RESEARCH ARTICLES

Quantitative Evaluation of Pharmaceutical Effervescent Systems I: Design of Testing Apparatus

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Abstract ☐ Two new devices were developed to monitor the reactivity of pharmaceutical effervescent systems. The first method monitored carbon dioxide pressure generation during the effervescent reaction in a plastic pressure vessel fitted with a pressure gauge. The second method monitored weight loss, attributed to carbon dioxide loss to the atmosphere, by means of a double cantilever beam and an electromagnetic proximity transducer. In the pressure device, the quantification of an effervescent reaction was accomplished by measuring the dissolution time of the effervescent system and the pressure generated. Quantification of an effervescent reaction using the beam device utilized the total carbon dioxide weight loss, the rate of weight loss, and the effervescent reaction lag time.

Keyphrases ☐ Effervescent pharmaceuticals—quantitative evaluation, design of testing apparatus ☐ Reactivity—quantitative evaluation of effervescent pharmaceuticals, design of testing apparatus ☐ Instrumentation—design of testing apparatus to quantitate reactivity of effervescent pharmaceuticals

Acid–base reactions between alkali metal carbonates or bicarbonates and citric or tartaric acid have been used for many years to produce effervescent pharmaceutical preparations on the addition of water. The greatest problem with effervescent products is the loss of reactivity with time due to their premature reaction on exposure to moisture. Even exposure to atmospheric moisture when opening and closing a multiple-dose container can rapidly destroy reactivity.

BACKGROUND

Studies to design improved effervescent tablet systems have suffered from the absence of methodology to quantitate effervescent reactions. To study the rate of an effervescent reaction such as between sodium bicarbonate and citric acid in excess water, producing carbon dioxide, water, and sodium citrate, one can theoretically measure the increase in one reaction product or the decrease in one reactant. The obvious element to measure continuously would be the carbon dioxide generated. This procedure would permit measurement of the amount of carbon dioxide generated by a particular system as well as the rate of the reaction.

Chemical analysis of carbon dioxide, following total evolution of the gas, can be accomplished by several means. However, none of the methods permits the direct kinetic determination of carbon dioxide evolution during various time points in the process of a rapidly reacting system. Carbon dioxide can be measured by a volumetric method using the Chittick apparatus (1), by a combination of gas measurement and gas absorption, or by a weight loss method (2). Carbon dioxide is also determined by absorption on liquid or solid media, measuring the amount of gas evolved by weighing (3). The use of the absorption method has been modified many times by using different detection methods to determine the amount of gas absorbed (4–6). None of these methods is satisfactory for quantitating an effervescent reaction that is completed in <30–60 sec.

One possible method of continuously monitoring carbon dioxide evolution is to monitor the pressure generated in a closed system. However, this approach may not simulate the normal effervescent tablet reaction occurring in an open container of water at constant atmospheric pressure.

A simple, continuous, immediate response weight loss procedure was thought to offer the most direct and applicable technique to determine the total amount of carbon dioxide evolved, the reaction rate, and other characteristics of the reaction process. Development of such a system requires the development of an adequately sensitive weighing system, providing immediate response and continuous recording. The response characteristics must be rapid to quantitate totally a reaction that is completed in 30 sec or less and sensitive enough to measure accurately weight losses <1 g from an initial mass of ~100 g.

Transducers capable of responding quickly to applied forces have been used in the pharmaceutical industry for more than 20 years. Strain-gauge transducers have been shown (7, 8) to be widely and successfully used in instrumenting tableting machines in research, development, and production capacities. A device was developed (9) for the continuous recording of the flow of powders or granular material from various hoppers with strain gauges. Later, an instrument was developed (10) to determine granule strength using strain gauges in a beam apparatus similar to the flow device. Taylor (11) developed a flowing measure instrument with strain gauges and a specially designed double-cantilever beam, and the same equipment was adapted to quantify suspension pourability (12). While the newer strain-gauge devices permit continuous recording of applied loads, such systems are not adequately sensitive to monitor carbon dioxide loss during an effervescent reaction.

This report describes a new balance system utilizing an electromagnetic proximity transducer and a specifically designed double-cantilever beam that is sensitive enough for the continuous gravimetric measurement of carbon dioxide loss during an effervescent reaction. Utilizing the proximitor balance system as well as pressure generation measurements, effervescent systems and reactions were quantitated as to their reaction
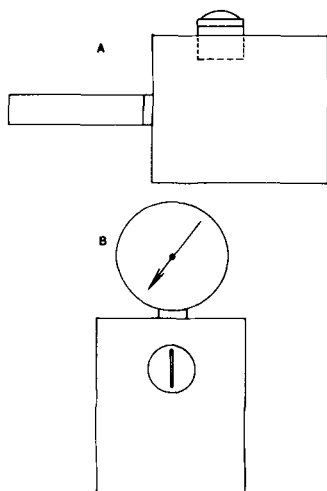
Figure 1—*Pressure monitoring device in the filling position (A) and in the testing position (B).*

rates, carbon dioxide losses, dissolution times, and lag times to initiation of reaction. A reactivity index was developed, and a correlation between the two new methods of examining effervescent reactions was found.

EXPERIMENTAL

Instrumentation—Reactivity testing based on monitoring pressure generation of effervescent tablet systems was done in a cylindrical plastic pressure vessel especially designed for effervescent tablets. The pressure generated during the effervescent reaction in the vessel was measured by a 0–60 psi pressure gauge[1] mounted on the pressure vessel. The volume of the pressure vessel was ~250 ml. Attached to the side of the vessel was the sample tablet holder(Figs. 1A and 1B). The tablet holder was cylindrical in design and built perpendicularly into the side of the pressure vessel. The end opening to the interior of the vessel consisted of two perpendicular crosspieces, which held the sample tablet out of the interior of the vessel in the filling position (Fig. 1A), but allowed the water in the vessel to flow into the sample holder to cover the tablet when placed in the vertical test position (Fig.1B). A pressure-tight, clear plastic screw cap sealed the system at the exterior end of the cylindrical sample holder.

The new balance system for the continuous recording of carbon dioxide weight loss utilized a double-cantilever beam with a proximity transducer to monitor beam deflection. The proximity transducer consisted of a probe and a proximitor. The actual transducer consisted of a flat coil of wire located in the ceramic tip of the probe. This probe then became a gap-to-voltage transducer used to measure distances and change in distances to any electrically conductive material. The probe was driven by a radio frequency (RF) voltage developed by the proximitor. The output signal from the proximitor to a chart recorder was at a voltage proportional to the distance between the probe and the conductive surface.

Basically, the proximitor takes the voltage supplied to it from a power supply and converts it to an RF signal. This signal is then applied to the probe and the probe coil, which radiates this signal into the surrounding area as a magnetic field. If there is no conductive surface to interfere with the magnetic field there is no RF signal loss. However, as a conductive surface approaches the probe and interferes with the magnetic field, eddy currents are generated on the surface of the material, the RF signal is lost, and power is consumed. As the surface moves closer to the probe, more and more power is absorbed and the RF signal decreases. The proximitor measures the RF signal voltages and sends out an output voltage equal to the negative RF signal peaks (13). The output voltages can then be directly measured on a volumeter or used to drive a chart recorder.

The new beam/proximitor (b/p) balance system (Fig. 2) consisted of a double-cantilever beam specifically designed for a maximum load of 100 g to be placed on the 5.1-cm sample pan. The proximity transducer probe[2] was mounted directly below the electrically conductive surface needed for the proximity measurement. The proximitor[2] itself was housed

Table I—Theoretical and Observed Recorder Span Responses of the Beam/Proximitor Balance to Various Weights Applied to a 99-g Load

Weight Applied, g	Theoretical Span Response, division	Actual Span Response, division
1.00	90.0	90.0
0.75	67.5	67.5
0.50	45.0	45.0
0.25	22.5	22.5
0.10	9.0	9.0
0.05	4.5	4.5
0.02	1.8	1.75
0.01	0.9	1.0

Table II—Beam/Proximitor Balance Recorder Span Precision and Reproducibility [a]

Trial	Number of Tests Run	Average Span Response ± SD, division
1	30	90.09 ± 0.154
2	35	89.98 ± 0.195
3	31	90.00 ± 0.144

[a] One gram produces a 90-division span response.

with an 18-v power supply. A line filter[3] was needed to filter out electrical noise, and a voltage divider was needed to reduce the input voltage to the recorder to match the 100-mv span on the recorder[4]. The b/p balance was housed during tests in a plexiglass hood to reduce the possibilities of air currents affecting the balance.

The double-cantilever beam system of the balance was designed and constructed to provide a linear response in beam deflections to various load weights. The b/p balance was then designed to measure weight loss by monitoring beam deflections with the proximitor and probe. Using this design, the b/p balance could monitor up to a 1-g weight loss from an initial load of up to 100 g.

Pressure Vessel Test Method—With the pressure vessel placed in the horizontal filling position (Fig. 1A), the cap of the tablet holder was removed and 150 ml of deionized, distilled water (20°) was quickly transferred into the pressure device through the tablet holder. Any water adhering to the tablet holder was removed to prevent premature reaction. The tablet to be tested was placed in the tablet holder, and the cap was replaced and secured. The pressure vessel was then lifted to the vertical test position (Fig. 1B), causing the water to contact the tablet in the tablet holder and produce the effervescent reaction. At 5-sec intervals, the pressure was read from the pressure gauge and recorded. The dissolution time of the effervescent tablet, as observed through the transparent cap of the tablet holder, was recorded, as well as the pressure that developed at the dissolution time. Finally, the entire device was shaken for a few seconds and the final pressure was recorded.
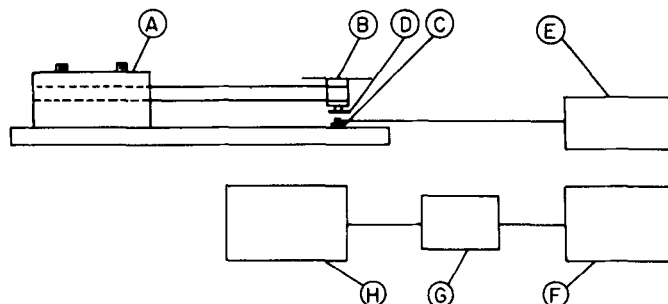

Figure 2—*The balance system utilizing a double-cantilever beam and proximity transducer. Key: A, double-cantilever beam assembly; B, sample pan; C, proximity probe; D, electrically conductive surface; E, power supply; F, electrical line filter; G, voltage divider; and H, recorder.*

Table III—Carbon Dioxide Weight Loss [a] After 2 Min from Effervescent Tablets

Trial	Number of Tablets	Commercial Analytical Balance			Beam/Proximitor Balance		
		Average Tablet Weight, g	Average Carbon Dioxide, mg	Loss, % (w/w)	Average Tablet Weight, g	Average Carbon Dioxide, mg	Loss, % (w/w)
1	4	3.5006	553.3	15.81	3.5413	606.4	17.12
2	3	3.4345	560.5	16.32	3.4605	574.4	16.60
3	5	3.4987	581.5	16.62	3.4870	584.4	16.76

[a] As measured by an analytical balance and the beam/proximitor balance.

Balance Test Method—Polypropylene beakers (100-ml) were used as the effervesecent tablet reaction vessels. Because the effervescent reaction was violent enough to cause a loss of water as well as carbon dioxide from the beaker, a circular beaker cover (7.0 cm in diameter) was made from high density polyethylene material. This cover had a rectangular slot, 2.9 × 0.6 cm, cut in the center through which the effervescent tablets were dropped into the beaker.

After prestressing the balance beam with a 100-g load for 30–40 min to stabilize the base (0% span) and top lines (90% span) on the recorder, ~80 ml of deionized, distilled water at 20° was measured into the reaction beaker and the total weight of the beaker, cover, water, and tablet was adjusted to 100 g or 90% of full recorder span with 20° water. With the recorder on "standby" and the chart speed set at 12.7 cm/min, the tablet was set on its edge at the edge of the slot in the cover. After initial beam vibration had subsided, the tablet was gently dropped through the slot into the beaker. Immediately after the tablet entered the water, the recorder was turned to "record," and the effervescent reaction was monitored for at least 2 min. The tablet dissolution time was determined visually and indicated on the recording.

Calibration of Balance—After prestressing the beam with a 99-g load, the b/p balance was calibrated by placing various known loads, 10 mg–1 g, on the balance. The recorder span was set at 90%. The actual recorder response to the various loads was in very close agreement to the theoretical response. Only slight deviations occurred at even the 20- and 10-mg loads (Table I).

The recorder span (90%) reproducibility was measured by repeatedly adding and removing a 1-g weight from the b/p balance loaded with 99 g. Table II shows the precision and reproducibility resulting from the three trials performed.

Tests were run to compare reacting effervescent tablet carbon dioxide weight loss values obtained with the b/p balance to values obtained with a commercial balance. Effervescent tablets[5] were reacted in a beaker of water, and the weight loss was noted after 2 min of reaction time on a commercial analytical balance[6] and compared to the weight loss of tablets run on the experimental balance. The data in Table III show close agreement in the total weight loss after 2 min between the b/p balance and the commercial analytical balance, which further verified the accuracy of the b/p unit.

Materials—Several different experimental effervescent tablets were made for effervescent reactivity testing with the pressure vessel and b/p balance methods. Each tablet system was a 3-g tablet containing a stoichiometric ratio of acid and base (Table IV). A standard 3-g tablet was made of citric acid–sodium bicarbonate (1.3:1.7). All materials were either USP, NF, or pharmaceutical grade.

The materials were first passed through a 30-mesh screen and then through an 80-mesh screen, mixed, and compressed on a hydraulic press[7] between 25.4-mm, flat-faced, beveled-edge tooling. The compression force generated for each tablet was 897 kg/cm^2 and was held for a 5-sec dwell time. All operations were conducted at 23–25° and a relative humidity of ≤30%.

RESULTS AND DISCUSSION

The standard tablets were run in the pressure device first. Table V shows the pressure and dissolution time results of the 28 standard formulation tablets run. The standard tablets were then run on the b/p balance to measure carbon dioxide loss (Table VI).

The experimental effervescent tablets were then run in the pressure device and on the b/p balance. The resultant carbon dioxide weight loss values and gas pressure values were divided by the corresponding values obtained from the standard tablets to generate relative pressure values

and relative weight loss values listed in Table VII. Figure 3 shows the relationship between the relative values obtained from the two test methods. The calculated correlation coefficient for the graph was 0.937.

Table IV—Experimental Effervescent Tablets Run in The Pressure Monitoring Device and the Beam/Proximitor Balance

Composition	Composition Ratio, g:g
Citric acid–sodium bicarbonate (standard)	1.3:1.7
Malic acid–potassium bicarbonate	1.72:1.28
Glutaric acid–potassium bicarbonate	1.19:1.81
Maleic acid–potassium bicarbonate	1.10:1.90
Glutaric acid–sodium bicarbonate	1.32:1.68
Malic acid–sodium bicarbonate	1.85:1.15
Maleic acid–sodium bicarbonate	1.22:1.77

Table V—Average Pressure Generation and Dissolution Time of Sodium Bicarbonate–Citric Acid Run [a] in the Pressure Monitoring Device

	Pressure Developed, psi	Dissolution Time, sec
Average	26.75	28.89
Variance	0.435	5.65
SD	0.669	2.38
SEM	0.125	0.45

[a] Twenty-eight samples were run.

Table VI—Average Carbon Dioxide Weight Loss of the Standard 3-g Tablets of Sodium Bicarbonate–Citric Acid Run on the Beam/Proximitor Balance

	Amount
Tablet weight	
Number of tablets tested	30
Average weight, g	2.9914
Variance, g	0.0004
SD, g	0.0062
SEM, g	0.0011
Calculated carbon dioxide weight loss (W_F)	
Number of tablets tested	30
Average loss, g	0.5419
Variance, g	0.0003
SD, g	0.0177
SEM, g	0.0032

Table VII—Relative [a] Pressure Values and Carbon Dioxide Weight Loss Values of the Experimental Effervescent Tablets Run in the Pressure Monitoring Device and the Beam/Proximitor Balance

Tablet Composition	Relative Pressure (psig) Values	Relative Weight Loss Values
Citric acid–sodium bicarbonate (standard)	1.00	1.00
Malic acid–potassium bicarbonate	0.93	0.95
Glutaric acid–potassium bicarbonate	1.02	0.98
Maleic acid–potassium bicarbonate	0.98	1.02
Glutaric acid–sodium bicarbonate	1.01	1.00
Malic acid–sodium bicarbonate	0.84	0.84
Maleic acid–sodium bicarbonate	0.86	0.83

[a] Experimental tablet values for pressure and weight loss were divided by the standard tablet values of 26.75-psi pressure and 0.5419-g weight loss to calculate the relative values.

[5] Alka-Seltzer tablets, Miles Laboratories, Elkhart, Ind.
[6] Model H-10 Mettler Instrument Corp., Princeton, N.J.
[7] Carver laboratory press model C, Fred S. Carver and Co., Summit, N.J.
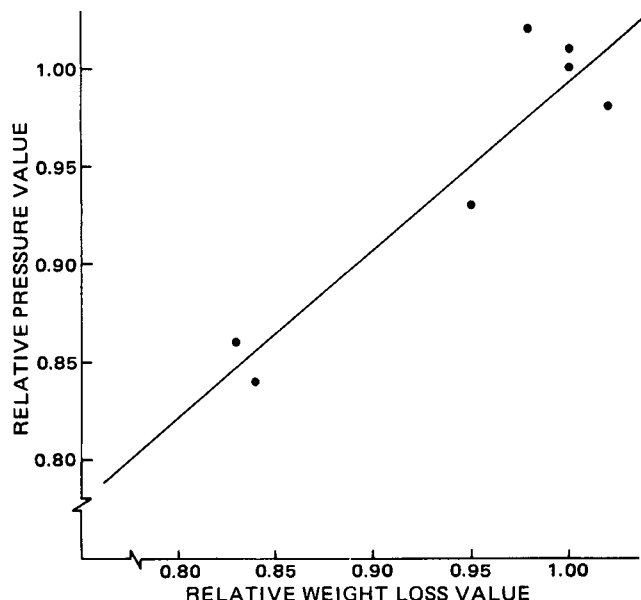
Figure 3—*Relationship between the relative pressure values from the pressure monitoring device and the relative weight loss values from the beam/proximitor balance (Table IV).*

The correlation was judged to be good considering that the sensitivity of the pressure gauge on the pressure device was 2 psi/division and the sensitivity of the b/p balance was 0.0111 g/division.

The milligrams of carbon dioxide lost at any time (t) during an effervescent reaction were designated W_t and could be calculated from the chart recording (Fig. 4) by multiplying the number of divisions corresponding to the weight loss at time t by 11.1 mg/division. The final weight loss measured 2 min after the reaction was started was designated W_F. Plotting log ($W_F - W_t$) *versus* time produced a graph like the one in Fig. 5. The graph can be divided into three segments corresponding to the three events observed during the effervescent reactions. Period A of Fig. 5, the distance between the y-axis and the time at which the graph first approaches linearity, represents an induction period or lag time during which the tablet is wetted by the water and the effervescent reaction is initiated. Period C represents the period after the effervescent reaction has ceased and when carbon dioxide is slowly coming out of solution. Period B represents the actual time of the effervescent reaction of the tablet. In this section of the graph, a straight line can be drawn, the slope determined by linear regression, and an observed first-order rate constant (k) can be calculated for the reaction.
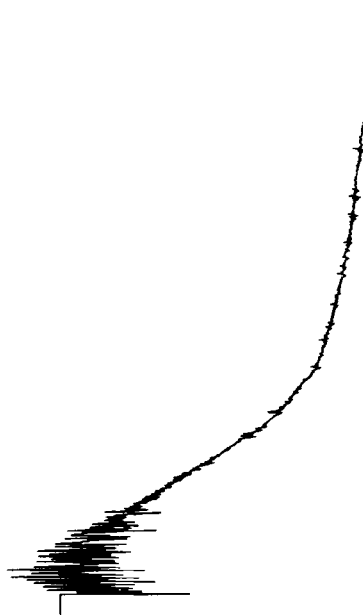

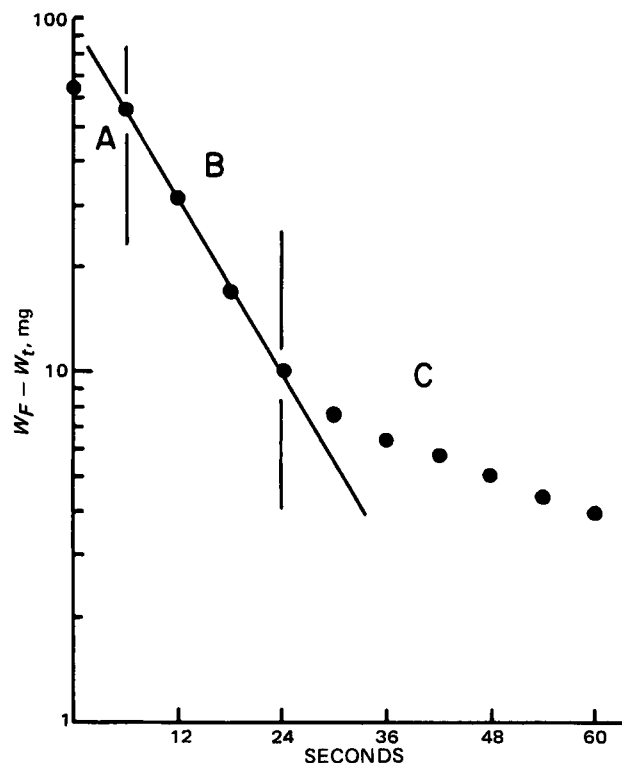**Figure 4**—*Typical chart recording from a beam/proximitor balance effervescent tablet run.*

Figure 5—*Example plot of beam/proximitor balance data treatment using log ($W_F - W_T$) versus time relationship.*

In a statistical evaluation of reactivity, a single measurement of both the reaction rate and the total carbon dioxide evolved is required since differing effervescent systems could conceivably have a fast reaction rate and yet produce little carbon dioxide (and vice versa). Therefore, Eq. 1 can be used to quantitate each effervescent tablet system for both k and W_F in a single indicator, the index of reactivity (I_R):

$$I_R = kW_F \qquad \text{(Eq. 1)}$$

SUMMARY

While the described pressure monitoring device did not lend itself to effervescent reaction characterization or rate determinations, the results obtained did correlate with weight loss data obtained from the balance device. The pressure monitoring device could be used as an effective, quick screening device for experimental effervescent system reactivity or as a possible quality control instrument.

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