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PHARMACEUTICAL PREFORMULATION STUDIES WITH SPECIAL EMPHASIS ON EXCIPIENTS COMPATIBILITY

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Abstract

Preformulation is the stage of development during which the physicochemical properties are characterized by some parameters some of these include solubility, dissolution behavior, stability, partition coefficient, ionization constant, solid state-state properties such as crystal form, water sorption behavior, surface property, particle size and shape, other mechanical properties etc. Drugs are rarely administered solely as pure chemical substance but are almost always given a formulated property. These can vary from relatively simple solution to complex drug delivery systems. Though the use of appropriate additives or excipients in the formulations to provide valid and specialized pharmaceutical functions. The principle objective of a dosage form design is to achieve a predictable, therapeutic response to a drug included in a formulation, which is capable of large-scale manufacture with reproducible product quality. The drug substance characterization and stability is usually determined as part of preformulation studies. Before any new compound is taken up for clinical trials, stability profile of new drug substance is very much needed to proceed further to enter into product development, as stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical products. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product from early phase development through the lifecycle of the drug product. Stability data for the drug substance are used to determine optimal storage and packaging conditions for bulk lots of the material. Studies are designed to degrade the solid drug substance and appropriate solutions, allowing the determination of the degradation profile.

Keywords: Chemical Stability; Physicochemical Properties; Oxidation; Formulation; Excipients

Introduction

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.[1] It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the person those who want to prepare the formulation in developing stable and bioavailable dosage forms for the patient those who require the drug. Obviously the dosage form to be developed depends on the information available from the preformulation studies. Pre-formulation discipline utilizes biopharmaceutical principles in the determination of physico-chemical properties of a drug substance. During the pre-formulation phase of product development, characterization of the drug molecule is very important step Therefore, goal of pre-formulation studies are to choose the correct form of the drug. Pre-formulation studies generally include accelerated stability (stress) studies, stability-indicating analytical method development, and other physico-chemical characterization designed to pinpoint stability problems and enable formulation optimization.

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system. Characterization of drug molecule is a very important step at the preformulation phase of product development. In preformulation, relevant physico-chemical properties of drug substances are determined, for example solubility or stability that is important criteria to select the right substances for development. After oral application, only the substances with sufficient solubility can be absorbed by the digestive tract and into the body, where they become effective. Stability is important, as a drug substance must remain stable during handling, formulation, storage and administration of the drug product.

Prior to this a validated method of analysis is required. Guidelines are available from ICH to harmonize and set a uniform standard of method validation and quantization. For doing validation we need to follow some of the components for the sake of validation. Following studies are conducted as basic preformulation studies; solubility, partition coefficient, dissociation constant, crystal properties, polymorphism, and stability studies.[2, 3]

1. Physico-chemical parameters

1.1 Purity: The purity of drug substance plays the most significant role in all studies carried out on it. For every new compound, depending on its dose and toxicity, the limit of impurity is defined. Until and unless the purity of the drug is assured other studies like stability, degradation and toxicity cannot be performed. Various parameters, which are considered to find the purity of the drug substance, are melting point, UV absorption, IR spectra, TLC. Other determinations of impurities is done to check each batch for limit of impurities etc. the various parameters checked are limit of insoluble matter, limit of soluble matter, limits of moisture, volatile matter and residual solvents, limit of nonvolatile matter, limit of residue on ignition, loss on ignition, ash values. Both TLC and HPLC are used for detection of impurities. Now a day these are used for identification and quantification of impurities, which are often very closely related in structure to the main compound of interest.

1.2 Solubility Determination

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. The solubility of a molecule in various solvents is determined as a first step. This information is valuable in developing a formulation. Solubility is usually determined in a variety of commonly used solvents and some oils if the molecule is lipophilic.

The solubility of a material is usually determined[4-6] by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved. Common solvents used for solubility determination are: water polyethylene glycols, propylene glycol, glycerin, sorbitol, ethyl alcohol, methanol, benzyl alcohol, isopropyl alcohol, tweens, polysorbates, castor oil, peanut oil, sesame oil, buffers at various pHs

1.3 Partition Coefficient: Partition coefficient[7] (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$P_{o/w} = (C_{oil}/W_{ater})_{equilibrium}$

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/hydrophilic nature of the drug[8, 9]. Since biological membranes are lipoidal in nature, the rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water.

Drugs having values of $P_{o/w}$ much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pKa, and solubility on absorption must not be neglected.

1.4 pKa Determination (dissociation constant)

For a compound containing basic or acidic functional groups, solubility at a given pH is influenced by the compound's ionization characteristics. The solubility of a compound in aqueous media is greater in the ionized state than in the neutral state.[10, 11] Thus, solubility of ionizable compounds is dependent on the pH of the solution. Many drugs are weak acids or bases and thus are ionizable within the pH range of the gut. Solubility and dissolution, and therefore absorption, of a weak base can be altered by changes to gastric pH. While a weakly basic compound might fully dissolve in the acidic environment of the stomach and result in high exposure levels under such conditions, co-administration of drugs that raise the stomach pH can lead to greatly decreased solubility, leading to significantly lower exposure.

Determination of the dissociation constant for a drug capable of ionization within a pH range of 1 to 10 is important since solubility, and consequently absorption, can be altered by orders of magnitude with changing pH. There are many experimental methods used for determining the pKa. Simple fitting of the pH-solubility profile can be used if

solubility measurements have already been made at multiple pH values. Other typical methods include potentiometric titration, spectrophotometric titration, and capillary electrophoresis.[12] The Henderson-Hasselbalch equation provides an estimate of the ionized and un-ionized drug concentration at a particular pH.

For acidic compounds:

pH = pKa + log ([ionized drug]/[un-ionized drug])

For basic compounds:

pH = pKa + log ([un-ionized drug]/[ionized drug])

pKa of a compound is thus a measure of drug un-ionized at a certain pH

pKa = -log K_a , where Ka is the acidity or ionization constant of a weak acid.

For a weak base, **$K_a = K_w/K_b$**, where K_w is the ionic product of water

($K_w=[H_3O^+] \times [OH^-]$) and K_b is the basicity or ionization constant of the weak.

1.5 Particle size, shape and surface area

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also on their biopharmaceutical behavior. Bulk flow, formulation homogeneity, and surface area controlled processes such as dissolution and chemical reactivity are directly affected by size, shape and surface morphology of the drug particles.[13] In general, each new drug candidate should be tested during preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug's surface area for interactions. It is generally recognized that poorly soluble drugs showing a dissolution-rate limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state rather than as a coarse material.

Size can also be a factor in stability; fine materials are relatively more open to attack from atmospheric oxygen, heat, light, humidity and interacting excipients than coarse materials. The more common methods of determining particle size of powders used in the pharmaceutical industry include sieving, microscopy, and sedimentation[14, 15].

The coulter-counter[16] is used widely in the field of particle-size analysis in the pharmaceutical industry. Light scattering methods are generally fast, inexpensive and induce minimal artifacts.

1.6 Crystal Properties and Polymorphism

Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction (XRD) patterns, and solubilities, even though they are chemically identical. Differences in the dissolution rates and solubilities of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving form may be utilized to improve the rate and extent of bioavailability. For drugs prone to degradation in the solid state, the physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is a solution in many cases.

Different polymorphs also lead to different morphology, tensile strength and density of powder bed which all contribute to compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its preformulation evaluation, especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy (including hot-stage microscopy), IR spectrophotometry, single-crystal X-ray and X-ray powder diffraction (XRPD), thermal analysis, and dilatometry.

2. Stability Studies

The stability studies are done to determine shelf-life, and co-related specifications, and it must be taken into account of the chemistry of the active ingredient and its likely vulnerability to degrade by oxidation, hydrolysis, isomerisation, polymerization, decarboxylation, moisture, heat and light. Properly conducted stability study must

also include an examination of specific decomposition products by appropriate techniques to establish identity and relative toxicity of the decomposition products and the concentrations in which they are formed.

Stability studies should not only take the account of the physical state in which the compound is likely to be used, but also the immediate biological environment likely to be met on administration. The substance for tablet, encapsulation and preparation of suspension, should be examined primarily in solid state. Substances for injection, which must be subjected to some form of sterilization procedure, must be examined particularly for stability at elevated temperature for possible hydrolysis or rearrangement in aqueous media and effects of exposure to CO_2 and light. Similarly all substances intended for oral administration must be chemically stable to the pH and enzymatic conditions likely to be met in the gastro-intestinal tract.

Hence, stability studies must be conducted on the drug substance in the solid state over a range of temperature, at varying degrees of humidity, and in both light and dark. Also, if a product is to be used in multiple dose form in the tropics with fluctuation in temperature, which should be stored ideally in cool or refrigerated conditions, then the stability tests should include a study of the effects of fluctuating temperature.

Stability studies are an integral part of the drug development program and are of the most important area in the registration of pharma products. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. Stability studies can influence the specification, limits and control method for drug.

The physico-chemical parameters, such as the presence of additives as well as the storage conditions, which may affect the stability of drugs, have received considerable attention in the field of pharmaceutics. The formulation of a stable dosage form is essential for the patient's safety and drug efficacy.

In the ICH Harmonized Tripartite Guidelines on Stability Testing of New Drug Substances and Products fundamental recommendation are summarized. According to the ICH guideline, long term (12months) and accelerated stability studies (least 6 months) have to be carried out.

Table 1: Long term, accelerated and where appropriate, intermediate storage conditions for the drug substances.

Study	Storage conditions	Time period
Long term*	25°C ± 2°C/60%RH ± 5%RH	12 months
	OR	
	30°C ± 2°C/65%RH ± 5%RH	
Intermediate**	30°C ± 2°C/65%RH ± 5%RH	6 months
Accelerated	40°C ± 2°C/75%RH ± 5%RH	6 months

* Long term stability studies are performed at 25°C ± 2°C/60%RH ± 5%RH or 30°C ± 2°C/65%RH ± 5%RH.

** If 30°C ± 2°C/65%RH ± 5%RH is the long-term condition, there is no intermediate condition.

2.1 Chemical stability profile

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid-state experiments under conditions typical for the handling, formulation, storage, and administration of a drug candidate as well as stability in presence of other excipients.

Factors affecting chemical stability critical in rational dosage form design include temperature[14], pH[17] and dosage form diluents.[18, 19] The method of sterilization for parenteral products will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral and parenteral dosage forms; acid labile drugs intended for oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for parenteral dosage forms will be largely based on the stability characteristics of the drug.

2.2 Solid-State Stability

The primary objectives of this investigation are identification of stable storage[20] conditions for drug in the solid state and identification of compatible excipients for a formulation. Solid-state studies may be severely affected by changes in purity and crystallinity, [21] which often result from process improvements. Repetitive testing of the initial bulk lot in parallel with newer bulk lots should be expected, and adequate material should be set aside for these studies. In general, solid-state reactions are much slower and more difficult to interpret than solution state reactions, and it is customary to use stress conditions in the investigation of stability. The data obtained under stress conditions are then extrapolated to make a prediction of stability under appropriate storage conditions.[22]

2.3 Stability Studies by applying Stress

a. Elevated Temperature Studies

The elevated temperatures most commonly used are 40°, 50° and 60°C in conjunction with ambient humidity. Occasionally, higher temperatures are used. The samples stored at the highest temperature should be examined for physical and chemical changes at weekly intervals, and any change, when compared to an appropriate control (usually a sample stored at 5°C), should be noted[23]. If a substantial change is seen, samples stored at lower temperatures are examined. If no change is seen after 30 days at 60°C, the stability prognosis is excellent. Corroborative evidence must be obtained by monitoring the samples stored at lower temperatures for longer durations. Samples stored at room temperature and at 5°C may be followed for as long as 6 months. The data obtained at elevated temperatures may be extrapolated using the Arrhenius[24] treatment to determine the degradation rate at a lower temperature.

Arrhenius Equation: $K = A\, e^{-Ea/RT}$

Ea: activation energy, R: gas constant

$logK = logA - (E_a/2.303RT)$

Plotting the rate of reaction (K) against 1/T allows the calculation of rate at any temperature and therefore a prediction of shelf-life.[25] This forms the basis of many accelerated stability tests. Not all solid-state reactions are

amenable to Arrhenius treatment. Their heterogeneous nature makes elucidation of the kinetic order and prediction difficult. Long-term lower temperature studies are, therefore, an essential part of a good stability program.

b. High-Humidity Conditions

In the presence of moisture, many drug substances hydrolyze, react with other excipients, or oxidize.[26] Exposing the solid drug to different relative-humidity conditions can accelerate these reactions. Controlled humidity environments can be readily obtained using laboratory desiccators containing saturated solutions of various salts.[27] Preformulation data of this nature are useful in determining if the material should be protected and stored in a controlled low-humidity environment, or if the use of an aqueous-based granulation system, in the case of a solid dosage form, should be avoided. They may also caution against the use of excipients that absorb moisture significantly. During manufacture, storage and transport of the compound (drug), its protection from moisture is necessary as it may lead to decomposition of the drug and the impurity may be harmful or toxic; if taken as such. The single most important cause of loss of potency of a drug substance is the presence of moisture. It can be presented as surface moisture, which dissolves the drug to the extent of its solubility S, if the moisture is abundant (water is in excess) then rate of decomposition can be pseudo first order. When moisture content is very high, decomposition of solid dosage form may be treated as kinetics of saturated solution. In such cases it follows zero order kinetics. It is seen that for '$C= C_0- k_0^n t$', when weight is plotted vs time, a straight line results with time. The slope is independent of C_0, as opposed to the reactions of first order; in such cases it follows zero order kinetics. But in other cases the effect of humidity follows first order kinetics. Hence it becomes necessary to study the effect of moisture on the compound.

c. Photolytic Stability

The intrinsic photo stability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. The ICH Harmonized Tripartite guidelines covering the stability testing of new drug substances and products notes that light testing should be an integral part of stress testing.

According to ICH, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparison to be made between the drug substance and drug product. Samples may be exposed to side by side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters.

Many drug substances fade or darken on exposure to light. Usually the extent of degradation is small and limited to the exposed surface area[28-30]. This can be controlled by using amber glass or an opaque container or by incorporating a dye in the product to mask the discoloration. Exposure of the drug substance to photo stability in a chamber or when exposed to 400 and 900 foot-candles of illumination, is adequate to provide some idea of photosensitivity (One footcandle is equal to 10.76 lux) [31]. Over these periods, the samples should be examined frequently for change in appearance and for chemical loss, and they should be compared against samples stored under the same conditions but protected from light[32].

d. Oxidative Stability

The sensitivity of each new drug entity to atmospheric oxygen must be evaluated to establish if the final product should be packaged under inert atmospheric conditions and if it should contain an antioxidant[1]. Sensitivity to oxidation of a solid drug can be ascertained by investigating its stability in an atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for a rapid evaluation. Results should be compared against those obtained under inert or ambient atmospheres.

2.4 Solution Phase Stability

The primary objective of this phase of preformulation research is identification of conditions necessary to form a stable solution. These studies should include the effects of pH, ionic strength, co-solvent, light, temperature and oxygen. Solution stability investigations usually commence with probing experiments to confirm decay at the extremes of pH and temperature (e.g., 0.1N HCl, water, and 0.1N NaOH all at 90°C) [33]. These intentionally degraded samples may be used to confirm assay specificity as well as to provide estimates for maximum rates of

degradation. This initial experiment should be followed by the generation of a complete pH-rate profile to identify the pH of maximum stability. Aqueous buffers are used to produce solutions over a wide range of pH values with constant levels of drug, co-solvent and ionic strength.

pH Rate Profile

To generate a pH-rate profile, stability data generated at each pH and temperature condition are analyzed kinetically to yield the apparent decay rate constants. All of the rate constants at a single temperature are then plotted as a function of pH. The minimum in this curve is the pH of maximum stability. An Arrhenius plot is constructed by plotting the logarithm of the apparent decay rate constant versus the reciprocal of the absolute temperature at which each particular buffer solution was stored during the stability test. If this relationship is linear, one may assume a constant decay mechanism over this temperature range and calculate activation energy (E_a) from the slope ($-E_a/R$) of the line described by.

$$\ln k = -(E_a/R)(1/T) + C$$

Where **"C"** is a constant of integration and R is the gas constant.

A broken or nonlinear Arrhenius plot suggests a change in the rate-limiting step of the reaction or a change in decay mechanism, thus making extrapolation unreliable. Reactions in solutions proceed considerably more rapidly than the corresponding solid-state reactions. Degradation in solution thus offers a rapid method for the generation of degradation products[34]. The latter are often needed for the purpose of identification (to study their toxicity) and the development of analytical methods. Even for a drug substance intended to be formulated into a solid dosage form such as a tablet, a limited solution-phase stability study must be undertaken. Among others, these studies are necessary to assure that the drug substance does not degrade intolerably when exposed to gastrointestinal fluids. Thus, the stability of drug in buffers ranging from pH 1 to 8 should be investigated. If the drug is observed to degrade rapidly in acidic solutions, a less soluble or less susceptible chemical form may show increased relative bioavailability. Alternately, an enteric dosage form may be recommended for such a compound. The availability of pH-rate profile data is sometimes useful in predicting the solid-state stability of salt forms or the stability of a drug

in the presence of acidic and basic excipients. If a drug substance is adjudged to be physically or chemically unstable when exposed to moisture, a direct compression or non-aqueous solvent granulation procedure is to be recommended for the preparation of tablets. Before using a non-aqueous solvent for this purpose, stability of the drug in the solvent must be ascertained.

2.5 Compatibility Studies

Drug-excipient studies are designed to determine a list of excipients that can be used routinely in the final dosage forms. Various means have been used for detecting potential interactions and incompatibilities.

The use of differential scanning calorimetry (DSC) as a novel means of detecting excipient incompatibility. In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. Example: a typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much at the discretion of the preformulation scientist. Drug-excipient interaction can be determined with different methods such as DSC, TLC, HPLC, and XRPD. The results with the DSC method are comparable and in good agreement with the results obtained with other methods[35, 36].

a. Differential scanning calorimetry (DSC)

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Both the sample and reference are maintained at very nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned. The basic principle underlying this technique is that, when the sample undergoes a physical transformation such as phase transition, more (or less) heat will need to flow to it than the reference to maintain both at the same temperature. Whether more or less heat must flow to the sample depends on whether the process is exothermic or endothermic.

For example, as a solid sample melts to a liquid it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid. Likewise, as the sample undergoes exothermic processes (such as crystallization) less heat is required to raise the sample temperature. By observing the difference in heat flow between the sample and reference, differential scanning calorimeters are able to measure the amount of energy absorbed or released during such transitions. DSC is widely used in industrial settings as a quality control instrument due to its applicability in evaluating sample purity and for studying polymer curing[37].

An alternative technique, which shares much in common with DSC, is differential thermal analysis (DTA). In this technique it is the heat flow to the sample and reference that remains the same rather than the temperature. When the sample and reference are heated identically phase changes and other thermal processes cause a difference in temperature between the sample and reference. Both DSC and DTA provide similar information; DSC is the more widely used of the two techniques.

A typical DSC consists of two sealed pans, a sample pan and a reference pan (which is generally an empty sample pan). These pans are often covered by or composed of aluminum, which acts as a radiation shield. The two pans are heated, or cooled; uniformly while the heat flow difference between the two is monitored. This can be done at a constant temperature (isothermally), but is more commonly done by changing the temperature at a constant rate, a mode of operation also called temperature scanning.

During the determination, the instrument detects differences in the heat flow between the sample and reference. This information is sent to an output device, most often a computer, resulting in a plot of the differential heat flow between the reference and sample cell as a function of temperature. When there are no thermodynamic physical or chemical processes occurring, the heat flow difference between the sample and reference varies only slightly with temperature, and shows up as a flat or very shallow base line on the plot. However, an exothermic or endothermic process within the sample results in a significant deviation in the difference between the two heat flows. The result is a peak in the DSC curve. Generally, the differential heat flow is calculated by subtracting the sample heat flow

from the reference heat flow. When following this convention, exothermic processes will show up as positive peaks (above the baseline) while peaks resulting from endothermic processes are negative (below the baseline).

The result of a DSC experiment is a heating or cooling curve. This curve can be used to calculate enthalpies of transitions. Integrating the peak corresponding to a given transition does this. It can be shown that the enthalpy of transition can be expressed using the following equation:

$$\Delta H = KA$$

Where ΔH is the enthalpy of transition, K is the calorimetric constant, and A is the area under the curve. The calometric constant will vary instrument to instrument, and can be determined by analyzing a well-characterized sample with known enthalpies of transition.

b. Applications of DSC

Differential scanning calorimetry can be used to measure a number of characteristic properties of a sample. Using this technique it is possible to observe fusion and crystallization events as well as glass transition temperatures (T_g). DSC can also be used to study oxidation, as well as other chemical reactions[37].

Glass transitions may occur as the temperature of an amorphous solid is increased. These transitions appear as a step in the baseline of the recorded DSC signal. This is due to the sample undergoing a change in capacity no formal phase change occurs.

As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (T_c). This transition from amorphous solid to crystalline solid is an exothermic process, and results in a peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (T_m). The melting process results in an endothermic peak in the DSC curve. The ability to determine transition temperatures and enthalpies makes DSC an invaluable tool in producing phase diagrams for various chemical systems. DSC may also be used in the study of liquid crystal. As matter transitions between solid and liquid it often goes through a third state, which displays properties of both phases. This anisotropic liquid is known

as a liquid crystalline or mesomorphous state. Using DSC, it is possible to observe the small energy changes that occur as matter transitions from a solid to a liquid crystal and from a liquid crystal to an isotropic liquid. Using DSC to study the oxidative stability of samples generally requires an airtight sample chamber. Usually, such tests are done isothermally (at constant temperature) by changing the atmosphere of the sample. First, the sample is brought to the desired test temperature under an inert atmosphere, usually nitrogen. Then, oxygen is added to the system. Any oxidation that occurs is observed as a deviation in the baseline. Such analyses can be used to determine the stability and optimum storage conditions for a compound. DSC is widely used in the pharmaceutical and polymer industries. For the polymer chemist, DSC is a handy tool for studying curing processes, which allows the fine-tuning of polymer properties. The cross-linking of polymer molecules that occurs in the curing process is exothermic, resulting in a positive peak in the DSC curve that usually appears soon after the glass transition.

In the pharmaceutical industry it is necessary to have well-characterized drug compounds in order to define processing parameters. For instance, if it is necessary to deliver a drug in the amorphous form, it is desirable to process the drug at temperatures below those at which crystallization can occur. In food science research, DSC is used in conjunction with other thermal analytical techniques to determine water dynamics. Changes in water distribution may be correlated with changes in texture. Similar to material science studies, the effects of curing on confectionery products can also be analyzed. DSC curves may also be used to evaluate drug and polymer purities. This is possible because the temperature range over, which a mixture of compounds melts, is dependent on their relative amounts. This effect is due to a phenomenon known as freezing point depression, which occurs when a foreign solute is added to a solution. Consequently, less pure compounds will exhibit a broadened melting peak that begins at lower temperature than a pure compound.

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