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An Approach for Solubility Enhancement of Poorly Water-Soluble Drug Cefdinir with Polyvinyl Alcohol

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Abstract

Solid dispersions (SDs) prepared with water-soluble polymers have been successfully used to increase the solubility of many poorly water-soluble drugs. Although Cefdinir (CEF) is used in many microbial diseases, its bioavailability is quite low due to its low solubility in water. Therefore, CEF is a suitable candidate for the preparation of the SD. In this study, SDs were prepared with polyvinyl alcohol (PVA) to increase the solubility and bioavailability of CEF and SDs were characterized by analyzes such as solubility and *in vitro* dissolution studies.

***Keywords*:** *Cefdinir, Probe sonication, Polyvinyl alcohol, Solid dispersion*

Introduction

In today's market, many drugs used in treatment suffers from low solubility. In pharmaceutical area many ways are used in order to enhance water solubility such as salt formation, reduction in particle size, preparing inclusion complexes using host molecules like cyclodextrins. One of the popular ways to enhance solubility is to prepare SDs using suitable polymers. SDs help improving solubility of insoluble active pharmaceutical ingredients, by enhancing solubility their bioavailability increases in significant rates. Consequently, active treatment is achieved by lower doses. They are prepared by different methods that are basically based on dispersing the active pharmaceutical ingredient within polymeric matrix (1, 2). SDs are prepared using biocompatible polymers like PVA, polyvinyl pyrrolidone, cellulose derivates and polymethacrylates (2). PVA has excellent properties that make it a strong candidate to use in drug delivery systems. PVA is highly stable and chemically inert, which makes it safe and

biocompatible. Its adhesiveness, solubility, swelling and film forming properties make PVA an often-used polymer in pharmaceutical area (3).

CEF is an antimicrobial agent often used in treatment of soft tissue infections, otitis media and respiratory tract infections. It is a semi-synthetic third generation cephalosporin that is classified in Class IV in Biopharmaceutical Classification System, which means both its solubility and permeability are low. Its bioavailability is approximately 20-25% with a short half-life of 1 to 2 hours (4, 5). A study about SDs of CEF with Kollicoat®Protect was presented by us at 8th BBBB International Conference on Pharmaceutical Sciences (6).

In this study, SDs of CEF using PVA are prepared by probe sonification and their *in vitro* properties are determined. The aim of the study is to enhance solubility and evaluate the prepared SDs' characteristic properties compared to pure CEF.

Results and Discussion

Preparation of solid dispersion: CEF is a kind gift from Sanovel İlaç (İstanbul, Turkey) and both PVA and methanol are purchased from Sigma (Germany). All chemicals used were of analytical grade. Since it's not possible to dissolve it in water, CEF was suspended in methanol. While mixing with magnetic stirrer, CEF suspension was added to polymer solution and the mixture was sonicated using probe sonicator (Sonics®, USA). Following these steps, formulations were refrigerated at -80°C and lyophilized (Scanvac CoolSafePro Labogene, Denmark) to obtain a fine powder. Physical mixture was prepared by mixing 0.5 g CEF and 0.5 g PVA homogenously. Table 1 shows formulation ingredients and conditions.

Table 1: Formulation ingredients and conditions.

Code	PVA	Water	CEF	Methanol	Amp. & Min.
PM-PVA	0.5 g	-	0,5 g	-	-
PVA-1	0.5 g	50 ml	0,5 g	50 ml	75 %, 4 min.
PVA-2	0.5 g	50 ml	0,5 g	50 ml	75 %, 8 min.

PM: Physical Mixture, **Amp:** Amplitude %, **Min:** Minute

UV–visible spectrophotometric method: Prior to solubility and *in vitro* dissolution studies, a specific and selective UV spectrophotometric method was validated for CEF. UV method was performed on a UV/vis Recording Spectrophotometer UV-160A (Shimadzu) at 287 nm and using quartz cell. Following validation of the UV-Visible spectrophotometric method developed, linearity was determined to be at a concentration range of 1–17 µg.mL^{-1} with a linearity of y=0.0528x+0.004 (r^2=0.9997). The method was decided to be precise due to relative standard deviation (RSD) values of <2% for repeatability and intermediate precision. Recovery and accuracy of the method was satisfactory owing to <2% RSD value. Based on the partial validation results, the easy and inexpensive procedure proposed in this study can be routinely used for CEF determination (7).

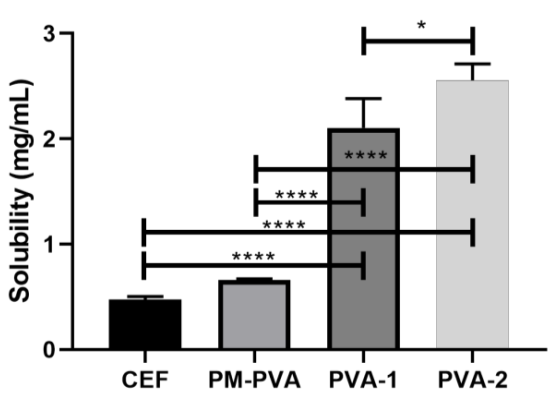

Figure 2. Solubility Results

Solubility study: To assess the solubility properties of the formulations, CEF, PM, PVA-1 and PVA-2 were weighed to 50 mg and added to 10 mL of distilled water, then shaken (250 rpm) at room temperature for 24 h at room temperature using a horizontal shaker. After 24 h, the samples were centrifuged, and the supernatants were filtered using a 0.45 µm syringe filter. The filtrate was diluted with an appropriate amount of distilled water for analysis. The solubility of CEF, PM and SDs is shown in Figure 1. SDs displayed a higher solubility compared with CEF itself. While the solubility of CEF in water was 0.47%±0.03, this value was found to be 0.66%±0.01, 2.10%±0.28 and 2.55%±0.16 for the PM, PVA-1 and PVA-2, respectively. When analyzed both mathematically and statistically, the solubility of CEF in water is increased with PVA-1 and PVA-2 coded SDs. When PVA-1 and PVA-2 coded SDs were compared among themselves, the solubility of CEF was found higher in PVA-2 coded formulation. There was also a significant difference between PVA-1 and PVA-2 ($p<0.05$). The reason for this is thought to be the probe sonication time applied. Long sonication times have been reported in previous studies to

increase solubility of drugs in SDs (8). Enhanced solubility of CEF in SDs using PVA could be attributed to the chemical structure of highly water soluble PVA (9).

In vitro dissolution study: *In vitro* dissolution studies were performed on pure CEF and the optimum SD, PVA-2, using dialysis membrane method in 3 different mediums; water, pH 1.2 and simulated intestinal fluid (SIF, pH 6.8). The experiment was carried out considering the sink condition in 50 mL medium per content, at 37°C and 100 rpm. Figure 2 shows the *in vitro* dissolution profile of the pure CEF and PVA-2 in different media. In the *in vitro* dissolution study in water, when CEF dissolution from the pure CEF and PVA-2 coded solid dispersion formulation was compared for the first 120 min, it was observed that the CEF dissolution in the SD was always about 10% higher than pure CEF for each time interval. The difference was observed after 120 min. After 120 min, plateau status was observed in pure CEF dissolution profile, and CEF dissolution from PVA-2 coded SD formulation continued. In the 180th min, pure CEF dissolution almost stopped, while CEF dissolution from SD continued. Similar results were obtained in the dissolution study at pH 1.2. As a result, when Figure 2 is examined, it is clear that CEF solubility increases in water and pH 1.2 environment with PVA-2 coded SD formulation. In the dissolution study carried out at SIF-pH 6.8, CEF dissolution from pure CEF and PVA-2 coded SD did not show much difference. The reason for this is explained as follows in the literature. CEF has three ionizable groups with

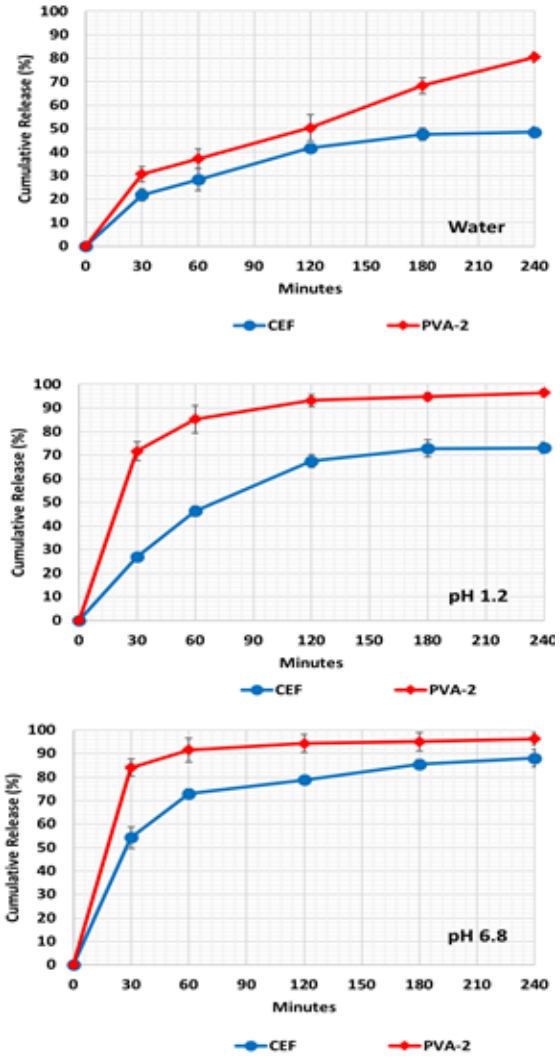

Figure 3. In vitro dissolution results

following pK_a values: −COOH group of cephem moiety (pK_a*:1.9*), −NH2 group of the aminothiazole moiety (pK_a*:3.3*), and =N–OH group of the oxime moiety (pK_a*:9.9*). According to the Henderson-Hasselbalch equation, the –COOH group of the cephem moiety (pK_a*:1.9*) is almost completely ionized over about pH 4, likely causing the observed increased aqueous solubility of CEF over about pH 4 (5). The physicochemical properties of CEF, including its pK_a values, seem to contribute to the pH-dependent solubility, as shown in *in vitro* dissolution study (Figure 2). As a conclusion, it can be said that this system we prepared can increase oral absorption of CEF and thus increase bioavailability.

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