

Review article

## Preformulation: The use of FTIR in compatibility studies

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**Key words:** Compatibility studies, preformulation, Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, Isothermal Stress Testing-Fourier Transform Infrared Spectroscopy, Isothermal Stress Testing-High Performance Liquid Chromatography.

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### Abstract

Studies of active pharmaceutical ingredient (API) - excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms. The potential physical and chemical interactions between an API and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety. Solid dosage forms are generally less stable than their API components. Despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), Isothermal Stress Testing-Fourier Transform Infrared Spectroscopy (IST-FT-IR), Isothermal Stress Testing-High Performance Liquid Chromatography (IST-HPLC), are commonly used as screening techniques for assessing the compatibility of an active pharmaceutical ingredient (API) with some currently employed excipients. Through the assignment of spectral bands, FTIR provides information on chemical reactions taking place between the API and the excipient. Thus, this procedure gives formulation scientists information on which chemical groups to avoid in the excipients, favoring the development of more stable blends.

Vol. 4(3), 01-06, Jul-Sep, 2019.

### Introduction

The stability, chemical structure and bioavailability of an API are affected by interactions taking place between the API and the excipients. These alterations lead to a reduced therapeutic efficacy and safety [1]. As a rule, solid dosage forms are less stable than the isolated API. Although it has already been established that API-excipient compatibility testing must always be carried out during the development of new dosage forms, a consensus on the test to be employed is still lacking [2,3]. The most common signs of deterioration of an API are changes in color, taste, odor, polymorphic form, or crystallization (pharmaceutical incompatibility). These changes arise from chemical reactions with the excipient, leading to degradation of the API [4].

Thermo-analytical techniques have been developed to predict the suitability of the excipients to be employed in dosage forms in order to minimize undesired reactions (stability issues) between the API and the excipient [4]. In this sense, physico-chemical interactions between the API and excipients can be readily evaluated by differential scanning calorimetry (DSC) [5-16]. Some authors claim; however, that the data obtained by thermal techniques are difficult to interpret and that the interactions observed at high temperatures during DSC assays may not be

representative of those occurring under normal storage conditions [17].

Isothermal stress testing-high performance liquid chromatography (IST-HPLC), Fourier transform infrared spectroscopy (FTIR) and powder X-ray diffraction (PDRX) are other methods to study API-excipient compatibility. The IST-HPLC involves storing the API-excipient blends at high temperature followed by the determination of the API content by HPLC [18-21]. Some authors use PDRX to evaluate compatibility of API with excipients [22-25].

FTIR spectroscopy is not only useful to study the behavior of solid state APIs and their excipients but also as a compatibility screening tool, since the vibrational changes detected by this method serve as evidence for potential intermolecular interactions among the dosage components.

FTIR is recommended as a simple technique for the detection of interactions between the API and the excipients [16, 21, 22, 26-36] or between different APIs [37]. A reduction of the peak intensity, the appearance of an absorption peak, or the appearance of new peaks indicate the existence of interactions between the excipient and the API [17, 18, 34, 38].

## FTIR and DSC

It has been suggested that the interactions observed at high temperatures during DSC experiments might not be representative of those occurring at normal storage temperatures [17, 18, 39, 40].

The instrument that determines the absorption spectrum for a compound is called a spectrophotometer. Fourier transform spectrophotometer provides the IR spectrum much more rapidly compared to the traditional spectrophotometer.

The IR spectrum obtained from FTIR spectrometer lies in the mid-IR region 2.5-15  $\mu\text{m}$  between 4000 and 666  $\text{cm}^{-1}$ . Transition energies corresponding to changes in vibrational energy state for many functional groups are in the mid-IR region (4000-400  $\text{cm}^{-1}$ ) and hence the appearance of an absorption band in this region can be used to determine whether specific functional groups exist within the molecule. There are four regions of types of bonds that can be analyzed from the FTIR spectra, single bond (OH, CH, and NH) is detectable in higher wavenumber (2500-4000  $\text{cm}^{-1}$ ). The triple bond and double bond are detectable in the middle wavenumber region 2000-2500  $\text{cm}^{-1}$  and 1500-2000  $\text{cm}^{-1}$ , respectively. At low wavenumber region 650-1500  $\text{cm}^{-1}$  can be used for the identification of the molecule as a whole.

FTIR is a simple methodology for the detection of variations within drug-excipient blends. The disappearance of an absorption peak, a reduction of the peak intensity, or the appearance of new peaks are indicative of the existence of interactions between the API and the excipient under study [17, 18, 34, 38].

By DSC, Daniel *et al.* [41] have studied the compatibility of binary mixtures (1:1) of risperidone and pharmaceutical excipients. These binary mixtures were also kept at room temperature and then analyzed by FT-IR in combination with principal component analysis (PCA) to evaluate solid-state incompatibilities.

Lima *et al.* [42] have studied the compatibility of trioxalen with sodium lauryl sulfate by DSC, DTA, and FTIR at 25°C, 240°C (after the fusion event) and 260°C. Figure 1 shows that trioxalen peak of fusion disappear in the mixture (1:1) with sodium lauryl sulphate. The trioxalen bands in the FTIR spectrum of the mixture (1:1) with sodium lauryl sulphate were well retained, indicating no change in the structure of the drug at room temperature (Figure 2). Same results were obtained before the mixture were heated at 240°C and 260°C (data not shown). It was concluded that trioxalen is compatible with sodium lauryl sulphate.

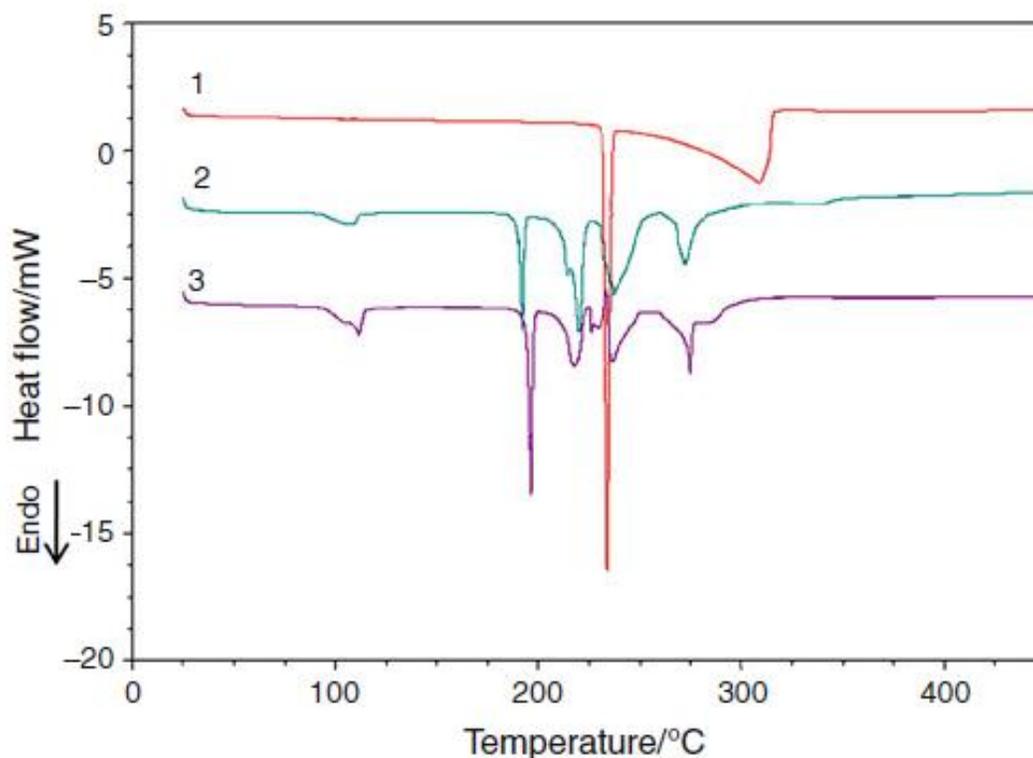


Figure 1. DSC curves of (1) TX, (2) TX/SLS, 3 (SLS). Reprinted with permission from Lima NGPB, Lima IPB, Barros DMC, Oliveira TS, Raffin FN, de Lima e Moura TFA, Medeiros ACD, Gomes APB, Aragão CFS: Compatibility studies of trioxsalen with excipients by DSC, DTA, and FTIR, J Therm Anal Cal 2014; 115:2311-2318. Copyright (2019) Springer Nature.

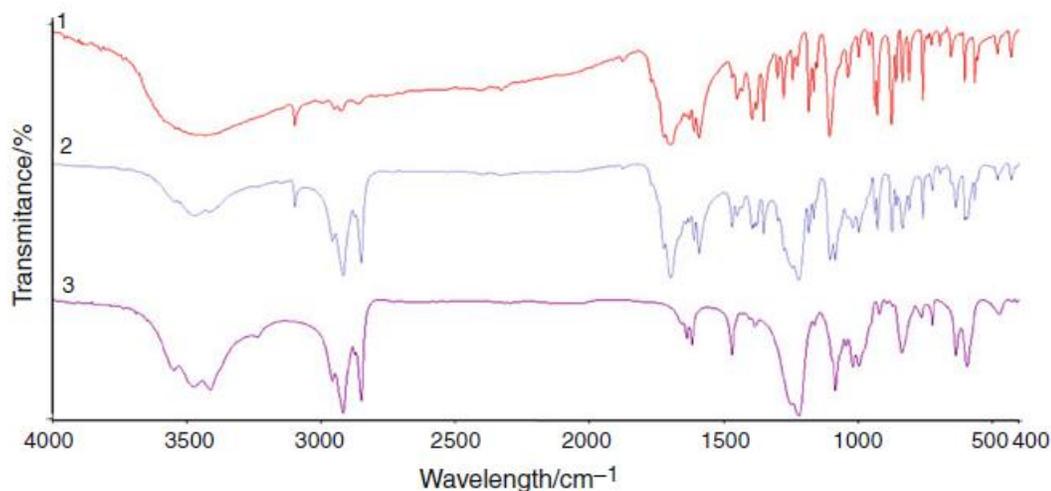


Figure 2. IR spectra of (1) TX, (2) TX/SLS, (3) SLS at 25°C. Reprinted with permission from Lima NGPB, Lima IPB, Barros DMC, Oliveira TS, Raffin FN, de Lima e Moura TFA, Medeiros ACD, Gomes APB, Aragão CFS: Compatibility studies of trioxsalen with excipients by DSC, DTA, and FTIR, *J Therm Anal Cal* 2014; 115:2311-2318. Copyright (2019) Springer Nature.

FTIR is a valuable tool to evaluate the compatibility of drugs without melting point. By DSC, Veiga *et al.* [21] have studied the compatibility of omeprazole sodium monohydrate with excipients such as, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, starch 1500, sodium starch glycolate, magnesium stearate, sodium carbonate, Acryl-Eze, stearic-acid and citric acid. The authors considered the decomposition exothermic peak of the API as an incompatibility parameter. These results were then confirmed by Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFT).

#### IST – FTIR and HPLC

Isothermal stress testing (IST) is another method used in compatibility testing. For this method, the drug-excipient blends are stored at high temperatures with or without moisture. The drug content is then determined by a suitable method, usually HPLC [18-21] or FTIR [16, 20, 26, 29, 30, 43].

Stress testing could be performed by storing physical mixtures in accelerated conditions at 40°C and 75% RH for 3 months [16], at ambient temperature, at 40°C and 75% RH and at 40°C and 75 % RH with the addition of 100  $\mu$ L of distilled water for 4 days [43], 14 days at 50°C [20], three weeks at 55°C [26, 29], and four weeks at 50°C [30].

Unlike the results obtained after 12 weeks using HPLC, Liltorp *et al.* [17] have demonstrated that IST/FT-IR can detect potential compatibility problems between an API and the excipients after only 3 days of storage at 50°C and 95% RH. The authors indicate that the spectrum of Lu AA44608 HBr-Mg stearate, before and after the storage at 50°C and 95% RH present the appearance of a

new peak at  $\sim 3270\text{ cm}^{-1}$  that was also observed in the spectrum of the free-base compound. Several other peaks corresponding to the free base compound are marked in the spectrum. These changes correspond to the desalting of the hydrogen bromide salt.

#### FTIR supported by multivariate statistics

Rojek and Wesolowski [44] have suggested that the presence of overlapping bands in the FTIR spectra may difficult the analysis. The spectra obtained in their work were more accurate and informative because the authors used an interferometer instead of a monochromator.

To improve the information quality indirectly acquired from the FTIR spectra, a multivariate statistics method, such as principal component analysis (PCA), should be carried out. Rojek and Wesolowski performed a compatibility study in different blends of atenolol and  $\beta$ -cyclodextrin, methylcellulose, starch and chitosan. The authors selected two spectral regions ( $3600\text{--}2800\text{ cm}^{-1}$  and  $1800\text{--}1000\text{ cm}^{-1}$ ) for multivariate statistical calculations. Changes in the structure of atenolol were readily detected because the region between  $1800\text{--}1000\text{ cm}^{-1}$  does not present typical absorption bands of excipients.

The results obtained by FTIR spectroscopy, supported by multivariate statistical methods, were verified by DSC, TG and PDRX.

#### FTIR and Pearson's correlation analysis

Silva *et al.* [34] have studied the compatibility between atorvastatin and excipients. They compared the atorvastatin spectra at 25°C with heated atorvastatin in binary mixtures. The Pearson's correlation analysis was employed in an algorithm to compare spectra over ever

decreasing spectral ranges. Two spectra are compared firstly as a whole and then each half of the spectra, each of half of the halves and so forth. The correlation values for each section are assigned to a vector with the same length of the spectra range being compared. A final average correlation vector is then obtained. This average is used to compare the spectra. The experimental spectrum can also be derived from a theoretical spectrum of the pure compound through a multivariate linear regression. This methodology assumes that the spectrum corresponding to the mixture is the result of the superposition the spectra of the pure compounds. When the experimental and theoretical spectra are different, it can be assumed that the atoms or the whole molecules have undergone a rearrangement within the mixture.

Correlation values near 1.0 indicate lack of significant interactions between the mixture constituents. Low correlations may arise from noise (or baseline); if such is the case, no further evaluations are made. Correlation values between 0.80 and 1.00 are considered high and indicate the presence of simple solid mixtures. Moderate correlations are between 0.50 and 0.80, and they may indicate the presence of interactions. Values below 0.50 indicate low similarity between spectra, demonstrating chemical degradation. The Pearson's correlation between atorvastatin and nine excipients can be seen in Figure 3. Barros Lima *et al.* [45] have studied the compatibility between tretinoin and pharmaceutical excipients using the Pearson's correlation.

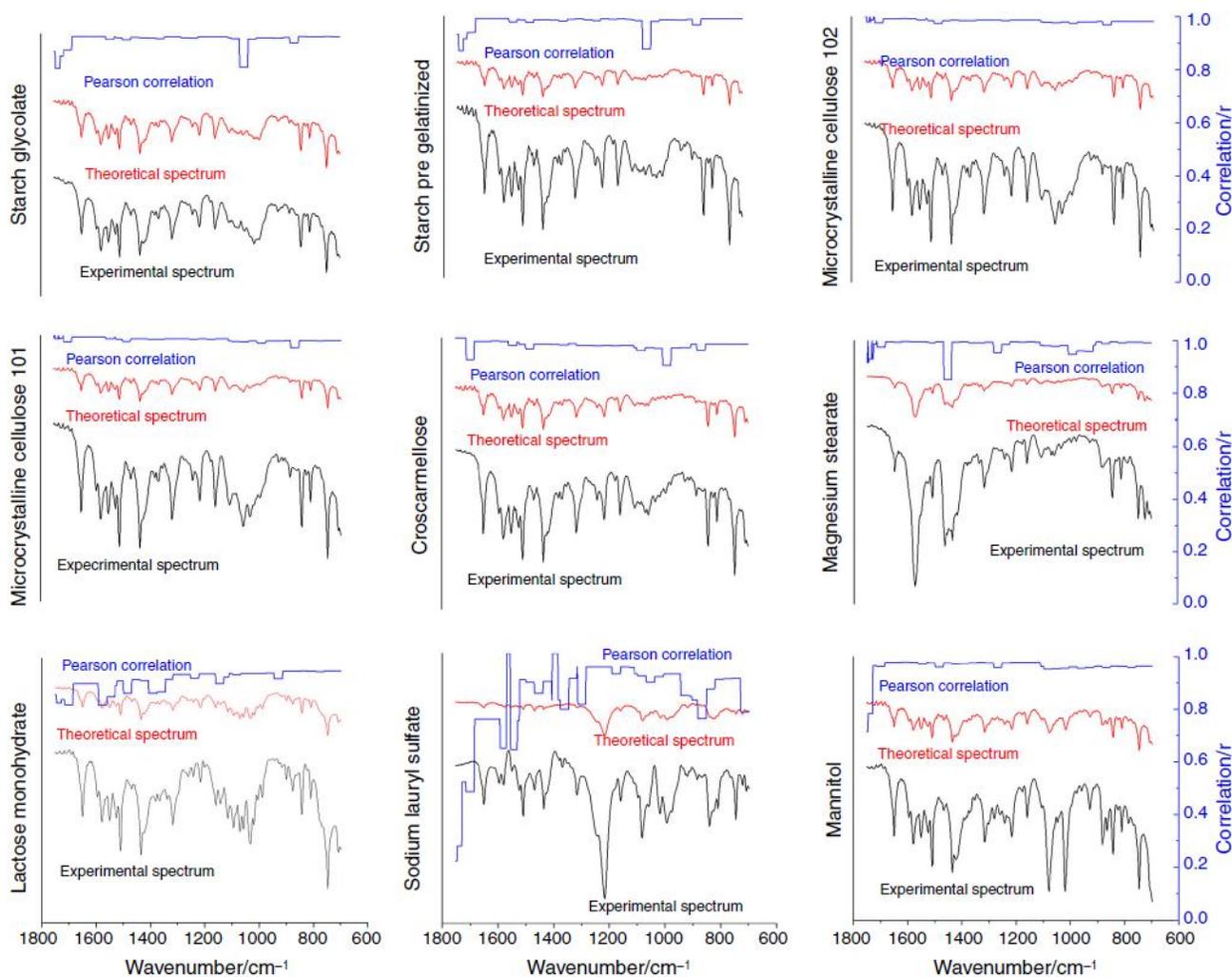


Figure 3. Pearson's correlation of atorvastatin + excipients sodium lauryl sulphate, croscarmellose, pre-gelatinized starch, microcrystalline cellulose 101 (MC101), lactose, sodium starch glycolate, microcrystalline cellulose 102 (MC102) and (9) magnesium stearate (10) mannitol. Reprinted with permission from da Silva EP, Pereira MAV, de Barros Lima IP, Barros Lima NGP, Barboza EG, Aragã CFS, Gomes APB: Compatibility study between atorvastatin and excipients using DSC and FTIR J Therm Anal Cal 2016; 123:933-939. Copyright (2019) Springer Nature.

## FTIR advantages and disadvantages in compatibility studies

When compared to other analytical methods, FTIR has several advantages: a) it is a common quality control equipment, b) this method detects changes in the crystal structure, i.e. polymorphic changes, desalting, and degree of hydration; c) the preparation of samples is easy; d) useful for API without melting point, e) can detect potential incompatibility between an API and pharmaceutical excipients after a few days of storage with control temperature and humidity, f) the use of the interferometer instead of the classical monochromator makes the spectra obtained more accurate and informative.

FTIR has the disadvantages: a) It is not helpful with overlapping peaks, b) sometimes it requires the application of statistical analysis for interpretation, c) It is necessary to combine with IST.

## Conclusion

Studies on drug–excipient compatibility represent an important step in the formulation stage for the development of all dosage forms. Despite its disadvantages, FTIR is a simple technique available in analytical laboratories.

Through the assignment of spectral bands, FTIR provides information on chemical reactions taking place between the API and the excipient. Thus, this procedure gives formulation scientists information on which chemical groups to avoid in the excipients, favoring the development of more stable blends.

## Acknowledgements

This work was carried out thanks to the subsidies 20020170100161BA for A. I. Segall of UBA.

## References

- Bharate SS, Bharate SB, Bajaj AN: Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. *J. Excip. Food. Chem.* 2010; 1:3-26.
- Moyano MA, Broussalis AM, Segall A: Thermal analysis of lipoic acid and evaluation of the compatibility with excipients. *J. Therm. Anal. Cal.* 2010; 99: 631-637.
- Ceresole R, Han Y, Rosasco MA, Orelli LR, Segall AI: Drug-excipient compatibility studies in binary mixtures of Avobenzone. *J. Cosmet. Sci.* 2013; 64: 317-328.
- Chadha R, Bhandari S: Drug–excipient compatibility screening—Role of thermoanalytical and spectroscopic techniques *J. Pharm. Biomed. Anal.* 2014; 87: 82-97.
- McDaid FM, Barker SA, Fitzpatrick S, Petts C, Craig DQM: Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug–excipient interactions. *Int. J. Pharm.* 2003; 252:235-240.
- O'Neill MA, Gaisford S: Application and use of isothermal calorimetry in pharmaceutical development. *Int. J. Pharm.* 2011; 417:83-93.
- Ferraz Pinto M, Afonso de Moura E, Santos de Souza F, Oliveira Macêdo R: Thermal compatibility studies of nitroimidazoles and excipients. *J. Therm. Anal. Cal.* 2010; 102:323-329.
- Oliveira Santos AF, Basilio Jr ID, Souza FS, Medeiros AFD, Ferraz Pinto M, de Santana DP: Application of thermal analysis of binary mixtures with metformin. *J. Therm. Anal. Cal.* 2008; 93:361-364.
- Chou YP, Huang JY, Tseng JM, Cheng Y, Shu CM: Reaction hazard analysis for the thermal decomposition of cumene hydroperoxide in the presence of sodium hydroxide. *J. Therm. Anal. Cal.* 2008; 93:275-280.
- Sashima ES, Janowska G, Zaborski M, Vnuchkin AV: Compatibility of fibroin/chitosan and fibroin/cellulose blends by thermal analysis. *J. Therm. Anal. Cal.* 2007; 89:887-891.
- Medeiros AFD, Santos AFO, de Souza FS, Júnior IDB, Valdilânio J, Procópio JVV, de Santana DP, Macêdo RO: Thermal studies of pre-formulates of metronidazole obtained by spray drying technique. *J. Therm. Anal. Cal.* 2007; 89: 775-781.
- Silva MAS, Kelmann RG, Foppa T, Cruz AP, Bertol CD Sartori T, Granada A, Carmignan F, Murakami FS: Thermoanalytical study of fluoxetine hydrochloride. *J. Therm. Anal. Cal.* 2007; 87:463-467.
- Lira AM, Araújo AAS, Basílio IDJ, Santos BLL, Santana DP, Macêdo RO: Compatibility studies of lapachol with pharmaceutical excipients for the development of topical formulations. *Thermochim. Acta.* 2007; 457:1-6.
- Mura P, Furlanetto S, Cirri M, Maestrelli F, Marras AM, Pinzauti S: Optimization of glibenclamide tablet composition through the combined use of differential scanning calorimetry and d-optimal mixture experimental design. *J. Pharm. Biomed. Anal.* 2005; 37:65-71.
- Araújo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, dos Santos Filho M, Matos JR: Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. *Int. J. Pharm.* 2003; 260: 303-314.
- Matos APS, Costa JS, Boniatti J, Seiceira RC, Pitaluga Jr A, Oliveira DL, Visçosa AL, Holandino C: Compatibility study between diazepam and tablet excipients. *J. Therm. Anal. Cal.* 2017; 127:1675-1682.
- Liltorp K, Larsen TG, Willumsen B, Holm R: Solid state compatibility studies with tablet excipients using non thermal methods. *J. Pharm. Biomed. Anal.* 2011; 55:424-428.
- Verma RK, Garg S: Selection of excipients for extended release formulations of glipizide through drug–excipient compatibility testing. *J. Pharm. Biomed. Anal.* 2005; 38:633-644.
- Verma RK, Garg S: Compatibility studies between isosorbide mononitrate and selected excipients used in the development of extended release formulations. *J. Pharm. Biomed. Anal.* 2004; 35:449-458.
- Silva LAD, Teixeira FV, Serpa RC, Esteves NL, dos Santos RR, Lima EM, da Cunha-Filho MSS, de Souza Araújo AA, Taveira SF, Marreto RN: Evaluation of carvedilol compatibility with lipid excipients for the development of lipid-based drug delivery systems. *J. Therm. Anal. Cal.* 2016; 123:2337-2344.
- Veiga A, Oliveira PR, Bernardi LS, Mendes C, Silva MAS, Sangoi MS, Janissek PR, Murakami FS: Solid-state compatibility studies of a drug without melting point. *J. Therm. Anal. Cal.* 2018; 131:3201-3209.
- Rus LM, Tomuta I, Iuga C, Maier C, Kacso I, Borodi G, Bratu I, Bojita M: Compatibility studies of indapamide/pharmaceutical excipients used in tablet preformulation. *Farmacia.* 2012; 60:92-101.
- Tomasetti M, Catalani A, Rossi V, Vecchio S: Thermal analysis study of the interactions between acetaminophen and excipients in solid dosage forms and in some binary mixtures. *J. Pharm. Biomed. Anal.* 2005; 35:949-955.
- Ding T, Chen L, Zhai LH, Fu Y, Wang-Sun B: Compatibility study of rivaroxaban and its pharmaceutical excipients. *J. Therm. Anal. Cal.* 2017; 130: 1569-1573.
- Pires SA, Mussel WN, Yoshida MI: Solid-state characterization and pharmaceutical compatibility between citalopram and excipients using thermal and non-thermal techniques. *J. Therm. Anal. Cal.* 2017; 127:535-542.
- Joshi BV, Patil VB, Pokharkar VB: Compatibility studies between carbamazepine and tablet excipients using thermal and non-thermal methods. *Drug Devel. Ind. Pharm.* 2002; 28:687-694.
- Stulzer HK, Rodrigues PO, Cardoso TM, Matos JSR, Silva MAS: Compatibility studies between captopril and pharmaceutical excipients used in tablets formulations. *J. Therm. Anal. Cal.* 2008; 9:323-328.
- Reddy RA, Ramesh B, Kishan V: Drug-excipient interaction during formulation development *in vitro* and *in vivo* evaluation of gastroretentive drug delivery system for nizatidine. *Int. J. Pharm. Sci. Nanotech.* 2013; 6: 2281-2293.
- Prathyusha CH, Murthy TEGK: Compatibility studies of Donepezil with different excipients by using HPLC and FTIR. *J. Adv. Pharm. Tech. Res.* 2013; 3:273-278.
- Jangde R, Singh D: Compatibility studies of quercetin with pharmaceutical excipients used in the development of novel formulation. *Research J. Pharm. and Tech.* 2014; 7:1101-1105.
- Tiwari SP, Vidyasagar G: Identification, characterization, and drug-excipient compatibility of diltiazem hydrochloride by physico-chemical techniques UK. *J. Pharm. Biosci.* 2014; 2:49-53.
- Gupta A, Kar HK: Solid state compatibility studies of miconazole using

- thermal and spectroscopic methods. *Adv. Anal. Chem.* 2015; 5:51-55.
33. Khan MI, Madni A, Ahmad S, Khan A, Rehman M, Mahmood MA: ATR-FTIR based pre and post formulation compatibility studies for the design of niosomal drug delivery system containing nonionic amphiphiles and chondroprotective drug. *J. Chem. Soc. Pak.* 2015; 37:527-534.
  34. da Silva EP, Pereira MAV, de Barros Lima IP, Barros Lima NGP, Barboza EG, Aragã CFS, Gomes APB: Compatibility study between atorvastatin and excipients using DSC and FTIR. *J. Therm. Anal. Cal.* 2016; 123:933-939.
  35. Amir IM, Amir ME, Osama AA, Suzan A, Alaa IM: Investigation of drug-polymer compatibility using chemometric-assisted UV-Spectrophotometry. *Pharmaceutics* 2017; 9:1-13.
  36. Canbay HS, 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; 13:1-7.
  37. Gomes EC de L, Mussel WN, Resende JM, Fialho SL, Barbosa J, Yoshida MI: Chemical interactions study of antiretroviral drugs efavirenz and lamivudine concerning the development of stable fixed-dose combination formulations for AIDS treatment. *J. Braz. Chem. Soc.* 2013; 24:573-579.
  38. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siah-Shadbad MR, Mojarad JS, Robertson TH, Roberts MS: Compatibility studies of acyclovir and lactose in physical mixtures and commercial tablets. *Eur. J. Pharm. Biopharm.* 2009; 73: 404-413.
  39. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S: Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. *Int. J. Pharm.* 1995; 119:71-79.
  40. Malan CEP, de Villiers MM, Lötter AP: Application of differential scanning calorimetry and high performance liquid chromatography to determine the effects of mixture composition and preparation during the evaluation of niclosamide-excipient compatibility. *J. Pharm. Biomed. Anal.* 1997; 15:549-557.
  41. Daniel JSP, Veronez IP, Lopez Rodriguez L, Trevisan MG, García JS: Risperidone – Solid-state characterization and pharmaceutical compatibility using thermal and non-thermal techniques. *Thermochim Acta.* 2013; 568:148-155.
  42. Lima NGPB, Lima IP., Barros DMC, Oliveira TS, Raffin FN, de Lima e Moura TFA, Medeiros ACD, Gomes APB, Aragão CFS: Compatibility studies of trioxsalen with excipients by DSC, DTA, and FTIR. *J. Therm. Anal. Cal.* 2014; 115: 2311-2318.
  43. Rosasco MA, Bonafede SL, Faudone SN, Segall AI: Compatibility Study Between Tobramycin and Pharmaceutical Excipients Using Differential Scanning Calorimetry, FT-IR, DRX and HPLC. *J. Therm. Anal. Cal.* 2018; 134: 1929-1941.
  44. Rojek B, Wesolowski M: Fourier transform infrared spectroscopy supported by multivariate statistics in compatibility study of atenolol with excipients. *Vib. Spectrosc.* 2016; 86:190-197.
  45. de Barros Lima IP, Lima NPG, Barros DMC, Oliveira TS, Barbosa EG, Gomes APB, Ferrari M, do Nascimento TG, Aragão CFS: Compatibility study of tretinoin with several pharmaceutical excipients by thermal and non-thermal techniques. *J. Therm. Anal. Cal.* 2015; 120:733-745.