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Review

Drug–excipient compatibility screening—Role of thermoanalytical and spectroscopic techniques

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ABSTRACT

Estimation of drug–excipient interactions is a crucial step in preformulation studies of drug development to achieve consistent stability, bioavailability and manufacturability of solid dosage forms. The advent of thermoanalytical and spectroscopic methods like DSC, isothermal microcalorimetry, HSM, SEM, FT-IR, solid state NMR and PXRD into pre-formulation studies have contributed significantly to early prediction, monitoring and characterization of the active pharmaceutical ingredient incompatibility with pharmaceutical excipients to avoid expensive material wastage and considerably reduce the time required to arrive at an appropriate formulation. Concomitant use of several thermal and spectroscopic techniques allows an in-depth understanding of physical or chemical drug–excipient interactions and aids in selection of the most appropriate excipients in dosage form design. The present review focuses on the techniques for compatibility screening of active pharmaceutical ingredient with their potential merits and demerits. Further, the review highlights the applicability of these techniques using specific drug–excipient compatibility case studies.

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1. Introduction

A complete characterization and understanding of physico-chemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new drug 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 [1,2]. Although excipients are pharmacologically inert, they can interact with drugs in the dosage

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form to affect drug product stability in physical aspects such as organoleptic properties, dissolution slowdown or chemically by causing drug degradation [3,4]. 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 [5,6]. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the forefront of drug product science and technology research. In addition, a complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype of drug development and is encouraged by United States Food and Drug Administration as well as various regulatory bodies worldwide. The advent of thermoanalytical methods into the initial steps of pre-formulation 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 [7].

2. Drug–excipient interactions

Solid dosage forms are generally less stable than their pharmacologically active components. The excipients or reactive impurities in excipients may interact with drugs and often catalyze the degradation of susceptible API [8]. The interactions of drug with excipients or other actives that lead to changes in the chemical, physical, therapeutic properties of the pharmaceutical dosage form are termed as incompatibilities. The drug interactions that occur during formulation or storage can be categorized as, physical or chemical interactions [9]. A physical interaction describes the scenario where no chemical reaction occurs but rather there is alteration in the physicochemical parameters of the active components like solubility, dissolution rate and finally the bioavailability. Such interactions may arise due to changes in colour, odour, taste, polymorphic form, or crystallization of a drug in the presence of excipients (pharmaceutical incompatibility). This may lead to adverse findings and call upon batch removals or product withdrawals. However, there are instances where a physical interaction between the drug and the excipient are planned with an aim to increase the solubility and bioavailability of API, e.g. drug–cyclodextrin complexes and solid dispersions [8].

A chemical interaction/incompatibility involves a direct chemical reaction between the excipient and the drug molecule/modification of microenvironmental pH to enhance the rate of chemical reaction. Additionally, trace amounts of impurities present in excipients can react with the drug or other functional excipients [8]. The existence of chemical incompatibility between actives with other actives/and excipients may manifest itself in undesirable effects which may be toxic (formation of degradation products) or result in compromised clinical efficacy (loss of potency) [10]. The identification of these incompatibilities and prediction of the drug product stability not only guide the formulation scientists towards selection of appropriate formulation components for clinical development and commercialization but also help in the regulatory filings to justify proposed shelf life of the drug product. The present review focuses on the techniques for compatibility screening of API with their potential merits and demerits (Table 1). Further, the review highlights the applicability of these techniques using specific drug–excipient compatibility case studies.

3. Drug–excipient compatibility studies

These studies are sought after to identify the significant drug–excipient interactions/drug degradation and are based on standard protocols and/existing knowledge on drug degradation pathways [11]. The compatibility studies of new chemical entities are invariably designed on the grounds of existing chemical information of the drug candidate to identify the potential degradation pathways. Initially, useful information for the selection of excipients can be exploited from the presence of reactive functional groups of API, pK_a values and reactivities of similar compounds which are previously known. Use of computational programs like CAMEO®, SPARTAN®, EPWIN® and Pharm D^3® and internal databases are also helpful in prediction of main degradation routes.

The compatibility screening studies involve the use of physical mixtures of drug with one or more excipients. The proportion of excipient in the mixtures is usually kept high (drug:excipient, 1:1, w/w) as compared to that in the formulation to maximize the proportion of excipient/reacting species, thereby increasing the chance of incompatibility. It is essential to understand the roles of water and temperature in case of solid samples [12]. Water may interact with an active pharmaceutical ingredient to alter its properties and high temperature leads to faster degradation [13,14]. Thus, the samples are usually equilibrated at various stress conditions like elevated temperature and humidity that can accelerate the drug–excipient interactions. These samples are visually observed for any change in colour, aggregation of powder mixture or any change in the physical state which are indicators of incompatibility. Additionally, the physical mixtures are analyzed by various thermoanalytical and spectroscopic techniques before and after equilibriation. The chemical interactions with the drug can be analyzed by chromatographic techniques like HPLC/TLC based on assessment of drug potency in the equilibriated samples.

4. Analytical tools for compatibility assessment of APIs

Formulation scientists have explored diverse thermo-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, thermogravimetric analysis [15–17], differential thermal analysis, isothermal microcalorimetry [18,19], hot stage microscopy [20] and other analytical methods namely powder X-ray diffraction [21,22], Fourier transform-infrared spectroscopy [23], scanning electron microscopy [24] and high performance liquid chromatography [25]. 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