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ADVANCES IN ANALYTICAL TECHNIQUES USED IN PREDICTING DRUG-EXCIPIENT INTERACTIONS

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Abstract

Drug-excipient interaction has paramount importance in pharmaceutical industry. Excipient although considered inert, it alone or along with its degradation products and contaminants can exhibit various incompatibilities with the drug. This review elaborates various types of drug degradation mechanisms. Various advanced analytical techniques like thermal methods (TG, DTA, DSC, Thermomicroscopy, Isothermal microcalorimetry, Isothermal Titration Calorimetry, High sensitivity DSC), Isothermal stress testing, Optical microscopy, XRD, IR, NMR and chromatography can detect potential drug excipient incompatibilities. Conditions for carrying out drug excipient interaction studies along with advantages and limitations of each technique are discussed. Using these techniques in preformulation stage, rationalized excipient selection can be performed. Although many analytical methods can be applied, hyphenated techniques like DSC-GC, DSC–FTIR are more advantageous methods since they not only can simulate the accelerated drug stability testing but also at the same time enable to detect and quantify the degradation products.

Keywords: Thermal methods, Drug- excipient incompatibility, DSC, IR, Chromatography, NMR.

1. Introduction:

Definition of excipient as developed by IPEC (International Pharmaceutical Excipients Council) America and IPEC Europe is, “These are the substance(s) other than the API which has been appropriately evaluated for safety and are included in a drug delivery system to either aid processing of the system during manufacturing or protect, support or enhance stability, bioavailability or patients compliances or assist in product identification and enhance any other attributes of overall safety and effectiveness of drug product during storage or use” [1].

Excipients may be added in formulation to improve the stability of API in the dosage form, to modulate bioavailability of API, to maintain the pH of liquid formulation, to maintain the rheology of semisolid dosage form, as tablet binders and disintegrant, antioxidant and emulsifying agents, to facilitate the manufacturing of dosage form, for aesthetic reason and for identification [2].

Ideally the excipient should be pharmacologically inert substance. Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds which may compromise the effectiveness of a medication [3]. Degradation may be facilitated by excipients possessing the requisite functional groups, or containing residues that catalyze/participate in degradation processes. If excipients are also susceptible to environmental changes, this provides additional possibilities for the generation of species that participate in break-down processes. Excipients are not exquisitely pure [4]. Like drug substances, it also has allowed limit of certain impurities like oxidizing substances, organic and inorganic impurities and alkaline impurities. Polymer may contain free acid which may accelerate degradation of acid sensitive drug. Hygroscopicity of excipient is of a paramount importance as it can accelerate degradation of water sensitive drug after intermediate and long term stability. Incompatible excipient must be omitted from formulation. If alternative excipient is not available, careful attention must be provided in formulation design.

2. Types of Interaction

Drug-excipients interaction can either be beneficial or detrimental.

Beneficial interactions

Numerous papers dealing with studies of interactions between active medicaments and excipients have been published in the last two decades. Beneficial interactions are aimed to improve the solubility of poorly soluble drugs, increase dissolution rates, increase rate of drug release, alteration of therapeutic activity, increase of bioavailability and decrease of unwanted side effects [5-9].

Non Beneficial interactions

Interaction between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. It may cause substantial loss of potency, undesired change in the performance, substantial changes in physical appearance of dosage form causing product failure, degradation products may result in adverse events or

toxicity. Excipient impurities can react either directly with drugs or act as catalysts for other drug degradation processes, e.g., hydrolysis or oxidation. In particular, peroxides, small aldehydes and carboxylic acids can be present in many excipients at levels up to several hundred parts per million. Because of the low molecular weight of these reactive impurities, for low dose formulations, unacceptable degradation levels of drug can occur [10]. Reaction of drugs with excipient degradation products can in many ways mimic the reaction of drugs with excipient impurities.

Duloxetine Hydrochloride is acid labile compound that degrades to a highly toxic compound 1-naphthol as it contains secondary amino functional group. It was formulated with enteric polymers like Hydroxypropyl Methylcellulose Acetate Succinate and Hydroxypropyl Methylcellulose Phthalate to prevent the acid degradation in the stomach. These were found to accelerate degradation of duloxetine due to the free acids contained in the polymers [11]. Preformulation studies should be performed for early detection of such interactions. A number of experimental techniques can be applied to provide information on physicochemical properties of substances with respect to compatibility by predicting future problems of stability prior to the final dosage formulation.

3. Mechanism of drug-excipients interaction

Exact mechanism of drug excipients interaction is not clear. However, there are several well documented mechanisms in the literature. Drug-excipients interaction are common than excipient-excipient interaction.

Physical interactions are common, but are very difficult to detect. Physical interactions are frequently useful in manufacturing of dosage form, for example to modify drug dissolution. However many of the physical interactions are unintended which usually causes the problems. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration [4].Chemical interactions can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect. Primary and secondary amine group of drugs undergoes Maillard reaction with glycosidic hydroxyl group of reducing sugar like dextrose to form imine, which finally breakdown to form amidori compounds [11]. The Maillard reaction with lactose has been studied for several drugs like fluoxetine hydrochloride, lisinopril, neomycin, dextroamphetamine, aminophylline, thiamine hydrochloride, benzocaine, sodium p-aminosalicylate, procaine hydrochloride, sulphaguanidine, chloroquine phosphate or ephedrine sulphate in combination with lactose [12,13]

Medicinal agents have structural features that confer some degree of lability, making them vulnerable to degradation. Common modes of degradation are described below-

Hydrolysis: Drugs containing functional groups like esters, amides, lactones or lactams are vulnerable to hydrolysis. Most of the medicinal agents contain either of these groups. Hence hygroscopicity of excipients should be checked. Excipeints like povidone- and poloxamer were found to mediate degradation of hydrochlorothiazide in an antihypertensive combination tablet product due to hydrolysis [14]. In the presence of moisture, degradation of moexipril occurred more in acidic excipients than the basic excipients [15]. Acid and base impurities are often associated with hydrolysis and cyclizations e.g., lactone or lactam formation [16].

Cyclization: Drugs like diclofenac [17],moexipril, spirapril hydrochloride and quinapril hydrochloride were found to undergo intramolecular cyclization [15].

Dissociation/ Disproportionation: This is important for drug salts. Disproportionation is dissociation of drug salts into the corresponding free form. Salts are ionic compounds which generally have a higher aqueous solubility than the uncharged free form of the compound. It is one of the methods to improve the solubility of poorly soluble drugs. While formulating salts, pHmax should be given atmost consideration. It is the pH of maximum solubility, where there is equilibrium between the ionized and neutral species in solution with both the solid salt and the solid neutral form.

In aqueous environments below pHmax, the excess solid phase in equilibrium with the saturated solution is the free acid form, whereas the excess solid above pHmax is the salt. The opposite pH relationship is true for basic compounds. The microenvironmental pH of weakly acidic drug must be maintained at a value higher than pHmax. The microenvironmental pH is affected by acidic or basic excipients, and improper excipient selection has been shown to lead to disproportionation [18].

Oxidation: The oxidation reaction can be catalyzed by radiation from the sun and artificial light, and by trace quantities of metal ions, leading to free radical formation. Free radicals react with oxygen to form peroxy radicals which in turn react with oxidizable compound to generate additional free radicals to fuel further reactions [4]. Aldehydes, alcohols, phenols, alkaloids and unsaturated fats and oils are all susceptible to oxidation.

Crystalline esters of vitamin A decomposed by both polymerization and oxidation pathways [15]. Vitamin A was found as a gummy yellow solid after 5 months of exposure to room light, temperature, and air. Peptides and some steroids

were also shown to be prone to oxidation. Ascorbic acid [19], chlorophenols [20], rapamycin [21]were found to undergo oxidation. Trace impurity levels of hydrogen peroxide have been observed to catalyze the instability of pharmaceutical products via a reaction between the API and excipients, excipient and excipient or between impurities. Hydrogen peroxide can oxidize functional groups, such as the double bond of an unsaturated ketone to an epoxide, an amine to an amine N-oxide or a hydroxylamine and a thiol to a sulfoxide. Additionally, hydrogen peroxide can be reduced to the more reactive hydroxyl radical in the presence of metal and initiate a radical chain reaction with the API [16]. Hydrogen peroxide in crospovidone was found to degrade Raloxifene hydrochloride to its N-oxide when exposed to accelerated storage conditions [22]. Gold nanoparticles deposited on inorganic supports are efficient catalysts for the oxidation of various substituted phenols with aqueous hydrogen peroxide [23].Various drugs like anti-ulcer (proton pump inhibitor), antibacterial, antifungal, anti-atherosclerotic, anthelmintic, antihypertensive, cardiotonic agents, psychotonics and vasodilators contains organic sulfoxide group. Due to presence of hydrogen peroxides in excipients, it may oxidize to sulfones [24]. Metal contaminants in excipients are often associated with oxidation reactions.

Polymerization and Isomerization

Intermolecular reactions can lead to dimeric and higher molecular weight species. Concentrated solutions of ampicillin, an amino-pencillin, progressively form dimer, trimer and ultimately polymeric degradation products. Isomerization involves conversion of a chemical into its optical or geometric isomer more widely in chiral environment which may br provided by excipients. Isomers may have different pharmacological or toxicological properties [4].

Photolysis

Reactions such as oxidation-reduction, ring alteration and polymerization can be catalyzed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and degradation by low wavelength radiation is common. Table 1 lists examples of medicinal agents susceptible to degradation.

4. Compatibility Studies

The rational approaches to the excipients choice as well as to their interactions with medicaments have been shown as the basis for modern modeling of pharmaceutical formulation. Drug-excipient studies are designed to determine a list of excipients that can be used routinely in the final dosage forms. The compatibility of the drug substance with the used excipients for the selected formulation should be evaluated as per ICH guidelines [25].

There are numerous factors which affect drug-excipient interactions. These include chemical nature of excipient, drug to excipient ratio, moisture, microenvironmental pH of drug excipient mixture, temperature and light. Excipient may affect solid state stability of drug by acting as a surface catalyst, acting as a source of extra moisture, altering the pH of moisture layer or by having direct chemical reaction with drug.

For rapid collection of compatibility data High Throughput approach as used in combinatorial chemistry can be used. It uses a 96 well plate, each well acting as a separate reaction centre. Simultaneously 96 excipients can be subjected to a given study protocol at a time. It requires as little as 0.1 mg of drug substance [26, 27].

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.

Conventional stability testing includes prolonged storage at elevated temperatures and determination of the undegraded or degraded fraction of drug as a function of time. The degradation rate under ambient conditions may then be estimated by extrapolation of the elevated temperature data using the Arrhenius equation. Present techniques are time consuming and, moreover, suffer from the uncertainty of the final shelf-life prediction due to temperature dependent inconsistencies in the Arrhenius relationship.

Consequently it would be desirable to have a rapid and less complicated method to perform stability testing.

5. Analytical Techniques used in drug-excipient interaction studies.

Techniques used in Drug-excipient interaction are listed below.

5.1 Thermal methods:

Thermogravimetry (TG), Differential Thermal Analysis (DTA), Differential Scanning Calorimetry (DSC), Microthermal Analysis, TG/DTA–GC/MS (Hyphenated method),

Thermomicroscopy (TM), Optical Miscroscopy (OM), Isothermal microcalorimetry, Isothermal Titration Calorimetry (ITC), High sensitivity DSC (HSDSC), DSC–FTIR microspectroscopic technique

5.2 Isothermal Stress Testing (IST)

5.3 X Ray powder Diffraction (XRD)

5.4 Vibration spectroscopy

Fourier Transform Infrared Spectroscopy (FT-IR), Raman Spectroscopy, Diffuse Reflectance Spectroscopy (DRS)

5.5 Nuclear Magnetic Resonance (NMR)

5.6 Chromatography

Thin Layer Chromatography (TLC), High Pressure Liquid Chromatography (HPLC)

Thermal methods

The term thermal analysis refers to a group of techniques in which a physical property of a substance and/ or its reaction products is measured as a function of temperature whilst the substance is subjected to a controlled temperature program. Information regarding the effects of storage at elevated temperatures can be obtained.

The early forms of thermal analysis were based mostly on Thermal Gravimetric Analysis where the change in weight of a substance with temperature was measured. Thermograms are generated for pure components and their physical mixtures with other components. In the absence of any interaction, the thermograms of mixtures show patterns corresponding to those of the individual components.

In DTG, the derivative of the mass change with respect to time is recorded as a function of time or temperature or the derivative of the mass change with respect to temperature is recorded as a function of time or temperature.

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 is measured as a function of temperature. The basic principle underlying this technique is that, when the sample undergoes a physical transformation such as phase transition, more or less heat will flow to it than the reference to maintain both at the same temperature. Heat flow to the sample depends on whether the process is exothermic or endothermic. 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. Endothermic process like Melting or an exothermic process like crystallization can be easily monitored. The temperature and energy associated with events, such as melting, oxidation and reduction reactions, glass transition, boiling, sublimation, decomposition, crystallization or gel to liquid crystal transition can be evaluated. When such events are evaluated for mixtures of drugs

and excipients, possible interactions may be discerned [28,29]. Various types of processes that can be monitored using DSC. Interaction between acyclovir and monohydrate lactose was evidenced by DSC as shown in Fig 1. Lactose showed two peaks due to dehydration and melting phenomenon [31]. In the DSC of mixture acyclovir melting peak was missing which was related to drug excipient interaction.

Studies can be carried out using sealed volatile aluminum pans or standard pan which are not hermetically sealed allowing volatile components to escape during the process of analysis.

A surface contact between drug and excipient is an important variable that affects DSC pattern. Prepared sample can be in the form of the powder mixtures, small discs prepared by compressing powder mixtures in a press, broken discs or aqueous solution [32, 33]. Sample preparation for the pure drug should be always identical to those of drug-excipient mixtures to ensure that the data obtained could always be related to the behavior of the pure drug under similar conditions. The effect of drug excipient ratio should be thoroughly investigated.

In the event that interaction occurs, this is indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components or shifting of peaks from their original positions. The disappearance of the melting peak of drug is indicative of a strong interaction, but not necessarily corresponding to incompatibility. Such disappearance of peaks can be attributed to drug dissolution in the melted polymer [15]. Interpretation of DSC thermogram is elaborated in Fig 2.

Interactions between coprecipitated drug and polymer can influence the glass transition temperature (*T*g) of the polymer–drug blend. The influence of the drug on the *T*g of the drug-excipient co-precipitated blends was examined [34]. The *T*g of the polymer may be expected to decrease in the presence of a small molecule due to the plasticising effect of the drug on the polymer. The change in glass transition temperature of the fully amorphous blends as a function of molar percentage of drug was studied by DSC. The glass transition temperature and how it changes with moisture content, related to mobility, is an important factor for the stability and formulation of amorphous materials [35].

As the Thermal analysis is used to investigate and predict any physicochemical interactions between components in the formulation and therefore can be applied to the selection of suitable chemically compatible excipients.

Microthermal analysis with thermally assisted nanosampling was used to study drug–excipient compatibility [36]. The method is a derivative of atomic force microscopy whereby the probe is replaced with a miniaturised thermistor,

allowing the temperature of the tip to be both controlled and measured. The classical measuring mode is localised thermomechanical analysis (L-TMA), whereby the position of the tip is measured as a function of temperature. As the material undergoes a transition such as melting the probe penetrates into the sample, thereby allowing the temperature at which the mechanical properties of the material immediately under the tip to be assessed. Another approach is localised differential thermal analysis (L-DTA) whereby the temperature difference between the probe tip and a remote reference is measured as a function of temperature, thereby allowing the detection of thermal transitions via a differential temperature signal in a manner analogous to conventional DTA.

In nanosampling the tip is introduced to a sample surface, heated so as soften that surface and become partially covered with material and then removed. Typically the tip retains some of the sample in the nanogram to picogram range. Thermally assisted particle manipulation uses a tip to pick up a particle by placing the tip on the particle then heating it to soften the material so it sticks to the tip. In photothermal IR, an IR beam is applied to a sample which is in close proximity to the tip and the measurement of the temperature fluctuations as a function of frequency via Fourier transformation is done. This enables the spectra of samples on or close to the tip to be obtained. These methods are suggested as a high throughput screening method for drug-excipient interaction based on its ability to both manipulate small quantities of material and to measure thermal properties at high heating rates [36].

The solid state interactions between the thiazide diuretics were investigated by measuring *T*g*s* of a range of binary co-spray-dried PVP–thiazide composites [37]. It was found to deviate which was attributed to interactions between the constituents of the spray-dried composites. FTIR analysis suggested hydrogen bonding between the sulphonamide groups of the thiazide diuretics and the PVP molecule and interaction between the phenyl group of aromatic diuretic and polymer ring.

The miscibility of indomethacin and lacidipine with excipient to predict glass solutions formation was investigated by DSC [38]. A glass solution is formed when two or more components are entirely miscible in the molten state and cool to form an amorphous one-phase system. However, to form a glass solution that is physically stable over prolonged periods of time, the *T*g should be higher at least 50 °C than the storage temperature. DSC analysis of onset of drug melting was found to have limitations in assessing miscibility when both the drug and the excipient melt at similar temperatures. But, *T*g analysis from DSC prepared quench cooled melts of drug and excipient provided an alternative means of predicting

miscibility. DSC *T*g analysis was found to be an important tool to predict physical stability of a glass solution formed with a specific drug and excipient for a given mass ratio.

Compatibility of glipizide with excipients was successfully evaluated using the combination of thermal and isothermal stress testing (IST) methods [39]. The data of thermal method was found to relevant with long term stability under IST.

DSC and FT-IR studies were used to investigate the compatibility of aceclofenac with various tableting excipients. The incompatibility was observed only between aceclofenac and magnesium stearate [40]. The potential compatibilities of excipients with picotamide were evaluated using differential scanning calorimetry, Hot-stage microscopy and scanning electron microscopy. The effects of aging and of mechanical treatment (blending, grinding, or kneading) of samples were also evaluated [41]. Thermoanalytical behavior of olanzapine with excipients like microcrystalline cellulose, croscarmellose, dicalcium phosphate dihydrate, lactose, magnesium stearate, and povidone was carried out by DSC, TG and X-ray diffraction tests. Thermoanalytical methods showed evidence of interaction of olanzapine with magnesium stearate, lactose, and povidone [42] and interaction of atenolol with mannitol [43].

The thermal properties of Ibuprofen with some excipients were evaluated by TG/DTG and DSC [44]. Venlafaxine hydrochloride -excipient compatibility studies by DSC have shown a possible physical interaction of the drug with magnesium stearate, microcrystalline cellulose and starch [45]. The compatibilities of several commonly used pharmaceutical excipients (microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, lactose monohydrate) and empty hard-gelatin capsules with sibutramine hydrochloride monohydrate was evaluated using DSC, TG/DTG, Isothermal and non-isothermal methods [46].

Nifedipine in tablets formulation was evaluated after storing them in amber-colored glass containers at 40°C and 75% RH for 180 days. DSC and TG were used in order to evaluate the thermal properties of nifedipine and excipients [47]. Incompatibility of Primaquine with lactose, magnesium stearate and mannitol was confirmed by thermal methods with FT-IR. The thermal decomposition in this case has followed a zero order kinetic in air and nitrogen atmospheres in non-isothermal method [48]. The thermal decomposition of glimepiride was studied using DSC and TG/DTG [49].

Techniques of thermal (DSC) and isothermal stress testing (IST) were used to assess the compatibility of glipizide with selected excipients. DSC has shown interaction with magnesium stearate, meglumine, TRIS buffer, and lactose. Stressed binary mixtures glipizide and meglumine also showed yellow coloration indicating potential incompatibility [39].

Ibuproxam with some currently employed pharmaceutical excipients was tested by DSC. The influence of processing effects (simple blending, cogrinding or kneading) on drug stability was also evaluated [50]. Incompatibility studies of acyclovir in physical mixtures with lactose and in different tablet brands were studied by DSC and FTIR. Acyclovir-lactose Maillard reaction product was studied by LC-MS. The incompatibility of acyclovir with lactose was evaluated using a combination of thermal methods and LC-MS/MS [31].

The compatibility of haloperidol with PVP was assessed by thermal methods, electron microscopy, IR spectroscopy and X-ray diffraction. The DSC was proven to be the most sensitive and specific in assessing the compatibility [51]. Thermal analysis of cyclodextrins with drug is extensively reviewed by Giordano et. al. [9].

Although DSC is a potential tool for these studies, interactions observed at elevated temperatures should be cautiously interpreted because they may not always be relevant at ambient conditions. [32,52]. DSC is generally regarded as one of the methods of first choice in assessing drug-excipient in compatibilities, but the evaluation of the curves is often difficult and 'hard' conclusions are rarely obtained. Better results can be achieved if the curves are compared with those of samples stored at 55^0C for 3 weeks [53]. Thermal method can be coupled with GC/MS. The evolved gaseous material from drug-excipient interaction can be adsorbed to Tenax trap cooled at dry ice temperature. The trap can be subsequently heated to desorb the gaseous material. The desorbed components can be separated and detected using GC-MS. Volatile products of the thermal decomposition of antiretroviral zidovudine were studied by a system composed of the TG/DTA coupled gas chromatography/mass spectrometry (GC/MS) to evaluate the compatibility with excipients used in solid dosage forms [28]. It results in conversion to thymine followed by its thermal decomposition to furan and 2-furanmethanol like volatile species.

Thermomicroscopy: Drug and drug-excipient mixture can be observed using hot stage microscopy. Melting, degradation and appearance of melt upon cooling can be visually monitored. This technique has been used for evaluating the interaction between microcrystalline cellulose and enalapril maleate [32]. Interaction with the excipient can be studied by measuring morphological characteristics of drug and excipient separately and in mixture using optical microscopy. Incompatibility of β-lapachone with Magnesium stearates was studied [54]. The drug and Magnesium stearate after heating upto $160\ ^0$ C has not shown any morphological changes of both. But when both were heated together the sample was blackened due to degradation. Techniques such as hot stage microscopy and scanning electron

microscopy can be used in conjunction with DSC to determine the nature of an apparent incompatibility. These techniques study the morphology of the drug substance and can determine the nature of physical transformations, thus indicating the type of incompatibility that has occurred [55].

Isothermal microcalorimetry (ITC)

Microcalorimetry is measurement of heat in micro-Watt scale. Isothermal calorimeter measures power as a function of temperature. ITC is emerging as the method of choice for characterizing intermolecular interactions and recognizing reactions with exquisite sensitivity, since both low and high affinity interactions can be quickly and accurately characterized using ITC. Materials can be studied in solution and suspensions, because the turbidity or the color of the samples does not affect measurement. It is based on measurement of the heat that is generated or absorbed in an interaction between two molecules [56]. It has been applied to determine the stability constants, stoichiometry, interaction enthalpies and under some conditions, entropies, Gibbs free energies and heat capacity changes.

ITC can be used to measure binding thermodynamics, particularly of cyclodextrin–guest interactions [57]. It is the most modern and sensitive method available at the present time for the determination of thermodynamics of the host–guest interaction. ITC shows whether an association process occurs and allows the evaluation of the association constant, the enthalpy and entropy of the interaction from which the Gibbs free energy of the process can be derived. A stronger interaction of a molecule with the cyclodextrins is indicated by a higher value of the binding constant and by a more negative value of enthalpy and Gibbs free energy indicating that the interaction is stronger and more spontaneous, respectively. In a typical ITC experiment, aliquots of a concentrated solution of cyclodextrins are added in a time-controlled manner to a cell containing the interacting molecule, which is maintained at constant temperature. During cyclodextrin addition, the two materials interact and the observed released heat is directly proportional to the amount of binding compound added with the solution aliquot [58].

It can be used to evaluate chemical stability and excipient compatibility of a solid drug. In general, calorimetry produces thermodynamic and kinetic data. For an exothermic process, the heat flow value is positive, for an endothermic process the heat flow value is negative. The method is non-specific as all chemical and physical processes can contribute to heat flow signals. This may be considered disadvantageous since the interpretation with respect to the chemical decomposition of a drug is more difficult, on the other hand thermal events in pharmaceutical systems indicates that a

process is occurring that may ultimately adversely influence the quality of the final drug product. Consequently, it is necessary to investigate the origin of the thermal events by additional specific assays.

The decomposition of a drug is usually combined with an exothermic enthalpy of reaction $\Delta_R H$ which is the sum of the endothermic bond breaking and the exothermic bond forming reaction. The amount of evolved heat, Q, is directly proportional to the concentration of the decomposition product and thus the heat flow is directly proportional to the decomposition rate dx/dt (constant of proportionality is $\Delta_R H$). Interactions can be predicted by change in the heat flow to the drug [59].

Thus advantages for isothermal calorimetry are data generation can be done in time frame of several hours to weeks as opposed to traditional accelerated temperature methods that can require 6-12 weeks. The sensitivity of method can allow one to monitor the reaction at ambient temperature rather than highly elevated temperature.

Disadvantages includes interpretation with respect to the chemical decomposition of a drug is more difficult. It is non-specific method of measurement as the evolution or absorption of heat could be a result of other chemical and physical processes during measurement such as dissolution, evaporation, phase transition or crystallization and can contribute to heat flow signals. The effect of various excipients on Pyridoxine Hydochloride stability based on Plackett-Burman factorial design was studied using this method. The drug excipient blends were stored in oven at 25-55 ^{0} C in hygrostats [60]. When the samples are investigated with monitoring combined effect of temperature and moisture, the results may be more realistic. ITC was used to identify and thermodynamically characterize the binding of phenol to folded Protein X [61]. It was used to measure binding constant of excipient to drug. Thus the type of interaction can be predicted which is useful to predict in *vivo* dissociation of the active protein from the stabilizing excipients in the formulation. Experiment was performed by titrating drug with excipient filled in syringe with controlled addition of titrant. Heat per injection measured by ITC versus molar ratio of excipient: drug is obtained. From this data, the binding affinity constant, enthalpy of binding and number of binding sites per protein and the entropy change of binding can be calculated.

Isothermal stress testing

Isothermal stress testing (IST) involves storage of drug–excipient blends with or without moisture at high temperature for a specific period of time (normally 3–4 weeks) to accelerate drug ageing and interaction with excipients. The

samples can then be visually observed and the drug content determined quantitatively [62, 63, 64]. Although more applicable, the disadvantage with this method is that it is time consuming and requires quantitative analysis using HPLC. Ideally, the techniques of DSC and IST should be used in combination for the selection of excipients.

Chemical interaction between isosorbide mononitrate and cellulose acetate was confirmed by IST [65].

A screening model to determine a potential stability problem due to interactions of drug substances with excipients in solid dosage forms has been developed [63]. The model involved storing drug-excipient blends with 20% added water in closed glass vials at 50^0 C and analyzing them after 1 and 3 weeks for chemical and physical stability. Effect of factors like chemical nature of the excipient, drug-to-excipient ratio, moisture, microenvironmental pH of the drug-excipient mixture, temperature, and light, on dosage form stability could be identified by using the model. The compatibility of nateglinide with selected excipients was done by thermal and isothermal stress testing techniques [66].

High sensitivity DSC/ HS-DSC

High-sensitivity differential scanning calorimetry is a modern powerful method of evaluation of protein energetics, structure and interactions. This technique has been developed in the Former Soviet Union to study co-operative conformational transitions of biopolymers in extremely dilute solutions. It has more sensitivity and precision exceeding most other commercial scanning calorimeters. A specific property of these instruments is uses of built-in calorimetric cells and relatively high heating rates (1-2 K/min). Such a design of the calorimetric cells provides high stability of a base line of the instrument that is a key factor for determination of the partial heat capacity of a substance. A further benefit of HS-DSC is rather short measurement time and modest sample consumption. It has considerable benefit whereby even gross incompatibilities could be detected in a matter of hours rather than weeks. Thermal methods either involve temperature ramping programmes or isothermal microcalorimetry. They have strengths and weaknesses. Ramping methods lack the sensitivity of microcalorimetry, while the isothermal microcalorimetry is not easily utilised at elevated temperatures, hence if the incompatibility is energetically weak at room temperature the response may not be detected. HSDSC could be used as a means of detecting the interaction between a model drug and an excipient as it overcomes the drawbacks of both the methods mentioned above. Any change like chemical degradation, dissolution, temperature re-equilibration, etc. can be seen on the HSDSC trace as a deviation of the heat flow from its baseline value [67]. Degradation of an experimental drug was observed in the presence of magnesium stearate and water in

combination by this technique. These results agreed with conventional stability studies, in which extensive degradation was observed in the Drug–magnesium stearate system after storage at 40 °C/75% RH for 4 weeks.

The compatibility between nebicapone and common excipients using DSC, HSDSC and a conventional heat stress test was demonstrated [68]. Nebicapone was found to be incompatible with magnesium stearate. HSDSC in stepwise isothermal mode was used as a potential tool for detecting excipient incompatibilities.

Incompatibilities of Aspirin with magnesium stearate at concentrations as low as 1% w/w was detected using this approach. Compacts of magnesium stearate and aspirin showed more pronounced thermal events as compared to the powder mixes [69]. As shown in Fig 3 there was no deviation from baseline during each isothermal step after achieving thermal equilibrium for Aspirin and Lactose mixture. It was concluded as absence of incompatibility.

While for Aspirin and Magnesium stearate mixture (Fig 4) an endothermic signal has indicated presence of incompatibility.

X-ray powder diffraction

This analytical tool is widely used for phase analysis and polymorph screening, crystallinity determination, crystallography and crystal structure determination, compatibility studies, manufacturing and production, stability studies, process control and for control of ingredients.

The nondestructive nature of XRPD makes it an ideal tool for systematic drug–excipient compatibility studies in preformulation [70]. It explores the real-life properties of a sample without the need to dissolve, digest, or destroy it in order to obtain essential information. Analysis of final dosage in solid form, hygroscopic materials, emulsions, suspensions, and gels can be done. Detection of crystalline impurities down to 0.05% is possible. It is the primary tool for characterizing the crystalline and amorphous materials. X-ray diffraction patterns of the mixture, prepared at room temperature, when compared with those of its individual components can show appearance of new lines and disappearance of some of the lines present in the individual components which can be interpreted as a sign of incompatibility.

Vibrational spectroscopy (IR and Raman Spectroscopy): Common techniques used to characterize drugs and excipients are infrared (IR) and Raman spectroscopy, which are sensitive to the structure, conformation and environment of organic compounds. Qualitative as well as quantitative analysis can be performed with both techniques.

IR spectroscopy is based on the conversion of IR radiation into molecular vibrations. For a vibration to be IR active, it must involve a change in molecular dipole. Whereas IR has been traditionally used as an aid in structure elucidation, vibrational changes also serve as probes of intermolecular interactions in solid materials.

Presence of drug excipient interaction can be confirmed by appearance of a new IR absorption band, characteristic of the complex or salt formation, disappearance of band, Shift of characteristic band, broadening of band, alterations in intensity [71]. Use of IR in predicting these interactions has been reviewed by G.N. Kalinkova [72].

An IR spectrum represents a fingerprint of a sample with absorption peaks which correspond to the frequencies of vibrations between the bonds of the atoms constructing the material. Since each material is a unique combination of atoms, no two compounds may produce the same IR spectrum. Drug–polymer interactions in the solid state can be revealed using FT-IR by examination of wavelength shifts in the characteristic peak positions of either the drug or the polymer. Regions of the spectra where the peaks do not overlap are potentially useful [34]. Therefore, IR spectroscopy can be used to qualitatively identify different materials. FTIR can identify the chemical structure of a molecule by measuring the absorbance of light at different frequencies. The absorbance is proportional to the concentration of the chemical species active at the selected frequency.

Combination of vibrational spectroscopy and chemometrics was used to investigate excipient-induced disproportionation of the calcium salt of atorvastatin [73] and for Thiaminchloride hydrochloride, Nicotinamide and Acetylsalicylic acid [74].The Raman and IR spectral profiles of atorvastatin calcium trihydrate and atorvastatin free acid were monitored at 1712 cm^{-1} in the IR spectrum which was indicative of the presence of a free carboxylic acid group.

Incompatibility of β-lapachone with dicalcium phosphate dehydrate as shown in Fig 5 was demonstrated by measuring the change in the bands corresponding to the functional groups of the drug especially in thermally stressed samples [75].

Simultaneous DSC–FTIR microspectroscopic technique

In the early 1950s, the concept and first successful applications of IR spectroscopy coupling with optical microscopy had been respectively introduced by Gore and the research groups of Blout. This combination allows analysis of small particles down to micronized scale and even detection of molecular changes. The sample was illuminated by focusing

the light and the transmitted or reflected light was delivered to the detector. This has resulted in the modern development and application of advanced FTIR microspectroscopy.

DSC–FTIR microspectroscopy simulates the accelerated stability test, and simultaneously detects the decomposed products in real time. A DSC is frequently used to provide information of the thermal properties of the materials but the main chemical functional characterizations present in the materials is generally determined by FTIR spectroscopy. DSC–FTIR technique gives simultaneous thermodynamic and spectroscopic information about a solid or liquid sample undergoing thermal modification. DSC measures the exothermic and endothermic responses of the samples, while the FTIR analysis observes their changes in chemical and physical composition at the same time. FTIR can clearly provide qualitative information that complements the heat flow changes measured by DSC. Simultaneous DSC and FTIR experiments have generally involved the use of a miniature DSC positioned under the objective of an infrared spectrometer coupled to a microscope. The DSC cell is mounted on a microscope stage [30].

FT-Raman spectroscopy

Raman spectroscopy is based on the inelastic scattering of laser radiation with loss of vibrational energy by a sample. A vibrational mode is Raman active when there is a change in the polarizability during the vibration.

Fourier Transform – Raman Spectroscopy (FT-Raman) is an important complementary tool for the solid state characterization of pharmaceutical solids and for the identification of the chemical structures. Spectroscopic investigations deliver chemical and physical information and combine high speed of analysis and the non-invasive measurements with high selectivity and sensitivity.

The combined use of Raman chemical imaging and Multivariate curve resolution technique was effectively used in detailed characterization of interactions between a drug and different types of cyclodextrins [76].

Metoprolol tartrate and Eudragit mixtures were extruded and monitored in-line in the die using Raman spectroscopy [77]. The Metoprolol tartrate Raman peaks in the solid solution broadened compared to the corresponding solid dispersion peaks, indicating the presence of amorphous drug. Peak shifts appeared in the spectra of the solid dispersion and solid solution compared to the physical mixtures indicated interactions between Eudragit and drug which was interpreted as hydrogen bonding.

Diffuse Reflectance Spectroscopy (DRS)

When radiation is made incident on the sample, portion of incident radiation flux penetrates into the interior of the solid sample. Return of some portion of radiation from the surface of sample following partial absorption and multiple scattering at boundary of individual sample particles is measured. This method detects the decomposed products, along with physical and chemical adsorption of excipients on to drug and vice versa. A shift in the Diffuse Reflectance Spectrum of the drug due to the presence of excipients indicates the physical adsorption. Where as the appearance of the new peak indicates chemisorption or formation of the degradation products. DRS is a more useful than HPLC assay to detect the surface discoloration due to oxidation or reduction with the excipient.

Nuclear Magnetic Resonance (NMR)

NMR spectroscopy of solutions is commonly used for structure elucidation as it determines atomic environments based on the different resonance frequencies exhibited by nuclei in a strong magnetic field. Various NMR techniques including two-dimentional NMR, solid-state NMR measurements are extremely useful for characterizing the crystal forms of pharmaceutical solids.

Drug excipient binding constant can be determined for complexation reaction. The determination is usually based on measurement of chemical shift of protons that are closely associated with excipient. Chemical shift, spin coupling and relaxation times are affected by short range interactions encountered [78].

NMR has been used in identification of esters as reaction products between citric acid and 5-aminosalicylic acid. It is also useful to determine the solubility of compounds in various *in vivo* formulations [79].

Intact tablets can be studied using solid state NMR (SSNMR). The tablet may be broken into pieces for ease of packing into the rotor. It is also possible to use SSNMR for the analysis of inclusion complexes, particularly to determine if there is any sort of interaction occurring between the API and the host molecules. It is also possible to look at very small quantities of individual components of a system by isotopically labeling specific species. If a drug is ^{13}C labeled, the signal from the labeled carbon will be approximately 90 times greater than that of a natural abundance signal. Hence interactions that might occur between drugs and excipients, even at low drug loadings can be followed. Complexation of a drug with cyclodextrin can be studied by NMR. In the absence of a guest in the cavity of cyclodextrin, it assumes a

less symmetrical conformation. After inclusion of a guest, it adopts a symmetrical conformation with each glucose of cyclodextrin unit in a similar environment giving single peak for each glucose carbon [80].

The increased line widths of the resonance lines when compared to pure drug suggest the presence of a drug in a more amorphous (less ordered) environment, which suggests the formation of a true inclusion complex.

NMR is inherently a quantitative technique, with the observed signal corresponding directly to the relative number of like nuclei in the sample. Quantitation of drug is also possible by careful optimization of the experimental conditions and use of calibration curves.

Solid state NMR is useful for the study of the molecular mobility of solids. Understanding the mobility of groups in solids can lead to insight into the mobility of molecules in solution, the forces responsible for conformational interconversions, and the factors responsible for solid state reactions. Solid state degradations of pharmaceuticals are often related to molecular mobility.

SSNMR has been used to study reaction of (+)- and (±)- ibuprofen during reaction with MgO. Ibuprofen reacts with magnesium oxide resulting in formation of magnesium diibuprofenate. [15]. Solid-state NMR was proved to be the best method for studying these reactions which was evidenced from the growth of the new carbonyl resonance at 190 ppm. Chiral (+)-crystals of ibuprofen react significantly faster than the racemic crystals.

Interaction of Salicylic acid and theophylline with chitosan was studied by solid-state ^{13}C NMR spectroscopy. It has demonstrated the drug–polymer interaction between salicylic acid and chitosan, resulting in salicylate formation at an amino group and absence of interaction between theophylline and chitosan films [81].

The ^{1}H is an excellent tool which was used to study inclusion phenomena of paeonol with β-CD. It showed that the aromatic ring of the guest molecule insert itself into the torus of β-CD from the narrow side of the cavity. The induced shift which is the difference in chemical shifts in the presence and absence of the other reactants was measured. Due to significant changes in microenvironment between the free and bound states, chemical shift variation occurs. The protons of paeonol which were located inside the cavity, and on the cavity rim at the narrow end of β-CD were shifted upfield. The upfield shifts was an evidence of the existence of a hydrophobic interaction between the guest molecule and the interior of the host cavity. It occurs due to replacement of water molecules by the hydrophobic aromatic benzene ring of drug molecule inside the cavity [82].

The amine salt interaction between the carboxyl group of the acid polymers and N-atom of erythromycin was studied by the NMR technique. Shifting in peak of ^{1}H NMR spectrum from at 2.23 ppm in pure erythromycin powder to a region of 2.35 ppm in erythromycin-shellac mixture was observed. This peak shifting to the higher ppm value reflected the protonation of amine group of erythromycin molecule by the carboxylic acid groups of polymers [83].

Chromatography

Thin Layer Chromatography (TLC)

TLC is generally used as confirmative test of compatibility after performing DSC. Solution of drug, excipient and drug: excipient mixture are prepared and spotted on the TLC plate. The plate is then developed in suitable mobile phase.

Any change in the chromatograph such as the appearance of a new spot or a change in the Rf values of the components is indicative of an interaction [84].The technique may be useful in quantification if deemed necessary. If significant interaction is noticed at elevated temperatures, evidence must be obtained by examining mixtures stored at lower temperatures for longer durations.

Evidence of degradation is unequivocal by TLC. The spots corresponding to degradation products can be isolated for possible identification.

A thin-layer chromatographic assay for the determination of rifampicin and its degradation components in drug-excipient interaction was studied by K.C.Jindat et.al. [85].

High Pressure Liquid Chromatography (HPLC)

It is one of the most widely used methods for detecting drug excipients compatibility. It separates degradation products from drug due to its ability to discriminate them based on polarity which is related to chemical structures. Any chemical interaction is indicated in the chromatogram form number of peaks. Decrease in peak area of a drug or any additional peak other than API is an indication of instability. The ability to use of various types of detectors UV, MS, Light scattering, flourescence etc. imparts the flexibility and sensitivity to the technique. A fully integrated automated DECCAS system was developed by V. H.Thomas et.al. for complete on-line performance testing of drug–excipient mixtures [86]. Mixture were weighed, blended and subjected to accelerated stress stability for up to 1 month, followed by sample extraction and HPLC analysis. The overall design of the platform was capable of accurate powder dispensing, accelerated stress stability, sample extraction and HPLC data generation, all in a 96- well block plate format.

Niclosamide compatibility with numerous excipients was studied by HPLC and DSC [87].

Using HPLC–SPE–NMR, the analytes are separated from the HPLC mobile phase by means of post-column solid-phase extraction and then submitted, in an automated fashion, to NMR measurements in a deuterated solvent. The structures of formed products can be elucidated. The reaction between 5-aminosalicylic acid and citric acid during storage was studied using this technique. It has resulted in formation of an ester and an amide [77].

The reactivity between cetirizine and sorbitol or glycerol has been studied to verify acylation reaction between a carboxylic acid and a polyalcohol [88]. The reaction products between cetirizine and the polyols have been identified by mass spectrometry and the kinetics of the acylation reaction has also been studied by liquid chromatography–mass spectrometry (HPLC–MS). The Multiple Reaction Monitoring chromatogram has been used in characterising the peak with molecular mass corresponding to an acyclovir–lactose Maillard reaction product. The incompatibility of acyclovir with lactose was successfully evaluated using a combination of thermal methods and LC–MS/MS [31].

The compatibility of rabeprazole and excipients was assessed by spectrocolorimeter and HPLC. The color change values of rabeprazole-excipient mixtures were measured using a spectrocolorimeter [89].

Recently stability indicating HPLC method was emphasized in order to better characterize the API-excipient interaction by providing not only the qualitative but also quantitative results for test substance and related degradation products. Results can be reported as potency or concentration of parent peak, also all amount of unknown peaks can be determined. If adequate forced degradation studies are performed in the early preformulation stage, the identification of early degradation products that might arise due to excipient compatibility studies might have been already determined [90].

Conclusion

There are many stability issues between drug and excipient which a preformulation scientist should be aware of. A careful consideration should be given presence of chemically interacting groups in drug and excipients. Also complexities of chemical and physical interactions, presence of a residual solvents or impurities in excipients, degradation of excipients should be investigated. Even at low levels these impurities can initiate degradation of drug. Degradation products formed by drug–excipient interactions pose questions on safety a formulation. Such awareness

may help to anticipate undesirable interactions and avoid their occurrence. A judicious choice of excipients and its quality will exclude or limit residues promoting degradation.

Many sophisticated analytical techniques are emerging to detect the drug excipient interaction and quantitate reaction products at low level. The high throughput approach using 96 wells can be used for initial rapid screening of excipients. The most commonly used analytical techniques for compatibility testing are thermal methods although less predictive due to speed and unrealistic experimental conditions. Conditions during thermal stress like presence of water, extent of contact between drug and excipient, their ratio may modify the results and should be clearly stated. Although thermal method is a potential tool for these studies, interactions observed at elevated temperatures should be cautiously interpreted because they may not always be relevant at ambient conditions. Still there are many examples where the data of thermal method was found to relevant with long term stability under isothermal stress testing. Thermal techniques reveal no information concerning the cause or nature of any incompatibility.

Nonthermal methods like NMR, IR can provided some insight into the reaction mechanisms by allowing the assignment of the bands in the spectra. Chromatography also gives indication of amount of degradation and number of degradation products. IST involves storage of drug–excipient blends with or without moisture at high temperature for a specific period of time to accelerate interactions. Still these methods are time consuming and less widely used.

Early detection of incompatibilities is still a persistent challenge to the pharmaceutical formulation development. But the usefulness of existing methods is undoubtful as a predictive tool in identifying most of the drug excipient interactions. Thus the obtained data after this study can be used as rational for the optimization of the stable and effective formulation.

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