

The Importance of Pharmaceutical Excipients and their Interactions with Drug Substance During Formulation

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Abstract: Dosage forms are accompanied by excipients to facilitate their production, administration, or absorption. Excipients can begin, propagate, or engage in chemical or physical interactions with medicinal components, even if they may appear to have no pharmacological effect. This can make a medication less effective. Not every recipient of an award is exceptionally well-groomed. It is essential to comprehend the manufacturing process of excipients, especially the most widely used ones, in order to identify possible interactions between trace components and active pharmaceutical substances. The amount of the active component that is accessible for therapeutic effect may be reduced due to degradation brought on by chemical interactions. Physical interactions can affect the rate of dissolution, dosage homogeneity, or convenience of administration.

Keywords: Pharmaceuticals; Excipient; Formulation; Pharmacological effect; Physical interaction; Stability.

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1. Introduction

An essential component of the pre-formulation stage of developing new dosage forms is a detailed characterization and comprehension of the physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms, as this is most desirable for consistent efficacy, safety, and stability of a drug product. In a dosage form, an API comes into direct touch with other formulation constituents, sometimes known as excipients. The active component is protected from the environment by these substances, which also aid in its administration and release. Although excipients are not pharmacologically active, they can interact with drugs in the dosage form to change the drug product's physical or chemical stability by slowing down the dissolution process or causing drug degradation. A strong and efficient formulation of dosage forms that facilitate administration, enhance patient compliance, boost drug release and bioavailability, and lengthen its shelf life necessitates careful selection of the excipients. Therefore, it is acknowledged that compatibility screening of an API with excipients or other active ingredients is one of the essential components and is at the forefront of research on pharmacological products and technology [1-5].

The dosage, stability, and release of API from the formulation are three crucial roles that the perfect excipients must be able to perform. Excipients can start, spread, or take part in chemical or physical interactions with therapeutic components, even if they are thought to be pharmacologically inactive. This could reduce a medication's efficacy. The recipients aren't exceptionally pristine. Starting materials, reagents, and solvents are used in the manufacturing of synthetic, semi-synthetic, and natural origin materials, as they are in the production of almost all minerals. Functional groups found in excipients may interact directly with the active compounds in pharmaceuticals. Alternatively, they could create degradation products or include residues or impurities that lead to the medicinal substance's breakdown [6]. Drug inactivation caused by chemical or physical breakdown, or drug loss as a result of drug conversion to a less desirable form. The term "incompatible" refers to a mixture of two or more API and/or excipients that negatively impacts the other's safety, therapeutic effectiveness, appearance, or elegance [7].

2. Reason for Adding Excipients:

- Improvement of the stability of API in the dosage form
- Modulation of bioavailability of active pharmaceuticals

- ingredients
- Maintain the pH of liquid formulation
- Maintain the rheology of semisolid dosage form
- Act as tablet binders, tablet disintegrant
- Act as antioxidant and emulsifying agents
- To allow the adequate administration
- To facilitate the manufacturing of dosage form
- For aesthetic reasons
- For identification

These are the substance(s) other than the API that have undergone a suitable safety evaluation and are added to a drug delivery system to help with system processing during manufacturing or to safeguard, support, or improve stability, bioavailability, patient compliance, or aid in product identification and improve any other aspects of the drug product's overall safety and effectiveness during storage or use [8]. API are in close contact with one or more excipients in pharmaceutical dosage forms. Excipients can have a significant impact on the performance of API when present in dosage form because they are typically present in larger quantities than the amount of API in the dosage form (for instance, binders, disintegrants, lubricants, and fillers are typically found in tablets). Depending on the mode of administration, it may have an impact on the medication's safety and efficacy. For instance, in solid dosage forms, excipients may have an impact by speeding up or slowing down gastrointestinal release.

3. Decomposition of Drug

Hydrolytic breakdown is a likely process for drugs containing functional groups, such as lactones, amides, esters, or lactams. Given the prevalence of water and the presence of these groups in pharmaceuticals, it is perhaps the most often seen mechanism of drug degradation. Water may also facilitate interactions and encourage the development of microorganisms. Oxidation-reduction, ring modification, and polymerization are among the processes that can be catalyzed or accelerated by exposure to natural or artificial light. Because many drugs absorb UV light, low wavelength sunlight commonly damages them. Lower wavelengths also result in more energy absorption. Exposure to light almost always causes dis-colouration, even in situations where there is little or even no chemical modification. Intermolecular interactions can produce dimeric and higher molecular weight species. Amino-penicillin ampicillin concentrate solutions gradually produce dimer, trimer, and finally polymeric breakdown products [9]. Degradation might be an indication of susceptibility to environmental stressors such as heat, humidity, light, or interactions between drugs [10]. Furthermore, excipients with the necessary functional groups for contact or residues that accelerate or engage in degradation processes might aid or encourage decomposition. The formation of species that take part in break-down processes is given more opportunities if excipients are also subject to modification.

Oxidative processes, in contrast to hydrolysis, are more intricate and include either the addition of an electronegative moiety or the removal of an electropositive atom, radical, or electron. Light, heavy metal ions, and oxygen can all function as catalysts in oxidation processes to produce free radicals. Peroxy radicals are created when free radicals mix with oxygen to create more free radicals, which are then used to drive subsequent reactions with oxidizable compounds. Oxidation can occur to aldehydes, alcohols, phenols, alkaloids, unsaturated fats, and oils.

4. Excipients Types:

- Binders
- Disintegrants
- Fillers (diluents)
- Lubricants
- Glidants
- Compression aids
- Colors
- Sweeteners
- Preservatives
- Flavors
- Film formers/coatings
- Suspending/dispersing agents/surfactants

Excipients have the ability to change a drug's safety and efficacy depending on how it is administered. For example, they may influence safety and efficacy in a solid dose form by accelerating or delaying gastrointestinal release. Therefore, understanding drug-excipient interactions is essential for selecting appropriate excipients for a recommended dose form.

5. Physical Interactions

Drug particles can be made smaller and have more surface area accessible to the dissolving media by adsorbing onto the surface of excipients. On the other hand, desorption may be slowed down and absorption might be jeopardized if attraction forces are strong. Finely split excipients may also adsorb onto active substances; if these excipients are hydrophobic, this may slow down the rate of dissolution and reduce the amount of bioavailability [11, 12]. Drugs and complexing agents combine to generate a complex, often in a reversible way. The medication must first dissociate from the complex in order for it to disintegrate while it is in it. When the drug complex comes into touch with gastrointestinal fluids, it often dissociates, releasing the drug ingredient, which can then be absorbed through the gastrointestinal membranes [13].

Interactive mixing is a common illustration of a physical interaction. Physical forces are used in this situation to interact with the surface of the bigger carrier particles (usually the excipients) and the smaller particles, which are usually the APIs. We are able to get a more uniform powder blend in this method. Following the patient's administration of medication, such as a tablet, the aqueous environment of the gastrointestinal tract (GIT) either dissolves the smaller API particle or other carrier particles or modifies surface interactions to release the smaller particles from the larger carrier particles [14]. In one study, it was shown that the drug's adsorption on the surface of microcrystalline cellulose reduced the drug's ability to dissolve. In a similar setting, partial drug release from the capsules was caused by the new κ -opioid agonist's adsorption by microcrystalline cellulose. Chemical disintegration may also be started via adsorption. In tablet dosage form, it was demonstrated that colloidal silica catalyzed the breakdown of nitrozapam. This may have been accomplished via adsorptive interactions that changed the electron density around the labile azo group, opening the door for hydrolyzing entities to attack.

6. Excipient Residues Interaction

The substances used are not exceptionally pure. After isolation, residues inevitably persist. Contrary to popular belief, low residue levels can have a bigger effect in some situations. These situations include high excipient to drug ratios, low molecular weight residues, and catalyst residues. This is especially true in situations when toxicological tests are required to qualify an interaction product that may raise concerns about safety [15]. Additionally, pH-modifying residues may have more esoteric effects or hasten hydrolytic breakdown. Long-term storage of residues that alter pH may result in the development of free base or acid. These materials could be flammable and lose their potency during sublimation. When degradation products do not simultaneously occur, this "disappearance" might be confusing and take a long time to understand. It is not always the case—or not in a meaningful way—that degradation occurs when a residue with interaction capacity is present. The physical form, circumstances, and setting for the contact might not be suitable. Investigation is necessary if residues are volatile, liquid, or otherwise "mobile" since instability is a possibility that cannot be ruled out.

7. Water based Reactions

Certain materials have demonstrated the ability to break down bound water during processing steps like drying and grinding, making it "free" to take part in hydrolytic processes. Process stressors of this kind may also be anticipated to release bound water in excipients, which might lead to the degradation of the moisture-sensitive medications that are manufactured with them. The trigger for contact may be compression, attrition, or other crystal-disturbing stressors, however, they are rarely cited as things that need more research [16]. Lipid excipients may be used to create different drug targeting systems, such as micro-emulsions. Peroxides, found in the majority of food-grade lipids, break down in the presence of heat and UV light. This may result in the production of free radicals, which may then oxidize unsaturated groups and damage the delivery mechanism and perhaps the active component [17]. It has been demonstrated that the concentration of the solution and the length of storage time affect the peroxide levels in polyethylene glycol solutions. The production of potent oxidizing agents indefinitely may be highly detrimental to protein structures that include histidine, cysteine, methionine, or other oxidizable terminal groups.

8. Conclusion

Drug-excipient interactions in conventional stability testing programs may not always be predicted by stress and pre-formulation studies and may take some time to manifest. They can make managing a development program more challenging or put the viability of a commercial product in jeopardy. In summary, a comprehension of drug-excipient interactions is necessary for the development of stable and superior dosage forms. The purpose of this review is to provide some understanding of this important area of pharmaceutical science.

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