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R E S E A R C H A R T I C L E

Development of Enhanced Site Specific Periodontal Drug Delivery Systems for Minocycline HCl and Ciprofloxacin Gels

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A B S T R A C T

Ciprofloxacin hydrochloride, fluoroquinone antibiotic and Minocycline hydrochloride, tetracycline antibiotic that could be used in the treatment of periodontitis for localized therapy. The ciprofloxacin gel was formulated using biodegradable PVP, CMC (5%, 10%, 20%, 30% w/w) and poloxamer. The gel was evaluated for polarizing light microscopy, gelation and gel melting, mechanical characterization of bioadhesive formulations, rheological studies, *in vitro* release of CPX-MHCl, drug(s) release data analysis, antibacterial activity tests and susceptibility tests. *in vitro* antibacterial activity was determine to use S. aureus and E. coli represented Gram-positive and Gram negative bacteria exclusively, and were used as locality strains for antibacterial bustle testing. P. gingivalis was subcultured tabloid on augmented blood agar. *in vitro* antibacterial activity and bio-degradability study. The gels displayed dose dependent antibacterial activity and was found to be stable. The approach provides an opportunity and potential for development of periodontal gel containing both Ciprofloxacin and minocycline HCl for extended release.

Keywords: Gel, Ciprofloxacin, Minocycline, Periodontal diseases.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Drug delivery is an application of biochemical engineering with technologies aimed at the improvement of safety and efficacy, better compliance and life extension of products [1]. Parenterals depot systems (PDS) have been subject of intensive research efforts over the past two decades. PDS can be classified into gels or micro particles [2]. PDS allow the control and modulation of drug release using biodegradable polymers [3]. These polymers have become increasingly important in the development of controlled release systems. Conventional therapy, based on scaling

surgery and the use of antibiotics or antimicrobials has been proposed. But due to bacterial resistance and toxic side effects of the administered antibiotics local delivery system are designed to maintain the antibiotic, in the gingival crevicular fluid at a concentration higher than that achieved by systemic administration.

Periodontitis is set of inflammatory diseases affecting the periodonitium (the tissues that surround and support the teeth). It is caused by micro-organisms that adhere to and grow on the tooth's surfaces, along with an overly aggressive immune response against microorganisms [4]. The presence of periodontal pathogens such as Porphyromonas gingivalis, Prevetella intermedia and Actinobacillus actinomycetemcimitans are responsible for periodontal destruction [5].

The treatment of periodontitis is aimed at controlling the population of microorganisms. High doses of antibacterial agents for a longer period of time required for the treatment of periodontitis. Ciprofloxacin is one of the second generation fluoroquinolone derivative and Minocycline hydrochloride, tetracycline antibiotic anti-infective, exhibiting activity against a wide range of gram-negative and gram-positive facultative bacteria as well as periodontal pathogens. It is reported as more effective in the treatment of periodontitis [6].

Ciprofloxacin and Minocycline is available in the market as a conventional dosage forms such as tablets (extended release), parenterals (intravenous) and suspension for the treatment of bacterial infections but not for the treatment of local infection. Hence it was a challenge to develop implants containing ciprofloxacin with rate controlling polymers which has a prolonged action and shows the antibacterial activity directly at the site of infection without loss of dosage [7].

The present work aims to biodegradable gel of ciprofloxacin and Minocycline for sustained release. The literature review shows that with ciprofloxacin hydroxyl propyl methyl cellulose and poly vinyl alcohol the drug release at the 6th hour was found that 78%. In oder to improve the drug release rate, the fabricated gels are studied for various physicochemical parameters like weight variation, thickness, drug content uniformity, drug polymer interaction, *invitro* dissolution rate studies are performed on the gel.

2. Materials and Methods

2.1. Materials:

Ciprofloxacin (CPX) was obtained as gift sample from seimens Laboratories, Gurgaon, India. Minocycline HCl (MHCl) was obtained as gift sample from Welcure Drugs and Pharmaceuticals, New Delhi, India. Gelatin and Sodium alginate were purchased from S.D fine chemical Ltd., (Mumbai). PVP, CMC was purchased from Hi Pure fine chemical industry, (Chennai). Luria Bertani agar was purchased from Qualigens fine chemicals, Mumbai. Other materials used in the study were of analytical reagent grade.

2.2. Preparation of bioadhesive gels containing CPX and MHCl

HEC, MC (5%, 10%, 20%, 30% w/w) and poloxamer 407 (10% w/w) were thawed in the applicable weight of phosphate buffered saline (PBS, pH 6.8, 0.03 M) using an automatic stirrer. This gel was borne onto an ointment slab and into this, PC (1, 5% w/w), and CPX laterally with MHCl (5%, w/w; particle size, 63 mm) were steadily mixed (table 1). PVP, CMC (5%, 10%, 20%, 30% w/w) and poloxamer 407 (10% w/w) were dissolved in phosphate buffered saline (PBS, pH 6.8, 0.03 M). To this gel PC (1, 5% w/w) and CPX laterally with MHCl (5%, w/w; particle size, 63mm) were sundry (table 1). Ensuing amputation of air under vacuum, formulations were each characterized as entitled beneath or, on some occasions, were stored at 48°C in grade 2 amber glass ointment jars overnight prior to analysis [8-10].

2.3.1. Polarizing Light Microscopy

Gel samples were observed beneath a polarizing light microscope (Nikon, Melville, NY) expending a λ¼ compensator to alteration the actuality of birefringence beneath crossed polarized light, fetching a magnification of 100x. The lamellar, cubic and hexagonal phases were acknowledged convening to the sorting reputable by Rosevear [11-12].

2.3.2. Gelation and Gel Melting

Gelation and gel melting were gauged expending a discrepancy of the Miller and Donavan technique. A 5 ml aliquot of gel was redistributed to test tubes, submerged in a water bath at 4°C, and airtight with aluminum foil. The temperature of the water bath (Haake Phoenix c25P, Karlsruhe, Germany) was enlarged in augmentations of 0.5°C and left to equilibrate for 1 minute at each innovative setting. The sections were then examined for gelation, which was said to have supervened when the meniscus would no extensive move upon slanting through 90°. The gel melting temperature, the temperature at which a gel starts sophisticated upon tilting through 90°, was exhaustive [13-14].

2.3.3. Mechanical Characterization of Bioadhesive Formulations

The automatic properties of all formulations beneath scrutiny were surveyed using texture contour analysis. Formulations were transferred into McCartney (30 ml volume, grade 2 clear glass) bottles to a static height, enchanting care to dodge the hasty of air into the samples. Texture profile scrutiny was accomplished using a Stable Micro Systems Texture Analyzer (Haslemere, Surrey, UK), in texture profile inquiry mode in which the analytical probe (10 mm diameter) was twice crushed into each trial at a distinct rate (2mm s^{-1}) to a depth of 15 mm[169]. A delay period (15s) was permitted among the end of the first and the creation of the second compression and all scrutinizes were achieved at least in quadruplicate. From the ensuing force-time plots, some mechanical constraints may be consequent. These are as follows,

1. **Product Hardness:** (Force prerequisite to conquer a given deformation) was restrained by a Rotovisco (R'V3) cone and plate viscometer.
2. **Compressibility or Spreadability:**

(The force criterion to warp the sample during the compression). 24 hrs old gels (1 g) was constrained amid two horizontal plates of 20 cm^2 of which the greater one weighed 46.36 g and a 200 g weight was positioned over it at ambient temperature. A circle of 5 mm in diameter was through and the diameter of the gel was reserved after 5 min.

3. **Cohesiveness:**

The ratio of the area beneath the force-time curve formed on the second compression cycle to that on the first compression cycle, where progressive compressions are detached by a demarcated rescue period [15-16].

2.3.4. Examination of the Work of Syringeability of Drug(S) Containing Bioadhesive Formulations

The syringeability of apiece formulation was gritty using the texture analyzer. In brief, formulations were displaced into duplicate plastic syringes to a persistent height (3cm). The content of each syringe was effusively expressed expending the texture analyzer in compression mode and the conflict to expression was untiring from the area beneath the consequent force-time plot. Enlarged work of syringeability was titled by enlarged areas under the curves. All extents were attained at least in quadruplicate [17].

2.3.5. Rheological Studies

Rheological magnitudes had been agreed out by using two divergent instruments, contingent on the sample viscosity. Oscillatory scopes were carried out at low amplitude (within the linear viscoelastic region) with an angular velocity (w) of between 0.1 and 100 rad/s. Scopes were conducted at four sundry temperatures, namely 10, 20, 30 and 37°C. Pay for to the Bohlin theory that deliberates flow as a supportive spectacle, the coordination coefficient z was cautious from the slope of the curve assimilated by plotting the elastic modulus (G') vs 0) in a log-log plot[170]. The sol-gel transition temperature (T_c) was designed by 'time cure tests' achieved by plotting elastic (G') and loss (G") moduli as function of temperature. Purposes were realised at 1 Hz and at low amplitude, the temperature range was 4-40°C and the temperature ramp was 1°C/ min. The viscosity has been restful at a low shear rate ($0.1\text{-}10^{-1}$) in order to evade slipping assets at the wall surface, perchance instigated by high shear rates [18-19].

2.3.6. *In Vitro* Release of CPX-MHCl:

In vitro release of CPX-MHCl from the bioadhesive gel formulations was executed (in triplicate) using a 37 ml Franz diffusion cell. The diameter of the donor cell was 26 mm and the dissolution standard was PBS. The diffusion cell was water jacketed at 37±°C. 1.5 g of the gel was displaced to the Durapore HVLP membrane (0.45 um) of the vessel. At unwavering time intervals, 2 ml illustrations of the receptor fluid were taken and analyzed for CPX and MHCl spectrophotometrically at 318 nm and 273.8 nm individually by synchronised equation routine. The standard was bartered after each specimen to endure sink ailment [20].

2.3.7. Drug(S) Release Data Analysis

Data acquired from dissolution revisions were fitted to the universal release equation (Eq.1) advocated by Gurny et al. using logarithmic transformations and least squares regression analysis [21, 22].

$Mt/ M\omega = kt^n$.....Eq. 1

Where,

Mt = the percentage of drug(s) released at time t,

K= a constant incorporating structural and geometric characteristics of the delivery system.

n= the release exponent.

2.3.8. Antibacterial Activity Tests

Bacterial strains and advance situations P. gingivalis, S. aureus and Escherichia coli were used in this learning. S. aureus and E. coli represented Gram-positive and Gram negative bacteria exclusively, and were used as locality strains for antibacterial bustle testing. P. gingivalis was subcultured tabloid on augmented blood agar [SBA; trypticase soya agar, supplemented with yeast extract 1 mg/ml, vitamin K_1 5 ug/ml, hemin 5mg/ml and 5% (v/v) human blood. The other bacteria were cultured on Mueller-Hinton agar (MHA; Merck, Germany) slant at 37°C. To standardize the cells, the allusion strains were advanced to reach log phase and then the suspension was adjusted to 25% transmittance at an OD_{560} compatible to bumpily 10^8 colony-forming units/ml, and this was used assisting for antibacterial bustle testing [23,24].

2.3.9. Susceptibility Tests

Antibacterial bustle was curtained by the cylinder plate scheme. Plates encircling agar were brushed using sterile swabs with 25% transmittance test retiring organisms (P. gingivalis, S. aureus and E. coli). Solution of optimized gel (Sample 1) was prepared at a concentration of 20 mg/300ul DW. Solutions of the allusion antibiotics were prepared at a concentration of 30 ug/300 ul DW. These samples were sterilized by filtration complete wetting agent free cellulose acetate 0.2 um filter (Sartorius, Germany). 300 u1 of reference antibiotic solution or 300 ul of the test model solutions were engaged in the cup on the agar plate. P. gingivalis on SBA was nurtured in an anaerobic glove box (Thermo Forma, Germany) with 80% N_2 10% CO_2 and 10% H_2 at 37°C for 72 h, whereas S. aureus and E. coli on MHA were incubated in an aerobic incubator (Heraeus B5060 E, Germany) at 37°C for 24 h. After the incubation period, the diameter of the inhibition zone was unemotional with an antibiotic zone reader (Fisher Scientific™, USA) and substantiated in mm. Sample 1 was convinced for auxiliary testing of the minimum inhibitory concentration (MIC). MICs were steadfast in a microtitre assay by inoculation of 100 ul of P. gingivalis adjourned in supplemented BHI (sBHI; yeast extract 5 mg/ml, vitamin K1 5 ug/ml and hemin 5 ug/ml, final concentration $5x10^5$ colony forming units/ml) in a 96 well microtitre tray with two-fold serial dilutions by adding 100 ul of a solution of Sample 1 or control antimicrobial agents (MHCl, Ciprofloxacin). The final concentrations of the test sample 1 was 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125 and 0.625 mg/ml, and for the antimicrobials were 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625, 0.03125 and 0.0156 ug/ml. The plates were nurtured anaerobically for 72 h. The MICs were exhaustive as the lowest concentration for 90% inhibition. Minimum bactericidal concentrations (MBCs) were gritty by culturing on SBA for 48 h. The percentage of inhibition is stated by the ensuing equation:

Percentage inhibition = OD in control group - OD in interested group/ OD in control group

For studies of the kinetic death rate of Sample 1, a cellular suspension (100 ul, 10^5 colony forming units/ml) of P. gingivalis was inoculated into sBHI. The test sample 1 (aqueous solutions, final concentration 2-8 mg/ml) were added, and the mixtures were incubated at 37°C for 0, 2, 5, 9, 24, 48 and 72 h. At designated intervals, 100 ul portions were taken, diluted and dropped on to sBA, the plate was incubated for 48 h, and colonies were counted [25, 26].

3. Results and Discussion

3.1.1. Polarizing Light Microscopy

Polarizing photographs of gel destitute of CMC, PVP and a gel encircling 10% CMC and 5% PVP are shown in Figure-1. Photographs presented a dark background in the case of plain gel, however some fan like structures were superficial in the polarizing photograph of the P_5C_{10} formulation. Amalgamation of drug(s) did not distress the liquid crystalline phase of gel; it underwent in the cubic phase. Incorporation of CMC and PVP did disrupt the phase structure where it acclimatises from the cubic phase into the hexagonal phase. However, an improvement in the concentration of PVP did not craft any amendment in the phase edifice. It was uncovered that plain gel is in the cubic phase, which refurbishes to the hexagonal phase after the scheming of CMC and PVP. For PVP, the type of structures accomplished in the presence of discriminatory solvent looks to be a function of the volume fraction of the polar/apolar module. This is endorsed to the aptitude of the macromolecule lumps to swell to a diverse magnitude (created on the expanse of solvent unfilled) with the particular solvents and thus to annoyance the interfacial curvature and ensuing structure. The interfacial curvature is divergent as positive when the interface curvatures near the apolar provinces that is, the micelles are encircled by the polar sticks restricting the apolar provinces inside them, and vice versa. In the cubic phase, interfacial curvature is remarkably positive because of the spherically shaped micelles. The normal hexagonal phase has been assimilated at a high content of CMC (10%) and at 5% PVP because of decreased solvation of the PVP blocks. PVP engrosses water from the system; as a result, less water was presented for CMC, which begun the restoration of the cubic phase to the hexagonal phase.

3.1.2. Gelation and Gel Melting

The effect of drug(s) concentration on gelation and gel melting is publicized in Figure-2. The gelation temperature was dropped in the prevalence of drug(s) and waned linearly with its swelling concentration; nevertheless the melting temperature improved with the concentration of drug(s). Substantially, gel formation is concomitant to micellar packing and volume fraction. Scholars have endorsed gelation to the dehydration in the micelle core, a tuning in the micellar volume, or a dwindling in the critical micelle concentration and an escalation in the aggregation number. The finding that drug(s) depressed the gelation temperature was parallel to the result conversant by Esposito. This piece was timidly progressive by a empowering of the collaboration among the hydrophobic portion of the polymer molecules, which might dislocate the micellar edifice and escalation the entanglement of micelles. At established concentration of drug(s), depressing of the critical micellar concentration streamlines closer packing of micelles, which possessions that more energy is prerequisite to interruption the gel structure. The gel structure was rumoured to sustain infrangible with temperature up until an arbitrarily high temperature triggered the wreckage of the gel structure. At higher temperatures, the gel tolerated dehydration, but undue hydrogen bonding and closely packed micelles embarrassed the destruction of the gel structure. As the concentration of the HEC engorged and concentration of MC waned, the gel structure became more strictly packed, with the organization in a lattice decoration. In turn, the interruption of the lattice melting of the gel arises at higher temperatures.

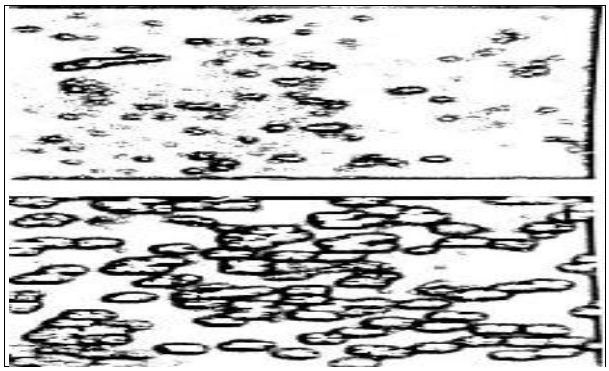

Figure 1: Polarizing Light Microphotographs of Poloxamer Gel Showing Different Phases: (A) Cubic Phase (Plain Gel), (B) Hexagonal Phase (Pvp-Containing Gel).

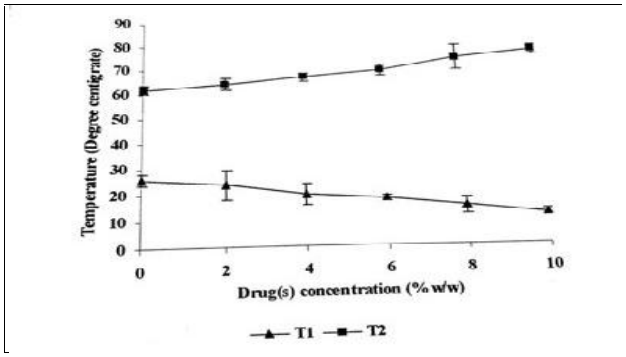

Figure-2: Effect of drug(s) concentration on gelation point (t_1) and gel melting point (t_2)

3.2.3. Mechanical Characterization of Bioadhesive Formulations

In this study, the mechanical properties of the entrant formulations for the management of periodontal disease were resolute. Texture profile analysis (TPA) outlines the mechanical constraints in empathies of hardness, compressibility and adhesiveness, properties that will anguish the ease of product solicitation into, and preservation within, the periodontal pocket, unconventionally. TPA also accords an assessment of the scope of organizational reformation subsequent product

administration (cohesiveness), and facet which will impact product recital. Therefore, in this character, TPA is a pertinent observes for the depiction of formulations deliberated for solicitation to the periodontal pocket. Increased product hardness, compressibility and syringebility were allied with enlarged concentrations of HEC or CMC and PC in apiece formulation. Each of these parameters elected the fighting of each formulation to compression and, consequently, reflects regulations in product viscosity, as previously recognized. Statistical exchanges seemed among the possessions of the polymeric constituents on these mechanical properties and were due to the unexpectedly large firmness, work of compression and syringe ability escorting with formulations encircling 30% (w/w) HEC or CMC and 5% PC. These formulations encircled the greatest extents of suspended, un-swollen particles and the larger ensuing semisolid properties accounted for the unexpected solidity properties.

Product cohesiveness has been carried to designate spatial traits of structural re-organisation resulting product compression. As the PC content was amplified, the mass of adjourned solids enlarged. Subsequently, the semisolid fauna of the product enlarged, which, in turn, decreases formulation cohesiveness. Decreased product cohesiveness akin with increased concentrations of HEC or CMC is a meaning of increased product viscosity, as the viscoelastic properties of these formulations will be expensive by this parameter. The statistical collaboration term imitates the unexpectedly outstanding decline in cohesiveness of formulations encircling the higher concentrations of respectively polymer and is once more due to the comparably superior semisolid character of these formulations.

The mechanical parameters of apiece formulation are handy in table-2. Aggregate concentrations of HEC or CMC and/or PC alluringly increase formulation hardness, compressibility and adhesiveness, yet, they diminutions cohesiveness. Archetypally extreme and tiniest hardness, compressibility and adhesiveness were akin with formulations encompassing 30% (w/w) HEC or CMC and 5% (w/w) PC, and 5% (w/w) HEC or CMC and 1% (w/w) PC, respectively. In the case of cohesiveness, the inverse was witnessed, i.e. extreme and tiniest values being complementary with formulations encompassing 5% HEC or CMC and 1% PC, and 30% HEC or CMC and 5%, PC, individually. With the omission of formulations surrounding 5% (w/w) HEC or CMC and 1% PC, HEC encircling formulations divulged expressively grander hardness, adhesiveness and compressibility than their equivalents encircling CMC.

The syringeability of each formulation is prevailing in table-3. Once more, aggregate concentrations of each polymeric element (HEC/CMC and/PC) vividly escalations the force essential to exorcise apiece formulation from a periodontal syringe over a fixed aloofness. Formulations encircling (5% w/w) HEC or CMC presented statistically analogous values of work of syringeability (P.0.05), nevertheless the work of syringeability of formulations encircling 30% HEC encouragingly outdone those formulations encircling (30% w/w) CMC.

In this investigation, the adhesive properties of the entrant formulations were dissected using two methods, unambiguously texture profile analysis, which entitles the work criterion to sequester a polymeric probe from the test formulation, and also by estimation of the detachment force prerequisite to daze the adhesive bond between each formulation and a compressed mucin disc. In tallying, for all formulations, time of exchange with the mucin disc sensitively predisposed the strength of the mucoadhesive bond. This may be progressive by hydration of the mucin, due to the promise of moisture from each formulation, which in turn approvals interpenetration of the polymeric chains in mucin and those in each formulation. The absolutions from these annotations were additional with formulations encircling (5% w/w) CMC in which cohesive bond disaster befallen.

The consequence of HEC on the bioadhesive properties of formulations encircling PC was vividly greater than that of CMC. The probable mechanisms originating this inconsistency were emphasized within the statistical interaction term amid polymeric constituents with admiration to adhesiveness and impartiality force. Once more, in these interactions, formulations encircling 5% (w/w) PC and either 30% (w/w) HEC or CMC unveiled surprisingly large numerical values of adhesiveness and impartiality forces. It has been recounted that the bioadhesive properties of formulations including PC increases as the number of uncharged carboxylic acid groups increases. Therefore, formulations encircling the higher concentration of HEC or CMC and 5% (w/w) PC haunted the greatest multitudes of unswollen, uncharged particles and, subsequently, these formulations definite the greatest adhesion to both mucin and the polymeric probe. The preservation of the product in the periodontal pocket was the foremost distress, as it was prerequisite to guarantee that the product would sustain there for the planned period of drug release. The results of the detachment force revision provisions the hypothesis that the probable mechanism of the mucoadhesion uncovered by the dehydration of the mucosa (i.e. water uptake by the mucoadhesive material). The extent of water taken up by the liquid crystalline gels directed the mucoadhesive force; the gel having grander water uptake capacity revealed greater mucoadhesion.

3.2.4. Rheological Studies

In this alteration, a sequence of preliminary possessions on the rheological portrayal of poloxamer based gels is attainable (Table-4). This reading was accomplished in order to delineate the universal rheological behavior of these judiciously novel constituents and to pay for information on their edifice, as a function of temperature and of the survival of solubilized guest molecules (i.e. CPX and MHCl).

3.1.5. *In Vitro* Drug(S) Release Studies

HEC and/ or CMC encompassing gels ensuing dissolution in PBC or water correspondingly deliberate primary gels, the viscosity of which was aquiline on of the concentration of polymers specified the upshot of dissimilar types of bioadhesive polymers and their emergent concentrations on the release of drug(s) from gel formulations. PC is a cross linked imitative of polyacrylic acid which does not liquefy but disclosures swelling, the latitude of which is contingent on the extent of presented water extant in the formulation i.e. the water does not escorting with the dissolved polymer. Consequently, in the formulations encircling 30% (w/w) HEC or CMC, the amount of free water is decayed and the magnitude of swelling of PC in these formulations is wilted in evaluation to the formulations incorporating 5% (w/w) HEC or CMC. In formulations encircling 5% (w/w) HEC or CMC, PC ensued mostly in swollen state. In all formulations CPX and MHCl was existent in a suspended form. The state of PC in every formulation was predisposed, at least in part for voluminous of the annotations of this adjustment. Decreased drug(s) release from formulations comprehending enlarged concentrations (30% w/w) of either HEC or CMC may be nominated to the assenting increase in product viscosities that are related with enlarged polymer concentrations. Decreased release affiliated with increased concentrations of PC in formulations grasping 5% (w/w) HEC or CMC may also be illuminated by the conglomerated increased product viscosities consequent swelling of this polymer within the formulation.

Drug(s) release from CMC systems was grander than from their HEC parallel item and was due to loftier viscosities of HEC/PC formulations. An improved PC concentration predominantly declines the release of drugs. The release of drug(s) from formulations restricted 30% (w/w) HEC and 5% (w/w) PC was sensitively countless than those encompassing 30% (w/w) HEC and 1% (w/w) PC. These interpretations may be liberal by the practised degrees of swelling of PC in each formulation. Product swelling was countless for formulations comprehending HEC, in appraisal to those comprehending CMC, due to the grander masses of unswollen PC. Incontestably as an upshot of unnecessary swelling of this polymer concluded dissolution testing, partial product disintegration arisen for formulations comprehending 30% (w/w) HEC and 5% (w/w) PC.

Therefore, surface areas of these formulation amplified, which in turn growths the rate of drug(s) release. The time criterion for the 50% release of drug(s) i.e. $t_{50\%}$ from respectively formulation is revealed in table-5. The times critical for 50% drug(s) release from formulations comprehending HEC were encouragingly greater than those enfolding equivalent concentrations (%w/w) of CMC and PVP. DE after 24 hrs (DE_{24}%) and $t_{50\%}$ were used to comrade the drug release characteristics of sundry formulations.

3.1.6. Drug(S) Release Data Analysis

In order to scrutinize the mechanism of drug(s) release (Figure 3-6) from controlled delivery formulations, the tenets of the kinetic parameters n, K and R from Eq. (1) were premeditated. The all-encompassing viscosity is escalations with polymer concentration. Thus, the dwindling in drug(s) release rate is paramount projected due to dwindled rates of penetration of dissolution fluid into the higher viscosity products. PVP and CMC formulations exhibited Higuchi release kinetics and are too hard and not from a mechanical fact of view. The gels comprehending 10% HEC necessity low work of syringeability but drug(s) release persists only 24-36 hrs. (Figure-3).

Nevertheless, merchandises with 30% (w/w) HEC not only have decorous mechanical properties but sanction sustained release profiles for 46-58 hrs. (Figure-3). Increase the polymer concentration of HEC escalations the k value further meritoriously than MC. Increasing concentrations of PVP from 5-30% in gels encircling CMC, decreases the k and decreases t (Figure 3-6). With the persistent concentration of PVP accumulative the CMC from 5-30% amplified the k and t. Consequent solicitation of the general release equation (1) to the release data of all formulations, it was alleged that there was a release exponents (n) ranged from 0.5 to 1.0 postulating non-fickian drug(s) transport. The mechanism of drug(s) release from gels has been hitherto cognizant as diffusion-controlled, i.e. where n= 0.5. Consequently it is advocated that other mechanisms, e.g. Polymeric swelling and or dissolution endow to the complex release exteriors of drug(s) from formulations underneath contemporary assessment.

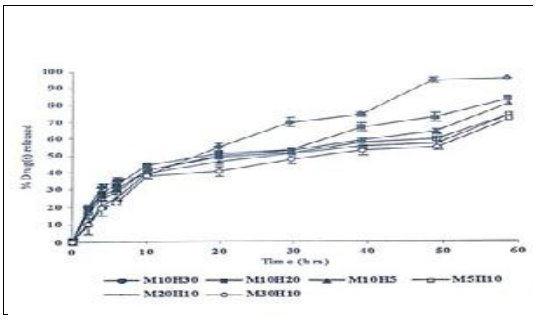

Figure-3: Release profiles of CPX from bioadhesive gels containing methyl cellulose (mc) and hydroxy ethyl cellulose (HEC) (n=3).

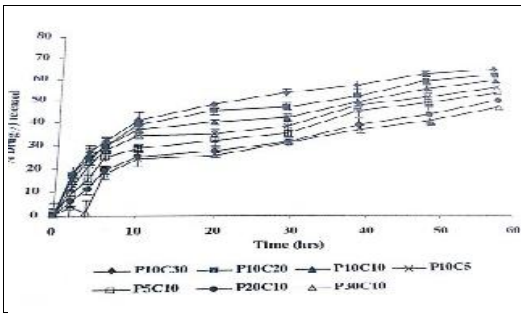

Figure-4: Release profiles of MHCl from bioadhesive gels containing carboxy methylcellulose (CMC) and polyvinyl pyrrolidone (PVP) (N=3)

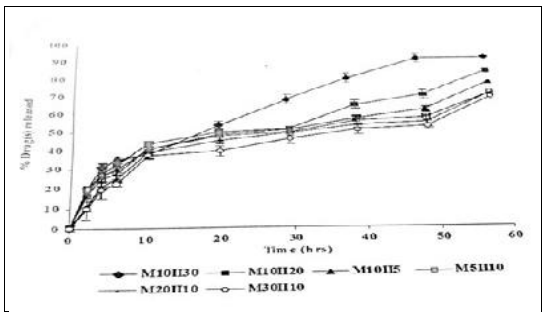

Figure 5: Release profiles of CPX from bioadhesive gels containing methyl cellulose (MC) and hydroxy ethyl cellulose (HEC) (N=3)

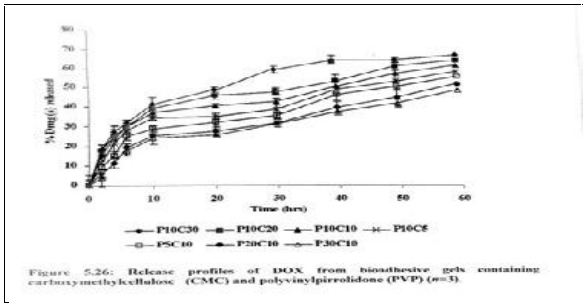

Figure 6: Release profiles of MHCl from bioadhesive gels containing carboxymethyl cellulose (CMC) and polyvinyl pyrrolidone (PVP) (N=3)

3.1.7. Antibacterial Activity

Antibacterial deeds are concise in table 6. Briefly, Sample 1 had a growth inhibition zone on agar with all three strains. Remarkably, MHCl pay for related zones of inhibition with reverence to E. coli and S. aureus [16.4 and 23.7 mm for MHCl, 18.2 and 18.4 mm for Sample 1]. However, with P. gingivalis, MHCl was substantially more persuasive [45 mm for MHCl , 24.7 mm for Sample 1]. The E. coli and P. gingivalis used were inclined to MHCl with MICs of 0.2-2 uM and MBCs of 1-8 uM. P. gingivalis was inclined to CPX with an MIC of 0.7 uM and an MBC of 1.4 uM. At the critical concentration (0.14 uM) through incubation times of 10 mm, 1 h and 2 h, the numbers of P. gingivalis declined vividly with no practicable counts after 2 h.

4. Conclusion

The ciprofloxacin and minocycline HCl gels were categorized by a atypical rheological comportment, as a function of polymer concentration, temperature and existence of drug(s) and retain apt properties as intrapocket drug(s) delivery system for periodontal healing. In the present study, a substantial lessening in mean plaque index, gingival index, sulcus bleeding index, and probing pocket depth, and a substantial gain in clinical affection were perceived.

Table-1: Formulation design of CPX and MHCl bioadhesive gels

Formulation code	MHC (%w/w)	MC (%w/w)	MC (%w/w)	MC (%w/w)	MC (%w/w)	Poloxamer (%w/w)	CPX and MHCl (%w/w)
$M_{10}H_2$	10	5	-	-	5	10	5
$M_{10}H_{20}$	10	20	-	-	1	10	5
$M_{10}H_{30}$	10	30	-	-	5	10	5
M_5H_{10}	5	10	-	-	1	10	5
$M_{20}H_{10}$	20	10	-	-	5	10	5
$M_{30}H_{10}$	30	10	-	-	1	10	5
$P_{10}C_5$	-	-	10	5	5	10	5
$P_{10}C_{10}$	-	-	10	10	1	10	5
$P_{10}C_{20}$	-	-	10	20	5	10	5
$P_{10}C_{30}$	-	-	10	30	1	10	5
P_5C_{10}	-	-	5	10	5	10	5
$P_{20}C_{10}$	-	-	20	10	1	10	5
$P_{30}C_{10}$	-	-	30	10	5	10	5

Table 2: Mechanical properties of the bioadhesive gel formulations of CPX and MHCl

Formulation code	Hardness Mean(±S.D.)	Adhesiveness Mean (± S.D.)	Compressibility Mean (± S.D.)	Cohesiveness Mean (± S.D.)
$M_{10}H_5$	2.05 ± 0.03	4.11 ± 0.01	16.87 ± 0.32	0.81 ± 0.01
$M_{10}H_{20}$	2.11 ± 0.01	4.32 ± 0.25	17.25 ± 0.65	0.76 ± 0.01
$M_{10}H_{30}$	2.55 ± 0.52	4.45 ± 0.15	17.46 ± 0.85	0.74 ± 0.02
M_5H_{10}	2.01 ± 0.06	3.89 ± 0.11	16.81 ± 0.11	0.82 ± 0.03
$M_{20}H_{10}$	1.87 ± 0.05	3.77 ± 0.02	16.74 ± 0.02	0.86 ± 0.01
$M_{30}H_{10}$	1.82 ± 0.07	3.75 ± 0.18	16.71 ± 0.07	0.87 ± 0.02
$P_{10}C_5$	0.70 ± 0.08	2.58 ± 0.09	6.75 ± 0.11	0.88 ± 0.03
$P_{10}C_{10}$	0.87 ± 0.04	2.71 ± 0.11	7.24 ± 0.05	0.86 ± 0.01
$P_{10}C_{20}$	0.93 ± 0.10	2.79 ± 0.23	7.96 ± 0.45	0.85 ± 0.10
$P_{10}C_{30}$	1.26 ± 0.12	2.97 ± 0.56	8.42 ± 0.52	0.83 ± 0.02
P_5C_{10}	0.68 ± 0.05	3.81 ± 0.48	11.41 ± 0.23	0.79 ± 0.01

$P_{20}C_{10}$	0.64 ± 0.09	1.88 ± 0.20	6.67 ± 0.33	0.89 ± 0.03
$P_{30}C_{10}$	0.61 ± 0.14	1.29 ± 0.53	6.25 ± 0.25	0.94 ± 0.02

Table 3: Mucoadhesive strength of formulations containing CPX and MHCl

Formulation code	Force required to break the mucoadhesive bond following contact between formulations and mucin for a range of times(s)			Work of syringe ability (N mm)
	60	180	240	
$M_{10}H_5$	0.37 ± 0.02	0.42 ± 0.01	0.57 ± 0.01	77.43 ± 3.24
$M_{10}H_{20}$	0.40 ± 0.01	0.47 ± 0.02	0.58 ± 0.05	81.23 ± 2.31
$M_{10}H_{30}$	0.48 ± 0.01	0.56 ± 0.01	0.61 ± 0.04	89.49 ± 1.02
M_5H_{10}	0.34 ± 0.02	0.37 ± 0.01	0.54 ± 0.02	74.69 ± 4.20
$M_{20}H_{10}$	0.32 ± 0.03	0.38 ± 0.02	0.51 ± 0.01	71.23 ± 1.22
$M_{30}H_{10}$	0.30 ± 0.02	0.36 ± 0.03	0.49 ± 0.02	69.45 ± 2.41
$P_{10}C_5$	0.15 ± 0.02	0.21 ± 0.02	0.26 ± 0.05	52.11 ± 3.25
$P_{10}C_{10}$	0.18 ± 0.01	0.22 ± 0.01	0.29 ± 0.03	53.98 ± 1.23
$P_{10}C_{20}$	0.21 ± 0.02	0.28 ± 0.03	0.35 ± 0.01	55.06 ± 3.62
$P_{10}C_{30}$	0.27 ± 0.03	0.36 ± 0.05	0.30 ± 0.01	56.71 ± 2.55
P_5C_{10}	0.14 ± 0.01	0.20 ± 0.0	0.24 ± 0.02	49.36 ± 1.02
$P_{20}C_{10}$	0.12 ± 0.02	0.18 ± 0.01	0.22 ± 0.01	47.89 ± 1.85
$P_{30}C_{10}$	0.11 ± 0.03	0.16 ± 0.02	0.20 ± 0.03	44.33 ± 2.32

Table-4: Rheological characterization of CPX AND MHCl containing gels

Gel	Composition	Guest molecule	Tc [°C]	G'[Pa]			G"[Pa]			z [Pa. s]			η [x10s^{-1}]
				10°C	30°C	37°C	10°C	30°C	37°C	10°C	30°C	37°C	37°C
Poloxamer	20	No	15.8	0.0004	26.240	30.060	0.6	1703	1053	-	73.8	185.4	68.6
	25	No	21.01	0.0007	12.440	15.390	0.5	1149	1443	4.1	11.2	23.6	46.6
	25	Yes	15.81	0.0063	24.090	24.120	1.1	1869	1040	0.7	61.5	106.6	67.5
	30	No	12.20	0.992	24.120	24.770	177	1992	2316	8.8	40.0	37	63.1

Table-5: Model independent parameters and release data analysis of bioadhesive gels (n=3)

Formulation code	DE_{24}%±S.D.		K±S.D.		$t_{50\%}$±S.D.		n	
	CPX	MHCl	CPX	MHCl	CPX	MHCl	CPX	MHCl
$M_{10}H_5$	60.11±0.11	64.36±0.41	18.20±0.11	23.44±0.11	32.84±0.94	33.65±0.94	0.564	0.554
$M_{10}H_{20}$	62.78±0.23	67.36±0.24	17.98±0.20	17.98±0.20	34.21±0.25	36.36±0.56	0.636	0.654
$M_{10}H_{30}$	68.20±0.56	72.36±0.55	18.95±0.02	18.95±0.02	38.76±0.89	39.25±0.44	0.587	0.557
M_5H_{10}	58.77±0.54	66.36±0.25	17.57±0.55	18.34±0.54	29.87±0.98	30.21±0.11	0.649	0.657
$M_{20}H_{10}$	56.29±0.89	60.36±0.25	17.38±0.002	19.34±0.36	27.86±0.78	28.25±0.81	0.548	0.557
$M_{30}H_{10}$	55.25±0.54	56.25±0.54	17.01±0.50	19.36±0.55	24.72±0.46	25.36±0.44	0.570	0.573
$P_{10}C_5$	39.21±0.23	43.56±0.58	1.57±0.06	3.65±0.56	18.27±0.82	18.55±0.88	0.51	0.514
$P_{10}C_{10}$	41.01±0.25	42.58±0.58	1.62±0.85	2.36±0.55	19.11±0.45	19.21±0.45	0.500	0.543
$P_{10}C_{20}$	44.60±0.45	47.65±0.54	1.78±0.12	4.25±0.52	21.89±0.72	21.89±0.72	0.500	0.515
$P_{10}C_{30}$	46.91±0.56	49.81±0.60	16.11±0.002	18.23±0.02	22.77±0.48	22.77±0.48	0.539	0.554
P_5C_{10}	25.61±0.89	25.61±0.89	1.51±0.06	5.36±0.08	17.28±0.25	17.28±0.25	0.516	0.551
$P_{20}C_{10}$	22.13±0.78	22.13±0.78	1.47±0.01	1.55±0.05	15.78±0.28	15.78±0.28	0.532	0.523
$P_{30}C_{10}$	21.45±0.80	25.36±0.88	1.41±0.23	2.73±0.25	14.60±0.26	14.60±0.26	0.521	0.524

Table 6: Antibacterial activity of $M_{10}H_{30}$ formulations

Agent	pH (±S.D.)	Bacterial Strains	Amount/inhibition zone		MIC	MBC
			n = 3	mm (±S.D.)		

Sample 1 ($M_{10}H_{30}$)	3.52±0.5	E.coli S. aureus P. gingivalis	20mg 20mg 20mg	18.2 (0.5) 18.4 (0.6) 24.7 (0.8)	ND ND ND	ND ND ND
MHCl	2.1-2.3*	E.coli S. aureus P. gingivalis	30µg 30µg 30µg	16.4(0.4) 23.7(0.3) 45.0(2.4)	2 µM ND 0.2 µM	8 µM ND 1 µM
Ciprofloxacin	5.8*	E.coli S. aureus P. gingivalis	30µg 30µg 30µg	(-) (-) 75.0(1.6)	ND ND 0.7 µM	ND ND 1.4 µM

*ND: Not determined; MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration*Values from Merck Index*

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