USE OF KINETIC METHODS IN STORAGE STABILITY STUDIES ON DRUGS AND PHARMACEUTICALS

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Utility of kinetic methods for predicting shelf life of drugs and pharmaceuticals and its importance in our country with varying conditions of climate ranging from hot and humid to extreme cold and dry have been brought out in this review.

As the troops operate under varying conditions of climate, ranging from hot and humid to extreme cold and dry the shelf life of pharmaceutical preparations intended for storage at room temperature is not always applicable under the field conditions. Frequently DGAFMS requires information at a very short notice on the shelf life of certain drugs before purchasing them, or taking a decision on accepting indigenously developed substitute for the existing imported item, or introducing a new item in the PVMS list.

In the present report the methods based on kinetic treatment of experimental data obtained from observations spread over from few weeks to few months have been reviewed, mentioning in detail where these have been utilized to predict the shelf life of drugs and pharmaceuticals. No attempt has been made to enumerate all the references available; they have been selected to demonstrate the wide applicability and interest of a large number of research workers throughout the world.

FACTORS AFFECTING STABILITY

A great variety of drugs and pharmaceutical preparations are available in various forms depending upon their physical state, route of administration and stability under normal conditions of room temperature. They are available as solids (powders, tablets, capsules) or liquids such as elixirs, mixtures, parenteral solutions, biological fluids, etc. A particular preparation is dispensed depending upon the route of administration, which itself depends on its efficacy, e.g. a drug may not necessarily be as effective if administered orally but on being injected via a suitable route may be miraculously effective. The conditions of storage are specified by the manufacturers and are covered by the various schedules of the Drugs and Cosmetics Act. In substance, any drug is recommended to be stored in dry cool place protected from direct sunlight. Due to its chemical characteristics a drug may lose its potency if it is not stored properly as advised. Drugs and pharmaceuticals have their shelf life for varying periods, from 14 days for human whole blood, BCG vaccine, etc. to 3 years for parenteral morphine preparations. A drug may not be dispensed as liquid, for in solution deterioration can be rapid, as in the case of ascorbic acid, but stabilizing effect of other chemical substances is often useful.

Drugs are affected by heat, *p*H changes, direct sunlight, humidity, other chemicals, metals, presence of other drugs as in the mixture of a pharmaceutical preparation, presence of fillers as in tablets, preservatives in various liquid preparations, ultrasonic waves, loss of colouring dye on storage or exposure to light.

Effect of various parameters on the stability of a drug preparation has been brought out in individual cases.

HISTORY OF DEVELOPMENT OF KINETIC METHOD FOR STORAGE STABILITY

The conventional method for determining the shelf life of pharmaceutical preparations is to study their stability by actually storing them at desired temperatures or humidity, etc., for the required period of time, usually one to three years. The obvious disadvantages of such a method are the loss of time and

cost. Another method that has been suggested is to study the stability of preparations stored in ovens at high temperatures and correlating this data with those obtained by actual storage in field conditions. Such correlations have often been intuitive being based on an insufficient data or on empirical relations found in supposedly similar preparations[1].

Prediction of shelf life from accelerated studies has been placed on a quantitative basis by the application of fundamental physicochemical principles[1-4]. A rationale of predicting stability of pharmaceutical preparations using chemical kinetics has been presented by Ho and Goeman[5] using hydrocortisone sodium succinate as an example. Prediction of pharmaceutical stability of parenteral solutions was done by Ho[6], Carstensen and Su[7] who found that for preparations having less than 10% degradation, zero order kinetics was applicable to accelerated test data and by extrapolating it to room temperature, the prediction of shelf life was possible. Lin[8] proved the efficacy of the short term data for prediction of shelf life by comparing it with long term storage data[9-19]. By the use of a modified form of the Arrhenius equation, and simultaneous determination of activation energy and rate constant dependence on temperature prediction of stability can be determined from the values of the concentration as shown by Rogers[20] and applied to first order decomposition of sugar and riboflavin; see also Cole and Leadbeater[21,22]. The Arrhenius equation can be modified suitably to formulate non isothermal technique of accelerated testing[23-27].

PREDICTION FOR A NEW PRODUCT DURING DEVELOPMENT

By making use of the accelerated test data, the physical stability of a new pharmaceutical product could be predicted[28-32]. Various parameters such as biological contamination, container height, age, temperature, moisture and oxidation, were taken into consideration for studying stability of pharmaceuticals[18] and for emulsions, suspensions and solids[33-35]. Lintner *et al*[36] have shown how the data could be computerized for predicting shelf life of a new product.

METHODOLOGY

Briefly the method is based on the observation that a suitable metameter of the potency (usually the potency itself or its logarithm) falls off, at any chosen temperature linearly with time, and the different rates of degradation of the potency (or its metameter) obtained at different temperatures are related to those temperatures in accordance with Arrhenius equation[1,2].

$$k = \mathrm{A}.e^{-(\triangle Ha/RT)}$$

$$\text{or, } \log k = -(\triangle Ha/2{\cdot}303R)\,(1/T) + \text{Constant}$$

where k is the reaction rate constant, T is temperature in absolute units, R is gas constant (1·987 kcal./mole), $\triangle Ha$ is heat of activation, and A is a constant depending on the entropy of the reaction and/or collision factors.

These relationships can be used to calculate the degradation rate at the required storage temperature from the experimentally determined degradation rates at elevated temperatures. Thus the shelf life may be predicted at the required storage temperatures with the aid of determined degradation rates.

Alternately, the logarithmic form of the Arrhenius equation shows that any value proportional to the specific rate (k) would permit slope evaluation of a plot between $\log k$ versus $1/T$, and also evaluation of the heat of activation. If such a relation among several values determined at elevated temperatures and the absolute temperature is reasonably linear, it is possible to predict shelf life at any desired temperature. In stability prediction studies, it is not necessary to elucidate the mechanism of the reaction and it is only necessary to determine reaction rates, etc. The graphical procedure for predicting thermal stability for a particular component in a pharmaceutical preparation as enunciated by Garrett and Carper[1] is based on the reproducibility of the degradation rates at the various elevated temperatures and extrapolation of the Arrhenius plot to obtain the rate constants at the desired lower shelf temperatures. The validity of this method of predicting stability was demonstrated by the agreement of classical assay values from long term method with the predicted values[3]. A graphical method may also be used to evaluate the order of the

reaction by linearity of a plot of concentration or its logarithm with time, the former giving pseudo zero order reaction and the latter giving pseudo first order reaction[3].

In Rogers' method[20] Arrhenius equation was modified to evaluate the rate constant and energy of activation at room temperature from values of the concentration of the reactant. The experiment itself is so designed that the temperature of the reacting system is raised in accordance with a pre-determined programme; the temperature of the reactants is allowed to increase from the initial temperature, T_o, to the final temperature, T_t both in absolute units, t being time period, say, 6 hours, in accordance with the equation

$$1/T_0 - 1/T_t = 2{\cdot}303b \log (1 + t)$$

where b is a constant of proportionality which can be chosen as desired. The whole experiment is finished in a period of 6-7 hr. The method was applied by Rogers to first order decomposition of riboflavin and inversion of sucrose[20], and was critically assessed by Cole and Leadbeater for a number of first order and second order reactions such as inversion of sucrose, hydrolysis of ethylbenzoate, cholinesterase activity of horse serum[21,22]. Here no preliminary experiment is necessary to determine the optimum temperatures for the method, the linearity of the plots confirm that correct order for the reaction has been assumed, and deviations from the linearity may therefore be looked into [23,25-27].

The statistical method may be utilized as an alternative to a graphical method. In the case of imprecise analytical methods such as microbiological assay[37], an experimental design based on statistical method[13,31,37-43] was presented. Lordi and Scott[44] constructed nomographic charts to facilitate the analysis of stability data obtained at elevated temperatures. The effects of errors on predictions made by using the nomogram were described, with particular reference to those arising from faulty assays, timing and temperature control. Carstensen *et al*[45] on the other hand applied Hammett graphs for predicting the best substituents for allyl barbituric acid derivatives to get optimal stability.

The quantitative physico-chemical relationships permit the rates of degradation to be calculated by substitution of the appropriate values for temperature, concentration, time, *p*H, light intensity, etc. A knowledge of mechanism of degradative process is necessary to work out stability pattern in the presence of buffers, vehicles and excipients.

Other parameters followed for the predicting shelf life include solubility analysis[46], heats of activation[39], optimum[40,47] *p*H, melting point depression for pharmaceutical powders[48], refractometry[49], light reflectance for tablets[50], conductivity measurements[51], polarography[52], microdiffusional study in solid state[53], stirred flow techniques for developing mathematical equations for complex kinetic runs[54] and N. M. R. analysis[55].

In addition to usual stability studies, the formulations have also been studied for loss of colour of dyes[56-59], the effect of fillers on the active ingredients[60-61] stability of preservatives like cholorobutanol, in parenteral solutions[62] and effect of vehicle[63].

STABILITY STUDIES ON VITAMINS AND COMPLEX VITAMIN MIXTURES

General areas of vitamin stability were reviewed by Parrak[64]; see also[65]. Vitamins are of varied chemical nature, and degrade by photolytic, oxidative and solvolytic mechanisms.

Tardiff[9] used elevated temperature storage tests and a graphical method to determine thermal degradation rates of vitamin A, thiamine and ascorbic acid in three multi-vitamin formulations. The role of moisture was brought out in this study; if it was maintained below 1% the pseudo first order rate was reduced considerably for the vitamins separately. Assay of samples stored at room temperature for 15-38 months confirmed accelerated storage data[66-68]. Accelerated test method was utilized to estimate the shelf life of vitamins B_6, B_{12}, and K_3 by Ebel *et al*[69]; zero order decomposition for vitamin A in organic dispersion, stabilized with α—tocopherol acetate was found independent of vitamin A concentration. For vitamin B_1, the decomposition was of first order in aqueous solution, and shelf life of one and three years was predicted from specific rate data, for the two vitamins[70-75].

Ascorbic Acid

Kinetic method was employed to study the stability of ascorbic acid in a liquid multivitamin emulsion by Tingstad *et al*[76]. The vitamin was found to degrade initially by a zero order reaction, but other evidences showed the rate to be nearly one. Thus predictions made by making use of the Arrhenius plot were correct[77-79]. Kinetics of copperion catalyzed auto-oxidation of ascorbic acid-3-phosphate[86] have been reported ; *see also*[78-98]. Investigations on kinetics of ascorbic acid have been reviewed by Hutterrauch[99].

Vitamin A

This vitamin degrades by oxidation and elimination in hydroxylated solvents. Effect of *dl* - α - tocopherol on the stability of vitamin A in aqueous solution was investigated by Klotz *et al*[100—101]. An hydrovitamin A in preparations, was found to be more stable than the vitamin A itself [102]. Solid state stability of crystalline vitamin A derivatives was studied by Guillory and Higuchi[102]; Carstensen[104] found that the logarithm of pseudo first order rate was related to water vapour pressure in the case of vitamin A in tablet; see also[105-108].

Thiamine

The main route of destruction is hydrolytic and is catalyzed by buffer salts. Kinetics of hydrolysis of thiamine was investigated by Windhauser and Higuchi[109]. The hydrolysis followed a first order reaction, and was influenced by general base catalysis[110-114]. Stability of the vitamin was studied in presence of dipyrone[115] and in presence of some antibiotics in capsules by accelerated stability test methods[116-120].

Riboflavin

Base catalyzed decomposition of riboflavin was found by Guttman[121] to be of first order at constant hydroxyl ion concentration; the kinetic parameters in presence of caffeine, the latter complexing with the substrate and hence enhancing riboflavin stability, were also evaluated, see also[122,123].

Cyanocobalamin

General acid-base catalysis has been demonstrated for this vitamin. The stability of cyanocobalamin at different times and *p*H was studied by Loy *et al*.[124], Marcus and Stanley[125] and Sen[126]. Predictions of stability were made utilizing Arrhenius parameters applied to the apparent first order degradation of the vitamin in liquid multivitamin preparations[127-130].

Other Vitamins

Among studies on other vitamins, photodegradation of vitamin K_1,[131] hydrolysis of niacinamide[132] and kinetic study of pyridoxine hydrochloride in presence of some antibiotics[133] may be mentioned. Tetracycline and chlortetracycline hydrochloride had stabilizing and oxytetracycline and chloramphenicol, had deleterious effects on pyridoxine. Stability studies on vitamin D have also been reported[134-136].

STABILITY STUDIES ON ANTIBIOTICS

Stability studies and predictions of shelf life have been reported for many of the antibiotics, both natural and semi-synthetic. Most of the antibiotics are thermolabile and are effected by *p*H changes and presence of metallic ions, etc.

Penicillins

Among the early studies reference may be made to the work of Brodersen[137] who studied the kinetics of penicillin degradation in various *p*H ranges, the maximum stability being at about *p*H 7. Kinetics of degradation of penicillin to penicillenic acid was studied by Krejci [138]. In another investigation Swintosky *et al*. [139] found the degradation of saturated solution of procaine penicillin to follow a zero order reaction.

Mechanism of catalysis of penicillin degradation in presence of catechol[140], catecholamines[141] and metallic ions has been investigated[142-148], Kinetics of degradation of 6-aminopenicillanic acid was reported by Dennen[149]; in another study Rasmussen[150] evaluated kinetic parameters of interaction of penicillinase with penicillins. Similar work led to the theory explaining the penicillin allergy[151-152].

Semi-Synthetic Penicillins

Degradation kinetics of phenethicillin and methicillin were evaluated by Schwartz *et al.*[153], the rates being of first order[154]; for aqueous solution of methicillin, the optimum *p*H was found to be 7·44[155]; *see also*[141]. Kinetics and mechanism of degradation of ampicillin[156] and that of oxacillin in aqueous solution between the *p*H range 1·44-10·93 were studied[1157-161]. In solid state stearic acid inactivated sodium dicloxacillin and sodium oxacillin in tablets; the results were confirmed by accelerated tests on combination[162]. Decomposition of hetacillin leads to a rapid formation of a substance with a characteristic absorption at 317 nm and ampicillin gives a polymerized product[163-165]. Recently Hem *et al*[166] found sucrose to form 1 : 1 molar complex with various penicillins, the rate being 5-6 times greater than the uncomplexed penicillin; however, the complexation does not change the degradation pathway.

Tetracyclines

The C_4 epimerization of tetracycline[168-171] acid base catalyzed and *p*H dependent. Stability of tetracycline and its derivatives was studied by Zelinka *et al.*[167] as early as 1961, kinetics of epimerization by n.m.r. was studied by Schlecht and Frank[55]; see also [168-172].

Chloramphenicol

Major route of degradation in solution is by substitution giving chloride ions. Microbiological kinetics of chloramphenicol analogues was quantified and shelf life predicted [173,174]. In a recent study on effect of *p*H on degradation the reaction was found to follow two paths, viz., oxidation to *p*—nitrobenzaldehyde, and reduction to arylamine[175-179].

Stability Studies on other Antibiotics

Stability kinetics of cycloheximide in pharmaceutically useful *p*H range and temperature[180], and degradation of lincomycin[181] in acid medium were reported; see also[182,183]. Garrett *et al.*[184] studied the kinetics of effect of erythromycin on lincomycin. Seydel[185] found the acid catalyzed hydrolysis of rifampicin in 0·1 N HCl to be pseudo first order reaction. The conversion of cephaloglycine esters to cephaloglycine at *p*H 7·45 and 37° was studied by Binderup[186]. Oesterling[183] studied the kinetics and mechanism of aqueous solution degradation of clindamycin and its derivatives in buffered solution. Stability studies on streptomycin[187-189], nystatin[190-193], and gramacidin[194] have been reported. Stability studies of other antibiotics, have also been reported by various authors[195-206].

STABILITY KINETICS OF MISCELLANEOUS DRUGS

Salicylic Acid Derivatives

Much work has been reported on the stability of aspirin and other salicylic acid derivatives e.g., *p*—aminosalicylic acid. Fundamental kinetics of aspirin and its solvolysis to salicylic acid was completely studied by Edwards[207]; specific acid base catalysis and a *p*H independent solvolysis was shown; the rate constants of hydrogen ion and hydroxyl ion catalyzed reactions varied with the nature of the charge on the molecule. Garrett[208,209] constructed log *k*-*p*H profile for the solvolysis of acetyl salicylic acids. Effect of various talcs on acetyl salicylic acid stability was studied by accelerated temperature and humidity[210-217].

Arrhenius plot for aspirin decomposition in polyethylene glycols at 4,27,45 and 60°C, was evaluated by fluorescence measurements[43, 217-223]. Solid state decomposition of benzoic acid derivatives has recently been reported[224].

Degradation of PAS acid takes place via decarboxylation the kinetics is *p*H dependent, by apparent attack of hydroxide ion on the anion[225-228], the product is m-aminophenol, the oxidation products giving rise to a brown coloration. Decomposition of PAS in solution was found to be of first order while that of sodium PAS was of zero order[229-232].

Barbituric Acid Derivatives

The barbiturates are attacked by hydroxyl ions, the ring being destroyed[233-234]. Prediction of stability of phenobarbital sodium in water, applying the Arrhenius equation to apparent first order rate constants obtained at higher temperatures[235], and of allyl barbituric acids was shown[236-243].

Epinephrine

The racemisation of epinephrine in acidic solution is specific hydrogen ion catalyzed. Degradation kinetics of epinephrine in solution by molecular oxygen[244], and its stabilization by chelation of catechol nucleus with boric acid[245] and glutimide[246] were studied. For racemization of the drug in acidic solutions the log *k*—*p*H profile was found to be linear[247] and the data could be used for prediction upto *p*H 4; *see also*[248-255]. Stability of this drug in parenteral solutions[256] and in tablets containing aspirin[257] have also been reported.

Amines and Esters Containing Amino Group

Solvolysis of procaine leads to the formation of *p*-aminobenzoic acid and diethyl aminoethanol[258-259] and seems to depend on the hydroxyl ion concentration, in the various *p*H ranges. Accelerated stability predictions on this drug were conducted by Arancibia *et al.*[260], using Arrhenius relation; *see also*[261-270].

Rates of hydrolysis of benzocaine in cetrimide solutions[271] and of procaine under different *p*H and temperature[272] have been calculated.

Among studies on other amines mentioned may be made of work on α-chymotrypsin[273], chloramine-*T* in acid solution [274], chloropyramine[274], methionine[275]; *see also*[276-279].

Kinetics of solvolysis of urea by Welles[280] in concentrated aqueous solution at 25, 35 and 45°C was followed by conductometry in another series of experiments. Garrett[281] constructed log *k*—*p*H profile and Arrhenius parameters by polarographic and colorimetric assays, solvolysis was catalyzed by hydrogen ion, hydroxyl ion, solvent and buffer; the maximum stability was demonstrated at a *p*H of 4·0.

Similarly stability of phenyl butazone[278,282,283] in suppository bases and aminophenazone[279,284-286] in aqueous solution has been studied; for the former it was found to be dependent on the vehicle used.

Amides and Imides, etc.

Hydrolysis of various amides in both acid and base have been reported, acid hydrolysis having higher activation energy than alkaline hydrolysis[287,288]. For *N*-acetyl *p*-aminophenyl, the overall rate was found to be due to the catalytic effects of both hydrogen and hydroxyl ions[289]. Degradation kinetics of glutethimide and sodium sulphacetimide[290-293] were evaluated. Hall[294] studied the possible reactions of amines buffered with carboxylic acids; mechanism of degradation of succinamide and other amides and esters were studied[290,292,295,295,296]. In another work stability of cardenolide was investigated by Lutumski[291]. Garrett *et al.*[293] have studied the stability of N-butyl formamide to acid and enzymic hydrolysis. Recently, Rattie *et al.*[297] investigated the kinetics of hydrolysis of acetaminophen precursors in aqueous buffers; stability of angiotensinamide[298], phenoxy-benzamine[299] and tolbutamide[300] was also reported.

Among the aldoximes of the nitrogen containing compounds work of Ellin *et al.*[301] and Bernasconi[302] may be mentioned. Chin *et al.*[303] evaluated comparative hydrolytic rates of thiouracils in acidic and alkaline medium. Recently Garrett and Tsau[304] investigated the solvolysis of cytodine and cytosine to uridine and uracil, respectively at all *p*H values. Kinetics of sydnonimine derivatives[305], azetidinones[306], sydnones[307] and imidazalidinones[308], have been reported.

Alkaloids and Similar Compounds

Solvolysis of compounds such as scopolamine methylbromide, atropine methylbromide, acetylcholine chloride, etc., catalysed by hydroxyl ion were studied by Moffet and Garrett[309] in alcohol water system at 25°C; *see also*[310-315]. Accelerated stability study of atropine sulphate over wide range of *p*H values by Struhar *et al.*[316] and at elevated temperatures by Simon *et al.*[317] were done ; *see also*[318,319]. Hydrolysis of pilocarpine solution was found to be catalysed both by hydrogen and hydroxyl ions[320-322].

In such cases as atropine where the reaction is different in acidic and alkaline medium, the rate constant for the hydroxyl ion is greater when the attack is on the oppositely charged species, i.e., protonated atropine than when the attack is on the neutral species i.e., unprotonated atropine.

Kinetic parameters for morphine[323,324] apomorphine[325], diamorphine[326] have been reported. Kinetics of effect of 10 metal ions on second order auto-oxidation of aqueous papavarine hydrochloride was studied, the most prominent being for copper bivalent ions[327,328]. Kinetics of dihydroergotamine-methane-suphonate at a wide range of *p*H[329] and quinidine sulphate decomposition in aqueous solution[330] have been reported. Stability of tecamine [331] and taurinophenetidine[332] was recently studied; *see also*[333,334].

Amongst other alkaloids mention may be made of study on adiphenine and cycloadiphenine[335] and colchicine and related tropolone methyl derivatives[336,337], decomposition of meperidine hydrochloride [338] and idoxyridine[339] hydrolysis of khellin[340], ergonovine maleate[341] and various quaternary nitrogen compounds[342,343].

Stability kinetics for solutions of aqueous succinyl choline chloride by Suzuki[344] and recently for acetylcholinesterase inhibition by atropine[345] and for acetylcholines in acidic and basic solution in presence of borate buffer were reported[346]. Recently photoreaction of reserpine in parenteral solution[347] and in stability of atropine and chloramphenicol in aqueous solution have been reported; *see also*[348].

Chlorpromazine and Phenothiazines, etc.

Kinetics of photodegradation of chlorpromazine with *p*H variation was found to be of zero order by Felmeister and Discher[349]. In a study by Huang and Sands[350], U.V. light catalyzed degradation under anaerobic conditions was found to be different from aerobic conditions; *see also*[351]. Kinetic parameters were calculated for decomposition of chlorthiazide and its decomposition products and for isoniazid[352-360].

Effects of *p*H and light on the decomposition of several phenothiazines[361,362] and benzothiadiazines[363] have recently been studied. Among studies reported on the other azines, hydrolysis of 9-methyl isoalloxazine by Wadke *et al.*[364] and kinetics of decomposition of a piperazine derivative[365] and propionyethyl piperazine derivative[355] may be mentioned.

Sulfathiazole and Pyrazole Derivatives

In a study of Kostolowska *et al.*[366] colour change of aqueous solution of sodium sulphathiazole was found due to degradation; kinetics of polymorphic transformation of this compound was followed by calorimetry by Shamo *et al.*[367]. Stability and mechanism of a aminopyrazolone compound[368] degradation and alkaline stability of another pyrazolol were reported[369], the latter being followed spectrophotometrically; *see also*[370].

Hormones and Steroids

Kinetics of stability prediction has been attempted for many of the steroids and hormones; insulin stability was predicted by Krogh and Hemmingson[371] the degradation being apparent first order initially and half life, for example, in water at 30° was evaluated to be 2 years. Many of the steroids undergo photolytic, oxidative or solvolytic degradation.

For anterior pituitary growth hormone, the stability appears to be dependent on mode of preparation[372,373]. Rates of oxidative destruction and alkali saponification of some steroidal esters were calculated by Pesez *et al.*[374]. Study of factors influencing the stability of prednisolone in aqueous solution[375] and that of fluprednisolone acetate aqueous solution[376] by accelerated study were reported; subsequent experiments at ambient temperatures also confirmed the predicted stability. Recently the hydrolytic behaviour of corticosteroid derivatives was studied by Yamamoto *et al.*[377]; *see also*[378-382].

Enzymes

Recently acylation of co-enzyme A and *p*H rate profile for reaction of succinic anhydride with cysteine have been studied[383]. In another study programme for predicting degradation of lyophilized co-enzyme B_{12} was presented[384]. Kinetics of degradation of amylase in aqueous solution at three *p*H values[385] and of acetylcholinesterase inhibition by atropine [386] have been reported. In another study *p*H effect of trypsin catalysis of an ester was reported[387].

Acids and Esters

Shah[388] studied the reactions of cyclic acid anhydrides in aqueous solution to understand prediction of pathways of decomposition. Auto-oxidation of sorbic acid in citric acid was found to be accelerated by very low concentrations but inhibition by high concentrations of ferric and cupric ions. Stability kinetics studies on aminoethylesters of phenyl acetic acid[284,389-394], have been reported; *see also*[395,396]. First order base catalyzed addition reaction of diethyl phosphonate was followed spectrophotometrically by Hopkins[396]. Carstensen and Muna[397] have recently studied decomposition of benzoic acid derivatives in solid state. Acid catalyzed hydrolysis of sodium dodecyl sulphate and effect of 1-hexadecanol on the hydrolysis was reported by Barry and Shotton[398].

Sugars

Thermal degradation of glucose exhibited general acid base catalysis[399]; the kinetics of degradation in acid solution were also followed by the initial rate of formation of 5-hydroxymethylfurfural, the degradation product of glucose[400]. Accelerated storage tests on 5% glucose and glucose saline solution have been conducted in this laboratory by following the formation of 5-hydroxymethylfurfural and Arrhenius parameters were calculated; however, the high temperature data could not be used to predict storage at lower ambient temperature, and *p*H effect cannot be ruled out (Mitra and Chatterjee, unpublished work).

The specific rate and other data have been evaluated for the reversible reaction between glucuronoe lactone and glucuronic acid[401]. In mildly acidic solution, 2-deoxyribose degraded to give a chromophor- with a characteristic absorption[402,403] at 261 nm. Alkaline hydrolysis of sugar[404] and rate of inversiou of sucrose in aqueous solutions of strongly dissociated acids[405] have been described; *see also*[20,21]. Validity of theory and advantages of non isothermal stability method for prediction at any desired temperature for sucrose inversion was brought out[21,406]. In another study acid degradation of aldopentoses to furfural and then further degradation of furfural was found to be a first order reaction with respect to acid and pentose concentration[407]. Armstrong[408] has studied the first order kinetics of hydrolysis of monosterin in aqueous media, the reaction found to decrease with a decrease in the *p*H. Stability of reconstituted drugs and intravenous fluids[409] and that of dextran after prolonged storage[410] have been studied. Similar studies on catalyzed hydrolysis of glycosides[411] and mechanism of hydrolysis of cytosine arabinoside in aqueous buffer[412] were reported.

Miscellaneous Drugs

In this section various other drugs not covered earlier, have been reported. In a study benzoyl peroxide stability in pharmaceuticals[413] was attempted. For ecothiophate iodide two pathways for degradation depending on *p*H were found. Kinetics of 4-aminoethane sulphonyl-amino-antipyrine in different *p*H values[414], a sulphone derivative[415], stability of levamisole aqueous solution[416], and alcoholic fezatione solution have been presented.

Degradation of sodium bisulphite in dextrose solution was investigated by Schumacher and Hull[417]. Studies on hydrolysis of antioxidants such as paraben[418] and chlorobutanol[419] have been reported. The hydrolysis of latter was affected by surface active agents but not by polyethylene glycols. Similarly oxidation reactions of white lotion, paraffin and linoleic acid have been studied by Rhodes[420] and Guth *et al.*[421]. Effect of antioxidants on the stability of hydrated and anhydrous ointment bases was studied by Wisniewski and Golucki[422]. In another investigation stability study of certified dyes was reported by Goodhart *et al.*[423], the reaction being followed colorimetrically; stability of dyes with gelatin was reported in another paper by Valeiras[424].

Conclusions and Recommendations

Prediction of shelf life from accelerated studies has been placed on a quantitative basis by the application of fundamental physico-chemical principles[1-4]. A great volume of literature has accumulated showing

the efficacy of the kinetic method, the short term data being comparable with long period data[5-13]. The technique is useful for predicting the physical stability of a new pharmaceutical product during development[28-33]. The parameters could be fed into a computerized unit for still quicker prediction[36,425,426]. However, for a fairly moderate size manufacturing research unit, it should be possible to make use of the emperical procedure enunciated by Kennon[39]. In a country like ours with varying conditions of climate ranging from hot and humid to extreme cold and dry, it is imperative on the part of the drugs manufacturers in the country to evolve out stability patterns *vis-a-vis* climatic/weather conditions. Needless to say this will be in their interest and as such they could modify their production targets depending upon shelf life pattern round the year or at different areas/zones of such a vast country.

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