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Preparation and characterization of Metronidazole and Minocycline HCl Mucoadhesive Gel for the Treatment of Periodontitis

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Abstract

The aim of the paper was to develop Metronidazole and Minocycline HCl containing mucoadhesive gel for the treatment of periodontitis. Different Mucoadhesive gels were prepared, using various gelling agents like, Hydroxy ethyl cellulose (HEC), Methyl cellulose (MC) and Poloxamer 407. The selected formulations were studied for different mechanical properties, such as product hardness, compressibility or spreadability and cohesiveness the other characterizations like mucoadhesive, rheology. *In vitro* Metronidazole release from the prepared formulations was also determined. The gels containing 10% HEC need low work of syringeability but drug(s) release lasts only 24-36 hrs. However, products with 30% (w/w) HEC not only have suitable mechanical properties but show sustained release profiles for 46-58 hrs. Increase the polymer concentration of HEC increased the k value more effectively than MC. So, this work confirmed the acceptability and effectiveness of Metronidazole and Minocycline HCl gel for treatment of periodontitis.

Keywords: Mucoadhesive gel, periodontitis, Metronidazole, Minocycline HCl, texture analysis

Contents

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1. Introduction

Periodontal diseases are now one of the greatest challenges for modern dentistry. Tooth loss impacts on systemic diseases in many patients. It seems therefore that the treatment of chronic periodontitis is beneficial not only for overall dental health but also for overall general health. Currently, the treatment of periodontal diseases emphasizes a maximum of local treatment without systemic complications. The creation of local drug carriers is of great importance and is very useful in periodontic practice. Elimination of side effects from overall treatment creates a good basis for long-term treatment especially in patients with systemic diseases. However, the oral environment does not create favourable conditions for topical pharmacotherapy. The continuous flow of saliva, cheek movement, mealtimes, talking – all these factors make it difficult to maintain medicine long enough on the mucosa or in the

periodontal pocket. The application of the medicine itself to the periodontal pocket is difficult; additionally, both the ability to control the amount of medicine released and the medicine continuation time in the pocket is often unpredictable. Modern pharmacology and biotechnology are in search of new solutions and ways to deliver medicines topically (1).

The use of systemic antibiotics raises a number of issues, like bacterial resistance to administered antibiotic and unpleasant or toxic side effects. Large doses must be taken in order to achieve sufficient concentrations in the gingival crevicular fluid of the periodontal pockets; this brings with it the associated side effects of antibiotics and problems regarding antibiotic resistance (2). Because of these considerations, a variety of specialized local delivery systems (i.e., intrapocket devices) were designed to maintain the antibiotic in the gingival crevicular fluid at a concentration higher than that achieved by systemic administration (3). With respect to solid devices, semisolid (gel) formulations have some advantages, such as relatively faster release of the incorporated drug (particularly with respect to fibres or microparticles); easy preparation; easier administration and a higher biocompatibility and mucoadhesivity, allowing adhesion to the mucosa in the dental pocket and rapid elimination through normal catabolic pathways, decreasing the risk of irritative or allergic host reactions at the application site. The current practice for the treatment of gingivitis and periodontitis involve the removal of plaque by scaling and root planning, along with application of Metronidazole gel directly on the gums several times. The Metronidazole (MZ) gel is a very bitter formulation and, thus, reduces patient compliance (4).

Metronidazole is an antimicrobial drug often used in local chemotherapy of chronic periodontitis. It is a drug of nitroimidazole derivatives. It exhibits bactericidal activity against protozoonicidal and anaerobic microorganisms. It can be delivered either orally–250 mg Tablets, and localized mostly in the form of a gel, 1%, 5% and 10%, 25% Metronidazole gel Elyzol, and often clinically in the form of pocket irrigation–0.5% solution for injection. Metronidazole gel Elyzol® 25% – the preparation is in a syringe with a dispenser, which allows quick and accurate application. Immediately after administration into the pocket the drug is a sol, and contact with saliva or gingival fluid causes its transformation into a gel, which then undergoes crystallization, thus securing its long-term therapeutic effect. Metronidazole acts primarily on anaerobic flora and its mechanism of action is inhibition of DNA synthesis in the bacterial cell (5). The mucoadhesive gels were prepared for administration to the periodontal pocket by using different gelling agents like poloxamer 407(PL407), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC).

2. Materials and Methods

Materials:

Metronidazole, Minocycline HCl were obtained as a kind gift samples from, SEIMENS Laboratories, Gurgaon, Welcure Drugs and Pharmaceuticals, New Delhi, India respectively. Ethyl cellulose, , Hydroxy propyl cellulose, Hydroxyethylcellulose (HEC), Methylcellulose (MC), were obtained from S.D. fine chem. ltd, Mumbai, Titan biotech ltd, Bhiwadi, Rajasthan, S.D. fine chem. ltd Mumbai, India, respectively. Poloxamer 407 was obtained from BASF USA, Hydroxy propyl methyl cellulose E15LV was obtained from Sigma Aldrich, Steinheim, Germany.

Methods:

1. Preparation and evaluation of periodontal gel of Metronidazole and Minocycline HCl:

HEC, MC (5%, 10%, 20%, 30% w/w) and poloxamer 407 (10% w/w) were dissolved in the appropriate weight of phosphate buffered saline (PBS, pH 6.8, 0.03 M) using a mechanical stirrer. This gel was transferred onto an ointment slab and into this, PC (1, 5% w/w), and MTZ along with MINOCYCLINE HCl (5%, w/w; particle size, 63 mm) were thoroughly mixed (Table 4.7). 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 MTZ along with Minocycline HCl (5%, w/w; particle size, 63 mm) were mixed (Table 1). Following removal of air under vacuum, formulations were either characterized as described below or, on some occasions, were stored at 48°C in grade 2 amber glass ointment jars overnight prior to analysis.

2. Characterization:

2.1. Evaluation of Periodontal Gel

2.1.1 Polarizing Light Microscopy

Gel samples were examined under a polarizing light microscope (Nikon, Melville, NY) using an λ¼ compensator to study the existence of birefringence under crossed polarized light, employing a magnification of x100. The lamellar, cubic, and hexagonal phases were identified according to the classification established by Rosevear.

2.1.2 Gelation and Gel Melting

Gelation and gel melting were assessed using a modification of the Miller and Donavan technique. A 5 ml aliquot of gel was transferred to test tubes, immersed in a water bath at 4°C, and sealed with aluminium foil. The temperature of the water bath (Haake Phoenix c25P, Karlsruhe, Germany) was increased in increments of 0.5°C and left to equilibrate for 1 minute at each new setting. The samples were then examined for gelation, which was said to

have occurred when the meniscus would no longer move upon tilting through 90°. The gel melting temperature, the temperature at which a gel starts flowing upon tilting through 90°, was recorded.

3. Mechanical Characterization of Bioadhesive Formulations

The mechanical properties of all formulations under examination were examined using texture profile analysis. Formulations were transferred into McCartney (30 ml volume, grade 2 clear glass) bottles to a fixed height, taking care to avoid the introduction of air into the samples. Texture profile analysis was performed using a stable Micro Systems Texture Analyzer (Haslemere, Surrey, UK), in texture profile analysis mode in which the analytical probe (10 mm diameter) was twice compressed into each sample at a defined rate (2mm s^{-1}) to a depth of 15 mm. A delay period (15s) was allowed between the end of the first and the beginning of the second compression and all analyses were performed at least in quadruplicate. From the resultant force—time plots, several mechanical parameters may be derived.

4. Product Hardness: (force required to attain a given deformation) was measured by a Rotovisco (R'V3) cone and plate viscorneter.

5. Compressibility or Spreadability

The force required to deform the sample during the compression). 24 hrs old gels (1 g) was pressed between two horizontal plates of 20 cm^2 of which the upper one weighed 46.36 g and a 200 g weight was placed over it at ambient temperature. A circle of 5 mm in diameter was made and the diameter of the gel was measured after 5 min.

6. Cohesiveness:

The ratio of the area under the force time curve produced on the second compression cycle to that on the first compression cycle, where successive compressions are separated by a defined recovery period.

7. Examination of the work of Syringeability of Drug(S) Containing Bioadhes1ve Formulations

The syringeability of each formulation was determined using the texture analyzer. In brief, formulations were transferred into identical plastic syringes to a constant height (3 cm). The content of each syringe was fully expressed using the texture analyzer in compression mode and the resistance to expression was determined from the area under the resultant force time plot Increased work of syringeability was denoted by increased areas under the curves. All measurements were performed at least in quadruplicate..

8. Evaluation of the Mucoadhesion of Mtzminocycline HCl Formulations

The mucoadhesion of the formulations under investigation was determined using the re analyzer in tension mode as follows. Mucin discs were prepared by compression of a known weight of crude pig gastric mucin (250 mg) in a Carver press for 30 s using a compression force of 10 tonnes. These were then attached to a al probe (length 5 cm, diameter 1 cm) using double-sided adhesive tape. MTZ-MINOCYCLINE HCl containing formulations were packed into McCartney bottles and centrifuged (3000 g for 5 min.) to remove any entrapped air. The mucin discs were then placed in contact with the gel formulations and a downward force was applied (0.1 N) for a range of times (0.5, 1, 2, 3 and 4 mm). The probe was removed vertically at a constant upward speed (1 mm 1) and the force required to detach the mucin disc from the gels was measured as the peak value in the force—time plot.

9. Rheological Studies

Rheological measurements had been carried out by using two different instruments, depending on the sample viscosity. Oscillatory measurements were carried out at low amplitude (within the linear viscoelastic region) with an angular velocity (w) of between 0.1 arid 100 rad/s. Measurements were conducted at four different temperatures, namely 10, 20, 30 and 37°C. According to the Bohlin theory that considers flow as a cooperative phenomenon, the coordination coefficient z was calculated from the slope of the curve obtained by plotting the elastic modulus (G') vs 0) in a log-log plot. The sol.-gel transition temperature (T_c) was calculated by 'time cure tests' obtained by plotting elastic (G') and loss (G") moduli as function of temperature. Determinations were performed 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 measured at a low shear rate ($0.1\text{-}10^{-1}$) in order to avoid slipping effects at the wall surface, possibly caused by high shear rates.

***10. In Vitro* Release of Mtz-Minocycline HCl**

In vitro release of MTZ-MINOCYCLINE HCl from the bioadhesive gel formulations was performed (in triplicate) using a 37 ml Franz diffusion cell. The diameter of the donor cell was 26 mm and the dissolution medium was PBS. The diffusion cell was water jacketed at 37±°C. 1.5 g of the gel was transferred to the Durapore HVLP membrane (0.45 um) of the vessel. At predetermined time intervals, 2 ml samples of the receptor fluid were taken and analyzed for MTZ and MINOCYCLINE HCl spectrophotometrically at 318 nm and 273.8 nm respectively by simultaneous equation method. The medium was replaced after each sampling.

11. Drug (S) Release Data Analysis

Data obtained from dissolution studies were fitted to the general release equation (Eq. (1) proposed by Gurny et al. using logarithmic transformations and least squares regression analysis.

$$\frac{Mt}{M\omega} = kt^n \quad \text{.....Eq. 1}$$

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.

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12. Statistical Analysis

The rates of release of drug(s) (k), the time required to dissolve 50% of the drug(s) ($t_{50\%}$) the dissolution efficiency, the correlation coefficient of different kinetic models of release data, and mechanical properties were evaluated statistically using a one- way ANOVA. Post-hoc statistical analysis of the means of individual groups was performed using Fischer's least significant difference test ($P<0.05$ denoting significance) using SPSS computer software (Version 10, 1999).

3. Results and Discussion

Mechanical Characterization of Bioadhesive Formulations

In this study, the mechanical properties of the candidate formulations for the treatment of periodontal disease were determined. Texture profile analysis (TPA) defines the mechanical parameters in terms of hardness, compressibility and adhesiveness, properties that will affect the ease of product application into, and retention within, the periodontal pocket, respectively. TPA also allows an estimation of the extent of structural reformation following product administration (cohesiveness), a factor which will influence product performance. Therefore, in this regard, TPA is an applicable technique for the characterization of formulations designed for application to the periodontal pocket. Increased product hardness, compressibility and syringebility were associated with increased concentrations of HEC or CMC and PC in each formulation. Statistical interactions were observed between the effects of the polymeric components on these mechanical properties and were due to the unexpectedly large hardness, work of compression and syringeability associated with formulations containing 30% (w/w) HEC or CMC and 5% PC. These formulations contained the greatest proportions of suspended, unswollen particles and the greater resultant semi-solid properties accounted for the unexpected compression properties.

Decreased product cohesiveness associated with increased concentrations of HEC or CMC is a function of increased product viscosity, as the viscoelastic properties of these formulations will be affected by this parameter. The mechanical parameters of each formulation are presented in Table 2. Increasing concentrations of HED or CMC and/or PC significantly increased formulation hardness, compressibility and adhesiveness, yet, they decreased cohesiveness. Typically maximum and minimum hardness, compressibility and adhesiveness were associated with formulations containing 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 reverse was observed, i.e. maximum and minimum values being associated with formulations containing 5% HEC or CMC and 1% PC, and 30% HEC or CMC and 5%, PC, respectively. With the exception of formulations containing 5% (w/w) HEC or CMC and 1% PC, HEC containing formulations exhibited significantly greater hardness, adhesiveness and compressibility than their counterparts (% w/w) containing CMC. The syringeability of each formulation is presented in Table 3. Once more, increasing concentrations of each polymeric component (HEC/CMC and/PC) significantly increased the force required expel each formulation from a periodontal syringe over a fixed distance. Formulations containing (5% w/w) HEC or CMC displayed statistically similar values of work of syringeability (P.0.05), whereas the work of syringeability of formulations containing 30% HEC significantly exceeded those formulations containing 30% (w/w) CMC. The effect of HEC on the bioadhesive properties of formulations containing PC was significantly greater than that of CMC.

1. Rheological Studies

In this study, a series of preliminary results on the rheological characterization of poloxamer based gels is presented (Table 4). This study was performed in order to define the general rheological behavior of these relatively novel materials and to provide information on their structure, as a function of temperature and of the presence of solubilized guest molecules (i.e. MTZ and MINOCYCLINE HCl). In particular, we determined the sol-gel transition temperature (T_o) by 'time cure tests', the frequency dependence of the elastic modulus G' by frequency sweep tests', and the temperature dependence of G' and the z coefficient.

2. In Vitro Drug (S) Release Kinetics

The release of drug(s) from formulations contained 30% (w/w) HEC and 5% (w/w) PC was significantly greater than those containing 30% (w/w) HEC and 1% (w/w) PC. These observations may be explained by the relative degrees of swelling of PC in each formulation. Product swelling was greater for formulations containing HEC, in comparison to those containing CMC, due to the greater masses of unswollen PC. Indeed as a result of excessive swelling of this polymer during dissolution testing, partial product disintegration occurred for formulations containing 30% (w/w) HEC and 5% (w/w) PC. Therefore, surface areas of these formulation increased, which, in

turn increased the rate of drug(s) release. The time required for the release of drug(s) ($t_{50\%}$) from each formulation is shown in Table 3.31. The times required for 50% drug(s) release from formulations containing HEC were significantly greater than those containing comparable concentrations (%w/w) of CMC and PVP. DE after 24 hrs (DE_{24}%) and $t_{50\%}$ were used to compare the drug release characteristics of different formulations. (Table 5&6).

Table 1: Containing the compositions of formulations

Formulation code	MHC (%w/w)	(%w/w)	(%w/w)	(%w/w)	(%w/w)	(%w/w)	MTZ and Minocycline HCl (%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 Mtz and Minocycline HCl

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 Mtz and Minocycline HCl

Formulation code	Force required to break the mucoadhesive bond following contact between formulations and mucin for a range of times(s)			Work of syringeability (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: 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	
	MTZ	Minocycline HCl	MTZ	Minocycline HCl	MTZ	Minocycline HCl	MTZ	Minocycline HCl
$M_{10}H_5$	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±0.006	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±0.006	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 5: Comparing the Correlation Coefficient (R) of Drug(S) Release Data According to Different Kinetics Model of Different Bioadhesive Gel Formulations of Mtz and Minocycline Hcl In Phosphate Buffer Saline (PH =6.8) (N=3).

Formulation code	r±S.D. Zero order ($Q=Q_0-Kt$)		r±S.D. First order ($Q=Q_0 e^{-k1}$)		r±S.D. Higuchi ($Q= Kf^{1/2}$)	
	MTZ	Minocycline HCl	MTZ	Minocycline HCl	MTZ	Minocycline HCl
$M_{10}H_5$	0.982±0.001	0.984±0.002	0.975±0.002	0.981±0.003	0.973±0.002	0.985±0.003
$M_{10}H_{20}$	0.989±0.02	0.996±0.05	0.979±0.003	0.972±0.005	0.979±0.03	0.984±0.02
$M_{10}H_{30}$	0.998±0.003	0.991±0.001	0.985±0.001	0.982±0.007	0.980±0.01	0.981±0.03
M_5H_{10}	0.981±0.005	0.982±0.002	0.970±0.02	0.976±0.004	0.978±0.005	0.984±0.004
$M_{20}H_{10}$	0.976±0.002	0.989±0.002	0.969±0.01	0.975±0.002	0.975±0.04	0.981±0.03
$M_{30}H_{10}$	0.975±0.003	0.987±0.003	0.965±0.003	0.963±0.002	0.969±0.006	0.987±0.005
$P_{10}C_5$	0.855±0.001	0.878±0.001	0.975±0.006	0.971±0.005	0.987±0.005	0.995±0.004
$P_{10}C_{10}$	0.859±0.01	0.878±0.05	0.977±0.002	0.981±0.001	0.989±0.001	0.979±0.003
$P_{10}C_{10}$	0.862±0.002	0.876±0.003	0.979±0.001	0.988±0.003	0.994±0.002	0.990±0.002
$P_{10}C_{30}$	0.866±0.03	0.887±0.04	0.980±0.03	0.986±0.02	0.993±0.02	0.989±0.06
P_5C_{10}	0.852±0.001	0.875±0.005	0.981±0.004	0.975±0.005	0.973±0.02	0.986±0.03
$P_{20}C_{10}$	0.851±0.005	0.842±0.004	0.971±0.002	0.982±0.003	0.986±0.002	0.981±0.003
$P_{30}C_{10}$	0.848±0.006	0.894±0.007	0.969±0.03	0.975±0.02	0.977±0.001	0.984±0.003

4. Conclusion

Gels were characterized by a peculiar rheological behaviour, as a function of polymer concentration, temperature and presence of drug(s) and possess appropriate properties as intra pocket drug(s) delivery, system for periodontal therapy. In the present study it was demonstrated, in a preliminary study, that this poloxamer gel released MTZ and Minocycline HCl for the period of seven days in vitro. Decreased release associated with increased concentrations of PC in formulations containing 5% (w/w) HEC or CMC may also be explained by the concomitted increased product viscosities following swelling of this polymer within the formulation. From the results it is concluded compare to all formulations the formulations (code) $M_{10}H_{20}$, $M_{30}H_{10}$ are the best for mutations for future study.

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