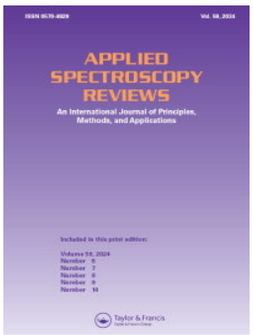

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REVIEW ARTICLE

Fourier transform infrared spectroscopy used in drug excipients compatibility studies

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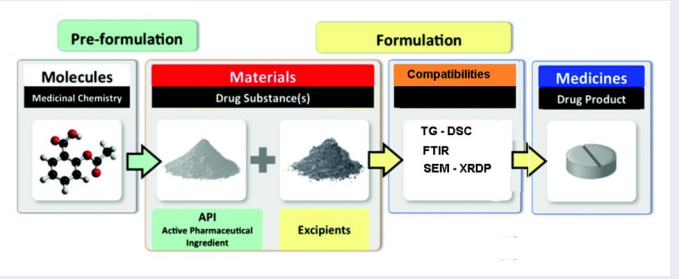
ABSTRACT

Drug-excipient interaction/incompatibility is a major concern for drug stability and effectiveness. Assessing the compatibility of excipients is an essential phase in the formulation process for all pharmaceutical dosage forms. Incompatibility can be investigated using a variety of thermal and nonthermal approaches. Infrared spectroscopy can provide insights into potential intermolecular interactions between components by identifying specific vibrational modes that correspond to physico-chemical properties (chemical bonds and their strength) and molecular symmetry of a molecule. This article reviews some of the most relevant studies on Fourier Transform Infrared spectroscopy utilized as a tool for compatibility screening between 2017 and 2024.

GRAPHICAL ABSTRACT



KEYWORDS

FTIR spectroscopy; drug-excipient compatibility; pre-formulation studies; nonthermal approaches

Introduction

Most modern pharmaceutical formulations are complex systems containing various components, known as excipients, alongside the active pharmaceutical ingredient (API).

The term 'excipient' comes from the Latin '*excipere*', meaning 'to except', which is simply explained as 'other than'. Excipients play a crucial role in the development and design of dosage forms.[1] They are often included to enhance the stability of the formulation. While they are ideally supposed to be inert, it has been recently indicated

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that they can cause adverse reactions. In other words, they are pharmacologically inactive ingredients added to drug products for various functional purposes. For example, they can enhance the volume or size of a dosage form, assist in the breakdown of solid forms, bind particles together, lubricate machinery during manufacturing, mask unpleasant flavors, adjust the release of a drug, etc.

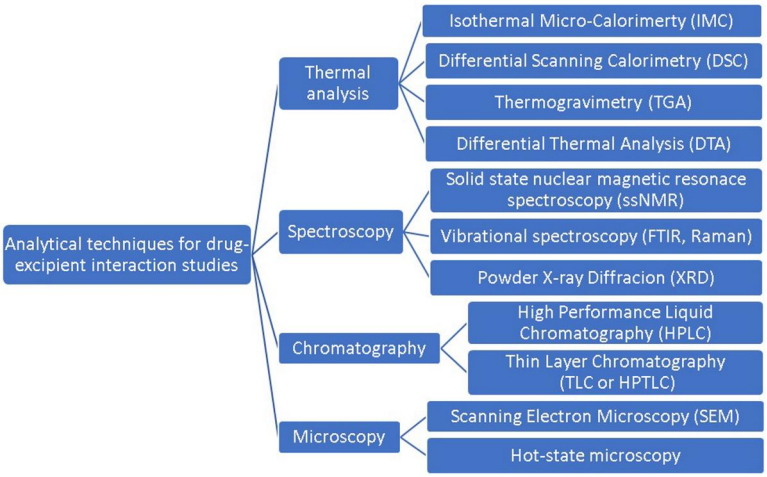
Research on excipient compatibility aims to identify dosage form components compatible with the drug. Thoroughly planned and executed experiments provide insights into the drug's stability profile, including the degradation products and mechanisms. It is a common misconception that excipient compatibility studies are monotonous and routine.

Drug-excipient compatibility is critical during pre-formulation studies as it can impact the physico-chemical characteristics and bioavailability of the drugs involved. The development of drug-excipient compatibility is essential in designing pharmaceutical products, but the associated costs and time constraints make predictive techniques particularly appealing.[2] When choosing the type, grade, and concentration of excipients for a formulation, excipient-compatibility tests and formulation development studies are crucial. The concentration of excipients is determined based on their functional characteristics and compatibility with the drug. Uniform and reliable performance in terms of identity, purity, and functionality is essential for the safe use of excipients in dosage forms. Typical indicators of API degradation are alterations in color, flavor, smell, polymorphic structure, or the formation of crystals, all of which suggest pharmaceutical incompatibility. These changes are typically due to chemical interactions between the excipient(s) and API, leading to API degradation.[3,4]

Excipients are more than just inactive substances used to facilitate pharmaceutical production, administration, or absorption; they can interact with the API or other environmental elements, potentially catalyzing the breakdown of pharmaceutical compounds.[4] Various analytical techniques can be employed to study drug-excipient interactions, including spectroscopic methods (FT-IR, NMR, X-ray diffraction), thermal analysis (DSC, DTA, DTG, ITC), and chromatographic methods (HPLC, LC-MS/MS).[5–7] These techniques range from complex and time-consuming to less predictive. Given the importance of this type of research, developing a quick and straightforward procedure with accurate results is essential. Scheme 1 presents the primary analytical methods used for compatibility evaluation.

API-excipient interactions are categorized as either physical or chemical. Physical interactions can alter physicochemical characteristics such as solubility and dissolution rate, affecting drug bioavailability. Additionally, these interactions can impact organoleptic properties (taste, color, odor), solid-state characteristics, polymorphic forms, tensile strength, and drug release. Chemical interactions, on the other hand, can lead to drug degradation and the formation of harmful degradation products, resulting in potency loss.[4,8]

For investigating these interactions, thermal and spectroscopic methods have been utilized for over thirty years. Spectroscopic techniques, such as Fourier transform infrared (FTIR), near-infrared (NIR), and Raman examine the behavior of pharmaceutical compounds in the solid state and serve as a compatibility screening method to identify vibrational changes that suggest potential intermolecular interactions.[4]



Scheme 1. Analytical techniques commonly employed for drug-excipient interaction studies.

Thermal analysis techniques, like thermogravimetry (TG), are commonly used for compatibility studies by comparing thermogravimetric curves of drug-excipient mixtures with those of individual ingredients.[9] Nonetheless, TG has limitations since the samples are exposed to high temperatures not encountered in real-world settings.[10]

Selecting suitable excipients for a specific application can be challenging due to the variety of available excipients and the common issue of poor water solubility in modern drugs. In modern pharmaceutics research, lipid-based drug delivery systems and solid dispersions are often used to address bioavailability issues.[11]

Qualitative and quantitative spectroscopic techniques are typically quick and offer advantages when combined with chemometric tools. FTIR is particularly recommended for detecting interactions between APIs and excipients, indicated by changes in peak intensity, the appearance of new peaks, or absorption peaks.[12]

Primary chemical processes affecting API-excipient compatibility include hydrolysis, photolysis, oxidation, isomerization, and polymerization. Factors influencing these processes include temperature, pH, moisture content, relative humidity, catalysts, light, oxygen, the drug's physical form, and the particle size of the drug and excipients. Thus, this review addresses other incompatibilities of various APIs with different excipients, apart from previously published reviews from 2017 to 2024.[7,12–14]

Excipients compatibilities studied by FTIR spectroscopy

The objectives of this review are to present a curated selection of the most important studies conducted on the application of infrared spectroscopy technique for assessing excipient compatibility. These studies, spanning from 2017 to 2024, vary in depth, with some of them providing more details while others just mentioned in a tabular format.

Acetazolamide, a carbonic anhydrase inhibitor named Diamox, is extensively used in ophthalmology to lower elevated intraocular pressure in glaucoma patients. It is also employed postoperatively following intraocular surgeries like cataract surgery.[15]

The research was performed to determine the compatibility between acetazolamide and various excipients, including magnesium stearate, lactose, mannitol, chitosan, meglumine, β-cyclodextrin, PVP (polyvinylpyrrolidone) K-30, methylcellulose, and starch.[16]

Figure 1 presents a comparative display of the FTIR spectra of acetazolamide and two of the excipients, magnesium stearate and meglumine, employed in this study.

Most of the combinations under investigation have distinctive acetazolamide absorption bands, as shown by the FTIR spectra presented in Figure 1. The bands of acetazolamide and excipients, however, overlapped in the spectra of all the combinations since they were in the same spectral regions. A shift in the acetazolamide band's breadth, shape, and intensity was noted in the 1700–1000 cm^{-1} range in the combinations including β-cyclodextrin and chitosan. New bands occurred at 1504 cm^{-1}, most likely caused by stretching of the acetazolamide C=N ring, and at 1032 cm^{-1}, most likely caused by stretching of the β-cyclodextrin C–O–C in the spectra of mixtures containing β-cyclodextrin. β-cyclodextrin combinations generally have spectra that closely resemble the components' spectra.[17] The large hydroxyl band of β-cyclodextrin narrowed at

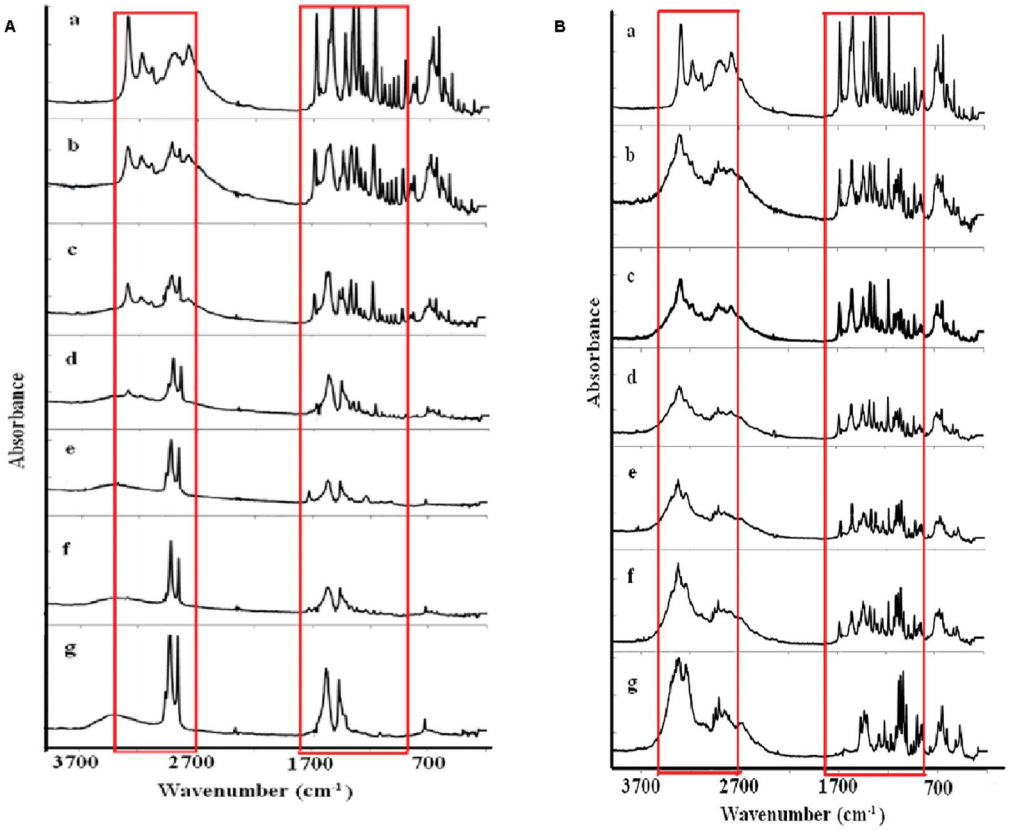


Figure 1. (A) FTIR spectra of (a) acetazolamide, (g) magnesium stearate and their mixtures at the ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7 and (f) 1:9. (B) FTIR spectra of (a) acetazolamide, (g) meglumine and their mixtures at the ratios: (b) 9:1, (c) 7:3, (d) 1:1, (e) 3:7 and (f) 1:9 (reproduced from[16] with permission).

roughly 3370 cm^{-1}, a common occurrence for inclusion complexes, confirming the existence of the inclusion complex.

The unique absorption patterns of acetazolamide are prominent in most of the tested mixtures, as evident in the combinations with magnesium stearate. Spectra of acetazolamide paired with meglumine exhibit variations within specific ranges 3600 and 2800 cm^{-1} and 1700 and 800 cm^{-1}. Incompatibility arises when acetazolamide is combined with starch, resulting in the emergence of a new band at 1736 cm^{-1}. Similar incompatibility is observed in mixtures of seproxetine maleate and clenbuterol with starch.[18]

Estrogens, which are natural hormones produced within the body, exert diverse physiological impacts. Estriol (E3), chemically known as 1,3,5(10)-Estratriene-3,16,17-triol, is the primary estrogen during pregnancy. Despite less attention outside pregnancy, estriol exhibits agonistic, antagonistic, and estrogenic actions. The placenta secretes the majority of it.[19]

Potential interactions were evaluated between estriol and various excipients (calcium phosphate dibasic, magnesium stearate, mannitol, lactose, sucrose, sodium carboxymethyl cellulose, butylated hydroxyanisole, cellulose, and talc).[20] Every constituent, whether in its pure form or in select solid binary combinations of estriol with excipients, underwent DSC and FTIR analyses.

According to the FTIR compatibility data, the characteristic peaks of estriol are preserved in the presence of calcium phosphate dibasic, cellulose, butylated hydroxyanisole, talc, and sodium carboxymethyl cellulose. These peaks either showed a decrease in intensity, a shift to different wavenumbers, or disappeared in binary mixtures containing mannitol, sucrose, lactose, cellulose, and magnesium stearate.

Diazepam (DZM), is the most common benzodiazepine, and its prescription is for alleviating symptoms of convulsions, insomnia, and anxiety as well as for sedation and muscle relaxation.[21]

A study investigated potential solid-state interactions between 1:1 (*w/w*) physical mixtures of DZM and various tablet excipients using TG, DSC, and IR spectroscopy.[22] The excipients included colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and talc. These combinations underwent analysis at intervals of 1, 2, and 3 months under accelerated conditions (40 °C/75% RH) to assess the impact of accelerated aging. Figure 2 presents the FTIR spectra of DZM, as well as mixtures with sodium alginate, guar gum, and of course, the solid dispersion formulation, and no interaction was found.

The amide C=O group of the DZM molecule exhibited a consistent sharp peak at 1685 cm^{-1} in the spectra of all physical binary mixtures. The presence of DZM peaks in all mixtures indicates no interactions or incompatibilities with the tablet excipients. These results aligned with findings from TG analysis. Another similar study was performed to analyze the mixture between DZM and CSD (colloidal silicon dioxide).[23] Due to lower enthalpy values than anticipated, the DSC curves of the mixtures containing DZM and CSD suggested a potential interaction. However, the fact that IR and TG were unable to confirm this interaction shows that these methods are insufficiently sensitive to detect it. These findings imply that diazepam and CSD may interact but are not incompatible.

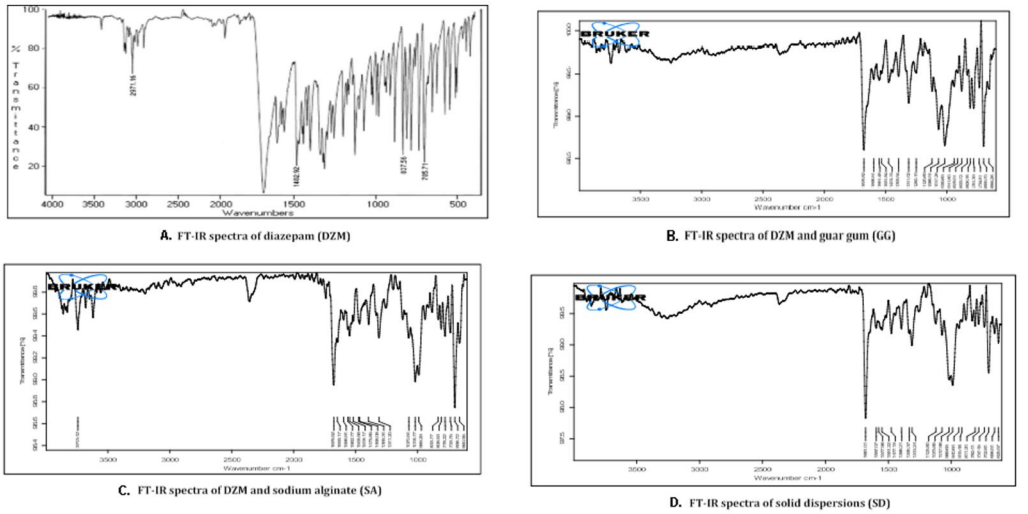


Figure 2. FTIR spectra of diazepam and mixtures with different excipients (reproduced from[22] under CC-BY-4.0 license).

Donepezil, ((±)-2-[(1-Benzyl-4-piperidyl) methyl]-5,6-dimethoxy-1-indanone hydrochloride), is recognized as a key medication for treating Alzheimer's disease, functioning as an acetylcholinesterase inhibitor that prevents the enzyme from breaking down acetylcholine.[24]

Donepezil's compatibility was investigated with several pharmaceutical excipients like anhydrous lactose, calcium lactate, magnesium stearate, magnesium citrate, mannitol, polyvinylpyrrolidone K30, silica, sorbitol, sodium carboxymethylcellulose, starch, and talc under ambient conditions, by XRPD and ATR–FTIR spectroscopic data; and later by thermoanalytical techniques (TG/DTG/HF) was later employed for evaluating the thermal-induced interactions.[25] Reactive functional groups in the molecules of the active medicinal ingredient and excipient are typically the focus of interaction searches. Due to protonation or deprotonation, ester hydrolysis, etc., the interaction causes some bands to disappear and other ones to arise. It also causes peak shifting to lower or higher wavenumbers. In this case, chemical interactions, particularly with the reactive groups – in this case, the keto group – as well as polymorphic transitions are possible during sample preparation.[26] To determine if donepezil bands were present in the spectrum of binary mixtures, binary mixtures were compared to pure donepezil with an analysis. Based on these results, it is evident that there are no interactions between donepezil and the excipients during trituration at ambient conditions. According to thermal analysis, donepezil was concluded to be compatible with magnesium citrate, polyvinylpyrrolidone, and talc under both ambient conditions and at high temperatures.

Another study was performed for studying to discover if donepezil and other certain excipients – such as talc, sodium starch glycolate, mannitol, magnesium stearate, and microcrystalline cellulose – may interact when stored at high temperatures.[27] There was no discernible difference between the infrared spectra of pure donepezil and combinations of the drug in powder form. Additionally, on day 20 of storage at 55^0C, neither missing bands nor the emergence of new bands were observed in the IR spectra of the

powder combinations. Since no change in the peak area, no change in Rt, and no additional peaks were observed due to the drug and excipient degradation products, it was concluded that the samples were stable for 20 days at 55^0C.

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a common plant compound derived from cinnamic acid.[28] It is the most prevalent phenolic acid found in whole grains, grapes, parsley, spinach, and rhubarb.[29] It not only neutralizes free radicals but also boosts the activity of enzymes that neutralize them and inhibits the enzymes that facilitate their production.[30] It has been widely incorporated into skin care products for its photoprotective properties and its ability to slow down skin photoaging. In a study, Bezerra and colleagues employed thermoanalytical techniques (TG/DTG and DSC) along with Pearson's correlation – used to measure the strength of the linear relationship between two data sets – [31] using FTIR data to assess whether ferulic acid is compatible with various excipients in skincare formulations.[32] The thermoanalytical data indicated that ferulic acid was compatible with the following excipients: Dow Corning® RM 2051, Carbopol® Ultrez 30, Crodabase CR2®, Crodamol™, GTCC, EDTA, and passion fruit seed oil. However, it was also suggested that potential interactions could occur between ferulic acid and the excipients such as glyceryl stearate, Optiphen®, and Rapithix® A-60. Pearson's correlation confirmed that Dow Corning® RM 2051, Carbopol® Ultrez 30, Crodabase CR2®, Crodamol™ GTCC, EDTA, glyceryl stearate, passion fruit seed oil, and Rapithix® A-60 did not exhibit any incompatibilities that could compromise the properties of ferulic acid. It was recommended to avoid using caprylyl glycol (Optiphen®) in the cosmetic formulation of ferulic acid owing to a marked incompatibility between these two substances demonstrated through Pearson's correlation.

In another study, the suitability of flurbiprofen (FLB) and triclosan (TCS) was evaluated with chitosan (CS), Kolliphor® P188 (KP), and poly-ε-caprolactone (PCL) for possible application in the design of nanoformulations.[33] The 1:1 physical mixtures' FTIR spectra showed simple superimposition with the original bands well retained (as displayed in Figure 3), indicating a lack of drug-excipient interactions in the mixtures (TCS+PCL, TCS+KP, FLB+KP, FLB+PCL). Minor variations in the IR spectra of other combinations, such as decreased intensity, peak broadening, or slight shifts, could be attributed to dilution and mixing effects. Some peaks overlapped due to their presence in similar spectral regions. As a result, the FTIR findings confirmed the chemical compatibility of the selected components in drug-excipient or drug-drug pairings.

There were no interactions observed in the FTIR spectra of the mixtures of the pure drugs and other components; the spectra simply represented the superimposition of their components. It is crucial to note that some of the absorption bands of the drugs and excipients overlap in the 3800–2800 cm^{-1} range. These overlaps are mostly caused by the O–H, C–H, C–CH_3, and CH_2 groups, as well as the NH_2 group in the case of CS. Similarly, the spectra of the mixtures of drugs and excipients displayed distinct absorption bands for pure FLB, TCS, CS, KP, and PCL.

Thymol (TML) is a monoterpene known for its antibacterial, antifungal, antiparasitic, antioxidant, anti-inflammatory, and wound-healing properties. TML is highly liposoluble and volatile, which significantly limits its application in topical preparations.[34] These limitations were addressed by incorporating TML into nanostructured lipid

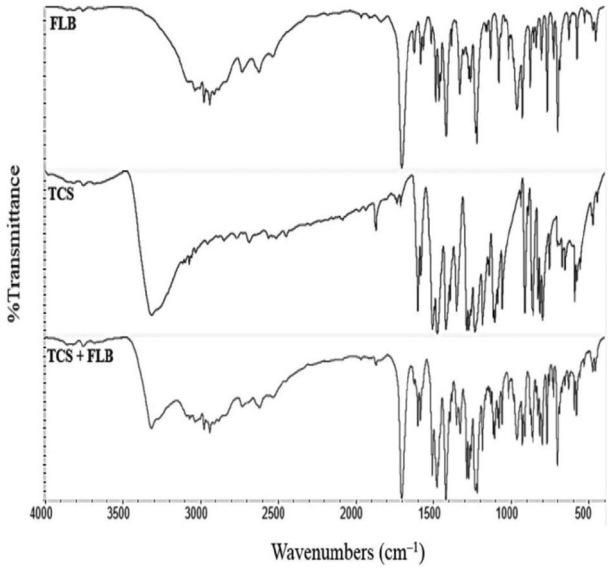


Figure 3. FTIR spectra of 1:1 *w/w* physical mixture of triclosan (TCS) and flurbiprofen (FLB), and their respective pure forms (reproduced from[33] under CC-BY-4.0 license).

carriers (NLC) because drug release into the surrounding environment was intercepted, thereby reducing volatilization.[35] Because NLC is made up of a combination of liquid and solid lipids or short- and long-chain glycerides that can be natural, semisynthetic, or synthetic, a study on TML-lipid excipient compatibility was highly desired. The correlation coefficient (r) was determined based on the spectral similarity of pre- and post-thermal stress to get a numerical representation of the FTIR data for evaluating the mixture design. Values of $r > 0.9$ suggested that the samples had a high level of structural similarity.[36]

Figure 4 displays the FTIR spectra of chosen mixtures pre- and post-thermal treatment, with alterations in the spectra marked and enumerated to denote the corresponding functional groups. The TML – sodium taurodeoxycholate (TAU) binary mixture, along with the TML – stearic acid (SA) – TAU ternary mixture, showed shifts in peaks corresponding to the C–O and –OH stretches (at 1205 and 3360 cm^{-1}, respectively) after thermal stress. Similarly, the TML – SA – polysorbate 80 (P80) ternary mixture displayed changes in the peaks associated with the C–O and –OH stretches (at 1222 and 3430 cm^{-1}, respectively). These shifts may result from hydrogen bonding between the donor (hydroxyl group) and the acceptor (carbonyl group).[37,38] The combined spectral changes, peak shifts, and variations in relative intensity, particularly in the TML – SA – TAU sample, indicate more than mere physical interaction, suggesting sample degradation.

Levodopa (L-Dopa or LD) is currently recognized as one of the World Health Organization's essential drugs, as it is an essential ingredient in the treatment of Parkinson's disease.[39] The primary challenge to LD's therapeutic effectiveness is its short plasma half-life of 1–3 h, limited bioavailability, and is highly soluble in acidic pH.[40] Given the fact that many products contain LD as the API and differ mainly in their excipients, compatibility analysis is essential for both future and existing

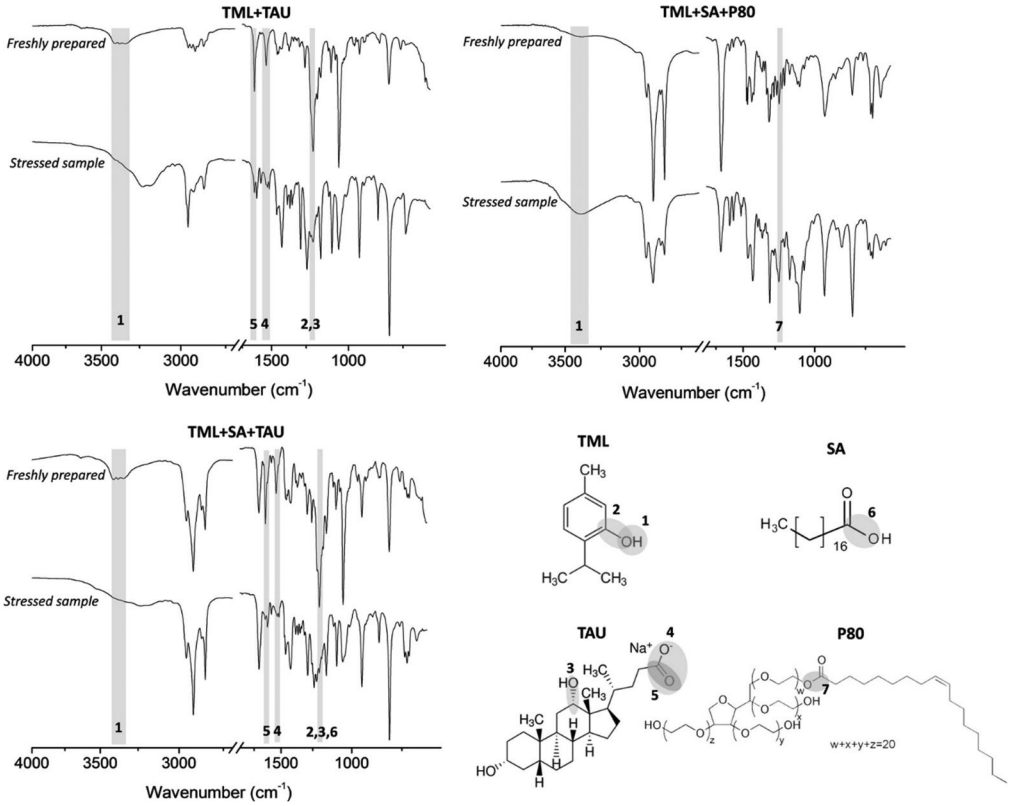


Figure 4. Chemical structures of the compounds and FTIR spectra of selected mixtures pre- and post-thermal treatment (reproduced from[36] with permission).

formulations.[41] Excipients for LD formulations were commonly chosen based on their classification into different categories and their various functions in the final solid formulation; e.g. anhydrous lactose, calcium lactate, magnesium citrate, magnesium stearate, mannitol, polyvinylpyrrolidone K30, silica, sodium carboxymethylcellulose, sorbitol, starch and talc. Several conclusions were obtained from the FTIR results, suggesting potential relationships between LD and anhydrous lactose, calcium lactate, magnesium stearate, mannitol, silica, and talc. Thermal stress determined the interactions in all samples, except for the magnesium citrate mixture.

During FTIR data analysis, several observations can be made. Most binary mixtures exhibit a broad band in the spectral range of 3500–2400 cm^{-1}, which becomes significantly more intense when excipients with O–H groups are present. When LD is combined with talc and silica, this broad band disappears from the spectrum. The presence of the strong band characteristic of Si–O bonding around 1100 cm^{-1} and the intense band of talc around 1000 cm^{-1} likely causes this attenuation. Nonetheless, the remaining bands of LD within the 1875–650 cm^{-1} range are still visible, especially those not obscured by the excipients' dominant bands.

In a different study, the interaction between LD and various excipients was investigated to develop coground binary mixtures for intranasal applications.[42]

Figure 5 presents the FTIR spectra comparison between pure components and coground binary mixtures: LD: α-cyclodextrin (α-CD) 70:30, LD: PVP 50:50 and LD: d-mannitol 50:50. It was demonstrated that FT-IR analysis could identify hydrogen bonding, a specific stabilizing interaction between the API and carrier polymer.[43] Chemical compatibility tests confirmed that the drug content in the samples remained unchanged compared to the reference (unground raw LD), demonstrating that the formulation stabilized for 30 days without any chemical incompatibilities.

Arbidol hydrochloride, also known as umifenovir hydrochloride, is a broad-spectrum antiviral medication developed in Russia. It is used to treat and prevent respiratory illnesses caused by COVID-19, hepatitis C, influenza A and B, and other human

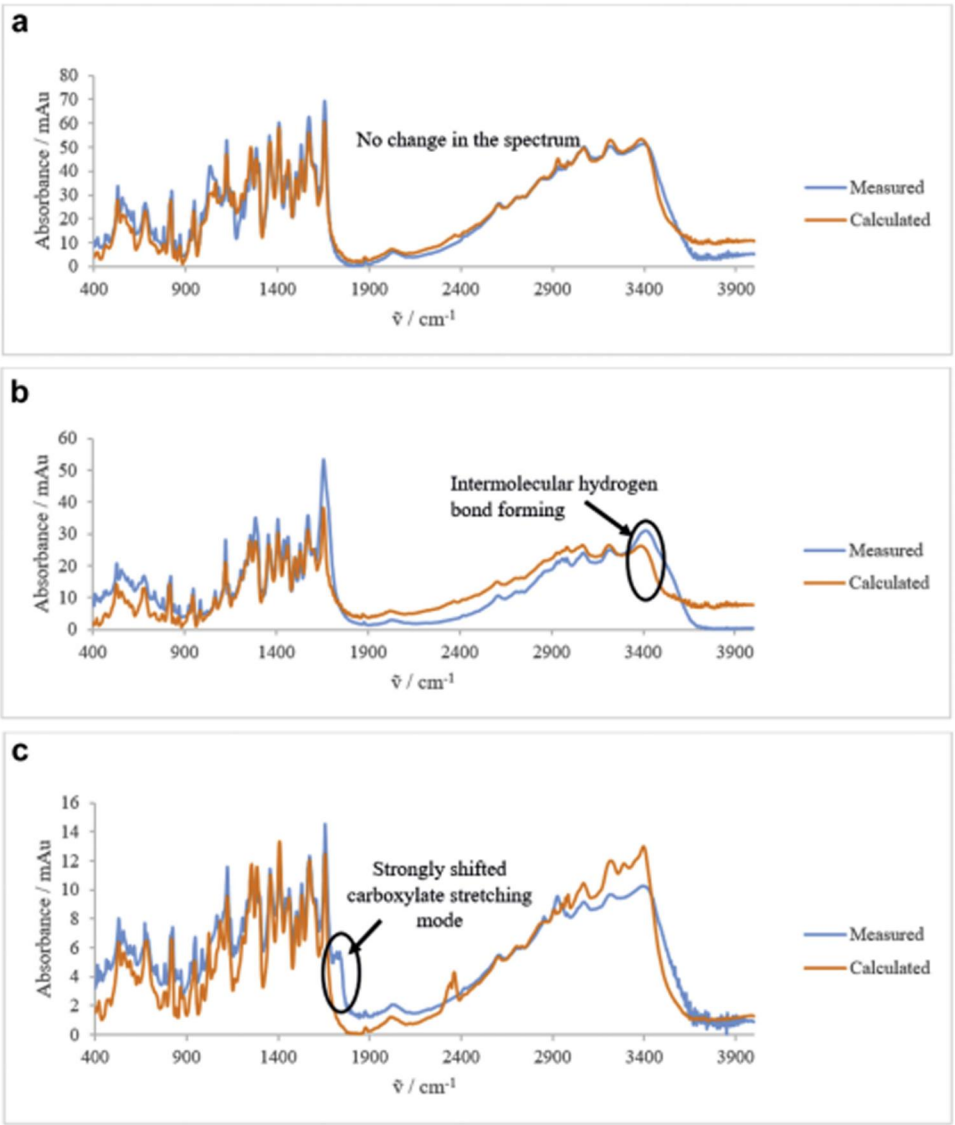


Figure 5. Comparison of calculated IR spectra to measured spectra of products: (a) LD: α-CD, 70:30; (b) LD: PVP, 50:50; and (c) LD: d-mannitol, 50:50 (reproduced from[43] with permission).

pathogenic respiratory viruses.[44–46] It was combined with various pharmaceutical excipients, such as chitosan, magnesium stearate, and polyvinylpyrrolidone K-30 to create binary mixtures. These mixtures were then analyzed using TGA-FTIR, FTIR, and DSC techniques. Additional analyses, including intrinsic dissolution rate studies and XRPD, were conducted on arbidol hydrochloride both alone and with excipients. It was revealed that arbidol hydrochloride might transform into different forms and is incompatible with magnesium stearate and chitosan. However, combining it with polyvinylpyrrolidone K-30 ensures stable and effective medicinal formulations.[47]

Chemometric factor analysis was used to further interpret the FTIR data, and the two-dimensional plot of Factors 1 and 2, shown in Figure 6, displays three distinct groupings. Arbidol hydrochloride, polyvinylpyrrolidone K-30, and their combination form one of the clusters, indicating agreement between their spectra and the FTIR spectrum of the arbidol hydrochloride mixture. In contrast, the mixture of arbidol hydrochloride with other excipients forms the other two clusters. Using non-thermal techniques such as FTIR spectroscopy, the incompatibilities detected using DSC and XRPD were verified. This helped determine whether these incompatibilities occur immediately after mixing the ingredients at room temperature and identify the chemical groups responsible for the incompatibilities.

Astaxanthin is a nutritional supplement known for preventing diabetes, cardiovascular disease, and neurological disorders. It acts as an antioxidant and anticancer agent while also boosting the immune system.[48] Over one month, it showed excellent stability under specific conditions.[49] FTIR spectra and DSC confirmed that there was no significant drug interaction with Eudragit L-100 and hydroxypropyl methylcellulose (HPMC). Astaxanthin's FTIR spectral data reveals a hydroxy group at 3448 cm^{-1}, a keto group at 1744 cm^{-1}, an alcoholic C–O stretch at 1068 cm^{-1}, and a C–H stretch at 2931 cm^{-1}. In contrast, the Eudragit L-100 spectra show carbonyl vibrations around 1715 cm^{-1} in the carboxylic acid group, OH stretching at 3060 cm^{-1}, C–O stretching at

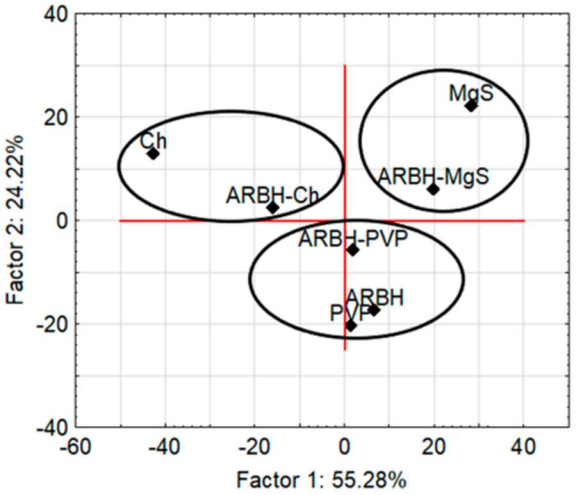


Figure 6. Score biplot of the first two factors from the factor analysis, based on FTIR data for arbidol hydrochloride (ARBH), chitosan (Ch), magnesium stearate (MgS), polyvinylpyrrolidone K-30 (PVP), and their binary combinations (reproduced from[47] under CC-BY-4.0 license).

1161 cm^{-1}, and an aliphatic C–H stretch at 2954 cm^{-1}. Conducting such a preformulation compatibility analysis is essential before developing a transdermal patch for microneedle astaxanthin delivery to identify the appropriate solvent, polymer, and optimal concentrations.

The compatibility of ganciclovir (an antiviral drug) was accessed, in another investigation, with various excipients using well characterized analytical techniques such as nuclear magnetic resonance (NMR), FTIR spectroscopy, and DSC.[50] The FTIR spectra showed the distinct absorption bands of both the drug and drug-excipient mixtures. They demonstrated the compatibility of ganciclovir with all the excipients under study, including dicalcium phosphate, magnesium stearate, microcrystalline cellulose, lactose, and talc.

Tamsulosin is a prolonged-action selective α1-adrenergic receptor antagonist used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia.[51] An investigation was performed to determine the compatibility of tamsulosin with several common excipients, including Eudragit (RS100, RL 100, S100), ethyl cellulose, gelatin, HPMC (5 cps and 15 cps), methyl cellulose, and lactose.[52] Each combination showed its functional group peaks at the expected positions, though with a slight decrease in intensity in the drug-containing binary mixtures. Changes in the vibration frequencies of C–H bending, C–H (aromatic) stretching, and N–H bending in the infrared spectra of the binary mixtures with ethyl cellulose, HPMC 5 cps, and lactose indicated chemical interactions in the solid state. However, no absence or shift in the tamsulosin vibration band was observed. It suggested that ethyl cellulose, gelatin, and lactose were incompatible with tamsulosin and had to be discarded in the production of thermally stable medicinal formulations. Because this interaction was just marginally verified by IR spectra, additional in-depth research was required for confirmation.

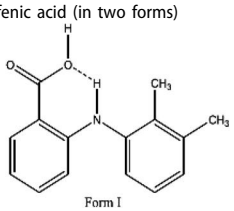
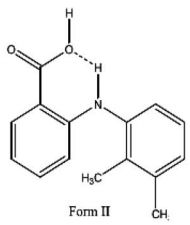
Table 1 shows additional examples of drug-excipient mixtures that have been investigated for compatibility.

Conclusions

Modern pharmaceutics require a thorough understanding and evaluation of excipients in formulations. This is because drug and excipient interactions can occur physically, chemically, or therapeutically. Incompatibilities may be evident at high temperatures or extreme excipient to API ratios, but not at room temperature or standard ratios over the product's shelf life. Gathering information on potential drug-excipient incompatibilities is crucial in formulation development to avoid physical, chemical, and microbiological instability in pharmaceutical dosage forms.

This article provides an in-depth analysis of using Fourier Transform Infrared (FTIR) spectroscopy to study drug-excipient interactions, offering detailed insights into molecular interactions. FTIR spectroscopy identifies incompatibilities by detecting changes in the functional groups of the compounds, proving to be a valuable tool in pre-formulation stages. It guarantees the stability and compatibility of drug products for intended use, by verifying the purity and potential interactions of drug and excipients co-formulated. Undoubtedly, the FTIR technique will continue to be an useful analytical tool, along with thermal analysis and other instrumental tools, actively supporting pharmaceutical research in the future.

Table 1. Some drug-excipient compatibility studies in the period 2017–2024.

Drug	Excipient(s)	Methods	Conclusions	Ref.
Lisinopril Metoprolol	Mannitol, calcium phosphate, butylated hydroxyanisole (BHA), cellulose sodium carboxymethyl cellulose	DSC FTIR	Possible interaction metoprolol with BHA; possible interaction of lisinopril with BHA and mannitol.	[53]
Penciclovir Lysine.HCl	Cetostearyl alcohol, EDTA, sodium lauryl sulfate, di-tert-butyl methyl phenol, paraffin, liquid petrolatum, propylparaben, methylparaben, propylene glycol	DSC, TG, XRD, FTIR, SEM	No interactions were detected between lysine.HCl and penciclovir using any technique, except DSC/TG.	[54]
Valacyclovir	Dicalcium phosphate, magnesium stearate, lactose, microcrystalline cellulose, talc.	DSC, NMR, UV and FTIR, TLC.	The characteristic peaks in both the infrared spectroscopy and NMR signals remained unchanged or showed insignificant variation.	[55]
Clopidogrel bisulfate	Avicel 102, aerosil, aspartame, crospovidone, croscarmellose, hydroxy propyl cellulose, sodium stearyl fumarate, pregelatinized starch, mannitol, sucralose, orange flavor, peppermint, sodium saccharin	HPLC, FTIR	The FTIR analysis of the mixtures showed no chemical interaction between the API and excipients, as evidenced by the absence of significant changes in characteristic peaks. This observation suggested that the mixtures displayed characteristic behavior that aligns with expectations for binary mixtures.	[56]
Hydroxy-chloroquine sulfate	Colloidal silicon dioxide, corn starch, magnesium stearate, mannitol, microcrystalline, cellulose PH101	DSC, TG, FTIR, IST	Thermal analysis techniques (including DSC, TG/DTG), FTIR, and IST were effectively utilized to evaluate how well hydroxy-chloroquine sulfate interacts with specific excipients.	[57]
Dexamethasone	Colloidal silicon dioxide, mannitol, magnesium stearate, microcrystalline cellulose, polyvinyl pyrrolidone k-30, pregelatinized starch, sodium starch glycolate	TG, DTA, FTIR	While dexamethasone maintained its effectiveness with most excipients tested, the FTIR analysis of the magnesium stearate mixture was inconclusive due to overlapping spectral bands.	[58]
Mefenic acid (in two forms)  Form I  Form II	Corn starch, magnesium stearate, methylcellulose, microcrystalline cellulose, silicon dioxide, sodium croscarmellose, sodium lauryl sulfate	NMR, DRX, thermal analysis, FTIR	The highest point of polymorphic transformation was noted at the 84-h mark. The crystalline structure present in the tablet corresponds to Form I. While DSC analysis could indicate potential interactions, a more detailed understanding, both qualitatively and quantitatively, necessitated the use of MIR spectroscopy combined with multivariate curve resolution-alternating least squares.	[59]

(*continued*)

Table 1. Continued.

Drug	Excipient(s)	Methods	Conclusions	Ref.
Rosmarinic acid	Croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, lactose monohydrate, polyvinylpyrrolidone, talc	DSC, TG, FTIR, ssNMR, IST coupled with LC.	FTIR revealed physical interaction of rosmarinic acid with talc and magnesium stearate. ssNMR confirmed the physical interaction showed by FTIR and excluded the presence of incompatibility.	[60]
Gliciazide	Lactose, magnesium stearate, polyvinylpyrrolidone, sodium starch glycolate, polyethylene glycol 2000, dicalcium phosphate	DSC, HPLC, FTIR	The drug showed incompatibility with all the excipients tested, except for dicalcium phosphate	[61]
Sildenafil	Butylated hydroxyanisole, cellulose, sodium carboxymethyl cellulose, ascorbic acid, citric acid	TG, DSC, FTIR, XRPD	There is incompatibility with sildenafil-butylated hydroxyanisole, sildenafil-ascorbic acid and sildenafil-citric acid	[62]
Rosuvastatin calcium	Crospovidone, dibasic calcium phosphate, lactose monohydrate, magnesium stearate, microcrystalline cellulose (Vivapur 121)	SEM, DSC, TGA, FTIR, XRPD	The FTIR comparison of the API-excipient mixtures showed some variations for calcium phosphate and lactose monohydrate, as did the thermal analysis; however, these variations did not mean any drug-excipient incompatibility.	[63]
Verapamil hydrochloride	HPMC-K15M, karaya gum, sodium bicarbonate, magnesium stearate, lactose, PVP K30.	FTIR, DSC	The pure drug and its formulation exhibited similar distinctive peaks with minor variations in FT-IR spectra. DSC thermograms indicated no drug-excipient interaction.	[64]
Mirtazapine hydrochloride	α-Lactose monohydrate, aerosil, calcium lactate, D-mannitol, magnesium stearate, magnesium citrate, polyvinylpyrrolidone K30, sorbitol, starch, stearic acid	FTIR, TG, DTG, DSC	No interactions were observed at room temperature for calcium lactate, magnesium citrate, magnesium stearate, lactose, starch, and sorbitol. Nonetheless, higher temperatures altered the thermal behavior of the drug when combined with the specified excipients.	[65]
Atorvastatin trihydrate calcium	Aerosil 200, avicel PH, aspartame, crospovidone, croscarmellose sodium, camphor, talc, sodium starch glycolate	SEM, FTIR, TGA	The porous atorvastatin trihydrate calcium tablets exhibited all characteristic peaks, apart from the free hydroxyl group (O–H stretch). This missing peak probably overlapped with the amide peak (N–H stretch), causing a broadening effect. It was likely due to weak Waals forces formed between the drug and other excipients co-formulated.	[66]
Albendazole	Random methyl-beta-cyclodextrin and hydroxyl-propyl-beta-cyclodextrin, mannitol, magnesium stearate, polyvinylpyrrolidone K30, starch, talc, colloidal silica (SiO_2)	ATR-FTIR; XRPD, DTG, DSC, HF	Caution is advised when developing new solid albendazole formulations with either PVP K30/SiO_2 and hydroxyl-propyl-beta-cyclodextrin or Talc/SiO_2 and random methyl-beta-cyclodextrin, due to observed interactions under ambient conditions.	[67]

(*continued*)

Table 1. Continued.

Drug	Excipient(s)	Methods	Conclusions	Ref.
Diclofenac	Microcrystalline cellulose; stearic acid	DSC, FTIR, SEM, XRPD	An interaction was seen with diclofenac –sodium microcrystalline cellulose – stearic acid ternary mixture prepared using microwave irradiation. Conversely, the corresponding mixtures prepared by physical mixing and co-evaporation methods showed compatibility.	[68]

Abbreviations

API	Active pharmaceutical ingredient
DSC	Differential scanning calorimetry
TG	Thermogravimetry
DTG	Derivative Thermogravimetry
HF	Heat flow
HPLC	High-performance liquid chromatography
FTIR	Fourier transform infrared spectroscopy
IST	Isothermal Stress Test
NMR	Nuclear magnetic resonance
ssNMR	Solid-state nuclear magnetic resonance
XRPD	X-ray powder diffraction
SEM	Scanning electron microscopy
IST coupled with LC	Isothermal stress testing coupled with liquid chromatography

Author contributions

Conceptualization, AAB, VDH, and HYAE; methodology, AAB, VDH, and HYAE; writing—original draft preparation, AAB; data curation, VDH, and HYAE; writing—reviewing and editing.

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No potential conflict of interest was reported by the author(s).

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References

1. Mahato, R. I.; Narang, A. S. *Pharmaceutical Dosage Forms and Drug Delivery*, 2nd ed.; CRC Press: Boca Raton, FL, **2012**; p. 472.
2. Kumar, N.; Goindi, S.; Saini, B.; Bansal, G. Thermal Characterization and Compatibility Studies of Itraconazole and Excipients for Development of Solid Lipid Nanoparticles. *J. Therm. Anal. Calorim.* **2014**, *115*, 2375–2383. DOI: 10.1007/s10973-013-3237-6.
3. Rowe, R. C.; Sheskey, P. J.; Quinn, M. E. *Handbook of Pharmaceutical Excipients*, 6th ed.; Libros Digitales, Pharmaceutical Press: London, UK. **2009**.

4. Chadha, R.; Bhandari, S. Drug–Excipient Compatibility Screening – Role of Thermoanalytical and Spectroscopic Techniques. *J. Pharm. Biomed. Anal.* **2014**, *87*, 82–97. DOI: 10.1016/j.jpba.2013.06.016.
5. Dinte, E.; Bodoki, E.; Leucuta, S.; Iuga, C. A. Compatibility Studies between Drugs and Excipients in the Preformulation Phase of Buccal Mucoadhesive Systems. *Farmacia*. **2013**, *61*, 703.
6. Patel, P.; Ahir, K.; Patel, V.; Manani, L.; Patel, C. Drug-Excipient Compatibility Studies: First Step for Dosage Form Development. *Pharm. Innov. J.* **2015**, *4*, 14.
7. Thakur, S. K.; Pal, P.; Pandey, P.; Singh, A.; Chanana, A.; Singh, R. P. Approaches of Drug-Excipients Interaction in Pharmaceutical Drug Product Formulation. *World J. Pharm. Res.* **2023**, *12*, 347.
8. Narang, A. S.; Desai, D.; Badawy, S. Impact of Excipient Interactions on Solid Dosage Form Stability. *Pharm. Res.* **2012**, *29*, 2660–2683. DOI: 10.1007/s11095-012-0782-9.
9. Faraat, A.; Kumar, R.; Sahu, P. L.; Singh, G. N. Physicochemical Characterization and Compatibility Study of Roflumilast with Various Pharmaceutical Excipients. *J. Therm. Anal. Calorim.* **2017**, *130*, 1627–1641. DOI: 10.1007/s10973-017-6274-8.
10. Shantikumar, S.; Sreekanth, G.; SurendraNath, K. V.; Jafer Valli, S.; Satheeshkumar, N. Compatibility Study between Sitagliptin and Pharmaceutical Excipients Used in Solid Dosage Forms. *J. Therm. Anal. Calorim.* **2014**, *115*, 2423–2428. DOI: 10.1007/s10973-013-3329-3.
11. Ermens, H. A Report of IPEC, Pharmaceutical Excipients – The Past and Future, Business Briefing. *Pharmagenerics.* **2004**, 1–3.
12. Segall, A. I. Preformulation: The Use of FTIR in Compatibility Studies. *J. Innov. Appl. Pharm. Sci.* **2019**, *4*, 01.
13. Singh, C.; Rao, K.; Yadav, N.; Bansal, N.; Vashist, Y.; Kumari, S.; Chugh, P. A Review: Drug Excipient Iincompatiblity by FTIR Spectroscopy. *CPA*. **2023**, *19*, 371–378. DOI: 10.2174/1573412919666230228102158.
14. Gorain, B.; Choudhury, H.; Pandey, M.; Madheswaran, T.; Kesharwani, P.; Tekade, R. K. Drug – Excipient Interaction and Incompatibilities. In *Dosage Form Design Parameters*, *volume II. Advances in Pharmaceutical Product Development and Research*; Academic Press, **2018**; pp 363–402.
15. Zamvar, U.; Dhillon, B. Postoperative IOP Prophylaxis Practice following Uncomplicated Cataract Surgery: A UK-Wide Consultant Survey. *BMC Ophthalmol.* **2005**, *5*, 24. DOI: 10.1186/1471-2415-5-24.
16. Rojek, B.; Wesolowski, M. FTIR and TG Analyses Coupled with Factor Analysis in a Compatibility Study of Acetazolamide with Excipients. *Spectrochim. Acta. A Mol. Biomol. Spectrosc.* **2019**, *208*, 285–293. DOI: 10.1016/j.saa.2018.10.020.
17. Sambasevam, K. P.; Mohamad, S.; Sarih, N. M.; Ismail, N. A. Synthesis and Characterization of the Inclusion Complex of β-Cyclodextrin and Azomethine. *Int. J. Mol. Sci.* **2013**, *14*, 3671–3682. DOI: 10.3390/ijms14023671.
18. Bharate, S. S.; Bharate, S. B.; Bajaj, A. N. Interactions and Incompatibilities of Pharmaceutical Excipients with Active Pharmaceutical Ingredients: A Comprehensive Review. *J. Excip. Food Chem.* **2010**, *1*, 3. https://ojs.abo.fi/ojs/index.php/jefc/article/view/26.
19. Falah, N.; Torday, J.; Quinney, S. K.; Haas, D. M. Estriol Review: Clinical Applications and Potential Biomedical Importance. *Clin. Res. Trials.* **2015**, *1*, 29–33. DOI: 10.15761/CRT.1000109.
20. Canbay, H. S.; Doğantürk, M. Compatibility Studies of Sildenafil with Different Excipients by Using TGA, DSC, XRD and FTIR. *Celal Bayar Uni. J. Sci.* **2019**, *15*, 401–407. DOI: 10.18466/cbayarfbe.613951.
21. Bosmann, H. B.; Case, K. R.; DiStefano, P. Diazepam Receptor Characterization: Specific Binding of a Benzodiazepine to Macromolecules in Various Areas of Rat Brain. *FEBS Lett.* **1977**, *82*, 368–372. DOI: 10.1016/0014-5793(77)80623-6.

22. Uditi, H.; Kamal, S. Research and Development of Diazepam Solid Dispersion Powder Using Natural Polymers. *Int. J. Appl. Pharm.* **2018**, *10*, 220. DOI: 10.22159/ijap.2018v10i5.27975.
23. Matos, A. P. S.; Costa, J. S.; Boniatti, J.; Seiceira, R. C.; Pitaluga, A.; Jr., Oliveira, D. L.; Viçosa, A. L.; Holandino, C. Compatibility Study between Diazepam and Tablet Excipients. Infrared Spectroscopy and Thermal Analysis in Accelerated Stability Conditions. *J. Therm. Anal. Calorim.* **2017**, *127*, 1675–1682. DOI: 10.1007/s10973-016-5350-9.
24. DRUGBANK online - Donepezil. https://www.drugbank.ca/drugs/DB00843. (accessed June 1, 2024).
25. Ledeti, I.; Bolintineanu, S.; Vlase, G.; Circioban, D.; Dehelean, C.; Suta, L.-M.; Caunii, A.; Ledeti, A.; Vlase, T.; Murariu, M. Evaluation of Solid-State Thermal Stability of Donepezil in Binary Mixtures with Excipients Using Instrumental Techniques. *J. Therm. Anal. Calorim.* **2017**, *130*, 425–431. DOI: 10.1007/s10973-017-6250-3.
26. Park, T. J.; Ko, D. H.; Kim, Y. J.; Kim, Y. G. Polymorphic Characterization of Pharmaceutical Solids, Donepezil Hydrochloride, by C CP/MAS Solid-State Nuclear Magnetic Resonance Spectroscopy. *B Kor. Chem Soc.* **2009**, *30*, 2007. DOI: 10.1007/s10973-017-6250-3.
27. Prathyusha, C. H.; Murthy, T. E. G. K. Compatibility Studies of Donepezil with Different Excipients by Using HPLC and FTIR. *J. Adv. Pharm. Edu. & Res* **2013**, *3*, 275.
28. Gómez-Caravaca, A. M.; Verardo, V.; Segura-Carretero, A.; Fernández-Gutiérrez, A.; Caboni, M. F. Phenolic Compounds and Saponins in Plants Grown under Different Irrigation Regimes. In *Polyphenols in Plants: Isolation, Purification and Extract Preparation*; Watson, R. R., Ed.; Elsevier: USA, **2014**.
29. Graf, J. Antioxidants and Skin Care: The Essentials. *Plast. Reconstr. Surg.* **2010**, *125*, 378–383. DOI: 10.1097/PRS.0b013e3181c2a571.
30. Ou, S.; Kwok, K. C. Ferulic Acid: Pharmaceutical Functions, Preparation and Applications in Foods. *J. Sci. Food Agric.* **2004**, *84*, 1261–1269. DOI: 10.1002/jsfa.1873.
31. Benesty, J.; Chen, J.; Huang, Y.; Cohen, I. Pearson Correlation Coefficient. In *Springer Topics in Signal Processing*; Benesty, J., Kellermann, W., Eds. Springer-Verlag: Berlin Heidelberg, **2009**; Vol. 2, pp 1–4.
32. Bezerra, G. S. N.; Pereira, M. A. V.; Ostrosky, E. A.; Barbosa, E. G.; de Moura, M. F. V.; Ferrari, M.; Aragão, C. F. S.; Gomes, A. P. B. Compatibility Study between Ferulic Acid and Excipients Used in Cosmetic Formulations by TG/DTG, DSC and FTIR. *J. Therm. Anal. Calorim.* **2017**, *127*, 1683–1691. DOI: 10.1007/s10973-016-5654-9.
33. Aminu, N.; Chan, S. Y.; Mumuni, M. A.; Umar, N. M.; Tanko, N.; Zauro, S. A.; Aminu, A.; Toh, S. M. Physicochemical Compatibility Studies of Triclosan and Flurbiprofen with Excipients of Pharmaceutical Formulation Using Binary, Ternary, and Multi-Combination Approach. *Futur. J. Pharm. Sci.* **2021**, *7*, 148. DOI: 10.1186/s43094-021-00302-7.
34. Bethanis, K.; Tzamalis, P.; Tsorteki, F.; Kokkinou, A.; Christoforides, E.; Mentzafos, D. Structural Study of the Inclusion Compounds of Thymol, Carvacrol and Eugenol in β-Cyclodextrin by X-Ray Crystallography. *J. Incl. Phenom. Macrocycl. Chem.* **2013**, *77*, 163–173. DOI: 10.1007/s10847-012-0230-9.
35. Wu, L.; Zhang, J.; Watanabe, W. Physical and Chemical Stability of Drug Nanoparticles. *Adv. Drug Deliv. Rev.* **2011**, *63*, 456–469. DOI: 10.1016/j.addr.2011.02.001.
36. Pires, F. Q.; Angelo, T.; Silva, J. K. R.; Sá-Barreto, L. C. L.; Lima, E. M.; Gelfuso, G. M.; Gratieri, T.; Cunha-Filho, M. S. S. Use of Mixture Design in Drug-Excipient Compatibility Determinations: Thymol Nanoparticles Case Study. *J. Pharm. Biomed. Anal.* **2017**, *137*, 196–203. DOI: 10.1016/j.jpba.2017.01.037.
37. Mecozzi, M.; Pietroletti, M.; Monakhova, Y. B. FTIR Spectroscopy Supported by Statistical Techniques for the Structural Characterization of Plastic Debris in the Marine Environment: Application to Monitoring Studies. *Mar. Pollut. Bull.* **2016**, *106*, 155–161. DOI: 10.1016/j.marpolbul.2016.03.012.

38. Kumbhar, D. D.; Pokharkar, V. B. Engineering of a Nanostructured Lipid Carrier for the Poorly Water-Soluble Drug, Bicalutamide: Physicochemical Investigations. *Colloids Surf. A Physicochem. Eng. Asp.* **2013**, *416*, 32–42. DOI: 10.1016/j.colsurfa.2012.10.031.
39. Fahn, S. The History of Dopamine and Levodopa in the Treatment of Parkinson's Disease. *Mov. Disord.* **2008**, *23*, S497–S508. DOI: 10.1002/mds.22028.
40. Bhavana, V.; Khopade, A. J.; Jain, W. D.; Shelly.; Jain, N. K. Targeted Oral Drug Delivery. *Indian Drugs.* **1996**, *33*, 365.
41. Chaitanya, K.; Velmurugan, S. Formulation and Evaluation of Levodopa Effervescent Floating Tablets. *Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 189.
42. Ledeti, I.; Bolintineanu, S.; Vlase, G.; Circioban, D.; Ledeti, A.; Vlase, T.; Suta, L. M.; Caunii, A.; Murariu, M. Compatibility Study between Antiparkinsonian Drug Levodopa and Excipients by FTIR Spectroscopy, X-Ray Diffraction and Thermal Analysis. *J. Therm. Anal. Calorim.* **2017**, *130*, 433–441. DOI: 10.1007/s10973-017-6393-2.
43. Kiss, T.; Alapi, T.; Varga, G.; Bartos, C.; Ambrus, R.; Szabó-Révész, P.; Katona, G. Interaction Studies between Levodopa and Different Excipients to Develop co-Ground Binary Mixtures for Intranasal Application. *J. Pharm. Sci.* **2019**, *108*, 2552–2560. DOI: 10.1016/j.xphs.2019.03.005.
44. Zhu, Z.; Lu, Z.; Xu, T.; Chen, C.; Yang, G.; Zha, T.; Lu, J.; Xue, Y. Arbidol Monotherapy is Superior to Lopinavir/Ritonavir in Treating COVID-19. *J. Infect.* **2020**, *81*, E21–e23. DOI: 10.1016/j.jinf.2020.03.060.
45. Deng, L.; Li, C.; Zeng, Q.; Liu, X.; Li, X.; Zhang, H.; Hong, Z.; Xia, J. Arbidol Combined with LPV/r versus LPV/r Alone against Corona Virus Disease 2019: A Retrospective Cohort Study. *J. Infect.* **2020**, *81*, E1–e5. DOI: 10.1016/j.jinf.2020.03.002.
46. Wang, X.; Cao, R.; Zhang, H.; Liu, J.; Xu, M.; Hu, H.; Li, Y.; Zhao, L.; Li, W.; Sun, X.; et al. The anti-Influenza Virus Drug, Arbidol is an Efficient Inhibitor of SARS-CoV-2 in Vitro. *Cell Discov.* **2020**, *6*, 28. DOI: 10.1038/s41421-020-0169-8.
47. Rojek, B.; Bartyzel, A.; Sawicki, W.; Plenis, A. DSC, TGA-FTIR and FTIR Assisted by Chemometric Factor Analysis and PXRD in Assessing the Incompatibility of the Antiviral Drug Arbidol Hydrochloride with Pharmaceutical Excipients. *Molecules.* **2024**, *29*, 264. DOI: 10.3390/molecules29010264.
48. Ambati, R. R.; Moi, P. S.; Ravi, S.; Aswathanarayana, R. G. Astaxanthin: Sources, Extraction, Stability, Biological Activities and Its Commercial Applications – A Review. *Mar. Drugs.* **2014**, *12*, 128–152. DOI: 10.3390/md12010128.
49. Rajwant, K.; Saahil, A.; Manish, G. Compatibility Study of Astaxanthin with Pharmaceutical Excipients Using Thermal and Nonthermal Techniques for the Development of TDDS. AIP Conference Proceedings, 3050, 050007, 2nd International Conference on Advanced Earth Science and Foundation Engineering (ICASF 2023), 26–27 May 2023, Mohali, India; **2024**.
50. Anoop, M.; Vivek, R. S.; Sumit, S.; Alen, T. M.; Rajnish, K.; Ashok, K. Y. A Comprehensive Compatibility Study of Ganciclovir with Some Common Excipients. *Am. J. Biopharm. Pharm. Sci.* **2023**, *3,* 1–10. DOI: 10.25259/AJBPS_4_2023.
51. Duan, Y.; Grady, J. J.; Albertsen, P. C.; Helen Wu, Z. Tamsulosin and the Risk of Dementia in Older Men with Benign Prostatic Hyperplasia. *Pharmacoepidemiol. Drug Saf.* **2018**, *27*, 340–348. DOI: 10.1002/pds.4361.
52. Shrivastava, A.; Mittal, A. Incompatibility Studies of Tamsulosin HCl Using TGA, DSC and IR. *Hacettepe Uni. J. Fac. Pharm.* **2023**, *43*, 22.
53. Canbay, H. S.; Doğantürk, M. Application of Differential Scanning Calorimetry and Fourier Transform Infrared Spectroscopy to the Study of Metoprolol-Excipient and Lisinopril-Excipient Compatibility. *Eurasian J. Anal. Chem.* **2018**, *13*, em39. DOI: 10.29333/ejac/92739.
54. Meira, R. Z. C.; Biscaia, I. F. B.; Nogueira, C.; Murakami, F. S.; Bernardi, L. S.; Oliveira, P. R. Solid-State Characterization and Compatibility Studies of Penciclovir, Lysine Hydrochloride, and Pharmaceutical Excipients. *Materials.* **2019**, *12*, 3154. DOI: 10.3390/ma12193154.

55. Anoop, M.; Vivek, R. S.; Sumit, S.; Alen, T. M.; Rajnish, K.; Ashok, K. Y. Molecular and Qualitative Characterization of Compatibility between Valacyclovir Hydrochloride and Excipients as Raw Materials for the Development of Solid Oral Dosage Formulation. *Am. J. Biopharm. Pharm. Sci.* **2023**, *3,* 1–11.
56. Noman, M. A.; Mahmoud, M. A.; Mohammed, A. A. Preformulation and Characterization Studies of Clopidogrel Active Ingredient for Orodispersible Tablets Development. *World J. Pharm. Pharm. Sci.* **2024**, *13*, 996.
57. Moraes, A. N. F.;·Dantas Silva, L. A.; de Oliveira, M. A.; de Oliveira, E. M.; Nascimento, T. L.; Lima, E. M.; Torres, E. M. S.; Diniz, D. G. A. Compatibility Study of Hydroxychloroquine Sulfate with Pharmaceutical Excipients Using Thermal and Nonthermal Techniques for the Development of Hard Capsules. *J. Therm. Anal. Calorim.* **2020**, *140*, 2283–2292. DOI: 10.1007/s10973-019-08953-8.
58. Santos, W. M.; Nóbrega, F. P.; Andrade, J. C.; Almeida, L. F.; Conceição, M. M.; Medeiros, A. C. D.; Medeiros, F. D. Pharmaceutical Compatibility of Dexamethasone with Excipients Commonly Used in Solid Oral Dosage Forms. *J. Therm. Anal. Calorim.* **2021**, *145*, 361–378. DOI: 10.1007/s10973-020-09753-1.
59. Antonio, M.; Calvo, N. L.; Maggio, R. M. Chemometric Study of the Excipients' Influence on Polymorphic-Behavior. Mefenamic Acid as Case of Study. *J. Pharm. Biomed. Anal.* **2019**, *170*, 8–15. DOI: 10.1016/j.jpba.2019.03.021.
60. Veras, K. S.; Fachel, F. N. S.; Pittol, V.; Garcia, K. R.; Bassani, V. L.; dos Santos, V.; Henriques, A. T.; Teixeira, H. F.; Koester, L. S. Compatibility Study of Rosmarinic Acid with Excipients Used in Pharmaceutical Solid Dosage Forms Using Thermal and Non-Thermal Techniques. *Saudi Pharm. J.* **2019**, *27*, 1138–1145. DOI: 10.1016/j.jsps.2019.09.010.
61. Jabbari, H. N.; Shabani, M.; Monajjemzadeh, F. Gliclazide Compatibility with Some Common Chemically Reactive Excipients; Using Different Analytical Techniques. *Anal. Sci. Technol.* **2019**, *34*, 46–55.
62. Canbay, H. S.; Polat, M.; Doğantürk, M. Study of Stability and Drug-Excipient Compatibility of Estriol. *Bilge Int. J. Sci. Technol. Res.* **2019**, *3*, 102–107. DOI: 10.30516/bilgesci.582054.
63. González, R.; Peña, M. a. Á.; Torres, N. S.; Torrado, G. Design, Development, and Characterization of Amorphous Rosuvastatin Calcium Tablets. *PLoS One.* **2022**, *17*, e0265263. DOI: 10.1371/journal.pone.0265263.
64. Singh, S. Y.; Salwa, S.; Shirodkar, R. K.; Verma, R.; Kumar, L. Enhancement in Dissolution Rate of Atorvastatin Trihydrate Calcium by Formulating Its Porous Tablet Using Sublimation Technique. *J Pharm Innov.* **2020**, *15*,498, 520. DOI: 10.1007/s12247-019-09397-1.
65. Mahmoud, Z. H.; Mahdi, A. B.; Alnassar, Y. S.; Al-Salman, H. N. K. Formulation and Sustained-Release of Verapamil Hydrochloride Tablets. *The Chemist.* **2023**, *94,* 76–88.
66. Circioban, D.; ·Ledeți, A.; ·Ridichie, A.; ·Vlase, T.; Ledeți, I.; Bradu, I. A.; Pahomi, A.; Sbârcea, L.; Vlase, G. Compatibility Study of Mirtazapine with Several Excipients Used in Pharmaceutical Dosage Forms Employing Thermal and Non-Thermal Methods. *J. Therm. Anal. Calorim.* **2024**. DOI: 10.1007/s10973-024-13181-w.
67. Trandafirescu, C.; Ledeți, I.; Șoica, C.; Ledeți, A.; Vlase, G.; Borcan, F.; Dehelean, C.; Coricovac, D.; Racoviceanu, R.; Aigner, Z. Albendazole-Cyclodextrins Binary Systems. Thermal and Spectral Investigation on Drug-Excipient Interaction. *J. Therm. Anal. Calorim.* **2019**, *138*, 3039–3054. DOI: 10.1007/s10973-019-08326-1.
68. Fayrouz, D.; Abdallah, D.; Aicia, H. Experimental Investigation of Ternary Mixture of Diclofenac Sodium with Pharmaceutical Excipients. *Phys. Sci. Rev.* 2023, *8*, 763–774. DOI: 10.1515/psr-2020-0111.