4 Impact of surface properties on drug dissolution in amorphous solid dispersion of Riluzole prepared with different polymers

4.1 Background of the study

The characteristics of solids can be divided into two main groups: bulk properties and surface properties. Bulk properties are mainly determined by interactions within the solid's lattice structure and include features like solubility, compactness, and elasticity. While surface properties are influenced by the chemical composition and energy-related factors at the solid's surface, encompassing aspects like interfacial tension, adhesion, and cohesion. Surface behavior is of significant importance because many phenomena of pharmaceutical importance gets initiated at the surface [198]. For example, according to the Noyes-Whitney equation, factors important for the dissolution of drug are diffusion, solubility in gastrointestinal tract and surface area of the drug available for wetting from the luminal fluids[199]. So, the surface property of a solid-liquid interface is very critical. Wettability is assessed using two essential parameters: the degree of wetting, which is associated with the equilibrium contact angle formed between the liquid and solid interface, and the rate of wetting. The former is primarily determined by factors such as the properties of the liquid, the test temperature, and the surface energies of the solid. The latter, on the other hand, is affected by potential reactions occurring at the interface, capillary forces, and interfacial energies. For instance, the lower the interfacial tension between the particles the higher is their wetting [200]. The surface energy of the particles plays a major role in the wetting of the particles. For example, increase in the polar surface energy of co-milled ibuprofen with excipient MCC, leads to an increase in their wetting as well as dissolution [201]. The surface energy is the sum of components *viz.* polar energy and dispersive energy. Materials demonstrating similar surface energy may have

different surface energy components hence could have different wetting/anti wetting properties [202]. The analysis of the presence of polar groups present on the surface of any material further supports the data observed for the surface free energy. .

In vitro dissolution and drug release tests have guided the development of oral solid dosage forms, which is considered as the very important factor. It monitors the quality, consistency and quality of the drug product. Apart from this, the test can act as a surrogate for bioequivalence assessment [203,204]. *In vitro* dissolution from the dosage form is the rate-limiting step of the drug absorption from the gastrointestinal tract. Since, dissolution in gastrointestinal fluid is a primary requirement for absorption, drugs with poor aqueous solubility possess a major challenge to be administered through oral route.

4.1.1 Plan of work

In the current study the dissolution behaviour of RLZ in presence of polymers i.e. PAA, PVP VA and HPMC AS were evaluated and compared. Initially, solution ^{1}H NMR was done to evaluate the possible drug-polymer interaction which might be responsible for the dissolution enhancement. Based on results obtained in ^{1}H NMR and the previous studies, only PAA and PVP VA were chosen to evaluate the effect of polymer on the supersaturation and dissolution of RLZ. Even though, many literatures give evidences of the role of drug-polymer interactions in the ASD systems, very little information is available about the surface properties of the drug molecule and their ASDs which contributes to a higher dissolution profile. This work focuses on the surface properties of the hence formed RLZ ASDs, which were evaluated using total surface energy, and was later supported by XPS analysis. The obtained results established that the interaction of drug and polymer in solution state as well as their surface properties give rise to the variation in dissolution profile observed for different systems.

4.2 Experimental section

4.2.1 Nuclear Magnetic Resonance

The molecular level interaction in solution state was deciphered by performing ^{1}H-NMR (500 MHz) using Bruker 500 FT NMR spectrometer. The NMR spectra of RLZ, polymers and physical mixtures of 70:30% w/w of drug and individual polymers were taken. All the samples were dried to remove moisture and then dissolved in dimethyl sulfoxide-d6. The values of chemical shifts have been reported in parts per million (ppm) which are referenced to internal standard tetramethylsilane (TMS). The values of coupling constants (J) have been reported in Hz.

4.2.2 Preparation of amorphous solid dispersion of RLZ

The preparation of ASDs were done using a rapid solvent evaporation method in a rotary evaporator (IKA RV 10 auto pro V). To dissolve the drug and polymer with varying weight ratios of (10:90, 70:30, 50:50, 30:70, and 90:10), a mixture of methanol and dichloromethane in a 1:1 ratio was employed, while maintaining continuous stirring. Subsequently, this prepared solution was evaporated applying vacuum conditions, with a bath temperature set at 55 °C, and a gradual reduction in vacuum pressure from 500 mBar to a minimum of 2 mBar was applied. The resulting ASDs were then subjected to 24 hours of drying in a vacuum oven at 25°C for the removal of any remaining solvents. Afterward, the samples were sieved through a 150 micron seive and stored at a temperature of 4°C.

4.2.3 Saturation solubility in presence of polymer

The solubility of RLZ and in a phosphate buffer of pH 6.8 was checked at 37±0.2 ^{o}C. Briefly 10 mg/ml and 15 mg/ml of PAA and PVP VA polymer solution were prepared by mixing 100mg and 150mg of PAA and PVP VA in 10 ml of pH 6.8 phosphate buffer. To

this polymer containing buffer solution, an excess amount of drug (50mg) was added to each glass vial. The solution was shaken on a mechanical shaker for 72 hours. The collected sample was centrifuged at 5000 rpm and filtered through 0.45 µm nylon filter, diluted appropriately and drug concentration was determined using the HPLC method. For evaluation of saturation solubility of RLZ without any polymer, same procedure was followed. The only difference was that, there was no polymer present in the buffer solution.

4.2.4 *In vitro* dissolution study

The dissolution studies for RLZ and its prepared ASDs were conducted in USP II (Paddle type) dissolution apparatus (Electrolab India Ltd). 500 ml of phosphate buffer (pH 6.8) was taken as dissolution media. 20 mg equivalent of RLZ and its ASD formulations were added to the dissolution media maintained at a temperature of 37±0.5^{o}C. 5 ml of aliquot were withdrawn at each time point of 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 360 mins. The samples were filtered through a 0.45 µm nylon filter and analyzed at 264 nm by the HPLC method mentioned in the next chapter.

4.2.5 Wetting property and surface free energy

The contact angle of the drug and different ASD formulations were measured to determine the effect of different polymer ratio on wetting property of RLZ. For this experiment, a Drop Shape Analyzer device (contact angle goniometer assembled by DuraVision) was used to measure the contact angle on the compacted samples using sessile drop method. The testing liquids having different polar and dispersive components namely, double distilled water, ethylene glycol (EG) and diiodomethane (DIM) were used for the surface energy estimation [205]. All the readings were taken in triplicate under ambient conditions. The values of contact angle of different solvents were used to calculate total

surface energy (γ^S), dispersive free energy (γ_s^{LW}), and polar surface energy (γ^{AB}). The polar component of the surface energy is subdivided into acidic element (γ^-_S or γ^A) and basic element (γ^-_S or γ^B). The acidic and basic component reflects the tendency of a sample to have more polar interaction with a surface of higher basic character by donating electrons and acidic character by accepting electrons respectively. This is a standard method called Owens, Wendt, Rable and Kaelble (OWRK) method, where surface free energy of a solid is calculated using its contact angles with different liquids [206–208]. equation 4.1 was used to calculate the energies [31,32].

$$(1 + cos\theta)\gamma_{LV} = 2\left[\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + \sqrt{\gamma_S^A}\gamma_L^B + \sqrt{\gamma_L^A}\gamma_S^B\right] \quad \text{Equation 4.1}$$

Where, γ_{LV} is surface tension, γ_S^{LW} is dispersive surface energy of solid, γ_L^{LW} is the surface energy of liquid. The polar energy is calculated using the acidic and basic component following equation 4.2. The total surface energy γ_S is calculated by using dispersive free energy and polar surface energy using equation 4.3.

$$Polar\ energy = \sqrt{2\gamma_S^A}\gamma_S^B \quad \text{Equation 4.2}$$

$$\gamma_S = \gamma^{LW} + \gamma^{AB} \quad \text{Equation 4.3}$$

4.2.6 X-ray Photoelectron Spectroscopy

The surface chemistry of the ASDs was analyzed using XPS (K-Alpha, Thermo Fisher Scientific) with a probe depth of less than 100 Å. The electron energy was detected using 180° double focusing hemispherical analyzer with 128-channel detector. Al Ka micro-focused monochromators were used as X-ray source in the instrument with variable spot size along with the energy range 100-4000 eV of the ion gun. Binding energy of 0-1350 eV was used to obtain the high energy resolution spectra of C 1s, N 1s, O 1s, F 1s and S 2p.

4.3 Results and Discussion

4.3.1 Nuclear Magnetic Resonance

To comprehend the mechanism of drug dissolution and to spot interactions between drug and polymer, solution ^{1}H NMR spectra were used. ^{1}H NMR holds accountability to identify the possible interactions due to any kind of chemical bond formation between drug and polymer. Figure 4.1 shows the overlay spectra of proton (^{1}H) NMR of the three physical mixtures and pure RLZ. The up-field shifts of NH_2 proton at 7.64 ppm was observed in all three physical mixtures. The maximum relative shift could be seen from 7.74 to 7.62 ppm in case of RLZ:PAA (green colored peak). The doublet peak of aromatic hydrogen of RLZ appearing at 7.37-7.35 ppm was flattened in the physical mixture. The maximum relative shift in RLZ:PAA could be due to the hydrogen bonding interaction between the NH_2 group of RLZ with the carbonyl oxygen of polymers. The flatness of the doublet peak of aromatic hydrogen of RLZ might occur due to C-H···O non-bonding interactions between drug and the polymer or the change in the electron density due to distinct binding interactions between the drug with each polymer [209–211]. The higher order of chemical shift corresponds to the comparatively stronger non-bonding interactions [212]. As the alteration in the chemical shift due to the presence of PAA and PVP VA were more with respect to HPMC AS. It can be inferred that PAA and PVP VA are showing more interactions with RLZ and will stabilize its amorphous state.

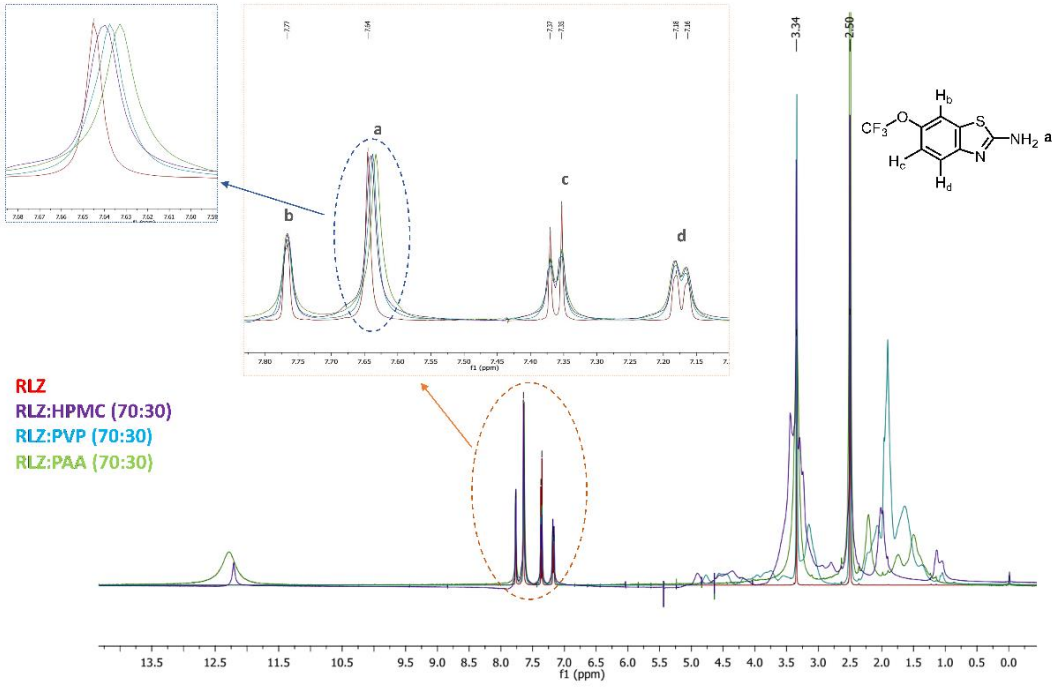

Figure 4.1. Overlay of ^{1}H NMR spectra of RLZ and its physical mixtures with each polymer in solution state, showing the change in the chemical shifts due to non-bonding interactions

4.3.2 Saturation solubility in presence of polymer

The values of saturation solubility of RLZ in presence of 10mg/ml PAA and PVP VA was 395 and 390 µg/ml respectively. Which is nearly 1.2 and 1.18 times of the RLZ solubility in pH 6.8 in absence of any polymer i.e., 330 µg/ml. After increasing the concentration of polymer to 15 mg/ml, a drastic change in the RLZ concentration was noticed. The saturation solubility of RLZ in the presence of 15 mg/ml of PAA and PVP VA was found to be 1828 and 761 µg/ml respectively. This makes a 5.5 and 2.3-fold increase in the solubility of RLZ in the aqueous medium. In the saturation solubility study, data in the presence of polymers did not show much significant effect at a lower concentration of 10 mg/ml. However, at 15 mg/ml polymer concentration, a significant change in the saturation solubility was observed. The results indicated that the solubilizing effect of PAA on RLZ is slightly more than PVP VA. The reason behind this solubilizing efficacy of polymers is often explained by the formation of weakly soluble

complexes in the aqueous solution in which polymeric carriers are dissolved [213,214]. The polymers PAA and PVP VA are also proven to have an inhibitory effect on the crystallization of drugs like dipyridamole and cinnarizine [210]. This result indicates the benefit of PAA to increase the solubility of RLZ over PVP VA.

Table 4.1. Saturation solubility of crystalline RLZ at pH 6.8 with and without polymer

Polymer concentration (mg/ml)	**Saturation solubility of RLZ at pH 6.8 (mg/ml)**
Without polymer	0.33±0.04
PAA	
10	0.40±0.016
15	1.83±0.17
PVP VA	
10	0.39±0.018
15	0.76±0.05

Values taken in n=3, mean values with SD are presented

4.3.3 *In vitro* Dissolution Study

As a quality control test, dissolution study holds utmost importance since it provides quantitative information about the percentage of drug released in a defined period of time and under certain conditions. In the current study the dissolution profile of pure RLZ and RLZ ASDs in four different drug:polymer ratio of 10:90, 30:70, 50:50 and 70:30 was tested. Figure 4.2 shows that after 360 mins dissolution of pure RLZ is only 59%. While, in the case of RLZ:PAA and RLZ:PVP VA in the ratio 10:90 both the ASDs showed exponentially higher dissolution rate with 102% and 88% release, respectively in the initial 30 mins only. The dissolution of RLZ:PAA and RLZ:PVP VA in the ratio 30:70 is having a complete release of 103% and 95% at the end of 60 mins only. In the case of 50:50 ratio of ASDs, significant difference was observed as at the end of 90 mins RLZ:PAA was having 101% dissolution while RLZ:PVP VA ASD was having a dissolution of only 40%. When the drug polymer ratio was further changed to 70:30, RLZ:PAA ASD showed complete dissolution of 97% at the end of 360 mins, while

RLZ:PVP VA ASD was having a dissolution of 84%. Additionally a comparison of ASDs with crystalline RLZ in terms of model-independent similarity factor (f2) was found to be 18 and 14 for 10:90, 14 and 11 for 30:70, 16 and 51 for 50:50 and 32 and 52 for 70:30 of RLZ:PAA and RLZ:PVP VA respectively. This data shows that PAA is giving higher dissolution profiles in all the weight ratios while PVP VA struggles to provide higher dissolution at its lower weight ratio of 50:50 and 70:30. In the *in vitro* dissolution studies, the extreme of the drug and polymer combination, i.e., 90% w/w of the drug was not shown because, at this drug loading, significant crystallinity was found in the XRD pattern (Chapter 3). The results obtained in the dissolution study clearly indicate the major impact of the type of polymer and the drug:polymer ratio used to prepare ASD on their dissolution profile. The observed data shows that with the increase in the weight ratio of the polymer, the dissolution profile improves and vice versa. This is also evident in terms of ASD stability, as a higher percent of the drug may result in drug recrystallization, which can result in a major drop in the dissolution [45] [215]. However, the trend of increase or decrease in the dissolution profile is similar for both the polymers, yet in the case of PAA, there is a major improvement in the dissolution profile with an increased ratio compared to PVP VA. The observations of the saturation solubility and dissolution studies can be backed up by the ^{1}H nuclear magnetic resonance (NMR) data, where non-bonding interactions between the RLZ and polymers (PAA and PVP VA) were observed in terms of chemical shifts. These drug-polymer interactions stabilize the drug in its amorphous form; hence, the saturation solubility in the presence of polymers and dissolution of ASD samples increase [216].

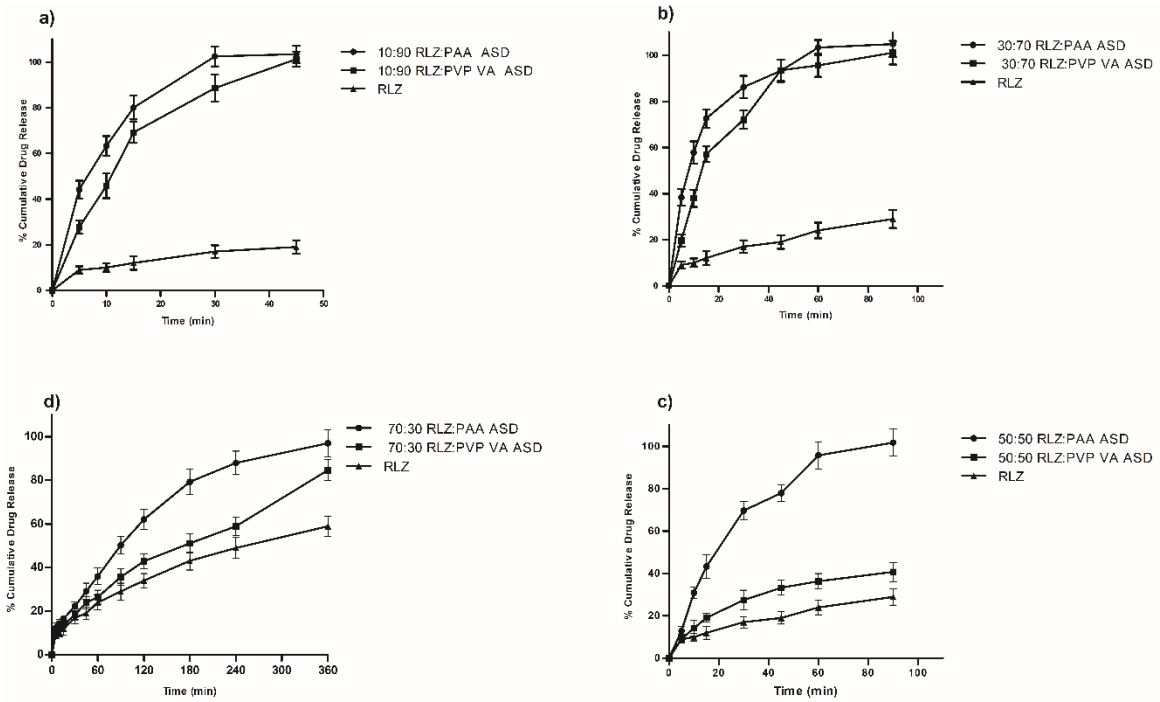

Figure 4.2. Comparative dissolution profile of RLZ ASD with PAA and PVP VA and pure crystalline RLZ in the ratio a) 10:90, b) 30:70, c) 50:50, and d) 70:30

4.3.4 Wetting property and surface free energy

The surface free energy, dispersive energy and polar energy of all the samples have been mentioned in Table 2. The value of water contact angle defines the actual wetting property of the samples. Small contact angle (<90^o) shows high wettability while large contact angle (>90^o) shows low wettability of the samples. RLZ being a poorly water-soluble molecule shows a higher contact angle values with water while with DIM the contact angle value is low. When combined with PAA in a different ratio to make ASD the contact angle with water decreases significantly. Similarly, when RLZ was combined with polymer PVP VA to form ASD, the water contact angle also decreases while with DIM the contact angle increases with increasing ratio of polymer. Along with the contact angle, the polar component of the surface free energy also increases, with an increase in the polymer concentration in ASD. From the table it can be seen that in case of both the polymers, with increasing polymer concentration, the dispersive energy contribution keeps on decreasing and the polar energy contribution keeps increasing (Figure 4.3).

However, in case of PAA, at all the concentrations, the polar energy values are higher with their respective PVP VA concentrations. This indicates better capacity of PAA over PVP VA for increasing the hydrophilicity of RLZ when prepared as ASD, which could lead to dissolution rate enhancement of RLZ [217].

The interfacial wetting pattern of the various ASDs can be correlated with their dissolution mechanism. By measuring contact angles, the wetting extent of a solid surface is determined after it interacts with the liquid. The contact angle data provides information about many surface properties like wettability, adhesion, and friction related to the surface energy [27,30]. The contact angle of water on RLZ:PAA ASD is lower than RLZ:PVP VA. The higher contact angle with water indicates poor wetting properties, and the contact angles are closely correlated with the dispersive and polar components of the surface energy. In Table 4.2, it is evident that with the increasing weight ratio of the polymer, there is an increase in the surface energy. A higher value of surface energy indicates more molecular interaction of the drug and polymer complex with water; hence it contributes to higher solubility [41] and hence, higher rate of dissolution. It is also observed that as the weight ratio of the polymer increases, the dispersive energy component decreases, which is due to the passivation of high energy sites due to polymers [42]. However, the higher values of polar energy components are attributed to high hydrophilicity. This observation supports the results obtained in the dissolution study.

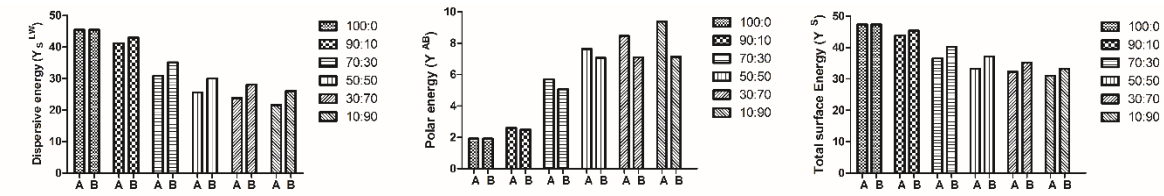

Figure 4.3. Comparison of dispersive energy (γ_S^{LW}), polar energy (γ^{AB}), and surface free energy (γ^S) between drug and ASD formulations with PAA and PVP VA in their respective drug:polymer ratio

Table 4.2. Values of polar energy, dispersive energy and total surface energy of different RLZ and RLZ ASDs with different polymers in different ratio

Sample	Energy		
	Polar energy (γ^{AB})	**Dispersive energy (γ_s^{LW})**	**Total surface energy (γ^s)**
RLZ Pure	1.91	45.48	47.39
90:10 RLZ:PAA	2.61	41.23	43.85
70:30 RLZ:PAA	5.70	30.91	36.61
50:50 RLZ:PAA	7.64	25.57	33.22
30:70 RLZ:PAA	8.46	23.81	32.27
10:90 RLZ:PAA	9.38	21.59	30.97
90:10 RLZ:PVP VA	2.50	42.96	45.45
70:30 RLZ:PVP VA	5.07	35.14	40.22
50:50 RLZ:PVP VA	7.07	30.03	37.10
30:70 RLZ:PVP VA	7.10	28.07	35.17
10:90 RLZ:PVP VA	7.14	26.08	33.23

To further evaluate the effect of polymers on the wetting property of drug, the water contact angle profiles of RLZ and combination of drug and polymer in different weight ratio were plotted and fitted. Angles recorded between 2-20 seconds at an interval of every 2 seconds were plotted for this purpose. In Figure 4.4 it can be seen that RLZ and ASDs at higher concentration of RLZ (90:10) with both the polymers are following linear fitting with higher regression coefficient values. This shows that at higher drug concentration wetting could be predominantly controlled by drug's property. In the case of 70:30 ratio of RLZ with both the polymers, the plot follows polynomial curve fitting. However, when the polymer concentration is further increased to as in 50:50 RLZ:polymer ASD, the one with PAA followed polynomial, while PVP VA followed exponential curve fitting. At this point the difference in the trend of wetting between both the polymers can be marked. While in case of 30:70 and 10:90 RLZ:PAA, the plots showed fitting with power function equation. However, at 30:70 and 10:90 RLZ:PVP VS ASDs followed exponential

function. These results indicate that at and after the presence of 50% w/w of polymer, the wetting property differentiates according to the nature of the polymer. This can define the point where the dissolution of ASDs can transit from drug-controlled to carrier-controlled in nature [218]. A difference between the polymer properties came into light by this study.

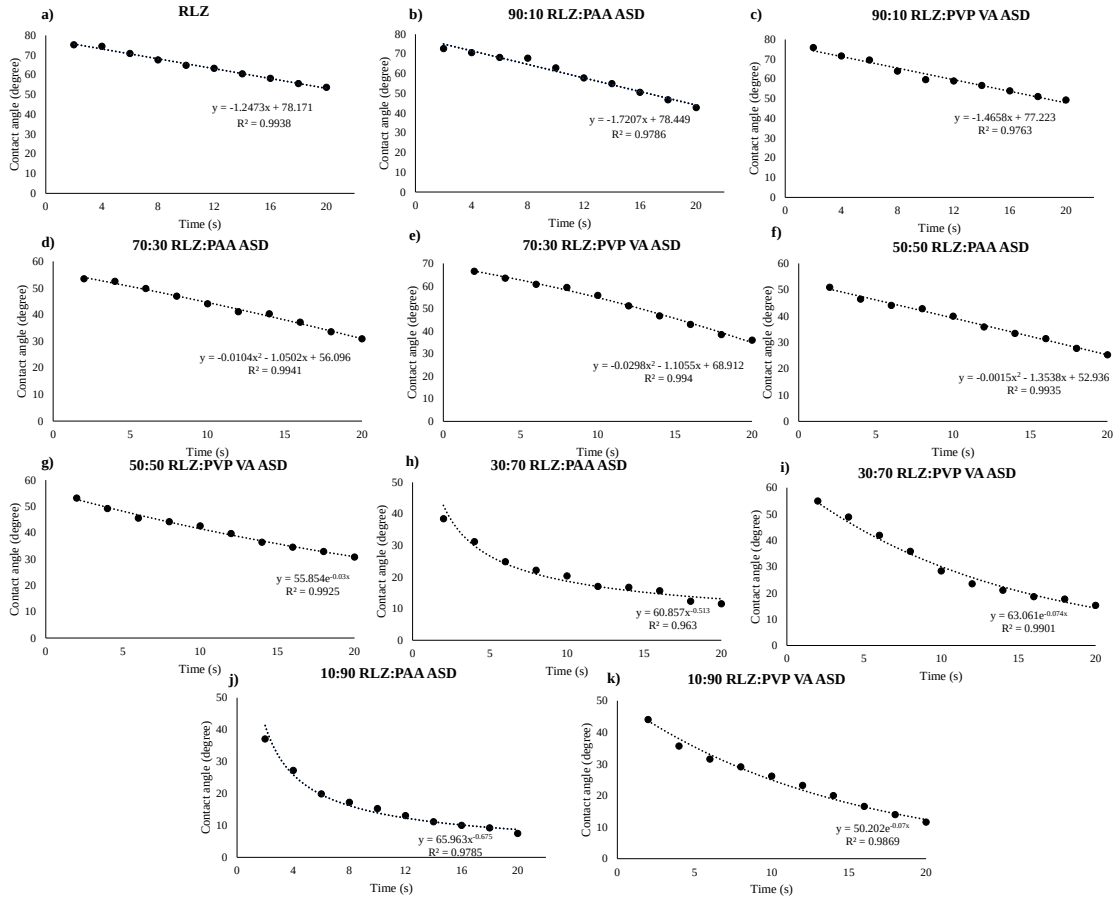

Figure 4.4. Water contact angle fitting of trend profiles of RLZ and ASD of RLZ with different polymers

4.3.5 X-Ray Photoelectron Spectroscopy

Surface polarity and the interaction of any surface with its external environment is mainly governed by the surface chemistry. The XPS data of RLZ and ASDs of RLZ with PAA and PVP VA is summarized in Table 4.3. In the crystalline RLZ, the concentration of oxygen is lower while concentration of nitrogen, fluorine and sulphur is higher than both the ASD formulations. RLZ:PVP VA ASD have displayed highest oxygen concentration

while concentration of carbon is highest in RLZ:PAA ASD. The atomic concentration of fluorine is of major concern in imparting the hydrophilicity/hydrophobicity on the surface of the drug and the ASD formulations. The highest atomic concentration of fluorine in RLZ can be seen in Figure 4.5a which declines drastically after its combination with polymers PAA and PVP VA. RLZ:PAA exhibits least concentration of fluorine (Figure 4.5b). This further supports the higher interaction of ASD formulations with water with respect to the crystalline RLZ. These results also corroborate with the polar energy calculations showing polarity order as RLZ:PAA>RLZ:PVP VA>RLZ.

A correlation was established between the obtained XPS results with the single crystal structure of RLZ. The crystal structure of RLZ was obtained from Cambridge Crystallographic Data Centre (CSD Deposition number: 1820861) and Mercury software (Version 4.2.0) was used to identify the groups exposed on the RLZ crystal. In the software, various facets of the crystal were analyzed and the values of relative area were obtained. The crystal structure database particle (CSD) allows the simulation of morphology using Bravais Friedal Donnay Harker (BFDH) method. According to the BFDH method the largest and the most morphologically important facet [219,220] was (00-1) and (001) with a relative area of 0.228. Hence, facet (00-1) and (001) was considered as the predominant planes of the crystal. It can be seen in figure 4.5d that trifluoromethoxy group is exposed on the crystal surface. While the amine group which is capable of forming hydrogen bond by donating electrons lies in the inside layer of the crystal. Hence this packing arrangement of RLZ completely supports the results obtained in the XPS study.

In the current study, the XPS analysis was used to obtain information about the surface chemical composition of the drug and ASD samples qualitatively and quantitatively [221]. XPS can provide data on surface chemistry up to a penetration level of 10 nm [222].

This information is useful in understanding the nature of the surface, which is most likely to interact with the aqueous medium during dissolution. The chemical name of RLZ is 2-amino-6-(trifluoromethoxy)benzothiazole, with an empirical formula of $C_8H_5F_3N_2OS$. It consists of an amide functional group (NH_2) containing N, and a trifluoromethyl group (CF_3) containing F. Fluorine atoms are highly electronegative, and the CF_3 group is nonpolar and does not readily interact with water. The electronegativity of fluorine atoms makes the CF_3 group strongly hydrophobic, meaning it tends to repel water and prefers to interact with nonpolar solvents [223,224]. This is because the CF_3 group does not add any hydrogen-bondable atoms. Even though fluorine is more electronegative than hydrogen, introducing a CF_3 group does not necessarily result in a molecule with a larger polarity [225]. This is the reason behind the use of CF_3 groups for increasing the lipophilicity of molecules [226]. In contrast to the trifluoromethoxy group, the amine (NH_2) group present in the structure of RLZ is highly efficient in the formation of hydrogen bonds with the surrounding water molecule. The hydrogen bonding capacity of the NH_2 group present in RLZ has been proven by solid-state NMR and *in silico* studies [227] shown in previous section. Along with nitrogen in the NH_2 group, the azole ring also has nitrogen and is a polar water-soluble compound [228]; hence the atomic percentage of nitrogen is also important for deciding the surface property. In Table 3 it can be seen that the presence of nitrogen is comparatively more than on ASD samples. However, the surface polarity expressed in terms of nitrogen to fluorine ratio is 0.57, 3.61, and 1.65 for RLZ, RLZ:PAA, and RLZ:PVP VA ASD, respectively. Hence, the higher surface polarity of both ASD samples with respect to pure drug supports the higher dissolution of ASDs over RLZ.

The results obtained from XPS were correlated with the lattice arrangement of the functional groups exposed on the RLZ crystal. As seen in figure 4.5d the crystal structure

of RLZ have a trifluoromethoxy group exposed on its surface hence this is not available to interact with water molecules. However, when converted to amorphous form it will show more conformational flexibility. This is attributed to having multiple molecular conformation centres arranged in a very short range [229,230]. This will lead to the exposure of groups at the surface that are capable of forming hydrogen bonds with the polymers as well as the water molecules. This confirms the more hydrophilic nature of the amorphous form of RLZ with respect to its crystalline counterpart which contributes to higher dissolution rates of ASD samples over the pure drug RLZ. These evidences are in reasonable agreement with the results obtained in the contact angle study

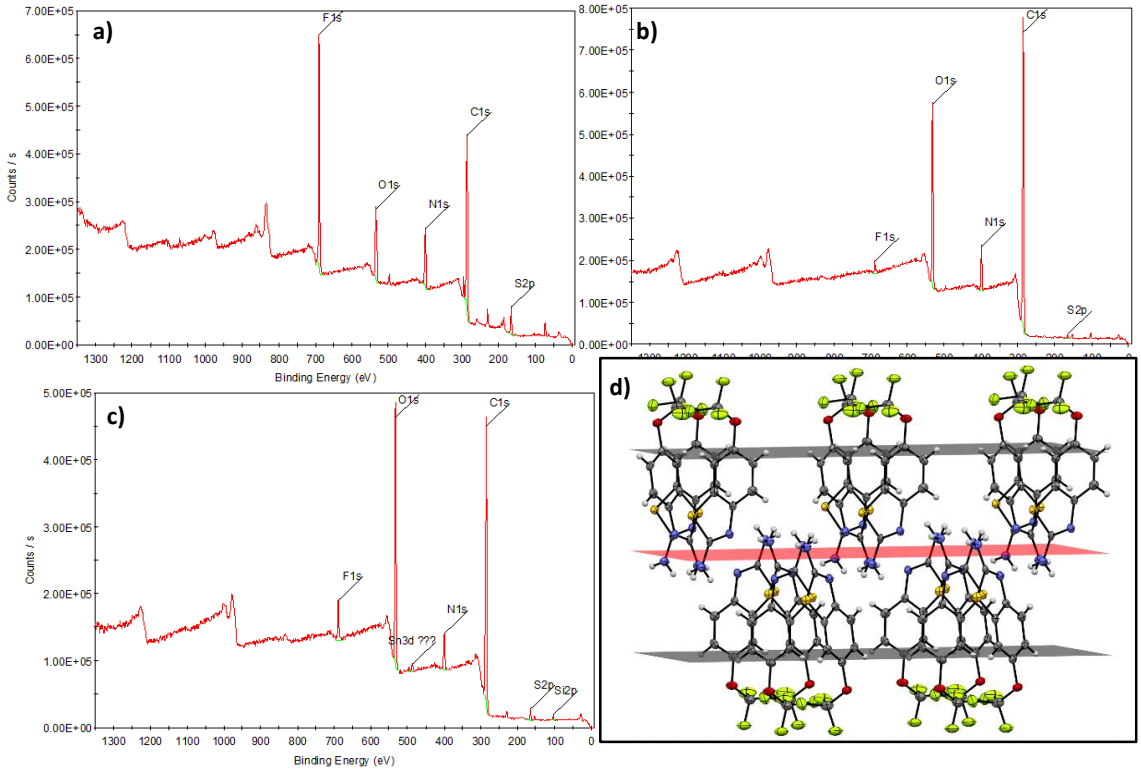

Figure 4.5. XPS peaks of a) RLZ, b) RLZ:PAA ASD, and c) RLZ:PVP VA ASD showing different atomic concentrations d) Predominant plane (001) of RLZ crystal predicted by Mercury software using BFDH method

Table 4.3. Surface chemical composition of RLZ and ASD of RLZ with different polymers

Sample	Carbon (C 1s)	Oxygen (O 1s)	Nitrogen (N 1s)	Flourine (F 1s)	Sulphur (S 2p)
RLZ Pure	55.63	11.32	10.74	18.63	3.68
RLZ:PAA ASD	72.7	18.87	6.26	1.73	0.45
RLZ:PVP VA ASD	63.63	24.91	5.61	3.39	1.26

4.4 Conclusions

This study is an attempt to correlate the solubility and dissolution mechanism of the ASD of RLZ taken as a model drug to its surface properties. Polymers like PAA and PVP VA, in different weight ratios ranging from 10% w/w to 90% w/w were studied to check the trend of the obtained results. The enhanced saturation solubility and dissolution of drug was explained based on the drug-polymer interactions identified by NMR in our previously published work. In addition to this, the wetting property of the surface of drug and ASD samples were studied by using contact angle method. Surface chemistry study using XPS gave an important perspective to compare the hydrophobicity/hydrophilicity of the drug and its ASD samples by quantifying the atomic percentages of the responsible elements. Nonetheless, as a future prospect of this work, the XPS analysis of the samples after different time points of the dissolution study could be performed to have a more detailed information about the surface chemical composition at each time point. This information would be helpful in determining the time point where the dissolution transitions from being carrier controlled to drug controlled. Overall, these studies in correlation with each other provide reasonable explanation about effect of polymers on the dissolution profile of drug in any ASD formulation.