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Enhancement of Water Solubility for Lopinavir by Co-solvency Approach

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ABSTRACT

In quantitative terms, the solubility is to dissolve an object can be measured by the solute concentration in a saturated solution at a given temperature. The term of qualitative mean, solubility is known as homogeneous molecular dispersion formed by combining of two or more substances when they interact spontaneously. This study performed and compared by the cosolvency approach using various cosolvents like polyethylene glycol (PEG 400), propylene glycol (PG), and glycerin. Because increasing the water solubility of a drug with low water solubility, is a critical task in the design of new formulation of liquid dosage forms. Lopinavir's solubility found 2.02 mg/100 mL in water, which was enhanced by PG, PEG 400, and glycerin. Less polar solvents have a higher water solubility, which aids the hydrophobic interaction mechanism. The most effective solvent-cosolvent blend tested was found to be water-PEG 400. Hence, this study will be helpful in the development of new formulation of liquid dosage forms for Lopinavir.
Keywords: *Lopinavir, glycerin, propylene glycol, polyethylene glycol 400.*

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INTRODUCTION

In quantitative terms, the solubility is to dissolve an object can be measured by the solute concentration in a saturated solution at a given temperature. The term of qualitative mean, solubility is known as homogeneous molecular dispersion formed by combining of two or more substances when they interact spontaneously [1,2]. This relationship holds true for any given drug's bioavailability. Poor bioavailability is frequently caused by drug molecules that are poorly water soluble in patients' digestive fluids. A water solution is required at the absorption site to achieve therapeutic plasma concentrations after oral administration of a poorly water-soluble drug. Drugs that are difficult to dissolve in water are a common occurrence in drug development and screening studies for new chemical entities. Complexation, addition of surfactant [3]. Adjustment of pH, and cosolvency are all methods that can help solubilize drug candidates with low water solubility [4]. Cosolvents are advantageous in pharmaceutical liquid formulations for drugs with a low solubility in water [5]. Cosolvents, which are mixtures of miscible solvents, have been shown to significantly increase the solubility of drugs that are poorly soluble in water [6,7,8]. Water solubility is low for weak electrolytes and nonpolar molecules. Generally, a drug's solubility can be increased by mixing it with a water-miscible solvent that has a high solubility for the drug. As a result, cosolvents are used to increase the solubility of compounds. Because the interfacial tension in the water solution is reduced, the hydrophobicity of the solute is reduced. Solvent blending is another term for the same thing [9,10]. Hydrogen bond donor and acceptor groups and small hydrocarbon regions and are common in cosolvents. Their hydrophobic regions disrupt the water hydrogen-bonding network, lowering intermolecular attraction overall, because their water miscibility ensured by hydrogen-bonding groups. Cosolvents increase solubility by interfering with water's ability to squeeze out hydrophobic compounds [11,12]. Cosolvent technology increases drug solubility while also preventing contamination during dispensing and saving money on pharmaceutical technology that would otherwise be required to create the dosage form when used in liquid dosage forms. PEG, DMA, and DMSO are the most commonly used low-toxicity intravenous cosolvents. The chemical name of Lopinavir is 5-{[2-(2,6-dimethylphenoxy) acetylamino]-4-hydroxy-1,6 diphenylhexan-2-yl}-3-methyl-2-(2-oxo-1,3-diazinan-1-yl) butanamide [13]. It is used to treat HIV infections when combined with another protease inhibitor. The chemical structure of this substance is depicted in Figure 1. Because of its insolubility, Lopinavir's formulation and therapeutic applications must be improved. Cosolvency should be investigated as thoroughly as the various Lopinavir solubilization methods. Cosolvency has never been used to increase

lopinavir's water solubility. The water solubility of Lopinavir will be investigated using glycerin, PG and PEG 400 in this study [14].

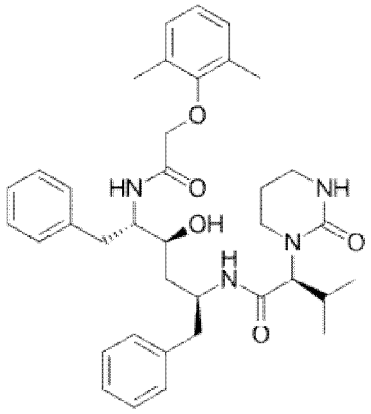

Figure No. 1. Lopinavir Chemical Structure

MATERIAL AND METHODS

India's Jigs Chemicals Ltd. provided Lopinavir samples as a gift. Glycerin, propylene glycol, polyethylene glycol 400 sold by Neoscience Labs Private Limited in India. All of the chemicals were analytical reagent grade, and distilled water was used throughout the study.

Determination of A1%, 1cm

Weigh accurately 100±2 mg of Lopinavir in 100 ml volumetric flask. Add sufficient methanol and vigorous shaking and made up the volume with methanol. Aliquot the portion of 100, 200, 300, 400, 500 µg/mL and made up the volume. These concentrations were analyzed (Table 1) by UV-VIS spectrophotometer at 260.

Table 1: Absorbance of Lopinavir in water

S. No.	Concentration (µg/mL)	Absorbance
1	100	0.097
2	200	0.194
3	300	0.297
4	400	0.395
5	500	0.499

By using Water and Glycerin

Prepared the mixture of water and glycerin in the ratio of [100:0, 80:20, 60:40, 40:60, 20: 80] %v/v respectively. Transferred 100 ml of each ratio of the above mixture to each 250 ml stoppered conical flask. Weighed accurately 100±2 mg of Lopinavir and added directly to each 250 ml stoppered conical flask containing solvent mixtures. These flasks kept in magnetic stirrer at room temperature and 50 rpm for 20 minutes. After 20 minutes, samples were withdrawn, filtered each sample (0.22 µm pore size). From the resulting solution took 10 ml (100 µg/mL) and transferred into each 100 ml volumetric flask and made up the volume with respective ratio of the solvent mixtures. These samples were analyzed (Table 2) using UV-VIS spectrophotometer at 260 nm.

Table 2: Absorbance of Lopinavir in Water and Glycerin

Water (% v/v)	Glycerin (% v/v)	Sample Weight (±2mg)	Absorbance
100	0	100	0.002
80	20	100	0.007
60	40	100	0.015
40	60	100	0.026
20	80	100	0.039

By using Water and Propylene Glycol

Prepare the mixture of water and propylene glycol (PG) in the ratio of [100:0, 80:20, 60:40, 40:60, 20: 80] %v/v respectively. Transferred 100 ml of each ratio of the above mixture to each 250 ml stoppered

conical flask. Weighed accurately 100±2 mg of Lopinavir and added directly to each 250 ml stoppered conical flask containing solvent mixtures. These flasks kept in magnetic stirrer at room temperature and 50 rpm for 20 minutes. After 20 minutes, samples were withdrawn, filtered each sample (0.22 µm pore size). From the resulting solution took 10 ml (100 µg/mL) and transferred into each 100 ml volumetric flask and made up the volume with respective ratio of the solvent mixtures. These samples were analyzed (Table 3) using UV-VIS spectrophotometer at 260 nm.

Table 3: Absorbance of Lopinavir in Water and PG

Water (% v/v)	Propylene Glycol (% v/v)	Sample Weight (±2mg)	Absorbance
100	0	100	0.002
80	20	100	0.019
60	40	100	0.032
40	60	100	0.047
20	80	100	0.061

By using Water and Polyethylene Glycol 400 (PEG 400)

Prepare the mixture of water and PEG 400 in the ratio of [100:0, 80:20, 60:40, 40:60, 20: 80] %v/v respectively. Transferred 100 ml of each ratio of the above mixture to each 250 ml stoppered conical flask. Weighed accurately 100±2 mg of Lopinavir and added directly to each 250 ml stoppered conical flask containing solvent mixtures. These flasks kept in magnetic stirrer at room temperature and 50 rpm for 20 minutes. After 20 minutes, samples were withdrawn, filtered each sample (0.22 µm pore size). From the resulting solution took 10 ml (100 µg/mL) and transferred into each 100 ml volumetric flask and made up the volume with respective ratio of the solvent mixtures. These samples were analyzed (Table 4) using UV-VIS spectrophotometer at 260 nm.

Table 4: Absorbance of Lopinavir in Water and PEG 400

Water (% v/v)	PEG 400 (% v/v)	Sample Weight (±2mg)	Absorbance
100	0	100	0.002
80	20	100	0.023
60	40	100	0.045
40	60	100	0.063
20	80	100	0.084

RESULT AND DISCUSSION

Concentrations of Lopinavir in the ratio (Table No. 2, 3, 4) of water : glycerin, water : PG, and water : PEG 400 were calculated from absorptivity value and pathlength (1cm) of the Lopinavir in the wavelength of 260 nm [15].

$$Concentration\ of\ Lopinavir\ (c) = \frac{Absorbance}{Absorptivity\ (a) * Pathlength\ (b)} - - - - - - (1)$$

$$Absorptivity\ (a) = \frac{Absorbance}{Concentration} - (2)$$

$$Dilution\ Factor = \frac{x}{100} * \frac{10}{100} - (3)$$

From the table no. 1, the values were substituted in Eq. 2 and made the average of those values and got absorptivity (A1%, 1cm) was 9.86 and it's complied [16] with the limit of International Pharmacopoeia (WHO). Hence, the concentrations of Lopinavir in different cosolvents ratio were calculated by using Eq. 1 and 3 (See Table 5) from the absorptivity value of 9.86. Lopinavir had a low water solubility. Because nonpolar molecules cannot break the water's lattice structure. Lopinavir was found to be more soluble in PEG 400 (Figure 2) than in the other solvents. The drug molecules can be dissolved in the solution by weaker hydrogen bonds in water. As expected, PG and glycerin have lower solubilization powers than the less polar PEG 400. According to these findings nonpolar environments rather than polar ones, appear to be better suited for the solubilization of drug molecules. PEG 400 can be used to incorporate hydrophobic compounds because of its ability to reduce the dipole moment of water.

Table 5: Concentration of solubility in different cosolvents (mg/100 mL)

S. No.	Solvent Ratio Water : Solvents (%v/v)	Solubility (mg/100 mL)		
		Glycerin	Propylene Glycol	PEG 400
1	100 : 0	2.02	2.02	2.02
2	80 : 20	7.09	19.26	23.32
3	60 : 40	15.21	32.45	45.63
4	40 : 60	26.36	47.66	63.89
5	20 : 80	39.55	61.86	85.19

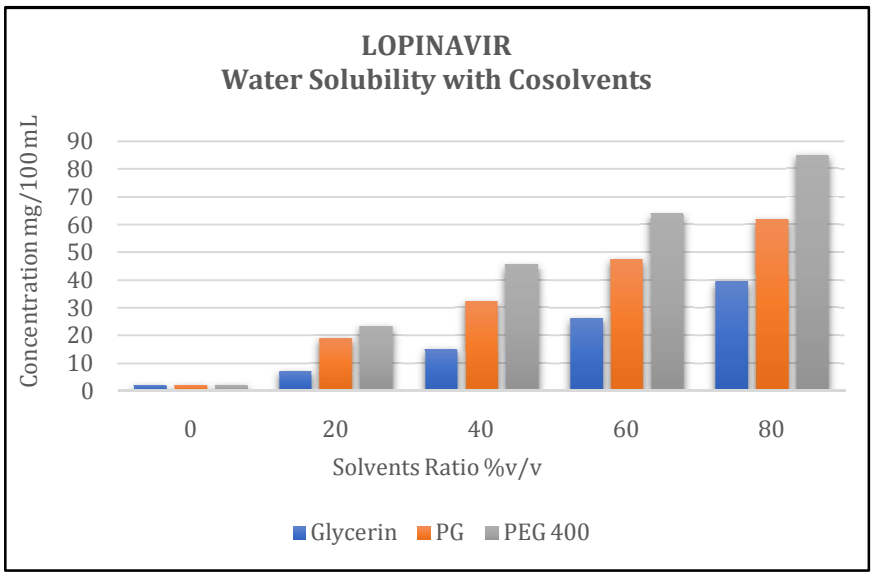

Figure No. 2. Lopinavir water solubility with cosolvents

CONCLUSION

The solubility enhancement study was performed by cosolvency approach such as glycerin, PG, and PEG 400 were used to improve Lopinavir's water solubility. The Lopinavir highly solubilize in PEG 400 with water. As a result, the most effective and acceptable cosolvent for solubility has been identified as PEG 400. As a result of this research, the solubilization of lopinavir in PEG 400, PG, and glycerin and these solvents were pharmaceutically acceptable cosolvents could be investigated. Hence, this study will be helpful in the development of new formulation of liquid dosage forms for Lopinavir.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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