

# Effects of Dissolved Gases in Surfactant Dissolution Media

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## Abstract

The effects of dissolved gases on the performance of aqueous dissolution media have been studied extensively, but little has been published regarding the effect of dissolved gases on surfactant containing dissolution media. There are various methods available to control the level of dissolved gases in surfactant media, but regardless of the method used or level of dissolved gases achieved, the media will equilibrate to atmospheric conditions within approximately one hour. Therefore, elaborate techniques to control the level of dissolved gases are unnecessary, and the variability associated with dissolved gases can be minimized by performing the dissolution experiment at equilibrium.

## Introduction

Dissolved gases, with dissolved oxygen serving as the primary marker, have been widely documented to influence dissolution experiments. The dissolved gases can cause changes in the performance of the dissolution medium by changing pH, forming bubbles on the dosage form or altering the interaction of the medium and the active pharmaceutical ingredient [1]. Extensive studies have been performed examining appropriate techniques for the removal of dissolved gases from aqueous media which include a combination of heating and vacuum filtration followed by stirring under vacuum (USP method), vacuum filtration, heating alone, sonication, helium sparging, and membrane filtration [2-6].

Regardless of technique, reaeration of the media is a concern. Reaeration can be defined as the process of gases from the atmosphere dissolving into the liquid phase raising the level of dissolved gases. Studies have shown that regardless of technique used to remove dissolved gases, reaeration will occur, and the equilibrium dissolved oxygen value will be relatively unaffected [7]. The only influence the technique will have is the amount of dissolved gas removed, and the time it will take for the media to equilibrate to atmospheric conditions. Media that have reached equilibrium do not exhibit performance changes stemming from the technique used to remove the dissolved gases.

While the effect of dissolved gases on aqueous media has been studied extensively, the effect on surfactant containing media has not been addressed directly. The USP General Chapter <711> states, "dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing" [8]. This statement does not specify type of media, but suggests that if dissolved gases do not

affect the results, the level of dissolved gases can be largely ignored.

This study investigates whether the level of dissolved gases is a source of variability that should be monitored when performing dissolution tests that utilize a surfactant-containing medium by examining the dissolution performance of oral dosage forms in media with a range of dissolved oxygen levels. Furthermore, the USP method of dissolved gases removal along with other accepted methods will be examined to determine their influence on equilibrium values of dissolved gases.

## Experimental Media Equilibration Study-

Three representative surfactant-containing dissolution media were prepared in water: 0.5% sodium dodecylsulfate (Sigma Chemical Co., St. Louis, MO), 2.0% sodium dodecylsulfate and 0.5% Tween 80 (TCI, Tokyo, Japan). The first treatment of media was placed in dissolution vessels immediately after preparation, the media were agitated at 50 rpm using Apparatus II. A second treatment of media was sparged with helium for 5 and 30 minutes after preparation and then placed in dissolution vessels and agitated at 50 rpm using apparatus II after each treatment. A third treatment of media was prepared according to the USP degassing procedure, placed in dissolution vessels and agitated at 50 rpm using Apparatus II. The dissolved oxygen content of all three media was measured upon placement in the vessels, and at predetermined timepoints (Figure 1-3). Only the USP method of degassing required preheating of the media, all other treatments were placed in the vessels at room temperature. The dissolved oxygen content was determined using the Winkler titration method [9,10].

All dissolved oxygen measurements were

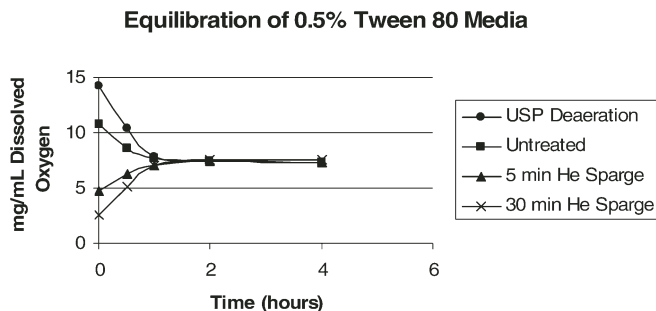


Figure 1. Dissolved oxygen equilibration in 0.5% Tween media.

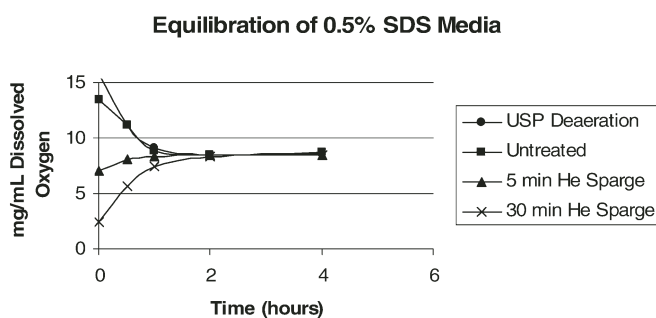


Figure 2. Dissolved oxygen equilibration in 0.5% SDS media

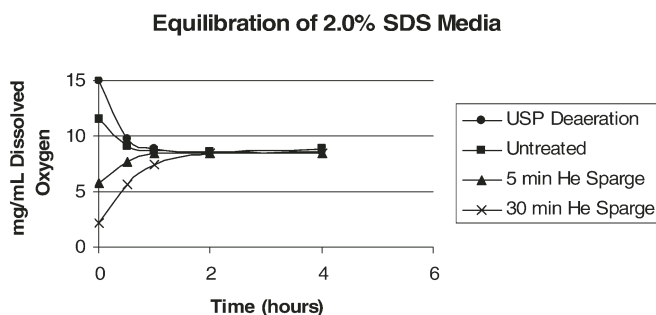


Figure 3. Dissolved oxygen equilibration in 2.0% SDS media.

conducted using the Winkler titration method. Attempts were made at using dissolved oxygen meters, but unexpected and inconsistent values were obtained. It is suspected that the presence of the surfactant interfered with the probe on the dissolved oxygen meter. The Winkler titration is a reaction between manganese and oxygen and is not likely to be affected by other components of the solution.

### Effect of Dissolved Gases Content on Dissolution Rate

To determine if the level of dissolved gases affects surfactant media differently than aqueous media, the series of experiments described below was conducted. The experiments were conducted side by side using media that had

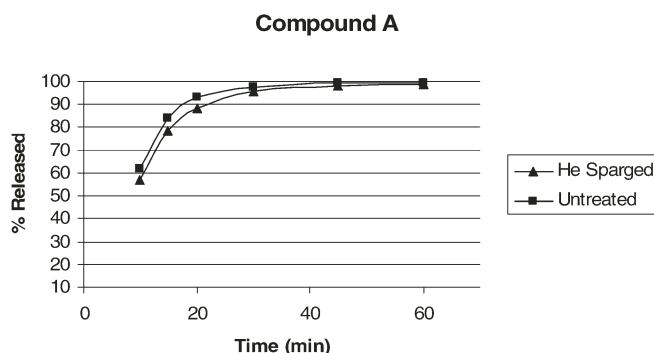


Figure 4. Release profile of compound A in helium sparged and untreated 1.0% SDS media.

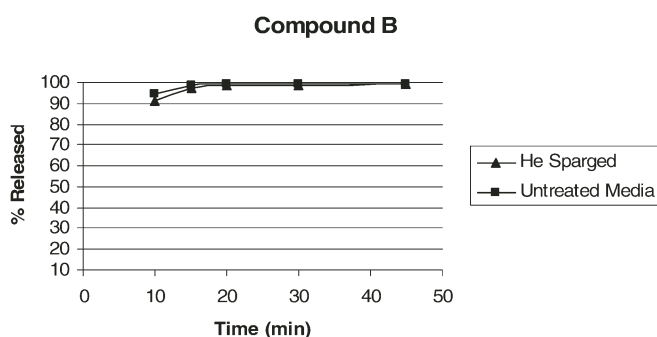


Figure 5. Release profile of compound B in helium sparged and untreated 0.5% SDS media.

been treated by helium sparging, and media that was left untreated (unless otherwise stated). The dissolved oxygen content was measured upon preparation and at the start of the dissolution test.

To examine if any effects from dissolved gases were dependent upon dosage form, a series of experiments was conducted using three different dosage forms. First, compound A (a compressed tablet with a 10% drug load and standard pharmaceutical excipients) was examined. This method utilizes 1.0% sodium dodecyl sulfate (50 rpm, Apparatus II) and the dissolved oxygen content at the start of experiments was 8.81 mg/L and 3.99 mg/L for the untreated and helium sparged media respectively. The % of compound A released was monitored by HPLC-UV at 10, 15, 20, 30, 45 and 60 minutes (Figure 4).

Next, compound B (a film coated tablet with a 25% drug load and standard pharmaceutical excipients) was examined. This method utilizes 0.5% sodium dodecyl sulfate (75 rpm, Apparatus II) and the dissolved oxygen content at the start of the experiment was 11.1 mg/L and 6.2 mg/L for the untreated and helium sparged media respectively. The percent of compound B released was monitored by HPLC-UV at 10, 15, 20, 30 and 45 minutes (Figure 5). Finally, a

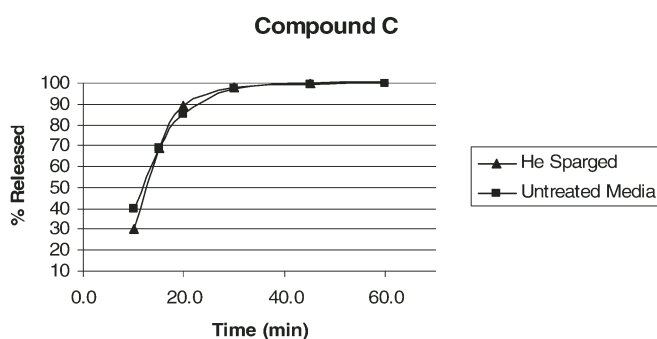


Figure 6. Release profile of Compound C in helium sparged and untreated 0.5% Tween 80 media.

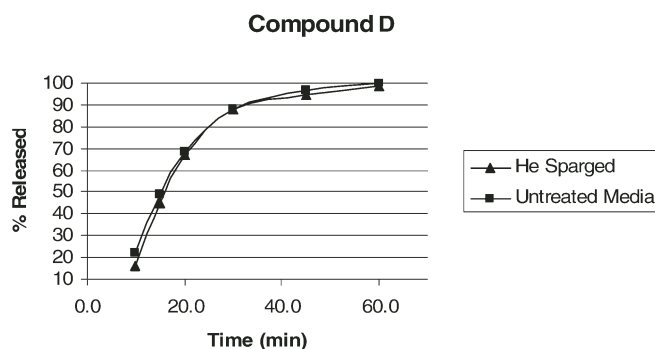


Figure 7. Release profile of compound D in helium sparged and untreated 0.5% Tween 80 media.

formulation with two active components, compound C (10% drug loading) and compound D (5% drug loading) in a hard gelatin capsule was examined. This method utilizes 0.3% Tween 80 medium (in 25 mM  $\text{NaH}_2\text{PO}_4$ , pH 7.0, 100 rpm, Apparatus II) and the dissolved oxygen content at the start of the experiment was 8.8 mg/L and 4.9 mg/L for the untreated and helium sparged media respectively. The percent of compounds C and D released was monitored by HPLC-UV at 10, 15, 20, 30, 45 and 60 minutes (Figures 6 and 7).

A second set of experiments was conducted to examine the effect of dissolved gases on a product that was known to be influenced by dissolved gases in aqueous media. This experiment involved the USP calibrator prednisone tablet formulation. The formulation is used to calibrate dissolution baths, and its release rate is known to be influenced by the level of dissolved gases in water. Although the standard dissolution method does not call for surfactants to be used, the experiment was performed with very low levels of surfactant (0.1% and 0.3% SDS in water). Along with sparged media, aerated media were used in place of untreated media to maximize the difference in dissolved oxygen levels. The aerated media were generated by bubbling air through the media for 2 minutes. The dissolved oxygen content at the start of the experiment using 0.1% SDS was 13.4 mg/L and 3.4 mg/L for the aerated and helium sparged media respectively. The dissolved oxygen content at the start of the experiment using 0.3% SDS was 13.9 mg/L and 3.1 mg/L for the aerated and helium sparged media respectively. The media were heated prior to placing them in the dissolution bath to minimize the time the media sat in the vessels before beginning the experiment. The percent of prednisone released was monitored by direct UV at 10, 15, 20, 30 and 45 minutes (Figure 8).

A final set of experiments was conducted to examine the effect that allowing the dissolution media to reach equilibrium would have on a system that had previously been shown to be influenced by the level of dissolved gases. This experiment was a repeat of the previous experiment involving prednisone (using only the 0.3% SDS) with a change in how the media were treated prior to the start of the dissolution. In this experiment the first set of media were helium sparged and placed immediately in the

vessels. The second set of media was aerated and placed in the vessels. The two sets of media were not preheated prior to placing them in the vessels. Upon placement in the vessels the dissolved oxygen content was 13.4 mg/L and 3.9 mg/L for the aerated and sparged media respectively. These media were then allowed to equilibrate for 30 minutes past the temperature equilibrium (approximately 1 hour total from placement in the vessels). At the initiation of the dissolution experiment, the dissolved oxygen content was 7.8 mg/L and 6.9 mg/L for the aerated and sparged media respectively. The percent of prednisone released was monitored by direct UV at 10, 15, 20, 30 and 45 minutes (Figure 9).

## Results and Discussion

The results from the equilibration of media study show that all three media equilibrated in the dissolution bath (stirring at 50 rpm) in approximately 1 hour regardless of the starting level of dissolved gases. The USP method of degassing showed an increase in the amount of dissolved gases present in the media. This is likely due to the filtration step where a significant amount of foaming was observed in all three media. In contrast, the helium flow during sparging was kept minimal to avoid excess foaming of the media. This required a longer sparging time for low levels of dissolved gases to be reached.

The equilibration times that were observed for the surfactant media are significantly faster than those observed for aqueous media. When similar equilibration experiments were conducted on aqueous media, equilibration times of up to 5.5 hours were observed [11].

A higher equilibration concentration of dissolved gases was also observed for the surfactant containing media compared with that of aqueous media. A level of approximately 5.5 mg/L [11] of dissolved oxygen was observed for aqueous media, while levels ranging from 7.5 to 8.5 mg/L were observed for surfactant containing media.

The three formulated products that were examined show a 3-9% faster release at early timepoints when the dissolution is performed in untreated media as opposed to helium sparged media. The difference in release rates diminishes at later timepoints with nearly identical values obtained after

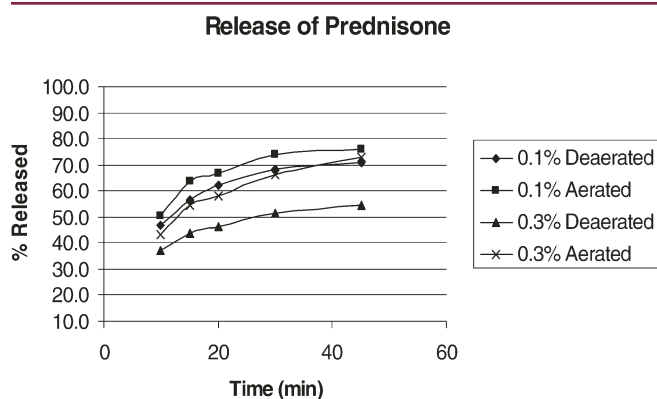


Figure 8. Release profile of Prednisone in 0.3% and 0.1% SDS.

20 minutes. The similarity in the profiles after 20 minutes is expected as equilibrium has been established and the environment in the dissolution vessels is indistinguishable. The overall dissolution curves show a strong similarity to one another indicating no significant effect from the starting level of dissolved gases.

The experiments performed with prednisone, a product with a known sensitivity to levels of dissolved gases, indicate a difference in release rate depending on level of dissolved gases. This difference was observed to a greater extent in the 0.3% SDS medium than in the 0.1% SDS medium. An F2 value of 62 (5 points used in the calculation) was obtained for the 0.1% SDS medium and a value of 45 (5 points used in the calculation) was obtained for the 0.3% SDS medium when comparing release profiles from sparged and aerated media. The value obtained for the 0.3% SDS medium experiment is below 50, and indicates a dissimilar profile according to SUPAC guidelines. When the 0.3% SDS media (helium sparged and aerated) were allowed to equilibrate in the dissolution bath for 30 minutes (post temperature equilibration), the curves had an F2 value of 89 (5 points used in the calculation).

## Conclusions

The level of dissolved gases present in the dissolution media can have an effect on the release profile of a dosage form. An experiment performed in media containing a high level of dissolved gases will likely yield a faster release than the same experiment run at equilibrium concentrations. Not performing the dissolution at equilibrium conditions could cause difficulties during method validation or method transfer. However, the influence of dissolved gases is less of a concern when using surfactant containing dissolution media because of the rapid equilibration time compared with aqueous media. This increase in equilibration rate is most likely due to the decrease in surface tension caused by the addition of surfactant [12]. The formation of micelles is probably not a contributor to the faster equilibration as the faster equilibration times were also observed in media with concentrations as low as 0.1% which is below the critical micelle concentration for SDS.

This study showed that regardless of technique used to

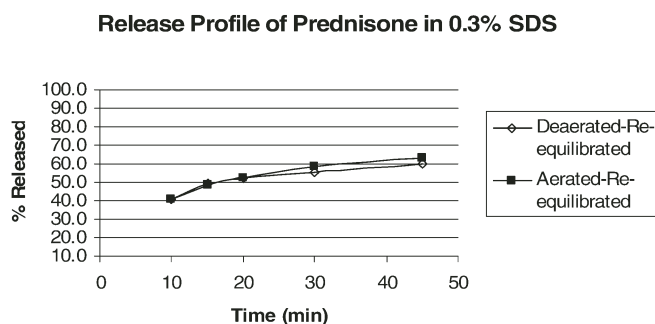


Figure 9. Release profile of Prednisone in equilibrated 0.3% SDS.

alter the initial concentration of dissolved gases, equilibrium will be reached in less than one hour. Equilibration of dissolution media with regards to dissolved gases can most easily be achieved by stirring at 50 rpm (Apparatus II) in the dissolution vessels for one hour or less. The time needed to ensure minimal variability from dissolved gases may be less than one hour as no experiments were conducted to determine how much of a discrepancy in dissolved gases will cause a change in release rate. Allowing the media to reach equilibrium in the dissolution vessels is a technique that can be readily used by all laboratories with only a minimal amount of additional time required and no additional equipment.

The end goal of a dissolution method is to produce a reliable measure of the quality of the dosage form. To prevent artificial changes in the test results it is important that the media reach equilibrium with regards to the dissolved gases before a test is initiated.

If media are not allowed to equilibrate prior to the initiation of the test, variability may be observed at early time-points. This work has shown that even in the case of a product that is significantly affected by dissolved gases, allowing time for the media to come to equilibrium eliminates this variability. Ensuring that dissolved gases are at equilibrium can increase the reproducibility and quality of dissolution results generated at all laboratories.

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