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Solution calorimetry as a tool to study the neutralising capacity of magnesium trisilicate mixture BP and its components

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Abstract

Magnesium trisilicate mixture BP, a liquid antacid, contains three active components; magnesium trisilicate BP (MT) (5% (w/v)), light magnesium carbonate BP (LMC) (5% (w/v)) and sodium bicarbonate BP (SB) (5% (w/v)). The role of each component in the mixture is not well understood although each contributes to the overall acid neutralising capacity (ANC) of the product, the standard measure by which antacid performance is rated. Previous work has suggested that the inclusion of magnesium trisilicate BP in the mixture is unwarranted [Int. J. Pharm., 29 (1986) 253], because of its extremely slow reaction with hydrochloric acid. In light of these observations, there is a need to study the basic mechanisms of neutralisation of the components of the mixture. Since the heat change associated with simple mono-protic acid–base neutralisation is approximately $-57\,\mathrm{kJ\,mol^{-1}}$ [Chemistry Data Book, John Murray, London, 1982], calorimetry may be used to study the reactions. In this work, the relative contributions to the ANC of the product of each component were measured using solution calorimetry. It was found that light magnesium carbonate BP contributed most to the overall ANC of the product, sodium bicarbonate BP the least. Magnesium trisilicate BP was found to neutralise acid over an extended time period, and contributed most to the duration of action of the dose. Moreover, it appears that light magnesium carbonate BP and magnesium trisilicate BP in combination exhibit a greater than expected ANC, showing positive synergy.
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1. Introduction

Antacids are designed to neutralise stomach acid, thereby increasing local pH and reducing the effects of gastroesophageal reflux [3]. They are used pre-operatively for the prevention of Mendelson's syndrome (whereby acid is aspired into the lungs) [4–6], to provide relief from dyspepsia and stress gastritis [7,8] and are widely taken as a self-prescribed medication, providing symptomatic relief of gastrointestinal complaints [9].

Liquid antacids, usually, are suspensions of inorganic salts that are insoluble at neutral pH. These salts become, however, solubilised under acid conditions, releasing anions which are consequently available to neutralise hydrogen ions. This mechanism ensures that gastric acid proportionately generates reactive base [3]. An exception to this general mechanism is sodium bicarbonate, which is freely soluble at neutral pH. The neutralising effect of sodium bicarbonate is therefore not regulated by local pH and some authors have suggested that it should not be included in antacid formulations [3].

Magnesium trisilicate mixture BP (MTM) is a readily available, over-the-counter liquid antacid. MTM contains three principal active components; light magnesium carbonate BP (LMC), sodium bicarbonate BP (SB) and magnesium trisilicate BP (MT). LMC and MT are insoluble and are present in suspension. SB, as mentioned above, is present in solution. Each component is present at a concentration of 5% (w/v), giving a total concentration of active of 15% (w/v) in the final product. The three neutralising reactions

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are expressed as:

$$(MgO)_2(SiO_2)_{3\,(s)} + 4HCl_{(aq)} \rightarrow 2MgCl_{2\,(aq)} + 3SiO_{2\,(s)} + 2H_2O_{(l)}$$

$$MgCO_{3\,(s)} + 2HCl_{(aq)} \rightarrow MgCl_{2\,(aq)} + H_2O_{(l)} + CO_{2\,(g)}$$

$$NaHCO_{3\,(aq)} + HCl_{(aq)} \rightarrow NaCl_{(aq)} + H_2O_{(l)} + CO_{2\,(g)}$$

Antacid efficacy is determined (for BP purposes) using the BP neutralising capacity test [10]. Antacid (5 g) is added to water (100 ml) and is heated to 37 °C. Dilute hydrochloric acid (100 ml, 0.1 M), previously heated to 37 °C, is added to the warmed suspension and the mixture is stirred at 200 rpm. The pH of the suspension at 37 °C at 10 and 20 min should not be less than 2.0 and 2.4, respectively and at no time must it exceed 4.0. Note that the term acid neutralisation is used here to mean a significant reduction in gastric acidity, rather than the attainment of chemical neutrality. Each component in the mixture contributes to the overall ANC of the product, but the role of each is not well understood. On its own each component is reported to have a relatively low ANC [9]. Indeed, all OTC antacid formulations containing solely MT were withdrawn from the United States Market [1].

The BP test [10], while providing a useful standard by which to compare commercial formulations does not accurately reflect the case in vivo. This is because the contents of the stomach are continuously being emptied and acid is being replaced. To model more accurately the action of antacids in vivo a derivative of the BP neutralisation capacity test was devised by Rossett and Rice [11] and was subsequently modified by Washington et al. [1]. In the Rossett and Rice test, antacid is added to a volume of acid at 37 °C. The pH of the suspension is recorded as a function of time as dilute acid is pumped into the reaction suspension at a constant rate. In the modified Rossett and Rice test, dilute acid is continuously pumped into the reaction mixture while the volume of the mixture is kept constant by continual removal of some liquid. In both cases the mixtures are continuously stirred (although the rates are not stated). The duration of action of the antacid is defined as the period of time during which the pH is greater than 3.0.

Washington et al. [1] used the modified Rossett and Rice test to investigate the neutralising capacity of magnesium trisilicate BP and magnesium trisilicate mixture BP. They noted that MTM reacted rapidly with acid, at an input of 4 ml min^{-1}, reaching a maximum pH 7.0 and an extent of action of 27 min. In the conventional Rossett and Rice test, MTM increased the pH to a maximum of 7.4 with a duration of action of 46 min. MT, however, did not produce any significant change in the pH of the medium until the input rate of acid was lowered to 0.5 ml min^{-1}, whereupon the pH was greater than 3.0 for approximately 20 min.

The neutralising capacities of SB and LMC were also investigated using the Rossett and Rice test [1]. SB caused a rapid rise in pH to 6.4 within 1 min and had a duration of action of 11 min. LMC increased the pH to 7.2 within 3 min and had a duration of action of 22 min. When SB and LMC were added in combination the pH was increased to 7.4 and the duration of action was increased to 41 min.

These data suggested that it was the combination of LMC and SB that was responsible for the long-lasting, fast-acting response of magnesium trisilicate mixture BP and the authors concluded that it was questionable as to whether the principal component, MT, should be included in the formulation.

We are currently investigating the mechanisms associated with antacid neutralisation and the action of MTM in particular. Clearly, it is important to understand the role of each component in MTM, not only to ensure that the current product continues to meet pharmacopoeial specifications but to facilitate the formulation of new, more efficacious products. Basic research into the mechanisms of action of antacids is also required in light of Washington's evidence [1] that the inclusion of MT in MTM is unwarranted.

Simple mono-protic acid–base neutralisation is associated with an enthalpy change of approximately −57 kJ mol^{-1} [2]. However, more complex, non-ideal species (such as suspensions) would be expected to show overall heat changes that deviated slightly from this value. Measuring the heat liberated from the neutralising reactions of MTM will aid the interpretation of the existing pH methods because the calorimeter records the changes associated with all of the processes involved, not just the pH change. Moreover, careful experimental design will allow any possible synergy between the components to be detected. Therefore, the simple aim of the present study is to investigate whether the heat liberated upon neutralisation can be used as a measure of the ANC for antacid formulations.

In this work, the relative ANC of each of the components of MTM was studied using solution calorimetry. It should be noted that in solution calorimetry it is the temperature change associated with a reaction or process that is recorded. This means that ANC values could not be calculated directly. Rather, the relative contributions to the ANC of each component in the mixture, normalised to the mass of the sample, were assessed. The technique was chosen because of its high sensitivity towards chemical changes occurring in solution. Components were studied in isolation, in binary pairs and in a tertiary mixture to assess whether there were any synergistic effects.

2. Experimental

BP grade materials (sodium bicarbonate BP, light magnesium carbonate BP, magnesium trisilicate BP and magnesium trisilicate mixture BP) were supplied by Thornton & Ross Ltd., and were used as received. Hydrochloric acid solution (0.05 M) was prepared by dilution of a standard (0.1 M). Suspensions (5% (w/v) of each active component) were prepared in distilled, deionised water (listed in Tables 1 and 2).

Table 1
Suspensions of single components prepared for this study and the heat changes calculated for each upon dispersion into 0.05 M HCl at 25 °C (confidence limit ± 3%)

Suspension components (5% (w/v))	Heat-change calculated (J)
MT	−5.04
SB	−2.41
LMC	−21.31

Table 2
Suspensions of binary and tertiary mixtures of components prepared for this study and the heat changes (both calculated and expected) for each upon dispersion into 0.05 M HCl at 25 °C (confidence limit ± 3%)

Suspension components (5% (w/v))	Heat change calculated (J)	Heat change expected (J)
MT and LMC	−31.17	−26.34
MT and SB	−7.98	−7.45
LMC and SB	−23.21	−23.72
MT, LMC and SB	−29.01	−28.76

Calorimetric data were recorded using a 2225 precision solution calorimeter, (Thermometric AB, Sweden). The calorimeter was thermostatted in a Heto precision water bath at 25 or 35 °C, dependent upon the desired experimental temperature. Standard glass crushing ampoules were filled with aliquots of suspension (0.6 ml) and were stoppered with teflon plugs. Ampoules were then double sealed with beeswax using the method described previously by Hogan & Buckton [12]. Suspensions were dispersed into dilute hydrochloric acid solution (0.05 M, 100 ml) by breaking the ampoules, using an internal stirring speed of 500 rpm. Electrical calibrations were performed before and after each experiment. Data capture and manipulation were performed using the dedicated instrument software. Samples were run in duplicate.

3. Results and discussion

The solution calorimeter operates under semi-adiabatic conditions, so the raw data output from an experiment is a plot of temperature offset (of the instrument, relative to that of the thermostatting bath) versus time, Fig. 1. The initial temperature offset is adjusted by the user, typically to 150 mK. The baseline sections in Fig. 1 were used to ensure that the temperature of the calorimeter was exponentially approaching that of the bath. Before and after the ampoule was broken (marked ‘break’) the calorimeter was calibrated using a small electrical heater. The dedicated instrument software uses the calibration and baseline sections to determine an accurate value for the heat of reaction for the system under study. Any subsequent conversion of the raw data to (the more conventional) power–time data is dependent upon the conversion parameters selected. The instrument software performs this conversion automatically using well-known heat-balance equations [13]. A more complete description of the theory of the solution calorimeter can be found in the manufacturer’s manual.

A typical data set recorded by the instrument, in this case for the addition of MTM suspension to acid at 25 °C, is shown in Fig. 1. Following the break, the data represent contributions from suspension dilution, dispersion and acid neutralisation. It is (not unreasonably) assumed that the contribution to the overall response from the first two components is negligible (based on experiments with samples introduced into distilled water, data not shown). The heat change measured is thus directly proportional to the amount of acid neutralised.

Temperature offset versus time plots were obtained for all the suspensions prepared (listed in Tables 1 and 2) at 25 °C and the software was used to calculate the heat changes associated with each, Tables 1 and 2. It is immediately

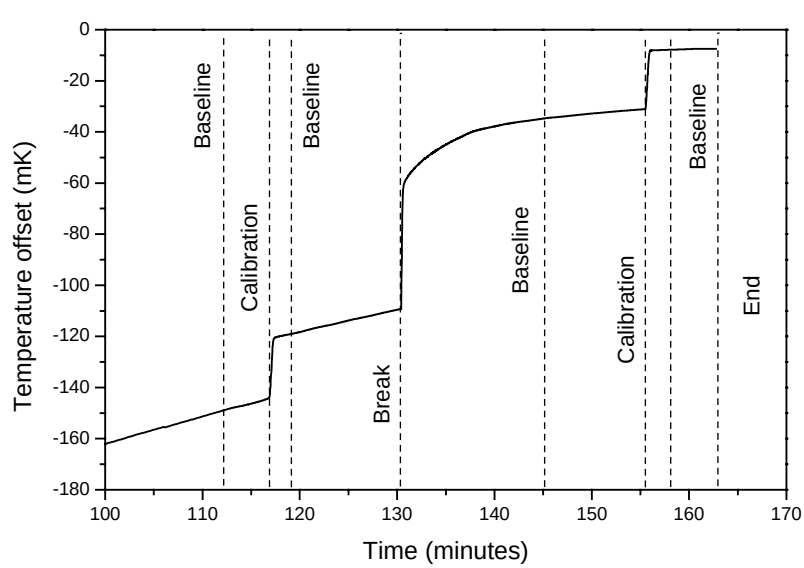

Fig. 1. Temperature offset vs. time data for the dispersion of magnesium trisilicate mixture BP in 0.05 M hydrochloric acid at 25 °C.

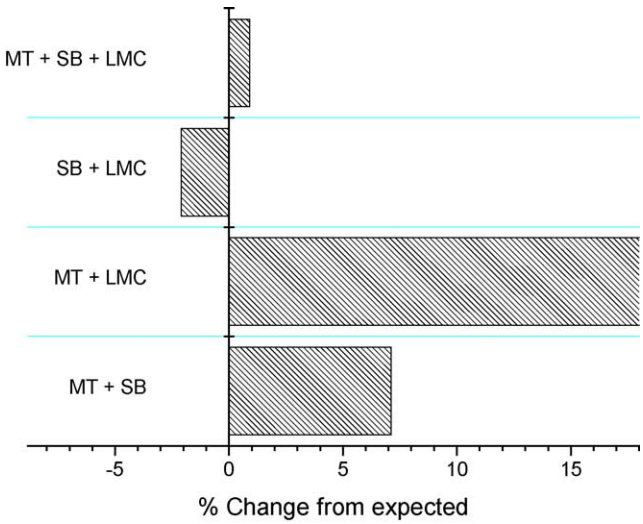

Fig. 2. The percent difference between the calculated and expected heat changes for binary and tertiary suspensions.

apparent that, for suspensions of single components, LMC gives the greatest heat change while SB exhibits the least. MT has a small but appreciable heat change.

The data in Table 2 show the heat changes calculated for binary and tertiary mixtures of the components. Since the heat changes are additive, it is possible to predict the heat change expected for each sample by summation of the heat changes recorded for the individual species. These expected values are given in Table 2. Any differences between the expected and calculated heat changes for a given system reflect positive or negative synergistic interactions between those components. The percent changes between expected and calculated values are represented graphically in Fig. 2. Any binary or tertiary system that contains MT appears to give a greater than expected heat change, while the SB/LMC mixture gives a slightly lower than expected heat change, although this is within the error limit of the experiment.

The most significant effect is observed in the LMC/MT binary system, which shows a significantly higher than expected heat change. This implies that the two components act cooperatively, giving a greater neutralising effect in combination. The power–time data for this system, as calculated by the instrument software, is shown in Fig. 3. Also shown in Fig. 3 is the power–time data for the *sum* of the responses for the separate components. In both cases, the data show a large exotherm, showing that there is considerable acid neutralisation initially, followed by a prolonged, but smaller, heat output, suggesting that acid neutralisation continues for a period of time following administration of the antacid. In the case of the binary mixture it can be seen from the (inset) data in Fig. 3 that the extended heat output, after the initial exotherm, is much greater than that observed for the sum of the two components, and it is this region that contributes most to the apparent excess heat change for this system.

The tertiary mixture shows a greater than expected heat change based on summation of the heat changes noted for the three individual components. However, the MT/LMC binary system was observed to give a greater heat change than the tertiary system.

4. Summary

It has been shown that the heat changes associated with acid neutralisation can be measured directly using solution calorimetry and that the technique is sufficiently sensitive to measure differences between antacids. One immediate benefit of this would be rapid batch to batch screening of raw materials used in the manufacture of antacid formulations. The data show that LMC contributes most to the overall ANC of MTM and that antacids containing both LMC and

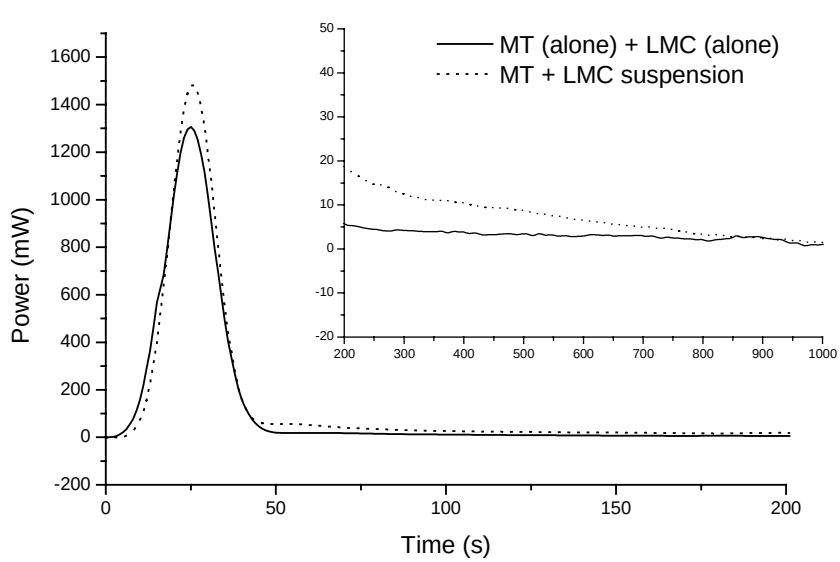

Fig. 3. Power–time data for the dispersion of (·····) MT (alone) + LMC (alone) and for (—) MT/LMC binary mixture in 0.05 M hydrochloric acid at 25 °C.

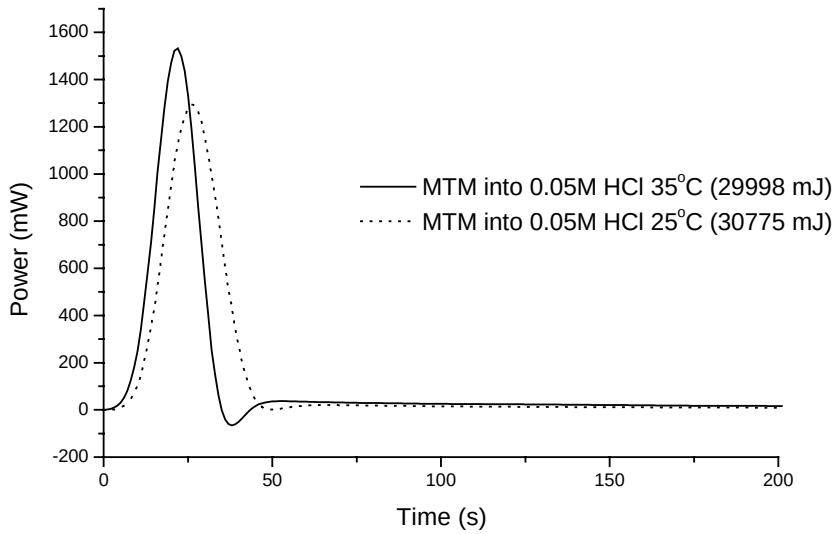

Fig. 4. Power–time data for the dispersion of magnesium trisilicate mixture BP in 0.05 M hydrochloric acid at (·····) 25 and (—) 35 °C.

MT perform better than would be expected based on summation of the ANC for each component. LMC provides the initial neutralising effect of the product while MT gives a sustained neutralising action. The data also suggest that the inclusion of SB in the mixture seems to be unnecessary, since it appears slightly to reduce the efficacy of the mixture. This contrasts with previous observations, which suggested that it was the inclusion of MT that was debatable [1].

The experiments performed as described above were designed to replicate the conditions of the BP neutralising capacity test, although they were performed at a lower temperature. Fig. 4 shows the derived power–time data for the dispersion of MTM into 0.05 M acid at both 25 and 35 °C. It can be seen that at the higher temperature the rate of reaction is quicker but the total heat output is the same (within experimental error, ±3%). While, as noted earlier, this test does not accurately represent the case in vivo it does offer a system with fewer variables than one which better mimics the case in vivo (such as the Rossett and Rice test discussed in the introduction) making comparison of data easier. Using a modified test, Washington et al. [1] noted that, again, LMC was the principal contributor to the ANC of MTM. However, they observed that the ANC of MT alone was negligible unless the rate of acid being introduced to the system was slow (0.5 ml min^{-1}). They also suggested that a binary mixture of LMC/SB was the most effective antacid under their experimental conditions.

It would appear that the conditions dramatically affect the actions of the individual components—the complex nature of the in vivo case may mean that a tertiary blend of the three components produces a product that is better able to perform consistently under different conditions than one containing either one or two components. We intend to repeat the experiments using a modified reaction vessel into which a pH meter is placed, allowing both pH and calorimetric data to be obtained simultaneously.

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