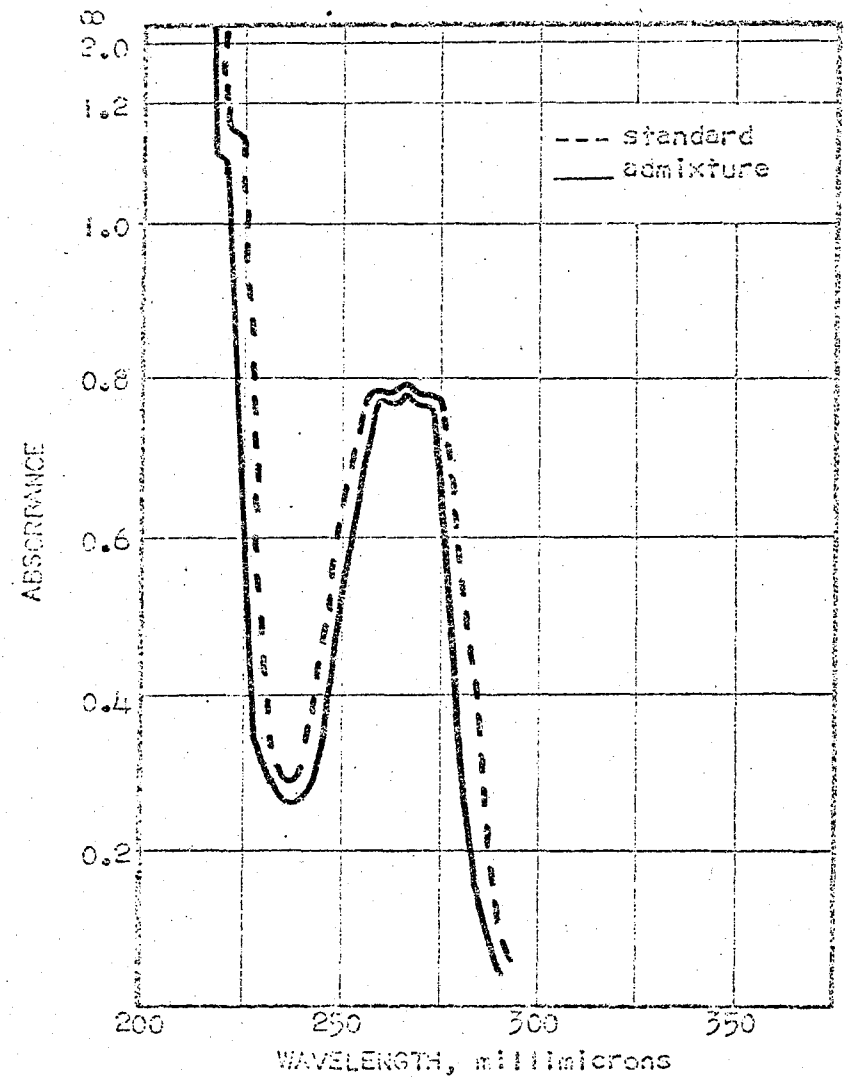


Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.

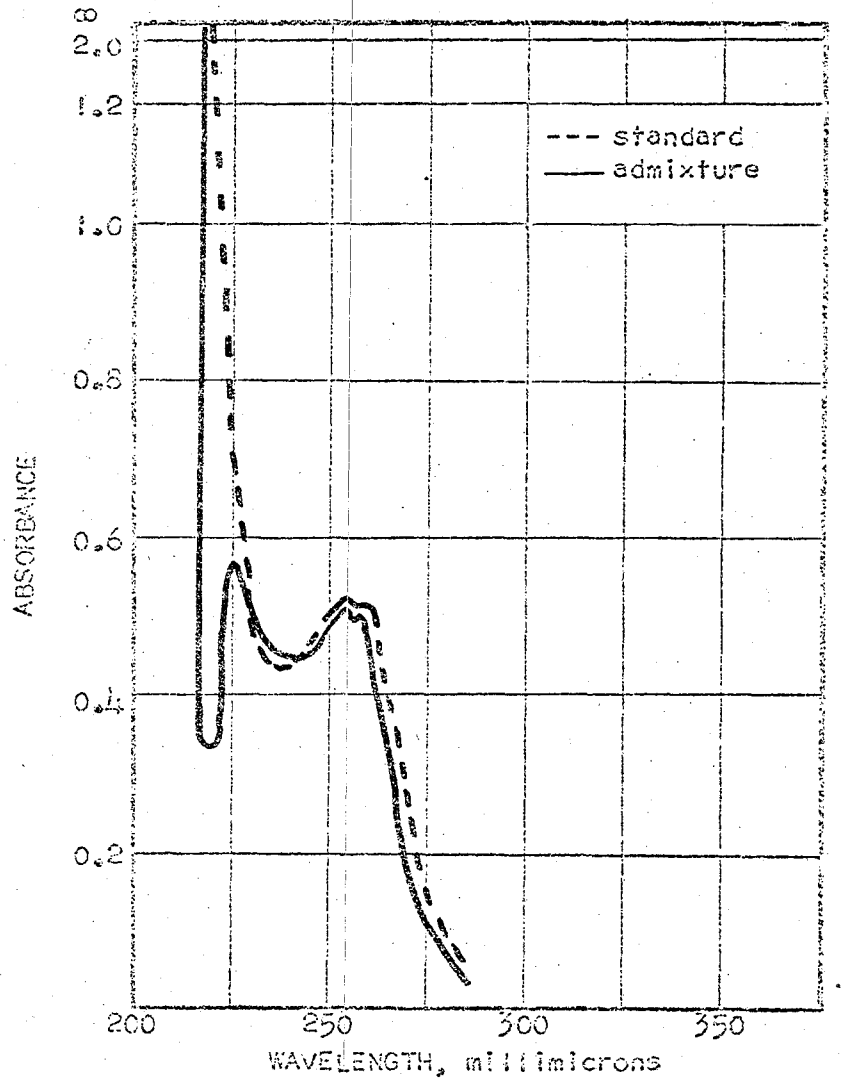


Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 5. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in 5% Dextrose Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Prednisolone Sodium Phosphate
8 mcg./ml.



Prednisolone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 6. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Prednisolone Sodium Phosphate (λmax 256 mμ) in 5% Dextrose Injection at eight hours.

Metaraminol Bitartrate and Dexamethasone Sodium Phosphate in Sodium Chloride Injection

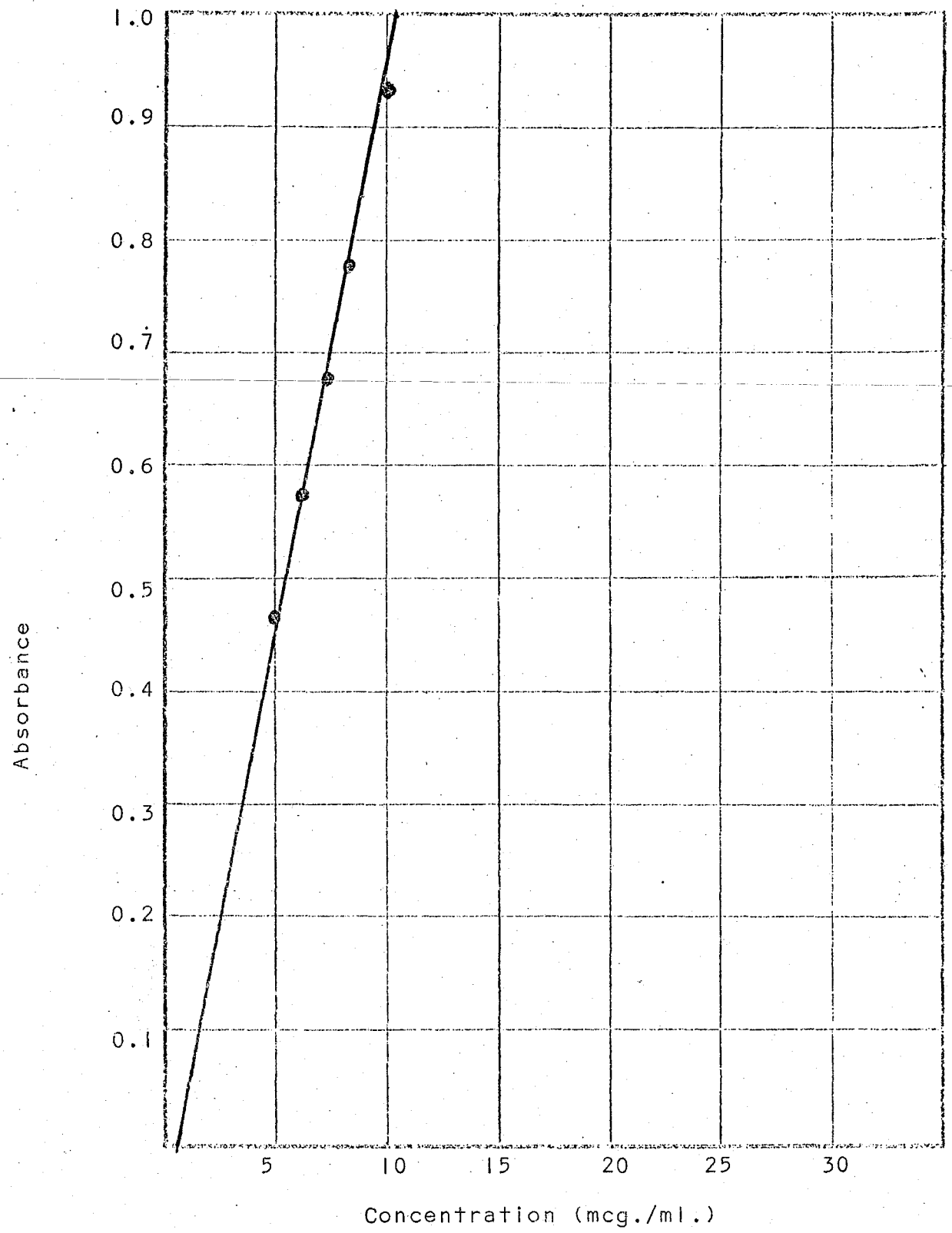
Metaraminol bitartrate, 100 mcg./ml., and dexamethasone sodium phosphate, 20 mcg./ml., were mixed in Sodium Chloride Injection. From the Beer plots obtained initially, the optimum spectrophotometric concentration for metaraminol bitartrate was determined to be 40 mcg./ml. and 8 mcg./ml. for dexamethasone sodium phosphate.

The absorption spectrum obtained was compared with the standard spectrum and demonstrated a shift in the λmax and loss of absorbance for dexamethasone sodium phosphate. This altered spectrum would be suggestive both of a loss of concentration and a change in the chemical structure for this component. The absorption spectrum for metaraminol bitartrate was not altered appreciably (Figures 7, 8, 9).

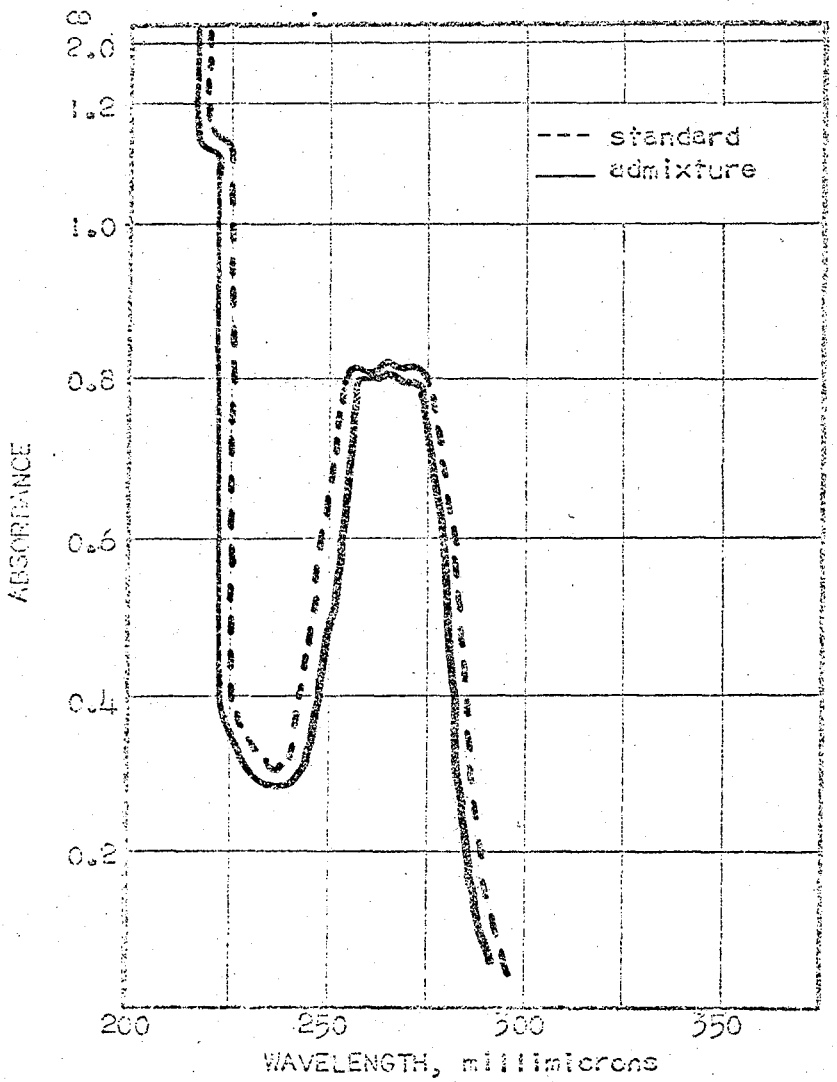
Admixtures of these two therapeutic agents, in Sodium Chloride Injection, produced a rather acidic solution which showed little variation over the period of the study (Table III).

Table III: pH Change of Metaraminol Bitartrate and Dexamethasone Sodium Phosphate in Sodium Chloride Injection.

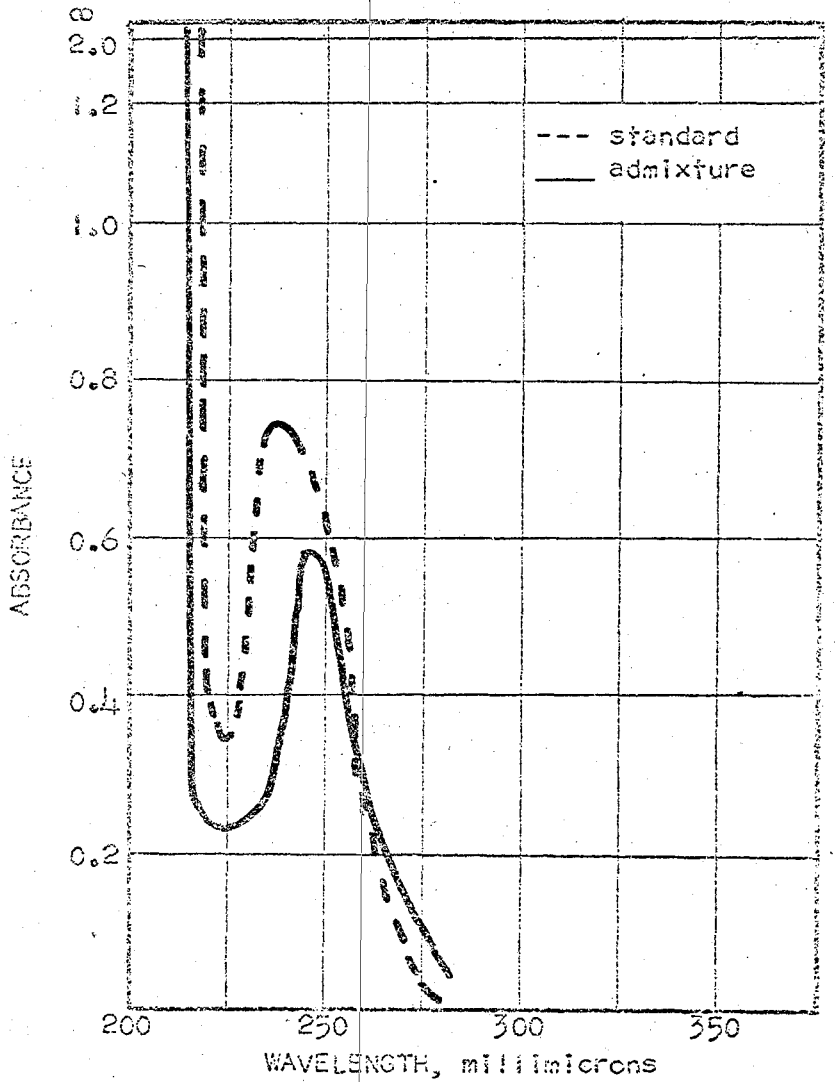
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Dexamethasone Sodium Phosphate	100 20	4.7	4.8	4.8
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	100	3.9	3.9	3.9
Dexamethasone Sodium Phosphate	20	7.1	7.1	7.1



Graph 5. Beer plot for Dexamethasone Sodium Phosphate in Sodium Chloride Injection.

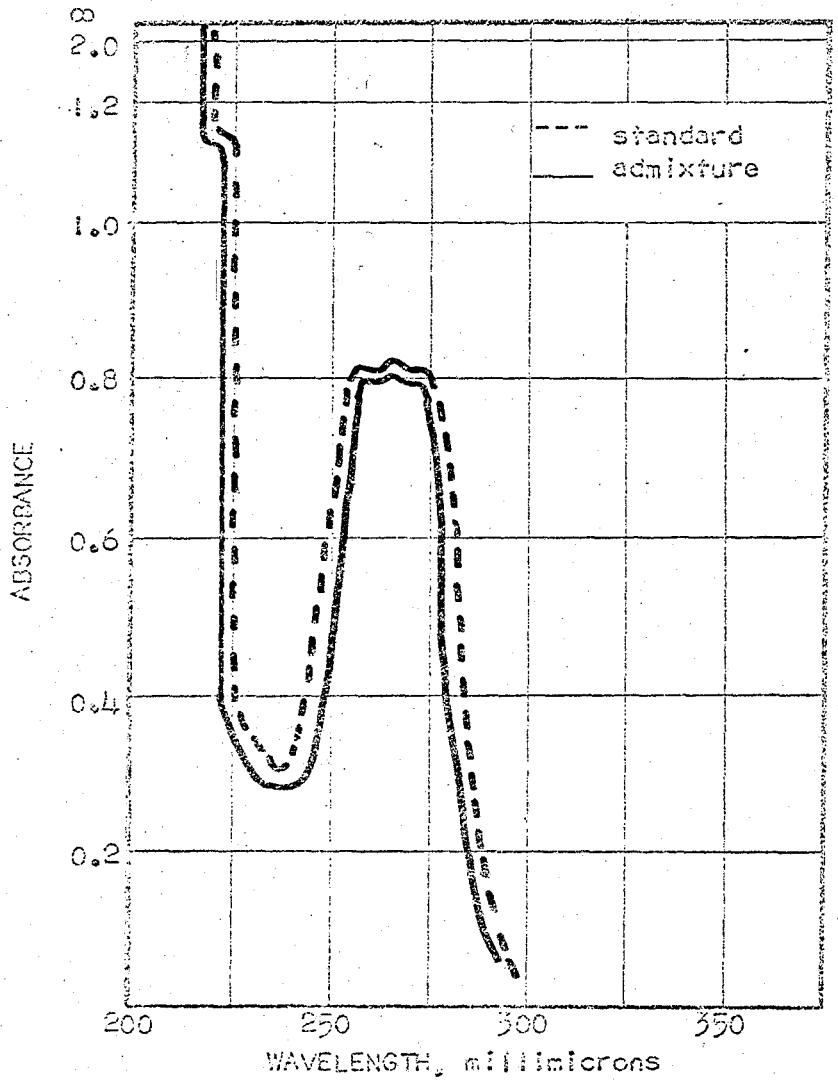


Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.

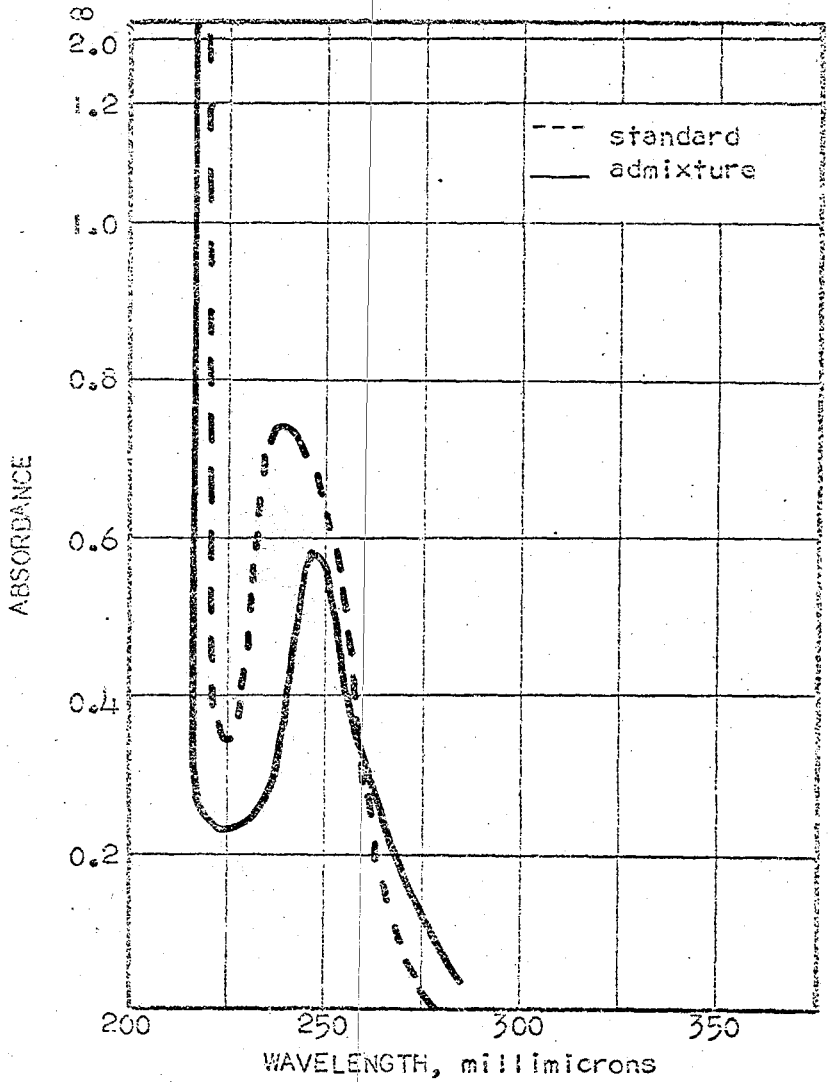


Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 7. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in Sodium Chloride Injection at one hour.

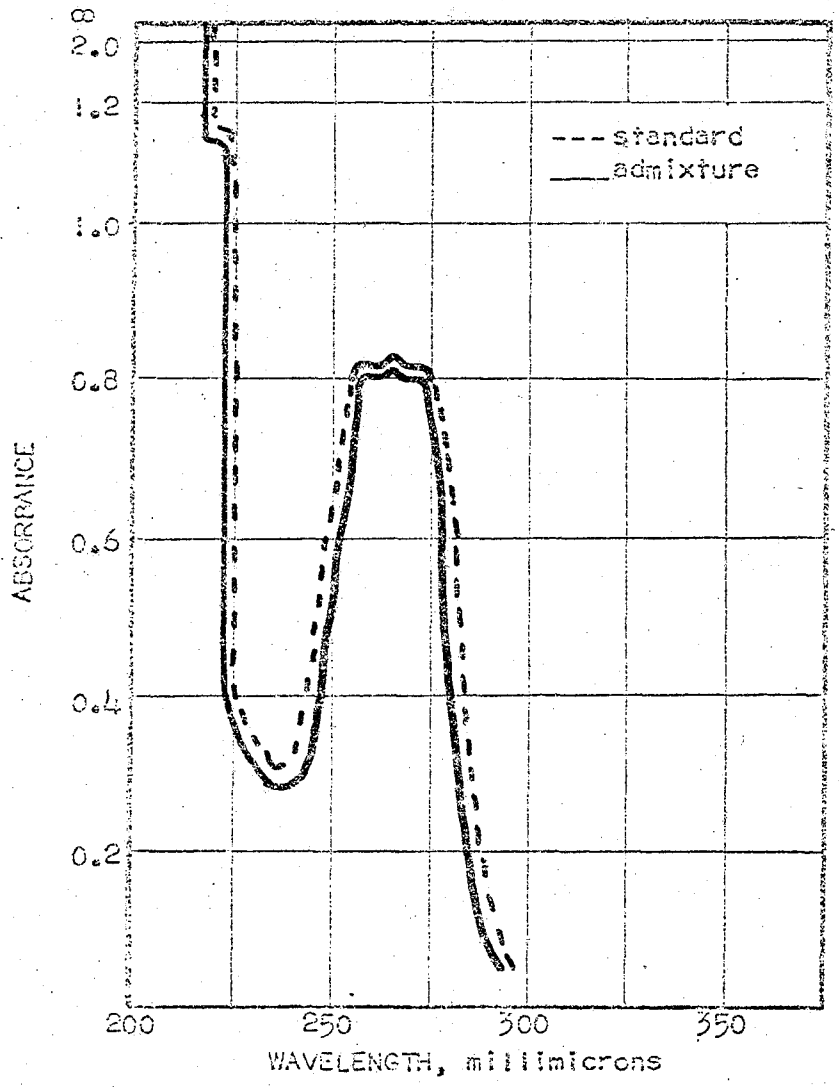


Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.

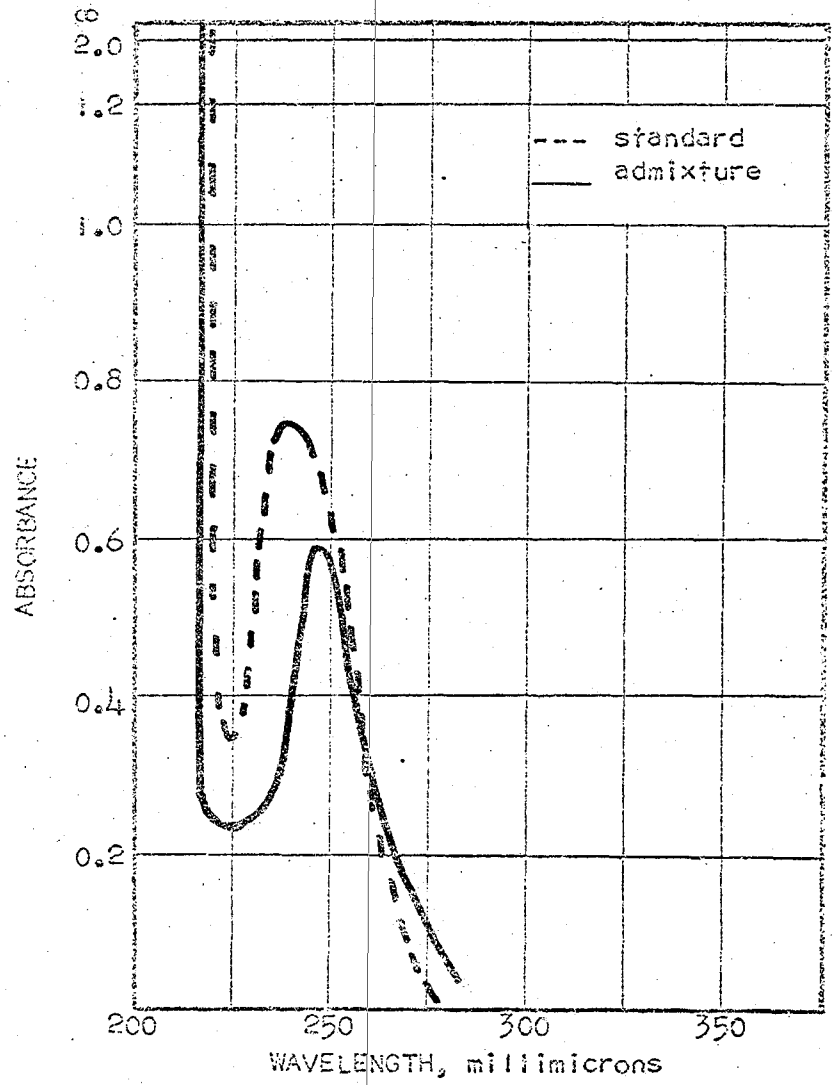


Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 8. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.



Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 9. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in Sodium Chloride Injection at eight hours.

Metaraminol Bitartrate and Dexamethasone Sodium Phosphate in 5% Dextrose Injection

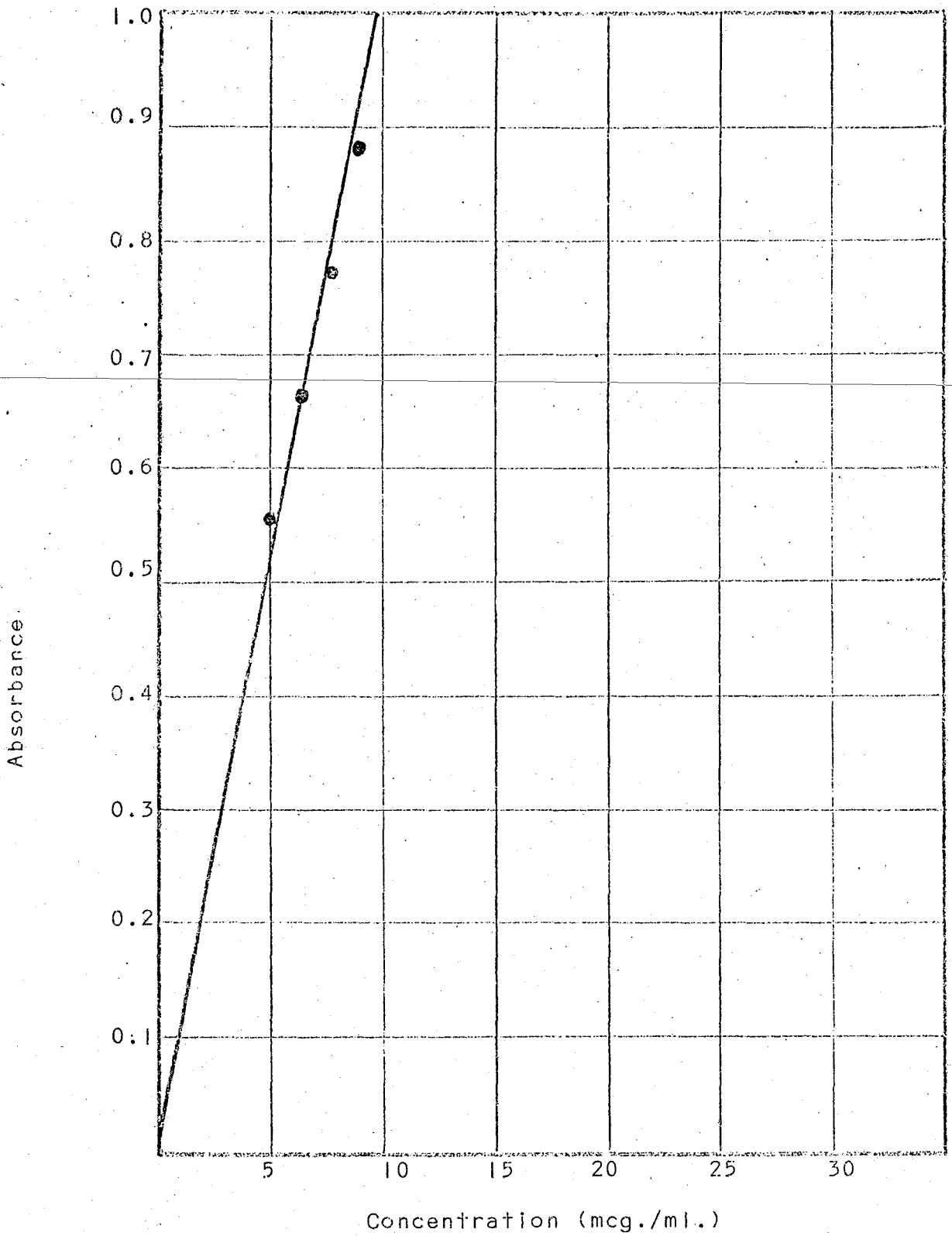
The admixture of metaraminol bitartrate, 500 mcg./ml., and dexamethasone sodium phosphate, 100 mcg./ml., in 5% Dextrose Injection, represented a concentration which was five times greater than the previous admixture containing Sodium Chloride Injection as the diluent. The concentration ratio, 5:1, however, remained the same. The optimum spectrophotometric concentration used to obtain the absorption spectrum also remained the same; metaraminol bitartrate, 40 mcg./ml., and dexamethasone sodium phosphate, 8 mcg./ml.

The absorption spectrum determined for each drug component resembled the spectrum obtained for the components when admixed at a lower concentration. Dexamethasone sodium phosphate demonstrated a shift in the λmax and a loss of absorbance, while metaraminol bitartrate remained appreciably unchanged (Figures 10, 11, 12).

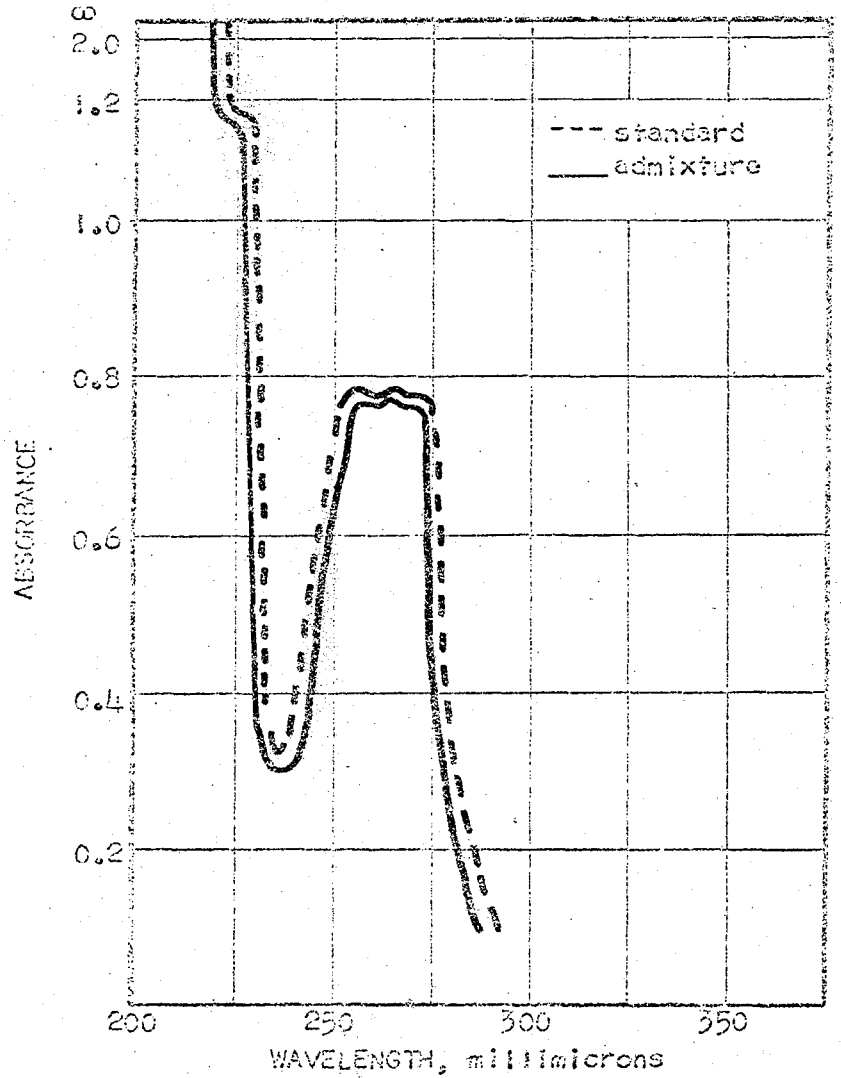
It was noted that the increased concentration of each drug component did not create an appreciable alteration in the pH values for either the individual drug components or the therapeutic admixture (Table IV).

Table IV: pH Change of Metaraminol Bitartrate and Dexamethasone Sodium Phosphate in 5% Dextrose Injection.

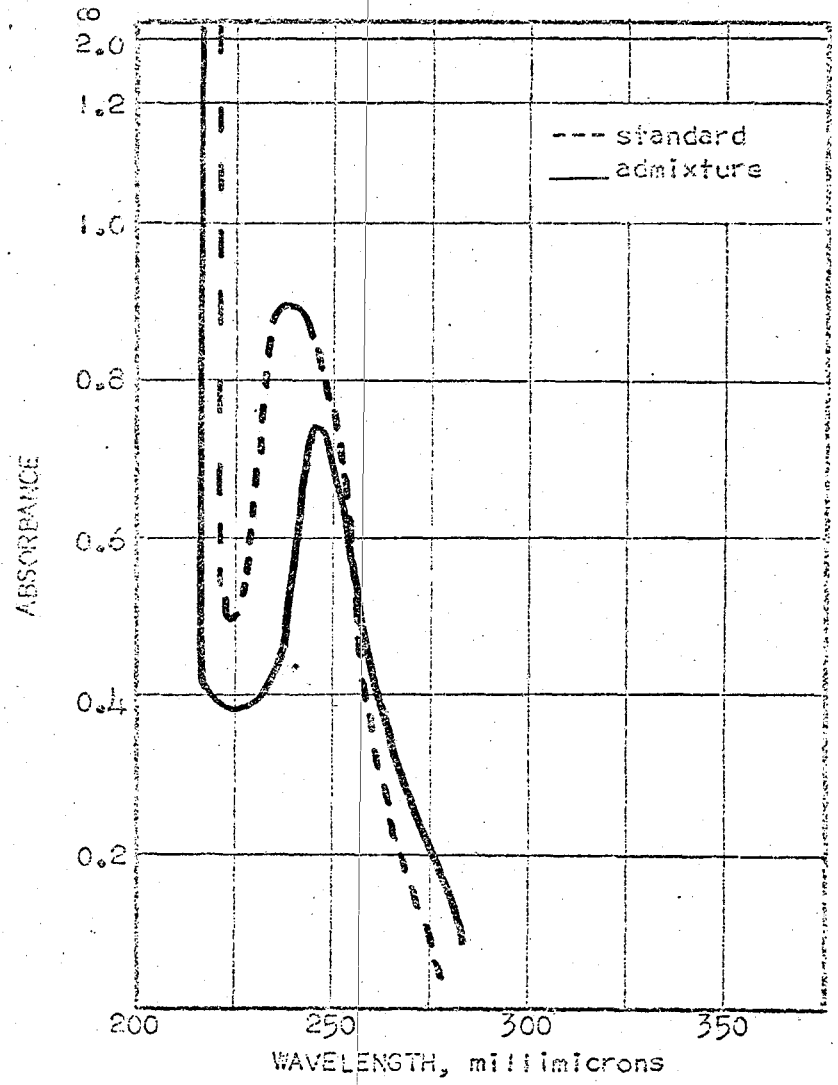
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Dexamethasone Sodium Phosphate	500 100	5.0	5.1	5.0
5% Dextrose Injection		5.0	5.0	5.0
Metaraminol Bitartrate	500	3.6	3.6	3.6
Dexamethasone Sodium Phosphate	100	7.7	7.6	7.5



Graph 6. Beer plot for Dexamethasone Sodium Phosphate in 5% Dextrose Injection.

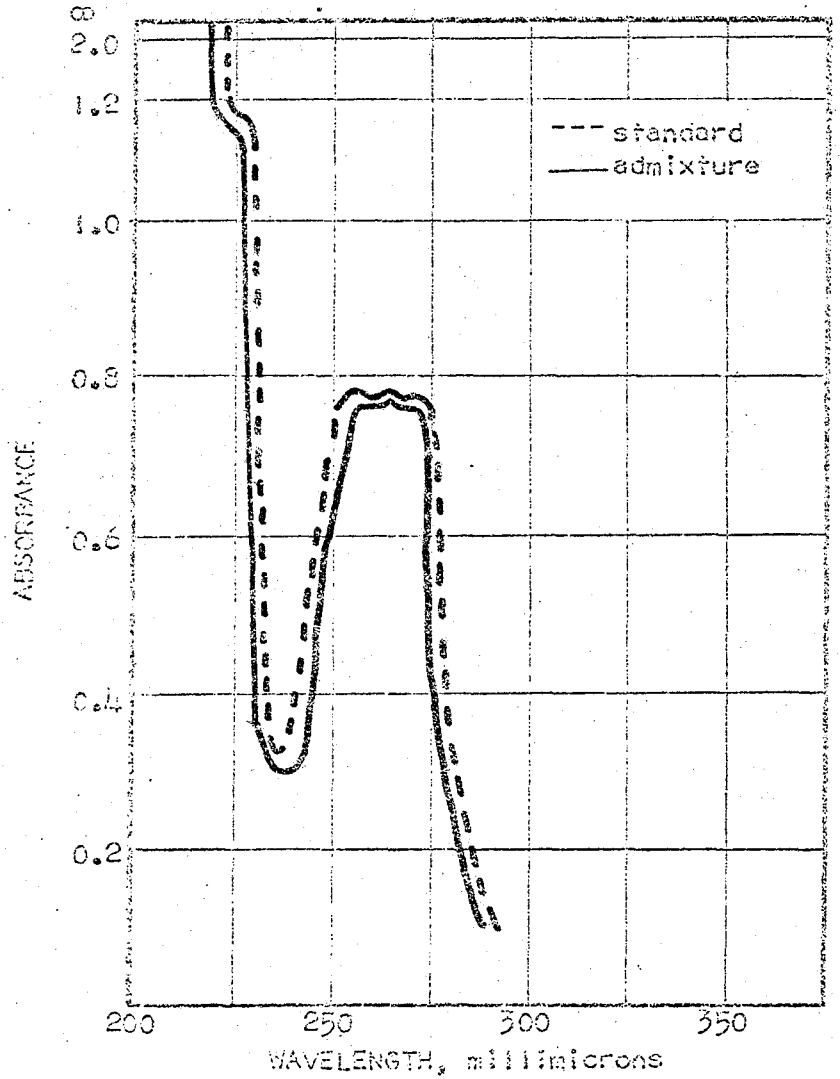


Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.

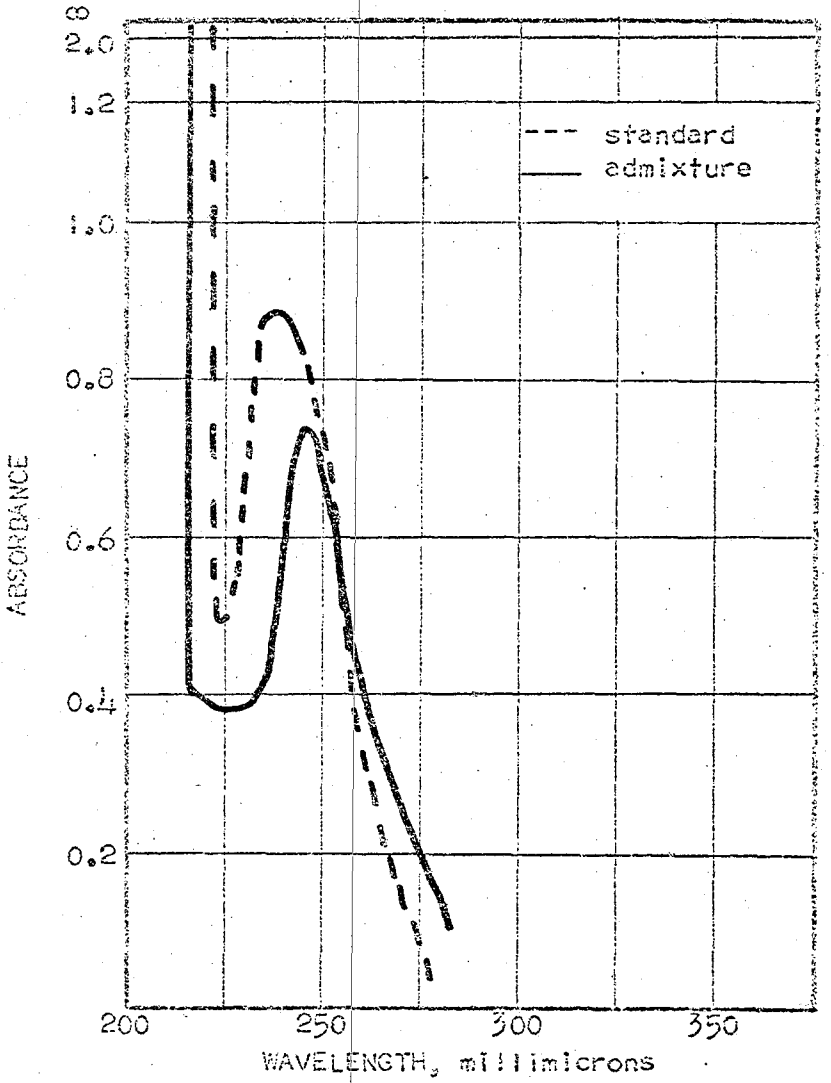


Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 10. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in 5% Dextrose Injection at one hour.

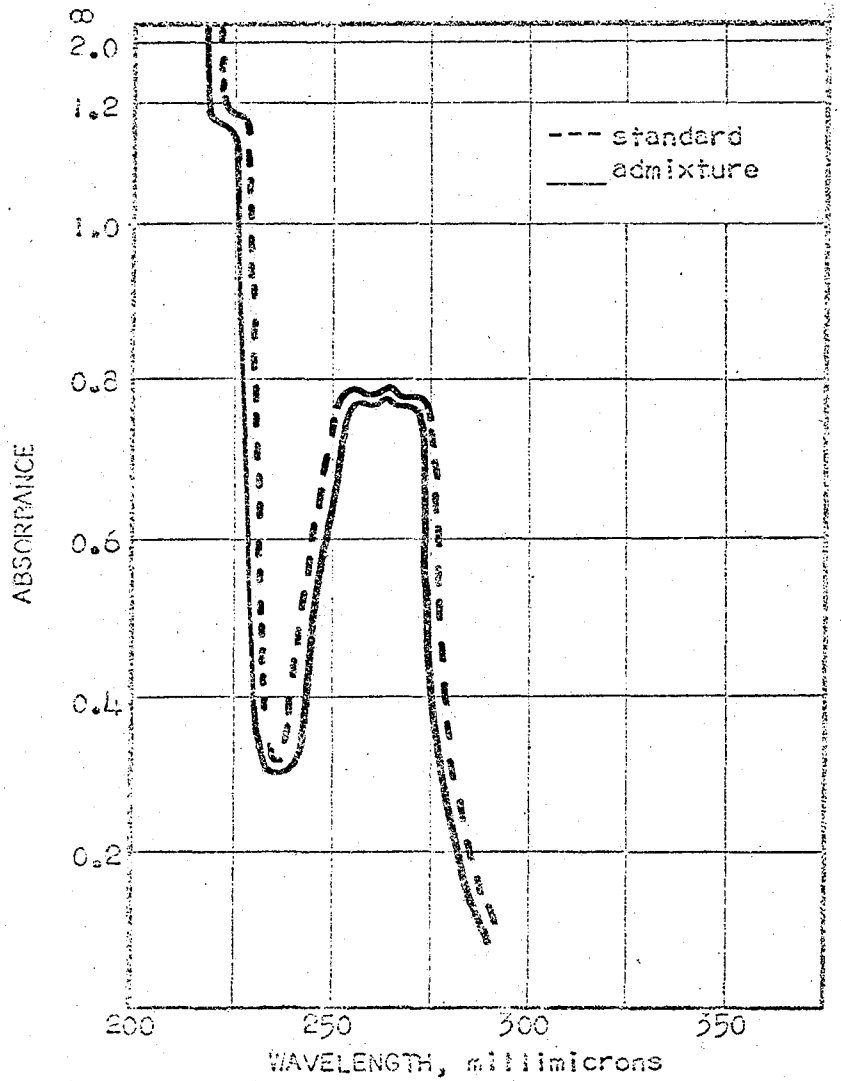


Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.

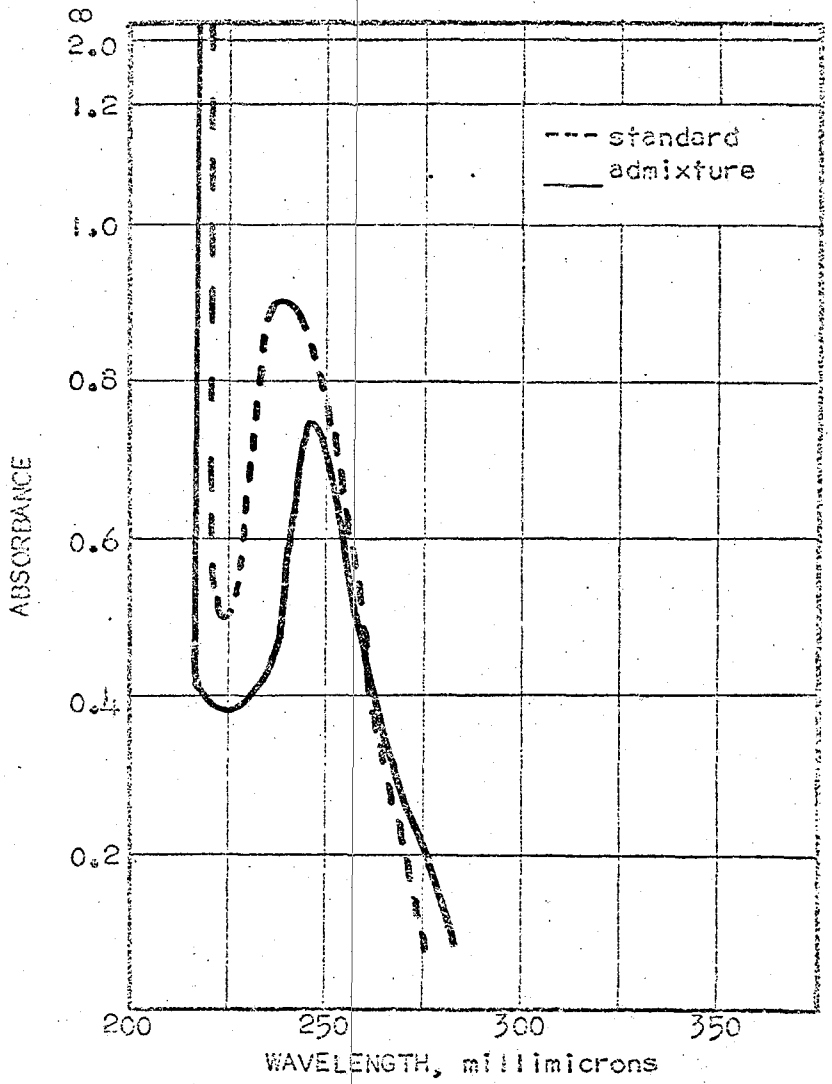


Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 11. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in 5% Dextrose Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Dexamethasone Sodium Phosphate
8 mcg./ml.



Dexamethasone Sodium Phosphate
8 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 12. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Dexamethasone Sodium Phosphate (λmax 239 mμ) in 5% Dextrose Injection at eight hours.

Metaraminol Bitartrate and Methylprednisolone Sodium Succinate in Sodium Chloride Injection

Metaraminol bitartrate, 400 mcg./ml., and methylprednisolone sodium succinate, 125 mcg./ml., were mixed in Sodium Chloride Injection. Within four hours a precipitate developed in this admixture. Therefore, aliquots, at the stated time intervals, were withdrawn by using a Swinnex-25,[a] 0.22 micron membrane filter. Dilution of these filtered aliquots provided the optimum spectrophotometric concentration for each component; metaraminol bitartrate, 40 mcg./ml., and methylprednisolone sodium succinate, 12.5 mcg./ml.

Comparison of the absorption spectrum obtained with the standard spectrum demonstrated an appreciable loss of absorbance for methylprednisolone sodium succinate, suggesting a reduction in the concentration for this component. The absorption spectrum for metaraminol bitartrate also demonstrated a minor loss of absorbance (Figures 13, 14, 15).

The pH of the admixture, which remained constant throughout the study, essentially resembled the initial pH of metaraminol bitartrate (Table V).

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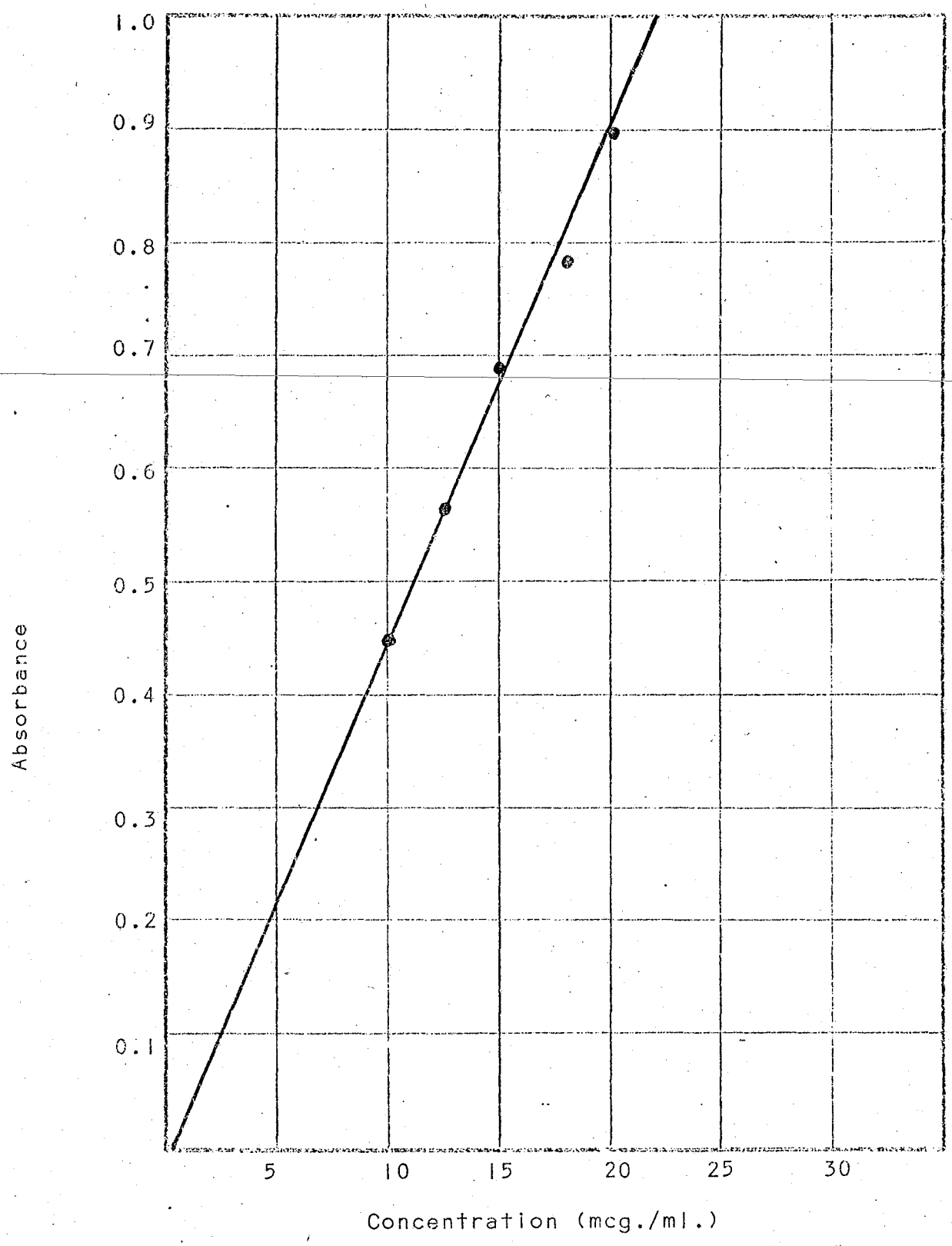
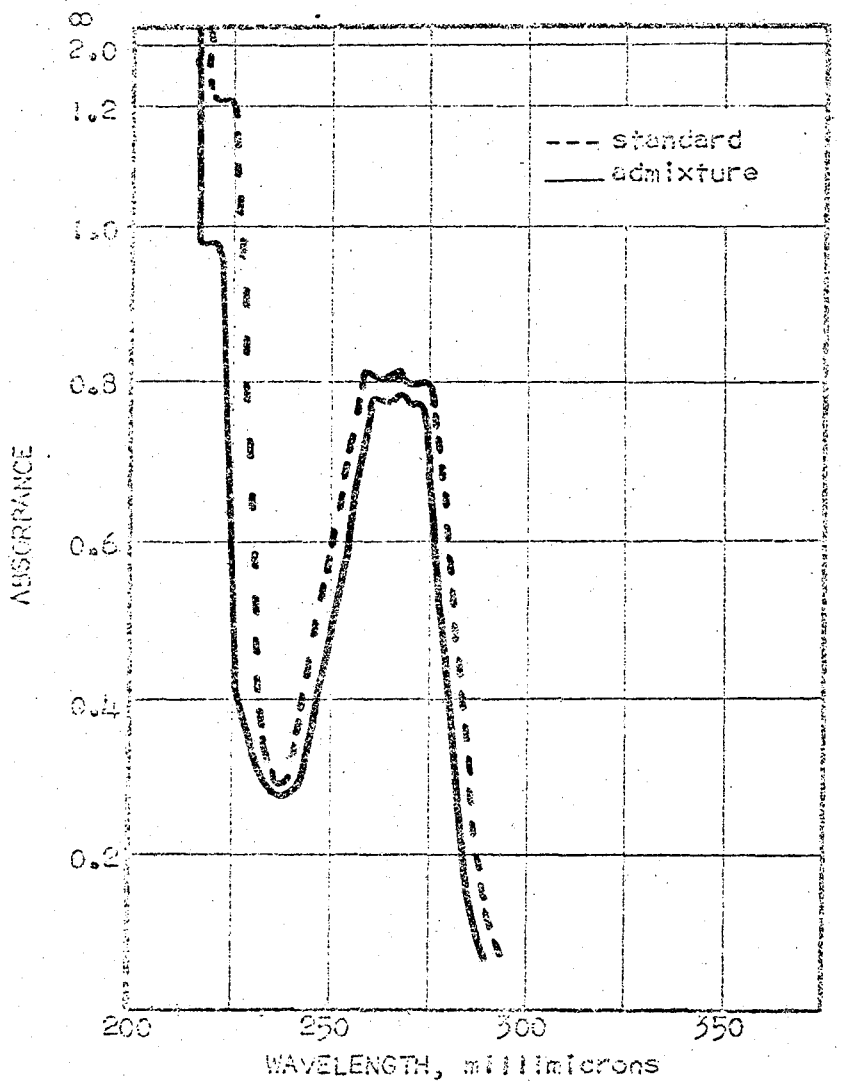
a - Millipore Corp., Bedford, Massachusetts.

Table V: pH Change of Metaraminol Bitartrate and Methylprednisolone Sodium Succinate in Sodium Chloride Injection.

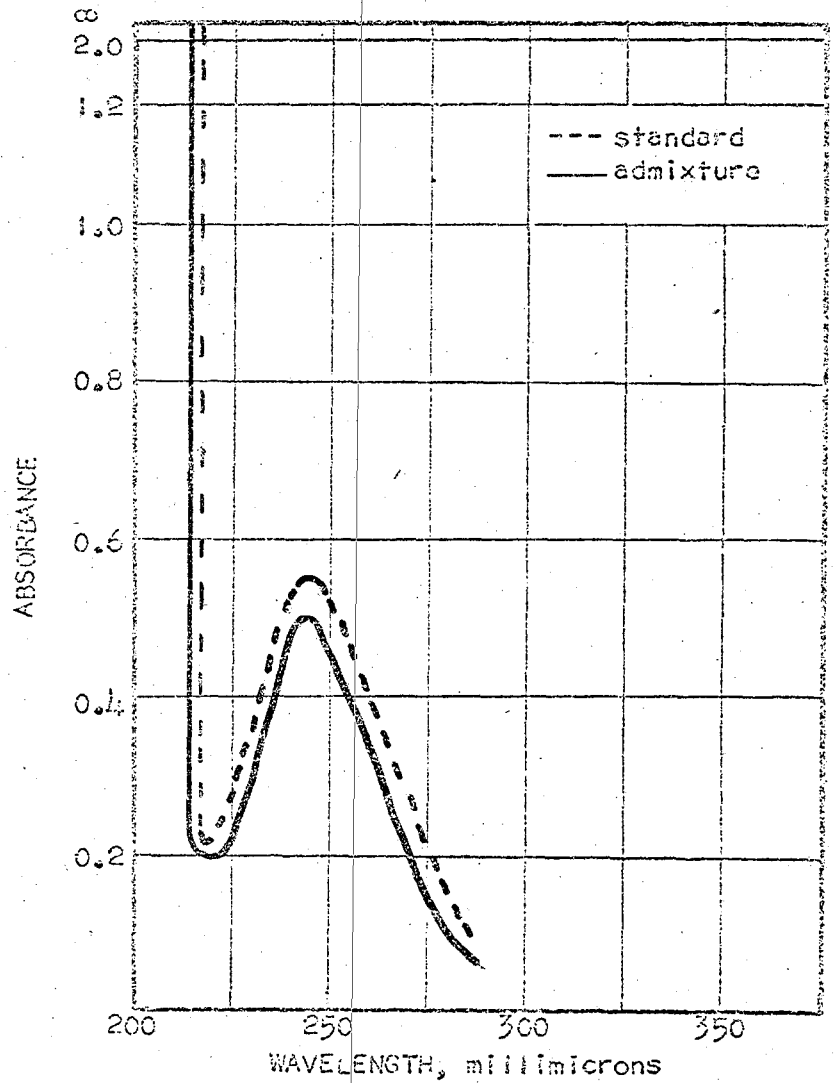
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Methylprednisolone Sodium Succinate	400 125	3.8	3.8	3.8
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	400	3.6	3.6	3.6
Methylprednisolone Sodium Succinate	125	7.3	7.3	7.3



Graph 7. Beer plot for Methylprednisolone Sodium Succinate in Sodium Chloride Injection.

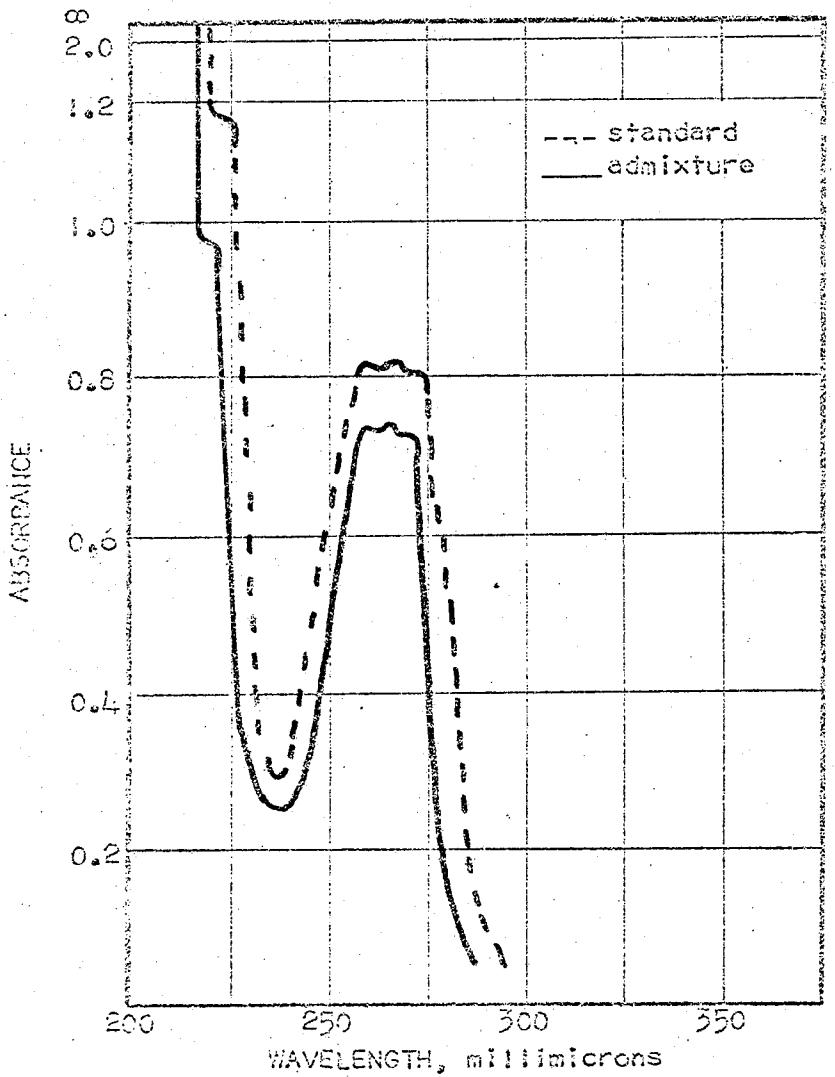


Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium
Succinate 12.5 mcg./ml.

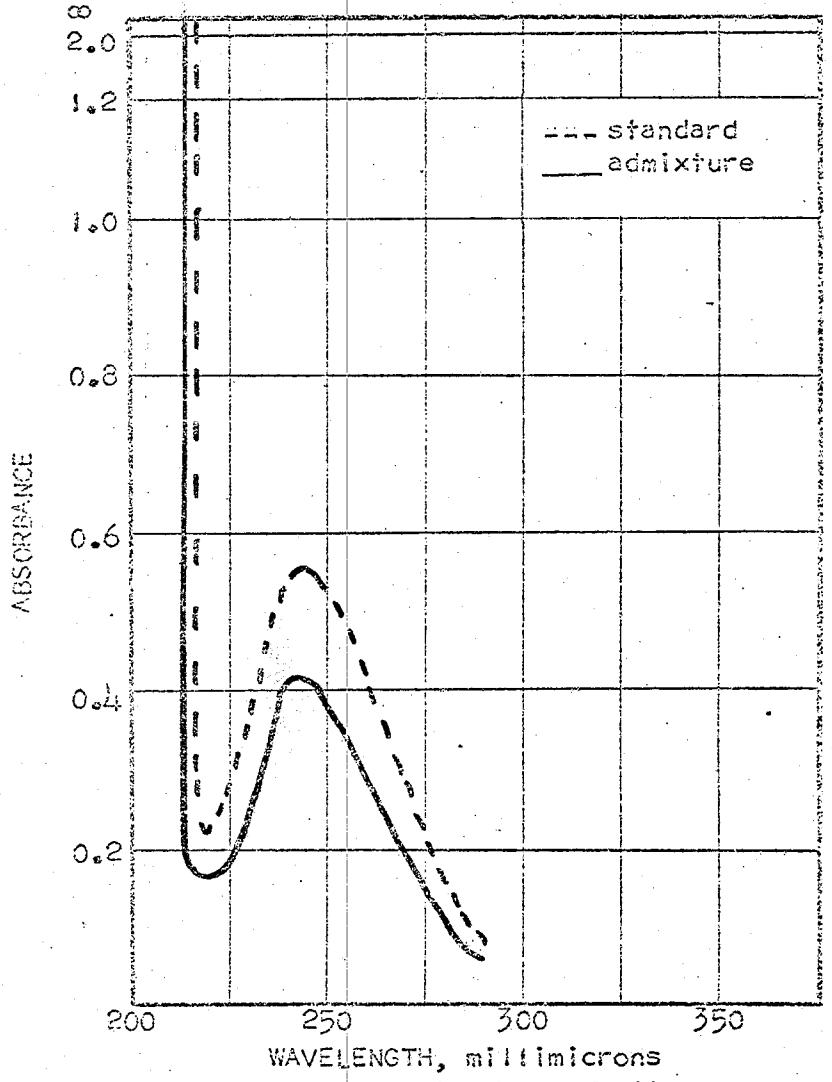


Methylprednisolone Sodium
Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 13. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at one hour.

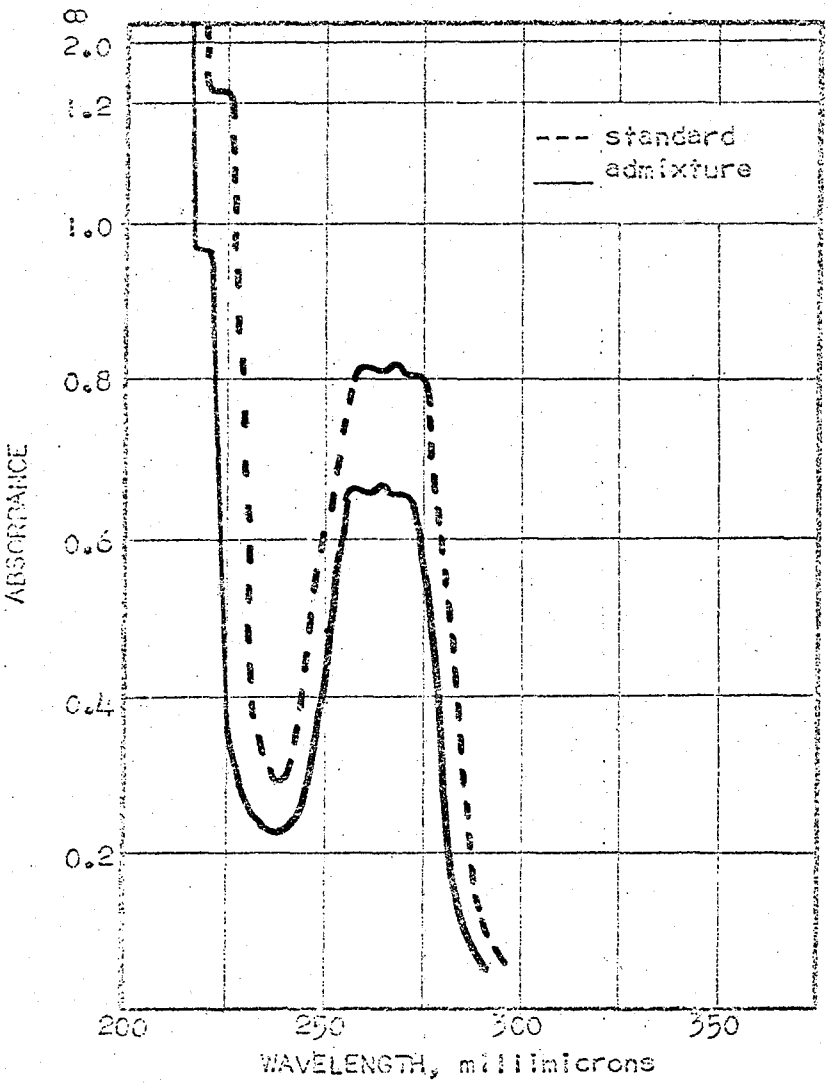


Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium
Succinate 12.5 mcg./ml.

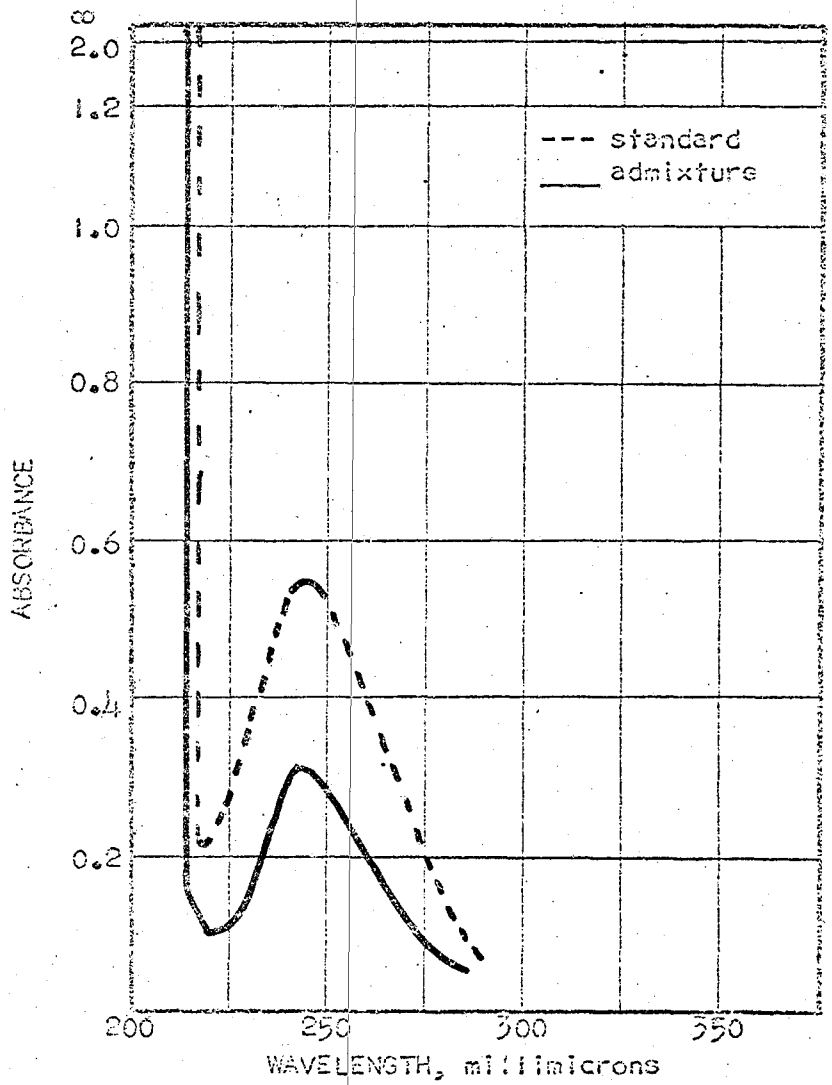


Methylprednisolone Sodium
Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 14. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium
Succinate 12.5 mcg./ml.



Methylprednisolone Sodium
Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 15. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at eight hours.

Metaraminol Bitartrate and Methylprednisolone Sodium Succinate in 5% Dextrose Injection

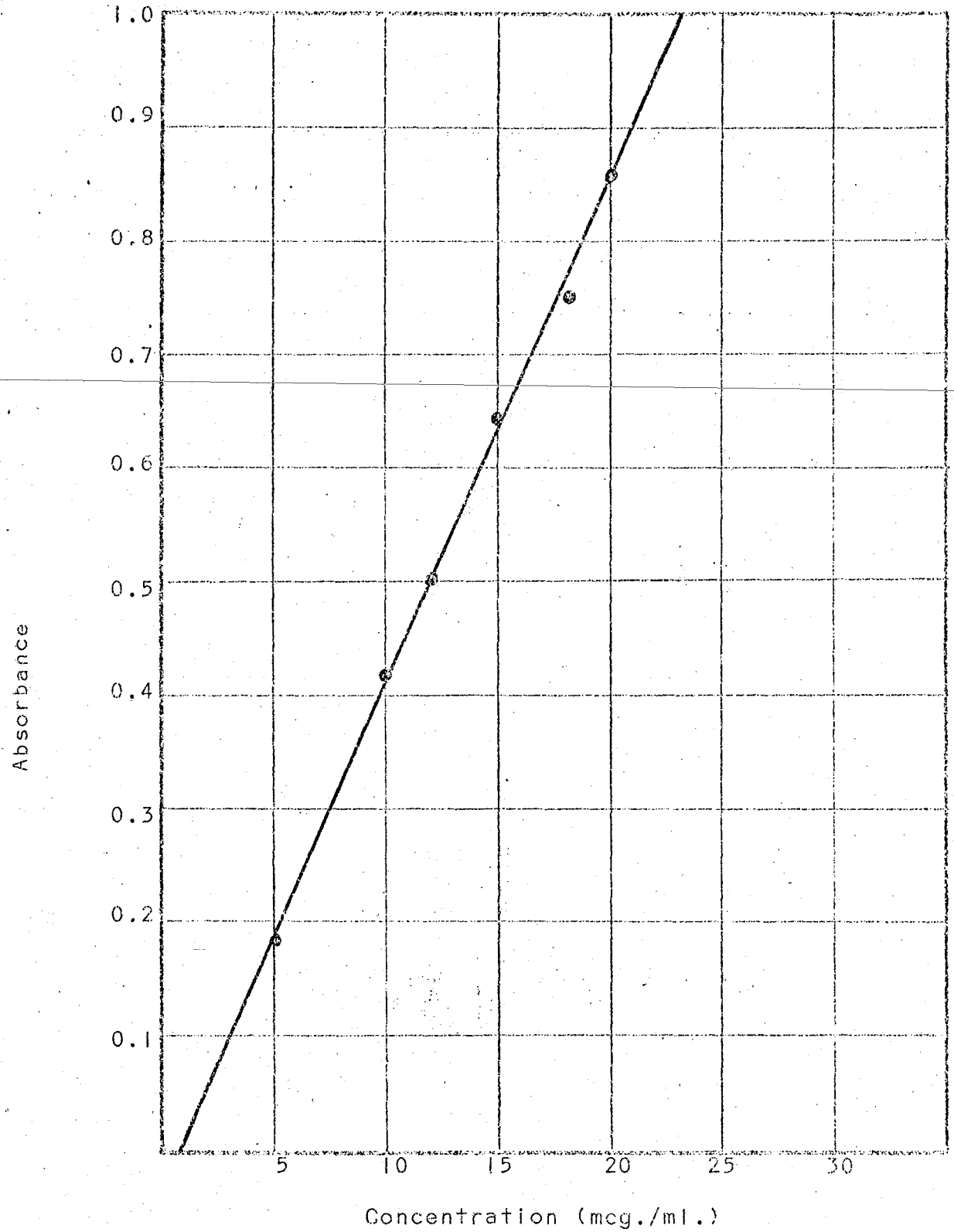
A precipitate was observed within four hours after the mixture of metaraminol bitartrate, 400 mcg./ml., and methylprednisolone sodium succinate, 125 mcg./ml., in 5% Dextrose Injection. Filtered aliquots were withdrawn from the admixture and diluted to provide a concentration of 40 mcg./ml. for metaraminol bitartrate and 12.5 mcg./ml. for methylprednisolone sodium succinate.

In comparing the absorption spectra for the two drugs after admixture, it was noted that an appreciable change occurred in the spectrum for methylprednisolone sodium succinate. The loss of absorbance observed for this component would suggest a reduction in concentration. A minor loss of absorbance was demonstrated for metaraminol bitartrate. The results of this admixture analysis and that of the saline admixture would strongly suggest that the precipitate consisted primarily of the corticosteroid component (Figures 16, 17, 18).

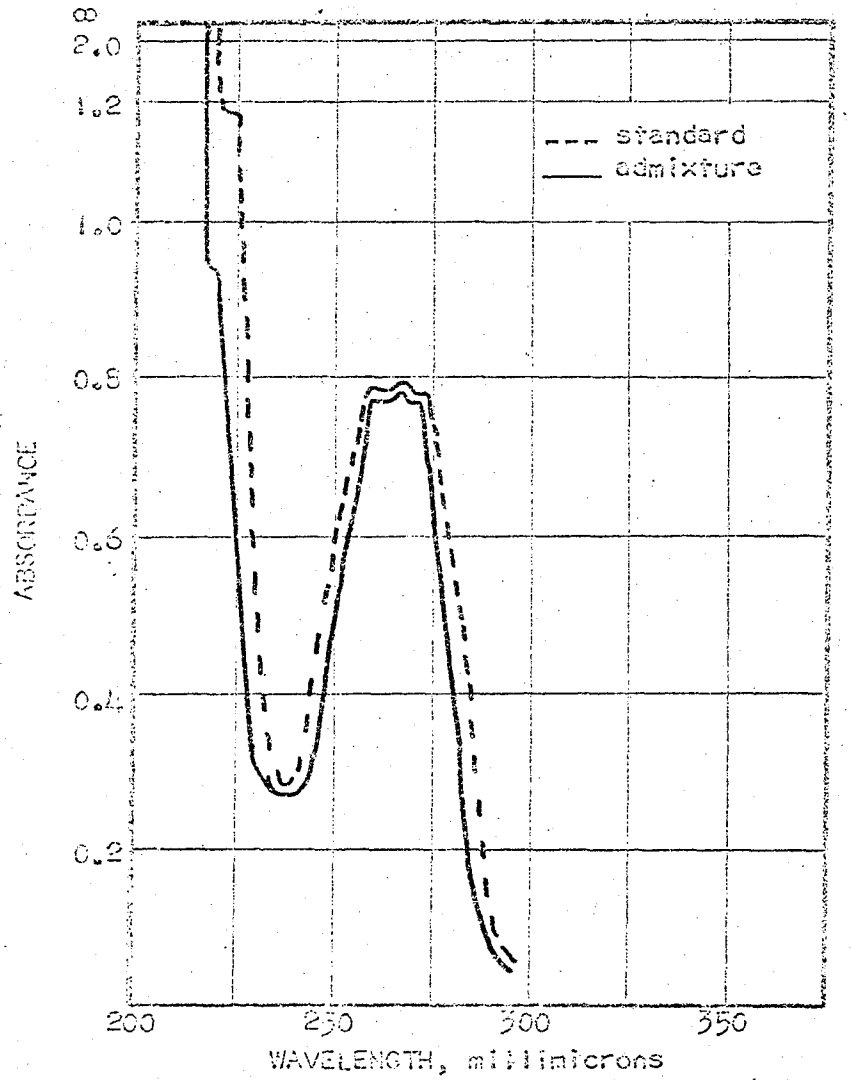
The admixture pH for this drug combination approximated the initial pH recorded for metaraminol bitartrate. The pH change for methylprednisolone sodium succinate in the dextrose admixture was observed to be slightly less than in the saline admixture. It was noted that the loss of absorbance for this component was also correspondingly less in the dextrose admixture (Table VI).

Table VI: pH Change of Metaraminol Bitartrate and Methylprednisolone Sodium Succinate in 5% Dextrose Injection.

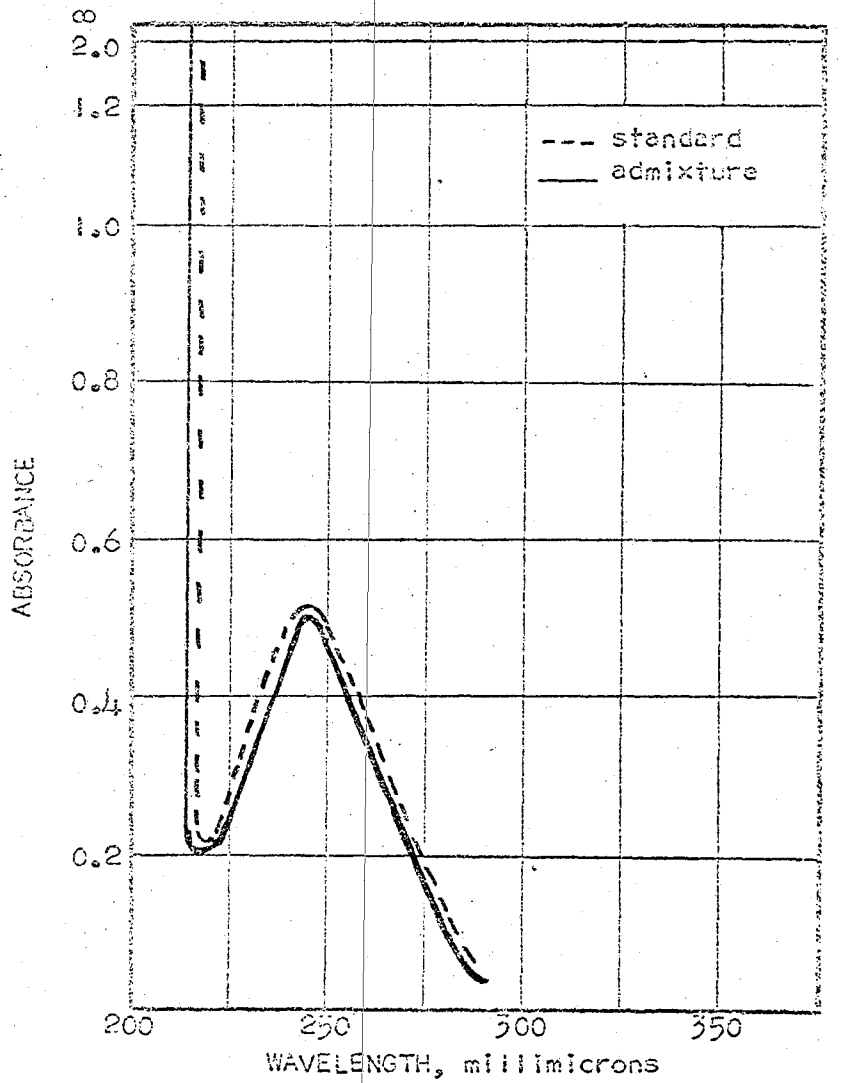
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Methylprednisolone Sodium Succinate	400 125	4.2	4.2	4.2
5% Dextrose Injection		5.0	5.0	5.0
Metaraminol Bitartrate	400	3.6	3.6	3.6
Methylprednisolone Sodium Succinate	125	7.1	7.1	7.1



Graph 8. Beer plot for Methylprednisolone Sodium Succinate in 5% Dextrose Injection.

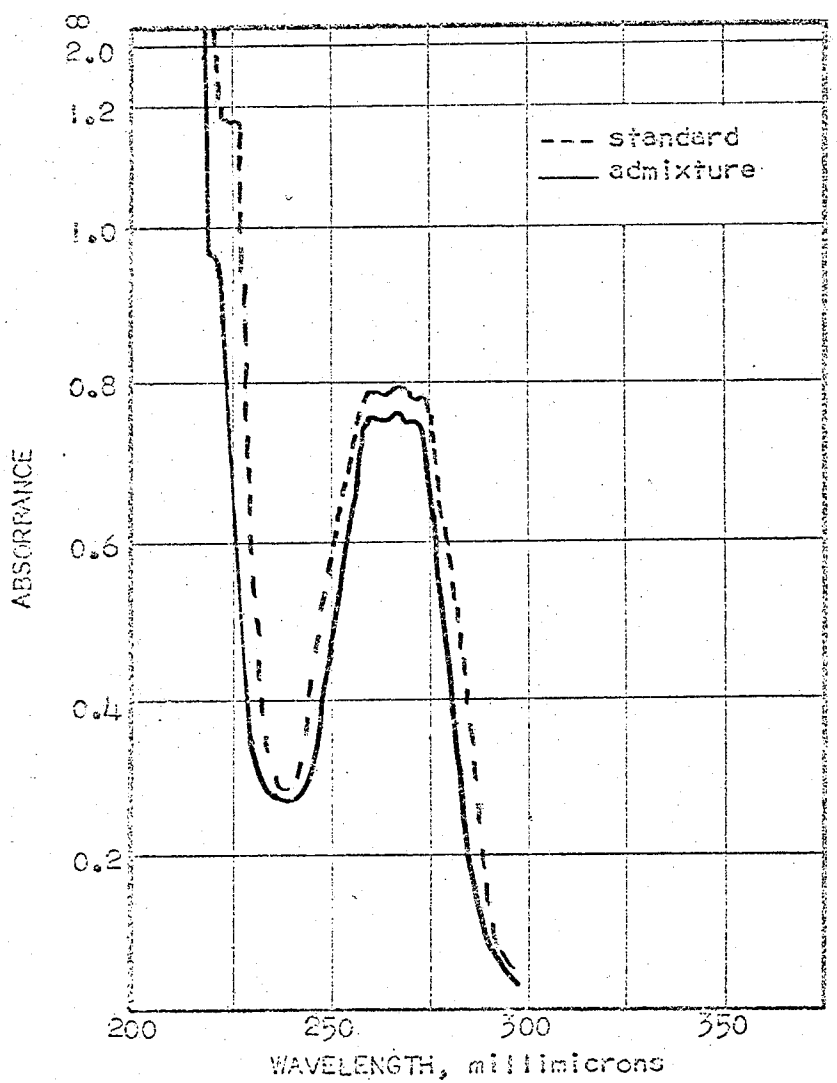


Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium Succinate 12.5 mcg./ml.

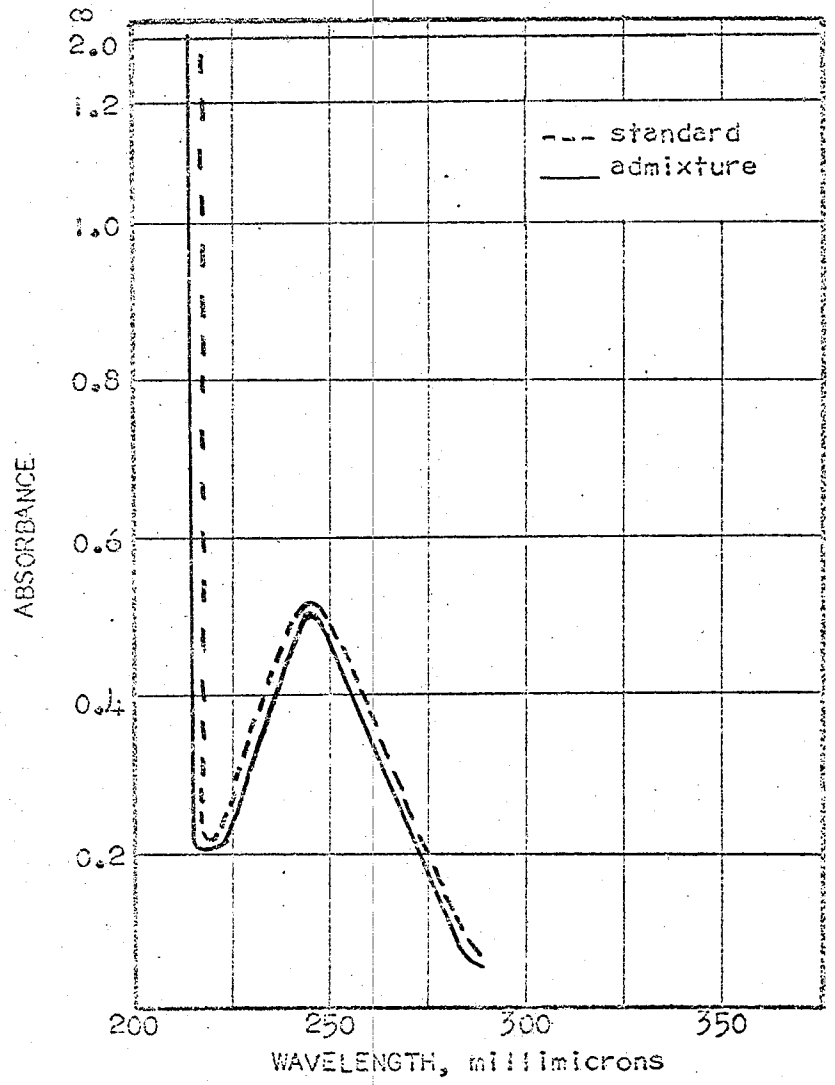


Methylprednisolone Sodium Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate 40 mcg./ml.

Figure 16. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at one hour.

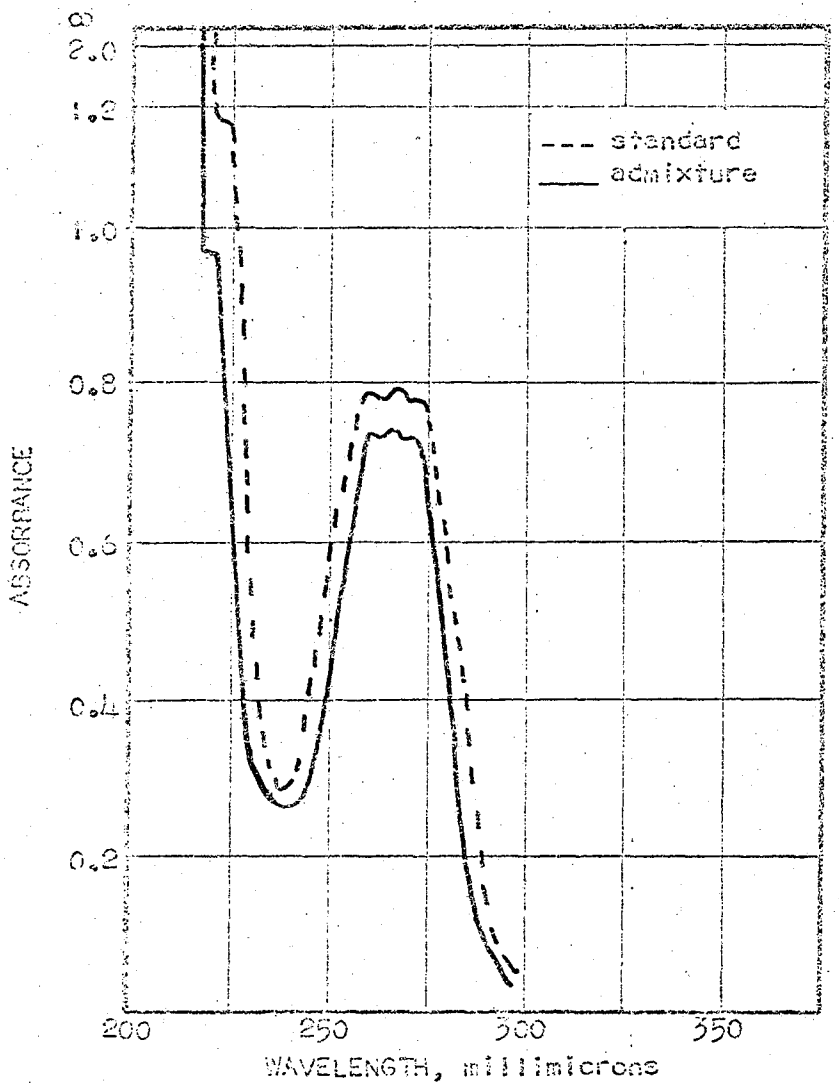


Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium Succinate 12.5 mcg./ml.

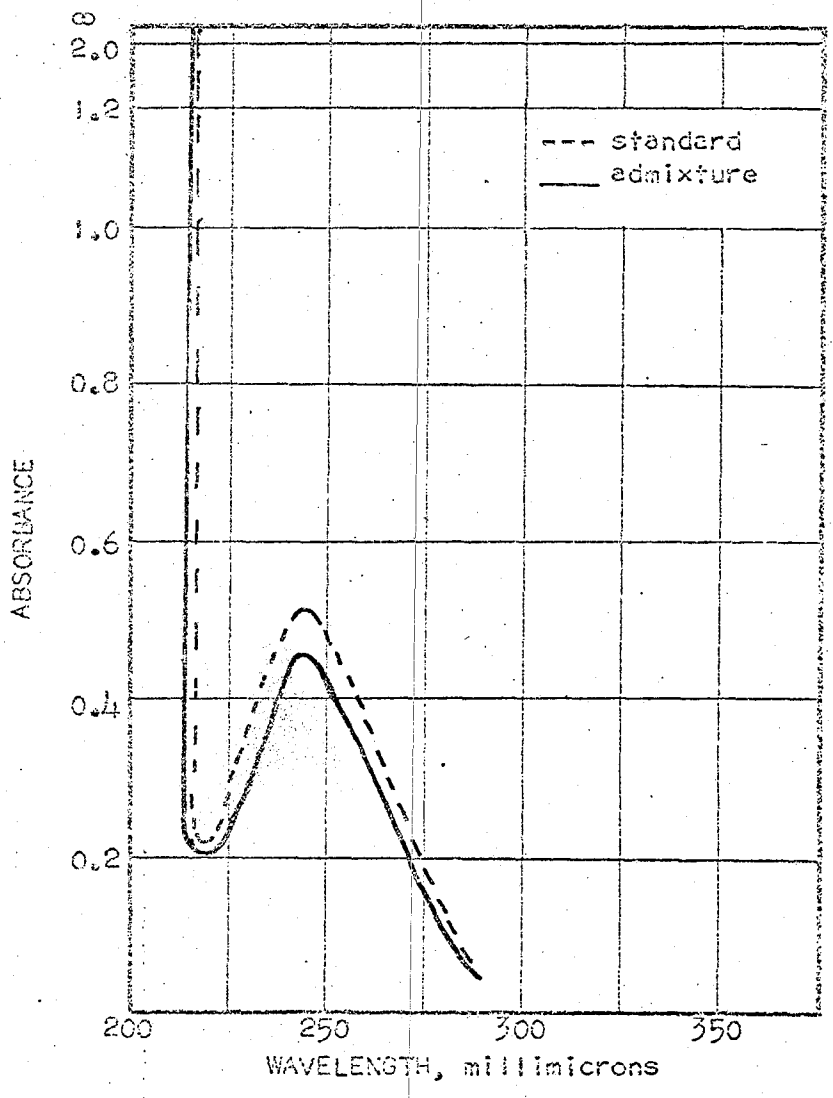


Methylprednisolone Sodium Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate 40 mcg./ml.

Figure 17. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at four hours.



Metaraminol Bitartrate 40 mcg./ml.
ref: Methylprednisolone Sodium
Succinate 12.5 mcg./ml.



Methylprednisolone Sodium
Succinate 12.5 mcg./ml.
ref: Metaraminol Bitartrate
40 mcg./ml.

Figure 18. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Methylprednisolone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at eight hours.

Metaraminol Bitartrate and Hydrocortisone in Sodium Chloride Injection

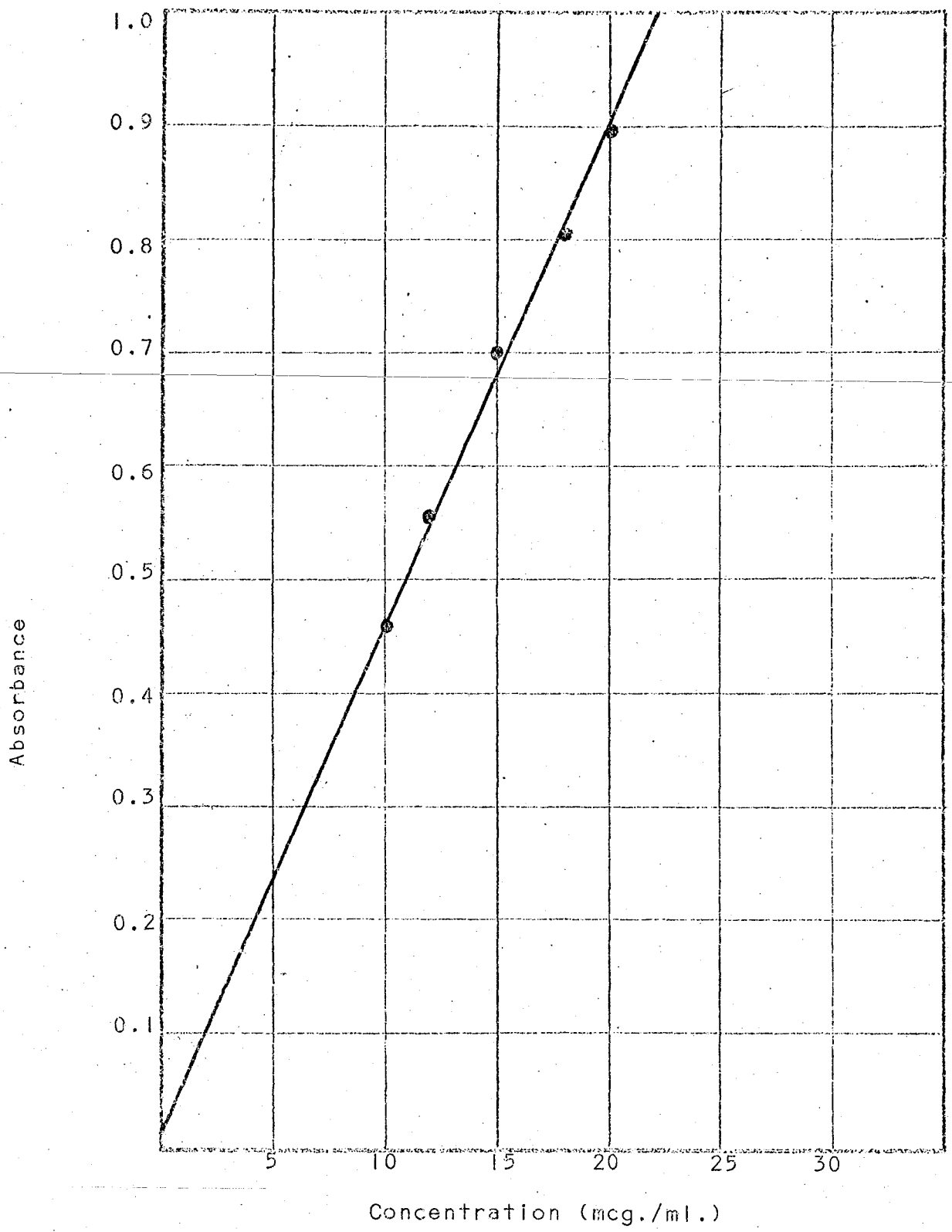
An admixture of metaraminol bitartrate, 500 mcg./ml., and hydrocortisone, 250 mcg./ml., was prepared in Sodium Chloride Injection. Aliquots were withdrawn from this admixture and diluted to provide the optimum spectrophotometric concentration for each drug component. This concentration was 30 mcg./ml. for metaraminol bitartrate and 15 mcg./ml. for hydrocortisone.

Admixture analysis provided an absorption spectrum for each drug component which demonstrated no appreciable change for either metaraminol bitartrate or hydrocortisone throughout the eight hours of study (Figures 19, 20, 21).

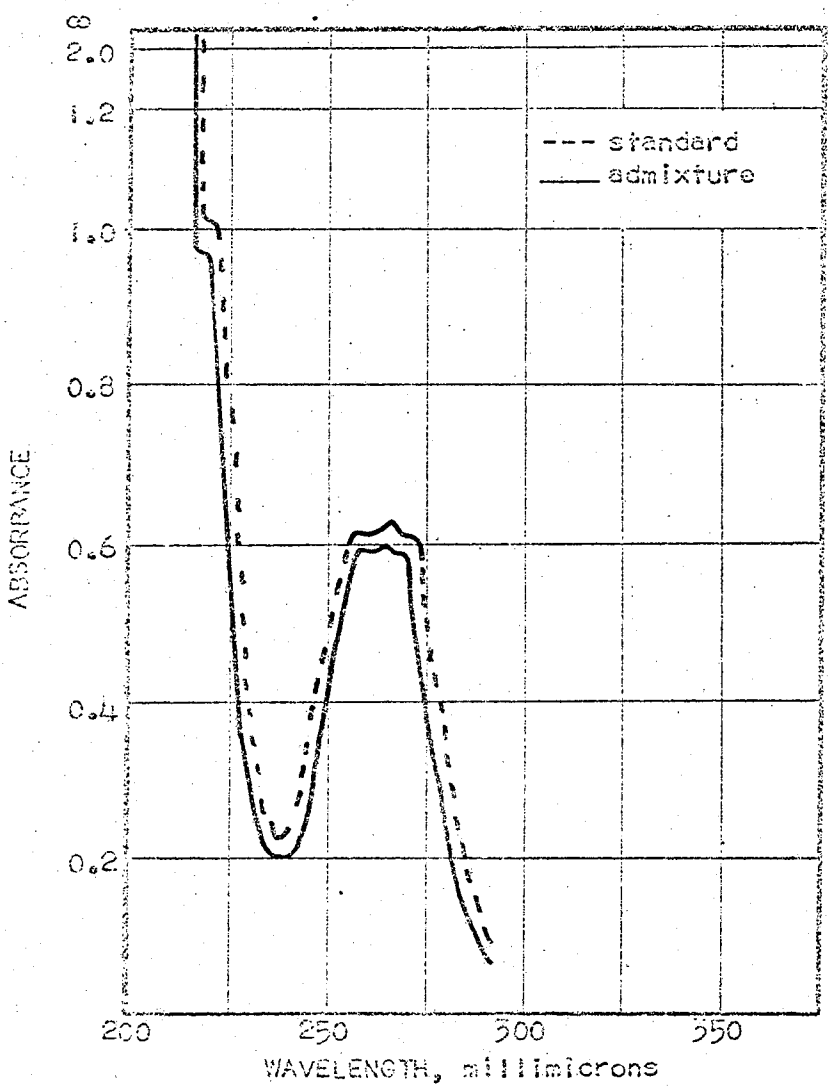
Because of the acidic nature of the hydrocortisone component, the pH change was of a lesser magnitude than that observed for the other corticosteroid containing admixtures (Table VII).

Table VII: pH Change of Metaraminol Bitartrate and Hydrocortisone in Sodium Chloride Injection.

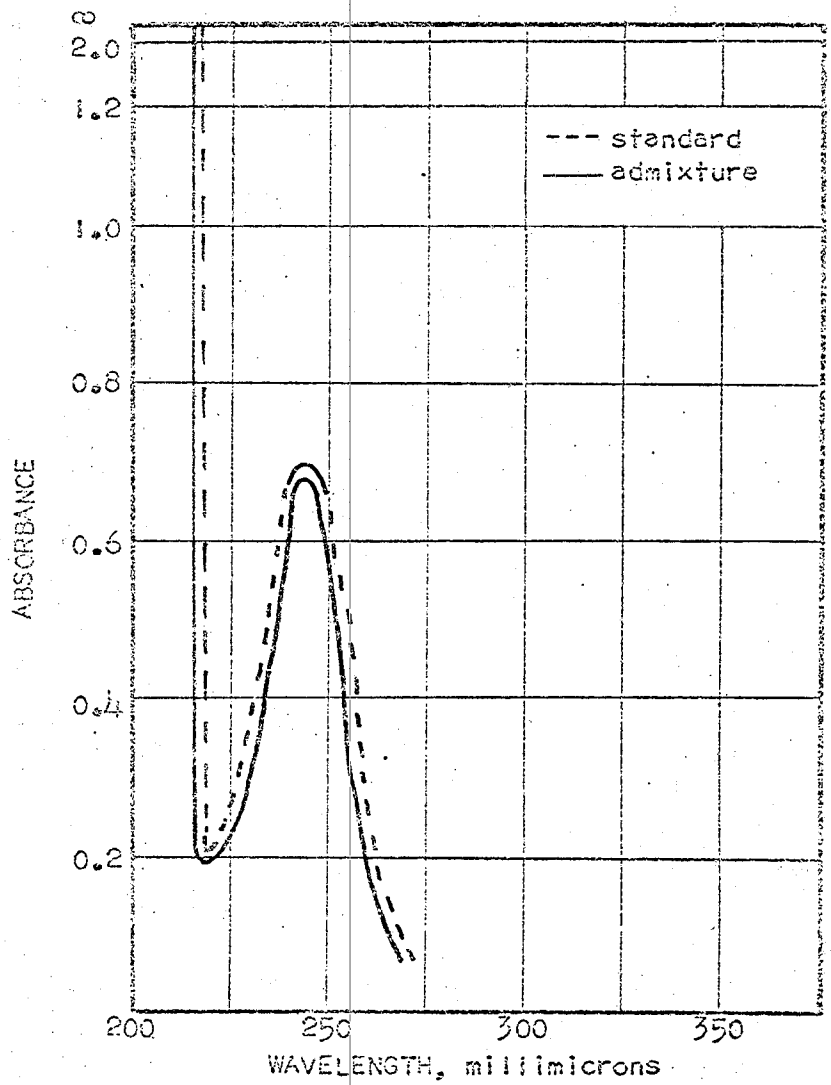
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone	500 250	3.6	3.6	3.5
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	500	3.7	3.7	3.6
Hydrocortisone	250	5.1	4.9	4.9



Graph 9. Beer plot for Hydrocortisone in Sodium Chloride Injection.

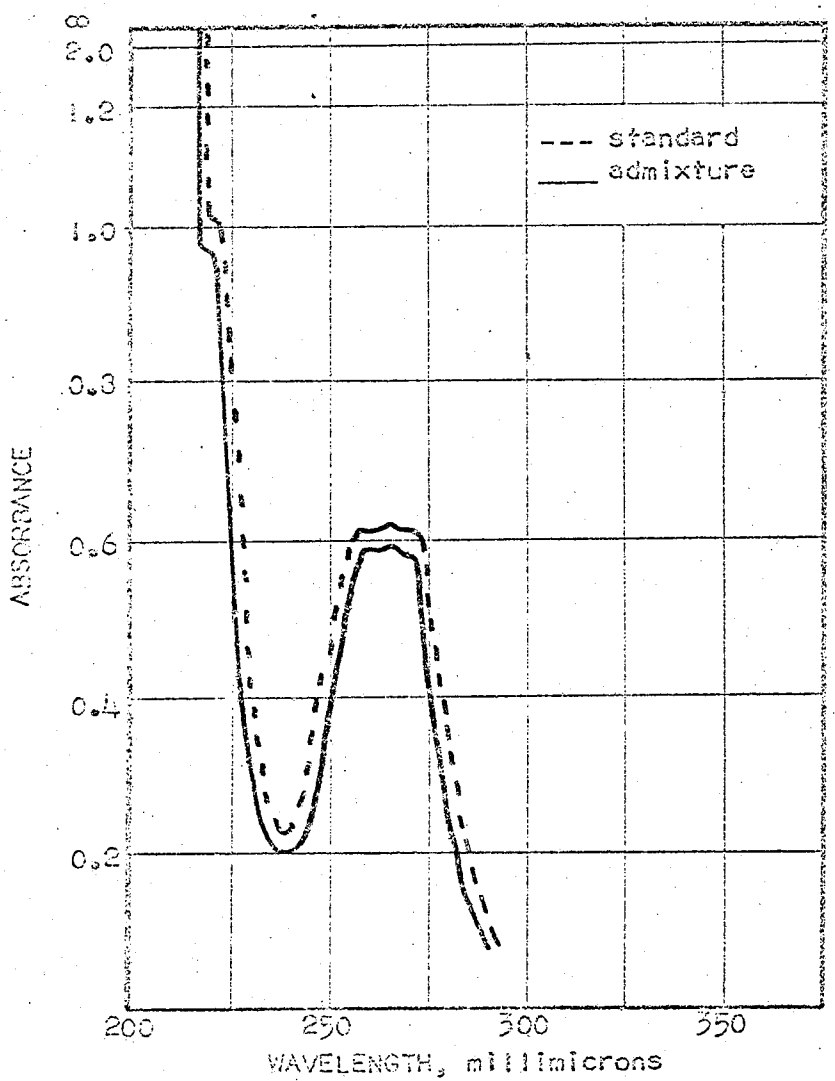


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.

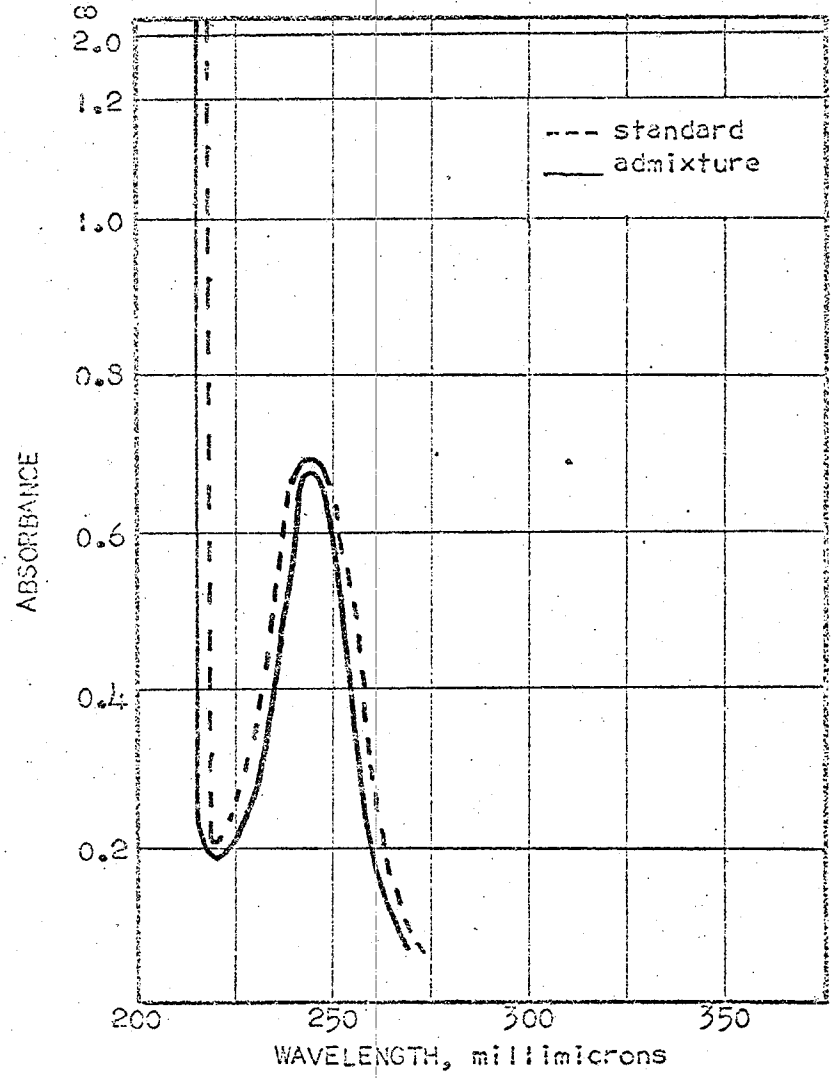


Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 19. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in Sodium Chloride Injection at one hour.

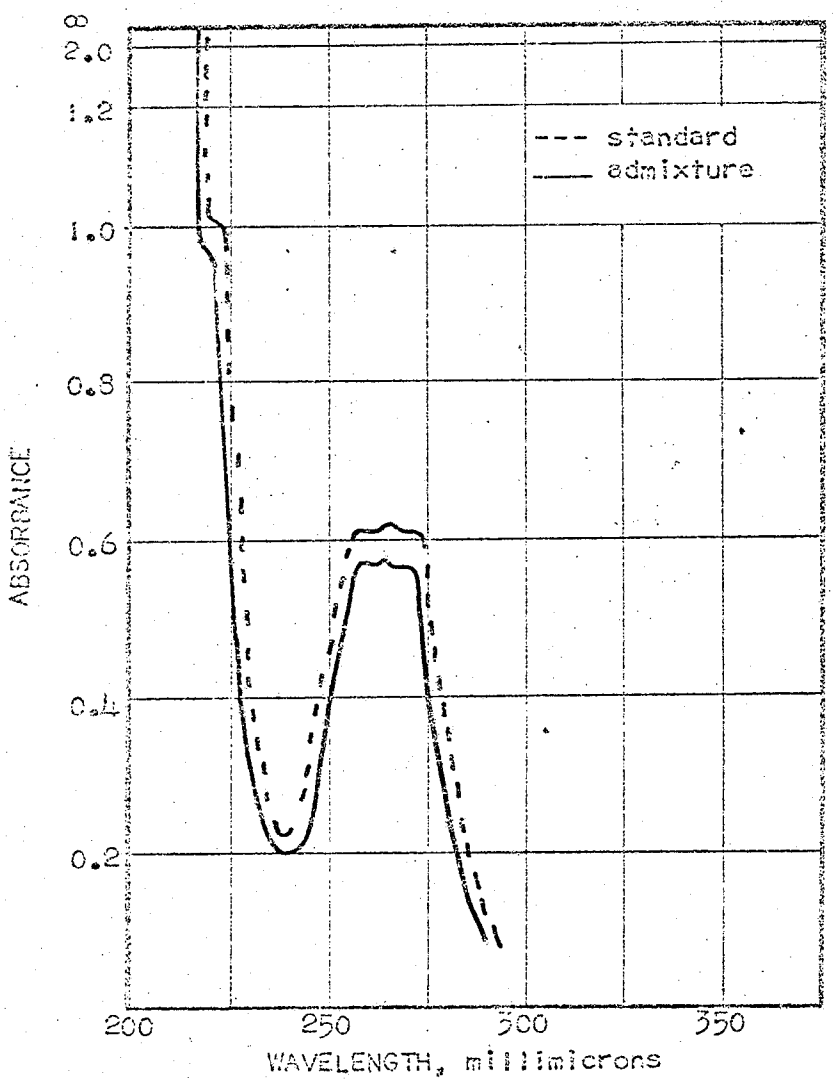


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.

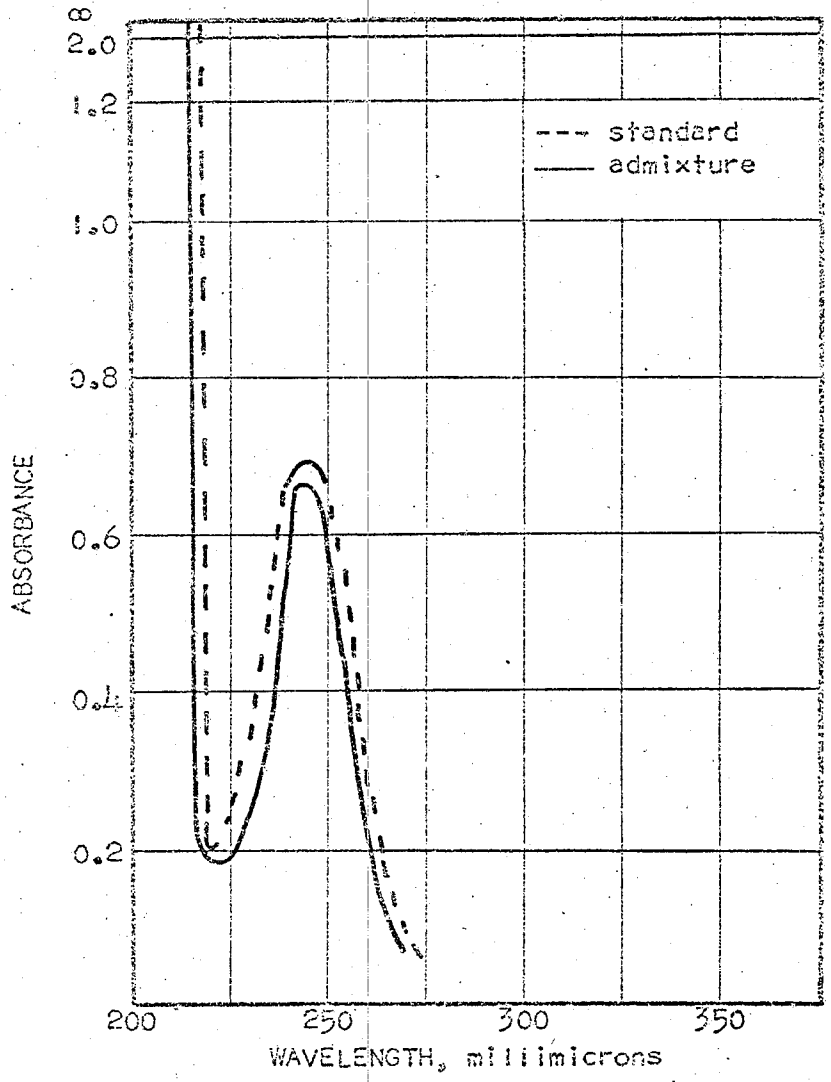


Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 20. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.



Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 21. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in Sodium Chloride Injection at eight hours.

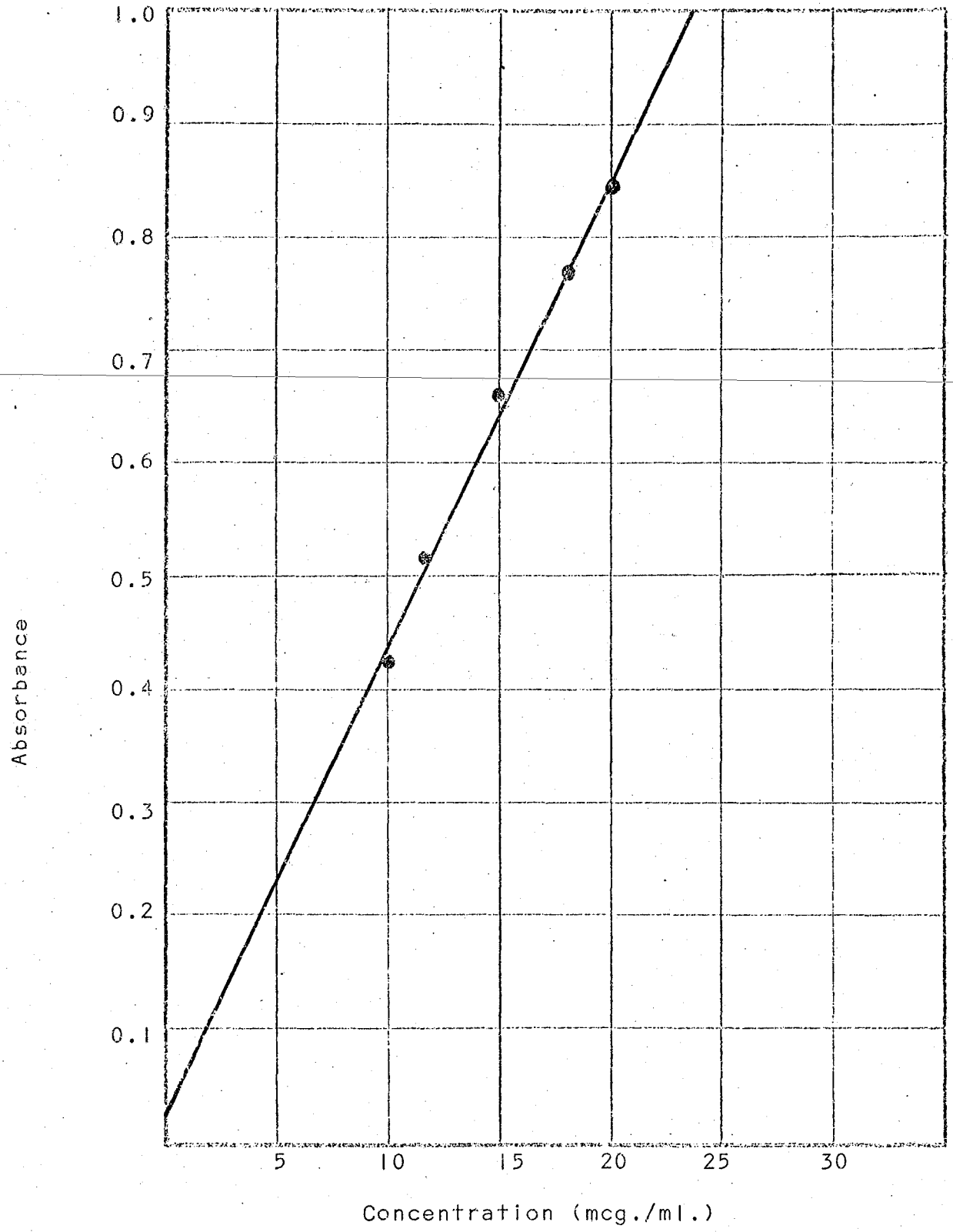
Metaraminol Bitartrate and Hydrocortisone in 5% Dextrose Injection

At a concentration of 500 mcg./ml. and 250 mcg./ml., respectively, metaraminol bitartrate and hydrocortisone were admixed in 5% Dextrose Injection. Admixture analysis was performed on aliquots of this mixture which contained 15 mcg./ml. The absorption spectrum obtained from this analysis paralleled the results of the saline admixture. Admixture of these two components at the specified concentrations does not present evidence of any recordable chemical interaction (Figures 22, 23, 24).

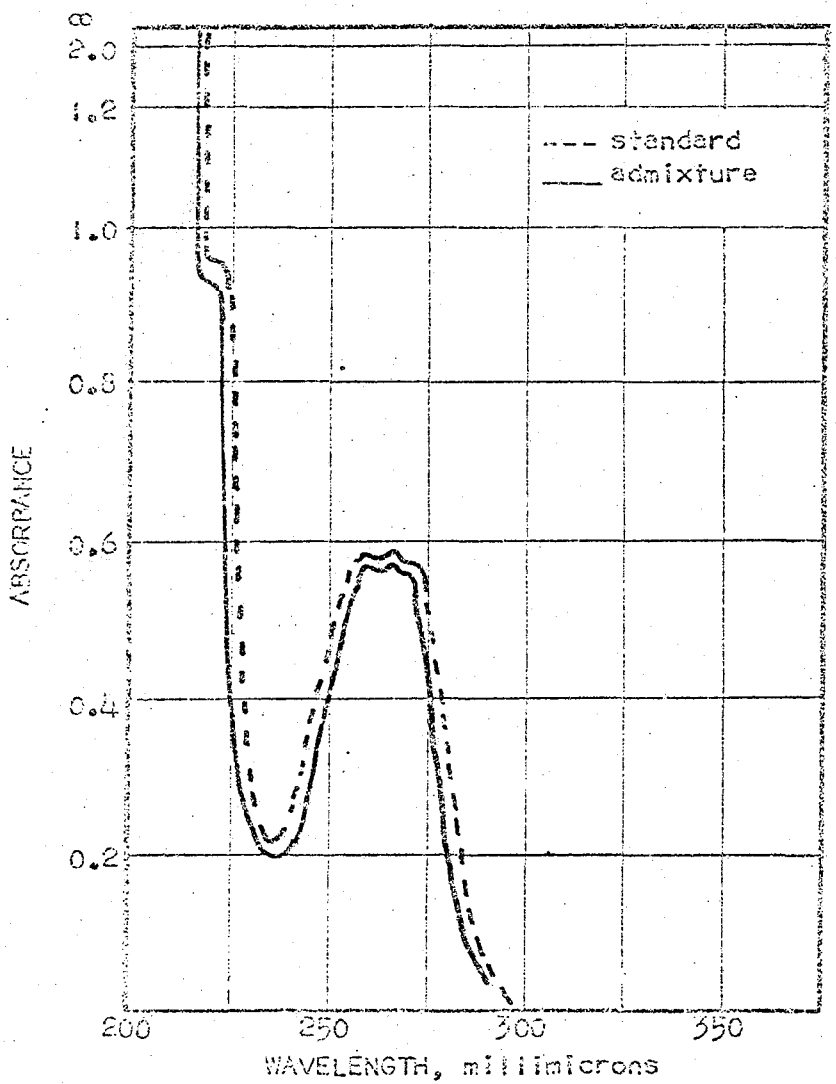
Measurements of pH in this admixture closely paralleled those noted when the saline solution was used as the infusion solution (Table VIII).

Table VIII: pH Change of Metaraminol Bitartrate and Hydrocortisone in 5% Dextrose Injection.

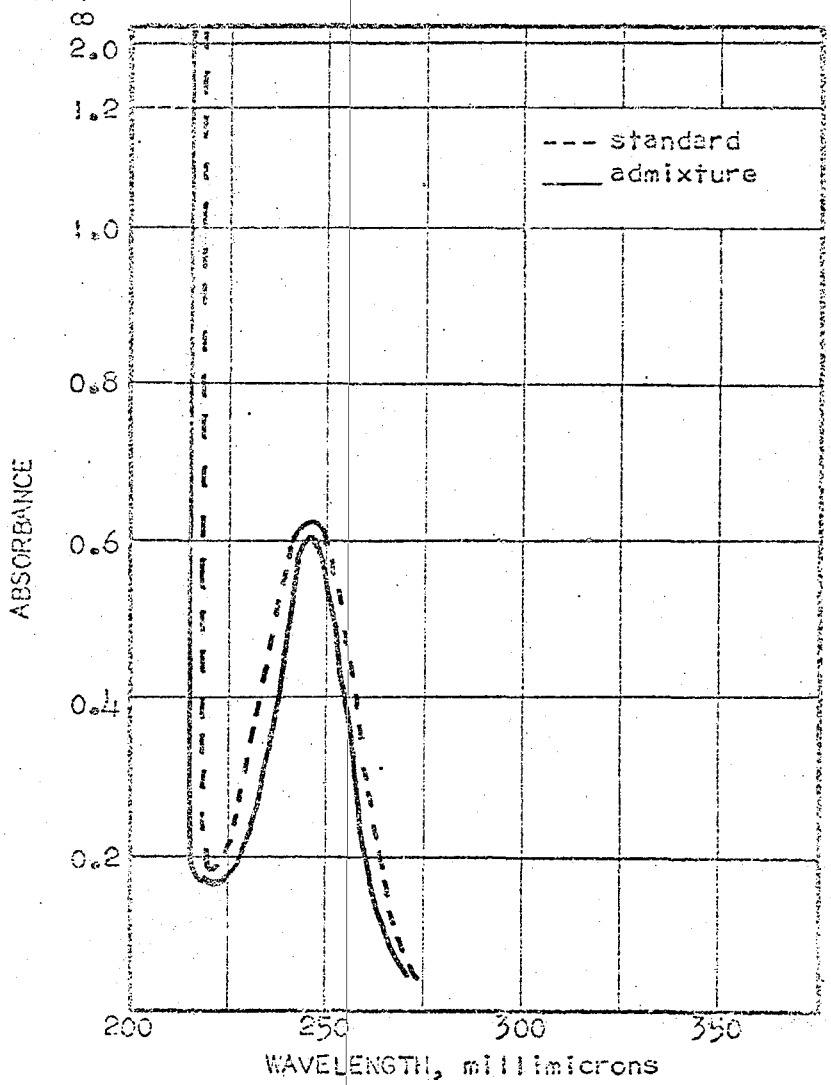
Component	conc. (mcg./ml.	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone	500 250	3.8	3.8	3.8
5% Dextrose Injection		5.0	5.0	5.0
Metaraminol Bitartrate	500	3.6	3.6	3.6
Hydrocortisone	250	4.8	4.8	4.8



Graph 10. Beer plot for Hydrocortisone in 5% Dextrose Injection.

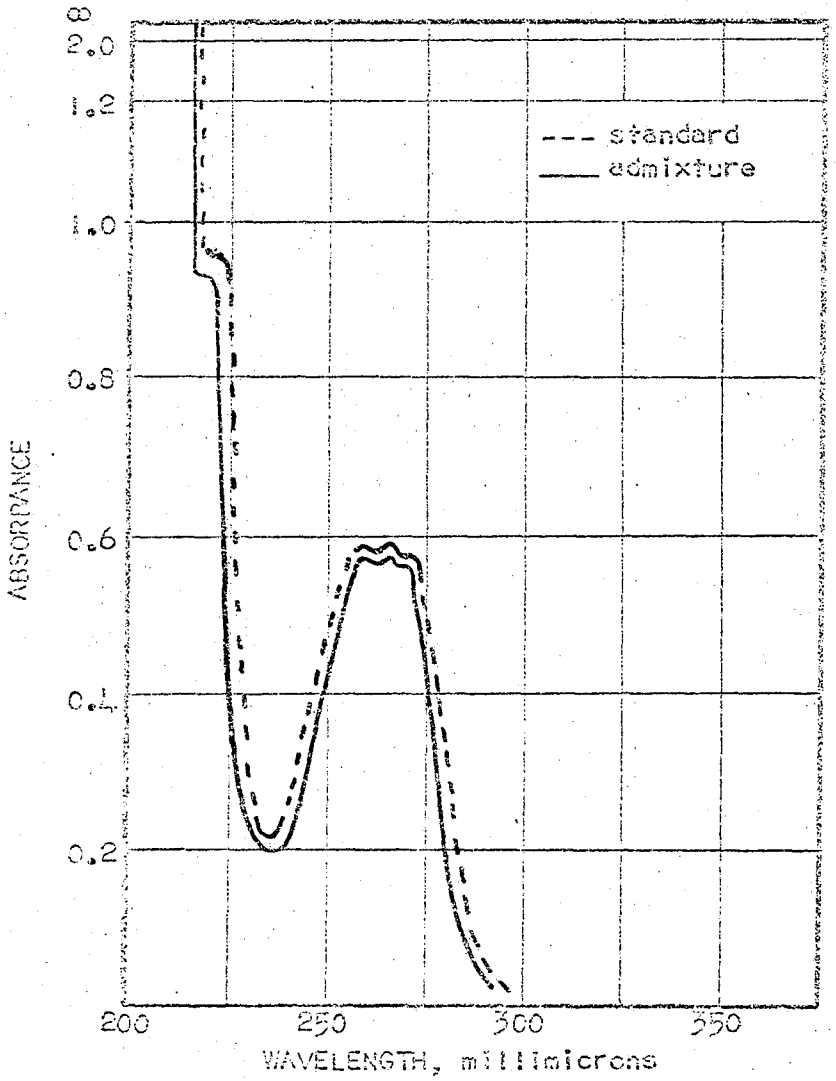


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.

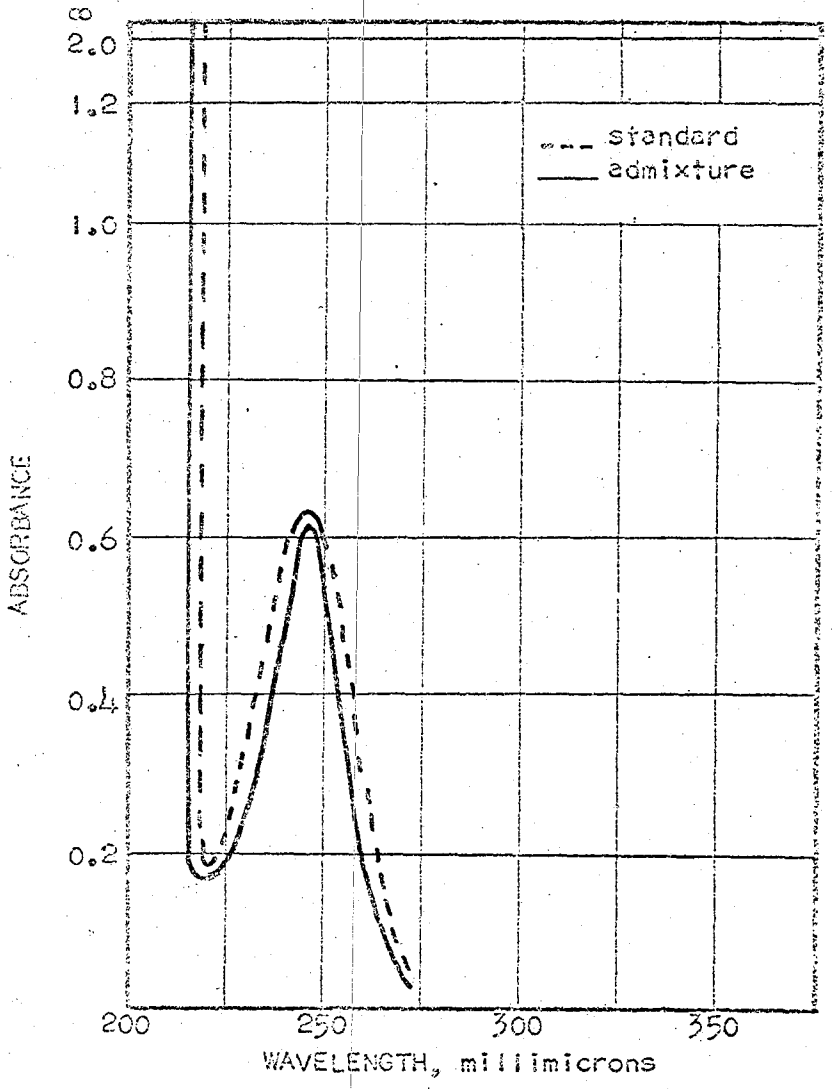


Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 22. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in 5% Dextrose Injection at one hour.

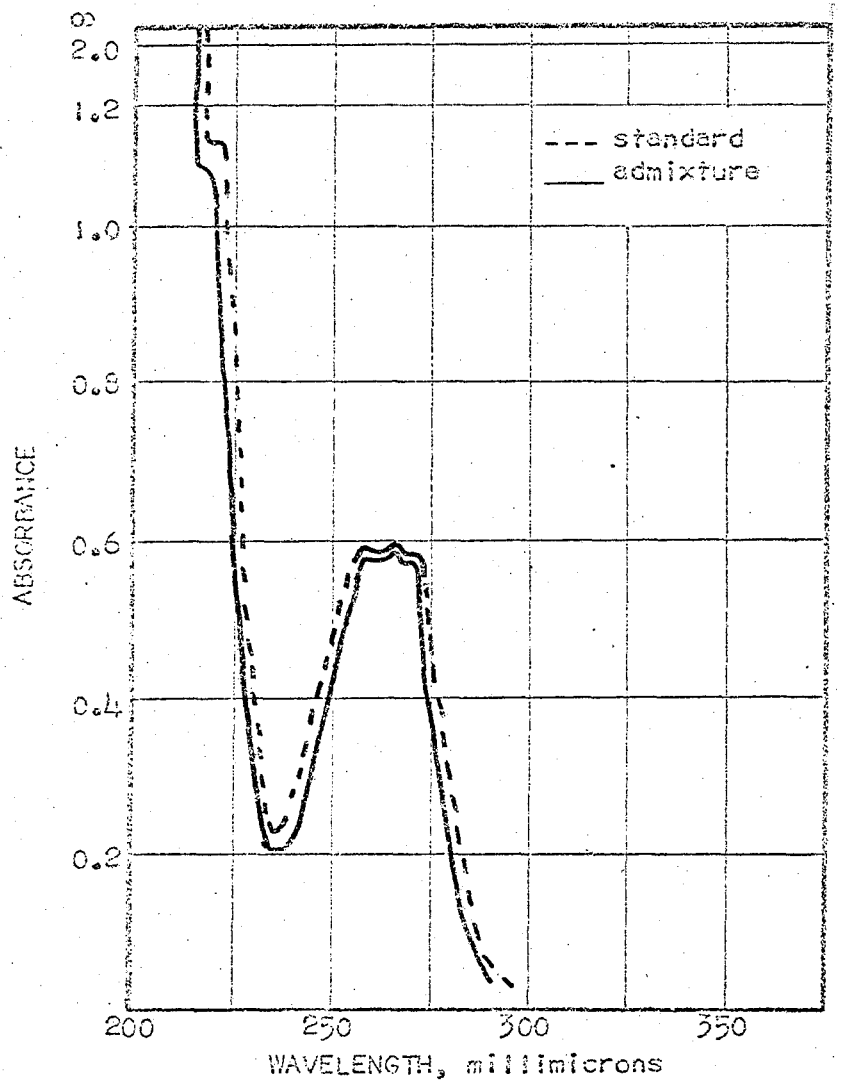


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.

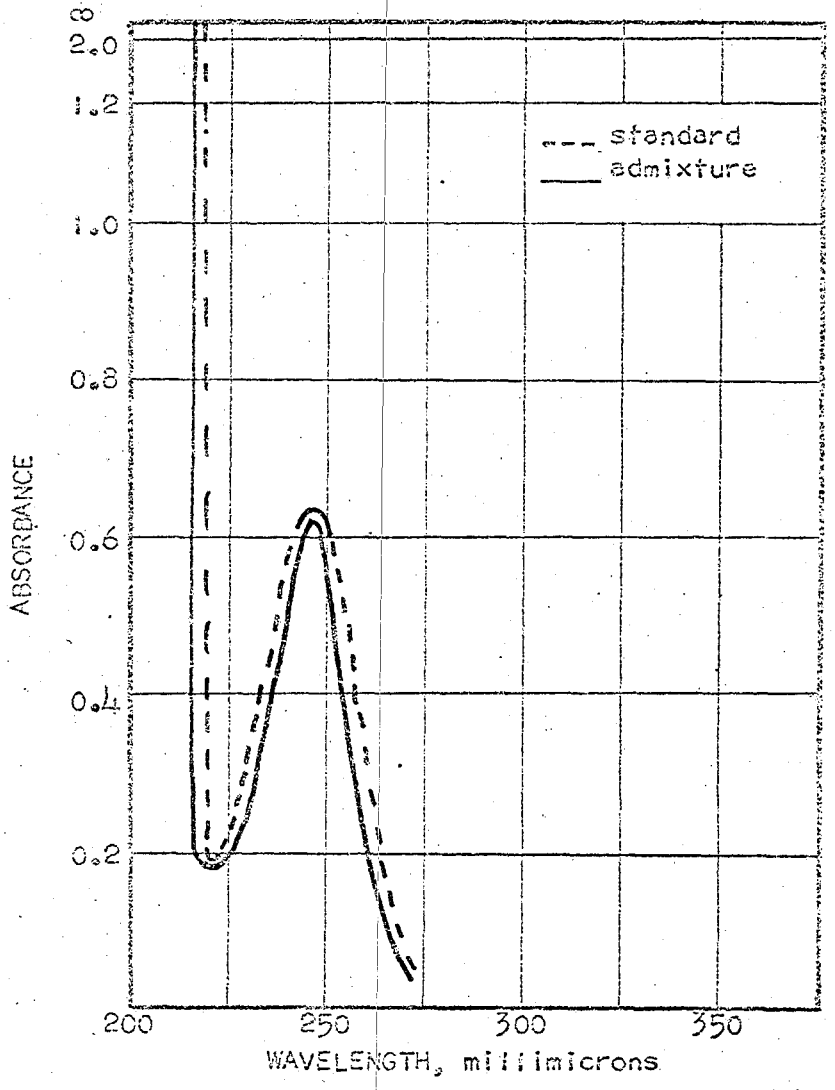


Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 23. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in 5% Dextrose Injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone 15 mcg./ml.



Hydrocortisone 15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 24. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone (λmax 248 mμ) in 5% Dextrose Injection at eight hours.

Metaraminol Bitartrate and Hydrocortisone-21-Phosphate in Sodium Chloride Injection

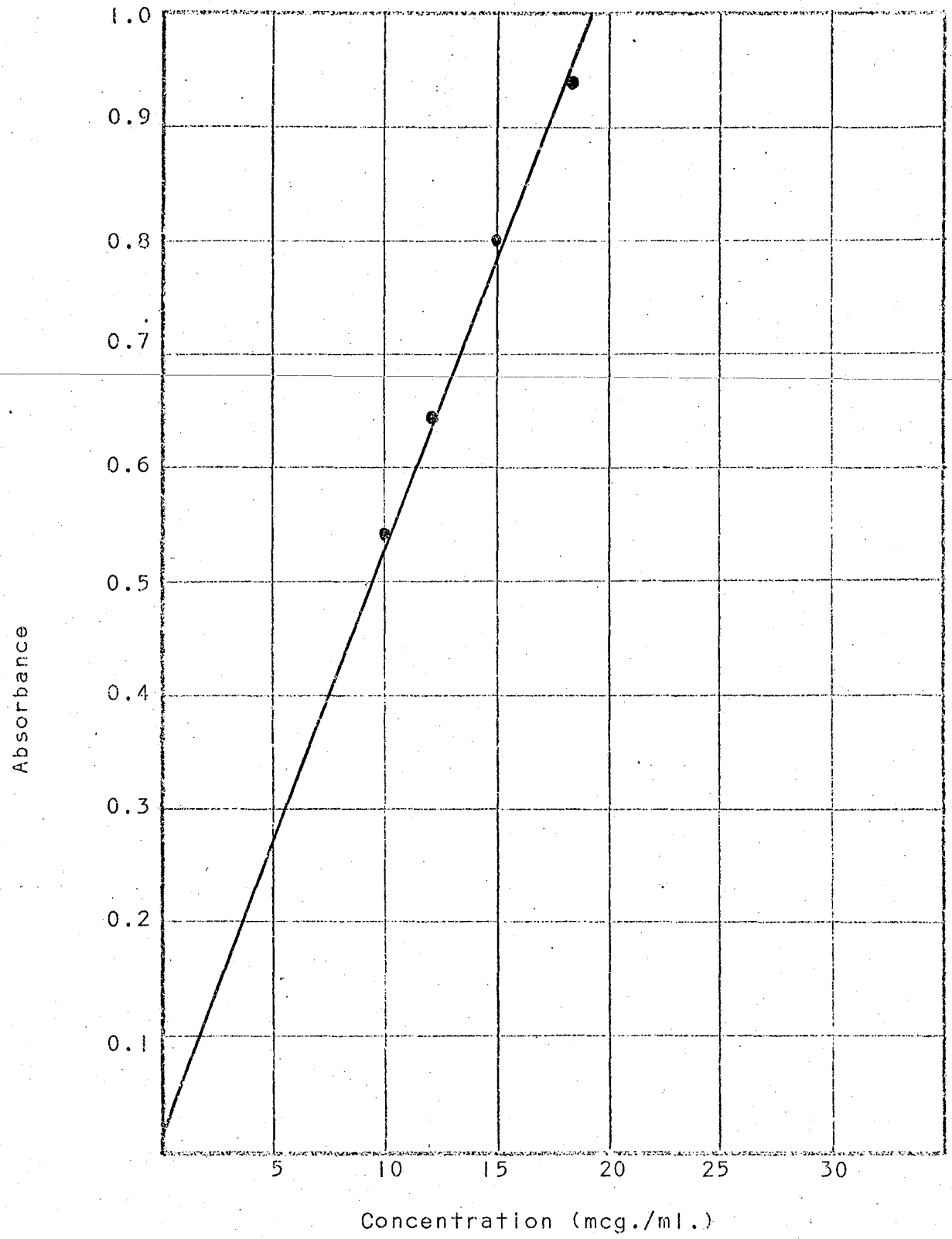
Metaraminol bitartrate, 500 mcg./ml., and hydrocortisone-21-phosphate, 250 mcg./ml., were mixed in Sodium Chloride Injection. Aliquots were withdrawn from this admixture at specified time intervals as before and diluted to obtain the optimum spectrophotometric concentration for each component. This concentration was 30 mcg./ml. for metaraminol bitartrate and 15 mcg./ml. for hydrocortisone-21-phosphate.

Comparison of the absorption spectrum with the standard spectrum demonstrated no appreciable change for either metaraminol bitartrate or hydrocortisone-21-phosphate throughout the eight hours of study (Figures 25, 26, 27).

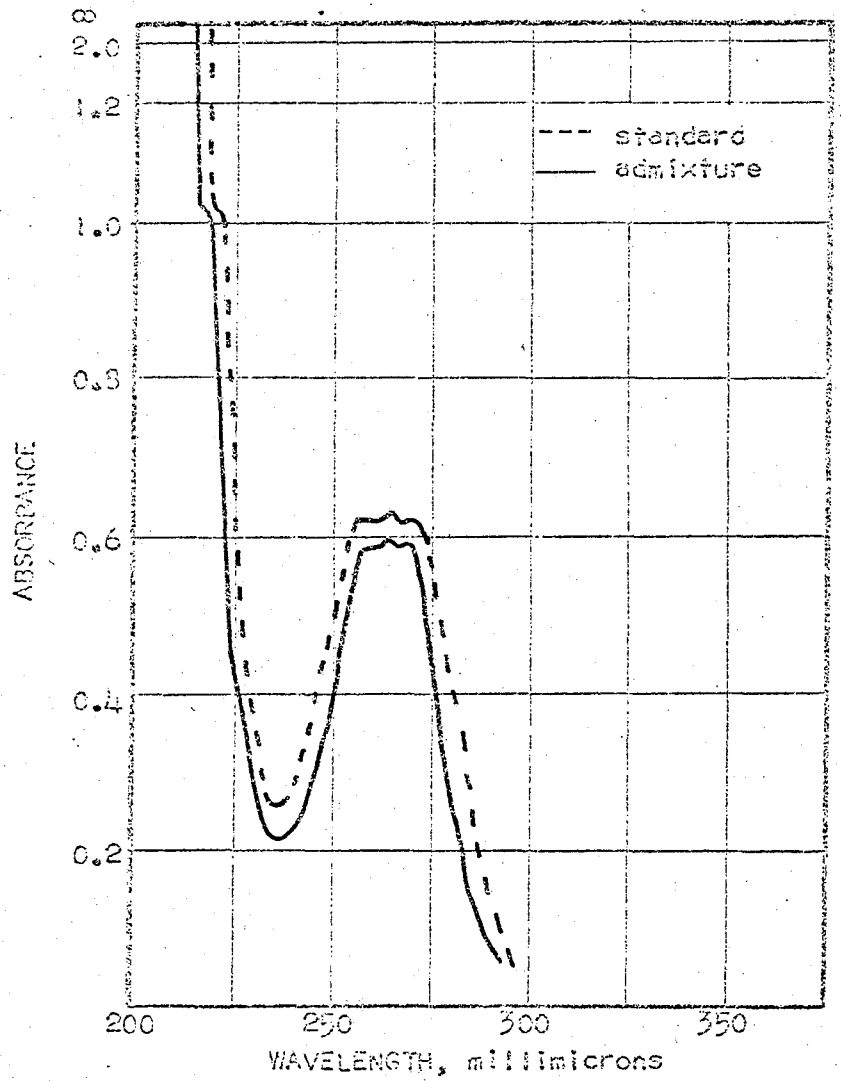
In the admixtures previously studied, a pH change of the magnitude seen here was associated with an altered absorption spectrum suggesting the occurrence of a chemical interaction. It would appear that the stability of hydrocortisone-21-phosphate in this admixture was not influenced by a pH change (Table IX).

Table IX: pH Change of Metaraminol Bitartrate and Hydrocortisone-21-Phosphate in Sodium Chloride Injection.

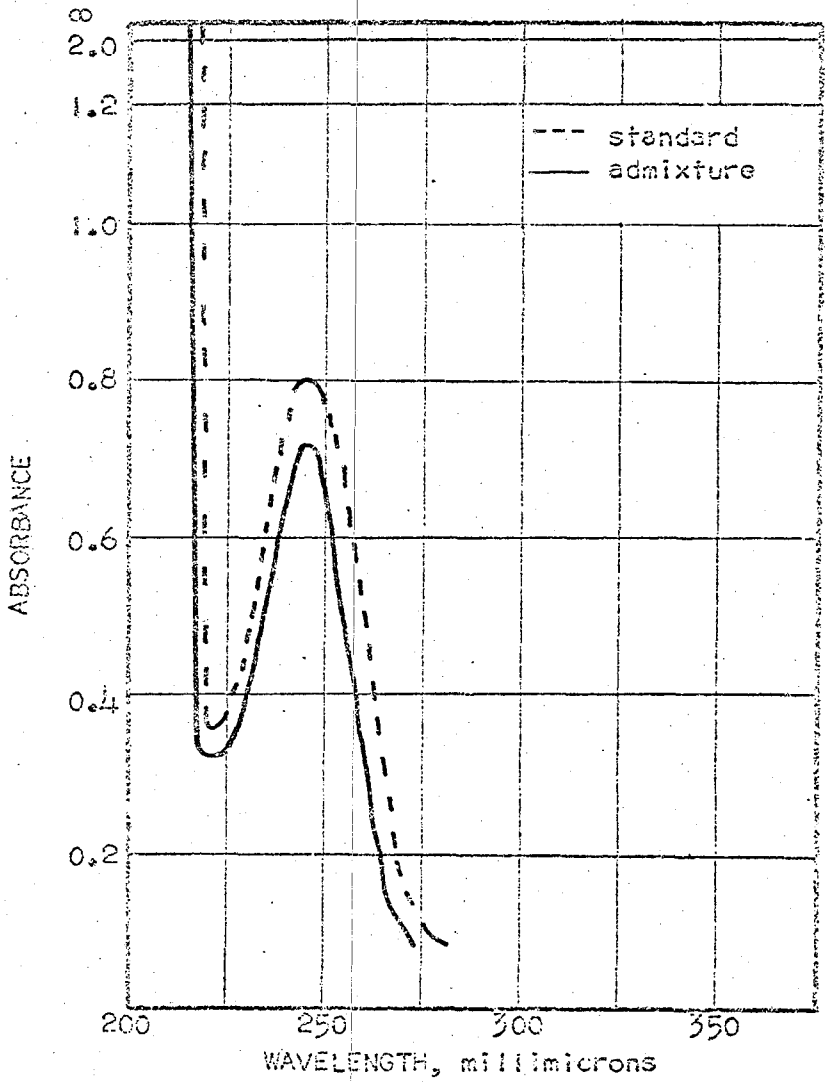
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone-21-Phosphate	500 250	4.0	4.0	4.0
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	500	3.7	3.7	3.6
Hydrocortisone-21-Phosphate	250	7.4	7.4	7.4



Graph II. Beer plot for Hydrocortisone-21-Phosphate in Sodium Chloride Injection.

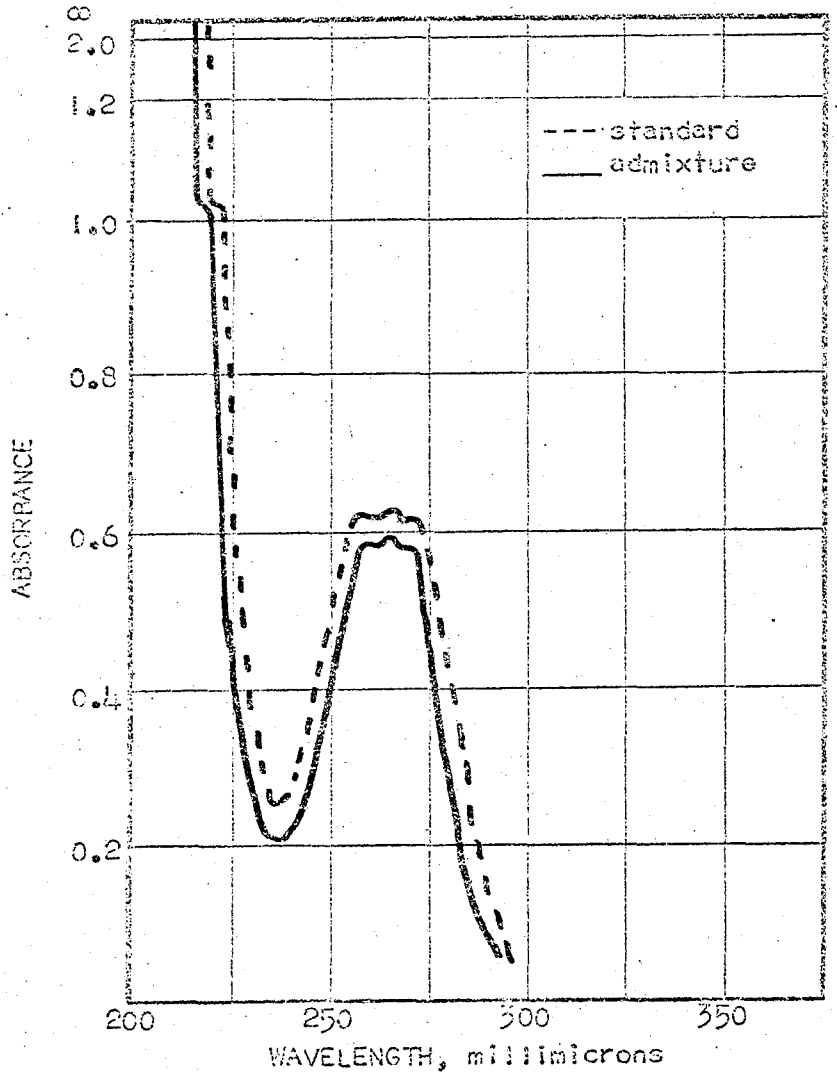


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.

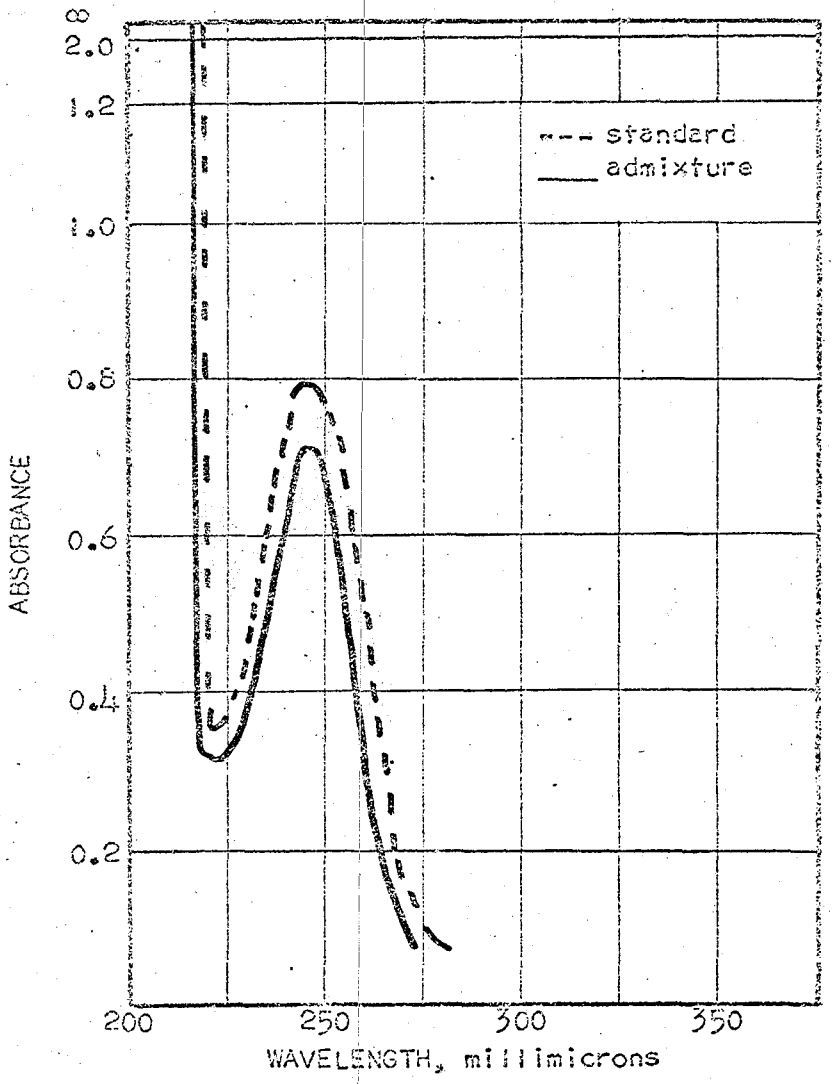


Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 25. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone-21-Phosphate (λmax 248 mμ) in Sodium Chloride Injection at one hour.

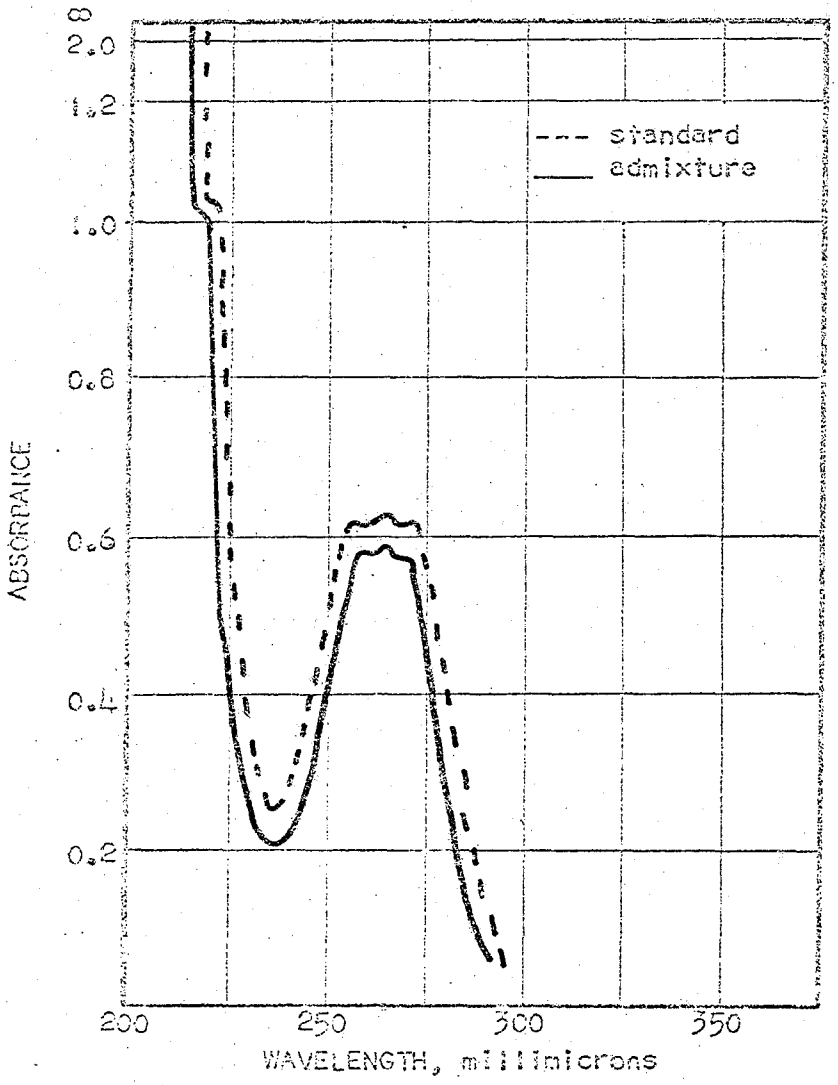


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.

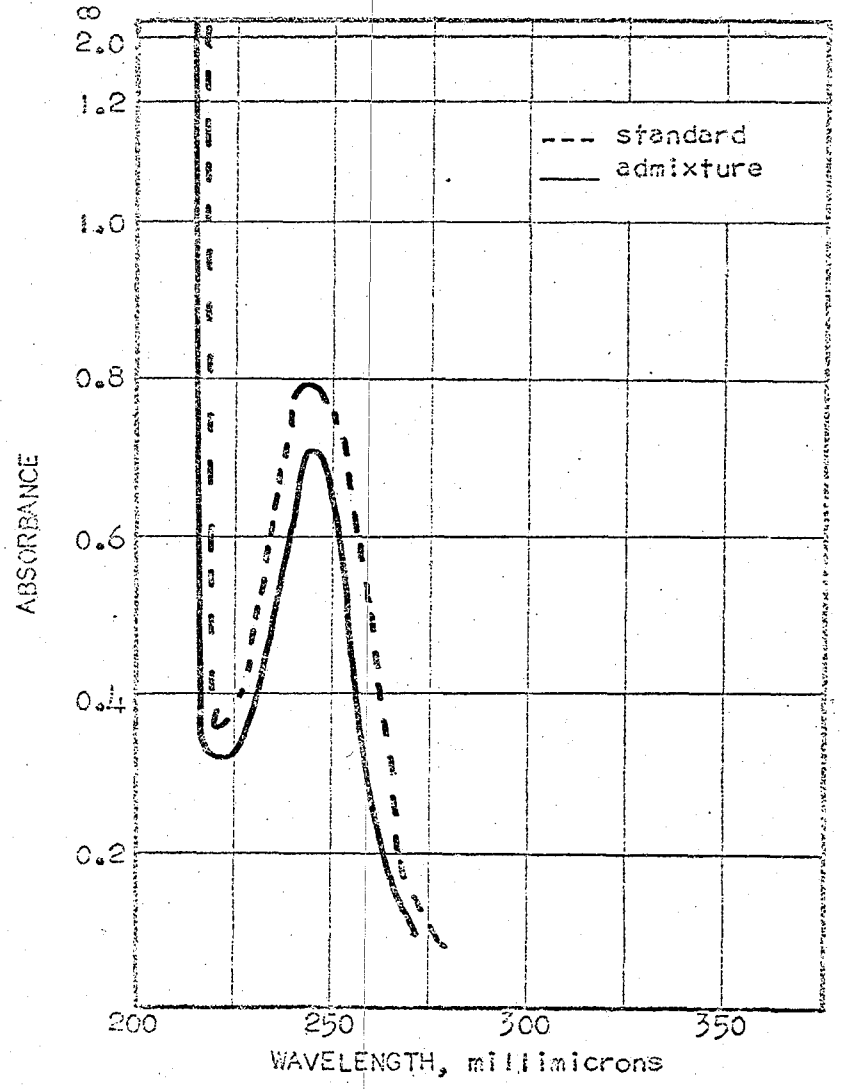


Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 26. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone-21-Phosphate (λmax 248 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.



Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 27. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone-21-Phosphate (λmax 248 mμ) in Sodium Chloride Injection at eight hours.

Metaraminol Bitartrate and Hydrocortisone-21-Phosphate in 5% Dextrose Injection

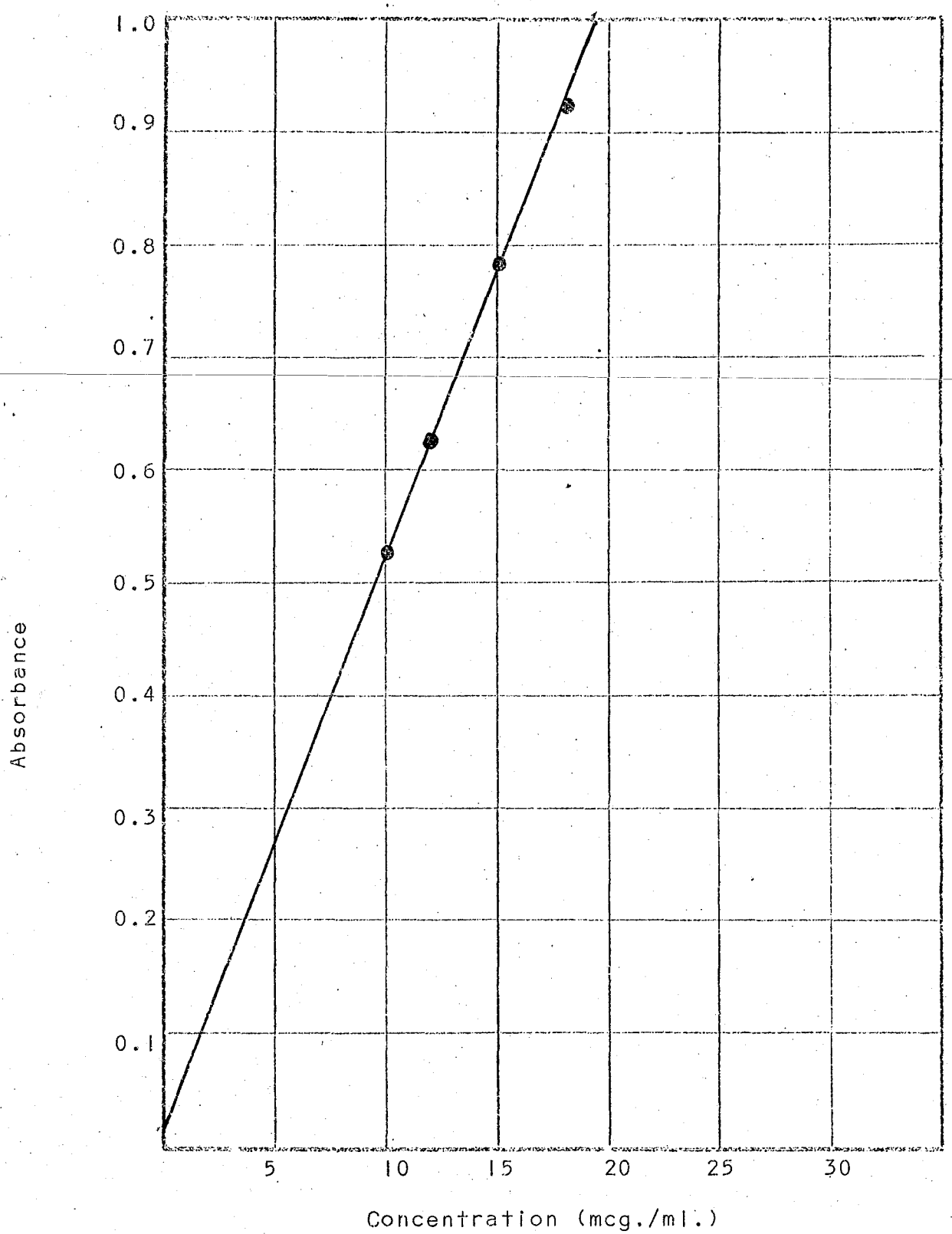
Metaraminol bitartrate and hydrocortisone-21-phosphate were mixed in 5% Dextrose Injection at a concentration of 500 mcg./ml. and 250 mcg./ml., respectively. Admixture analysis was performed on the diluted aliquot samples which provided a concentration for 30 mcg./ml. for metaraminol bitartrate and 15 mcg./ml. for hydrocortisone-21-phosphate.

As with the saline admixture, no appreciable change in the absorption spectrum for either metaraminol bitartrate and hydrocortisone-21-phosphate occurred throughout the eight hours of study (Figures 28, 29, 30).

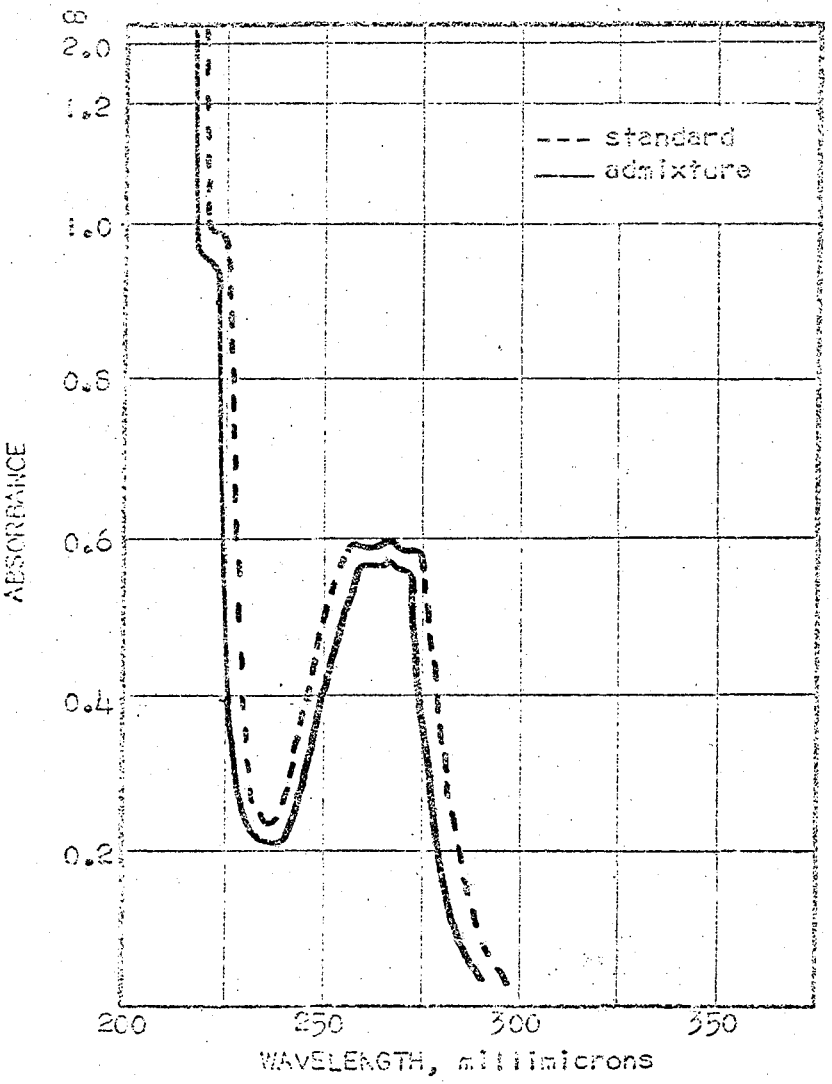
Again, the marked drop in pH, with reference to the corticosteroid, did not appear to be associated with an alteration in the absorption spectrum for this component (Table X).

Table X: pH Change of Metaraminol Bitartrate and Hydrocortisone-21-Phosphate in 5% Dextrose Injection.

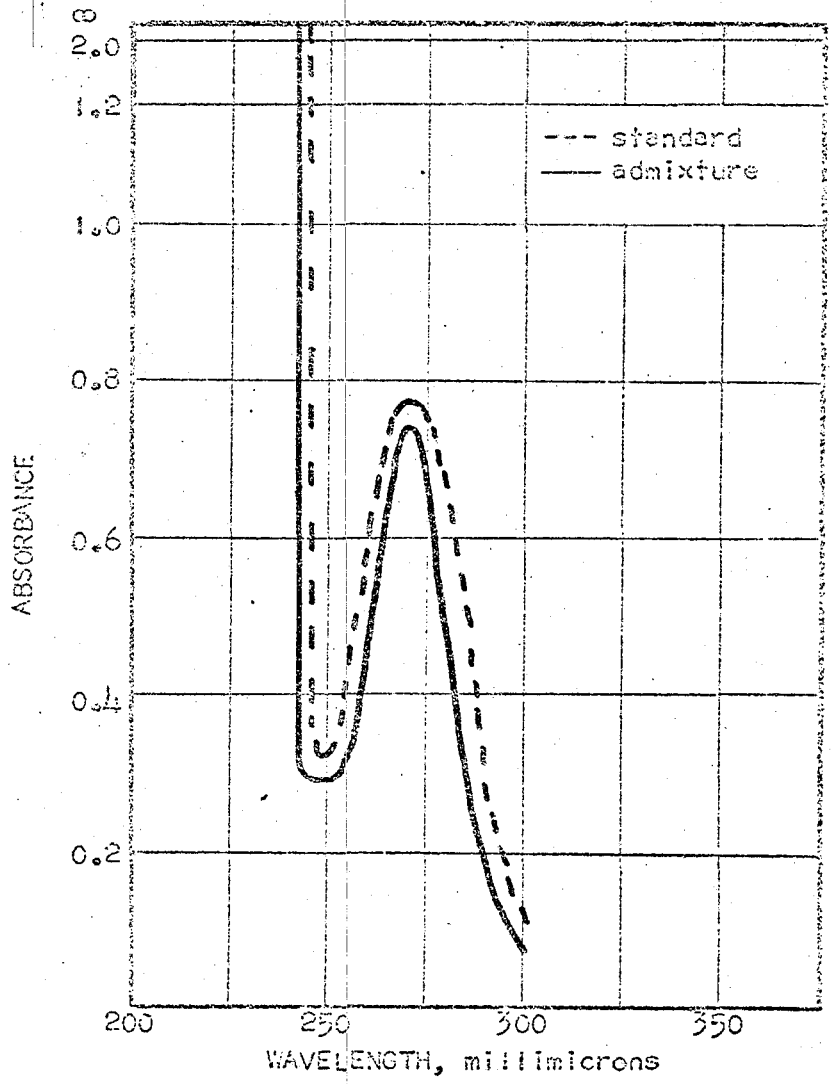
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone-21-Phosphate	500 250	4.3	4.4	4.4
5% Dextrose Injection		5.0	5.0	5.0
Metaraminol Bitartrate	500	3.6	3.6	3.6
Hydrocortisone-21-Phosphate	250	7.5	7.5	7.5



Graph 12. Beer plot for Hydrocortisone-21-Phosphate in 5% Dextrose Injection.

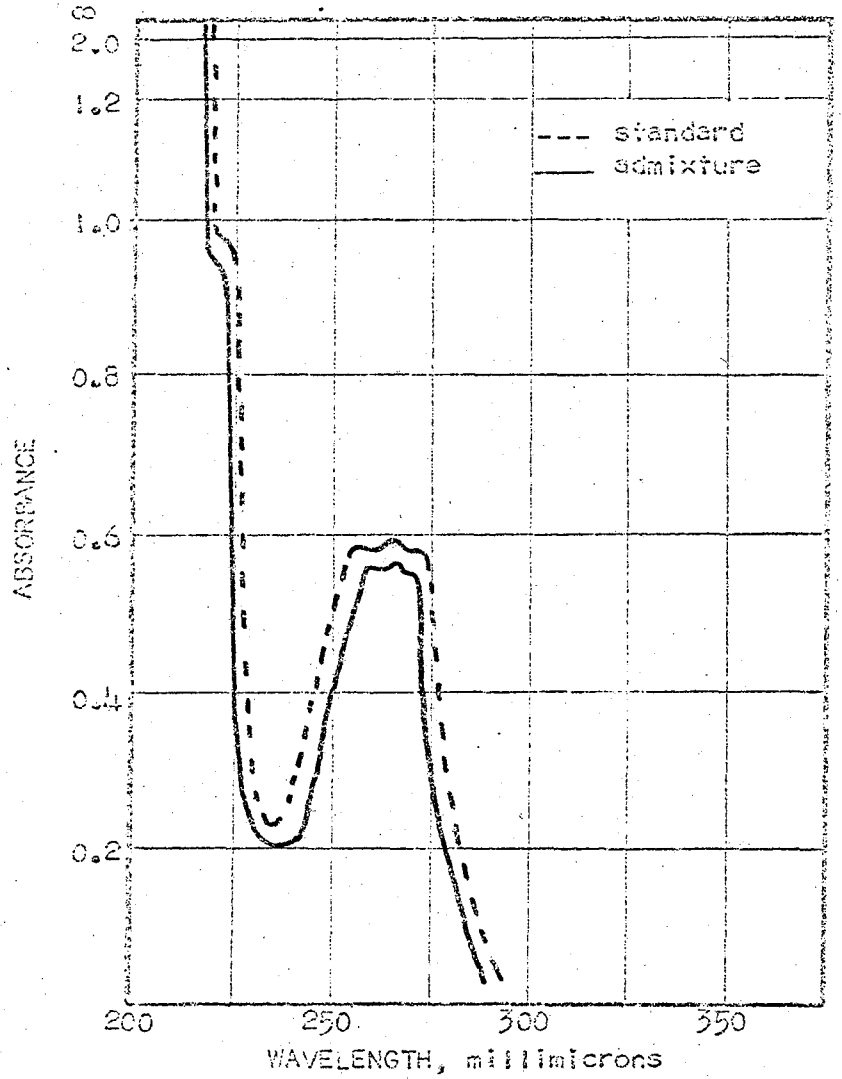


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.

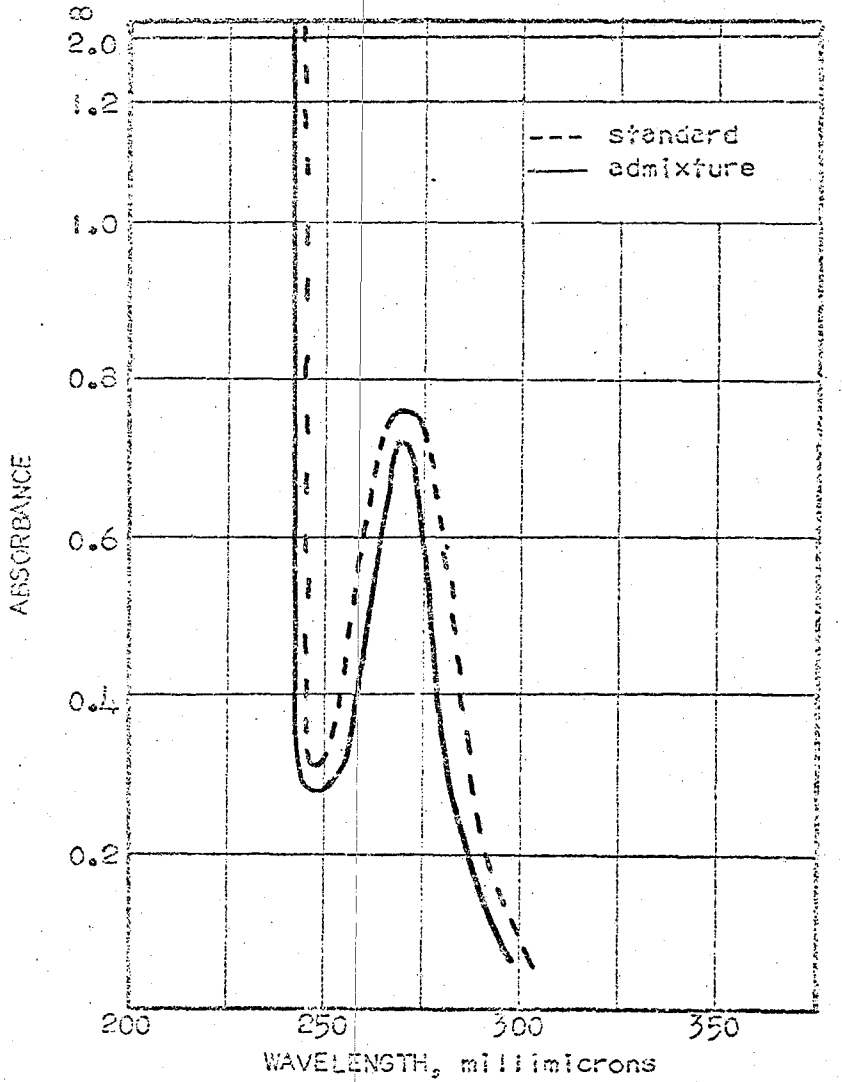


Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 28. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone-21-Phosphate (λmax 248 mμ) in 5% Dextrose Injection at one hour.

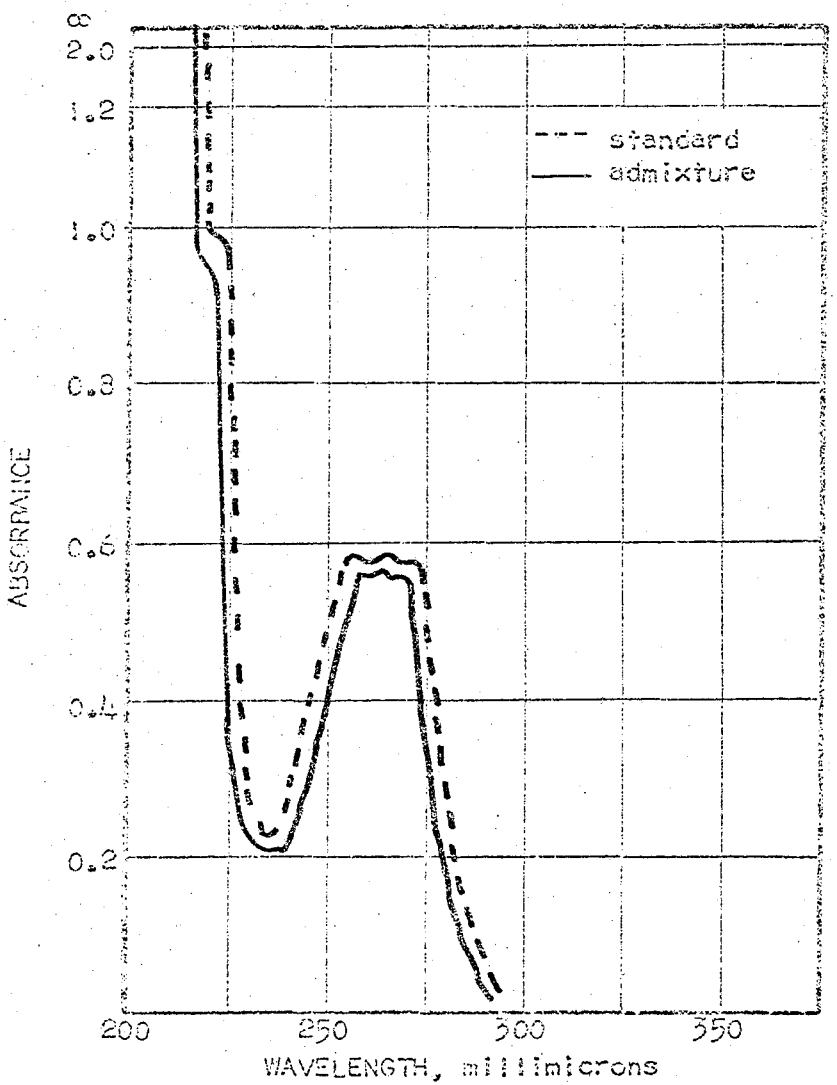


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.

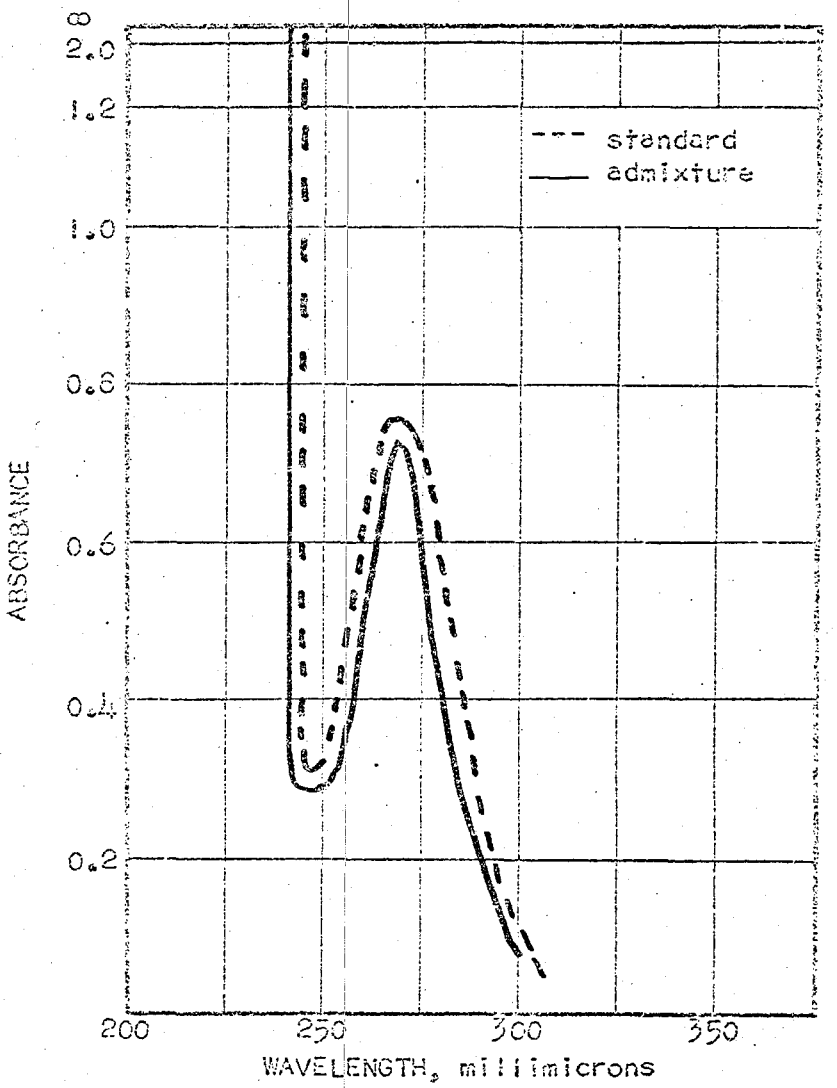


Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 29. U.V. Spectrum of Metaraminol Bitartrate (max 267 mu) with Hydrocortisone-21-Phosphate (max 248 mu) in 5% Dextrose injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone-21-Phosphate
15 mcg./ml.



Hydrocortisone-21-Phosphate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 30. U.V. Spectrum of Metaraminol Bitartrate (max 267 mu) with Hydrocortisone-21-Phosphate (max.248 mu) in 5% Dextrose Injection at eight hours.

Metaraminol Bitartrate and Hydrocortisone Sodium Succinate In Sodium Chloride Injection

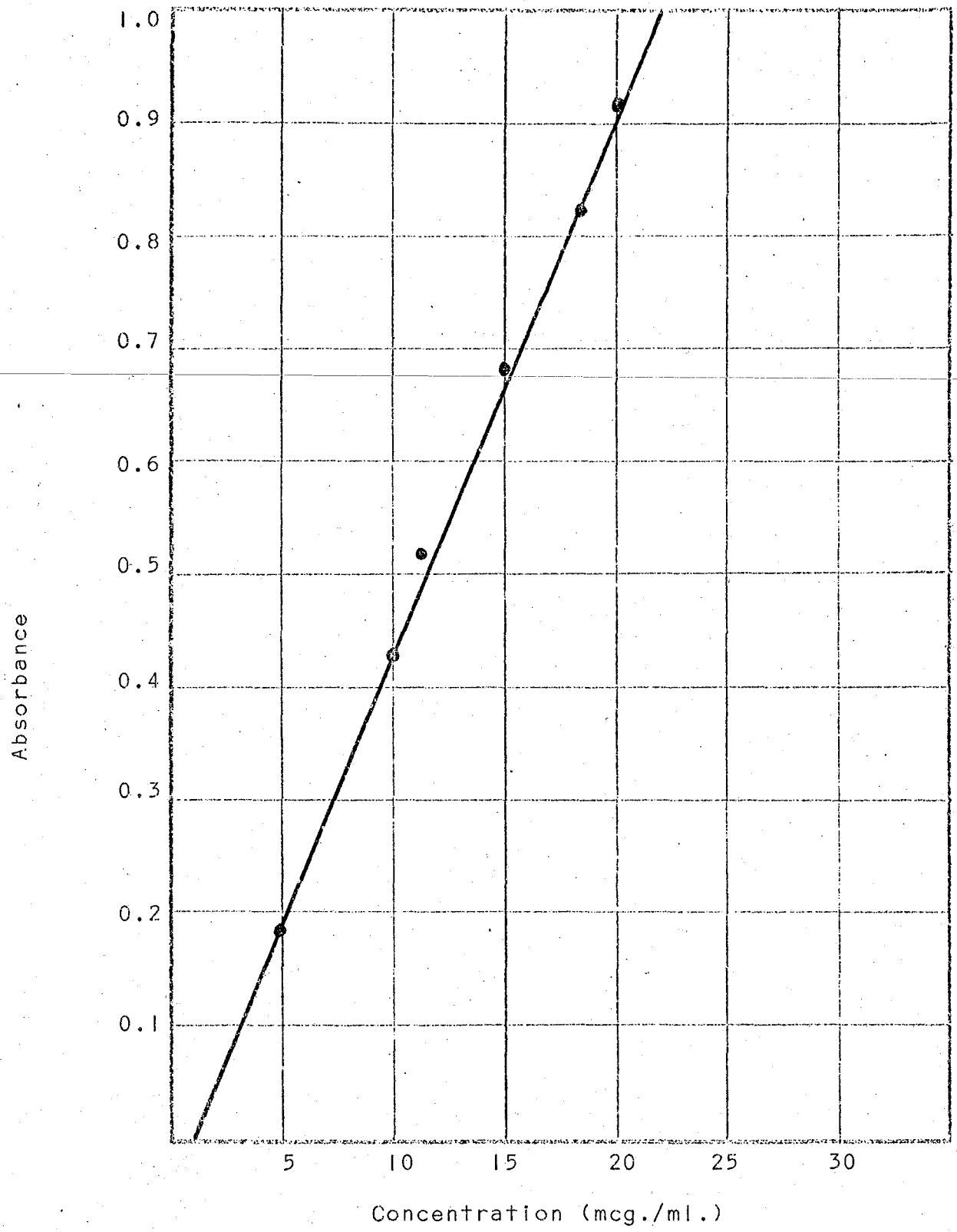
A precipitate was observed within one hour after metaraminol bitartrate, 500 mcg./ml., and hydrocortisone sodium succinate, 250 mcg./ml., were mixed in Sodium Chloride Injection. Therefore, aliquots at the specified time intervals were withdrawn by using a Swinnex-25 filter. Dilution of these filtered aliquots was calculated to provide the optimum spectrophotometric concentration for each component had no precipitation occurred, metaraminol bitartrate 30 mcg./ml. and hydrocortisone sodium succinate 15 mcg./ml.

The absorption spectrum obtained was compared to the standard spectrum and demonstrated an appreciable loss of absorbance for hydrocortisone sodium succinate. This would suggest an appreciable reduction in concentration for this component. Metaraminol bitartrate demonstrated both an altered absorption spectrum and a loss of absorbance. The impossibility of using a reference solution in a concentration to compensate for the loss of the hydrocortisone component was the probable cause of the altered spectrum seen for metaraminol (Figures 31, 32, 33).

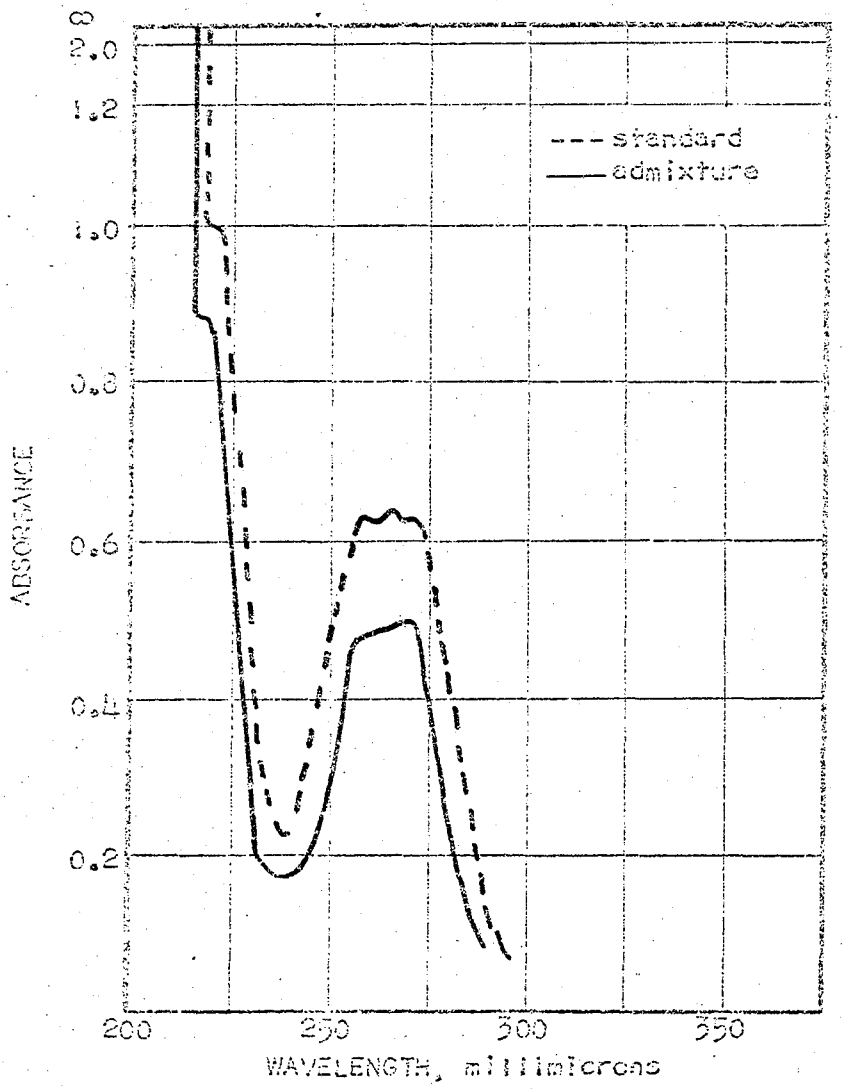
The pH of the therapeutic admixture at specific time intervals after initial mixing was compared to the pH of the individual components. It was noted that the pH of the admixture was somewhat greater than three pH units below that seen with the corticosteroid, in the absence of the pressor agent (Table XI).

Table XI: pH Change of Metaraminol Bitartrate and Hydrocortisone Sodium Succinate in Sodium Chloride Injection.

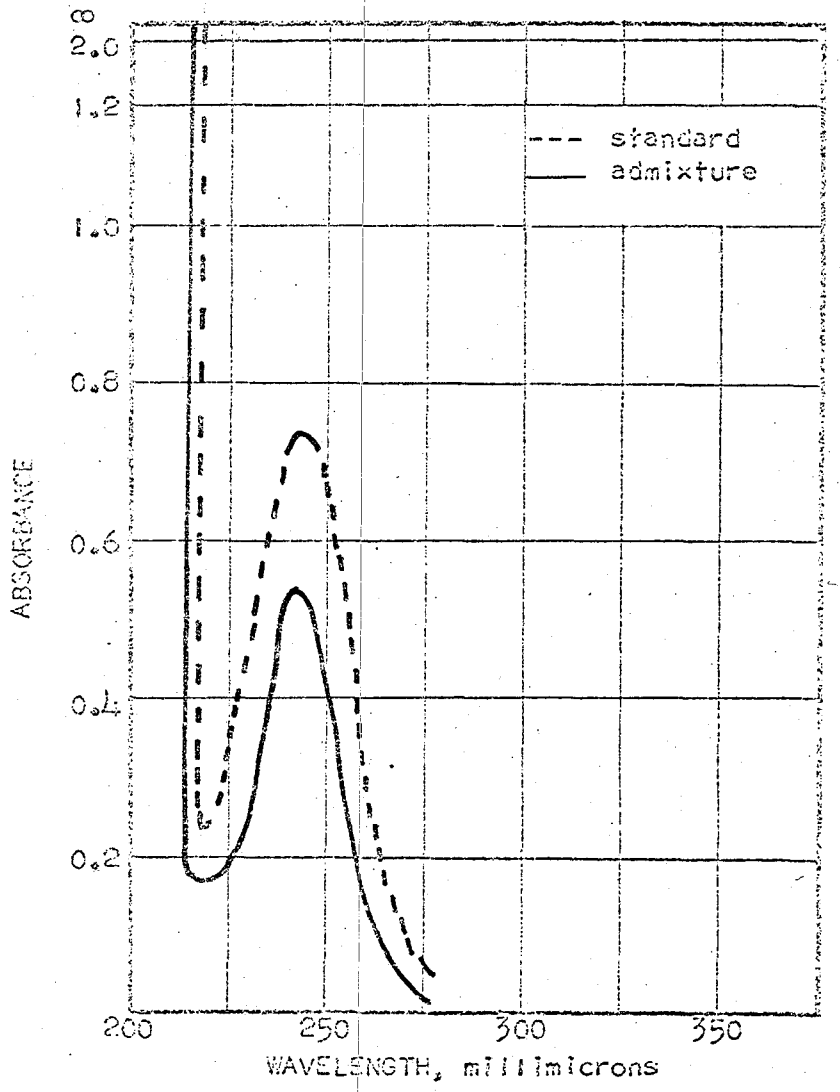
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone Sodium Succinate	500 250	3.8	3.8	3.8
Sodium Chloride Injection		6.4	6.4	6.4
Metaraminol Bitartrate	500	3.7	3.7	3.6
Hydrocortisone Sodium Succinate	250	7.2	7.2	7.2



Graph 13. Beer plot for Hydrocortisone Sodium Succinate in Sodium Chloride Injection.

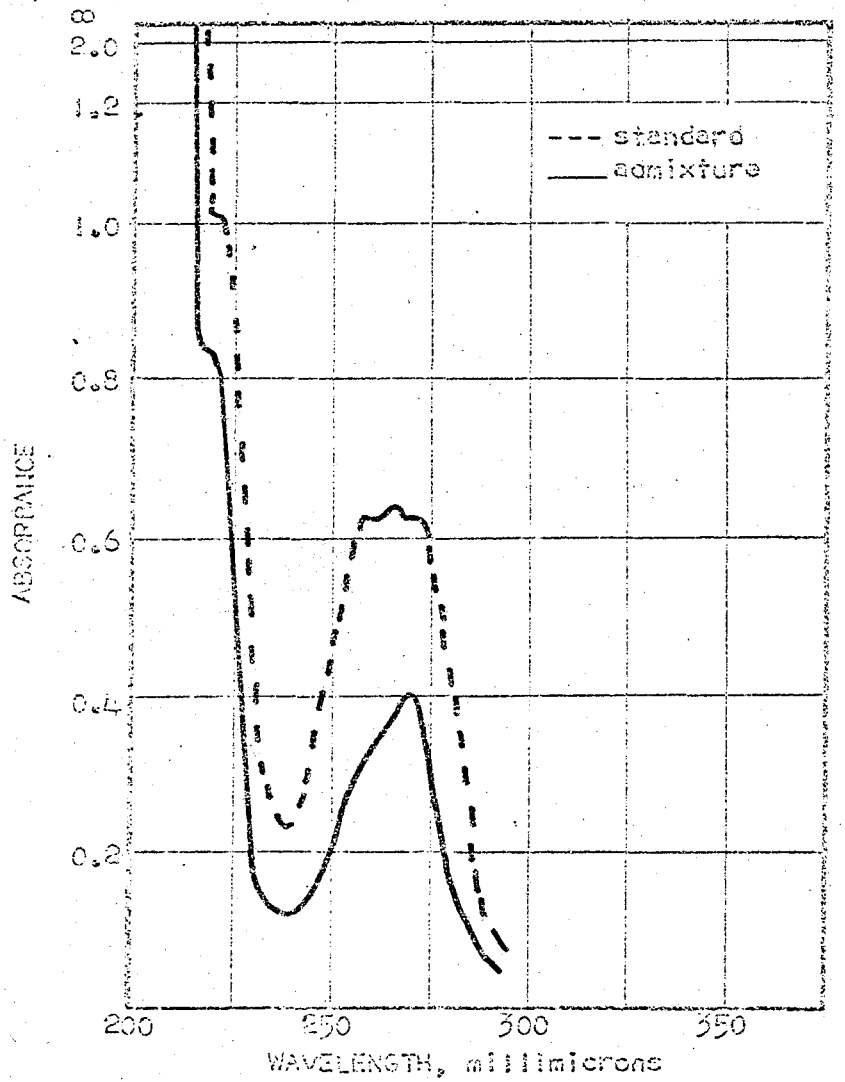


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.

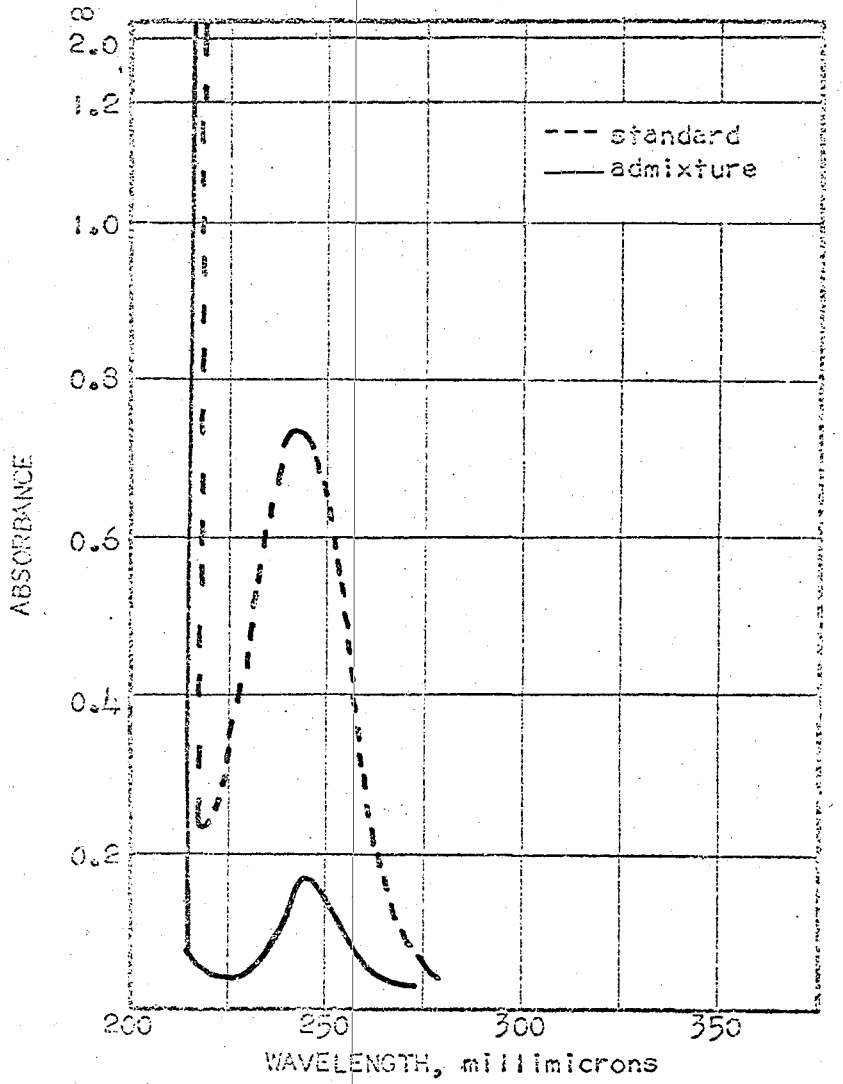


Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 31. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at one hour.

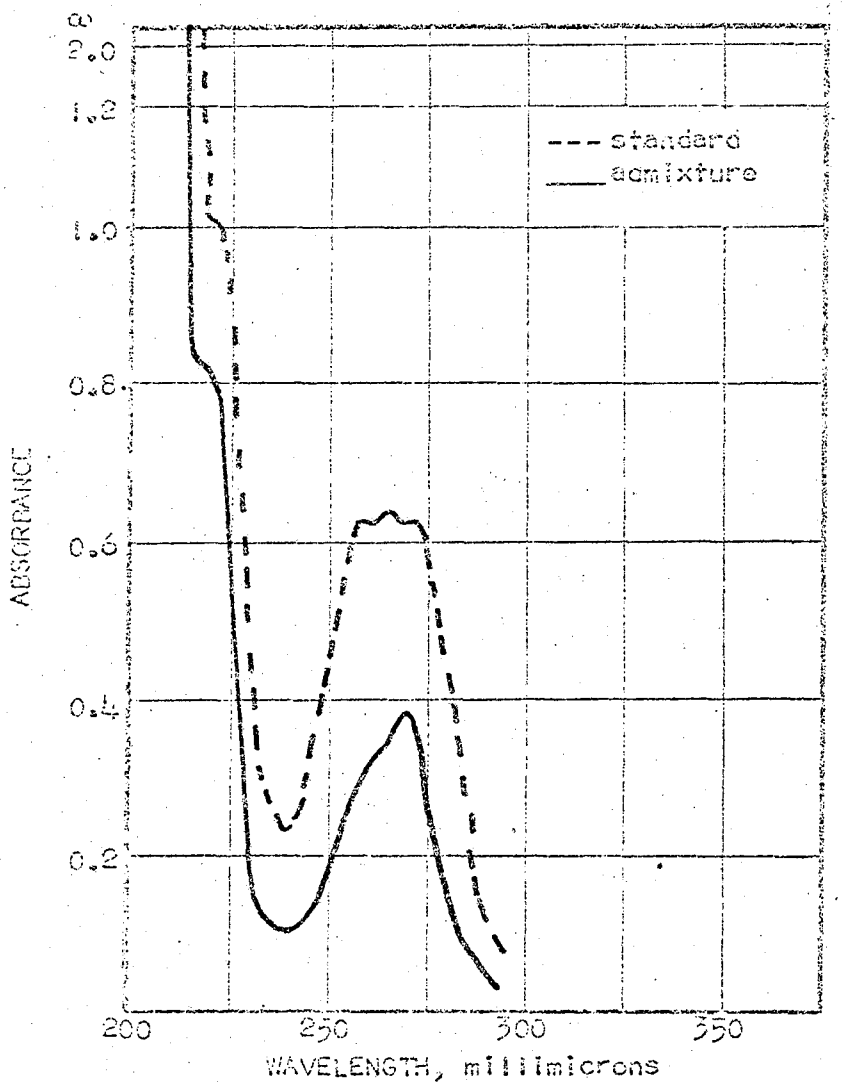


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.

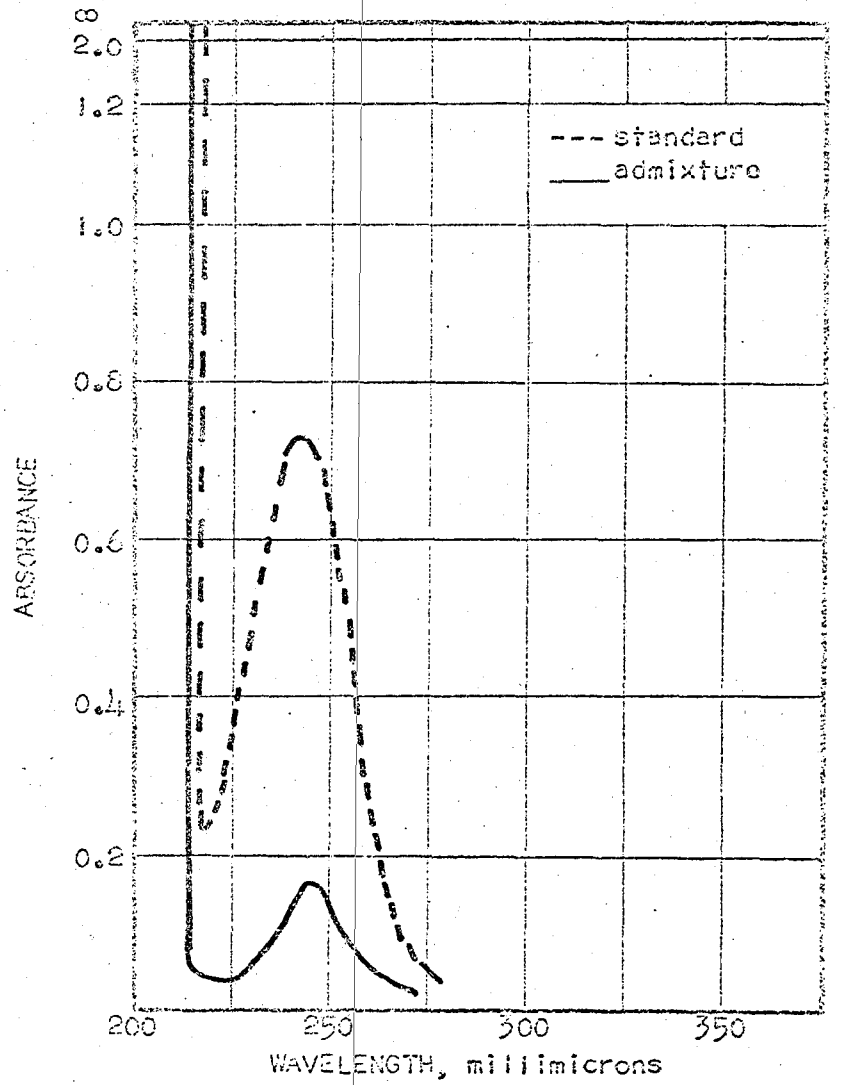


Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 32. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.



Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 33. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in Sodium Chloride Injection at eight hours.

Metaraminol Bitartrate and Hydrocortisone Sodium Succinate in 5% Dextrose Injection

The admixture of metaraminol bitartrate, 500 mcg./ml. and hydrocortisone sodium succinate, 250 mcg./ml. in 5% Dextrose Injection demonstrated the presence of a precipitate after one hour of admixture. Filtered aliquots were withdrawn and diluted to provide a concentration of 30 mcg./ml. for metaraminol bitartrate and 15 mcg./ml. for hydrocortisone sodium succinate, based on calculations which ignored the formation of the precipitate.

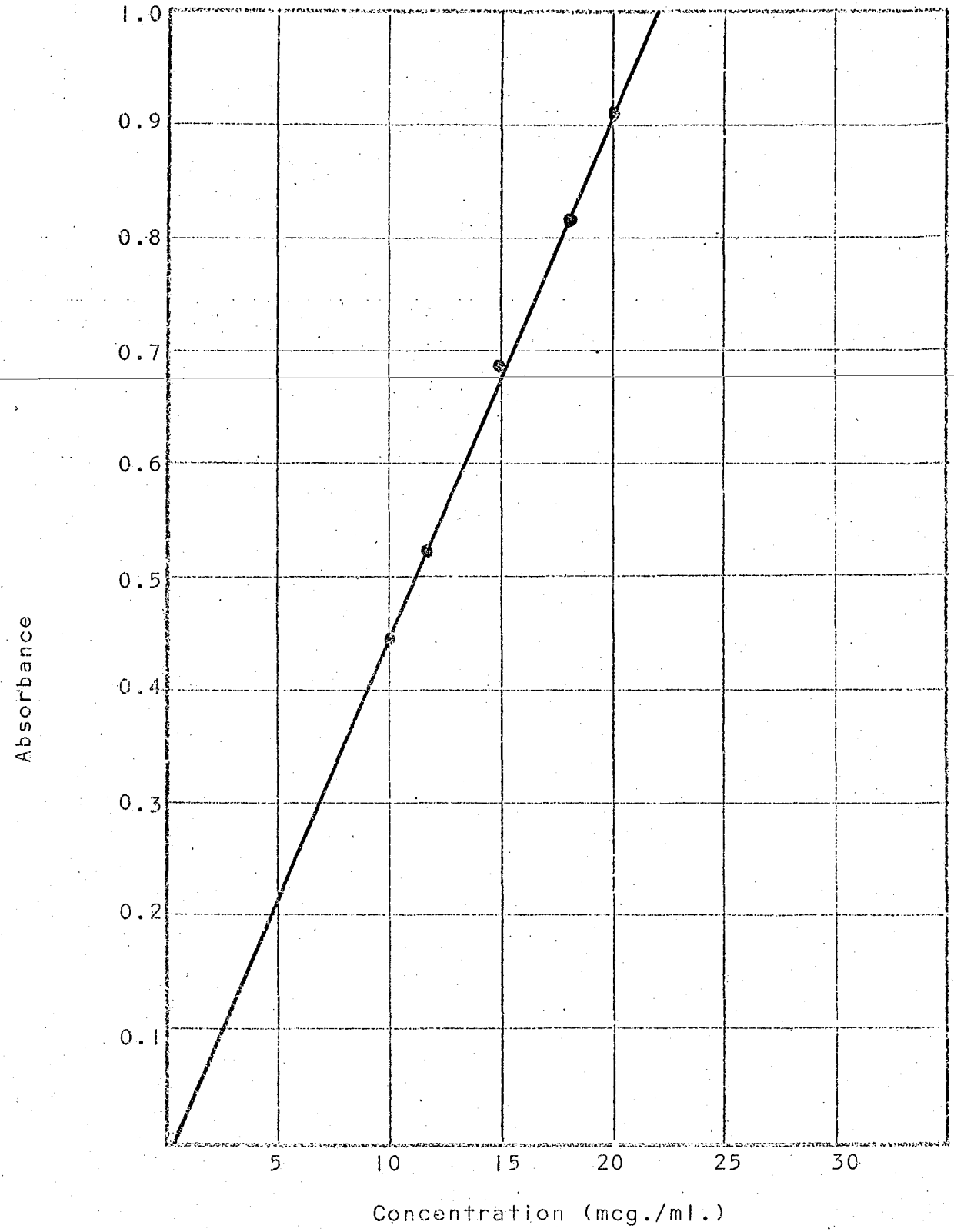
Comparison of the absorption spectrum obtained with the standard spectrum demonstrated an appreciable loss of absorbance for hydrocortisone sodium succinate, suggesting an appreciable reduction of concentration for this component. The loss of absorbance for this component in the dextrose admixture was slightly less and developed more slowly than observed in the saline admixture. Metaraminol bitartrate demonstrated both an altered absorption spectrum and a loss of absorbance. As with the saline admixture, no effort was made to compensate for the loss of the hydrocortisone component by altering the concentration of the reference. This failure was the probable cause of the altered spectrum seen for metaraminol. The data obtained from both the saline and dextrose admixtures would suggest that the precipitate consisted primarily of the corticosteroid component (Figures 34, 35, 36).

In this admixture, the development of the precipitate was somewhat slower than with the same combination in Sodium

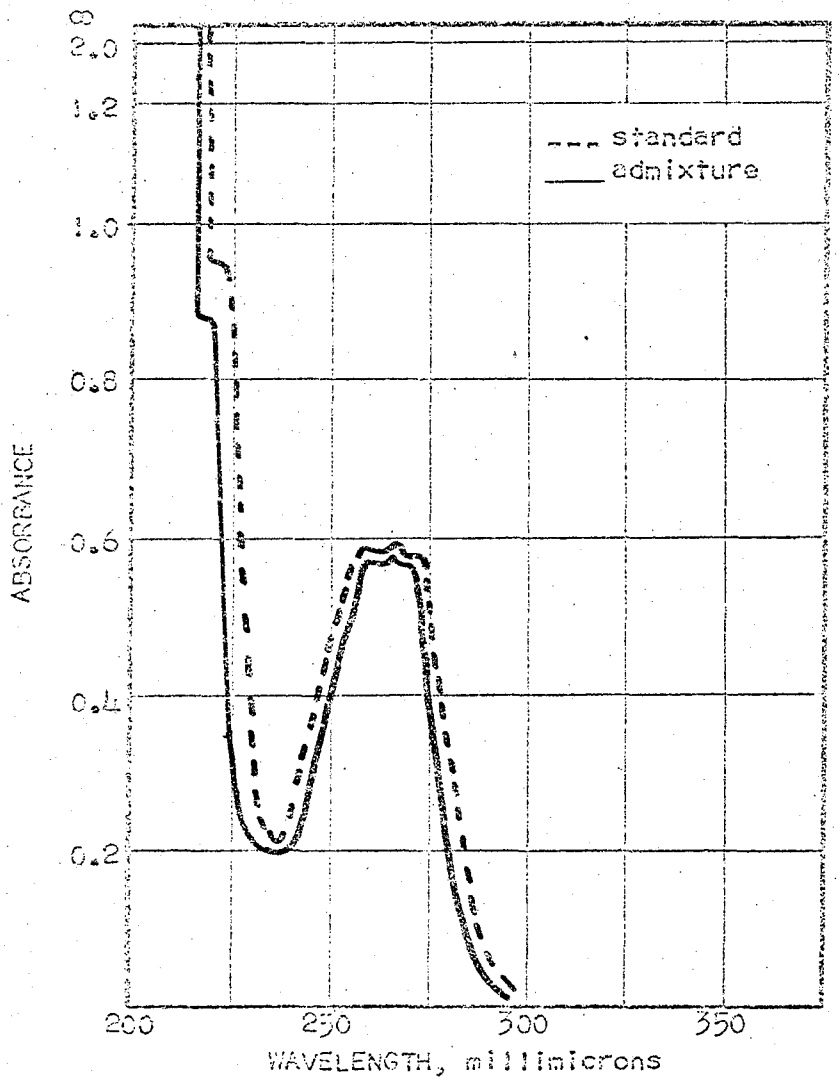
Chloride injection. The alteration in pH, using Dextrose Injection as the infusion fluid, was slightly less than seen in the saline solution (Table XII).

Table XII: pH Change of Metaraminol Bitartrate and Hydrocortisone Sodium Succinate in 5% Dextrose Injection.

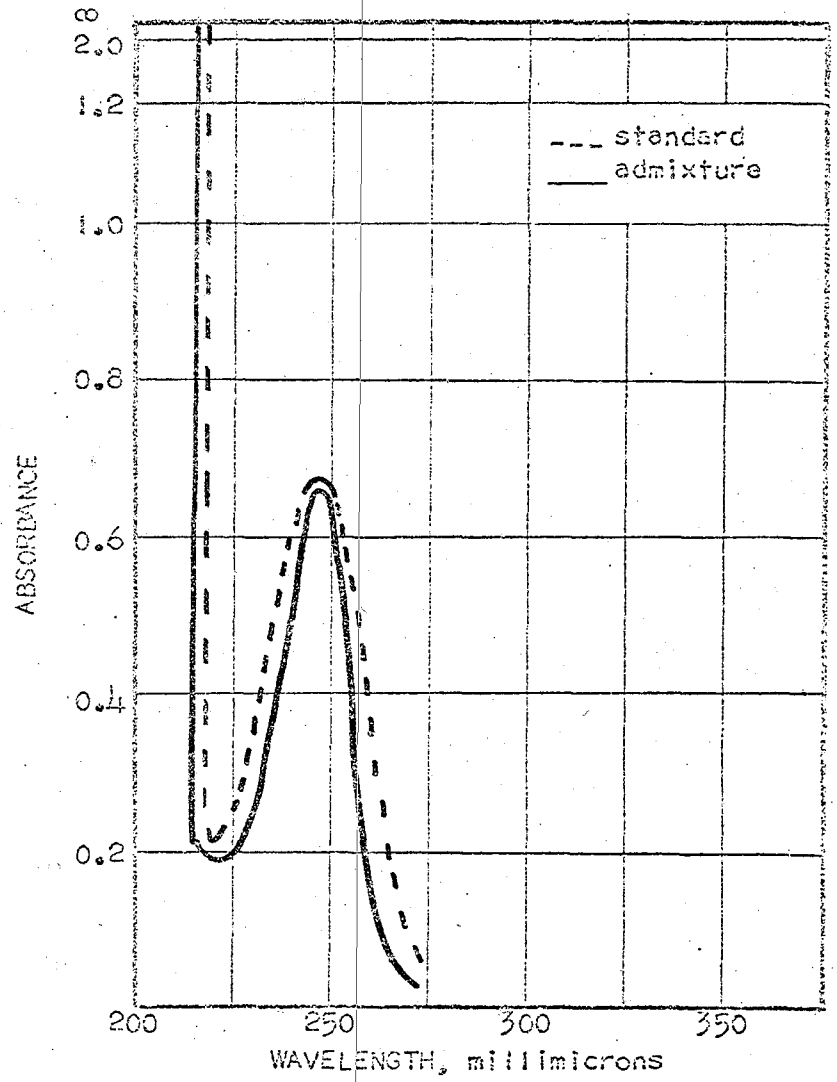
Component	conc. (mcg./ml.)	pH after admixture 1 hr.	4 hr.	8 hr.
Metaraminol Bitartrate and Hydrocortisone Sodium Succinate	500 250	4.0	4.1	4.1
5% Dextrose Injection		5.0	5.0	5.0
Metaraminol Bitartrate	500	3.6	3.6	3.6
Hydrocortisone Sodium Succinate	250	6.8	6.8	6.8



Graph 14. Beer plot for Hydrocortisone Sodium Succinate in 5% Dextrose Injection.

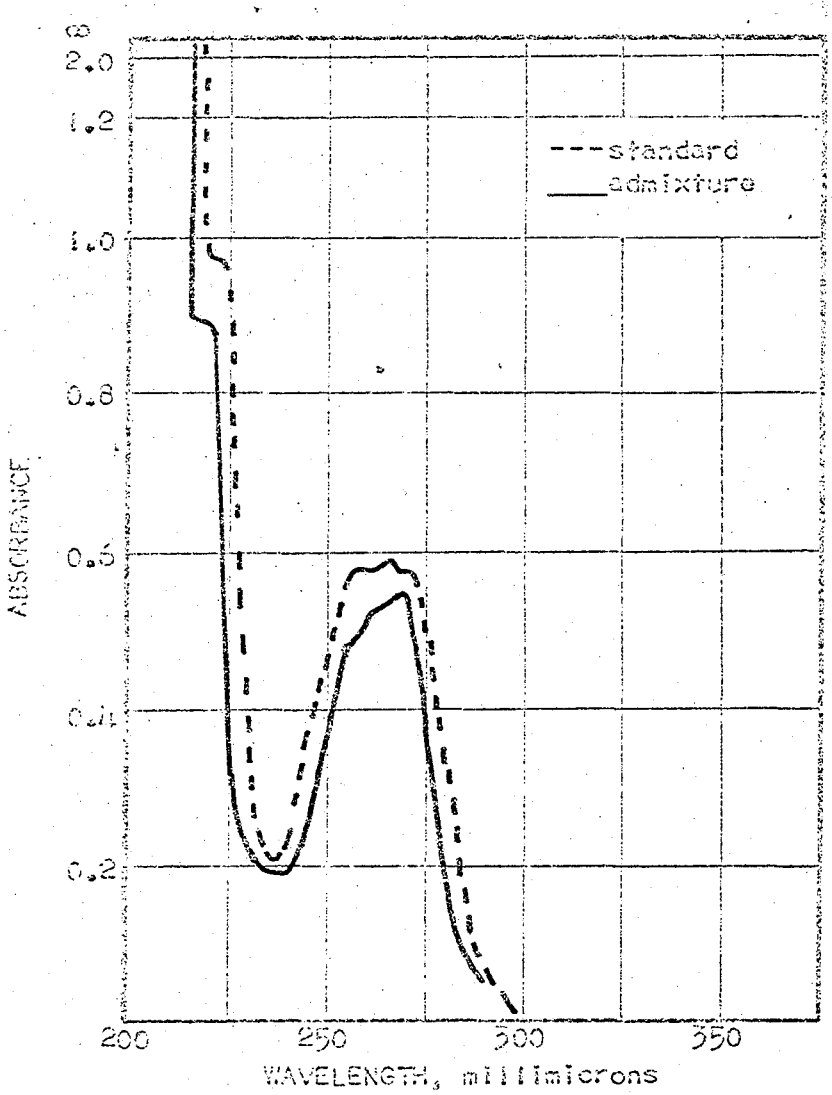


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.

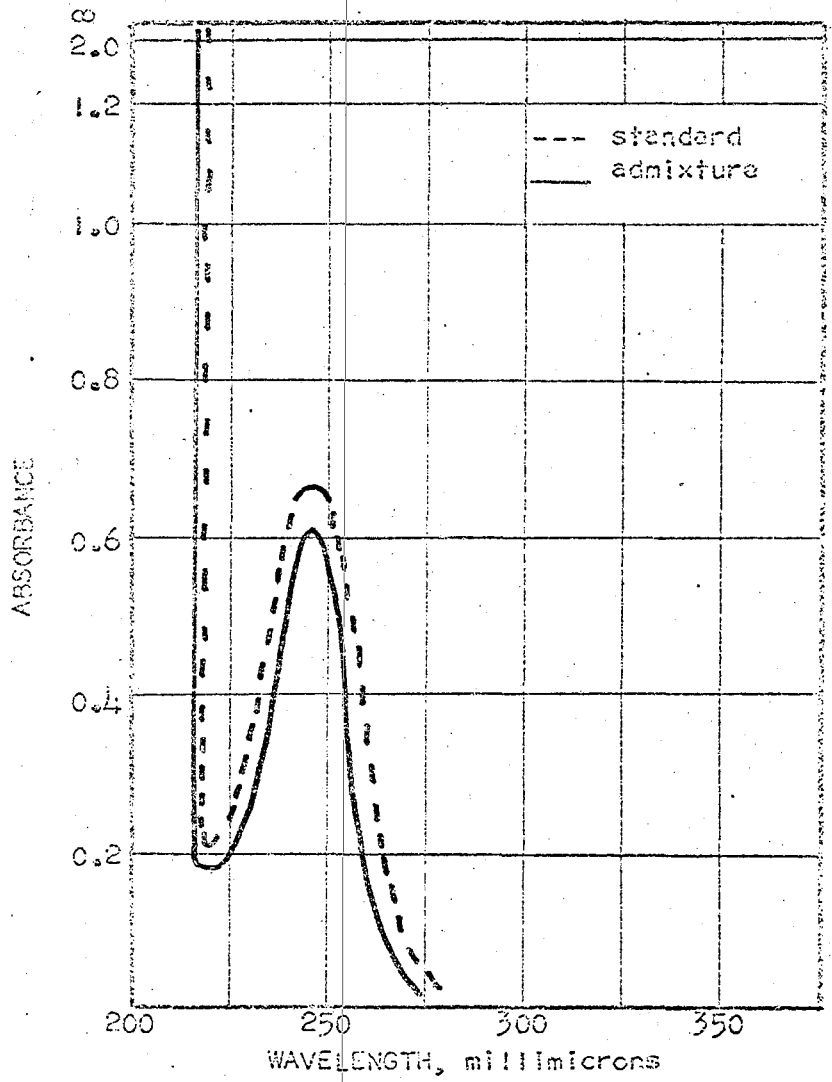


Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 34. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at one hour.

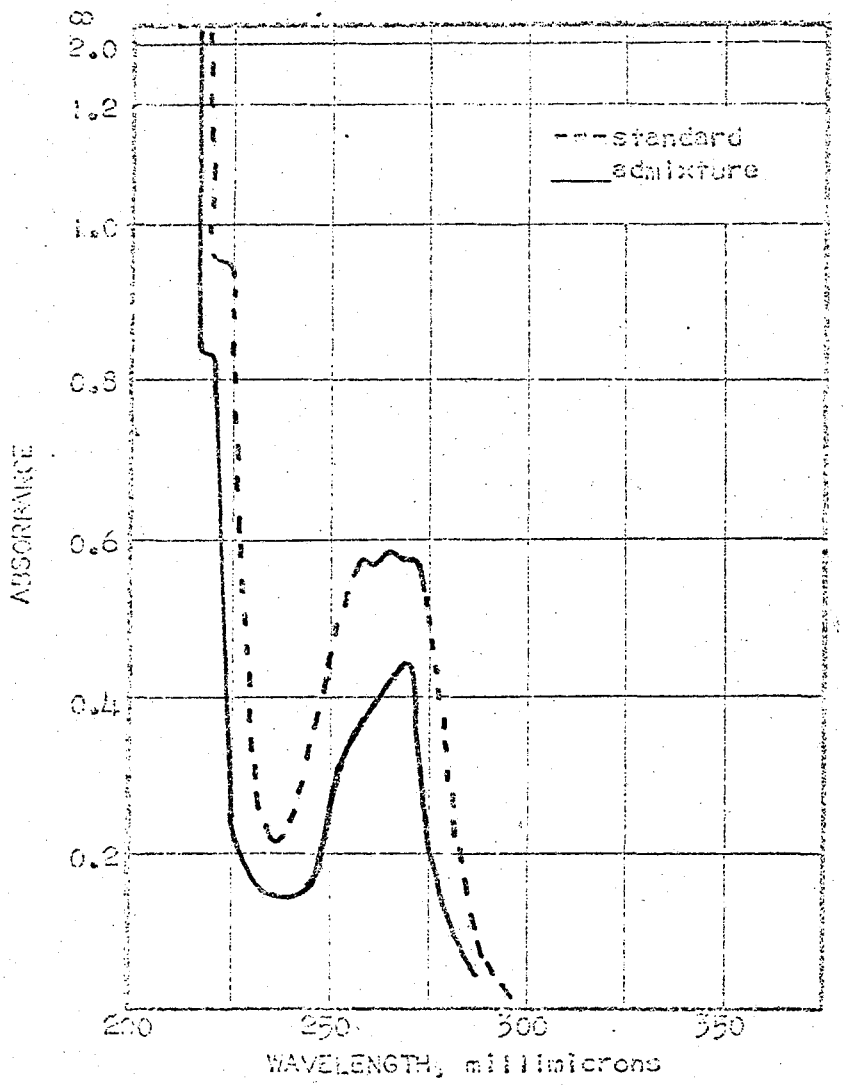


Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.

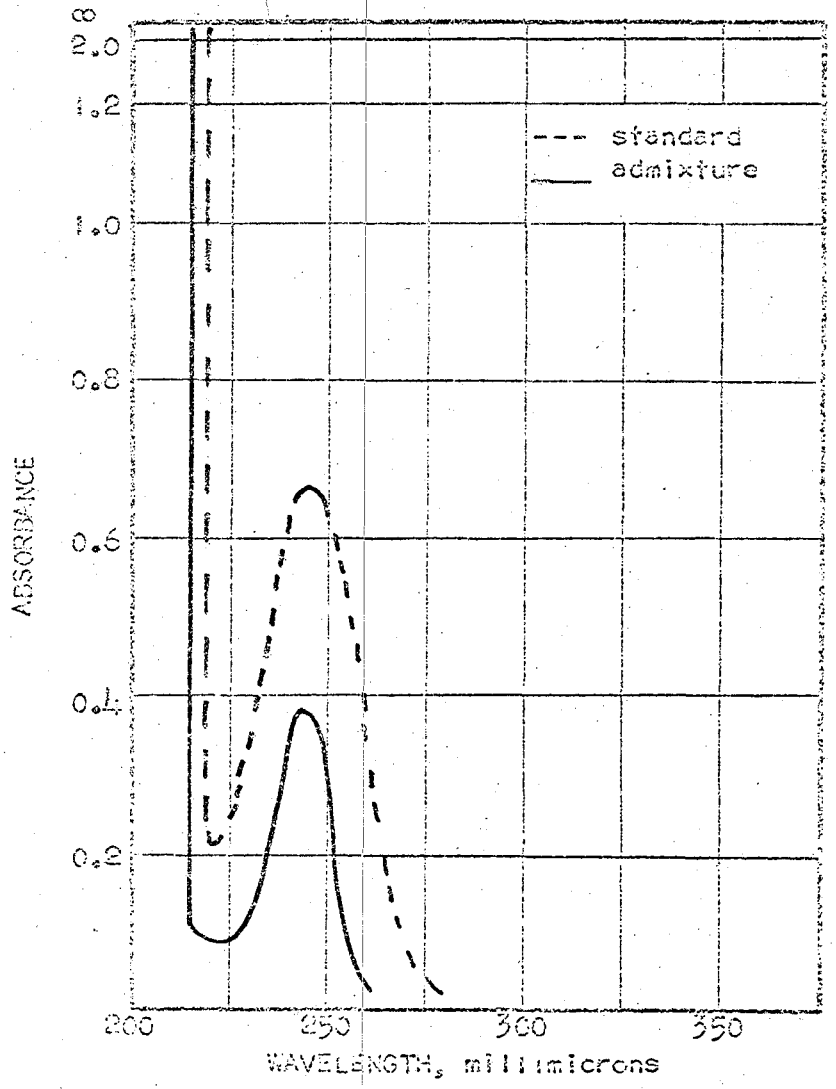


Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 35. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at four hours.



Metaraminol Bitartrate 30 mcg./ml.
ref: Hydrocortisone Sodium Succinate
15 mcg./ml.



Hydrocortisone Sodium Succinate
15 mcg./ml.
ref: Metaraminol Bitartrate
30 mcg./ml.

Figure 36. U.V. Spectrum of Metaraminol Bitartrate (λmax 267 mμ) with Hydrocortisone Sodium Succinate (λmax 248 mμ) in 5% Dextrose Injection at eight hours.

Table XIII: Summary of the Spectrophotometric Analysis on Admixtures Containing Metaraminol Bitartrate and Selected Corticosteroids in Sodium Chloride Injection.

Admixture	conc. in admixture* (mcg./ml.)	optimum spectrophotometric conc.** (mcg./ml.)	spectrum***
Prednisolone Sodium Phosphate	100	8	altered
Metaraminol Bitartrate	500	40	unchanged
Dexamethasone Sodium Phosphate	20	8	altered
Metaraminol Bitartrate	100	40	unchanged
Methylprednisolone Sodium Succinate	125	12.5	altered
Metaraminol Bitartrate	400	40	unchanged
Hydrocortisone	250	15	unchanged
Metaraminol Bitartrate	500	30	unchanged
Hydrocortisone-21-Phosphate	250	15	unchanged
Metaraminol Bitartrate	500	30	unchanged
Hydrocortisone Sodium Succinate	250	15	altered
Metaraminol Bitartrate	500	30	altered****

*The concentration of the admixture components reflects a therapeutic concentration which could be added to 1000 ml. of infusion solution.

**The optimum spectrophotometric concentration is the concentration range which would produce an absorbance between 0.3 and 0.9.

***Alteration in absorption spectrum was considered significant if an appreciable loss of absorbance or changes in the continuous absorption spectrum occurred.

****Failure to use a reference solution, in a concentration to compensate for the loss of the hydrocortisone component, was the probable cause of the altered spectrum seen for metaraminol.

Table XIV: Summary of the Spectrophotometric Analysis on Admixtures Containing Metaraminol Bitartrate and Selected Corticosteroids in 5% Dextrose Injection.

Admixture	conc. in admixture* (mcg./ml.)	optimum spectrophotometric conc.** (mcg./ml.)	spectrum***
Prednisolone Sodium Phosphate	100	8	altered
Metaraminol Bitartrate	500	40	unchanged
Dexamethasone Sodium Phosphate	20	8	altered
Metaraminol Bitartrate	100	40	unchanged
Methylprednisolone Sodium Succinate	125	12.5	altered
Metaraminol Bitartrate	400	40	unchanged
Hydrocortisone	250	15	unchanged
Metaraminol Bitartrate	500	30	unchanged
Hydrocortisone-21-Phosphate	250	15	unchanged
Metaraminol Bitartrate	500	30	unchanged
Hydrocortisone Sodium Succinate	250	15	altered
Metaraminol Bitartrate	500	30	altered****

*The concentration of the admixture components reflects a therapeutic concentration which could be added to 1000 ml. of infusion solution.

**The optimum spectrophotometric concentration is the concentration range which would produce an absorbance between 0.3 and 0.9.

***Alteration in absorption spectrum was considered significant if an appreciable loss of absorbance or changes in the continuous absorption spectrum occurred.

****Failure to use a reference solution, in a concentration to compensate for the loss of the hydrocortisone component, was the probable cause of the altered spectrum seen for metaraminol.

CHAPTER IV

DISCUSSION

The use of the sympathomimetic pressor amines and the glucocorticosteroids is currently being advocated for the treatment of cardiogenic shock. The intravenous use of these drugs, either singly or in combination as components of an intravenous admixture, has been shown to provide a rapid and continuous increase in blood pressure which results in a favorable perfusion of the heart, kidneys, and brain. The rapid restoration of blood perfusion to these organs has reduced the morbidity of this syndrome (34, 35).

Chemically, drug formulations of the sympathomimetic pressor amines are acidic (pH 3-4), while formulations containing the corticosteroids are generally more alkaline (pH 5-8). The simultaneous use of these drugs as components of an intravenous admixture could result in a pH range which might adversely affect the stability of either or both of these agents. Because of their clinical use and possible chemical reactivity, representative drug formulations from each group were chosen for this study.

After an initial spectrophotometric screening, metaraminol bitartrate and six corticosteroids, including three different drug formulations of hydrocortisone, were selected. Admixtures containing these drug formulations could be mixed at a

therapeutic concentration and diluted to provide the necessary optimum spectrophotometric concentration for both components without altering the initial therapeutic concentration ratio. Sodium Chloride Injection and 5% Dextrose Injection were selected as the dilution vehicles because of their clinical use and lack of appreciable buffering capacity.

The criterion used to judge the occurrence of a chemical interaction was an alteration in the U.V. absorption spectrum for a drug formulation after admixture. Appreciable loss of absorbance would indicate a corresponding loss of concentration. Changes in the continuous absorption spectrum, such as a shift in the λmax or development of secondary peaks, would indicate an alteration in the chemical structure for the drug formulation.

Obtaining the absorption spectrum specific for each drug component in an admixture presented a problem in that the presence of two different drugs in solution can produce an absorption spectrum which is a composite of the individual spectrum for each drug. The method used in this study to effectively mask or block the presence of one admixture component was the technique of differential spectrophotometric analysis. In this, the solution in the reference beam of the spectrophotometer, is the same composition and concentration as one component of the admixture tested. By alternating this reference solution, the absorption spectrum specific for each drug component can be obtained.

The importance of using a reference solution of appropriate

composition was demonstrated by the absorption spectrum obtained for admixtures of metaraminol bitartrate and hydrocortisone sodium succinate. In these, the precipitate observed was believed to be composed primarily of the corticosteroid component. Failure to use a reference solution to compensate for the apparent loss of this component resulted in an altered for composite spectrum observed for metaraminol bitartrate.

The pH of the individual drug formulations before and after admixture were recorded at specific intervals. Throughout the study, the pH of admixtures represented in the order of two to more than three pH units of change for the corticosteroid component. The pH change for metaraminol did not exceed one pH unit. Comparison of the changes in pH with the results obtained by spectrophotometric analysis of the same admixture components suggested some possible correlation. With the exception of admixtures containing metaraminol bitartrate and hydrocortisone or hydrocortisone-21-phosphate, a pH change of three pH units for an admixture component was associated with an alteration in the absorption spectrum for the same component.

Three different drug formulations of hydrocortisone were used in the study, hydrocortisone, hydrocortisone-21-phosphate, and hydrocortisone sodium succinate. Each was mixed with metaraminol bitartrate in the same hydrocortisone equivalent concentration. Admixtures containing hydrocortisone demonstrated a change of two pH units for this component and no

appreciable alteration in the U.V. absorption spectrum. Admixtures containing hydrocortisone-21-phosphate demonstrated a 3 pH unit change and a slight loss of absorption in the absorption spectrum was observed. Hydrocortisone sodium succinate containing admixtures demonstrated a 3 pH unit change for this component and a precipitate was observed.

It would appear that different drug formulations of the same parent compound could have quite different stability characteristics after admixture.

CHAPTER V

SUMMARY AND CONCLUSIONS

The purpose of this investigation was to demonstrate the use of spectrophotometric analysis in detecting the occurrence of chemical interactions between two drug components of an intravenous admixture. The ultraviolet absorption spectrum was obtained for each drug formulation before and after admixture. Comparison of the resultant spectrum was made for a change in absorbance at the λmax, and for alteration or shift of the λmax. The occurrence of a chemical interaction was suggested when an appreciable loss of absorbance at the λmax occurred. This would indicate a loss of concentration for the drug component. An alteration of the absorption spectrum with the development of a new or secondary λmax would suggest modifications in the structural nature of the drug component and would also be suggestive of a chemical interaction.

Of the twelve admixture combinations containing metaraminol and one of six selected corticosteroids, eight admixtures demonstrated evidence of chemical interaction.

Admixtures of metaraminol bitartrate with hydrocortisone sodium succinate and methylprednisolone sodium succinate in Sodium Chloride Injection and 5% Dextrose Injection produced precipitates within one and four hours respectively. Subsequent analysis of filtered admixture samples demonstrated a

considerable loss of absorbance for the corticosteroid component.

Admixtures of metaraminol bitartrate with prednisolone sodium phosphate and dexamethasone sodium phosphate in Sodium Chloride Injection and 5% Dextrose Injection demonstrated an altered absorption spectrum for the corticosteroid component. Prednisolone sodium phosphate exhibited a secondary λmax, while dexamethasone sodium phosphate exhibited a wavelength shift in the λmax.

The absorption spectrum for admixtures of metaraminol bitartrate with hydrocortisone and hydrocortisone-21-phosphate in Sodium Chloride Injection and 5% Dextrose Injection was not significantly altered throughout the study.

Mixture of metaraminol bitartrate with the corticosteroids selected for inclusion in this study produced solutions with pronounced acidity. The pH measurements for the admixtures revealed that the acidity of the solutions was controlled, to a great extent, by the metaraminol bitartrate. This assertion is made on the basis that the resulting pH values were quite close to those observed when metaraminol bitartrate was added to the infusion fluids, in the same concentrations, but without the addition of other drugs. Except in the cases of hydrocortisone and hydrocortisone-21-phosphate, the pH change observed, with respect to the corticosteroid component, was associated with some alteration of the absorption spectrum.

Providing that the spectrophotometric optimum concentration can be attained for each drug component of an intravenous

admixture, the results of this study suggest that differential spectrophotometric analysis offers a useful method of detecting the occurrence of chemical interaction after admixture.

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