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Pharmaceutical Materials Science – Resuscitation or Reincarnation?*

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To optimize the biological activity of a drug molecule it is necessary to develop dosage forms which will result in the delivery of that drug to the appropriate site in the body at the appropriate rate. One aspect of the development of these systems which is receiving increasingly greater attention is the study of the physical structure and behaviour of materials of pharmaceutical interest in relation to product performance. This review discusses the basic philosophy underpinning the activities of this research group and outlines some of the work conducted in the fields of thermal and dielectric analysis. In particular, the use of conventional differential scanning calorimetry (DSC) in the study of glyceride-based excipients is described, and the principles and applications of the new technique of modulated temperature DSC are also outlined, with examples of studies on lactose and polylactic acid. The theory and uses of dielectric spectroscopy are described, with examples given including lactose, glycerides, bioadhesive polymer gels and inhalation aerosols.

The development of successful drug therapies might be considered to be dependent on two factors. Firstly, it is clearly essential to have an active ingredient which will elicit the desired effect at the site of action. Secondly, it is necessary to administer that drug such that the active ingredient will be delivered to the appropriate site at the appropriate rate. The first of these factors is a function of the chemical structure of the drug molecule and forms the basis of most research within the pharmaceutical industry. The second consideration is, however, at least partially a function of the nature of the dosage form in which that drug is administered. It is now well recognized that by manipulation of the dosage form it is possible to alter the biological fate of the incorporated active ingredient. For example, if a drug is poorly water-soluble, the dissolution of that drug from the dosage form in the gastrointestinal tract might become the rate-limiting step of absorption, hence the biological activity of the drug might be directly related to the nature of the dosage form.

The awareness of the importance of dosage-form design has led to the evolution of this field in diverse directions. Tableting and capsule-filling technology, for example, have enabled efficient manufacture of these dosage forms in terms of both processing optimization and drug-release characteristics, and newer approaches to drug delivery such as polymeric controlled-release dosage forms, bioadhesives, colloidal and transdermal systems have enabled much more sophisticated control of the site and rate of drug administration. Similarly, recent developments in fields such as antibody targeting and polymer-drug conjugates have effectively reduced dosage-form design to a molecular level.

Common to all these approaches is a need to understand the nature of these dosage forms in relation to their processing and in-vivo performance. Although the chemical structures of the drugs and excipients used in dosage forms are usually well defined, considerably less is known about the physical characteristics of many of these systems. Such characteristics are of fundamental importance to both the design and the manufacture of successful dosage forms. For example, numerous studies have indicated that the bioavailability of drugs can be altered by the choice of particle size, polymorph, or solvate form. Similarly, incorporation into water-soluble polymers such as polyethylene glycols, solid waxes such as gelucires or self-emulsifying systems which form oil-in-water emulsions in the gastrointestinal tract might improve the oral bioavailability of poorly absorbed drugs. Problems of scale-up are common within the industry, as are difficulties relating to inter-batch variation and changes in product performance with time, even when the chemical composition of the material in question is unaltered. Similarly, there is a persistent problem of maximizing drug entrapment in colloidal drug-delivery systems such as liposomes, while the effects of processes such as freeze and spray drying on the physical characteristics of drugs and excipients are often poorly understood.

If one accepts the premise that the study of the physical and material properties of drugs and dosage forms is an area in which more work is required, then the question arises as to why this lack of understanding exists. There are arguably two reasons. Firstly, the range of techniques available for the study of the physical properties of these systems is somewhat limited. Several techniques are available for studying, for example, the solid state rheological properties of compacted powders, and techniques such as differential scanning calorimetry and X-ray diffraction have been widely used in the study of phenomena such as polymorphism. Many of the problems arise, however, when the system under study is multicomponent, either in terms of having more than one chemical entity or when more than one physical form of the same substance is present. Such complex systems are invariably more difficult to characterize, yet are of considerable practical relevance, given the complex nature of most dosage forms.

The second reason for the difficulties associated with material characterization is that this has not always been regarded as an area of great priority within the pharmaceutical field. For example, many drugs are orally absorbed with no discernible difficulties relating to the dosage form, and the

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formulation of many systems for injection have involved well defined production techniques which have not necessitated further investigations in themselves. There are, however, three points which should be considered with regard to this. Firstly, control of the dosage form might considerably improve oral bioavailability, as discussed above, hence a greater understanding of the relationship between dosage-form design and bioavailability could considerably alleviate some absorption problems. Secondly, our lack of understanding of the relationship between physical characteristics and material properties has led to the persistence of certain difficulties such as changes in drug characteristics on changing the manufacturing process, inter-batch variation of widely used materials such as lactose and difficulties in establishing effective quality-control protocols for materials such as magnesium stearate, for which the relationship between chemical and physical structure and lubricant performance is not fully understood. Thirdly, the advent of newer dosage forms such as liposomes, bioadhesive gels and polymeric matrices has resulted in a renewed need for greater material characterization, as the functionality of the dosage forms may be intrinsically associated with their physical characteristics.

Overall, therefore, there are many challenges associated with the characterization of the physical structure and behaviour of pharmaceutically relevant materials, both in terms of improving our understanding of conventional and novel dosage forms and also in the development of new approaches with which to study these systems. This review will outline some of our activities in both these respects, particularly relating to the introduction of two novel techniques to the pharmaceutical arena, namely modulated temperature differential scanning calorimetry and dielectric spectroscopy.

Activities of this Research Group

The basic philosophy of the research strategy stems entirely from the arguments outlined above. Over the last six years we have been attempting to meet some of the needs for greater understanding of the physical structure of pharmaceuticals in relation to product performance, while also developing novel techniques and approaches to studying such systems. As such, our activities are fairly broad in terms of dosage forms and systems under study but are linked together by the use of various combinations of four principal analytical approaches, namely thermal analysis, dielectric analysis, rheology and microscopy. Of these, the first two form the core of the work and will be discussed in more detail later in the review. It is, however, important to stress that we consider it highly advisable to use these techniques in combination, as the information obtained from each individually is often indirect and requires further validation before firm conclusions can be drawn, particularly when a new technique is being explored.

Thermal Analysis

Thermoanalytical techniques have been widely used within the pharmaceutical field and involve the measurement of either the heat content of a sample, usually over a range of temperatures, or the response of a material to a heating signal in terms of, for example, weight loss in thermogravimetric analysis. The use of thermal analysis for the study of pharmaceutical systems has been extensively reviewed (Ford & Timmins 1989) and the approach is arguably one of the most useful and versatile means available for elucidation of the physical structure of pharmaceuticals.

Principles of differential scanning calorimetry

The most commonly used method of thermal analysis is differential scanning calorimetry. This technique involves the application of a linear (or occasionally isothermal) heating signal to a sample and the measurement of the heat flow as a function of temperature (or time). There are two main categories of DSC. Heat-flux DSC involves the positioning of a sample and empty reference pan symmetrically in a furnace which is then heated at a specified rate. The differential temperature between the two is measured and converted to heat flow. In power-compensation DSC the sample and reference are placed in separate furnaces and the heat flow required to maintain thermal equilibrium between the two is measured, hence during an endothermic melting process heat is supplied to the sample to maintain temperature balance. DSC data are presented as differential power (heat flow) against temperature, hence both the temperature and energy associated with a thermal event may be easily measured, the energy involved being determined by integrating the measured peak. Thermal events such as melting or crystallization are seen as endothermic or exothermic peaks respectively, whereas glass-transition phenomena, which involve a change in the heat capacity of a sample, are seen as shifts in the baseline. These phenomena will be discussed in more detail later in the review.

There are two main applications of DSC in the pharmaceutical field. Firstly, it enables information to be obtained about the behaviour of a sample at different temperatures. This might be of use if information is needed about, for example, the conditions required for crystallization of a sample or, for liposomes, the phospholipid transition temperature below which liposomes will not form. In addition, however, the behaviour of the sample at low or elevated temperatures might be used to obtain information on the corresponding structure at room or body temperature. An example of this is the detection of polymorphism, whereby different crystal forms present at room temperature might be identified by their melting behaviour. The use of DSC in the detection and characterization of pharmaceutical polymorphs has been thoroughly reviewed by Giron (1995). An example of recent work involving the use of DSC is given below.

The use of DSC in the characterization of gelucires

The gelucires comprise a family of excipients which may be used in the manufacture of controlled-release dosage forms or as a means of enhancing the bioavailability of poorly soluble drugs (Sutananta 1993; Craig 1995a). These materials are composed of mixtures of glycerides and fatty acid esters of polyethylene glycols and, as such, have highly complex physical structures. This complexity arises largely as a result of the glyceride component, as these materials are well known to exhibit complex polymorphism (Garti & Sato 1988). The simple triglyceride tristearin has, for example, been reported to exist in at least three different polymorphic forms (α, β, β') and subclasses of these forms might also exist; it has been suggested, for example, that there are five different subforms of β-trilaurin (Hagemann 1988). In the light of this behaviour of

pure triglycerides, one would expect the structural complexity to be compounded for natural products such as olive oil and safflower oil, as these materials contain mixtures of different glycerides, each of which might be capable of existing in different physical forms. The same argument is applicable to the gelucires, because these materials are manufactured from such natural products rather than pure glycerides. This might not only lead to problems associated with the quality control of these materials but also result in difficulties with the understanding of the corresponding product performance, particularly in terms of drug-release mechanisms and changes in dissolution patterns on storage. Because these difficulties have traditionally been considered to be associated with polymorphism of the gelucire base, there is a perceived need to explore methods of characterizing the structure of these materials and to relate that structure to drug-release properties.

The approach adopted involved the study of five different gelucires (43/01, 54/02, 50/02, 50/13 and 55/18), these materials being subjected to controlled heating and cooling cycles in order to study the effects of thermal history on structure and behaviour (Sutananta et al 1994a, b). Fig. 1 shows the DSC traces of gelucire 50/13 subjected to fast and slow cooling from the melt, as well as solvent-crystallized from chloroform. Clearly, the material adopts different structures as a result of the various treatments, but it is also noted that, given the chemical complexity of these materials, the DSC traces are not as complex as one might expect, given the vast number of possible structural permutations that could arise if each chemical entity present in the sample exhibited polymorphism. It is, in fact, highly unlikely that the peaks seen in Fig. 1 represent different polymorphs. The DSC traces are more likely to be indicative of different mixed crystals within the sample; as a result different chemical entities co-crystallize on cooling to form solid solutions on a microscopic scale. Such behaviour has been reported in the food science literature (Garti & Sato 1988).

Further work involved modelling the profiles of the release of a model drug, theophylline, from the bases with a view to ascertaining the mechanism of drug dissolution (Sutananta et al 1995a, b). It was noted that for many gelucires the rate and mechanism of release were both dependent on the thermal history of the sample. Gelucire 50/13 was found to release the drug principally by an erosion mechanism, the rate of which depended on the cooling conditions used when solidifying the base from the melt (Fig. 2). By adopting the approach described above, it has been possible to build up a correlative body of data associating the solid-state structure with the dissolution and ageing behaviour of these systems.

Principles of modulated temperature differential scanning calorimetry

Modulated temperature differential scanning calorimetry (MTDSC) is a novel thermoanalytical technique which is generating great excitement in the field of thermal analysis, particularly in the polymer sciences and, more recently, in pharmaceutical thermal analysis (Coleman & Craig 1996). The original concept (modulated DSC, or MDSC) was introduced by Dr Mike Reading, formerly of ICI Paints (Gill et al 1993; Reading et al 1994), and marketed by TA Instruments. Other instruments have since appeared on the market and, because these operate on principles sufficiently similar to MDSC to

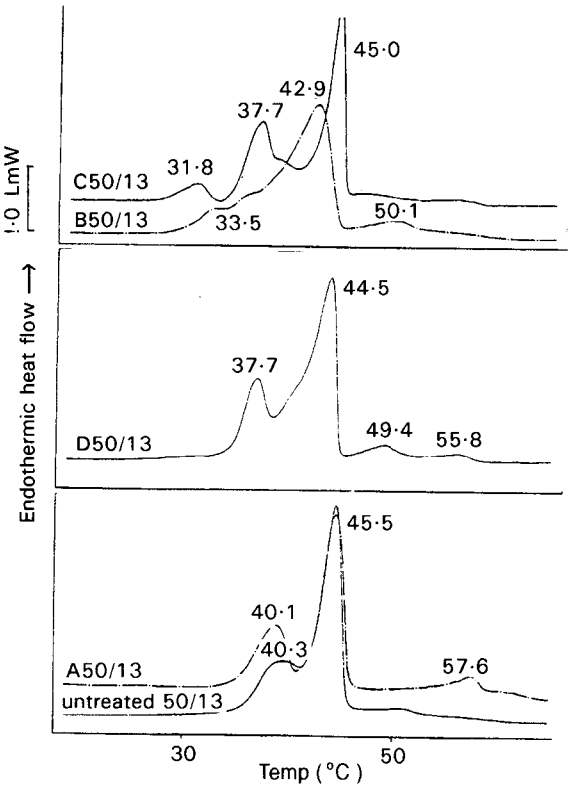

FIG. 1. DSC curves of gelucire 50/13. A, solvent-crystallized; B, slow-cooled from melt; C, fast-cooled from melt; D, cooled under ambient conditions. Reproduced from Sutananta et al (1994a), with permission.

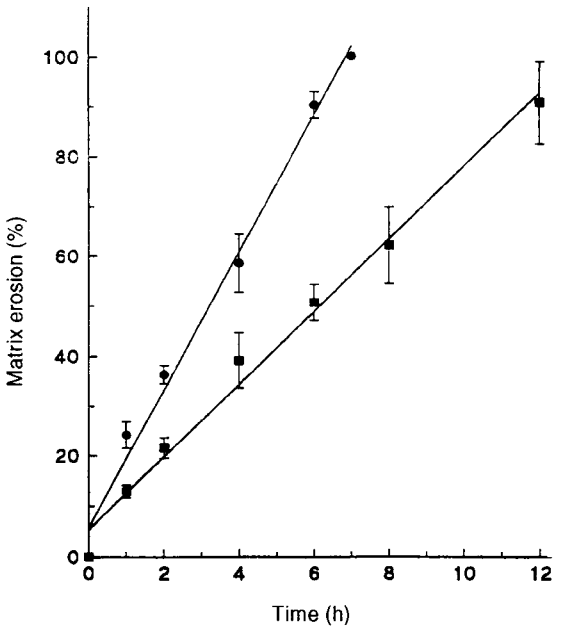

FIG. 2. The effect of cooling rate on the erosion of gelucire 50/13 matrices: ■, ambiently cooled matrices; ●, slowly cooled matrices. Reproduced from Sutananta et al (1995b), with permission.

cause considerable confusion between models, it has been suggested that all these instruments should be termed under the generic title MTDSC, with distinct names being given for the various models. The term MTDSC has, therefore, been used in this review; it should, however, be noted that our work to date has been performed on the TA Instruments model and it is not therefore possible to guarantee that the same results would be obtained using other instruments.

The method is a software development of conventional DSC and involves, in the case of MDSC, the superimposition of an oscillation on the linear DSC heating programme. Thus whereas the average temperature increase is identical with that of conventional DSC, the heating rate fluctuates sinusoidally, as illustrated in Fig. 3. By applying a discrete Fourier transform algorithm to the heat-flow signal it is possible to deconvolute the modulated and underlying heat-flow signals. The significance of this deconvolution might be summarized as follows. The heat-flow signal of a conventional DSC response might be considered to comprise two components, kinetic and heat-capacity components, given by:

$$dQ/dt = C_p dT/dt + f(t, T) \quad (1)$$

where dQ/dt is the heat flow, C_p is the heat capacity, dT/dt is the heating rate (temperature/time) and f(t,T) is some function of temperature and time and denotes any kinetically controlled processes. The first term on the right-hand side of the equation is known as the reversing heat-flow and is related to changes in heat capacity, such as are seen in glass-transition phenomena; the second term is known as the non-reversing heat-flow. MTDSC enables separation of these two signals at any temperature, thereby enabling far more sophisticated analysis of thermal events. It should be emphasized that because conventional DSC simply measures dQ/dt, the reversing and non-reversing heat-flow signals are seen in summation.

The principal interest in MTDSC thus far has focused on the capacity of the technique to detect and quantify glass transitions in polymers, a field in which great success has been achieved (Song et al 1995). The glass transition is a function of the amorphous component of a material and is associated with a change in molecular mobility, rather than a change of phase such as melting or crystallization. Such transitions are not only of importance in themselves in terms of processing but also yield highly important information on the structure of the polymer over a range of temperatures. It is, for example, possible to assess the extent of miscibility of two polymers by observing their respective glass transitions. These transitions are also of great importance within the pharmaceutical sciences (Ahlneck & Zografi 1990; Hancock & Zografi 1994; Saleki-Gerhardt et al 1994; Kerc & Srcic 1995). Many drugs exist in amorphous forms which exhibit different bioavailability profiles compared with crystalline materials; the amount of amorphous material in substances such as lactose is now widely believed to be associated with inter-batch variation. Similarly, milled, spray-dried and freeze-dried materials might be partly or totally amorphous, whereas polymers used in pharmaceutical systems such as film coats, microspheres and controlled-release matrices might also exhibit glass transitional behaviour. A knowledge of such behaviour is of considerable relevance to dosage-form design in terms of stability, quality control and drug-release kinetics. Glass transitions are, however, relatively difficult to measure; they are seen as (often small) shifts in the DSC baseline, which might be difficult to distinguish from noise or other thermal events, and they can be associated with an enthalpic stress–relaxation response which, while of interest in its own right, might render visualization and quantification of the glass transition difficult. Given the potential ability of MTDSC to separate these responses, it could be argued that the technique has been introduced at a highly fortuitous time.

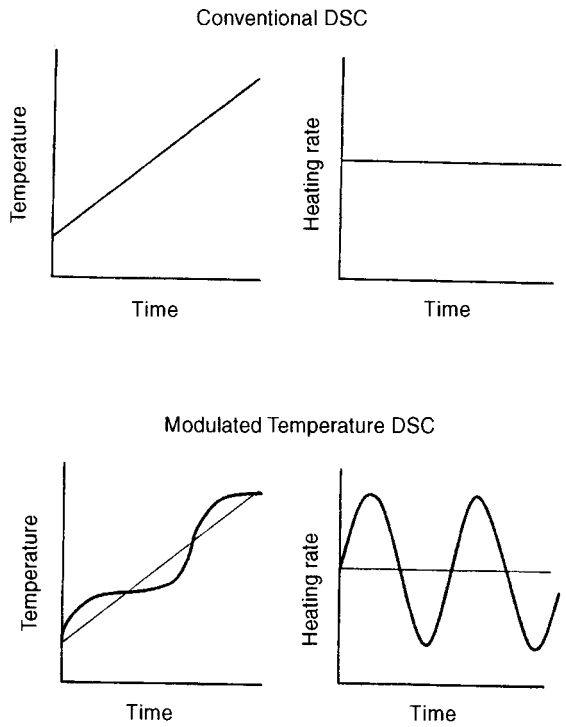

FIG. 3. Schematic representation of the temperature and heat-flow signals for conventional and modulated DSC.

Examples of the use of MTDSC

The use of MTDSC is very much in its infancy within the pharmaceutical sciences, hence the examples cited here represent preliminary studies which nonetheless demonstrate the possibilities associated with the technique. Fig. 4 shows

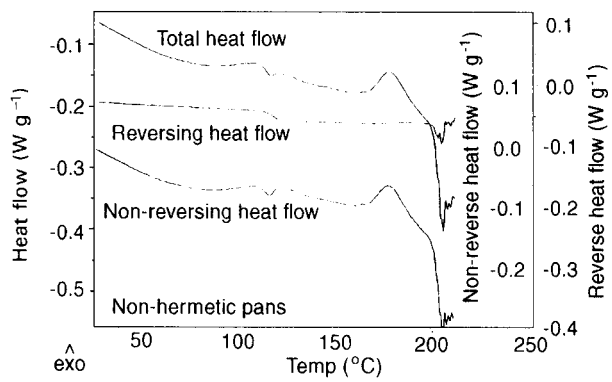

FIG. 4. MTDSC of spray-dried lactose, showing the total, reversing and non-reversing heat-flow signals. Sample size 2·83 mg, underlying heating rate 2° min^{-1}, period 30 s, amplitude 0·16°C.

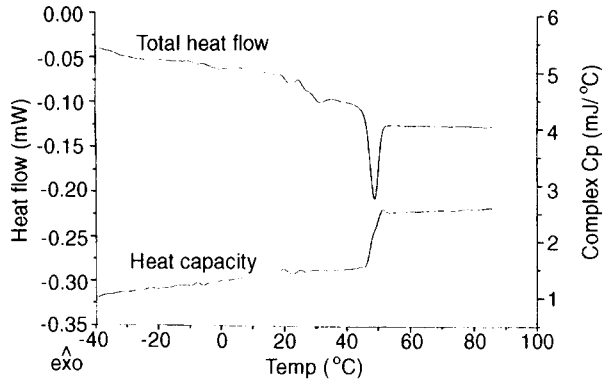

FIG. 5. MTDSC of DL-polylactic acid, showing the total heat-flow and heat-capacity signals. Sample size 3·40 mg, underlying heating rate 2° min^{-1}, period 60 s, amplitude 0·32°C.

MTDSC data for spray-dried α-lactose monohydrate (Hill, Craig & Feely, unpublished data). The total heat-flow signal (equivalent to that obtained using conventional DSC) shows a complex transition at approximately 116°C which represents the glass transition but which is difficult to analyse more precisely because of the presence of a relaxation endotherm. Examination of the reversing and non-reversing heat-flow signals, however, clearly shows a distinct glass transition in the reversing signal and a superimposed endotherm in the non-reversing signal.

Polylactic acid (PLA) is a polymer which has been extensively used in the production of microspheres (Bodmeier & McGinity 1987; Jalil & Nixon 1990). There is, however, a considerable need to have a greater understanding of the physical structure of these systems in terms both of processing and of drug-release characteristics. Fig. 5 shows the response of DL PLA powder as received (Hill, Craig, McGinity & Feely, unpublished data), showing a relaxation endotherm in the total heat-flow signal. Examination of the reversing heat-flow signal, however, clearly shows the glass transition in isolation from the relaxation endotherm. These examples serve to illustrate the many possibilities afforded by this exciting new technique; both studies will be reported in full in the near future.

Dielectric Spectroscopy

Principles of dielectric analysis

Dielectric spectroscopy is an analytical technique which for several years has been widely used in the study of semiconductors, ceramics, polymers and colloids but which has only recently begun to be used in the study of pharmaceutical systems (Craig 1995b). The technique involves the application of an oscillating electric field to a sample over a range of frequencies (or temperatures) and measurement of the sample response to obtain a spectrum, from which information about the structure and behaviour of the sample may be obtained. When a unidirectional field is applied to a sample, the dipoles within that material will tend to re-orientate in the direction of that field, hence the system will polarize. Similarly, when the field is oscillating, the dipoles will re-orientate with the changes in field direction. This process is not, however, totally efficient, hence a phase-lag will develop between the reorientation process and the applied field. This phase-lag may be resolved into in- and out-of-phase components as follows. The polarization, P, at any frequency, ω, is related to the field strength, E, by the susceptibility, χ, which is an intrinsic property of the sample and yields information on sample structure, and ε_0, which is the permittivity of free space and is a constant, by the equation:

$$P(\omega) = \varepsilon_0 i\chi(\omega)E(\omega) \quad (2)$$

The susceptibility is a complex variable and can, therefore, be expressed as:

$$\chi(\omega) = \chi'(\omega) - i\chi''(\omega) \quad (3)$$

where $\chi'(\omega)$ and $\chi''(\omega)$ are the real and imaginary susceptibilities at a frequency ω, and i is the square root of -1. The real and imaginary susceptibilities might be related to the measured parameters capacitance, C, and dielectric loss, G/ω, where G is the conductance, by:

$$C(\omega) = (A\varepsilon_0/d)(\chi'(\omega) + \varepsilon(\infty)) \quad (4)$$

and

$$G/\omega(\omega) = (A\varepsilon_0/d)(\chi''(\omega)) \quad (5)$$

where A and d are the area and distance between the electrodes, respectively, and $\varepsilon(\infty)$ is the permittivity at infinite frequency. C and G/ω are measured over a range of frequencies and information may be gained from the resulting spectrum, both by observing and modelling the spectral shape and by noting the absolute values obtained. The capacitance, C, is related to the dielectric constant of the system, whereas the dielectric loss can be thought of as an indication of the various conductance processes that take place within the sample. There are, in addition, several other equivalent properties, such as permittivity and impedance, that can be measured using the technique. Furthermore, each instrument tends to only operate over a limited frequency range, hence different groups tend to work in a specific frequency window. Up until recently, we have concentrated on the low-frequency (10^{-4} to 10^5 Hz) region and the comments below refer to this approach. We have, however, recently acquired equipment which enables not only high frequency measurements (up to 10^9 Hz) but also enables us to ramp the temperature of the sample; this will considerably extend our measuring capability.

The technique is of interest in the study of pharmaceutical systems for several reasons. The method is non-invasive, as the voltage applied tends to be very small (0·1 V is commonly used). This is important when analysing delicate samples such as creams, the microstructure of which can be altered during measurement by thermal or rheological methods. The technique is also highly versatile, because all that is required is the establishment of electrode contact with a sample; hence liquids, semi-solids, solids or even gases might be measured over a range of temperatures and pressures. The samples can also be run in the time and temperature domains, thereby enabling observation of kinetic or thermal events such as glass transitions. All these advantages are, however, secondary to the usefulness of the data. The technique might yield novel information on a range of samples, because the dielectric response is a function of the structure and environment in which a dipole is embedded. Because this information is indirect, however, one needs to develop the interpretation of the electrical behaviour in relation to physical parameters. This is one area where the use of several techniques in conjunction

has proved useful, as the structures or phenomena suggested by the dielectric analysis may be supported by the use of supplementary techniques.

Examples of pharmaceutical uses

The uses, both realized and potential, of dielectric analysis within the pharmaceutical field has been reviewed (Craig 1995b) and only a few selected examples will be discussed here to illustrate the directions in which the work appears to be going. For reasons of brevity, the modelling aspects of the work will not be discussed; more information on this aspect of dielectric analysis is available in the aforementioned text. There are essentially three approaches to using dielectric analysis for the study of pharmaceutical systems. Firstly, the dielectric properties of these materials can be studied in their own right, hence such studies are in many ways of more interest in physics than in the pharmaceutical sciences. This is a perfectly valid approach, as not only is knowledge of dielectric behaviour enhanced but it also increases awareness among dielectricians of the possible use of the technique within applied fields. Our own studies on polyethylene glycols (Craig et al 1993a, b) and alginate gels (Binns et al 1992) arguably fall into this category. Secondly, the technique might be used for fingerprinting and quality control. This again is a valid approach, because it identifies possible areas of interest and demonstrates an important use of the technique. An example of this approach concerns early work on fast-flo lactose (Craig et al 1991). A pharmaceutical company was observing anomalous disintegration behaviour when using a particular batch of lactose for which a range of standard analytical techniques was not showing any differences. Four lactose samples were therefore compacted and analysed using low-frequency dielectric spectroscopy, one of which (Batch A) was taken from the rogue batch. Fig. 6 shows the response of the lactose samples, with Batch A showing a reproducibly lower response than the other three. This approach is useful but limited, because such studies do not themselves provide an explanation of the observed differences in terms of structure (although further work to this effect on lactose is continuing). The third approach is to attempt to relate the dielectric response directly to the sample structure. This is by far the most difficult option because it requires both effective modelling of the dielectric response and a thorough understanding of the physical structure of the material in question, but this is undoubtedly the direction that will eventually lead to optimum use of the technique within the pharmaceutical sciences.

Other examples of pharmaceutical uses include the study of gelucires (Sutananta et al 1995c, 1996). Fig. 7 shows the dielectric response of slow- and fast-cooled gelucire 50/13; the response is markedly higher for the slow-cooled material. It is interesting to note that, as for the lactose example given above, the sample with the lower dielectric response, which broadly speaking indicates lower polarity, has a lower disintegration or erosion rate. By using the dielectric data in conjunction with the DSC studies for a range of gelucires, a pattern was observed whereby the sensitivity of the dielectric response to changes in thermal history corresponded to the tendency of the material to exhibit extensive fractionation into distinct microcrystalline regions. It is well known in the dielectrics field that electrical response is sensitive to the presence of interfaces within a sample (Hill & Pickup 1985), hence it is reasonable to

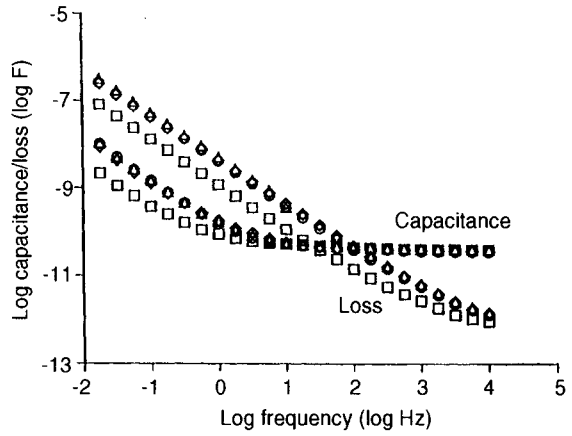

FIG. 6. Dielectric response of fast-flo lactose, showing a lower response for the rogue batch A. □, Batch A; ○, batch B; △, batch C and ◇, batch D. Reproduced from Craig et al (1991), with permission.

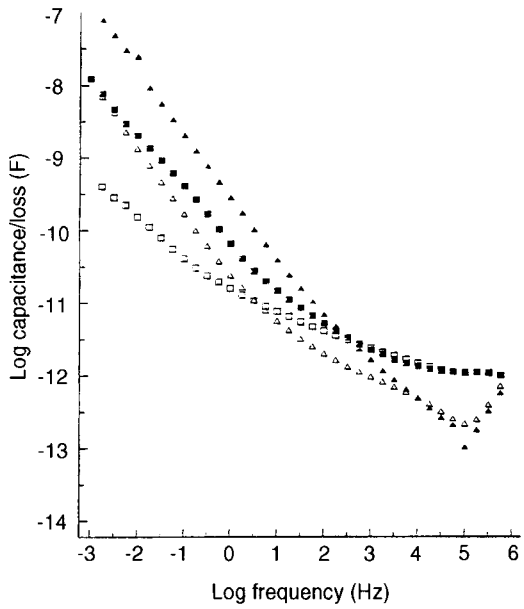

FIG. 7. Dielectric response of gelucire 50/13. □, △, capacitance and loss of fast-cooled sample; ■, ▲, capacitance and loss of slow-cooled sample. Reproduced from Sutananta et al (1995c), with permission.

suggest that, in this case, the dielectric response is giving information on the distribution of microcrystals within the material. This is an area about which comparatively little is known, hence this could represent an important application of the technique.

Work has also been conducted on bioadhesive gels, in particular using dielectric analysis in conjunction with oscillatory rheology. Our previous work on alginate gels (Binns et al 1992) had suggested that whereas rheology gives information about the polymer network of a gel sample, dielectric analysis might yield information about the passage of molecules through that network, hence the use of the two in conjunction is potentially highly useful. Bioadhesives adhere to the mucus layers of the body, thereby theoretically enabling control of both the site and drug-release characteristics of dosage forms

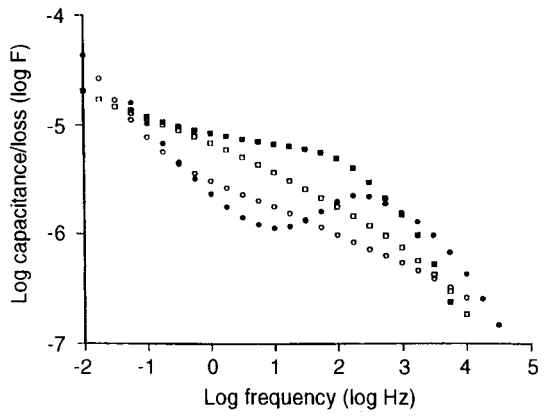

FIG. 8. Dielectric response of carbopol 934 (2·5% w/v) in water in the presence and absence of 0·1% w/v chlorhexidine gluconate. ■, ◆, C, G/ω carbopol 934, □, ◇, C, G/ω carbopol 934 with drug. Reproduced from Craig et al (1994), with permission.

containing these gel-forming polymers. We have worked on carbopol gel systems, looking at the effects of incorporating additives (Craig et al 1994), changing the nature of the neutralizing agent added to promote gelation (Tamburic & Craig 1995) and studying the effects of storage on the structure of the gels (Tamburic & Craig 1996), at the same time trying to relate these parameters to bioadhesive strength. An example is shown in Fig. 8, where the model drug chlorhexidine gluconate has been added to carbopol 934 at a concentration of 0·1% w/w. Clearly, not only the magnitude but also the shape of the spectrum has been altered, indicating an interaction between the drug and the polymer network. It is difficult to characterize the internal structure of gel systems, hence dielectric analysis could have an important role in this respect.

As a final example, we have used the technique to examine aerosol systems with the intention of exploring the possibility of making measurements in pressurized systems (Craig & Taylor 1995). Because of a lack of canister-filling facilities, and also because this was a proof-of-concept study, we used the comparatively non-volatile CFC P113 as a propellant, with salbutamol sulphate as model drug. Our intention was to examine the effects of adding a surfactant (sorbitan trioleate), which is used as a dispersant in these systems, on the dielectric response. We found that the CFC alone gave a very low response which was almost indistinguishable from that of the empty cell. The response was, furthermore, not significantly altered by the addition of 1% drug, whereas addition of surfactant caused substantial increases in dielectric loss. This is useful in as much as it demonstrated the sensitivity of the technique to the presence of surfactant (addition of 0·05% w/v caused more than a tenfold increase in G/ω) but is not surprising in dielectric terms because the surfactant might be expected to act as a charge carrier. On addition of the drug to systems containing surfactant, however, the response was dramatically reduced, indicating that the surfactant was adsorbed on to the surface of the drug particles and was, therefore, no longer free to carry charge (Fig. 9). This was investigated for a range of surfactant concentrations and a correlation was found between the reduction of G/ω and the aggregation behaviour of the drug.

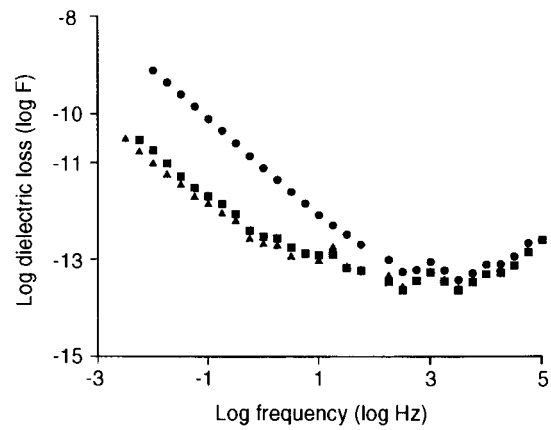

FIG. 9. The effect of addition of 1% salbutamol sulphate on the dielectric response of CFC P113 containing 0·05% sorbitan trioleate. ■, P113; ●, 0·05% surfactant and ▲, 0·05% surfactant with 1% drug.

Conclusions

This review has highlighted the philosophy underlining the main areas of activity of this research group, particularly in thermal and dielectric analysis. The acquisition of modulated temperature DSC and improved dielectric equipment has considerably extended our measuring capability, and the imminent arrival of high-sensitivity DSC for the measurement of molecular transitions such as protein and polysaccharide conformational changes in solution will add a further facet to our activities. Underlying all of this, however, is the belief that by understanding more about the structures of the systems we are dealing with, we can optimize existing formulations and develop new strategies for delivering drugs on a more rational basis.

The subtitle to the review, "Resuscitation or Reincarnation?", refers to the question of whether this field is an extension of existing areas or whether it represents a new contribution to the successful development of drug therapies. There are arguments on both sides: physical characterization studies have been steadily conducted for decades, whereas on the other hand the availability of several new analytical techniques such as those outlined here, along with other methods such as microcalorimetry and solid-state NMR, allow us new insights into physical structures, which were not previously possible. Our needs in terms of the characterization of materials have, furthermore, become increasingly more sophisticated in line with developments in dosage-form design. It is, therefore, arguable that the simultaneous advent of both new techniques and new applications has resulted in pharmaceutical materials science moving in a novel direction. In any case, however, the field appears to be thriving at present and will hopefully become increasingly recognized as an important component of the successful design of new drug therapies.

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