

Investigation of Adsorption of the Cardiotonic Drug Milrinone Onto Montmorillonite: An FTIR and Raman Spectroscopic Study

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ABSTRACT

Milrinone is a cardiotonic drug that is used for the treatment of congestive heart failure. Clay minerals are widely used materials as a low-cost nanocarriers in designing drug delivery systems. Drug-clay interaction is important since it affects drug action. Montmorillonite, a clay mineral with high adsorption and swelling properties, is useful as a low-cost nanocarrier in designing drug delivery systems. The adsorption of a molecule on a clay surface, or formation of intercalates, gives rise to changes in the vibrational wavenumbers of the adsorbed molecule. In this study, interaction between the adsorbed milrinone molecules and montmorillonite was investigated by FT-IR and Raman spectrometry. The X-ray diffraction patterns of montmorillonite before and after treatment with milrinone showed a significant change in the $d(001)$ reflectance of clay. This reflection peak shifted to a lower angle due to the adsorption of milrinone onto the clay. The result indicated the intercalation of the milrinone molecules by increasing the interlayer spacing of the clay. Vibrational spectroscopic results indicated that intercalated milrinone interacted with clay by direct or indirect coordination (through water molecules) to exchangeable cations or the Lewis acidic centers.

Keywords: Clays; Milrinone; Montmorillonite; FTIR; Raman

1. INTRODUCTION

Milrinone ($C_{12}H_9N_3O$), a phosphodiesterase-3 inhibitor, is used for the short-term treatment of heart failure (Young & Ward 1988). It is a positive inotropic cardiotonic agent that acts as selective phosphodiesterase 3 inhibitor in cardiac and vascular smooth muscle. Milrinone acts as a vasodilator, by helping alleviate increased pressures (afterload) on the heart, thus improving its pumping action. It was approved by the FDA on December 31, 1987 (Shipley et al. 1996).

Montmorillonite, an expandable type of clay mineral, has a 2:1 layered structure consisting of one octahedral sheet and two tetrahedral sheets (T:O:T). The layers have a small net negative charge due to isomorphous substitution of ions in the framework. This negative charge is compensated by interlayer hydrated cations, which are known as exchangeable cations. The interlayer space can expand by the adsorption of a suitable solvent or organic molecules. It is well known that wide variety of organic molecules can intercalate between the interlayer regions of expandable clays and increase the interlayer region (Theng 1974; Schulze 2005).

Vibration frequencies of molecules are determined by infrared (IR) and Raman spectroscopy. Since molecular vibrational frequencies change depending on molecular interactions,

we investigate the interaction mechanism of milrinone with the clay framework.

2. MATERIAL METHOD

The natural montmorillonite sample was sourced from the Çankırı region of Anatolia, Turkey. Details on its chemical composition are provided in our previous study (Akyuz & Akyuz 2008). Milrinone (solid state) was reagent grade (Sigma Aldrich Chemicals) and used as received. Milrinone treated clay was prepared analogous method described (Akyuz & Akyuz 2008).

The FT-IR spectra of KBr discs were recorded on a Bruker Tensor 27 FT-IR spectrometer. Spectral data were collected over 4000–400 cm^{-1} spectral range based on averaging 200 scans with a resolution of 1 cm^{-1} . The micro-Raman spectra of the powdered sample was recorded on a Jasco NRS-3100 μ -Raman spectrometer (1200 lines/mm grating and high sensitivity cooled CCD). A 532 nm line of the diode laser was used as the excitation wavelength. The XRD spectra of the starting montmorillonite and milrinone treated montmorillonite were recorded on a Rigaku D/Max 2200 powder X-ray diffractometer using $Cu K\alpha$ radiation.

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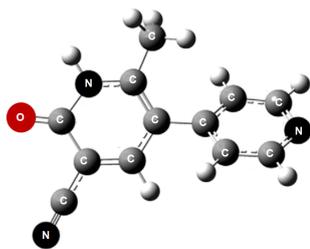


Figure 1. Molecular model of milrinone.

3. RESULTS AND DISCUSSION

The XRD pattern of starting montmorillonite indicated a basal spacing of 12.0 Å, which increased to 16.0 Å after treatment with milrinone. The increase in the basal spacing indicates formation of intercalates (Aguzzi et al. 2007; Borrego et al. 2018). The result clearly demonstrates the effective inclusion of drug in the interlayer spaces of the montmorillonite.

Clay minerals contain hydroxyl groups that can easily bond with water molecules through H-bonding interaction. These hydroxyl groups can also react with organic groups via H-bond bridges, either directly or indirectly through water bridges. These interactions are detected by the IR and Raman spectroscopy thanks to their vibrations in the infrared region.

Recently Esme (2017) calculated the optimized structure of milrinone using DFT/B3LYP/6-31G(d,p) level of theory. The molecular model of milrinone according to Esme (2017) is shown in Figure 1. Milrinone can interact through its ring nitrogen, cyano group nitrogen and/or carbonyl group oxygen. To determine the interaction mechanism of milrinone molecules adsorbed by montmorillonite, the vibrational wavenumbers of adsorbed milrinone were examined in comparison with the wavenumbers of milrinone in solid phase, taking into account the coordination effects via ring nitrogen, CN group nitrogen and > C=O group oxygen. The FTIR spectra of starting montmorillonite (untreated montmorillonite), milrinone treated montmorillonite and solid milrinone are given in Figure 2, comparatively. As seen in Figure 2, milrinone bands are clearly observed in the IR spectrum of milrinone treated montmorillonite, shifted compared to the solid phase. The result indicated that milrinone interacts with the clay, thereby becoming chemisorbed. Additionally, we observed slight alteration in the vibrational wavenumber of the asymmetric Si-O stretching mode of montmorillonite due to adsorption of milrinone (see upper frame of Figure 2). In previous studies it was shown that the Si-O stretching mode frequency was significantly affected by changes in swelling and orientation of the clay platelets and shifted to higher wavenumbers due to intercalated organic molecules (Katti & Kati 2006; Akyuz & Akyuz 2008). In our study the Si-O asymmetric stretching wavenumber observed at 1032 cm⁻¹ in the IR spectrum of montmorillonite was observed at 1041 cm⁻¹ in that of milrinone treated montmorillonite.

When a ligand coordinates through the oxygen of a carbonyl

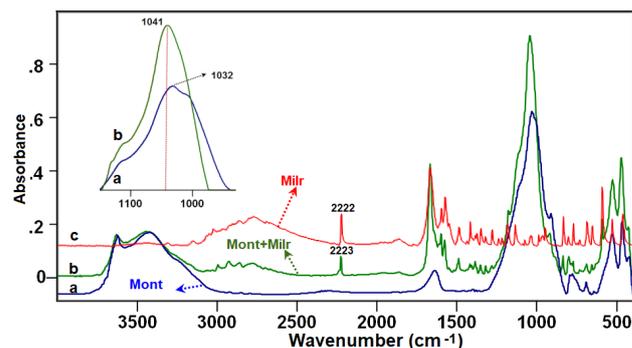


Figure 2. The FTIR spectra of montmorillonite (a), milrinone treated montmorillonite (b) and solid milrinone (c). Upper frame is the detailed 1100-1000 cm⁻¹ region of untreated (a) and milrinone treated (b) montmorillonite.

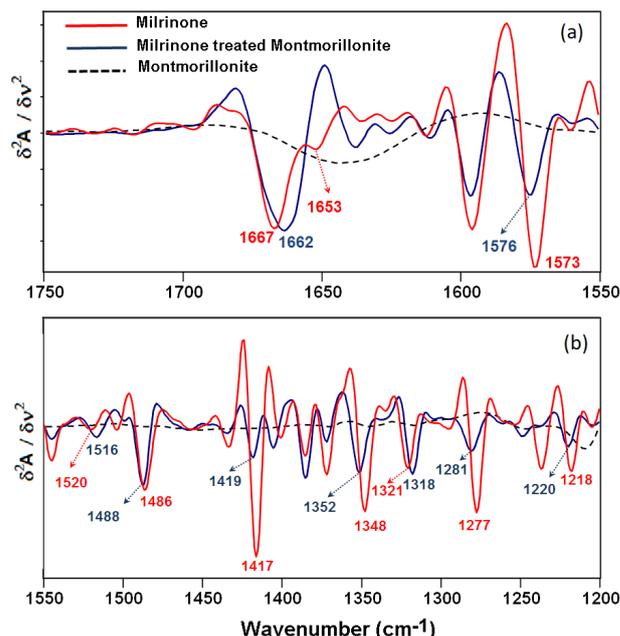


Figure 3. The 1700-1550 cm⁻¹ (a) and 1550-1200 cm⁻¹ (b) regions of the second derivative profiles of montmorillonite (dashed line), milrinone (red line) and milrinone treated montmorillonite (dark blue line).

group, a negative shift in the $\nu(\text{C}=\text{O})$ wavenumber of the coordinated molecule compared to the free ligand is expected. On the other hand, coordination through pyridine ring nitrogen of the ligand alters particularly the ring stretching vibrations. Dines et al. (2003) investigated the adsorption of 2-chloropyridine on oxide surfaces by vibrational spectroscopy and it was reported that the ring stretching vibrations around 1400-1600 cm⁻¹ increase in wavenumber upon hydrogen bond formation or adsorption at Lewis acid sites. In our previous study, the effect of the coordination of the pyridine ring nitrogen on the vibrational frequencies was calculated on the pyridinecarboxamide-Al(OH)₃ model compound (Akalin et al. 2005). It was found that in addition to the ring stretching vibrations around 1400-1600 cm⁻¹, the ring deformation modes around 1000 cm⁻¹, 800 cm⁻¹, and 400 cm⁻¹ were also the most sensitive modes to the coordination through pyridine ring nitrogen.

The IR absorption bands are relatively broad, due to over-

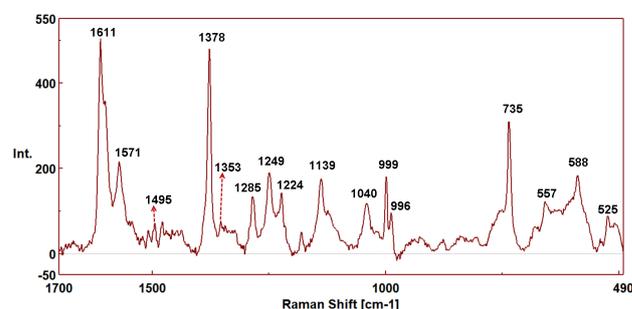
Table 1. Some vibrational wavenumbers (cm^{-1}) of solid milrinone and adsorbed milrinone onto montmorillonite.

Assignment	Milrinone	Milrinone	Adsorbed milrinone		
	This study	(Esme 2017)	This study		
	IR	IR	Ra	IR	Ra
$\nu\text{C=O}$	1667	1666	–	1662	–
νring	1595	1595	1606	1609	1611
νring	1573	1573	1568	1576	1571
$\delta\text{CH}(\text{ring})$	1486	1487	1485	1488	1495
νring	1373	1372	1375	1385	1378
δCH	1348	1349	1347	1352	1353
$\delta\text{CH}(\text{ring})$	1277	1279	1282	1281	1285
νring	1218	1219	1219	1220	1224
τring	989	988	960	–	999-996

*Obscured by the strong SiO stretching band (IR) of the clay. ν = bond stretching; δ = in plane angle bending; τ = torsion vibrations.

lapping several vibrational modes. In this study, we utilized the second derivative of the absorption spectrum as a resolution enhancement technique. This approach helps distinguish overlapping bands in the IR spectrum and clearly delineate the frequency alterations in milrinone due to its interaction with the clay framework. Figure 3 shows the second derivative profile of solid phase milrinone in comparison with that of adsorbed milrinone onto montmorillonite. The second derivative profile of the pure montmorillonite was also added to Figure 3 for comparison.

The C=O stretching mode of milrinone is observed at 1667 cm^{-1} in the solid phase, whereas it appears at 1662 cm^{-1} in the adsorbed phase (see Figure 3a). This shift indicates that the carbonyl oxygen of the adsorbed molecule engages in H-bonding interactions. On the other hand, ring stretching vibrations of milrinone determined at 1573 cm^{-1} and 1486 cm^{-1} in the second derivative profile of the IR absorption spectrum of milrinone were observed at 1576 cm^{-1} and 1488 cm^{-1} in that of milrinone treated montmorillonite (see Figure 3b). Similar shifts were also predicted upon formation of H-bonding through pyridine (Akyuz & Akyuz 2010) and pyrimidine (Des-texhe et al. 1994) ring nitrogen. The coordination sensitive vibrational modes of milrinone are tabulated in Table 1. The vibrational wavenumbers of adsorbed milrinone show coordination effects through both ring nitrogen and carbonyl oxygen. The results indicate that adsorbed milrinone molecules are coordinated through both the ring nitrogen and carbonyl oxygen lone pairs. Investigations of clay-organic complexes by Raman spectroscopy have the advantage that the strong SiO stretching and bending modes observed in the IR spectrum, were not observed in Raman spectrum, due to being weak scatter of silica. Thus, the Raman spectrum of a clay-organic complex, mainly involves organic molecule's vibrations. Figure 4 shows the Raman spectrum of milrinone treated montmorillonite. We compared adsorbed milrinone bands with those of solid milrinone given by Esme (2017) (see Table 1).

**Figure 4.** The Raman spectrum of milrinone treated montmorillonite.

4. CONCLUSION

In this study, the interaction of milrinone, a cardiotoxic drug used to reduce cardiac contractility, with montmorillonite was investigated using vibrational spectroscopy. The comparison of the XRD patterns of untreated- and milrinone treated montmorillonite indicated that as a result of the interaction of clay with the drug, diffraction pattern of montmorillonite shows significant changes. The reflection corresponding to $d(001)$ of montmorillonite shifted to lower angles after interaction with the drug. The interlayer spacing (basal spacing) of untreated clay was determined as 12.0 \AA . As a result of the adsorption of milrinone, the basal spacing of the milrinone-treated clay increased to 16.0 \AA . The result clearly indicates that the intercalation of milrinone molecules in the montmorillonite interlayer spacing. The comparison of the IR and Raman spectra of the adsorbed milrinone to those of solid milrinone elucidated the interaction mechanism of the milrinone with the clay framework. The results indicated that the adsorbed milrinone molecules on montmorillonite are coordinated through both nitrogen and oxygen ends to exchangeable cations directly or indirectly through water bridges.

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REFERENCES

- Aguzzi C., Cerezo P., Viseras C., Caramella C., 2007, *Applied Clay Science*, 36, 22
- Akalin E., Yilmaz A., Akyuz S., 2005, *Journal of Molecular Structure*, 244, 881
- Akalin E., Akyuz S., Akyuz T., 2007, *Journal of Molecular Structure*, 834, 477
- Akyuz S., Akyuz T., 2008, *Vibrational Spectroscopy*, 48, 229
- Akyuz S., Akyuz T., 2010, *Vibrational Spectroscopy*, 53, 136
- Borrego-Sánchez A., Carazo E., Aguzzi C., Viseras C., Sainz-Díaz C. I., 2018, *Applied Clay Science*, 160, 173
- Destexhe A., Smets J., Adamowicz L., Maes G., 1994, *Journal of Physical Chemistry*, 98, 1506
- Dines T. J., MacGregor L. D., Rochester C. H., 2003, *Spectrochimica Acta A*, 59, 3205
- Esme A., 2017, *Indian Journal of Pure & Applied Physics*, 55, 478
- Katti K., Katti D., 2006, *Langmuir*, 22, 532
- Massaro M., Colletti C. G., Lazzara G., Riela S., 2018, *Journal of Functional Biomaterials*, 9, 58
- Rocha M. C., Galdino T., Trigueiro P., Honorio L.M.C. et al., 2022, *Pharmaceutics*, 14, 796
- Schulze D. G., 2005, *Clay Minerals* (Ed: Hillel, D.) in *Encyclopedia of Soils in the Environment*, Elsevier, 246
- Shipley J. B., Tolman D., Hastillo A., Hess M. L., 1996, *The American Journal of the Medical Sciences*, 311, 286
- Theng B. K. G., 1974, *The Chemistry of Clay Organic Reactions*, Hilger, London, 1974
- Young R. A., Ward A., 1988, *Drugs*, 36, 158