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Prediction of Chemical Stability of Ibuprofen in Solution: An Accelerated Aging Study

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Ibuprofen, propionic acid derivative, was subjected to different temperature (20, 30, 37, 40, 50 and 60 ºC) and pH (3, 4, 5, 6, 7 and 8) conditions. The samples were assayed at time intervals 0, 12, 24, 36 and 48 h by taking their UV/VIS absorbance at wavelengths 272 and 258 nm. Ratios of absorbance at any time were taken as a parameter, proportional to the concentration of intact substance. The degradation processes were assumed to follow pseudo-first-order kinetics and rate constants (K) were calculated by plotting logarithm of absorbance ratio *versus* time and slope of the regression lines were considered to be equivalent (K/2.303). The energy of activation (E_a) at particular pH, was calculated by Arrhenius equation *i.e.*, $K = Ae^{-Ea/RT}$. Ibuprofen is found to be moderately resistant to the acid treatment. Respective E_a values at pH 3, 4, 5, 6, 7 and 8 were calculated to be 19.17, 20.60, 21.81, 24.22, 22.45 and 21.16 Kcal/mol. The compound under study exhibited thermolability and is recommended to be maintained at 20 ºC.

Key Words: Ibuprofen, Stability, Temperature, pH, Arrhenius equation.

INTRODUCTION

Knowledge of the physical stability of formulation is very importance for three primary reasons: First, a pharmaceutical product must appear fresh, elegant and professional, so long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to loss confidence in the product. Second, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be assured. A cloudy solution or a broken emulsion can lead to a non-uniform dosage pattern. Third, the active ingredient must be available to the patient throughout the expected shelf life of the preparation. A breakdown in the physical can lead to non availability of the medicament to the patient[1].

The pharmaceutical products can be protected by taking the following measures into consideration: (i) protection from light, (ii) exclusion of oxygen, (iii) addition of antioxidants and (iv) control of pH[2]. The rates of most chemical reactions increase with rise in temperature. It is, therefore, important to be aware of this when formulating pharmaceutical products for use in tropical areas, or when a product has to be heat sterilized before use. There are however, a few instances where low temperature storage may have a tendency to accelerate decomposition. The increased rate of polymerization of formaldehyde at temperatures below 15 ºC was observed[3].

The degradation of most drugs is catalyzed by extremes of pH *i.e.*, high [H^+] and many drugs are most stable between pH 4 and 8. Where maximum stability dictates wider values, it is important for injectables that the buffers should have a low capacity to prevent unnecessary challenge to the homeostatic pH 7.4 of blood[4]. Weakly acidic and basic drugs are most soluble when ionized and it is then that instability is most likely since the species are charged. This lead to a potential dilemma, since many potent drugs are extremely poorly soluble and pH dependent ionization is the obvious method to produce a solution[5]. In some cases, therefore, the inclusion of a water-miscible solvent in the formulation will increase stability by suppressing ionization, reduce the extreme of pH required to achieve solubility, contribute to the solubility and decrease the water activity by reducing the polarity of the solvent mixture, *e.g.*, 20 % propylene glycol in chlordiazipoxide injection. However, solvents can increase degradation in some drugs[6]. Decarboxylation is the elimination of CO_2 from a compound. This problem is most commonly encountered when parenteral solutions of sodium bicarbonate are autoclaved[7,8].

The absorption of CO_2 from the atmosphere by a pharmaceutical product is a more frequent occurrence then the loss of CO_2 by decarboxylation. Solutions of potassium hydroxide, sodium hydroxide, calcium hydroxide and lead subacetate become turbid due to the formation of insoluble carbonates.

To avoid this reaction they are stored in well-filled, well-closed containers. Similarly, I/V solution of soluble barbiturates face this problem and are distributed as sterile powders in ampoules and dissolved in water for injection just prior to use[9].

Ibuprofen is a propionic acid derivative. It contains methyl group in its structure. On heating in solution form, CO_2 evolves and ibuprofen (I) is converted to its degradation product (II) (Fig. 1)[2].

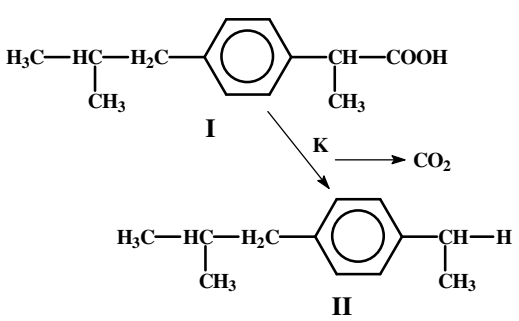

Fig. 1. Degradative products of ibuprofen

The present project was undertaken to assess the stability of ibuprofen in the prevailing physical factors like temperature and pH. The work involved the lower, normal and accelerated conditions of temperature and different pH. Present work may provide ample information to the manufacturer, physician, retail pharmacist and the patient regarding formulation storage.

EXPERIMENTAL

Ibuprofen (pure powder drug) was supplied by Schazoo Laboratories (Pvt.) Limited, Lahore, Pakistan. Potassium hydrogen phthalate was obtained from Sigma, USA. Potassium dihydrogen phosphate, sodium hodroxide (NaOH) and hydrochloric acid (HCI) were obtained from Merck, Dranstedt, Germany.

Preparation of buffers: Potassium hydrogen phthalate, potassium dihydrogen phosphate, sodium hydroxide and hydrochloric acid solutions, each of 0.2 M strength, were prepared by adding their weighed quantities (40.85 g, 40.85 g, 8.00 g and 7.29 g, respectively) to a 1000 mL measuring volumetric flask and distilled water was added in quantity sufficient to make up the volume. Buffers of pH 3-8 were also prepared as narrated in Table-1.

Method of analysis: The 0.18 g of ibuprofen was dissolved in 100 mL of 96 % ethanol and the resulting solution was titrated with 0.1 M sodium hydroxide using 0.2 mL of phenolphthalein solution as indicator until a red color is produced. Repeat the procedure without the substance being examined *i.e.*, ibuprofen. The difference between the titrations represents the amount of sodium hydroxide required. Each ml of 0.1 M sodium hydroxide is equivalent to 20.63 mg of ibuprofen.

Temperature exposure to ibuprofen: The 500 mg of ibuprofen was taken in 1000 mL volumetric flask and 0.1 M sodium hydroxide was added in small installments while shaking continuously. The volume was made up to mark after dissolution of solute and resultant strength of solution was approximately 0.05 % w/v. Fresh solution was dispensed immediately in 24 dark volumetric flasks each measuring 25 mL. Filled flasks were divided into six groups (designated as 1st, 2nd, 3rd, 4th, 5th and 6th group), each containing four flasks. The 1st, 2nd , 3rd , 4th, 5th and 6th group flasks were maintained at respective temperatures of 20, 30, 37, 40, 50 and 60 ºC[11].

Remaining solution was immediately subjected to spectrophotometeric studies, where absorbance was measured at two separate wavelengths (272 and 258 nm) and the readings were regarded as 0 time measurement. One flask was selected from each group after every 12 h interval (*i.e.*, at 12, 24, 36 and 48 h), volume was made up to the mark by adding more distilled water to compensate water loss due to evaporation and subsequently subjected to spectrophotometeric measurement. The above experiment was repeated four times to assure reproducibility[10].

pH variation and ibuprofen: The 500 mg of ibuprofen was taken in 1000 mL volumetric flask and 0.1 M sodium hydroxide was added in small installments while shaking continuously. The volume was made up to the mark after dissolution of the solute and resultant strength of the solution was approximately 0.05 % w/v. The 10 mL of the above solution was taken in 1000 mL volumetric flask and added further quantities of buffer solution of pH 3 to make up the volume. Fresh solution was dispensed immediately in 16 volumetric flasks each measuring 25 mL and the filled flasks were maintained at 20 ºC in refrigerator. Remaining solution was immediately subjected to spectrophotometeric studies, where absorbance was measured at two separate wavelengths (272 and 258 nm) using UV/VIS spectrophotometer[11], 1601 Shimadzu, Japan and the readings were regarded as 0 time measurement. Four flasks were selected after every 12 h intervals (*i.e.*, at 12, 24, 36 and 48 h), volume was made up to the mark by adding more buffer to compensate water loss due to evaporation and subjected to spectrophotometeric measurements. The above mentioned procedures were repeated at 30, 37, 40, 50 and 60 ºC. Each experiment was repeated four times to assure reproducibility.

RESULTS AND DISCUSSION

It has been the practice to assess stability of a product by placing it in certain storage conditions. These tests involve the

TABLE-1
PREPARATION OF BUFFERS WITH DIFFERENT pH

Contents	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8
0.2 M potassium hydrogen phthalate (mL)	250	250	250	–	–	–
0.2 M potassium dihydrogen phosphate (mL)	–	–	–	250	250	250
0.2 M hydrochloric acid (mL)	111.5	0.5	–	–	–	–
0.2 M sodium hydroxide (mL)	–	–	113.5	28	145.5	230.5
Final volume with distilled water (mL)	1000	1000	1000	1000	1000	1000

examining of quality and potency at suitable time intervals for a period corresponding to the normal time that the product is likely to remain in stock or in use. Since this period may be as long as 2 years, a storage test of this nature is time-consuming and expensive. Therefore, it becomes essential to seek methods that are helpful for rapid prediction of long term stability of medicinal agents[12]. It is now possible to identify the most stable and suitable pharmaceutical formulation without resorting to the lengthy and conventional storage testing procedures. The life of pharmaceutical products can be predicted by a accelerating the decomposition process and extrapolating the results to normal storage conditions[5].

When chemical stability of a medicinal agent is to be assessed, it is essential that the used assay should be sufficiently specific to distinguish between the drug and its decomposition product(s). Identification of the decomposition product(s) is a more sensitive approach than assaying for the intact drug. However, this may be time-consuming when there are several pathways of decomposition[3].

The expiration date for a drug in its solution is conventionally based on the time ($t_{10\,\%}$) during which formulation maintains 90 % of its labeled concentration. Using $t_{10\,\%}$ convention, solution would expire if 10 % of drug degrades during storage[4]. All degradative reactions were assumed to run under pseudo-first-order conditions, which followed first-order kinetics[1]. The kinetic parameters describing degradation of active ingredients were determined by taking ratio of absorbance at two different wavelengths (A_1/A_2 at wavelengths λ_1 and λ_2, respectively). The absorbance ratio of the compounds under study was recorded as a function of time and data were plotted as first order reaction at constant pH according to the following scheme (Beer-Lambert's Law)[7]:

$$A = \log \frac{1}{10} = \in lC$$

where A is absorbance of the solution, $\in$ is molar extinction coefficient, l is cell path length and C is the concentration of the active ingredient.

At wavelength λ_1, $A_1 = \in_1 lC$

At wavelength λ_2, $A_2 = \in_2 lC$

Therefore, $A_1/A_2 = \in_1 lC/\in_2 lC = \in_1/\in_2 = C$ (constant).

Actually, the ratio between absorbance of a solution at two wavelengths represents the ratio between molar extinction co-efficient of that particular compound, independent of original concentration. Any chemical change in active ingredient may cause alteration in spectrophotometeric behavior, resulting in modification of extinction coefficient as well as the absorbance ratio[7].

The well established first-order rate equation ($dc/dt = -KC$) can be modified by substituting C with absorbance ratio and the resulting form is $d(A_1/A_2)/dt = -K[A_1/A_2]$. On integration, this is changed to $\log (A_1/A_2)/t = -K/2.303 \times t + \log (A_1/A_2)0$. Where, $(A_1/A_2)/t$ is absorbance ratio at any time "t" and $(A_1/A_2)0$ is the initial absorbance ratio[7].

The linear equation plots gave a slope of -K/2.303 from which the first order rate constant (K) and $t_{10\,\%}$ (0.105/K) were determined. Energy of activation (E_a) is the amount of energy required by molecules to participate in chemical reactions. It can be calculated by Arrhenius equation[7]:

$$K = Ae^{-Ea/Rt}$$

where A is constant, which is termed as the frequency factor, R is gas constant and T is absolute temperature. The logarithmic form of the above equation can be written as:

$$\log K = \log A - \frac{E_a}{2.303R} \times \frac{1}{T}$$

The common logarithms of reaction velocity constant (K) for various temperatures at a particular pH plotted against the reciprocals of the absolute temperatures (1/T), yields a straight line whose slope is $E_a/2.303$ R. The activation energy in Kcal/mol can be obtained by multiplying the slope with a factor ($2.303 \times 1.987/1000 = 4.57 \times 10^{-3}$).

Ibuprofen has been known to undergo remarkable degradation in aqueous solutions. Prediction of stability of ibuprofen in solution is based on kinetic data (pH and temperature) constants, pertaining to each experimental condition. Thus, stability investigation have been carried out in this study at different temperature (20, 30, 37, 40, 50 and 60 ºC) and pH (3, 4, 5, 6, 7 and 8) conditions.

Effect of temperature: There exists temperature dependence of ibuprofen degradation at pH 3, 4, 5, 6, 7 and 8 in the temperature range of 20-60 ºC (Table-2). According to Arrhenius equation, Fig. 2 shows the linear relationship between the logarithms of K and I/T. Form the slopes of these lines, activation energies (E_a) were calculated to be 19.17, 20.60, 21.81, 24.22, 22.45 and 21.16 Kcal/mol at respective pH values of 3, 4, 5, 6, 7 and 8.

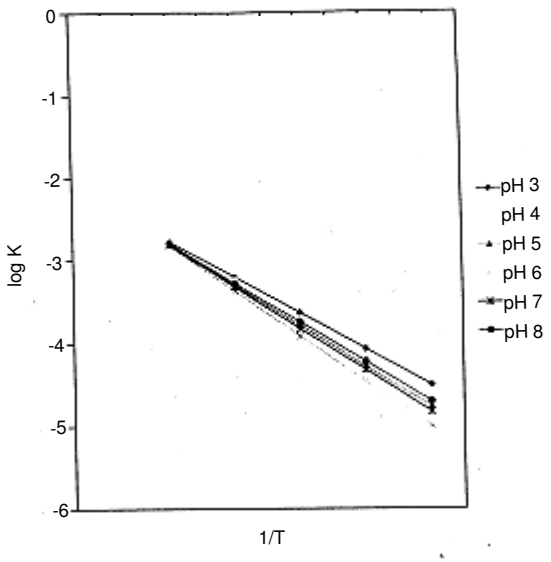

Fig. 2. log K of ibuprofen *versus* temperature (1/T) at various pH values

TABLE-2
LOG OF OBSERVED PSEUDO-FIRST-ORDER RATE CONSTANT (K) OF IBUPROFEN DEGRADATION AT DIFFERENT TEMPERATURES AT pH 3

Temperature (ºC)	Rate constant (K)	log K
20	3.16×10^{-5}	-4.50
30	8.36×10^{-5}	-4.07
37	1.58×10^{-4}	-3.80
40	2.26×10^{-4}	-3.64
50	6.13×10^{-4}	-3.21
60	1.65×10^{-3}	-2.78

TABLE-3
OBSERVED PSEUDO-FIRST-ORDER RATE CONSTANTS (K/h^{-1}) OF IBUPROFEN DEGRADATION AT DIFFERENT TEMPERATURES AND pH

pH	Temperature (ºC)					
	20	30	37	40	50	60
3	3.16×10^{-5}	8.36×10^{-5}	1.58×10^{-4}	2.26×10^{-4}	6.13×10^{-4}	1.65×10^{-3}
4	2.31×10^{-5}	6.65×10^{-5}	1.39×10^{-4}	1.92×10^{-4}	5.56×10^{-4}	1.62×10^{-3}
5	1.71×10^{-5}	5.24×10^{-5}	1.21×10^{-4}	1.59×10^{-4}	4.85×10^{-4}	1.54×10^{-3}
6	9.85×10^{-6}	3.39×10^{-5}	8.85×10^{-5}	1.18×10^{-4}	4.11×10^{-4}	1.46×10^{-3}
7	1.45×10^{-5}	4.68×10^{-5}	1.14×10^{-4}	1.45×10^{-4}	4.59×10^{-4}	1.49×10^{-3}
8	1.98×10^{-5}	5.96×10^{-5}	1.43×10^{-4}	1.76×10^{-4}	5.03×10^{-4}	1.56×10^{-3}

Effect of time and pH: At particular pH, plots of logarithm of absorbance ratio of ibuprofen *versus* time at different temperatures gave straight lines according to pseudo-first-order kinetics (Fig. 3). From the slopes of these regression lines, apparent first-order rate constants (K) were calculated (Table-3). In Fig. 4, logarithms of these rate constants are plotted *versus* pH. Its pH-rate profile shows specific base catalysis. In Table-4, same pH-rate profile is presented which may facilitate its use in the prediction of practical instability problems. The logarithm of $t_{10\,\%}$ which means the time needed for 10 % degradation of drug is here plotted as the ordinate. The pH rate profile indicates maximum stability at pH 6 and temperature 20 ºC corresponding to a $t_{10\,\%}$ *ca.* 444 days (Table-4).

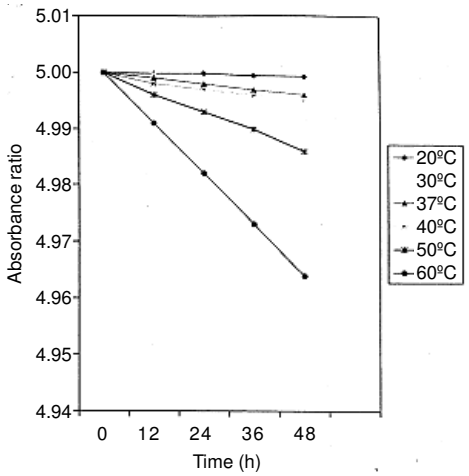

Fig. 3. Absorbance ratio of ibuprofen *versus* time (h)

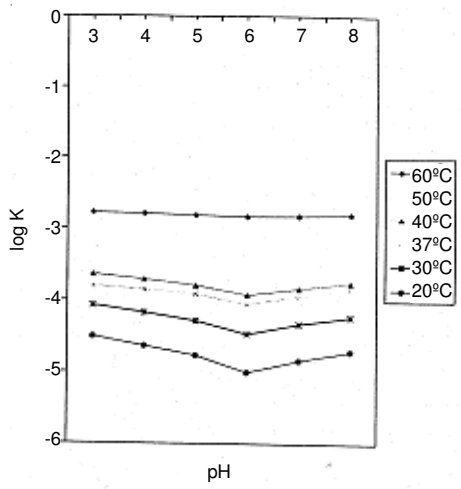

Fig. 4. log K of ibuprofen *versus* different pH at various temperatures

TABLE-4
CALCULATED $t_{10\,\%}$ (SHELF-LIFE = 0.105/K) OF IBUPROFEN DEGRADATION AT DIFFERENT TEMPERATURES AND pH

pH	Temperature (ºC)					
	20	30	37	40	50	60
3	3322.78	1255.98	664.55	464.60	171.28	63.63
4	4545.45	1578-94	755.39	546.87	188.84	64.81
5	6140.35	2003.81	867.76	660.37	216.49	68.18
6	10659.89	3097.34	1186.44	889.83	255.47	71.91
7	7241.37	2243.58	921.05	724.13	228.75	70.46
8	5303.3	1761.74	734.26	734-26	208-74	67.30

Conclusion

From the stability of ibuprofen, chemical degradation of ibuprofen was found to be increased with the increase in temperature and hence they are required to be maintained at lower temperature, if they are available in solution. At studied temperatures, ibuprofen solutions showed some chemical instability. It was found that higher temperature have an adverse effect on the stability of ibuprofen. This indicates that higher temperature enhances the rate of degradation of ibuprofen. In liquid state, decomposition of ibuprofen has been shown to follow first-order kinetics at low concentration. Ibuprofen is most stable at pH range 5, 6 and 7. So, if the reconstituted solutions are maintained at these pH as well the temperature below 30 ºC, their prolonged effective utility periods may be expected. In liquid preparations, pH should be adjusted to 6 for maximum stability. To prevent degradation of ibuprofen, water should be prevented from coming in contact with solid ibuprofen. Temperature also plays an important role in the rates of degradation in the solid and solution states. Because of the limited half lives in solutions and suspensions, solid dosage forms are the only formulations stable over extended periods of time. Buffering at the pH where degradation rate is minimum, is an alternative method for enhancing the stability of liquid formulations. Ibuprofen is most unstable in aqueous solution and at higher temperature. Its half-life can however, be prolonged by appropriate choice of vehicle, besides control of other parameters such as pH, stabilizer and temperature. It should be stored at cool and dry place.

REFERENCES

1. W.J. Pugh, In ed.: M.E. Aulton, Kinetics of Product Stability, Aultons´s Pharmaceutics. The Design and Manufacture of the Medicines, Churchil Livingstone Elsevier, London, UK, edn. 3 (2007).
2. L.S. Goodman and A. Gilman, The Pharmacological Basis of Therapeutics, MacMillan Publishing Co., New York, USA, Vol. 1, edn. 4, p. 3144 (1970).

3. S.J. Prince and H.C. Ansel, Pharmaceutical Calculations: The Pharmacist's Handbook. Baltimore: Lippincott Williams & Wilkins, New York, USA, edn. 1 (2004).
4. E. Gleditsch and P.J. Waaler, *Int. J. Pharm*., **212**, 275 (2001).
5. W. Zhao, L. Cui, C. Zhou, J. Lin and X. Zhan, *Dier Junyi Daxue Xuebao*, **24**, 210 (2003).
6. K.C. Waterman, R.C. Adami, K.M. Alsante, J. Hong, M.S. Landis, F. Lombardo and C.J. Roberts, *Pharm. Dev. Technol*., **7**, 1 (2002).
7. S. Vyazovkin, Concept of Variable Activation Energy (Why it Just Can't Stay Put), Proc. NATAS Ann. Conf. Thermal Anal. Appl., Vol. 27, p. 55 (1999).
8. P. Simon, M. Veverka and J. Okuliar, *Int. J. Pharm*., **270**, 21 (2004).
9. V. Morillon, F. Debeaufort, G. Blond and A. Voilley, *J. Membr. Sci*., **168**, 223 (2000).
10. M.N. Nassar, V.N. Nesarikar, R. Lozano, W.L. Parker, Y. Huang, V. Palaniswamy, W. Xu and N. Khaselev, *Pharm. Dev. Technol*., **9**, 189 (2004).
11. USP30-NF25, The Official Compendium of Standards. The United States Pharmacopoeial Convention (2007).
12. T.R. Darrington and J. Jiao, *J. Pharm. Sci*., **93**, 838 (2004).