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Original Article

TASTE MASKING BY FUNCTIONAL CROSS-LINKED COPOLYMERS AND SUSTAIN RELEASE OF DRUG THROUGH INTERPENETRATING POLYMER NETWORK WITH SODIUM ALGINATE AND κ-CARREGANEEN BIOPOLYMERS

A. MICHAEL RAJESH[†§], SHREYA A. BHATT[†], G. VENKATA RAMANA[‡], HARSHAD BRAHMBHATT[‡], KHUSHBOO GAJJAR[†], C. B. TRIPATHI[¶], PRITPAL SINGH ANAND[†], KIRITKUMAR MANGALDAS POPAT[*†§]

[†]Reverse Osmosis Membrane Division, Central Salt and Marine Chemicals Research Institute, Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar 364 002, India, [‡]Analytical Discipline & Centralized Instrumentation Facility, Central Salt and Marine Chemicals Research Institute, Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar 364 002, India, [¶]Department of Pharmacology, Government Medical College & Sir Takhtasinhji General Hospital, Bhavnagar 364001, India, [§]Academy of Scientific and Innovative Research, Central Salt and Marine Chemicals Research Institute, Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar 364 002, India.
Email: kmpopat@csmcri.org

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ABSTRACT

Objective: The objective of this study was to carry out taste masking of ciprofloxacin (Cfx) by functional cross-linked copolymers (FCCs) followed by sustain release of Cfx by forming interpenetrating polymer network (IPN) beads.

Methods: Drug-copolymer complexes (DCCs) with three different ratios of drug to copolymer (1:1, 1:2, 1:4) were prepared for the copolymers showing high drug loading with Cfx. Taste masked IPN beads were prepared by using sodium alginate (AL) and sodium alginate-κ-Carreganeen (AL-κ-Ca) with DCC 1:4, prepared from methacrylic acid divinyl benzene copolymer (MDC-1) and Cfx. The IPN beads were characterized with FTIR and further studied for sustain release of Cfx at different pH.

Results: *In vivo* taste masking carried out by Human volunteers showed that DCC 1:4 significantly reduces the bitterness of Cfx. Characterization studies such as FTIR, SEM, DSC, P-XRD and taste masking study differentiates DCC 1:4 from physical mixture prepared from MDC-1 and Cfx (PM 1:4). In vitro study at gastric pH showed complete release of Cfx from DCC 1:4 within 60 min where as the release of drug was extended upto 10 h in case of IPN beads. Kinetic study for drug release from IPN beads shows non-Fickian type.

Conclusions: Taste masking of Cfx was achieved by complexing with DCC 1:4 and control release of Cfx by forming IPN beads.

Keywords: Functional cross-linked copolymers, Cross linking agents, *In vivo* taste masking, Biopolymers, Release kinetics.

INTRODUCTION

Ciprofloxacin hydrochloride (Cfx), chemically it is called 1-cyclopropyl-6-fluoro-1,4 dihydro-4-oxo 7-(1-piperazinyl)- 3-quinoline carboxylic acid hydrochloride monohydrate, is a leader among the third generation fluoroquinolones. It functions by inhibiting DNA gyrase, a type II topoisomerase and type IV topoisomerase enzymes necessary to separate bacterial DNA, thereby inhibiting cell division and with a broad spectrum of antibacterial activity and good penetration in most tissues [1]. Even though Cfx has good broad spectrum of antibacterial activity, it has bitter taste which becomes palatability challenge and has patients compliance for oral administration.

Taste of an oral formulation administered to a child or adult has an important impact on the adherence to drug therapy. It is important to mask the unpalatable taste of active pharmaceutical ingredient (API) in order to improve the product quality. This will increase the value of the product with palatable and better patient compliance [2]. Various taste masking techniques have been made for orally unacceptable therapeutics, such as microencapsulation with various polymers [3], using lipophilic vehicles by obstructing the taste buds [4], lipids, lecithin's and hydrophilic vehicles [5] chemical modification of insoluble pro drugs [6,7]. Taste masking is to minimize the drug release during the dwell time of oral cavity (<10 %) to avoid direct contact of drug and taste buds [8].

FCCs or Ion-exchange resins (IERs) have been widely studied in medical and pharmaceutical applications since 1950 [9]. 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 [10]. They also possess high capacity of drug loading, controlled or sustained release of drug in the gastrointestinal tract, physico-chemical stability and their insolubility in any solvents show their capability to be better candidates for using as taste masking and sustained release of drugs.

Among the various available taste masking agents FCCs can be used as one of the tool to develop a simple, rapid and cost-effective method for the masking of bitter drugs [11]. FCCs contains carboxylic functional groups can form complexes by ionic or hydrogen bonding and mask the bitterness of the drugs [12, 13]. In past researchers have studied FCCs for taste masking and sustain release of various drugs. Betty et al used a mixture of coated and noncoated sulfonic acid resins loaded with dextromethorphan for taste masking and sustained release [14]. Bermudez et al developed extended release tablets of 500 mg of Cfx based on swellable drug polyelectrolyte matrices [15]. Pisal et al studied sustain release of drug at gastric pH by treating polyethylene glycol and also for taste masking with Cfx-Indion 234 complex [16, 17].

FCCs restrict the exchange of ions in salivary pH but in the presence of acidic pH release of drug from the FCC is very fast which can be controlled by using a polymeric film, waxy layer onto the surface of DCCs and also by entrapment with biopolymers [18-21]. In recent years many researcher have used IPN beads for sustain release of drug which showed that IPN beads seemed to be novel carrier for drug delivery [22]. IPN beads are stable, biocompatible, non-toxic, biodegradable and have excellent swelling properties which have attracted their use in pharmaceutical field. AL and κ-Ca are environment friendly materials; non-toxic, biodegradable, biocompatible, hydrophilic and semi-rigid polysaccharides are being

studied for the control release of drugs. AL is linear polysaccharide and composed of (1-4)-linked-D mannuronic acid (M-units) and α-L–guluronic acid (G units) polymer chain which can vary in proportion and sequential distribution [23]. AL forms spherical beads in the presence of divalent cations such as Ca^{2+} through ionic gelation. Calcium cross-linked beads have been used in many biomedical applications [24]. κ-Ca is a collective term for linear sulphated polysaccharides with repeated units and used in the biomedical applications [25]. IPN beads of κ-Ca and AL have been studied previously by some researchers. Kulkarni et al used IPN beads of κ-Ca and AL for the controlled release of propranolol HCl [26]. Sipahigil et al studied *in vitro* release of verapmil HCl and Ibuprofen by using Carrageenan Beads [27].

However, the taste masking and sustain release of Cfx through FCCs based IPN beads using κ-Ca 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 FCCs for taste masking of Cfx and sustain release by forming IPN beads with AL and κ-Ca biopolymers. FCCs were prepared by using different cross linkers and crosslinking % during the synthesis of FCCs. These FCCs possess high ion exchange capacity (>11 meq/gm), stability and insolubility properties as well as high drug loading capacity. FCCs have been used for complexation of Cfx (pKa 5.61-6.18) by simple batch method. Taste masking by using human volunteers, sustain release of Cfx through entrapment with biopolymers and kinetics study have been reported.

MATERIALS AND METHODS

Materials

Cfx was obtained from WALLACE Pharmaceuticals PVT. LTD. Ponda, Goa, India. Methacrylic acid (MAA), ethylene glycoldimethacrylate (EGDMA) and N,N'-methylene bis acrylamide (MBA) were procured from Central Drug House, Mumbai, India and DVB from Merck Germany was used as received, Benzoyl peroxide (BP) from Heney fine chemicals India, potassium dihydrogen orthophosphate, sodium hydroxide, potassium hydroxide, potassium chloride and other chemicals were obtained from S. D Fine Chemicals Mumbai, India.

AL (viscosity: 20.0-40.0 CP in 1% water, MW: 7334) and cellulose acetate dialysis tube (cut off molecular mass of 12000) were obtained from Sigma Aldrich, USA. κ-Ca purchased from TCI, Japan. 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).

Synthesis of functional cross linked copolymers (FCCs)

FCCs 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 [28]. Series of MAA based FCCs were prepared by varying quantities of EGDMA, MBA and DVB. They are coded as MECs, MBCs and MDCs respectively.

The details of the synthesis of FCCs are given in Table 1. FCCs were conditioned by giving alternate treatment of acid (1N HCl) and base (1N NaOH) with intermittent water (Millipore water) rinsing for three cycles and finally converted to K^+ form with KOH for further study. Elemental analysis to determine the percentage of C, H and N of FCCs was carried out by vario micro cube model, made by Elementar, Germany and their physico-chemical properties are tabulated in Table 2.

Complexation of Cfx with FCCs

Complexation of Cfx with MECs, MBCs and MDCs of FCCs are prepared by following reported method [29]. FCCs were preswelled by using millipore water and known quantity of Cfx was dissolved in millipore water, added slowly in the beaker at ratio of 1:1and maintained the pH at 6. Each mixture was stirred at a speed of 500 rpm at room temperature for 24 h. The DCCs 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.

Table 1: Synthesis of FCCs by varying ratios of monomers, cross linkers and solvents

FCCs	MAA, gm	EGDMA, gm	MBA, gm	DVB, gm	n-Heptane, gm	Isobutanol, gm	Cross-linking, %
MEC-1	63	7	-	-	41.6	-	10
MEC-2	72	8	-	-	27.7	-	10
MEC-3	56	14	-	-	41.6	-	20
MEC-4	64	16	-	-	27.7	-	20
MBC-1	36	-	4	-	-	60	10
MBC-2	63	-	7	-	-	30	10
MBC-3	32	-	8	-	-	60	20
MBC-4	54	-	16	-	-	30	20
MDC-1	47.5	-	-	2.5	-	50	5
MDC-2	66.5	-	-	3.5	-	30	5
MDC-3	45	-	-	5	-	50	10
MDC-4	63	-	-	10	-	30	10

Table 2: Physico-chemical properties of FCCs

FCCs	Ion exchange capacity, meq/gm	Swelling percentage, ($H^+ \leftrightarrow K^+$%)	%,C	%,H	%,N	Yield, %
MEC-1	10.4	35	33.98	6.54	-	94
MEC-2	10.3	30	34.28	6.77	-	92
MEC-3	8.0	20	35.88	6.49	-	94
MEC-4	7.5	20	37.96	6.80	-	93
MBC-1	11.2	75	32.03	6.54	0.74	93
MBC-2	11.8	90	30.91	6.77	0.58	94
MBC-3	10.4	50	32.40	6.99	1.73	92
MBC-4	10.7	70	40.73	6.85	2.04	93
MDC-1	11.7	66	20.95	4.12	-	96
MDC-2	10.1	75	34.45	6.78	-	95
MDC-3	9.2	70	19.12	4.04	-	93
MDC-4	11.1	50	32.82	6.27	-	94

Preparation of taste masking DCCs on maximum drug loading FCCs

Different DCCs were prepared by varying the ratios of Cfx with MEC-1, MBC-2 and MDC-1FCCs i. e. 1:1, 1:2 and1:4 (w/w) which showed maximum drug loading. The DCC prepared with MDC-1copolymer were designated as DCC 1:1, DCC 1:2 and DCC 1:4. Loading of drug was calculated by following eqn.

Loading of drug was calculated by following eqn.

$$\%\text{Loading} = \frac{\text{Drug retained on FCCs}}{\text{Initial Drug concentration}} \times 100$$

Different physical mixtures (PMs) denoted as PM 1:1, PM 1:2 and PM 1:4 ratios of drug with MDC-1were prepared by mixing the both with mortar-pestle.

Preparation of DCC-AL beads

A known amount, 60 mg, of DCC 1:4 containing 20 mg of Cfx was mixed with 20 ml of 2 % AL aqueous solution and stirred for 2 h to get homogenous suspension. The mixture was added by drop wise at a distance of 15 cm height using a 2.5 ml syringe of needle size 1.2 mm in 0.25 M $CaCl_2$ solution under mild stirring at desired temperature. The beads were formed by ionotropic gelation were cured for 30 minutes at room temperature followed by washing with distilled water and finally dried at room temperature until constant weight was obtained.

Preparation of DCC-AL- κ-Ca beads

A known amount, 60 mg, of DCC 1:4 containing 20 mg of Cfx was mixed with 20 ml of 2 % AL solution and 20 ml of 2 % κ-Ca solution. The mixture was stirred for 2 h to get homogenous solution. The solution was filled in 2.5 ml syringe of needle size 1.2 mm and poured at a distance of 15 cm with mild stirring at desired temperature (30°C to 55°C) to get IPN beads by ionotropic gelation of AL and κ-Ca with ionic solutions of 0.25 M $CaCl_2$ and 0.25 M KCl. The beads were cured for 30 minutes at room temperature followed by washing with distilled water and finally dried at room temperature till constant weight was obtained.

Mean diameter of dry beads was measured with the help of micrometer screw (Mitutoyo, Japan) and entrapment efficiency (%) of Cfx in DCC-AL and in DCC-AL-κ-Ca was determined by HPLC at 275 nm by measuring Cfx left in $CaCl_2$/KCl solutions during the preparation of composites. The encapsulated efficiency was calculated by using following eqn.

$$\%\,\text{Entrapment efficiency} = [(C1 - C2)]/C1 \times 100$$

Where *C1* is the known concentration of Cfx in DCC 1:4 and *C2* is the concentration of Cfx in $CaCl_2$/KCl solutions.

Instrumental analysis

P-XRD analysis

MDC-1, Cfx, DCC 1:4 and PM 1:4 were investigated by Powder X-ray diffraction (P-XRD, Phillips-X' Pert MPD System). P-XRD was recorded from 2° to 60°(2θ) at a scanning speed of 0.3 deg/s. PW3123/00 curved Ni-filtered Cu-Kα (λ=1.54056 Å) radiation was used as the X-ray source.

FT-IR analysis of MDC-1, Cfx, PM 1:4, DCC 1:4, DCC-AL and DCC-AL- κ-Ca

The Fourier transform infrared spectra (FT-IR) were recorded on Perkin-Elmer, GX-FTIR as KBr pellet over the wavelength range 4000-400 cm^{-1}.

Scanning electron microscopy (SEM) study

Scanning electron microscopy (SEM) images of dried FCCs, Cfx, DCCs and PMs were recorded by using a LEO Instruments (Kowloon, Hong Kong) microscope after the gold sputter coating on desired samples. The samples were prepared in Milli-Q water and dried on aluminium grids at room temperature prior to SEM analysis.

Differential scanning calorimetry (DSC)

MDC-1, Cfx, DCC 1:4 and PM 1:4 were assessed by Differential scanning calorimetry (DSC) measurements. They were dispersed in Milli-Q water separately and 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 behaviour under nitrogen flow (20 ml/min).

High Pressure Liquid Chromatography (HPLC)

The quantitative analysis of drug (Cfx) was performed using High Pressure Liquid Chromatography (HPLC) (1) 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 water and acetonitrile in the ratios of 60:40 (contain 0.25M H_3PO_4). 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 20µl/ml. The sample temperature was maintained at 10°C.

***In vitro* and *in vivo* taste masking study**

In vitro taste masking of DCCs comparison with Cfx was carried out at salivary pH 6.8. Pre-decided amount of DCCs and Cfx was dispersed in 5 ml phosphate buffer of pH 6.8 in conical flasks [30] separately. Samples of 1 ml were withdrawn from the conical flask at time interval 30 s and filtered with 0.45µm whatman filter paper. The filtrates were analyzed for Cfx at 275 nm by using HPLC. This study was performed in triplicate for each sample, and the average values for respective DCCs were reported.

In vivo taste masking study of Cfx, DCCs and PMs was performed by a panel of nine Human volunteers in the age group of 18 to 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. Cfx, DCCs and PMs were placed on tongue by each volunteer separately and taste was evaluated for 30 s resident time by reported method [31]. 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). The threshold of the bitterness of DCCs was determined as point at which most number of the volunteers described the taste as bitter or slightly bitter.

***In vitro* release studies**

In vitro release of Cfx, DCC 1:4 and PM 1:4 was studied at gastric pH 1.2using dialysis bag technique [32]. (2) Pre-decided amount, 10 mg of Cfx, 10 mg of Cfx containing DCC 1:4 and PM 1:4, were dispersed separately in 5 ml buffer solution in activated cellulose dialysis bags. The dialysis bags were dipped into receptor compartment containing 100 ml of buffer medium and were shaken at 37±0.5°C at a shaking speed of 100 rpm on Remi shaking water bath (RSB-12). DCC-AL and DCC-AL- κ-Ca were studied at different pH such as gastric pH and intestinal pH i. e. 7.4. containing 10 mg of Cfx. 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 analysed by HPLC.

Drug release kinetics

$$Q = k_H t^{1/2} \ldots\ldots (3)$$

The drug release mechanism of encapsulated DCC-AL and DCC-AL-κ-Ca were performed. 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.

$$\frac{Mt}{M\infty} = Kt^n \ldots\ldots (4)$$

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 [33].

Where Mt/M ∞ is the fraction of drug released at time*t, K is* rate constant *and n* is the diffusion exponent characteristic of release mechanism.

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 range tests. A probability level of $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Loading of Cfx on FCCs

The loading of Cfx on FCCs was studied and shown in Fig 1. Drug loading was carried out at 1:1 ratio maintaining the pH at 6 to find out loading percentage of Cfx on FCCs. The FCCs were swelled prior to drug loading to get better loading and found in the range of 54 % to 92 %. The loading of drug on FCCs may be due to ion exchange reaction taking between the drug and copolymers. FCCs with low degree of cross-linking showed high percentage loading of Cfx. This trend is due to decrease in the functional groups on the polymer matrix at higher degree of cross linking.

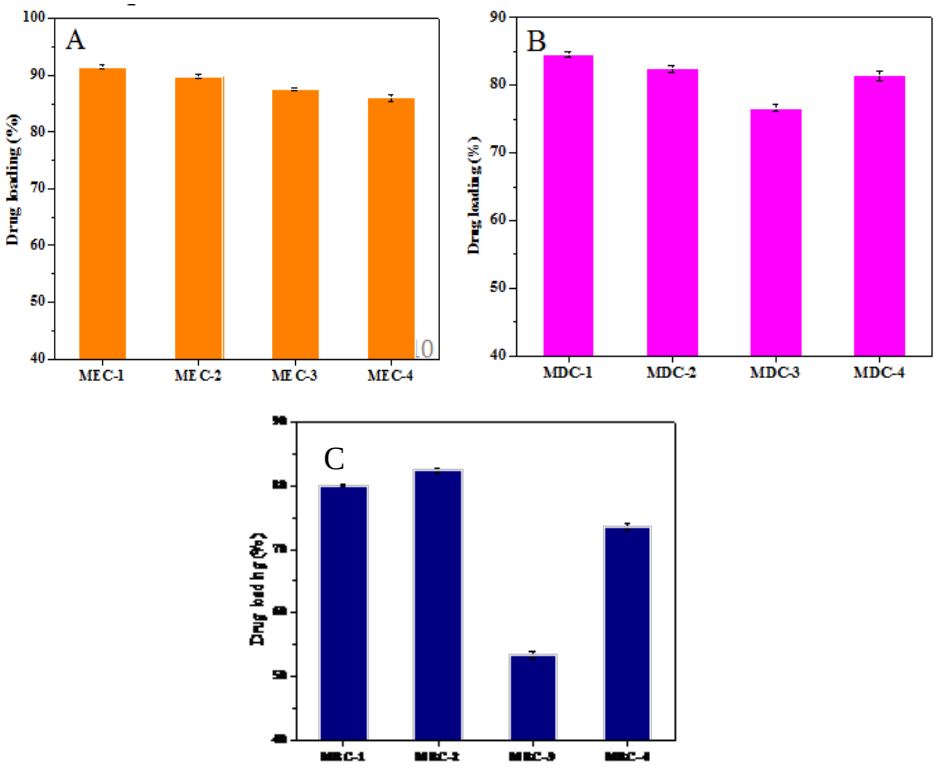


Fig. 1: Drug loading percentage with different FCCs at 1:1 ratios (A) MEC, (B) MDC and (C) MBC (n=3, $\bar{X}$ =±S. D).

Preparation of DCCs

MDC-1, MBC-2 and MEC-1 copolymers were selected for taste masking and dissolution studies as they showed better drug loading. The loading of Cfx on FCCs was carried out by batch method.

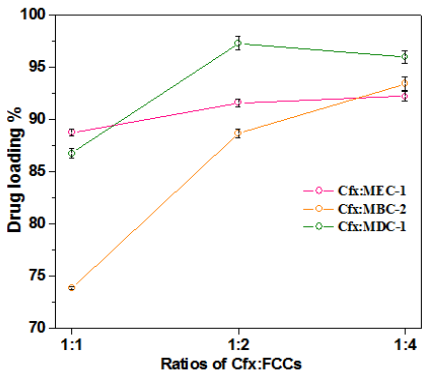


Fig. 2: Drug loading (Cfx) with MEC-1, MBC-2 and MDC-1 i. e. 1:1, 1:2 and1:4 ratios (w/w) (n=3, $\bar{X}$ =±S. D)

The drug loading on three different FCCs are shown in Fig 2. FCCs did not showed any major difference in loading of Cfx, however maximum loading on MDC-1 at 1:2 ratio was obtained.

In vivo taste masking and in vitro taste masking at salivary pH 6.8

In vivo taste masking study was carried for Cfx, DCCs and PMs. The written consent of human volunteers participated in the taste masking was obtained and results are shown in Fig 3(A). Statistical significance was assessed by two-way ANOVA test by using Duncan's multiple range tests with probability level of $p<0.05$. ANOVA results show that *in-vivo* taste masking studies have very high statically significance with Cfx. The taste masking values of DCCs are in the order MEC-1>MBC-2>MDC-1. The DCCs prepared with MDC-1 copolymer showed excellent taste masking compared to other copolymers i. e MBC-2 and MBC-1.

In vitro taste masking of three different cross-linked copolymers was carried out at salivary pH 6.8 by using phosphate buffer and shown in Fig 3(B). Release of Cfx from DCCs at salivary pH are observed to be in the following order MEC-1>MBC-2>MDC-1 respectively. DCC 1:4 showed only 2.36±0.17 % of Cfx release for a contact time of 30 s. At salivary pH 6.8 the phosphate group may not exchange with the amine groups present in Cfx of MDC-1 due to the presence of bulky DVB cross-linker, which imparts steric hindrance and ultimately

resulting in slow release of drug as well as relatively better taste masking of copolymer [34]. Whereas faster drug release in case of MEC and MBC is observed as the copolymers possess aliphatic cross-linkers such as EGDMA and MBA which allow fast release of drug than MDC-1.

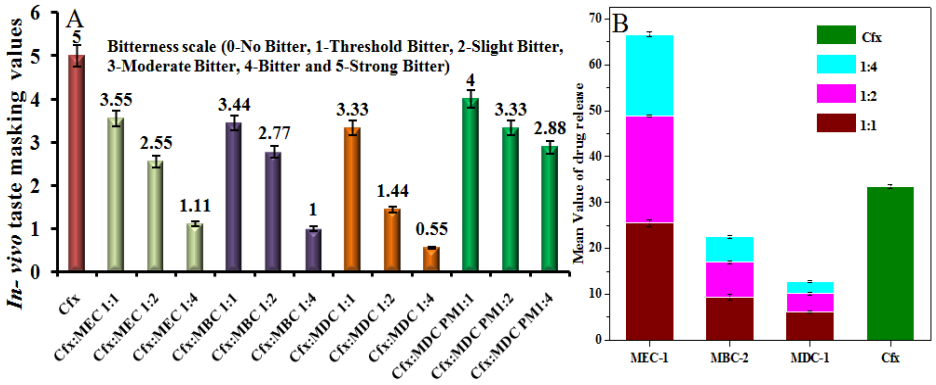


Fig. 3: (A) *In vivo* taste masking of Cfx, DCCs and PMs at ratios 1:1, 1:2 and 1:4 (w/w) involved by nine human volunteers for 30 s. (B) *In vitro* taste masking of different DCCs prepared by varying the ratios of Cfx with MEC-1, MBC-2 and MDC-1 i. e. 1:1, 1:2 and1:4 ratios (w/w) at salivary pH 6.8 (n=3, $\bar{x}$ =±S. D).

Instrumental characterization

FT-IR spectrum of MDC-1, DCC 1:4, PM 1:4, and Cfx are shown in Fig. 4 (A). MDC-1 shows peaks at 3408 cm^{-1}, 2929 cm^{-1}, 1719 cm^{-1} which represent the stretching frequency of –OH group, -C=C of aromatic ring and -C=O group of aryl acid which confirms the formation of MDC-1. CP showed peak at 3373 cm^{-1} which is corresponds to -NH stretching and the peak in the range of 2470 cm^{-1} to 3093 cm^{-1} is due to dimerization of $-COO^-$ groups present in drug. The peaks at 2925 cm^{-1} and 2840 cm^{-1} show aliphatic -CH- stretching. The peak at 3537 cm^{-1} is due to -OH stretching. The peak at 3379 cm^{-1} corresponds to -NH of CP is absent in DCC 1:4, which confirms the formation of complex by interacting secondary amine of CP with MDC-1. The peaks at 3093 cm^{-1} to 2470 cm^{-1} are absent due to breaking of acid dimers during complexation. The stretching frequency at 3537 cm^{-1} corresponds to -OH group of CP is also absent which signifies the complexation. Spectra of PM 1:4 showed superimposition of Cfx on MDC-1 ensuring that there is no formation of complexes.

SEM images of Cfx, MDC-1, DCC 1:4 and PM 1:4 are shown in Fig. 4(B). Small rod shape structure of pure Cfx is visualized and it signifies the crystalline structure of the drug. The SEM images of MDC-1 show porous surface and observed that there is no crystalline nature rather than a conchoidal surface fracture is present. This shows that the copolymer is amorphous in nature. A significant change in the morphologies of DCC 1:4 is observed which is not resembles to pure Cfx or MDC-1. The images of DCC 1:4 are entirely different as compared to Cfx, MDC-1 and PM 1:4 which clearly indicates that there is no crystalline form of drug but an amorphous form is formed during the complexation of Cfx with MDC-1. PM 1:4 showed dense clusters and crystals of drugs are visible above the cluster which indicates that complex was not formed between Cfx and MDC-1.

DSC studies of Cfx, MDC-1, DCC 1:4 and PM 1:4 were performed and shown in Fig. 4 (C). The endotherm of MDC-1 was observed at 270°C for MDC-1 and for Cfx it was found to be 159°C and 339°C respectively. The thermogram showed shift in the endothermic peak of DCC 1:4 from 270°C of MDC-1 to 79°C. Similar results with shifting of endotherm and Tg of the drug loaded with polymers have been reported [35]. Endothermic peaks of Cfx and MDC-1 are absent in case of DCC 1:4 which confirm that Cfx has been complexed with MDC-1. Whereas the endothermic peaks of PM 1:4 were found close to the endothermic peaks of Cfx indicates that complex formation in PM 1:4 does not take place.

P-XRD analysis of Cfx, MDC-1, DCC 1:4 and PM 1:4 are shown in Fig. 4(D). Cfx is observed to be crystalline in nature showed several sharp peaks ranging from 8.33°, 9.12°, 11.4 8°, 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° 2θ respectively. While MDC-1 does not show sharp peaks indicates amorphous nature of the copolymer. The P-XRD of DCC 1:4 shows that there are no peaks of Cfx due to complex formation between Cfx and MDC-1 which indicates that crystalline nature

of drug has been converted to amorphous form. This finding confirms that the entrapped Cfx is dispersed mono molecularly on MDC-1 matrix [36]. P-XRD of PM 1:4 of Cfx and MDC-1 shows several sharp peaks due to the crystal nature of Cfx and some diffused peaks owing to the amorphous nature of MDC-1 and confirms that complex formation does not take place between Cfx and MDC-1.

In vitro drug release study was carried out for Cfx, PM 1:4 and DCC-1:4 at Gastric pH 1.2 and the results are shown in Fig. 4(E). The release of Cfx is observed to be in the following order Cfx>PM 1:4>DCC 1:4. The higher release of Cfx was observed from PM 1:4 compared to DCC 1:4. This may be due to the complex formation between Cfx and MDC-1 copolymer. The displacement of H^+ with DCC 1:4 results in quick release of CP in gastric pH. The release of Cfx in DCC 1:4 may be due to the more reduction in crystalline to amorphous state of the DCC 1:4. The amorphous nature of DCC 1:4 was confirmed by PXRD and DSC analysis.

Preparation and characterization of DCC-AL and DCC-AL- κ - Ca

DCC 1:4 (MDC-1) having excellent taste masking properties was chosen for the sustain release studies by forming IPN beads with AL and κ-Ca polysaccharides using ionic crosslinking method. The schematic diagram for the preparation of DCC-AL and DCC-AL-κ-Ca beads are shown in Fig. 5(A). The photographs clearly show that DCC 1:4 is almost distributed uniformly within the beads matrix for both DCC-AL and DCC-AL-κ-Ca beads. Fig. 5(B). show the mechanism of IPN beads consisting of DCC-AL-κ-Ca polysaccharides. This shows that Ca^{2+}/K^+ crosslinked within the carboxylic groups of AL and κ-Ca are crosslinked within sulphate group encapsulated with DCC 1:4 which have been further confirmed by the FTIR. The FTIR spectra of DCC-AL and DCC-AL-κ-Ca beads are shown in Fig. 5(C). In case of DCC-AL the AL shows asymmetric and symmetric stretching vibrations at 1621 cm^{-1} and 1458 cm^{-1} are due to carboxyl anions groups. Cyclic ether bridge of AL is observed at 1018 cm^{-1} and confirms the encapsulations of DCC 1:4 by AL. In case of DCC-AL-κ-Ca new peaks were observed at 1026 cm^{-1} and 1253 cm^{-1} which indicate the glycosidic linkage and ester sulphate group of κ-Ca respectively. The shifting of peaks from carboxyl anion groups of AL from 1621 cm^{-1} and 1458 cm^{-1} to 1635 cm^{-1} and 1412 cm^{-1} indicates that ionic crosslinking between AL and peak at 1253 cm^{-1} ester sulphate group of κ-Ca which confirms the ionic crosslinking.

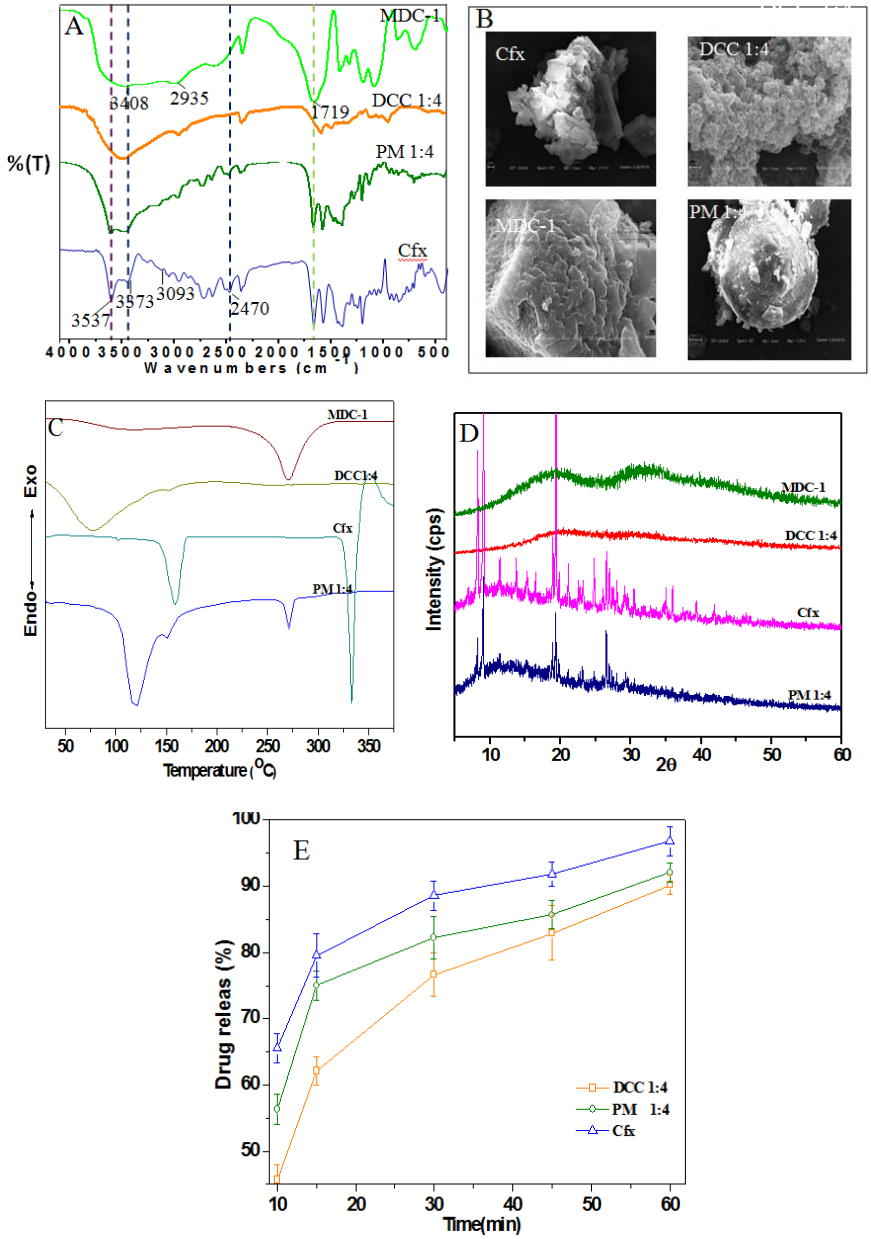
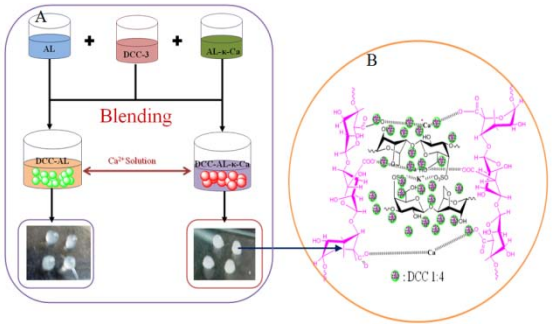


Fig. 4: (A) FTIR spectra (B) SEM images (C) DSC, (D) P-XRD of MDC-1, CP, DCC 1:4, and PM 1:4. (E) Drug release of Cfx, PM 1:4 and DCC 1:4 at gastric pH 1.2 (n=3, $\bar{x}$ =±S.D)



The encapsulation efficiency of both DCC-AL and DCC-AL-κ-Ca beads are found to have 96.41±1.34% and 93.62±1.17% respectively (Table 3) which indicates that DCC 1:4 has been well encapsulated with the biopolymers matrices. The bead sizes are shown in Table 3. The size of DCC-AL beads was found to be higher than the DCC-AL-κ-Ca beads. This may be due to more crosslinking in IPN beads of DCC-AL-κ-Ca beads and show the smaller size [37].

Drug release study of DCC-AL and DCC-AL-κ-Ca

Cfx release of DCC-AL and DCC-AL-κ-Ca at gastric pH 1.2 was carried out and the results are shown in Fig. 6 (A). The release was found to be 46.66±2.45% and 28.59±1.98% for DCC-AL and DCC-AL-κ-Ca after the time period of 10 h.

The slow release of drug in IPN beads may due to the slow penetration of dissolution medium along with ion exchange mechanism involving in displacement of drug from DCC. Another reason may be the in acidic condition the networks are totally contracted and the drug release will be slow due to the non- swelling of IPN beads [38].

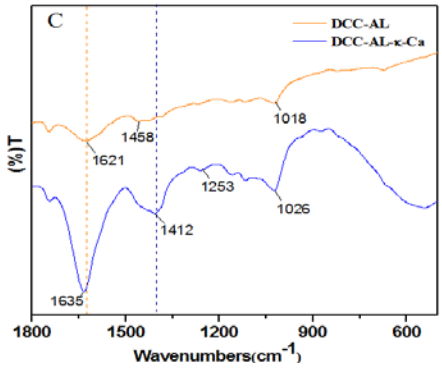


Fig. 5: (A) Schematic diagram for the preparation of DRC-AL and DRC-AL- κ-Ca IPN beads by ionic crosslinking method. (B) Scheme representing IPN bead formation mechanism under the influence of Ca^{2+}/KCl crosslinking of AL and κ-Ca (C) FTIR spectra of DRC-AL and DRC-AL- κ-Ca IPN beads.

The drug release for IPN beads at intestinal pH is shown in Fig. 6 (B). The release of drug was found to be 98.39±2.42 and 87.06±1.23 for DCC-AL and DCC-AL-κ-Ca after the time period of 10 h. The slow release of DCC-AL-κ-Ca compare to DCC-AL is due to ionic crosslinking between $–COO^-$ groups of AL, and also ionic crosslinking between the sulphate groups of κ-Ca which forms cage like structure and ultimately restrict the release of drug molecules from DCC-AL-κ-Ca IPN beads. The drug release may be due to the swelling of IPN beads and degradation of ionic crosslinking of IPN beads [38]. The degradation of IPN beads may be due to affinity of phosphate group compare to Ca^{2+} groups towards the $–COO^-$ groups of AL [39].

Table 3: Parameters for encapsulated efficiency and bead diameter of complexes (n=3, $\bar{x}$ =±S.D)

Parameters	DCC-AL	DCC-AL-κ-Ca
Encapsulation efficiency(%)	96.41±1.34	93.62±1.17
Bead diameter(μm)	932±0.23	845±0.50

Kinetics studies

The kinetics studies of DCC-3, DCC-AL and DCC-AL-κ-Ca are carried out by using two models Higuchi and Korsmeyer Peppas model. The values of correlation coefficient (r^2), rate constants (k) and diffusion exponent are shown in Table 4.

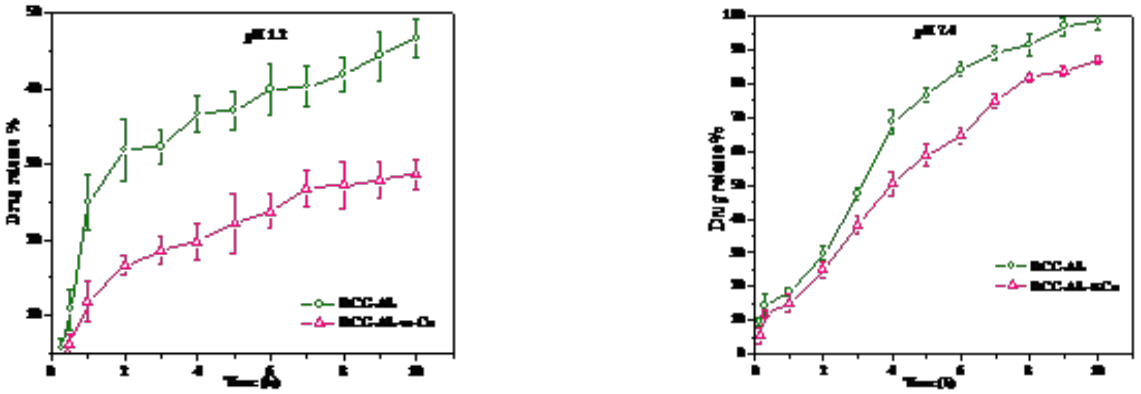


Fig. 6: (A) Drug release profile of DCC 1:4, DCC-AL and DCC-AL-κ-Ca at gastric pH 1.2 (n=3, $\bar{x}$ =±S.D) (B) Drug release profile of DCC-AL and DCC-AL-κ-Ca at intestinal pH 7.4(n=3, $\bar{x}$ =±S.D).

Table 4: Drug release kinetic study for DCC-AL and DCC-AL-κ-Ca beads

Kinetic models	Parameters	DCC-AL		DCC-AL-κ-Ca	
		pH 1.2	pH 7.4	pH 1.2	pH 7.4
Higuchi	r^2	0.98986	0.9015	0.9940	0.9950
	k_H	11.3072	4.3473	9.2597	3.3870
Korsmeyer Peppas	r^2	0.9889	0.9098	0.9978	0.9939
	n	0.5252	0.5902	0.5755	0.6675
	K_{kp}	0.5645	0.4026	0.6328	0.6343

The r^2 shows that values are near to one in both Higuchi and Korsmeyer Peppas model. The diffusion exponent "n" (Cfx release from DCC-AL and DCC-AL-κ-Ca) followed anomalous diffusion controlled mechanism (non-Fickian-type diffusion mechanism) in all medium. This indicates that mechanism depends on both diffusion and swelling control release. The n value increased from DCC-AL to DCC-AL-κ-Ca IPN beads which indicates that there is increase in crosslinking as DCC-AL-κ-Ca IPN beads have more numbers of crosslinking sites.

CONCLUSION

FCCs with highest drug loading were studied for the taste masking of CP. *In-vitro* and *in-vivo* taste masking showed DCC1:4 of MDC-1 have good taste masking properties compared to other DCCs. This may due to low exchange of ions at salivary pH in case of hydrophobic DVB cross linker compared to other aliphatic cross linker such as EGDMA and MBA. FT-IR spectra confirmed the possible interaction between the drug and MDC-1. P-XRD and DSC confirmed that drug was in amorphous state in the MDC-1 by forming complexes. DCC 1:4 studied for sustain release by forming IPN beads with AL and κ-Ca. The Cfx release was very slow in gastric media and intestinal 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 Cfx depends on non Fickian diffusion. Thus MDC-1 may be further utilized for the taste masking and sustain release of other bitter drugs also.

CONFLICT OF INTERESTS

Declared None

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