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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.

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. Exicipients are not exquisitely pure. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Often, it is the multi-component nature of the excipient that drives many of the interactions with APIs. Even

for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential API interactions with trace components. Excipients may have functional groups that interact directly with active pharmaceutical ingredients. 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 are

a. Properties and limitation of API
b. Properties and limitation of excipients
c. Advantage and limitation of method(s) used

In term of development of dosage form, all three considerations are of equally important. Excipients are the substances other than API which are intentionally incorporated intopharmaceutical dosage form for specific purposes such as;

a. Improvement of the stability of API in the dosage form
b. Modulation of bioavailability of active pharmaceuticals ingredients
c. Maintain the pH of liquid formulation
d. Maintain the rheology of semisolid dosage form
e. Act as tablet binders, tablet disintegrant
f. Act as antioxidant and emulsifying agents
g. To allow the adequate administration
h. To facilitate the manufacturing of dosage form
i. For aesthetic reason
j. For identification

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
- Fillers (diluents)

- Lubricants
- Glidants
- Compression aids
- Colors
- Sweeteners
- Preservatives
- Flavors
- Film formers/coatings
- Suspending/dispersing agents/surfactants

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. It can influence the safety and effectiveness of drug depending upon route of administration, for example in solid dosage form excipients can affect safety and effectiveness by promoting or delaying gastrointestinal release. Therefore, understanding of drug-excipients interactions is very important during selection of appropriate excipients for proposed dosage

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

Hydrolysis

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.

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.

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.

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.

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

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. For high-dose drugs, this may not be a major issue, but for low dose drugs it can lead to dissolution failures. This has caused problems in the past, but the phenomenon can be remedied by carrying out dissolution using a weak electrolyte solution for the dissolution medium (e.g., 0.05 M HCl). Under these revised dissolution test conditions, adsorption onto the microcrystalline cellulose is very much reduced and 100% dissolution may be achieved even for low-dose APIs A general example of a physical interaction is interactive mixing. In this smaller particles (typically the APIs) interact with the surface of the larger carrier particles (typically the excipients) through physical forces. In this way we obtain a more homogenous powder blend. After the medicine, e.g., a tablet has been administered to the patient, the aqueous environment of the gastrointestinal tract (GIT) either causes the smaller API particle or other carrier particles to dissolve or causes the surface interactions to change to allow the smaller particles to be released from the larger carrier particles.But as we have already stated, physical interactions can also be detrimental, and magnesium stearate is recognized within the pharmaceutical industry for causing problems such as reduced tablet "hardness" and dissolution from tablets and capsules.Adsorption of drug molecules onto the surface of excipients can render the drug unavailable for dissolution and diffusion, which can result in reduced bioavailability. For example, antibacterial activity of cetylpyridinium chloride was decreased when magnesium stearate was used as lubricants in tablet containing cetylpyridinium chloride; this was due to adsorption of cetylpyridinium cation by stearate anion on magnesium stearate particle .In one of the investigation, it was observed that dissolution of drug was decreased due to adsorption of drug on the surface of microcrystalline cellulose. In a similar context, adsorption of novel k-opoid agonist by microcrystalline cellulose led to incomplete drug release from the capsules. Adsorption may also initiate chemical breakdown. Colloidal silica was shown to catalyze nitrozepam degradation in tablet dosage form, possibly by adsorptive interactions altering electron density in the vicinity of the labile azo group and thus facilitating attack by

hydrolyzing entities. Complexing agents usually bind reversible with drugs to form complex, which do not allow them to dissolve, complexing agent such as cyclodextrin are often used to increase the bioavailability of poorly water soluble drugs However, it was found that complexation of cyclodextrin with non-steroidal anti-inflammatory drug (NSAID) naproxen and tolbutamide increased the dissolution, but there was no corresponding increase in bioavailability. 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.

Chemical interactions

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

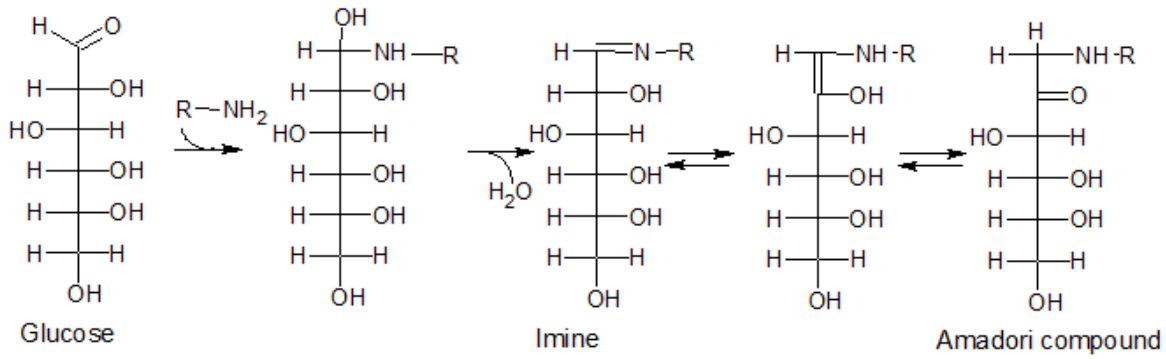

Fig. 1: Maillard reaction.

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. These reactions are more complex in some ways, and less easy to predict. 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, co-formulation 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 auto-oxidation 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

CONCLUSION

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. Such incidents have probably been increased by the growing sophistication of analytical techniques to detect, identify and quantitate low level impurities. 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 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. A judicious choice of excipients or control of their quality will exclude or limit residues promoting degradation. It is surprising, therefore, that there is a

paucity of information in compendia or other publications on potentially damaging residues in even the most common excipients. It is a sphere of activity that groups attempting to harmonize excipient monographs do not seem to have addressed, and it is to be hoped that 'least common denominator' considerations in harmonization initiatives do not exacerbate the situation. Perhaps it could be a subject for a future initiative.

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