IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Nachiappan Chidambaram and Aqeel Fatmi

Serial No.: Continuation of 11/367,238 Art Unit: Not yet assigned

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For: *SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

The undersigned, Robert Edward Kalkreuter, do hereby declare and state that:

1. I am currently a chemistry PhD candidate at North Carolina State University.

2. I have a Bachelor of Science in Chemistry from Emory University and have studied chemistry for seven years, including the last three in a Chemistry PhD program.

3. I have read U.S. Patent No. 6,383,515 to Sawyer *et al.* ("Sawyer"), which was cited by the Examiner during the prosecution of U.S. Patent Application No. 11/367,238 ('238 Application).

4. Sawyer describes solutions suitable for encapsulation in softgel capsules (col. 1, lines 6-7). Sawyer describes formulations containing a low molecular weight polymer, an active agent, and the salt of an organic acid containing at least three carbon atoms (col. 3, lines 23-26). The active agent is generally in the form of the free acid or base, and the

salt of the organic acid is a base which serves to ionize the active agent, when the active agent is an acid (Col. 4, lines 22-24).

5. Example 17 of Sawyer describes a solution containing naproxen sodium, polyethylene glycol, potassium hydroxide, and sodium propionate. Potassium hydroxide and sodium propionate are bases, *i.e.*, ionizing agents, which function to maintain naproxen as the sodium salt. The Examiner alleged during prosecution of the '238 Application that because the formulation disclosed in Sawyer contains sodium propionate in aqueous solution, the formulation would inherently contain propionic acid.

6. The Examiner provided no evidence to demonstrate that propionic acid is present in an amount between 0.2 to 1.0 mole equivalents of the active agent(s), as required by the claimed subject-matter.

7. Propionic acid is a weak acid. Propionate is the corresponding conjugate base of propionic acid. The equilibrium reaction is as follows:

$$\underset{\text{Propionate}}{C_3H_5O_2^{\ominus}} + H_2O \rightleftharpoons \underset{\text{propionic acid}}{HC_3H_5O_2} + OH^{\ominus}$$

8. Acid-base chemistry teaches that the K_a of a weak acid and the K_b of its conjugate base are related according to the equation:

$$K_a \times K_b = K_w,$$

where K_w is the ionic constant of water and has a value of approximately 1.0×10^{-14} at room temperature. Therefore, the K_b of propionate can be calculated to be 7.46×10^{-10} based solely upon the equation above and the K_a of propionic acid of $\sim 1.34 \times 10^{-5}$. Accordingly, when calculating either the propionic acid concentration or the propionate concentration present in Example 17 of Sawyer, one may use either the K_a of the acid or the K_b of the conjugate base as long as the equations are set up appropriately such that:

The equation for determining the concentration of propionic acid based upon the K_b or K_a using the equations shown below:

$$K_b = \frac{[\text{propionic acid}][OH^-]}{[\text{propionate}]} \quad \textbf{or} \quad (2)\ K_a = \frac{[\text{propionate}][H^+]}{[\text{propionic acid}]}$$

8. Example 17 of Sawyer, in part, reads as follows:

> A formulation was prepared with the ingredients set forth in Table 17. The ingredients were mixed and the sample was heated in a steam bath and swirled until dissolved. The potassium hydroxide was added as a solution of 6.8 g KOH in 100 mls of water. The sodium propionate was added as a solution of 500 g sodium propionate in 700 mls of water. A clear solution was obtained.

TABLE 17

Formulation of Example 17

Ingredient	Amount	Weight Percent (%)
Naproxen sodium	3.0033 g	21.67
Polyethylene Glycol 300	10.0332 g	72.40
Potassium hydroxide	6.66 mg	0.05
Sodium propionate	0.8153 g	5.88

Based on the information provided in Example 17, the amount of water present from the potassium hydroxide solution can be calculated by:

(6.66 mg KOH) × (100 mL H_2O / 6.8 g KOH) × (1 g / 1000 mg) = *0.0979 mL of water*

The volume of water added from the sodium propionate solution is calculated by:

(0.8153 g sodium propionate) × (700 mL H_2O / 500 g sodium propionate) = *1.14142 mL of water*

Therefore, the total volume of water present in the formulation of Sawyer was 1.23932 mL.

9. In Example 17 of Sawyer both a strong base (6.66 mg KOH) and a weak base (0.8153 g sodium propionate) were added to the formulation having a volume of water equal to 1.23932 mL. KOH is a strong base that will completely dissociate in water. Therefore, to a first approximation the pH can be determined from the concentration of KOH, wherein KOH has a molecular weight of 56.1056 g/mol. Thus, the molar concentration of KOH dissolved in solution is calculated as:

$$(6.66 \text{ mg KOH} / 1.23932 \text{ mL } H_2O) \times (1 \text{ mol KOH}/56.1056 \text{ g KOH}) \times (1000 \text{ mg}/1\text{g}) \times (1000 \text{ mL} / 1 \text{ L}) = 0.09578 \text{ M}.$$

Thus, the pH of the solution is calculated as follows:

$$pH = 14.0 - pOH = 14.0 + \log [OH^-] = 14.0 + \log (0.09578) = 14.0 - 1.02 = \mathbf{12.98}.$$

with the pH of the solution being *strongly basic*.

10. In order to calculate the concentration of propionic acid present in the formulation one further requires knowing the amount of sodium propionate added to the solution in Example 17. As only sodium propionate was added, conservation of mass requires that the sum of the concentration of sodium propionate and the concentration of propionic

acid, which may form in equilibrium in solution, must be equal to the initial concentration of sodium propionate that was dissolved.

11. The initial concentration of sodium propionate dissolved in the solution is calculated using the 0.8153 g of sodium propionate dissolved in 1.23932 mL of water wherein sodium propionate has a molecular weight of 96.060 g/mol. Accordingly, this gives a concentration of sodium propionate added of **6.84844 M**.

12. Using the relationship that the sum of concentrations of [propionic acid] + [propionate] = 6.84844 M and either the equation for K_a of propionic acid or the equation for K_b of propionate it is then possible to calculate the concentration of propionic acid in solution.

13. Using the equation for K_b, one finds:

$$K_b = \frac{[\text{propionic acid}][OH^-]}{[\text{propionate}]}$$

$$7.46\times10^{-10} = [\text{propionic acid}]\ [0.09578]\ /\ (6.84844 - [\text{propionic acid}])$$

$$\textbf{[propionic acid] = 5.3}\times\textbf{10}^{-8}\textbf{ M}$$

Alternatively, using the equation for Ka, one finds:

$$K_a = \frac{[\text{propionate}][H^+]}{[\text{propionic acid}]}$$

$$1.34\times10^{-5} = (6.84844 - [\text{propionic acid}])[10^{-12.98}]/[\text{propionic acid}]$$

$$\textbf{[propionic acid] = 5.3}\times\textbf{10}^{-8}\textbf{ M}$$

14. Therefore, in a volume of 1.23932 mL of solution having a molar concentration of 5.3×10^{-8} M propionic acid the solution only contains about 6.5×10^{-11} moles of propionic acid. This concentration of propionic acid accounts for the effect of potassium hydroxide present in the formulation.

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