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MIDAZOLAM SOLUBILITY ENHANCEMENT PRE-FORMULATION TECHNIQUES AT NASAL PHYSIOLOGICAL pH

Elahehnaz Parhizkar, Leila Emadi, Shohreh Alipour *

School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Keywords:

Complexation, Cosolvency, Midazolam, Nasal Physiological pH, Polymeric Micellization, Solubilizing Techniques

Correspondence to Author:
Shohreh Alipour

School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

E-mail: alipour_sh@sums.ac.ir

ABSTRACT: Midazolam is used as short-acting pre-anesthetic benzodiazepine with solubility of <0.1mg/mL at neutral-pH, which increases considerably in acidic media. Midazolam commercial acidic aqueous parenteral formulation (pH~3.3) causes pain and inflammation at administration site, which induces low patient-compliance. According to the absence of non-parenteral formulation, available parenteral dosage-form administered orally that showed bitter-taste with low bioavailability. Alternatively, intranasally administration was rapidly absorbed, with improved bioavailability. However, not only causes nasal mucosa irritation due to acidic media, but also needs large solution amount because of midazolam low solubility. On contrary of previous studies, which focused on solubility improvement in acidic pH, the aim of this study is to compare solubility enhancement techniques at nasal physiological pH (6). Different techniques evaluated including buffer solutions (Britton-Robinson, citrate and phosphate), inclusion-complexation (β-CD), polymeric-micellar-solubilization(HPMC) and co-solvency (PEG400 and P.G) separately in mentioned buffers. Ternary-diagram with the best-selected system examined in different ratios. As a result, phosphate buffer in combination with applied techniques indicated solubility enhancement ratio of 17.9, 22.7, 16.8 and 30.9 for β-CD, HPMC, PEG400 and P. G respectively. Best ternary-system was 0.3:0.1:0.6 P.G:PEG400:Phosphate buffer, obtained 28.2-fold solubility enhancement. It may suggested that solubilizing techniques especially co-solvency showed acceptable enhancement at nasal pH.

INTRODUCTION: Midazolam hydrochloride is a short-acting benzodiazepine used as a preoperative sedative drug in many pediatric medical procedures. It is also administered in status epilepticus in children [1, 2]. Midazolam is a weak acid (pKa 6.2) in pH>4 and exists in un-ionized form [3], with hydrophobic properties in neutral and physiological pH [4] therefore, it is commercially formulated in acidic pH (approximately 3) for better solubility, which cause pain and irritation in administration site [2, 5].

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Nasal route is recently recommended for midazolam because of highly vascularized nasal mucosa that helps rapid systemic absorption and direct drug delivery to the cerebrospinal fluid leading faster onset of action. However, acidic pH of the formulation may cause inflammation and irritation in nasal cavity [2, 6].

Aqueous systems are the most suitable choice for liquid pharmaceutical formulations. Hence various improvement techniques are investigated for solubility enhancement of poorly water-soluble drugs include pH adjustment, buffer solutions, complexation, co-solvency, micellarsolubilization, solid dispersion, chemical modification, etc [7, 8].

Various studies examined one or two solubility enhancement techniques separately or in combination in acidic pH (pH<4) for midazolam [9].

The aim of this study was to improve midazolam solubility applying four common enhancing strategies with different mechanisms at nasal physiologic pH (6) which are included:

- Buffer solutions- drug ionic interactions in the microenvironment at the solid–liquid interface [10].
- Hydrophilic polymers such as hydroxy propyl methylcellulose (HPMC) can make polymeric micelles [11-13].
- Inclusions (Cyclodextrins) contain a hydrophilic exterior and a relatively lipophilic interior cavity to form inclusion complexes [14].
- Co-solvents (PEG400 and P.G) are water miscible solvents which can change the water dielectric constant [13].

The effect of four mentioned techniques was evaluated separately and in combination.

2. MATERIALS AND METHODS:

2.1. Materials: Midazolam was purchased from Exir Company (Iran). Citric acid, Trisodium citrate, potassium dihydrogen phosphate, Boric acid, Acetic acid, sodium hydroxide, potassium hydroxid, phosphoric acid, HPMC, PEG400, P.G, were purchased from Merck. Beta Cyclodextrin was purchased from sigma-aldrich.

2.2. Midazolam analysis: For quantification processes of midazolam, UV-Vis spectrophotometry method was used at maximum absorbance wavelength for different solvents and the solubility values were calculated using calibration curves.

2.3. Calibration curve validation: Midazolam different concentrations (75, 37.5, 18.8, 9.4 and 4.7 µg/ml) in different medium (Water, Citrate buffer 0.2M, Britton- Robinson buffer and Phosphate buffer 0.2M at pH 6) were prepared using serial dilution. All concentrations were prepared in three different days. Each concentration was tested triplicate.

Calibration curve was validated by linearity, precision, accuracy, limit of detection (LOD) and limit of quantitation (LOQ). The linearity was calculated by the least square regression method. The precision of assay -the degree of repeatability of an analytical method- was determined by repeatability (intraday), intermediate precision (inter-day) and reported as %RSD for a statistically significant number of replicate measurements. The LOD and LOQ were determined using equations (1) and (2):

$$\text{Eq 1: } LOD = \frac{3.3\,\sigma}{S}$$

$$\text{Eq 2: } LOQ = \frac{10\,\sigma}{S}$$

Where σ is standard deviation of Y-intercept and S is slope of calibration curve [15].

2.4. Saturation solubility studies: Saturation solubility studies were carried out as described by Higuchi & Connors [4]. Briefly, excess amount of midazolam was added to flask containing different solvents and samples were continuously agitated at 100 rpm for 24 h at 25°C. At the end of 24 h, the samples were centrifuged and the supernatant was filtered (0.45 micron) and analyzed for drug content using analysis method.

2.5. Solubility enhancement techniques: Solubilization techniques which have used to improve solubility and further bioavailability of poor water soluble midazolam included buffer solutions, inclusion complexation, polymeric micellization and co-solvency [7, 16].

The solubility enhancement ratios (SER) were calculated according to the following equation [17]:

$$SER = \frac{\text{Solubility in particular solvent}}{\text{Solubility in control solution}}$$

In this study, control solution was water pH 6.

2.5.1. Buffer solution: Midazolam saturation solubility studies were performed in 5 ml distilled water, Britton- Robinson, Citrate and Phosphate buffers at pH 6.

2.5.2. Binary fraction systems:

2.5.2.1. β-CD Complexation effect: Excess amount of midazolam was added to 5 mL Citrate, Britton- Robinson and phosphate buffer in screw-capped vials, containing increasing concentrations of β-CD ranged from 1.5 to 5.5% w/v which is equivalent to 1:1, 1:1.5, 1:2, 1:2.5, 1:3 and 1:4 of midazolam:β-CD moles).

Phase-solubility profile was obtained by plotting the solubility of midazolam against the concentration of β-CD used. The slope of this equation is considered as stability constant (K1:1) of the complex. Each experiment was implemented triplicate [18].

The intrinsic solubility (S_0) of the drug in the aqueous complexation media (i.e. drug solubility when no cyclodextrin is present using equation 3 [19]:

$$K1{:}1 = \frac{\text{slope}}{S_0(1-\text{slope})}$$

2.5.2.2. Polymeric micellization effect: Excess amount of midazolam was added to 5 mL citrate, Britton- Robinson and phosphate buffer in screw-capped vials, containing 1.5, 2 and 3% w/v HPMC. Phase-solubility profile was obtained by plotting the solubility of midazolam against the concentration of HPMC used. Each experiment was carried out triplicate.

2.5.2.3. Co-solvents effect

The effect of two co-solvents (PEG 400:Phosphate buffer and P.G:Phosphate buffer) were evaluated in volumetrically mixed binary system containing 0.1, 0.2, 0.3, and 0.4 mole fractions of co-solvents (**Table 1**).

TABLE 1: DIFFERENT MIXTURE SOLUTIONS FRACTIONS IN TERNARY DIAGRAM

Mixture	P.G	PEG400	Phosphate buffer
M1	-	0.1	0.9
M2	-	0.2	0.8
M3	-	0.3	0.7
M4	-	0.4	0.6
M5	0.1	-	0.9
M6	0.2	-	0.8
M7	0.3	-	0.7
M8	0.4	-	0.6
M9	0.05	0.05	0.9
M10	0.1	0.1	0.8
M11	0.15	0.15	0.7
M12	0.1	0.2	0.7
M13	0.2	0.1	0.7
M14	0.2	0.2	0.6
M15	0.1	0.3	0.6
M16	0.3	0.1	0.6

The logarithmic relationship between total drug solubility in a mixed-solvent system and the volume fraction of the stronger solvent can be described by Equation 4:

$$\text{Eq. 4:} \quad \text{Log } S_{mix} = \text{Log } S + \varphi V_{ss}$$

Where S_{mix} and S are the solubility of drug in solvent mixture and pure solvent, $V_{ss}$is the volume fraction of the stronger solvent and Φ is the solubilization power of the stronger solvent.

2.5.3. Ternary phase system: The phase diagram of ternary co-solvent was used as a map to indicate the solubility of drug in the ternary co-solvent systems.

As mentioned in **Table 1**, ternary diagram for midazolam solubility with mixture of different concentrations of P.G, PEG400 and P.G:PEG 400 (that concluded better results in previous sections) were studied in phosphate buffer.

2.6. Statistics analysis: All data were analyzed by one-way ANOVA test followed by Tukey's honestly significant difference test using SPSS version 16.0 software. $p<0.01$ has been considered as significant statistically.

3. RESULTS:

3.1. Calibration Curve validation: Calibration curve data were constructed in the range of the expected concentrations of 4.7µg/mL to 75µg/mL in water, citrate, Britton- Robinson and phosphate buffer solutions pH 6. The regression equation and the correlation coefficient (r^2) of the standard curve were reported in **Table 2**. Furthermore, validation results of calibration curves results containing precision, accuracy, LOD and LOQ are illustrated in **Table 3**.

TABLE 2: REGRESSION EQUATION AND THE CORRELATION COEFFICIENT (R^2) FOR DIFFERENT CALIBRATION CURVES

Solvent	Equation	r^2
Water	y = 0.013x + 0.0178	0.9990
Britton- Robinson Buffer	y = 0.0138x + 0.0022	0.9996
Citrate Buffer	y = 0.0154x + 0.0196	0.9997
Phosphate Buffer	y = 0.0116x + 0.0006	0.9992

TABLE 3: VALIDATION RESULTS (PRECISION, ACCURACY, LOD AND LOQ)

Solvent	Precision Intraday%	Precision Interday%	Accuracy%	LOD (µg/ml)	LOQ (µg/ml)
Water	99.3±0.4	98.39±0.5	94.14±6.2	1.32	3.99
Citrate Buffer	98.9 ± 0.9	99.0±0.6	98.0±2.8	0.94	2.83
Britton- Robinson Buffer	98.7±1.0	94.3±2.7	96±5.7	1.10	3.33
Phosphate Buffer	98.0±3	96.9±3.5	96.3±5.3	1.21	3.66

3.2. Saturation solubility studies:

3.2.1. Buffer solutions: Saturation solubility studies for midazolam in different solvents were determined. As reported in **Table 4,** results indicated midazolam solubility and midazolam solubility enhancement ratio comparing to water.

TABLE 4: MIDAZOLAM SOLUBILITY (mg/ml) IN DIFFERENT SOLVENTS (pH 6)

Solvent	Solubility ±SD (mg/ml)	SER
Water	0.17±0.01	-
Citrate Buffer	0.32±0.09	1.9
Britton- Robinson Buffer	0.35±0.02	2.1
Phosphate Buffer	0.69±0.01	4.1

3.2.2. Binary systems:

3.2.2.1. β-CD complexation: The phase-solubility profile of midazolam with β-CD at pH 6is presented in **Fig. 1.** As it was predictable, β-CD enhancement effect on midazolam solubility is completely distinctive. SER for β-CD in citrate, Britton- Robinson and phosphate buffer was 6, 11.9 and 17.9 respectively. According to phase-solubility diagram K1:1 was calculated 337, 95 and 260 M^{-1} for Britton- Robinson, citrate and phosphate buffer, subsequently.

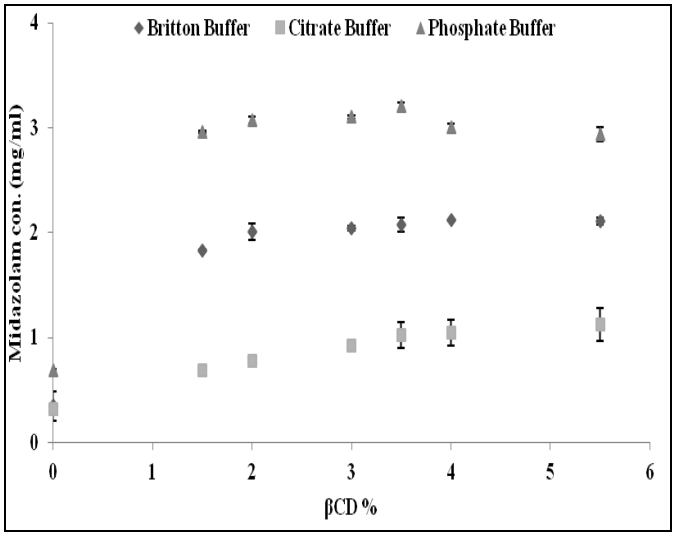

FIG. 1: PHASE-SOLUBILITY PROFILES OF MIDAZOLAM WITH DIFFERENT β-CD% IN DIFFERENT SOLVENTS

In comparison with buffers alones, β-CD could increase midazolam solubility in citrate, Britton-Robinson and phosphate buffer 2.9, 5.8 and 4.4 fold respectively.

3.2.2.2. HPMC effect: The phase-solubility profile of midazolam with HPMC at pH 6is illustrated in **Fig. 2**. As it is obvious, HPMC caused enhancement in midazolam solubility. SER for HPMC in Britton- Robinson, citrate and phosphate buffer was 6.1, 18.2 and 22.7 respectively. The average of solubilizing enhancement power ratios for HPMC in comparison with Britton- Robinson, citrate and phosphate buffer were 3.0, 9.7 and 5.6 respectively.

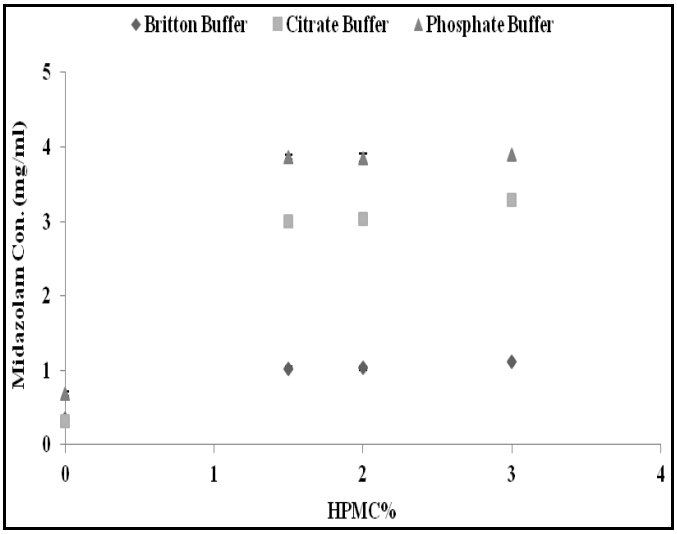

FIG. 2: PHASE-SOLUBILITY PROFILE OF MIDAZOLAM WITH DIFFERENT % OF HPMC IN DIFFERENT BUFFERS

3.2.2.3. Co-solvents effect

PEG 400 and P.G were mixed with phosphate buffer in different amounts. As it is shown in **Fig. 3**, the solubilizing enhancement was significant in presence of 0.3 and 0.4 mole fractions of P.G and PEG400. In 0.1 and 0.2 mole fraction the solubility was less comparing phosphate buffer alone. Solubility and solubilization power are reported in **Table 5**.

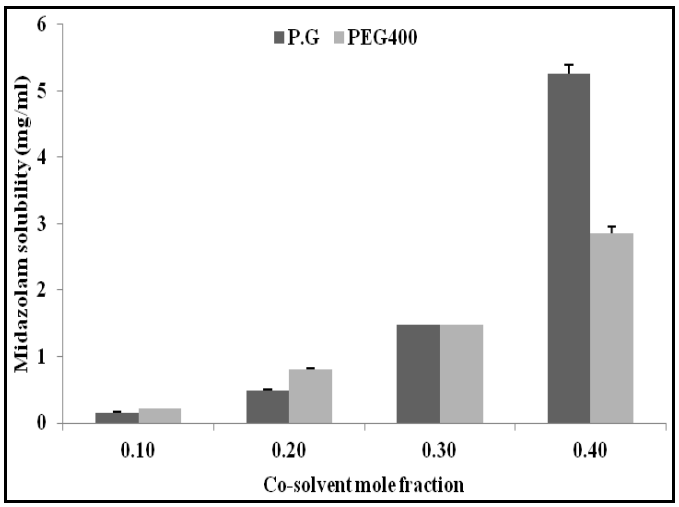

FIG. 3: MIDAZOLAM SOLUBILITY IN PRESENCE OF DIFFERENT CONCENTRATIONS OF P.G AND PEG400.

Fig. 4, displays the logarithmic relationship between total midazolam solubility in a binary co-solvent and the volume fraction of each co-solvent system. For all P.G and PEG400 based co-solvent systems, a good correlation (r^2= 0.9991 and r^2= 0.9608) between fand log S_{mix} were obtained.

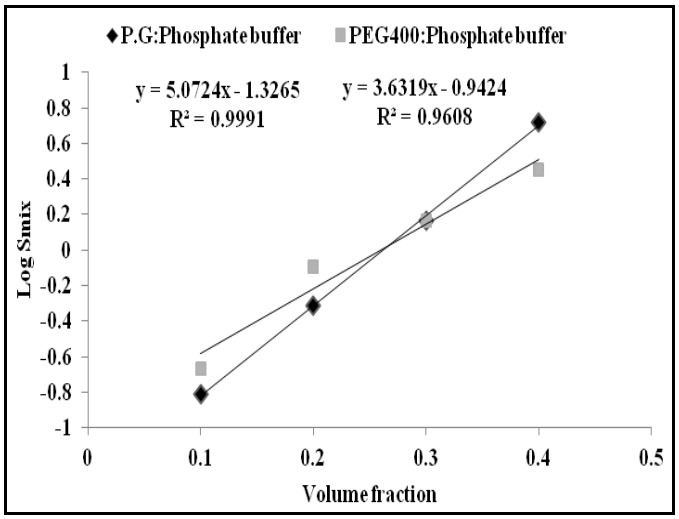

FIG. 4: COMPARATIVE SOLUBILITY PROFILE OF MIDAZOLAM IN BINARY SOLVENT SYSTEMS OF PEG 400 AND P.G IN PHOSPHATE BUFFER pH 6.

TABLE 5: CO-SOLVENT EFFECT ON SOLUBILITY OF MIDAZOLAM

	Midazolam Solubility (mg/ml)	SER	Solubilization power (φ)
M1	0.21± 0.01	1.3	-5.0
M2	0.81±0.01	4.8	0.4
M3	1.47±0.005	8.7	1.0
M4	2.85± 0.1	16.8	1.5
M5	0.17±0.014	1.0	-6.5
M6	0.49±0.012	2.9	-0.8
M7	1.47±0.007	8.7	1.0
M8	5.26±0.14	30.9	2.2
M9	0.25±0.014	1.5	-6.5
M10	0.42±0.012	2.5	-1.1
M11	1.20±0.006	7.0	1.8
M12	3±0.14	18.0	1.1
M13	2.3±.13	13.7	1.0
M14	3±0.07	17.4	1.6
M15	1.8±0.13	10.6	2.2
M16	4.8±0.21	28.2	2.1

3.2.3. Ternary phase system: Ternary phase diagram is presented in **Fig. 5,** midazolam solubility in phosphate buffer:P.G:PEG400 solvent system showed effective enhancement ratio in to different range of 1-4.1 and 4.2-31 compared with midazolam solubility in pure water at pH=6.

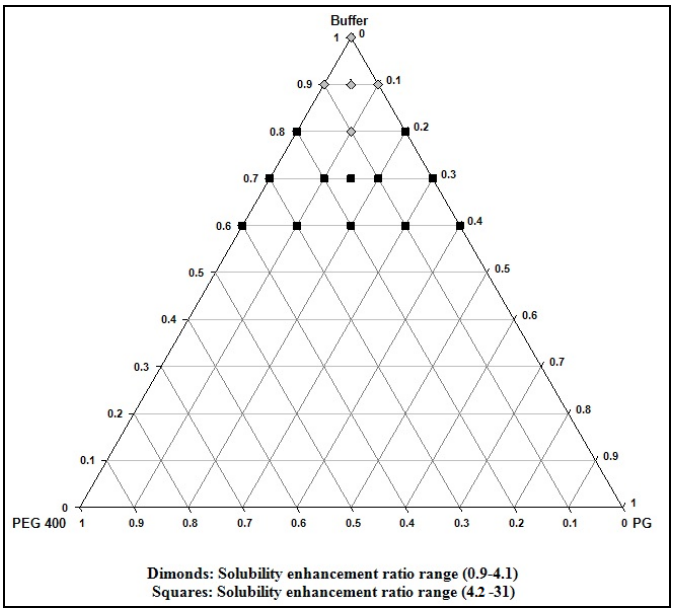

FIG. 5: TERNARY DIAGRAM FOR PHOSPHATE BUFFER: P.G: PEG400

4. Discussion: Midazolam is 2, 3-dihydro-1*H*-1, 4-benzodiazepine which exhibits anticonvulsant, anxiolytic, muscle relaxant and sedative properties [4, 20]. It's important usage is in the treatment of status epilepticus. Midazolam is usually administered intravenously which leads to minimal patient compliance [2, 21]. Since midazolam has short half-life and delay of action, it is commonly employed in children pre-anesthesia [4]. It is generally used sublingually and orally by dose of 0.2 mg/kg and 0.4 mg/kg, respectively. However, in oral administration midazolam undergoes extensive first pass metabolism in the liver (bioavailability of 15-27% in children) [21] -and also its strong bitterness may be repulsive for children [4].

Rectal administration of midazolam is currently the only out-of-hospital treatment that has been evaluated for efficacy in seizures in dogs [22].

Midazolam is a hydrophobic drug at neutral and physiological pH having a weak solubility in water and may increase to 10.3mg/ml in pH 3.3, at 25°C [3, 4]. The aqueous solubility of midazolam is a function of both the ionization of the drug molecule and the ring-opening of the diazepine ring. The ring-opening of the benzodiazepine ring is pH-dependent and fully reversible [9, 23]. Midazolam low aqueous solubility is a problem in formulations design. For pharmaceutical applications, acid buffer such as citric acid/sodium citrate can be added to improve midazolam solubility in aqueous oral solution [4].

In this study, at first different waters and buffers were evaluated for their solubility enhancement effects. Due to ionic interactions between the drug and the buffer species in the microenvironment at the solid–liquid interface; and also self-buffering capacity of the dissolved drug in the microenvironment [10] the dissolution rate of a sparingly soluble drug is affected by buffered aqueous medium . As it is reported in results section, the solubility enhancement order was citrate buffer ≈ Britton- Robinson buffer < phosphate buffer. It seems that phosphate buffer was the most effective buffer for midazolam solubility improvement which is consistent with previous studies [24].

β-CDs consist of seven (α-1,4)-linked α-D-glucopyranose units. Cone-shaped CD molecules with hydrophilic outer surface and hydrophobic central cavity can take up a whole drug molecule, or more frequently some hydrophobic part of it, into the hydrophobic cavity and are capable of forming inclusion complexes with many drugs. So, the complexation will affect many of the physicochemical properties of the drugs such as solubility [25]. It has been reported that cyclodextrins can also solubilize drugs via non-inclusion mechanisms, such as self-association and the formation of micelle-like structures in addition to inclusion complexation[26-28]. However, it has been reported that cyclodextrin complexation in the best conditions, will result in over four-fold increase in the formulation bulk of solid dosage forms [19].

Fig. 1 shows that the presence of 1.5% of β-CD (1:1 midazolam: β-CD) led to appropriate enhancement effect in solubility. The higher concentrations of β-CD did not significantly affect the solubility of midazolam which can be related to limited solubility of β-CD [29]. The most common type of cyclodextrin complexes is the 1:1 drug:cyclodextrincomplex (D:CD) where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD). Since the value of K1:1 is most often between 50 and 2000 M^{-1}[19] it seems that K1:1 values for different buffers was in the acceptable range and the formed Midazolam-β-CD complex is stable.

Hyroxypropylmethyl cellulose (HPMC) is a nonionic cellulose derivative with hydrogen bonding potential and stabilizing ability to prevent crystallization of amorphous material [30]. Previous studies showed increased drug solubility in phosphate buffer solution (pH 6.8) in presence of 1% water soluble polymers such as HPMC. Furthermore, it was reported HPMC inhibitory effect on the precipitation of drug from supersaturated solutions [31]. Our results indicated that midazolam solubility enhancement ratio was 6.1, 18.2 and 22.7 for Britton- Robinson, citrate and phosphate buffer in presence of HPMC. There was no significant different ($p>0.05$) in solubility of midazolam with increasing HPMC concentration.

Co-solvency -use of co-solvent- is one of the most popular and highly effective techniques for solubility improvement of poorly soluble drugs in pharmaceutical liquid formulations. Co-solvents are miscible solvents mixtures, which can vividly increase the solubility of poorly aqueous soluble drugs when added to water. Co-solvents reduce the ability of nonpolar solutes squeezing in aqueous system by small nonpolar hydrocarbon region. They can reduce the interfacial tension between the aqueous solutions and disrupt waters self-association and reduce hydrophobic solute squeeze out. The most frequently used low toxic and due to their cilio-friendlyco-solvents for nasal use are propylene glycol, glycerin, polyethylene glycol (PEG), etc [16, 32, 33].

As it is seen in Table 5, M1, M5, M6, M9 and M10 which containing 0.1 PEG400, 0.1 and 0.2 P.G and

0.05:0.05, 0.1:0.1 P.G:PEG400 respectively, showed lower midazolam solubility even less than solubility in phosphate buffer solution alone.

Ternary diagram for phosphate buffer: P.G: PEG400 is presented in **Fig. 5** indicated two different ranges for solubility enhancement ratio for midazolam. Solubility enhancement ratio range 1-4.1 refers to solvent system which showed suitable increase in midazolam solubility compared with water while point to lower solubility comparing phosphate buffer solution. The other range was related to solvent systems with solubility enhancement ratio of 4.2-31. As mentioned before solubility enhancement ratio was compared with midazolam water solubility. This different range can be explained by P.G and PEG400 dielectric constant which is 32 and 12.4, respectively [16]. The dielectric constant of phosphate buffer solution with the same ionic strength has been assumed78.5 in previous reports [34]. Therefore, the lower P.G and PEG400 in solvent mixture cause the lower total difference dielectric constant comparing phosphate buffer solution alone.

As it is showed in **Table 5** and **Fig. 5**, increasing P.G and PEG400% caused concurrent reducing in dielectric constant value in system, which leads to midazolam solubility improvement. The supplementary explanation for this phenomenon is related to increasing the enthalpy and entropy of the system due to low water hydrophobic effect in presence of <20% P.G as co-solvent. The co-solvent like "icebergs", disorder the water-water hydrogen bonds around the nonpolar groups of the drug, while increasing co-solvent concentration higher than 30% leads to better drug solvation and solubility [35]. The solubilization power (Φ) in co-solvent systems is a quantitative estimation for the stronger solvent to improve the drug solubility. The solubilization power is correlated to co-solvent polarity; it means that the greater the power of solubilization in a given mixed solvent system, the greater the difference in polarity or octanol-water partition coefficient of the two solvents [32].

CONCLUSION: As a Conclusion, solubilization techniques for midazolam solubility showed a successful process separately or in combination. All selected buffer solutions, inclusion complexation (β-CDs), polymeric micellization (HPMC) and co-solvents (P.G and PEG400) showed acceptable solubility enhancement ratio for midazolam. The most effective choice for each technique in this study contains phosphate buffer, 1.5% w/v β-CD, 1.5% w/v HPMC in phosphate buffer, 0.4:0.6 P.G: phosphate buffer in binary system and 0.3:0.1:0.6 P.G:PEG400:phosphate in ternary system.

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CONFLICT OF INTERESTS: The Authors declare that there is no conflict of interest.

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