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Review Article

FTIR Spectroscopic Investigation of Hydrogen Bonding Interactions

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ABSTRACT

Hydrogen bonding is a dominant non-covalent interaction controlling solubility, stability, and receptor recognition in pharmaceuticals. Fourier Transform Infrared (FTIR) spectroscopy provides direct experimental evidence of such interactions through frequency shifts and band broadening in characteristic vibrational regions . This study employs FTIR to examine hydroxyl, amine, and carbonyl functional groups in model drugs such as paracetamol, aspirin, and ibuprofen. Concentration-, temperature-, and isotopic-variation experiments reveal distinct red shifts and broadening patterns confirming intra- and intermolecular hydrogen bonding. The findings demonstrate that FTIR spectroscopy is a rapid, reliable tool for assessing hydrogen bonding in pharmaceutical solids and solutions.

INTRODUCTION

Among the most effective of the non-covalent forces of biology and chemistry, hydrogen bonding takes place when a covalently attached hydrogen atom that is attached to an extremely electronegative atom such as fluorine, nitrogen, or oxygen becomes involved with some other electronegative atom possessing a lone pair of electrons. Although weaker than covalent bonds, hydrogen bonds determine the stabilization of geometry of molecules and physicochemical nature of compounds.(Atkins et al., 2022; Silverstein & Webster, n.d.) Within pharmaceuticals, hydrogen bonding is the most significant because it controls such vital properties as drug–receptor interaction, solubility, melting point, crystalline structure, and overall

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bioavailability. Intramolecular hydrogen bonds, for instance, can freeze specific conformations of drug molecules, whereas intermolecular hydrogen bonds can influence water or other solvent solubility. Knowledge of such interactions enables researchers to design optimal drugs with desired pharmacological characteristics.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.)

Spectroscopic techniques are commonly used to investigate hydrogen bonding interactions, and among these techniques, Fourier Transform Infrared (FTIR) spectroscopy has come to be one of the most standard and dependable techniques. FTIR analyzes molecular vibrations of bonds, and hydrogen bonding induces measurable vibrational frequency shifts and absorption band profiles. (*Pavia DL 2015*, n.d.; Silverstein & Webster, n.d.)

Significance of Hydrogen Bonding in Drug Molecules.

Drug molecules bear many functional groups, i.e., hydroxyl (–OH), amine (–NH), amide (–CONH), and carbonyl (C=O), which are able to engage in hydrogen bonding.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.) These are not chemical curiosities but are important contributors to the therapeutic action of a drug.(*Brahmankar*, n.d.)

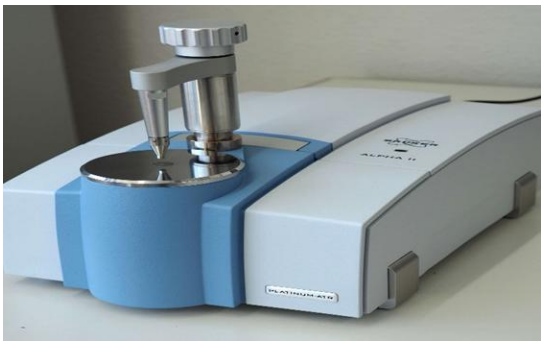
- Solubility: Increased hydrogen-bonding with water increases solubility and favors enhanced absorption in the body.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

- Stability: Intramolecular hydrogen bonds stabilize a molecule's conformations and render drugs resistant to degradation.(*Brahmankar*, n.d.)

- Drug–Receptor Binding: Hydrogen bonding is employed by many receptors and enzymes for selective drug recognition and binding. Geometry and strength of such bonds usually determine binding affinity.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Berkholz et al., 2010)

Solid-State Properties: Hydrogen bonding controls crystal packing in drug solids, influencing melting point, rate of dissolution, and mechanical properties like compressibility of tablets.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.)

Why FTIR Spectroscopy ?



FTIR spectroscopy is a rapid, sensitive, and non-destructive method that directly demonstrates hydrogen bonding. FTIR is based on the measurement of infrared radiation absorption by chemical bonds in a molecule. Upon hydrogen bonding, the donor group's vibrational frequency (e.g., –OH or –NH) goes down (red shift) and the absorption bandwidth increases. Similar frequency shifts are also observed with acceptor groups like C=O upon hydrogen bonding. (Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.) In comparison with other analytical methods like Nuclear Magnetic Resonance (NMR) or X-ray crystallography, FTIR has a number of advantages for this reason:-

i. Identification of hydrogen bond effects in the vibrational spectrum is simple.(*Pavia DL 2015*, n.d.; Silverstein & Webster, n.d.)
ii. Rapid measurement with little or no sample preparation.(Silverstein & Webster, n.d.)
iii. Versatility to the extent that both solid and liquid samples can be measured.
iv. Capacity to study dynamic effects, i.e., depend on concentration, temperature, or isotopic substitution.(*Pavia DL 2015*, n.d.)
v. Due to all such reasons, FTIR spectroscopy is a suitable technique to study the hydrogen bonding in drug molecules.(Atkins et al., 2022; *Pavia DL 2015*, n.d.)

Study Scope.

The project entails use of FTIR spectroscopy to study hydrogen bonding in certain drug molecules. The study comprises:-

Recording FTIR spectra of solid drug samples. Examination of common functional groups (–OH, –NH, and C=O). Free and hydrogen-bonded states comparison via peak shifts and band broadening. Investigating the effect of concentration, temperature, and isotopic substitution (with D_2O). (Atkins et al., 2022; *Pavia DL 2015*, n.d.)Interpretation of data to determine the role of hydrogen bonding in pharmaceutical activity. Learning through doing with focus on interpretation, the most important aspect being mastery of the use of FTIR as a standard tool in pharmaceutical research.

Project Aims:

The principal aims of this project are:

1.Investigation of hydrogen bonding between drug molecules by FTIR spectroscopy.

2.To determine spectral variations in functional groups under hydrogen bonding.

3.To determine comparison of hydrogen bonding behavior in solution state and solid state.

4. To assess the effect of concentration, temperature, and isotopic exchange on hydrogen bonding.

5. To emphasize the significance of hydrogen bonding towards drug stability and efficacy.(Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; Silverstein & Webster, n.d.)

1. Review

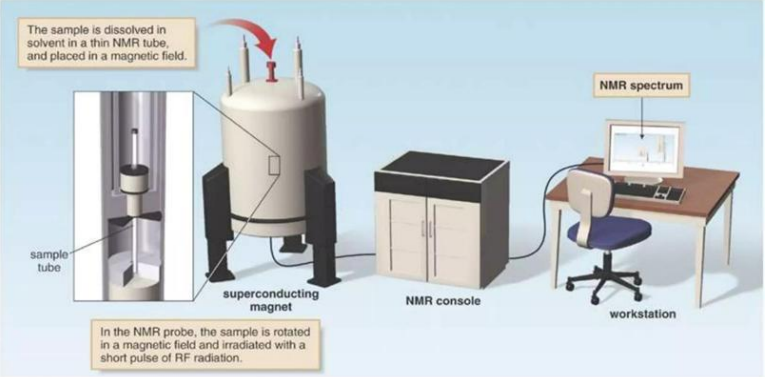
Hydrogen Bonding Basics Hydrogen bonding, an important non-covalent interaction in molecular sciences, takes place when an electronegative atom with an unshared electron pair is attracted to a hydrogen atom that is covalently bonded to an electronegative atom (such as oxygen, nitrogen, or fluorine). The conventional representation is in the form of: D–H···A where A represents the acceptor atom, H represents the hydrogen atom that is involved, and D represents the donor atom (including O, N, or F). Nature of Hydrogen Bonds Hydrogen bonds may be considered a hybrid of van der Waals forces and purely covalent interactions. While more extreme cases (e.g., O–H···O bonds) can approach a strength of 60 kJ/mol, in general hydrogen bonds vary from 5 to 40 kJ/mol in strength. These interactions are directional. Spectroscopic Techniques for Investigating Hydrogen Bonding.(Atkins et al., 2022; *Brahmankar*, n.d.)

Spectroscopic Techniques for Investigating Hydrogen Bonding.

There are many analytical techniques to investigate hydrogen bonding. Each offers certain advantages and disadvantages.

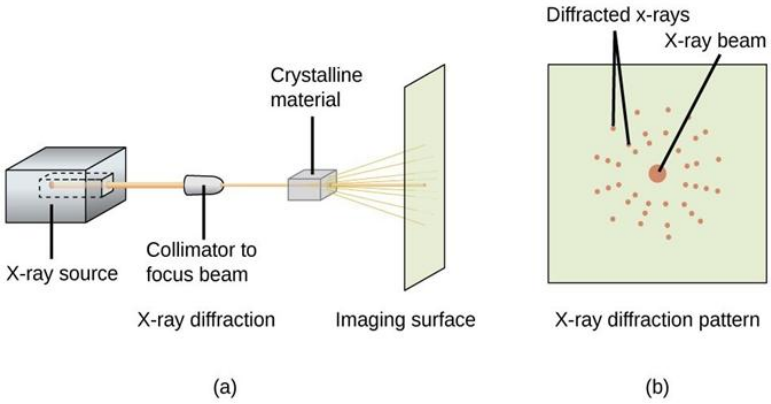
1. Nuclear Magnetic Resonance (NMR).

NMR identifies alterations to chemical shifts, and coupling constants as a result of hydrogen bonding. NMR variable temperature studies offer a dynamic investigation of hydrogen bonding. The method is notable for its need for relatively high concentrations and, in many cases, not sensitivity for weak hydrogen bonds.(Atkins et al., 2022)



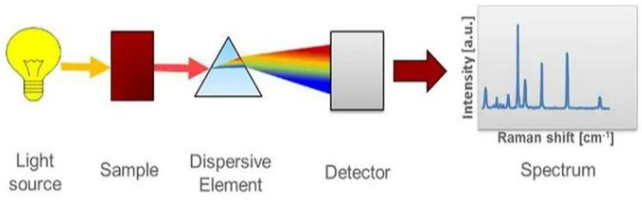
2. X-ray Crystallography.

This technique offers direct measurements of hydrogen bonding in the solid-state through measuring interatomic distances and angles. While excellent for accuracy, it requires crystals or crystalline samples, which are sometimes not possible to obtain. (*Jeffrey GA*, n.d.)



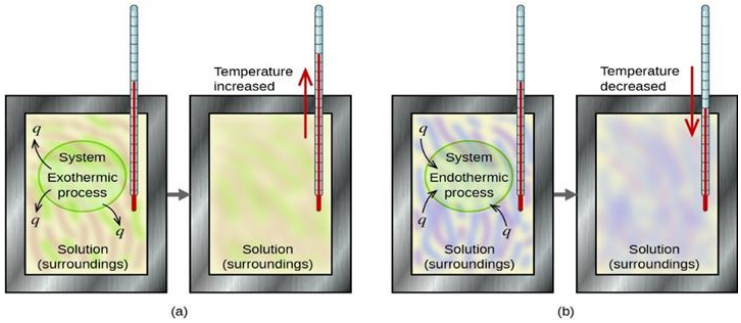
3. Raman Spectroscopy.

Raman spectroscopy identifies vibrational frequencies in a similar manner to FTIR, and is particularly complementary because bands that are weak in infrared may be quite strong in raman and vice versa. Raman spectroscopy works especially well for symmetric stretching vibrations.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)



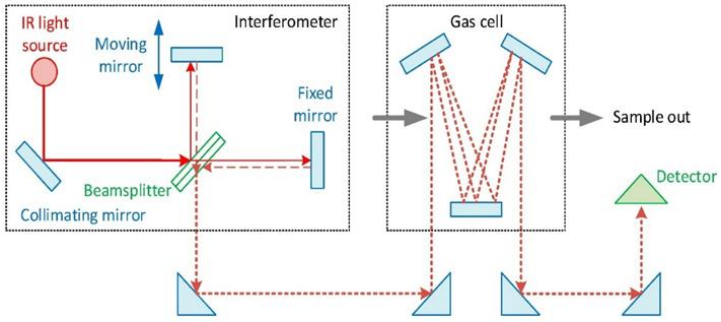
4. Calorimetry and Thermal Studies.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) offer indirect evidence of hydrogen bonding by measuring alterations in melting point and thermal stability. (*Brian C Smith*, n.d.)



5. Fourier Transform Infrared (FTIR) Spectroscopy.

FTIR is often seen as the most versatile of all methods because it can analyze rapidly, requires limited sample preparation, and can analyze solids, liquids and solutions. For all these reasons, FTIR is the main method used.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)



6. What is FTIR Spectroscopy?

FTIR spectroscopy involves passing infrared radiation through a sample while recording absorbance as a function of frequency (or wavenumber, cm^{-1}). Different functional groups absorb IR radiation at characteristic frequencies which correspond to vibrational transitions. (Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

○ Instrumentation Overview

FTIR instruments store IR spectra using an interferometer that can collect all of the frequencies of interest at the same time. An

interferometer converts the absorbance at frequencies to raw data which is called the interferogram and is the Fourier transformed for a spectrum.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)

- **Functional Group Areas**

OH Stretching (3200-3600 cm^{-1}): Free OH gives rise to a sharp band near 3600 cm^{-1}, whereas hydrogen-bonded OH may appear broader and with lower frequency. NH Stretching (3300-3500 cm^{-1}): The NH functionality will show shifts and broadening as hydrogen bonding occurs. C=O Stretching (1650-1750 cm^{-1}): This will always be a strong band, however when hydrogen bonding takes place there will be shifting lower in the wavenumbers. Fingerprint Region (600-1500 cm^{-1}): Very sensitive to subtle changes in Hydrogen bonding and particularly for amides and aromatic drugs.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

- **FTIR offers these advantages**

destructive analysis Minimal sample size Solid, liquid, and solution methods That you can analyze dynamic effects (the effects of temperature, concentration and, isotopic substitutions) (*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

7. Case Studies

In various studies FTIR spectroscopy has been successfully implemented to analyze hydrogen bonding for pharmaceuticals:

Aspirin (acetylsalicylic acid): Showed hydrogen bonding in the characteristic functional group, where OH is a broad absorption in the 2500-3300 frequency range.

Paracetamol (acetaminophen): Exhibits intramolecular hydrogen bonding between the hydroxyl and amide groups; see shifts in both OH and C=O as evidence. (*Brian C Smith*, n.d.)

Sulfonamides: FTIR studies show NH···O hydrogen bonding, impacting polymorphism

Peptide drugs: Direct evidence of hydrogen-bonded secondary structures when considering amide I and amide II bands in FTIR spectra.(*Brahmankar*, n.d.; *Brian C Smith*, n.d.)

The examples described above illustrate how FTIR is a diagnostic method for the identification of functional groups, but importantly can also be used to examine the effects of hydrogen bonding in medicinal chemistry.

Summary of Review .

From the review presented above, we can see that:

Hydrogen bonding is a major interaction and governs the physical and biological properties of drug molecules.

There are a variety of methods for studying hydrogen bonding, however FTIR has advantages of simplicity, sensitivity and flexibility. Previous studies have shown that FTIR provides options to detect and interpret hydrogen bonding in many different drugs. As stated, the information in this literature background provides information to develop the experimental work found in the later chapters of this report.(Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; *Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

1. Methods

1. Materials

The materials for this study can fall into general categories of drug samples, solvents and reagents, and equipment.(Atkins et al., 2022; Stuart, 2004)

2. Drug Samples

A selection of common drug molecules was selected for FTIR analysis. The selection criteria were drugs with functional groups that participate in hydrogen bonding (–OH, –NH, –CONH, –C=O). Considering this, there were four candidate drug molecules:

Paracetamol (acetaminophen): has hydroxyl and amide groups.

Aspirin (acetylsalicylic acid): has carboxyl and ester groups.

Sulfonamide derivatives: have amine and sulfonyl groups.

Ibuprofen: has a carboxylic acid group. These drugs were selected because they are commonly used, available as pure drugs, and represent different functional groups that participate in hydrogen bonding.(Atkins et al., 2022; *Brahmankar*, n.d.; *Brian C Smith*, n.d.)

3. Solvents and Reagents

Potassium bromide (KBr): an analytical reagent used for pellet preparation.

Deuterium oxide (D_2O): used for isotopic substitution experiments. Non-hydrogen bonding solvents (e.g., carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2)): solvents used for solution-state FTIR measurements.

Ethanol (C_2H_5OH): solvent used in some cases for sample dissolution (but keep in mind its own hydrogen bonding).

4. Equipment

FTIR spectrometer (Shimadzu, Bruker or PerkinElmer model), with an Attenuated Total Reflectance (ATR) accessory. KBr press for preparing transmission pellets. Mortar and pestle for grinding samples. Analytical balance for weighing samples accurately. Sample holder/heating stage for variable temperature experiments.(Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)

5. Analytical Methods of Sample Preparation

Sample preparation has a significant impact on FTIR spectra and several different methods of analysis were used for both solid and liquid samples.

1. Solid State (KBr Pellet Method)

1-2 mg of drug sample was accurately weighed. Mixed with approximately 100 mg of dry KBr powder. Thoroughly ground in an agate mortar to obtain a uniform mixture. Pressed the mixture into a clear pellet, using a hydraulic press, ensuring vacuum was used.Placed the pellet in the FTIR sample holder and spectra were recorded. This method provided high quality spectra but handling needs to be careful as moisture can or cannot contamination is an issue.(*Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

2. ATR-FTIR Method

For quick measurement and quickly we placed the solid forms of the drug directly on the ATR crystal. To make sure contact was appropriate, an ATR clamp was used. No preparation based on simple

were used, and spectra were recorded directly ATR is not as sensitive to sample thickness and sample thickness and give rapid results and not need to perform any sample preparation or correction of a sample. As with all IR analysis there is still limited penetration depth that IR radiation can give.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

3. Solution-State Samples

The drugs were dissolved in non-hydrogen bonding solvents (CCl_4).Solutions of different concentrations were made for the purpose of studying intermolecular hydrogen bonding.For the purpose of isotopic substitution, small amounts of D_2O were added to exchange labile hydrogens (OH and NH). (*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)

4. Temperature Change

Some experiments were conducted with a heating stage. The solutions of the drugs were heated in stages (25 °C, 50 °C, 75 °C). Clearly, each solution was heated progressively. FTIR (spectra) spectra of the samples were taken at each stage of the temperature change, allowing us to observe any hydrogen bond breaking with increasing temperature.(Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

5. Instrumentation

FTIR spectrometer was used under these conditions (parameters will vary from instrument to instrument, based on the model): Wave number range: 4000 to 400 cm^{-1}. Resolution: 2 cm^{-1} (sufficient to detect small shifts). Number of Averaged Scans: 32–64 scans were averaged per sample, for signal-to-noise precision. Background scans were taken before every sample measurement. ATR crystals used were diamond, or zinc selenide (ZnSe). Detector used: DTGS (Deuterated Triglycine Sulfate). Spectra were digitally stored on other software for further processing and analysis.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Kong & Yu, 2007; Silverstein & Webster, n.d.; Stuart, 2004)

6. Experimental Design

A series of specific experiments were conducted to systematically investigate hydrogen bonding in drug molecules:

1. Solid-State Spectra

Analyzed pure drug samples in behalf of solid state (ATR and KBr pellet). Wavenumber regions that were analyzed: OH/NH stretching (3000–3700 cm^{-1}) and C=O stretching (1600–1750 cm^{-1}).(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; Silverstein & Webster, n.d.)

2. Concentration-Dependent Spectra

Prepared solutions of drugs at different concentrations (0.01 M, 0.05 M, 0.1 M) in non-hydrogen bonding solvents. Integrated FTIR spectral analysis were conducted on the samples to compare shifts in bands due to intermolecular hydrogen bonding.

3. Temperature-Dependent Spectra

Heated drug samples in a calorimeter, incrementally. Monitored and documented band shifts and changes in intensity as hydrogen bonds weakened to the point of breaking at increased temperatures.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.)

4. Isotopic Substitution (D_2O Exchange)

Added D_2O into samples of drug compounds containing OH or NH functional groups. The exchange of hydrogen with deuterium progressively brought about the band vibrational frequency shifts (OD and ND bands appear at lower frequencies). This was useful in confirming which bands corresponded to the labile (acidic) hydrogen.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brian C Smith*, n.d.; Nakamoto, n.d.)

7. Data Analysis

Data analysis focused on identifying hydrogen bonding signatures (if any) and quantifying them if they could be located.

Use of Peak Position: Used the wavenumber of functional group vibrations and compared shifts with literature values for free or bonded states.

Use of Band Shape: Broadened peaks were used as evidence of multiple hydrogen bonding environments.

Use of Second Derivative Spectra: Slightly better for resolving overlapping peaks.

Use of Peak Deconvolution: Gaussian/Lorentzian fitting was used to estimate free vs bonded contributions.

Comparative Studies: Solid vs solution, low vs high concentration, room vs elevated temperature, H vs D substituted. (*Brian C Smith*, n.d.; Coates, 2000; Silverstein & Webster, n.d.)

2. Streaching Regions

- Solid State FTIR Observations.

Drug	Functional Group	Free (cm^{-1})	Observed (cm^{-1})	Shift (cm^{-1})	Interpretation
Paracetamol	OH stretch	3600	3320 (broad)	-280	Strong H-bonding.
Paracetamol	Amide C=O	1680	1650	-30	Intramolecular H-bond
Aspirin	Carboxyl OH	3550	2500-3200 (broad)	~500	Large Dimeric H-bonding.
Ibuprofen	Carboxyl OH	3550	3100	-450	Strong H-bonding dimer.

- OH and NH Stretching Regions.

The OH and NH stretching (3000 to 3700 cm^{-1}) regions are extremely sensitive to hydrogen bonding. Free OH groups will typically absorb at approximately 3600 cm^{-1}. Hydrogen-bonded OH groups will absorb as broad absorptions ranging from 3200 to 3400 cm^{-1}. Carboxylic acids will generally have very broad bands in the 2500 to 3300 cm^{-1} due to dimer formation. NH stretching bands at 3300-3500 cm^{-1} will also shift down and broaden due to hydrogen bonding.

Example: The OH stretch in paracetamol was observed at 3320 cm^{-1} indicating hydrogen bonding with the amide carbonyl.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brian C Smith*, n.d.; Coates, 2000; Silverstein & Webster, n.d.)

- Carbonyl Region Observations.

Drug	Group	Free (cm^{-1})	Observed (cm^{-1})	Shift (cm^{-1})	Interpretation
Paracetamol	Amide C=O	1680	1650	-30	Intramolecular H-bond
Aspirin	C=O	1725	1710	-15	Intermolecular H-bond
Ibuprofen	C=O	1720	1700	-20	Intermolecular H-bond

- Concentration-Dependent Studies.

In order to study intermolecular hydrogen bonding, we collected FTIR spectra of drug solutions in non-hydrogen bonding solvents (CCl_4, CH_2Cl_2) at varying concentrations.(Kazarian & Chan, 2006)

Observations were made that:

At low concentrations, we observed a sharper OH/NH band near free values, suggesting that more intermolecular H-bonding occurred (fewer intermolecular H-bonds). At higher concentrations, the bands shifted down and broadened as H-bonding intermolecularly increased.

Example: Ibuprofen (<3550 cm^{-1} at low conc.; ≈3200 cm^{-1} at high conc.)

- Temperature-Related Studies.

FTIR spectra were recorded at elevated temperatures and revealed a weakening of hydrogen bonds.

- Isotopic Substitution (D_2O Exchange)

The introduction of D_2O resulted in an isotopic substitution of labile hydrogens (OH → OD, NH → ND).(Atkins et al., 2022; *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; Silverstein & Webster, n.d.)

- **Overview**

Solid-state spectra illustrate strong hydrogen bonding in all selected drugs. Broadened and red shifted OH and NH stretching regions consistent with H-bonding. Carbonyl stretching bands red shifted in the presence of forming hydrogen bonding. Concentration dependent studies also showed intermolecular hydrogen bonding. Temperature depend studies showed that hydrogen bonds weaked and were reversible. Isotopic change to D_2O confirmed the assignments of hydrogen-bonded groups. These results provide solid confidence that FTIR spectroscopy is a valid approach for investigating hydrogen bonding in drugs molecules.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; *Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

3. Inter and intramolecular bonding

The FTIR intermolecular and intramolecular hydrogen bonding must have a large influence on the vibrational spectra of the chosen drug molecules. This discussion chapter will attempt, based on our theoretical knowledge and the literature, to make sense of these findings. In particular, we will ask what the impact of hydrogen bonding is for drug chemistry, and in doing so, we will consider the merits and drawbacks of FTIR spectroscopy to studying this phenomenon. Evidence of hydrogen bonding in drug molecules.The evidence presented has

confirmed that hydrogen bonding is a principal characteristic of the selected drugs.

1) OH and NH stretching regions: The broad red-shifted bands seen with paracetamol, aspirin and ibuprofen are strong evidence of hydrogen bonding. The free OH groups were expected to be seen near 3600 cm^{-1}, yet the absorptions were shown to be shifted to 3200-3400 cm^{-1}; this is consistent with intermolecular or intramolecular H-bonding.

2) C=O stretching region: The observed shifts of 10-30 cm^{-1} were compared to the literature value for free carbonyl groups were determined to be consistent with the interpretation of the carbonyl group being a hydrogen bond acceptor.

3) Isotopic substitution (D_2O exchange): The disappearance of OH bands and appearance of OD bands at 2500 cm^{-1} was strong evidence confirming that labile hydrogens were present in the structures.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; *Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

   - The Study of Intra- vs Intermolecular Hydrogen Bonding :-

Intramolecular hydrogen bonding involving Paracetamol was stable due to the influence of the hydroxyl group acting intramolecularly with the force of its amide carbonyl group, resulting in the strong shift of the C=O band due to that interaction and the stable conformation which followed. Intermolecular hydrogen bonding happened in both ibuprofen and aspirin, as demonstrated by an observable dimerization through the carboxylic acid groups, and the broadest OH bands with the highest intensity extending to as low as ~2500-3200 cm^{-1}, which would be the stronger intermolecular warnings. Intermolecular hydrogen bonding was particularly apparent in the solid state, and at high concentrations. This distinction is significant as intramolecular hydrogen bonding influences predominantly conformational stability, whereas intermolecular hydrogen bonding can influence solubility, melting points, and solid-conformational domains in solution, as well as solid state properties stated previously.

- Concentration and Temperature dependence

The confirmed results for the concentration- and temperature-factors conditional FTIR studies allow us to further comment on the intermolecular behaviours of hydrogen bonding.

- Concentration factor:

Although we used low concentrations of the solutes in non-hydrogen bonding solvents, the sharper-free OH peaks were observed at the low concentrations, therefore involving less intermolecular interactions at lower concentrations. The low concentration OH/stretch band peaked sharply and were closer to the free OH bands compared to higher concentration OH/ stretch bands occupying more volume, thus broadening and shifting down. Therefore, the difference in concentration clearly factors in the OH stretch and confirms the interesting connection to intermolecular hydrogen bonding.

- Temperature effect:

The heating process caused a gradual movement of the OH/NH bands back towards higher wavenumbers, which was expected with the breaking of hydrogen bonds. This is a reversible change that demonstrates that hydrogen bonding strength is influenced by thermal energy and demonstrates the dynamic character of hydrogen bonding. These findings are consistent with

published reports in literature, reinforcing the validity of the use of FTIR in monitoring hydrogen bond strength.

Pharmaceutical Implications

The above observations have direct relevance in pharmaceutical science;

1. **Drug solubility:** Intermolecular hydrogen bonding in carboxylic acid drugs, such as ibuprofen, would imply that solubility in water would to a large extent be determined by the disruption of the hydrogen-bonded dimers.

2. **Drug stability:** Intramolecular hydrogen bonding in paracetamol provides stability in the atomic conformation of the molecular structure. It is possible that hydrogen-bonding interactions may limit degradation.

3. **Polymorphism:** FTIR can determine different crystalline forms of drugs depending on the hydrogen bonding geometries involved. This is very important in the development, formulation and patent of drugs.

4. Drug – receptor binding: While this study did not explicitly investigate binding, these results do support the general pharmacological concept that hydrogen bonding plays an important role in drug – target binding interaction.

For all of the above reasons, FTIR has been shown to be a useful tool in studying hydrogen bonding interactions in academic settings, as well as provides useful insight into applied aspects of drug developments.(Atkins et al., 2022; *Brahmankar*, n.d.; *Brian C Smith*, n.d.)

Scope and Limitations of the Study

While FTIR is noteworthy, there are limitations of which we need to be cognizant:

Overlapping bands: In larger and more complex molecules, OH, NH, and CH vibrations overlap and make assignments challenging.

Solvent effects: Even "non-hydrogen bonding" solvents can sometimes have faint interactions with solvents that require care when interpreting result.

Quantification issues: Shifts in peaks identify hydrogen bonding, however, unless by other means such as using NMR or computational studies to obtain both bond lengths and angles to obtain bond energies, this is difficult to achieve.

Sample purity: Impurities, moisture, and errors during experimentation can significantly alter spectra.

The limitations suggested that FTIR is not intended as the only instrument for identifying or describing hydrogen bonding.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.; *Brahmankar*, n.d.; *Brian C Smith*, n.d.; Silverstein & Webster, n.d.)

3. Future Directions

While this study has successfully established the role of hydrogen bonding in drug molecules with the use of FTIR spectroscopy, there is further scope to build upon this work:

1. A Broader Range and Dysregulated Drug Use: Future studies could target many drugs that have not been included in this study, including peptide-based drugs, antibiotics, and anti-viral drugs, which we know have a more complex hydrogen bonding framework. (*Brahmankar*, n.d.)

2. Polymorph Studies: There are many drugs for which there are one or two polymorphs (multiple crystalline forms). A more comprehensive FTIR study of polymorphs could yield more information about hydrogen bonding differences regarding stability, dissolution rates, and ultimately, therapeutic efficacy.

3. Quantitative Analysis: More advanced data analysis methods like two-dimensional correlation spectroscopy (2D-IR) or peak deconvolution could be used to quantify the extent of hydrogen bonding more accurately.(*Brian C Smith*, n.d.)

4. Complementary Techniques: FTIR could be completed with complementary techniques like NMR, Raman spectroscopy, or X-ray crystallography to help us develop a more complete understanding of hydrogen bonding characteristics in pharmaceuticals. Theoretical computational approaches (Density Functional Theory, DFT) could also offer predictive vibrational frequencies and hydrogen bond energies.(Atkins et al., 2022; *Brahmankar*, n.d.)

5. In-Situ and Dynamic Studies: FTIR with special sample cells can provide a dynamic situation where we can witness hydrogen bonding as they occur during drug dissolution, crystallization, or thermal degradation.(*Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, n.d.)

6. Formulation Studies: It would be helpful to understand if the hydrogen bonding between active pharmaceutical ingredients (APIs) and excipients is relevant in determining the effects of formulation components on drug stability (shelf-life) or bioavailability.(*Brahmankar*, n.d.)

CONCLUSION

In conclusion, this illustrates the role of hydrogen bonding in drug chemistry and establishes the practical use of FTIR spectroscopy as an inexpensive, convenient, and simple tool to study it. This work is the basis for further studies and highlights the role of vibrational spectroscopy in research and applied pharmaceutical science. Incorporating and linking the FTIR data to complementary methods and models of computer simulations will help future researchers to continue to understand the complex phenomena of hydrogen bonding and further its implications for medicinal products.

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