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DRUG EXCIPIENT COMPATIBILITY SCREENING OF FEXOFENADINE HYDROCHLORIDE FOR ORALLY DISINTEGRATING TABLETS

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ABSTRACT

Selection of right excipients of functionality is an important task to ensure the performance of dosage form across shelf life. This selection happens at pre-formulation stage of pharmaceutical development to ensure there is no potential physical and chemical interaction between drugs and excipients leading to better stability and bioavailability. The objective of this work was to study the compatibility of Fexofenadine hydrochloride with pharmaceutical excipients employed in orally disintegrating tablets by Fourier transform infrared spectroscopy (FT-IR). Different categories of excipient functionality [Diluent, disintegrant, glidant, sweetener, flavor, color and lubricant, which were indispensable part of orally disintegrating tables] were selected and physical binary mixtures were prepared with Fexofenadine hydrochloride. Compatibility was investigated by storage of drug excipient binary mixtures at isothermal stress conditions and subsequently analyzed by FT-IR. Samples were packed and exposed for accelerated stability condition [40°C/75%RH] for four weeks and analyzed by FTIR to evident solid state interaction. Based on the results all the excipients found to be compatible with Fexofenadine hydrochloride and can be further used for orally disintegrating tablet dosage form.

Key Words: Excipient, Interaction, Stability, Bioavailability, Incompatibility, Infra-red spectroscopy, Orally disintegrating tablets, Fexofenadine hydrochloride.

INTRODUCTION

The drug excipient compatibility study identifies the physical, chemical interaction between drug and excipient early thereby helps to avoid surprise formulation problems and maximize the shelf life of dosage forms. Early assessment of incompatibility between drug and excipients ensure the lowest cycle time of pharmaceutical development of drug product. Physical and chemical interactions between drug and excipients can affect the chemical nature, the stability and bioavailability of drug products, and consequently, their therapeutic efficacy and safety (Rowe RC, 2009). The ideal drug product does not have either drug-excipient or excipient-excipient interactions. Drug–excipient compatibility assessment at pre-formulation stage provides compatible list of excipients that can be incorporated in drug product development with the highest probability of developing a stable dosage form. Till now there is no defined procedure to experiment drug excipient compatibility (Karin Liltorp *et al*., 2011). Incompatible combinations of drug and excipient may alter both the stability and the bioavailability of the drug in the formulation (Serajuddin *et al.*, 1999; Verma *et al.*, 2005). A rapid and reliable experimentation procedure is desired for drug excipient compatibility study. Differential scanning calorimetry (DSC) is one of the most

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commonly used thermal analytical technique for assessing incompatibility between drug and excipients with minimal sample requirement and time (Thumma *et al.*, 2009; Tomassetti *et al.*, 2005). DSC results are perhaps misleading due to interactions observed at higher temperature may not be relevant at typical storage temperatures of oral solid dosage form (Van Dooren, 1983). DSC does not allow evaluating the presence of humidity on dosage form where humidity is an integral part of storage environment (Cheng *et al*., 2008). If DSC results in an incompatibility between drug and excipient there is further confirmatory experiment is required to conclude (Laszcz *et al.*, 2007). Hence the beneficial way forward is to directly conduct the confirmatory experiment to select suitable excipients for desired formulation composition.

Accelerated stability testing is often used experimental condition for compatibility evaluation that involves storage of the drug excipient blends with or without moisture at elevated temperature and subsequent investigation or determination of the drug content by a suitable method (Serajuddin *et al.*, 1999). There are different methods are used to detect the compatibility after isothermal stress testing include High Performance Liquid Chromatography [HPLC] (Ceschel *et al.*, 2003), X-Ray Powder Diffraction[XRPD] (Marini *et al.*, 2003), Fourier Transform-Infra Red spectroscopy [FT-IR] (Kerc *et al.*, 1992; Late *et al.*, 2008; Sims *et al.*, 2003), Mass Spectroscopy [MS] (Monajjemzadeh *et al*., 2009) and microcalorimetry (Schmitt *et al.*, 2001). Out of all the techniques FT-IR and MS has the advantage of predicting structural changes. Fourier Transform-Infra Red spectroscopy [FT-IR] is a rapid and simple technique to screen different categories of formulation excipients perfectly fit to provide desired functionality in the dosage form. Appearance of new peak [other than excipient], disappearance of significant absorption peak and reduction of peak intensity gives a clear indication of interaction between the excipient and drug investigated. FT-IR has the rich advantage of rapid, very less quantity of sample requirement, identification of structural changes including desalting, hydrate formation etc. The purpose of the current study is to screen [selection/deselection] excipients necessary to formulate Fexofenadine hydrochloride orally disintegrating tablets.

Fexofenadine hydrochloride, a non-anticholinergic H1-receptor antagonist devoid of sedative effects, is a long acting antihistamine widely used for the treatment of several allergic rhinitis symptoms (Taglialatela *et al*., 2000). It is chemically, Benzene acetic acid, 4-[1-hydroxy-4-[4-(hydroxy-diphenyl methyl)-1-piperidinyl] butyl]-a, a-dimethyl-, hydro-chloride, (±)-. Fexofenadine hydrochloride was originally approved for the treatment of Idiopathic urticaria, chronic (Adult, Pediatric) and Seasonal allergic rhinitis (Adult, Pediatric). This drug is successfully formulated as tablets [Immediate release, orally disintegrating and long acting], capsules and oral suspension. Fexofenadine (terfenadine carboxylate; an active acid metabolite of terfenadine) is an antihistamine with selective peripheral H1- receptor antagonist activity. It is a racemate, and exists as a zwitterion in aqueous media at physiological pH. In animal studies, fexofenadine inhibits antigen-induced bronchospasm and histamine release from peritoneal mast cells. It appears to be devoid of anticholinergic or alpha-1-adrenergic antagonist activity. In addition, no sedative or other central nervous system (CNS) effects were observed in preclinical studies. Radioactive tissue distribution studies indicate that fexofenadine does not cross the blood-brain barrier. Fexofenadine is the active antihistamine when oral Terfenadine is administered.

MATERIALS AND METHODS

Materials

Fexofenadine hydrochloride was a gifted sample from Sai mirra pharmaceuticals, Chennai. Mannitol [Mannitol 25, extra fine crystalline Mannitol with mean diameter of 25 μ, Roquette], Sorbitol [NEOSORB Powder, Roquette], Microcrystalline Cellulose [Avicel PH105, mean diameter 20 μ, FMC bio polymer], Lactose monohydrate [Pharmatose 200M, DFE Pharma], Sodium starch glycolate [Primojel, DFE Pharma], Croscarmellose sodium [Ac-Di-Sol, FMC BIO Polymer], Crospovidone [Polyplasdone XL 10, ISP], Saccharin sodium [Spectrum], Sucralose [Tate and Lyle], Aspartame [NutraSweet Company], citric acid [Fisher Scientific], Sodium bicarbonate[Spectrum], Tannic acid [Tetrahydron], Polacrillin potassium [Dow chemicals], Orange flavor[Firmenich], peppermint flavor [Firmenich], Pineapple flavor [Firmenich], FD&C Blue #1 [Koelcolours], FD&C Yellow #5[Koelcolours], Colloidal silicon dioxide [Evonik], Magnesium stearate [Mallinckrodt Baker], Stearic acid[Mallinckrodt Baker] were used as supplied.

Fexofenadine hydrochloride orally disintegrating tablets

Fexofenadine orally disintegrating tablet is an immediate release tablet intended for twice a day oral dosing. Fexofenadine hydrochloride is a bitter drug and the orally disintegrating tablet should be taste masked for better patient compliance. So the drug product shall have the excipients from different functionalities including taste masking agent, diluent, super disintegrant, binder, colour, sweetener and lubricant. As a part of pre-formulation study drug excipient compatibility screening is performed to identify potential physical and chemical interactions between drug and excipients that can affect the stability of finished drug product.

Drug excipient mixture

A binary mixture of Fexofenadine hydrochloride and excipient was prepared by geometrical mixing technique to ensure homogeneity. The ratio of drug and

excipient was selected based on typical concentration in orally disintegrating tablet dosage form. The proportion of excipient in the binary mixture was selected based on typical functionality level used in orally disintegrating tablet dosage form to study the interaction. The details are given in table 1.

Since the Fexofenadine hydrochloride orally disintegrating tablet formulation manufacturing was proposed to be by direct compression process the binary mixture was done by physical mixing and there was no water used. The drug excipient mixture was packed in double lined self-seal polybag.

Accelerated stability testing

The samples were loaded at 40 ± 2°C / 75± 5 % RH stress conditions having elevated temperature and humidity that can accelerate the drug–excipient interactions for four weeks. These samples were unloaded, visually observed for any change in color, aggregation and deliquescence of powder mixture or any change in the physical state which are indicators of incompatibility. Drug–excipient blends stored in refrigerator served as controls for evaluation. Stressed and control samples were taken for FT-IR analysis to study chemical drug–excipient interactions.

FT-IR experiments

Fourier Transform-Infrared is nondestructive, sensitive to the structure and environment of organic compounds. It is used as compatibility screening tool as the vibrational changes serve as probe of potential intermolecular interactions among the drug excipient components. The pharmaceutical interactions that result in desalting, hydrate formation, dehydration, polymorphic changes or transformation of crystalline to amorphous forms and vice versa during processing can easily be detected with the aid FT-IR (Kogermann *et al.*, 2007). The drug, drug excipient binary mixture initial and isothermal stress exposed samples were taken for recording the IR spectra. These samples were prepared as potassium bromide (KBr) pellets. Pellets were prepared by taking 1mg of homogenized substance and 100 mg of spectroscopy-grade KBr. The IR spectra were recorded at room temperature in the 4000 – 400 cm^{-1} region using ambient atmosphere as back ground.

RESULTS AND DISCUSSION

In infra-red spectrum of Fexofenadine hydrochloride characteristic absorption bands can be distinguished. They are associated with aromatic C-H stretching, aromatic C-C stretching and also relevant to specific functional groups like aliphatic, acid ketone and tertiary amine. The specific frequencies are given in Table 2.

As a result all the excipients taken for this study did not exhibit any interaction with fexofenadine hydrochloride. The characteristic absorption of observed peaks in all excipient binary mixtures indicates that there is no major structural change affecting the functional groups of Fexofenadine hydrochloride. FTIR spectra showed that the characteristic bands of Fexofenadine hydrochloride were not altered in binary mixtures indicating no interactions between Fexofenadine hydrochloride and the selected excipients.

Table 1. Drug and excipient description and ratio

S.No	Drug + Excipient	Functionality	Description	Ratio
1	Fexofenadine hydrochloride	Active pharmaceutical Ingredient	White crystalline powder	Not applicable
2	Fexofenadine hydrochloride +Mannitol	Diluent/Filler	White crystalline powder	1:1
3	Fexofenadine hydrochloride +Sorbitol		White colored powder	1:1
4	Fexofenadine hydrochloride +Microcrystalline cellulose		White colored powder	1:1
5	Fexofenadine hydrochloride + Lactose monohydrate		White colored powder	1:1
6	Fexofenadine hydrochloride + Sodium starch glycolate	Super disintegrant	White colored powder	1:0.3
7	Fexofenadine hydrochloride + Croscarmellose sodium		White to off white colored powder	1:0.3
8	Fexofenadine hydrochloride + Crospovidone		White to off white colored powder	1:0.3
9	Fexofenadine hydrochloride + Saccharin sodium	Sweetener	White colored powder	1:0.2
10	Fexofenadine hydrochloride + Sucralose		White colored powder	1:0.2
11	Fexofenadine hydrochloride + Aspartame		White colored powder	1:0.2

12	Fexofenadine hydrochloride + citric acid	Acidulant	White crystalline powder	1:0.2
13	Fexofenadine hydrochloride + Sodium bicarbonate	Taste masking agent	White crystalline powder	1:0.2
14	Fexofenadine hydrochloride + Tannic acid		White to off white colored powder	1:0.3
15	Fexofenadine hydrochloride + Polacrillin potassium		White to off white colored powder	1:0.3
16	Fexofenadine hydrochloride + Orange flavor	Flavouring agent	White to off white colored powder	1:0.2
17	Fexofenadine hydrochloride + peppermint flavor	Flavouring agent	White to off white colored powder	1:0.2
18	Fexofenadine hydrochloride + Pineapple flavor		White to off white colored powder	1:0.2
19	Fexofenadine hydrochloride + FD&C Blue #1	Colorant	Blue colored powder	1:0.1
20	Fexofenadine hydrochloride + FD&C Yellow #5		Yellow colored powder	1:0.1
21	Fexofenadine hydrochloride + Colloidal silicon dioxide	Glidant	White to off white colored powder	1:0.2
22	Fexofenadine hydrochloride + Magnesium stearate	Lubricant	White to off white colored powder	1:0.3
23	Fexofenadine hydrochloride + Stearic acid		White to off white colored powder	1:0.3

Table 2. Fexofenadine hydrochloride – characteristic absorption bands

S.No	Functional group	Frequency
1	Aromatic C-H stretching	3300-3200 cm^{-1}
2	Aliphatic	2900-3000 cm^{-1}
3	Acid ketone	1700±10 cm^{-1}
4	Tertiary amine	1280±10 cm^{-1}
5	Aromatic C-C stretching	1447±10 cm^{-1}

Table 3. Characteristic absorption frequency observed

S.No	Binary mixture with	Characteristic absorption frequency (cm^{-1})	Description	Interference	Compatible / Incompatible
1	Mannitol	3289	White crystalline powder	No	Compatible
		2970			
		1705			
		1417			
		1280			
2	Sorbitol	3289	White colored powder	No	Compatible
		2934			
		1705			
		1447			
		1278			
3	Microcrystalline cellulose	3302	White colored powder	No	Compatible
		2937			
		1705			
		1447			
		1280			
4	Lactose monohydrate	3344	White colored powder	No	Compatible
		2934			
		1705			
		1447			
		1279			

5	Sodium starch glycolate	3297 2936 1706 1447 1279	White colored powder	No	Compatible
6	Croscarmellose sodium	3293 2936 1707 1447 1279	White to off white colored powder	No	Compatible
7	Crospovidone	3306 2931 1706 1447 1280	White to off white colored powder	No	Compatible
8	Saccharin sodium	3297 2937 1707 1447 1279	White colored powder	No	Compatible
9	Sucralose	3289 3000 1700 1447 1279	White colored powder	No	Compatible
10	Aspartame	3297 2937 1704 1448 1279	White colored powder	No	Compatible
11	Citric acid	3299 2938 1707 1448 1279	White crystalline powder	No	Compatible
12	Sodium bicarbonate	3298 2937 1706 1447 1279	White crystalline powder	No	Compatible
13	Tannic acid	3297 2937 1707 1448 1279	White to off white colored powder	No	Compatible
14	Polacrillin potassium	3302 2937 1707 1279	White to off white colored powder	No	Compatible
15	Orange flavor	3299 2937 1706 1448 1279	White to off white colored powder	No	Compatible
16	Peppermint flavor	3294 2937 1707 1448 1279	White to off white colored powder	No	Compatible
17	Pineapple flavor	3295	White to off white	No	Compatible

		2937 1707 1448 1279	colored powder		
18	FD&C Blue #1	3297 2937 1706 1448 1279	Blue colored powder	No	Compatible
19	FD &C yellow#5	3301 2937 1706 1448 1279	Yellow colored powder	No	Compatible
20	Colloidal Silicon dioxide	3298 2936 1705 1448 1279	White to off white colored powder	No	Compatible
21	Magnesium stearate	3296 2918 1705 1448 1279	White to off white colored powder	No	Compatible
22	Stearic acid	3299 2937 1706 1448 1279	White to off white colored powder	No	Compatible

The analysis of IR spectra of few Fexofenadine hydrochloride excipient binary mixture overlay are illustrated in Fig 2 -11and the presences of characteristic peaks are tabulated in table 2.

Fig 1. Chemical structure of Fexofenadine hydrochloride

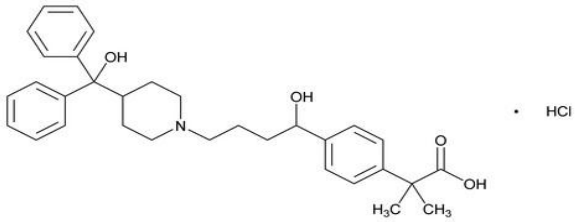


Fig 2. FT-IR Spectra of Fexofenadine hydrochloride

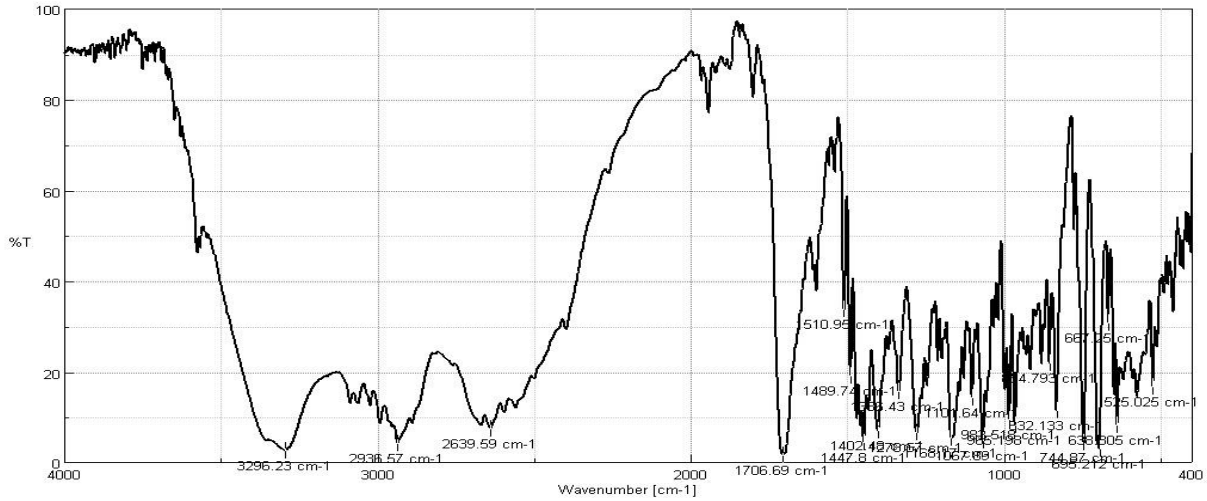


Fig 3. IR overlay spectra of Fexofenadine hydrochloride and Crospovidone

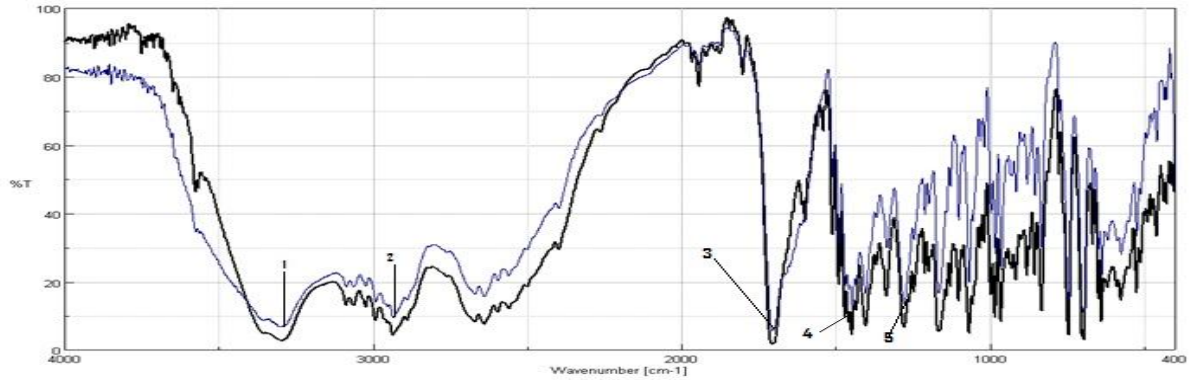


Fig 4. IR overlay spectra of Fexofenadine hydrochloride and saccharin sodium

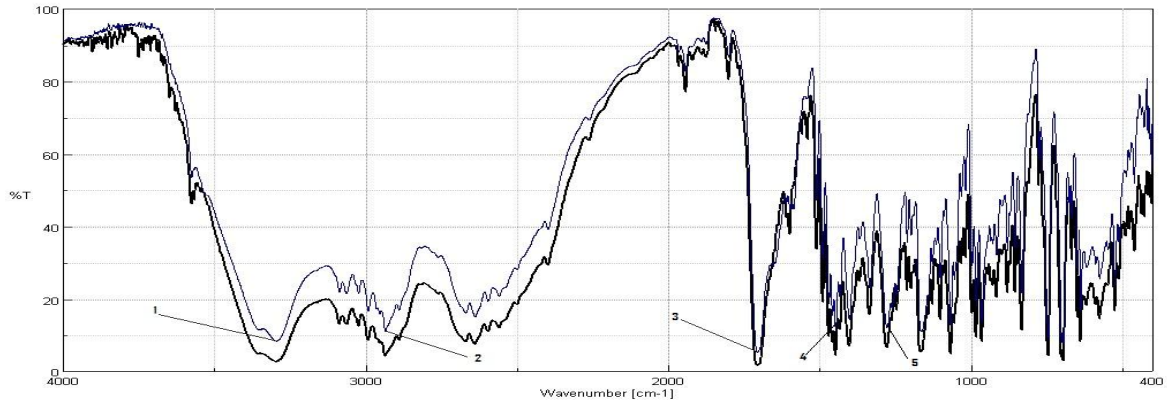


Fig 5. IR overlay spectra of Fexofenadine hydrochloride and sucralose

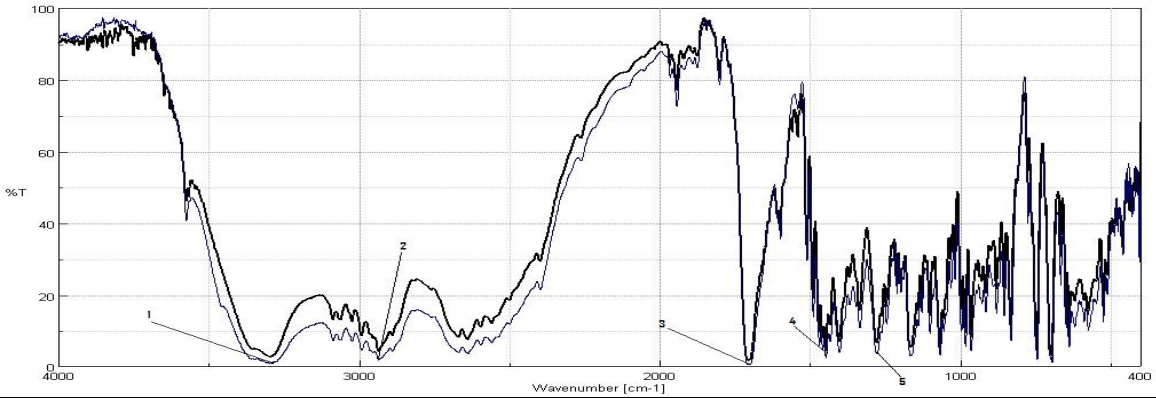


Fig 6. IR overlay spectra of Fexofenadine hydrochloride and Aspartame

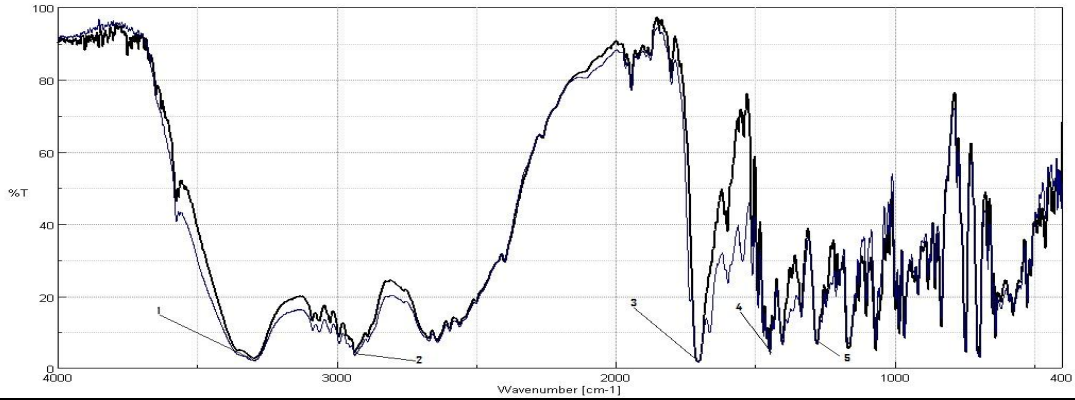


Fig 7. IR overlay spectra of Fexofenadine hydrochloride and Citric acid

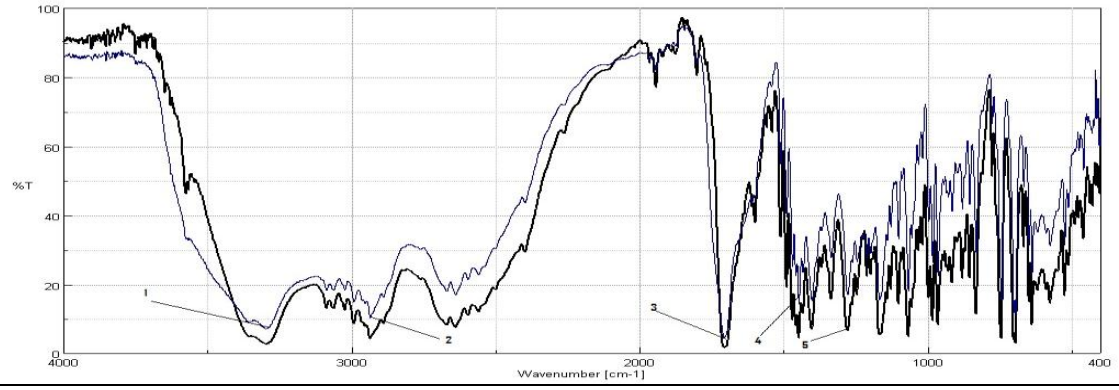


Fig 8. IR overlay spectra of Fexofenadine hydrochloride and Tannic acid

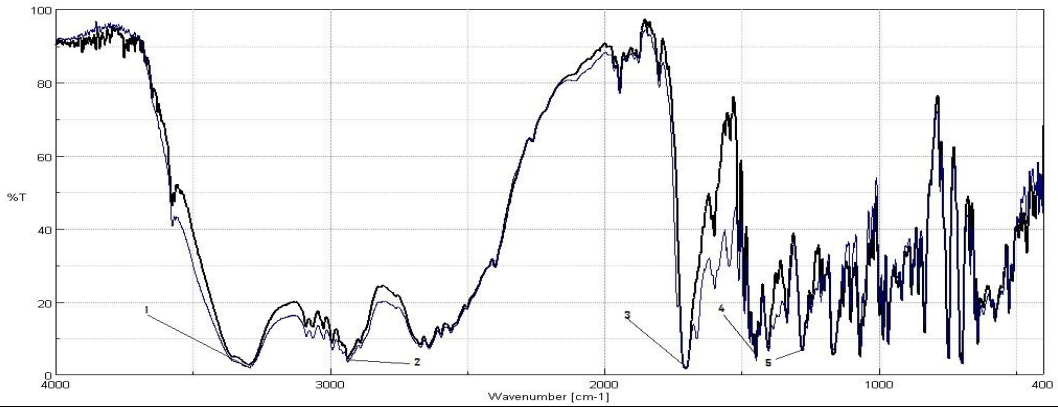


Fig 9. IR overlay spectra of Fexofenadine hydrochloride and Orange flavor

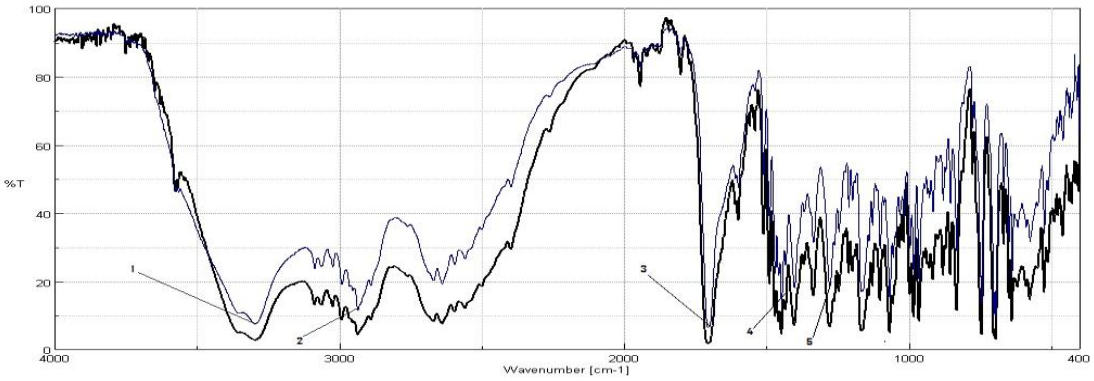


Fig 10. IR overlay spectra of Fexofenadine hydrochloride and peppermint flavor

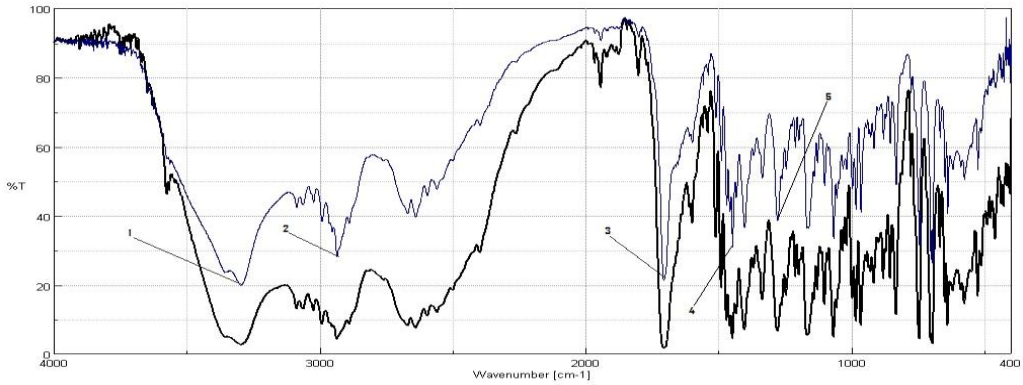
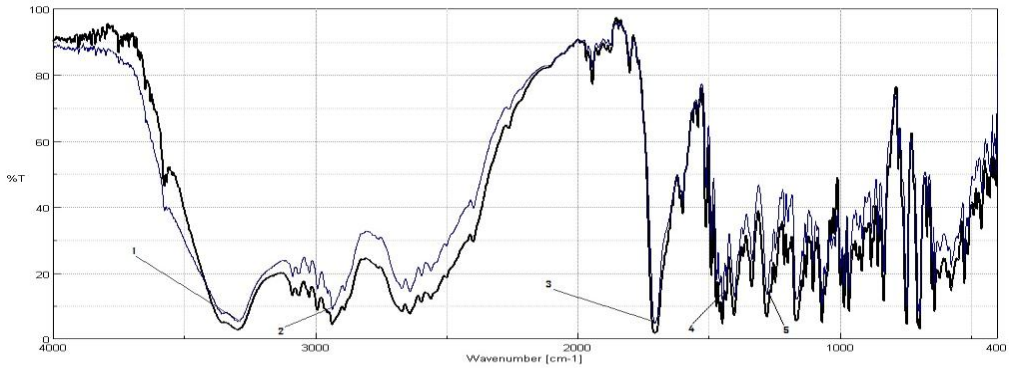


Fig 11. IR overlay spectra of Fexofenadine hydrochloride and pineapple flavor



The characteristic absorption observed are labelled as 1- Aromatic C-H stretching, 2- Aliphatic, 3- Acid ketone, 4- Tertiary amine, 5- Aromatic C-C stretching.

CONCLUSION

The outcome of the experiment demonstrated the applicability of FTIR method as fast screening tool to screen compatibility in early stages of a preformulation process. The drug excipient interaction results degradation related issue of dosage form at later stage of pharmaceutical development emphasized the need of better understanding of excipient interaction with active pharmaceutical ingredient. Literature search on interaction is an option to avoid possible excipients for selected dosage form but it has a limitation of availability. In-depth awareness on analytical tools and brought the drug excipient compatibility data aid the perfect selection of excipient for stable drug product. Based on this experimentation all the excipients taken for the study found to be fully compatible with Fexofenadine hydrochloride and the selected excipients can be further used for Fexofenadine hydrochloride orally disintegrating tablets.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES

Ceschel GC, Badiello R, Ronchi C, Maffei P. Degradation of components in drug formulations: a comparison between HPLC and DSC methods, *J. Pharm.Biomed. Anal.* 2003; 32: 1067–1072.

Cheng WT, Wang SL, Lin SY. Effect of moisture content on the solid-state interaction at the interface between magnesium stearate and captopril. *Appl. Surf. Sci.* 2008; 255: 2782–278.

Karin Liltorp, Trine Gorm Larsen, Birgitte Willumsen, René Holm. Solid state compatibility studies with tablet excipients using non thermal methods, *J. Pharm.Biomed. Anal.* 2011; 55: 424 –428.

Kerc J, Srcic S, Urleb U, Kanalec A, Kofler B, Smid-Korbar J. Compatibility study between acetylcysteine and some commonly used tablet excipients, *J. Pharm. Pharmacol.* 1992; 44: 515–518.

Kogermann K, Zeitler JA, Rantanen J, Rades T, Taday PF, Pepper M, Heina-maki J, Strachan CJ. Investigating dehydration from compacts using terahertz pulsed, Raman, and near-infrared spectroscopy. *Appl. Spectrosc.* 2007; 61: 1265–1274.

Laszcz M, Kosmacinska B, Smigielska B, Glice M, Maruszak W, Groman A, Beczkowicz H, Zelazko L. Study on compatibility on imatinib mesylate withpharmaceutical excipients, *J. Therm. Anal. Calorim*. 2007; 88: 305–310.

Late SG, Banga AK. Thermal and non-thermal methods to evaluate compatibility of granisetron hydrochloride with tablet excipients, *Pharmazie*, 2008; 63: 453–458.

Marini A, Berbenni V, Moioli S, Bruni G, Cofrancesco P, Margheritis C, Villa M. Drug-excipient compatibility studies by physico-chemical techniques – The case of indomethacin. *J. Therm. Anal.Calorim.* 2003; 73: 529–545.

Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, Robertson TA, Roberts MS. Compatibility studies of acyclovir and lactose in physical mixtures. *Eur. J. Pharm. Biopharm*. 2009; 73: 404–413.

Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th Edition ed.; Pharmaceutical Press: London, Preface 2009; X.

Schmitt EA, Peck K, Sun Y, Geoffroy J-M. Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry. *Thermochim. Acta*. 2001; 380: 175–183.

Serajuddin ATM, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, Varia SA. Selection of solid dosage form composition through drug excipient compatibility testing, *J. Pharm. Sci.* 1999; 88: 696–704.

Sims J, Carreira J, Carrier D, Crabtree S, Easton L, Hancock S. A new approach to accelerated drug-excipient compatibility testing. *Pharm. Dev. Tech.* 2003; 8:119–126.

Taglialatela M, Timmerman H, Annunziato L. Cardiotoxic potential and CNS effects of first-generation antihistamines. *Trends Pharmacol. Sci*.2000; 21: 52–56.

Thumma S, Repka MA. Compatibility studies of promethazine hydrochloride with tablet excipients by means of thermal and non-thermal methods, *Pharmazie.* 2009; 64: 183–188.

Tomassetti 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; 37: 949–955.

Van Dooren AA. Design for drug–excipient interaction studies, *Drug Dev. Ind. Pharm.*1983; 9: 43–55.

Verma RK, Garg S. Selection of excipients for extended release formulations of glipizde through drug-excipient compatibility testing, *J. Pharm. Biomed. Anal.* 2005; 38: 633–644.