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Polyvinylpyrrolidone oral films of enrofloxacin: Film characterization and drug release

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ABSTRACT

Enrofloxacin is a fluoroquinolone derivative used for treating urinary tract, respiratory and skin infections in animals. However, low solubility and low bioavailability prevented it from using on humans. Polyvinylpyrrolidone (PVP) is an inert, non toxic polymer with excellent hydrophilic properties, besides it can enhance bioavailability by forming drug polymer conjugates. With the aim of increasing solubility and bioavailability, enrofloxacin thin films were prepared using PVP as a polymer matrix. The obtained oral thin films exhibited excellent uniformity and mechanical properties. Swelling properties of the oral thin films revealed that the water uptake was enhanced by 21%. The surface pH has been found to be 6.8 ± 0.1 indicating that these films will not cause any irritation to oral mucosa. FTIR data of the oral thin films indicated physical interaction between drug and polymer. SEM analysis revealed uniform distribution of drug in polymer matrix. *In vitro* drug release profiles showed enhanced release profiles (which are also pH dependant) for thin films compared to pure drug. Antibacterial activity was found to be dose dependent and maximum susceptibility was found on *Klebsiella pneumonia* making this preparation more suitable for respiratory infections.

1. Introduction

Enrofloxacin is a fluoroquinolone antibiotic with broad spectrum of activity (Bauditz, 1987). Enrofloxacin is the first fluoroquinolone developed for veterinary applications for treating urinary tract, respiratory and skin infections in dogs and cats (Boothe, 1994). This antibiotic is also used in poultry to treat respiratory and enteric bacterial infections like mycoplasmosis, pasteurellosis and colibacillosis (Bauditz, 1987). Fluoroquinolones are characterized by their low solubility and low bioavailability (Kung et al., 1993; Seedher and Agarwal, 2009). To overcome the bioavailability factors enrofloxacin is generally administered to humans at high concentrations which can cause molecular stacking and crystal formation affecting many organs with undesirable consequences (Maurer et al., 1998). However, because of the above mentioned side effects it has been banned in humans. But if we could enhance the bioavailability and solubility we can restore this antibiotic for human use.

Advances in polymer science have led to the development of novel delivery systems. Polyvinylpyrrolidone (PVP) is known to have pharmaceutical importance and chemically PVP has been found to be inert, non-toxic, exhibits hydrophilic properties, universal solubility and strong tendency for complexes with wide range of smaller molecules (Majhi et al., 2001; Wohrle, 2005; Wu et al., 2001). An easy way to enhance bioavailability is by forming drug polymer conjugates (Veeran and Guru, 2011). For this reason polymeric films are interesting drug delivery systems to achieve a systemic effect through sublingual and buccal route. Formulating enrofloxacin thin films to enhance drug release could be an useful alternative to be explored because of the following advantages: (1) reducing peak plasma levels, (2) maintaining the dose under

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therapeutic window, (3) to avoid destruction in acidic environment of stomach and (4) reduced hepatic first pass effect (Bhupinderet al., 2011; Martinez et al., 2012).

Taking these research challenges into consideration, we have prepared enrofloxacin oral thin films using PVP as a polymer matrix. These prepared films were evaluated for their physico-chemical properties by employing scanning electron microscopy (SEM), Fourier transform infra-red spectroscopy (FTIR) and differential scanning calorimetry (DSC). These films were also evaluated for drug release profiles and antibacterial activity on gram positive and gram negative bacterial species.

2. Materials and methods

2.1. Materials

Enrofloxacin (assay purity ≥98.0%), polyvinylpyrrolidone (PVP) (Mw = 13,00,000) and dialysis membrane have been purchased from Sigma–Aldrich, Bangalore, India. Methanol, chloroform, monobasic sodium phosphate (NaH_2PO_4) and dibasic sodium phosphate (Na_2HPO_4) were purchased from Emplura®, Merck Specialities Private Limited, Bangalore, India.

2.2. Preparation of oral thin films

2.5 g of PVP was dissolved in a mixture of 20 ml methanol and 5 ml chloroform. Enrofloxacin drug solution was prepared by dissolving 50 mg in a mixture of 10 ml of methanol and 2.5 ml of chloroform. A blend of above solutions in ratio of (1:2) was made. The obtained homogenous solution was poured into a plastic mould, covered and kept overnight at room temperature for solvent evaporation. The resulting films were used for further physico-chemical analysis.

2.3. Characterization PVP oral thin film

2.3.1. Scanning electron microscopy (SEM)

The surface morphology of the pure drug, oral thin films containing drug and pure polymer films were characterized by field emission scanning electron microscope (FESEM, FEI Sirion) at operating voltage of 5–30 KV. All images were recorded at working distance of 8–10 mm.

2.3.2. FTIR analysis

The procedure involving sample preparation and spectral recordings was carried out by previously described method (Stuart, 2004). IR spectra of enrofloxacin, PVP and oral films were recorded using FTIR Nicolet 6700 (Thermo Fisher Scientific, Madisson, WI, USA) operated by Omnic software 8.1. Briefly, the formulations were placed individually on the sample plate of the smart orbit and screwed lightly to record IR spectra in ATR mode.

2.3.3. Differential scanning calorimeter (DSC)

DSC (Mettler-Toledo DSC 821e, Switzerland) analysis was carried out with initial and final temperatures at 25 °C and 300 °C with temperature raise of 10 °C/min in argon atmosphere. DSC curves were evaluated with STARe software supplied by the Mettler-Toledo company.

2.4. Surface pH

The surface pH of enrofloxacin oral thin films was measured by using combined pH electrode. Films were moistened with Milli-Q-water and pH was measured at the interphase of water and film (Dinge and Nagarsenker, 2008).

2.5. Thickness

Thickness was by calibrated digital vernier calipers (Mitutoyo 550-203-10, Mitutoyo, Japan). Thickness was measured at five different points in the films and mean value was expressed (Raju et al., 2011).

2.6. Folding endurance

Folding endurance was determined by repeatedly folding the film (4 × 4 cm) at the same point until a breaking point is achieved. Number of times the film could be folded at the same point without breaking was considered as folding endurance value. All the tests were performed four times and mean of the values was reported (Shinde et al., 2008).

2.7. Swelling percentage (% S)

Swelling index for the films was conducted in simulated salivary fluid at pH 6.75. Briefly, films (surface area 3 cm^2) was weighed and transferred onto a stainless steel mesh (sieve size approximately 800 μm). This setup was submerged into 50 ml of simulated salivary medium. At definite time interval (30 s), the stainless steel mesh was removed, excess moisture was removed carefully with filter paper reweighed. Increase in weight of the film was determined at each time interval until a constant weight. The swelling percentage was calculated by using the following formula (Mona et al., 2012; Peh and Wong, 1999; Semalty et al., 2005).

$$\%S = \frac{(X_t - X_0)}{X_0} \times 100$$

where % S – swelling percentage, X_t – the weight of swollen film after time t, and X_0 – weight of film at zero time.

2.8. In vitro disintegration time

In vitro disintegration time was measured by following monograph from United States Pharmacopeia (USP) using disintegration test apparatus (LABINDIA, DS8000) (The United States Pharmacopoeia, 2009).

2.9. Solubility studies

Drug concentration of 1 mg/ml enrofloxacin pure drug and PVP-enrofloxacin thin film was taken in a beaker containing phosphate buffer solution (PBS) (pH 5.8, 6.4 and 7.4) and these beakers were incubated at 37 ± 0.1 °C under dynamic conditions and amount of drug dissolved is noted visually (Mosharraf and Nystrom, 2003).

2.10. In vitro drug release

In vitro drug release studies were performed using USP apparatus-I at 50 rpm and 600 ml of PBS (pH 5.8, 6.4 and 7.4) at 37 ± 0.5 °C. A calculated 10 mg (conc. 1 mg/ml) of pure drug and enrofloxacin-PVP thin film were separately placed in dialysis tube and immersed in PBS at above mentioned pH. At predetermined time intervals (0, 5, 10, 30 min, 1 h, 2 h, 4 h, 6 h, 20 h, 24 h, 48 h and 72 h), an aliquot of 3 ml of the release media was withdrawn and the concentration of the drug in release media was estimated by UV spectroscopy (UV-1700 Pharma Spec, Shimadzu) at 290 nm. The dissolution medium was replaced with fresh buffer (3 ml) to maintain constant volume.