The ion sensitive field effect transistor (ISFET) pH electrode: a new sensor for long term ambulatory pH monitoring

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Abstract

Intraluminal pH monitoring in man should be performed with disposable multichannel assemblies that allow recordings at multiple sites and prevent transmission of infection. Currently available glass electrodes are unsuitable for this purpose because of their size and price. We have thus constructed and tested a small, combined ion sensitive field effect transistor (ISFET) pH electrode incorporating an integral reference electrode. In vitro studies showed that both ISFET and glass electrodes (440-M4, Ingold, Switzerland) have a linear response over the pH range 1.3-8.0 and that they are comparable with regard to response time and 24 hour drift. Twenty one hour intragastric pH recordings were performed simultaneously in eight healthy volunteers using a glass electrode and an ISFET electrode, placed no more than 2 mm apart in a combined assembly. This was located in the gastric corpus under fluoroscopic control. The 21 hour pH curves recorded by each electrode type showed identical patterns: an early morning rise in pH with three meal-associated pH peaks lasting for about two to three hours. The means of the 21 hour pH medians were 2.09 and 2.07 as measured by the glass and the ISFET electrodes respectively. Thus, ISFETs are suitable for the construction of inexpensive and hence disposable multichannel pH monitoring assemblies of small diameter. Provided that they can be produced in large numbers with appropriate technical support, ISFETs have the potential to replace glass electrodes for long term monitoring of gastrointestinal luminal acidity.

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At present, the standard electrodes for intraluminal pH monitoring are combined glass electrodes which incorporate an integral reference electrode,¹⁻³ but although these are highly accurate, they have some disadvantages. Studies of regional pH variations in the upper gastrointestinal tract require pH assemblies with more than two channels which, until now, have had to use glass electrodes. These assemblies cannot, however, be passed transnasally as they are too large and, if they are passed orally, they cannot be tolerated for more than a few hours, thus precluding long term ambulatory recordings with more than two channels.⁴⁻⁶ Another problem with glass electrodes is that manufacturing costs are still so high that they are not disposable. On the other hand, most types of glass electrodes can only be disinfected: heat and

gas sterilisation and the thermosinfection method newly developed for fiberoptic endoscopes⁷ are not recommended. Therefore, transmission of infectious diseases such as hepatitis can never completely be excluded. Because of this, the availability of low cost and hence disposable electrodes is highly desirable.

Attempts to develop a small and inexpensive pH electrode are not new; two examples are the monocrystalline antimony^{8,9} and the plastic^{10,11} electrodes. Neither type of electrode, however, is without its problems. Although the behaviour of antimony electrodes in vivo has been reported to be comparable with that of glass electrodes,¹² they are known to be non-linear over a pH range from 1 to 7 and they have a prolonged response time compared with glass electrodes.^{2,3} Furthermore, they require an external reference electrode attached to the skin and they may, therefore, suffer from the fact that the pH electrode and the reference electrode must work in environments that differ in respect of ionic background and temperature. Although integral reference electrodes are also susceptible to changes in the composition of gastric contents, it has been shown that the use of a distant skin or buccal reference electrode leads to significant differences in recorded pH.² The main problem with plastic electrodes is that they cover only a selected pH range depending on membrane composition and other ions present in the sample.¹³ Thus, their output may be predicted in vitro when the composition of the measured solution is known but not in vivo when, for example, the intragastric environment changes in the presence of food or refluxed duodenal contents.

We have thus developed a new type of pH electrode, the ISFET (ion sensitive field effect transistor) electrode,¹⁴⁻¹⁶ which is theoretically as reliable and accurate as glass electrodes with the additional advantages that it is smaller and, if commercially produced, cheaper. Since combined glass pH electrodes represent the gold standard for 24 hour ambulatory pH monitoring,² we have compared the performance of the ISFET electrode with a combined glass electrode under in vitro and in vivo conditions.

Methods

ELECTRODES

ISFET electrode

In principle, an ISFET is a modification of the normal field effect transistor used in many

Figure 1: Encapsulation of an ISFET in a catheter suitable for gastrointestinal intubation. CMOS = complementary metal oxide silicone (integrated circuit construction type).

amplifier circuits. In the ISFET, the metal gate, which is normally used as input, is replaced by an ion-sensitive membrane, the measured solution, and a reference electrode. Thus, an ISFET combines in one device the sensing surface and a signal amplifier which produces a high current, low impedance output and allows the use of connecting cables without excessive shielding. The ISFET used in this study contains a pH sensitive membrane made of Al_2O_3 .¹⁷ Its rugged solid state structure and small size ($1.5 \times 0.6 \times 0.3$ mm) permitted its encapsulation (Fig 1) in a polymer cylinder which was placed 4.5 mm from the tip of the catheter (1.5 mm outside diameter (OD)) just proximal to the reference electrode. The latter consisted of an Ag/AgCl wire immersed in a saturated KCl solution behind a porous glass membrane (CSEM, Neuchâtel, Switzerland). A constant-current power supply is required for the ISFET so that it will produce a voltage that is linearly proportional to the pH of the surrounding fluid over the range of pH values found in the gastrointestinal tract. The behaviour of both ISFET and glass electrodes can be described by the Nernstian equation and the sensitivity of the ISFET electrode is, therefore, comparable with that of a glass pH electrode, although the zero point of the ISFET electrode is different from that of most glass electrodes.

This similarity in behaviour allowed a direct comparison of the electrodes using the same recording device and evaluation program. The only modification required was the addition of a constant voltage of 1600 mV to the ISFET output so that it was in the same range as the output of a glass electrode.

Glass electrode

The combined glass electrode used for validating the ISFET is commercially available (440-M4, Dr Ingold AG, Urdorf, Switzerland) and is used routinely for upper gastrointestinal pH monitoring studies. It has an OD of 4 mm at the tip of the electrode and is mounted on a polyvinyl tube with an OD of 3 mm. The reference electrode is situated 15 mm proximal to the glass electrode.

Combined ISFET and glass electrode assembly

For the in vivo studies of gastric acidity, a measuring assembly (OD 5 mm) consisting of an ISFET electrode and a glass electrode was constructed, care being taken that the two sensing surfaces were never more than 2 mm apart.

IN VITRO STUDIES

Drift

Each of five new ISFET electrodes was immersed

in a neutral buffer solution for at least six hours before starting a measurement. The electrodes were then put in a buffer of pH 4.01 (S1316, Radiometer, Copenhagen, Denmark) at 22°C. The drift exhibited by ISFET electrodes has a characteristic form with an initial exponential change in electrode potential followed by a much slower but linear drift. In all cases the maximum deviation from the initial reading was observed at the end. Therefore, for the assessment of electrode drift the voltages were noted at the beginning and at the end of a 24 hour test period. The drift of an individual electrode was defined as the difference in voltage between first and second measurements. The same procedure was used to determine the drift of five glass electrodes.

Response time

Response times were defined as the time taken for the electrode voltage to reach 90% and 95% of its final reading in a given neutral or acid buffer solution. The electrodes, which were connected to a pH meter (PHM 85, Radiometer, Copenhagen, Denmark) and thence to a chart recorder (REC 80, Radiometer, Copenhagen, Denmark), were transferred between stirred buffer solutions of pH 7.38 and pH 1.10 at 37°C (S1356 and S1386, Radiometer). Five electrodes of each type were examined and triple measurements made with each individual electrode from which mean values and ranges were calculated. These data as well as group medians are presented for each electrode type. Differences in response time for each electrode type were tested statistically using the Wilcoxon-Mann-Whitney test.

Sensitivity

Electrode sensitivity was assessed using five electrodes of each type over the pH range of 1.3 to 8. Sodium hydroxide (0.01 N NaOH solution) was added gradually to a stirred solution of artificial gastric juice at 22°C (NaCl 2 g, Pepsin 3.2 g, 80 ml 1 N HCl and 1000 ml H_2O , pH 1.3). The electrical potentials of each electrode were plotted against pH values of the test solution, which were measured with a standard laboratory glass electrode (GK2401C, Radiometer). This procedure was used to compare the linearity of response of the two electrode types over a physiological pH range. Linear regression was used to determine the slope of the data points.

IN VIVO STUDIES

Long term pH monitoring

Eight healthy volunteers (three men and five women, mean age 27 years) participated in the study. No subjects received medication, none were alcohol or drug abusers, and none had any evidence of gastrointestinal disease. Two volunteers were smokers; smoking, however, was not allowed during the study. Informed consent was obtained from all volunteers; the study was approved by the local ethics committee.

Ambulatory 21 hour pH monitoring was conducted in each volunteer, during which they received standard meals.¹ No additional food was

allowed except tap water. The volunteers followed their usual daily activities.

At 4 pm, the combined ISFET/glass electrode measuring assembly was introduced through the nostril after local anaesthesia and positioned in the gastric corpus under fluoroscopic control. The electrode cables were connected to separate solid state data loggers, each with a storage capacity of 128 kByte (LZ 105, Kaufhold, Berlin, Germany), which were both carried in a bag along with the box containing the ISFET power supply and output amplifier.

The electrodes were immersed in buffer solutions of pH 7.38 and 1.10 (S1356 and S1386, Radiometer) for five minutes at the beginning and end of each measurement. Electrode potentials during these calibration periods, as well as during the 21 hour intragastric measurement, were sampled at a measuring interval of two seconds and stored, without transformation to pH values, in the data loggers.

At the end of each measurement the data were transferred from the data loggers to a host computer (EuroMak, Dr Weiss GmbH, Schriesheim, Germany). Data were evaluated using programs written in the language C and running under the OS-9 operating system (Microware, Des Moines, Iowa, USA).

In the initial evaluation step, the first and last 30 minutes of the recordings were displayed on the computer screen, and the operator was asked to mark, manually, the start and end of each calibration period. From this the computer then calculated the electrode zero point and sensitivity. These values were used later to transform each recorded electrode potential into its equivalent pH value.

Data presentation and statistics

Standard analysis was performed by calculating the median pH for a defined time interval: in this case, the full 21 hour recording. In addition, successive median values were calculated from 300 consecutive raw data points (corresponding to 10 minute intervals) resulting in 126 data points from each ISFET and each glass electrode recording in every subject. These data points were used for graphical display and also for statistical analysis. For each recording, differences were calculated between the 126 data pairs (glass electrode reading minus ISFET electrode reading) and plotted against their means¹⁷; bias was expressed as the mean of these differences. As a measure of overall agreement, the median of these mean differences was calculated regardless of their sign. Pearson's correlation coefficients were calculated for each recording solely in the interest of comparability with previous studies.

Results

IN VITRO STUDIES

Drift

The ISFET electrodes showed drifts of up to 15 mV/hour during the first four hours after their first immersion in buffer solution, but after this

Figure 2: 24 hour drift of five ISFET electrodes (open hourglass symbols) and five glass electrodes (■). EMF=electromotive force.

stabilisation period there was only minimal long term drift which never exceeded 15 mV/24 hours (0.26 pH units/24 hours). The 24 hour drifts obtained from all five glass and ISFET electrodes are displayed in Figure 2. Mean drift was 7.1 mV/24 hours (0.13 pH units/24 hours) and 5.2 mV/24 hours (0.09 pH units/24 hours) for ISFET and glass electrodes, respectively.

Response time

ISFET and glass electrodes attained 90% of their final reading comparably rapidly after transfer from acid to neutral buffer but the ISFETs reached 90% of their final reading more rapidly than the glass electrodes after transfer from neutral to acid buffer (p<0.01). Glass electrodes attained 95% of their final readings more rapidly than ISFETs (p<0.01) in both acid and neutral buffer solutions (Table I).

Sensitivity

Both glass and ISFET electrodes showed a linear

TABLE I Response times of glass and ISFET electrodes

Buffer	Neutral to acid		Acid to neutral	
	90%	95%	90%	95%
Glass electrode:				
1	0.87 (0.1)	4.67 (1.7)	0.83 (0.1)	1.70 (0.4)
2	1.00 (0.2)	3.73 (1.5)	0.83 (0.1)	1.53 (0.1)
3	1.07 (0.1)	3.70 (1.0)	0.70 (0.2)	1.30 (0.2)
4	0.97 (0.1)	4.10 (1.6)	0.70 (0.2)	1.70 (0.3)
5	0.90 (0.2)	3.93 (0.4)	0.80 (0.2)	1.33 (0.1)
Median	0.97	3.93	0.80	1.53
ISFET electrode:				
1	0.53 (0.3)	10.67 (4.2)	0.37 (0.1)	2.37 (1.5)
2	0.53 (0.1)	10.80 (9.0)	0.77 (0.6)	2.60 (1.2)
3	0.73 (0.1)	10.23 (3.1)	0.93 (0.2)	2.13 (0.2)
4	0.57 (0.1)	10.67 (3.1)	0.57 (0.3)	2.33 (0.1)
5	0.63 (0.4)	8.67 (1.4)	0.83 (0.3)	2.50 (1.0)
Median	0.57	10.67	0.77	2.37
Significance	*	*	NS	*

The time (seconds) taken to reach 90% and 95% of the final reading is given as the mean (range) of three measurements with each electrode and the median value for all five electrodes (*p<0.01: ISFET v glass). Buffers of pH 7.38 (neutral) and pH 1.10 (acid) were used.

Figure 3: Mean pH curves of simultaneous measurements with ISFET (thick line) and glass (thin line) electrodes in eight healthy volunteers.

response over the pH range from 1 to 8. The mean sensitivity of the glass electrodes was 54.5 mV/pH and that of the ISFET electrode was 57.8 mV/pH.

IN VIVO STUDIES

Mean pH curves from eight volunteers (Fig 3) show that the recordings from the two electrode types are nearly identical. Both show the typical diurnal pH variations, with a rise in pH during the night and meal-associated pH rises lasting for two to three hours at 19:00, 08:00, and 13:00. The means of the individual 21 hour medians were 2.09 and 2.07 measured with the glass and the ISFET electrode, respectively.

The readings of the two electrodes were compared for each recording by comparing the median pH values from corresponding, consecutive 10 minute intervals; the differences between these corresponding pH values are

TABLE II Agreement between electrode readings and correlation coefficients		
Subject no	Mean difference	Correlation coefficient
1	0.574	0.900
2	0.117	0.979
3	0.240	0.846
4	-0.0786	0.960
5	-0.0282	0.988
6	-0.364	0.978
7	-0.0512	0.957
8	-0.219	0.979
Median	0.168*	0.969

Mean difference between electrode readings (glass minus ISFET) and Pearson's correlation coefficient for each subject. * The mean differences were ranked regardless of their sign to calculate the median.

plotted against the means of the same two values (Fig 4). These figures indicate that there is not a systematic bias – that is, neither electrode type records pH values consistently higher or lower than the other. It can also be seen that in most of the recordings the differences between the electrode readings are generally small; furthermore, these differences are relatively constant and do not increase with increasing gastric pH.

The mean difference between electrodes was greatest in subjects 1 and 6, although this was not reflected by Pearson's correlation coefficient, which indicated a high degree of correlation for all recordings (Table II).

Discussion

Ambulatory long term pH monitoring is now the main method for evaluating gastric secretory profiles and as such it represents an important research tool for investigating the influence of physiological¹⁹ and pharmacological factors on gastric acidity. It has also become an essential clinical tool in the management of gastro-oesophageal reflux disease.²⁰ Upper gastrointestinal tract luminal acidity is, however, highly

Figure 4: Agreement between ISFET and glass electrodes in each of the eight subjects; subjects 1 to 4 are shown on the upper row and subjects 5 to 8 on the lower row. The abscissa displays the mean value for the two electrode readings; the ordinate the difference between them (glass minus ISFET). The outer horizontal lines represent 2 SD either side of the mean difference, shown by the central line.

variable with temporal and regional differences even within one organ such as the stomach. Thus, pH electrode assemblies with more than two channels allowing for simultaneous long term measurements of pH at different sites would be highly desirable. In addition, as variations in pH are thought to be dependent on local motility patterns²¹ it would also be of great interest to use combined pH and pressure measurement assemblies for prolonged ambulatory monitoring. Neither of these goals is feasible without the availability of small reliable electrodes. Single electrode assemblies with an integral reference electrode would also be useful for localised endoscopic pH measurements as, for example, when investigating Barrett's oesophagus. At present, this can only be achieved by using single glass electrodes with a distant reference electrode. The potential problem of disease transmission by non-disposable probes, which may be disinfected but are difficult to sterilise, could also be resolved by the use of low cost disposable electrodes. Thus, the ideal pH electrode should be small, reliable, and cheap while retaining the accuracy and stability of glass electrodes, which must, at present, be regarded as the gold standard for pH monitoring.

ISFETs fulfil all these needs. This study shows that the performance of the ISFET electrode is comparable with that of the standard glass electrode in vitro and in vivo. Both types of electrode show 90% response times of less than 1 second when transferred from neutral to acid and from acid to neutral buffer solutions. This allows an ideal sampling frequency of 1 Hz, which is particularly important for oesophageal or duodenal pH monitoring, both of which require relatively high sampling rates.²² The response time to reach 95% of the final value of the buffer solution is longer with ISFETs than with glass electrodes but even the response time of the latter is longer than the 2 second sampling interval (0.5 Hz) usually used in pH monitoring.

The ISFET electrode potential shows a large initial drift, which is logarithmic in nature,²³ but thereafter the drift is negligible. Provided the ISFET is placed in a neutral buffer solution at least four hours before each monitoring, the drift is linear and does not exceed 1 mV/hour in long term recordings.

Median pH values from consecutive 10 minute intervals were used for the comparison of time-matched values from the individual recordings to minimise the effects of previously documented, rapid gastric pH fluctuations.²⁴ The use of raw pH data values, recorded every 2 seconds, would have overestimated considerably the differences between the electrode types and obscured the fact that they provided comparable measurements of luminal pH over the longer time periods normally used in studies of gastric acidity. The data show, in fact, that the differences between the ISFET and glass electrodes in the current study are no greater than those found when two glass electrodes, in close proximity, are used for simultaneous gastric pH monitoring.¹ Furthermore, there is no systematic difference between the readings of the two electrode types, and, in the light of the experience with glass electrodes,

it is probable that many of the differences between the recordings are due to regional variations in gastric luminal acidity²⁵⁻²⁷ rather than to differences between the electrodes.

Given that the glass electrode is an ideal pH sensor, the 'worst case' assumption would be that an ISFET electrode introduces an error of 0.168 pH units (Table II) into gastrointestinal pH recordings. This should not have a notable effect on the required sample size in gastric pH measurement studies since even with recording systems using a glass electrode, the smallest detectable difference between test groups over similar 24 hour measurement periods was in excess of 0.1 pH units.²⁴ Indeed, for shorter periods, variations in intragastric pH are so large and rapid that group pH differences of less than 1.5-2.0 pH units cannot be detected.

In conclusion, the advent of ISFET electrodes represents a major advance in intraluminal pH measurement. Commercial availability and support will determine whether the ISFET pH electrode will fulfil its long term potential as a replacement for the glass electrode. In the short term, however, it also provides a new technique for mapping rapid, localised pH variations which occur simultaneously in different parts of the gastrointestinal tract.

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Further information about the combined ISFET pH electrode is available from Centre Suisse d'Electronique et de Microtechnique, Neuchâtel, Switzerland.

- 1 Fimmel CJ, Etienne A, Cilluffo T, *et al.* Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H₂-antagonists. *Gastroenterology* 1985; 88: 1842-51.
- 2 McLauchlan G, Rawlings JM, Lucas ML, McCloy RF, Crean GP, McColl KEL. Electrodes for 24-hour pH-monitoring - a comparative study. *Gut* 1987; 28: 935-9.
- 3 Emde C, Garner A, Blum AL. Technical aspects of intraluminal pH-metry in man: current status and recommendations. *Gut* 1987; 28: 1177-88.
- 4 Rhodes J, Prestwich CJ. Acidity at different sites in the proximal duodenum of normal subjects and patients with duodenal ulcer. *Gut* 1966; 7: 509-20.
- 5 Rune SJ. In vivo investigations by continuous measurements of gastric and duodenal pH. *Scand J Gastroenterol* 1982; 75 (suppl): 48-9.
- 6 Hannibal S, Rune SJ. Duodenal bulb pH in normal subjects. *Eur J Clin Invest* 1983; 13: 455-60.
- 7 Working Party of the British Society of Gastroenterology. Cleaning and disinfection of equipment for gastrointestinal flexible endoscopy. *Gut* 1988; 29: 1134-51.
- 8 Ask P, Edwall G, Johansson KE, Tibbling L. On the use of monocrySTALLINE antimony pH electrodes in gastro-oesophageal functional disorders. *Med Biol Eng Comput* 1982; 20: 383-9.
- 9 Johansson KE, Tibbling L. Evaluation of the 24-hour pH test at two different levels of the esophagus. In: De Meester TR, Skinner DB, eds. *Esophageal disorders: pathophysiology and therapy*. New York: Raven, 1985: 579-82.
- 10 Rawlings JM, Lucas ML. Plastic pH electrodes for the measurement of gastrointestinal pH. *Gut* 1985; 26: 203-7.
- 11 Oesch U, Brzózka Z, Xu A, *et al.* Design of neutral hydrogen ion carrier for solvent polymeric membrane electrodes of selected pH-range. *Anal Chem* 1986; 58: 2285-9.
- 12 Andersen J, Naesdal J, Strom M. Identical 24-hour gastric pH profiles when using intragastric antimony or glass electrodes or aspirated gastric juice. *Scand J Gastroenterol* 1988; 23: 375-9.
- 13 Oesch U, Brzózka Z, Xu A, Simon W. Solvent polymeric membrane pH catheter electrode for intraluminal measurements in the upper gastrointestinal tract. *Med Biol Eng Comput* 1987; 25: 414-9.
- 14 Bergveld P. Development of an ion-sensitive solid-state device for neurophysiology. *IEEE Trans Biomed Eng* 1970; 19: 70-1.
- 15 Matsuo T, Wise DK. An integrated field-effect electrode for biopotential recording. *IEEE Trans Biomed Eng* 1974; 21: 485-7.
- 16 Janata J, Moss SD. Chemically sensitive field-effect transistors. *IEEE Trans Biomed Eng* 1976; 21: 241-5.
- 17 de Rooij NF, Haemmerli A, Grisel A. C-MOS compatible pH-ISFET with Al₂O₃ gate. In: Ko W H, ed. *Implantable sensors for closed-loop prosthetic systems*. New York: Futura, 1985: 139-51.

- 18 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307-10.
- 19 Duroux Ph, Bauerfeind P, Emde C, Koelz HR, Blum AL. Early dinner reduces nocturnal gastric acidity. *Gut* 1989; **30**: 1063-7.
- 20 Schindlbeck NE, Heinrich C, König A, Dendorfer A, Pace F, Müller-Lissner SA. Optimal thresholds, sensitivity and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. *Gastroenterology* 1987; **93**: 85-90.
- 21 Bumm R, Emde C, Bauerfeind P, Stein H, Duroux Ph, Blum AL. Nocturnal gastroesophageal reflux and motility of the tubular esophagus: the question of hen and egg [Abstract]. *Gastroenterology* 1988; **94**: A54.
- 22 Emde C, Bauerfeind P, Bumm R, Blum AL. Minimal sampling rate required in ambulatory long-term pH-metry [Abstract]. *Dig Dis Sci* 1987; **32**: 909.
- 23 Krawiec J, Odes HS, Schwartz B, Lamprecht SA. Regional difference in ambient intraluminal gastric acidity after cimetidine monitored by intragastric pH-metry. *Am J Gastroenterol* 1983; **78**: 272-5.
- 24 Merki HS, Witzel L, Walt RP, et al. Day-to-day variation of 24-hour intragastric acidity. *Gastroenterology* 1988; **94**: 887-91.
- 25 Armstrong D, Castiglione F, Biollaz J, et al. Functional separation of gastric antrum and corpus observed in gastric double pH-metry studies in healthy volunteers [Abstract]. *Gastroenterology* 1989; **96**: A15.
- 26 McLauchlan G, Fullarton GM, Crean GP, McColl KEL. Comparison of gastric body and antral pH: a 24 hour ambulatory study in healthy volunteers. *Gut* 1989; **30**: 573-8.
- 27 Scheepel SJ, de Rooij NF, Koning G, Oeseburg B, Zijlstra WG. In vivo experiments with a pH-ISFET electrode. *Med Biol Eng Comput* 1984; **22**: 6-11.