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Pharmaceutical and Related Drugs

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Review Contents

The current article represents an overview of the pharmaceutical methods that have been published since the last review in *Analytical Chemistry* two years ago (*1*). As has been the case in the past, it does not cover biochemical or clinical aspects of the topic but concentrates only on procedures that are concerned with either unformulated or formulated products. Because of space and citation limitations, the selected references represent only a very small fraction of the total number of papers that have been published. Additionally, in most cases, routine procedures, less often used techniques, and more common approaches are not included. Neither are books.

The review is divided into eight major topical areas: General Information; Alkaloids; Antibiotics; Nitrogen−Oxygen-Containing Compounds; Peptides, Proteins, and Related Compounds; Steroids, Sulfur-Containing Compounds; and Vitamins. Even though a paper may deal with more than one class of compounds, it typically will be discussed in only one section.

GENERAL INFORMATION

A number of comprehensive reviews have been published during the last two years. Many of these discuss various aspects of separation methodology. An important topical area has been enantiomeric purity (*2*−*7*), which has been a general trend in past reviews in this series. One of these accounts (*2*) contains over 550 references and considers basic mechanisms and applications of high-performance liquid chromatography (HPLC), gas chromatography (GC), thin-layer chromatography (TLC), capillary electrophoresis (CE), and capillary electrochromatography. In another paper (*4*), various types of protein phases are discussed including those based on immobilized albumins, glycoproteins, enzymes, and several other miscellaneous proteins. Details are provided about the synthesis, enantioselective properties, and chiral recognition mechanisms governing the analyte protein interactions. By technique and in terms of the number of review articles published about chiral purity, capillary electrophoresis received the most attention (*2*, *5*−*7*). These four references are only a few examples of a much larger body of work that has appeared in the scientific literature since the 2001 *Analytical Chemistry* Review (*1*).

An emerging and important instrumental topic is microchip electrophoresis technology, which has been discussed in terms of electrochemical detection (*8*, *9*) as well as in terms of its application in DNA analysis (*10*). In the latter instance, fundamental aspects of the technology are examined including DNA sizing, genetic analysis, and DNA sequencing. Likewise, the paper contains information on chip format, substrates and fabrication technologies, fluid control, and methods of detection. Likewise, a broad range of other technique-related reviews have been published that considered various aspects of mass spectrometry (*11*, *12*), microarrays (*13*), solid-state NMR spectroscopy (*14*), thermal analysis (*15*), and many other techniques used in pharmaceutical analysis. The latter two of these citations address the specific application of the techniques for characterizing pharmaceuticals in the solid state. In the case of NMR, the article discusses structure and conformation, molecular dynamics, spectral editing and two-dimensional correlations, and the measurement of internuclear distances. Besides these papers, two other reviews have appeared that consider important aspects of characterizing pharmaceutical solids (*16*, *17*). The first one concentrates on the physical nature of amorphous solids and addresses questions related to preparation, characterization, and stabilization especially as they relate to crystillinity, microheterogenity, and polymorphism. It also considers how changes can result from differences in manufacturing and storage conditions. The latter review (*17*) examines important aspects of the use of infrared, near-infrared, Raman, solid-state NMR, and chemical imaging techniques for physically characterizing the final dosage forms of pharmaceuticals.

Computational methods related to prediction and data analysis continue to be important topics. Both quantitative structure−activity relationships (QSAR) (*18*) and multivariate methods (*19*) have been discussed. In the latter instance, the article covers a five-year period and presents a comprehensive overview of theoretical and background information related to experimental design, optimization, and application of multivariate methods. The article contains many illustrative examples and is a useful tutorial for those interested in learning more about multivariate ap-

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proaches. The QSAR article targets angiotensin II−antagonist interactions in rabbits, rats, guinea pigs, and humans.

A large number of other topical reviews have been published. Examples of these are ones concerned with questions related to the validation of stability indicating methodology *(20*), bioavailability and bioequivalence (*21*), and drug stability both in a general sense as it relates to the theory, mechanisms, and initiation of autoxidation and chain oxidation processes (*22*) and in a specific sense in terms of the stability of vaccines, which is an important problem that often leads to inadequate supplies of them (*23*). In both of these latter two reviews strategies for increasing stability are discussed. It has been noted that in order to meet the growing worldwide shortage for many of the vaccines that are currently used, empirical approaches to stabilize them need to be replaced with more molecular-based approaches.

Besides the more general reviews discussed above, many others have appeared that are related to specific compounds or class of compounds. Some examples of these are papers that consider the following: the systemic delivery of insulin via the eye (*24*); the bioavailability of rifampicin from formulated products (*25*); recent developments in separation methology related to the anthracyclines (*26*) and camptothecin and related compounds (*27*); the application of capillary electrophoresis to study basic pharmaceuticals (*28*) and molecular interaction of glycopeptide antibiotics (*29*); the use of HPLC for measuring antibiotics (*30*) and steroids (*31*); and general separation methodology for sesquiterpenes and sesquiterpene lactones (*32*).

ALKALOIDS

Several comprehensive articles have been published that deal with a variety of topics related to the analysis of pharmaceutically useful alkaloids. One of them is a historical review of mass spectrometry and its evolution over the last four decades (*A1*), and another compares operational advantages and disadvantages of capillary electrophoresis and high-performance liquid chromatography (*A2*). CE and HPLC results are given for several different analyte mixtures. Three other papers have been published that discuss general aspects of the separation of polyhydroxylated, *Rauvolfia serpentine*, and *Fritillaria* isosteroidal alkaloids (*A3*−*A5*) including the combined use of mass spectrometry (*A3*, *A4*). Both quantitative and preparative-scale separation conditions are given for the polyhydroxylated alkaloids. Similarly, a paper has appeared that discusses the use of high-speed countercurrent extraction for isolating alkaloids including the development of a general purpose two-phase solvent system consisting of four parts chloroform, three parts methanol, and two parts water containing NaH_2PO_4 or HCl (*A6*).

An article has been published that provides a comprehensive overview of most major analytical approaches used to assay ergot alkaloids including the following: colorimetric, UV, and fluorometric analysis; NMR and infrared spectroscopy; mass spectrometry; and gas, liquid, and thin-layer chromatography (*A7*). The paper is a useful reference and includes information such as proton and carbon-13 NMR chemical shift tables. Similarly, a review has appeared that discusses a variety of separation techniques as they relate to the analysis of *Cinchona* alkaloids (*A8*). Of the techniques considered (i.e., HPLC, GC, TLC, and CE) it was noted that a majority of the published methods were carried out by reversed-phase LC using some type of ODS column in combination with an acidic mobile phase and UV detection. Other HPLC assays described for *Cinchona* alkaloids includes a method based on the use of a molecularly imprinted monolitic stationary-phase column prepared using 4-vinylpyridine, methacrylic acid, and ethylene dimethacrylate in combination with a low polar porogenic solvent mixture of toluene and dodecanol (*A9*). In two other accounts, thin-layer methodology has been employed to identify an unknown compound in hydroquinine that has a higher R_f value and forms during migration when dichloromethane and methanol are used as the development solvent (*A10*) and to estimate the level of quinine, cinchonine, and cinchonidine in natural products and marketed formulations in combination with fluorescence-enhanced detection (*A11*).

Although HPLC and CE have been the two most often employed techniques to assay alkaloids in combination with other naturally occurring compounds, spectrometric approaches have been popular alternatives for quantifying them in pure form and in formulated products. Some examples of assays developed for individual alkaloids are methods for papaverine based on a flow injection approach using the chemiluminescence reaction of the analyte with permanganate−sulfite (*A12*) and a proton NMR procedure based on the integration of the analyte's methoxy protons relative to the methyl protons of the internal standard, acetanilide (*A13*). The latter procedure can be used to assay the analyte in the presence of other alkaloids or impurities. A capillary electrophoresis procedure that uses cyclodextrins added to the separation buffer (*A14*) also has been developed for papaverine. Chemiluminescence (*A15*, *A16*), and NMR (*A17*−*A19*) procedures also have appeared for a variety of other alkaloids including sophoridine and related compounds (*A15*), isoquinolines (*A17*), vinfluine (*A18*), and a new stereoisomer of isoreserpiline pseudoindoxyl (*A19*). In the latter three instances, structural assignments are given.

ANTIBIOTICS

Included in this section are drugs derived from natural and synthetic sources (i.e., antibacterials, antiinfective, antifungals, antiparisitics, and antimicrobials) and anticancer drugs if they were originally discovered in fermentation broths.

A large number of analytical procedures have been developed in this therapeutic area. Many of them have utilized some form of separation methodology. Although HPLC is the most popular of these and has been used often, a general trend has been the increasing use of capillary electrophoresis as well as emerging interests in electrochromatography. A paper has appeared that compares several approaches for assaying cephalexin in pharmaceutical preparations (*B1*), and four others review recent developments in the separation of anthracyclines (*B2*) and anthraquinone-related anticancer drugs (*B3*) as well as the application of CE methods for assaying antitubercular drugs (*B4*) and aminoglycosides (*B5*). In the latter instance, copper microparticle-modified carbon fiber microdisk array electrodes were used for detection. Likewise, macrolide antibiotics have been evaluated by several

different separation techniques including liquid chromatography (*B6*), capillary electrochromatography using monodispersed porous polymethacrylate microspheres (*B7*), and coil centrifugal countercurrent chromatography (*B8*). The influence of operating parameters on separation efficiency and sample migration is discussed in the latter case and optimal conditions are given for separating six closely related macrolide antibiotics, ascomycin, and rapamycin analogues. Countercurrent methods also have been used to separate the main components of spiramycin using a four-component separation system (*B9*) and to isolate and purify three novel glycosylated polyketides antifungal agents from fungal fermentation extracts of *Arthriniumand* (*B10*). Arthrinosides A and B, which differ in the epoxidation of an endocyclic double bond, were separated from arthrinoside C using two commercially available multilayer coil planet centrifuges.

A method has been developed for assaying acyclovir in commercial topical liposomal gel formulations (*B11*). Initially, the drug is extracted into water using ultrasonication, the extract is diluted to approximately100 μg/mL, and 20 μg/L portions of the solution are analyzed by LC. The separation is carried out on a C18 column using acetonitrile−0.01 M pH 4.8 phosphate buffer as the mobile phase and detection at 255 nm. The procedure is reported to be linear from 50 to 200 μg/mL, have a detection limit of 75 ng and recoveries of 100.2−103.2%. Numerous other liquid chromatographic methods have appeared for the many different types and classes of antibiotics. In one instance, a relatively simple and sensitive method has been described for assaying parenteral amikacin formulations that uses 1-naphthoyl chloride as a derivatizing reagent (*B12*). After incubation in pyridine at 30 °C for 1 h, a solution of dimethylamine and acetonitrile is added to eliminate excess reagent and the resulting derivative analyzed on a butyl column with 15:85 water−acetonitrile as the eluent and detection at 295 nm. The linear range of the procedure is 17−170 nmol/mL with a detection limit of 5 nmol/L. To optimize the method, reaction temperature, reaction times, and concentration of derivatizing reagent were investigated.

In another instance, liquid chromatography has been used to quantify amphotericin B in liposomal pharmaceutical formulations (*B13*). The separation can be completed in less than 10 min and is carried out on a C18 column with a mixture of acetonitrile and 20 mM disodium EDTA pH 5.0 buffer as the eluent. The method uses 1-amino-4-nitronaphthalene as the internal standard and is linear from 2.5 to 7.5 μg/mL with a detection limit of 5 ng/mL. As part of the study, both short- and long-term variability were evaluated and found to be about 1.3%.

Several papers have appeared that discuss different aspects of the analysis of amoxicillin and clavulanic acid. Included among these is a spectrophotometric method that is based on the formation of ion pairs with a molybdenum and thiocyanate complex (*B14*). The method is reported to give results that are in good agreement with those obtained by compendia procedures and is useful for quantifying amoxicillin in the 2−80 μg/mL range. It also can be used to measure ampicillin, dicloxacillin, and flucloxacillin in various dosage forms. Published studies that have been concerned with separation methodology include a comparison of CE and LC methods for the simultaneous determination of amoxicillin and clavulanic acid (*B15*), an investigation of the basic factors affecting ion exchange as a separation mechanism for clavulanic acid (*B16*, *B17*), and the analysis of oral suspensions and tablets that contain the analytes (*B18*). In the latter instance, amoxycillin and clavulanic acid were measured by reversed-phase chromatography using a C18 column, a mixture of methanol−phosphate buffer as the eluent, and electrochemical detection. The method has been reported to be linear from 16 to 500 ng/mL and to have detection limits of 0.8 ng/mL for amoxycillin and 15 ng/mL for clavulanic acid. Reversed-phase chromatography followed by electrochemical detection also has been used to assay the macrolide antibiotics clarithromycin and roxithromycin (*B19*), lincomycin and spectinomycin (*B20*), spectinomycin (*B21*), and tobramycin (*B22*). Although most of these procedures use more conventional RP packing, the latter separation was carried out on a poly(styrene−divinylbenzene) column using an aqueous solution containing sodium sulfate, sodium octanesulfonate, and pH 3.0 phosphate buffer as the eluent. The procedure can be used to separate nine different components in less than 30 min. In the case of clarithromycin, an alternate HPLC method has been reported for evaluating its stability in bulk samples (*B23*).

During the review period, the analysis of doxorubicin and daunorubicin has received considerable attention (*B24*−*B28*) including fundamental chromatographic investigations of analyte−peptide conjugate conformational changes (*B25*, *B26*) as well as the analysis of these two anlaytes by capillary electrophoresis using either UV or laser-induced fluorescence detection (*B27*, *B28*). Likewise, an electrophoretic procedure has been reported for bacitracin that employes mixed micelles in the acidic migration solvent (*B29*). In addition, a stability-indicating gradient reversed-phase method has been developed for measuring the active (A, B_1, B_2) and inactive (F) polypeptide components of bacitracin in complex samples (*B30*). In carrying out this work, various operating parameters were studied including eluent pH and column type.

A number of assays have been reported for isoniazid. Included among them are spectrometric, chromatographic, and capillary electrophoretic methods. A very simple chemiluminescence flow system has been developed for measuring isoniazid in pharmaceutical preparations that is based on its oxidation by alkaline hexacyanoferrate(III) solution (*B31*). The system has a linear response in the 0.05−2 μg/mL range and a detection limit of 0.01 μg/mL. Similarly, a novel chemiluminescence sensor also has been made by electrostatically immobilizing luminol and periodate on an ion-exchange resin (*B32*, *B33*). The optosensor has a linear response in the nanogram to microgram per milliliter range and can be use to carry out very rapid measurements of isoniazid. In addition to these approaches, LC also has been used to determine isoniazid, pyrazinamide, and rifampicin in pharmaceutical formulations (*B34*), and in another case, it has been measured using micellar electrokinetic chromatography (MEKC) (*B4*). Similarly, metacycline (*B35*), gentamicins, and related compounds (*B36*) have been determined electrophoretically. In the first case, the analyte was measured at 254 nm following its separation at 15 °C using an applied potential of 12 kV and a pH 10.4 conducting buffer (160 mM sodium carbonate−1 mM EDTA), and in the second

instance, an in-capillary derivitization procedure was employed prior to carrying out the separation. A 40% solution of methanol containing the analyte was sandwiched between two plugs of *o*-phthalaldehyde and hydrodynamically injected using 15 kV. Subsequently, the internal standard (picric acid) and the reaction products were separated at 20 °C using an applied potential of 19.5 kV and a pH 10 run buffer (30 mM sodium tetraborate, 7.5 mM γ-cyclodextrin, and 15% methanol). This latter procedure was used to separate five gentamicins, sisomicin, and three impurities within 17 min. The calibration graphs were linear from 0.1 to 2.4 μg/mL for the gentamicins, and the remaining compounds were quantifiable. Other CE methods have been used to assay streptomycin and related substances in commercial products (*B37*) and the separation of tetracycline derivatives from their main degradation products (*B38*).

A micro LC method has been reported for simultaneously measuring cephalexin and bromhexine in multicomponent formulations (*B39*). The analytes are separated on a cyano column using 60:40 methanol−water, a flow rate of 0.15 mL/min, and a detection wavelength of 214 nm. Besides this procedure, HPLC assays have been developed for cephalexin and cefadroxil (first generation), cefaclor (second generation), and cefataxim (third generation) cephalosporin antibiotics in pharmaceuticals (*B40*) and for cefixime trihydrate in bulk drugs (*B41*). The latter method, which can be used to quantify cefixime in the presence of several related compounds, utilizes a C18 column, a mobile phase consisting of 7:93 acetonitrile−pH 7.0 phosphate buffer, and a flow rate of 0.8 mL/min. The limits of detection and quantification are 37 (0.3%) and 128 ng (1.1%), respectively, at 287 nm. Similarly, an LC approach has appeared for simultaneously assaying ceftazidime and its principal degradation product, pyridine (*B42*). It was used to evaluate the stability of infusion solutions containing 40 mg/mL ceftazidime, 0.9% NaCl, and 5% glucose. Another account has appeared that discusses fundamental aspects of the migration behavior of ceftazidime and related cephalosporins under capillary electrophoretic conditions. To resolve cefazidime from mixtures containing cephazolin, cefuroxime sodium, ceftriaxone sodium, and cefoperazone sodium and ceftazidime, it was necessary to add both sodium dodecyl sulfate and pentasulfonic acid to the pH 6.5 run buffer (*B43*).

In addition, to above separation-based assays, a paper has appeared that discusses recent developments in the electroanalytical determination of cephalosporins and cephamycins (*B44*). Likewise, a molecularly imprinted polymer has been prepared using cephalexin as the template molecule and 2-(trifluoromethyl)acrylic acid as the functional monomer, and equilibrium binding have been carried out (*B45*). A Scatchard analysis of the data has shown that two classes of binding sites are formed in the imprinted polymer with estimated dissociation constants of 0.14 and 2.38 mmol/L. Additional work is being carried out to evaluate the potential usefulness of the polymer for developing a rapid QC assay for the drug. A FIA method also has been reported for cefotaxime, cefuroxime, ceftriaxone, cefaclor, cefixime, ceftizoxime, and cephalexin (*B46*). Each cephalosporin is first hydrolyzed using 0.1 M NaOH at 80 °C and oxidized with Fe^{3+} in sulfuric acid to produce Fe^{2+}. Subsequently, the resulting ferrous ion is complexed with *o*-phenanthroline and detected at 510 nm. The method was successfully applied to pharmaceutical preparation analysis and yielded comparable results with official methods.

A number of chromatographic procedures have been reported for the erythromycins. Among them was a simple isocratic LC method for in-process monitoring of erythromycins in fermentation broths (*B47*). Following an initial extraction with a mixture of acetone and methyl ethyl ketone, the extract is separated on a RP column operated at 65 °C using acetonitrile−phosphate buffer as the mobile phase. The method can be used to resolve erythromycins A, B, C, D, and E as well as *N*-desmethylerythromycin A and several other known and unknown components. A fundamental study has been carried out to characterize the migration behavior of erythromycin and several related antibiotics (troleandomycin, tylosin, vancomycin, rifamycin B, rifampicinon) on polyamide TLC plates using five different binary solvent mixtures (methanol−water, ethanol−water, propanol-water, acetonitrile−water, tetrahydrofuran−water) varying in composition from 0 to 100% of the organic component (*B48*). Additionally, an HPTLC method has appeared for the erythromycin that employs silica gel 60 plates and either methanol or 9:7:8 ethyl acetate−ethanol−10% pH 9.5 sodium acetate as the development solvents (*B49*). In the latter instance, erythromycin A, B, and C can be resolved. Following the initial separation step, quantitation is carried out using a 10% sulfuric acid solution in combination with heating for 15 min at 100 °C and subsequent scanning a wavelength of 410 nm. Since common excipients do not interfere, the method is applicable to a variety of formulations.

A simple LC method has been used to assay the aminoglycoside kanamycin in varicella vaccine (*B50*). The analyte is derivatized by treating it with a solution containing phenyl isocyanate and triethylamine for 10 min at 70 °C and measuring the reaction products at 240 nm following their separation. During the course of this investigation, electrospray mass spectrometry was used to study the reaction product, which was found to be kanamycin with four phenylisocyanate groups covalently bound to it. Since the derivative is stable for 24 h, precision of the method is good and it is linear from 10 to100 μg/mL with recoveries ranging from 97.5 to 99.8%. Reversed-phase LC also has been used to assay a large number of different formulated products. A few examples of these include methods for oxamniquine (*B51*), streptomycin (*B52*, *B53*), troleandomycin (*B54*), ofloxacin, and tinidazole (*B55*). In many cases, the procedures employ isocratic separation that is carried out on a C18 using a binary acetonitrile−buffer eluent and UV detection

Besides the examples presented above, many other methods have appeared during the time of this review. Examples of some these include spectrophotometric and liquid chromatographic procedures for quantifying fleroxacin in tablets (*B56*), measuring fluconazole in capsules and intravenous solutions (*B57*), and assaying sparfloxacin (*B58*) and lactam-based antibiotics (*B59*) as well as the use of electrochemical and thermal analysis to study quinine antibiotics (*B60*) and to evaluate the stability of phosphomycin (*B61*).

NITROGEN−OXYGEN-CONTAINING COMPOUNDS

As a broad therapeutic class, analgesics, antipyretics, and antiinflammatories continue to be studied often, including those that have been on the market for many years as well as those that have been introduced more recently. Many analytical procedures continue to be developed for the more common compounds such as acetaminophen (*C1*−*C10*), diclofenac (*C11*−*C17*), phenacetin (*C18*), ibuprofen (*C19*−*C25*), indomethacin (*C11*, *C26*), ketoprofen (*C11*), mefenamic acid (*C7*, *C14*, *C27*), and naproxen (*C26*, *C28*, *C29*), as well as for newer or less common compounds such as aceclofenac (*C17*), cizolirtine (*C30*), flufenamic acid (*C11*), and tramadol (*C31*). Often these methods utilized some form of separation (*C1*−*C5*, *C11*−*C13*, *C19*−*C22*, *C26*, *C30*), the most common of which is HPLC (*C1*−*C4*, *C11*, *C12*, *C21*), or they are based on spectrometric measurements (*C6*−*C8*, *C14*, *C15*, *C23*, *C24*, *C27*−*C29*, *C31*). Besides these approaches, flow injection assays also have been used in a number of cases including for measuring 4-aminophenol in acetominophen drug substance and formulations (*C8*) as well as for assaying acetominophen (*C10*) and diclofenac or mefenamic (*C14*) in formulated products. Likewise, a number of other methods have been developed for the latter two analytes. Among these are LC (*C11*, *C12*), TLC (*C13*), electrochemical (*C15*, *C17*), and fluorometric (*C15*) approaches. Fluorometric assays also have been reported for naproxen (*C28*, *C29*) as well as a room-temperature phosphorescence method (*C29*). In the latter instance, the characteristics of host−guest complexation between β-cyclodextrin and ibuprofen were investigated and a method was developed that is linear between 0.1 and 2 μg/mL and has a detection limit of 0.03 μg/mL. In one account, an acoustic wave sensor was constructed for phenacetin based on a molecularly imprinted acrylate polymer coating (*C18*). It had a linear response between 5.0×10^{-8} and 5.0×10^{-4} M with a detection limit of 5.0×10^{-9} M.

In the case of acetaminophen, most of the separation-based methods were used to measure it in cough−cold products; however, in one instance, the kinetics and thermodynamics of the hydrolysis of acetaminophen were studied by capillary electrophoresis (*C5*). Besides this particular application, CE also has been utilized to evaluate the enantiomeric purity of ibuprofen (*C22*) and to determine the apparent binding constants of indomethacin and naproxen to β-cyclodextrin using three different linear plotting approaches (*C26*). Examples of some of the other methods for acetaminophen is a FT-Raman spectrometric procedure that employs partial least-squares and principal component regression to measure it and acetylsalicylic acid in tablets (*C6*) as well as spectrophotometric (*C7*, *C8*) and electrochemical (*C9*, *C10*) assays for quantifying various pharmaceutical formulations. The latter two citations discuss respectively the fabrication of glassy carbon paste electrodes modified with polyphenol oxidase and a low-cost flow-through cyclic voltammetric cell.

Cough−cold, antihistamines, and related pharmaceuticals also have received considerable attention (*C32*−*C48*). Several methods have been reported for determining pseudoephedrine singularly and in combination with other compounds (*C32*, *C38*−*C40*, *C45*). Among them was a capillary electrophoresis approach that uses laser-induced fluorescence detection after derivatization with 4-chloro-7-nitrobenzo-2-oxa-1,3-diazol (C32) as well as HPLC, HPTLC, and spectrophotometric procedures (*C38*−*C40*, *C45*) that employ respectively either a C18 column and methanol−ammonium acetate buffer as the eluent, silica gel 60 F-254 plates in combination with ethyl acetate−methanol−ammonia as the development solvent, derivative ratio measurements, or multivariate methods involving net analyte preprocessing. This latter approach also has been used to analyze ternary mixtures of chlorpheniramine, naphazoline, and dexamethasone (*C46*) and to resolve a four-component mixture of phenylephrine, diphenhydramine, naphazoline, and methylparaben (*C44*) in nasal solutions. Other analytes measured in combination with pseudoepherine were ephedrine (*C32*), cetirizine (*C39*, *C40*), and fexofenadine and loratadine (*C40*). In one account, two new pseudoephedrine degradation products were identified using a combination of liquid chromatography−mass spectrometry and liquid chromatography−nuclear magnetic resonance spectroscopy. The two degradation products were 2-(carboxyamino)propiophenone (molecular ion of m/z 194) and 2-formyl-2-(methylamino)acetophenone (molecular ion of m/z 178) (*C38*).

Examples of other separation methods that have been developed for cough−cold products include capillary electrophoresis procedures for the determination of dextromethorphan, diphenhydramine, and phenylephrine in expectorant and decongestant syrups (*C33*), naphazoline, diphenhydramine, and phenylephrine in nasal solutions (*C47*), and ambroxol or bromhexine in pharmaceuticals (*C48*), as well as for the evaluation of the enantomeric purity of dexchlorpheniramine maleate (*C34*) and assaying cough−cold combination products by micellar (*C35*, *C36*) and ion pair (*C37*) LC, Similarly, examples of additional spectrometric methods include the quantitation of the antihistamine triprolidine in bulk and in drug formulations (C41) and astemizole in pharmaceutical preparations (*C43*). The first one of these methods is based on the alkaline oxidation of the analyte with $KMnO_4$ and measuring the manganate ion that forms spectrophotometrically at a fixed time of 20 min at 612 nm. Last, the polarographic behavior of acrivastine has been evaluated and a method developed for determining the analye in capsules (*C42*).

Because of their therapeutic importance, antihypertensive agents continue to be studied often (*C49*−*C86*). An important class of these is the β-blockers. Several general assays have been published for them including capillary electrophoretic (*C49*, *C50*), spectrophotometric (*C51*), and potentiometric (*C52*) procedures. In the first two instances, the chiral purity of propranolol was evaluated using either carboxymethyl-β-cyclodextrin or methylated glucuronyl glucosyl β-cyclodextrins, respectively, as the chiral selector. These same conditions also were employed to measure the chiral purity of various neurotransmitters and other optically active drugs. Of the β-blockers, propranolol received the most attention (*C49*−*C59*). In one instance, the solubilities of propranolol, phenazopyridine, and methimazole in supercritical carbon dioxide was studied (*C54*), and in another case, its compatibility and thermal stability in binary mixtures were evaluated (*C58*). Besides these studies, assays have been developed for the analyte

based on the application of polarography (*C55*), heavy atom-induced room temperature (*C56*), a sensitive fluorescence optosensor (*C57*), and ion selective electrodes (*C59*).

Some examples of the other types of antihypertensive compounds that have been studied often are benazepril (*C60*−*CN62*), cilazapril (*C62*−*C67*), lacidipine (*C68*), lisinopril (*C69*−*C75*), nisoldipine (*C76*, *C77*), nitrendipine (*C76*−*C80*), quinapril (*C81*−*C83*), ramipril (*C81*−*C86*), and enalapril (*C74*, *C86*). The cited examples represent only a small fraction of the many dozens of papers published in this area during the last two years that discuss various aspects of the therauputic use, pharmaceutical properties, and analysis of antihypertensive agents. There were a large number of chromatographic, electrophoretic, spectrometric, and electrochemical methods published for the angiotensin-converting enzyme (ACE) drugs. Several assays developed for measuring ACE drugs in combination with hydrochlorothiazide (*C60*, *C61*, *C65*, *C67*, *C70*, *C85*), as well as to evaluate their enzymatic, hydrolytic, photolytic, or thermal stability (*C62*, *C68*, *C76*, *C77*, *C79*, *C82*, *C83*, *C85*).

A wide variety of methodology has been reported for other important classes of pharmaceuticals including various anticancer agents (*C87*−*C92*), antidepressants (*C93*−*C106*), benzodiazepines (*C107*−*C116*), and vasodilators (*C117*−*C121*). Two reviews have been published that discuss general quantative aspects of camptothecin (*C87*) and cyclophosphamide (*C88*) and related compounds, and a third examines the use of capillary gas chromatography−mass spectrometry for monitoring anticancer drugs (*C89*). Similarly, mass spectrometry has been used in combination with HPLC to measure *cis*-[amminedichloro(2-methylpyridine)]-platinum(II) (*C90*) and with capillary electrophoresis for analyzing fluoxetine and compounds related to it (*C93*). In the latter procedure, the separation was carried out at 20 °C using 25 mM ammonium acetate and 1 M acetic acid in acetonitrile buffer electrolye and an applied voltage of 30 kV. The paper discusses the affect of nebulizing gas pressure, sheath liquid composition, and flow rate on the electrospray performance. Fluoxetine also has been assayed by an alternate capillary electrophoresis method (*C96*) as well as by HPLC (*C102*) and spectrofluorometry (*C96*, *C97*). In the latter article, the characteristics of host−guest complexation between methyl-β-cyclodextrin and the analyte were investigated. The association constant for the 1:1 complex that forms is 4.35×10^{-3}.

Capillary electrophoresis, as well as electrochromatography, also has been used to measure a variety of antidepressants (*C94*, *C95*, *C98*, *C101*), benzodiapzepines (*C110*, *C111*), and vasodilators (*C117*, *C121*). In one of these accounts, reboxetine, a novel antidepressant that selectively inhibits the norepinephrine reuptake at the presynaptic level, also was measured by a fourth-derivative technique (*94*). This and the CE method were specifically developed for assaying the analyte in pharmaceutical formulations. In another account, fundamental aspects of four propanesulfonic cation-exchange materials were evaluated using tricyclic antidepressants and related quaternary ammonium analogues as test analytes (*C98*). In doing this, studies were carried out as a function of pore size, pH, ionic strength, and concentration of acetonitrile in the mobile phase. Several other methods have appeared for tricyclic antidepressants including two HPLC procedures (*C100*, *C104*). In the latter one of these, the analytes is first separated on a C18 column with acetonitrile−phosphate buffer as the eluent and then electrochemically detected using highly boron-doped diamond electrodes. The analytes that can be assayed by this technique are imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, and doxepin.

A variety of spectrometric methods have appeared for the anticancer drug flutamide (*C92*), the antidepressants fluoxetine (*C96*, *C97*) and fluvoxamine (*C106*), the diazepines alprazolam (*C109*) and diazepam (*C113*), and the vasodilators isoxsuprine (*C118*, *C119*) and nicergoline (*C121*). In the latter instance, HPLC and TLC also were used to measure the analyte in the presence of its hydrolysis-induced degradation product. For the most part, these latter methods have been developed to assay formulations (*C92*, *C96*, *C97*, *C113*, *C118*, *C119*) or to study product degradation (*C109*); however, in one instance, proton NMR was used to evaluate the isomer ratio of the analyte (*C106*).

In addition to the separation- and spectrometric-based methods discussed above, other topics considered over the last two years include the following: hydrolysis and acid dissociation of cisplatin in aqueous media (*C91*); development of a new sorbent for in situ determination of impurities in flurazepam by HPTLC-FT-IR (*C114*); and voltammetric techniques for determination of psychoactive 1,4-benzodiazepine drugs (*C115, C116*).

PEPTIDES, PROTEINS, AND RELATED COMPOUNDS

Capillary electrophoresis offers many advantages over other types of separation methodology and has been used to assay a host of pharmaceutically useful proteins, protein fragements, and peptides. In one instance, a study was carried out to evaluate how solution conditions affect the CZE resolution of recombinant human deoxyribonuclease variants (*D1*). Titration of the run buffer was used to alter the surface charges of the protein, leading to measurable changes in its electrophoretic mobility. Likewise, electrophoretic mobility also was altered via addition of divalent metal ions. Typically, conditions that led to decreased electrophoretic mobility also led to enhanced resolution of broad zones associated with protein heterogeneity. Several electrophoretic methods have been reported for insulin including those used to quantitate it in oil formulations (*D2*) and for monitoring of recombinant human insulin production (*D3*). In the latter instance, narrow-bore reversed-phase HPLC and MALDI TOF mass spectrometry also were used to carry out the study. Besides these CE methods, a review has appeared that considers new developments in affinity chromatography with potential application in the production of biopharmaceuticals including insulin. In two additional studies, the effect of process variables on the degradation and physical properties of spray-dried insulin intended for inhalation was evaluated (*D4*), and in the other, both RP and GPC were used to analyze insulin and its degradation products (*D5*) in combination with static and dynamic light scattering measurements. The absolute molecular weight of human insulin monomer and dimer were 5800 and 12 400, respectively, and their *z*-average root-mean-square radii were 21.6 ± 0.4 and 40.5 ± 0.7 nm.

Two reviews have been published that discuss the following: new developments in affinity chromatography and its potential use for monitoring the production of biopharmecuticals (*D6*); and important aspects of different types of capillary electrophoretic methods for separating proteins (*D7*). Likewise, a capillary gel electrophoresis method has been introduced for the monoclonal antibody Synagis as an alternative to SDS−PAGE−densitometry (*D8*). The method has been approved by the FDA and is routinely used in the quality control testing of the product. In addition, a reversed-phase gradient HPLC procedure has been described for quantifying recombinant plasminogen activator inhibitor type 1 (PAI-1) in cultures of *Escherichia coli* (*D9*). The analyte can be resolved in less than 2 min using a short C18 column. When compared to gel electrophoresis procedures, the new method is reported to be superior in monitoring recombinant PAI-1 titers in cultures of *E. coli*. Finally, MEKC has been used to separate vaccines consisting of *Streptococcus pneumoniae* or *Neisseria meningiditis* polysaccharide covalently linked to formaldehyde-inactivated diphtheria toxoid carrier protein from the nonconjugated toxoid (*D10*). The separation is achieved using an alkaline sodium borate solution containing sodium dodecyl sulfate. An advantage of the procedure is that no sample pretreatment is required prior to analysis.

STEROIDS

Historically, the steroid section has been divided by technique. However, due to space and reference limitations, only a relatively few of the many papers published are included in the current review. A majority of the methods have involved some form of separation. The most popular of these, based on the number of papers appearing, has been liquid chromatography, especially RP methodology. In one case, a relatively general reversed-phase screening procedure has been reported for the detection of 49 corticosteroids in topical pharmaceutical products (*E1*). It uses two linear gradients (i.e., 18−82% acetonitrile and 33−88% methanol) that are each completed in 12 min. Likewise, as part of this work, two extraction procedures also were developed for isolating the corticosteroids from both water-soluble and lipid-soluble components including the removal of excipient interferences. In another study, the effects of different operating parameters on the supercritical CO_2 extraction efficiencies of two steroidal drugs, medroxyprogesterone and cyproterone, were evaluated for spiked matrixes and tablet formulations (*E2*). The influences of temperature (308−348 K), pressure (100−300 bar), static extraction time (5−15 min), dynamic extraction time (10−30 min), and percent methanol modifier (1−10% v/v) were evaluated.

Other published methods for corticosteroids included a direct injection micellar LC procedure for analyzing creams, ointments, and other pharmaceuticals (*E3*) and a chemiluminescence flow injection approach that can be used to measure nine corticosteroids simultaneously (*E4*). The second method, has a working range of about 3−8 mg/L and is based on the reaction of a solution of luminol that is prepared in NaOH with hexacyanoferrate(II) and hexacyanoferrate(III) added as oxidants. The procedure is useful for measuring triamcinolone, prednisolone, prednisone, cortisone, betamethasone, dexamethasone, corticosterone, flumethasone, and triamcinolone acetonide.

A number of approaches have been reported for measuring dexamethasone singularly and in combination with other active ingredients. Many of these have used liquid chromatography and include an isocratic reversed-phase procedure for quantifying dexamethasone in cream formulations (*E5*) and a gradient method for evaluating its stability as the unformulated drug substance and in formulated products (*E6*). The latter method also can be used to measure impurities, degradation products, and product preservatives at levels between 0.05 and 0.1%. Likewise, alternate chromatographic methods have been reported for measuring dexamethasone in combination products such as those containing either betamethasone (*E7*, *E8*), trimethoprim (*E9*), or xylometazoline (*E10*). In one of these procedures (*E8*), electrospray tandem mass spectrometry and multivariate statistical analysis were employed. Besides these separation approaches, dextramethasone has been studied using many different spectrometric procedures. Examples of these are UV and colorimetric assays for quantifying it in products containing excipients and other active ingredients (*E11*−*E13*), and nuclear magnetic resonance spectroscopy has been used to characterize the structure of dexamethasone sodium phosphate inclusion complexes formed with 2,6-di-*O*-β-cyclodextrin, γ-cyclodextrin, and hydroxypropyl-β-cyclodextrin with either 2.7 or 4.6 degrees of substitution (*E14*).

Four different approaches have been published for determining gestodene and cyproterone acetate in raw material and dosage forms (*E15*). Three of these are spectrophotometric based, and the fourth employs thin-layer chromatography. In addition, a LC method has been introduced for studying the stability of cyproterone acetate tablets (*E16*). It is linear between 50 and 650 μg/mL with mean recoveries greater than 99%. When used to evaluate the stability of the analyte, results showed that maximum degradation occurred following treatment with 1 M HCl/Zn and hydrogen peroxide, whereas no degradation occurred after 24-h exposure to daylight or dry heat at 110 °C. A number of other papers have appeared. Among these is one that discusses the reaction kinetics of a RIA for aldosterone and androstenedione (*E17*). Biexponential irreversible kinetics was found for androstenedione, and single-exponential reversible kinetics for aldosterone. A recent paper discusses the solid-state properties of flunisolide under different experimental conditions, including differentiation of its three polymorphic forms using infrared, X-ray powder diffraction, and thermal methods (*E18*). Two additional papers have appeared on the spectroscopic estimation of spironolactone and hydroflumethiazide (*E19*) and the electroanalysis of mifepristone at a DNA-modified carbon paste electrode (*E20*).

SULFUR-CONTAINING COMPOUNDS

A number of single-component assay procedures have been developed for various sulfur-containing pharmaceutical products. In many cases, these procedures are relatively simple to carry out and give quantitative results similar to approved methods. In one instance, a reversed-phase LC approach has been described for assaying carbocysteine in syrup preparations that is linear

between 0.8 and 25.6 mg/mL with a detection limit below 1 mg/mL (*F1*). An advantage of the method is it requires no sample pretreatment. Likewise, a simple and robust assay has been reported for the determination of captopril in pharmaceutical tablets that gives results similar to those obtained by the compendial method (*F2*). As an alternative, captopril can be measured in pharmaceutical tablets by anion-exchange HPLC using indirect photometric detection (*F3*) and its isomer forms can be resolved by RP-LC using a teicoplanin column (*F4*). Besides these methods, there are many nonchromatographic assays developed for this analyte among the various techniques; flow injection analysis was especially popular (*F5*−*F10*). In addition to these assays, two papers appeared that discussed the formation of inclusion complexes with cyclodextrins (*F11*) and the solid-state cis−trans isomerization of the analyte (*F12*).

Several methods have been published for celecoxib, a new nonsteroidal antiinflammatory drug that acts as a selective cyclooxygenase-2 inhibitor. Among them are LC (*F13*), TLC (*F14*), and MEKC (*F15*) procedures that have been used to analyze formulated products. In the first two citations, details also are given for spectrometrically measuring the analyte, which due to its specific mechanism of action, has the potential to cause less gastropathy and risk of GI bleeding. Besides these methods, normal-phase chromatography has been used to determine the ortho and meta isomeric content of celecoxib in bulk and formulations (*F16*). Following extraction of the analyte into ethanol, it is analyzed using a Chiralpak-AD column.

Sildenafil, the active ingredient in Viagra tablets, was another important compound that received considerable attention. A wide variety of methods were reported for assaying it in both unformulated and formulated forms. One of these was a micellar electrokinetic chromatography procedure that used sample stacking and polarity switching in combination with a 15 mM pH 12.3 phosphate buffer containing sodium dodecyl sulfate (*F17*). Another employed UV detection in combination with FIA to quantify sildenafil (*F18*). The best solvent system was found to be 10:90 methanol−0.2 M pH 8 phosphate buffer. The linear range of the method is 1−5 μM. Additional methods reported for sildenafil included both liquid chromatography- (*F19*) and spectrophotometry (*F20*, *F21*)-based procedures.

Many other procedures have appeared over the last two years. A few examples of these are a capillary GC approach for gliclazide (*F22*), enzyme (angiotensin convertase) inhibitors (*F*23), and hydrochlorthiazide (*F24*, *F25*), an HPTLC assay for hydrochlorthiazide (*F26*), a CE procedure for glansoprazole (*F27*), and the quantification of olanazapine by four divergent techniques (*F28*). Additionally, meloxicam has been assayed by both pulse polarography (*F29*) and three colorimetric procedures that are based on the formation of an ion pair complex with either bromocresol purple, bromothymol blue, or bromophenol blue) and monitoring the absorbances at 386, 394, and 395 nm, respectively (*F30*). The polarographic assay is linear in the 110−550 μM range and the colorimetric procedures between 1 and 30 μg/mL. Likewise, several different methods have been reported for promazine. Among these is one that uses UV derivative spectroscopy to measure the analyte and its sulfoxide using the first- and third-derivative spectra at 268 and 342−344 nm, respectively (*F31*). The method produces results that are similar to those obtainable by LC approaches. A DNA-modified carbon paste electrode has been fabricated to assay 6-mercaptopurine in tablet formulations (*F32*). As part of the method, a differential pulse voltammetric scan is carried out between 0.2 and 0.9 V versus SCE using a pulse amplitude of 25 mV and a scan rate of 5 mV/s. The working range for this method is from 5 to 80 μM, with a detection limit of 2 μM.

VITAMINS

A number of general articles have appeared including two that review the application of supercritical fluid extraction in combination with chromatography to assay fat-soluble vitamins (*G1*) and chromatographic procedures for measuring vitamin E in various matrixes (*G2*). Likewise, several separation procedures have been developed for simultaneously analyzing multivitamin preparations of water-soluble (*G3*−*G5*) and fat-soluble (*G4*−*G7*) vitamins. In two cases, fundamental aspects of electrokinetic capillary chromatography were considered including the application of different surfactant additives (*G5*) and performance differences between micellar and microemulsion modes of operation. Micellar electrokinetic chromatography in combination with ampeometric detection also has been used to assay mixtures of nicotiamide, pyridoxine, and ascorbic acid (*G8*).

Other multicomponent assays that have been reported include HPLC (*G9*, *G10*), asynchronous fluorescence (*G11*), and multicommuted flow spectrophotometric (*G12*) methods for the B vitamins and a spectrofluorometric procedure for piroxicam and vitamin B_6 in pharmaceutical formulations (*G13*). Likewise, the concentrations of vitamin A, β-carotene, and *all-trans*-retinoic acid have been determined in oral preparations using an isocratic reversed-phase procedure. The separation is carried out on a C18 column and the analyte monitored at 330 nm (*G14*). Another procedure also has been reported for vitamin A and β-carotene, that involves an initial solid-phase extraction followed by the separation of the analytes on a C18 column using binary mixtures of methanol−ethanol and acetonitrile−ethanol as eluents (*G15*). Detection is carried out fluorometrically using excitation and emission wavelengths of 350 and 480 nm, respectively.

Both second-derivative ultraviolet spectrophotometry and HPTLC have been used to assay mixtures of vitamin C and dipyrone (*G16*). In terms of the second approach, the equivalent of 200 mg of vitamin C and 200 mg of dipyrone from 20 powdered tablets is sonicated in methanol, applied to silica gel 60 F HPTLC plates, developed with 95:5 water−methanol, and read densitometrically at 260 nm. Vitamin C also has been assayed by many different approaches such as colormetrically as its iron(II)−4-(2-pyridylazo)resorcinol complex (*G17*), using modified electrodes (*G18*, *G19*), and by flow injection analysis in combination with either electrochemical (*G20*, *G21*) or indirect atomic absorption (*G22*) measuements.

Many other procedures have been reported for quantating individual vitamins. Some examples of these include the following: analysis of vitamin B_{12} by both HPLC (*G23*) and fluorometric (*G24*) approaches; determination of riboflavin using chemilumi-

nescence reactions (*G25*, *G26*) and automated LC in combination with precolumn derivitization (*G27*); and measurement of nicotinamide polarographically (*G28*). In addition to these assay methods, a number of other topics were studied. One of these was a comparison of the performance of narrow-bore and standard-bore silica columns for resolving α-, β-, γ-, and Δ-tocopherol (*G28*). The performance of the narrow-bore columns was deemed to be superior in terms of sensitivity and analysis times. A second study evaluated the effect of riboflavin on the photolysis of folic acid (*G30*), and a third investigation characterized the voltammetric behavior of riboflavin at a gold electrode modified with a monolayer of L-cysteine (*G31*).

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PEPTIDES, PROTEINS, AND RELATED COMPOUNDS

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