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

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Original Research Paper

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.

Keywords:
Ion exchange resins
Biopolymers
In vitro & in vivo taste masking
Ciprofloxacin
Sustain release
Release mechanism and kinetics
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 fluoroquinolone 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. Pusal 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 used by many researchers for sustain release of drugs in electrolyte matrices by Bermudez et al. [15]. Although CP has good broad spectrum antibacterial activity, it has bitter taste which becomes palatability challenge and has patients compliance for oral administration.

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.
Drug retained on IERs

Synthesis of IERs by varying ratios of monomers, cross linkers and solvents.

<table>
<thead>
<tr>
<th>IERs</th>
<th>AA (g)</th>
<th>EGDMA (g)</th>
<th>MBA (g)</th>
<th>DVB (g)</th>
<th>Heptane (g)</th>
<th>Isobutanol (g)</th>
<th>Crosslinking (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEC-1</td>
<td>63</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>41.6</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>AEC-2</td>
<td>72</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>27.7</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>AEC-3</td>
<td>56</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>41.6</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>AEC-4</td>
<td>64</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>27.7</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>ABC-1</td>
<td>36</td>
<td>–</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>10</td>
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<tr>
<td>ABC-2</td>
<td>63</td>
<td>–</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>30</td>
<td>10</td>
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<tr>
<td>ABC-3</td>
<td>32</td>
<td>–</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>ABC-4</td>
<td>54</td>
<td>–</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>30</td>
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<td>–</td>
<td>–</td>
<td>3.5</td>
<td>–</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>ADC-2</td>
<td>45</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>–</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>ADC-3</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>–</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

They were designated as AEC 1:1, AEC 1:2, AEC 1:4, ABC 1:1, ABC 1:2, ABC 1:4, ADC 1:1, ADC 1:2 and ADC 1:4 respectively.

Loading of drug was calculated by following eqn.

\[
\% \text{ Loading} = \left( \frac{\text{Drug retained on IERs}}{\text{Initial drug concentration}} \right) \times 100 \quad (1)
\]

ADC-3 was chosen for the preparation of physical mixtures (PMs) with CP by mixing in mortar-pestle. They were prepared by three different ratios and coded as PM 1:1, PM 1:2 and PM 1:4.

2.2.2. In vitro and in vivo taste masking studies

In vitro taste masking study of CP and DRCs prepared with AEC-1, ABC-2 and ADC-3 in different ratios i.e. 1:1, 1:2 and 1:4 (w/w) was carried out at simulated salivary fluid (SSF) pH 6.8. Pre-decided amount of DRCs was dispersed in 5 ml SSF in conical flasks separately [24]. Samples of 1 ml were withdrawn from the conical flask at time intervals of 30 s and filtered with 0.45 μm Whatman filter paper. The filtrates were analysed for CP at 275 nm by using HPLC. This study was performed in triplicate for each sample, and the average values for respective DRCs were reported.

In vivo taste masking study of CP, DRCs prepared with AEC-1, ABC-2 and ADC-3 and PMs prepared with ADC-3 was performed by a panel of 9 Human volunteers in the age group of 18–30 years of both the sexes from whom written consent was obtained after getting approval from Human Ethic Committee (HEC no. 423/2014) of the Government Medical College, Bhavnagar, Gujarat. CP, different ratios DRCs prepared by CP with AEC-1, ABC-2 and ADC-3 IERs i.e. 1:1, 1:2 and 1:4 (w/w) and PMs prepared with ADC-3 IER at ratio 1:1, 1:2 and 1:4 were placed on tongue by each volunteer separately and taste was evaluated for 30 s resident time by reported method [25]. Volunteers were asked to gargle immediately after each evaluation. The bitterness of DRCs experienced by the volunteers was assessed their glass transition behaviour under nitrogen flow (20 ml/min).

2.2.3. Powder X-ray diffraction (P-XRD)

ADC-3, CP, ADC 1:4 and PM 1:4 were investigated by Powder X-ray diffraction (P-XRD, Philips-X’ Pert MPD System) Netherland. P-XRD was recorded from 2θ to 60(2θ) at a scanning speed of 0.3 deg/s. PW3123/00 curved Ni-filtered Cu-Kx (λ = 1.54056 Å) radiation was used as the X-ray source.

2.2.4. Fourier transforms infrared spectroscopy (FT-IR)

FT-IR was recorded on Perkin–Elmer, GX-FTIR, GX series 49387 (Spectrum GX, USA). The samples were mixed with KBr and converted into pellets at 100 Kg pressure using a hydraulic press. The spectra were obtained at the wavelength range 4000–400 cm⁻¹.

2.2.5. Scanning electron microscopy (SEM)

SEM images of dried ADC-3, CP, ADC 1:4 and PM 1:4 were recorded by using LEO Instruments (Kowloon, Hong Kong) microscope after the gold sputter coating on desired samples. The samples were prepared in Millipore water and dried on aluminium grids at room temperature prior to SEM analysis.

SEM images of dried ADC-3, CP, ADC 1:4 and PM 1:4 were assessed by DSC measurements by Mettler Toledo (DSC 822®) Japan. The samples were dried in oven for overnight at 60 °C. Ten milligrams of each sample was taken in alumina crucible and heated in the temperature range of 30–450 °C, at a 5 °C/min heating rate to assess their glass transition behaviour under nitrogen flow (20 ml/min).

2.2.7. Preparation of ADC 1:4-AL and ADC 1:4-AL-CS IPN beads

A known amount of ADC 1:4 containing 20 mg of CP was mixed with 20 ml of 2% AL aqueous solution and stirred for 2 h to get homogenous suspension. The solution was filled in 25 ml syringe having needle size 1.2 mm and poured at a distance of 15 cm height in 0.25 M CaCl₂ solution under mild stirring at room temperature. The beads formed by ionic gelation were cured for 30 min at room temperature followed by washing with Millipore water and finally dried at room temperature until constant weight was obtained.

For the synthesis ADC 1:4-AL-CS IPN beads, ADC 1:4 containing 20 mg of CP was mixed with 20 ml of 2% AL solution. The mixture was stirred for 2 h to get homogenous suspension solution. CS solution containing 2% was prepared separately in acidic media at pH 4.5 under constant stirring at room temperature and mixed in 0.25 M CaCl₂ solution. The ADC 1:4 containing AL solution was dropped by using 25 ml syringe of needle size 1.2 mm at a distance of 15 cm height with mild stirring in the mixture containing of CS and CaCl₂ solution. The beads were cured for 30 min at room temperature followed by washing with distilled water and finally dried at
room temperature till the constant weight was obtained. Fig. 1 shows the schematic diagram for the preparation of ADC 1:4-AL and ADC 1:4-AL-CS IPN beads by ionic crosslinking method.

Mean diameter of dry beads was measured with micrometer screw (Mitutoyo, Japan) and entrapment efficiency (%) of CP in ADC 1:4-AL and in ADC 1:4-AL-CS was determined by HPLC at 275 nm by measuring the left CP in CaCl2 solution during the preparation of IPN beads. The entrapment efficiency was calculated by using following eqn.

\[
\% \text{ Entrapment efficiency} = \left( \frac{|C_1 - C_2|}{C_1} \right) \times 100
\]

where \(C_1\) is the known concentration of CP in ADC 1:4 and \(C_2\) is the concentration of CP in CaCl2 solution.

2.2.8. High pressure liquid chromatography (HPLC)
The quantitative analysis of drug (CP) was performed using HPLC system of Waters Alliance model with Waters 2996 Photo Diode array Detector. The stationary phase was Enable C18H (Shimadzu). The mobile phase was a mixture 0.25 M H3PO4 and acetonitrile in the ratios of 60:40. UV detector was set at 275 nm and oven temperature was maintained at 30 °C. The flow rate of mobile phase was 1.0 ml/min and the injection volume was 20 μl/ml. The sample temperature was maintained at 10 °C.

2.2.9. In vitro release studies
Buffer solution of pH 1.2 simulated gastric fluid (SGF) was prepared by mixing solutions of 0.2 M HCl and 0.2 M KCl. Buffer solution of pH 7.4 and 6.8 simulated intestinal fluid (SIF) and simulated salivary fluid (SSF) were prepared by mixing solutions of 0.1 M KH2PO4 and 0.1 M NaOH. In vitro release of CP, ADC 1:4 and PM 1:4 were studied at gastric pH 1.2 by using dialysis bag method. Pre-decided amount of CP, ADC 1:4 and PM 1:4 were dispersed separately in 5 ml buffer solution in activated cellulose dialysis bags [26]. The dialysis bags were dipped into receptor compartment containing 100 ml of medium and was shaken at 37 ± 0.5 °C at a shaking speed of 100 rpm on Remi shaking water bath (Model no: RSB-12, Mumbai, India), whereas ADC 1:4-AL and ADC 1:4-AL-CS were studied by incubating 10 mg of CP containing IPN beads in 100 ml of SGF (pH 1.2) in 125 ml conical flask kept in a shaking water bath at 37 ± 0.5 °C at a shaking speed of 100 rpm/min. After 3 h, the beads were filtered and transferred to 100 ml of SIF (pH 7.4) and incubated at 37 ± 0.5 °C at a shaking speed of 100 rpm/min. At desired intervals of time, 1 ml sample was withdrawn and replaced with same amount of fresh medium and analysed by HPLC. Receptor compartment was closed to prevent the evaporation losses from the medium. The study was performed for three times.

2.2.10. Drug release kinetics
The drug release kinetics was performed for ADC 1:4-AL and ADC 1:4-AL-CS IPN beads. The results obtained were fitted into two kinetics models; Higuchi and Korsmeyer-Peppas. Higuchi model describes the release of drugs as a square root of time based on Fickian diffusion.

\[
Q = k_H t^{1/2}
\]

\(k_H\) is a constant reflecting the design variables of the system. The release of drug from complexes was fitted by Korsmeyer-Peppas model to find out the mechanism of drug release by following equation [27].

\[
\frac{M_t}{M_\infty} = Kt^n
\]

where \(M_t/M_\infty\) is the fraction of drug released at time \(t\), \(K\) is rate constant and \(n\) is the diffusion exponent characteristic of release mechanism. The \(n\) value indicates the type of release mechanism. The values of \(n\) between 0.45 and 0.85 are due to the diffusion controlled and swelling controlled transport mechanism (anomalous/non-Fickian transport), the values above 0.85 indicate case II transport mechanism (zero order) which indicates polymer relaxation takes place during polymer swelling.

2.2.11. Statistical analysis
All data are presented as mean ± standard deviation. Statistical significance was assessed by using IBM SPSS statistics version 21 software by two-way ANOVA with Duncan’s multiple range test. A probability level of \(p < 0.05\) was considered to be statistically significant.

3. Results and discussion

3.1. Drug loading on synthesized IERs

Fig. 2 shows the percentage of drug loading on all IERs. The loading of CP was carried out to select the IERs from each series with highest drug loading capacity and to study them in detail for taste masking. The drug loading on IERs was found
to be in the range of 72 %–92 %. IERs with low degree of crosslinking showed high loading of CP whereas the drug loading is low for the IERs of high degree of crosslinking. This trend is due to decrease in the availability of functional groups on the IERs matrix at higher degree of crosslinking. The loading of CP may be due to breaking of the van der Waals forces between the drug molecules of carboxylic groups and ion exchange reaction also takes place during the complex formation between IERs and drug.

3.1.1. Effect of drug loading on different ratios of IERs

The loading of CP on AEC-1, ABC-2 and ADC-3 at 1:1, 1:2 and 1:4 ratios are tabulated in Table 2. Loading of CP increases with the increase in the quantity of IERs and ADC-3 at 1:2 ratio showed higher loading of CP compared to other IERs.

### Table 2 – Percentage of CP loading on AEC-1, ABC-2 and ADC-3 at 1:1, 1:2 and 1:4 ratios (n = 3, X = ±S.D).

<table>
<thead>
<tr>
<th>IERs</th>
<th>Ratios of CP: IERs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1:1 (%)</td>
</tr>
<tr>
<td>AEC-1</td>
<td>87.40 ± 0.43</td>
</tr>
<tr>
<td>ABC-2</td>
<td>88.08 ± 0.56</td>
</tr>
<tr>
<td>ADC-3</td>
<td>91.78 ± 0.14</td>
</tr>
</tbody>
</table>

3.1.2. In vivo and in vitro taste masking at SSF pH

Taste masking efficiency of CP, DRCs prepared with AEC-1, ABC-2 and ADC-3 and PMs prepared with ADC-3 were carried out by in vivo and the results are shown in Fig. 3A. The statistical analysis showed significant suppression (P < 0.05) for the drug. The taste masking of CP by different IERs was observed in the following order AEC-1>ABC-2>ADC-3. Taste evaluation by volunteers graded ADC 1:4 of ADC-3 (value 0.66 Fig. 3A) as tasteless as compared to other DRCs. The taste masking value is found to be below 2 which signify the good taste masking of DRCs and this has been explained by Maniruzzaman et al. [25].

In vitro taste masking efficiency of the DRCs prepared with AEC-1, ABC-2 and ADC3 was studied for the release of CP at SSF pH and the results are shown in Fig. 3B. The release of CP from DRCs was in the following order AEC-1>ABC-2>ADC-3. ADC 1:4 showed only 4.26 ± 0.38% of CP release for a contact time of 30 s ultimately resulting in better taste masking. The probable reason is that at pH 6.8, counter ions available to exchange amine groups present in CP of ADC-3 complex are not sufficient due the presence of crosslinked bulky and hydrophobic DVB group which ultimately results in slow release of CP. Whereas faster drug release in case of AEC-1 and ABC-2 is observed as the copolymers possess aliphatic cross-linkers such as EGDMA and MBA which may allow fast release of drug as compared to ADC-3.
3.2. Instrumental analysis and in-vitro drug release studies

Based on in vivo and in vitro taste masking studies CP, ADC-3, ADC 1:4 and PM 1:4 are extensively characterized to prove the complexation of ADC 1:4 with FTIR, SEM, DSC, P-XRD and in vitro drug release.

Fig. 4 shows the FT-IR spectrum of ADC-3, ADC 1:4, PM 1:4, and CP. ADC-3 shows peaks at 3423 cm\(^{-1}\), 2922 cm\(^{-1}\) and 1676 cm\(^{-1}\) which represent the stretching frequency of \(-\text{OH}\) group, \(-\text{C} = \text{C}\) of aromatic ring and \(-\text{C} = \text{O}\) group of aryl acid respectively which confirms the formation of ADC-3. CP shows peak at 3379 cm\(^{-1}\) which is correspond to \(-\text{NH}\) stretching and the peaks from 2449 cm\(^{-1}\) to 3093 cm\(^{-1}\) are due to dimerization of \(-\text{COO}\) group present in drug. The peak at 3537 cm\(^{-1}\) is due to \(-\text{OH}\) stretching. The peak at 3379 cm\(^{-1}\) corresponds to \(-\text{NH}\) of CP is absent in ADC 1:4, which confirms the formation of complex by interacting secondary amine of CP with ADC-3. The peaks at 3093 cm\(^{-1}\) to 2449 cm\(^{-1}\) are absent due to breaking of acid dimers during complexation. The stretching frequency at 3531 cm\(^{-1}\) corresponds to \(-\text{OH}\) group of CP is also absent which signifies the complexation [13]. Spectra of PM 1:4 showed superimposition of CP on ADC-3 ensuring that there is no formation of complex.

Fig. 5A shows the SEM images of CP, ADC-3, ADC 1:4 and PM 1:4. Rod-shape structure of pure CP is visualized and it signifies the crystalline structure of the drug whereas ADC-3 showed amorphous nature. PM 1:4 showed dense clusters and crystals of CP are visualized on the surface of the image which indicates that there is no formation of complex between CP and ADC-3 IER. A significant change in the morphologies of ADC 1:4 is observed and found to be different from images of CP, ADC-3 and PM 1:4 which clearly indicates an amorphous form of CP have been formed during the complexation of CP with ADC-3.

Fig. 5B shows the DSC studies of CP, ADC-3, ADC 1:4 and PM 1:4. ADC-3 did not show sharp peak but showed broad peak in the range of 70 °C–146 °C which represent the baseline transition of ADC-3. Similar studies for INDIION 294 has been reported by Thukaramji et al. [28]. CP shows two thermograms peaks at 142 °C and 286 °C indicating glass transition temperature (Tg) and melting point of drug respectively. The thermograms of ADC 1:4 has shifted to lower temperature 73 °C concluding the forming the amorphous nature when complexed with drug. Whereas the endothermic melting peaks of PM 1:4 were found close to the endothermic peak of CP indicates that complex formation in PMs does not take place. The resemblance in the sharpness of the peaks of PM 1:4 and CP further supports this observation.

Fig. 5C shows the P-XRD analysis of CP, ADC-3, ADC 1:4 and PM 1:4. CP is observed to be crystalline by showing several sharp peaks ranging from 8.33°, 9.12°, 11.48°, 13.73°, 15.30°, 16.53°, 18.90°, 19.46°, 20.03°, 21.15°, 22.61°, 24.88°, 25.9°, 26.66°, 27.11°, 30.48°, and 35.09° respectively, while ADC-3 is amorphous in nature with no peaks. The ADC 1:4 did not showed diffraction peaks of CP concluding that physical state of CP from crystalline form to amorphous form during the
formation of complex. This finding confirms that the entrapped CP is dispersed monomolecularly on ADC-3 matrix [29]. PM 1:4 retained the peaks of CP due to its crystal nature and some diffused peaks due to ADC-3 which indicate that there is no complex formation.

Fig. 5D shows the in-vitro drug release studies for CP, ADC 1:4 and PM 1:4 at gastric pH 1.2. The release is observed to be in the following order CP > PM 1:4 > ADC 1:4. The higher release of CP was observed from PM 1:4 compared to ADC 1:4. This may be due to the complex formation between CP and ADC-3. The displacement of H⁺ with ADC 1:4 results in quick release of CP in SGF media and it is within 60 min and similar result was also reported by Pisal et al. for the release of CP from IERS [14].

3.3. Preparation and characterization of ADC 1:4-AL and ADC 1:4-AL-CS beads

ADC 1:4 were designed for sustain release studies by forming IPN beads with AL and CS biopolymers. IPN beads of ADC 1:4-AL and ADC 1:4-AL-CS showed spherical shape. The bead size shown in Table 3 of ADC 1:4-AL was found to be 533 ± 12 μm whereas it was increased up to 932 ± 26 μm for ADC 1:4-AL-CS; this may be due to formation of ionic crosslinking between AL of −COOH and CS of NH₃⁺ with Ca²⁺ which ultimately resulted in the increases of bead size. The increases in bead sizes have also reported by previous researchers [30,31].

Fig. 6A shows the mechanism of ionic crosslinking with Ca²⁺ between two polymer strands of AL and ionic interaction between CS of NH₃⁺ and COOH of AL during the formation of IPN beads [30]. The mechanism was confirmed by the FTIR spectra.

Table 3 - Parameters for entrapment efficiency and bead diameter of IPN beads (n = 3, x = ±S.D).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ADC 1:4-AL</th>
<th>ADC 1:4-AL-CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrapment efficiency (%)</td>
<td>91.85 ± 1.22</td>
<td>90.28 ± 0.85</td>
</tr>
<tr>
<td>Bead diameter (μm)</td>
<td>533 ± 12</td>
<td>932 ± 26</td>
</tr>
</tbody>
</table>
Fig. 6B shows FTIR spectra of ADC 1:4 (explained in Section 3.2), ADC 1:4-AL and ADC 1:4-AL-CS beads. In case of ADC 1:4-AL beads, AL show asymmetric and symmetric stretching vibrations of carboxyl anions at 1622 cm\(^{-1}\) and 1468 cm\(^{-1}\) respectively. Cyclic ether bridge at 1022 cm\(^{-1}\) is observed in case of ADC 1:4-AL, confirms the entrapment of ADC 1:4 by AL. In case of ADC 1:4-AL-CS, peaks are observed at 1022 cm\(^{-1}\) and 1263 cm\(^{-1}\) which indicate the stretching of C–O–C of CS. Peak at 1635 cm\(^{-1}\) shows the primary amine group of CS and the peak of carboxyl anion is shifted from 1468 cm\(^{-1}\) to 1419 cm\(^{-1}\) due to ionic bonding of AL with CS.

The entrapment efficiency of ADC 1:4-AL and ADC 1:4-AL-CS is tabulated in Table 3 and found to be 91.85 ± 1.22% and 90.28 ± 0.85% respectively which indicate that ADC 1:4 has been well entrapped by the biopolymers matrices. The high entrapment value indicates that during gelation ionic cross-linking takes place between \(\text{COOH}\) group of AL and \(\text{NH}_3^+\) group of CS. The other reason may be the low pH of the solution causes ionic crosslinking between CS and AL [31].

3.3.1. Drug release profile
The drug release profile of ADC 1:4, ADC 1:4-AL and ADC 1:4-AL-CS at gastric pH i.e. 1.2 is presented in Fig. 7. The release of CP was completed within 60 min for ADC 1:4 and was found to be 92.53 ± 1.98%. In case of IPN beads of ADC 1:4-AL and ADC 1:4-AL-CS the release of CP was studied for the initial period of 3 h at SGF pH. The rate of drug release was slow (<20%) for the IPN beads and it follows the following order i.e. ADC 1:4-AL > ADC 1:4-AL-CS. In SGF pH 1.2 the H\(^+\) was not able to exchange with DRC-AL-CS IPN beads because there is ionic bonding between \(\text{COOH}\) groups of AL and \(\text{NH}_3^+\) groups of CS which restrict the release of drug molecules from DRC-AL-CS beads.

The release of CP from the IPN beads of ADC 1:4-AL and ADC 1:4-AL-CS at SIF pH 7.4 was carried out for 7 h after removing the IPN beads from SGF pH. After 10 h the release of CP from ADC 1:4-AL and ADC 1:4-AL-CS was found to be 88.44 ± 1.74% and 75.24 ± 1.53% respectively. In SIF media the release CP from IPN beads of ADC 1:4-AL was fast compared to the ADC 1:4-AL-CS may be due to the presence of phosphate ions of buffer solution which have high affinity for Ca\(^{2+}\) and increased the release rate of CP. The slow release of CP from ADC 1:4-AL-CS may be due to the strengthening of IPN beads by ionic interaction between \(\text{COO}^-\) groups of AL and \(\text{NH}_3^+\) groups of CS. To demonstrate the above explanation the schematic diagram and photographs representing the drug release mechanism in SGF and SIF media of IPN beads (ADC 1:4-AL-CS) are shown in Fig. 8.

Fig. 6 – (A) Schematic diagram for the preparation of ADC 1:4-AL and ADC 1:4-AL-CS IPN beads by ionic crosslinking method. (B) Scheme representing IPN bead formation mechanism under the influence of Ca\(^{2+}\) crosslinking between the AL and CS (C) FTIR spectra of ADC 1:4-AL and ADC 1:4-AL-CS.

Fig. 7 – Drug release profile of ADC 1:4, ADC 1:4-AL and ADC 1:4-AL-CS at gastric pH 1.2 and at intestinal pH 7.4.
diagram of IPN beads at pH 1.2. Fig. 8B shows the photographs of IPN beads at pH 1.2 after 3 h. Fig. 8C shows the complete degradation of ionic crosslinking at SIF pH. Fig. 8D shows the photograph of degraded IPN beads at pH 7.4 after 10 h.

3.3.2. Kinetics studies by Higuchi and Korsmeyer Peppas model
The kinetics studies of ADC 1:4-AL and ADC 1:4-AL-CS were carried out by using two models: Higuchi and Korsmeyer Peppas model. The values of correlation coefficient ($r^2$) and rate constants ($k$) are tabulated in Table 4. The diffusion exponent “$n$” of ADC 1:4-AL and ADC 1:4-AL-CS follows anomalous (non-fickian) diffusion in all medium. The $n$ value increased from the ADC 1:4-AL to ADC 1:4-AL-CS IPN beads show the crosslinking effect between the AL and CS. This indicates that mechanism depends on both diffusion and swelling control. The $r^2$ was near to unity and shows the best fit to non fickian model [32].

### Table 4 – Drug release kinetics for IPN beads.

<table>
<thead>
<tr>
<th>Kinetic models</th>
<th>Parameters</th>
<th>ADC 1:4-AL</th>
<th>ADC 1:4-AL-CS</th>
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<td>pH 1.2</td>
<td>pH 7.4</td>
<td>pH 1.2</td>
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</tr>
<tr>
<td></td>
<td>$K_p$</td>
<td>0.7434</td>
<td>1.4917</td>
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</tbody>
</table>

4. Conclusion
IERs with highest drug loading were studied for the taste masking of CP. In vitro and in vivo taste masking studies showed ADC 1:4 have good taste masking properties compared to other DRCs. FT-IR spectra confirmed the possible interaction between the drug and IERs. P-XRD and DSC confirmed that drug was in amorphous state in the IERs by forming complexes. ADC 1:4 studied for sustain release by
forming IPN beads with AL and CS. The CP release was very slow in SGF media and when transferred into SIF media the release of CP was due to the degradation of ionic crosslinking of IPN beads. The kinetic study of model showed the release of CP depends on non Fickian diffusion.

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References