RESEARCH ARTICLE

Enhancement of Solubility of Drug Acetazolamide by Different Techniques and Comparison thereof

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Abstract

Solubility enhancement has attracted considerable interest as an efficient mean of improving the solubility and hence bioavailability of poorly water soluble drugs. Oral route is most of the preferred route of drug administration but it presents a considerable challenge in case of poorly soluble drugs. In the present work the solubility of Acetazolamide was enhanced using two different techniques. In which solid dispersion of Acetazolamide is prepared by physical mixture method and by kneading method using PEG-6000 and PVP K-30 as a carrier for solid dispersion and Complex is prepared by physical mixture method and kneading method using β-Cyclodextrin as a complex forming agent. Comparison different formulation is done in term of solubility and the results revealed that solid dispersion physical mixture of Acetazolamide and PEG-6000 (1:1 ratio) shows high saturation of solubility as compare to others, which leads to increase in the rate of solubility. Formulation with maximum solubility was analyzed using FT-IR, XRD and DSC studies. Thus, increases the dissolution and bioavailability of poorly soluble drug acetazolamide.

Keywords: Solid dispersion, Solubility, Complexation, Kneading, *In-vitro* release.
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Introduction

Acetazolamide (ACZ) is a carbonic anhydrase inhibitor reduces abnormal and excessive neurotransmission in the central nervous system while also having sedative and helps in maintains breathing during sleep. ACZ is indicated for epilepsies (petit mal and unlocalized seizure), open angle glaucoma and secondary glaucoma. [1] Acetazolamide has a slight diuretic effect as well as it is a non-bacteriostatic sulphonamide with a pharmacological action and chemical structure that are quite different from bacteriostatic sulphonamide. ACZ has been the subject of the most in-depth research as a carbonic anhydrase inhibitor out of the many sulphonamides that have been developed and studied.[2]

According to Biopharmaceutical classification system (BCS) Acetazolamide belongs to BSC class- IV drugs which indicates low permeability and low solubility.[3] This has a significant impact on gastrointestinal absorption and bioavailability, limiting its therapeutic success. As a result, numerous pharmaceutics techniques are employed to increase the solubility.[4] However these methods are complicated, time consuming and expensive, which stimulates researchers to look for current, simple, and economical methods to enhance the physicochemical features of the Acetazolamide.[5]

A large number of researchers are interested in solid dispersion technology, which works with drugs that are classified as BCS Class-IV drugs because of their low permeability across biological membranes and poor water solubility. The rate-limiting stage for absorption of these drugs is their disintegration. Therefore, enhancing the dissolution rate will raise the rate of absorption. Solid dispersion technologies thus hold potential for enhancing the rate of dissolution and bioavailability of BCS-Class IV drugs, resulting in increased oral absorption.[6] However complexation is a commonly employed technique to improve the solubility of drugs that are poorly soluble, where complexation with cyclodextrins is widely use technique among all co-complexes.[7] The cyclodextrins improve aqueous stability, improve drug absorption, make the drug soluble in water, and reduce gastrointestinal irritation.[8] Therefore the current research aims to enhance the solubility of drug Acetazolamide by different techniques using different polymers and this to compare the formulation with maximum solubility, characterizing X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FT-IR), as well as estimating solubility and comparing results with pure drug.

Materials And Methods

Acetazolamide (ACZ) purchased from Swapnroop Drugs & Pharmaceuticals, Maharashtra, India. Polyethylene Glycol (PEG)-6000, Polyethylene Glycol (PEG)-6000, Polyvinylpyrrolidone (PVP) K-30, and β-Cyclodextrin were

acquired from Central Drug House Pvt. Ltd. and all reagents are of AR quality,

Phase Solubility Study

The phase solubility study was conducted with the addition of acetazolamide in excessive amounts of solvent..The solution was kept for 24 hours at 25°C temperature and solubility were analyzed at 10 µg/ml and 20 µg/ml concentration using UV spectrophotometric technique at 265nm wavelength. The apparent solubility constant was determined from the slope of the phase solubility diagram using equation 1. The slope is calculated from the original straight line of acetazolamide in methanol.

$$Kc = Slope/So\ (1\text{-}Slope) \quad [1]$$

Co-solvency

The mixture of miscible solvent used to solubilize the lipophilic drugs is known as co-solvent. In this method the excess amount of drug (100 mg) was dissolved in 10ml of methanol which was used as co-solvent, and further the volume was carried out up to 100ml using distilled water.

Solid Dispersion by Physical Mixture

The drug (ACZ) and polymer (PVP K30 and PEG 6000) were weighed to prepare the physical mixture. and by mixing them. The formulation was obtained by mixing the components using spatula in mortar for 5 minutes. The following mixture were passed through 50 meshsieve. The solubility was determined by adding excess amount of mixture (10mg) inphosphate buffer 6.8 pH concentration 10ml. The dilution was kept at 25°C temperature for 24 hours in a mechanical shaker and solubility was analyzed by making the dilution of solution upto 10µl/ml and 20µl/ml respectively. The solubility of 1:1, 1:2, 1:3 and 1:4 complex was analyzed at 365 nm wavelength. The apparent solubility was determined from the phase solubility diagram using equation 1. The slope is calculated using the initial straight line plot of acetazolamide and PVP K30 or acetazolamide and PEG-6000 in varying ratios. [9,10,11]

Solid Dispersion by Kneading

In kneading method, the weighed amount of drug (ACZ) and polymer (PVP K30 and PEG 6000) were kneaded in different ratio (1:1, 1:2, 1:3 and 1:4) utilizing a mortar and pestle for ten minutes while adding the appropriate quantity of methanol.The mass was dried at the room temperature overnight, crushed, sieved, and then dried again in the oven for 24 hours. The solubility was determined by adding excess amount (10mg) inphosphate buffer 6.8 pH concentration 10ml. The dilution was kept at 25°C temperature for 24 hours in a mechanical shaker and and the solubility was analyzed by making the dilution of solution upto 10µg/ml and 20µg/ml concentration respectively. The solubility of 1:1, 1:2, 1:3 and 1:4 complex was analyzed at 365 nm wavelength. The apparent solubility was determined from the phase solubility diagram using equation 1. The slope is calculated using the initial straight line plot of acetazolamide and PVP K30 or acetazolamide and PEG-6000 in varying ratios.

Complexation Physical Mixture

In this method acetazolamide and β-CD were weighed in varying ratios (1:1, 1:2, 1:3 and 1:4) respectively, β-CD was lightly triturated in a mortar before acetazolamide was gradually added, sieved, and well combined.The uniform physical mixture was created by constantly mixing the mixture for one hour. The mixture was passed through 120# sieve. The solubility was determined by adding excess amount of mixture (10mg) in phosphate buffer pH 6.8 concentration 10ml. The solution was kept at 25°C temperature for 24 hours in mechanical shaker and solubility was analyzed by making the dilution of solution upto 10µg/ml and 20µg/ml concentration respectively. The solubility of 1:1, 1:2, 1:3 and 1:4 complex was analyzed at 265 nm wavelength. The apparent solubility was determined from the phase solubility diagram using equation 1. The slope is calculated using the initial straight line plot of acetazolamide andβ-CD complex in different ratio. [9,10,12]

Complexation Kneading Method

In the kneading technique β-Cyclodextrin in different weight in the separate mortar was moistened with sufficient water (10% w/w) to form a pasteAcetazolamide was gradually introduced to the paste to make the different ratio of complex (1:1, 1:2, 1:3 and 1:4). Kneading was done manually for an hour, and water was added as needed to keep the paste consistency.The mixture was oven-dried overnight at 40°C. The dried complex was crushed using a mortar and pestle. After screening through 55#, the inclusion complex was stored in a closed container. The solubility was determined by adding excess amount of mixture (10mg) in phosphate buffer pH 6.8 concentration 10ml.The solution was kept at 25°C temperature for 24 hours in mechanical shaker and solubility was analyzed by making the dilution of solution upto 10µg/ml and 20µg/ml concentration respectively. The solubility of 1:1, 1:2, 1:3 and 1:4 complex was analyzed at 265 nm wavelength. The apparent solubility was determined from the phase solubility diagram using equation 1. The slope is calculated using the initial straight line plot of acetazolamide andβ-CD complex in different ratio. [5,6,13]

Characterization of Drug and PEG-6000 Physical Mixture (1;1)

X-Ray diffraction (XRD)

The powder XRD pattern of pure acetazolamide and a solid dispersion of acetazolamide and PEG-6000 Physical Mixture (1:1) was obtained using a diffractogram (Bruker AXS D8 Advance Germany) and Cu-Kα radiation. The diffractogram was done at a scanning rate of 2 degrees per minute and a chart speed of 2°/2cm per 2θ.

Differential scanning calorimetry (DSC)

DSC of pure acetazolamide and solid dispersion of acetazolamide and PEG 6000 physical mixture (1:1) was performed using a differential scanning calorimeter (Mettler Toledo DSC 1 Star System) at a heating rate of 10°C/min from 25°C to 300°C. [14,15]

Infrared spectroscopy (IR)

Acetazolamide Fourier transform infrared spectroscopy and a solid dispersion of Acetazolamide and polyethylene glycol (PEG 6000) Physical Mixture (1:1) were obtained on an FTIR (84005, Shimadzu Japan) using the KBr disc method. The scanning range was 450–4000 cm-1, and the resolution was 1 cm-1. [16,17]

Results and Discussion

Co-solvency

Acetazolamide is a drug belongs to the BSCclass- IV drugs which indicates low solubility and low bioavailability, It is insoluble in water, phosphate buffer, hydrochloric acid. The pure drug is soluble in methanol. Hence the solubility of pure drug was measured in methanol using a 10 µg/ml sample at 265 nm wavelength and found to be 5.693 µg/ml. Acetazolamide solubility in distilled water with methanol as a cosolvent was found to be 4.891 µg/ml at 265 nm. as shown in Table 1.

Solid Dispersion Kneading and Physical Mixture

The weighed amount of drug and polymer, (PVP K30 and PEG 6000) was kneaded in different ratio (1:1, 1:2, 1:3 and 1:4) utilizing a mortar and pestle for ten minutes while adding the appropriate quantity of methanol.The mass was dried at the room temperature overnight, crushed, sieved, and then dried again in the oven for 24 hours. The solubility was determined by adding excess amount (10mg) inphosphate buffer 6.8 pH concentration 10ml. Theλmax of various samples were analyzed using UV spectrophotometer and the solubility of different samples were determined. A similar ratio of drug and polymer (PVP K30 and PEG 6000) were used in the physical mixture technique and the solubility of kneading and physical mixture was analyzed using given λmax. The solubility results of kneading and physical mixture are mentioned in Table 2.

Complexation Kneading and Physical Mixture

In the complexation technique, the β-cyclodextrin polymer was used for solubility enhancement of drug in different ratio using kneading andphysical mixture technique. In the complexation by physical mixture technique, the drug (ACZ) and polymer (β-CD)were prepared by trituration in different ratio (1:1, 1:2, 1:3 and 1:4) respectively . A similar ratio of β-cyclodextrin (β-CD) was used in the kneading method. Polymer and drug were kneaded in mortar pestle using methanol as a solvent. The λmax of different samples were analyzed using UV visible spectrophotometer and the solubilities of respected samples were determined. The solubility studies were conducted using the phosphate buffer pH 6.8 as a solvent.. The solubility results of acetazolamide using β-cyclodextrin (β-CD) as a complexing agent in the ratio of 1:1, 1:2, 1:3 and 1:4 (kneading and physical mixture is mentioned in Table 3.

Table 1: Solubility of acetazolamide in methanol and distilled water taking methanol as co-solvent

S.No	*Solvent*	*Wavelength (λmax)*	*Solubility (10µg/ml)*
1	Methanol	265	5.693
2	Distilled water with cosolvent methanol	265	4.891

Powder XRD Study

Figure 1 shows powder XRD pattern of Acetazolamide and Acetazolamide and PEG 6000 solid dispersion physical mixture 1:1. XRD result of acetazolamide and acetazolamide and PEG 6000 solid dispersion 1:1. XRD results of acetazolamide shows that acetazolamide has changed from being crystal clear to being amorphous. Compared to the crystalline form, the amorphous form has higher molecular mobility and energy. This characteristic produces an amorphous form with higher apparent solubility and dissolution rate.

Differential Scanning Calorimetry (DSC)

Figure 2 illustrates the DSC of pure drug Acetazolamide and Acetazolamdie with PEG 6000 solid dispersion, physical mixture (1:1). In the DSC thermogram of pure acetazolamide due to the melting of single drug endothermic peak was shown at 265°C and DSC thermogram of acetazolamide and PEG-6000 physical mixture solid dispersion in the ratio (1:1) due to melting of PEG 6000 the peak appeared at 53°C that indicated the melting of polymer while no peak has shown that of drug, which indicated conversion of pure acetazolamide to solid dispersion amorphous form.

Infrared Specreocsopy

The bands above 3100 cm^{-1} represents O-H stretching, the bands at 2771 represents C-H aldehyde stretching, the bands at 1685 represents C=N stretching, the bands at 1585 represtns N-H streaching. Fig 3

As the proportion of PEG 6000 was added in solid dispersion OH streach was increased, the characteristic absorption band undergoes widening at position 3300 O-H bond and 3291 C-H aldehyde starching with relatively more signigicant widening of solid dispersion with proportion 1:1.

FT-IR Study

Solubility Comparison Using Different Solubility Enhancement Techniques

The solubility of acetazolamide was determined by employing various solubility enhancement techniques. The results of solubility were compared and elaborated in Table 4 and Figure 4-6.

Table 2: Results of solubility study by solid dispersion method using PEG 6000

S. No	*Solubility enhancement technique*	*Brief description*	*Drug polymer ratio*	*Wavelength (λmx)*	*Solubility (10µg/ml)*	*Solubility (20µg/ml)*
1	Solid Dispersion	Physical Mixture (Drug and PVP-K30)	1:1	265	8.775744	15.57208
2	Solid Dispersion	Physical Mixture (Drug and PVP-K30)	1:2	265	9.792157	11.12549
3	Solid Dispersion	Physical Mixture (Drug and PVP-K30)	1:3	265	7.859244	10.52731
4	Solid Dispersion	Physical Mixture (Drug and PVP-K30)	1:4	265	8.448133	12.88797
5	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:1	265	10.54849	31.61367
6	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:2	265	10.2655	15.29457
7	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:3	265	7.27259	9.125
8	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:4	265	9.257764	13.71946
9	Solid Dispersion	Kneading (Drug and PVP K30)	1:1	265	8.4547321	13.90740741
10	Solid Dispersion	Kneading (Drug and PVP K30)	1:2	265	9.86908078	17.25069638
11	Solid Dispersion	Kneading (Drug and PVP K30)	1:3	265	9.772009	15.83296
12	Solid Dispersion	Kneading (Drug and PVP K30)	1:4	265	10.02289	16.80401
13	Solid Dispersion	Kneading (Drug and PEG 6000)	1:1	265	9.545455	17.25237
14	Solid Dispersion	Kneading (Drug and PEG 6000)	1:2	265	9.318957	14.11334
15	Solid Dispersion	Kneading (Drug and PEG 6000)	1:3	265	10.19818	17.31663
16	Solid Dispersion	Kneading (Drug and PEG 6000)	1:4	265	8.10526316	9.82271468

Table 3: Solubility of acetazolamide in phosphate buffer pH 6.8 using solubility enhancement technique complexation

S. No	*Solubility enhancement technique*	*Brief description*	*Drug polymer ratio*	*Wavelength (λ max)*	*R^2 value*	*Solubility (10 Mg/ml)*	*Solubility (20 Mg/ml)*
1	Complexation	Physical Mixture Trituration (Drug and β cyclodextrin complex)	1:1	265	0.992	10.1535	16.11177
2	Complexation	Physical Mixture Trituration (Drug and β cyclodextrin complex)	1:2	265	0.989	10.18011	16.43152
3	Complexation	Physical Mixture Trituration (Drug and β cyclodextrin complex)	1:3	265	0.981	10.05521	16.36593
4	Complexation	Physical Mixture Trituration (Drug and β cyclodextrin complex)	1:4	265	9.965	9.717201	16.41691
5	Complexation	Kneading Method (Drug and β cyclodextrin complex)	1:1	265	0.973	9.956621	17.05137
6	Complexation	Kneading Method (Drug and β cyclodextrin complex)	1:2	265	0.932	9.994695	18.24403
7	Complexation	Kneading Method (Drug and β cyclodextrin complex)	1:3	265	0.984	9.861111	29.67857
8	Complexation	Kneading Method (Drug and β cyclodextrin complex)	1:4	265	0.976	10.07004	16.28167

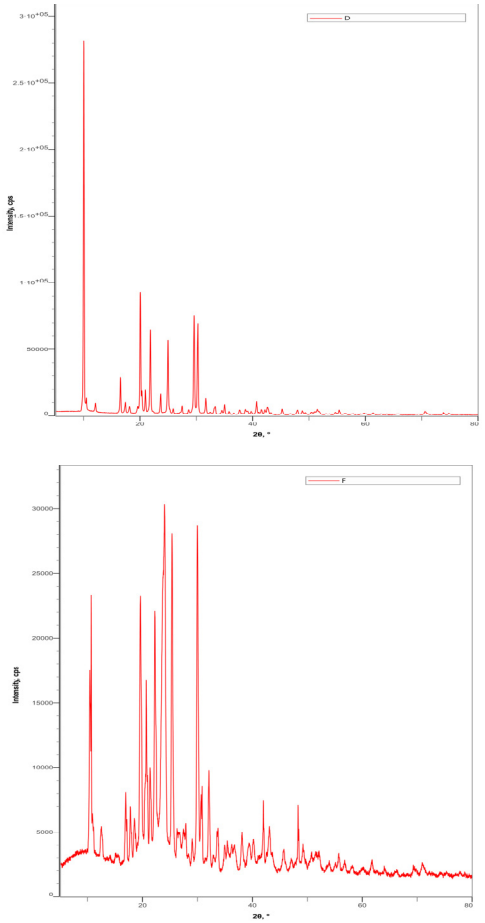

Figure 1: XRD ofa) Pure drug and b) Solid Dispersion physical mixture drug and PEG 6000 (1:1)

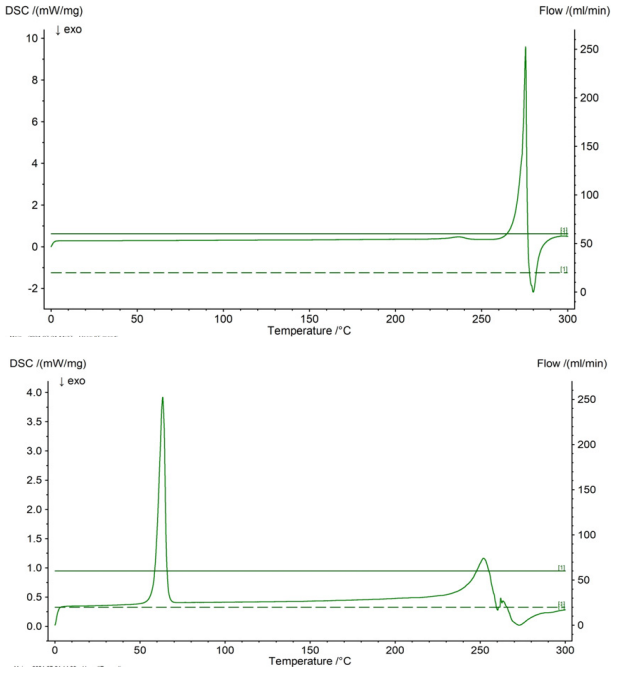

Figure 2: a) Differential Scanning Calorimetry of pure drug b) Differential Scanning Calorimetry of Solid Dispersion physical mixture drug and PEG 6000 (1:1)

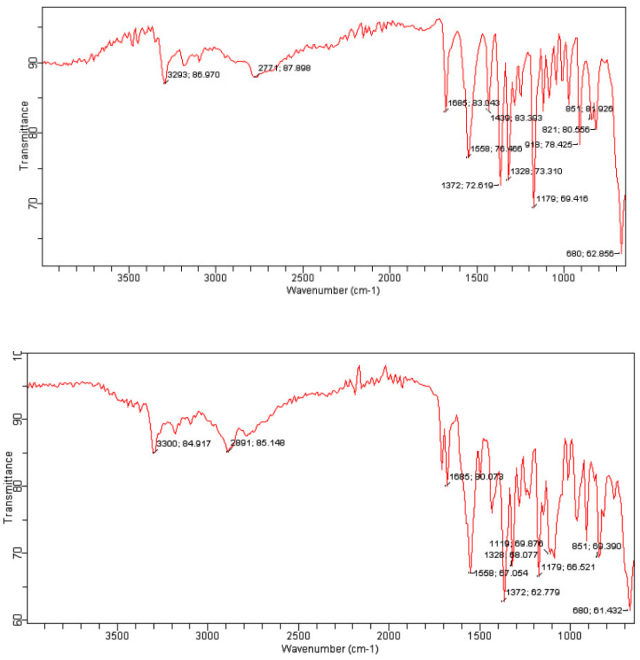

Figure 3: a) Infrared Spectroscopy (IR) of pure drug b) Infrared spectroscopy of drug and PEG 6000 solid dispersion physical mixture (1:1)

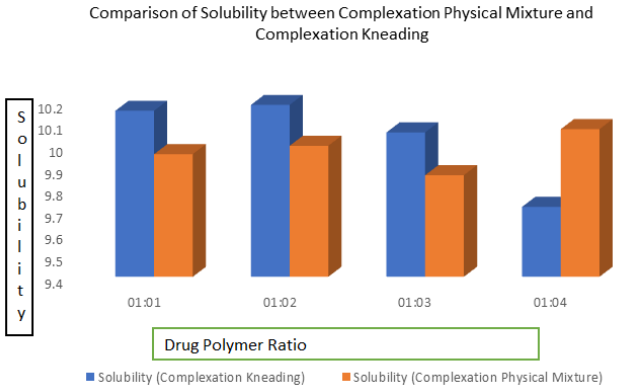

Figure 4: representing the solubility comparison between complexation physical mixture and complexation kneading

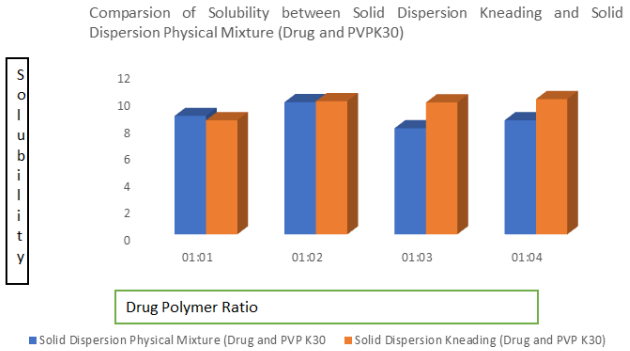

Figure 5: representing solubility comparison between solid dispersion physical mixture (drug and PVP K-30) and solid dispersion kneading technique (drug and PVP K-30)

Table 4: Solubility of acetazolamide in phosphate buffer pH 6.8 using solubility enhancement technique solid dispersion

S.No	*Solubility Enhancement Technique*	*Brief Description*	*Drug Polymer Ratio*	*Wavelength (λmax)*	*R^2 value*	*Solubility (10µg/ml)*	*Solubility (20µg/ml)*
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5	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:1	265	0.974	10.54849	31.61367
6	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:2	265	0.981	10.2655	15.29457
7	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:3	265	0.995	7.27259	9.125
8	Solid Dispersion	Physical Mixture (Drug and PEG 6000)	1:4	265	0.997	9.257764	13.71946
9	Solid Dispersion	Kneading (Drug and PVP K30)	1:1	265	0.993	8.4547321	13.90740741
10	Solid Dispersion	Kneading (Drug and PVP K30)	1:2	265	0.992	9.86908078	17.25069638
11	Solid Dispersion	Kneading (Drug and PVP K30)	1:3	265	0.983	9.772009	15.83296
12	Solid Dispersion	Kneading (Drug and PVP K30)	1:4	265	0.975	10.02289	16.80401
13	Solid Dispersion	Kneading (Drug and PEG 6000)	1:1	265	0.991	9.545455	17.25237
14	Solid Dispersion	Kneading (Drug and PEG 6000)	1:2	265	0.974	9.318957	14.11334
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16	Solid Dispersion	Kneading (Drug and PEG 6000)	1:4	265	0.988	8.10526316	9.82271468
17	Complexation	Physical Mixture Trituration (Drug and β cyclodextrin complex)	1:1	265	0.992	10.1535	16.11177
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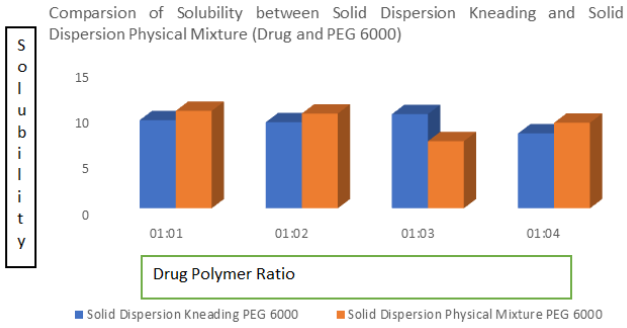

Figure 6: Representing solubility comparison between solid dispersion physical mixture (drug (ACZ) and PEG-6000) and solid dispersion kneading technique (drug and PEG 6000)

Conclusion

The approach of present research to improve the solubility of Acetazolamide, a poorly soluble drugs belonging to BCS class IV, by the use of various techniques such as co-solvency, solid dispersion and co-complexation. Different polymers were employed in varying ratios to improve the drug›s solubility. In comparison to other solid dispersion physical mixtures, the 1:1 ratio of ACZ and PEG-6000 shows a high saturation of solubility. Acetazolamide underwent a change from a crystalline to an amorphous state, as shown by XRD and DSC studies. As a result, acetazolamide, a poorly soluble drug, can be made into a solid dispersion by mixing a physical mixture with PEG 6000 (1:1)can be used in various pharmaceutical

formulation with maximum enhanced solubility compared to all formulation.

Conflict of Interest

The authors have no conflict of interest.

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