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## RESEARCH ARTICLE

# ANALYSIS OF THE IVERMECTIN-ASCORBIC ACID BINDING INTERACTION USING FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT-IR)

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## ABSTRACT

Ivermectin (IVM), a lipid-based anthelmintic agent, effectively manages both endoparasites and ectoparasites. There is a clear association between instances of Ivermectin (IVM) overdoses, concerns over its effectiveness, and the emergence of resistance. The co-administration of Ivermectin (IVM) and Ascorbic Acid (AA) in the treatment groups exhibits a significant improvement at elevated dosages. The main objective of this study was to assess the possible interaction or viability of co-administering ascorbic acid and ivermectin at a uniform dosage. The infrared spectra of Ivermectin and ascorbic acid were analyzed in the spectral region of 4000 $cm^{-1}$ to 400 $cm^{-1}$. The spectra were compared to reference peaks that corresponded to specific functional groups. The visual characteristics of the band's performance may exhibit variation contingent upon the number of bands participating. The primary purpose of this study was to assess the possible interaction between ivermectin and ascorbic acid in order to ascertain the need and viability of polypharmacy or a combination of these two medications in varying proportions. The ratios examined in this study included 1:1, 1:3, 1:5, 3:1, and 5:1. The investigation incorporated evidence regarding the possibility for interaction between ivermectin and ascorbic acid, whether provided concurrently or in combination.

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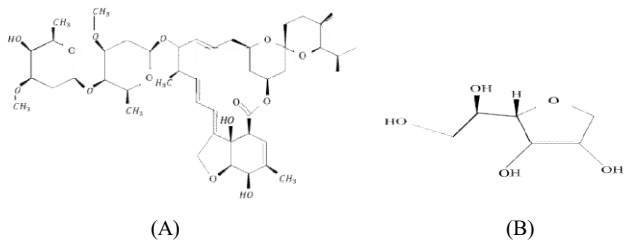
# INTRODUCTION

Ivermectin (IVM) is a lipophilic anthelmintic that is extensively utilized in both human and veterinary medicine to combat internal and external parasites. Conversely, the issues pertaining to resistance and efficacy are intricately connected to cases of excessive utilization of Integrated Vector Management (IVM), as emphasized by Chahrazed *et al*. (2020). A notable improvement was noticed when the oral dose of Ivermectin (IVM) was combined with the treatment groups receiving ascorbic acid (AA). According to the research conducted by Chahrazed *et al*. (2020), it is proposed that AA may have the ability to alleviate the negative consequences linked to the repetitive administration of IVM in high doses. These consequences include pruritus, painful skin edema, arthralgia, bone pain, thoracic pain, malaise, headache, and fever, as previously observed by Bauernfeind *et al*. (1953). Chahrazed *et al*. (2021) reported that the provision of complimentary ivermectin to animals leads to a decrease in the intensity of consequences. Furthermore, it has been shown that the simultaneous administration of antioxidants, such as vitamin C, might mitigate the effects of the medicine. The oral administration of ivermectin induces hepatic, renal, and scrotal tissue pathologies, characterized by the manifestation of congestion and necrosis. Based on the findings of Allen *et al*. (2018), the utilization of vitamin A and vitamin C as antioxidants had a favorable effect on the result subsequent to the consumption of unbound ivermectin. A number of aforementioned investigations have established a correlation between IVM and AA. Prior research has demonstrated that the concurrent administration of ascorbic acid can successfully mitigate the effects of overdose or elevated dosages of Ivermectin (IVM). Nevertheless, this prompts an additional investigation into the potential influence of consistent amounts of ascorbic acid on the dose of IVM. If ascorbic acid is capable of neutralizing IVM at typical concentrations, it is plausible that the intended therapeutic effect of IVM may not be attained. The intermolecular interaction between two pharmaceutical compounds is of utmost importance in the advancement of pharmacological combinations or concurrent administration. This study provides a chance to get insights into this subject by investigating the interaction between IVM and ascorbic acid through the utilization of infrared spectroscopy. Ivermectin (IVM), a pharmaceutical compound that has undergone partial synthesis, exhibits notable efficacy against endoparasitic and parasitic organisms, which are of considerable importance in both veterinary and human therapeutic domains (Rothova *et al*., 1989). Ette *et al*. (1990) reported that the substance under investigation exhibits oral efficacy in the elimination of microfilariae, as opposed to macrofilariae. According to Newland *et al*. (1988), the use of pharmaceutical interventions is frequently adopted as the primary approach for treating patients affected by the worm Onchocercid volvulus. This particular nematode is a significant cause of vision impairment in specific tropical areas. Ivermectin is a chemical substance that is obtained through the process of fermentation, originating from a natural source. This substance belongs to the class of anthelmintics and is distinguished by its chemical formula ($C_{47}H_{72}O_{14}H_2B_1b$) (Martin *et al*., 2021). The aforementioned chemical assumes a pivotal function in mass treatment activities aimed at addressing and preventing onchocerciasis (Taylor *et al*., 1989). Research done by Goa *et al*. in 1991 shown the effectiveness of Ivermectin in treating cutaneous larva migrans. Prior research has

provided empirical support for the notion that ivermectin possesses the capacity to augment the transmission of neural signals, promote the activation of chloride channels, diminish the resistance to electrical current in muscle fibers, and demonstrate comparable effects to those of gamma-aminobutyric acid (GABA) (BAUERNFEIND *et al*., 1982). The primary route of elimination for ivermectin and/or its metabolites is by fecal excretion. Based on research done by Guzzo *et al*. (2002), it was shown that the plasma half-life of Ivermectin in males is approximately 18 hours after oral administration. The efficacy of this therapeutic intervention has been observed in patients diagnosed with connective tissue illnesses, such as dermatomyositis, autoimmune bullous disorders, such as pemphigus, and persons affected by HIV-1 infection. Nevertheless, the management of scabies in patients with HIV-1 infection presents a heightened challenge (Dourmishev *et al*., 2005). According to Pehlivan and Pehlivan *et al*. (2017), ascorbic acid serves as an oxygen acceptor and has the ability to hinder the traditional oxidation process by absorbing oxygen from the surrounding environment. The chemical under investigation possesses the capacity to act as a synergistic agent with major antioxidants through its role as a hydrogen donor. The chemical in question was first obtained from lemons by Waugh and King, and subsequently isolated from the adrenal gland by Svirbely and Szent-Gyiirgyi. Based on recent research discoveries, it has been demonstrated that the synthesis of ascorbic acid occurs endogenously in the human body through the condensation of glucose, which has led to its widely recognized nomenclature (Waugh & King *et al*., 1932). Organic sources abundant in the antioxidant ascorbic acid ($C_6H_8O_6$) have been recognized to include citrus fruits, berries, melons, tomatoes, and green vegetables (Hughes & Jones *et al*., 1971). The study conducted by Batiha *et al*. (2020) presents solid evidence suggesting that minor deficiencies in ascorbic acid have detrimental effects on health, particularly in relation to the development of scurvy. The expression of these characteristics can be ascribed to a decrease in the production of collagen due to a deficiency in vitamin C. The oxidation of deaminated amino acids plays a crucial role in the metabolic pathway of tyrosine, serving as a coenzyme (Bauernfeind *et al*., 1953). The molecule L-ascorbic acid, which possesses reducing characteristics, experiences oxidative degradation when present in a solution (Naidu *et al*., 2003; Linster& Van Schaftingen *et al*., 2007). There has been considerable backing for its function as a detoxifying agent, perhaps also performing a non-specific purpose (Rumsey & Levine *et al*., 1998; Linster& Van Schaftingen *et al*., 2007). Prior study on animal experimentation has indicated that the administration of vitamin C may offer protective benefits against oxidative stress and exposure to environmental contaminants (Chambial *et al*., 2013). The approach adopted in this study involves the use of two phases of demonstration. The initial stage of the study utilizes Fourier-transform infrared (FT-IR) spectroscopy to gain a fundamental understanding of the interaction between ivermectin and ascorbic acid. Moreover, to augment one's comprehension of the therapeutic capacity of the synergistic utilization of ivermectin and ascorbic acid, it is imperative to delve further into the topic at hand.



(A) (B)

**Figure 1. Structure of (A) Ivermectin and (B) Ascorbic acid**

# MATERIALS AND METHODS

All chemicals and reagents utilized in this study were of analytical quality and were used as received. Solvents, on the other hand, were purified in accordance with the established standard technique. The Ivermectin sample was obtained from ACI Pharmaceuticals Ltd., while the Ascorbic acid, methanol, and ethanol samples were acquired from the pharmaceutical analysis laboratory of Stamford University Bangladesh.

***Instrument:*** The evaluation of potential interactions between the pharmaceutical compound and hydrophobic polymers was performed by Fourier Transform Infrared (FT-IR) research. To obtain infrared spectra ranging from 4000 to 600 $cm^{-1}$, the Perkin Elmer apparatus (model L160000A) situated in Waltham, MA, USA, was utilized. Individual samples were carefully positioned on the specimen platform for analysis. The baseline was systematically altered and normalized throughout the experiment for each sample. In order to accomplish spectral smoothing, a smoothing function with a 9-point configuration was utilized. The experiment was performed with the IRSpirit Fourier transform infrared (FT-IR) Spectroscopy apparatus produced by Shimadzu, USA.

***Sample preparation:*** Different ratios of ivermectin and ascorbic acid were delivered in separate test tubes. Following the introduction of two chemicals, specifically Ivermectin and Ascorbic acid, into the test tube, a precise volume of 1 ml of methanol was meticulously incorporated gradually. Following that, the chemical granules, which consisted of ivermectin and ascorbic acid, were exposed to moisture by the application of a droplet of methanol. The ivermectin and ascorbic acid mixture was subjected to homogenization using a glass rod-shaped stirrer for about 2 to 4 hours. The procedure above persisted until the liquid product achieved a condition of complete dryness or until the methanol component had evaporated entirely. The visual characteristics of the material bore a resemblance to clay when its granules were dissolved in methanol. To achieve sufficient drying, the test tubes were enveloped in aluminum foil and stored in a light-free environment for about 24 hours or more until they appeared visually devoid of moisture. After the experimental procedures were concluded, the test tubes containing different proportions of ivermectin and ascorbic acid were sufficiently dried, and the methanol solvent was evaporated. The subject under consideration is to the employment of Ivermectin in combination with Ascorbic Acid, as provided by my supervisor. In particular, the supervisor has provided a set of ratios for the mixture of Ivermectin and Ascorbic Acid, labeled as A (1:1), B (1:3), C (1:5), D (3:1), and E (5:1).

# RESULT AND DISCUSSION

FT-IR spectra were recorded to assess the compatibility of the drugs. FT-IR spectra for ivermectin, ascorbic acid & a physical mixture of ivermectin & ascorbic acid at the ratio of –

A (1: 1), B (1: 3), C (1: 5), D (3: 1) and E (5: 1)

The scanning area was between 650 and 4000 $cm^{-1}$. Samples were mixed in a mortar then pressed for 2-3 minutes to form a semitransparent pellet, which lets light be transmitted to the detector.

***Individual Data of Selective Compounds:*** The raw samples of ivermectin were given a strong and broad peak at 3476.43 $cm^{-1}$, 2938.51 $cm^{-1}$, 1731.06 $cm^{-1}$, and 1675.27 $cm^{-1}$ wavelength which indicated the following functional groups: O – H Stretching (Alcohol), N – H Stretching (Amine salt), C = O Stretching (Aldehyde) and C = O Stretching (Conjugated Ketone) respectively. The raw samples of ascorbic acid were given peak at 3525.07 $cm^{-1}$, 3409.19 $cm^{-1}$, 3311.91 $cm^{-1}$, and 3012.91 $cm^{-1}$ wavelength which respectively indicated the following functional groups: O – H Stretching (Alcohol), O – H Stretching (Alcohol), O – H Stretching (Alcohol), and O – H Stretching (Carboxylic acid). The mixtures of ivermectin and ascorbic acid were given a strong and broad peak at 2938.51 $cm^{-1}$ in sample A, 3525.07 $cm^{-1}$ in sample B, 3523.64 $cm^{-1}$ in sample C, 3482.15 $cm^{-1}$ in sample D and 3310.48 $cm^{-1}$ in sample E which respectively indicated following functional groups: N – H Stretching (Amine Salt), O – H Stretching (Alcohol), O – H Stretching (Alcohol), O – H Stretching (Alcohol), O – H Stretching (Alcohol). These functional groups are formed by $sp^3$ hybridization. The following results of the FT-IR spectrometer are given below:

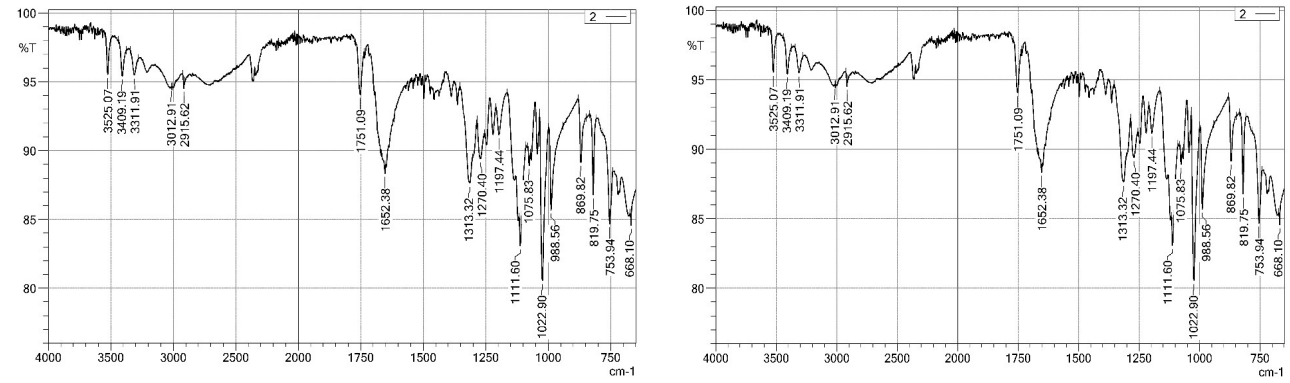



**Figure 2. IR Sample (1) Ivermectin and Sample (2) Ascorbic Acid**

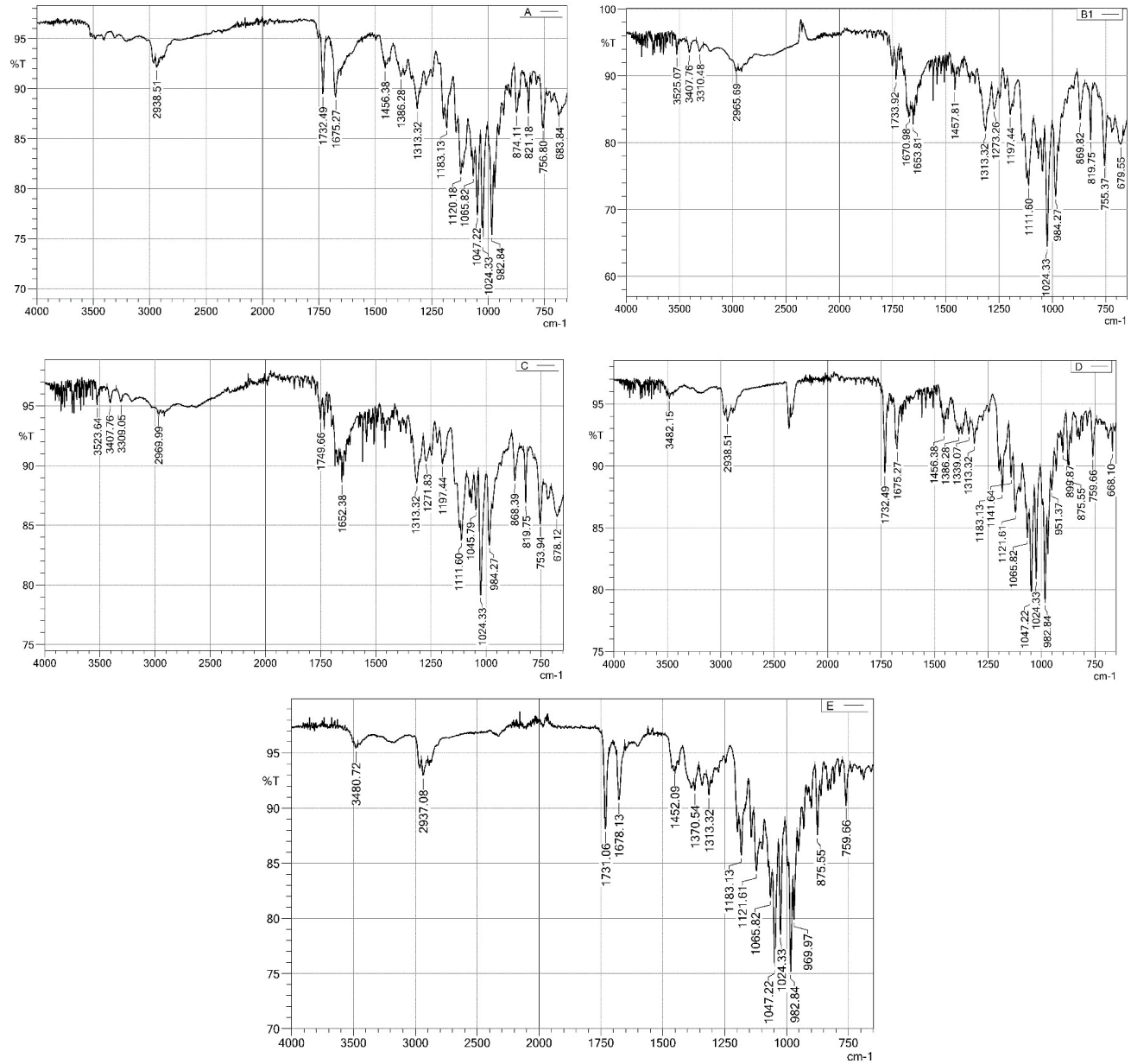



**Figure 3. IR Sample Mixture of Ivermectin and Ascorbic Acid [A – (1 : 1)], [B – (1 : 3)], [C – (1: 5)], [D – (3: 1)] and [E – (5: 1)]**

***Combination Data Analysis of Selective Compounds:*** The following table and graphics provide a detailed explanation of how ivermectin and the antioxidant ascorbic acid are combined.

# DISCUSSION

Ivermectin has been employed as a therapeutic agent for many infectious ailments in animals over an extended period of time. The discovery of Ivermectin occurred in the later years of the 1970s, and subsequent authorization for its use in animals was acquired in 1981 (Tawfeek et al., 2021). As a result, it has been determined that this has the potential to offer advantages to individuals. Crump and Ōmura, distinguished researchers, were awarded the Nobel Prize in 2015 for their notable achievements in the identification and subsequent progress of ivermectin, as acknowledged by Canga et al. (2008). The core focus of this curriculum centers on the transmission cycle of parasites.

**Table 1. Comparison data table**

| Interpretation | Ivermectin | Ascorbic Acid | Sample A | Sample B | Sample C | Sample D | Sample E |
|---|---|---|---|---|---|---|---|
| O – H | 3476.43 | 3525.07 | N/A | 3525.07 | 3523.64 | 3482.15 | 3310.48 |
| N – H | 2938.51 | N/A | 2938.51 | 2965.69 | 2969.99 | 2938.51 | 2937.08 |
| C = O | 1731.06 | N/A | 1732.49 | N/A | N/A | 1732.49 | 1731.06 |
| C – H | N/A | N/A | N/A | 3310.48 | 3310.48 | N/A | N/A |
| O – H | N/A | 3012.91 | N/A | N/A | N/A | N/A | N/A |
| C = O | 1675.27 | N/A | 1675.27 | N/A | N/A | 1675.27 | 1678.13 |

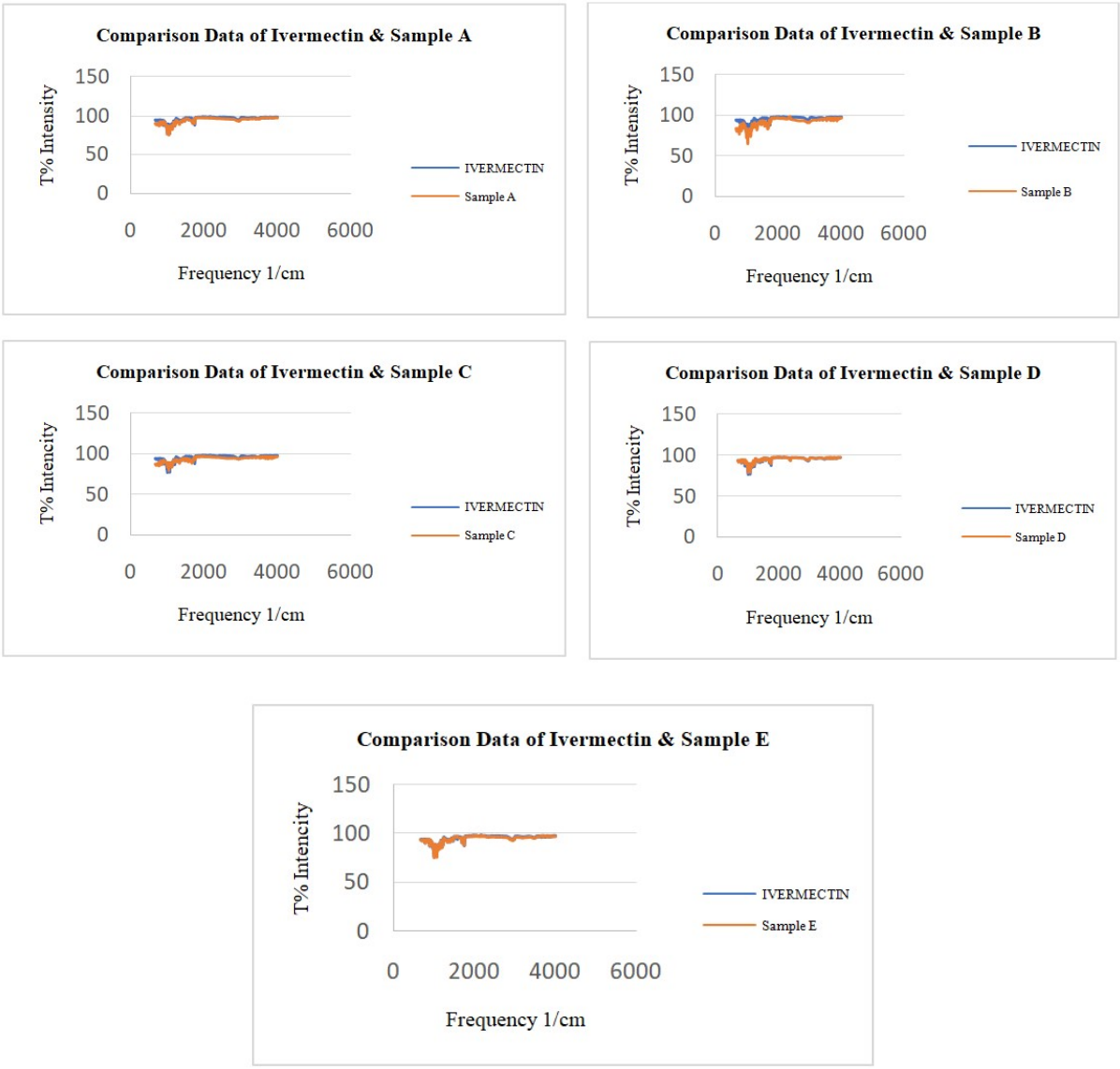



**Figure 4. Comparison Data of Ivermectin & Sample A, Sample B, Sample C, Sample D, and Sample E**

The utilization of a combination therapy including Ivermectin and aerial treatment, has demonstrated a significant reduction in the incidence of the illness within human populations since 1987. This approach has played a crucial role in impeding disease transmission (Canga et al., 2008; M Winnen et al., 2002). Ivermectin demonstrates a pronounced degree of efficacy and demonstrates very low levels of effective dosage. The recommended therapeutic dosage of ivermectin for the therapy of onchocerciasis is 150 grams per kilogram. However, an ongoing discourse persists over the optimal frequency of delivery, encompassing possible variations that span from a single dosage of 150 g/kg to a maximum of three administrations per year. Determining the optimal duration of therapy must be established (Enk et al., 2006). Dourmishev et al. (2005) suggest a generally recommended approach for scabies treatment, which involves administering further doses of medication at regular intervals of one or two weeks following an initial oral dosage of 200 g/kg. According to Guzzo et al. (2002), the inappropriate dosage of ivermectin has been associated with several adverse effects, including pronounced cognitive disorientation, compromised motor function, seizures, and hypotension. The administration of large doses of Ivermectin has the potential to surpass the therapeutic threshold, leading to the saturation of P-glycoprotein pumps. The potential saturation of the pumps may impede their ability to regulate the delivery of medications to the central nervous system (CNS). This occurrence can lead to many neurological effects, such as coma, encephalopathy, seizures, myoclonus, ataxia, and tremors (Ryne Cole et al., 2021). The research conducted by KhaldounOularbi et al. (2017) shown a potential mitigation of hepatotoxicity associated with ivermectin with the concurrent administration of vitamin C. Additionally, the study also observed that the administration of vitamin C supplements resulted in a reduction in abnormal biochemical markers and structural irregularities. Previous studies conducted by Adikwu and Deo et al. (2013), as well as Hussein H.K et al. (2012), have documented the substantial efficacy of vitamin C in mitigating hepatotoxicity induced by various pharmaceuticals and chemical substances. However, it is widely recognized that many drugs may demonstrate unfavorable

interactions when used concurrently with Vitamin C at the recommended dosages. Protease inhibitors supplied by oral route, such as Indinavir (often referred to as Crixivan), are utilized in the therapeutic management of Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS). In research done by Collins et al. (2003), it was demonstrated that these inhibitors can diminish the efficacy of some antiviral drugs. Furthermore, the effectiveness of warfarin, also known as Coumadin, seems to be significantly diminished in the presence of vitamin C. Several rare cases have demonstrated a potential impact on the effectiveness of this anticoagulant due to the presence of vitamin C. According to the research conducted by Sattar et al. (2013), following follow-up investigations did not identify any noticeable effects linked to administering vitamin C at dosages of up to 1,000 mg per day. Considering the possible interference induced by introducing additional pharmacological drugs is of utmost importance.

The agents included in this group comprise acetaminophen, commonly known as Tylenol, barbiturates, aluminum-containing antacids, chemotherapeutic medications, nitrate therapies used for heart disease, and hormone replacement therapy (Richards et al., 1941; Sadowski et al., 1994; Unlu et al., 2016). It is imperative for individuals to refrain from concomitant use of Vitamin C and the aforementioned drugs without prior consultation with a healthcare professional. As previously stated, the coadministration of ascorbic acid and ivermectin has been shown to diminish the efficacy of ivermectin, aligning with the documented effects observed when ivermectin is administered alongside other pharmacological agents or medications that impact its functionality, such as oral Phenobarbital. Mandro et al. (2020) have reported that the elimination of ivermectin from the body is facilitated by the P-glycoprotein (MDR1) transporter, resulting in a decrease in the quantity or effectiveness of ivermectin. The main aim of this study was to examine the potential interaction between ascorbic acid and ivermectin, with a particular focus on their interaction at recommended dosages. Following the initial oral administration of a dosage equivalent to 200 grams per kilogram, many persons diagnosed with scabies have favorable treatment outcomes. However, the treatment protocol sometimes requires the subsequent administration of two or three further doses, with intervals of one to two weeks between each administration. The analysis of the comparative data table reveals that the medications exhibit a comparable alteration in their immediate-release (IR) pattern. The spectral analysis of Ivermectin yielded discernible peaks at wavenumbers of 3476.43 cm–1, 2938.51 cm–1, 1731.06 cm–1, and 1675.27 cm–1. These peaks indicate the presence of specific functional groups, namely O – H, N – H, and C = O, respectively. The presence of the O – H functional group in ascorbic acid was confirmed by detecting spectral peaks at 3525.07 cm–1 and 3012.91 cm–1. When examining the spectrum properties of the combinations of Ivermectin and Ascorbic acid, it can be observed that there are distinct differences. Sample A exhibits distinct peaks at 2938.51 cm–1 wavenumber, 1732.49 cm–1, and 1675.27 cm–1. Sample B's observed peaks are at wavenumbers of 3525.07 cm–1, 2965.69 cm–1, and 3310.48 cm–1. The spectral analysis of Sample C demonstrates the presence of distinct peaks detected at wavenumbers of 3523.64 cm–1, 2969.99 cm–1, and 3310.48 cm–1. Sample D's observed peaks are at wavenumbers of 3482.15 cm–1, 2938.51 cm–1, 1732.49 cm–1, and 1675.27 cm–1. In conclusion, Sample E demonstrates distinct peaks at wavenumbers of 3310.48 cm–1, 2937.08 cm–1, 1731.06 cm–1, and 1678.13 cm–1. The merger did not provide significant modifications that had a meaningful impact on the overall Fourier Transform Infrared (FT-IR) spectra. Therefore, it is evident that there is no conceivable interaction among these entities.

# CONCLUSION

When undertaking the development and evaluation of novel medications, it is imperative to give due consideration to potential drug interactions as a pivotal component. A thorough understanding of pharmaceutical interactions can alleviate unfavorable outcomes, specifically regarding the metabolism, absorption, excretion, and transportation of medications. Comprehending the fundamental mechanisms of action is frequently crucial for precisely anticipating pharmacodynamic interactions. Researchers have made significant progress in enhancing their knowledge of the well-stirred and physiologically based pharmacokinetic (PBPK) models. As a result, there have been considerable breakthroughs in understanding drug-drug interactions that occur through metabolic processes. Due to the rising frequency of polypharmacy, the evaluation of drug-drug interactions will continue to be a vital component in the analysis of prospective pharmacological candidates. Nevertheless, recent studies have provided evidence supporting the absence of any significant interaction between Ivermectin and ascorbic acid. Hence, it is feasible to synthesize many medicinal dose forms, including Ivermectin and Ascorbic acid.

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