Taste masking of ofloxacin and formation of interpenetrating polymer network beads for sustained release

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ABSTRACT

The objective of this study was to carry out taste masking of ofloxacin (Ofi) by ion exchange resins (IERs) followed by sustained release of Ofi by forming interpenetrating polymer network (IPN) beads. Drug-resin complexes (DRCs) with three different ratios of Ofi to IERs (1:1, 1:2, 1:4) were prepared by batch method and investigated for in vivo and in vitro taste masking. DRC of methacrylic acid-divinyl benzene (MD) resin and Ofi prepared at a ratio of 1:4 was used to form IPN beads. IPN beads of MD 1:4 were prepared by following the ionic cross-linking method using sodium carboxymethyl xanthan gum (SCMXG) and SCMXG-sodium carboxymethyl cellulose (SCMXG-SCMC). IPN beads were characterized with FT-IR and further studied on sustained release of Ofi at different pH. In vivo taste masking carried out by human volunteers showed that MD 1:4 significantly reduced the bitterness of Ofi. Characterization studies such as FT-IR, DSC, P-XRD and taste masking showed that complex formation took place between drug and resin. In vitro study at gastric pH showed complete release of drug from MD 1:4 within 30 min whereas IPN beads took 5 h at gastric pH and 10 h at salivary pH for the complete release of drug. As the crosslinking increased the release kinetics changed into non-Fickian diffusion to zero-order release mechanism. MD 1:4 showed better performance for the taste masking of Ofi and IPNs beads prepared from it were found useful for the sustained release of Ofi at both the pH, indicating a versatile drug delivery system.

1. Introduction

The taste masking of bitter drugs is an important factor for the development of drug therapy. It is a major challenge especially for the development of orally administered active pharmaceutical ingredient (API) in pharmaceutical industry [1]. Most of the APIs are either bitter or salty in taste. So there is a need for pleasant taste for oral dosage to increase the value of the product with palatable property and for better compliance of patients [2]. Many taste masking methods have been used for orally unacceptable APIs, which include microencapsulation with various polymers [3], lipophilic vehicles by obstructing the taste buds [4] and forming inclusion compounds of drugs with cyclodextrins [5].

Ion exchange resins (IERs) are high molecular weight, insoluble, porous, cross-linked swellable and amorphous poly-electrolytes that exchange their mobile ions of equal charge to the ions present in the surrounding medium reversibly and stoichiometrically [6]. IERs are functional copolymers; their ionizable groups have the properties of complexation with bitter drugs, which ultimately results in masking the bitter taste of drugs [7]. The drug resin complexes (DRCs) are stable at salivary pH and the patient does not sense bitter taste of drug when it is swallowed. The other taste masking methods are tedious and require a long time of processing [8].

Ofloxacin (Ofi) is chemically racemate, (±)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido[1, 2, 3-de]-1, 4-benzoxazin-6-carboxylic acid [9]. It has activity against a broad spectrum of Gram positive, Gram negative and anaerobic bacteria [10]. Ofi is a fluoroquinolone and is used for the treatment of urinary tract infections, prostatitis and gonorrhea. It is least absorbed from the lower part of the gastrointestinal tract and better absorbed from the stomach. Taste masking methods of Ofi by using microspheres and forming rapid disintegrating tablets have been studied by some researchers [9,11].

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 Recently, researches have focused on the use of biopolymers to form interpenetration polymer network (IPN) beads for drug delivery applications [12]. Biopolymers are preferred because of their stable, biocompatible, non-toxic and biodegradable properties which have fascinated their use in pharmaceutical field [13]. They also have some limitations such as microbial contamination, drop in viscosity and uncontrolled rate of hydration. These problems can be overcome by modifying the biopolymers into IPN beads for the sustained release of drugs [14]. Xanthan gum (XG) is used in pharmaceutical industry as a thickening, suspending, and emulsifying agent [15]. XG is a high molecular weight, anionic extracellular polysaccharide produced by the Gram-negative bacterium Xanthomonas campestris. Hydrophilic matrices have been formulated from XG for controlled release of drugs [16,17]. XG can be modified to sodium carboxymethyl xanthan gum (SCMXG) which can be ionically crosslinked with Al\(^{3+}\) to form IPN beads being useful for drug delivery [18].

Sodium carboxymethyl cellulose (SCMC) is an anionic derivative of natural polymer cellulose. It is prepared by partial substitution of hydroxyl methyl group of cellulose by hydrophobic carboxy methyl group. SCMC behaves as polyanion at pH more than 4 and its sodium salt is water soluble [19]. IPN beads of SCMXG and SCMC have been used by some researchers for the sustained release of drugs such as diltiazem, ketoprofen and diclofenac sodium [20–22]. However, the taste masking by using DRCs followed by sustained release of O

In this study, different methacrylic acid (MAA) based-IERs were prepared by varying cross linkers. These IERs possess high ion exchange capacity (> 11 meq/g), stability and insolubility properties as well as high drug loading capacity. DRCs of IERs and O

2. Materials and methods

2.1. Materials

Ofl was received as research sample from Elder Pharmaceuticals Ltd. (Navi Mumbai, India). MAA, ethylene glycol dimethacrylate (EGDMA) and N,N'-methylene bis acrylamide (MBA) were purchased from Central Drug House (Mumbai, India). Divinyl benzene (DVB) supplied by Merck (Germany) was used as received. XG, SCMC, and benzoyl peroxide (BP) were 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). Cellulose acetate dialysis tube (cut-off molecular mass of 12000) and monochloroacetic acid were procured from Sigma Aldrich (USA). All other reagents used in this study were of HPLC grade and used without further purification. Millipore water was prepared by Milli-Q plus system (Millipore Corporation Breford, USA) and used for every experiment.

2.2. Synthesis of IERs

MAA-based IERs were synthesized by following the suspension polymerization technique with some modifications as reported in our earlier work in the presence of n-heptane and isobutanol as diluents and BP as an initiator [23]. Different cross-linking agents like EGDMA, MBA and DVB were used separately during the synthesis of MAA-based IERs. They are coded as methacrylic acid-ethylene glycol dimethacrylate resin (ME), methacrylic acid-N,N'-methylene bis acryl-

2.3. Preparation of DRCs

DRCs were prepared by the complexation of Ofl with IERs by following reported batch method [24]. Known quantity of Ofl was dissolved in a mixture of water and ethanol (3:1, v/v). To it pre-swelled IERs were added and stirred with magnetic stirrer. Each of the mixture of IERs and Ofl at ratios of 1:1, 1:2 and 1:4 (m/m) was stirred at a speed of 500 rpm at room temperature for 24 h, separately. The DRCs formed were separated by centrifugation and washed with copious amount of Millipore water to remove un-complexed drug. DRCs were dried in oven at 45 °C and stored in the desiccators for further experiments. They were designated as ME 1:1, ME 1:2, ME 1:4, MB 1:1, MB 1:2, MB 1:4, MD 1:1, MD 1:2 and MD 1:4, respectively. The supernatant solution was filtered and set for HPLC analysis at 292 nm in order to find out loading of Ofl on IERs. Loading of drug was calculated by the following equation.

\[
\text{Loading\%} = \frac{\text{Drug retained on IERs}}{\text{Initial drug concentration}} \times 100% \tag{1}
\]

2.4. Modification of XG to SCMXG

XG was modified to SCMXG by substituting –OH group with carboxy methyl group by following reported method [25]. Known amount of XG was dispersed in ice cold solution of 45% (m/v) NaOH. The dispersion was kept at 5 °C with continuous stirring for 1 h. Monochloroacetic acid was dissolved in water to prepare 75% (m/v) solution and added to the reaction mixture with stirring. The temperature was raised to 15–18 °C. After 30 min, the temperature was increased up to 75 °C and maintained there for 30 min. The reaction mixture was allowed to cool up to room temperature; the sample was filtered, washed with Millipore water, cut into pieces and dried in oven at 50 °C. The dried product was swelled by using 80% of methanol. The product, SCMXG, was again dried and used for the further experiments.

2.5. Preparation of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC IPN beads

A solution of 2% SCMXG (m/v) in water was prepared and mixed with known quantity of MD 1:4. The mixture was stirred for 2 h to get homogenous suspension. It was transferred to a 2.5 mL syringe containing needle of 1.2 mm diameter and poured at a distance of 10 cm height in AlCl\(_3\) solution under slow stirring at room temperature. The same method was followed for the preparation of MD 1:4-SCMXG-SCMC IPN beads. The beads were washed with Millipore water and finally dried at room temperature until constant weight was obtained. The formulations of beads prepared are given in Table 3.

2.6. Preparation of physical mixtures of MD

MD showing better taste making of Ofl was chosen for the preparation of physical mixtures (PMs) with Ofl by mixing with mortar-pestle. They were prepared in three different ratios of drug: MD and coded as PM 1:1, PM 1:2 and PM 1:4.
Drug entrapment efficiency (%) = \( \frac{1 - \text{2}}{\text{1}} \times 10^2 \)

2.9.2. Fourier transform infrared spectra (FT-IR)

The samples were mixed with KBr and their complexes were recorded on a Perkin Elmer, GX-FT-IR, GX series 49387 (Spectrum GX, USA). The spectra were recorded in the range of 4000–400 cm\(^{-1}\).

2.9.3. Differential scanning calorimetry (DSC)

MD, Ofi, MD 1:4 and PM 1:4 were assessed by DSC analysis using Mettler Toledo (DSC 822\(^\circ\), Japan). The samples were dried in oven for overnight at 60 °C. 10 mg 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 behavior with continuous flow of nitrogen (20 mL/min).

2.9.4. High pressure liquid chromatography (HPLC)

The quantitative analysis of drug (Ofi) 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 of 0.25 M H\(_3\)PO\(_4\) and acetonitrile at ratio of 60:40 (v/v). UV detector was set at 292 nm whereas oven temperature was maintained at 30 °C during the analysis of samples. 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.

2.10. In vivo taste masking studies

In vivo taste masking study of Ofi, DRCs and PMs was performed by a panel of nine 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, India. Ofi, DRCs and PMs were placed on tongue by each volunteer separately and taste was evaluated for 30 s resident time following the reported method [25]. Taste masking information was provided to the volunteers and concern sheet was given to score the bitterness scale to each one. The volunteers have been well explained about the nature of drug, IERs and DRCs before the study. Volunteers were asked to gargle immediately after each evaluation. The bitterness was recorded immediately according to the bitterness scale ranging from 0 to 5 (0-no bitter, 1-threshold bitter, 2-slight bitter, 3-moderate bitter, 4-bitter and 5-strong bitter).

2.11. In vitro taste masking studies

The taste masking ability of DRCs was evaluated by in vitro methods where a delayed drug release from the DRCs within 30 s was considered as in vitro parameter for successful taste masking ability. In vitro taste masking study of DRCs was carried out at simulated salivary pH 6.8. Pre-decided amount of DRCs was dispersed separately in 5 mL of phosphate buffer of pH 6.8 in conical flasks [2]. Samples of 1 mL were withdrawn and dispersed separately in 5 mL of buffer solution in activated cellulose dialysis bags. The drug was also studied similarly for comparison.

### Table 1

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

| IERs | MAA (g) | EGDMA (g) | MBA (g) | DVB (g) | n-Heptane (g) | Isobutanol (g) | Cross-linking (%) |
|------|---------|-----------|---------|---------|-------------|--------------|-----------------|
| MD   | 47.5    | –         | –       | 2.5     | –           | 50           | 5               |
| ME   | 63      | 7         | –       | –       | 41.6        | –            | 10              |
| MB   | 63      | –         | 7       | –       | –           | 30           | 10              |

MMA: Methacrylic acid, EGDMA: Ethylene glycol dimethacrylate, MBA: N,N’ methylene bis acrylamide, DVB: Divinyl benzene.

### Table 2

Physico-chemical properties of synthesized IERs.

| IERs | Ion exchange capacity (meq/g) | Swelling percentage (H\(^+\)=Na\(^+\)) | C (%) | H (%) | N (%) | Yield (%) |
|------|-------------------------------|-------------------------------------|-------|-------|-------|-----------|
| MD   | 11.7                          | 70                                  | 20.95 | 4.12  | –     | 96        |
| ME   | 10.4                          | 45                                  | 33.98 | 6.54  | –     | 94        |
| MB   | 11.8                          | 90                                  | 30.91 | 6.77  | 0.58  | 94        |

Table 3: Parameters for preparing IPN beads.

| Formulation codes | SCMG (%, m/v) | SCMC (%, m/v) | DRC (mg) | AlCl\(_3\) (%, m/v) | Gelation time (min) |
|-------------------|--------------|--------------|--------|-----------------|-------------------|
| MD 1:4-SCMXG      | 2            | –            | 42     | 2               | 30                |
| MD 1:4-SCMXG      | 2            | –            | 42     | 3               | 60                |
| MD 1:4-SCMXG-SCMC | 2            | 2            | 42     | 2               | 30                |
| MD 1:4-SCMXG-SCMC | 2            | 2            | 42     | 3               | 60                |

* DRC containing 10 mg of drug.

### 2.7. Measurement of bead size

Mean diameter of dry beads was measured with the help of micrometer screw (Mitutoyo, Japan) having accuracy of 0.001 mm.

### 2.8. Drug entrapment efficiency (%)

Drug (Ofi) entrapment efficiency (%) of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC was determined using HPLC at 292 nm by measuring Ofi left out in AlCl\(_3\) solution during the preparation of beads. The entrapment efficiency was calculated by using the following equation.

\[
\text{Drug entrapment efficiency} = \frac{(C1 - C2)}{C1} \times 100
\]

where \(C1\) and \(C2\) are the concentration of Ofi in MD 1:4 and AlCl\(_3\) solution, respectively.

### 2.9. Analytical methods

#### 2.9.1. Powder X-ray diffraction (P-XRD)

MD, Ofi, MD 1:4 and PM 1:4 were investigated by P-XRD (Phillips-\(\lambda\) X’ Pert MPD Model, Netherlands). P-XRD was recorded from 2° to 60°(2θ) at a scanning speed of 0.3 deg/s. PW3123/00 curved Ni-filtered Cu-K\(_\alpha\) (\(\lambda=1.54056\) Å) radiation was used as the X-ray source.

#### 2.9.2. Fourier transform infrared spectra (FT-IR)

FT-IR spectra of the MD, Ofi, MD 1:4, PM 1:4, biopolymers and their complexes were recorded on Perkin-Elmer, GX-FT-IR, 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 recorded in the range of 4000–400 cm\(^{-1}\).
purpose. The dialysis bags were dipped into receptor compartment containing 100 mL of buffer medium and were shaken at 37 °C ± 0.5 °C at a shaking speed of 100 rpm on Remi shaking water bath (RSB-12). Similarly, IPN beads of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC were studied for in vitro release of Olf at different pH such as gastric pH 1.2 and intestinal pH 7.4. The receptor compartment was closed to prevent the evaporation losses from the medium. The study was performed three times. Samples of 1 mL were withdrawn and drug released was analyzed by HPLC.

2.13. Drug release kinetics

The drug release mechanism of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC was performed. The results obtained were fitted into the following kinetics model; Korsmeyer-Peppas [27].

\[
\frac{M_t}{M_{\infty}} = K t^n
\]  
(3)

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.

2.14. Statistical analysis

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

3. Results and discussion

3.1. Preparation of DRCs

DRCs were prepared in different ratios of Olfs and IERs, i.e. 1:1, 1:2 and 1:4 (m/m). Drug loading on MD, MB and ME are shown in Fig. 1. The drug loading was found to be in the range of (47.11 ± 0.98)%–(97.710 ± 0.63)%). The drug loading was due to the ion exchange process between the positively charged amine groups and negatively charged carboxylic groups. The drug loading at 1:1 ratio of Olfs to IERs was found to be less as compared to 1:2 and 1:4 ratios. Maximum drug loading was found at 1:2 ratio of drug to IERs, and the uptake of Olfs was found to be more on MD resin. It was obvious that at higher concentration of drug ion exchange capacity of IERs can be utilized maximally.

3.2. In vivo and in vitro taste masking

In vivo taste masking study was carried out for Olfs, DRCs and PMs. A team of nine human volunteers participated in the taste masking studies after receiving their consent and results are shown in Fig. 2A. Statistical significance was assessed by two-way ANOVA test by using Duncan’s multiple range with probability level of \(P < 0.05\). ANOVA results showed that in vivo taste masking studies had very high statically significance with Olfs. The taste masking values of Olfs, DRCs and PMs were in the order MD > MB > ME > PMs > Olfs. The volunteers graded MD 1:4 as tasteless compared to other DRCs. This may be due to the ionic interaction between the drug and IERs. The cationic functional group of the drug might have interacted with the anionic functional group of the IERs. These interactions facilitated a hydrogen bonding interaction between the active amine group of the drug and carboxylic group of resin. This reason may have facilitated for in vivo taste masking [28].

Fig. 2B shows the result of in vitro taste masking studies of DRCs carried out at salivary pH 6.8. The release pattern of Olfs from respective DRCs was observed to be decreased in the following order ME > MB > MD. MD 1:4 showed only (1.22 ± 0.51) % release of Olf for a contact time of 30 s whereas for ME and MB it was (3.46 ± 0.54) % and (2.31 ± 0.21) %, respectively. At salivary pH 6.8 the phosphate group did not exchange with the amine groups present in Olf of MD due to the presence of bulky DVB cross-linker, which imparted steric hindrance and ultimately resulted in slow release of the drug [29]. The release of the drug was fast in case of ME and MB, as the copolymers possess aliphatic cross-linkers such as EGDMA and MBA, which allow faster release of drug than that of MD.

3.3. Analytical methods

Based on in vivo and in vitro taste masking studies of the drug copolymer MD, complex MD 1:4, Olfs, and PM 1:4 were extensively characterized with FT-IR, DSC and P-XRD to prove that the complex formation of MD 1:4 took place successfully.

Fig. 3A shows the FT-IR spectra of Olfs, MD, MD 1:4 and PM 1:4. MD shows peaks at 3408 cm\(^{-1}\) and 2929 cm\(^{-1}\), which represent the stretching frequency of hydroxyl group and aromatic ring, respectively whereas the broad peak at 1719 cm\(^{-1}\) was assigned to carbonyl functional group which confirms the formation of MD. Olf shows peaks in the range of 2685–3043 cm\(^{-1}\) and they were for the dimerization of carboxylic groups. Peak observed at 1623 cm\(^{-1}\) corresponded to N-H bending vibration of quinolone group whereas peak at 1712 cm\(^{-1}\) indicates stretching frequency of -CO group of Olf. In case of MD 1:4, the peaks from 2685 cm\(^{-1}\) to 3043 cm\(^{-1}\) of Olf are absent due to breaking of acid dimmers during complexation and confirm the formation of DRC. The peak observed at 1623 cm\(^{-1}\) was due to the fact that -NH group of Olf was also absent in MD 1:4. The shifting of carbonyl peak from 1719 cm\(^{-1}\) to 1711 cm\(^{-1}\) indicates quinolone group of Olf had reacted successfully with carboxylic group of MD and formed DRC. PM 1:4 shows the peaks of both MD and Olf, which indicates that complex formation did not take place during the preparation of PM 1:4.

Fig. 3B shows the DSC analysis of Olfs, MD, MD 1:4 and PM 1:4. The endothermic peaks of MD and Olfs were observed at 241 °C and 276 °C, respectively. The endothermic peak of Olf was shifted from 276 °C to 236 °C for MD 1:4, which indicates that Olf might be converted to amorphous form during the complexation with MD. Whereas the endothermic melting peaks of PM 1:4 were found close to the endothermic peaks of Olf and MD (276 °C and 241 °C), which indicates that the drug retained its crystalline property in physical mixture.

Fig. 3C shows the P-XRD analysis of Olfs, MD, MD 1:4 and PM 1:4. Olf was observed to be crystalline and diffraction index file showed several peaks at 5.8°, 10.9°, 13.1°, 13.9°, 15.8°, 18.2°, 19.2°, 20.5°, 21.9°, 23.8°, 25.8°, 26.6°, 27.5° and 29.9° 20. In case of MD, it did not exhibit any peaks indicating its amorphous nature. P-XRD of PM 1:4
showed several sharp peaks due to the crystal nature of Ofl and some diffused peaks owing to the amorphous nature of MD clearly indicated that there was no complex formation. MD 1:4 showed a hollow diffused pattern and there were no sharp peaks of Ofl, which indicates that crystalline nature of drug had been converted to amorphous form during complexation. These findings confirmed that the entrapped Ofl was dispersed monomolecularly on MD matrix [30].

3.4. In vitro release for DRCs

Fig. 3D shows the in vitro drug release carried out for Ofl, MD 1:4 and PM 1:4 at gastric pH 1.2. The release was observed to be in the following order Ofl > PM 1:4 > MD 1:4. The release of Ofl from MD 1:4 was fast and it depended upon several factors like concentration of ions, ionization and swelling ability of the polymer matrix [8]. This may be due to the conversion of crystalline form of drug to amorphous form during the preparation of MD 1:4 and it is in well agreement with the results of P-XRD and DSC analyses, where the drug in MD 1:4 was found to be amorphous [31].

3.5. Synthesis of XG to SCMXG and preparation of IPN beads

Fig. 4A shows the reaction scheme for the modification of XG to SCMXG. Fig. 4B shows the FT-IR spectra of XG and SCMXG. FT-IR
spectra of SCMXG show the peak at 1338 cm\(^{-1}\), which represents the -C=O stretching of O-carboxyl methyl group and indicates that O-6-acetyl group of XG was hydrolyzed by NaOH solution and converted to carboxymethyl group [16]. In case of XG, there was no such peak, which confirms the formation of SCMXG.

Fig. 5A shows the mechanism for the formation of IPN beads of MD 1:4-SCMXG-SCMC. MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC were dispersed in Millipore water and dropped into AlCl\(_3\) solution separately to form IPN beads. The formation of IPN beads for MD 1:4-SCMXG was due to the ionic cross-linking of Al\(^{3+}\) with carboxylic groups of SCMXG and in case of MD 1:4-SCMXG-SCMC, it may be due to the ionic cross-linking of Al\(^{3+}\) between the carboxylic groups of SCMXG and SCMC.

### 3.6. Size of IPN beads

Table 4 shows the size of IPN beads. The size of IPN beads varied from (524 ± 12) \(\mu\)m to (1122 ± 10) \(\mu\)m. It was found that at higher concentration of Al\(^{3+}\) the bead size was small compared to that at lower concentration. This may be due to the rapid shrinking of IER network by treating with higher concentration solution and also due to the increase in the gelation time. This result is in agreement with those of earlier reports of some researchers [32,33]. The bead size of MD 1:4-SCMXG-SCMC was high as compared to the size of MD 1:4-SCMXG IPN beads. This may be due to increase in concentration of solution by mixing SCMC biopolymer, which resulted in bigger droplets.

| Formulation codes | Drug entrapment efficiency (%) | Bead size (\(\mu\)m) | Kinetic model (Korsmeyer-Peppas) |
|-------------------|---------------------------------|--------------------|----------------------------------|
|                   |                                 | n\(^a\)            | r\(^2\)                           |
| MD 1:4-SCMXG      | 91.90 ± 0.75                    | 636 ± 15           | 0.74                             |
| MD 1:4-SCMXG      | 80.42 ± 0.52                    | 524 ± 12           | 0.88                             |
| MD 1:4-SCMXG-SCMC | 90.23 ± 0.55                    | 1122 ± 10          | 0.84                             |
| MD 1:4-SCMXG-SCMC | 79.58 ± 0.26                    | 937 ± 15           | 1.04                             |

\(^a\) Diffusion exponent. \(^b\) Correlation coefficient.

b,d 2% cross-linking with AlCl\(_3\) and gelation time 30 min.
c,e 3% cross-linking with AlCl\(_3\) and gelation time 60 min.

**Table 4** Drug entrapment efficiency (%), bead size (\(\mu\)m, n=6) and kinetic model (Korsmeyer-Peppas) of IPN beads (n=3, mean ± SD).
3.7. Drug entrapment efficiency of IPN beads

The drug entrapment efficiency of IPN beads for MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC was found to be in the range of (79.58 ± 0.26)%–(91.90 ± 0.75)% (Table 4). As the concentration and gelation time of Al\textsuperscript{3+} increased the drug entrapment efficiency decreased. This was obvious as drug diffused out from IPN beads into AlCl\textsubscript{3} solution, which ultimately resulted in the decrease of drug entrapment efficiency. Similar result of decrease in drug entrapment efficiency was also reported [34]. Moreover, the prolonging in gelation time increased the concentration of Al\textsuperscript{3+} in beads which displaced more molecules of drug and resulted in the decrease of drug entrapment efficiency of IPN beads.

3.8. FT-IR spectra of IPN beads

Fig. 5B shows the FT-IR spectra of SCMXG, SCMC, IPN beads of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC. The formation of SCMXG from XG and IPN beads was confirmed by the FT-IR spectra. SCMXG beads show the peaks at 1521 cm\textsuperscript{-1} and 1461 cm\textsuperscript{-1} due to asymmetric and symmetric stretching vibration of -COO\textsuperscript{-} group. The peak at 1642 cm\textsuperscript{-1} was assigned to -C=O group of SCMXG. The peak at 1332 cm\textsuperscript{-1} shows the C=O stretching of O-carboxyl methyl group and indicates that O-6-acetyl group of XG was hydrolyzed by NaOH solution and converted into carboxy methyl group [35]. The SCMC shows the peaks at 1643 cm\textsuperscript{-1} and 1555 cm\textsuperscript{-1}, which represent carboxyl stretching frequency, whereas the peaks at 1454 cm\textsuperscript{-1} and 1045 cm\textsuperscript{-1} were due to -OH bending vibration and -C=O-C stretching respectively.

In case of MD 1:4-SCMXG, the peak at 2925 cm\textsuperscript{-1} was due to aromatic ring of MD. SCMXG shows the asymmetric and symmetric stretching vibrations at 1630 cm\textsuperscript{-1} and 1380 cm\textsuperscript{-1} of carboxyl groups. In case of MD 1:4-SCMXG-SCMC, carboxyl group peaks of SCMXG are shifted from 1630 cm\textsuperscript{-1} to 1636 cm\textsuperscript{-1} and from 1380 cm\textsuperscript{-1} to 1431 cm\textsuperscript{-1} during the preparation of 1:4-SCMXG-SCMC, which indicates that ionic cross-linking between SCMXG and SCMC had formed due to Al\textsuperscript{3+}.

3.9. In vitro drug release studies for IPN beads

Fig. 6A shows the release of Ofl from IPN beads of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC at gastric pH 1.2 prepared with different cross-linking percentages of AlCl\textsubscript{3}. IPN beads with higher cross-linking percentage of Al\textsuperscript{3+} showed slow release of the drug as compared to lower cross-linking percentage. At higher cross-linking percentage, the free volume of IPN beads would decrease and limit the diffusion of the drug through the IPN network. The reason for the slow release of the drug was that the H\textsuperscript{+} was not sufficiently available to exchange with IPN beads as -COO\textsuperscript{-} groups of SCMXG and SCMC had been ionically cross-linked by Al\textsuperscript{3+} and was also due to increase in gelation time.

Fig. 6B shows the drug release profile of IPN beads MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC at intestinal pH 7.4. The release was found to be prolonged compared to gastric pH and extended up to 10 h. This might be due to the integrity of IPN beads in the matrix and also slower displacement of the drug from IPN beads by counter ion present in the dissolution fluid [36]. IPN beads having higher concentration of Al\textsuperscript{3+} released the drug slowly as compared to the beads possessing lower concentration of Al\textsuperscript{3+}.

3.10. Kinetics studies

The kinetics studies for the release of drug from IPN beads of MD 1:4-SCMXG and MD 1:4-SCMXG-SCMC were performed by Korsmeyer Peppas model. The values of correlation coefficient (r\textsuperscript{2}) and diffusion exponent (n) are shown in Table 4. 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 signifies that polymer relaxation takes place during polymer swelling. The n value depends on cross-linking concentration of Al\textsuperscript{3+} in IPN beads and it increases with the increase of cross-linking concentration. The n value also increases with the increase of cross-linking time. The release of Ofl was found to be governed by anomalous (non-fickian) diffusion controlled mechanism in case of 2% of cross-linking and 30 min of gelation time, whereas for IPN beads prepared with 3% cross-linking and 60 min gelation time the n value increased and showed the zero order release mechanism. The drug release for MD 1:4-SCMXG with 3% AlCl\textsubscript{3} solution was found to be more than MD 1:4-SCMXG-SCMC with 3% AlCl\textsubscript{3} solution. The slow drug release of MD 1:4-SCMXG-SCMC with 3% AlCl\textsubscript{3} solution might be due to having more cross-linking sites as compared to those of MD 1:4-SCMXG with 3% AlCl\textsubscript{3} solution. So at higher cross-linking concentration, a rigid IPN matrix with less porosity was formed, which restricted the swelling of IPN beads and also movement of the drug molecules. As the crosslinking concentration increased the drug release mechanism was changed to (non-fickian) diffusion to zero order release mechanism [37].

4. Conclusions

Among the DRCs prepared, the most efficient in masking the bitter taste of Ofl was MD 1:4. The taste masking was due to the formation of

![Fig. 6](image-url)
complex between drug and MD. MD 1:4 was characterized using different analytical techniques to confirm the formation of DRC. FT-IR confirmed the possible interaction between the drug and MD. P-XRD and DSC described that the drug was in amorphous state in MD 1:4. In vitro release study showed complete release of Ol at gastric pH within 30 min. IPN beads were prepared with MD 1:4 by following ionic cross-linking method for the sustained release study of Ol. MD 1:4-SCMXG-SCMC showed sustained release at both the intestinal and gastric pH without initial burst. The kinetics study showed the release of Ol depended on the percentage of cross-linking during formation of IPN beads. Cross-linking carried out in 30 min with 2% AlCl₃ showed anomalous drug release whereas with 3% AlCl₃ and in 60 min the drug release followed zero order mechanism.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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