JOURNAL OF Pharmaceutical Sciences

March 1963 volume 52, number 3

Review Article

X-ray Emission Spectroscopy in Pharmaceutical Analysis

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X-RAY EMISSION spectroscopy (also called X-ray fluorescent spectroscopy) is a rapid, nondestructive, highly sensitive, and precise technique amenable to and applicable to the pharmaceutical control laboratory.

A concise consideration of X-ray fundamentals is presented as an introduction and orientation for those readers with only a superficial knowledge of X-ray methods. The advanced reader is referred to two excellent and very comprehensive books on the subject by Birks (1) and by Liebhafsky and co-workers (2).

FUNDAMENTALS

The Origin of X-rays.—X-rays are produced when fast-moving electrons impinge on matter. The phenomena resulting from the deceleration of such electrons are very complex, and X-rays result from two general types of interaction of the electrons with the atoms of the target material. A high-speed electron may strike and displace a tightly bound electron deep in the atom near the nucleus, thereby ionizing the atom. When a certain inner shell of an atom has been ionized in this manner, an electron from an outer shell may fall into the vacant place, with the resulting emission of an X-ray characteristic of the atom involved. This process produces the characteristic line spectrum of the target element. This production of X-rays is a quantum process similar to the origin of the optical spectra; however, there is a second process in which the high-speed electron is simply slowed down in passing through the strong electric field near the nucleus of an atom. X-radiation produced in this manner is independent of the nature of the atoms being bombarded, and appears as a band of continuously varying wavelength whose lower limit is a function of the maximum energy of the bombarding electrons as shown in Fig. 1.

Continuous Spectrum.—The short-wavelength limit of the continuous spectrum, as seen for tungsten in Fig. 1, is clearly a quantum phenomenon. This short-wavelength limit discovered by Duane and Hunt (3) obeys the relationship

$$\lambda \text{ min.} = \frac{12{,}350}{V} \qquad \text{(Eq. 1)}$$

where λ min. is the minimum wavelength in Ångströms and V is the voltage in volts. This

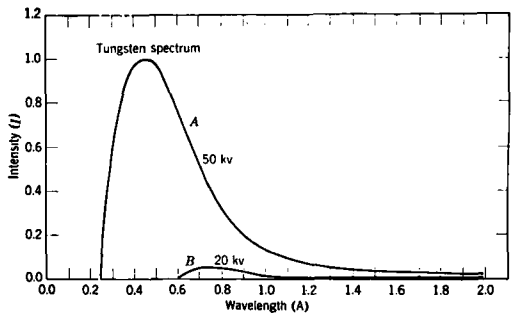

Fig. 1.—The continuous X-ray spectrum. [Reprinted with permission from Liebhafsky, Pfeiffer, Winslow, and Zemany, "X-Ray Absorption and Emission in Analytical Chemistry," Wiley, 1960.]

Received from the Research Department, Ciba Pharmaceutical Co., Summit, N. J.

equation is merely the standard equation relating quantum energy to frequency and is expressed in convenient units. Although the minimum wavelength is independent of the target element, the overall intensity of the spectrum does depend upon the atomic number, Z. This dependency is usually expressed in terms of the frequency, ν, rather than as a function of the wavelength, λ. This relationship is

$$I = AZ(\nu_{max.} - \nu) + BZ^2 \qquad \text{(Eq. 2)}$$

where I is the intensity obtained at a frequency, υ, when $\upsilon_{max.}$ is the maximum frequency (minimum wavelength) obtainable and A and B are constants. One can see from the above expression that the heavier elements will yield more intense primary radiation at all the wavelengths considered.

Characteristic Radiation.—Characteristic radiation from the target element is produced when the high-voltage electrons from a filament have sufficient energy to knock out the inner electrons of the target atoms. Moseley made the first systematic investigation into the production of characteristic radiation (4, 5). He studied the K and L series spectra of 38 different elements by using them successively as the target element and observed that the same type of lines occurred for all of these elements but that they occurred at different wavelengths. From this work Moseley derived the relationship between the atomic number of an element, Z, and the wavelength, λ, at which the characteristic lines of the element occur, or

$$\frac{1}{\lambda} \propto Z^2 \qquad \text{(Eq. 3)}$$

The proportionality constant needed in the above expression is dependent upon which series is being considered. Figure 2 is an illustration of characteristic line dependency on atomic number.

When the applied voltage is sufficient, the filament electrons knock out the inner electrons of the target atoms, and the characteristic lines of the target element will then be superimposed on the continuous radiation curve as in Fig. 3 for molybdenum.

For any element, there is more than one characteristic line because an electron can be ejected from more than one electron shell, and this shell vacancy can be filled by an electron from more than one energy level. Thus the lines of the K series occur if an electron is ejected from a K shell and an electron, in accordance with certain selection rules, from an outer shell fills the vacancy in the K shell. If an L-shell electron fills the K-shell vacancy, the emitted line will be K_α radiation; and if a K-shell vacancy is filled by an M-shell electron, the K_β line is emitted. Similarly, such electronic transitions from outer shells to vacancies in the L shell of atoms lead to the production of the lines of the L series. Figure 4 is a schematic representation of the energy levels for an iron atom showing the transitions that correspond to the four lines of the K spectrum.

BASIC X-RAY EMISSION SPECTROSCOPY SYSTEM

Arrangement and Method of Use.—A brief description of the arrangement of the components of an X-ray emission spectrograph and the manner in which it functions is now in order. It should be noted that although many of the

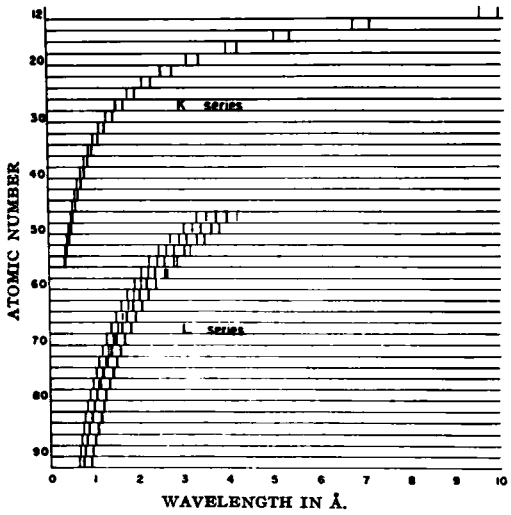

Fig. 2.—The K and L series X-ray lines that are commonly used for X-ray spectrochemical analysis. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

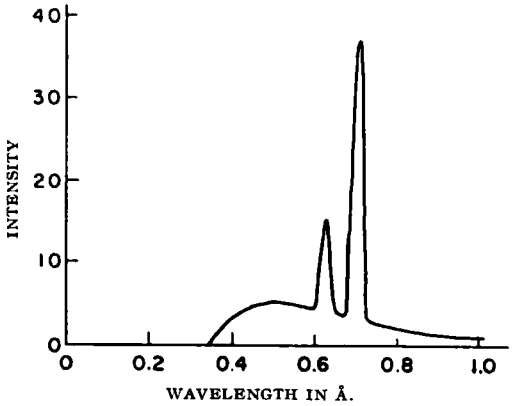

Fig. 3.—The characteristic K series lines of molybdenum superimposed on the continuous spectrum. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

components are similar, the arrangement described here for X-ray fluorescent work is different from that used in other X-ray techniques such as diffraction and absorption.

A schematic representation of the arrangement used for fluorescent X-ray spectroscopy is shown in Fig. 5. The main components are *A*, the primary X-ray tube; *B*, the sample; C, the collimator; *D*, the analyzing crystal; and *E*, the detector. The functioning of these components as a unit can best be described by a consideration of the sequence of events which occur when a sample is analyzed. This sequence is as follows:

1. The target material within the X-ray tube is excited, causing the emission of primary radiation. This emitted radiation will consist of characteristic radiation of the target material as well as continuous radiation.

2. This primary radiation strikes the sample with sufficient energy to cause the excitation of the sample. (The foregoing consideration of electron excitation of a primary target and the resulting characteristic lines is applicable to the X-ray photon excitation of the sample as well.) Hence the generation of the characteristic radiation of the elements present in the sample occurs.

3. This characteristic radiation which is emitted in all directions is collected into a parallel bundle by use of the collimator. The collimator is nothing more than a tube filled with parallel metal blades evenly spaced. Thus the radiation emerges from the collimator as a parallel bundle of radiation.

4. This parallel bundle of radiation is polychromatic since each of the elements present in the sample has a different characteristic line. Thus it is necessary to separate this polychromatic radiation into its component parts. This is done by applying the Bragg equation to an analyzing crystal

$$n\lambda = 2d \sin \theta \qquad \text{(Eq. 4)}$$

where n is the order of diffraction, λ is the wavelength of the radiation in Ångströms, d is the interplanar spacing of the analyzing crystal in Ångströms, and θ is the angle formed by the incident radiation and the crystal surface. Rotation of the crystal will change θ, the angle of incidence, and therefore the wavelength of the diffracted radiation will be changed. In this manner the incident polychromatic radiation is separated into its component parts since any one

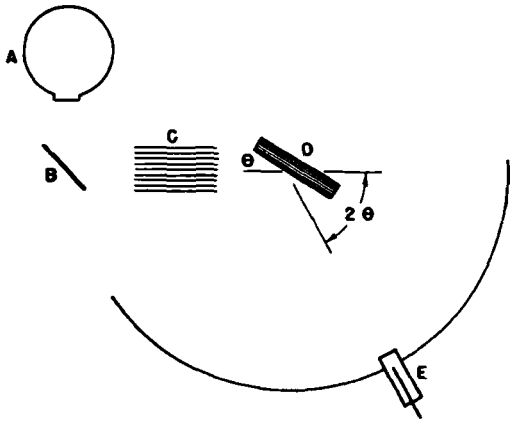

Fig. 5.—Schematic representation of the arrangement used for fluorescent X-ray spectroscopy. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

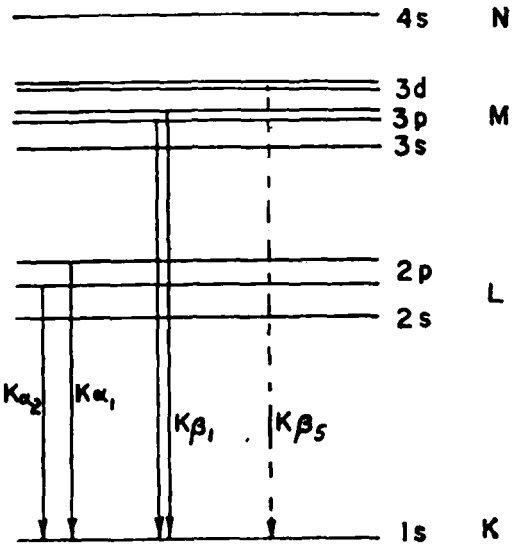

Fig. 4.—Schematic representation of the energy levels for an iron atom showing the transitions that correspond to the four lines of the *K* spectrum. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

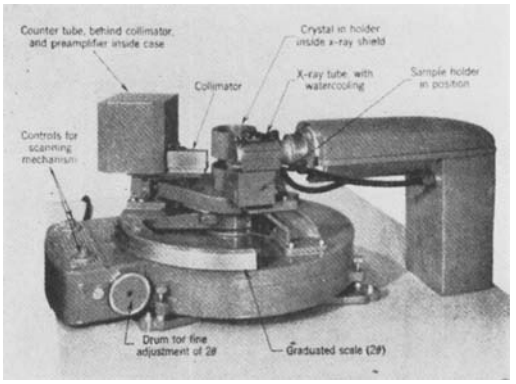

Fig. 6.—XRD-5 D/S spectrogoniometer arranged for X-ray emission work. [Reprinted with permission from Liebhafsky, Pfeiffer, Winslow, and Zemany, "X-Ray Absorption and Emission in Analytical Chemistry," Wiley, 1960.]

crystal rotation position will yield radiation of only one wavelength.

5. The diffracted radiation emerges at an angle of 2 θ with respect to the incident beam and is measured by means of a radiation detector. As stated above, the crystal is rotated, from $\theta = 0°$ to $\theta = 90°$, while the detector is rotated at twice the speed of the crystal so it will always be in position to intercept the diffracted radiation. The goniometer is that part of the equipment which indicates the 2 θ position of the detector. The crystal and detector move as the goniometer moves. The wavelengths of the intercepted X-ray lines indicate the elements that are present in the sample, and the intensities of these lines are an indication of the concentration of each element within the sample.

The actual physical appearance of the instrumentation which performs the above function is depicted in Figs. 6 and 7.

Components.—A more detailed description of several of the components, mentioned just briefly above, is necessary in order for the reader to obtain a more complete understanding of the operation of the X-ray emission spectrograph.

X-ray Tube.—The X-ray tube commonly used in X-ray fluorescent analysis is the hot-cathode or Coolidge tube. These tubes are thoroughly evacuated and sealed. The electrons for excitation are supplied by application of the Edison effect, that is, by emission from a heated filament. A schematic representation of a Coolidge tube is shown in Fig. 8. Two serious drawbacks of this tube are target contamination and the absence of target interchangeability.

Analyzing Crystals.—Crystals which are used as analyzing crystals are not truly perfect crystals but are what are referred to as ideally imperfect crystals. Perfect crystals would give very low diffracted intensities because of primary extinction. Crystals such as lithium fluoride and sodium chloride are ideally imperfect crystals and are commonly used as analyzing crystals.

By inspection of Bragg's equation, Eq. 4, it will be seen that the maximum wavelength that may be diffracted is equal to $2d$, that is, twice the interplanar spacing of the analyzing crystal. Consequently, the wavelengths of the characteristic radiation of the lighter elements become too great for the commonly used crystals. For example, lithium fluoride, $2d = 4.02$ Å, may only be used effectively down to the K lines of potassium, which are at 3.7 Å. Obviously in considering the analysis of lower atomic number elements it is necessary to find suitable crystals with greater d spacings. An example of such a crystal is ethylenediamine ditartrate, $2d = 8.76$ Å, which enables one to work with

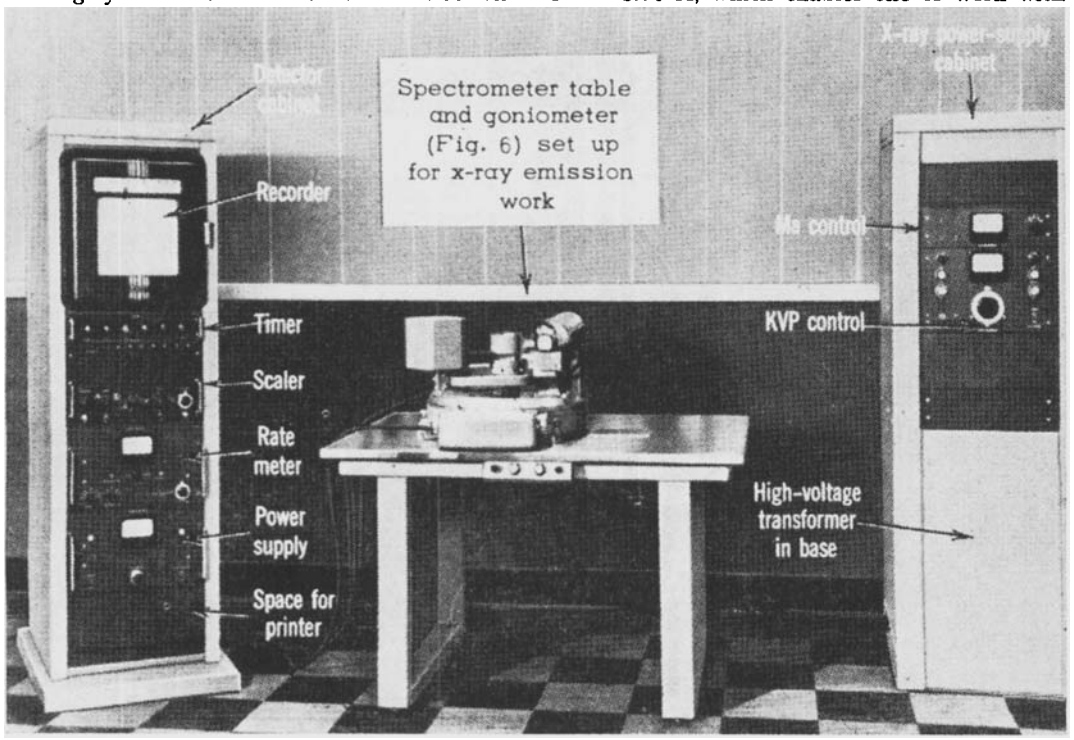

Fig. 7.—XRD-5 D/S spectrometer arranged for X-ray emission work. [Reprinted with permission from Liebhafsky, Pfeiffer, Winslow, and Zemany, "X-Ray Absorption and Emission in Analytical Chemistry," Wiley, 1960.]

aluminum, which has a characteristic line at 8.3 Å.

Detectors.—The detectors in common use for X-ray spectrochemical analysis are the Geiger, proportional, and scintillation counters. These three detectors all operate on the principle of electronic amplification of the energy pulse generated when an X-ray quantum is absorbed. In this way, signals strong enough to operate scaling or integrating circuits are obtained.

It should be noted that photographic film as a means of detection has wide use in X-ray diffraction work but is of little use in emission work.

LIMITING FACTORS OF X-RAY FLUORESCENT ANALYSIS

Fluorescent Yield.—The X-ray fluorescent analysis of all elements is not possible at the present time; however, the analysis of those elements with an atomic number of 23 or above can be performed quite simply and without any special equipment adaptations. On the other hand, the analysis of those elements with an atomic number of 11 or below cannot be assayed by X-ray fluorescent methods. The "light elements," elements with an atomic number of 12 to 22, represent the intermediate range where analysis is possible only after certain difficulties are overcome.

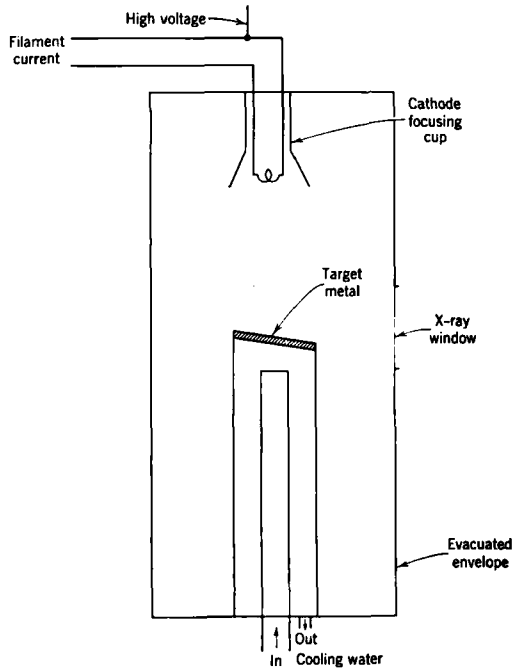

Fig 8.—Schematic diagram of a Coolidge X-ray tube. [Reprinted with permission from Liebhafsky, Pfeiffer, Winslow, and Zemany, "X-Ray Absorption and Emission in Analytical Chemistry," Wiley, 1960.]

The main reason that an elemental distinction must be made, according to atomic number, is that the fluorescent yield of the elements is less than unity, and as the atomic number decreases so does the fluorescent yield as illustrated in Fig. 9. It has been shown that 70% of the K radiation escapes from the atoms with an atomic number of 55, but only 10% escapes from atoms with atomic numbers less than twenty (6). The Auger effect is responsible for this difference in fluorescent yield. Normally when a K electron is knocked out of an atom, another electron will replace it, giving rise to one of the K series emission lines. The Auger effect occurs when the K emission radiation does not leave the atom but instead knocks out an L electron to generate an L series. The probability of the Auger effect occurring increases with a decrease in atomic number.

There are other factors besides the Auger effect which limit the applicability of X-ray fluorescence to the determination of the lower atomic number elements. One of these factors is the air absorption of the X-ray radiation as it travels through this medium. The weaker radiations of the lower atomic number elements are, of course, more easily absorbed. It is for this reason that a helium atmosphere or a vacuum path is necessary in order to determine the "light elements."

Background Radiation.—As in other spectroscopic methods of analysis, the line-to-background ratio is critical when considering the lower limits of detection of a method. Hence some mention should be made of the processes which produce the background radiation in X-ray fluorescence and therefore limit the range of detection. There are two scattering processes, coherent and Compton, which increase the background intensity.

Coherent scattering or unmodified scattering occurs when a photon undergoes an elastic collision with the sample. In this process the primary radiation is not absorbed nor does it cause fluorescence. It is merely reflected unchanged off the sample. Thus continuous background and weak characteristic primary radiation lines are always found superimposed on the fluorescent spectrum of a sample.

Compton or incoherent scattering occurs when an X-ray photon strikes an atom, especially the lower atomic number atoms such as oxygen, carbon, or hydrogen, and it is inelastically scattered, losing part of its energy. This loss of energy results in an increase in wavelength of the scattered X-ray photons. For a sample containing a high percentage of hydro-

carbons or other light elements, the Compton scattering will increase relative to the coherent scattering and may even be stronger than the coherent scattering.

Background scattering has a decided influence on the line-to-background ratio and therefore on the limit of detectability. The limit of detection of an element by X-ray fluorescence has been related to the background intensity by Birks (1). Birks states that the minimum composition detectable by X-ray fluorescence is that concentration that yields an intensity equal to three standard deviations of the background intensity. Thus to be detectable, a line must be at least three standard deviations above the background. Using this criterion, some typical orders of magnitude values for the minimum detectable limit, in parts per million, are shown in Table I.

METHODS OF ANALYSIS

Qualitative Analysis.—In order to determine which X-ray detectable elements are present in a sample, one merely has to scan through a wide 2 θ degree range recording the reflected intensities. That is, with the present-day commercial X-ray equipment it is possible to automatically scan and record, obtaining a plot of intensity *versus* 2 θ angle as shown in Fig. 10. From a chart recording of this kind, one obtains information as to what elements are

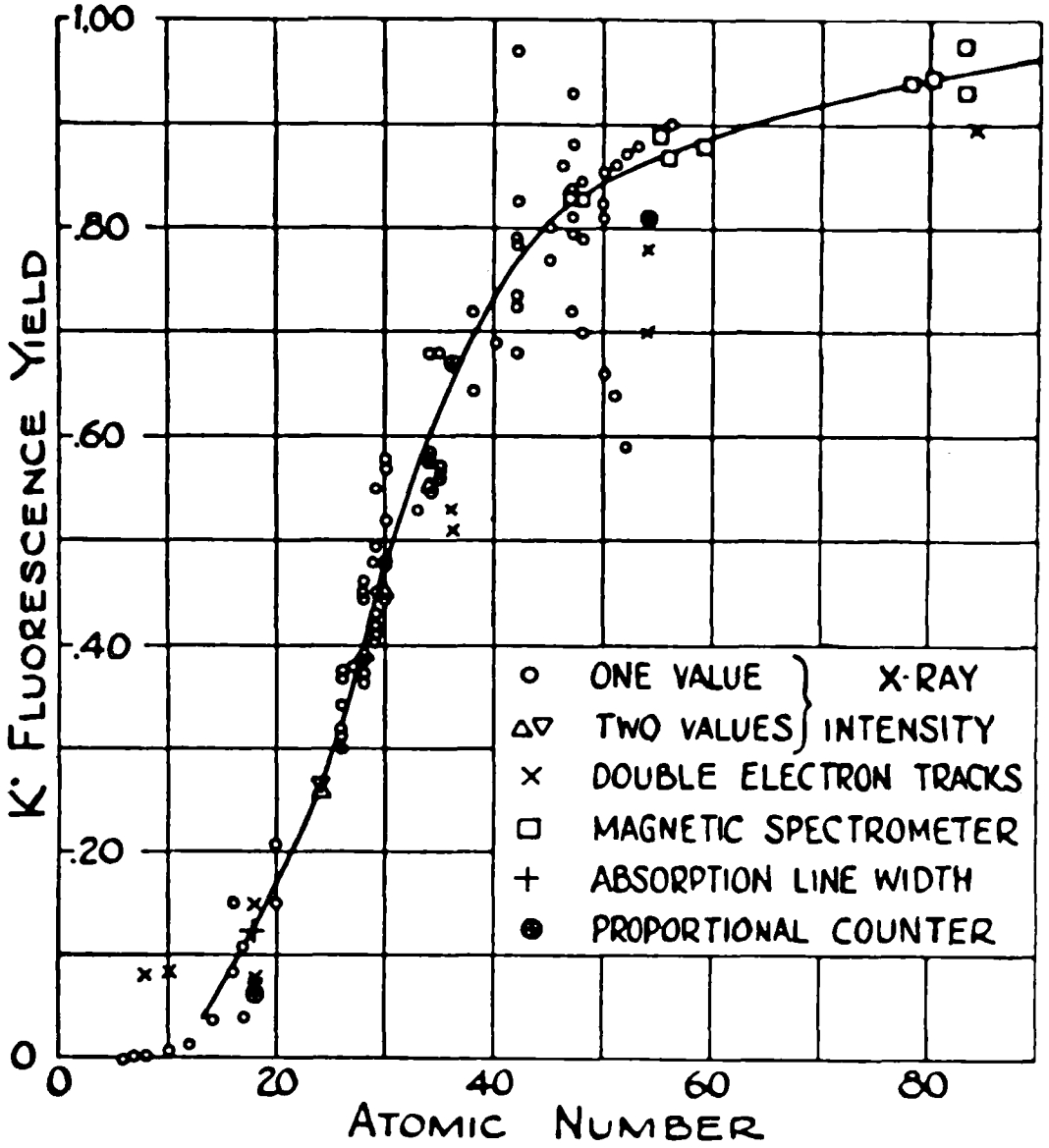

Fig. 9.—Fluorescent yield as a function of atomic number. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

TABLE I.—MINIMUM DETECTABLE LIMIT

Nonconcentrated	Concentrated
10 p.p.m.	0.01 p.p.m.[a]
100 p.p.m. for light element in heavy matrix	
1 p.p.m. for medium element in light matrix	

[a] There is, of course, no absolute lower limit if large enough starting quantities are used. There are, however, practical limitations on both quantity and preparation time. The value listed represents a limit actually achieved in what is considered a practical analytical procedure (1).

present and their relative concentrations. It should be borne in mind that a great variety of sample forms can be analyzed both qualitatively and quantitatively by means of X-ray fluorescence (7). For example, analyses of rocks, powders, metal plates, wires and bars, briquets, solutions, films, evaporated residues, and massive solids are all possible with only slight if any instrumental modifications.

Quantitative Analysis—To quantitatively determine the concentration of a particular element in a sample, the goniometer must be positioned at a 2 θ angle peculiar to the element in question. Usually this 2 θ angle is the angle corresponding to the wavelength at which the $K\alpha$ first-order line of the sample element is reflected by the analyzing crystal. The counter is then allowed to accumulate either a fixed number of counts, the time for such a count being recorded, or to count for a fixed period of time. It is necessary to relate this intensity measurement to a per cent composition value for this element in the sample.

The relationship between measured intensity and elemental content of sample is controlled by what is known as the matrix effect. The matrix is everything which is present in the sample with the exception of the element of interest. Thus the matrix effect, which consists of both absorption and enhancement effects, is the effect which the elemental composition or matrix of the sample has upon the incident and diffracted radiation. Figure 11 is an illustration of the effect that the matrix has on the intensity-composition relationship. The matrix effect must be corrected for either by computation or physical methods. The computation methods are rather involved and are less popular than the physical methods.

The three principal physical methods are use of calibration standards, use of an internal standard, and the dilution technique.

In the calibration standard method, a series of standards is prepared with varying concentrations of the element in question but with a matrix identical to that of the sample. From this standard series a calibration curve of concentration *versus* intensity can be made. Thus, once the intensity from the unknown sample is obtained, the elemental concentration can be found by use of the calibration curve. In this method the matrix effect is eliminated by duplicating the sample matrix in the prepared standards.

When it is difficult or impossible to reproduce the matrix of the sample, one often resorts to the use of the internal standard. In this procedure the internal standard is added to the sample matrix and the prepared standard matrix. In this case the sample and standard matrix do not have to be identical. What actually is plotted in order to obtain the concentration of the element in the sample is the ratio of the internal standard intensity to the desired element intensity *versus* the desired element composition.

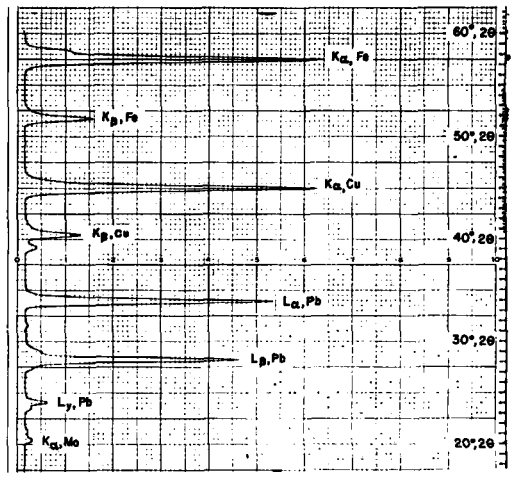

Fig. 10.—X-ray fluorescent chart recording of a sample consisting of copper, lead, and iron.

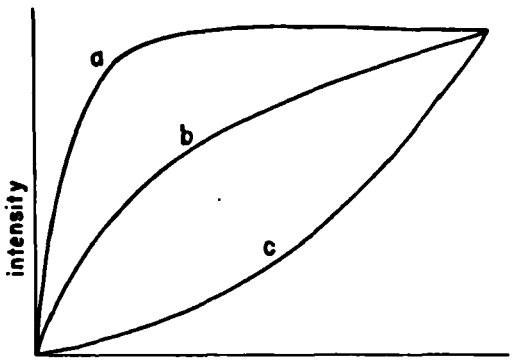

Fig. 11.—Variation of the intensity *vs.* composition curve with matrix effect. Curve *a*, a heavy element in a light-element matrix; in curve *b*, the absorption of the matrix is only slightly less than the self-absorption of the desired element; in curve *c*, the matrix absorption is slightly greater than the self-absorption of the desired element. [Reprinted with permission from Birks, "X-Ray Spectrochemical Analysis," Interscience, 1959.]

It is important that the internal standard chosen have an atomic number close to that of the element in question so that the absorption and enhancement effects of the matrix will be similar for the two elements.

The third physical method, the dilution technique, is simply a method whereby the samples' absorption and enhancement effects are reduced to a negligible amount by a physical dilution of the sample in a relatively transparent material. Materials often used for this purpose are water, organic solvents, starch, alumina, and borate glass.

APPLICATIONS

The use of X-ray fluorescent analysis in the pharmaceutical industry is certainly not extensive, and, consequently, there are not a great many published applications; however, the authors will supplement the published works of others with some of their own unpublished experiences in order to give the reader a full appreciation of the usefulness of X-ray fluorescence.

Qualitative Inspection.—X-ray spectroscopy is often utilized for the qualitative inspection of raw materials, intermediates, and final products. The reason for this is that a quick X-ray fluorescent scan will immediately reveal whether or not metal contamination has occurred or whether or not the concentration of a metal in a product has varied. Thus fluorescent scans are routinely taken of certain raw materials to assure the chemist that the same quality of material is being received.

Routine Quantitative Procedures.—There are several good examples of quantitative X-ray methods that have been adopted as routine control procedures. In almost all of these cases the analysis by any other method was either impossible or prohibitively time consuming.

R. B. Scott developed an X-ray method of analysis for the alkaloid hyoscine hydrobromide in a tablet formulation which contained one hundred times as much diphenhydramine hydrochloride (8). It was possible to analyze for halide conventionally, but the predominance of chloride was so great that the assay was meaningless for the small percentage of bromide. The X-ray fluorescent method using the $K\alpha$ line of bromine was found to be precise, convenient, fast, and unhampered by the presence of chloride.

The analysis of most of the minerals in vitamin-mineral supplement products is one of the most outstanding applications of X-ray fluorescence in this indusitry. Manganse, iron, potassium, zinc, calcume, and copper have been quantitatively assayed in a vitamin-mineral preparation by use of an internal standard technique (9). A wet chemical method of analysis of the minerals in such a product is at least ten times more time consuming than the X-ray method.

The arsenic content of arsenosobenzene, a coccidiostat used in veterinary food products is determined by an X-ray spectrographic method (9). The wet chemical method for arsenic in this product took 2 to 3 days to complete, whereas the X-ray method requires only 1 hour.

The analysis of merthiolate, a mercurial preservative, at the fifty parts per million level in pharmaceutical preparations is a relatively simple task if one assays for the mercury present by X-ray fluorescence (10).

The use of selenium dioxide and selenium dioxide in the presence of mercury as dehydrogenation catalysts in the chemical manufacture of certain steroids necessitated the analysis of selenium and mercury in the final product. Olson and Shell developed an X-ray fluorescent method of analysis for the determination of selenium and selenium and mercury in the presence of each other at the parts per million range (11, 12). This method has an accuracy of ± 1 p.p.m. in the range of 2 to 40 p.p.m. for both selenium and mercury.

Special Problems.—X-ray fluorescence has been quite useful as a tool in the solution of certain perplexing problems. The following are some examples of these problems.

A large pharmaceutical firm was confronted with the problem of a precipitate appearing in their diphtheria-tetanus toxoid preparation after the material had been packaged (8). An X-ray fluorescent scan of the precipitate revealed that zinc was present. This discovery led to an investigation of the rubber stoppers of the container since zinc is often used in rubber compounding. An X-ray examination of the rubber closures revealed zinc to be present. Obviously, the precipitation in the preparation was caused by zinc that was leached out of the rubber stoppers. The problem was quickly eliminated by changing closure specifications with respect to zinc content.

Another firm was faced with the problem of reporting to the Federal Food and Drug Administration the amount of ink present on an imprinted capsule (9). This problem was solved by an X-ray fluorescent determination of the titanium content in the ink itself and on the capsule. Calculations revealed that each capsule bore 13 mcg. of ink.

Trace Analysis.—Possibly one of the most dramatic applications of X-ray emission spec-

troscopy in the pharmaceutical industry has been in the determination of trace quantities of metallic elements either present as impurities or intentionally added in pharmaceutical formulations. X-ray emission spectroscopy acts as a a fingerprint of the formulation and has been used to positively identify the source of manufacture of the product. This technique, due to its high sensitivity, quantitative aspects, and nondestructive nature, has proven infallible to date.

Organic Analysis Through Inorganic Association.—As previously mentioned, those elements with an atomic number of 11 or below cannot be assayed by X-ray fluorescent methods because of the minimal fluorescent yield of these elements. Thus, the direct analysis of organic compounds by X-ray fluorescent methods is impossible at the present time. This is a great advantage when considering the analysis of a heavy element in an organic matrix, but it is also a serious limitation on a fine tool. Consequently, work has been done in this laboratory to illustrate the feasibility of determining organic substances indirectly through their association with an X-ray detectable element (13). Three different methods of associating an X-ray detectable element with an organic compound and assaying for this element have already been explored. They are the determination of phenolic and unsaturated compounds by bromination, the determination of 5-chloro-7-iodo-8-quinolinol by chelation, and the determination of ammonium acetate by salt formation. These methods provide specificity, selectivity, and sensitivity. Specificity and selectivity are obtained by the proper choice of the inorganic association reaction. Thus in many cases lengthy, time-consuming, error-introducing separation procedures may be eliminated. Such methods also have the potential of assaying, without isolation, microgram quantities in highly colored, many component solutions. This method should be quite useful in the analysis of drugs and metabolites in body fluids. In support of this statement, it might be mentioned that Natelson and Bender have already determined the calcium, chlorine, sulfur, and potassium content of a 20-μl. sample of serum by X-ray fluorescence (14, 15).

CONCLUDING REMARKS

Advantages and Disadvantages.—A consideration of the advantages and disadvantages of X-ray emission methods will emphasize the major points presented in the main body of this text.

The advantages of X-ray emission spectroscopy can be listed as follows:

1. Rapid.
2. Nondestructive.
3. Trace determinations possible.
4. Many sample forms are acceptable; *e.g.*, solutions, powders, intact tablets, *etc.*
5. Organic compounds do not interfere in the analysis of heavy atoms.
6. Equipment can easily and rather inexpensively be modified for diffraction use as well.
7. Once methods are developed, they can easily be performed by a technician.

The principal disadvantages are the initial cost of the equipment, which is \$15,000 to \$20,000, and the fact that direct analysis of organic compounds and elements with an atomic number less than 12 is not possible at the present time.

Future.—A number of uses for X-ray emission spectroscopy in pharmaceutical analysis have already been cited; however, as more investigators become involved in its use, one can be sure that many more applications will be uncovered.

As a matter of fact, it has already been shown that X-ray emission lends itself quite nicely to automation for the analysis of large numbers of samples as well as to the analysis of dynamic systems (1). It is highly probable that in the near future extensive use will be made of X-ray emission as an automatic analyzer in quality control laboratories. Also, greater use will be made of X-ray fluorescence in dynamic systems studies such as rate of solution, rate of precipitation, *etc.*

The vast amount of research that is now in progress on analyzing crystals, detectors, and X-ray tubes will someday make it possible to determine some, if not all, of the lower atomic number elements by X-ray emission methods.

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