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Research paper

Online monitoring of dissolution tests using dedicated potentiometric sensors in biorelevant media

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ABSTRACT

The performance of the Ion-Selective Electrode (ISE) for *in vitro* dissolution testing using biorelevant media was evaluated in this study. *In vitro* dissolution was carried out using USP apparatus 2 (paddle method) with classical and with updated biorelevant media to simulate the pre- and postprandial states. The ISE was used as an analytical stand-alone system and in combination with a single-point HPLC–UV measurement. A modified method enabling the use of the ISE for very poorly soluble substances is also proposed.

In terms of f_2-factor, the results acquired using the ISE for the drug diphenhydramine-HCl were found to be very similar to the results obtained by manual sampling followed by HPLC–UV analysis. In Fed State Simulated Gastric Fluid (FeSSGF), a medium containing 50% milk, the ISE is more practical since the need to separate proteins from the analyte prior to HPLC–UV analysis is eliminated. Further work will be needed to establish ISE methodology for Fed State Simulated Intestinal Fluid (FeSSIF) media.

In summary, the ISE has promise as an analytical tool for research and development applications.

1. Introduction

Dissolution testing is an important analytical tool for the development of orally administered solid dosage forms. Originally introduced as a more discriminating, add-on test to the disintegration test, dissolution testing has become closely interwoven with the development of *in vitro–in vivo*-correlations [1]. Nowadays, dissolution testing is one of the most important tools in formulation development of new chemical entities.

According to the quality-by-design principle, it is essential to gather as much information about the dosage form as early as possible in the process of development. New dosage forms aiming at instant release of the drug tend to form a stable supersaturation (e.g. through complexation with cyclodextrins) or possess very rapid dissolution rates (e.g. melt extrudates and nanosized drugs) [2,3]. The latter formulations are often difficult to characterize accurately in dissolution testing. For instance, nanocrystals are often sufficiently small enough to pass through 0.45-μm filters, which are usually employed to separate the analyte from undissolved material [4]. In our laboratories, we have also observed that some lipid formulations and melt extrudates are hard to filter due to clogging of the filter. When just a limited number of samples are taken and the subsequent filtration proves to be difficult, the results are often incomplete and may even be misleading.

In other cases, it is not the dosage form itself that causes difficulties but the dissolution medium. Biorelevant media were introduced to investigate dissolution behavior and possible food effects of poorly soluble drugs [5,6]. In 2008, these media were updated to better resemble the human physiology and, among others, Fed State Simulated Gastric Fluid (FeSSGF) was introduced to simulate the fed state gastric fluids [7]. The use of milk as part of the dissolution medium in FeSSGF (50%) prohibits sample filtration through the standard pore size of 0.45 μm, since milk proteins clog the filter membrane. Therefore, a more labor-intensive sample preparation including filtration through larger pore size filters followed by protein precipitation, application of cosolvents and subsequent centrifugation has to be used [8]. This kind of sample preparation prohibits accurate characterization of the dissolution of nanosized drugs because the filter pore size used is 2.7 μm, which is by definition far larger than the average size of a nanosized API. Other authors have reported techniques as well to separate dissolved

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from solid drug in milky media, but none of them appears to be less labor-intensive or appropriate for very rapidly dissolving drug formulations [9,10].

For all these reasons, continuous *in situ* monitoring of the dissolution process would be highly desirable.

To monitor a dissolution process online, flow-through UV analysis and fiber optics can be employed, but both these methods are sensitive to light scattering effects caused by the medium or the formulation [11]. Since there is no filtration step in these methods, the baseline must be corrected for UV measurement [12].

In 2007, Bohets et al. introduced a potentiometric, Ion-Selective Electrode sensor system (ISE) to monitor the process of dissolution online. The ISE is sensitive for a given charged model drug (i.e. each ISE is conditioned for its target drug analyte), but insensitive to uncharged molecules and undissolved material [13]. Peeters et al. have shown that these potentiometric sensors are suitable for dissolution testing of various drugs (loperamide, cinnarizine and domperidone) in simple buffer media. Moreover, ISE can be used to obtain accurate results in turbid media [14]. It is not the first time an electrode has been used for monitoring the dissolution of a drug [15,16], but this is the first electrode which can be applied to any ionizable lipophilic drug since specificity is obtained by conditioning.

In this article, we utilized the ISE with two objectives:

(A) To test the suitability of the Ion-Selective Electrode as an analytical method which can be directly applied in biorelevant media, as an alternative to sampling with subsequent analysis by conventional methods such as HPLC–UV (Method A).
(B) To investigate the ISE as an analytical system to obtain a full dissolution profile in biorelevant media with the aid of one single draw which is analyzed by a conventional method, here HPLC–UV (Method B).

Dissolution profiles obtained by using ISE were compared to those acquired by HPLC–UV assay after conventional, manual sampling.

2. Materials and methods

2.1. Chemicals

Diphenhydramine-HCl (DPH) was chosen as the model drug. The dissolution tests were carried out with Nustasium© tablets (lot # 07H30) containing 50 mg diphenhydramine-HCl from Labima, Belgium. Diphenhydramine-HCl drug substance, NaCl, NaOH, glacial acetic acid, NaH_2PO_4, H_3PO_4 KH_2PO_4 and acetonitrile were purchased by Sigma–Aldrich, Germany. Egg phosphatidylcholine (Lipoid E PC®, 97.9% pure, lot # 108015-1-/042) was kindly donated from Lipoid GmbH, Ludwigshafen, Germany. Glycerylmonooleate (GMO, Rylo MG19 Pharma®, 99.5% monoglyceride, lot # 173403-2202/107) was provided by Danisco Specialities, Brabrand, Denmark. Hydrochloric acid (31–33%) was obtained from Hedinger, Stuttgart, Germany. Ortho-phosphoric acid (85%) and pepsin (Ph. Eur., 0.51 U/mg, lot # 1241256) were purchased from Fluka Chemie AG, Buchs, Switzerland. Sodiumoleate (82.7% pure, lot # 51110) was obtained from Riedel-de Haën, Seelze, Germany. Sodium taurocholate (NaTC, >97% pure, lot # 2007100274) was purchased from Prodotti Chimici e Alimentari SpA, Basaluzzo, Italy. Long-life whole milk was obtained from Milfina, Germany and from Lidl, Germany.

2.2. Filter adsorption studies

Filter adsorption of diphenhydramine-HCl onto regenerated cellulose filters (Minisart© RC 25, 0.2 μm, lot # 17764, Sartorius, Germany) was investigated by filtration of each medium at a concentration of about 100 μg/ml diphenhydramine-HCl. The samples were analyzed by HPLC–UV and compared to the unfiltered medium ($n = 3$) [17].

2.3. Calibration of the Ion-Selective Electrodes

Ion-Selective Electrodes were provided by Janssen Pharmaceutica and have been described previously by Bohets et al. [13]. Prior to dissolution testing, the electrodes were conditioned at 37 °C in the dissolution medium at a DPH concentration of about 110 μg/ml for at least 48 h. In preliminary experiments, it had been shown that this time-frame was sufficient to condition the ISE to DPH in simple buffer media (no data shown). The DPH concentration is equivalent to 110% dissolution of Nustasium© tablets. This procedure resulted in low drift and fast response of the ISE to DPH. Calibration curves were constructed by stepwise addition of a standard solution into a vessel containing 500 ml of the test medium. Two milliliters of aliquots were added in five steps, with each 2 ml containing approximately 11 mg of DPH. As in the conditioning step, the final concentration was approximately 110% of the concentration expected at the end of the dissolution of Nustasium© tablets. Dissolution tests were initiated when the correlation coefficient (R^2) of the linear fit of the calibration data exceeded 0.9995. A secondary criterion was that the mean slope of this calibration curve did not exceed the value of 63 mV. Furthermore, the sensor response obtained from the stepwise addition of the standards had to be fast and stable; $t_{90} < 60$ s and drift less than 0.3 mV for the 2nd to 5th addition.

2.4. Dissolution testing

Dissolution tests were carried out at 37 °C with a USP type II (paddle) dissolution tester Erweka R6©, (Erweka, Heusenstamm, Germany). In some experiments, 2 or 3 ISE were placed in a single dissolution vessel to evaluate reproducibility among electrodes. In other experiments, the ISEs were compared to manual sample removal and subsequent HPLC analysis. Manual samples were taken at 5, 10, 15, 20, 25, 35 and 45 min without volume replacement. The filtered samples were diluted appropriately with mobile phase.

2.5. Quantitative analysis

2.5.1. Ion-Selective Electrodes (ISE)

The conversion of the measured potential to percentage dissolution was carried out according to the procedure described in Bohets et al. [13], using an in-house Potential-to-Concentration software (LabView©, Version 6.1, National Instruments). The system is able to measure the electrochemical potential of the solution every four seconds. An endpoint calibration to correct the drift of the ISE system was conducted in two different ways:

Method A: With this method, the ISE was placed into a solution containing a known concentration of DPH, typically the calibration solution, after completion of the dissolution run.
Method B: With this method, a manual sample was drawn at one time-point (corresponding approximately to the completion of drug release, e.g. t_{45} for Nustasium© tablets) and the concentration of DPH was determined by HPLC–UV. The dissolution profile was calculated on the basis of this value.

2.5.2. HPLC–UV

Samples from dissolution test were analyzed by HPLC–UV. The HPLC–UV-System consisted of a LaChrom© L-7100 pump, a LaChrom© L-4250 UV–Vis-Detector, a LaChrom© L-200 autosampler

and the EZ-Chrome Elite© Data System Software (Merck Hitachi, Darmstadt, Germany). The analysis was performed on a LichroChrosphere© RP-8 5 μm, 250–4 mm column. The mobile phase consisted of 55% acetonitrile and 45% aqueous KH_2PO_4-solution (30 mM). The pH value was adjusted with phosphoric acid to pH 2.5. The flow rate was set at 1.5 ml/min, resulting in elution of DPH approximately at 3.5 min. The concentration of released drug was determined using a UV detector at the wavelength of 254 nm.

2.6. Analysis of in vitro dissolution data

f_1- and f_2-factors were used to compare dissolution profiles generated by filtration and subsequent HPLC–UV and by ISE. To allow for better comparison and to include the dissolution at higher percent release, five time-points were always included (i.e. t_5–t_{25}), even if the last time-point exceeded 85% dissolution relative to the label strength [18,19].

To compare Nustasium© dissolution endpoints at t_{45}, ANOVA at a significance level of $\alpha = 0.05$ was applied using Origin© 6.0 (Microcal, Northhampton, MA, USA). All other calculations were conducted in Excel© 2003 (Microsoft, Redmond, WA, USA).

2.7. Dynamic light scattering (DLS)

To monitor a possible change of micellar formation in FeSSIF-V2, dynamic light scattering measurement was conducted using a Malvern Zetasizer© 3000 HSA (Malvern Instruments Ltd., Malvern, UK) at 25 °C with a Ne–He-Laser at 633 nm and at a measurement angle of 90°. The samples were placed into single-use PCS-Cells (10 × 10 × 48 mm) (Sarstedt, Nürnbrecht, Germany).

3. Results and discussion

3.1. Filter adsorption studies

The recoveries of diphenhydramine-HCl after filtration are shown in Fig. 1. For every medium, filter adsorption was low, indicating suitability for sample preparation.

3.2. Dissolution in Fasted State Simulated Gastric Fluid (FaSSGF)

After conditioning the electrodes to FaSSGF, the calibration curve was found to yield an R^2 of 0.99994 or better, with a slope

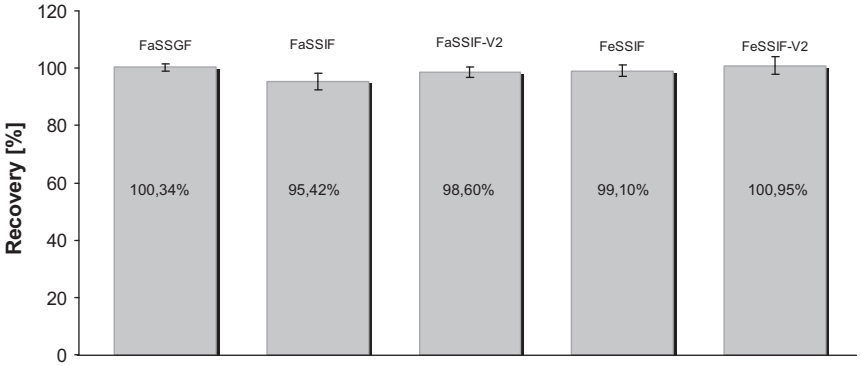

Fig. 1. Recovery of diphenhydramine-HCl after filtration through Minisart® RC 25 regenerated cellulose, 0.2 μm.

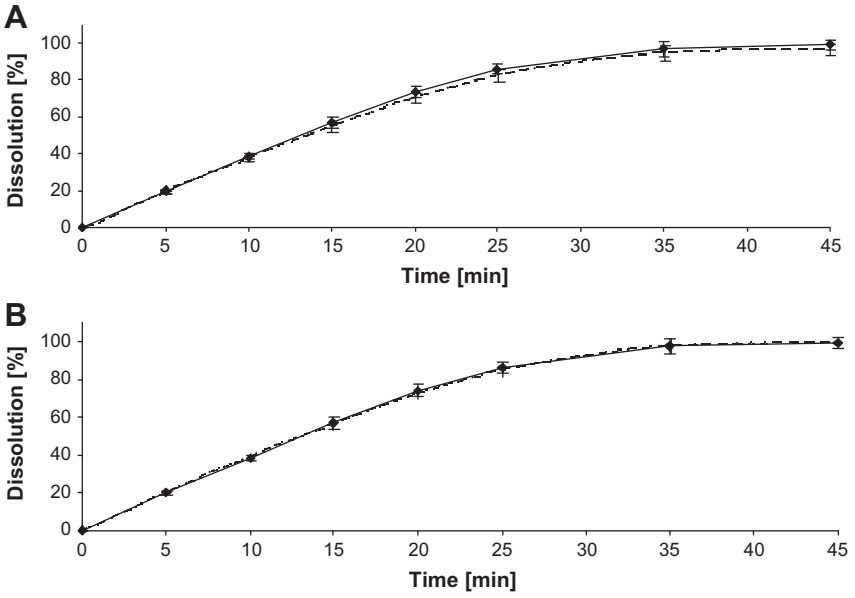

Fig. 2. (A and B) Dissolution profiles of Nustasium® in FaSSGF obtained by manual sampling and subsequent HPLC–UV analysis (solid line) and ISE (dotted line). (A) Method A. (B) Method B.

Table 1
f_1–f_2-values for each medium/each electrode in comparison with manual sampling and subsequent HPLC–UV analysis.

Medium	Method A		Method B	
	f_1	f_2	f_1	f_2
FaSSGF	4.24	64.57	1.63	86.50
FaSSIF-V2 electrode 1	3.31	73.72	1.85	94.09
FaSSIF-V2 electrode 2	3.67	68.86	1.71	99.77
FaSSIF electrode 1	1.51	86.10	2.65	69.27
FaSSIF electrode 2	1.80	97.04	2.46	70.75
FaSSIF electrode 3	5.59	54.01	8.08	45.53

of 59.83 ± 0.99, and therefore, the quality of the conditioning was considered to be sufficient for dissolution measurements [14].

The results from the dissolution tests are shown in Fig. 2. The f_1- and the f_2-factors indicate that the dissolution results obtained with the ISE (Method A) can be considered similar to manual sampling with HPLC–UV analysis (Table 1). A combination of ISE and HPLC–UV, as done with Method B, leads to a slight improvement in agreement of the ISE results with those obtained by manual sampling with HPLC–UV analysis and fulfils the goal of obtaining a full dissolution profile with a single sample draw.

3.3. Dissolution in Fasted State Simulated Intestinal Fluid – Version 2 (FaSSIF-V2)

After conditioning the electrodes to FaSSIF-V2, the calibration curve was found to yield an R^2 exceeding 0.9995 or better, with a slope of 62.61 ± 0.63, fulfilling the conditioning criteria. In this medium, the ISE yielded identical dissolution profiles to those obtained with manual sampling and subsequent HPLC–UV analysis (Fig. 3, Table 1). High standard deviations in the results obtained with HPLC–UV analysis were observed. These can likely be attributed to variations in positioning of the ISE electrodes in the vessel and their subsequent influence on the hydrodynamics, although small variations in sample preparation could also have contributed.

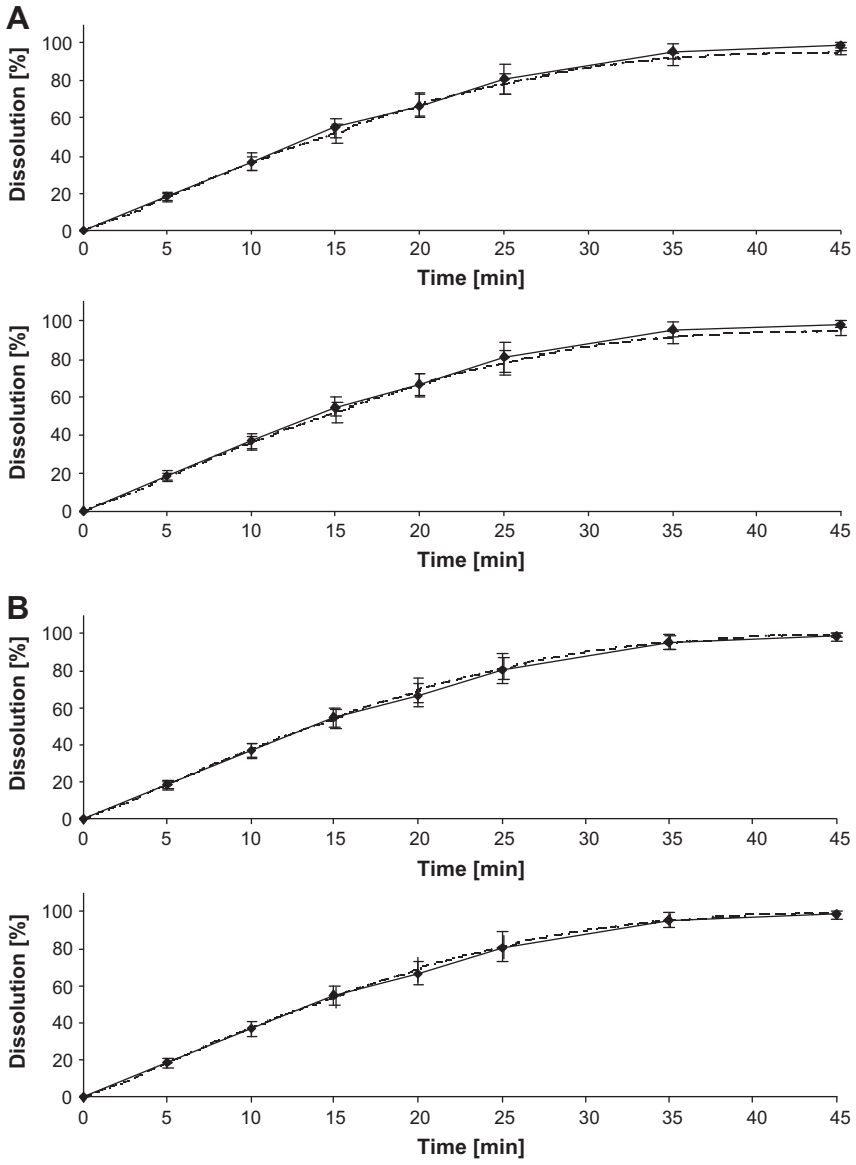

Fig. 3. (A and B) Dissolution profiles of Nustasium® in FaSSIF-V2 obtained by manual sampling and subsequent HPLC–UV analysis (solid line) and ISE (dotted line). (A) Method A electrodes 1 and 2. (B) Method B electrodes 1 and 2.

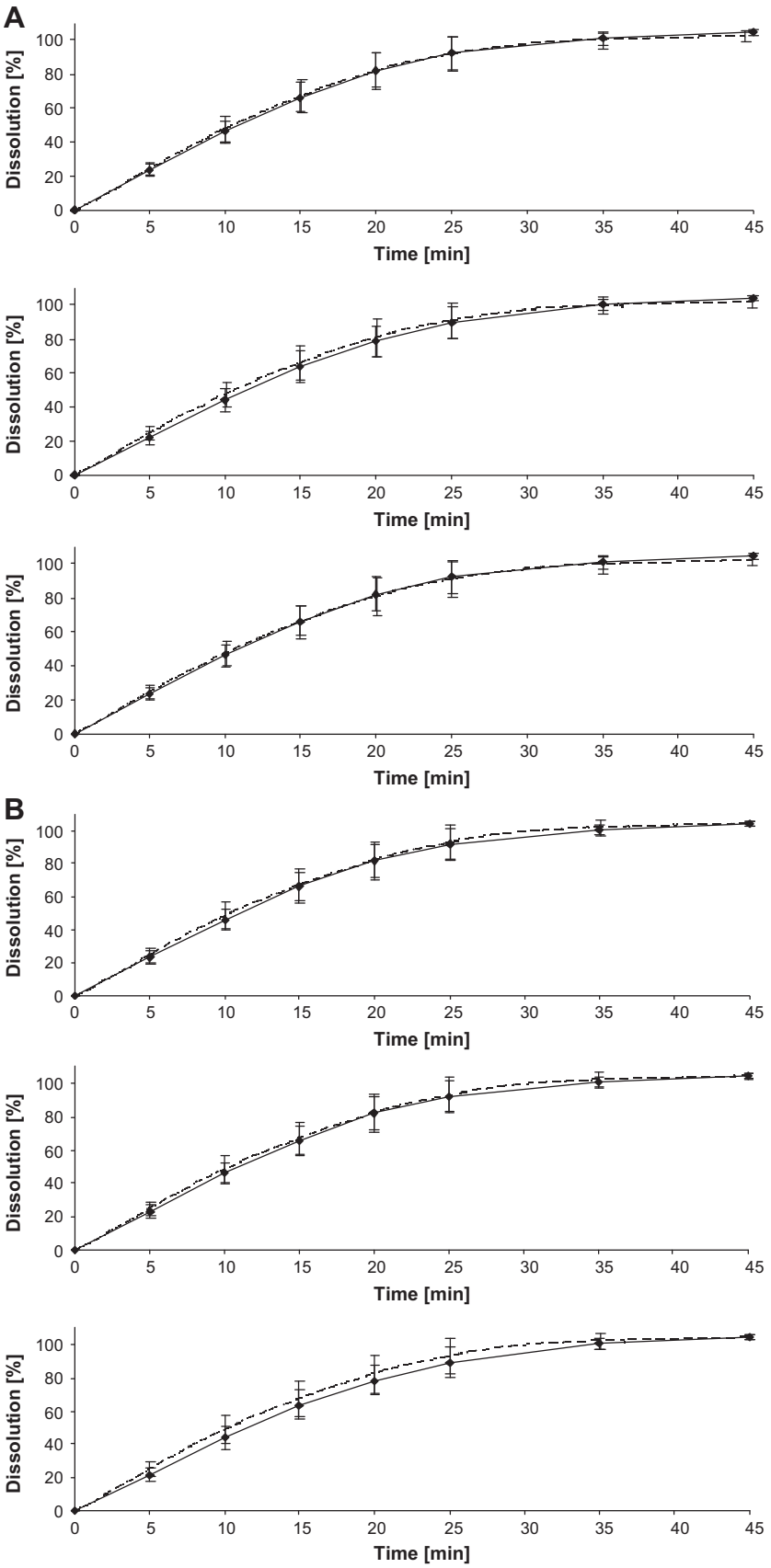

Fig. 4. (A and B) Dissolution profiles of Nustasium® in FaSSIF obtained by manual sampling and subsequent HPLC–UV analysis (solid line) and ISE (dotted line). (A) Method A electrodes 1–3. (B) Method B electrodes 1–3.

Table 2
(A and B) Comparison of the ISE to manual sampling and subsequent HPLC–UV analysis and ISE within the same vessel during dissolution test with Method A and Method B.

Time	HPLC–UV	Electrode 1	Electrode 2	Electrode 3	SD electrodes
Method A					
5	17.91	18.55	18.63	18.71	0.08
10	36.91	36.54	36.49	36.80	0.17
15	53.42	52.28	51.84	52.21	0.24
20	67.53	65.69	65.54	65.79	0.13
25	78.05	77.22	76.79	77.30	0.27
35	95.71	94.50	93.93	94.52	0.34
45	103.77	102.44	102.02	102.43	0.24
f_1		1.93	2.40	1.84	
f_2		86.33	82.28	88.78	
Method B					
5	17.91	18.79	18.95	18.95	0.09
10	36.91	37.01	37.11	37.28	0.14
15	53.42	52.95	52.72	52.89	0.12
20	67.53	66.53	66.66	66.65	0.07
25	78.05	78.21	78.10	78.30	0.10
35	95.71	95.72	95.53	95.75	0.12
45	103.77	103.76	103.76	103.76	0.00
f_1		1.03	1.13	1.22	
f_2		99.77	99.83	99.86	

3.4. Dissolution in Fasted State Simulated Intestinal Fluid (FaSSIF)

Three electrodes were used simultaneously for dissolution in FaSSIF to assess reproducibility in the manufacture of the ISE and in the conditioning procedure. The calculated R^2 values of the calibration curves were 0.99990, 0.99994 and 0.99991, respectively, with a mean slope of 62.85 ± 0.52 and therefore met the performance criteria for use in dissolution testing. The dissolution profiles are shown in Fig. 4. Methods A + B produced similar results to manual sampling and subsequent HPLC–UV analysis for all three ISEs, showing an f_1-factor less than 15. For ISE 1 and 2, the f_2-value was higher than 50, while for electrode 3, the value was over 50 for Method A but slightly under for Method B. When comparing a single dissolution test profile obtained by manual sampling and HPLC–UV analysis with the corresponding results from the three individual electrodes, it can be seen that the performance of the ISE is very close to HPLC–UV with low standard deviations among the electrodes (see example in Table 2).

3.5. FeSSGF

Difficulties in the measurement of the exact drug concentration in FeSSGF are often encountered, since this medium is a multiphase system. Therefore, HPLC–UV measurement is not possible unless a time-consuming and tedious sample preparation using acetonitrile to precipitate proteins followed by centrifugation is utilized [8]. As an alternative, a 25 step ISE calibration was conducted ($n = 5$) by subjecting the ISE to FeSSGF containing known concentrations of DPH. The mean slope of the resulting calibration curves was 61.15 ± 0.27 with an R^2 of 0.99978 or better, with concentrations calculated from ISE measurement all within the range of 95–105% of the known concentration (Fig. 5). Therefore, the ISE can be used for online measurements in FeSSGF and related, milk-containing media.

3.6. Fed State Simulated Intestinal Fluids (FeSSIF/FeSSIF-V2)

For the conditioning of the electrode, it is crucial that the surrounding medium is stable over time. In the FeSSIF media, we observed an increase in turbidity over 24 h (e.g. Fig. 6). We used a dynamic light scattering measurement to confirm this visual observation and found an increased micellar size (e.g. fresh medium average 26.2 nm, after 24 h at 37 °C 44.1 nm for FeSSIF-V2). Using a conventional sampling method (e.g. syringe filters), these changes do not alter results (since, in absence of a conditioning procedure, the medium does not have to be maintained at 37 °C for long periods), but they can lead to different results with the ISE.

Although calibration curves were obtained with all ISEs in the biorelevant fed state media, their performance did not meet all

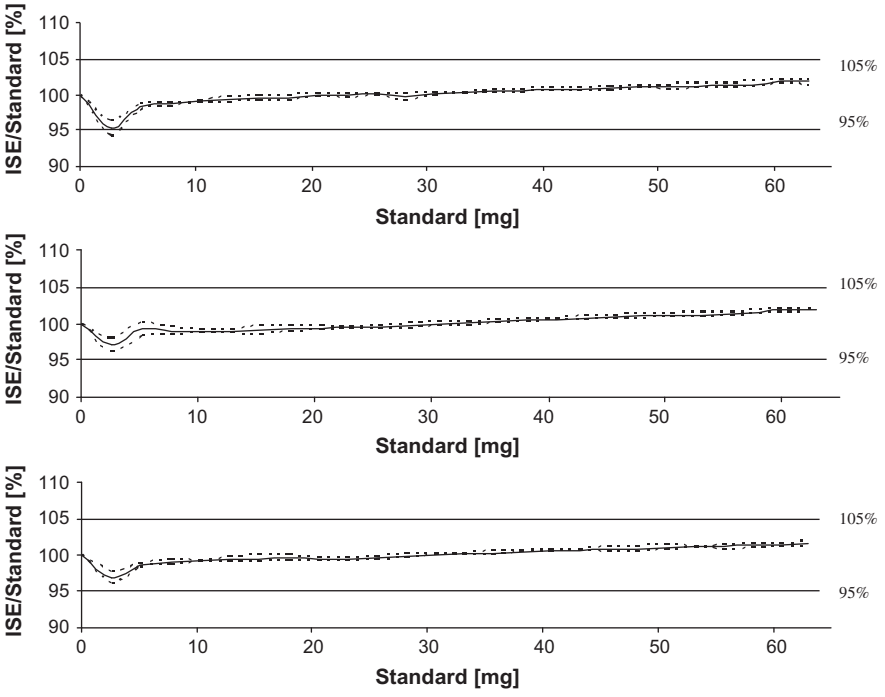

Fig. 5. Plot of measured concentration against amount of added standard electrodes 1–3. The dotted lines above and under the solid lines show the standard deviations.

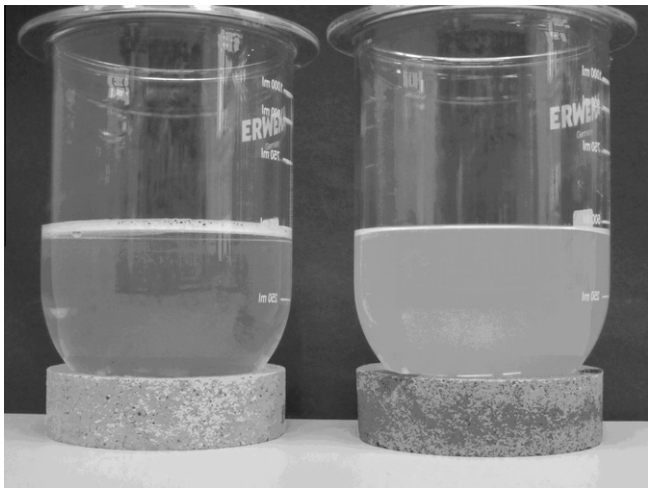

Fig. 6. Picture of freshly prepared FeSSIF-V2 (left vessel) and FeSSIF-V2 after 24 h at 37 °C and 75 rpm (right vessel).

criteria for analysis with ISE (see Section 2.3). The highest R^2 value obtained for the calibration curve was 0.99947, just failing to meet the criterion of $R^2 \geqslant 0.9995$. Slopes were 52.74 ± 2.47 in FeSSIF and 52.21 ± 4.10 in FeSSIF-V2, both meeting the performance criteria (max. slope of 63). The third criterion, a fast and stable plateau showing a drift of less than 0.3 mV to the next addition, was not fulfilled (e.g. drift of 0.6 mV between steps 3 and 4 in Fig. 7).

3.7. Limitations and opportunities of the Ion-Selective Electrode system

Bohets and Peeters have already shown the suitability of the ISE for quality control purposes. It offers satisfactory accuracy at low cost and avoids the need for organic solvents [13,14]. In addition, the measurements are performed online, enabling real-time generation of data. In consequence, the throughput of dissolution tests in quality control can be increased.

In our study, the focus was set on dissolution testing in research and development, especially with respect to measurement in biorelevant media. Online monitoring in biorelevant media is often associated with difficulties since fiber optics and flow-through UV methods are sensitive to light scattering effects. Wavelength-independent interference of UV-absorption in simple buffers can easily be corrected by baseline offset to the entire UV-range. But micellar solutions, including all biorelevant media, show Tyndall scattering. The correction of this wavelength-dependent scattering requires complicated mathematical approaches such as multivariate analysis or second-derivative algorithm [12,20]. Manual sampling with HPLC–UV analysis is applicable to analysis of fasted state media but more difficult to apply to the fed state media, especially for FeSSGF, for which a time-consuming and tedious sample preparation is necessary. The suitability of ISE for use in turbid media was demonstrated by Peeters et al. [14] and has been further confirmed in our studies with FeSSGF as a medium. Additionally, as an off-line system, manual sampling with HPLC–UV analysis generates only a limited number of samples and the dissolution profile will not be continuous. As a non-spectroscopic online system without the need for sample preparation, the ISE offers the potential to circumvent these problems.

With regard to limitations to the application of ISE-based analysis of dissolution in biorelevant media, these are at present threefold: the first is the general limitation of the ISE to ionisable compounds, recognizing that approximately 40% of drugs are neutral compounds over the physiological pH range [21]. The second is that the ISE failed to meet the suitability criteria for use in FeSSIF and FeSSIF-V2. Further developmental work will be needed to overcome this limitation. Third, the calibration procedure of the ISE is usually based on dilution of a concentrated stock solution. This procedure is obviously not suitable for application to very poorly soluble substances. To overcome this difficulty, the ISE Method B was adapted using a single sample analysis by HPLC–UV. This sample should be drawn just before the plateau is reached (i.e. at t_{25}).

Method B was applied to FaSSGF, FaSSIF and FaSSIF-V2. For all these media, equivalence of Method B to conventional HPLC–UV analysis was established (Table 3). This broadens the application range for the ISE to potentially encompass even supersaturated systems of poorly soluble substances.

Table 3
f_1–f_2-values for each medium/each electrode in comparison with manual sampling and subsequent HPLC–UV analysis with the adapted Method B, using t_{25} instead of t_{45}.

Medium	Adapted Method B	
	f_1	f_2
FaSSGF	1.53	83.79
FaSSIF-V2 electrode 1	2.83	86.07
FaSSIF-V2 electrode 2	3.84	72.33
FaSSIF electrode 1	1.44	83.99
FaSSIF electrode 2	1.65	79.91
FaSSIF electrode 3	6.13	51.91

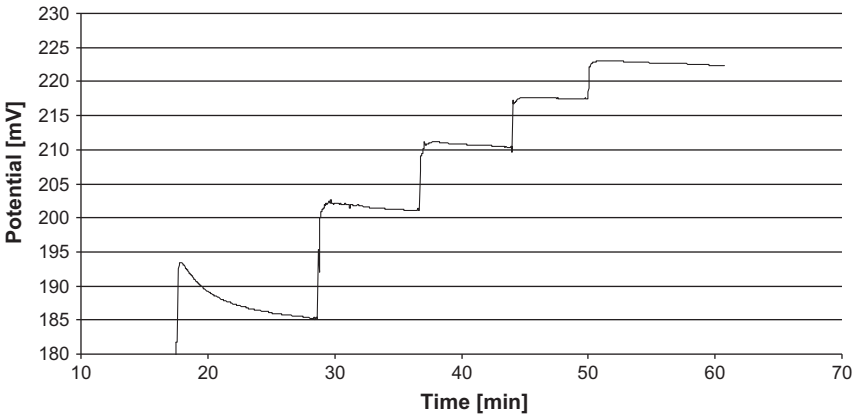

Fig. 7. Calibration curve of diphenhydramine-HCl in FeSSIF-V2.

4. Conclusion

The results demonstrate that the Ion-Selective Electrode is suitable for measurements of diphenhydramine-HCl in fasted state biorelevant media (FaSSGF, FaSSIF and FaSSIF-V2) as both a stand-alone system (Method A) and in conjunction with a single-point conventional assay (Method B). The results acquired are similar to those obtained by manual sampling and subsequent HPLC–UV analysis. The ISE also delivers satisfactory results in a milk-based medium (FeSSGF), in which it has distinct advantages over manual sampling with HPLC–UV analysis by obviating the need for sample preparation. Application of the ISE in FeSSIF type media will need further study.

Finally, as an online technology, ISE offers more efficient generation of dissolution profiles than conventional sample-based methods.

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