WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 2, 347-366. Review Article ISSN 2277– 7105

APPROACHES OF DRUG-EXCIPIENTS INTERACTION IN PHARMACEUTICAL DRUG PRODUCT FORMULATION

Shiva Kant Thakur[1]*, Rahul Pal[2], Prachi Pandey[3], Arun Singh[4], Arsh Chanana[5], Ravindra Pal Singh[6]

[1,2,3,5,6]Department of Pharmaceutics, NIMS Institute of Pharmacy, NIMS University, Jaipur, Rajasthan India.

[4]Department of Pharmacy, Mahatma Jyotiba Phule Rohilkhand University, Bareilly, Utter Pradesh, India.

Article Received on
23 Nov. 2022,

Revised on 14 Dec. 2022,
Accepted on 04 Jan. 2023

DOI: 10.20959/wjpr20232-26923

***Corresponding Author**
Shiva Kant Thakur
Department of Pharmaceutics, NIMS Institute of Pharmacy, NIMS University, Jaipur, Rajasthan India.

ABSTRACT

Drug excipients interaction is essential for the formulation of the formulation of the pharmaceutical product which work as the preformulating factor of formulation. Excipients are the general term used to describe these non-therapeutic compounds. Excipients can interact with the active ingredient or with other substances in the environment; they are not inert substances/ingredients added to drugs to aid in production, administration, or absorption. As a result, a number of analytical techniques can be used to analyses the interaction between a drug and excipients, consisting thermal methods like TG, DTA, DSC, Thermomicroscopy, optical microscopy, XRD, IR, NMR, isothermal stress testing, isothermal microcalorimetry, isothermal titration calorimetry, high sensitivity DSC, and chromatography. Another more techniques although many analytical methods can be applied for detection working as hyphenated techniques like DSC-GC, DSC–FTIR are more advance methods. This Review discussed the basic drug-excipients interaction, Understanding the chemical and physical nature of excipients, different kinds of existing excipients, the classification systems in which we will be reviewed also however, here mainly named as including chemical, physical, and biopharmaceutical will be defined and subclassified accordingly. The three primary types of physical interactions are complexation, adsorption, and solid dispersions. Hydrolysis, oxidation, the Maillard process, isomerization, and polymerization are the most common chemical reactions, and Biopharmaceutical interactions occur after drug

administration and mainly affect the pharmacokinetics of the drugs. The study of drug-excipients analyzed by the involving the different analytical methods like thermal methods, Chromatography and FTIR.

KEYWORDS: Pharmaceutical Drug-Excipients, Drug excipient Interaction, Drug- excipient incompatibility, Advance Techniques.

1. INTRODUCTION

The API moieties cannot be administrated as such, so they are modified to different dosage forms for the reasons of patient compliance, dose accuracy and consistency, improving bioavailability, aesthetics and reduction of side effects commonly they modified with the help some excipients especially for the improvement application. Excipients are defined as "***The components of a formulation other than the active ingredien***t".[1] International Pharmaceutical Excipients council of America (***IPEC***) has defined the excipients as any substance other than the active drug or prodrug, which has been appropriately evaluated for safety and is included in a drug formulation system to aid processing of the system during manufacture. Excipients are the non-active ingredients, they are essential in the successful production of acceptable dosage forms such as tablets, powders, parenteral, semi solids and liquid orals, always play a very important role in the designing of different pharmaceutical dosage forms, without the excipient's drugs cannot be administered in pure form. Though there are number of excipients available in the system although the selection of excipients with the drug application may tough. Broadly, most of the new drugs are poorly soluble in water thereby having dissolution related bioavailability problems. So, various technologies such as lipid drug delivery systems, solid dispersions and other chemical also involves.[2]

"Drug-Excipient Interaction (***DEI***)", "As interaction, desirable or undesirable, which will occur between active pharmaceutical ingredients (API) and non-drug substances (additives, excipients, impurities) during processing (Preformualtion, formulation, manufacturing, packaging), after processing (shelf storage) and/or after administration of the pharmaceutical dosage form (drug product) to the patient delivery at period of time, which may lead to changes in drug and/or drug product properties".

According to this definition, DEI can be divided into two main groups

a). Desirable drug-interactions: Generally, those interaction's which can be primarily planned, designed, controlled and utilized to modify certain property or properties of the drug

or pharmaceutical product to the desired direction or purpose. This includes color, odor, and taste-masking by coating, increase or decrease dissolution rate, enhancement of absorption rate etc. considering in the desirable interaction primarily.

b). Undesirable drug-interactions: Other interaction/incompatibilities which include physical, chemical, or biopharmaceutical interaction that will take place during the formulation, storage, or after administration of the drug product to the patients resulting in changes in physical, chemical, microbiological, or therapeutic properties of the dosage form.[3]

Interaction/Incompatibilities in pharmaceutical products are undesired physical, chemical or biopharmaceutical processes which take place during preparation, storage or administration resulting in decomposition of drags and a failure to improve the patient's condition. Incompatibilities may take place in a manner of ***drug-drug interactions*** and ***additive-additive interactions***. Chemical interaction can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect; reaction products may compromise safety or tolerance. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration.[4]

2. MECHANISM OF DRUG-EXCIPIENTS INTERACTION

More of the mechanism of the drug-excipients interaction including physical, chemical and biopharmaceutical which having lots of data in their description.[5] The mechanism of drug-interaction is commonly discussed in the below-

Table No. 01: List of Interaction with their Nature.

Physical Drug-Excipients Interaction	Chemical Drug-Excipients Interaction	Biopharmaceutical Drug-Excipients Interaction
• Complexation • Adsorption • Solid dispersion	• Hydrolysis • Oxidation • Millard reaction **Other Chemical interaction:** • Polymerization • Isomerization • Photolysis	• Pharmacokinetics interaction

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines.[6] Lots of interaction which are important for formulation of pharmaceutical dosage form product discussed in (**Table 01**). Briefly data mentioned in the above description.

2.1 PHYSICAL DRUG INTERACTION

Physical drug-interactions are frequently used in the manufacturing or formulation of dosage forms for example, to modify drug dissolution. Many of such interactions can be categorized as noncovalent. Physical interaction may include van der Waals attractions, hydrogen-bonding and electrostatic interactions (known as ionic bonding).[7] All including interactions involve an electrical charge due to temporary dipoles or ion formation as physical changes. Physical interaction between two or more pharmaceutical substance linkage by hydrogen bonding can improve the physicochemical properties.

Table 02: List of Physical Drug-Interaction Example.

Interaction	Beneficial Effect Example	Detrimental Effect Example
Complexation	Cyclodextrin	Tetracycline Formulation of chlorpromazine with Tween 80 and SLS
Adsorption	Formulation of the indomethacin (NSAID's) using Kaolin as adsorbent	Formation of cetyl pyridinium chloride tablet suing magnesium stearate as a lubricant.
Solid dispersion	Formulation of piroxicam, norfloxacin and ibuprofen using PEG of different grades	Interaction between povidone and stearic acid in a capsule.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site.

Physical interactions may include but are not limited to ***complexation, adsorption, and solid dispersions***. A short preview of the physical drug-interaction shown in the (**Table 02**), before the complete description. All parts of physical interaction discussed briefly in below section-

2.1.1 Complexation: Complexation is an extensively used technique in the pharmaceutical field to improve solubility of several pharmaceutical ingredients, and subsequently the bioavailability of poorly water-soluble drugs. Complexation with the help of complexing agents interact, usually not reversibly, with a drug to form a complex. When in the complex, the drug is not free to dissolve, because it must first dissociate from the complex. In many instances, the drug complex will dissociate upon coming into contact with gastrointestinal fluids, releasing the drug substance, which can then be absorbed across the gastrointestinal membranes.[8]

Explain as example complexing agents such as **Cyclodextrins** and their derivatives (**Octakis)** mostly used in pharmaceutical formulation due to their suitable physicochemical and biological properties. Many of other drug properties were studied with using cyclodextrins such as solubility, permeability, and stability. Drug complexation with cyclodextrins was given in many drug delivery systems such as ophthalmic, Nasal, rectal, transdermal, and oral.[9]

2.1.2 Adsorption: The process of atoms, ions, or molecules from a substance adhering to the surface of the adsorbent is known as adsorption. Adsorption is a surface-based process where a film of adsorbate is created on the surface of adsorbent while absorption involves the entire volume of the absorbing studied the adsorption such of propranolol, cellulose acetate to be a superior adsorbent surface than chitosan when using HCl. Drug particle size can be decreased and the amount of drug surface area accessible to the dissolving medium can be increased by the adsorption of drug molecules onto the surface of excipients.[10] Ziprasidone solid self-

micro emulsifying drug delivery system (SMEDDS) was formulated by first making liquid SMEDDS using Oleic acid, Tween 80, and methanol as a penetrant, surfactant.

2.1.3 Solid Dispersion: A solid dispersion is a mixture of one or more active substances dispersed in a solvent, melting process, or other mechanism into a solid state. Today, glass solutions of poorly soluble chemicals using amorphous carriers with high glass transition temperatures are most frequently associated with the phrase "***solid dispersion***." Based on how the solute molecules are distributed inside the carrier matrix, solid dispersions have been categorized as eutectic mixtures, solid solutions, and microfine crystalline dispersions.[11]

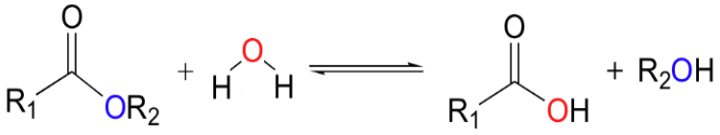
2.2 CHEMICAL DRUG-INTERACTION

Chemical interactions are defined as the involvement of particular drug with the numbers of chemical components, alcohol substances, tobacco and also the environmental chemical presence. Depending on the chemical structure of the API molecule and the reaction mechanism, the height of this energy barrier can vary widely, and thus, influences how fast an API degrades.[14] chemical drug-interaction mainly includes hydrolysis, oxidation, Millard reaction, photolysis, physical transformation, polymerization and isomerization will be discussed in the following subsections of chemical drug-interaction.[12] Some drugs produce effects without altering cellular function and without binding to a receptor, mostly the antacids drug medicament decrease gastric acidity (GI) through simple chemical reactions; antacids are bases that chemically interact with acids to produce neutral salts into the stomach. Bile acids are mostly bound in the digestive tract by cholestyramine, a bile acid sequestrant.

Chemical drug interaction is consisting numbers of reaction involving such as ***hydrolysis, oxidation, Millard reaction, polymerization, photolysis*** *and* ***isomerization.*** The data comes under their explained in the next below section-

2.2.1 Hydrolysis

The most susceptible drugs are those containing carbonyl groups like esters, amides lactones, etc. with a good leaving group. The parent medication is divided into two halves and added to the process along with water molecules.



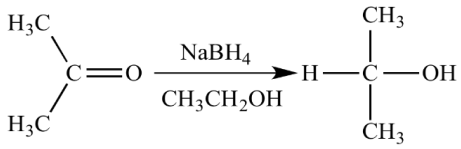
Excipients may facilitate the process directly, by changing the aqueous environment, or by influencing other factors like pH, ionic strength, or dielectric constant. Another important factor is water activity, as related to excipient moisture contents where the hydrolysis rate depends on the water activity around the drug.

As an example of the influence of water availability on hydrolysis rates is aspirin compacts containing dibasic calcium phosphate dihydrate degrade approximately 10 times faster than formulations containing lactose and two-fold faster than formulations containing microcrystalline cellulose.[14]

Other examples of drugs which gave hydrolysis reaction affected by excipients include methylphenidate with glycerin in oral solutions, fosinopril sodium with Magnesium Stearate and nitrazepam with hygroscopic excipients.

2.2.2 Oxidation

Oxidation described as increase in the number of electronegative atoms in a molecule. These electronegative heteroatoms are typically oxygen or halogens in organic systems.[15]



Free radical production can result from oxidation reactions that are catalyzed by oxygen, heavy metal ions, and light (induction). Free radicals react with oxygen to form per oxy radicals which in turn interact with the oxidizable compound (propagation). Aldehydes, alcohols, alkaloids, and unsaturated fats are of most susceptible to oxidation.[16]

Excipients can also be involved in generating mobile oxidative species such as peroxyl radicals, superoxide, and hydroxyl radicals. However, a lot of excipients also contain contaminants such reducing sugars, peroxides, aldehydes, organic acids, and aldehydes. Because of how reactive these contaminants are, even minute amounts could result in drug deterioration. To stabilize medications against oxidation, excipients (generally speaking, and antioxidants specifically) can be useful.[17]

2.2.3 Maillard reaction

This reaction is so named after Louis Maillard, to form colored pigments from sugars and amines. Primary amines in the formulation with carbonyl compounds, basically reducing

sugars, undergo Maillard reaction, to form Schiff base ($R_2C=NR'$).[18] The outbreak due to phenytoin intoxication was attributed to its interaction with excipients. When CaSO4 was used as a diluent, phenytoin absorption was decreased due to the formation of calcium salt and precipitate. However, when CaSO4 was replaced in the formulation by lactose, the amount of phenytoin absorbed was much higher, resulting in the observed intoxication.[19]

Phenytoin sodium also interacted with lactose through Maillard reaction in an aqueous. Levofloxacin and methyldopa were also found incompatible with lactose by the Maillard reaction mechanism.[20]

2.2.4 Other Chemical Interactions

This may include isomerization, photolysis, and polymerization. ***Isomerization*** involves the conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties116. For example, the activity of Levo(L) form of adrenaline is 15-20 times greater than for the Dextrose (D) form. Another example where optical isomerization of an experimental compound was observed at an asymmetric carbon atom that linked the pyrrolobenzodiazepine ring to a heterocyclic ring through an amide bond. This was in a soft gelatin capsule dosage form which contained a mixture of PEG 400 and glycerol.[21] The degradation of the active was accelerated by the formic acid in the formulation. This degradation can be decelerated by the addition of cyclodextrin as an inclusion complex.

Photolysis (called photodissociation and photodecomposition) is a chemical reaction in which an inorganic chemical (or an organic chemical) is broken down by photons and is the interaction of one or more photons with one target molecule. ***Polymerization*** reactions occur as a result of intermolecular reactions lead to dimeric and higher molecular weight species.

Concentrated solutions of ampicillin, aminopenicillin, progressively form dimer, trimer, and ultimately polymeric degradation products. Some organoleptic agents also may undergo polymerization degradation. An example is the natural color Betalains which is susceptible to color fading or browning due to subsequent polymerization.[22]

2.3 BIOPHARMACEUTICAL DRUG-INTERACTIONS

Drug-drug interaction is commonly classified into two broadly area one is **pharmacodynamics** and another on is **pharmacokinetics** under the class of

biopharmaceutical interaction. Pharmacodynamic interaction is defined as which occurring drug have either additive effect in which case the overall effect is increased or opposing effects in which case the overall effect is decreased or even cancel out, another pharmacokinetics interaction described as which altering concentration when on drug change the systemic concentration of another drug altering ***how much*** and for ***how long***, it is present at the site of action. A type of interaction which are indicate after administration of the medication into the patients (human) body.

Biopharmaceutics Interaction within the body is between medicine and body fluids which influence the rate of absorption. Biopharmaceutical drug–excipient interactions have the potential to affect many physiological processes and factors, including pH of the microenvironment, protein binding, GI transit time, stability in the GI tract, effects on gut flora after drug interaction into the body with the fluid. Ultimately the potential outcome of biopharmaceutical drug-interactions altering the bioavailability of the drug within the given period of time. It explained as an example taken increasing gastric pH by antacids affecting enteric coat integrity, the interaction of tetracycline with calcium ions forming unabsorbable complex, and increasing GI motility by sorbitol and glycols which affect drug transit time and absorption. The bioavailability of a medication in a biopharmaceutical drug-interaction varies based on a variety of factors, including the drug's strength and dose, therapeutic window, site of absorption, rate-limiting factor in drug absorption efflux, complexation, or degradation at the site of absorption.[20] Pharmacokinetic interactions are frequently taken into account based on an understanding of each medicine and are discovered by monitoring changes in serum drug concentrations as well as the clinical symptoms of the patient. In a recent study, machine learning techniques were used to examine the effects of vitamin A palmitate and abietic acid as inhibitors of P glycoprotein and uridine diphosphate-glucuronosyl-transferase-2B7 (UGT2B7), respectively.[23]

In overall 20% of medications that are FDA-approved have their pharmacokinetics affected in some way by the proteins P-gp and UGT2B7. Ranitidine and colchicine are two P-gp substrates that have been discovered to be more permeable when vitamin A palmitate is present. Further for the detection or analysis of drug-excipients interaction in the formulation as per guide different software used in the detection. They are work as Preformualtion factors in the formulation after that drug should manufactured with good quantity.[24] Here the

(**Table 02**) described the software, in above description. They include the major role DSC for the detection or analysis and another many more discussed-

3. RECENT APPROCHES IN DRUG EXCIPIENTS INTETACTION

Drug excipients are analyzed by the using of the different types of analytical methods as well as the techniques, which may include thermal analysis (TG, DTA, DSC, TM AND ITC), XRD and chromatography techniques for the detection or analyzed the drug excipients incompatibility using their application. The methods or analytical approaches discussed in (**Table 03**) for the basic idea to interaction studied.

Table 03: Techniques involve in Drug-Excipients Interaction.

Drug Excipients Interaction Approaches		
Thermal Analysis	**X-Ray Powder Diffraction**	**Chromatography**
Differential Scanning Calorimetry (DSC)*, Thermogravimetry (TG) Differential Thermal Analysis (DTA), Microthermal Analysis, TG/DTA–GC/MS (Hyphenated method), **Thermomicroscopy (TM),** Optical Microscopy (OM), High sensitivity DSC (HSDSC), Infrared spectrophotometric study (IR)	Vibration spectroscopy Fourier Transform Infrared Spectroscopy (**FT-IR**) Raman Spectroscopy. Diffuse Reflectance Spectroscopy (**DRS**)	Thin Layer Chromatography (**TLC**) High Pressure Liquid Chromatography (**HPLC)**

Thermal analysis is an important parameter or method for the detection work as a tool in the detection of drug excipients interaction.

Differential Scanning Calorimetry (DSC) is one of the well-developed techniques used in detection of incompatibilities in drug/ drug and drug/excipient interactions comes under in the thermal analysis.[26]

Herby numbers of analytical techniques used to characterize drug-excipient interaction with the proper uses and utility of data mentioned in the (***Table 04***) in proper manner. Complete data describes as follow-

Table 04: Investigational Techniques and Utility Data.

Sr. No	**Investigational Techniques**	**Measurement**	**Utility of data**
01.	DSC	Energy is absorbed or release by a sample as it is heated, cooled or held at a constant temperature.	Physicochemical compatibility of drug and excipients.

02.	TGA	Weight changes by a sample as it is heated, cooled or held at a constant temperature.	Physicochemical compatibility of drug and excipients
03.	Chromatographic Analysis	Chemical interaction of the sample with the stationary phase and the mobile phase.	Excipients, drug product purity, excipients-drug a substance chemical compatibility
04.	X-Ray Diffraction	Scattering of x-ray radiation by a solid sample	Polymorph characterization
05.	Microscopy	Magnified appearance of the sample	Particle size, morphology

3.1 THERMAL ANALYSIS

There are several thermal methods of analysis may be defined as those techniques in which changes in physical and or chemical properties of a substance are measured as a function of temperature. Thermal analysis used to quantitative and qualitative analysis of samples. Sample may be identified and characterized by qualitative investigation of their thermal behavior. Quantitative results obtained from changes in weight and enthalpy as the sample is heated. The temperature of phase changes and reaction as well as the sample is heated. The temperature of phase changes, reactions and heat of reaction are used to determine the purity of material.

The different application of different software used in detection with many of the property measured, which apparatus used for the analysis and also which type of graph will plotted. These all data covered in the (**Table 05**) simultaneously and concise manner for the acquiring the knowledge.

Table No. 05 List of Analysis and Apparatus with Graph Between.

Sr. No.	Analysis Tool Name	Property Measured	Apparatus Involves	Graph Plotted
01.	Thermogravimetric analysis	Change in weight (mass)	Thermo balance	Mass vs. Temp.
02.	Derivative thermogravimetric analysis	Rate of exchange of weight (dm/dt)	Thermo balance	dm/dt vs temp.
03.	Differential thermal analysis or DSC	Heat absorbed or evolved (Delta T) or heat difference	DTA apparatus	Delta T vs Temp.

In the TGA method, the sample's mass gain or loss is calculated as a function of temperature or time. DTG refers to the curve that more clearly illustrates the degradation events that may overlap in the TGA, the first derivative of the TGA as a function of time or temperature. In

all of them the DSC is an important tool which showed incompatibility between the drug and all excipients selected by observing the formation of new events not present in the isolated thermograms.[25]

3.2 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The technique was developed by E.S. Watson and M.J. O'Neill in 1962, and the Pittsburgh Conference in 1963 was the first time it was made commercially available. A DSC is a device that directly detects energy and permits precise measurements of heat capacity. Excipients are inert parts that may significantly affect how well active pharmaceutical compounds perform when included in dosage forms, despite the fact that they are inert parts. The magnitude of this effect will depend upon physicochemical properties of drugs as well as quantity and quality of excipients used, although often regarded as 'inert', excipient can in fact readily interact with drugs. Therefore, a crucial component of every Preformualtion study is the assessment of drug-excipient compatibility. Isothermal stress testing of binary drug-excipient mixtures and thermal analysis utilizing either DSC or differential thermal analysis are the two regularly used compatibility screening procedures (DTA). A thermoanalytical method called differential scanning calorimetry (DSC) measures the variation in the amount of heat needed to raise a given temperature.[26]

Differential scanning calorimetry (DSC) is a very powerful analytical tool for the identification of various physical properties of drug excipient and thermal transitions of polymeric materials. Differential scanning calorimetry (DSC) is one of the well-developed techniques used in detection of incompatibilities of various interaction of drug and excipient like drug/ drug and drug/excipient interactions. In many ways, differential thermal analysis (DTA) and differential scanning calorimetry (DSC) are similar, and the same range of thermal events can be seen using analogous data. A thermal analytical technique known as differential scanning calorimetry, or DSC, measures the difference between the amount of heat needed to raise the temperature of a sample and a reference as a function of temperature. Throughout the experiment, the sample and reference are both kept at temperatures that are virtually identical. The sample holder temperature should rise linearly as a function of time according to the temperature programmed typically used for a DSC study.

Types of DSC

- Power compensated DSC, keeps power supply constant.
- Heat flux DSC, keeps heat flux constant.

DSC Curves: The result of a DSC experiment is a curve of heat flux versus temperature or versus time. There are two different conventions: exothermic reactions in the sample shown with a positive or negative peak, depending on the kind of technology used in the experiment. This curve can be used to calculate enthalpies of transitions. This is done by integrating the peak corresponding to a given transition. It can be shown that the enthalpy of transition can be expressed using the following equation:

$$\Delta H = KA$$

Where ΔH is the area under the curve, K is the calorimetric constant, and H is the enthalpy of transition. Analysing a sample with known enthalpies of transition will help you find the calorimetric constant, which varies depending on the equipment.

Interaction Phase Detection: The glass transition temperature (Tg) of the polymer-drug mixture can be influenced by interactions between coprecipitated drugs and polymers. It was investigated how the drug affected the Tg of the drug-excipient co-precipitated blends. Due to the drug's plasticizing action on the polymer, it is possible to anticipate that the Tg of the polymer will drop in the presence of a tiny molecule.[24]

The change in glass transition temperature of the fully amorphous blends as a function of molar percentage of drug was studied by DSC. For the stability and formulation of amorphous materials, the glass transition temperature and how it varies with moisture content, related to mobility, are crucial variables. 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. 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. In recently, the miscibility of indomethacin and lacidipine with excipient to predict glass solutions formation was investigated by DSC.[18]

Drug Analysis: In the pharmaceutical and polymer sectors, DSC is frequently utilised. DSC is a useful method for polymer chemists to analyse curing processes, which enables fine-tuning of polymer properties. Exothermic cross-linking of polymer molecules during the curing process causes a positive peak to develop on the DSC curve shortly after the glass transition.

3.3 THERMOGRAVIMETRIC ANALYSIS (TGA)

A technique in which a change in the ***weight of a substance*** is recorded as function of temperature or time. (***Table. 03)*** describes each technique is listed in terms of the parameter recorded and the instrumentation involved in the drug excipients analysis.

It is a simple analytical technique that measure the amount and rate of change in the weight of material as a function of temperature or time in a controlled atmosphere. Measurements are used primarily to determine the composition of material and to predict their thermal stability at temperature up to 1000-degree C. It is the most widely used thermal method which can characterized material that exhibit weight loss or gain due to decomposition, oxidation or dehydration. As material are heated, they can lose weight from a simple process such drying or from chemical reactions that liberate gases. Such analysis relies on a high degree of precision in three measurements: ***weight, temperature and temperature change.***[22]

There are three types of thermogravimetry

a. **Isothermal or static thermogravimetry**: in this technique the sample weight is recorded as a function of time at constant temperature.
b. **Quasistatic thermogravimetry**: in this technique, the sample is heated to constant weight at each of a series of increasing temperature.
c. **Dynamic Thermogravimetry**: in this technique, the sample is heated in an environmental whose temperature is changing in predetermined manner, generally at a linear rate. Most of the studies are carried out with dynamic thermogravimetry. Therefore, generally it is referred to as thermogravimetry.

Instrumentation for Thermogravimetry analysis (TGA)

The principle of thermogravimetry is based in the simple fact the sample weight continuously as it is being heated to elevated temperature. In the market both manual as well as automatic recording balance are available but for practical reasons, the latter types is preferred. A modern thermobalance have various components as follows:

- The balance
- Sample holder
- The furnace.
- Temperature measurements
- Thermobalance, Recorder.

3.4 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. 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. The drug and Magnesium stearate after heating up to 160 0 C has not shown any morphological changes of both. But when both were heated together the sample was blackened due to degradation. These methods examine the morphology of the drug substance and can identify the kinds of physical changes that have taken place, revealing the kind of incompatibility that has taken place.[23]

3.5 DSC–FTIR MICRO SPECTROSCOPY TECHNIQUE

Gore and the research groups of Blout had, respectively, introduced the idea and the first practical uses of IR spectroscopy coupling with optical microscopy in the early 1950s. This combination makes it possible to analyses tiny particles at the micron scale and even detect 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 micro spectroscopy. DSC–FTIR micro spectroscopy 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.[23] DSC–FTIR technique gives simultaneous thermodynamic and spectroscopic information about a solid or liquid sample undergoing thermal modification. 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.[24]

3.6 X-RAY POWDER DIFFRACTION (XRPD)

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 Preformualtion. 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.[25] X ray diffraction having one of the important tools is FT-Raman Spectroscopy for the detection, which described below description-

3.7 FT-Raman Spectroscopy

The foundation of Raman spectroscopy is the inelastic scattering of laser light with vibrational energy loss 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.

Chemical and physical information is delivered through spectroscopic studies, which also combine rapid analysis, non-invasive measurements, and excellent selectivity and sensitivity. The precise characterization of interactions between a drug and several types of cyclodextrins was successfully accomplished by the combination of Raman chemical imaging and Multivariate curve resolution approach. Raman spectroscopy was used to monitor the extrusion of mixes of metoprolol tartrate and eudragit while it was happening in the die. When compared to the comparable solid dispersion peaks, the Metoprolol tartrate Raman peaks in the solid solution widened, indicating the presence of an amorphous drug. When compared to the physical mixtures, peak changes in the spectra of the solid dispersion and solid solution suggested interactions between the medication and the eudragit that were interpreted as hydrogen bonding.[25]

3.8 CHROMATOGRAPHY

3.8.1 Thin Layer Chromatography (TLC)

TLC is generally used as qualitative test of drug-excipients compatibility after performing Diffraction Scanning Calorimetry. Solution of drug, excipient and drug: excipient mixture is prepared and spotted on the TLC plate. After that, the plate is developed in an appropriate mobile phase. Any modification to the chromatograph, such as the development of a new spot

or a shift in the Rf values of the constituents, indicates the presence of an interaction. If considered required, the technique might be useful in quantification. 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 recently determination of rifampicin and its degradation components in drug-excipient interaction was studied.[25]

3.8.2 High Pressure Liquid Chromatography (HPLC)

The HPLC is one of the most widely used methods to detecting of 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, fluorescence etc. gives the method flexibility and sensitivity. V. H. Thomas et al. created a fully automated DECCAS system for comprehensive on-line performance assessment of drug-excipient mixes.

Following sample extraction and HPLC analysis, the mixture was weighed, blended, and subjected to accelerated stress stability for up to one month. In a 96-well block plate format, the platform's overall design enabled accurate powder dispensing, rapid stress stability, sample extraction, and HPLC data processing.[35] Niclosamide compatibility with numerous excipients was studied by HPLC and DSC. 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. For the purpose of confirming the acylation reaction between a carboxylic acid and a polyalcohol, the reactivity between cetirizine and sorbitol or glycerol has been investigated. By using a spectrocolorimeter and HPLC, the compatibility of rabeprazole and excipients was evaluated. Using a spectrocolorimeter, the color change values of rabeprazole-excipient mixtures were determined.[26]

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 might be presented as potency or concentration of the parent peak, as well as the total number of unidentified peaks. If sufficient forced degradation tests are carried out in the early stages of formulation, it may already be possible to identify early degradation products that could result from excipient compatibility studies.

4. CONCLUSION

There are many stability issues between drug and excipient which a Preformualtion 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. Many sophisticated analytical techniques are emerging to detect the drug excipient interaction and quantitate reaction products at low level. Thus, the obtained data after this study can be used as rational for the optimization of the stable and effective formulation. All the terms discussed above portion which covers the mechanism of drug-excipients interaction as well as the methods involving in the drug-excipients interaction carefully with the proper explain data in my review.

REFERENCES

1. Sinko PJ and Singh Y: Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences. Walter Kluer, 2011.
2. Herman Ermens, A report of IPEC, Pharmaceutical Excipients – The Past and Future, Business Briefing. *Pharmagenerics*, 2004.
3. Baldrick P. Pharmaceutical excipient development: the need for clinical guidance, *Regul Toxicol Pharmacol*, 2000; 32: 210.
4. Niguram P, Polaka SN, Rathod R, Kalia K and Kate AS: Update on compatibility assessment of empagliflozin with the selected pharmaceutical excipients employed in solid dosage forms by thermal, spectroscopic and chromatographic techniques. Drug Dev Ind Pharm., 2020; 46(2): 209-18.
5. Sinko PJ and Singh Y: Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences. Walter Kluer, 2011.

6. Michele S, Francesco L, Anna Maria F, Chiara S and Elena P: Drug-excipients compatibility studies in proniosomal formulation: A Case Study with resveratrol. J Nanosci. Nanotechnol, 2021; 21(5): 2917-21.
7. Gupta KR, Pounikar AR and Umekar MJ: Drug excipient compatibility testing protocols and charaterization: A Review. Asian J of Chemical Sciences, 2019; 6(3): 1-22.
8. Bharate SS, Bharate SB and Bajaj AN: Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. Journal of Excipients and Food Chemicals, 2016; 1(3): 11-31.
9. Rahul P, James B and Amr E: Pharmaceutical excipients and drug metabolism: A mini-review. Int J Mol Sci., 2020; 21(21): 8224.
10. Sandesh NS, Ajeet MG, PankajSG and Sapna K: Significance of pharmaceutical excipients on solid dosage form development: A Brief Review. Asian J Pharm Res., 2016; 6(3): 193-02.
11. Gupta KR, Pounikar AR and Umekar MJ: Drug excipient compatibility testing protocols and charaterization: A Review. Asian Journal of Chemical Sciences, 2019; 6(3): 1-22.
12. Fung MH, DeVault M, Kuwata KT and Suryanarayanan R: Drug-excipient interactions: Effect on molecular mobility and physical stability of ketoconazole-organic acid coamorphous systems. Mol Pharm., 2018; 15(3): 1052-61.
13. Derar MO, Yazan A and Assayed S: Drug-Excipient Interactions: An Overview on Mechanisms and Effects on Drug Stability and Bioavailability. Annals of the Romanian Society for Cell Biology, 2021; 25(4): 8402-29.
14. Gaisford S: Isothermal microcalorimetry, In Analytical Techniques in the Pharmaceutical Sciences, Springer, New York, 2016; 389-409.
15. Harding, Qi S, Hill G, Reading M and Craig DQ: The development of microthermal analysis and photothermal microspectroscopy as novel approaches to drug–excipient compatibility studies. International Journal of Pharmaceutics, 2008; 354(1-2): 149-57.
16. Brusac E, Jelicic ML, Cvetnic M, Amidzic Klaric D, Nigovic B and Mornar A: A comprehensive approach to compatibility testing using chromatographic, thermal and spectroscopic techniques: Evaluation of potential for a monolayer fixed-dose combination of 6-mercaptopurine and folic acid. Pharmaceuticals, 2021; 14(3): 274.
17. Z. Aigner, R. Heinrich, E. Sipos, G. Farkas, A. Ciurba, O. Berkesi, P. Szabó-Révész, Compatibility studies of aceclofenac with retard tablet excipients by means of thermal and FT-IR spectroscopic methods, J. Therm. Anal. Calorim, 2011; 104(1): 265-271.

18. M P. Mura, M. T. Faucci, A. Manderioli, S. Furlanetto, S. Pinzauti, Thermal Analysis as a Screening Technique in Preformulation Studies of Picotamide Solid Dosage Forms, Drug Dev Ind Pharm., 1998; 24(8): 747-756.
19. R. O. C. Filho, P. I. B. M. Franco, E. C. Conceição, M. I. G. Leles, Stability studies on nifedipine tablets using thermogravimetry and differential scanning calorimetry, J. Therm. Anal. Calorim., August, 2008; 93(2): 381-385.
20. P. Mura, M.T. Faucci, A. Manderioli, G. Bramanti, L. Ceccarelli, Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy, J. Pharm. Biomed. Anal., October, 1998; 18(1-2): 151-163.
21. F.Balestrieri, A.D. Magri, A.L.Magri, D. Marini, A. Sacchini, Application of differential scanning calorimetry to study drug excipient interaction, Themochimica. Acta., 1996; 285: 337-345.
22. J.L. Sims, J. A. Carreira, D. J. Carrier, S. R. Crabtree, L. Easton, S. A. Hancock, C. E. Simcox, A New Approach to Accelerated Drug-Excipient Compatibility Testing, Pharm. Dev. Technol., 2003; 8(2): 119–126.
23. T. Durig, A.R.Fassihi, Identification of stabilizing and destabilizing effects of excipient-drug interactions in solid dosage form design, Int. J. Pharm., 1993, 97,161-170. Tambe Vrushali Sachin*et al. International Journal of Pharmacy & Technology IJPT, July, 2014; 6(1): 6388-6417 Page 6415.
24. J. M. Woods, M. Puri, D. Doucet, T. Derrick, S. Morar-Mitrica, D. Nesta, Applications of isothermal titration calorimetry and differential scanning calorimetry in biopharmaceutical formulation development, GE Healthcare, Application Note 28-9613-26.
25. Patil, S. P. C. a. P. S., Pharmaceutical Excipients: A review. International journal of advances in pharmacy, biology and chemistry, **2012;** *1*(1): 14.
26. Gunsel, W. a. K., G, Chapter 11: Tablets. In *The Theory and Practice of Industrial Pharmacy*, Second ed.; Leon Lachman, H. A. L., Joseph L. Kanig, Ed. CBS: Philadelphia, PA, 1985.