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The aqueous stability of bupropion

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ABSTRACT

In this study the aqueous stability of bupropion was determined and the pH-degradation profile was obtained. The effects of hydrogen ion, solvent and hydroxide ion concentration are discussed with particular emphasis on the kinetics of degradation of bupropion. Kinetics and degradation of bupropion were determined by HPLC-UV and LC–MS analysis both utilising high pH chromatographic methods. Degradation of bupropion in aqueous solutions follows first-order reaction kinetics. The pH-degradation profile was determined using non-linear regression analysis. The micro- and macro-reaction constants for degradation are presented. Bupropion was most stable in aqueous solutions below pH 5. Degradation was catalyzed by water but mainly by hydroxide ion on the unionised form of bupropion. The energy of activation for decomposition in aqueous solution pH 10.7 $I = 0.055$ was determined to be 53 kJ mol^{-1} with a frequency factor of 6.43×10^{10} s^{-1}. The degradants of bupropion were positively identified and a mechanism of degradation is proposed. The inherent instability of bupropion above pH 5 has implications for its therapeutic use, formulation, pharmacokinetics and use during analysis and storage.

1. Introduction

Bupropion was first patented in 1974 [1] and released onto the world market in 1985. It was briefly withdrawn due to seizures incidence but reintroduced in 1989 after the daily recommended dose was reduced to lower seizure likelihood. Bupropion is a dopamine and norepinephrine reuptake inhibitor [2]. It is about twice as potent an inhibitor of dopamine reuptake than of norepinephrine reuptake.

Bupropion has numerous therapeutic indications including, depression [3], smoking cessation [4], sexual dysfunction [5], obesity [6], attention deficit hyperactivity disorder [7] and seasonal affective disorder [8]. It has recently been shown to have anti-inflammatory properties [9]. In 2007 it was the fourth-most prescribed antidepressant in the USA. While there has been little published in peer reviewed journals, it is widely acknowledged that bupropion presents serious stability problems in manufacturing, formulation and use. This is partly reflected in the numerous patents directed at methods to improve the stability of bupropion formulations.

One method to improve the stability of bupropion in oral formulations involves addition of a stabilizer to the formulation, in this case cysteine or glycine hydrochloride which acts to buffer the formulation at a pH between 0.9 and 4.0 [10]. Other stabilizers used to improve the stability of bupropion in tablet formulations are organic acid [11], inorganic acids [12] and salts of organic bases [13].

Pharmaceutical compositions for transdermal administration containing fatty acid salts of bupropion free base and metabolites have also been developed [14]. The salt form of bupropion is more stable than the freebase.

The levels of moisture are evidently critical in controlling degradation during processing. Chawla et al. developed a dry granulation process for tabletting of bupropion, avoiding the use of stabilizers [15]. Indeed, an inclusion complex of bupropion hydrochloride with beta-cyclodextrin that stabilizes bupropion hydrochloride against degradation has been developed by Gidwani et al. [16].

Other physical methods have been developed to trap bupropion inside a moisture barrier within an oral tablet formulation. These usually involve polymer coatings around the tablet or sometimes polymer miscrospheres within the tablet. These formulations create dry micro-environments within the tablet matrix limiting access between bupropion and its outside environment. Stabilized bupropion hydrochloride pharmaceutical compositions are described that are free of acid additives and provide for a sustained release of bupropion hydrochloride [17]. The particulate bupropion hydrochloride is coated with a polymer membrane coating.

Bupropion half-life in plasma stored at 22 and 37 °C was 54.2 and 11.4 h, respectively. It was only shown to be stable at pH 2.5 [18].

Abbreviations: HPLC-UV, high performance liquid chromatography with ultraviolet spectrophotometric detection; LC–MS, liquid chromatography with mass spectrometric detection; pH, log[H$^+$]; pK_a, log[K_a]; K_a, acid dissociation constant; ESI, electrospray ionisation; SIM, selected ion monitoring; USP, United States pharmacopoeia; CE, carboxylesterase; TMPT, thiopurine methyltransferase; I, ionic strength; RSD, relative standard deviation.

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Another study on the chemical stability of bupropion in isotonic pH 7.4 at 32 °C over two weeks showed that its disappearance follows first-order kinetics [19].

The stability of bupropion in formalin has been studied and it was shown that at lower pH, bupropion is most stable; at higher pH, bupropion is converted into *N*-methyl bupropion [20]. Compounds with similar structure to bupropion, i.e. diethylpropion have shown similar degradation characteristics. Hydrolytic decomposition of diethylpropion in solution at 45 °C occurred at a very slow and constant rate at pH 3.5 and below but increased rapidly as the pH was raised above 3.5 [21].

The formulation, stabilisation and use of bupropion is therefore an active area of pharmaceutical research. There is currently no injectable delivery vehicle for bupropion in clinical use and its absolute oral bioavailability in humans has not been reported. Against this background and in the context of its expanding therapeutic uses this paper reports on the kinetics of degradation of bupropion in aqueous solution including routes of degradation and influence of parameters such as ionic strength and buffer identity.

2. Materials and methods

2.1. Chemicals

Methanol, acetonitrile and water were supplied by Fisher Scientific Ireland (LC–MS grade). Ammonium hydroxide solution (30% as NH_3), glacial acetic acid, formic acid, boric acid, citric acid monohydrate, sodium chloride and tripotassium phosphate were supplied by Sigma–Aldrich Ireland (reagent grade). Bupropion hydrobromide and related degradants were supplied as a gift from Biovail Technologies Ireland Ltd.

2.2. Instrumentation

A stability indicating HPLC-UV assay was used to monitor degradants of bupropion. The HPLC system consisted of a Waters Alliance 2695 separations module connected to a Waters 2996 Photodiode Array detector. The column was a Waters XBridge C18 250 mm × 4.6 mm, 5 μm fitted with a Waters XBridge C18 guard column heated at 50 °C. Mobile phase A was pH 10.0 ammonium acetate buffer (1.27 M)/water/acetonitrile, 10:80:10, mobile phase B was pH 10.0 ammonium acetate buffer (1.27 M)/water/acetonitrile, 10:20:70. Injection volume was 20 μL, flow rate 1.5 mL/min. Gradient; 0–42% B over 5 min, hold for 10 min, 42–100% B over 10 min, hold for 5 min and equilibrate to starting gradient. The retention time of bupropion standard was approximately 23 min. Detection wavelength 239 nm. This method was demonstrated to be linear over a working range of 0.01–0.50 mg/mL bupropion hydrobromide.

Degradation kinetics and mass spectrometric measurements were carried out on a Thermo Accela Liquid chromatograph. The detector was a Thermo LTQ-XL-Orbitrap Discovery mass spectrometer. The column used for chromatographic separation was a Waters Xbridge C18, 2.1 mm × 50 mm 2.5 μm at 20 °C. Mobile Phase A: 10:40:50, 0.5% Ammonium hydroxide solution in water, adjusted to pH 10.0 with formic acid: water: methanol. Mobile Phase B: 10:90, 0.5% Ammonium hydroxide solution in water, adjusted pH 10.0 with formic acid: methanol. Flow rate: 100 μL/min, Injection volume: 10 μL, run time: 15 min. Gradient, 0% B to 100% B over 8.00 min, hold until 12.00 min. 0% B at 12.01 min and equilibrate for 3 min. This method was validated as appropriate according to ICHQ2R and demonstrated to be linear over a working range of 1–250 ng/mL bupropion.

The LTQ-XL ion trap mass spectrometer was coupled to the Accela LC system via an electrospray ionization (ESI) probe. The capillary temperature was maintained at 400 °C, sheath gas flow rate 50 arbitrary units, auxiliary gas flow rate 5 arbitrary units, sweep gas flow rate 0 arbitrary units, source voltage 3.20 kV, source current 100 μA, capillary voltage 43.00 V and tube lens 100 V.

Bupropion was detected in positive ion mode using selected ion monitoring (SIM). Bupropion SIM 184, $(M+H)^+ = 240$, retention time = 9.4 min. The optimum detector conditions were found by tuning the instrument to the highest sensitivity for bupropion most abundant fragment ion at 184 (m/z).

2.3. Determination of rate constant

The observed first-order degradation rate constants, k_{obs}, were calculated from the slopes of the natural-logarithmic plots of the drug fraction remaining versus time in accordance with Eq. (1):

$$\ln\left(\frac{C_t}{C_0}\right) = -k_{obs}t \quad (1)$$

where C_0 was the initial concentration and C_t was the remaining concentration of bupropion at time t. Solutions were monitored for two weeks and stored protected from light.

2.4. pH-degradation profile

Bupropion solutions were prepared at a concentration of 250 ng/mL in aqueous buffers from a 1 mg/mL methanol stock solution. The final concentration of methanol in the buffered solutions was approximately 1%. Buffers over the pH range of 2–13 were prepared by mixing two stock buffered solutions to give solutions of different pH but equal ionic strength. This buffer system was adapted from a previously described universal buffer system by Carmody.

Stock buffer A: boric acid 0.2 M, citric acid 0.05 M, NaCl 0.594 M, $I = 0.6$. Stock buffer B: tripotassium phosphate 0.1 M, $I = 0.6$.

For example, to prepare a solution of pH ∼ 7.2 with an $I = 0.055$, add 0.5 mL solution A and 0.5 mL solution B to 10 mL deionised H_2O. Buffered solutions at the lowest and highest pH were prepared with 0.055 M HCl pH 2.0 and 0.055 M NaOH pH 13.1. Solution pH was measured at room temperature 20 ± 1 °C using a Radiometer Copenhagen PHM61 laboratory pH meter. The pH meter was calibrated before use with standard buffers, 4.0, 7.0 and 10.0. Solutions were incubated either in a digital oven (for long term storage) or in the Accela LC system autosampler (for short term). Aliquots were taken at appropriate times depending on the decomposition rate and analyzed immediately for remaining bupropion. Buffer concentrations throughout the study were low. However the effect of buffer concentration on rate was evaluated at kinetically and mechanistically distinguishable phases of the resulting pH-rate profile. Dilution did not affect degradation rate using the universal buffer system and therefore we did not extrapolate to zero buffer.

2.5. Effects of temperature and buffer on the stability of bupropion

The effect of temperature on the rate of bupropion degradation was determined at pH 10.7. Bupropion solutions were prepared in the appropriate buffers as described in Section 2.4, and incubated at 40, 46, 54 and 60 °C. Aliquots were taken at appropriate times depending on the decomposition rate and analyzed immediately for bupropion. The observed first-order degradation rate constants k_{obs} were calculated using Eq. (1). The Arrhenius factor A, and activation energy E_a for bupropion degradation were determined from a plot of $\ln(k_{obs})$ against $1/T$ (K) according to Eq. (2) using least

Table 1
Rate constants determined for the degradation of bupropion.

Temperature (K)	313	323	333
Ionic strength	0.055	0.12	0.055
pH_{RT}	k_{obs} (h^{-1})		
5.1	0.002	0.001	0.004
6.3	0.003	0.002	0.008
7.4	0.004	0.004	0.019
8.3	0.006	0.017	0.035
9.4	0.012	N/D	0.051
10.7	0.018	0.052	0.055
11.9	0.034	0.072	0.101
12.3	0.042	0.114	0.166
13.0	0.102	N/D	0.407

squares regression:

$$\ln\ k_{obs} = \ln A - \frac{E_a}{RT} \quad (2)$$

where R is the universal gas constant and T the absolute temperature (K).

Buffer catalysis was investigated by monitoring the amount of bupropion degradation in three different buffers pH 7.4 at 60 °C, ionic strength 0.055, 0.275 and 0.55 using the universal buffer system described in Table 1. From the slope of plots of $\ln[C_t/C_0]$ versus time, the rate constant was calculated. A plot of rate constants versus buffer concentration gave a straight line of which extrapolation back to zero gave the buffer-free rate constant.

The effects of different buffers were determined by monitoring the disappearance of bupropion at pH 7.4 at 60 °C in different buffer types with fixed ionic strength, 0.055. Four buffer systems were studied; citrate, phosphate, borate and a TRIS buffer system. Ionic strength was adjusted with NaCl. The slopes of plots of $\ln[C_t/C_0]$ versus time were determined to establish the effect of buffer anion on degradation of bupropion (Fig. 4).

2.6. Liquid chromatography with UV and mass spectrometric detection

Two HPLC systems were used in the study. The LCMS system as described in instrumentation section was used to assay bupropion and determine kinetic data. The HPLC-UV system was used to monitor and determine the degradation pathway of bupropion. The HPLC-UV system was a validated stability indicating assay for bupropion and it degradants. This system was better suited for assay of bupropion degradants as they had good UV absorbances but poor positive electrospray ionisation character. System suitability was determined on the day of use and throughout the analysis by repeat injection of a bupropion standard. The % RSD of area and retention time of repeat injections was not more than 5.0%. Degradant peaks were quantified off bupropion using relative response factors and relative retention times, which were generated during the validation of the stability indicating method using external standards.

3. Results and discussion

3.1. pH-rate profile of bupropion

The disappearance of bupropion in aqueous solution was monitored by HPLC–MS. The degradation in the pH range 2–13 followed apparent first-order rate kinetics. Rate constants from a matrix of different experiments are presented in Table 1, where the temperature, pH and ionic strength have been varied. Rate constants were estimated from the resulting slopes after a plot of $\ln[C_t/C_0]$ versus time (Fig. 1) and the resulting k_{obs} values (Table 1) plotted against

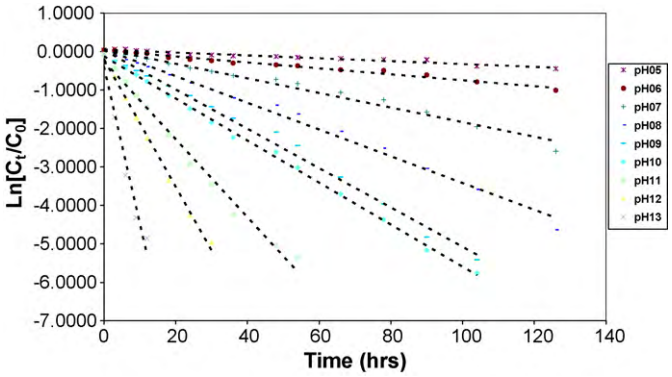


Fig. 1. First-order plots showing the degradation of bupropion at 60 °C in aqueous solution in the pH range 5–13.

pH. The pH-rate profile was fitted using a mechanistic interpretation of pH-rate profiles suggested by Loudon [22]. By analysing the shape of the pH-rate profile a mathematical equation that best describes the degradation can be formulated, Eq. (3):

$$k_{obs} = c_1[H^+] + \frac{c_2[H^+]}{K_a + [H^+]} + \frac{c_3 K_a}{K_a + [H^+]} + \frac{c_4 K_w}{[H^+]} \quad (3)$$

where K_a and K_w are the acid dissociation constant for bupropion and water respectively and c_1, c_2, c_3 and c_4 are the macro-reaction rate constants of the pH-rate profile. Constants c_1 and c_4 are kinetically distinguishable and are equal to the specific hydronium catalysed degradation on the protonated form and hydroxide catalysed degradation on the deprotonated form of bupropion respectively. Constants c_2 and c_3 contain contributions from kinetically indistinguishable micro-reaction rate constants. The macro-reaction rate constants were determined by fitting the k_{obs} values with the model and solving the rate equation using non-linear regression analysis. These rate constants are described in Table 2. Bupropion was shown to be stable over the course of the degradation study below pH 5, and therefore the specific hydronium catalysis rate constant c_1 is many orders of magnitude lower than c_2, c_3 and c_4. Therefore c_1 can be assumed to be zero and Eq. (3) simplifies to Eq. (4):

$$k_{obs} = \frac{c_2[H^+]}{K_a + [H^+]} + \frac{c_3 K_a}{K_a + [H^+]} + \frac{c_4 K_w}{[H^+]} \quad (4)$$

The macro-reaction rate constant c_2 combines two micro-reaction rate constants that are kinetically indistinguishable. Empirically these are the contribution of hydronium catalysed degradation on the deprotonated form of bupropion and solvent catalysed degradation on the protonated form of bupropion.

The macro-reaction rate constant c_3 combines two micro-reaction rate constants that are also kinetically indistinguishable. These are the contribution of hydroxide ion catalysis on the protonated form of bupropion and solvent catalysed degradation on the deprotonated form of bupropion. The magnitude of rate constants at 40, 50 and 60 °C follows $c_4 > c_3 > c_2 > c_1$, showing the rate of degradation is strongly influenced not only by hydroxide ion

Table 2
The macro-reaction constants determined by non-linear regression analysis.

	40 °C	60 °C
c_1	0.0000	0.0000
c_2	0.0000	0.0041
c_3	0.0187	0.0596
c_4	0.2914	0.2224
K_a	1.26×10^{-8}	1.26×10^{-8}
K_w	2.92×10^{-14}	1.26×10^{-13}

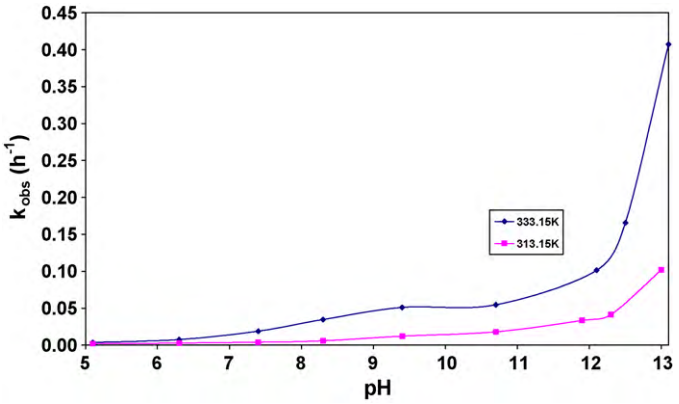


Fig. 2. pH-degradation profile of bupropion at 40 and 60 °C.

concentration but also from solvent catalysed degradation on the deprotonated form of bupropion. Bupropion degradation was not observed at pH ≤ 5.0 at 60 °C when it is principally in its protonated form (pK_a 25°C = 7.9).

Fig. 2 presents the pH-degradation rate profile of bupropion at 40 and 60 °C, ionic strength 0.055. The degradation rate exhibited a marked pH dependence. An inflection point at pH 7.9 corresponds to the bupropion pK_a. At pH ≥ 11 there was a significant increase in the rate of disappearance. Degradation of bupropion was markedly hydroxide ion dependent. Non-linear regression analysis of the pH-degradation profile of bupropion is shown in Fig. 3.

3.2. Influence of temperature and buffer concentration on the stability of bupropion

The degradation of bupropion was monitored in the temperature range 40–60 °C at pH 10.7 and ionic strength, 0.055. This pH was chosen as degradation happened at a sufficiently fast rate to enable analysis over a 24 h period. The rate constant for each temperature was calculated from the slope of the first-order degradation profile. When ln k was plotted against $1/T$ the equation of the line was

$$\ln k = \frac{-6497}{R} \cdot \frac{1}{T} + \ln 16.69,$$

the activation energy E_a for the degradation of bupropion was calculated to be 52.85 kJ mol^{-1}, the frequency factor A, was found to be 1.78×10^7 h^{-1} or 6.43×10^{10} s^{-1}.

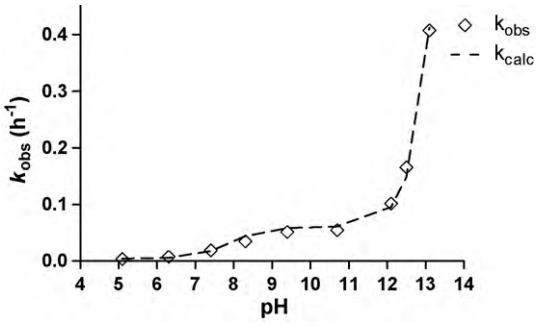


Fig. 3. The pH-degradation profile of bupropion at 60 °C, I = 0.055. Macro reaction constants have been calculated by non-linear regression analysis. The fitted line was constructed using Eq. (4) and the data appearing in Tables 1 and 2.

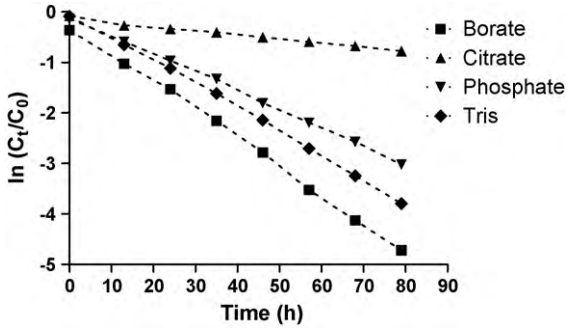


Fig. 4. The effect of different buffer systems on the rate of degradation of bupropion at pH 7.4 60 °C, I = 0.055, adjusted with sodium chloride.

3.3. Identification of bupropion degradants and mechanistic proposal

Degradation products of bupropion were identified by matching the retention time and photo-diode array UV spectra of eluted peaks from degraded samples with those of external standards run under similar conditions (Fig. 6). Four main degradants were identified as **2**, **4**, **3** and **1** (Scheme 1). Bupropion related compounds **3**, **1** and **4** are poorly ionized by +ESI due to loss of the amino functionality. These degradants were all seen at pH > 5 but above pH 10 only *m*-chlorobenzoic acid **2** was seen at significant levels. Fig. 5 shows the concentration versus time profiles for bupropion and its degradants at different pH values.

A proposed degradation pathway of bupropion is presented in Scheme 1. The mathematical model that best described the mechanism of degradation follows consecutive and parallel reactions. Degradation of bupropion was strongly pH dependent, and below pH 5 bupropion was protonated and stable. Above pH 5 and approaching its pK_a bupropion becomes increasingly deprotonated and suffers from water catalysed and hydroxide catalysed degradation. This was evident from the pH-rate profile of bupropion. Under these conditions the proposed reaction (Scheme 1) is kinetically possible.

$$\frac{d[\text{bup}]}{dt} = -k_1[\text{bup}] \quad (5)$$

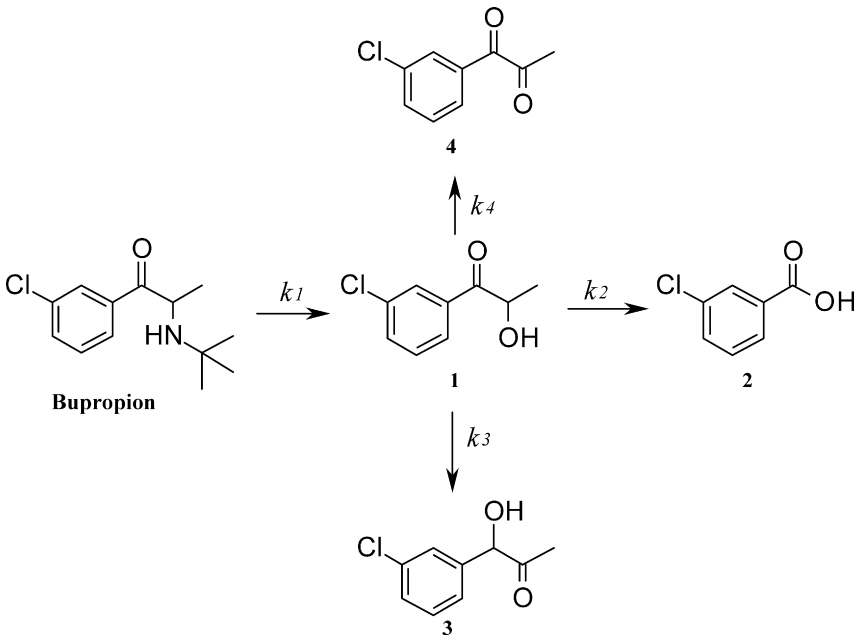
$$[\text{bupropion}] = [\text{bup}]_0 e^{-k_1 t} \quad (6)$$

Bupropion's rate constant of decomposition was calculated by fitting a first-order plot using non-linear regression analysis, Eq. (5). The first product of bupropion degradation at high pH is compound **1** formed from loss of the *t*-butylamine group during hydrolysis. The concentration of **1** during the course of the hydrolysis remained below 1% of the total degradation products of bupropion. The rate of decomposition of **1** was faster than the rate of formation of **1** and therefore can be assumed at steady state throughout the time course of the reaction. The hydrolysis and oxidation products of **1** are the major apparent degradation products of bupropion. These are the two oxidation products, **2** and **4** and the tautomeric pair **3** and **1**. Eqs. (7)–(9) were used to calculate the rate constants of these parallel reactions. The experimental data fitted with these equations using non-linear regression analysis allowed calculation of the rate constants.

$$[2] = [2]_0 + \frac{[\text{bup}]_0 k_2 (1 - e^{-k_1 t})}{k_1} \quad (7)$$

$$[3] = [3]_0 + \frac{[\text{bup}]_0 k_3 (1 - e^{-k_1 t})}{k_1} \quad (8)$$

$$[4] = [4]_0 + \frac{[\text{bup}]_0 k_4 (1 - e^{-k_1 t})}{k_1} \quad (9)$$



Scheme 1. Proposed pathway for base catalyzed degradation of bupropion in aqueous solution. **1** = 1-(3-chlorophenyl)-2-hydroxy-1-propanone, **2** = 3-chlorobenzoic acid, **3** = 1-(3-chlorophenyl)-1-hydroxy-2-propanone, **4** = 1-(3-chlorophenyl)-1,2-propanedione.

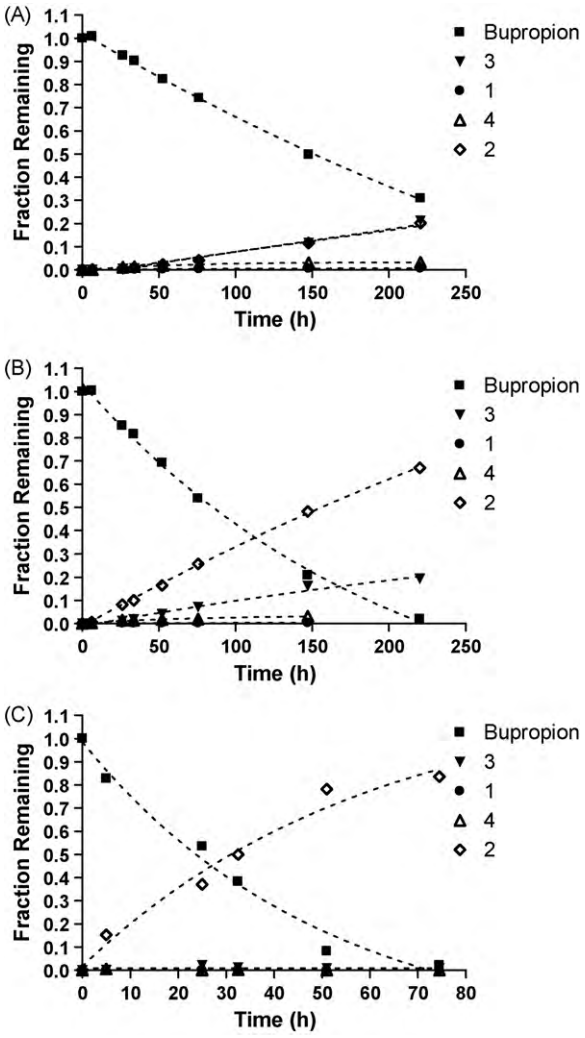


Fig. 5. The time course profile for degradation of bupropion at (A) pH 7.6, (B) pH 8.7 and (C) pH 10.9, 50 °C, I = 0.12.

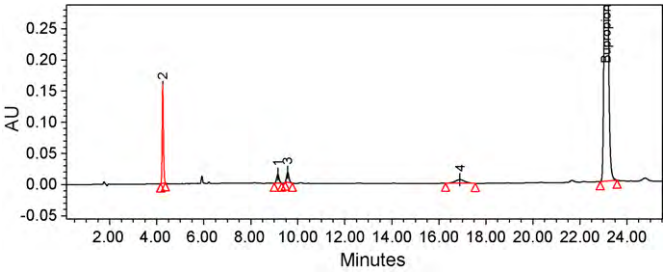


Fig. 6. A typical LC-UV chromatogram of bupropion hydrolysis at pH 8.7, 50 °C, I = 0.12, T = 144 h. **1** = 1-(3-chlorophenyl)-2-hydroxy-1-propanone, **2** = 3-chlorobenzoic acid, **3** = 1-(3-chlorophenyl)-1-hydroxy-2-propanone, **4** = 1-(3-chlorphenyl)-1,2-propanedione.

The rate constants calculated at pH 8.7, 50 °C, I = 0.12 were 0.0050, 0.0045, 0.00138 and 0.00023 h^{-1} for k_1, k_2, k_3 and k_4, respectively (Fig. 7).

The rate constants calculated at pH 7.6, 50 °C, I = 0.12 were 0.0046, 0.0012, 0.0012 and 0.00028 h^{-1} for k_1, k_2, k_3 and k_4, respectively.

The loss of the amino functionality during degradation is likely to render the degradants neuropharmacalogically inactive. The

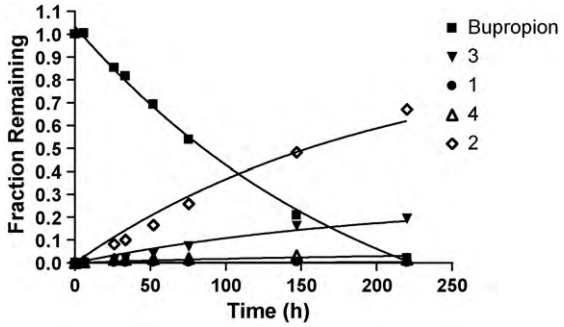


Fig. 7. Data at pH 8.7, 50 °C, I = 0.12. The solid lines were constructed using Eqs. (5)–(9) with the calculated k_{obs} values.

most polar and prominent degradant **2**, is likely the least problematic as this compound is reported to be easily metabolized and excreted in the urine as *m*-chlorohippuric acid [23]. However, high levels of **2** have been reported to inhibit thiopurine methyltransferase (TMPT) [24]. TMPT is best known for its role in the metabolism of the thiopurine drugs such as azathioprine, 6-mercaptopurine and 6-thioguanine.

Toxicological and pharmacological data on degradants **1**, **3** and the diketone **4** is absent. The latter is likely to be chemically active towards formulation components and in vivo towards proteins such as carboxylesterases (CEs) [25]. CE's are involved in the detoxification of xenobiotics in both prokaryotes and eukaryotes. Bupropion is rapidly and extensively metabolised in vivo. Its metabolites contribute significantly to its pharmacological and toxicological profile. The rate data at pH 7.4 do not indicate that its chemical reactivity in vivo is likely to affect its profile.

4. Conclusion

Bupropion undergoes degradation in aqueous solution in a pH dependent manner. Its most prominent degradation pathway involves hydroxide ion catalysis of the free base form. Degradation involves loss of the *t*-butylamino group and the degradants are therefore likely to be neuropharmacologically inactive. The effect of ionic strength, buffer type and temperature on the kinetics was also characterised.

The poor stability profile of bupropion above pH 5 has implications for its formulation in drug delivery systems, its distribution in vivo and its analysis and storage in assay systems. The data shows that careful buffering below pH 5 during processing and formulation is needed in order to have the most stable product containing bupropion. There is also a need during sample preparation and storage to consider appropriate solvents and buffers which again keep the pH low.

Acknowledgement

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