

# Effect of precipitation inhibitors on supersaturation and solubility of furosemide

Tuğba GÜLSÜN<sup>1</sup> , Naile ÖZTÜRK<sup>1,2</sup> , Aslı KARA<sup>1,3</sup> , Selma ŞAHİN<sup>1</sup> , İmran VURAL<sup>1</sup> 

<sup>1</sup> Department of Pharmaceutical Technology, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey.

<sup>2</sup> Department of Pharmaceutical Technology, Faculty of Pharmacy, İnönü University, Malatya, Turkey.

<sup>3</sup> Department of Medical Services and Techniques, Sungurlu Vocational High School, Hitit University, Çorum, Turkey.

\* Corresponding Author. E-mail: sahin.selma@gmail.com (S.S.); Tel. +90-312-305 12 41.

Received: 17 December 2020 / Revised: 04 March 2021 / 09 March 2021

**ABSTRACT:** Furosemide is a widely used diuretic drug for the treatment of edema associated with heart, liver cirrhosis, renal diseases and hypertension. It is a Class IV drug with low aqueous solubility and low permeability according to Biopharmaceutics Classification System (BCS). Furosemide was chosen as a model drug to examine the effect of polymeric precipitation inhibitors (PPIs) on the supersaturation and solubility. Solubility and concentration change of furosemide as a function of time at pH 1.2 and 6.8 were determined to show the effects of PPIs on furosemide solubility. The 24 h equilibrium solubility of furosemide was  $0.017 \pm 0.004$  and  $3.62 \pm 0.201$  mg/mL at pH 1.2 and pH 6.8 buffer solutions, respectively. PPI type and concentration (0.05%, 0.25%) did not increase furosemide solubility at pH 1.2. However, both hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrolidoneK17 (PVPK17) at two concentrations increased furosemide solubility at pH 1.2 and 6.8. In addition, viscosity of solutions was in the range of 2.2-3.7 centipoise, and it was not influenced by PPIs concentrations. Our results showed that designing supersaturated formulations using PPIs can be useful and promising to enhance solubility of furosemide.

**KEYWORDS:** Furosemide; precipitation inhibitors; solubility; supersaturation.

## 1. INTRODUCTION

One of the major challenges that pharmaceutical companies encounter during the drug development process is to develop a commercial product with a sufficient pharmacokinetic profile from poorly water-soluble drugs. This process is both time consuming and costly. In addition, most of the newly developed drug candidates have also poor permeability characteristics. Solubility is an important physicochemical property as it affects the absorption, bioavailability and onset of action of a low solubility compound [1]. Therefore, it is necessary to increase the solubility of compounds to overcome bioavailability problems. Various approaches are used to increase the solubility of compounds, including the use of different polymorphic/amorphous drug forms, reduction of particle size, addition of surfactants or cosolvents to the formulation, complexation, pH adjustment, solid dispersion, new formulation techniques, precipitation inhibitors to create supersaturable formulations [2].

Strategies to increase absorption of the poorly water-soluble drugs focus mainly on increasing equilibrium solubility and improving the rate of dissolution in the gastrointestinal fluids. In addition, maintaining the poorly water-soluble drugs in a transient supersaturated state in intestinal fluids, long enough to achieve sufficient absorption, emerges as another feasible approach [3,4]. Supersaturated state of solute is defined as the state where the solute concentration in solution is higher than the equilibrium solubility. If this situation is maintained even temporarily, absorption may increase. However, as drugs are not thermodynamically stable at high concentrations, they tend to precipitate in the body, resulting in low and variable bioavailability. To overcome this problem, precipitation inhibitors are commonly used to keep drugs in a supersaturated state [4]. Polymers such as cellulose derivatives, polyvinylpyrrolidones,

**How to cite this article:** Gülsün T, Öztürk N, Kara A, Şahin S, Vural İ. Effect of precipitation inhibitors on supersaturation and solubility of furosemide. J Res Pharm. 2021; 25(2): 209-217.

cyclodextrins and methacrylates are the most commonly utilized precipitation inhibitors in oral formulations [5]. When the supersaturated formulations prepared with precipitation inhibitors reach the gastrointestinal fluids, drug concentration exceeds its equilibrium solubility. As the drug precipitation is delayed by the precipitation inhibitors, high drug concentration provides improved absorption and potential increase in the bioavailability of poorly water-soluble drugs [6]. In this study, supersaturated formulations were prepared using precipitation inhibitors to improve solubility of furosemide.

Drugs are categorized into four classes as Class I (high permeability and high solubility), Class II (high permeability and low solubility), Class III (low permeability and high solubility), Class IV (low permeability and low solubility) according to BCS [7]. Ten years after BCS, Wu and Benet developed Biopharmaceutics Drug Disposition Classification System (BDDCS) by replacing permeability with metabolism. BDDCS classifies drug substances in four classes based on aqueous solubility and metabolism (Class I: high solubility and extensive metabolism; Class II: low solubility and extensive metabolism; Class III high solubility and poor metabolism; Class IV: low solubility and poor metabolism) and provides information in regard to drug-drug interactions, and role of transporters in drug absorption and elimination [8].

The model drug furosemide (5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid) is a diuretic drug used for the treatment of edema associated with heart, liver cirrhosis, renal diseases and hypertension for many years [9]. As shown in Figure 1, furosemide is commercially available as tablets (20, 40 and 80 mg single dose), solutions (10 mg/mL, 40 mg/5 mL) and injections (10 mg/mL). According to BCS and BDDCS, it is classified as a Class IV drug with low aqueous solubility, low permeability and poor metabolism [10–12]. Its bioavailability is low and highly variable (37-70%). Absorptive and efflux transporters effects could be important for furosemide. Therefore, increasing solubility of furosemide is quite critical for furosemide formulations to enhance its absorption and bioavailability.

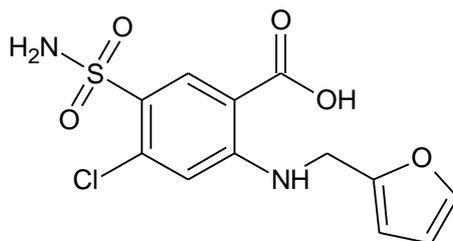


Figure 1. Chemical structure of furosemide.

The aim of this study was to investigate the effect of polymeric precipitation inhibitors (PPIs) such as PolyvinylpyrrolidoneK17 (PVPK17) and hydroxypropylmethylcellulose (HPMC) at various concentrations on the supersaturation and solubility of furosemide. For this purpose; solubility, concentration change and viscosity of furosemide as a function of time at pH 1.2 and 6.8 were determined in this study.

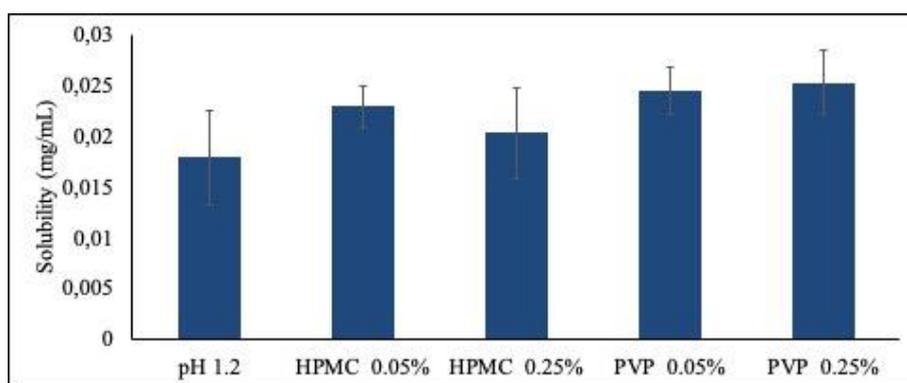
## 2. RESULTS AND DISCUSSION

### 2.1. Effects of PPIs on furosemide solubility

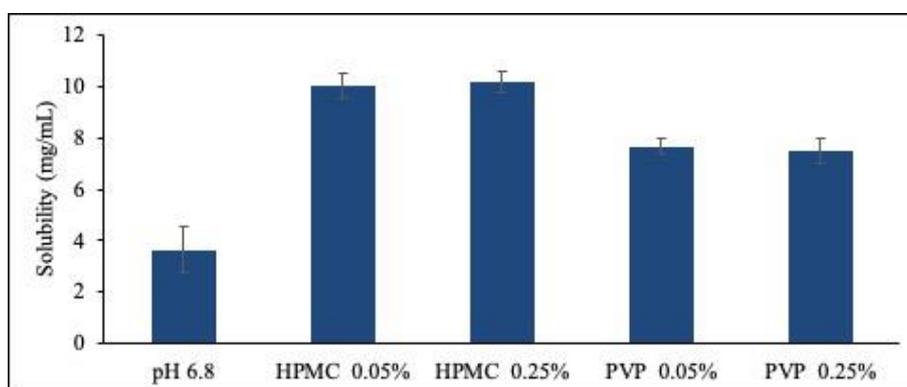
Poorly water-soluble drugs can be formulated as solid dispersions, lipid-based systems or nanoparticles to enhance their bioavailability [13–15]. These drug-delivery systems are called high energy drug delivery technologies, and solid-state or solution-state supersaturation are produced with these technologies. Solution-state supersaturation is especially important to obtain higher bioavailability [16, 17]. PPIs such as HPMC and PVP have supersaturation maintenance effect but, this effect varies for different drugs so, it is imperative to understand their effect on drugs with a case by case approach. Maintenance of solution supersaturation by PPIs are explained by different hypotheses [13]. In the first hypothesis, PPIs can enhance viscosity and thus, diffusivity of drugs is reduced and drug nucleation and crystal growth are inhibited. According to the second hypothesis, PPIs prevent crystal growth by acting at crystal-solution interface to inhibit attachment of molecules from solution to crystal body. And lastly, PPIs enhance equilibrium solubility by forming complexes with drugs so the system is not supersaturated, and thus, crystal growth and drug precipitation are inhibited. Considering all these hypotheses, the effect of PPIs on

the equilibrium solubility of drugs should be investigated to better understand the role of PPIs in maintaining supersaturation.

Furosemide is practically insoluble in water, and its aqueous solubility at room temperature is 0.01825 mg/mL [18, 19]. Furosemide is a weak acid and its solubility increases as the pH of the solution increases [20, 21]. The solubility of furosemide in buffers and PPI containing buffers are given in Figures 2 and 3. The 24 h equilibrium solubility of raw furosemide was  $0.017 \pm 0.004$  and  $3.62 \pm 0.201$  mg/mL at pH 1.2 and pH 6.8 buffer solutions, respectively. As expected, furosemide solubility was higher in the alkaline pH 6.8 buffer solution. In the literature, 48h equilibrium solubility of furosemide was reported as 0.024 and 3.94 mg/mL at pH 1.2 and pH 6.5 buffer solutions, respectively, using shake-flask method [20]. Although our experimental conditions (room temperature, 24 h) are different from the literature (37°C, 48 h), our solubility results agree well with the reported values [20], indicating that pH is the determining factor for furosemide solubility. Furosemide equilibrium solubility increased in the presence of PPIs at pH 6.8 at least 2-fold but at pH 1.2 buffer there was not such an increase. At pH 1.2 neither PPI type nor PPI concentration caused a significant increase in furosemide solubility, furosemide solubility increased from  $0.017 \pm 0.004$  mg/mL to  $0.025 \pm 0.003$  mg/mL,  $0.024 \pm 0.002$  mg/mL,  $0.020 \pm 0.004$  mg/mL and  $0.022 \pm 0.002$  mg/mL in 0.25% PVPK17, 0.05 % PVPK17, 0.25% HPMC, 0.05 % HPMC (pH 1.2 buffer) solution, respectively ( $p > 0.05$  for all comparison). Effect PPI on the solubility was more pronounced for pH 6.8 solutions. However, at pH 6.8, both HPMC and PVPK17 increased furosemide solubility from  $3.624 \pm 0.201$  mg/mL to  $10.164 \pm 0.218$  and  $7.658 \pm 0.105$  mg/mL for HPMC (0.05%, w/v) and PVPK17 (0.25%, w/v) solutions, respectively ( $p < 0.05$ ). Nevertheless, different PPI concentrations did not alter the solubility of furosemide significantly ( $p > 0.05$ ). As shown in Figure 3, in both concentrations (0.05% and 0.25%) at pH 6.8 for HPMC and PVPK17 did not affect the solubility of furosemide. However, HPMC increased the solubility of furosemide more in both concentrations when compared to PVPK17.



**Figure 2.** Solubility of furosemide in the absence and presence of PPIs at pH 1.2 (mean  $\pm$  standard deviation (SD), n=3).



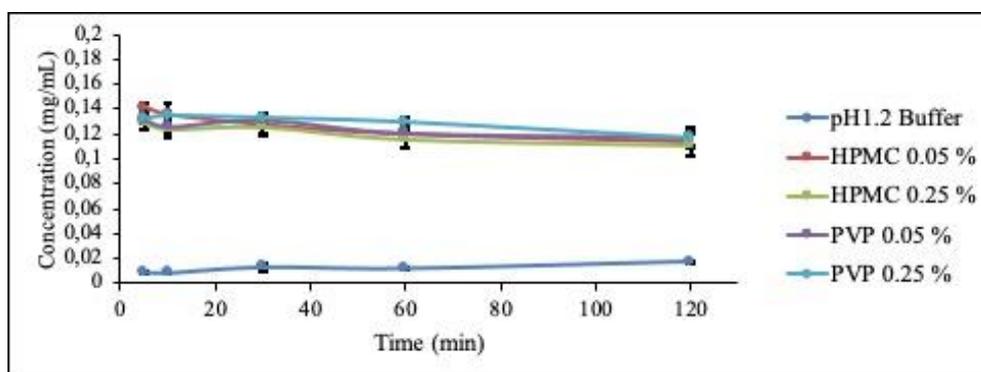
**Figure 3.** Solubility of furosemide in the absence and presence of PPIs at pH 6.8 (mean  $\pm$  standard deviation (SD), n=3).

Scham et. al investigated crystal growth rate of felodipine in the presence of hydroxypropyl methylcellulose acetate succinate (HPMCAS) at pH 3.0 and pH 6.8 [22]. HPMCAS was reported to be more effective at pH 6.8 due to its conformational state at this pH. Based on the results it was concluded that due to ionization of HPMCAS at pH 6.8, polymer chains were relaxed and crystal surface of drug was covered extensively by HPMCAS. However, due to globule formation by polymer chains at pH 3.0, surface of drug crystal was accessible to other solutes in the solution. Thus, polymer chains could not prevent crystal nucleation and growth at pH 3.0 as effectively as at pH 6.8 [18]. Due to ionization and relaxation of PVPK17 and HPMC, polymer chains at pH 6.8 cause a better crystal surface coverage, and as a result, solubility of furosemide increases.

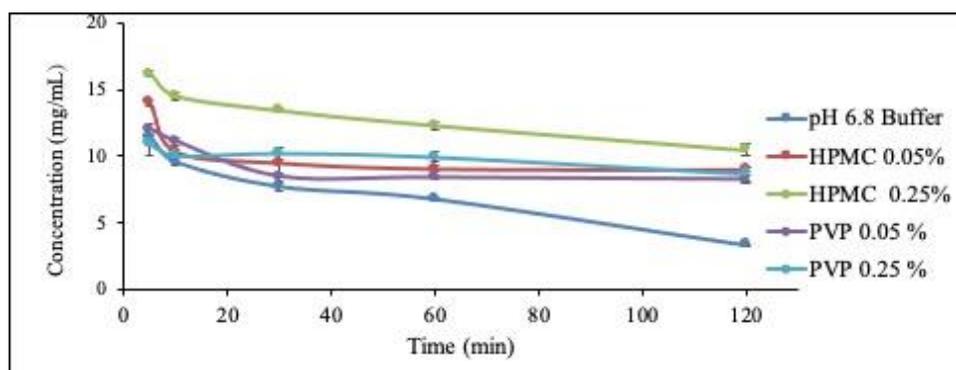
## 2.2. Effects of PPIs on furosemide supersaturation

Furosemide is generally used as a model drug to develop novel formulation methods and for optimization studies due to its low and variable bioavailability [23]. Furosemide has a poor solubility which undergoes site-specific absorption in the stomach and the upper small intestine [24, 25]. Especially when the poor water-soluble drugs like furosemide contact with the gastrointestinal tract or dissolution media, they can trigger the drug to precipitate. To overcome these limitations and to enhance the bioavailability of these types of drugs, various polymeric precipitation inhibitors used to develop to protect the supersaturated state of the drug [26, 27].

In a previous study, it is indicated that the type and amount of PPIs effect the supersaturation state of drugs, and higher amounts of PPIs cause higher supersaturation degree [28]. Based on this observation, to improve the solubility of furosemide, in our study, we investigated the effect PVPK17 and HPMC at two different concentrations (0.05 and 0.25%) to maintain supersaturated state of furosemide. As shown in Figures 4 and 5, furosemide supersaturation was determined at pH 1.2 and pH 6.8 in the absence and presence of PPIs for 120 min. For pH 1.2, the supersaturation concentration of furosemide in all formulations was almost 6 times higher (~0.11 mg/mL) than that of the equilibrium solubility ( $0.017 \pm 0.0008$  mg/mL), indicating the importance of polymeric inhibitors to enhance the supersaturated drug concentration ( $p < 0.05$  for all type and concentration of PPIs). In the presence of PPIs, the supersaturated concentration of furosemide increased significantly from pH 1.2 to pH 6.8 ( $p < 0.05$ ). This result is expected because furosemide is a weak acid and its solubility is higher at basic pHs. However, as seen in Figure 5, the increase in the supersaturated furosemide concentration at pH 6.8 was not pronounced when compared to equilibrium solubility. When HPMC concentration increased from 0.05% to 0.25%, supersaturated furosemide concentration increased from 8.97 mg/mL to 10.50 mg/mL, respectively. These results correlate well with the literature [29]. However, in the presence of PVPK17, furosemide concentration increased approximately 2.5 times when compared with equilibrium solubility, as shown in Figure 5. This result could be due to the higher affinity of the PVPK17 to hydrophilic compounds. As noted in a previous study, the dissolution rate of furosemide was lower in the presence of PVPK30 than other PPIs. Based on the results, the authors reported that only a 1.5-fold increase in dissolution rate may be due to the increased wettability and dispersibility of the hydrophobic drug by the more hydrophilic carrier [30].



**Figure 4.** Furosemide concentration change as a function of time at pH 1.2 buffer and PPI solutions prepared in the corresponding buffer (mean  $\pm$  standard deviation (SD),  $n=3$ ).



**Figure 5.** Furosemide concentration change as a function of time at pH 6.8 buffer and PPI solutions prepared in the corresponding buffer (mean  $\pm$  standard deviation (SD), n=3).

### 2.3. UV spectrophotometric method

Validation parameters were summarized in Tables 1 and 2. A determination coefficient ( $R^2$ ) value of 0.998 was taken as an indication linearity of the analytical method (Table 1). Intra- and inter-day relative standard deviation (RSD) values were lower than 2% and also intra- and inter-day recovery data were satisfactory, demonstrating the precision and accuracy of the method.

**Table 1.** Linearity data of method (n=6).

Regression equation	$y = 0.0533x - 0.0005$
Standard error of slope	0.0002
Standard error of intercept	0.0003
Determination coefficient ( $R^2$ )	0.998
Linearity range ( $\mu\text{g/mL}$ )	0.5-10
Number of data points	6
Limit of detection ( $\mu\text{g/mL}$ )	0.04
Limit of quantification ( $\mu\text{g/mL}$ )	0.12

**Table 2.** Accuracy and precision data (n = 3).

Theoretical drug amount ( $\mu\text{g/mL}$ )	Intra-day			Inter-day		
	Found <sup>a</sup> ( $\mu\text{g/mL}$ )	Accuracy <sup>a</sup> Recovery (%)	Precision <sup>b</sup> (RSD%)	Found <sup>a</sup> ( $\mu\text{g/mL}$ )	Accuracy <sup>a</sup> Recovery (%)	Precision <sup>b</sup> (RSD%)
2	1.92 $\pm$ 0.02	96.15 $\pm$ 0.94	0.98	2.05 $\pm$ 0.03	102.41 $\pm$ 1.43	1.40
4	3.97 $\pm$ 0.06	99.20 $\pm$ 1.62	1.64	3.97 $\pm$ 0.03	99.20 $\pm$ 0.81	0.82
8	7.90 $\pm$ 0.10	98.77 $\pm$ 1.29	1.31	7.85 $\pm$ 0.12	98.07 $\pm$ 1.51	1.54

<sup>a</sup>Mean  $\pm$  SD

<sup>b</sup>Relative standard deviation

### 2.4. Effects of PPIs on viscosity

PPIs can increase the viscosity of aqueous solutions and high viscosity lowers the diffusion of drug in the solution. Thus, viscosity increase can contribute to delaying of precipitation of supersaturated drug in solution. Viscosity values of PPI solutions at pH 6.8 and 1.2 buffers were given in Figure 6. Viscosity of solutions was in the range of 2.2-3.7 centipoise, and was not influenced by the PPIs concentrations ( $p > 0.05$ ). In supersaturation experiments (shown in Figure 4 and Figure 5), there was not a pronounced difference between PPI solutions regarding furosemide concentration at pH 1.2 buffer. However, regardless of the concentration, HPMC was slightly superior to PVPK17 in terms of maintaining higher furosemide amount in the solution at pH 6.8. This could be attributed to the higher viscosity of HPMC than PVPK17 at pH 6.8, and therefore, retain slightly higher amounts of furosemide in HPMC solutions.

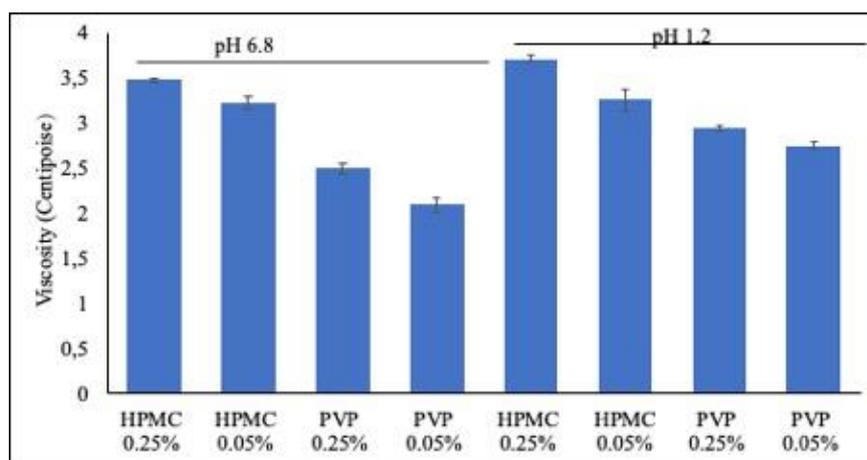


Figure 6. Viscosity of PPI solutions at pH 6.8 buffer and pH 1.2 buffer (mean  $\pm$  SD, n=3).

Ishikawa et al., evaluated the effect of HPMC on release profiles of a poorly water-soluble drug from tablets. The results showed that the increase in HPMC concentration in tablet increased the viscosity and delayed the dissolution of the drug with low water solubility from tablet [31], and supported our results with HPMC.

### 3. CONCLUSION

For development of a bioavailable product, solubility of furosemide (BCS Class IV drug) needs to be improved. This study was designed to solve solubility problem of furosemide using precipitation inhibitors such as PVPK17 and HPMC. Our results showed that furosemide PPIs can be used to enhance furosemide solubility and to maintain supersaturated state of furosemide. Based on these results, designing supersaturated formulations using PPIs which is a simple and effective method, can be useful and promising to enhance solubility of furosemide and other poorly water-soluble drugs.

## 4. MATERIALS AND METHODS

### 4.1. Materials

Furosemide was obtained as a gift sample from Deva Holding (Turkey). PVPK17 was purchased from by BASF (Germany). HPMC, dimethylsulfoxide (DMSO), sodium chloride, concentrated HCl, disodium hydrogen phosphate, potassium dihydrogen phosphate and sodium hydroxide were obtained from Sigma Aldrich (Germany). All other chemicals were of analytical grade.

### 4.2. Methods

#### 4.2.1. Saturation solubility studies

The shake flask method was used to determine the saturation solubility of furosemide in the absence and presence of PVPK17/HPMC at pH 1.2 and 6.8. After preparation of pH 1.2 and 6.8 buffer solutions according to United States Pharmacopeia (USP) [32], PVPK17 and HPMC were dissolved in pH 1.2 and pH 6.8 buffers to achieve concentrations of 0.05 and 0.25% for both. Subsequently, an excess amount of furosemide above its saturation solubility at pH 1.2 and 6.8 (100 mg) was added to the solutions of PPIs. The mixtures were agitated at a speed of 60 rpm for 24 h at room temperature. At the end of 24 h, sample was withdrawn and filtered using a 0.45  $\mu$ m PTFE syringe filter. Furosemide concentration was determined by UV spectrophotometry.

#### 4.2.2. Supersaturation studies

Solvent-shift method was used to create the supersaturated state [33]. Furosemide solution (381.6 mg in 1.2 mL DMSO) was added dropwise to a glass vial containing the 20 mL of the medium of interest (pH 1.2 buffer, pH 6.8 buffer in the absence/presence of PVPK17/HPMC) and stirred continuously at room temperature at 600 rpm. Resulting drug amount in each vial was at least 5 times higher than the solubility of furosemide in both pH 1.2 and pH 6.8 buffer solutions. The concentrations of PPIs were used as 0.05, 0.25%

both for PVPK17 and HPMC. Samples (1 mL) were withdrawn at predetermined sampling intervals (5, 10, 30, 60, 120 min), and were filtered using a 0.45 µm PTFE syringe filter. Furosemide concentration in samples was determined by UV spectrophotometry.

#### 4.2.3. UV spectrophotometric method

The analysis was carried out using a Shimadzu UV-visible spectrophotometer system (Shimadzu 1800, Japan) with quartz cuvette. Samples were filtered through a 0.45 µm PTFE syringe filter, and then furosemide concentrations in filtrates were determined at 274 nm [34]. Quantitative analysis of furosemide solubility results and furosemide concentration change as a function of time in different buffers were measured by this method. At concentrations of 0.5, 1, 2, 4, 8, 10 µg/mL furosemide solutions were prepared in 0.1 M NaOH solution to obtain the calibration curve. The analytical method was validated as to linearity, precision, and accuracy parameters according to ICH guidelines [35].

#### 4.2.4. Determination of viscosity

The viscosity measurements of PPI solutions (0.05 or 0.25 % HPMC and PVPK17 solutions at pH 1.2 and pH 6.8 buffer solutions) were performed with an Ubbelohde viscometer using a capillary based method for measuring viscosity at room temperature. This viscometer is recommended for higher viscosity cellulosic polymer solutions. The flow times were determined from the average of three measurements and viscosities were calculated by Equation 1.

$$\eta = k.t.d \quad \text{Eq.1}$$

Dynamic Viscosity: Poise ( $\eta$ )

k: Viscometer constant

t: Flow time (sec)

d: Density (g/cm<sup>3</sup>)

#### 4.2.5. Statistical analysis

All tabulated results were given as mean  $\pm$  standard deviation. GraphPad Prism 6 was used for comparing the solubility and viscosity results by Student's t-test, and a p value less than 0.05 was considered significant.

**Acknowledgements:** None.

**Author contributions:** Concept - S.S., I.V.; Design - T.G., N.O., A.K., S.S., I.V.; Supervision - S.S., I.V.; Materials - T.G., N.O., A.K., S.S., I.V.; Data Collection and/or Processing - T.G., N.O., A.K., S.S., I.V.; Analysis and/or Interpretation - T.G., N.O., A.K.; Literature Search - T.G., N.O., A.K., S.S., I.V.; Writing - T.G., N.O., A.K., S.S., I.V.; Critical Reviews - T.G., N.O., A.K., S.S., I.V.

**Conflict of interest statement:** The authors declared no conflict of interest.

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