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pK_a Determination of Pharmaceutical Active Agents: The Analytical Method of Choice

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Editorial
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Editorial

The acid-base dissociation constant (pK_a) of a drug is a major physicochemical parameter that influences biopharmaceutical characteristics of drugs and other chemical substances [1]. The pK_a distributions of drugs are influenced by two main factors namely; (i) the nature and frequency of occurrence of the functional groups commonly seen in drug molecules and the typical range of pK_a values involved, (ii).the biological targets the drug molecules are designed to interact. Since many of the drugs are weak acids and/or bases, knowledge of the pK_a provides understanding the ionic form of the drug molecule across a range of pH values. This is of vital importance in physiological systems where ionization state affects the pharmacokinetic characteristics (absorption, distribution, metabolism and excretion (ADME) of drug molecules [2]. Due to the importance of this parameter to biological system, a number of analytical methods have been investigated to measure or estimate the pK_a values of pharmaceutical active agents (drugs). Such analytical methods include: potentiometric [3], UV spectrometric [4], conductometric [5], proton magnetic resonance spectroscopic [6], partitioning [7], solubility [8], chromatographic [9], voltammetric [10], calorimetric [11], electrophoretic [12], fluorometric [13], polarimetric [14], kinetic [15] and computational [16] methods. In this paper, it was of interest to examine few of these methods on the basis of their simplicity, accuracy and reproducibility in determining pK_a values of pharmaceutical active agents.

The potentiometric method is the most common and useful technique for accurate and reproducible determination of aqueous ionization constant (pK_a) of drugs or other organic chemical substances. It is not applicable for the determination of ionization constant of poorly-water soluble drugs because reliable titration curves are not obtained. However, the use of cosolvent systems [17] and surfactants [18], have made it possible to determine the pK_a values of such water insoluble drugs. The plot of potential versus volume of titrant gives rise to a sigmoid curve, where the inflection point indicates the potential at equilibrium. With the use of standards with known pH, this potential can be linearly converted into a pH, equaling pK_a. Alternatively, the pK_a can be evaluated using Henderson-Hasselbalch equation.

In ultraviolet spectroscopic method, the presence of a chromophore close to the ionization site in the drug molecule is required in order that the spectra of the dissociated and the non-dissociated form can differ. It is one of the methods suitable for poorly aqueous soluble drugs. Any wavelength can be used for the determination of pK_a, except at the isosbestic point at which wavelength of both forms have the same molar absorptivity. An improved spectroscopic method involves absorption measurement at two different wavelengths as a function of pH and plotting the ratio in absorption at those two wavelengths against the pH. A sigmoid curve is obtained and the pK_a can be determined from the inflection point as normal. One of the wavelengths has to be assigned to the chromophore and the other wavelength should be invariant under change of pH.

The proton magnetic resonance (H-NMR) is useful for drugs whose UV spectra do not change upon ionization; however, the drug has to be water soluble. The method

requires one proton to show a significant chemical shift (δ) when going from the unionized to ionized species. Since the equilibrium is pH dependent, the chemical shift will also change with the pH level. For this situation, the pK_a can be obtained using the equation below.

$pK_a = pH + \log [(\delta_A - \delta_{obs})/(\delta_A - \delta_{HA})]$

In the partitioning method, measurement of the partition coefficient between water and immiscible organic solvent at various pH values of the aqueous phase is carried out.

The equation relating partition coefficient and hydrogen ion concentration (pH) is usually employed for pK_a calculation.

The solubility method requires maintaining a constant pH during the solubilization process to avoid underestimation of saturation solubility at a known pH value. A derivation of the Henderson-Hasselbalch equation allows the determination of the pK_a from solubility data, in chromatographic method, poorly-water soluble and impure drug samples can be accurately analyzed and the method also requires small quantities of drug samples. The chromatographic method could be paper chromatography (requires impregnation of the paper with aqueous solutions with known pH values), thin layer chromatography (requires impregnating the plates with mineral oil), gas chromatography (limited method because drugs are in the vapor phase rather than aqueous solution) and high performance liquid chromatography (ion-exchange or reverse phase type). Plotting capacity factor (k) versus pH gives a sigmoid curve with the inflection point of degree of dissociation (α) = 0.5 at pH = pK_a.

The polarimetric method depends on the difference in optical rotation between the ionized and non-ionized forms of an analyte. Determination of pK_a involves the measurement of the optical rotation of plane polarized light by the sample solution as a function of pH. The optical rotation of the sample is taken as the sum of the optical rotation of the ionic fractions derived from the analyte. The pK_a value may be determined by plotting the optical rotation against the pH. Although, the method is a reasonably sensitive, one of the limitations is that only optically active analytes can be analyzed.

In calorimetric method, isothermal titration is used to measure pK_a values. The technique requires a regular acid-base titration to be carried out inside the calorimeter while the energy needed to keep the temperature constant is measured. The pK_a is obtained indirectly from a measured enthalpy change ΔH or directly from the inflection point of a sigmoid curve when the minima or maxima is plotted against pH.

In conclusion, it has been found that a variety of analytical methods are available for the determination of pK_a values of pharmaceutical active agents. Potentiometry and ultraviolet–visible spectrometry appear to be the most used because of their accuracy and reproducibility. However, separation techniques such as thin layer chromatography, high performance liquid chromatography and capillary electrophoresis, currently are strongly recommended for pK_a evaluation because none requires pure samples for measurements. Finally, despite all the analytical methods available for pK_a determination, the analytical method of choice might depend mostly on the physicochemical properties of the analyte, method of analysis available to the analyst, duration of analysis and the cost-effectiveness.

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