I. Introduction

Electromagnetic Radiation

Electromagnetic radiation is a form of energy that is produced by oscillating electric and magnetic disturbance or by the movement of electrically charged particles traveling through a vacuum or matter. The electric and magnetic fields come at right angles to each other and combined wave moves perpendicular to both magnetic and electric oscillating fields thus the disturbance. Electron radiation is releases as photons which are bundles of light energy that travel at the speed of light as quantized harmonic waves. This energy is then grouped into categories based on its wavelength into the electromagnetic spectrum. These electric and magnetic waves travel perpendicular to each other and have certain characteristics including amplitude, wavelength and frequency (Figure 1).

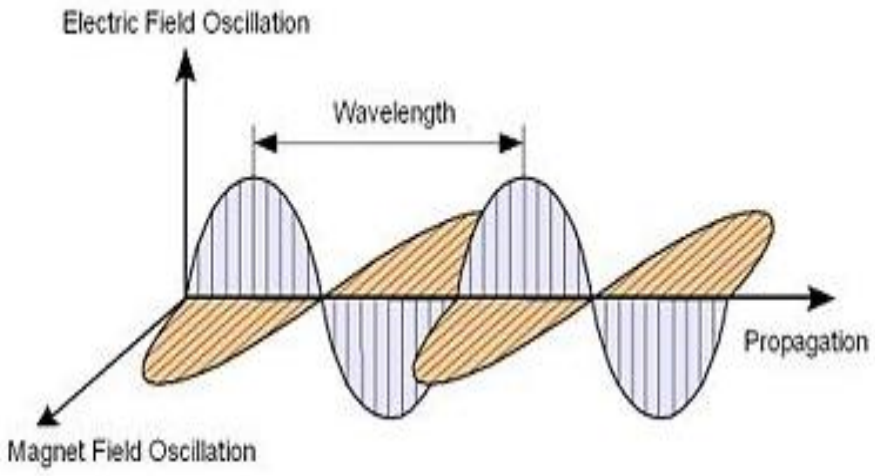


Fig. (1) Plane polarized electromagnetic radiation showing the electric field, the magnetic field and the direction of propagation.

Electromagnetic Spectrum

i- The spectrum is the written records of the EMR.

ii- EMR is divided into different regions based on the type of atomic or molecular transition that gives rise to the absorption or emission of photons.

iii- The boundaries describing the electromagnetic spectrum are not rigid, and on overlap between spectral regions is possible (Figure 2).

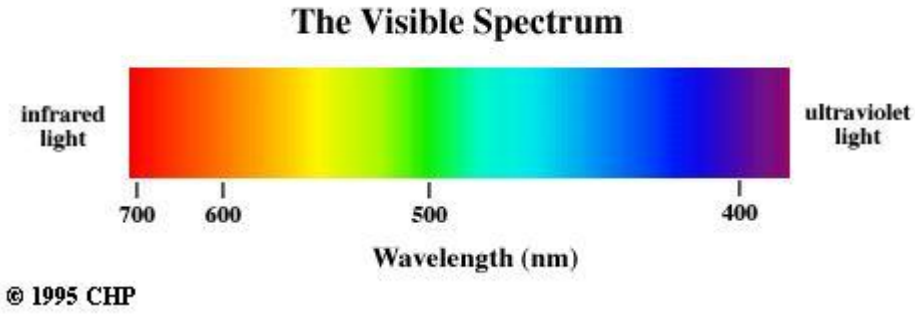
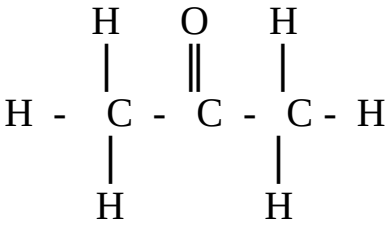


Fig. (2)

Absorption Spectrometry

The ultraviolet (UV) and visible region of the electromagnetic spectrum covers the were length range from about 100 nm to about 800 nm. The vacuum ultraviolet region which has the shortest wave lengths and highest energies (100 – 200 nm) is difficult to make measurements in and is little used in analytical procedures. Most analytical measurements in the UV region are made between 200 and 400 nm. The visible region occurs between 400 and 800 nm.

Such as propanone (acetone) has the structure



The single C-H and C- C bonds relate to σ orbitals the carbonyl double bond to II orbitals and the unpaired electrons on the oxygen to the nonbonding n-levels. The energy levels may be grouped approximately as shown in (Figures 3).

Transitions between σ and σ^* levels, and between π and π^* are favored, and those of the n electrons to the higher levels.

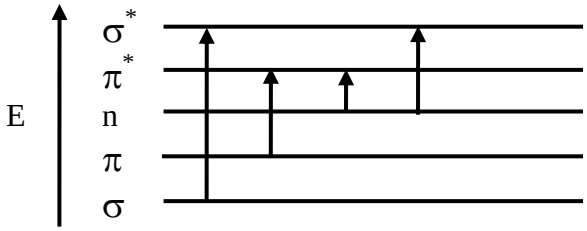


Fig. (3) Typical transitions For organic molecules. Shows that the σ - σ^* transitions require the largest energy change and occur at the lowest wavelengths usually less than 190 nm which is below the wavelengths measurable with most laboratory instrumentation. The π - π^* transitions are very important as they occur in all molecules with multiple bonds and with conjugated structures, such as aromatic compounds. The transitions occur around 200 nm but the greater the extent of the conjugation, the closer the energy levels and the higher the observed absorption wavelength. Transitions involving the lone pairs on heteroatom such as oxygen or nitrogen may be n-σ * which occurs around 200 nm, or n-π * which occur near 300 nm. These values are considerably altered by the specific structure and the presence of substituents (auxochromes) in the molecules.

Laws of Radiation Absorption

Lambert's law

Lambert reached the intuitively reasonable conclusion that each unit length of material through which radiation passes absorbs the same fraction of radiation. Given a parallel monochromatic beam of intensity I passing through a thickness db of absorbing material, the reduction in intensity can be stated mathematically as

$$dI = -KI\,db$$

where dI is the change in intensity, K is proportionality constant and the negative sign arises from the fact that I becomes smaller when b becomes larger.

Rearranging, we obtain

$$\frac{dI}{I} = -K\,db$$

which is mathematical statement of the fact that the fraction of radiation absorbed is proportional to the thickness traversed If Io is the incident intensity when b=o we integrate

$$\int_{Io}^{I} \frac{dI}{I} = -K \int_{o}^{b} db$$

Obtaining

$$\ln \frac{I}{Io} = -Kb$$

Removing the negative sign and converting to logarithms to the base 10, we obtain

$$\log \frac{Io}{I} = \frac{K}{2.303}\, b$$

Eq. (1) The final form of lamberts law, is on exact law and applies to any homogenous, non scattering medium, regardless of whether it is a gas, liquid, solid, or solution. The proportionality constant k depends on the wave length and temperature for a given absorbing substance, and for absolution the concentration must remain constant.

Beer's law

Lambert's law though exact is not of very great application in chemistry of much greater interest is the dependence of intensity on the concentration of absorbing solutes in solution. Beer found that increasing the concentration of radiation absorbing solution had the same effect as proportional increase in the radiation absorbing path. This should be obvious since an increase of solute in the same volume of solution will increase the effective thickness of the light absorbing layer by the same factor. Thus, the proportionality constant k in Eq. (1) is in turn proportional to the concentration C of absorbing solute which can be expressed as

$$\frac{\mathbf{K}}{\mathbf{2.303}} = \mathbf{ac} \quad (\mathbf{2})$$

where a is the new proportionality constant substituting Eq. (2) into Eq. (1) gives the logarithmic form of Beer's law

$$\mathbf{log}\frac{\mathbf{Io}}{\mathbf{I}} = \mathbf{abc} \quad (\mathbf{3})$$

Beer's law is fundamental to optical methods of analysis forming the basis for estimating the concentration of a substance by measuring the radiation absorbed by a solution of that substance. Eq. (3) the ratio I/Io called the transmittance is dimensionless the combination abc being a logarithm must also be a pure number. The cell width b is usually expressed in centimeters and is a constant in most work, when C is expresses in grams per liter, a is called the absorptivity and has units of liters per gram centimeter, the absorptivity is a constant. Characteristic of the absorbing substance and of the particular wavelength of radiation used. When the concentration C is expressed in moles per liter, the proportionality constant a is changed to Ɛ and called the molar absorptivity. Most often in experimental work the terms percent transmittance

($\%\mathbf{T} = \frac{\mathbf{I}}{\mathbf{Io}} * \mathbf{100}$) and absorbance ($\mathbf{A} = \mathbf{log}\frac{\mathbf{Io}}{\mathbf{I}} = \mathbf{2} - \mathbf{log}\,\%\mathbf{T}$)

Substitution of A into Eq. (3) gives the shortest statement of Beer's law

A= abc (4) or A = Ɛbc (5)

According as c is in grams per liter or moles per liter.

Limitation and Deviations of Beer – lambert law

Real Deviations: these are fundamental deviations due to the limitations of the law itself. Beer law and Lambert law is capable of describing absorption behavior of solutions containing relatively low amounts of solutes dissolved in it (<10 mM).

When the concentration of the analyte in the solution is high (> 10 mM) the analyte begins to behave differently due to interactions with the solvent and other salute molecules and at times even due to hydrogen bonding interactions;

1- At high concentrations, solute molecules can cause different charge distribution on their neighboring species in the solution. Since uv – visible absorption is an electronic phenomenon, high concentrations would possibly result in a shift in the a in the absorption wavelength of the analyte. At times even electrolyte concentrations such as those present in buffers play an important role in altering the charge distributions and affecting uv – visible absorbance.

Some large ions or molecules show deviations even at very law concentration for e.g ethylene blue absorptivity at 436 nm fails to observe Beer Lambert law even at concentrations as low as 10 μM.

2- High analyte concentrations can also possibly alter the refractive index (η) of the solution which in turn could affect the absorbance obtained. If the addition of solute causes significant change in the refractive index of the solution a correction to the Beer lambert formula can be placed as,

$$A = \varepsilon bc \left(\eta^2 + 2 \right)^2$$

This correction is normally not required below concentrations of 10mM (Figure 4).

Chemical deviations: From Beer's law are caused by shifts in the position of a chemical or physical equilibrium involving the absorbing species. Consider, For example the following equilibrium.

$2CrO_4^{2-} + 2H^+ \rightarrow 2HcrO_4^- \rightarrow Cr_2O_7^{2-} + H_2O$

The dichromate ion absorbs in the visible region at 450 nm. Upon diluting dichromate solution the equilibrium shifts to the left. The equilibrium can be controlled by converting all the chromium to CrO_4^{-2} by making the solution 0.05 M in potassium hydroxide. Beer's law is then followed. Chromium should not be expected to follow Beer's law in a highly acidic solution because the dimerization step is dependent on concentration even at a constant P^H. In general, if an absorbing species is involved in a simple acid – base equilibrium. Beer's law fails unless the PH and ionic strength are kept constant. In such situations the PH should be adjusted to at least three units more or less than the pk_a value of the monoprotic acid. Alternatively, the wavelength corresponding to an isosbestic (sometimes called isobestic) point can be used (Figure 5).

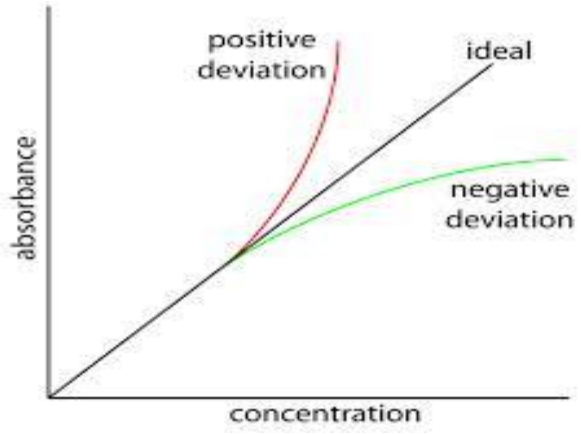


Fig. (4) Calibration curves For quantitative analysis.

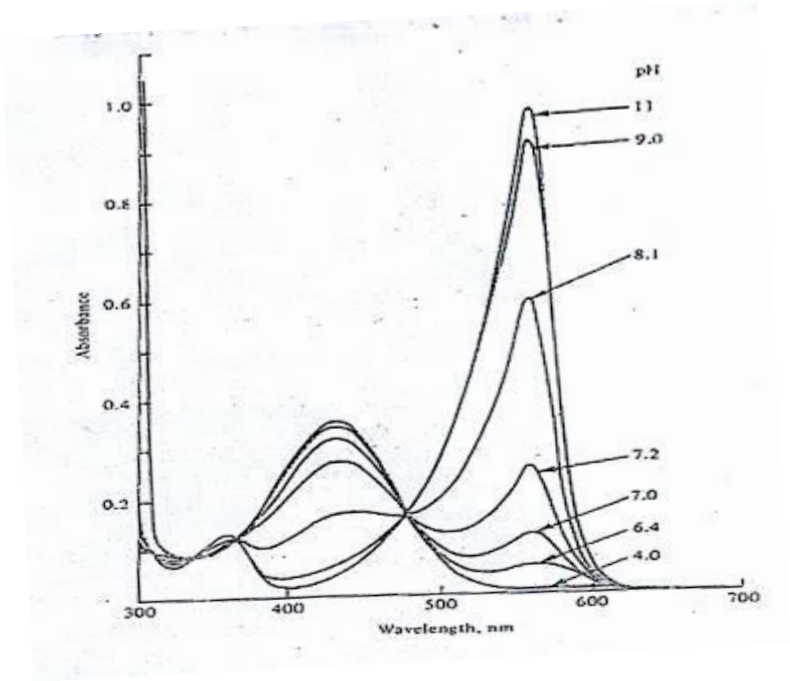


Fig. (5) chemical equilibrium between two solution components , the conversion of phenol red (PKQ = 7.9) From the yellow (acidic) to the red (basic) Form. Absorption maxima are at 433 and 558 nm, respectively for the acidic and basic forms. Isosbestic points are recorded at 338,367 and 480 nm.

Instrumentation

UV / visible spectrophotometers

All spectrometers require:-

(1) a source of continuous radiation over the wavelengths of interest.

(2) a monochromatic for selecting a narrow band of wavelengths from the source spectrum.

(3) a detector or transducer for converting radiant energy into electrical energy

Source

The source should have a readily detectable output of radiation over the wavelength region for which the instrument is designed to operate. No source, however, has a constant spectral output. The most commonly employed source for the visible region is a tungsten Filament incandescent lamp. The spectral output of atypical filament bulb is illustrated in (figure 6). The useful wavelength range is from about 325 or 350 nm to 3Mm, so it can also be used in the near ultraviolet and near infrared regions. The wavelength of maximum emission can be shifted to shorter wavelengths by increasing the voltage to the lamp and hence the temperature of the filament but its lifetime is shortened. For this reason a stable regulated power supply is required to power the lamp. This is true for sources for other regions of the spectrum also. Sometimes a 6 V storage battery is used as the voltage source. For the ultraviolet region, a low pressure hydrogen or deuterium discharge tube is generally used as the source. Each of these can be used from 185 nm to about 375 nm, but the deuterium source has about three times the spectral output of the hydrogen source. Ultraviolet sources must have a quartz window because glass is not transparent to ultraviolet radiation. They are frequently water cooled to dissipate the heat generated. In infrared spectrometers, which usually operate from about 2-15 μm, a nernst glower is used as the source. This is a rod consisting of a mixture of rare earth oxides. It has a negative temperature coefficient of resistance and is nonconducting at room temperature.

Therefore, it must be heated to excite the element to emit radiation, but once in operation it becomes conducting and furnishes maximum radiation at about 1.4 μm, or 7100 cm-1 (1500-2000°C). Another infrared source is the Globar. This is a rod if sintered silicon carbide heated to about 1300-1700°C. Its maximum radiation occurs at about 1.9 Mm (5200 cm^{-1}) and it must be water-cooled. The Globar is a less intense source than the Nernst glower but it is more satisfactory for wavelengths longer than 15 Mm because its intensity decreases less rapidly. We will see below how the instruments can be adjusted to account for the variations in source intensity with wavelength as well as for the variation in detector sensitivity with wavelength.

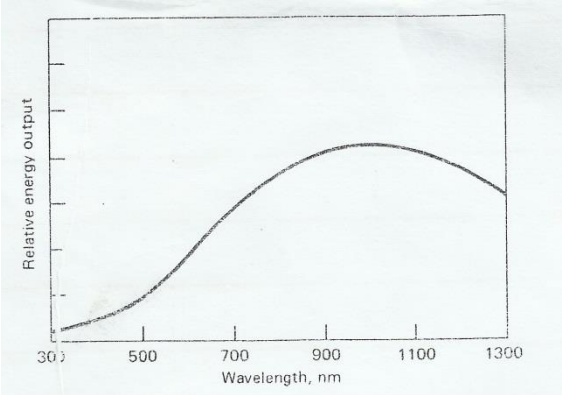


Fig. (6) Intensity of radiation as a function of wavelength for a typical tungsten bulb at 3000°k.

Monochromators

A monochromators consists chiefly of lenses or mirrors to focus the radiation, entrance and exit slits to restrict unwanted radiation and help control than spectral purity of the radiation emitted from the monochromators and a dispersing medium to "separate" the wavelengths of the polychromatic radiation from the source. There are two basic types of dispersing elements, the prism and the diffraction grating. Prisms When electromagnetic radiation passes through a prism, it is refracted. Because the index of refraction of the prism material is different from that in air.

The index of refraction depends on the wavelength and therefore so does the degree of refraction. Shorter wavelengths are refracted more than longer wavelengths the effect of refraction is to spread the wavelength apart into different wavelength (Figure 7). By rotation of the prism different wavelengths of the spectrum can be made to pass through an exit slit and through the sample. A prism works satisfactorily in the ultraviolet and visible regions and can also be used in the infrared region. However, because of its nonlinear dispersion, it works more effectively for the shorter wavelengths. Glass prisms and lengths can be used in the visible region, but quartz or fused silica transmit very little, and the prisms and other optics must be made from large cristls of alkali orb alkaline earth halides, which are transparent to infrared radiation. Sodium chloride (rock salt) is used in most instruments and is used useful for the entire region from 2.5 to 15.4 Mm (4000-650 cm^{-1}) for longer wavelengths, KBr (10-25 Mm) or Csl (10-38 Mm) can be used. These (and the monochromators compartment) must be kept dry. Diffraction gratings these consist of a large number of parallel lines (grooves) ruled on a highly polished surface such as aluminum, about 15000-30000 per inch for the ultraviolet and visible regions and 1500-2500 per inch for the infrared regions.

The grooves act as scattering centers for rays impinging on the grating. The result is equal dispersion of all wavelengths of a given order, that is linear dispersion (Figure 8). The resolving power depends on the number of ruled grooves but generally the resolving power of gratings is better than that of prisms, and they can be used in all regions of the spectrum. They are particularly well suited for the infrared region because of their equal dispersion of the long wavelengths. Gratings are difficult to prepare and original gratings are expensive. However, many replica gratings can be prepared from an original grating. This is done by coating the grating with a film of an epoxy resin that after setting is stripped off to yield the replica. It is made reflective by aluminizing the surface. These replica gratings are much less expensive and are even used in small inexpensive instruments. The intensity of radiation reflected by a grating varies with the wavelength of maximum intensity

being dependent on the angle from which the radiation is reflected from the surface of the groove in the blazed grating. Hence, gratings are blazed at specific angles for specific wavelength regions, and one blazed for the blazed for the blue region would be poor for an infrared spectrometer. Gratings also will produce radiation at multiples of the incident radiation (Figure 8). These multiples are called higher order of the radiation. The primary order is called the first order, twice the wavelength is the second order, three times the wavelength is the third order, and so on . So a grating produces first order spectra, second order spectra, and so on. The higher order spectra are more greatly dispersed and the resolution increased. Because of the occurrence of higher orders, radiation at wavelengths less than the spectral region must be filtered out, or else its higher orders will overlap the radiation of interest. This can be accomplished with various types of optical filters that pass radiation only above a certain wavelength. For example, if incident radiation from a radiating sample (replaces the source on a spectrophotometer) in the 400 - 700 nm range is being dispersed and measured e.g. fluorescence, any radiation by the sample at for example 325 nm would have a second order at 650 nm, which would overlap first order radiation at 650 nm.

This can be filtered out by placing a filter between the radiating sample and the grating that blocks radiation of $\leq$ 400 nm in the path of the incident beam; then the 325 nm radiation will not reach the grating. Ruled gratings have a problem of "ghosting" associated with periodic errors in the ruling engine drive screws, particularly if the gratings are used with high intensity radiation sources. This stray light is greatly reduced with holographic gratings. These are manufactured by exposing a photoresist layer, on a suitable substance to the interference pattern produced by two monochromatic laser beams, followed by photographic development to produce grooves and then a reflective coating process. The smoother line profile results in reduced light scatter. Also these gratings can be produced on curved surfaces and used to collimate light, eliminating mirrors or lenses that result in loss of light. The cost of the gratings is significantly higher than

the more conventional type, but they are finding use in spectrometers used for measurement of radiating samples such as in fluorescence analysis.

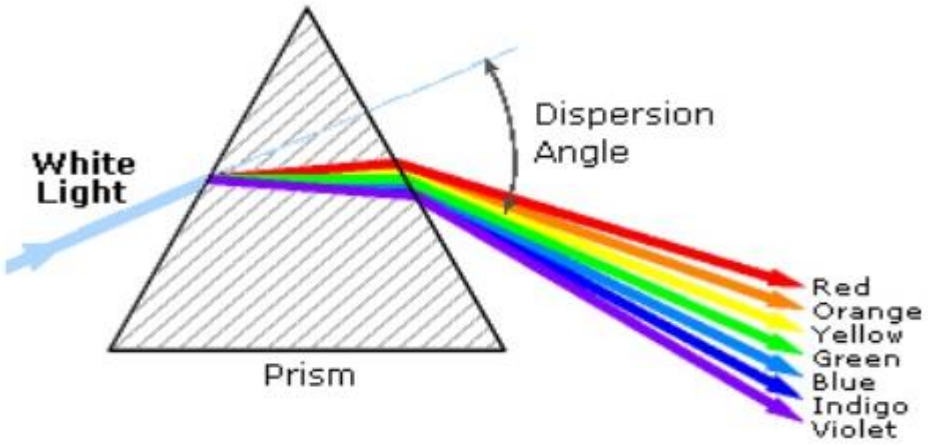


Fig. (7) Dispersion of polychromatic light by a prism.

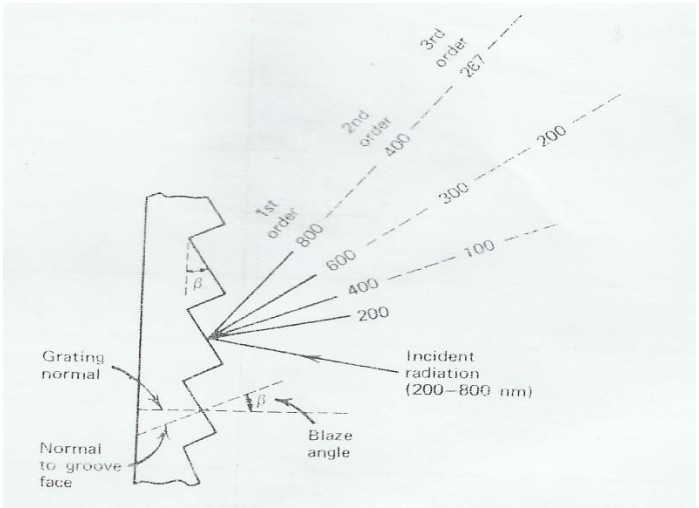


Fig. (8) Diffraction of radiation from a grating.

Detectors

The detector measures the light signal at a given wavelength. It is by nature a single channel device that converts the light intensity selected either by the monochromater exit or by the position, in the case of a spectrograph, into an electrical signal. In the latter case, the use of large number of detectors in the format of a diode array allows simultaneous multichannel detection (Figure 9). Two types of detectors exist: Photomultiplier tubes and semiconductors e.g. silicon photodiodes and charge transfer devices (CCD/CID). The Photomultiplier tube - a very sensitive device that has a linear response over seven decades - has for a long time been the most widely used detector in spectrophotometers. Its efficiency depends on the yield of the photocathode, which varies with wavelength (e.g. 0.1 e/ photon at 750 nm), and with the signal gain provided by the dynode cascade (e.g. gain of $6*10^5$). With such values, the impact of 10000 photons per second produces a current of 0.1 nA. In routine spectrophotometers photomultiplier tubes are replaced by photodiodes (Figure 9), which have excellent sensitivity, linearity and dynamic range. The photoelectric threshold, in the order of 1ev allows detection up to wavelengths of 1.1μm. In diode array systems each rectangular diode (15 pm * 2.5 mm) is associated with a capacitor. The electronic circuit sequentially samples the charge of each capacitor. While a photomultiplier tube measures the instant intensity in watts, a diode measures the emitted energy in joules over a time interval.

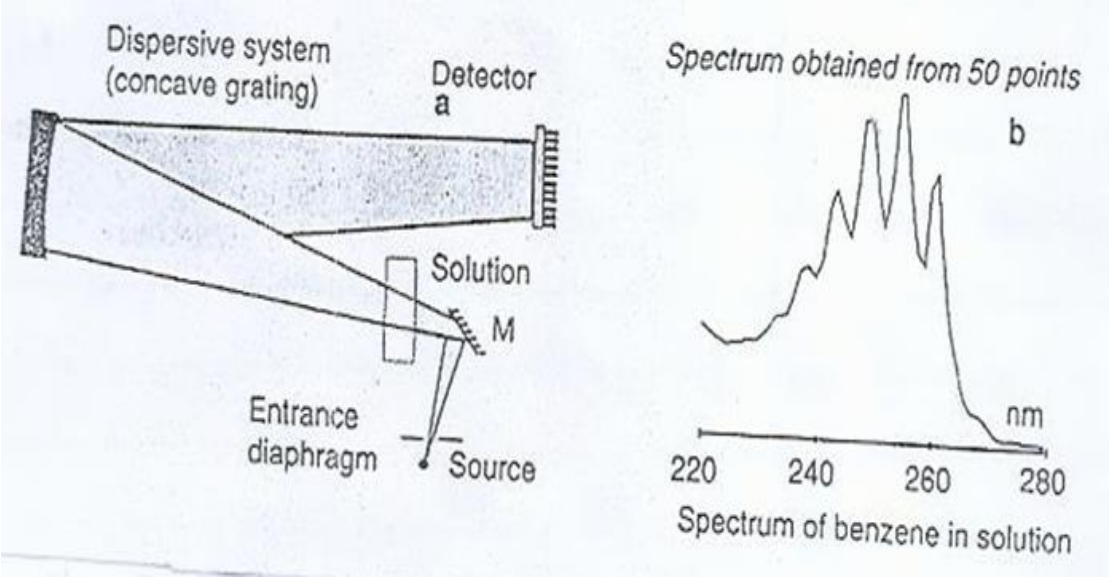


Fig. (9) Muluttichannel detection.

a-Multichannel detection with a diode array located in the focal plane. The light beam is ditiracted by the concave dispersive system after traveling through the sample.

b-Spectrum of a 1: 1000 solution of benzene in methanol. This spectrum represents atypical spectrum without smoothing quid is obtained with commercial photodiodes.

Single – Beam Spectrometers

Many routine measurements are conducted at fixed wavelengths using simple photocolorimeters equipped with wideband, interchangeable color filters. An analytical blank (or control) containing the solvent and reagents for the analysis (without the sample to be measured) is first placed in the optical path, then this is replaced by the solution to be analysed. These instruments For as light additional cost can be fitted with a grating and an electronic compensation mechanism for light source intensity variations (Figure 10). The compensation device is known as a split beam. Part of the light beam is diverted before it reaches the sample permitting stabilization of the source intensity (it is not a true reference beam). These spectrometers produce observance data by alternate measurements between the cells (control and sample). And lead to the desired concentration

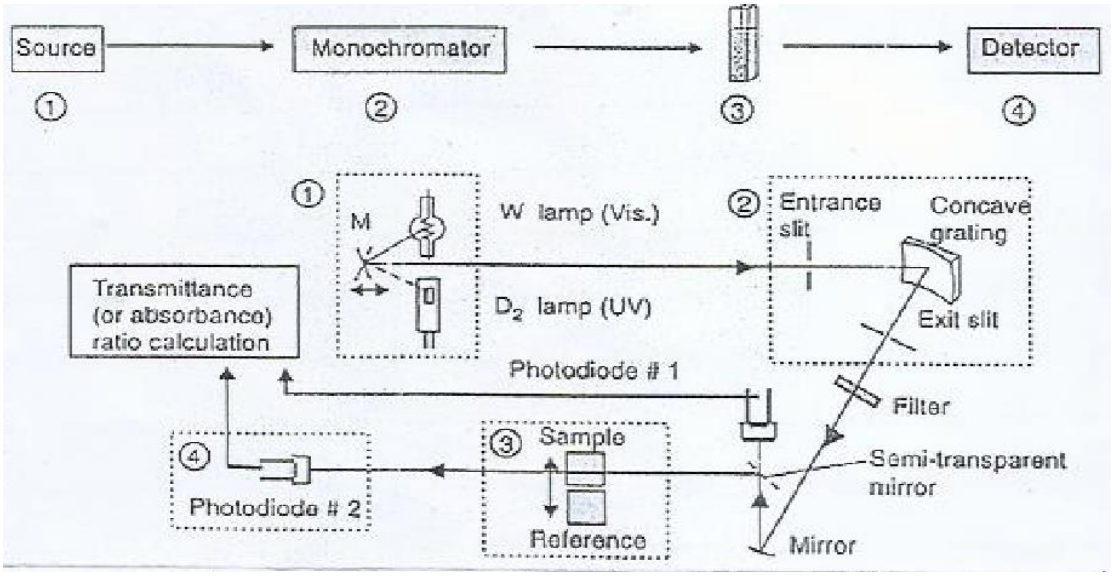


Fig. (10) Schematic and optical path of a single beam spectrophotometer equipped with electronic regulation (Hitachi U- 1000).

Double beam spectrometers

The best instruments in this area are still the double beam spectrometers in which one of the beams passes through the sample while the other passes through the reference two rotating mirrors called choppers which are synchronized with the displacement of the grating allow the comparison of transmitted light at the detector of the two beams with the same wavelength (Figure 11). Amplification of the modulated signal allows the elimination of stray light Double beam spectrophotometers allow differential measurements to be mode between the sample and the analytical blank. They are preferable to single beam instruments for measurements in problematic solutions For high performance instruments, the bandwidth con be as low as 0.01 nm.

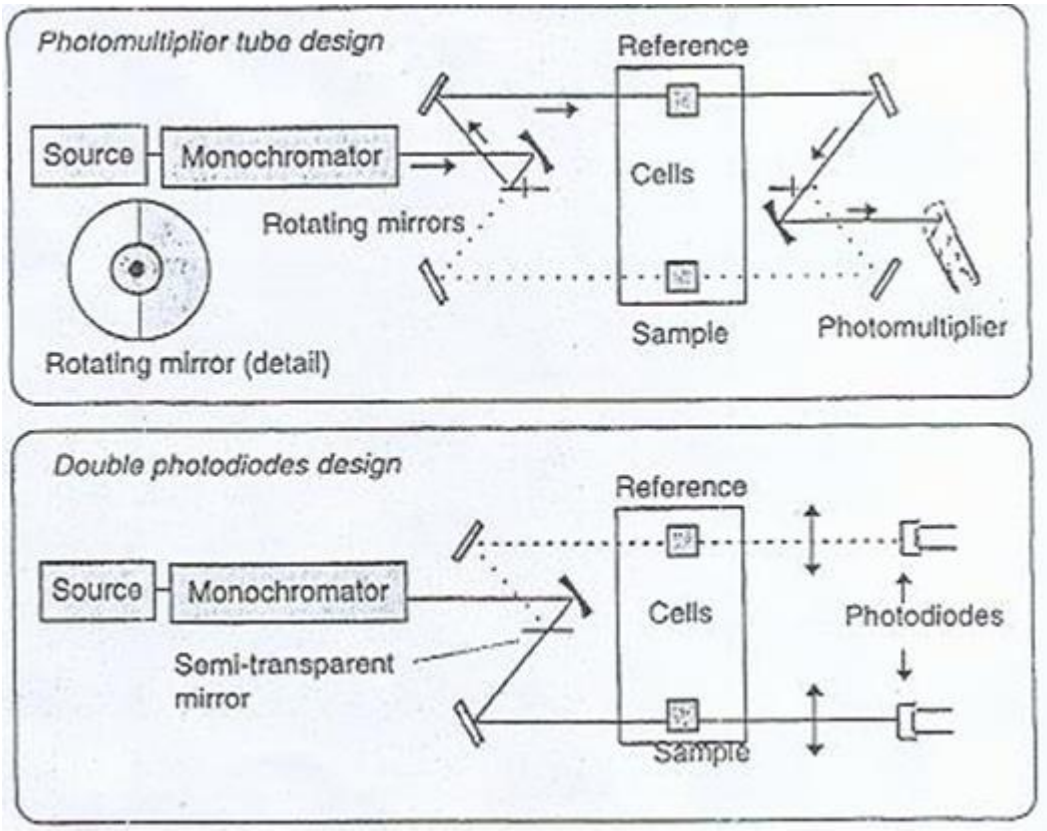


Fig. (11) Optical path between the monochromatic exit and the detector for two double beam instruments (rotating mirror model and semi - transparent mirror model).

Applications

Quantitative Analysis

Analysis for an absorbing substance can be carried out directly through Beer's law if no other absorbing material is present to interfere or if the interfering material can be removed or corrected for a good example of this approach is the measurement of ozone concentration in urban smog. A high pressure mercury are lamp was set up on the roof of a building, and its radiation received with a simplified prism spectrophotometer located on another building several hundred feet distant since a double beam system was impracticable zero calibration was made at night when atmospheric ozone was known to drop to negligible values. The ozone measurements were interfered with by other oxidants such as NO2 but this effect was eliminated by determining the ratio of absorbances at the ozone maxima of 313 and 265 nm. Ozone was found to rise to about 22 parts per 10^8 at noon, as the average of 50 days. Substances that do not show useful absorption can in many instances be determined spectrophotometrically following the addition of a reagent to produce an absorbing complex or other chromophore. One of the more important reagents is dithizone (diphenylthiocarbazone). This green compound soluble in chloroform reacts with cations of most of the transition metals to give red or violet complexes. The reagent can be made specific by adjustment of the pH. Details of the dithizone method are readily available and will not be repeated here. Another example of developed absorption is the determination of trace amounts of Hg(II) with the dye 4,4'-bis(dimethylamino)diphenylamine, known as Bindschedler's green in citrate buffer. The complex extracted into 1,2-dichloroethane, follows Beer's law from 8×10^{-7} to 4×10^{-6} M Hg(II). Only tin out of 21 metals checked interferes with the analysis.

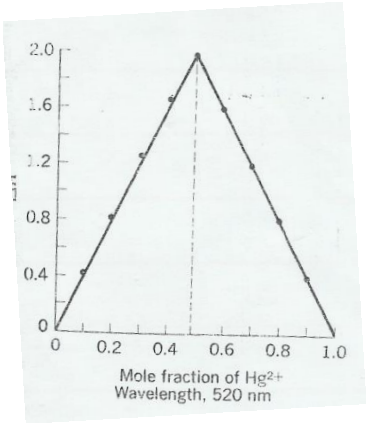


Fig. (12) Job plot for the mercury-diphenylthiocarbazone complex. The vertical coordinate ∆A represents the difference between the absorbance of the mixed solution and the sum of the absorbance that the reagents would have shown had they not reacted.

Determination of ligand/metal ratio in a complex

Since organometallic complexes in general show selective absorption in the visible or ultraviolet this property is widely employed to determine their composition as well as their stability constants. The stoichiometry of a stable complex can be determined by either of two related techniques:

(1) the mole-ratio method introduced by Yoe and Jones and (2) the method of continuous variations attributable to Job and modified by Vosburgh and Cooper. In the mole-ratio method the absorbances are measured for a series of solution which contain varying amounts of one constituent with a constant amount of the other. A plot is prepared of absorbance as a function of the ratio of moles of reagent to moles of metal ion. This is expected to give a straight line from the origin to the point where equivalent amounts of the constituents are present. The curve will then become horizontal because all of one constituent is used up and the addition of more of the other constituent can produce no more of the absorbing complex. If the constituent in excess itself absorbs at the same wavelenght. The curve after the equivalence point will show a slope that is positive but of smaller magnitude than

that prior to equivalence. (Figure 14). Shows the result of such an experiment utilizing the complex of diphenylcarbazone with mercuric ions.

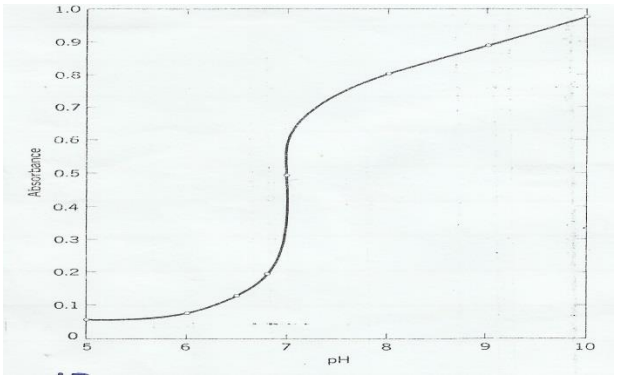


Fig. (13) Phenol red. Absorbance at 615 nm as a function of pH.

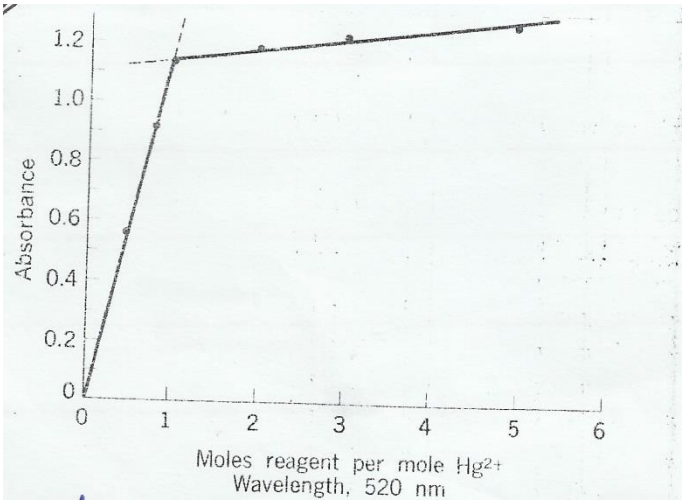
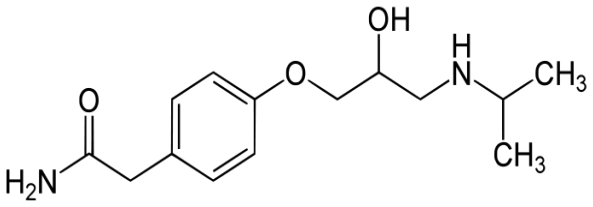


Fig. (14) Yoe-Jone plot for the mercury-diphenylcarbazone complex.

Atenolol



Trade names :	Tenormin
Molecular Formula :	$C_{14}H_{22}N_2O_3$
Molecular Weight :	266.336 g/mol

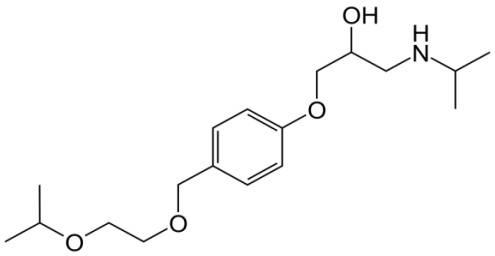
Medical Uses

Atenolol is used for a number of conditions including hypertension, angina, long QT syndrome, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and the symptoms of alcohol withdrawal. Off-label uses of atenolol, as with other cardioselective β-blockers, include symptomatic treatment of psychological issues such as anxiety. β-blockers are effective for some in treating the somatic (physical) effects of anxiety. In these instances, dosing is used as needed instead of regular daily dosing. Due to its hydrophilic (water-attracting) properties, the drug is less suitable in migraine prophylaxis compared to propranolol, because, for this indication, atenolol would have to reach the brain in high concentrations, which is not the case, because atenolol does not pass through the blood–brain barrier**.**

Side Effects

Atenolol was the main β-blocker identified as carrying a higher risk of provoking type 2 diabetes, leading to its downgrading in the United Kingdom in June 2006 to fourth-line agent in the management of hypertension. Antihypertensive therapy with atenolol provides weaker protective action against cardiovascular complications (e.g. myocardial infarction and stroke) compared to other antihypertensive drugs. In some cases, diuretics are superior. In addition, atenolol has been found to lack mortality benefits and even to increase mortality in older adults.

Bisoprolol



Trade names :	Zebeta, Concor, others
Molecular Formula :	$C_{18}H_{31}NO_4$
Molecular Weight :	325.443 g/mol

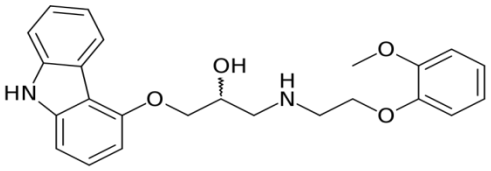
Medical Uses

Bisoprolol is beneficial in treatment for high blood pressure (hypertension), reduced blood flow to the heart (cardiac ischemia); congestive heart failure, and preventive treatment before and primary treatment after heart attacks, decreasing the chances of recurrence. In cardiac ischemia, the drug is used to reduce the activity of the heart muscle, so reduces oxygen and nutrient demand, and reduced blood supply can still transport sufficient amounts of oxygen and nutrients. Patients with compensated congestive heart failure may be treated with bisoprolol as a comedication (usually with an ACE inhibitor, a diuretic, and a digitalis-glycosid, if indicated). In patients with congestive heart failure, it reduces the need for and the consumption of oxygen of the heart muscle. It is very important to start with low doses, as bisoprolol reduces also the muscular power of the heart, which is an undesired effect in congestive heart failure.

Side Effects

Overdose of bisoprolol leads to fatigue, hypotension, low blood sugar, bronchospasms, and bradycardia. Bronchospasms and low blood sugar because at high doses drug can be an antagonist for β_2 adrenergic receptors located in lung and in liver. Bronchospasm is due to blockage in lungs of β_2 receptor and low blood sugar because of decreased stimulation of glycogenolysis and gluconeogenesis in the liver via β_2 receptor.

Carvedilol



Trade names :	Coreg
Molecular Formula :	$C_{24}H_{26}N_2O_4$
Molecular Weight :	406.474 g/mol

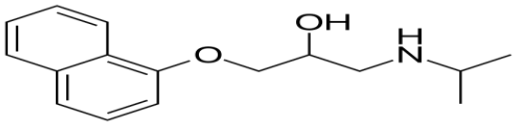
Medical Uses

Carvedilol is indicated in the management of congestive heart failure (CHF), commonly as an adjunct to angiotensin-converting-enzyme inhibitor (ACE inhibitors) and diuretics. It has been clinically shown to reduce mortality and hospitalizations in people with CHF. The mechanism behind its positive effect when used long-term in clinically stable CHF patients is not fully understood, but is thought to contribute to remodeling of the heart, improving upon its structure and function. In addition, carvedilol is indicated in the treatment of hypertension and to reduce risk of mortality and hospitalizations in a subset of people following a heart attack. It can be used alone or with other anti-hypertensive agents.

Side Effects

The most common side effects (>10% incidence) include: (dizziness, fatigue, low blood pressure, diarrhea, weakness, slowed heart rate, weight gain, and erectile dysfunction) .Carvedilol is not recommended for people with uncontrolled bronchospastic disease (e.g. current asthma symptoms) as it can block receptors that assist in opening the airways. Carvedilol may mask symptoms of low blood sugar (hypoglycemia), resulting in hypoglycemia unawareness. This is termed beta blocker induced hypoglycemia unawareness.

Propranolol



Trade names : Inderal, others

Molecular Formula : $C_{16}H_{21}NO_2$

Molecular Weight : 259.34 g/mol

Medical Uses

Propranolol is used for treating various conditions, including:

Cardiovascular

- Hypertension
- Angina pectoris (with the exception of variant angina)
- Tachyarrhythmia
- Myocardial infarction
- Tachycardia (and other sympathetic nervous system symptoms, such as muscletremor) associated with various conditions, including anxiety, panic, hyperthyroidism, and lithium therapy
- Portal hypertension, to lower portal vein pressure
- Prevention of esophageal variceal bleeding and ascites
- Anxiety
- Hypertrophic cardiomyopathy

Side Effects

Propranolol should be used with caution in people with:

- Diabetes mellitus or hyperthyroidism, since signs and symptoms of hypoglycaemia may be masked
- Peripheral vascular disease and Raynaud's syndrome, which may be exacerbated
- Phaeochromocytoma, as hypertension may be aggravated without prior alpha blocker therapy

- Myasthenia gravis, which may be worsened
- Other drugs with bradycardic effects

Pregnancy and lactation

Propranolol, like other beta blockers, is classified as pregnancy category C in the United States and ADEC category C in Australia. β-blocking agents in general reduce perfusion of the placenta, which may lead to adverse outcomes for the neonate, including lung or heart complications, or premature birth. The newborn may experience additional adverse effects such as low blood sugar and a slower than normal heart rate. Most β-blocking agents appear in the milk of lactating women. However, propranolol is highly bound to proteins in the bloodstream and is distributed into breast milk at very low levels. These low levels are not expected to pose any risk to the breastfeeding infant, and the American Academy of Pediatrics considers propranolol therapy "generally compatible with breastfeeding". Due to the high penetration across the blood–brain barrier, lipophilic beta blockers such as propranolol and metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such as insomnia and vivid dreams, and nightmares. Dreaming (rapid eye movement sleep, REM) was reduced and increased awakening. Adverse drug reactions associated with propranolol therapy are similar to other lipophilic beta blockers.

II. Chemical abstract

a. Spectrophotometric determination of atenolol

Bakir et al. (5) developed a simple and sensitive spectrofluorimetric method for determination of atenolol (ATE) using gold nanoparticles (AuNPs). The method is based on the quenching effect of atenolol on photoluminescence of AuNPs at λ_{em} = 705 nm. Variables affecting luminescence of gold nanoparticles such as the solvent, pH value and surfactant were studied and optimized. The method was preliminarily validated according to ICH guidelines. A linear correlation was recorded within the range of 1.0–10 mg mL^{-1} ATE with the coefficient of determination R^2 of 0.999. The limit of detection and limit of quantitation for atenolol were found to be 0.87 and 2.64 mg mL^{-1}, resp. Good recoveries in the range of 98.7–100.0 % were obtained for spiked samples. The proposed method was applied successfully to assaying atenolol in pharmaceuticals formulations.

Amirdehi et al. (6) determined the pK_a values of two important drugs in different binary aqueous/organic solutions, which mimic a range of industrial solvents and biological fluids encountered during drug synthesis and end use. Titrations of monoprotic (propranolol) and diprotic (atenolol) drugs were determined using a combination of potentiometric and spectroscopic methods at constant temperature and ionic strength. Single-parameter correlations between the measured pK_a values (at 25 °C) and hydrogen-bond acidity/basicity or solvent polarity parameters were poor in all cases. However, analysis using the multi-parameter method of Kamlet, Abboud, and Taft represents significant improvement enabling better interpretation of the solvent effects on the acid−base equilibria of the drugs. As a validation step and for a deeper understanding of the origins of the solvent effects on the drugs, all pK_a values were predicted by DFT calculations. Finally, acidity constants were determined by correlations between experimental and theoretical measurements. The developed method will measure and accurately

simulate the effect of the solvent environment on pK_a values and represent advancement for questions related to drug synthesis and drug compound's behavior in biological fluids.

Hasumati et al. (7) developed a simple, accurate, precise, economic, robust and rugged UV spectrophotometric method for the simultaneous estimation of Atenolol and Ivabradine HCl in synthetic mixture. Combination of Atenolol and Ivabradine HCl has not any analytical method developed yet, so this UV method is novel for combined synthetic dosage of Atenolol and Ivabradine HCl (10:1). The absorbance maxima of Atenolol and Ivabradine HCl were found to be 276.00 nm and 286.50 nm respectively. Beer law obeyed the concentration range of 20–100 μg/ml and 2–10 μg/ml for Ivabradine HCl. The result of analysis was validated statistically and by the recovery studies. The %RSD value of all validation parameter less than 2. The proposed method can be effectively applied for the estimation of these two drugs.

b. spectrophotometric determination of bisoprolol

Alahmad et al. (8) developed spectrophotometric methods for the simultaneous determination of Bisoprolol (BIS), Hydrochlorothiazide (HCT) and Ramipril (RAM) in their dosage form. These methods are chemometric based on treatment of data, the applied chemometric techniques are multivariate methods including Classical Least Squares (CLS), Principal Component Regression (PCR) and Partial Least Squares (PLS). In these techniques, the concentration data matrix were prepared by using the synthetic mixtures containing the three drugs dissolved in 0.1 M NaOH. The absorbance data matrix corresponding to the concentration data matrix was obtained by measuring the absorbance in the range 235-245 nm at 1 nm intervals in the zero-order. The spectrophotometric procedures are simple, do not require any separation step. The developed methods were validated by calculating

validation diagnositics after analyzing dosage form containing the studied drugs. The developed methods were successfully applied routinly in quality control laboratory.

Mostafa et al. (9) described the UV spectrophotometric analysis of a binary mixture containing bisoprolol fumarate (BS) and hydrochlorothiazide (HZ) by using multivariate calibration methods, such as principal component regression (PCR) and partial least-squares regression (PLS-1); and a graphical spectrophotometric method such as second derivative of the ratio spectra 2DD. A calibration set of 22 reference samples was used to develop the models for PCR and PLS-1. The calibration models optimization was achieved through the proper wavelength ranges selection, and excluding any information about the interfering excipients. In addition, a High Performance Liquid Chromatography (HPLC) was developed to analyze the same mixture. The chromatographic separation was achieved on a reversed phase, RP 18 column with mobile phase consisting of acetonitrile-0.01 M KH2PO4 (40:60, v/v, and pH 3.5). Quantitation was achieved with UV detection at 232 nm based on peak area. The proposed methods were validated and successfully used for the analysis of laboratory-prepared mixtures and pharmaceutical formulations.

Abdelmonem et al. (10) developed Sensitive, simple and rapid spectrofluorimetric and spectrophotometric methods for the determination of Irbesartan (IRB) and Bisoprolol hemifumarate (BPH) in their tablets dosage form. Both methodologies are based on charge transfer reaction between the studied drugs and 7-Chloro-4-nitrobenzen-2-oxa-1, 3-diazole NBD-Cl. The developed orange products were measured in the appropriate solvent fluorometrically at 534 and 538 nm after excitation at 465 and 470 nm for IRB and BPH, respectively. The fluorescence–concentration plots were rectilinear over the range of 2.5–8 μg/mL for IRB and 6–16 μg/mL for BPH with lower detection limits of 0.18 and 0.39 μg/mL and a lower quantification limit of 0.55 and 1.17 μg/mL for IRB and BPH, respectively. The

spectrophotometric method is based on measuring the orange colored products which were developed upon charge transfer complex formation between the studied drugs and (NBD-Cl) in organic media. This showed absorption maxima at 476 nm and 479 nm for IRB and BPH, respectively. The absorbance–concentration plots were rectilinear over the range of 20–90 μg/mL for IRB and 40–160 μg/mL for BPH with lower detection limits of 1.37 and 3.98 μg/mL and lower quantification limits of 4.17 and 12.06 μg/mL for IRB and BPH, respectively. Both methods were successfully applied to the analysis of the two selected drugs. The current study showed that the results were in good agreement with the reference methods.

c. spectrophotometric determination of carvedilol

Farahmand et al. (11) introduced an air assisted liquid-liquid microextraction by applying the solidification of a floating organic droplet method (AALLME-SFOD) coupled with a multivariate calibration method, namely partial least squares (PLS), for the fast and easy determination of Atenolol(ATE), Propanolol (PRO) and Carvedilol (CAR) in biological samples via a spectrophotometric approach. The analytes would be extracted from neutral aqueous solution into 1-dodecanol as an organic solvent, using AALLME. In this approach a low-density solvent with a melting point close to room temperature was applied as the extraction solvent. The emulsion was immediately formed by repeatedly pulling in and pushing out the aqueous sample solution and extraction solvent mixture via a 10-mL glass syringe for ten times. After centrifugation, the extractant droplet could be simply collected from the aqueous samples by solidifying the emulsion at a lower than the melting point temperature. In the next step, analytes were back extracted simultaneously into the acidic aqueous solution. Derringer and Suich multi-response optimization were utilized for simultaneous optimizing the parameters of three analytes. This method incorporates the benefits of AALLME and dispersive liquid–liquid microextraction considering the solidification of floating organic droplets (DLLME-SFOD).

Calibration graphs under optimized conditions were linear in the range of 0.30–6.00, 0.32–2.00 and 0.30–1.40 μg mL^{-1} for ATE, CAR and PRO, respectively. Other analytical parameters were obtained as follows: enrichment factors (EFs) were found to be 11.24, 16.55 and 14.90, and limits of detection (LODs) were determined to be 0.09, 0.10 and 0.08 μg mL^{-1} for ATE, CAR and PRO, respectively. The proposed method will require neither a highly toxic chlorinated solvent for extraction nor an organic dispersive solvent in the application process; hence, it is more environmentally friendly.

Kundu et al. (12) developed two spectroscopic methods such as simultaneous equation method and third order derivative spectroscopic method for the simultaneous estimation of carvedilol (CARV) and spironolactone (SPRN) in pharmaceutical dosage form and dissolution samples. The methods were validated as per the ICH guidelines for different parameters such as linearity, .specificity, accuracy, precission, limit of detection and limit of quantification. The equal concentration of both drugs (10 μg/ml) solutions were scanned separately in the UVregion and from the overlain spectra, two wavelengths, 243 nm (λmax of CARV) and 236 nm (λmax of SPRN) were selected for the formation of simultaneous equation (method I). The zero order spectrum was processed to obtain third-derivative spectrum (method II). The two third derivative spectra were overlaid which shows that CARV showed zero crossing point (ZCP) at 257.2 nm, while SPRN showed ZCP at 308.6 nm. The determinations were made at 308.6 nm for CARV (ZCP of SPRN) and 257.2 nm for SPRN (ZCP of CARV). Linear relationship was found in the concentration range of 5-30μg/mL for CARV and SPRN by both methods. Both methods were found accurate and precise. The bilayer tablet (in house) was analyzed and amount of CARV and SPRN determined by the proposed method was found to be 99.52 % for CARV and 99.74 % for SPRN, respectively by simultaneous equation method and 99.04 % for CARV and 98.28 % for SPRN by employing third derivative spectroscopic method. The described

methods are giving accurate and precise results for the determination of carvedilol and spiranolactone mixture in formulations. The proposed methods could be satisfactorily employed in dissolution studies to determine the percentage drug release.

Abdelwahab et al. (13) developed two simple, precise, rapid and economic spectrophotometric methods for simultaneous determination of Carvedilol (CV) and Hydrochlorothiazide (HCT) in bulk powder and combined dosage form. Method (I) is based on dual wavelength analysis while Method (II) depends on UV-spectrophotometric determination using Q-analysis (graphical absorbance ratio) method.

In Method (I), two wavelengths were selected for each drug in such a way that the difference in absorbance is zero for the second drug. At wavelengths 238 and 248.8 nm HCT has equal absorbance values, therefore, these two wavelengths have been used to determine CV, on similar basis 266 and 289.4 nm were selected to determine HCT in the combined formulation. Method (II) involves the formation of Q-absorbance equation using the respective absorptivity values at 229.2 nm (isoabsorptive point) and 241 nm (λ_{max} of CV). The drugs obey Beer's Lambert's law in the concentration range of 1–10 μg/mL for both CV and HCT (for Method I) and in the range of 1–10 and 2–10 μg/mL for CV and HCT, respectively (for Method II). The accuracy and precision were determined and recovery studies confirmed the accuracy of the developed methods that were carried out following the International Conference on Harmonization (ICH) guidelines. Statistical comparison of the suggested methods with the reported spectrophotometric one using F and t tests showed no significant difference regarding both accuracy and precision.

d. spectrophotometric determination of propranolol

Martins et al. (14) developed hypertension is one of the most important mortality risks in the world and is considered the leading cause of deaths associated with cardiovascular disease. In an attempt to improve the treatments and apply them to a large number of disorders, a propranolol hydrochloride (Prop) based medicine it in our laboratory, employing a multiparticulate system which operates in a biphasic manner, one portion of immediate and other of modified release. This study aimed at developing and validating a suitable method to quantify this new version of the drug using UV spectrophotometry, following what is recommended in RE 899/2003. The results showed that the method employed was linear, accurate, precise and robust in the range of 0.8 to 96.0 μg mL⁻¹which allows it for routine use in quality control laboratories.

Amirdehi et al. (15) determined the pK_a values of two important drugs were determined in different binary aqueous/organic solutions, which mimic a range of industrial solvents and biological fluids encountered during drug synthesis and end use. Titrations of monoprotic (propranolol) and diprotic (atenolol) drugs using a combination of potentiometric and spectroscopic methods at constant temperature and ionic strength. Single-parameter correlations between the measured pK_a values (at 25 °C) and hydrogen-bond acidity/basicity or solvent polarity parameters were poor in all cases. However, analysis using the multi-parameter method of Kamlet, Abboud, and Taft represents significant improvement enabling better interpretation of the solvent effects on the acid−base equilibria of the drugs. As a validation step and for a deeper understanding of the origins of the solvent effects on the drugs, all pK_a values were predicted by DFT calculations. Finally, acidity constants were determined by correlations between experimental and theoretical measurements. The developed method will measure and accurately simulate the effect of the solvent environment on pK_a values and represent

advancement for questions related to drug synthesis and drug compound's behavior in biological fluids.

Kumar et al. (16) studied deals with UV spectrophotometric method development & validation for simultaneous estimation of Hydrochlorothiazide and Propranolol in dosage form by Simultaneous Equation Method. The wavelengths selected for the method were at the λmax 271nm and 289nm for Hydrochlorothiazide and Propranolol respectively. The linearity of Hydrochlorothiazide and Propranolol was found to be in the range of 4-24 µg/ml & 8-48µg/ml respectively. The linear correlation was obtained (r^2> 0.998) in the range of 4-24µg/ml for Hydrochlorothiazide at 271nm. The method was found to be linear (r^2> 0.998) in the range of 8-48 µg/ml for Propranolol at 289 nm. The limit of detection was 0.052 µg/ml and 0.461 µg/ml for Hydrochlorothiazide and Propranolol respectively. The limit of quantification was 0.158 µg/ml and 1.397 µg/ml for Hydrochlorothiazide and Propranolol. The accuracy of the method was found to be 97-98%.The simple and economical method was successfully applied for simultaneous determination of Propranolol and Hydrochlorothizide in combined dosage form. The proposed method was validated as per ICH guidelines.

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