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The effect of pH change on the gastric emptying of liquids measured by electrical impedance tomography and pH-sensitive radiotelemetry capsule

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Abstract

Citrate phosphate buffer liquid adjusted to different pH values was used to investigate the gastric emptying profiles in human using simultaneous monitoring by electrical impedance tomography (EIT) and pH sensitive radiotelemetry capsule. No interference was observed between the two methods during data acquisition periods. A positive correlation between methods from the pooled data was demonstrated. Statistical moments analysis demonstrated a significant delay in the onset of gastric emptying and also the mean gastric residence time of the pH 3 buffer liquid (34.7–46.7 min) when compared with pH 7 buffer liquid (14.4–22.5 min). These data suggest that the negative feedback gastrin related response to acidity of the liquid was high. However, incorporation of an acid suppression compound (ranitidine), as part of the control study showed that the EIT imaging of this buffer could be successfully performed under normal physiological conditions. When 450 ml pH 7 buffer liquid was measured, no significant difference in gastric emptying rate was observed. This study demonstrated that, citrate phosphate buffers can be used as an alternative test liquid for EIT monitoring, and that pH has a systematic effect on gastric emptying and the lag phase. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Electrical impedance tomography (EIT); Gastric emptying; pH; Radiotelemetry

1. Introduction

γ-Scintigraphy is widely used in monitoring gastric emptying of solid and liquid meals in human, but the administration of radioactive isotopes prevents its use for multiple studies. Electrical impedance tomography (EIT) is a non-invasive technique that images the distribution of resistivity of the tissues within a body region. It was introduced for practical purposes almost two decades ago and has been successfully used to measure the gastric emptying in both adult and paediatric patients. Studies have shown a good correlation between changes in tissue resistivity and gastric emptying and filling (Avill et al., 1987;

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Nour et al., 1995). Recently, EIT has also been successfully used to evaluate the basal acid output due to its sensitivity to ionic changes (Sarker et al., 1997).

Previous studies suggest that factors such as meal types including the volume, osmolarity, pH and calorific values, gender, age, body mass, psychological states and acid secretion may influence the gastric emptying process. The aim of the current study was to evaluate the pH and volume effects of liquid buffers of varying pH on the gastric emptying rate and the contribution of acid secretion on the overall performance of EIT by simultaneous pH monitoring using a pH sensitive radiotelemetry capsule in healthy volunteers. The technique has the potential of monitoring non-invasively the gastric emptying of liquid formulations.

2. Methods

2.1. Subjects and principle outline of study

Twenty healthy male subjects with no history of current or past major GI disorders and who were not taking any medication or any substance, which might act on the GI tract were recruited for the study. The study was approved by East London and The City Health Authority Research Ethics Committee and all subjects gave written, informed consent before the study.

Subjects were all of normal weight for height and between 27 and 55 years of age. The subjects were divided into two groups of ten. In group I, the subjects underwent four studies of gastric emptying, without gastric acid suppression, using EIT. For group II, the subjects underwent four studies, with and without gastric acid suppression, using simultaneously the EIT and the pH-sensitivity radiotelemetry capsule. There was a minimum of 3 days between studies and subjects were fasted overnight for 12 h prior to each measurement.

Each subject was studied with a non-nutrient citrate phosphate buffer liquid adjusted to either pH 3 or 7 of varying volumes. The buffer was made of Analar grade, citric acid monohydrate, sodium hydrogen orthophosphate and sodium chloride (BDH Chemical Industries, Poole, UK). In group I, each subject was given on separate occasions 150, 250, 450 ml pH 7 or a 250 ml pH 3 buffer liquids, respectively. In group II, each subject was given on separate occasions 250 ml pH 3 and 7 buffer liquids. On two of the occasions, a 300 mg ranitidine (Zantac®, Glaxo-Wellcome, UK) tablet was also given 1 h 30 min, prior to the study, as the gastric acid suppressor.

The gastric emptying rate was monitored non-invasively using the EIT Mark I (Medical Physics University of Sheffield, UK). Sixteen pre-gelled silver/silver disposable ECG electrodes were placed in a ring around the upper abdomen 1/3 of the distance between the xiphisenus and the cusilium, in order to image the stomach. Subjects were seated comfortably and were refrained from major physical movement during image acquisition. Images were obtained at 1 min intervals and the baseline reference abdominal tissue impedance was recorded for 150 cycles (15 s) prior to the study. The net impedance change caused by the ingestion of a test liquid of different impedance to the body tissues is a marker of the system sensitivity and resolution. Up to 2 h data acquisition was obtained after administration of each test liquid.

Luminal gastric pH was measured using a pH sensitive radiotelemetry capsule, Type 7036 (Remote Control Systems Ltd., Amersham, UK). This consisted of a silver/silver chloride electrode located in the reference cap. The subject swallowed a pre-calibrated, tethered capsule with a minimum amount of plain water. The pH measurement was converted into a radio frequency and was detected by a double loop aerial band (Oakfield Instrument Ltd., Oxon, UK) worn around the abdomen of the subject. The detected signal was recorded on to a portable solid state Medilog 1000 receiver (Oakfield Instrument Ltd.). Baseline pH was monitored for a 30 min interval before attachment to the EIT system, and recording was continued for up to 2 h after the administration of the buffer liquid. At the end of the study period, the capsule was pulled out from the stomach via the oesophagus and sterilised for reuse. The step response time of the capsule after stabilisation and calibration procedure was assessed to ensure optimum performance and to check for drift before and after each study.

2.2. Analysis methods

For analysis of gastric emptying, a region of interest (ROI) was created from the EIT system by totalling the images of approximately ten image frames to produce a representative outline of the stomach. A conductance time curve for ROI was plotted for each study. A gastric emptying profile was derived from the values of the impedance, expressed as a percentage change in values from the initial baseline level, measured on the ingestion of the test liquid. A typical example is presented in Fig. 1 for the gastric emptying of buffer solutions in one volunteer. Studies, which failed to show a distinct area representing the filling and emptying of the meals, were discarded, as were those which contained gross conductance changes caused by artefacts. The area under the curve (AUC), gastric lag-time, gastric mean residence time (GMRT) and its variance (VGRT) were determined mathematically by statistical moments (Podczeck et al., 1995) rather than using the conventional method by determining the gastric emptying half time. Data were expressed as the mean, median and the range, and statistical analysis was performed using analysis of variance (ANOVA, SPSS 7.5, SPSS Inc., Woking, UK).

For the pH analysis, the luminal pH profiles recorded on the Medilog 1000 receiver were replayed on to a microprocessor controlled replay unit to give a hard copy of pH against time. This data was then transferred to a PC where it was converted into a readable form by appropriate software (Oakfield Instrumental Ltd.) for further analysis. The pH profile was divided into pre-administration and post-administration periods. The median, 25th and 75th quartiles of each 30 min of the recording and a pH distribution were calculated. The results for the median and S.D. of the pH values prior to administration of the buffer solutions and between 0–30, 30–60, 60–90 and 90–120 min are presented in Fig. 2. The pH time value is denoted as the gastric time interval where the pH value of the stomach was ± 0.5 of the pH value of the administered liquid and was determined by summing the time values at specific pH values from the pH distribution profiles. This value served as the parameter that described the gastric emptying behaviour using the pH sensitive radiotelemetry capsule, which was used for comparison with the GMRT value from EIT analysis using limits of agreement test (Bland and Altman, 1986) and Spearman's rank correlation regression analysis (Kirkwood, 1988). The administration of ranitidine tablet (150 mg) provided acid suppression over the monitoring period, therefore, the pH time value when pH 7 buffer was administered in these instances could not be calculated.

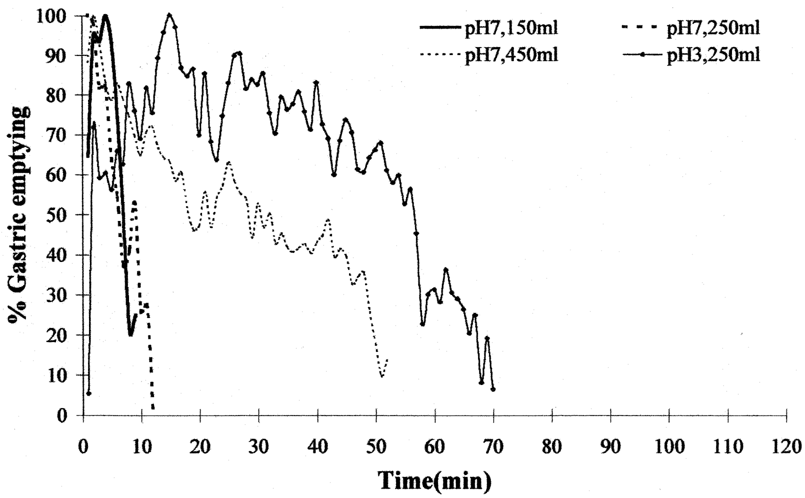


Fig. 1. An example of the gastric emptying profiles of the citrate phosphate buffer liquids derived from the ROI mapping of the EIT images of one subject in group I.

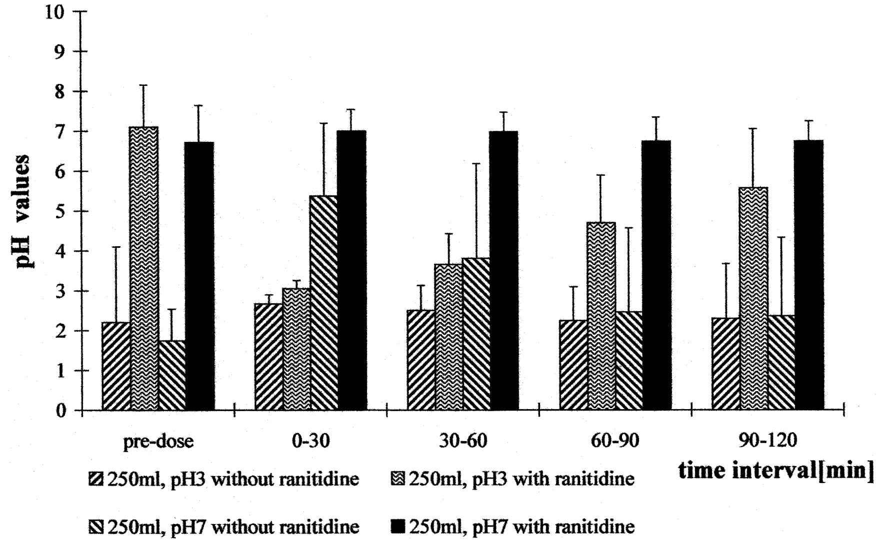


Fig. 2. The mean and the S.D. of median pH values of the citrate phosphate buffer liquid at different time interval derived from the pH profiles using the Flexilog II pH analysis for group II.

3. Results

3.1. Gastric emptying results for group I

Fig. 3a shows the GMRT distributions for different test liquids. Table 1 summarises the gastric emptying parameters for each test. The results from an ANOVA comparing the effect of administered pH was significant for all gastric emptying parameters at $P<0.01$ but not for the administered volumes, except for the AUC at $P<0.05$. The F-values and their significance are summarised in Table 2.

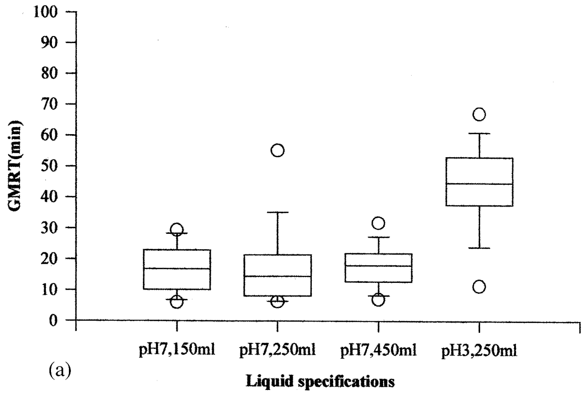
3.2. Gastric emptying and pH results from group II

Fig. 3b shows the GMRT distributions for group II and the gastric emptying parameters from each test are summarised in Table 3. The ANOVA results show a significant delay in gastric emptying rate for pH 3 liquid ($P<0.01$) in all gastric emptying parameters where $P<0.05$ for gastric lag time, hence, confirming the results obtained in group I. The effect of acid suppression on emptying parameters, was not significant at $P<0.05$ level (Table 4).

By using pH time values as an indicator for gastric emptying characterisation using pH analysis (Table 3), the results from ANOVA (Table 4) showed that the gastric emptying was significantly delayed by pH 3 buffer liquid ($P<0.01$) and this is consistent with the results from EIT analysis. However, this result also showed a significant level of inter-subject variation ($P<0.01$).

3.3. Comparison between EIT and pH profiles for group II

The GMRT and pH time values from three tests are studied and the results presented in Table 3. The results from Spearman's rank correlation analysis and limits of agreement are summarised in Table 5. The correlation analysis shows significant level of correlation with the pooled data but not when the data were sub-divided. This correlation from the pooled data was also not reflected in corresponding limits of agreement, as there were relatively large differences between the measurement from each method of determination of the pH time values. Determination can be difficult especially in cases where fluctuations in the specified baseline cut off pH values was either too variable or too small due to acid secretion, saliva-



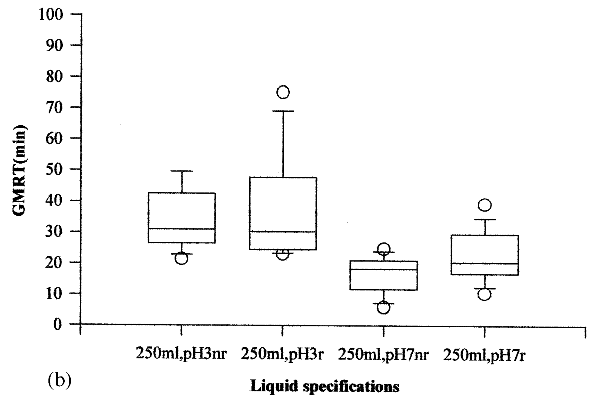


Fig. 3. The GMRT distributions for (a) group I (b) group II. The lower and the upper boundary of the box indicates the 25th and 75th percentiles, a line within the box marks the median. The error bars above and below the box indicates the 10th and 90th percentiles. The symbol o shows the outliner. The symbols r and nr indicate without and with ranitidine treatment, respectively.

tion and reflux from the oesophagus and intestine. Furthermore, the fluctuations causing irregularities in the gastric emptying curves also make

Table 2
The ANOVA of gastric emptying parameters from group I using buffer test liquid of different pH and volumes

Effect and F-values	GMRT	VGRT	AUC	Lag time
Acidity (pH)	40.4***	11.5**	79***	26.5***
Volume	0.4	0.5	4.7*	0.3
Subject	0.2	0.6	1.1	0.5

The F-values and theirs significance. ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$.

GMRT value determination, inadequate in some cases. However, the positive correlation of the pooled data indirectly confirmed the validity of EIT measurement using pH-sensitive radiotelemetry capsule. Examples of the simultaneously measurement using the two methods are shown in Fig. 4a–d.

4. Discussion

Hunt and Knox (1969) have described the effects of administering fluid of different properties such as calorific values, osmolarity, pH and volume to human using the naso-gastric aspiration technique, which is invasive and hence may suffer from artefacts due to the discomfort introduced during the test. This technique was superseded by the use of the gold standard technique, of 'γ-scintigraphy', which monitors gastric transit of materials using radio labelled isotopes. Advances in EIT technology leading to its development to the current system, with the advantages of speed in data processing, low cost and non-invasiveness, is an attractive alternative means for clinical research in monitoring gastric emptying. The cur-

Table 1
The mean and span of the gastric emptying parameters calculated from each subject from group I with different test liquids and volumes

Test liquids	pH 7 buffer (150 ml)	pH 7 buffer (250 ml)	pH 7 buffer (450 ml)	pH 3 buffer (250 ml)
GMRT (min)	18.1 (6.0–25.8)	14.4 (6.2–26.7)	19.5 (8.9–31.7)	46.7 (29.4–67.1)
VGRT (min^2)	50.6 (3.6–109.0)	59.1 (5.0–193.5)	118.6 (15.0–223.6)	267.8 (67.6–478.8)
AUC (% min)	90.6 (8.1–195.8)	110.2 (10.4–283.3)	313.5 (119.4–1061.9)	344.0 (143.5–542.6)
Lag time (min)	8.0 (3.0–14.0)	3.9 (3.0–10.0)	4.5 (3.0–18.0)	22.1 (6.0–39.0)

rent study used a buffered pH liquid adjusted to an osmolarity of 260 mOsmol kg^{-1} and showed that gastric emptying could be effectively monitored using the EIT system. The incorporation of ranitidine treatment into group II has demonstrated that measurement of the buffer liquid using EIT on different days is reproducible and can be performed under normal physiological conditions without any pharmacological intervention as reported previously by others, Evans and Wright (1990), Mitchell (1997).

The pH effect of the administered test liquid is predominant over the volume effect in current work. The acid effect is consistent in the two groups and with other reports using different acidic non-nutrient solution (Lin et al., 1990; Hunt and Knox, 1969). In contrast to previous reports (Oberle et al., 1990; Erskine and Hunt, 1981), the administration of different volumes using pH 7 buffer liquid has no significant effect on the gastric emptying rate. This has partially demonstrated that the rapid emptying of the stomach results in an increase in volume per minute emptying with a larger administered vol-

Table 3
The mean and span of the gastric emptying parameters calculated from each subject from group II with different test liquids and conditions

Test liquids and conditions	pH 3 buffer without ranitidine treatment (250 ml)	pH 3 buffer with ranitidine treatment (250 ml)	pH 7 buffer without treatment (250 ml)	pH 7 buffer with ranitidine treatment (250 ml)
GMRT (min)	34.7 (21.4–49.6)	37.9 (23.1–55.1)	16.6 (5.9–21.8)	22.5 (10.4–39.2)
VGRT (min^2)	233.9 (9.0–583.0)	241.0 (80.0–597.0)	72.9 (3.4–143.3)	149.0 (27.3–632.1)
AUC (% min)	273.1 (36.1–487.4)	383.7 (161.7–875.1)	103.3 (28.7–130.2)	199.5 (82.3–411.9)
Lag time (min)	11.8 (3.0–21.0)	11.1 (3.0–23.0)	5.1 (3.0–12.0)	6.4 (3.0–15.0)
pH time (min)	50.1 (22.0–80.0)	47.3 (26.0–77.0)	18.9 (8.0–32.0)	N/A

Table 4
The ANOVA of gastric emptying characterisations from group II using buffer test liquid of different pH values and with the use of ranitidine treatment

Effect and *F*-values	GMRT	VGRT	AUC	Lag time	pH time
Acidity pH	26.0***	9.15**	10.2**	6.4*	27.5***
Ranitidine	1.6	0.9	3.3	1.0	0.1
Treatment subject	1.0	1.5	1.2	0.9	7.7**

The *F*-values and their significance. ***, $P<0.001$; **, $P<0.01$; *, $P<0.05$.

Table 5
The Spearman's rank correlation coefficient (r_s) and the mean difference ± 2 S.D. from limits of agreement determination on the GMRT and pH time values of the three tests for group II

Test liquids and conditions	pH 3 buffer without ranitidine treatment (250 ml)	pH 3 buffer with ranitidine treatment (250 ml)	pH 7 buffer without ranitidine treatment (250 ml)	Pooled data from all three tests
r_s	0.70	0.50	0.30	0.82***
Mean difference ± 2 S.D.	7.08 ± 28.76	10.86 ± 6.94	-1.03 ± 25.60	5.36 ± 30.16

***, $P<0.001$.

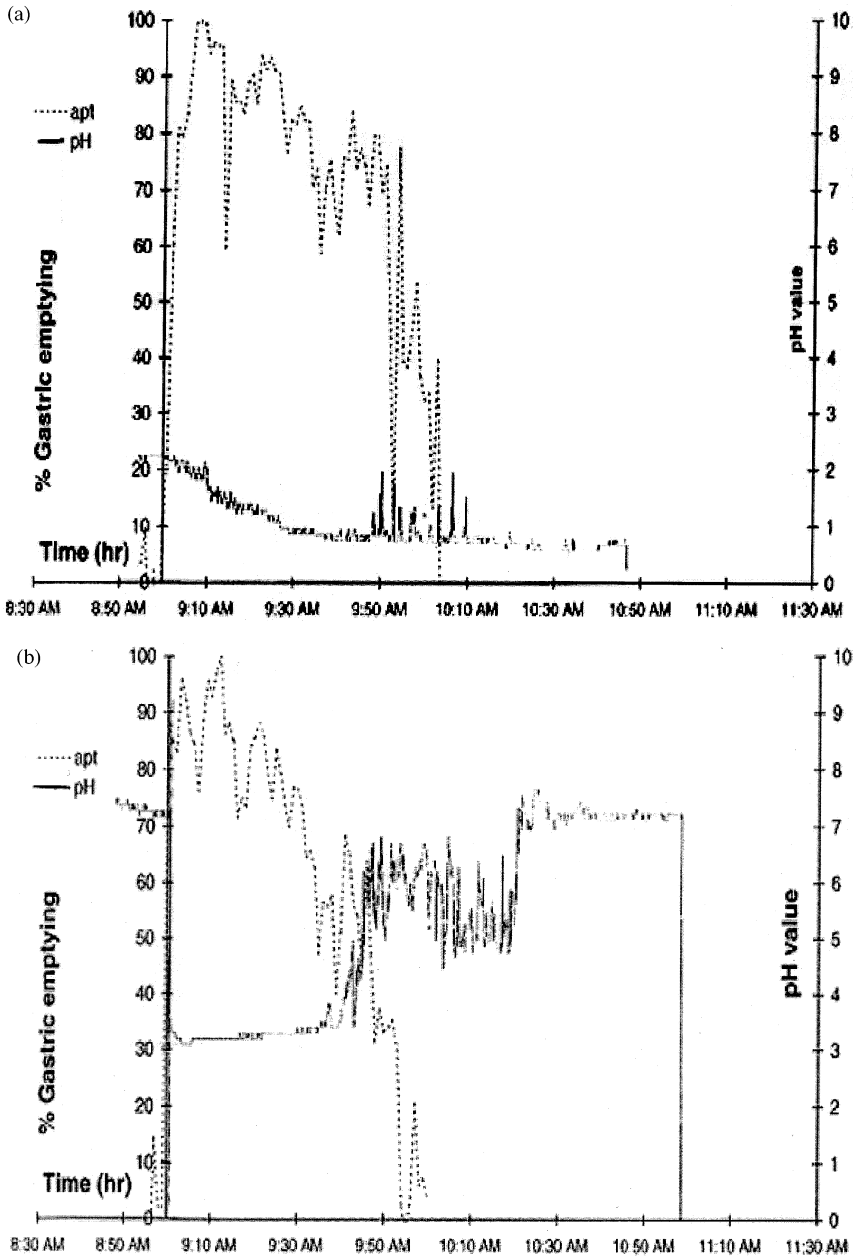


Fig. 4. Examples of the simultaneous monitoring of gastric emptying and pH using, EIT system and pH radiotelemetry capsule at different conditions in a healthy subjects (group II). (a) pH 3 buffer (250 ml) without ranitidine treatment; (b) 250 ml, pH 3 buffer with ranitidine treatment; (c) 250 ml, pH 7 buffer without ranitidine treatment; (d) 250 ml, pH 7 buffer with ranitidine treatment.

ume. The MMC phase of the stomach is known to affect the gastric emptying rate during the fasted state. This effect is profound in particular for small volume, which empties rapidly (Oberle and Amidon, 1987). No fed state induction is assumed in the current study as the administered volume is relatively small and has no calorific value. Despite the fact that the results from

ANOVA show that the intra- and inter-subjects variation are not significant in all gastric parameters except the pH time value, the GMRT distributions from Fig. 3a and b clearly demonstrate the existence of these variations. Failure to calculate the gastric parameters using the statistical moments analysis due to the irregularity of the gastric emptying profile occurred most frequently with the 150 ml pH 7 test liquid and with the subject of large body mass index. The small sample size coupled with the vast subject variability explained the non-significant level using different

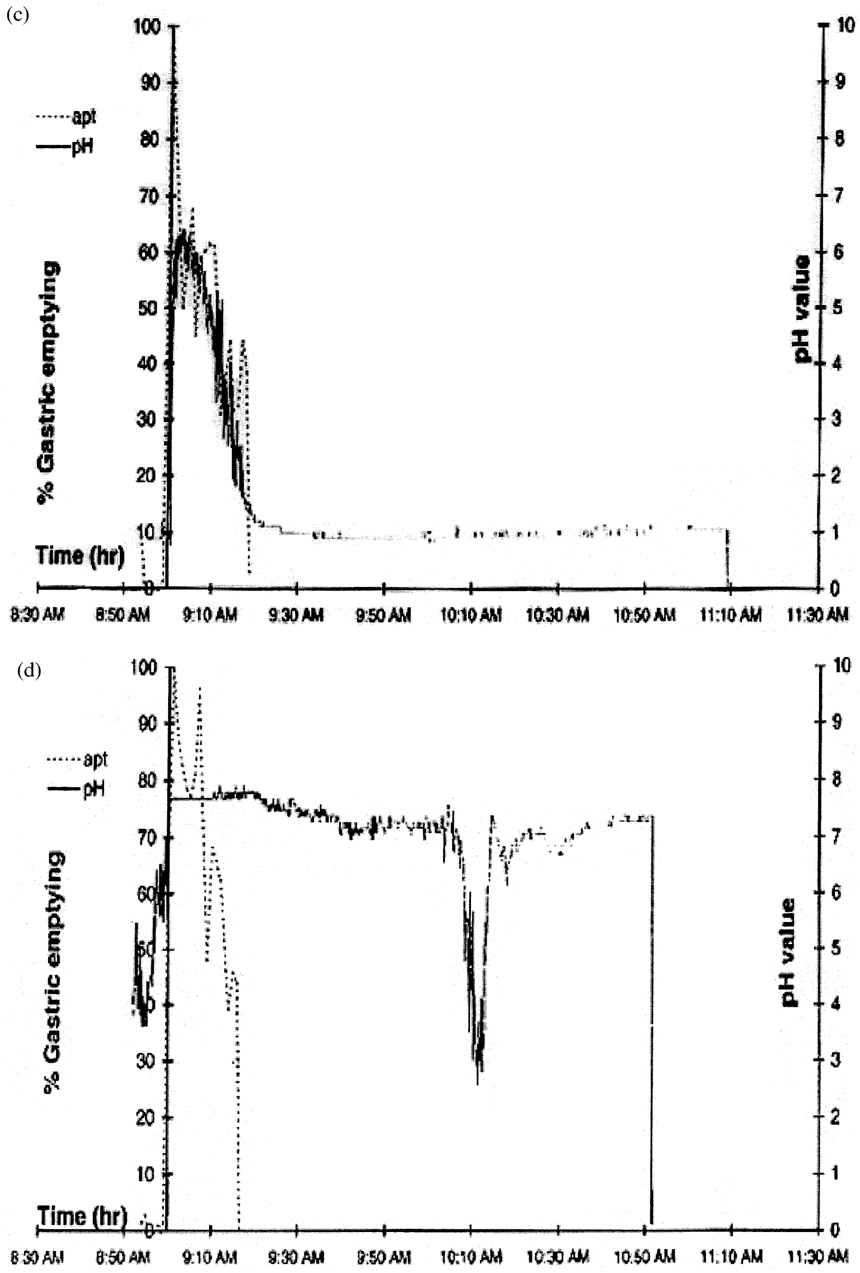


Fig. 4. (*Continued*)

volumes in the current work. The study has highlighted the need to control the MMC and inclusion of ranitidine treatment for an administered volume up to 150 ml in adults in order to obtain images of better quality.

The incorporation of a tethered pH radiotelemetry capsule has shown that fluctuations observed in the gastric emptying profiles do occur. This could be caused by the ionic changes in the gastric environment from acid secretion, bicarbonate reflux and salivation, which indirectly reflect the sensitivity of EIT system to the gastric fluid flux. Discomfort caused by the tethered string within the pharynx and psychological stress due to swallowing of the tethered capsule was observed in some subjects especially during the first attempt of incorporating the capsule. In this case, salivation increased the fluid flux into the stomach. However, this volume contribution is small, when the gastric emptying rate of the administered liquid is rapid.

5. Conclusion

A citrate phosphate buffer liquid can be used to monitor gastric emptying in order to investigate the pH effect using an EIT system. However, for a relatively small non-nutrient administered volume up to 150 ml, the method is less reliable as other control measures such as MMC and fluid flux have to be considered. No interference for data acquisitions was observed during simultaneous monitoring using the EIT system and pH sensitive radiotelemetry capsule. However, an increase in saliva flow stimulated by the tethered pH sensitive radiotelemetry capsule could contribute to irregular emptying profiles using the EIT system, if small liquid volumes are consumed. The EIT system could, therefore, be used to evaluate the gastric emptying of liquid dosage forms with volumes in excess of 250 ml.

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