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Applications of isothermal microcalorimetry in the pharmaceutical sciences

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Abstract

Isothermal heat conduction microcalorimetry is a technique which can be used to study very many physical and chemical processes. The experimental yield can potentially give information on thermodynamics of the process, kinetics (mechanism) and analysis. It is argued that with careful experimental design, and experienced data interpretation this technique is an extremely valuable tool for pharmaceutical scientists. The existing literature is discussed in terms of microbiological investigations, tissue culture studies, physical pharmacy (including immersion, adsorption, crystal properties, dissolution and targeting), and chemical stability studies.

Keywords: Isothermal; Kinetics; Microcalorimetry

1. Introduction

Given the likelihood that the readership of this issue will include those from the pharmaceutical sciences who may be unfamiliar with isothermal microcalorimetry, it is appropriate to describe the basic concepts of this technique in rather more detail that would otherwise appear in this journal. Isothermal microcalorimetry has the capacity, in principle, to be able to monitor all physical and chemical processes. The range of applications of this technique is limited by the investigator's imagination and the ability to control the experiment. The principle of the technique is to monitor the heat conduction into, or out of, a measuring cell, from, or to, a heat sink. The heat sink will usually be held isothermal (normally at a set

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temperature in the range 5–95°C) to an accuracy of $\pm 10^{-4}$°C, and by use of a reference cell to correct for variations in the heat sink temperature, an out of balance signal of 10^{-6}°C can be detected. The instrumental output is the rate of change of heat (dq/dt) as a function of time. The rate of change of heat is equivalent to power, thus the response is often referred to as a power–time ($p-t$) curve. A generalised equation to describe the output would be

$$dq/dt = \Delta H(d\alpha_t/dt)C \quad (1)$$

where ΔH is the enthalpy change for the process under investigation, ($d\alpha_t/dt$) is a generalised rate equation, for a process in which α_t describes the fractional extent of the reaction at time t. The initial concentration of the reactant is defined by C. Eq. (1) can be developed into a zero order form

$$dq/dt = \Delta H(-k_0)C \quad (2)$$

where k_0 is the zero order rate constant. For such a reaction, it can be seen that the power output will be a straight line parallel to the time axis, which is displaced from zero power by a factor due to the enthalpy change, the rate constant and the initial concentration. A similar situation exists for first order processes

$$dq/dt = \Delta H(-k_1)\alpha_t C \quad (3)$$

where k_1 is the first order rate constant. Here the power output will be an exponential function, again related to the enthalpy term, the rate constant, and the initial concentration (which obviously is scaled by the fractional term α_t). Similar equations can be developed for other orders of reaction, and variations are available for experiments other than simple batch responses. In each case, however, the output is a composite of enthalpy, concentration and rate, and thus thermodynamics, analysis and mechanism. It follows that the experimental yield of such an experiment is very rich in information, which is a great advantage if the different contributions can be separated. Returning to the versatility of the instrument, the sample can be of any physical form, and can be monitored for physical or chemical processes. The output can be used for quantitative analysis, rate and mechanism studies, and thermodynamic characterisation. For analysis the sample can be monitored in situ; thus it is totally non-invasive, and has no requirement for specific physical properties (unlike UV spectroscopy where the sample must be a colourless solution). To balance these enormous advantages there are some disadvantages as, for example, a low enthalpy fast rate process can initially appear identical to a high enthalpy slow rate process. However, with suitable experimentation this problem can be overcome. The other two-edged sword is the versatility, because it is possible to monitor a process other than that which you believe to be the subject of the experiment. For example, it would not be impossible to measure a zero order evaporation of a liquid through a faulty seal, and believe it to be a response from the sample.

The applications of isothermal microcalorimetry in the pharmaceutical sciences can be divided into three convenient areas: biological sciences, physical processes and chemical reactions. Each of these areas could be discussed in great length, but

such a comprehensive review would not be possible here given the limitation of space. The strategy adopted will be to describe general areas in which the technique could be applied, and to dwell on specific examples which the author finds especially interesting.

2. Biological sciences

2.1. Microbiology

Because heat is associated with life itself, the metabolic processes of micro-organisms can be followed by use of isothermal microcalorimetry. The experiment will normally be performed in an external incubator, with a peristaltic pump being used to circulate the suspension through a flow cell in the calorimeter. Different calorimetric responses will be obtained depending upon whether the cells are in bio-stasis or growth phases. It is possible to alter the output by changing the media in which the cells are suspended. The influence of drugs on the cells can be investigated, and from the change in the power–time curve, it is possible to obtain quantitative dose–response relationships, and also to obtain some understanding of mechanism of drug action. The schematic responses in Fig. 1 show the metabolism of the organism in nutrient (curve A), and then have two further traces superimposed; these correspond to the addition of a drug which is not bactericidal, but which does reduce the metabolic activity of the cells (curve B), and another which is bactericidal (curve C). The availability of quantitative and mechanistic information offers advantages over traditional plate methods of determining viable counts. Examples of qualitative work are given in a recent review [1] and a more substantial review was published in 1987 [2]. There is a need for caution with studies of microbiological processes, as the systems are not at equilibrium and thus thermodynamic laws must be applied with care [3].

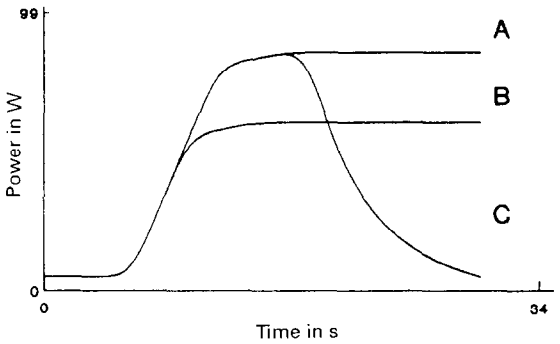

Fig. 1. Schematic representation of (curve A) microbial growth, (curve B) microbial survival in the presence of a bacteristatic agent, and (curve C) microbial death in the presence of a bactericidal agent. The calorimetric response is a consequence of heat produced during the metabolism of the living cells [1].

2.2. Tissue culture

The calorimetric work on micro-organisms was an obvious precursor to studies on tissue culture systems. Animal cells which have been investigated include cancerous cells such as lymphoma [4] and melanoma [5], and a wide range of blood cells (see Ref. [6]), thus allowing investigations of antineoplastic drugs, which should ideally be more toxic to cancerous cells than normal blood cells. Monti [7] has reported on the value of using calorimetry to obtain clinical information on non-Hodgkin lymphoma, chronic lymphocytic leukaemia, thyroid dysfunctions and acromegaly. An example was that calorimetric measurements showed statistically significant increases in heat output (metabolic activity) for samples from patients with progressive non-Hodgkin lymphoma, compared with those who improved during treatment.

The brief review presented here demonstrates that a wide variety of living cells can be studied, and that the yield can be used for quantitative purposes, or for valuable qualitative evaluation of certain biological processes. The brevity of the coverage given to the subject should not be taken to indicate a lack of importance. With the rapid development in large molecular weight drugs, and targeting concepts, it has never been so important to understand more about the drug–biology interface. There is no doubt that isothermal microcalorimetry has a vital role to play in research in this field.

3. Physical processes

In an earlier review [8], this subject was covered under the headings of wetting, adsorption (which is related to wetting), crystal properties, dissolution, and drug targeting. These remain suitable headings for consideration, but the literature has developed significantly since the 1991 review [8]. The "Literature Reference List", published by one instrument manufacturer in January 1993, lists six references on physical pharmacy dated 1991 or later [9–14], compared with seven publications in all years prior to 1991 [15–21], all of which were from only two laboratories ([15–19] from our own work, and [20,21] from Fubini et al.). This manufacturer's reference list is not inclusive, and does not cover much of the early work with other types of instrument, but it is indicative of a trend of developing interest. It is encouraging that the application of microcalorimetry in the field of physical pharmacy has developed so significantly over the last 2–3 years, and given its value it is probably that the list of published material will grow significantly over the next few years.

3.1. Wetting (immersion and adsorption)

The importance of wetting, in terms of dispersion of powders in liquids, aiding drug dissolution, the addition of binders during wet granulation, the adhesion of film coats to tablets and many other applications, has always been accepted. There

are, however, difficulties associated with assessing contact angles for powdered systems [22]. Calorimetry has always been viewed as an alternative to contact angle data as a method of gaining an understanding of solid–liquid and solid–gas interactions. The solid–gas interactions will be considered below. Heats of immersion have been measured calorimetrically for at least five decades; thus this is far from a new application. Work in the pharmaceutical field is rather limited, but includes a substantial study by Hollenbeck et al. [23], and others which include that by Hansford et al. [24] and Storey [25]. Hollenbeck et al. [23] investigated the immersion of microcrystalline cellulose in water, and showed that the heat of immersion was directly related to the extent of water vapour coverage already on the powder (increase water coverage, decreased response for the heat of immersion). This demonstrates an important fact, that the vapour phase wetting is the first, and very significant, stage in the wetting process. Immersion is usually measured by sealing the powder into a glass ampoule, and then equilibrating this in the calorimeter, under the surface of the test liquid. At a desired time, the ampoule is broken and the powder released into the liquid. If the powder is insoluble a heat of immersion will be measured, and if the powder dissolves, the sum of the wetting and solution processes will be observed. If, however, the powder partially wets, and partially floats, then the result is meaningless. This can be a major limitation, and prevents the measurement of the heat of immersion of many hydrophobic drug powders in water. The logical alternative is to consider vapour phase studies.

As stated above, the vapour phase wetting of a powder is the most significant step in the wetting process. After monolayer coverage of the surface, further adsoprtion is analogous to condensation, which is less indicative of the vapour–powder interaction. Immersion of a vapour laden surface will give a small response as a consequence of reordering the outer molecules of adsorbed vapour, to fit into bulk liquid structure. Comparatively few calorimetric studies of vapour phase adsorption have been published for pharmaceutical materials, even though such studies are common in many other fields of investigation (see, for example, Refs. [26–28]). Vapour phase studies on pharmaceuticals include the adsorption of water onto barbiturate powders [17], celluloses [16] and different samples of aspirin which differed in their physical processing history [18]. For each of these studies the powders were held in the cell of the microcalorimeter and treated under vacuum until dry, then water vapour was allowed into the cell and adsorption measured. The experimental design did not allow for any intermediate between dry and wet conditions, which proved to be a limitation. The major problems of the technique were that certain materials vaporised under vacuum, whilst others dissolved in the water vapour. Despite these problems, the technique adequately differentiated between the different barbiturate materials [17], and also provided information on the complex interaction between water vapour and celluloses [16]. Of great interest was the finding that different milling conditions affected the interaction between aspirin and water vapour. It was found [18] that differences existed not only between various milling processes, but also if sequential milling stages were undertaken in order to achieve the same particle size. It was concluded that total processing history was important in controlling the final properties of these powder

samples. This kind of observation had only been seen in "use tests" where products behaved in different manners depending upon processing conditions; however, reports of these situations are poorly documented, and not well investigated. It was, therefore, valuable that microcalorimetry was able to detect and quantify processing induced variability in material properties. The technology of calorimetric cells is constantly developing, and now it is possible to buy a system which will allow control of humidity in the cell, and which can be used to adjust the humidity at any desired step, or rate, from 0 to 100%. Cells of this type (termed gas-flow) allow any pharmaceutical material to be studied, in any desired humidity. It has been shown that the gas-flow approach is capable of detecting differences between sources of materials which are not apparent from contact angle studies [29]. It is now comparatively simple to investigate interactions between vapours and powders using this system.

3.2. Crystal properties

The microcalorimetric technique can be used for investigations of crystal properties. Angberg et al. [9–12] have utilised a novel approach to investigate the water induced transformation between beta and alpha lactose. In their experiments, wetting was not the process of interest, and thus the water (liquid) reservoir (a small tube containing a saturated salt solution) was placed in the calorimeter cell itself. This means that as the liquid evaporates, there is an enthalpy change, which almost balances (i.e. is almost equal and opposite to) the enthalpy associated with vapour wetting of the powder. By this approach the wetting response is almost lost, and other processes which may occur can be monitored. It follows that cell (experiment) design is critical, because changing the position for the vaporisation of the liquid from outside to inside the measuring cell will result in a totally different response. Further details of lactose crystal transitions will be given elsewhere in this volume by Angberg [44].

As well as monitoring crystal transitions, from one crystal form to another, it is also possible to follow recrystallisation of an amorphous region in a particle. Many particles, especially those which have recently been processed will be mostly crystalline, but will have amorphous surfaces. Indeed this is probably the basis of the differences in interaction seen by Buckton et al. [18] between water vapour and aspirin that had been milled by different techniques. The post-processing amorphous content of a powder may amount to a small percentage of the overall bulk, but it is the critical regions that have changed, because the amorphous material is likely to be at the powder surface. This surface material will be that which interacts (and potentially reacts) with other components of a formulation and/or with the biological environment. It follows that it is vital to characterise the nature of these processed surfaces in order to understand the extent of disruption caused by different processing conditions, and to know if and how the surfaces will recover to the original stable form. Recently, Briggner et al. [30] have investigated processing effects on lactose. By filling lactose samples into a sealed glass calorimeter cell, containing a tube of a saturated salt solution, it is possible to control the humidity

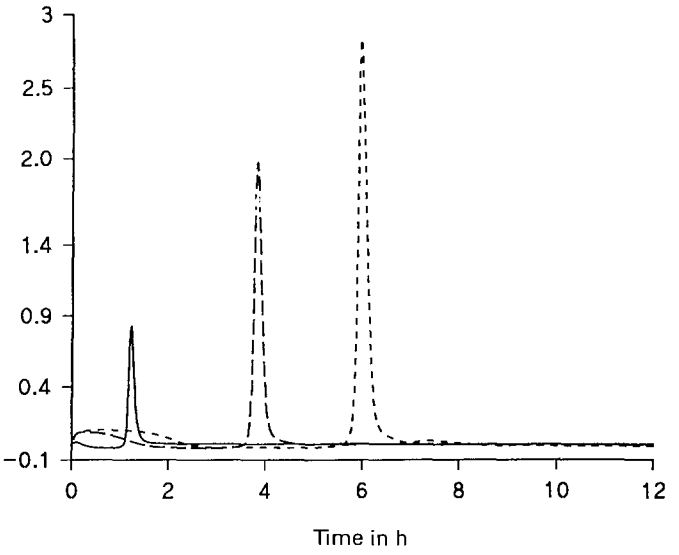

Fig. 2. Calorimetric output (power P as a function of time) for spray dried lactose, using powder loadings of 10 (——), 30 (– –) and 50 (- - - -) mg, at 85% RH and 25°C. The sharp peak is a consequence of recrystallisation of the amorphous content of the lactose [30].

in the cell, in exactly the same manner as used by Angberg et al. [11]. If the lactose is partially amorphous, exposure to humidities of above about 45% RH will cause it to recrystallise. The recrystallisation event will produce a thermal response which is directly proportional to the amount of amorphous material present. Typical responses for a recrystallisation event of lactose are shown in Fig. 2. It can be seen that the recrystallisation peak is extremely sharp, indicating a highly cooperative process. It follows that the powder bed must reach a certain critical moisture content throughout its mass, before recrystallisation occurs, i.e. the water vapour is probably sorbed at the upper surface of the powder, but transferred away through the powder bed at a faster rate than it is supplied to the upper surface of the powder, until bed saturation is achieved. It follows that the rate limiting steps for the recrystallisation can be the rate of supply of water vapour (i.e. the relative humidity of the air, and the surface area of the saturated salt solution from which evaporation can occur), and the mass of powder. Fig. 2 shows the recrystallisation of different masses of the same sample of lactose, from which it can be seen that the greater the mass, the slower the recrystallisation. If the areas of the different peaks in Fig. 2 are normalised per unit weight of material, then the total heat output is essentially the same in each case. A similar reponse is also seen in Fig. 3, for changes in humidity with identical sample weights. In this case (Fig. 3) the lower the humidity, the longer the delay before the recrystallisation. In the same paper [30], it was noted that the degree of crystallinity could be characterised to a resolution of at least as low as 1% amorphous material. This is significantly more accurate than can be achieved by X-ray diffraction, or any other available method.

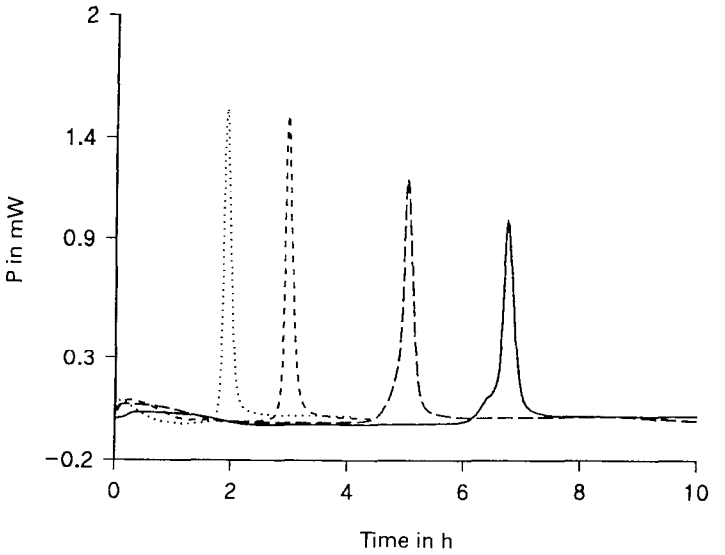

Fig. 3. Calorimetric output (power P as a function of time) for spray dried lactose, using 85 (· · · ·), 75 (- - -), 65 (– –) and 53 (— —)% RH, 20 mg of powder at 25°C. The sharp peak is a consequence of recrystallisation of the amorphous content of the lactose [30].

It was also noted [30] that the effect of processing, such as pressure used during micronisation in an air jet mill, could be quantified. The case for using microcalorimetry for this type of material characterisation appears to be overwhelming.

3.3. Dissolution

The majority of all drug administrations are by the solid oral route. The release of drug from a solid dosage form is vital to the efficacy of the formulation, and as such there is always great interest in dissolution testing. It has been suggested [31] that calorimetric methods may be an appropriate way of testing dissolution of materials during preformulation. The advantage claimed is that small quantities of materials can be used, and it may be possible to relate the hydrodynamics of the calorimeter to those obtained in compendial dissolution testing experiments. Conventional dissolution experiments utilise an analytical method which is often UV spectroscopy, rather than the heat production of the calorimetric experiment. It must be remembered that, as in all calorimetric experiments, the output will be a composite of wetting responses, dissolution phenomena (including disruption of the crystal lattice, removal of the surface molecules, disruption of the solvent and incorporation of the solute molecules in cavities in the solvent), and any interaction processes that may occur (e.g. adsorption, chelation etc). Furthermore, conventional testing considers the release of the drug from a multi-component product, whilst the calorimeter does not discriminate between the dissolution of the drug and excipients. Again, as with all calorimetric experiments, the complexity of the

instrument measuring all processes can be a disadvantage, but can also be an advantage if it is used correctly. The study of dissolution into complex media is an example of a case where microcalorimetry can have some advantage. For sustained/controlled release dosage forms, there is considerable interest in the effect of food on the drug release profile. This is rather difficult to study by conventional means, because the food will interfere with most assay procedures, requiring processes such as dialysis to extract the released drug. The use of microcalorimetry, however, does not require clear solutions, so the dissolution process can be followed directly in complex media [15,19]. Ashby et al. [15] investigated the dissolution of active and placebo Phyllocontin Continus tablets in the presence of buffer, a fat emulsion, and a commercial liquid feed (Ensure diluted with buffer). It was observed that the different fluids caused significant differences in the dissolution profiles, which in part agreed with certain differences in in vivo performance that had been noted for other Continus products with administration after various meals of differing fat contents [32]. The well known chelating action of certain materials (notably Ca^{2+} ions) with tetracycline has also been investigated calorimetrically [19], indicating that not only can dissolution be followed, but also interactions with various media may be investigated.

Dissolution of theophylline, and the swelling kinetics of hydroxypropylmethyl cellulose based matrix tablets have also been investigated calorimetrically [33].

A limitation with the use of microcalorimetry is the inevitable disruption at the start of the experiment which essentially means that no data can be collected for at least the first 30 min of the dissolution process.

3.4. Drug targeting

There is much interest in research directed towards site specific drug delivery. By its very nature research in this field is both multidisciplinary and complex. The disciplines involved will include biological and physical characterisation teams, and the complexity is a consequence of trying to understand processes which occur in the biological environment. The biological environment is one in which multi-component fluids interact with each other to produce responses. Experiments which simplify the situation by, for example, using selected plasma proteins rather than whole plasma, may remove components which are involved in the interactions and thus not mimic the in vivo response. Thus, the numerous components of plasma and the possibility of changes in conformation of materials being very significant, makes experiments difficult to design and interpret. Microcalorimetry is of use in such situations, as it is well suited to studies on processes which occur in complex media.

Examples of uses of calorimetry in this field include that of Norde and Lyklema [34], who investigated the adsorption of albumin onto model hydrophobic carrier particles (polystyrene latex), and Manzini et al. [35], who studied interactions of albumin with drug particles. Mitchard [36] has undertaken a microcalorimetric investigation of the binding of surfactants to model hydrophobic surfaces and studied the interaction of these materials with plasma proteins. Other workers have

also investigated the adsorption of surfactants to latex particles using microcalorimetry [14]. There are, however, many other uses of microcalorimetry in the areas that relate to drug targeting; these include all manner of biological applications of the type discussed above.

4. Chemical reactions

Chemical reactions have been studied calorimetrically for many years; however, only recently has the possibility of trying to predict pharmaceutical product stability been considered. The use of differential scanning calorimetry to predict interactions between drugs and excipients is well known, but is also known to be potentially unreliable. Isothermal microcalorimetry has greater sensitivity than standard DSC instruments, and thus offers the possibility that reactions may be observed at temperatures that are rather more realistic than those that are used during DSC scans (i.e. near to ambient temperature, rather than at the melting point of the materials) [8]. A few reports suggest that it is possible to utilise isothermal microcalorimetry as a technique for rapid stability screening. Gibson et al. [37] reported on calorimetry studies which revealed interactions between additives and a film forming material. Further studies on chemical stability include investigations of both solid state and liquid state decomposition of drugs [38–43]. The published studies are encouraging, and indicate that isothermal calorimetry does indeed have a role to play in solid state stability prediction of pharmaceutical formulations, but care must be taken not to overstate this role. It is clear from the published work on the hydrolysis of aspirin [42,43] that very rapid degradation processes can be followed, especially if the temperature is elevated. However, these processes can be followed just as easily by sensitive "conventional" analytical instruments. If microcalorimetry is to have an advantage, it must be able to probe solid state reactions, and to be used for drug–excipient mixtures, which are harder to probe by conventional analytical techniques. Hansen et al. [38] and Pikal and Dellerman [41] have had success in such investigations, and show that industrial laboratories are giving serious consideration to this technique. It can be assumed that much more work has been undertaken in industrial research centres which has been deemed too sensitive for publication. It must be remembered, however, that the calorimetric response is a composite of the concentration of reactants, the enthalpy of the process and the kinetics of the reaction. If only simple experiments are performed to search for the presence or absence of an unknown reaction, then the calorimetric output could be misinterpreted. It is probable that certain reactions will be of fast rate, but of low enthalpy (perhaps certain hydrolysis processes), whilst others may be of high enthalpy but slow rate. These may appear as identical responses, even though one may be critical and the other irrelevant to the stability of the product. A further problem is the complexity of order of reaction that can occur in solid state reactions, coupled with difficulties due to the reaction being linked to the extent of particle–particle contact. Whilst there is considerable promise in this field, as demonstrated by the extensive use of calorimetry for

stability testing in the explosives industry, in the pharmaceutical field if calorimetry is to be used effectively for stability testing, it must be used alongside some understanding of the reactions which may occur.

5. Conclusions

Isothermal heat conduction microcalorimetry is an extremely versatile technique. The information that can be obtained from well designed experiments is vast, and can allow much to be understood about the process(es) that have been studied. The range of application possibilities is also extremely large. This technique has not been used extensively in the pharmaceutical sciences; this is surprising because so many pharmaceutical investigations require information to be obtained on complex systems for which the isothermal microcalorimeter is well suited. It can be expected that more work will follow in physical material characterisation, the physical–biological interface and in aspects of stability prediction.

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