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A REVIEW: DRUG- EXCIPIENT INTERACTIONS STUDY

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ABSTRACT

Excipients are included in dosage forms to aid manufacture, administration or absorption. 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. Exicipients are not exquisitely pure. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential active pharmaceutical ingredients interactions with trace components. Chemical interactions can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration. Understanding the chemical and physical nature of excipients, the impurities or residues associated with them and how they may interact with other materials, or with each other, forewarns the pharmaceutical technologist of possibilities for undesirable developments. 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:

Excipient, Drug, Interaction, Physical, Chemical.

INTRODUCTION:

Pharmaceutical dosage form is a combination of active pharmaceutical ingredients (API) and excipients. Excipients are included in dosage forms to aid manufacture, administration or absorption (Crowley and Martini). The ideal excipients must be able to fulfill the important functions i.e. dose, stability and release of API from the formulation. 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. Incompatibilities may take place in a manner of drug-drug interactions or drugadditive 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. Excipients can initiate, propagate or participate in chemical or physical interactions with an active substance, possibly leading to compromised quality or performance of the medication. Incompatibilities in pharmaceutical products are undesired physical, chemical or biopharmaceutical processes which take place during preparation, storage or administration resulting in decomposition of drugs and a failure to improve the patient's condition. 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. Alternatively, they may contain impurities or residues, or form degradation products in turn cause decomposition of the drug substance. For the development of proposed pharmaceutical dosage form, three main components which should be consider area. Properties and limitation of API b. Properties and limitation of excipients. Definition of excipients 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 is 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.

Excipients are classified according to their functions as:

- Binders
- Disintegrants

- Colors
- Sweeteners
- Preservatives
- Flavors
- Film formers/coatings In pharmaceutical dosage form API are in intimate contact with one or more excipients. Moreover in most of dosage form the quantity of excipients are greater than the amount of API present in dosage form, for example typically a tablet contain binders, disintegrants, lubricants, and fillers, therefore excipients can have tremendous impact on the performance of API when present in dosage form.

Excipients Play an important role in formulating a dosage form.These are the ingredients which along with active pharmaceutical ingredients make up a dosage forms.

Excipients act as protective agents,bulking agents and can also be use to improve bioavailability of a drug

Excipients as like other active pharmaceutical ingredients need to be stabilized and standardized.

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.

Excipients:

"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.

Mode of drug decomposition:

Medicinal agents invariably have structural features that interact with receptors or facilitate metabolic handling. These inevitably confer some degree of lability, making them vulnerable to degradation (and interaction with other materials). Common modes of degradation are described below. Pharmaceutical substances, in general, have structural features that interact with receptors or facilitate metabolic handling. These inevitably confer some degree of lability, making them vulnerable to decomposition.

Hydrolysis:

Hydrolysis is one of the most frequently encountered type of chemical reaction responsible for drug decomposition processes. The following types of compounds undergo hydrolytic degradation, usually at different rates, esters, amides, lactams, lactose, imines, nitriles, ureides, halides, thio-halides, thio-esters. Hydrolytic decomposition can be avoided or slowed down by using an insoluble form of drugs. In addition, stability of drug solution can be increased by the use of suitable buffers. Drugs with functional groups such as esters, amides, lactones or lactams may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug n because of the prevalence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.

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. Oxidative decomposition of drug products may cause many changes in the products such as drug degradation and discoloration. Some important factors accelerating oxidation are temperature, oxygen concentration and heavy metal ions. Several compounds, particularly aldehydes, phenols, alkenes, alkynes, sugars, can undergo oxidative decomposition. Oxidation may be retarded by using antioxidants or nitrogen gas atmosphere during filling procedures.

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. Isomerization involves conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties. 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.

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. Light can cause photochemical decomposition of drugs. Reactions such as oxidation, reduction, ring alteration and polymerization can be catalysed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and, as many drugs absorb ultraviolet 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. Photolysis may be retarded by the use of amber glass or light-resistant containers. 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.

Polymerization:

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. 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. Intermolecular reactions can lead to dimeric and higher molecular weight species (1). 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 catalyse/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in breakdown processes. 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.

Acid-base character

Ionized drugs in solution may interact ionically with the ion of opposite charge to form flocullent coprecipitates or transparent complexes. In general, salts of acidic drugs are incompatible with salts of weak bases.

pH:

pH of solution influences the percentage ionization of drug owing to its pKa. Weak acids will be the most soluble in solutions with a pH at least two units above their pKa (>99% ionized form). On the other hand, weak bases at two or more pH units below their pKas will be the most soluble. Precipitation of drug should be aware according to pH change. Furthermore, many drugs are stable in a limit pH range, so the buffer system are used to maintain a certain pH in some drug products.

Concentration:

In general, a higher concentration of drugs in solution can undergo faster degradation rates because of the ease of intermolecular interaction. The degradation of most drugs in solution is concentration dependent.

Temperature :

The rate of reaction can vary greatly with changes in temperature. Elevated temperature increase reaction rate. In general, each rise of 10oC results in a two to four times increase in reaction rate.

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 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. Direct Interactions.
4. Bio – Pharmaceutical interactions.

1.Physical interactions:

It is quite common, but is very difficult to detect. A physical interaction doesn‟t involve any chemical changes. Physical interactions are frequently used 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 interaction can either be beneficial or detrimental to product performance. An example of a physical interaction between an API and an excipient is that between primary amine drugs and microcrystalline cellulose. When dissolution is carried out in water a small percentage of the drug may be bound to the microcrystalline cellulose and not released. Phenobarbital formed an insoluble complex with PEG-400, which resulted in slower dissolution and decreased absorption. In-vitro evaluation of complexation of steroids prednisolone with water soluble excipients, showed increased dissolution, but the complexes were having high molecular weight and might be too large to diffuse through GI membrane, therefore it may be possible that in-vivo bioavailability of prednisolone would be lower.

Adsorption:

The adsorption of drug molecules onto the surface of excipients can reduce drug particle size and increase the surface area of drug available to the dissolution medium. However, if forces of attraction are high, desorption may be retarded and absorption compromised (5,6). Adsorption of finely divided excipients on to active ingredients can also occur and, if such excipients are hydrophobic, dissolution rate and bioavailability may be retarded.

Complexation:

Complexing agents interact, usually reversibly, with a drug to form a complex (2). 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 than be absorbed across the gastrointestinal membranes.

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. Chemical interaction involves chemical reaction between drugs and excipients or drugs and impurities/ residues present in the excipients to form different molecules. Chemical interactions are almost detrimental to the product because they produce degradation products, different degradation product are classified as in ICH guideline ICHQ3B (ICH guideline ICHQ3B, 2008). Different types of chemical drug-excipients interaction have been reported in the literature. Chemical interactions between drug and excipients.Primary amine group of chlorpromazine undergoes Maillard reaction with glycosidic hydroxyl group of reducing sugar dextrose to form imine, which finally breakdown to form Amidori compounds Fig.

1: Maillard reaction. In one another study it was observed that release of diclofenac sodium from matrix tablet was inhibited by polymer chitosan at low pH, most possibly via formation of ionic complex between diclofenac sodium and ionized cationic polymer Secondary amines may also interact with reducing sugars. However, the reaction cascade does not proceed beyond the formation of the imine, and thus no coloration develops Primary amines may interact with double bonds in a reaction analogous to a Michael addition reaction (e.g., fluvoxamine maleate, where the fluvoxamine primary amine group can interact with the double bond in the maleic acid counterion). Examples of excipients that contain double bonds include sodium stearyl fumarate and sorbitan monooleate Certain APIs are susceptible to oxidation, e.g., atorvastatin and cytidine nucleoside analogues. Fumed metal oxides (e.g., fumed silica, fumed titania, and fumed zirconia) can promote such oxidation reactions. Lactone formation because of the close proximity of heteroatoms and an active hydrogen atom in the molecule, e.g., benazepril. Suspending agents such as sodium alginate dissolve in water to form large negatively charged anions, coformulation in aqueous systems with drugs such as neomycin and polymixin (active mioties of which are positively charged) result in precipitation.Silicon dioxide catalyzes oxidation of diethylstilbestrol to the peroxide and conjugated quinone degradation products. Air autooxidation of methyl linoleate to peroxides with subsequent decomposition to aldehydes has been shown to be accelerated in the presence of colloidal silicon dioxide .Interaction between chloramphenicol stearate and colloidal silica during grinding leads to polymorphic transformation of the chloramphenicol, demonstrating that unwanted effects of excipients are not restricted to chemical transformations.

3. DIRECT INTERACTIONS

Excipients may be inorganic or organic in composition, synthetic or semi-synthetic, or derived from biological or natural sources. Many of them possess functional groups that can interact with other materials. It may be possible on occasion to exploit such attributes to stabilize unstable materials (2), but more usually interactions lead to loss of quality. This is particularly true where an interaction product may pose safety questions and needs to be qualified by toxicology studies. Also, the presence of pH-modifying residues can accelerate hydrolytic degradation or have more esoteric effects. Residues that modify pH may lead to free base or acid formation during long-term storage. Such products may be volatile and lost by sublimation from the dosage form. This "disappearance" without concomitant formation of degradation products can be mystifying and requires much time and effort to elucidate.

Hydrogen-donating:

interactions Direct drug-excipient interactions seem to be most prevalent when the interacting species are water soluble and in liquid systems. However, adsorbed moisture may promote greater molecular flexibility and consequent facilitation of interactions in solid state systems. Solution interaction studies may have some predictive capability because of such possibilities. For example, polyvinylpyrrolidone (PVP or povidone) can interact with compounds containing hydrogen-donating functional groups (3,4).

Methods of estimation of drug excipient compatibility:

Formulation scientists have explored various thermal and nonthermal 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 transforminfrared 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. Biopharmaceutical interaction:- 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:-

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.

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.

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.

These are the interaction observed after administration of medication. Interaction within the body is between medicine and body fluids which influence the rate of absorption. All excipient physiological way when they are administered along with active pharmaceutical ingredients.

Beneficial effect example:-

Cyclodextrin is often used to improve bioavailability of poorly water soluble drug . This increase bioavailability and increase rate and extent of drug dissolution by increasing mucosal permeability or increasing stability of drug.

Biopharmaceutical interaction Examples:-

- These are the interaction observed after administration of medication.
- Interaction within the body is between medicine and body fluids which influence the rate of absorption.
- All excipient physiological way when they are administered along with active pharmaceutical ingredients.

Increase in gastrointestinal motility:-

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

CONCLUSION

Understanding the chemical and physical nature of excipients, the impurities or residues associated with them and how they may interact with other materials, or with each other, forewarns the pharmaceutical technologist of

possibilities for undesirable developments. All incompatibilities may take place in a visual or hidden manner. Visual or visible incompatibilities usually result from inadequate solubility, viscosity changes, color change, turbidity, etc. The hidden incompatibilities which are not visible apparent may be difficult in detection. Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and preformulation 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 effects by allying knowledge of the propensity of a drug to undergo degradation reactions with an awareness of excipient reactivity and of the residues that they may contain. Such awareness may help to anticipate undesirable interactions and avoid their occurrence.

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