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MOLECULAR RECOGNITION OF 2,6-DIHYDROXYBENZOIC ACID POLYMORPH IN ETHANOL, METHANOL AND P-XYLENE SOLUTION

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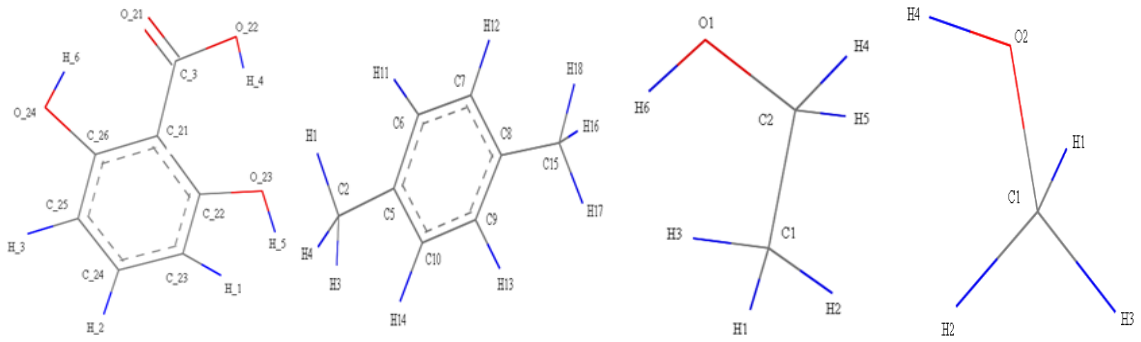
Abstract

2,6-dihydroxybenzoic (DHB) acid is an active pharmaceutical ingredient exhibits polymorphism when it is in crystalline form. The selection of appropriate solvent plays a significant role in the formation of the desirable FI and FII polymorph of 2,6-dihydroxybenzoic acid crystal solid. In this extended research study, molecular dynamics was applied to simulate the behavior of 2,6-dihydroxybenzoic acid solute in ethanol, methanol and p-xylene solvents at 20^{o}C using COMPASS force field in Material Studio package. The molecules were labelled as illustrated in Figure 1 to recognize the specific individual atoms which might impart to the significant intermolecular interaction and synthons that lead to the different hydrogen bonding networking in the crystal polymorph. The dynamics run for pure solvent and binary system were equilibrated initially in NVE ensemble at 500 ps and followed by NPT ensemble at 1500 ps to get the desired radial distribution function (rdf) of 2,6-DHB in the solution. At similar ratio number of solvent:solute, the rdf of solute-solute interaction in methanol solution indicates a stronger hydrogen bonding networking and different synthons compared in ethanol and p-xylene solutions which is in agreement that 2,6-DHB has highest solubility in methanol. Experimental study has found that FI form is crystallised from p-xylene meanwhile FII form was crystallised from ethanol and methanol solvents.

Keywords: radial distribution function, synthons, COMPASS



(a) (b) (c) (d)

Figure 1: Molecular structure defining the atomic numbering of 2,6-DHB(a), p-xylene(b), ethanol(c) and methanol(d).

1 Introduction

2,6-dihydroxybenzoic acid is an active pharmaceutical ingredients (APIs) which are frequently delivered to the patient in the solid state as part of an approved dosage form such as in the form of tablets or capsules. Solids provide a convenient, compact and generally stable format to store an API or drug product. When it is in crystalline form, it exhibits polymorphism. According to Bernstein (2002) and Alfred et al (2011), polymorphism in molecular crystals is a common phenomenon and is of great interest to the pharmaceutical field. The solid state form is a key quality attribute of a crystalline product.

2 Simulation Methodology

Prior to the simulation, the single molecules of methanol, ethanol and p-xylene were optimized and minimized using the generic COMPASS force field in Material Studio to obtain the most stable structure. The cubical boxes containing 216 number of molecules for methanol, ethanol and p-xylene pure solvents and 216:108 of solvent: 2,6-DHB solute ratios were created using Amorphous Cell in Material Studio. Then, energy minimization of simulation boxes was applied. The molecular structures of the solvents and solute molecules are labelled as shown in Figure 1 to recognize of any significant role in the polymorphism of 2,6-DHB based on their ability to form hydrogen bonding with particular neighbouring atoms in the solution system. Initially, the boxes were equilibrated using Forcite Module by performing the molecular dynamics simulation in NVE ensemble for 500ps and followed by NPT ensemble for 1500ps with the total of 2ns simulation time at the set point 293K and 1 atm. For the dynamics run in the NVE ensemble, the temperature and pressure of the system is scaled down until the values achieved are consistent with the setting conditions in order to get a reasonable total energy for the system. The dynamics run in the NPT ensemble will maintain the temperature and pressure of the system and control the simulation box size to achieve the density of the real system. Once the temperature, pressure and energy of the system were in equilibrium at the desired values, the radial distribution function of the systems were calculated and analyzed from the trajectory files. The details of simulation protocol is summarised in Table 1.

Table 1: Molecular dynamic simulation details for 2,6-DHB in methanol, ethanol and p-xylene mixtures using COMPASS force field.

System	Methanol mixture	Ethanol mixture	P-xylene mixture
Number of solute molecules	108	108	108
Number of solvent molecules	216	216	216
NVE ensemble (ps)	200	500	500
NPT ensemble (ps)	800	1500	1500
Total simulation time (ns)	1	2	2
Timestep (fs)	0.3	0.6	1.0
Cutoff (Å)	15.7	16.5	20.0
Interval (Å)	0.5	0.5	0.5
$\rho_{simulated}$ (g/cm^3)	1.219	1.167	1.068
$\rho_{theoretical}$ (g/cm^3)	1.222	1.150	1.064
ρ error (%)	0.25	1.48	0.38

3 Results and discussion

Adam (2012) has reported that molecular dynamics simulation able to recognize the polymorphism of 2,6-dihydroxybenzoic acid begins from the chloroform and toluene solution to crystallise FII and FI forms respectively. In this part, the radial distribution function plots are discussed in more details regarding the behavior of interaction between atoms of each molecule either in the pure systems or in the mixture systems. Three different solvents were chosen in this simulation study due to the different nature of polar and nonpolar properties to crystallise different polymorph. Adam (2012) found that ethanol and methanol contribute to the high solubility and supersaturation point to crystallise FII crystal. Meanwhile the nonpolar, para-xylene solvent contributed to the low solubility and low supersaturation point tends to crystallise FI polymorph.

In pure methanol, a strong intermolecular interaction occurs between O2---H4 at 2.25Å (Figure 2a) while at 2.75Å and 4.25-4.75Å between O2---H1, H2, H3 atoms (Figure 3c) respectively. The first peak represents the nearest neighbour interaction between the specific types of atoms in the liquid solution. Therefore, from the rdf pattern, it shows that the nearest neighbour interaction occurs between O2---H4 atoms representing a strong hydrogen bond in the pure methanol solution. This indicates that, in pure methanol, a strong attraction of H4 atoms is more favourable towards O2 atoms for hydrogen bonding to occur. While for the rest of atoms which are between O2---H3, H2, H1, the interaction between molecules is still happen but the distance is greater compared to the O2---H4. The rdf plots from this work is validated to Saiz et al (1997) work which applied different force field are shown in Figure 2(b). The calculated peak position of the 1st neighbour atom of O2---O2 using COMPASS force field from this work is not in agreement to the previous literature study (Saiz et al., 1997) at 2.75 Å. It is reported that in polar solvent (Abdulnour and John, 1996), the Ewald summation approach should be applied to in the calculation of charges.

In pure ethanol, a strong hydrogen bonding interaction of O1---H6 exists at 2.25Å which is similar to the hydrogen bonding in methanol liquid in Figure 3a). However, in Figure 3c), the strength of intermolecular interaction of oxygen from hydroxyl group, O1 and H1, H2 and H3 reduces compared to the oxygen from hydroxyl group, O2 and H1, H2 and H3 in methanol solution (Figure 2c). The structure validation of pure ethanol solvent is compared to Saiz et al. (1997) and the position of 1st neighbour atom is in agreement as in Figure 3b). The intensity or probability value of g(r) is higher compared to the literature value because of the unsuitable of the atomistic summation applied in the methanol solution as similar as in methanol liquid.

The structure of nonpolar solvent, p-xylene shows a broad peak of the 1st neighbour atom for each C2---H1, C2---H2 and C2---H3 intermolecular interaction between the alkyl group which locate at around 3.75Å. Similar rdf patterns also obtained for H1---H1, H3---H3 and H4---H4 intermolecular interaction with the 1st neighbour atom at 4.25 Å. These should reflect the repulsion between the alkyl group, in the nonpolar solvent compared in the methanol and ethanol solvents.

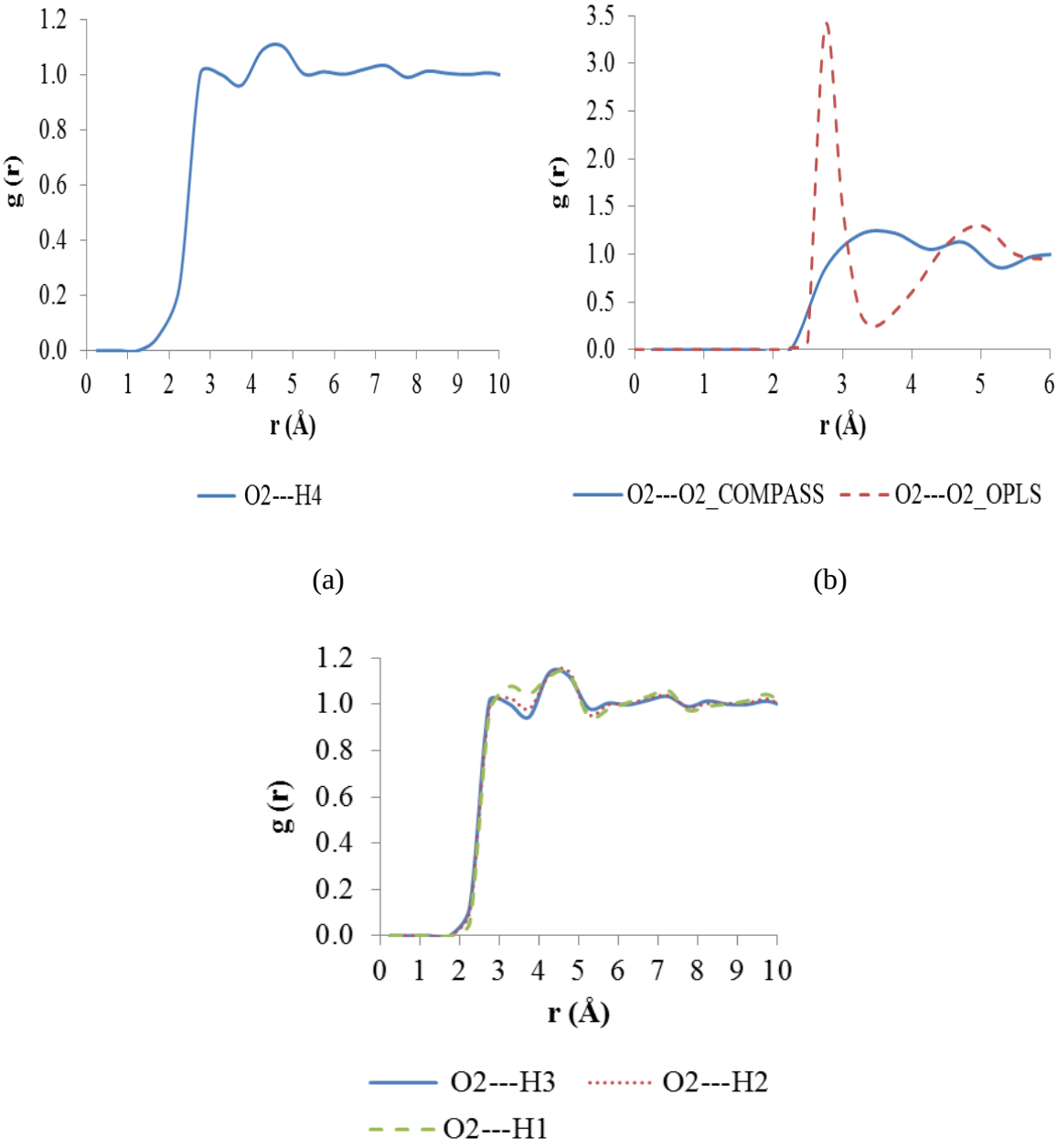


Figure 2: Radial distribution functions of pure methanol represents the intermolecular interaction between O2---H4 in a), O2---O2 in b) and O2---H3, O2---H2, O2---H1 in c).

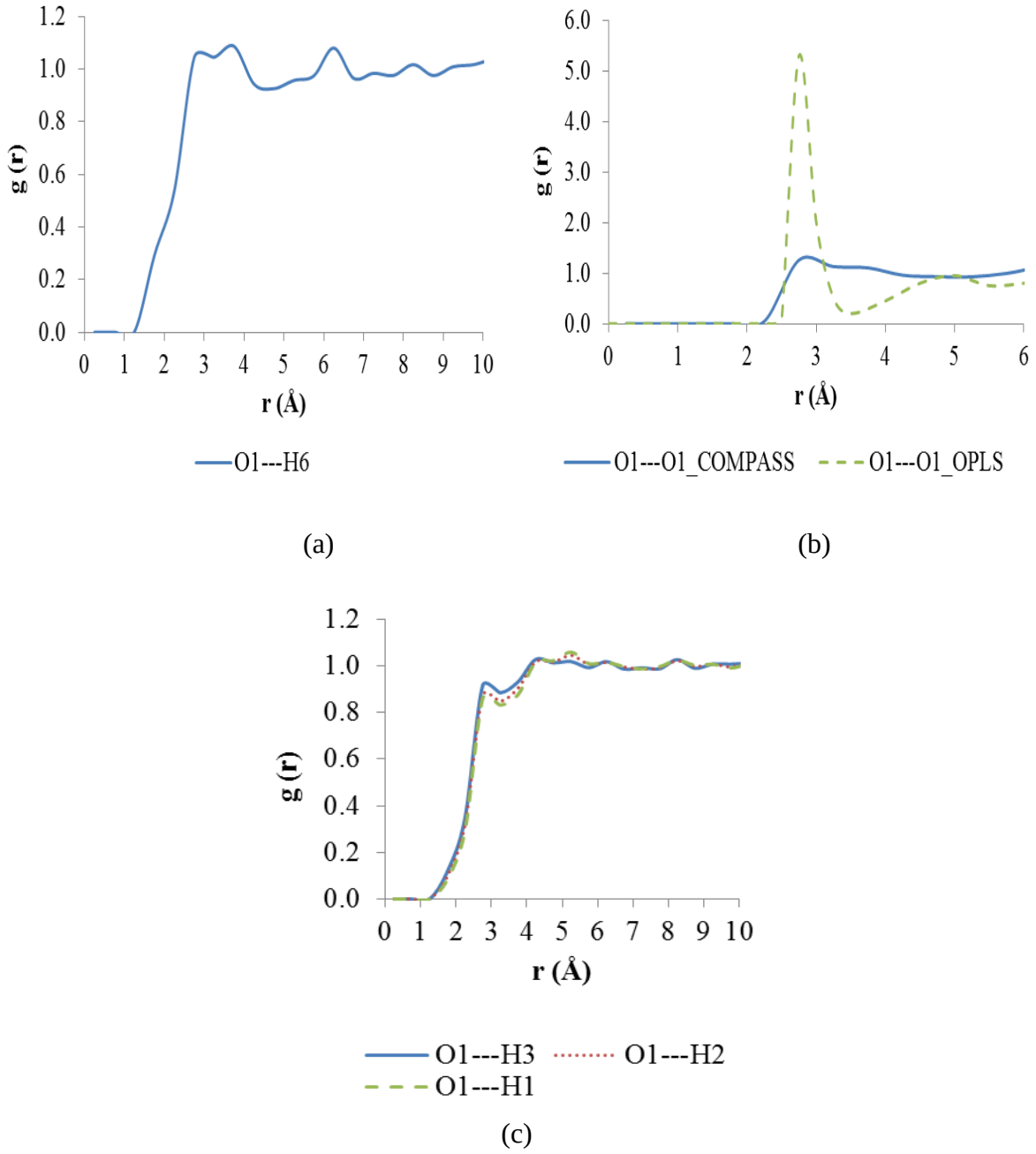


Figure 3: Radial distribution function of pure ethanol represents the intermolecular interaction between O1---H6 in a), O1---O1 in b) and O1---H3, O1---H2, O1---H1 in c).

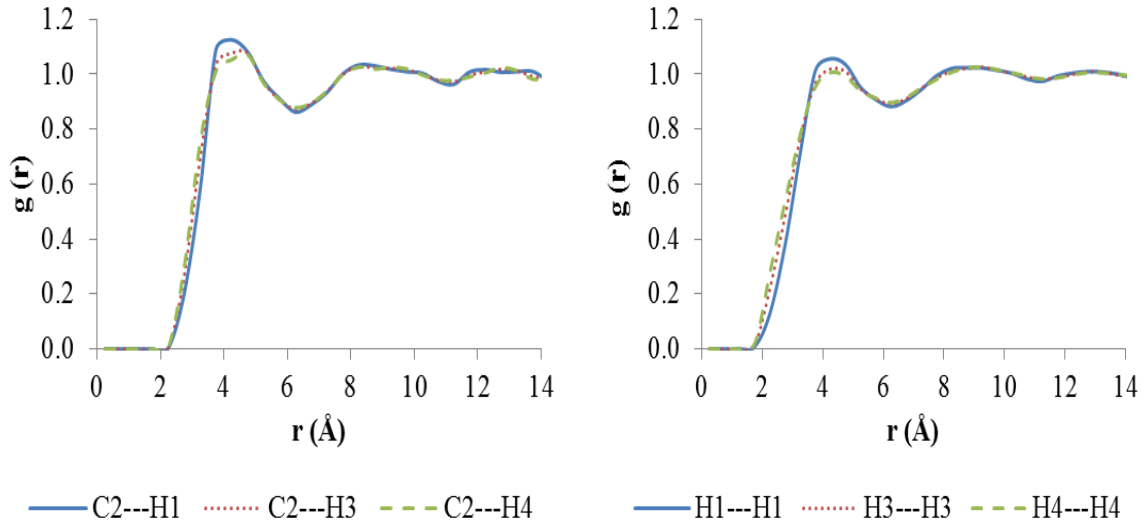
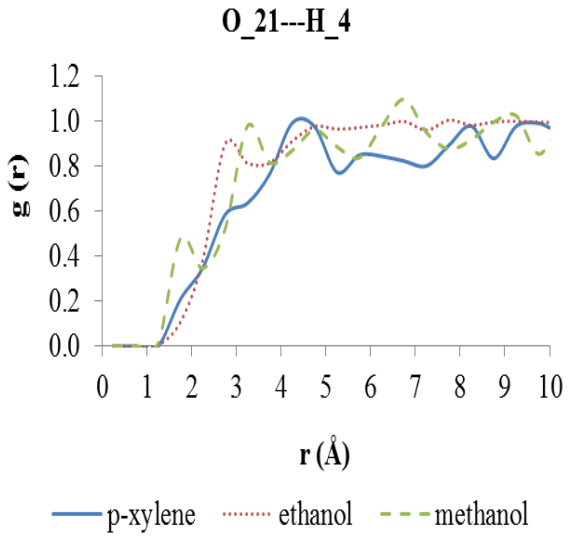


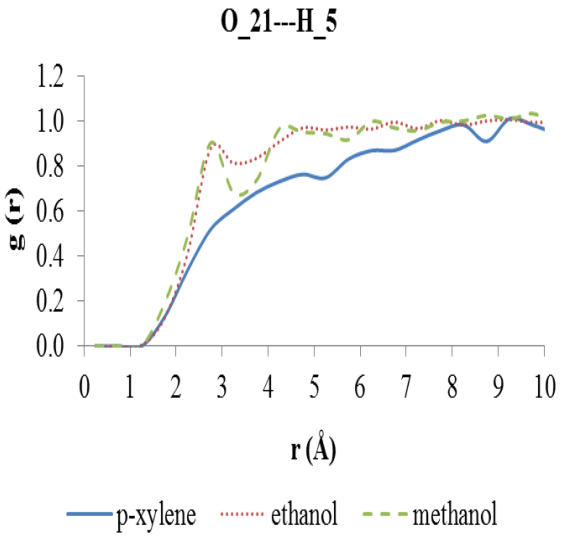
Figure 4: Radial distribution function of pure p-xylene represents the intermolecular interaction between C2---H1, C2---H2 and C2---H3 in a) and H1---H1, H3---H3 and H4---H4 represent the alkyl group in para-xylene structure.

Solute-solute Interaction

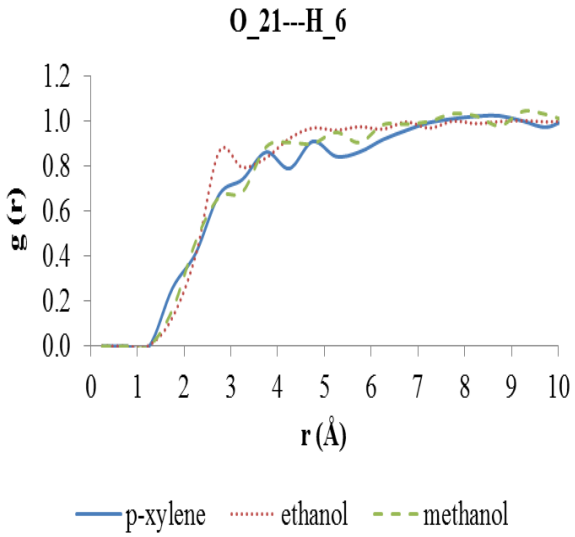
In Figure 5 a), and b), the hydrogen bonding amongst the 2,6-dihydroxybenzoic acid solute O_21---H_4 and O_21---H_5 are significant when crystallised from the polar methanol and ethanol solvents. Although the simulation timesteps are still not achieving 1fs in methanol and ethanol, under NPT ensemble, the rdf trends begin to show a strong hydrogen bonding presence in the crystallisation solution. According to the molecular dynamics principle, a flexible molecules should have the timestep of 1 or 0.5 fs in molecular dynamics simulation (Leach, 2001). In the nonpolar solvent para-xylene, the hydrogen bond trends amongst the solute molecule are not significant with weak intermolecular interaction and less structure pattern. The hydrogen bonding interaction of O_21---H_6 is quite significant only in ethanol solution and show a weak pattern in methanol and para-xylene solutions. For the interaction of O_21---H_1, O_21---H_2 and O_21---H_3, ethanol and methanol solution has more structured rdf patterns meanwhile less structured patterns in para-xylene solutions.


O_21---H_4
g (r)
r (Å)
p-xylene
ethanol
methanol

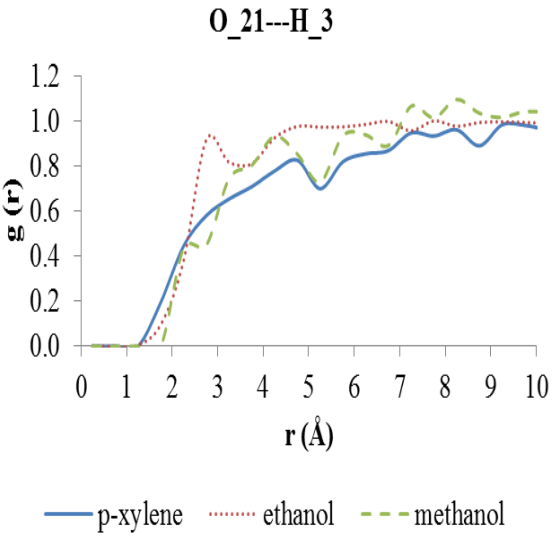
(a)


O_21---H_5
g (r)
r (Å)
p-xylene
ethanol
methanol

(b)


O_21---H_6
g (r)
r (Å)
p-xylene
ethanol
methanol

(c)


O_21---H_3
g (r)
r (Å)
p-xylene
ethanol
methanol

(d)

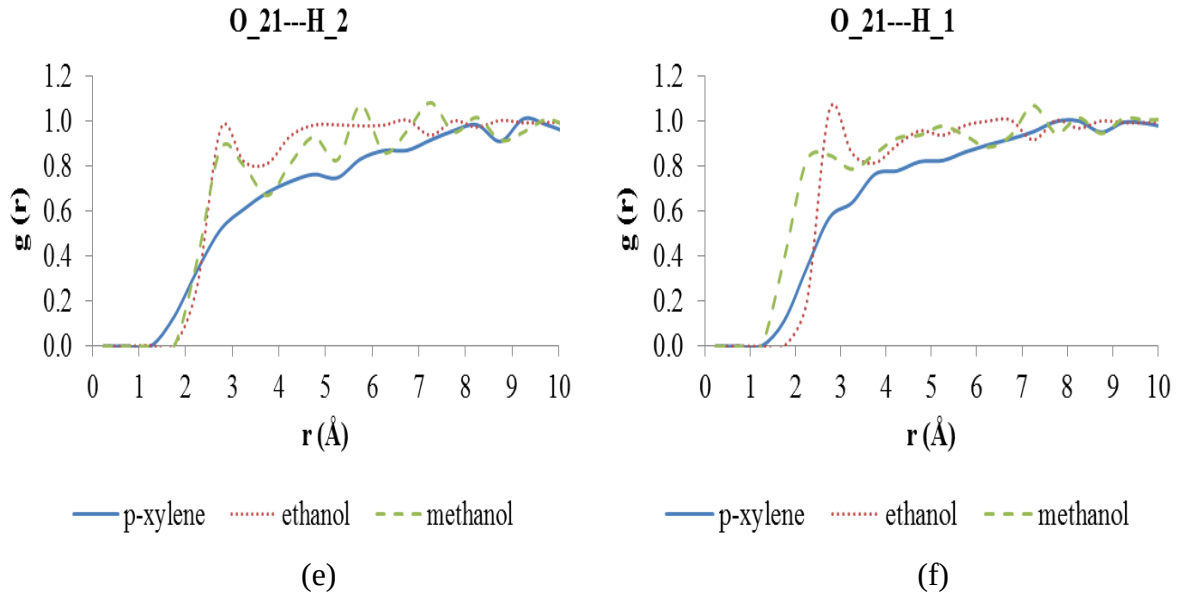


Figure 5: Radial distribution function represents solute-solute intermolecular interaction amongst the 2,6-dihydroxybenzoic solute in the non-polar and polar solvents.

4 Conclusion

From the molecular dynamic simulation, there is difference in the intermolecular interaction behavior between the solute of 2,6-DHB depending on the solvents used such as methanol, ethanol and p-xylene. Base on those differences, it shows that different polymorphs will be produced with different types of solvents which will act either as a hydrogen bond donor or acceptor and neither of the hydrogen bond formation between the solute and solvent interaction.

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Nomenclatures

r radial

rdf radial distribution function

ρ_y density of y type atom

N_y number of atoms of the y type