



Transparent ciprofloxacin-povidone antibiotic films and nanofiber mats as potential skin and wound care dressings



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ARTICLE INFO

Keywords:

Ciprofloxacin
Povidone
Polyvinylpyrrolidone
Wound dressing
Acetic acid
Nanofibers

ABSTRACT

Water insoluble monohydrochloride monohydrate free ciprofloxacin (Cipro) antibiotic was incorporated in polyvinylpyrrolidone (PVP) polymer matrix by using acetic acid co-solvent in water. The resultant solutions were cast into fully transparent antimicrobial films. Proper concentrations of acetic acid eliminated *in situ* crystallization of the antibiotic and the resultant phase separation upon solvent evaporation. The solutions could also be electrospun into nanofiber mats (non-transparent). Presence of residual PVP-bound acetic acid in dry PVP films induced unprecedented levels of plasticity (stretching capacity) and softness to the films. Additionally, PVP-bound acetic acid also acted as an antiseptic. Antibacterial properties of the films and fiber mats were confirmed on *Escherichia coli* and *Bacillus subtilis* (growth and viability). Films and nanofiber mats demonstrated promising wound resorption characteristics by using *in vivo* full-thickness excisional skin wound healing mice model. Nanofiber mats were resorbed much faster than transparent films. Wound exudate absorption in the films and resorption rate of the nanofiber mats were dependent on the starting acetic acid concentrations. The fact that PVP/Cipro solutions in aqueous acetic acid can be used either to produce transparent soft films or nanofiber mats renders this process highly suitable for the fabrication of new-generation potential dressings for wound management and care.

1. Introduction

Wound dressings have been evolving steadily in close conjunction with recent trends and advances in bio-based polymer synthesis and processing technologies (Ovington, 2007; Athanassiou et al., 2014). Dressings grew from materials or tapes that simply covered and concealed the wound, to materials that can interact with wounds so that important wound healing factors such as moisture management, active ingredient delivery and interaction with cells or proteins can be tuned or enhanced *in situ*. For chronic non-healing wounds or burns, for instance, one of the most important aspects is to prevent infection. As such, dressings should provide a continuous or sustained release of an antiseptic agent at the wound surface to provide a long-lasting antimicrobial action in combination with maintenance of physiologically moist environment for healing (Boateng et al., 2008).

Most commercially available wound dressings are frequently opaque. Visual observation of the healing process is therefore prevented.

Infection or other complications cannot be easily detected with opaque coverings. During inspection, dressing removal generally causes discomfort but also healing disruption, bleeding and granuloma formation. Therefore, transparent wound dressings would be highly appropriate. Particularly, antiseptic loaded and adhesive free transparent wound dressings that can be easily absorbed by the wound are highly desirable in the sense that instead of removal and replacement, an identical self-adhering transparent dressing can be immediately applied after the absorption of the previous one (Fabo and Svensby, 2008).

Wound dressings in the form of hydrogels tend to be transparent with many advantages such as flexibility, deterioration resistance as the wound fluids are absorbed permitting clean and neat removal of the wound dressing upon healing or during replacement, among others. Researchers are continuously developing new hydrogel wound dressings in order to address a number of gel related shortcomings, such as the need for a secondary dressing, dehydration in time, securing on the wound properly, and initiation of peri-wound maceration (Quarfoot

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et al., 1990). Flexible, water vapor permeable, self-adhering and polymeric thin film wound dressings are equally popular and generally classified as interactive and bioactive dressings (Gupta et al., 2010; Mogoşanu and Grumezescu, 2014) compared to passive traditional dressings like gauze and tulle products that account for the largest market segment today (Paul and Sharma, 2004). Therefore, development of new, inexpensive and intelligent transparent polymeric bandages from biodegradable polymers such as alginates and chitosan has been extensively researched and noticeable progress has been made so far (Boateng et al., 2008; Norouzi et al., 2015; Whitaker et al., 2001) (Giordano et al., 2007; Wang et al., 2007).

Polyvinylpyrrolidone (Povidone, PVP) is one of the most utilized pharmaceutical polymers (Guo et al., 1998; Park et al., 2015) not only in the form of a thermoplastic but also as crosslinked particles in tablets and most commonly as iodine complex (PVPI) as an effective antiseptic (Liakos et al., 2013). It is a water soluble transparent and non-toxic polymer which has been also approved as food additive (Sun et al., 2012). It has been shown to have excellent compatibility with moist wounds due to its inherent hydrophilicity (Alsarra et al., 2011; Haaf et al., 1985; Langer et al., 2006; Minghetti et al., 2003). However, apart from its iodine complex known as povidone iodine solution or ointment, antibiotic loaded or complexed transparent interactive povidone-based wound dressings are very rare due to the fact that hydrophobicity or water insolubility of such antibiotics is a major obstacle for dispersing them both in water and in povidone. Earlier reports also showed that use of povidone iodine along with certain antibiotics might create complications in wound healing and even promote wound infection (Lau et al., 1986). It is therefore imperative to develop new procedures to incorporate effective antibiotics into pristine polyvinylpyrrolidone rather than povidone iodine as potential wound dressings.

Ciprofloxacin is an antibiotic that belongs to the family of fluoroquinolones (Appelbaum and Hunter, 2000). It is considered to be one of the most important medications for basic health care (Davis et al., 1996). Its spectrum of activity includes most strains of bacterial pathogens responsible for respiratory, urinary tract, gastrointestinal, and abdominal infections, including gram-negative and gram-positive bacterial pathogens (Appelbaum and Hunter, 2000; Drlica and Zhao, 1997; Hooper, 2001). It functions by inhibiting DNA gyrase and topoisomerase IV (type II topoisomerases), necessary to separate bacterial DNA, thereby inhibiting cell division. Although frequently referred to as Cipro, the most common form of Ciprofloxacin is monohydrochloride monohydrate salt tablets (CiproHCl). While both Cipro and CiproHCl have common antibiotic related side effects (Schluter, 1989), pharmacokinetics of CiproHCl is very sensitive to the pH of physiological fluids (*i.e.*, protein binding) (Anand et al., 2012) and its antiseptic effect can be reduced in lower pH body fluids, particularly during ulcer or urinary treatments (Kamberi et al., 1999). Moreover, CiproHCl can also take part in unwanted reactions with metabolized vitamins and minerals in the body such as iron (Parojčić et al., 2011). Therefore, alternative oral administration of monohydrochloride monohydrate-free Cipro in oil-based syrups have been formulated and prescribed (Johnson et al., 1997) (Baker et al., 2009).

In this study, we demonstrate a facile water-based process to incorporate monohydrochloride monohydrate-free Cipro in PVP by using aqueous acetic acid (AcOH) as co-solvent. Use of acetic acid not only enabled solubilization of Cipro along with povidone in water but also prevented post-crystallization and phase separation of it in dry polymeric films after solvent (water) evaporation enabling fabrication of completely transparent antibiotic PVP films. Same solutions were used to electrospin nanofiber (non-transparent) mats for the first time.

2. Materials and methods

2.1. Materials

Polyvinylpyrrolidone (PVP; MW = 360,000), monohydrochloride monohydrate free ciprofloxacin ($\geq 98.0\%$ HPLC; MW = 331.34), acetic acid ($\geq 99.7\%$) were purchased from Sigma-Aldrich and used as received. Dimethylsulphone (DMS), heavy water (D_2O) and 3-(trimethylsilyl)propionic-2,2,3,3-d₄ acid sodium salt (TSP) were obtained from Sigma Aldrich (Milan, Italy). Deionized water was obtained from Milli-Q Advantage A10 ultrapure water purification system. Phosphate buffered saline (PBS) solution (pH 7.4) was acquired from Sigma-Aldrich and used as received.

2.2. Preparation of the films

Cipro/polymer solutions were prepared by dissolving Cipro powder and PVP in various water/acetic acid solutions containing 1, 5, 10 and 30% (v/v) AcOH in 10 mL of total volume. Cipro concentration in the solutions was maintained at 0.1% w/v while PVP concentration was 3% (w/v). Initially, Cipro powder was dispersed in vials containing water/AcOH solvents and upon complete dissolution of Cipro, PVP polymer was added and dissolved under mild stirring. A control solution of PVP in water at 3% (w/v) was also prepared. The solutions were cast on circular plastic Petri-dishes (50 × 50 mm), and dried for 3 days under an aspirated hood under ambient conditions (16–20 °C and 40–50% R.H). Then, the films were placed in vacuum desiccator for 3 more days for complete removal of excess acetic acid. Dry transparent films had a thickness of 130–170 µm.

2.3. Fabrication of the electrospun mats

For the fabrication of the electrospun mats, identical acetic acid solutions were prepared as above. A more concentrated PVP polymer solution was necessary to enable electrospinning. The optimum concentration of PVP was found to be 25% (w/v). Cipro powder was dispersed in these solutions *a priori* such that the final blend contained 0.4% Cipro with respect to PVP polymer by weight. Mats were produced by means of a vertical electrospinning setup. Syringes with a stainless-steel 18-gauge needle were filled with the different solutions and connected to a syringe pump (NE-1000, New Era Pump Systems, Inc.) working at constant flow rate of 250 µL/h. The needle was clamped to the positive electrode of a high-voltage power supply generating 30.5 kV, and an aluminum disk was used as collector (needle-collector distance of 24 cm).

2.4. Sample notation

Film and fiber mat samples were classified by using two different notations: Samples labeled as P0%, P1%, P5%, P10% and P30% represent Cipro free PVP films or mats, obtained from solutions containing acetic acid with concentrations ranging from 0% to 30% (v/v). Similarly, samples labeled as PC1%, PC5%, PC10% and PC30% represent Cipro containing PVP films or mats with identical acetic acid concentration range. For film casting, PVP concentration in solution was always maintained at 3% (w/v) and for electrospinning PVP concentration in solution was increased and always maintained at 25% (w/v). On dry basis, Cipro concentration with respect to PVP in the films and mats was 3.3 wt% and 0.4 wt%, respectively.

2.5. Morphological characterization

Morphology of the films and the nanofibers was analyzed by Scanning Electron Microscopy (SEM), using a variable pressure JOEL JSM-649LA microscope equipped with a tungsten thermionic electron source working in high vacuum mode, with an acceleration voltage of

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