Retraction Notice

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Determination of the Mesalazine Solubility at Biorelevant Temperature

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Abstract

Physicochemical properties of drug/drug candidates are still key inputs for drug discovery and development studies. The most important physicochemical properties of these substances are lipophilicity, solubility, acid/base character, permeability, and bio-accessibility. Among them, the knowledge about solubility is a crucial physicochemical property of drugs and this parameter is in high demand in industry and academia. The aims of the current study are: to determine the solubility of MES in the non-aqueous propylene glycol (PG) + 2-propanol and aqueous 1,4-dioxane binary mixtures at biorelevant temperature (310.2˚K) by using co-solvency method; to perform density analysis in non-aqueous and aqueous binary mixtures for saturated systems; to characterize MES equilibrated in the saturated solutions by XRD analyses. In this research, the solubility values of mesalazine were determined in the non-aqueous (propylene glycol (PG) + 2-propanol) and aqueous (1,4-dioxane + water) binary mixtures at biorelevant temperature (310.2˚K) using the common shake-flask method. The experimental molar solubility (C_M) of MES values in the diluted solutions was determined in the PG + 2-propanol and 1,4-dioxane + water binary mixtures using a plotted calibration curve (R^2 = 0.999) at 310.2˚K. The maximum solubility in the molarity scale was obtained in neat PG ($C_M = 1.03 \times 10^{-2}$ mol/l), and the minimum solubility in the neat 2-propanol ($C_M = 5.14 \times 10^{-4}$ mol/l) in non-aqueous binary mixtures. The maximum solubility value was obtained in 0.4 mass fraction ($C_M = 1.68 \times 10^{-2}$ mol/l) of 1,4-dioxane + water and the minimum solubility was obtained in neat 1,4-dioxane ($C_M = 3.34 \times 10^{-3}$ mol/l) at 310.2˚K. Density data were also determined and correlated with Jouyban-Acree model for saturated systems in non-aqueous and aqueous binary mixtures. The characterization tests of mesalazine equilibrated in the saturated solutions were performed by X-Ray Diffraction (XRD) analyses from 10˚ to 70˚. XRD analysis showed that the crystallinity of mesalazine remained unchanged and did not show any poly-

morphic transformation during the drug dissolution in the investigated binary mixture. Up to now, no data was reported for MES solubility in these binary mixtures at biorelevant temperature.

Keywords

Mesalazine, Solubility, Shake-Flask Method, Biorelevant Temperature, XRD

1. Introduction

Mesalazine (5-amino-2-hydroxybenzoic acid, $C_7H_7NO_3$, MES) is part of numerous antimicrobial agents [1], colorectal cancer chemopreventive [2], inhibit tumor growth [3], antioxidant, antifungal, antibacterial, anti-diverticulosis, anti-amyloid, anti-ulcer, and gastroprotective properties drug [4] [5] [6].

MES (**Figure 1**) shows its anti-inflammatory effect via the expression of peroxisome proliferator-activated receptors in gastrointestinal epithelial cells and it inhibits Cyclooxygenase enzymes (COX) enzymes, thus affecting prostaglandins and decreasing inflammation of the colon during the therapy of patients who are suffering from ulcerative colitis [7] [8]. The reported acid/base character (pK_a) of MES is due to the presence of the primary aromatic amino group ($-NH_3$ + pK_a = 6), carboxylic group (-COOH pK_a = 3), and phenolic group (-OH pK_a = 13.9) in the molecule [9]. Intrinsic solubility of MES is 0.844 (±0.021) $mg \cdot ml^{-1}$ and 1.41 (±0.021) $mg \cdot ml^{-1}$ at 25˚C and 37˚C, respectively [10].

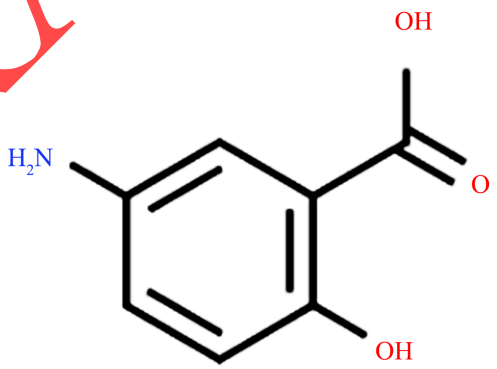

Figure 1. The chemical structure of the MES.

The analysis of the drug solubility in solvent mixtures has important applications in assessing the physical stability of liquid dosage forms and in pre-formulation studies of a drug candidate [11]. The approved drugs and drug candidates have poor aqueous solubility due to their higher molecular weights and complicated chemical structures. The poor solubility causes important problems in designing liquid dosage formulations and oral bioavailability. To overcome these problems, solvent mixtures can be employed to enhance the aqueous solubility [12] [13].

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Nanoparticle and complex formations [14] [15], modified-release formulations [15], and liposomal formulations [16] of MES were some of the reported papers to improve the solubility of this active pharmaceutical ingredient (API). Among them, co-solvency is one of the most preferred solubility enhancement techniques. In this technique, aqueous or non-aqueous binary mixtures can be used to improve the solubility of drug molecules. Aqueous-organic solvent mixtures could be used to formulate liquid dosage forms to prepare solution and/or crystallization processes. This aqueous binary mixture could also be used to prepare nanosuspensions of pharmaceuticals [17]. Non-aqueous binary mixtures are commonly used in the crystallization process, synthesis media, nanoparticle formation, or preparation of non-aqueous solutions of drugs in the pharmaceutical industry [18]. The studies related to the co-solvency approach for MES solubility were given in literature as follows: polyethylene glycol 400 + water [19], (PG) + water [20], in ternary mixtures of ethanol, PG, and water [21], 1-propanol + water [22], aqueous mixtures of a deep-eutectic solvent [23], N-methyl-2-pyrrolidone + water [24].

In this work, PG + 2-propanol and 1,4-dioxane + water were selected as non-aqueous and aqueous binary mixtures, respectively. PG is one of the most important pharmaceutical cosolvents and has been widely used in many liquid formulations [25] [26]. This non-aqueous binary mixture (PG and 2-propanol) was selected to contribute to pre-formulation studies of homogeneous liquid pharmaceutical dosage forms in the pharmaceutical industry [27].

For toxicological reasons, pharmaceutical companies aspire to minimize the number and amount of solvents applied in drug production. Apart from the fact that some of the solvents have no therapeutical value and may be toxic, they may accelerate the decomposition of the drug product [28]. Among these solvents, 1,4-dioxane is not accepted for oral use and has to be limited in the final drug product according to the International Council for Harmonisation (ICH) guideline Q3C. However, 1,4-dioxane has the ability to dissolve poorly soluble drugs [29] and could be used in the synthesis and/or crystallization of the drug and galenical processes as an intermediate solution. It could be mixed with water at any composition of interest because of its low polarity property as described by its dielectric constant, *i.e.*, 2.21 at 298.15˚K [30] [31].

The shake flask method is widely used for solubility analysis of drug molecules [32]. The novelty aspect of this study is related to the choice of organic solvents and temperature (310.2˚K). The point of this view is that the aims of the current study are: 1) to determine the molar solubility of MES in the non-aqueous (PG + 2-propanol) and aqueous (1,4-dioxane + water) binary mixtures at bio-relevant temperature (310.2˚K) by using co-solvency method; 2) to perform density analysis in non-aqueous and aqueous binary mixtures for saturated systems; 3) to characterize MES equilibrated in the saturated solutions by XRD analyses. The solubility of MES in selected binary mixtures has not been reported until this time at the selected temperature.

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2. Materials and Method

2.1. Materials

Chemicals were purchased from: MES Sigma Aldrich, China (mass fraction purity of 0.95), 1,4-dioxane Merck KGaA, Darmstadt, Germany, Ethanol Supelco, Darmstadt, Germany, Propylene glycol Merck KGaA, Darmstadt, Germany, 2-propanol Supelco, Darmstadt, Germany and distilled water Polifarma, Tekirdağ, Türkiye and were used for the preparation of saturated mixtures. Ethanol with a mass fraction purity of 0.935 was used for diluting the saturated solutions of MES in the 1,4-dioxane + water binary mixtures before UV-vis measurements.

2.2. Solubility Experiments

A common shake-flask method [33] is used to determine solubility values of MES in the PG + 2-propanol and 1,4-dioxane + water binary mixtures. Excess amounts of MES are placed into the volumetric flasks with 10 g of neat solvents or solvent mixtures with different mass ratios (w_1 = 0.1 - 0.9). Then, it will be tightly sealed and placed on an orbital shaker (Heidolph, Germany) in the incubator system (MhmtGhsm Company, Dublin, Ireland). The drug solution was shaken for 48 hours at 310.2˚K. Then, the saturated mixtures are centrifuged, diluted with ethanol: water (30:70 % v/v) mixture and spectrophotometric measurements are performed with a UV-vis spectrophotometer (UV 1800 Perkin Elmer Ins., USA) at a fixed wavelength of 299 nm. MES concentration in the diluted solutions is calculated using a plotted calibration curve (R^2 = 0.999). The density values of the saturated mixtures of MES were determined using a 5 ml pycnometer with an uncertainty of 0.001 g·cm^{-3}. The measured solubility data and density values are the averages of at least three replicate measurements.

2.3. X-Ray Powder Diffraction

The characterization tests of MES equilibrated in the saturated solutions were performed by XRD analyses (Rigaku Ultima IV, Tokyo, Japan) from 10˚ to 70˚. The voltage and current applied were 40 kV and 15 mA, respectively using CuKa radiation. The scan speed was 5.00˚/min with a step width of 0.02˚. All samples were dried in an oven at 100˚C, before XRD analysis. XRD analyses were performed at the R & D Training and Measurement Center, X-Ray Diffraction Laboratory (METU, Türkiye).

3. Results and Discussions

The solubility values of MES in the binary mixtures of PG + 2-propanol and 1,4-dioxane + water were determined using a shake flask followed by UV-Vis spectroscopy. The results showed that the maximum solubility was obtained in neat PG (C_M = 1.03 × 10^{-2} mol/l) and the minimum solubility in the neat 2-propanol (C_M = 5.14 × 10^{-4} mol/l) at 310.2˚K. The maximum molar solubility value was obtained in 0.4 mass fraction (C_M = 1.02 × 10^{-2} mol/l) of the

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1,4-dioxane + water binary mixture, and the minimum solubility was obtained in water (C_M = 0.99 × 10^{-3} mol/l) at 310.2˚K. The molar solubility values of the two systems for each mass fraction are given in **Table 1**. The reported values were in accordance with a previously published paper [34], which reported that mole fraction solubility value, but in this study, the data was reported as molar solubility value.

Table 1. Experimental molar solubility (C_M/mol/l) values as the mean of three experiments (±std. dev.) for MES in the PG + 2-propanol and 1,4-dioxane+water binary mixtures at biorelevant temperature.

w_{1*}	310.2˚K	
	PG + 2-propanol	1,4-Dioxane + water
0.0	5.14 (±0.02) × 10^{-4}	9.64 (±0.04) × 10^{-3}
0.1	8.48 (±0.63) × 10^{-4}	1.29 (±0.06) × 10^{-2}
0.2	1.14 (±0.09) × 10^{-3}	1.57 (±0.06) × 10^{-2}
0.3	1.23 (±0.06) × 10^{-3}	1.66 (±0.08) × 10^{-2}
0.4	1.60 (±0.06) × 10^{-3}	1.68 (±0.10) × 10^{-2}
0.5	2.25 (±0.03) × 10^{-3}	1.49 (±0.06) × 10^{-2}
0.6	2.76 (±0.24) × 10^{-3}	1.18 (±0.07) × 10^{-2}
0.7	3.72 (±0.16) × 10^{-3}	8.53 (±0.81) × 10^{-3}
0.8	5.13 (±0.58) × 10^{-3}	6.39 (±0.50) × 10^{-3}
0.9	7.48 (±0.96) × 10^{-3}	5.24 (±0.49) × 10^{-3}
1.0	1.03 (±0.07) × 10^{-2}	3.34 (±0.30) × 10^{-3}

*w_1 is the mass fraction of cosolvent.

The observed solubility patterns can be attributed to molecular interactions and solvation effects involving mesalazine, the cosolvent, and the solvent within the mixtures. These interactions significantly influence mesalazine's solubility and contribute to the observed behavior in these cosolvency systems, as explained in the reference [34].

Considering that MES with lipophilicity (log P) = 0.75 [35] and Hansen solubility parameters of δ_D (dispersion forces) = 16.71, δ_P (dipolar intermolecular forces) = 17.73, δ_H (hydrogen bonds) = 29.33, PG with log P = −0.92, dipole moment: 2.27 D, dielectric constant of 32 [36], δ_D = 14.06, δ_P = 11.40, δ_H = 20.96, 2-propanol with log P = 0.05, a dipole moment of 1.66 D, dielectric constant value is 19.92, and δ_D = 16.42, δ_P = 9.47, δ_H = 18.55, 1,4-dioxane with log P = −0.27, a dipole moment of 0.45 D, dielectric constant value is 2.25, and Hansen solubility parameters of δ_D = 12.43, δ_P = 14.25, δ_H = 26.82, and water with dipole moment: 1.85 D [37] and a dielectric constant of 78.4 [38] and Hansen solubility parameters of δ_D = 15.50, δ_P = 16.0, δ_H = 42.30, it was expected that the solubility of MES would rise with the incorporation of dioxane, which was less polar than

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water. As can be seen from Hansen solubility parameters, water is considered the most polar solvent due to its higher capability to form hydrogen bonds. 1,4-dioxane is also polar solvent; however, its polarity is lower than that of water. Furthermore, the solubility of MES was also impacted by the interactions between 1,4-dioxane and water. When 1,4-dioxane is present in water, it can disrupt the hydrogen bonding network among water molecules. Consequently, this affects the solvation of MES, leading to variations in its solubility behavior within 1,4-dioxane + water mixtures.

Moreover, in PG + 2-propanol system, PG has a polar hydroxyl group (-OH) and an ether group (-O-), which makes it more polar and capable of forming stronger intermolecular interactions, such as hydrogen bonds and dipole-dipole interactions, with MES according to Hansen parameters. The amide group in mesalazine can also form hydrogen bonds with the hydroxyl group in PG, further enhancing their solubility. On the other hand, 2-propanol has a similar polar hydroxyl group but a smaller and less polar aliphatic chain compared to PG. Although it can also form hydrogen bonds with the hydroxyl group in MES, the overall polarity and intermolecular interaction capability of 2-propanol are lower than those of PG. As a result, MES has higher solubility in PG-rich systems than in 2-propanol-rich mixtures.

Moreover, the density values for the MES saturated mixtures at 310.2˚K are also measured and given in Table 2 and correlated with the Jouyban-Acree model (Equation (3)).

Table 2. Measured density (g·cm^{-3}) of MES saturated solutions in the PG + 2-propanol and 1,4-dioxane+water binary mixtures at biorelevant temperature.

	310.2˚K	
w_1	PG + 2-propanol	1,4-dioxane + water
0.0	0.75 (±2.00) × 10^{-2}	0.990 (±5.77) × 10^{-3}
0.1	0.76 (±2.08) × 10^{-2}	0.995 (±1.00) × 10^{-2}
0.2	0.78 (±1.00) × 10^{-2}	1.003 (±1.53) × 10^{-2}
0.3	0.82 (±1.00) × 10^{-2}	1.007 (±5.77) × 10^{-3}
0.4	0.83 (±5.77) × 10^{-3}	1.015 (±5.77) × 10^{-3}
0.5	0.86 (±1.53) × 10^{-3}	1.007 (±5.77) × 10^{-3}
0.6	0.88 (±1.00) × 10^{-2}	1.007 (±1.15) × 10^{-2}
0.7	0.90 (±5.77) × 10^{-3}	1.010 (±1.15) × 10^{-2}
0.8	0.93 (±1.00) × 10^{-2}	1.010 (±5.77) × 10^{-3}
0.9	0.98 (±5.77) × 10^{-3}	1.010 (±2.08) × 10^{-2}
1.0	1.07 (±1.53) × 10^{-2}	1.000 (±5.77) × 10^{-3}

The trained models for PG + 2-propanol is:

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$$\ln \rho_{m,T} = w_1 \ln \rho_{1,T} + w_2 \ln \rho_{2,T} - 68.191 \frac{w_1 w_2}{T} \quad (3)$$

and the trained models for 1,4-dioxane + water is:

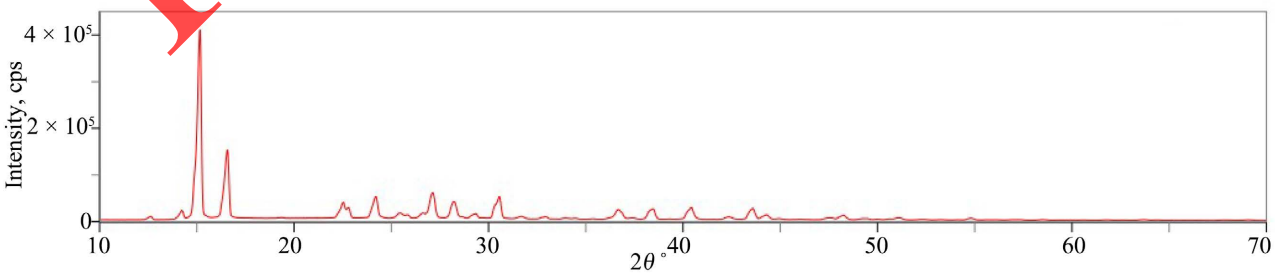
$$\ln \rho_{m,T} = w_1 \ln \rho_{1,T} + w_2 \ln \rho_{2,T} + 19.873 \frac{w_1 w_2}{T} \quad (4)$$

$\ln \rho_{m,T}$ describes the density of MES-saturated solutions and $\rho_{1,T}$ and $\rho_{2,T}$ are the density of MES saturated neat 1,4-dioxane and water for an aqueous binary mixture system and neat propylene glycol and 2-propanol for a non-aqueous binary mixture system at 310.2˚K. The back-calculated mean relative deviation percentage (MRD %) is obtained at 0.2 for the 1,4-dioxane and water system and 1.4% for the PG + 2-propanol system. These MRD% values (Equation (3)) show a good prediction ability for the density data.

The characterization tests of MES equilibrated in the saturated solutions from 10˚ to 70˚ by XRD analyses were performed [39]. XRD result of raw MES given in our previously published paper (data not shown here) [40], and the residuals from neat 1,4-Dioxane, neat PG, neat 2-propanol, water, and binary mixtures were given in this study. This analysis showed similar characteristic peaks in raw material and the residuals from neat solvents and binary mixtures. According to the XRD result, the crystallinity of MES remained unchanged. It showed no polymorphic transformation during the dissolution procedure in the investigated non-aqueous and aqueous binary mixture systems.

4. Conclusion

In this study, the mesalazine solubility profile was measured experimentally in propylene glycol + 2-propanol non-aqueous and 1,4-dioxane + water aqueous binary mixtures at biorelevant temperature. The maximum solubility in the molarity scale was obtained in neat propylene glycol (C_M = 1.03 × 10^{-2} mol/l) and the minimum solubility in the neat 2-propanol (C_M = 5.14 × 10^{-4} mol/l) in the non-aqueous binary mixture and the maximum solubility value was obtained in 0.4 mass fraction (C_M = 1.68 × 10^{-2}) of 1,4-dioxane + water and the minimum solubility was obtained in water (C_M = 3.34 × 10^{-3} mol/l) at 310.2˚K. According to the XRD characterization tests, the crystallinity of MES remained unchanged. It showed no polymorphic transformation during the dissolution procedure in the investigated co-solvent systems (**Figure 2**).



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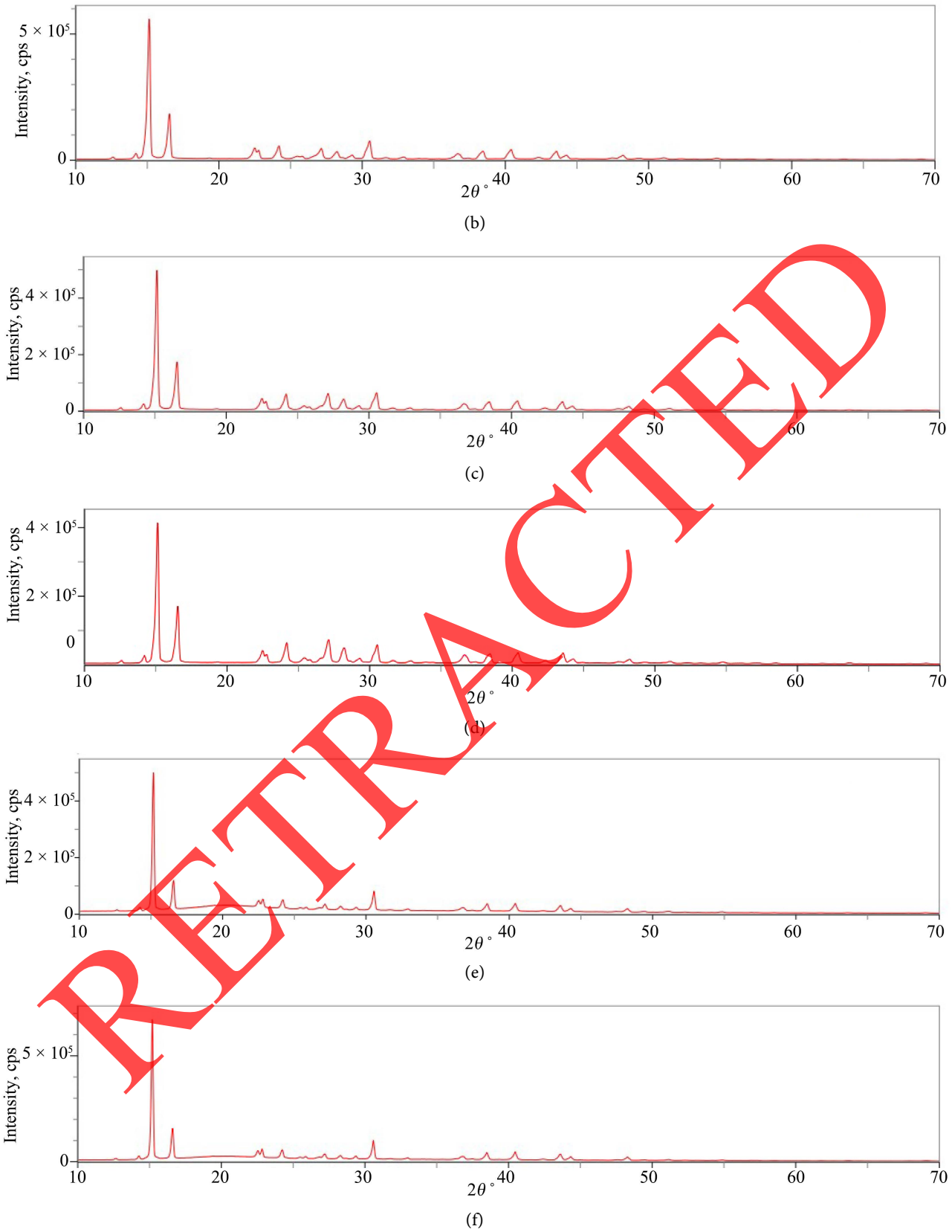

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Figure 2. XRD spectra of MES in equilibrated systems*. (*(a) water, (b) 1,4-dioxane + water (1-1 mass ratio), (c) 1,4-dioxane, (d) 2-propanol, (e) PG + 2-propanol (1-1 mass ratio), (f) PG).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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