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RESEARCH PAPER

Preformulation Studies on the S-Isomer of Oxybutynin Hydrochloride, an Improved Chemical Entity (ICE™)

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ABSTRACT

(S)-Oxybutynin HCl (S-OXY) is a white crystalline solid powder with an acicular particle morphology. Differential scanning calorimetry (DSC) thermograms revealed one characteristic endotherm at 116.2°C. On rescanning a sample heated to 120°C, no thermal events were distinguished in the temperature range 25°C to 150°C. Weight loss curves determined by thermogravimetric analysis showed a continuous, gradual weight loss of about 0.15% over the temperature range 30°C to 110°C, followed by a change in slope and more rapid weight loss beginning at 150°C. Observation by hot-stage microscopy confirmed the melting endotherm observed by DSC. Equilibrium moisture uptake studies indicated low water vapor uptake at low relative humidities (<52.8%). At relative humidities of 75.3% and 84.3%, S-OXY first deliquesced and then converted to a lower melting point crystal form. X-ray powder diffraction (XRPD) data supported the DSC findings. S-OXY underwent degradation by ester hydrolysis at alkaline pHs. The kinetics of this reaction were studied at 25°C in carbonate-bicarbonate buffers. Observed rate constants of 0.008 h^{-1} and 0.0552 h^{-1} were determined at pH 9.69 and 10.25, respectively.

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The pK_a of S-OXY was 7.75. The aqueous solubility of S-OXY was described as a function of pH and the free-base solubility. The mean partition coefficient log P *was 3.33 using 1-octanol. The surface tensions of aqueous solutions of S-OXY decreased with increasing concentration, but no concentration-independent region was observed, indicating that S-OXY does not form micelles in aqueous solution. The dissolution rate of S-OXY from a compressed disk in 0.1 N HCl was rapid, whereas it was considerably slower at pH 7.4. Addition of 1% hexadecyltrimethylammonium bromide (CTAB) at pH 7.4 significantly improved the dissolution rate. S-OXY displayed very poor flow properties when compared to standard pharmaceutical excipients. XRPD results indicated that S-OXY exhibited a loss in crystallinity following ball milling. Hiestand tableting indices indicated that S-OXY has good bonding properties and forms strong compacts, but is likely to be susceptible to capping on ejection from the die. This indicated the need for a plastically deformable excipient such as Avicel PH-101 in tablet formulations.*

KEY WORDS: *Oxybutinin; Preformulation; Solid-state characterization; Tableting indicies.*

INTRODUCTION

Pharmaceutical preformulation is an important part of the drug development process. The information relating to a drug compound acquired during this phase of development is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally (1,2). However, limited time and resources often dictate that only a focused set of studies can be conducted that must serve as the basis for future decision making (3,4).

There has been a dramatic increase in the number of single-enantiomer compounds finding indications in place of the previously marketed racemates (5). Racemic oxybutynin [(RS)-oxybutynin] is effective for controlling symptoms of urgency and frequency of patients with urinary incontinence, but its usefulness is limited by undesirable side effects. The single enantiomer (S)-oxybutynin (S-OXY) may represent an improvement over the racemate since it retains the spasmolytic action of (RS)-oxybutynin with reduced antimuscarinic activity (6). When the single enantiomer demonstrates significant improvement in activity relative to the racemate, it may be classified as an Improved Chemical Entity (ICE™).

Because the solid-state properties of single enantiomers are different from those of the corresponding racemic crystal (7), it is necessary to conduct separate preformulation studies even if information is available on the racemic crystal. Moreover, the solution properties of the enantiomers may be different. The objective of this study was to generate a wide array of characterization data relating to the solid-state and solution properties of S-OXY and to collect data that could be used to recommend an approach for development of a solid dosage form.

EXPERIMENTAL

Bulk Drug Material and Reagents

(S)-Oxybutynin hydrochloride (S-OXY) bulk drug substance was provided by Sepracor (Marlborough, MA). The compound had a total purity of 99% and an enantiomeric purity of 99.9%. All reagents were ACS grade or higher, and high-performance liquid chromatography (HPLC) grade solvents were used for chromatography. Deionized distilled water was used.

Solid-State Characterization

Hot-stage microscopy was conducted using a microscope equipped with a Mettler FP 82 hot stage and a Mettler FP 80 central processor (Mettler Instrument Corp., Hightstown, NJ). The heating rates used were 5.0°C/min and 1.0°C/min over a temperature range of 90.0°C to 130.0°C after initial observations over a wider temperature range. The samples were observed visually during heating.

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 analyzer (Perkin-Elmer Corp., Norwalk, CT). Samples were run at heating rates of 5.0°C/min and 1.0°C/min over a temperature range of 25.0°C to 300°C. Volatile content was determined using thermogravimetric analysis (TGA) with a Perkin-Elmer TGA 7 analyzer at a heating rate of 10.0°C/min over a temperature range of 30°C to 160°C (under nitrogen purge). X-ray diffractograms were obtained using a Phillips PW1710 diffractometer (Philips Electronic Instruments, Mount Vernon, NY) operated at 40 kV and 30 mA.

Moisture sorption determinations were conducted

gravimetrically using a batch technique. Approximately 0.2 g samples were carefully weighed and subsequently placed in relative humidity (RH) chambers made from saturated salt solutions at relative humidities of 11.3%, 21.6%, 32.8%, 52.8%, 75.3%, 84.3%, 93.7%. Samples were periodically weighed over 74 days.

The effect of milling on the solid-state properties of S-OXY was evaluted by ball milling portions of the powder for varying lengths of time in a Fritsch Planetary Micro Mill Pulverisette7 (Idar-Oberstein, Germany). The milled powders were subsequently analyzed by DSC and X-ray powder diffraction (XRPD).

Bulk and Physical Powder Properties

True density was determined using a micropycnometer (Quantachrome model MPY-2, Boynton Beach, FL). For bulk density measurements, a 100-ml graduated cylinder was tared on a five-place balance. The powder was gently placed into the cylinder until about one-third to one-half of the cylinder was filled and the powder mass was recorded. The volume of the powder was measured to the nearest milliliter using the graduated cylinder.

The bulk density of the powder was calculated by dividing the mass of the sample by its volume. The procedure was done in triplicate. Tap density was measured by weighing an aliquot of S-OXY and transferring it to a 100-ml graduated cylinder. The volume of the sample was measured to the nearest milliliter using the cylinder. The density (apparent) of the sample was calculated from the mass and volume of the sample. The cylinder was tapped five times by lifting it about 2–3 cm high and letting it fall onto the bench. The volume was then determined, and the apparent density of the sample was calculated. The procedure was repeated until a constant volume was reached for three consecutive five-tap increments. The apparent density at that point was taken as the tap density of the powder. This procedure was done in triplicate. A total of 40 taps was required to determine the tap density in all three cases.

Flow Properties

The flow properties of Avicel PH-101 (lot 1247, FMC, Philadelphia, PA), Emcompress (lot 7009X, Mendell, Patterson, NY), Fast-flow lactose (lot IRD205, Foremost Farms, Baraboo, WI), and (S)-oxybutynin HCl (lot 947-100, Sepracor) were compared using three different methods: angle of repose, flow through an orifice, and compressibility index. The angle of repose was measured by gently pouring a powder through a glass funnel to make a free-standing cone. The angle of repose ϕ is the maximum angle that can be obtained between the free-standing surface of the powder heap and the horizontal plane. In the experimental setup, the base of the cone consisted of a petri dish 9.0 cm in diameter. The height of the cone was measured with a ruler. The angle of repose was calculated using the following equation:

$$\mathrm{Tan}(\phi) = 2h/D$$

where h is the height of the cone, and D is the diameter of the cone.

The compressibility index I was calculated using the following equation:

$$\mathrm{I} = \left(1 - \frac{v}{v_o}\right) \cdot 100$$

where v is the volume occupied by a sample of powder after being subjected to a standard tapping procedure, and v_o is the volume before tapping. Known weights of powder were poured into a 100-ml graduated cylinder, and the volume of the powder v_o was recorded. The cylinder was subjected to 50 taps. The final volume v was subsequently recorded, and the compressibility index was calculated.

Flow through an orifice was measured using a device having a 2.5 cm $\times$ 20.0 cm steel cylinder mounted on a metal block. The block had grooves at the bottom such that a steel plate with a hole could be inserted at the base of the cylinder. Another plate, without a hole, could also be inserted to close the hole made by the first plate. The cylinder was then filled with powder, and the second plate was removed so that the powder was free to flow through the hole in the first plate. Plates with holes of different diameters were used until the smallest orifice through which the powder could freely flow was obtained.

Hiestand Indices

Hiestand indices were determined by conducting several mechanical tests on compacts made from the powder of interest. Details of the procedures and equipment have been previously reported (8). All compacts weighed approximately 2.5 g and were compressed to a solid fraction of 0.85. The pressure necessary to obtain a solid fraction of 0.85 was determined to be 600 psi. Five new compacts were used for each of the following tests: dynamic indentation hardness test, tensile strength test without a hole in the center, and tensile strength test with a hole in the center. Mean values of chordal radius, tensile strength

with a hole, and tensile strength without a hole were used to compute the tablet indices.

Solution-State Properties

Stability-Indicating High-Performance Liquid Chromatography Assay

A stability-indicating assay for S-OXY was installed on an HPLC system consisting of a Waters 510 pump and a Waters Wisp 712 autosampler (Milford, MA) with a Shimadzu UV/Vis detector (Kyoto, Japan). A Zorbax RX-C8 (DuPont, Inc., Wilmington, DE) was used with a mobile phase composed of 30:70 methanol:0.05 M sodium monobasic phosphate and 0.1% TEA (pH 3). Simulated S-OXY reaction mixtures were prepared from solutions of 0.003 M S-OXY and (RS)-cyclohexylphenylglycolic acid (CHPGA, a product of ester hydrolysis). Due to its low aqueous solubility, a mixture of water and methanol was used to solubilize the CHPGA. Appropriate aliquots of these solutions were used to prepare samples containing varying ratios of S-OXY to degradation product. The ratios (S)-oxybutynin:CHPGA used were 80:20, 60:40, 50:50, 40:60, 20:80, 10:90. To 50 ml of buffer containing glycine, sodium glycinate, and sodium chloride, 1 ml of each of these solutions was added.

Alkaline Hydrolysis

Solutions of S-OXY were prepared in carbonate buffer solution (pH 9.7). At predetermined times, samples were removed, quenched with 0.1 N HCl to bring the pH down to around 2.5, and stored in clean 20-ml screw-cap vials. Aliquots of the reaction mixture were removed at appropriate time intervals for about 2 weeks. At the end of the study, the pH of the reaction mixture was measured again. No appreciable changes were observed. The samples were then analyzed in triplicate using HPLC. Each batch taken for analysis was interspersed with reference standards having a concentration of 5×10^{-4} M. This procedure was repeated at pH 10. 25. With this reaction mixture, a pH change of 0.4 pH units was observed at the end of the study, and the final pH was 9.85.

pK_a Determination

The pK_a was determined using a Radiometer TTA80 titration assembly (Copenhagen, Denmark) along with a pH meter. To a 50-ml jacketed titration vessel that was maintained at a constant temperature of 25°C (under a slow stream of nitrogen) was added 25 ml of 0.001 M S-OXY. Titrant (0.1 N NaOH) was added in 0.02-ml aliquots; the solution was vigorously stirred, the stirring was stopped, and the pH was recorded after the reading had stabilized. Titrant volume and pH were recorded after each addition until the final pH reached 10. The titration mixture was then immediately filtered through a 0.45-μm filter. After rejecting the first 5–6 ml of filtrate, a sample was collected and subjected to an assay by HPLC to estimate the solubility of the free base. The titration and free-base solubility determination were conducted in duplicate.

Solubility

Solutions of S-OXY were prepared at concentrations of 0.05 M, 0.01 M, 0.002 M, and 0.0005 M. Each of these solutions was then used to prepare samples saturated with the free base at various pH values. The more concentrated solutions were used to make samples at lower pH, while the more dilute ones were used for samples at higher pH. The following steps were repeated with each of the solutions, starting with the most concentrated: (1) the initial pH of the solution was measured; (2) small aliquots of 0.1 N NaOH were added (under manual stirring) until the pH reached a predetermined value; (3) a 10-ml sample was removed after each adjustment and stored in a clean vial. All samples removed showed visible turbidity, indicating that the solution was saturated with the free base at that pH. Samples were stored at room temperature (varying between 22°C and 25°C) for 48 h. They were then filtered through 0.45-μm membrane filters, and the pH was remeasured. The solubility of the free base was determined by HPLC assay. As the range of concentrations encountered was wide, injection volume and detector absorbance units (AUFS) were varied to give suitable size peaks. A standard solution having a concentration of 5×10^{-3} M was used as a reference.

Partition Coefficient

The partition coefficient of S-OXY was determined by potentiometric titration of a two-phase system (octanol/water). The octanol was saturated with water for 24 h prior to use. Instrumentation was the same as used for the pK_a determinations. The pH was monitored as a function of titrant volume. Titration data were analyzed according to the method of Levy and Rowland (9). The experiment was repeated using different ratios of aqueous to octanol phase, and the mean partition coefficient was calculated.

Surface Activity

The surface tensions of the aqueous buffered solutions containing S-OXY were measured using a surface tensi-

ometer (Fisher Scientific Co., model 21 Tensiomat, Hanover Park, IL) with a platinum-iridium du Noüy ring (Fisher Scientific Co.) having an R/r value of 53.032. The apparent surface tension at the detachment point was corrected using a Zudiema-Waters factor. Phosphate buffer with a pH of 5.0 was used for preparing the sample solutions of S-OXY. The total buffer concentration and the ionic strength were 0.1 M and 0.1 M, respectively. The concentrations of the S-OXY sample solutions were 0.01, 0.1, 0.2, 0.5, 1.0, and 2.0 mg/ml. The aqueous solubility at pH 5.0 limited the sample solutions from having concentrations higher than 2.0 mg/ml.

Dissolution

The dissolution rate of S-OXY from compacts was determined using a stationary disk method. A known weight of S-OXY was transferred to a die and compressed to 5000 psi using a Carver press. For a dissolution test, the die was placed in a 500 ml beaker with the tablet's exposed face upward, and 350 ml of dissolution media were added to the beaker. Stirring was immediately engaged at 100 rpm using an overhead stirrer positioned 3 cm from the surface of the disk. Samples (3.0 ml) were withdrawn at different time intervals for HPLC analysis. Dissolution studies were conducted in 0.1 N HCl, pH 7.4 phosphate buffer, and buffered hexadecyltrimethylammonium bromide (CTAB) solutions.

RESULTS

Physical Characterization, Flow Properties, and Tableting Indicies

Microscopic analysis showed that the bulk drug substance was a white powder consisting of aggregates of long needles and some oblong-shape particles. Thermal analysis results (Fig. 1) indicated that S-OXY underwent an endothermic transition consistent with melting at approximately 119°C. An insignificant weight loss (0.15%) was observed by TGA up to the endothermic transition. Hot-stage microscopy conducted at the same heating rate showed that melting occurred in the range of 112°C–115°C, confirming the transition observed in the DSC as a melting endotherm. No other transitions were observed at either lower or higher temperatures. When a sample was heated in the DSC to slightly above the melting point, cooled and reheated, no subsequent transitions were observed. The XRPD pattern of S-OXY is shown in Fig. 2 and indicates that the powder was crystalline. To determine whether preferred orientation could cause a significant alteration in the XRPD pattern, a sample was lightly ground in a mortar and pestle, and a diffractogram was obtained. The diffractograms were visually indentical in peak position and relative intensity.

The moisture sorption results (Fig. 3) indicate that S-OXY did not exhibit significant moisture uptake (less than 1.0%) at the relative humidities of 0%, 11.3%, 21.6%, and 32.8%. At relative humidities of 75% and 84.3%, the samples deliquesced after 1 day and then turned to a glassy solid by the 7th day. At a relative humidity of 93.7%, the sample deliquesced in one day and yellowed by the 7th day. The equilibrium moisture content was in the rank order $0.0\% < 11.3\% < 32.8\% < 21.6\% < 52.8\% < 75.3\% < 84.3\% < 93.7\%$. The TGA weight loss data were in the rank order $21.6\% < 11.3\% < 0.0\% < 52.8\% < 32.8\% < 75.3\% < 84.3\%$. The data did not follow the expected order, but in both cases indicated that, at lower relative humidities (<53.0%), S-OXY does not exhibit significant moisture sorption. DSC data showed the existence of two endothemic transitions (at 60°C and 116°C) for samples conditioned at 52.8% relative humidity and only one (at 60°C) for samples stored at higher relative humidities. This suggested the formation of a hydrate. The formation of an additional crystal form in the presence of moisture was confirmed by XRPD. At a relative humidity of 52.8%, a mixture of the two forms was present, but at higher levels of moisture, only the presumed hydrate was observed by XRPD.

The various measured densities of S-OXY were 1.21 g/ml, 0.082 g/ml, and 0.126 g/ml for the true, apparent, and tap densities, respectively. Properties relating to its flow are shown in Table 1. Because of the subjective nature of individual types of measurements as indicators of powder flow, three methods were employed, and several excipients were evaluated using some of the methods to obtain an indication of how S-OXY might perform relative to some commonly used excipients. The compressibility index, calculated from the bulk and tap densities, indicated that S-OXY had the potential for poor flow. Angle-of-repose values of up to 40° indicate reasonable flow potential, and those above 50° suggest that the material flows only with great difficulty (10). The angle-of-repose data indicated that Avicel PH-101 and S-OXY flow with great difficulty. Compressibility index values below 15% usually give rise to good flow characteristics, while values above 25% indicate poor flow (10). Avicel PH-101 and S-OXY had values that indicated poor flow. The smaller the orifice through which a powder will freely flow, the better are its flow properties. The data for flow through an orifice indicated that Avicel PH-101 and S-OXY exhibited very poor flow. All three measures

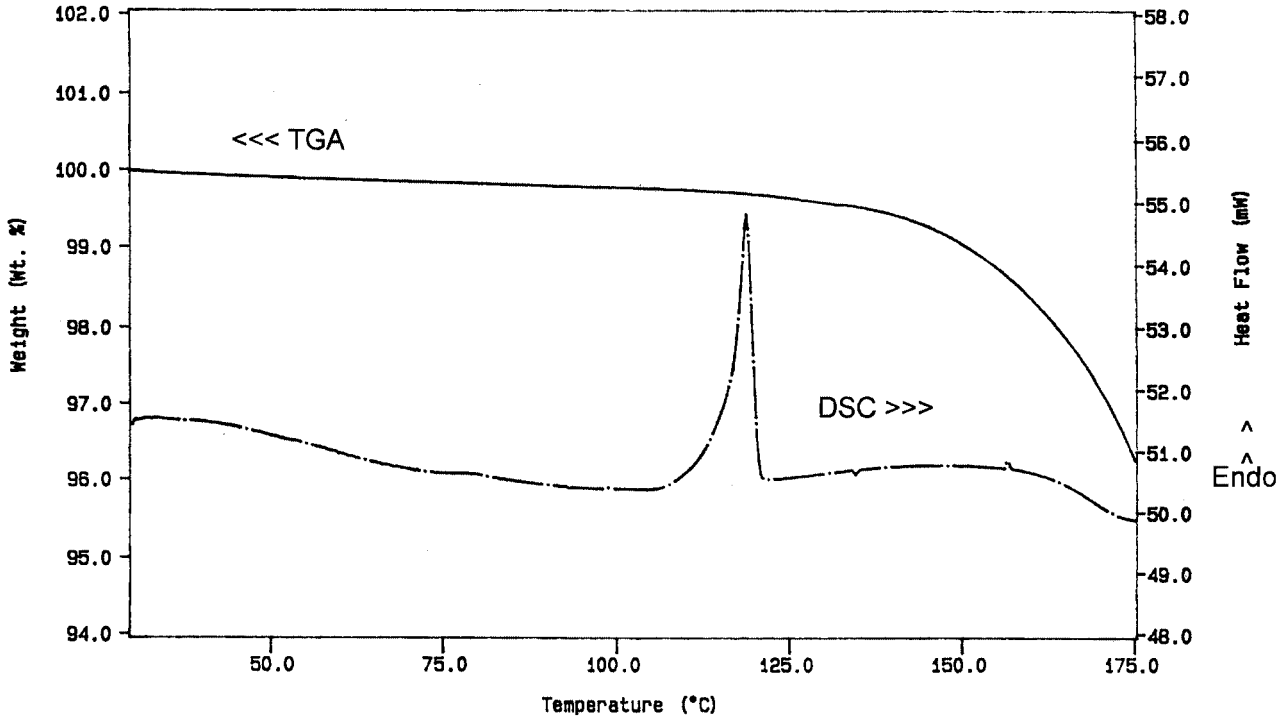

Figure 1. DSC and TGA thermograms for S-OXY. The scanning rate was 5°C/min.

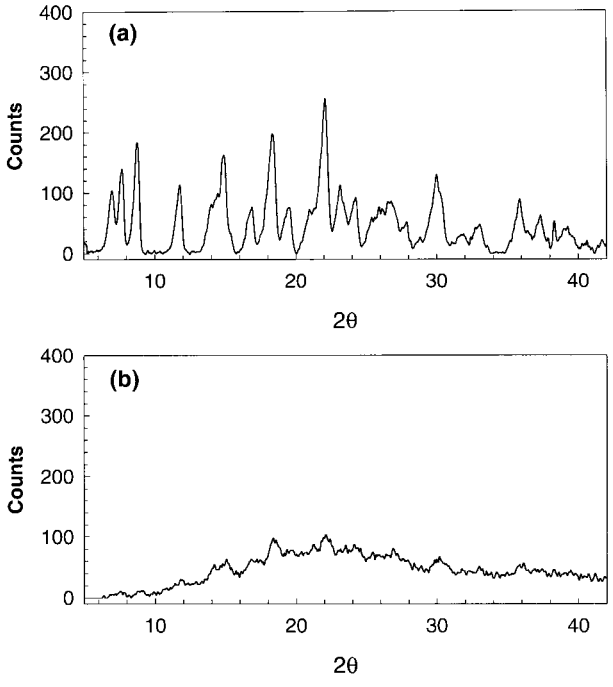

Figure 2. X-ray powder diffractograms for (a) S-OXY bulk drug substance and (b) S-OXY ball milled for 10 min.

of flow indicated that S-OXY exhibited the poorest flow of all the materials tested.

Because of the needlelike shape of the S-OXY bulk drug substance, it was expected that processing steps associated with solid dosage form manufacture would have an impact on the integrity of the particles. Therefore, it was important to assess the impact of milling on the phys-

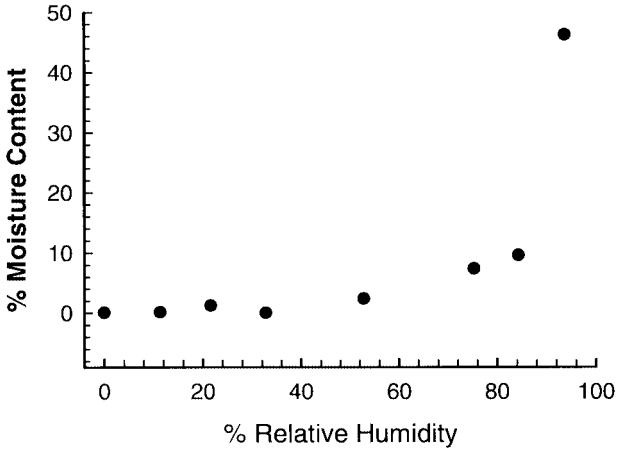

Figure 3. Moisture sorption profile for S-OXY.

Table 1

Powder Flow Measurement Results

Material	Angle of Repose (degrees)	Smallest Orifice (inches)	Compressibility Index
Emcompress	33.4	2/32	8.6
Avicel PH-101	54.0	3/4 < orifice < 1.0	22.9
Fast-flow lactose	45.5	7.32	14.5
(S)-Oxybutynin HCl	62.4	No flow in smallest orifice	36.2

ical form of SOXY. Ball milling S-OXY caused a reduction in the crystallinity, as evidenced by changes in the X-ray diffractograms (Fig. 2). Milling also had an effect on the DSC endotherm, shifting it from 118.7°C to 105.4°C after 10 min. Although ball milling represents the extreme end of processing conditions, the data indicate that comminution may result in a reduction of crystallinity.

The Hiestand tableting indices bonding index (BI), strain index (SI), and brittle fracture index (BFI) were calculated from parameters measured on S-OXY compacts. The relevant equations for these calculations are summarized elsewhere (8,11). The values for the Hiestand indicies were as follows: BI = 0.014 ± 0.002, SI = 0.020 ± 0.001, and BFI = 0.334 ± 0. 120. These values indicate that S-OXY has fairly good bonding properties and has the ability to form strong compacts. However, the BFI is quite high, indicating a strong potential for capping. This capping tendency can be reduced significantly by the addition of a plastic excipient, such as Avicel PH-101. At concentrations of 20% or more, Avicel PH-101 has been shown to reduce greatly the BFI of brittle powders (8).

Solution Properties and Dissolution

The profile of ln C versus time for the degradation of S-OXY in solution is shown in Fig. 4. On the basis of the profile and appearance of the known CHPGA ester hydrolysis product, S-OXY undergoes degradation by ester hydrolysis at alkaline pH by apparent first-order kinetics. The observed rate constants k_{obs} were found to be 0.008 h^{-1} and 0.0552 h^{-1} at pH 9.69 and 10.25, respectively. The half-lives of degradation were 85.2 and 12.5 h. The increase in rate constant with an increase in pH indicates that degradation is dependent on hydroxyl ion concentration. These results are consistent with the degradation of oxybutynin that has been previously reported in the literature (12).

The pK_a was determined by analyzing the titration data according to the method of Levy and Rowland (9). A plot of Z' versus (H^+) was made according to the relationship

$$Z' = M^+ + H^+ - OH^-$$

where M^+ is the absolute number of moles of base added to solution, H^+ is the absolute number of moles of hydrogen ion present in solution, and OH^- is the absolute number of moles of hydroxyl ion present in solution. The free-base solubility was determined to be 3.6 to 4.0 × 10^{-5} M. The pK_a was then calculated according to the following equation:

$$1/K_a = \text{Slope}/B_{sol}$$

where B_{sol} is the absolute number of moles of un-ionized species present in 25 ml of saturated solution and was determined to be 0.9 to 1.0 × 10^{-6} M. The estimated pK_a of S-OXY from the average of two runs was 7.75. Using the pK_a value, a predicted solubility profile was then generated using a free-base solubility of 3.8 × 10^{-5} M. The

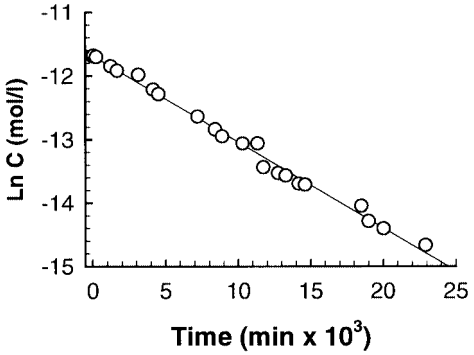

Figure 4. Solution state degradation kinetics of S-OXY in buffered aqueous solutions.

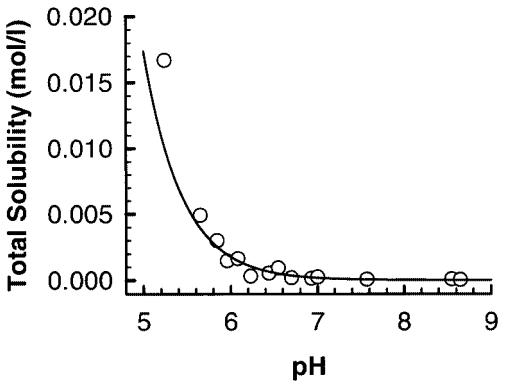

Figure 5. Measured (○) and calculated (——) pH solubility profile for S-OXY. Calculated values based on $pK_a = 7.71$ and $S_0 = 3.8 \times 10^{-5}$ M.

experimental and predicted solubility profiles corresponded closely (Fig. 5).

The octanol/buffer partition coefficient was determined using a titration method, and data were analyzed using the method of Levy and Rowland (9). Apparent K_a values were obtained from plots of titrant versus pH. The partition coefficient was calculated using suitable formulas (9). The mean partition coefficient log P was 3.33.

To examine whether S-OXY had any potential for self-association, the surface tension of S-OXY was measured over a range of concentrations. The values of the surface tensions determined for S-OXY are shown in Fig. 6. A solution pH of approximately 5 was utilized to ensure that adequately high concentrations could be

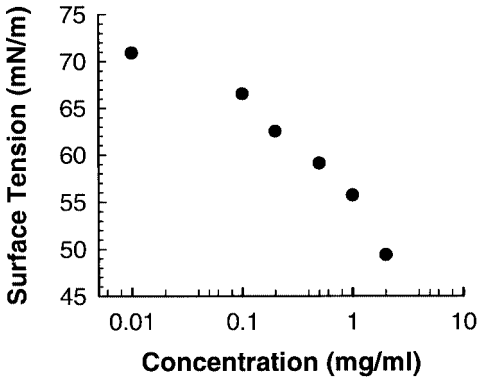

Figure 6. Surface tension of aqueous S-OXY at pH 5.0 as a function of concentration (log scale).

achieved. On the basis of these data, it was concluded that S-OXY exhibits surface activity, but does not form micelles since no critical point was observed in the plot of surface tension versus log C.

The dissolution of S-OXY was evaluated at representative pH values using compressed disks of fixed surface area under controlled stirring conditions. In 0.1 N HCl, S-OXY dissolved rapidly, and the surface of the disk was eroded. In pH 7.4 phosphate buffer, an insignificant amount of dissolution occurred, necessitating inclusion of a surfactant. When 1% CTAB was used in pH 7.4 phosphate buffer, dissolution progressed more rapidly. The initial dissolution rate, estimated from the initial slope of the curve of the mass versus time, was comparable to that obtained for 0.1 N HCl.

DISCUSSION

On the basis of the physical characterization studies, S-OXY bulk drug substance was found to be a crystalline solid that was sensitive to a presumed hydrate formation at relative humidities greater than 53%. Therefore, the bulk drug substance and potential dosage forms should be well protected from moisture. The bulk drug substance possessed poor flow properties, indicating the need for inclusion of an adequate glidant to improve powder processability. Its crystal form was altered on harsh mechanical treatment, indicating that milling should be avoided as a particle size reduction method to prevent induction of amorphous content. Analysis of the Hiestand tableting indices demonstrated that S-OXY may have a propensity for capping, necessitating the use of a plastically deformable tablet excipient such as Avicel PH-101. The potential for alteration of the S-OXY crystal form on contact with water potentially precludes the use of wet granulation methods. Altogether, these findings suggest that, in the development of a solid dosage form of S-OXY, a dry granulation process is recommended.

Characterization of the solution-state properties of S-OXY revealed that no special considerations, other than maintaining the pH of analytical solutions below pH 7, need to be made relative to manipulation of solution-state samples for analysis. The physicochemical properties of S-OXY in solution were similar to those of the racemate (12). Dissolution studies indicated that a surfactant was necessary for development of a pH 7.4 dissolution testing method.

In conclusion, these preformulation studies serve as a basis for recommendation of formulation development

strategies for S-OXY and demonstrate the necessity of thorough characterization of an improved chemical entity (ICE™).

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