Heidelberg Capsule I

In Vitro Evaluation of a New Instrument for Measuring Intragastric pH

By W. H. STEINBERG, F. A. MINA*, P. G. PICK, and G. H. FREY

The current methods available for measuring gastric pH are briefly reviewed. These methods provide limitations (*a*) restricted to the fasting stomach, (*b*) may provide stimulation of acid secretion, and (*c*) involves considerable patient resistance. Telemetering equipment has provided important data on many physiological processes. A new device called the Heidelberg capsule has been proposed to telemeter gastric pH. The studies include (*a*) standardization of equipment, (*b*) *in vitro* evaluation of the accuracy and precision of the device, and (*c*) determination of *in vitro* life and drift of the capsule. The *in vitro* data justify further studies of the instrument for *in vivo* evaluation of intragastric pH. The Heidelberg capsule may represent an important tool for tubeless *in vivo* evaluation of antacids and possibly other drugs.

OF THE NUMEROUS diagnostic tests performed by the physician on his patient, perhaps few if any are more disagreeable to the patient, and for that matter, to the doctor himself, than that of aspirating stomach secretions for gastric analysis.

The importance of gastric analysis cannot be stressed enough. However, aspiration techniques for gastric analysis pose a number of limitations that can provide results that often are not too accurate. For example, during intubation, hypersalivation can dilute the gastric contents and affect the hydrogen-ion concentration due to both the dilution factor and the higher pH of the saliva (1–3). Also frequent sampling and/or organoleptic perception may elicit excessive secretion of stomach acid in a fasting patient and provide inaccurate results.

Aspiration is more complex in patients who have undergone partial gastrectomy, and reflux of intestinal secretions into the antrum can neutralize gastric acid (4).

Since it is not practical to collect gastric samples from Pavlov or Heidenhain pouches, less esoteric methods must be utilized. Modifications of or substitutes for the aspiration technique have been proposed through the years. These include the dialysis bag technique which involves the use of a suitable membrane filled with distilled water and placed in the stomach *via* a connecting tube. After a time the content of the bag is withdrawn, and the hydrogen-ion content is determined (4, 5).

Attempts at measuring directly the pH of the stomach content *in situ* were made by the use of an intragastric electrode (6–11). This consisted of a special wire electrode passed into the stomach *via* the nasogastric route. These methods, however, continue to require some forms of intubation.

Tubeless gastric analyses were proposed by the use of indirect procedures. One such method involves the use of cationic exchange resins to determine the absence or presence of free hydrochloric acid. This procedure depends upon the dissociation of the resin by the hydrochloric acid in the stomach. The cation is absorbed and excreted in the urine in the presence of free acid only (12–16).

Another technique involves the use of a pill containing methylene blue wrapped in an indigestable sac tied by a catgut suture. Free acid, if present in the stomach, dissolves the suture and allows the release of the dye. The dye is then absorbed and excreted in the urine. Lack of free acid prevents the release of the dye. This procedure (Desmoid pill technique) was first devised by Sahli in 1905 and reintroduced in 1960 (17, 18).

Obviously, these methods are indirect, time consuming, and of limited value.

More recently, telemetry devices have been introduced for *in situ* physiological determinations. Such devices have been used in recording gastrointestinal sounds, motility, temperature, intraluminal pressure, and pH determinations (19–22). The latter is of special interest with reference to the subject of this paper.

EXPERIMENTAL

Materials

The three principal components necessary for telemetric measurements of intragastric pH are transmitter, antenna, and receiver.[1]

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[1] The Heidelberg equipment is supplied by The Upjohn Co., Kalamazoo, Mich.

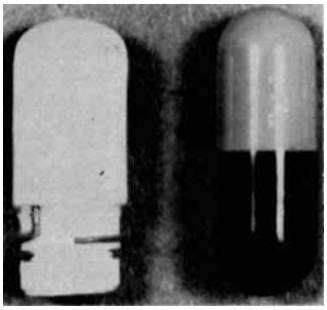

Fig. 1.—Transistorized high-frequency transmitter on the left compared in size with an antibiotic capsule.

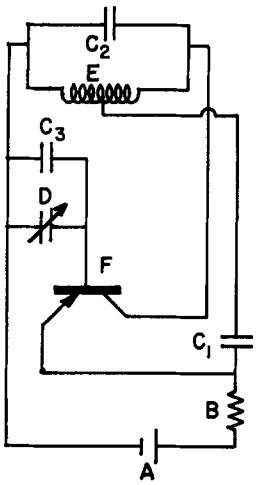

Fig. 2.—Transmitting capsule. Key: A, electrode; B, limiting resistor; C_1, C_2, C_3, fixed capacitors; D, variable capacitors; E, inductance; F, transistor; C_2-E, tank circuit.

Transmitter.—A transistorized high-frequency transmitter measuring only 8 × 18 mm. was used in the studies (Fig. 1). The transmitting device is encased in a nondigestible plastic capsule referred to as the Heidelberg capsule. The unique transmitting device utilizes a miniature Hartley circuit oscillating at a mean frequency of 1.9 megacycles per second. Electrical power is supplied by a self-contained silver chloride electrode collector battery having a constant voltage output of approximately 1.5 v.

A base battery is formed by separating the silver chloride electrode from an outer antimony electrode by means of a dialyzing membrane. The voltage output of the base battery is affected by the hydrogen-ion concentration of the surrounding medium. This variation in voltage output in turn affects the frequency of the transmitter circuit. The changes in frequency are then related to equivalent hydrogen-ion concentrations (Fig. 2).

The characteristics of the circuit are such that changes in hydrogen-ion concentration are linear in the range of pH 2.0 to 7.0.

Antenna.—A belt antenna was utilized containing three independent antenna systems polarized at right angles to each other. This arrangement provides for continuous signal strength when the apparatus is used *in vivo*, during which time the capsule transmitter changes its relative position and direction in the stomach.

Selection of the strongest signal is made automatically by the receiver to provide continuous telemetering, regardless of position and direction of the transmitting capsule.

A calibration antenna in direct contact with the capsule (Fig. 3) was used for determining the baseline of each capsule.

Receiver.—The receiving unit used in these studies was a transistorized recording receiver. Signals transmitted by the capsule *via* the antenna are modified so that the pH is equivalent to the frequency measured as kilocycles per second. The frequency is then observed as a related number on a dial and as a permanent record on the automatic graph recorder (Fig. 4).

Buffer Solutions

Harlco and Beckman buffers at pH 2.0, 4.0, and 7.0 were used in this study. Also a series of buffers from pH 1.2 to 8.8 in increments of 0.6 pH units was prepared according to U.S.P. standards, for determining the sensitivity response of the transmitting capsule to small changes in hydrogen-ion concentration.

Methods

Receiver Calibration.—Calibration of the receiving unit was accomplished in the following manner. A fresh transmitting capsule was acti-

Fig. 3.—Calibration antenna in direct contact with the capsule.

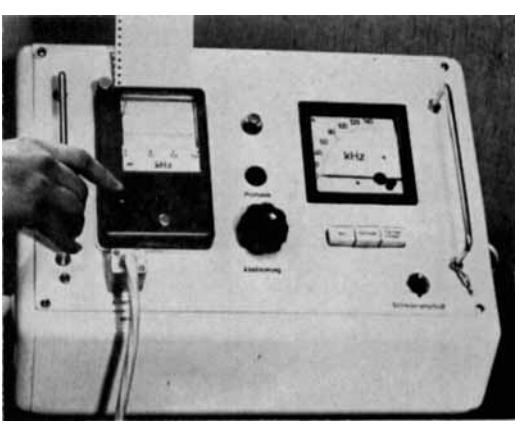

Fig. 4.—Automatic graph recorder.

TABLE I.—ACCURACY AND SENSITIVITY OF RECEIVER

Test Condition	Recording Chart Units and Equivalent Kc. Values in[a] Capsule *1*	Capsule *2*	Capsule *3*	Capsule *4*
pH 2.0	15 (25)	15 (25)	16 (30)	14 (25)
pH 7.0	84 (130)	84 (130)	76 (125)	74 (120)
5 pH units	69 (105)	69 (105)	60 (95)	60 (95)
1 pH unit	13.8 (21)	13.8 (21.0)	12.0 (19.0)	120 (19.0)
pH 7.0	84 (130)	84 (130)	76 (125)	74 (120)
pH 4.0	44 (71)	44 (70)	43 (65)	38 (59)
3 pH units	40 (49)	40 (60)	33 (60)	36 (61)
1 pH unit	13.4 (19.7)	13.4 (20.0)	11.0 (20.0)	12.0 (20.3)
% Error	2.9 (6.2)	2.9 (6.2)	2.0 (5.0)	0 (6.4)

[a] Equivalent kilocycle values in parentheses.

TABLE II.—CAPSULE RESPONSE TO RANDOM pH CHANGE

Capsule	Time hr.	Time min.	Actual pH	Kc. Value	Calcd. pH	Chart Value	Calcd. pH
1	0		1.85	25	[a]	15	[a]
		2	7.00	130	[a]	84	[a]
	1	2	7.00	132	[a]	85	[a]
	1	55	4.10	70	4.14	44	4.12
	3	0	4.10	71	4.15	45	4.20
	3	1	7.00	130	7.12	82	6.94
2	0		2.00	25	[a]	15	[a]
	2	6	7.05	122	[a]	84	[a]
	3	25	2.05	26	2.01	14	2.03
	5	47	4.05	59	3.70	38	3.72
3	0		2.00	30	[a]	16	[a]
	1	12	7.00	125	[a]	78	[a]
	1	14	4.00	68	3.95	40	4.08
4	0		2.00	25	[a]	14	[a]
	1	19	7.00	120	[a]	74	[a]
	1	31	4.00	64	4.05	40	4.00
	2	31	2.00	25	2.00	15	2.08
	2	40	4.00	59	3.79	35	3.76

[a] Calibrated baseline.

TABLE III.—LINEAR RESPONSE OF INDIVIDUAL TRANSMITTING CAPSULES

Capsule	Kc. Value pH 2.0	pH 7.0	pH 4.0	Calcd. pH	Actual pH	% Error in Linearity
1	25	132	70	4.10	4.10	0
2	25	122	59	3.75	4.10	8.55
3	30	125	65	4.10	4.00	2.50
4	20	110	65	4.22	4.00	5.56
5	25	120	64	4.05	4.00	1.25
6	25	125	64	3.95	4.00	1.25
7	25	137	70	4.02	4.00	0.50
8	25	121	64	4.05	4.00	1.25
9	25	131	68	4.13	4.00	3.25
10	25	125	55	4.00	4.01	0.25
11	25	134	72	4.14	4.02	3.00
12	25	124	65	4.02	4.00	0.50
13	25	125	67	4.09	4.05	1.00
14	25	130	67	4.00	4.08	2.00
15	25	130	73	4.28	4.06	5.43
16	25	125	68	4.23	4.04	4.00
17	25	130	77	4.46	4.04	10.35

vated by immersing the capsule in physiologic saline for 15 min. It was then thoroughly washed with distilled water, secured in the tip of the calibrating antenna directly connected to the receiving unit, and immersed in pH 2.0 buffer.

The instrument was adjusted so that a baseline reading of approximately 25 was obtained on the kilocycle meter on the face of the instrument.

After obtaining a continuous baseline for pH 2.0 buffer, the capsule was washed in distilled water and immersed in pH 7.0 buffer. Again after a steady baseline was obtained at this pH, the capsule was rinsed in distilled water and immersed in pH 4.0 buffer. All test solutions were maintained at a temperature of 38° by immersing the flask containing the test buffer in a constant-temperature water bath. Stock solutions of the other buffers also were maintained in the water bath for ready availability.

The next step was to measure the accuracy of the belt antenna. In this procedure, the belt antenna was looped around the water bath in which a conical

flask containing the appropriate pH buffer was immersed. The antenna position was arranged so as to simulate its use for *in vivo* application.

The activated capsule was held submerged by maintaining it in the calibrating antenna disconnected from the receiving unit.

The response interval was observed by immersing the capsule in different buffers after suitable rinsing with distilled water, recording the time lag between the change in environmental pH, and recording same on the continuous graph recorder.

The accuracy of the pH of the buffer solution was checked by a continuously monitored pH determination made on a Metrohm model E300 pH meter.

The procedures described above provided dependable means of determining accuracy, sensitivity, response interval, and life span of the individual transmitting capsules and sensitivity of the receiving instrument. A total of 25 capsules were used in this study phase.

The possibility of extraneous influence, *e.g.*, static, fluorescent fixtures, and other electrical interferences, was ruled out by repeated runs without capsules, using both the calibrating and belt antennas, and by moving the receiving instrument to different locations.

With proper grounding of the instrument, no electrical interference was found.

RESULTS AND DISCUSSION

Accuracy and sensitivity of the receiving instrument is indicated in Table I which records the results of four freshly activated capsules. The recording chart figures in Table I demonstrate an average error of 2.92 for the four capsules tested in comparing a spread of 5 pH units (pH 2 to pH 7) to a spread of 3 pH units (pH 7 to pH 4). The equivalent kilocycle value observed on the face of the receiving instrument showed an average error of 5.95% in the same comparison.

Table II shows the responsiveness of four transmitting capsules to random changes in environmental pH between buffers of pH 2.0, 4.0, and 7.0.

It is apparent from these results that the individual capsule accurately responds to abrupt changes in the pH of the surrounding medium.

In another experiment, a total of 17 transmitting capsules were activated separately and the receiving instrument calibrated for each capsule at pH 2.0 and 7.0. Each capsule then was placed in pH 4.0 buffer to determine individual capsule error in linearity. This was done by comparing the actual pH with that of the calculated pH in pH 4.0 buffer. The results are reported in Table III. These results show that the average per cent error is 2.98, and that the maximum per cent error in linearity response was 10.35 in one capsule which resulted in a difference of less than 0.5 pH units.

It is apparent from these observations that each capsule individually must be calibrated to the receiving instrument.

Attempts were made to standardize the instrument to a range of pH 2.0 to pH 8.8 using a freshly prepared sodium bicarbonate solution as the alkaline medium. Repeated tests indicated that the instrument was limited generally to a straight line response between pH 2.0 and 7.0. The abrupt change in recording of pH's above 7 serves as an indication of the transfer of the capsule from the stomach to the duodenum.

The life span and accuracy of transmitting capsules was found to be approximately 6 to 8 hr. This is considered an adequate span in view of the 1–3-hr. emptying time of the human stomach.

It was found that total transmission failure of the capsule occurred within 15 min. following an initial deviation of a 1.0 pH unit from the actual pH of the environmental medium.

The life span and response of a typical transmitting capsule immersed alternately in a pH 4 and pH 7 buffer is shown graphically in Fig. 5.

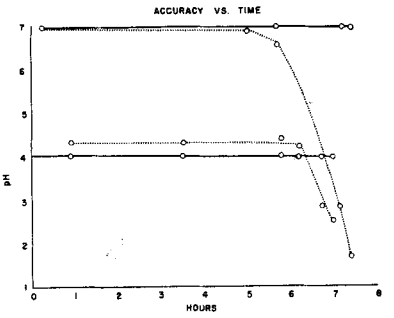

Fig. 5.—Transmitting capsule accuracy *vs.* time. Key: ————, actual pH; . . . . . , transmitted pH.

TABLE IV.—TRANSMITTING CAPSULE ACCURACY *versus* TIME

Time hr.	Time min.	pH of Buffer	Equivalent pH— Recording Chart	Equivalent pH— Kc. Value	% Error— Recording Chart	% Error— Kc. Value
0		2.00	[a]	[a]	...	...
	15	7.00	[a]	[a]	...	...
	55	4.03	4.33	4.20	7.45	4.23
3	30	4.02	4.33	4.20	7.45	4.48
3	42	2.03	2.13	2.23	4.85	9.90
5	5	2.00	2.00	2.00	0	0
5	38	7.04	6.60	6.98	6.25	0.85
5	45	4.04	4.48	4.02	10.90	0.50
6	10	4.04	4.28	3.68	5.95	8.82
6	40	4.03	2.86	3.17	29.00	21.30
6	55	4.03	2.53	...	37.30	...
7	7	7.04	2.86	...	59.43	...
7	20	7.04	1.67	...	76.30	...

[a] Calibrated baseline.

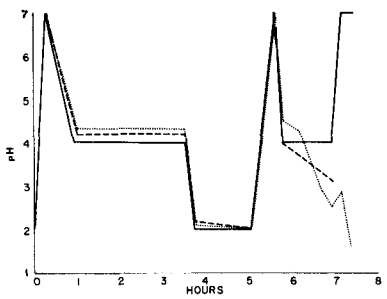

Fig. 6.—Transmitting capsule linearity response *vs.* time. Key: ————————, actual pH; – – – – – – – –, kilocycle value; . . . . . , chart value.

The results of varied pH media are given in Table IV and Fig. 6.

Response interval of the transmitting capsule to different buffers was found to be less than 5 min.

CONCLUSIONS

1. The Heidelberg capsules provide an accurate and sensitive means of telemetric recording of hydrogen-ion concentration of a surrounding medium.
2. Individual transmitting capsules vary in sensitivity and must be individually standardized.
3. The useful life span of a transmitting capsule is approximately 6 to 8 hr.
4. Linear response of the capsule is limited to between pH 2.0 and 7.0.
5. On the basis of the *in vitro* evaluation of the instrument and transmitting capsule, the Heidelberg capsule merits consideration for *in vivo* determinations of gastric pH.

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Evaluation of a High-Efficiency Solids–Solids Blender

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Solids–solids blending of pharmaceuticals is a time-consuming batch operation. Modern techniques using high-efficiency mixing devices as a method of process time-saving and cost reduction are becoming of prime concern. The Littleford-Lodige mixer was evaluated as a method of achieving rapid high-efficiency solids–solids blending; its application as a wet granulation device was also briefly investigated. The data obtained using the Littleford-Lodige mixer as a solids–solids blender is presented. Evaluation of the data indicate complete mixing is obtained in approximately 30 sec. Preliminary evaluation of this equipment as a method of wet granulation indicates granulation times in the order of 5 to 10 min. or less, depending on mixing characteristics and ingredients. Based on the results of this work, the Littleford-Lodige mixer appears to be a promising method of achieving rapid dry blending and wet granulation in one piece of equipment. Its use in the field of blending and wet granulation is worthy of further investigation.

SOLIDS–SOLIDS blending and the incorporation of liquids into dry solids is an important unit operation in many processes. In the field of pharmaceuticals, the blending of materials in the past has routinely been handled using the standard process equipment—namely, ribbon blenders, Hobart mixers, twin-shell blenders, etc. Mixing in these types of equipment, although adequate, generally is time consuming and of a batch nature. Today, with the ever-present problems of cost reduction and time savings being critically evaluated, the unit operation of blending is being reviewed for possible methods of time reduction and/or continuous operation.

In the past several years, high-efficiency equip-

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