Drug-Excipient Compatibility Studies in Formulation Development: Current Trends and Techniques

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Abstract
The safety, efficacy, quality and stability of a formulation are the cornerstones of any new drug development process. In order to consistently maintain these attributes in a finished dosage form, it is important to have a comprehensive understanding of the physico-chemical characteristics of the active pharmaceutical ingredient (API), as well as all other components (e.g. excipients, manufacturing aids, packaging materials) of the drug product. In a new drug development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. The preformulation stage involves characterization of several aspects of the API including solubility, dissolution, permeability, polymorph/salt screening, stability (solid-state and solution-state), ionization properties, particle size distribution, API-excipient compatibilities etc. [1]. Excipients are ubiquitous to virtually every pharmaceutical formulation, and facilitate the manufacture, stability, administration, delivery of the API, and/or provide other functionalities to the dosage form. Excipients are used to improve processing (e.g. improving powder flow [2, 3], powder compactibility [4-6] etc.), enhance aesthetics (e.g. identification, branding etc. [7]), optimize product performance (e.g. modified drug-release [8-11]), and/or to facilitate patient compliance (e.g. taste masking [12-15]). They may constitute anywhere from 1 to 99% of the total formulation mass.

Due to the intimate contact of the API with one or more excipients in a formulation, there exists a likelihood of physical and/or chemical interactions between them. Any such interactions may result in a negative impact on the physical, stability or performance attributes of the drug product [16, 17]. The choice of excipients is of crucial importance to avoid these negative effects, and to facilitate the development of a robust and an effective formulation [18-20]. Thus, for a rational selection of excipients, screening of excipient-API compatibility is recognized as an important aspect of formulation development. Moreover, the USFDA’s 21st century current Good Manufacturing Practices (cGMP) initiative and International Council on Harmonization (ICH) Q8 guidelines encourage the pharmaceutical manufacturers to apply Quality by Design (QbD) principles in their drug development process [21, 22]. These guidelines include expectations of a clear understanding of any interactions between the formulation components. Moreover, recent advances in various thermal and non-thermal analytical techniques have led to an improved efficiency in the detection, monitoring and prevention of the incompatibilities early in the drug development process [23, 24].

This article aims to provide a brief overview of the nature of drug-excipient incompatibilities; as well as current trends and techniques used to evaluate these compatibilities in formulation development.

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1. Introduction
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Due to the intimate contact of the API with one or more excipients in a formulation, there exists a likelihood of physical and/or chemical interactions between them. Any such interactions may result in a negative impact on the physical, stability or performance attributes of the drug product [16, 17]. The choice of excipients is of crucial importance to avoid these negative effects, and to facilitate the development of a robust and an effective formulation [18-20]. Thus, for a rational selection of excipients, screening of excipient-API compatibility is recognized as an important aspect of formulation development. Moreover, the USFDA’s 21st century current Good Manufacturing Practices (cGMP) initiative and International Council on Harmonization (ICH) Q8 guidelines encourage the pharmaceutical manufacturers to apply Quality by Design (QbD) principles in their drug development process [21, 22]. These guidelines include expectations of a clear understanding of any interactions between the formulation components. Moreover, recent advances in various thermal and non-thermal analytical techniques have led to an improved efficiency in the detection, monitoring and prevention of the incompatibilities early in the drug development process [23, 24].

This article aims to provide a brief overview of the nature of drug-excipient incompatibilities; as well as current trends and techniques used to evaluate these compatibilities in formulation development.

2. Drug-excipient incompatibilities
Pharmaceutical incompatibilities are generally referred to as changes in the physical, chemical and/or therapeutic properties of a dosage form resulting from the interaction of the API with excipients or other components of the drug product [25]. A wide variety of factors influence the nature and extent of drug-excipient interactions. These factors include the physico-chemical properties of the drugs and the excipients, relative ratios and proximity of these components in the formulations, and other processing and environmental factors. In addition, the reactive impurities present in the excipients are also known to initiate such interactions [26]. The drug-excipients interactions can be broadly classified as either physical or chemical interactions [27].

2.1 Physical interactions
The physical interactions between the API and excipients do not involve formation or breakage of chemical bonds in the drug molecular structure. These interactions however, may lead to changes in the organoleptic properties, polymorphic forms, crystallization behavior, or drug-release and stability profiles [29]. Hussain et al. studied the effects of several commercial grades and a high-purity magnesium stearate on in-vitro dissolution of acetaminophen directly-compressed tablets [29]. The study results showed that the adsorption of finely divided hydrophobic magnesium stearate on acetaminophen can lead to a decrease in the dissolution rate and bioavailability. Forni et al. reported the conversion of chloramphenicol acetate from polymorphic form B to form A after grinding with colloidal silica [30]. This transition was attributed to the induction of crystal defects with reduction in the
chloramphenicol acetate crystallinity due to the grinding with abrasive excipient. In contrast, the API form-conversion can be stabilized by excipient interactions. Tantry et al. found that high molecular weight polyvinyl pyrrolidone (PVP) inhibited the transition of metastable theophylline to the stable form during the wet granulation [31]. Thus physical interactions between the API and excipients can often be beneficial and purposefully introduced in the formulations to improve properties such as solubility and bioavailability [32].

2.2 Chemical interactions

The chemical interactions between the API and excipients involve changes in the molecular structure of the API. These molecular changes can lead to degradation of API or formation of new molecules called as ‘degradants’ [28]. Chemical incompatibilities eventually result in a decrease in the API content and subsequent potency in the dosage form, or may even cause toxicities due to the degradants. The most commonly known modes of degradation pathways include hydrolysis, oxidation, isomerization, photolysis, and polymerization [16]. These pathways can be further sub-classified into a range of mechanisms. For example, the oxidation reactions could occur due to free radical autoxidation, nucleophilic/electrophilic reactions and electron transfer mechanisms. Most underlying mechanisms involved in these drug-degradation pathways include alteration in the moisture content in a dosage-form, changes in the dosage-form micro-environmental pH, general acid/base catalysis, and/or direct reactions with the API or the impurities that can initiate or catalyze drug degradation [28]. The ‘Maillard reaction’ is a classic example of a chemical incompatibility due to the interaction between the drugs containing primary and secondary amine groups, and reducing sugars (e.g. lactose). The rates of these chemical degradations may also depend on the physical state of the API and excipients. API and excipients in liquid states show higher degradation rates than those in solid state due to the high molecular mobility. Wirth et al. reported the colored pigmentation of fluoxetine HCl tablets due to Maillard reaction between lactose and the secondary amine group of fluoxetine [33]. Ahlneck et al. reported a comparatively higher rate of hydrolytic degradation of aspirin in the presence of microcrystalline cellulose than microfibre cellulose [34]. This difference was attributed to the high water reactivity due to weakly adsorbed moisture on microcrystalline cellulose. It is known that unbound or weakly adsorbed water enhances the high molecular mobility within a system. On the other hand, excipients such as colloidal silica and silica gel adsorb water strongly and are known to act as a water scavengers, thus resulting in a lower water activity in the formulations [35, 36]. Yu et al. demonstrated that cetirizine reacts with sorbitol and glycerol in oral liquid formulation to form monoesters. This ester formation was attributed to the chemical interaction between the API carboxylic acid moiety and excipient hydroxyl group [37]. Excipients are also known to reduce the activation energy of the reaction to catalyze the API degradation. Killion et al. reported that the hydrolysis rate of p-nitrophenyl esters in neutral to alkaline solution was increased due to nucleophilic catalysis by various sugars such as dextrose, sucrose, and other polyhydric alcohols such as sorbitol, and mannitol [38]. Ionizable functional groups of excipients may also act as pH modifiers. This can alter the pH of the formulation and its degradation rate. Gu et al. reported the increase in the degradation rate of moexipril HCl, a dipeptide angiotensin-converting enzyme (ACE) inhibitor by pH modifying excipients [39]. On the other hand, pH modifiers may be intentionally added in certain formulations to enhance the dissolution rate. Citric, tartaric, and succinic acids are commonly used in the immediate- and controlled-release formulations of weakly basic drug to improve drug-release rates [40].

As mentioned above, the reactive impurities present in the excipients can propagate the API degradation. Polyethylene glycol (PEG), a common plasticizer used in the coating materials, is known undergo oxidative degradation to generate formaldehyde and formic acid at elevated temperatures and humidities. A smoking cessation drug, varenicline was found to react with this in-situ generated formaldehyde and formic acid to form two separate degradants [41]. Commonly used lubricant like magnesium stearate contains magnesium oxide as a reactive impurity. Kararli et al. has reported a reaction between magnesium oxide with ibuprofen [42]. This reaction, which is a classical acid-base reaction has also been used to stabilize API molecules [43, 44].

Although the above-mentioned description of physical and chemical interactions between drug and excipient is not comprehensive, it gives an idea of potential scenarios for such interactions and their effects on the final dosage forms.

3. Evaluation of drug-excipient compatibility/incompatibilities

The drug-excipient compatibility studies are carried out with an intent to identify, quantify and predict potential interactions (physical or chemical) along with the impact of these interactions on the manufacturability, quality and performance of the final drug product. These studies are typically based on the prior knowledge regarding the physico-chemical properties and the degradation mechanisms of the drugs and the excipients [27]. In addition to evaluating the direct interactions between the API and the excipients, the influence of factors such as water (moisture) and temperature is also explored in these studies. These factors are known to accelerate the likelihood, and the extent of drug-excipient interactions either by altering the physico-chemical properties or rate of degradation of the drugs and/or excipients [45-47]. These studies generally involve bringing the API and the excipient/s into intimate contact with each other either as physical admixtures in a predetermined ratio, or as a preliminary dosage form; and subjected them to various stress conditions. The physico-chemical and performance attributes of the API and the excipients are then evaluated using one or more analytical techniques.

4. Analytical techniques for the evaluation of drug-excipient interactions

The evaluation of drug-excipient compatibility encompasses a broad range of thermal and non-thermal analytical techniques. These techniques are diverse with respect to their principles of operation, sample size, duration of analysis, the type of stress i.e. thermal, mechanical etc. Moreover, due to the wide variation in the chemical and physical nature of drugs and the excipients, and the complex nature of their interactions, there is a lack of universal standards in the methodology utilized in the evaluation of compatibility between the API and the excipients.
In recent years however, there has been a significant increase in the number of individual studies reporting the use of one or more techniques for screening API-excipient compatibility. The commonly reported techniques include, thermo-analytical techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), differential thermal analysis (DTA), isothermal microcalorimetry (ITC), high performance liquid chromatography (HPLC), near infrared spectroscopy (NIR) and solid state nuclear magnetic resonance spectroscopy (ssNMR) [17, 48-56]. Applications of these techniques as drug-excipient compatibility screening tools, along with their advantages and drawbacks are briefly discussed below.

4.1 Thermal techniques

4.1.1 Differential scanning calorimetry
Differential scanning calorimetry (DSC) is the most common thermal technique utilized for testing excipient incompatibilities [57]. This technique usually only requires a small sample size and the results are obtained relatively rapidly [58]. Tita et al. used thermogravimetry / derivative thermogravimetry (TG/DTG) and DSC techniques to evaluate the compatibility between ketoprofen and several excipients including corn starch, microcrystalline cellulose, colloidal silicon dioxide, lactose, PVP K30, magnesium stearate and talc [19]. The study results demonstrated that DSC helps us ascertain any incompatibilities in the formulation components. These may include changes in appearance, in endothermic or exothermic peaks, or in enthalpy curves. In a similar study, Tita et al. evaluated the compatibility of the acetylsalicylic acid, a non-steroidal anti-inflammatory drug, with pharmaceutical excipients of common use including diluents, binders, disintegrants, lubricants and solubilizing agents [20]. The results confirmed the utility of DSC as a sensitive and a specific technique in assessing the drug-excipient compatibility.

Although DSC is frequently used due to its inexpensive and eco-friendly nature, it is important to understand that it may not provide accurate results in every situation. For instance, amorphous API are known to reduce the enthalpy of fusion of the API [59]. DSC often involves exposing the formulations to temperatures that may degrade excipients (as high as 300°C) and are physiologically unrealistic [58, 60]. As a result, DSC may sometimes be misleading and is often used in combinations with other techniques to ensure accuracy [61]. This technique however, can be used in combination with SEM to search for physical incompatibilities within a formulation [57].

4.1.2 Thermogravimetric analysis
Thermal testing is improved when thermogravimetric analysis (TGA) is conducted. This test, along with the DSC, examines the mass of formulation lost as a percentage with increasing temperature. Additionally, thermogravimetry and derivative thermogravimetry can determine the reactivity of each excipient with the API or with each other [20]. Tita et al utilized TGA, in addition to the DSC to check the compatibility of acetylsalicylic acid with 11 other excipients [20]. The thermogravimetric analysis, derivative thermogravimetric analysis, and DSC revealed that all excipients, aside from polyvinyl pyrrolidone (PVP) and magnesium stearate, were compatible with acetylsalicylic acid. In another study, Tita et al. assessed the compatibility of ketoprofen with similar, commonly used excipients using DSC, TGA, DTGA, PXRD and FTIR [19]. The TGA results along with other techniques revealed a possible interaction between the ketoprofen and PVP K30, and between ketoprofen and magnesium stearate.

In a study on the compatibilities between excipients and sildenafil citrate conducted by Julio et al, the DSC and TG curves showed that after heating to a range of 190-229.5°C, 28.8% of citric acid was evaporated. What remained was the sildenafil base that later decomposed at higher temperatures [61]. The TG curves in this analysis helped to understand each temperature range at which excipients would be lost.

4.1.3 Isothermal microcalorimetry
Isothermal microcalorimetry (IMC), or isothermal stress testing, is another method that helps determine the integrity of the pharmaceutical formulations. The test involves storing the excipients for three to four weeks, with or without moisture, at temperatures above 50°C. This process simulates drug aging and stimulates excipient interactions. The test has the capacity to determine compatibilities, but is limited by its time-consuming and arduous nature [60].

After a predetermined storage period, the contents of the formulation are analyzed using methods such as HPLC and DSC [62, 63]. Thumma et al. used IMC in combination with DSC to understand the compatibilities between promethazine HCl and certain excipients such as PMZ-Pearlitol® SD 200, lactose monohydrate, and zinc stearate. They found, through IMC, that after three months of storage at accelerated stability conditions, the tablet formulation had an acceptable level of reactivity and was thermally stable. This test not only helped with determining incompatibilities, but also offset the misleading results commonly associated with DSC.

4.1.4 Hot stage microscopy
Methods involving microscopy are used to study the drug formulation morphology and to identify any physical incompatibilities associated with the excipients [57]. Mura et al. conducted a study to evaluate the compatibility of ibuprofen and excipients using DSC [51]. Hot-stage microscopy (HSM) was used as an adjunct to DSC. The process required only a small amount of sample, and the microscopy results confirmed that the incompatibilities found in the DSC analysis was due in part by the dissolution of excipient at an elevated temperature. In a different study, conducted by Aigner et al, HSM was used to find thermal behavior of aceclofenac [53]. DSC revealed one sharp endothermic peak at 153.1 degrees Celsius. Magnesium Stearate, an excipient in this formulation, showed three endothermic peaks on the DSC analysis at 89.2, 104.5, and 203.5 degrees Celsius. The HSM analysis showed that the magnesium stearate melted first and subsequently dissolved the aceclofenac. HSM thus essentially explained the...
disappearance of aceclofenac and the peak associated with magnesium stearate on the DSC. It is thus advisable that when
developing formulations, both DSC and HSM be used in conjunction to ensure accuracy and compatibility of drug excipients.

4.2 Non-thermal techniques

4.2.1 Infrared, near-infrared and Raman spectroscopy

Infrared (IR), near-infrared (NIR) and Raman spectroscopy are the most commonly used non-thermal techniques for the screening
of drug-excipient compatibility. These techniques provide a unique fingerprint to the API and the excipients based on their physical
and chemical attributes. Due to the highly sensitive nature of these techniques, any subtle deviations in the physico-chemical
properties of the API as a result of the interactions with the excipients are readily detected. Commonly observed physico-chemical
changes due to drug-excipient interactions include polymorph transitions, dehydration, formation of hydrates/solvates, changes in
the deformation behavior of powders etc. [10, 64-67]. Some of the common advantages of these techniques include rapid analysis,
quick and easy detection of incompatibilities due to spectral shifts and the detection of interaction byproducts. Aigner et al.
investigated the compatibility of aceclofenac with various tableting excipients such as Carbopol® 940, hydroxypropyl
methylcellulose, microcrystalline cellulose, Aerosil® 200 and magnesium stearate using DSC and FT-IR [53]. The study results
showed the occurrence of interaction between aceclofenac and magnesium stearate resulting in the formation of magnesium salt of
aceclofenac. The other excipients were found to be compatible with the drug i.e. no significant interaction was observed between
aceclofenac and other excipients. Similarly Pani et al. assessed the compatibility of nateglinide with various excipients in the
development of immediate release tablets of nateglinide using DSC, IR and IST [68]. The IR results revealed the absence of
any significant incompatibilities between the API and the tested excipients.

Blanco et al. evaluated the polymorphic transition in Dexketoprofen Trometamol (DKP) production samples obtained by direct
compression and wet granulation using Multivariate Curve Resolution - Alternating Least Squares (MCR-ALS) methodology to
obtain the NIR spectra for samples without pretreatment [64]. The results showed that significant polymorphic transition occurred in
DKP during wet granulation; whereas, no changes were observed with samples processed via direct compression. Dave et al.
investigated the influence of plasticizer (triethyl citrate, TEC) level on the breaking force of extended-release matrix tablets prepared
by roller-compaction [10]. The multivariate analysis of the results demonstrated the feasibility of NIR spectroscopy in evaluating the
influence of TEC levels on the breaking force of prepared tablets. Kogermann et al. explored the dehydration of piroxicam
monohydrate in compacts using terahertz pulsed spectroscopy (TPS), Raman spectroscopy, and reflectance near-infrared (NIR)
spectroscopy [65]. The study results concluded that the Raman and NIR spectroscopy were suitable for monitoring the loss of
moisture along with the structural changes that occurred during the dehydration of samples.

4.2.2 Powder x-ray diffraction

In the preformulation stage of the drug development process, powder x-ray diffraction (PXRD) is used to characterize the crystalline
nature of materials. PXRD is a widely used polymorph screening technique for the API. Each crystalline material exhibits a unique
x-ray diffraction pattern, as displayed by the peak intensities against a range of diffraction angles (θ). Any interactions between the
API and excipients that results in a change in the crystalline form of the API is generally exhibited as a shift, appearance or
disappearance of these peak intensities. Thus PXRD analysis can provide useful information regarding the influence of drug-
excipent interactions on the polymorphic changes in the API. PXRD analysis may also be useful in the evaluation of API
polymorphic transitions occurring as under the influence of moisture and temperature changes during processing, albeit only in the
absence of interference from any excipient peaks [69, 70].

Tita et al. assessed the compatibility between ketoprofen and several excipients such as corn starch, microcrystalline cellulose,
colloidal silicon dioxide, lactose, polyvinyl pyrrolidone K30, magnesium stearate and talc using DSC, TGA, FTIR and PXRD [19].
The PXRD data confirmed the DSC and TGA results indicating a possible interaction between the KT with polyvinyl pyrrolidone K30
and magnesium stearate, as demonstrated by the changes in the intensity of peaks as well as disappearance of certain peaks
observed in the spectra of individual components. In a similar study, Tita et al. evaluated the compatibility of the acetylsalicylic acid
(ASA) with pharmaceutical excipients including diluents, binders, disintegrants, lubricants and solubilizing agents using DSC, TGA,
FTIR and PXRD [20]. The x-ray analysis results confirmed a possible chemical interaction between the ASA with polyvinyl
pyrrolidone K30 and magnesium stearate, and a possible physical interaction with colloidal silicon dioxide and stearic acid. In
another study, Roumelli et al. demonstrated the compatibility of trandalopril with α-lactose monohydrate, microcrystalline cellulose,
and pre-gelatinized starch using PXRD analysis of the physical mixtures of the drug with the selected excipients [71].

4.2.3 Solid-state nuclear magnetic resonance spectroscopy

Solid-state nuclear magnetic resonance (ssNMR) spectroscopy has emerged as a common analytical tool for the analysis of drug-
excipient interactions in recent years [72-78]. This technique identifies the interactions between the API and the excipients through
variations in the chemical shift occurring as a result of change in the electron density around the interaction sites. Some of the
known advantages of this technique include higher selectivity, limited interference from excipients and the ability to detect
polymorphic transitions in the API. In addition, the presence and influence of water on the drug-excipient interactions are easily
detected by this method. The main drawback of this technique is the duration of analysis, which often can be lengthy and complex.
Chen et al. investigated the acid–base reactions of solid materials, a common type of drug–excipient interaction using binary
mixtures (1:1) of pure α-form indomethacin and sodium bicarbonate as model drug and excipient respectively [74]. The ssNMR
results, along with those obtained from PXRD analysis confirmed the transformation of the mixtures into the microcrystals of sodium
indomethacin trihydrate, indicating the presence of drug-excipient interaction. In another study, Skotnicki et al. evaluated the
compatibility of bisoprolol fumarate with amorphous valsartan using DSC, TMDSC, ssNMR and PXRD [76]. The study results
indicated a strong interaction between bisoprolol fumarate and valsartan above 60°C. The ssNMR data provided the information on
the incompatibility at a molecular level. Schachter et al. characterized the nature of interaction between ketoprofen and polyethylene oxide (PEO) in a solid dispersion formulation using ssNMR along with other analytical techniques [79]. The $^{13}$C single pulse/magic angle spinning NMR indicated the presence of hydrogen bonds between the carboxylic group of ketoprofen and the ether oxygen of PEO, indicating a drug-excipient interaction.

4.3 Microscopic techniques

**Scanning electron microscopy**

The interactions between the API and the excipients often result in polymorphic transitions and changes in crystal habits of the API. Scanning electron microscopy (SEM) provides useful information on such changes by characterizing the surface morphology of pharmaceutical APIs. Although SEM may not independently provide information on the nature of drug-excipient interaction at a molecular level for e.g. chemical and thermal transitions; combining SEM with other analytical techniques such as DSC/TGA, HSM, and other thermal techniques can significantly benefit to the overall characterization of the incompatibilities [51, 80]. Mura et al. assessed the compatibility of ibuprofen with commonly used excipients such as corn starch, Avicel, sodium carboxymethyl cellulose, polyethylene glycol 4000 (PEG-4000), palmitic acid, stearic acid, Ca- and Mg-stearate, polyvinyl poly-pyrrolidone (PVPP) and polyvinyl pyrrolidone K30 (PVP K30) [51]. The results obtained from the SEM analysis were in general, in agreement with and confirmatory to those obtained from DSC and HSM.

4.4 Chromatographic techniques

4.4.1 High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) is the most widely used analytical technique for determining the API content in a formulation. This technique can be very useful in situations where the drug-excipient interaction may lead to a quantitative changes in the API [58, 61, 81]. In drug-excipient compatibility studies, the formulations or the drug-excipient mixtures are subjected to high temperatures for a predetermined period of time i.e. isothermal stress testing (IST) to accelerate any chemical incompatibilities. This is followed by determination of drug content using HPLC analysis, thus identifying any quantitative loss of drug as a result of interactions with the excipients [39, 82].

Gu et al. screened the compatibility of moexipril HCl, an angiotensin-converting enzyme (ACE) inhibitor, with commonly used filters, disintegrants, lubricants, glidants, and coating agents using IST along with HPLC [39]. The HPLC results confirmed the presence of interactions between the drug and the excipient. The results also indicated that neutralization of the acidic drug by the basic excipients suppressed drug degradation. In another study, Julio et al. evaluated the compatibility of sildenafil citrate with colloidal silicon dioxide, crosscarmellose sodium, lactose, mannitol and sucrose using DSC, HSM and HPLC [61]. The accelerated stability studies results showed the presence of incompatibilities between the drug and the selected excipients. However, it was also observed that some incompatibilities detected by HPLC, were not detected by DSC and vice-versa. The study demonstrated the benefits of complementing the thermal techniques with HPLC in detecting incompatibilities and providing more robust and accurate approaches for pre-formulation studies.

Along with the commonly recognized advantages of HPLC such as accuracy and robustness, the main drawback of the technique is that this technique is time consuming and complex. To evaluate the drug-excipient compatibility, this I is a very useful supportive tool in preformulation studies.

5. Conclusions

A clear understanding of the physicochemical characteristics of the API and the excipients, as well as the nature and the magnitude of their interactions, is critical to ensuring a robust product development. The range of available thermal and non-thermal analytical tools plays a major role in the detection of drug-excipient interactions in the early stages of drug development. A rational choice of a combination of analytical methods, based on their capabilities and limitations is the key to obtain comprehensive information on drug-excipient compatibility.

6. References

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