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ACCEPTANCE LETTER

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Corresponding author: İrem Namlı
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Solubility Improvement of Cefdinir Using Polyvinylpyrrolidone (PVP): Preparation of Solid Dispersions and Their Characteristic Properties

A. Alper Öztürk[1], İrem Namlı[2], Kadri Güleç[3]

[1]Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Eskişehir, Turkey

[2]Anadolu University, Graduate School of Health Sciences, Department of Pharmaceutical Technology, Eskişehir, Turkey

[3]Anadolu University, Graduate School of Health Sciences, Department of Analytical Chemistry, Eskişehir, Turkey

Corresponding author: aaozturk@anadolu.edu.tr

Abstract:

Cefdinir (CEF) is an antimicrobial drug with a wide spectrum of activity. It is mainly used in infections yet is not the first choice considering its solubility and bioavailability problems. The main aim of this study is to improve therapy with CEF by enhancing its solubility and improving dissolution properties. Solid dispersions have been preferred for this purpose and polyvinylpyrrolidone (PVP) has been used to develop two different formulations, PVP-1 and PVP-2. Physical mixture of PVP and CEF was also prepared for comparison. Formulations were prepared by lyophilization following probe sonication with different conditions. To ensure that our formulations have reached their purposes, further experiments were conducted. A specific and selective UV-visible spectrophotometric method was used to determine CEF concentration and the method was validated according to ICH guidelines for linearity, accuracy, and precision. Solubility studies were conducted with pure CEF, physical mixture (PM-PVP) and our solid dispersions, PVP-1, and PVP-2. Solubility studies confirmed CEF's low solubility, less than 1 mg/mL, and showed a significant difference between pure CEF and solid dispersions. While there was also a significant difference between PM-PVP and both PVP-1 and PVP-2, there were no significant differences between PVP-1 and PVP-2. Therefore, PVP-2 was chosen as the optimum formulation and dissolution studies were conducted with PVP-2 and pure CEF in three different mediums, water, pH 1.2 and simulated intestinal fluid (SIF, pH 6.8), respectively. Solubility and dissolution profiles of pure CEF and the formulations were compared and evaluated according to literature. Our formulations were found to be successful in the purpose of improving therapy with CEF by demonstrating a better solubility with better dissolution profiles in all mediums.

Keywords: Cefdinir; solid dispersions; solubility enhancement; probe sonication

1. Introduction

Cefdinir (CEF) is a semisynthetic third generation cephalosporine with a ß-lactam structure within. Its indications include respiratory infections, soft tissue infections and acute otitis media. It has activity on both gram-positive and gram-negative bacteria species (Garrepally et al. 2013). It is used via oral route and has many dosage forms available. CEF has a very low solubility in water and low bioavailability of nearly 25%, which makes it classify as a Class

IV drug according to Biopharmaceutical Classification System (BCS) (Thota et al. 2014). In addition to solubility and permeability problems, CEF's biological half life is limited to 1 – 2 hours. Its solubility is highly dependent on pH and is variable (Garrepally et al. 2013).

Solid dispersions are one of the many ways to improve a drug's solubility and even dissolution profiles by improving its aqueous solubility (Lakshman et al. 2020). Many polymers such as carboxymethyl cellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) and co-polymers and different combinations can be used to prepare solid dispersions of pharmaceutical active ingredients. The main challenge is to find the compatible and inert polymer that can be used with chosen active pharmaceutical ingredient (Schittny et al. 2020). While there are many available options to prepare solid dispersions, the method applied must be compatible with all the ingredients and one of the suitable methods is probe sonication.

Polyvinylpyrrolidone is a non-toxic, biologically compatible, and inert polymer with excellent properties. It is soluble in water and various solvents, also a great stabilizer in pharmaceutical systems. PVP is commonly used in preparation of nanosized drug delivery systems, such as nanoparticles (Koczkur et al. 2015).

In this study, preparation of solid dispersions containing CEF as active pharmaceutical ingredient and PVP as the polymer is aimed. The main goal is to improve therapy with CEF by improving its solubility and dissolution properties in different media.

2. Materials and Methods

2.1. Materials

Cefdinir is a kind gift from Sanovel İlaç (Istanbul, Turkey). All other chemicals used were of analytical grade.

2.2. Preparation of solid dispersions

0.5 g PVP was weighed and dissolved in 50 ml water. 0.5 g CEF suspension in 50 ml methanol was also prepared simultaneously and the suspension was added to the polymer solution, stirring continuously using magnetic stirrer. The obtained mixture was sonicated in a specific amplitude and duration (Sonics®, USA). All formulations were refrigerated at -80oC overnight to be lyophilized (Scanvac CoolSafePro Labogene, Denmark) to obtain the final powder form.

The physical mixture of PVP and CEF was prepared by weighing 0.5 g PVP and 0.5 g CEF in a falcon, shaken using a horizontal shaker at 250 rpm in room temperature for 24 hours. All conditions and formulation compositions are summarized in Table 1.

Table 1. Preparation conditions and compositions of the formulations.

Formulation Code	Amount (g)		Volume (mL)		Sonication conditions	
	CEF	PVP	Water	Methanol	Amplitude	Duration (min)
PM-PVP	0.5	0.5	-	-	-	-
PVP-1	0.5	0.5	50	50	75%	4
PVP-2	0.5	0.5	50	50	75%	8

2.3. Characterization

Prior to all experiments, a validated spectrophotometric method was used to determine CEF. The method was performed using a UV/vis Recording Spectrophotometer UV-160A (Shimadzu, Japan). In all experiments, quartz cells were used, and the analysis wavelength was 287 nm. Partial analytical method validation for linearity, precision, recovery, and accuracy was performed according to ICH guidelines (ICH 2005).

2.3.1. Solubility experiments

50 mg per formulation (PM-PVP, PVP-1 and PVP-2) and pure CEF were weighed and added to falcon tubes with 10 mL distilled water and shaken vigorously using a horizontal shaker at 250 rpm in room temperature for 24 hours. The mixtures were centrifuged, obtained supernatants were collected and filtered using syringe filters with 0.45 μm pore diameter. The filtrates were diluted using distilled water and analyzed using UV spectrophotometer. All experiments were performed in triplicates in room temperature.

2.3.2. Dissolution

In vitro dissolution studies were performed on pure CEF and optimum formulation (PVP-2). The experiment took place using dialysis membrane in three different mediums, water, pH 1.2 buffer and simulated intestinal fluid (SIF, pH 6.8) for over 4 hours.

3. Results

3.1. Characterization

In validation studies of UV-Visible spectrophotometric method for CEF analysis, several parameters have been investigated. Linearity study was conducted at a concentration range of 1 – 17 $\mu g.mL^{-1}$ and the linear equation is y=0.0528x+0.004 with an R^2 value of 0,9997. For the determination of precision, relative standard deviation (RSD) values were calculated and found to be smaller from 2%. Accuracy was investigated by calculating recovery values and found to be less than 2% for all concentrations.

3.1.1. Solubility experiments

The results clearly show that while pure CEF has a solubility of less than 1 mg/mL in water, both our formulations improved solubility significantly. It is also clearly seen that physical mixture of PVP and CEF improved solubility yet there are no significant differences between PM-PVP and pure CEF and the solubility still did not exceed 1 mg/mL. Our formulations, PVP-1, and PVP-2 show improvement and reached to solubility close to 3 mg/mL. Solubility results are presented in Figure 1.

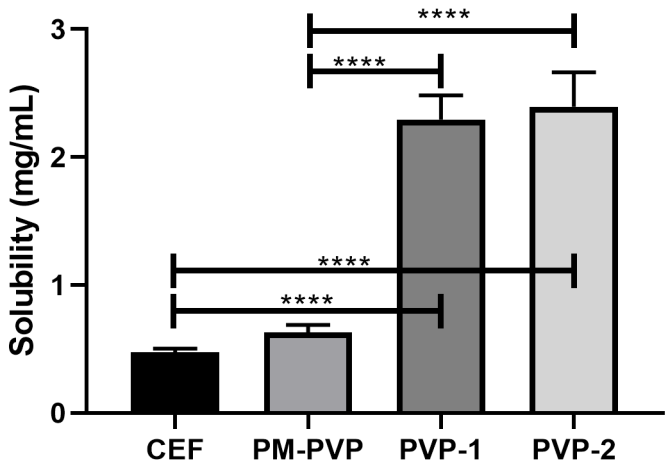

Figure 1. Results of solubility study and statistical analysis.

3.1.2. Dissolution

Since the solubility results demonstrated that there are no significant differences between PVP-1 and PVP-2 formulations, PVP-2 was chosen as the optimal formulation and dissolution studies were conducted using PVP-2 and pure CEF. In all three mediums PVP-2 showed better cumulative release in all time periods. While the difference is not very clear in water, in both pH 1.2 and pH 6.8 PVP-2 showed higher cumulative release. It is also seen that in pure CEF drug release has stopped after a while in water and pH 1.2, while PVP-2 kept releasing the drug. The *in vitro* dissolution results are shown in Figure 2.

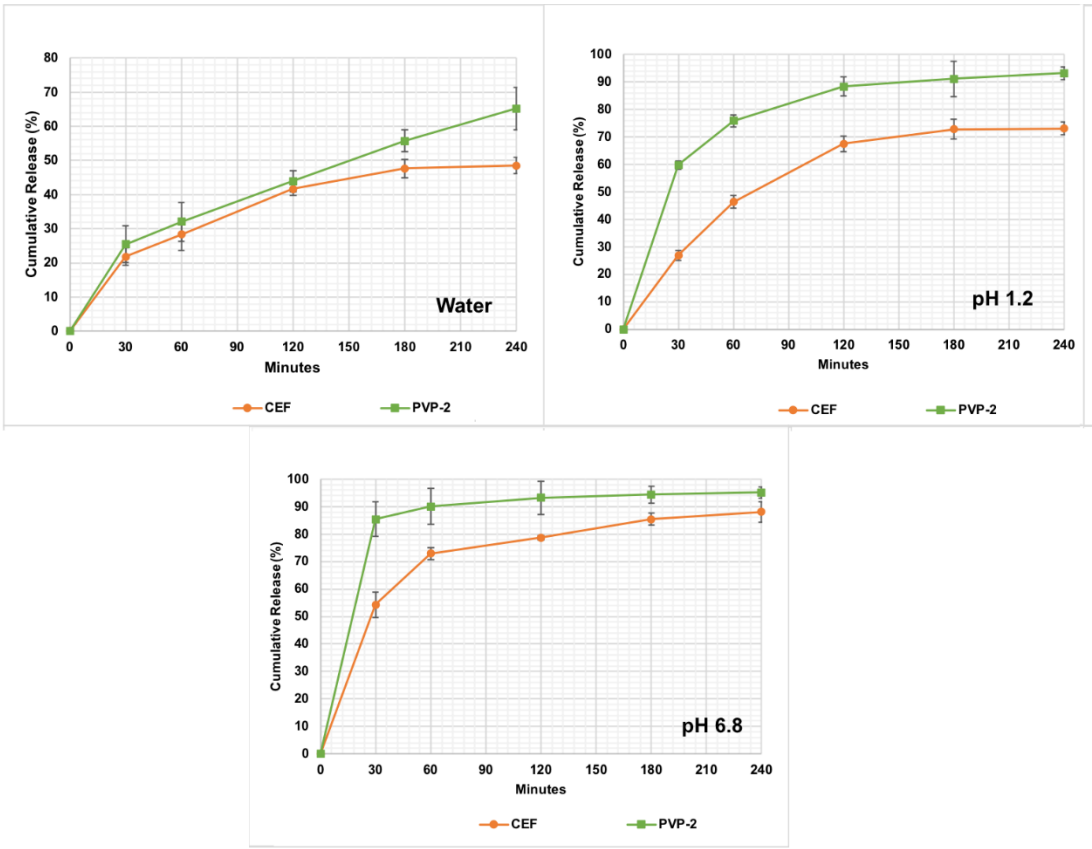

Figure 2. Results of *in vitro* dissolution study in different mediums (water, pH 1.2, pH 6.8).

4. Discussion

4.1. Characterization

Linearity, RSD, and recovery values were found to be within limits according to ICH. The results show that the current method is linear, precise, accurate and repeatable. Results of partial analytical method validation study proves that this method is not only easy and cost-friendly, and that it can be used for CEF determination routinely (Ozturk et al. 2019).

4.1.2. Solubility experiments

One of the main problems regarding CEF is its low water solubility, which is confirmed with our solubility experiments. In Figure 1, it is seen that CEF concentration in water didn't exceed 1 mg/mL. While the formulations improved CEF's solubility in water significantly compared to both pure CEF and PM-PVP, the difference between physical mixture and pure CEF did not reach to significant level. Although PVP can enhance solubility in a very low rate, it is not significant when compared and with previous studies showing that probe sonication has a positive effect on solubility enhancement (Pereira et al. 2016), it is clear that in this study the main difference is seen by probe sonication.

4.1.3. Dissolution study

Dissolution studies also confirm solubility results, showing CEF release reached higher cumulative release values in water. In water, the dissolution graphics were very similar until 2 hours. After that pure CEF dissolution has decreased while drug release from PVP-2 kept going at the same rate without any decreases. At 3rd hour it is seen that drug release in pure CEF stopped while PVP-2 kept releasing.

It is known that CEF has different solubility profiles and rates in different mediums with different pH values, showing the highest rate at pH 6.8 (Cho et al. 2017). Even though the release graphics are in very similar shapes for both pure CEF and PVP-2 in both mediums, pH 1.2 and pH 6.8, it is clearly seen that released amount of CEF is higher for PVP-2.

To take a closer look, in pH 1.2 the drug release stopped at 3rd hour for pure CEF while kept going for PVP-2, reaching above 90% cumulative release. Pure CEF reached only above 70% percent at the end of 4th hour, also showing that solubility has increased in pH 1.2 as well.

Since CEF solubility reaches a much higher value in pH 6.8 (Cho et al. 2017), drug release is much higher than in both water and pH 1.2. While pure CEF reaches above 50% at the end of 30 minutes, PVP-2 reaches above 80%, proving that solubility is also improved in an environment that CEF already has a higher solubility rate. Since cumulative amount reaches a very high level very early regarding PVP-2, a decrease is seen after 60 and 120 minutes, while pure CEF keeps releasing the drug until it reaches just below 90%, while the final cumulative release of PVP-2 hits above 90%.

5. Conclusion

CEF has many clinical uses in today's medicine, yet the problems regarding its properties limit its applications. As this study was conducted to improve solubility and improve CEF dissolution, the results show preparation of solid dispersions has been successful. This study is a small step in improving antimicrobial therapy with cefdinir and only a small part of a bigger project.

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