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Original Research Paper

Taste masking of ciprofloxacin by ion-exchange resin and sustain release at gastric-intestinal through interpenetrating polymer network

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ABSTRACT

The aim of the study was to taste mask ciprofloxacin (CP) by using ion-exchange resins (IERs) followed by sustain release of CP by forming interpenetrating polymer network (IPN). IERs based on the copolymerization of acrylic acid with different cross linking agents were synthesised. Drug-resin complexes (DRCs) with three different ratios of drug to IERs (1:1, 1:2, 1:4) were prepared & evaluated for taste masking by following *in vivo* and *in vitro* methods. Human volunteers graded ADC 1:4, acrylic acid-divinyl benzene (ADC-3) resin as tasteless. Characterization studies such as FTIR, SEM, DSC, P-XRD differentiated ADC 1:4, from physical mixture (PM 1:4) and confirmed the formation of complex. *In vitro* drug release of ADC 1:4 showed complete release of CP within 60 min at simulated gastric fluid (SGF) i.e. pH 1.2. IPN beads were prepared with ADC 1:4 by using sodium alginate (AL) and sodium alginate-chitosan (AL-CS) for sustain release of CP at SGF pH and followed by simulated intestinal fluid (SIF i.e. pH 7.4). FTIR spectra confirmed the formation of IPN beads. The release of CP was sustain at SGF pH (<20%) whereas in SIF media it was more (>75%). The kinetic model of IPN beads showed the release of CP was non-Fickian diffusion type.

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1. Introduction

Ciprofloxacin (CP) has been used for the several diseases such as infection of bones and joints, gastroenteritis and also approved for the treatment of infections, especially urinary tract infections, prostatitis [1]. It is a second-generation flouroquinolone antibiotic drug having excellent tissue penetration used for both oral and intravenous formulations [2,3]. Although CP has good broad spectrum antibacterial activity, it has bitter taste which becomes palatability challenge and has patients compliance for oral administration.

Oral administration of drug is considered to be the most preferred route for drug delivery. Taste of an oral formulation administered, particularly of bitter drugs, to a child or adult has an important impact on the adherence to drug therapy. Taste masking is an important challenge in drug delivery since drugs dissociate in the patients mouth in close proximity to the taste buds, thereby increasing the patients compliance. A variety of methods are available for taste masking purpose such as microencapsulation with various polymers, coating with polymers lipids, drug resin complexes and using lipophilic vehicles for obstructing the taste buds [4–6]. These methods are used to prevent instant drug release, when contact with the taste bud in the oral cavity [7–9]. Among various taste masking techniques, complexation method using ion exchange resins (IERs) is simple, cost effective and does not require more ingredients or organic solvents.

IERs have excellent properties like high ion-exchange capacity, good absorption capacity, physico-chemical stability and their insolubility in any solvents make them suitable candidates as taste masking and sustain release of drugs [10–12]. CP has been studied for taste masking and sustain release by some researchers. Pisal et al. studied taste masking of CP using Indion 234 resin and also studied for sustain release of CP at SGF pH by treating polyethylene glycol with CP-Indion 234 complex [13,14]. Extended release tablet was prepared by using 500 mg of CP on swellable drug polyelectrolyte matrices by Bermudez et al. [15].

Interpenetrating polymer network (IPN) beads have been used by many researchers for sustain release of drugs in recent years. IPN beads proved to be a novel drug carrier as they have many good properties [16]. They are stable, biocompatible, non-toxic and biodegradable which have attracted their use in pharmaceutical field. Chitosan (CS) is environment friendly bio material, non-toxic, biodegradable, biocompatible, hydrophilic and semi-rigid polysaccharide which has been studied for the controlled release of drugs in the present work. CS is derived from naturally occurring chitin by alkaline deacetylation. CS also possesses good mucoadhesive property and several researchers have used CS for the entrapment of drugs [17–20]. Sodium alginate (AL) is a polysaccharide and composed of β-D mannuronic acid and α-D-guluronic acid polymer which can vary in proportion and sequential distribution [21]. However, the taste masking and sustain release of CP through synthesized IERs based IPN beads using CS and AL biopolymers are relatively new area which prompted us to study them in details.

The objective of this study was to evaluate the performance of the synthesised resins for taste masking of CP followed by sustain release at different pH by forming IPN beads with AL and CS biopolymers. The IERs were prepared with different cross linkers and also by varying crosslinking %. These IERs have high ion exchange capacity (>11 meq/gm), stability and insolubility properties as well as possess high drug loading capacity.

2. Materials and methods

2.1. Materials

CP was procured from Corel Pharma (p) Ltd. Ahmedabad, India. Acrylic acid (AA), ethylene glycol dimethacrylate (EGDMA) and N,N'-Methylenebisacrylamide (MBA) were purchased from Central Drug House, Mumbai, India. Divinyl benzene (DVB) supplied by Merck, Germany was used as received. Benzoyl peroxide (BP) was purchased from Heny fine chemicals Vadodara, India. Potassium dihydrogen orthophosphate, sodium hydroxide, potassium hydroxide and other chemicals were acquired from S.D Fine Chemicals, Mumbai, India. AL (viscosity: 20.0–40.0 CP in 1% water, MW: 7334), CS (medium molecular weight) and cellulose acetate dialysis tube (cut off molecular mass of 12,000) were obtained from Sigma Aldrich, USA. All other reagents used in this study were of HPLC grade and used without further purification. Millipore water was used for every experiment by Milli–Q plus system (Millipore Corporation Breford, USA).

2.2. Synthesis of IERs

IERs were synthesized by following suspension polymerization technique with some modifications as reported in our earlier work in the presence of n-heptane and isobutanol as diluents [22]. Series of AA based IERs were prepared by varying quantities of EGDMA, MBA and DVB. They are coded as AEC-1, AEC-2, AEC-3, AEC-4, ABC-1, ABC-2, ABC-3 ABC-4, ADC-1, ADC-2 and ADC-3 respectively. The details of the synthesis of IERs are given in Table 1. IERs were conditioned by giving alternate treatment of acid (1 N HCl) and base (1 N NaOH) with intermittent water (Millipore water) rinsing for three cycles and finally converted to K^+ form with KOH for further study.

2.2.1. Preparation of drug resin complexes (DRCs)

DRCs were prepared from IERs and drug by following batch method [23]. CP was dissolved in Millipore water and swelled IERs were slowly added under constant stirring with a magnetic stirrer (Remi model no: FHMS-3762, Mumbai, India). Each mixture was stirred at a speed of 500 rpm at room temperature for 24 h. The resultant DRCs were separated by centrifugation. The supernatant solution was filtered and set for HPLC analysis at 275 nm in order to find out loading of CP on IERs.

IERs showing comparatively higher up take of drug (i.e. >80%) was chosen from each series to prepare DRCs by varying the ratios of AEC-1, ABC-2 and ADC-3 with CP i.e. 1:1, 1:2 and1:4 (w/w) to study their taste masking property in details.