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Dissolved Oxygen as a Measure for De- and Reaeration of Aqueous Media for Dissolution Testing

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Abstract

In order to obtain reliable and reproducible results from dissolution tests, it is often necessary to deaerate the dissolution medium. In the current work, four different methods of degassing the medium were compared by measuring the concentration of oxygen in the medium before and after the deaeration procedure. The oxygen concentration was determined under defined conditions by using an oxygen sensor based on a Clark electrode. The method described in the USP 23 (heating to 45°C plus filtration) achieved an 85% ±11% reduction in the oxygen concentration. Heating to 100°C resulted in a reduction of only 50% ±3%, while filtration reduced the oxygen content by 65% ±4%. A method developed in our laboratory combining ultrasound and application of a vacuum achieved a 95% ±2% reduction. After degassing, the medium must usually be transferred to the dissolution vessels before the test is run. The results indicated that even careful filling resulted in a 37% increase in the oxygen content, while typical filling procedures resulted in an almost three-fold increase. It was further shown that the medium gradually becomes re-saturated during the dissolution test itself, at a rate that is dependent on the apparatus (basket versus paddle) and the rotational speed. 120 minutes into the test, the oxygen concentration was already 60% of the saturation value. Conclusions: The measurement of oxygen was demonstrated to be a reproducible and direct method for measuring the efficiency of deaeration. It was further shown that the efficiency of deaeration is highly dependent on the method used, and that re-introduction of air into the medium occurs not only during filling of the dissolution vessels but also during the dissolution test.

Introduction

Many authors emphasize the importance of deaeration of the media when performing dissolution tests for solid oral dosage forms. Calibrator tablets are commonly used to investigate whether or not the deaeration procedure was successful (1). A potential drawback of calibrator tablets is that they exhibit differences in hardness, particle size distribution of the active ingredient and the excipients that are inherent from the manufacturing process etc.. Therefore it would be useful to compare deaeration methods by a method that is independent of the manufacturing process.

As oxygen is ubiquitous, exhibits a constant partial pressure at a given altitude, and is easy to quantify with sensitive electrodes, it can be used to represent the content of air dissolved in liquids. Furthermore, since oxygen possesses a low, virtually pH-independent solubility in water (2), its dissolution rate is not subject to fluctuations in the pH of the medium. The objectives of the present work were to compare various deaeration methods and to investigate the rate of reaeration of the medium during the dissolution test itself, using oxygen as the test solute.

Experimental

2.1 Deaeration of dissolution media

Purified water was deaerated according to four different methods.

2.1.1. "USP method"

The medium was heated to 45°C, filtered through 0.45µm membrane filters (diameter 50 mm/ Schleicher & Schüll, Dassel, Germany) under vacuum and stirred for about 5 minutes(3).

2.1.2. Filtering at Room Temperature (21°C):

To evaluate the efficiency of the filtration step separately, the medium was filtered at 21°C using the filters identical to those above.

2.1.3. Heating (45°C /100°C):

To evaluate the efficiency of the heating step separately, 2 L of medium were heated for 3 min. with vigorous stirring to 45°C and 100°C, respectively. Then the medium was cooled immediately with the aid of an ice-bath to 37°C.

2.1.4. "Ultrasound/ Vacuum method"

The dissolution medium was preheated to 37°C and transferred to a 2 L flask. The flask was placed in a sonicator bath (Transonic Digital 790/H,

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Elma, Singen) and the medium was deaerated using a combination of ultrasound and vacuum (approx.80 mbar, produced by a membrane vacuum pump (MZ 2C Synchro, Vacuubrand, Wertheim)). In an additional experiment, the procedure was repeated, with the exception of the temperature, which in this case was held at 21°C. All experiments were performed in triplicate.

2.2. Reaeration during dissolution test procedure

The rate of reaeration of the medium during the dissolution test was determined in 900 mL medium (water deaerated according to method 2.1.4.) using Type 1 and 2 apparatus (DT6, Erweka, Heusenstamm, Germany) according to the USP 23. The rotational speed was set at 50 rpm and 100 rpm for the paddle and for the basket experiments, since these speeds are frequently cited in current pharmacopeia (4). Additionally, the rate of reaeration due to diffusion only was assessed in stagnant media (0 rpm).

2.3. Reaeration during filling procedures

To evaluate the possibility that partial reaeration of the media occurs during manual filling of the media into the dissolution beakers we performed the following test:

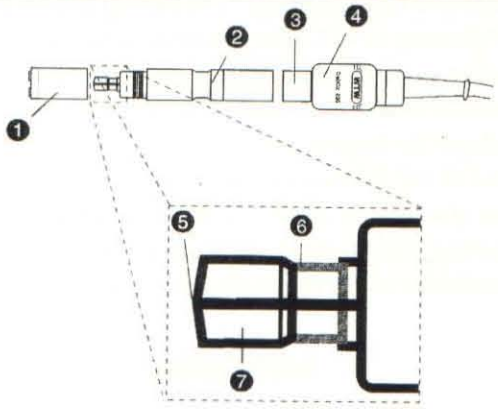
The dissolution vessels were carefully filled with both vessels held at an angle so that the medium could be transferred slowly and carefully, without inducing any turbulence (method B 1 and 2).

In a further set of experiments we tried to mimic the "typical filling procedure"; the dissolution vessel was held vertical and filled from 5 -10 cm above, without any special care (method N1 and 2)

2.4. Determination of the concentration of oxygen

The oxygen concentration was measured directly using a CLARK (4) electrode (Oxi 323 A, WTW, Weilheim, Germany) with an oxygen sensitive sensor (WTW CellOx 325). The sensor is calibrated by a two point procedure. The signal at zero current corresponds to less than 0.1 % of the saturation value, while at maximum current the signal corresponds to the partial pressure of oxygen in the atmosphere. The reproducibility of the individual determinations was better than ± 0.02 mg/L. The electrode itself consumes 11.4 µg/h of the available oxygen. This amount is negligible compared to the reported concentrations in the media. When determining the content of oxygen, the sensor always was located 7 cm underneath the liquid surface to account for the concentration gradient, and the temperature was maintained within ± 1°C of the desired value. Figure 1 demonstrates how the sensor works: The gold cathode reduces dissolved oxygen to solvated hydroxide ions while the lead anode is oxidated. The resulting current depends on the partial pressure and therefore the corresponding concentration of oxygen in the dissolution medium.

Aufbaud des Sauerstoffsensors CellOx 325
Construction of the oxygen sensor CellOx 325



1	Membrankopf WP 90	*Membrane head*
2	Temperaturfühler	*Temperature sensor*
3	Schaft	*Shaft*
4	Abschlußkopf	*Closing head*
5	Arbeitselektrode (Goldkathode)	*Working electrode (gold cathode)*
6	Gegenelektrode (Bleianode)	*Counter electrode (lead anode)*
7	Isolator	*Isolator*

Figure 1 Construction of the oxygen sensor used for the described experiments. Figure taken from "WTW Oxy 323/325 instruction manual" (WTW, Weilheim, Germany)

Results and Discussion

3.1. Deaeration

Table 1 summarizes the results for the deaeration procedures. Merely heating to 45°C resulted in almost no reduction of the content of oxygen (10 %). Boiling the water for 3 minutes yielded a 50 % decrease of dissolved oxygen whereas filtering effected a decrease of 65 % compared with the content before deaeration. The standard USP method (USPM) reduced the content of dissolved oxygen in the medium by almost 85 %. Typically it is possible to achieve a final concentration of oxygen of about 1 mg/L. Nevertheless, the most efficient method was the combination of ultrasound and vacuum (UVM). With this method, the starting content of oxygen was reduced by almost 95 % with a standard deviation of less than 4 % and 2 % at 21°C and 37°C, respectively.

3.2. Reaeration

Table 2 reports the rate of reaeration during frequently used dissolution tests. 120 minutes into the test the media are almost com-

Table 1. Decrease in content of oxygen in the medium after applying different deaeration techniques

method	samples (n)	temperature (°C)	oxygenconc.(21°C) before deaeration (mg/L ± sd)	decrease of oxygenconc. after deaeration (mg/L ± sd)	(% ± sd)
USPM	9	43	7,3 ± 0,8	6,2 ± 0,7	84,9 ± 11,3
F	3	21	8,4 ± 0,3	5,5 ± 0,2	65,5 ± 3,6
E 45	3	43	7,0 ± 0,1	0,7 ± 0,1	10,0 ± 14,3
E 100	3	43	7,0 ± 0,1	3,4 ± 0,1	48,6 ± 2,9
UVM 37	8	37	7,4 ± 0,2	7,0 ± 0,1	94,6 ± 1,4
UVM 21	3	21	9,0 ± 0,2	8,4 ± 0,3	93,3 ± 3,6

Legend

USPN	"USP Method"
F	Filtering at RT (21±1 °C)
E45/E100	Heating to 45°C (±C) and 100°C (±1 °C), respectively
UVM37/UVM21	"Ultrasound Vacuum Method" at 37°C (±1 °C) and 21°C (±1 °C), respectively

Table 2. Resaturation of the medium with oxygen during dissolution tests.

time (min.)	0 rpm (n=1) content (mg/L)	increase (%)	50 rpm paddle (n=3) content (mg/L)	increase (%)	100 rpm basket (n=1) content (mg/L)	increase (%)
0	2.3	-	1.4	-	2.2	-
30	2.8	21.7	2.5	72.2	2.8	27.4
60	3.1	10.7	3.2	30.6	3.4	18.3
90	3.5	12.9	3.9	19.1	3.8	13.1
120	3.8	8.6	4.3	12.2	4.2	9.7

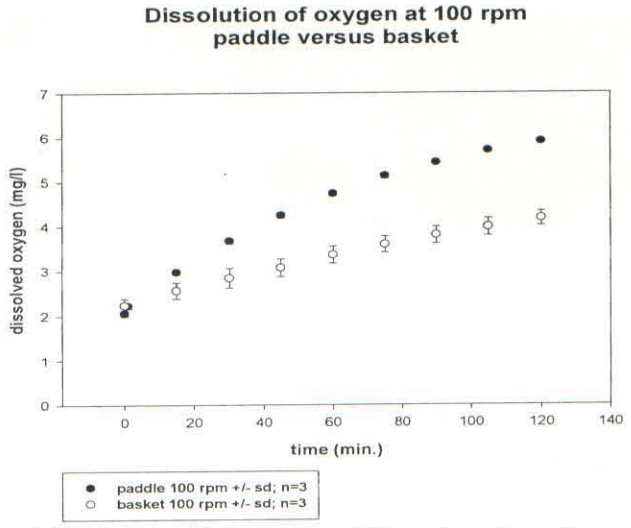


Figure 2. Dissolution profile for oxygen at 100 rpm for paddle and basket. Experiments performed in triplicate.

Table 3. Increase in the oxygen content for different filling procedures.

method	samples n	temperature at measuring (°C)	oxygenconc. before filling (mg/L ± sd)	at (°C)	oxygenconc. increase rate (mg/L ± sd)	(%)
B 1	15	37	1.1 ± 0.4	21	0.4 ± 0.1	36.4 ± 25.0
B 2	3	37	0.6 ± 0.1	21	0.5 ± 0.1	83.3 ± 20.0
N 1	10	37	0.4 ± 0.1	37	1.1 ± 0.1	275.0 ± 9.1
N 2	3	21	1.1 ± 0.3	21	1.3 ± 0.3	118.2 ± 23.1

B	carefully filled	oxygen conc. at start	B 1 = 1.1 mg/l
		oxygen conc. at start	B 2 = 0.6 mg/l
N	"normally" filled	temperature	N 1 = 37°C
		temperature	N 2 = 21°C

pletely reaerated. It is notable, that the paddle method induces much faster reaeration than the basket method. For example, 50 rpm paddle introduces 2.9 mg/L of oxygen into the medium within 120 minutes, whereas the 100 rpm basket procedure results in an uptake of 2 mg/L in the same time interval. The data also indicate that there is an uptake of oxygen even when the medium is not exposed to forced convection. In the absence of stirring, the oxygen concentration in the medium increases by 1. 5 mg/L after 120 min.. It can be hypothesized that natural convection - caused by small temperature differences in the water bath - as well as diffusion contributes to this effect.

The graph at left (Fig.2) describes the rate of reaeration of the dissolution test medium at 100 rpm. The paddle apparatus is compared with the basket at approximately the same starting concentration of oxygen. It is clearly shown that the different test conditions result in different rates of oxygen uptake. Further it is indicated that for long term dissolution tests with extended release dosage forms any efforts to deaerate the media are nullified by the dissolution test procedure itself.

The two filling methods clearly exhibit different levels of oxygen reaeration (Table 3): about 0.5 mg/L for the "careful technique" (B) and more than 1 mg/L for the "standard laboratory procedure" (N). If the "starting" concentration of oxygen is very low (under 1 mg/L oxygen content before filling the dissolution vessels) as may be the case when deaeration *and* filling are performed at 37°C (N 1), the increase in oxygen concentration during filling may be as great as 275 %.

For further details about the grounds for deaerating of dissolution media and the rationale for using oxygen as a "dissolution tool" see [6].

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Conclusions

A fast, efficient and reproducible deaeration method, without the need for expensive helium was developed. This method consist of a combination of ultrasound and vacuum. The efficiency of deaeration was measured directly by the decrease in oxygen concentration. The advantage of direct measurement over the use of calibrator tablets for this purpose is clear: it avoids the influence of any tablet-to-tablet differences on the results.

The reported data show that the rate of reaeration is influenced by the way the deaerated medium is filled into the dissolution vessels as well as is being highly dependent on the dissolution method.

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