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*Report*

# An Accurate Prediction of the pH Change Due to Degradation: Correction for a "Produced" Secondary Buffering System

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Esmolol hydrochloride degrades in aqueous solutions by the hydrolysis of a labile aliphatic carboxy-ester group. The products are methanol and ASL-8123. The resulting aliphatic carboxylic acid moiety (ASL-8123) has a p$K$ of 4.80, which is within 1 pH unit of the pH of the formulation. ASL-8123 therefore acts as a "secondary buffer" and minimizes the change in pH due to degradation. Equations are presented to calculate the change in the pH when the primary degradation product acts as a secondary buffer. This information can be used in the development of a parenteral product to predict, *a priori*, the concentration of buffer necessary for optimal pH maintenance. This knowledge can reduce the number of formulation screens required to determine the necessary buffer capacity for optimal drug stability.

KEY WORDS: stability; esmolol; secondary buffer; hydrolysis; aliphatic carboxy ester; pH change.

## INTRODUCTION

The pH and buffer concentration in a parenteral pharmaceutical product are set during manufacturing according to stability, solubility, and other formulation requirements. With time, most drugs will begin to degrade in solution, which can cause a change in the pH due to the production or consumption of acid or base. To prevent large deviations from the initial pH, a primary buffer is present. The concentration of this buffer is set according to the amount of pH change allowable for the formulation and whether buffer-induced degradation occurs. It is therefore useful to be able to predict accurately the change in the formulation's pH, for any percentage degradation, prior to starting preformulation or formulation studies.

Calculating the change in pH due to degradation is a straightforward problem when the degradation product(s) is neutral or has a p$K$ value significantly different from the formulation's pH. In these cases a simple Henderson–Hasselbalch equation can be used to predict the change in the pH of the formulation. However, if the degradation produces a compound with an ionizable group (secondary buffer) having a p$K$ value near the formulation pH, then the prediction of the pH change, by calculation, may need to include and correct for this.

The buffering capacity of a secondary buffer is related to the type of ionizable group (acidic or basic secondary buffer) produced and the protonation state of this group immediately subsequent to its formation. These two conditions create four possible scenarios:

(1) production of an acidic secondary buffer in the
  (a) neutral form (i.e., acid) or
  (b) protonated form (conjugate base) and
(2) production of a basic secondary buffer in the
  (a) neutral form (base) or
  (b) protonated form (conjugate acid).

The proximity of the p$K$ of the secondary buffer to the pH of the formulation will determine whether a hydronium or hydroxide ion is donated to, or consumed from, the solvent by the secondary buffer. This creates three possible cases for each major case described above:

(i) the p$K$ of the secondary buffer is much higher than the pH of the solution,
(ii) the p$K$ of the secondary buffer is much lower than the pH of the solution, and
(iii) the p$K$ of the secondary buffer is comparable to the pH of the solution.

In this paper we present several of the cases outlined above. Equations are derived to calculate accurately the change in pH due to degradation when a secondary buffer (acid in the neutral form, at a pH comparable to the p$K$ of the secondary buffer) is produced. These equations are then applied to the degradation of esmolol hydrochloride.

Esmolol degrades by a water-mediated hydrolysis of its

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aliphatic carboxy methyl ester, to ASL-8123 and methanol (1). The resulting degradation product has a p$K$ of 4.80 (2), which is within the pH range (pH of formulation ± 1) of the formulation. ASL-8123 acts as a secondary buffer and alters the magnitude of the pH change. Equations to correct the calculated pH, due to this secondary buffering effect, are presented.

## EXPERIMENTAL

The p$K$ for the aliphatic carboxy group of the degradation product of esmolol (ASL-8123 and Fig. 1) was determined by a routine potentiometric titration method, using the same equipment as described previously (2). This p$K$ was determined in a totally aqueous solution.

The degradation kinetics of esmolol were determined by monitoring the loss of esmolol by high-performance liquid chromatographic a (HPLC) routine (3). The HPLC procedure used a 15-cm, μBondapak Cyano column (Waters) and a Hitachi 655-11A pump with a Hitachi 655A variable-wavelength UV detector set at 280 nm. The mobile phase was acetonitrile:0.01 $M$ sodium acetate:glacial acetic acid, 15:84:1, at a 1-ml/min flow rate. Samples were diluted into 3 ml of Milli-Q water to quench the degradation and then kept at room temperature until they were analyzed. The rate of degradation at room temperature is minimal, and the samples were assayed within a week of sampling.

The change in pH due to degradation was determined using an ION 85 radiometer with a semimicro Ross electrode. All samples were allowed to cool to room temperature before the pH was measured.

## RESULTS AND DISCUSSION

### Case I: The p$K$ of the Secondary Buffer Is More than 2 pH Units Greater than the pH of the Formulation

In this case, degradation creates a product with an acidic ionizable group which has a p$K$ more than 2 pH units higher than the pH of the formulation. The "produced" secondary buffer will be formed in its fully protonated form, thereby preventing the pH of the formulation from changing. This is the "best case" possible. The pH will not change due to the primary hydrolysis of the drug, and therefore the concentration of initial buffer can be minimized. The actual buffer concentration required will be determined by the need for initial pH stability, ionic strength adjustments, or other buffer/formulation considerations.

### Case II: The p$K$ of the Secondary Buffer Is More than 2 pH Units Less than the pH of the Formulation

Degradation of the drug of interest may produce a secondary buffer, yet this buffer will have no ability to maintain the formulation's pH. This occurs when the p$K$ of the secondary buffer is more than 2 pH units below the pH of the formulation. In this case the secondary buffer is produced almost entirely in its conjugate base form. It should be noted that similar results occur when degradation does not produce an ionizable moiety (i.e., secondary buffer). In both of these scenarios the pH change due to hydrolysis can be calculated using a modified form of the Henderson–Hasselbalch equation:

$$[H^+] = K_a * \frac{[HA]_o + C_d}{[A^-]_o - C_d} \quad (1)$$

where

$$[HA]_o = \frac{[H^+]_o * C_t}{[H^+]_o + K_a} \quad (2)$$

and

$$[A^-]_o = \frac{K_a * C_t}{[H^+]_o + K_a} \quad (3)$$

where $[HA]_o$ and $[A^-]_o$ are the relative concentrations of acidic and basic components of the buffer, respectively. $[H^+]_o$ is the hydrogen ion concentration at the initial pH, $K_a$ is the ionization constant of the buffer, and $C_t$ is the total initial concentration of the buffer. $C_d$ is the molar concentration of base consumed, or acid produced, due to hydrolysis.

When the active drug or the excipients degrade in such a fashion that the products do not act as secondary buffers, then the only buffering capacity in the formulation will be that of the primary buffer. The concentration of primary buffer necessary will be determined by the need to prevent unacceptable pH changes, over the shelf life of the product.

### Case III: The p$K$ of the Secondary Buffer Is Comparable to the pH of the Solution

Figure 1 shows the degradation pathway for esmolol in a totally aqueous solution (1). Previous experiments have shown that esmolol degrades by hydrolysis of its aliphatic methyl ester. ASL-8123 and 1 mol of methanol are the only degradation products. This degradation pathway results in the net production of 1 mol of acid per mol of esmolol degraded. ASL-8123 increases the buffer capacity of the formulation as it is formed, thereby minimizing the change in pH due to degradation of esmolol. To calculate the pH change due to degradation, in the presence of a secondary buffer, Eq. (1) is modified to give

$$[H^+] = K_a * \frac{[HA]_o + C_d - [DH]}{[A^-]_o - C_d + [DH]} \quad (4)$$

where [DH] is the concentration of secondary buffer produced due to degradation. Assuming that 1 mol of this sec-

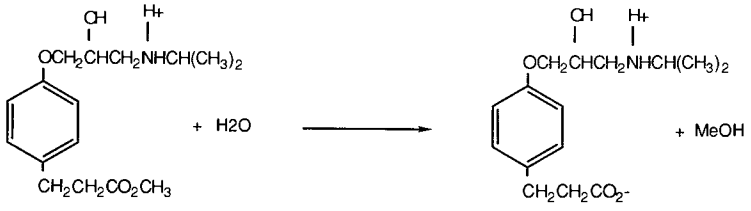


Fig. 1. The degradation pathway for esmolol in a totally aqueous solution.

Table I. Predicted Versus Actual Change in the Formulation pH Due to Degradation: Initial pH Is 5.0

| Esmolol (mg/ml) | Acetate buffer | Percentage degraded | Uncorrected pH[a] | Corrected pH[b] | Actual pH |
|---|---|---|---|---|---|
| 50 | 0.01 *M* | 5 | 2.68 | 4.48 | 4.56 |
| | | 10 | 1.98 | 4.26 | 4.21 |
| | | 15 | 1.72 | 4.11 | 4.05 |
| | | 20 | 1.56 | 4.00 | — |
| | 0.05 *M* | 5 | 4.70 | 4.83 | 4.86 |
| | | 10 | 4.38 | 4.72 | 4.67 |
| | | 15 | 3.93 | 4.62 | 4.59 |
| | | 20 | 2.72 | 4.55 | — |
| | 0.10 *M* | 5 | 4.85 | 4.91 | 4.90 |
| | | 10 | 4.70 | 4.83 | 4.83 |
| | | 15 | 4.55 | 4.77 | 4.73 |
| | | 20 | 4.38 | 4.72 | 4.69 |
| 100 | 0.01 *M* | 5 | 1.98 | 4.26 | 4.33 |
| | | 10 | 1.56 | 4.00 | 4.02 |
| | | 15 | 1.35 | 3.84 | 3.75 |
| | | 20 | 1.21 | 3.73 | 3.63 |
| | 0.05 *M* | 5 | 4.38 | 4.72 | 4.79 |
| | | 10 | 2.72 | 4.55 | 4.47 |
| | | 15 | 1.73 | 4.43 | 4.35 |
| | | 20 | 1.45 | 4.33 | — |
| | 0.10 *M* | 5 | 4.70 | 4.83 | 4.85 |
| | | 10 | 4.38 | 4.72 | 4.72 |
| | | 15 | 3.93 | 4.58 | 4.58 |
| | | 20 | 2.42 | 4.52 | 4.52 |

[a] Calculated by Eq. (1).
[b] Calculated by Eq. (2).

ondary buffer is produced per mol of drug degraded, then the relative concentration of the secondary buffer in its protonated form can be calculated by

$$[DH] = \frac{[H^+] * C_d}{[H^+] + K_d} \quad (5)$$

where $[H^+]$ is the hydrogen ion concentration and $K_d$ is the ionization constant of the secondary buffer. Combining Eqs. (4) and (5) and rearranging gives

$$[H^+]^2[A^-]_o + [H^+](K_d[A^-]_o - C_dK_d - [HA]_oK_a) - K_aK_d([HA]_o + C_d) = 0 \quad (6)$$

Equation (6) can be solved by the quadratic equation for any hydrogen ion and buffer concentration, to give a prediction of the pH at any percent degradation.

Table II. Predicted Versus Actual Change in the Formulation pH Due to Degradation: Initial pH Is 5.5 and Acetate Buffer Concentration Is 0.05 *M*

| Esmolol concentration (mg/ml) | Percentage degraded | Uncorrected pH[a] | Corrected pH[b] | Actual pH |
|---|---|---|---|---|
| 10 | 5 | 5.39 | 5.41 | 5.40 |
| | 10 | 5.30 | 5.34 | 5.33 |
| | 15 | 5.21 | 5.27 | 5.25 |
| | 20 | 5.13 | 5.22 | — |
| 50 | 5 | 5.06 | 5.17 | 5.15 |
| | 10 | 4.74 | 4.99 | 4.95 |
| | 15 | 4.42 | 4.86 | 4.89 |
| | 20 | 3.96 | 4.76 | — |

[a] Calculated by Eq. (1).
[b] Calculated by Eq. (6).

The experimentally determined change in the formulation pH, due to degradation, is shown in Table I. Also, the calculated changes in pH with, and without, correction for a secondary buffer are listed. In order to compare results it should be noted that the stability of esmolol in aqueous solution is optimal at a formulation pH of 5.0 ± 0.5 (1,4). Therefore, whenever the pH decreases 0.5 pH unit below the initial pH, it is assumed that stability of the product is lost. Results are presented for 5 to 20% loss of esmolol. It should be noted that esmolol is routinely formulated with a 10% manufacturing overage.

For the 50 mg/ml concentration of drug, the calculated change in the pH, in the absence of a secondary buffering affect, is large for all three buffer concentrations. For the 0.01 *M* buffer formulation, the predicted pH at 5% degradation is less than 3. For the 0.05 *M* buffer, the necessary buffer capacity is completely compromised by less than 10% degradation. For the 0.10 *M* buffer concentration, the pH does not decrease as dramatically, however, the pH, at 20% degradation, is not maintained within 0.5 pH unit of the initial pH. Therefore, in the absence of a secondary buffering effect, more than 0.10 *M* acetate buffer would be necessary initially for pH stability.

In the presence of a secondary buffering effect, the pH of the 50 mg/ml formulation is maintained within 0.5 pH unit of the initial pH by the 0.05 *M* acetate buffer. Even for 0.01 *M* acetate buffer, the formulation's buffer capacity is not completely neutralized by 5% degradation. Therefore, the concentration of acetate buffer necessary for pH mainte-

nance over the shelf life of this product can be reduced by more than a factor of two by the formation of a secondary buffer.

For the 100 mg/ml (10%) formulation of esmolol, the change in pH due to degradation in the absence of a secondary buffering effect is dramatic. Even at 0.10 *M* acetate buffer the pH decreases to less than 2.5 for 20% degradation. Substantially more than 0.10 *M* acetate buffer would be required to maintain the pH within optimal limits. However, due to the presence of a secondary buffering effect, the concentration of primary buffer can be set at 0.10 *M*.

Table II shows the predicted versus the actual change in the formulation pH due to degradation, when the initial pH is set at 5.5. At 10 mg/ml, the effect of the secondary buffer, even at 20% degradation, is minimal. However, at 50 mg/ml, it is obvious that the secondary buffer is helping to maintain the initial pH.

The stability of esmolol in aqueous solution is affected by several formulation factors. First, a pH of 5.0 ± 0.5 has been demonstrated to impart optimal stability to the drug in solution. Therefore, the pH of the formulation should be maintained in this pH range throughout the shelf life of the product. Second, the hydrolysis of the ester group in esmolol is accelerated in the presence of most buffers. Acetate shows the smallest buffer-induced hydrolysis, yet if higher levels of buffer were necessary (no secondary buffering effect), then this would be a problem.

In the formulation of many parenteral compounds this sort of formulation dichotomy exists. There is a need to increase one component of the formulation for stability, which then compromises the product's shelf life due to other competing solution stability factors. For esmolol there is a need to minimize the amount of buffer present (due to buffer catalysis) and yet maintain the pH within strict guidelines. For esmolol this problem is circumvented since ASL-8123 acts as a secondary buffer. The pH change due to degradation is minimized and an adequate shelf life is then possible.

Calculation of the pH change due to degradation, prior to preformulation or formulation experiments, can minimize the total number of experiments necessary, by predicting buffer requirements *a priori*. Also, in the synthesis of new drugs, especially prodrugs, the nature of the leaving group is critical. By carefully selecting this group, it should be possible to create drugs which degrade in solution, creating secondary buffers. Formulation of this drug product may be easier since the secondary buffer will help maintain the optimum formulation pH. This allows the concentration of the primary buffer to be set according to stability, isotonicity, and other possible formulation concerns.

## REFERENCES

1. L. S. Rosenberg, C. K. Hostetler, and D. M. Wagenknecht. (in preparation).
2. L. S. Rosenberg and D. M. Wagenknecht. *Drug Dev. Indust. Pharm.* 12(10):1449–1467 (1986).
3. N. N. Karnatz, D. M. Baaske, D. Herbranson, and M. Eliason. *J. Chromatogr.* 330:420–424 (1985).
4. E. Speicher. Personal communication, Formulation Group, Product Development Section, Du Pont Critical Care, Waukegan, Ill.