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Drug-Excipient compatibility studies: First step for dosage form development

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Abstract
Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutical properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipient interaction like physical, chemical and biopharmaceutical. Different Thermal and Non-thermal method of analysis, Tools and software for incompatibility is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form. From review, we conclude that consequent use of thermal and non-thermal method provide data for drug- excipient interaction which can further help in selection of excipient for the development of stable dosage form.

Keywords: Drug-excipient compatibility, thermal method, non-thermal method, interaction, incompatibility

1. Introduction
A complete characterization and understanding of physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In a dosage form, an API comes in direct contact with other components (excipients) of the formulation that facilitate the administration and release of an active component as well as protect it from the environment. Although excipients are pharmacologically inert, they can interact with drugs in the dosage form to affect drug product stability in physical aspects such as organoleptic properties, dissolution slow down or chemically by causing drug degradation. Careful selection of the excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the fore front of drug product science and technology research [1, 2].
A complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype of drug development. The analytical methods into the initial steps of preformulation studies have contributed significantly to early prediction, monitoring and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation.

1.1 Incompatibility [3]
- "Inactivation of drug through either decomposition or loss of drug by its conversion to a less favourable physical or chemical form." When we mix two or more API and / or excipient with each other and if they are antagonistic and affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible.

1.2 Importance of drug excipient compatibility [5, 6]
- Stability of the dosage form can be maximized. Any physical or chemical interaction between drug and excipient can affect bioavailability and stability of drug.
- It helps to avoid the surprise problems. By performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form.
- DECS data is essential for IND (investigational new drug) submission. Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

- Determine a list of excipient that can be used in final dosage form.
- To reduce associated side effect of drug due to DECS in dosage form.
- To overcome problems associated with incorporation of multiple excipients.

1.3 Excipients [7, 8]

"Pharmaceutical excipients are substance other than pharmacologically active drug or prodrug in finished dosage form as to impart specific qualities to them.**"**

Role of excipient

- Protect, support or enhance stability of the Formulation.
- Bulk up the formulation in case of potent drug for assisting in formulation of an accurate dosage form.
- Improve patient acceptance.
- Help improve bioavailability of active drug.
- Enhance overall safety and effectiveness of the formulation during its storage and use.

2. Mode of drug decomposition [9, 10, 11]

Medicinal agents invariably have structural features that interact with receptors or facilitate metabolic handling. These predictably confer some degree of liability, making them vulnerable to degradation (and interaction with other materials). They are hydrolysis/dehydration, isomerisation/epimerization decarboxylation, rearrangement and some kinds of polymerization reactions can be generalized into a condition that has been called "thermolytic". These reactions are generally sensitive to temperature and can be accelerated by elevating the temperature under various conditions in the solid state (low and high humidity). Hydrolytic reactions, can be accelerated both by exposure to elevated temperature as and by exposure to different pH values in a broad pH range. Oxidative degradation of pharmaceuticals is generally the result of autoxidation. It is driven by the formation of radicals (via initiators such as transition metals, low levels of peroxides, or molecular oxygen). Photolytic reactions are initiated by the absorption of photons from exposure to various sources of light.

2.1. Common modes of degradation are described below-

2.1.1 Hydrolysis-Drugs with functional groups such as esters, amides, lactones may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug degradation because of the occurrence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.

2.1.2. Oxidation

Oxidative degradation is second only to hydrolysis as a mode of decomposition. In contrast to hydrolysis, oxidative mechanisms are complex, involving removal of an electropositive atom, radical or electron or, conversely, addition of an electronegative moiety. Oxidation reactions can be catalyzed by oxygen, heavy metal ions and light, 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. Aldehydes, alcohols, phenols, alkaloids and unsaturated fats and oils are all susceptible to oxidation.

2.1.3. Isomerization

Isomerization involves conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties. For example, the activity of levo (L) form of adrenaline is 15-20 times greater than for the dextro (D) form.

2.1.4. 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, as many as drugs absorb UV light; degradation by low wavelength radiation is common. Exposure to light almost invariably leads to discoloration even when chemical transformation is modest or even undetectable.

2.1.5. Polymerization

Intermolecular reactions can lead to dimeric and higher molecular weight species. Concentrated solutions of ampicillin, an aminopenicillin, progressively form dimer, trimer and ultimately polymeric degradation products.

Table 1 lists examples of medicinal agents susceptible to such modes of degradation. Degradation may reflect vulnerability to environmental stresses such as heat, humidity, light or drug–drug interactions. Degradation may also be facilitated or promoted by excipients possessing the requisite functional groups for interaction, or containing residues that catalyze/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in break down processes.

Table 1: Modes of degradation of medicinal agents

Hydrolysis	Oxidation	Isomerization	Photolysis	Polymerization
Methyldopa	Calcitonin	Tetracycline	Riboflavin	Ceftazidime
Procaine	Ascorbic acid	Vitamin A	Folic acid	Ampicillin
Penicillins	isoprenaline	Adrenaline	Nifedipine	

3. Mechanism of drug excipient interaction

Exact mechanism of drug excipients interaction is not clear. However, there are several well documented mechanisms in the literature. Drug excipients interaction occurs more frequently than excipient-excipient interaction. Drug-excipients interaction can either be beneficial or detrimental, which can be simply classified as-

1. Physical interactions
2. Chemical interactions

3. Biopharmaceutical interactions

3.1 Physical interactions: Physical interactions are very common in dosage form and also difficult to detect. Physical interactions may or may not involve chemical changes thus permitting the components in the formulation to retain their molecular structure. Physical interactions involve change in a dissolution, solubility, sedimentation rate etc. Physical interactions can be either beneficial or detrimental to the product performance which is dependent on its application. Different physical interactions are as follows:

Table 2: Physical Interaction

Interaction	Beneficial effect examples	Detrimental effect examples
Complexation:- Complexing agent binds reversibly with drugs to form complex. Sometimes insoluble complexes are formed which lead to slower dissolution and decreased absorption of drug which is detrimental. Complexing agents can also be used to increase bioavailability of poorly water soluble drugs which is beneficial	Cyclodextrin is often used to improve bioavailability of poorly water soluble drugs. This increases bioavailability and increases rate and extent of drug dissolution.	Tetracycline formed insoluble complex with calcium carbonate leading to slower dissolution and decreased absorption.
Adsorption:- Adsorption of drug by excipient can lead to reduced bioavailability as the drug is not available for dissolution. Adsorption of drug on excipient surface can assist in increasing surface area of drug available for dissolution which eventually increases bioavailability.	Formulation of Indomethacin (NSAID) using kaolin as adsorbent increased its dissolution rate which leads to increase in bioavailability of drug.	Cetyl Pyridinium chloride cations get adsorbed on the surface of magnesium stearate which acts as a lubricant in tablet containing Cetyl Pyridinium chloride. This leads to marked reduction in the antibacterial activity of the drug.
Solid dispersion:- This kind of interactions improves the dissolution and bioavailability of hydrophobic drugs. Sometimes solid dispersion interactions can result in slow dissolution of drugs.	Improved dissolution rates of drugs like Piroxicam, Norfloxacin, Nifedipine and Ibuprofen were observed when these drugs were formulated into solid dispersions using Polyethylene glycol of different molecular weights.	Solid dispersion product formed due to interaction between Povidone and Stearic acid in a capsule showed slow dissolution of drugs.

3.2 Chemical interactions: - Active pharmaceutical ingredients and excipients react with each other to form unstable compounds. Several chemical drugs excipient interactions have been reported in literature which is mentioned in literature under heading 2. Generally chemical interactions have a deleterious effect on the formulation hence such kind of interactions must be usually avoided.

3.3. Biopharmaceutical interactions: These are the interactions which are observed after administration of the medication. Interaction of medicine with body fluid influences the rate of absorption. All excipients interact in physiological way when they are administered along with active pharmaceutical ingredients, various examples of biopharmaceutical interactions are stated as follows:-

3.3.1. Premature breakdown of enteric coat

The enteric coating polymers like cellulose acetate phthalate and hydroxylpropyl cellulose acetate phthalate, are soluble more at basic pH, but antacids raise pH of stomach resulting in breakdown of the enteric coat in stomach and release of active pharmaceutical ingredient in stomach itself, which results in degradation of drug in stomach. In case of NSAID's premature breakdown of enteric coat may cause side effects like gastric bleeding.

3.3.2. Interactions due to adjunct therapy

Tetracycline antibiotics form complexes with calcium and magnesium ions which are quite common excipients in various formulations which may be administered along with tetracycline as adjunct therapy the complex so formed is not absorbed from the G.I.T.

3.3.3. Increase in gastrointestinal motility

Many of the excipients like sorbitol, xylitol, have tendency to increase the gastrointestinal motility thus reducing the time available for absorption of drugs like metoprolol.

4. Methods of estimation of drug excipient compatibility [1, 13]

Formulation scientists have explored various thermal and non-thermal analytical techniques for early prediction of suitable excipients for the dosage forms to minimize or mitigate the untoward reactions (stability issues) which arise from drug–excipient incompatibility. Till date no universally accepted protocol is available for evaluating the compatibility of drug with other components. However, a flurry of reports have appeared in the last decade that highlight the use of analytical tools used in the compatibility screening of APIs in search of suitable excipients. Frequently used analytical techniques for prospective compatibility screening studies include thermal methods such as differential scanning calorimetry, thermo gravimetric analysis, differential thermal analysis, isothermal micro calorimetry, hot stage microscopy and other analytical methods namely powder X-ray diffraction, Fourier transform-infrared spectroscopy, scanning electron microscopy and high performance liquid chromatography. Relatively newer spectroscopic techniques like solid state Nuclear Magnetic Resonance spectroscopy and near Infrared spectroscopy having potential applications in the analysis of pharmaceutical solids, have been extended to study the drug–excipient or drug moisture interactions that may lead to instability of the active principles. These techniques vary in their working principles, mechanical and thermal stress that is applied to the sample, time of analysis and amount of sample required, sensitivity of the technique to minute changes, and the necessity of internal or external standards. Moreover, some of the reported methods for the assessment of compatibility have poor predictive value while a few of them possess time consuming exercise in the pharmaceutical product development. Therefore, combinations of thermal and non-thermal methods are successful in proper identification of incompatibility.

Analytical tools for compatibility assessment of APIs

4.1. Thermal methods of analyses

1. Differential scanning calorimetry (DSC)
2. Isothermal microcalorimetry
3. Hot stage microscopy (HSM)

4.2. Spectroscopic techniques

1. Vibrational spectroscopy
2. Powder X-ray diffraction (PXRD).
3. Solid state nuclear magnetic resonance spectroscopy (ss NMR)

4.3. Microscopic technique

1. Scanning electron microscopy (SEM)

4.4. Chromatographic technique

1. High performance liquid chromatography

4.1 Thermal methods of analyses [2]

Thermal analysis plays a critical role in compatibility screening studies and has been frequently employed for quick assessment of physicochemical incompatibility. Conventional compatibility testing methods require both multiple sample preparation and long storage times in order to obtain meaningful results. However, the thermal methods offer potential advantages over the conventional isothermal stress testing (IST) techniques. Thermal analysis eliminate the lengthy storage conditions and method development for all the active compounds required during IST and allow for a large number of excipient screening experiments to be performed in a short duration of time. The results obtained from thermal techniques are direct indicators of that excipient which are likely to be compatible, cutting down the conventional compatibility samples to prepare and thus saving the valuable time.

4.1.1 Differential scanning calorimetry (DSC) [14, 15]

DSC represents a leading thermal analysis technique that has been increasingly used for active pharmaceutical ingredient screening of incompatibilities for over 50 years. In this technique, the DSC curves of pure components are compared to the curves obtained from 1:1 physical mixtures. It is assumed that the thermal properties (melting point, change in enthalpy, etc.) of blends are the sum of the individual components if the components are compatible with each other. An absence, a significant shift in the melting of the components or appearance of a new exo/endothermic peak and/or variation in the corresponding enthalpies of reaction in the physical mixture indicates incompatibility. However, slight changes in peak shape height and width are expected due to possible differences in the mixture geometry. DSC stands to benefit over other conventional techniques in requirement of short time of analysis and low sample consumption. It also provides useful indications of the potential problems, so that an excipient can be rejected at an initial stage of product development. If the excipient under consideration is indispensable, the nature of interactions with the active API can be studied in depth. In spite of all the merits, the conclusions based on DSC results alone may be misleading and have to be interpreted carefully.

4.1.2. Isothermal microcalorimetry [16]

Isothermal microcalorimetry has proved to be an invaluable tool in the realm of solid state pharmaceutics with its important application in compatibility determination. It works on the principle that all physical and chemical processes are accompanied by a heat exchange within their surroundings. It allows determination of minute amounts of evolved or absorbed heat and heat flow signals in the range of μW are easily detectable. Further, micro reaction calorimeter gives meaningful results without requirement of multiple sample preparations and long storage times. In a typical compatibility experiment, a solution, suspension, or solid mixture of API and excipient is placed in the calorimeter and the thermal activity (heat flow) at a constant temperature is monitored.

The basic assumption is that the rate of heat production is proportional to the rate of chemical and/or physical processes taking place in sample. The thermal activity of API and excipient are measured individually, and then the output of the blend is compared to the "non-interaction" curve constructed from the individual components. If an experimentally significant difference is observed, the excipient is considered to be potentially incompatible with the API. Because the signal may be the sum of numerous chemical and physical processes, one should exercise proper caution before attempting to correlate the signal with rate of degradation. Instead, the method should be used as an indicator of potential incompatibility. Applying these simple testing criteria reduces the number of samples that must be screened using time consuming HPLC, X-ray and other methods, thus saving valuable time and effort during the formulation process.

4.1.3 Hot stage microscopy [17, 18]

Hot stage microscopy (HSM) or thermo microscopy is an analytical technique which combines the best properties of thermal analysis and microscopy. Thus, it is a complementary thermal analysis technique useful for visualizing thermal events recorded by DSC and TGA as well as a versatile tool for solid state screening. Although DSC and isothermal microcalorimetry are considered efficient methods, several studies have demonstrated that the concomitant use of HSM aids in the proper identification of incompatibilities. Being a visual thermal analysis technique, HSM allows efficient monitoring of solid state interactions like possible dissolution of one component into another that could be erroneously interpreted as incompatibility by DSC. Secondly, the degradation of one component is not masked by another thermal event. Thus, the visual system enables possible differentiation between solid state interactions and incompatibilities. Requirement of very small quantity of sample for visual observation is of great advantage when performing compatibility studies.

4.2. Spectroscopic techniques [19, 20]

4.2.1. Vibrational spectroscopy

Fourier Transform Infrared, Raman and near Infrared spectroscopy are sensitive to the structure and the environment of organic compounds. These techniques are not only focused on solid state behavior of APIs and their formulations, but are also used as compatibility screening tool as the vibrational changes serve as probe of potential intermolecular interactions among the components. Thus, pharmaceutical interactions that result in desalting, hydrate formation, dehydration, polymorphic changes or transformation of crystalline to amorphous forms and vice versa during processing can easily be detected with the aid of these spectroscopic techniques. However, the presence of overlapping peaks in the spectra may hinder the analysis.

Thus, FT-IR helped in the choice of suitable excipients for a stable formulation. DRIFT (diffuse reflectance infrared Fourier transform infrared spectroscopy) is the most suitable technique of the nondestructive spectroscopic methods and has attracted interest, as the materials are not subjected to thermal or mechanical energy during sample preparation, thereby preventing solid state transformations.

4.2.2. Powder X-ray diffraction (PXRD) [21, 22]

It is a direct measure of the crystal form of a material with atypical output being a plot of intensity vs the diffraction angle (2θ). A crystalline material exhibits unique set of diffraction peaks and the lack of crystalline API peaks when a dosage

form is analyzed could indicate that the material is amorphous or that the loading is too low to detect using the parameters chosen. PXRD analysis is of immense help in case of incompatibilities which occur during processes like compression, wet granulation etc. and bring on change in crystallinity/amorphicity and polymorphic forms of API in the presence of excipients with/without adsorbed moisture.

4.2.3. Solid state nuclear magnetic resonance spectroscopy (ssNMR) [23, 24]

Solid state NMR has shown immense potential in the qualitative and quantitative analysis of pharmaceutical solids (APIs and drug formulations) throws light on the chemical bonding and composition of drug products, is highly selective and offers limited interference from excipients as compared to other traditional analytical techniques. It has a unique advantage for detecting compatibility in crystalline as well as amorphous components in a mixture. This technique probes the existence of the drug–excipient interactions in the solid state through variations in the chemical shift due to change in the electron density at the interacting carbon atoms. Molecular mobility of water in a drug–excipient system that influences the chemical reactions can also be directly be measured by nuclear magnetic resonance (NMR). Although, it possesses numerous benefits over other spectroscopic techniques, the data acquisition is lengthy and can be complicated in many cases.

It is important to mention that weakly adsorbed water on the excipients like starch, lactose, cellulose plays a significant role in changing the molecular mobility within the system that accelerates the chemical reactions. Nuclear magnetic resonance (NMR) can directly measure the molecular mobility of water and its correlation with the drug stability in a drug–excipient mixture.

4.3. Microscopic technique

4.3.1. Scanning electron microscopy (SEM) [25]

This technique allows characterization of surface morphology of materials and is useful especially when there are distinctive differences in their crystal habits. It does not give any the chemical structure/thermal behaviour of drug materials and requires sample preparation along with stage condition setup. However, the combination of SEM studies with other thermal and spectroscopic techniques, such as DSC, HSM and FT-IR offers some opportunities for the characterization of incompatibilities of materials.

4.4. Chromatographic technique

4.1. High performance liquid chromatography [26, 27, 28]

This chromatographic technique is widely employed for compatibility testing by quantitative estimation of drug excipient samples that have been subjected to isothermal stress testing (IST)]. IST involves the storage of drug alone and drug–excipient blends with or without moisture at high temperature for a specific period of time (about 3–4 weeks) to accelerate any drug–excipient interaction. The chemical incompatibility is then evaluated by determination of the drug content in the stored samples. HPLC results that exhibit a percentage loss similar to the drug considered individually indicate no interaction between drug and the excipients and vice versa. Sophisticated analytical techniques like liquid chromatography mass spectrometry/mass spectrometry (LC–MS/MS) have been used to further characterize the incompatibility products. In spite of its optimal applicability, HPLC technique is time consuming. Thus, preliminary search of incompatibility using thermal techniques should be corroborated with chromatography to finally establish the chemical interactions of the API.

5. Predictive softwares (in-silico prediction) [31, 32]

5.1. CAMEO (Computer-Assisted Mechanistic Evaluation of Organic reactions): Historical degradation predictions involved the use of for modeling and predicting organic chemical reactivity, software developed by William L. Jorgensen. This software was discontinued, since predictions often over looked secondary or ternary degradants, and its major downfall was the inability to program the software with new chemistry reactions.

5.2. DELPHI (Degradation Expert Leading to Pharmaceutical Insight): It was another historical expert system, capable of predicting reaction products under given conditions. In contrast to CAMEO, DELPHI was specifically designed to predict reactivity and degradation of molecules and preceded beyond a primary reactive degradant to subsequent degradants of degradants. Even though described in the literature, DELPHI is a proprietary software system at Pfizer that has been discontinued due to its inflexibility.

5.3. Zeneth: This in silico software released in 2010 is the only commercially available program designed to predict degradation pathways of pharmaceutical compounds. It was developed by Lhasa Ltd. in consortium with a group of pharmaceutical companies and based on the framework of Meteor, a metabolite-prediction software program by Lhasa. Zeneth contains a chemical engine allowing the description and application of degradation transformations, a reasoning engine allowing the description and application of degradant transformation, a reasoning engine allowing assessment of transformation likelihoods and graphical interface allowing entry of query structures and display of prediction results. Zeneth predicts degradation under the influence of reaction conditions and optionally in the presence of other compounds such as excipients.

Two of the main advantages of Zeneth are, total recall and the absence of bias. A further major benefit is the steady accumulation of knowledge about degradation chemistry in an accessible form. Wet or bench chemistry is still needed and the power of prediction can be harnessed to develop focused stress testing protocols and to serve as a tool for the structure elucidation scientist to match predicted degradant structures with high performance LC-MS data.

6. Summary

Drug-excipient interactions/incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance. Many stability problems encountered during development and post-commercialization can be ascribed to inadequate matching of the ingredients in dosage forms, lack of awareness of the complexities of chemical and physical interactions, or the unheralded presence of a residue in one of the excipients. Many such issues concern low levels of novel entities formed by drug– excipient interactions that pose questions concerning safety or tolerance.

Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and pre-formulation studies.

They can complicate and compromise a development programme or the viability of a commercial product. It is possible to reduce the probability of such undesirable and costly scenarios by allying knowledge of the propensity of a drug to undergo degradation reactions with awareness of excipient reactivity and of the residues that they may contain.
Thermo analytical and spectroscopic techniques have played a pivotal role in characterization of solid state interactions and early detection of drug–excipient compatibility. The in-depth knowledge and appropriate use of these analytical techniques have brought forth extraction of valuable information concerning the drug–excipient interactions that aid in the selection of appropriate excipients for stable and an efficacious solid dosage form. In Non-thermal method of analysis HPLC and FTIR gives reliable data for structural conformation. SEM and Hot stage microscopy gives limited chemical information. DSC and DTA results are not useful if thermal changes are small, it should be confirmed using another non-thermal method. In summary, knowledge of drug–excipient interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality.

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