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Local Delivery of Chitosan Strips Carrying Ornidazole-Loaded Ethyl Cellulose Micro-Particles for the Enhanced Treatment of Periodontitis

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ABSTRACT

Locally used antimicrobials are rapidly cleared during the treatment of chronic periodontitis. The purpose behind this study was to prepare optimized ornidazole ethyl cellulose (EC) microparticles (MPs) with subsequent loading into chitosan strips formulation for local drug delivery. Three formulations of MPs were prepared using varying amount of EC and optimized for morphology and particle size, drug incorporation efficiency (IE) and loading capacity (LC), and in-vitro release. Chitosan carrying optimized ornidazole MPs strips then prepared using dispersion technique and characterized for surface pH and morphology, in-vitro and in-situ release, in-vitro and ex-vivo antimicrobial activity. The results were that the chitosan strips showed asymmetrical distribution of uniform shape holding ornidazole loaded EC containing MPs and great sustained release time. Moreover, the drug-loaded MPs having drug:polymer ratio 1:3 and films having 5% glycerol showed emphasize extended release. The excellent results of in-vitro and ex-vivo antimicrobial activity proved the stability of drug into the films. The prepared strips with assured sustained release should be a batter dosage form for enhanced treatment of periodontitis.

Keywords: Dental strip; Microparticle; Ornidazole; Ethyl cellulose; Chitosan

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INTRODUCTION

Site specific-local drug delivery system is attracting for enhanced treatment of periodontitis. Chitosan and EC have been primary choice of polymers for sustained release formulations like dental fibers, films and gels. As EC containing microcapsules can slow down the release rate of drug [1]. A different drug releasing pattern was obtained of diffusion pellets, which were coated by using various plasticizers and EC containing dispersion [2]. The dimenhydrinate shows zero-order kinetics, when it was loaded in EC matrix; as the concentration of EC increases, the drug release decreases [3]. Diclofenac sodium loaded EC microspheres formulated using different stabilizers such as gelatin, polyvinyl alcohol, pectin and alginate, which shows admirable release rate of drug [4]. The dispersions of EC and chitosan with different plasticizers always show phase separation. Though, the detection of interaction between them has been concluded [5]. Atypical sustained releasing rate was obtained, when comparison was made between microspheres and chitosan microspheres loaded in polyethylene glycol film [6]. In recent pharmaceutical research, to develop controlled drug release formulations chitosan has been played remarkable role [7-10]. Additionally, chitosan has better biodegradability, antibacterial properties, biocompatibility and accelerated wound healing properties [11-13]. Chlorhexidine containing chitosan films and gels have promising delivery system with excellent bioadhesive and antibacterial properties towards *porphyromonas gingivalis* a periodontal pathogen

[14]. Metronidazole containing chitosan mucoadhesive film has satisfactory drug releasing rate, mechanical strength and bioadhesive properties [15]. Although the various controlled release formulations were formulated using EC and chitosan, less numbers of research studies have been done on periodontal strip carrying MPs. In this recent study, ornidazole loaded three formulations having varying amount of EC containing MPs were prepared. Chitosan carrying optimized MPs, then fabricated using dispersion technique.

EXPERIMENTAL SECTION

Materials

Ethyl cellulose (Viscocity 46 cP, 5% in toluene/ethanol 80:20(lit.)), Chitosan (medium molecular weight), Glycerol (Reagent Plus, ≥ 99%), Dialysis tubes (Diameter 25 mm, M.W. cutoff: 12,400), Dialysis cellulose membranes (Diameter 25 mm, MW cutoff 12,000) and Mutans-Sanguis agar media were purchased from Sigma-Aldrich (India). CH_2Cl_2, methanol, acetone and glacial acetic acid were purchased from Loba Chemie PVT LTD, Mumbai, India. All other reagents utilized in this study were analytical grade.

Microparticles Preparation

Ornidazole loaded varying concentration of EC containing MPs were prepared using previously described method with necessary modifications [16]. Ornidazole and varying concentrations of EC (Drug:polymer ratio - 1:1, 1:3, and 1:5) were dissolved into the 40 ml ternary mixture of CH_2Cl_2, methanol, and acetone by using appropriate sonication. Chitosan solution (1% w/v) was prepared by dissolving 1 g chitosan in 100 ml diluted acetic acid (1% v/v) by using appropriate sonication. The drug and varying concentrations of EC containing solution (40 ml) was injected under continuous stirring for 30 min at 1000 rpm in 100 ml aqueous chitosan solution to get primary O/W emulsion. To evaporate the organic solvent, prepared emulsion was kept at 40°C in water incubator for 3 h. After proper evaporation of organic solvent, MPs being separated by using centrifugation, and then with the help of distilled water they were fully washed and stored in desiccator and evaluated for optimization.

Minimum Inhibitory Concentration (MIC) Value of Ornidazole

Agar dilution method [17] was utilized, to find out MIC value of ornidazole. In brief, 1 ml solution of ornidazole was taken from 10, 240, 2, 560, 320, 40, 5, and 0.625 µg/L stock solutions of ornidazole and then, appropriately diluted. From this diluted solution, 1 ml solution was thoroughly mixed with sterilized 19 ml of agar media and pours in prelabeled sterile petriplates on a leveled surface. At Darsh Superspeciality Dental Hospital; Vadodara (Gujarat, India), in pre-sterilized test tube, saliva samples were collected from the three volunteers; who were previously diagnosed with chronic periodontal disease.

Fabrication of Chitosan Strips Carrying EC containing MPs

Dispersion method was utilized for fabrication of chitosan strip carrying ornidazole loaded EC containing MPs. In this method, thoroughly mixed dispersion of chitosan solution, EC containing MPs and glycerol (plasticizer) 5% or 10% (w/w) were poured into a clean glass petriplate. Additionally, to neutralize the residual amount of acetic acid, 1% NaOH solution was added. Lastly, the dehydration of this co-matrix was done using desiccator for 24 h. The free drug containing chitosan strips were also fabricated by same procedure.

Characterization Analyses

Identification and compatibility study

Infrared (IR) spectra of physical mixture of ornidazole, chitosan, EC, and glycerol were recorded with FT-IR spectrophotometer (Bruker, Germany). At wavelength from 500 to 4000 cm^{-1}, all samples were scanned.

Morphological study

The mean particle size, and polydispersity index (PDI) of MPs were investigated using zetasizer (Malvern Instruments LTD, U.K). In addition, the morphological studies of EC containing MPs shaped and chitosan strip carrying EC containing MPs were characterized by scanning electron microscope (SEM) (ESEM EDAX XL-30, Philips, Netherlands). Samples were sprinkled on aluminium stubs and placed in the vacuum chamber of a SEM. The acceleration voltage of SEM was 20 kV for MPs samples and strip section, and 5 kV for surface of the strip.

Incorporation efficiency (IE) and loading capacity (LC)

The drug IE and LC of the MPs were investigated as previously described method [18]. In brief, accurately weighed 10 mg of MPs was crushed into the glass mortar. 5 ml of dehydrated alcohol was added into this powdered mass and thoroughly mixed the all contents. The mixture was then filtered through 0.2 µm membrane filter into a test tube. Additionally, 5 ml of dehydrated alcohol was used to rinse the mortar and filtered. Appropriate dilution of filtrate was done using phosphate buffer of pH 6.8 and analyzed at λ_{max} 320 nm using UV-spectrophotometry (Shimadzu, Japan). IE and LC of various samples were calculated using formulas IE = (Amount of incorporated drug in mg/theoretical drug content) × 100 and LC = (Theoretical drug content – Amount of incorporated drug)/Materials × 100, respectively.

***In-vitro* release of MPs**

The *In-vitro* drug release study of drug-loaded EC containing MPs was investigated as previously described method [19]. In brief, accurately weighed 20 mg of MPs was placed within dialysis tubing cellulose membrane (molecular weight cut-off 12,400; Sigma Aldrich; India) at the bottom of clean glass beaker containing 500 ml of phosphate buffer of pH 6.8, stirred at 100 rpm. The apparatus was kept at 37°C using thermostatic water bath and protected from light. At every 24 h, 1 ml samples were withdrawn (to maintain sink condition, immediately replaced it with 1 ml fresh medium) and analyzed UV-spectrophotometrically at λ_{max} 320 nm.

Physicochemical Parameters

To investigate weight uniformity of fabricated strips, single pan balance (Aarson Scientific works, Haryana, India) was utilized. Twenty strips (0.5 × 0.4 cm^2 size) were taken from the different places of both strips. Electronic outside micrometer (Model IP 54, Beijing C&C Trade center, China) was utilized to carry out the thickness of strips. Randomly selected three points from the fabricated strips were considered to determine the thickness. As previously reported [20], an acidic or alkaline pH of surface of strips may causes irritation to the buccal mucosa. Thus, investigation of surface pH of fabricated strips was carried out. In specially fabricated tube, by using 1 ml of distilled water (pH 6.5 ± 0.05), the strips were allowed to swell. A combined glass electrode was placed near the surface of the strip and equilibrium was attained for 1 min. As previously reported [21], to investigate the folding endurance; the strip was repeatedly folded at same place till it broke.

***In-vitro* Release Study**

The *in-vitro* release of chitosan strips carrying EC containing ornidazole MPs was investigated as previously reported method [22]. Briefly, the commercially available dialysis cellulose membranes (MW cutoff 12,000 Da; Sigma-Aldrich, India) were used as barriers in Franz diffusion cells. In the diffusion cells, between the donor and receptor compartments, the prehydrated membranes were mounted. The receptor compartment was filled with 12 ml of phosphate buffer, pH 6.8 and equilibrium was attained to 37°C; stirred continuously at 75 rpm. Strips having 0.5 × 0.4 cm^2 diffusional area were placed into the donor compartment. To avoid drug degradation, cells were placed into the dark place. From the receptor compartment, at predetermined time interval, 2 ml of samples were withdrawn and to maintained sink condition immediately replaced it with 2 ml of fresh medium. The UV- spectrophotometric analysis at λ_{max} 320 nm was carried out to determine the amount of drug release.

***In-situ* Drug Release Study**

As previously reported [20], by using flow-through apparatus, the *in-situ* drug release rate study was investigated. In brief, the bovine buccal mucosa (1.5 cm long and 1.5 cm wide) and fabricated strips (0.5 × 0.4 cm^2 diffusional area) were placed into the cavity (1.2 cm in length and 1 cm in depth) of apparatus; to stabilize and to remove soluble components of strip, phosphate buffer of pH 6.8 was used. As earlier describe [23], using 10 g of weight for 30 s and 25 µl of phosphate buffer of pH 6.8, the strip was stuck onto the buccal mucosa. The flow rate of gingival cervical fluid (GCF) is increases to 3.5 ml/day or more on inflammation [24]. To simulating GCF pH, phosphate buffer of pH 6.8 was constantly pumped through a cavity at flow rate of 15 ml/day using peristaltic pump. At predetermined time intervals, samples were collected from cavity using a micropipette. By using phosphate buffer of pH 6.8, sample volume was made up to 3 ml; Whatman no. 42 filter paper was used for filtration and UV-spectrophotometic analysis was carried out at λ_{max} 320 nm.

***In-vitro* Antimicrobial Activity**

As earlier reported [25], *in-vitro* antimicrobial activity was investigated using *Streptococcus mutans*. Briefly, fabricated strips were cut into 0.5 × 0.5 cm^2. This cut strips were positioned on Mutans-Sanguis agar plates, seeded with facultative anaerobic micro-organisms. After incubation at 37°C for 48 h in incubator (Allians Enterprise,

Vadodara), the strips were shifted on freshly seeded with micro-organisms plates for another 48 h incubation. This procedure was repeated until no growth inhibition area was obtained.

***Ex-vivo* Antimicrobial Activity**

Ex-vivo antimicrobial activity was investigated as previously reported [26]. Briefly, 0.5 ml samples were used as inoculums from the collected saliva samples of three volunteers (diagnosed positive for *Porphyromonas gingivalis*). These saliva samples were seeded into the presterilized nutrient agar medium and poured into the presterilized petriplates. Aseptically, three cups were made in each plates using presterilized metal borer. Cautiously fabricated strips were placed into the each two cups and 0.5 ml sterilized water as control into the third cup, and plates were then incubated at 37°C for 24 h in incubator.

Stability Study

Stability studies of fabricated strips were investigated in terms of ageing and temperature as previously reported [26]. At different temperatures (25°C, room temperature and 4°C, refrigerator) and at 40°C/75 relative humidity (RH), fabricated strips were kept for 3 months. Various physicochemical properties were investigated after one, two and three months.

RESULTS AND DISCUSSION

FT-IR Analysis

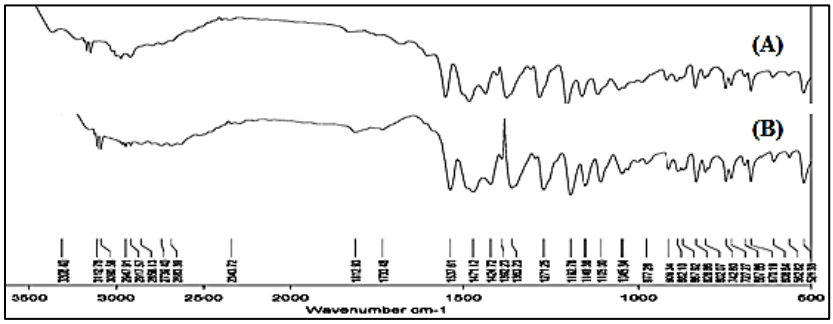

Figure 1: FT-IR spectra: (A) pure ornidazole (B) ornidazole + excipients

FT-IR spectra confirmed some interaction between hydroxyl groups of chitosan and EC as well as ammonium groups of chitosan with hydroxyl groups of EC. Chitosan matrix attributed a band at 3435 cm^{-1} to -NH_2 and -OH stretching vibration and EC matrix attributed a band at 3482 cm^{-1} to -OH stretching vibration Figure 1. A wider band shift from 3453 to 3424 cm^{-1} proved the enhancement of hydrogen bonding into the blending strip. Ornidazole attributed all principal bands at 3112 cm^{-1} to O-H stretching, 1537 cm^{-1} to -NO_2 stretching, 1296 to 1364 cm^{-1} to NO_2 stretching, symmetric and 1149 cm^{-1} to C-O stretching. These prove that there was not any chemical interaction in between ornidazole and the excipients employed in formulations.

Morphological Observation

As seen in Table 1, drug/polymer ratio was undesirably affecting the mean particle size and PDI of MPs. Like, formulation F_3 has lowest mean particle size and PDI while formulation F_1 has moderate mean particle size and PDI. Thus, MPs having drug/polymer ratio 1:5 were further used in fabrication of chitosan strips. SEM analysis shows that the formulated MPs were spherical, smoother and smaller in nature (Figure 2). As earlier concluded [27], sustained drug delivery was obtained from the microporous structure of the prepared MPs. As at higher magnifications; micro-pores were seen on the surface of MPs (Figure 2). The SEM result of chitosan strip carrying ornidazole loaded EC containing MPs are shown in Figure 3. The ornidazole loaded EC containing MPs uniformly dispersed in chitosan strip. There was no any conglomeration present into the strip. As seen in Figure 3A, MPs were clearly observed onto the upper surface of the strip. While in contrast, lower surface of strip has almost no MPs (Figure 3B).

Drug Incorporation Efficiency (IE) and Loading Capacity (LC)

The drug IE and LC of the ornidazole loaded MPs were detected by UV- spectrophotometry, and the value of IE and LC were seen in Table 2. As earlier described [18], the highest IE for eudragit E-100-based MPs prepared using solvent evaporation technique was 92%, and in our study for formulation F_3, it was 96.033 ± 2.08% (n=3) ± SD. This signifies the priority of our ornidazole loaded MPs design (Figure 4).

Table 1: Mean particle size and polydispersibility index of EC loaded MPs

Formulation code	Drug/polymer ratio	Mean particle size (nm)	Polydispersibility index (PDI)
F_1	01:01	786.4	0.865
F_2	01:03	793.9	1
F_3	01:05	513.4	0.703

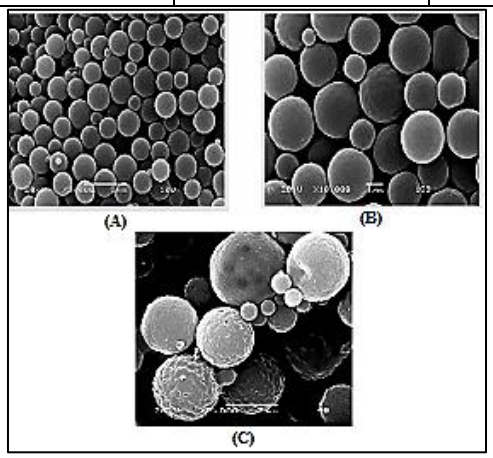

Figure 2: SEM photographs of ornidazole loaded EC microparticles (drug/polymer ratio- 1:5)

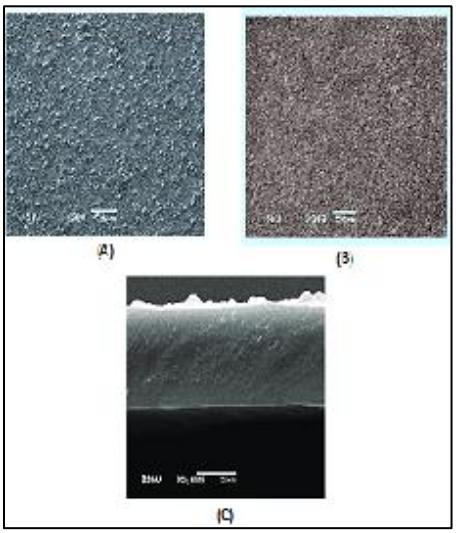

Figure 3: SEM photographs of chitosan carrying ornidazole loaded EC containing MPs (A) upper surface of the strip (B) lower surface of the strip (C) section of the strip

Table 2: Drug IE and LC

Formulation code	Drug/polymer ratio	IE (%) (n=3) ± SD	LC (%) (n=3) ± SD
F_1	01:01	86.066 ± 1.52	7.003 ± 0.20
F_2	01:03	89.013 ± 2.08	2.710 ± 0.02
F_3	01:05	96.033 ± 2.08	0.723 ± 0.03

Note: IE – Incorporation efficiency and LC – Loading capacity

In-vitro Release of MPs

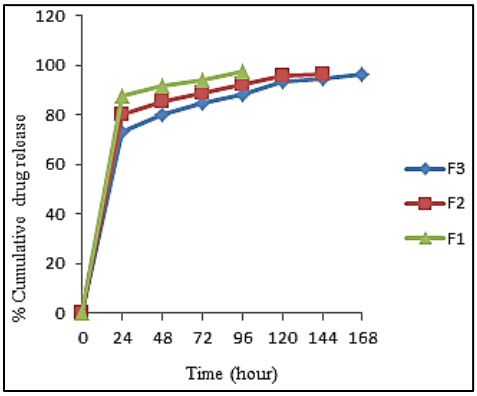

Figure 4: *In-vitro* release profile of ornidazole loaded MPs. F1-drug/polymer ratio-1:1, F2-drug/polymer ratio-1:3, F3-drug/polymer ratio-1:5

The cumulative release profile of ornidazole MPs in phosphate buffer of pH 6.8 at 37°C is shown in Figure 2. Formulation having drug/polymer ratio-1:5 was gave approximate 96.2% cumulative release after 7 days, which proved the remarkable sustained release profile of the ornidazole MPs. As previously described [25], ornidazole containing dental implant demonstrated the release of ornidazole for about 5 days. In compared with this result, the release of ornidazole MPs over 7 days represented a batter sustained release profile.

Physicochemical Evaluation of Strips

As previously described [28], glycerol may lead to undesirable increase in water absorption and water vapor permeability in gentamicin containing controlled release dressings. Farahnky A et al. [29] concluded higher concentration of glycerol in wheat starch edible films may lead to solubility, lightness and compact structure of film increases. As seen in Table 3, higher concentrations of glycerol containing strips have lower mean thickness value due to compact structure formation. Due to higher drug loading capacity, ornidazole loaded MPs containing strips have higher value of average weight in compared to free ornidazole containing strips. The low value of deviation in drug content indicates dispersion of ornidazole loaded MPs and free ornidazole were uniform into the strips. Free ornidazole containing strips have less amount of polymer in compared to ornidazole loaded MPs containing strips. Thus, the % moisture loss was higher in strips containing free drug then drug loaded MPs. All fabricated strips have folding endurance value more than 250 Nos.

Table 3: Physicochemical evaluation parameters of ornidazole strips

Parameters	FX_1	FX_2	FY_1	FY_2
Mean thickness (µm) (n=3)	1354.3 ± 2.08	1304.6 ± 1.52	1295.6 ± 2.51	1265.6 ± 1.15
Average Weight (mg) (n=20)	8.73 ± 1.63	14.92 ± 1.46	3.96 ± 1.53	11.26 ± 1.73
Content Uniformity (%) (n=3)	95.3 ± 0.45	96.8 ± 0.28	96.7 ± 0.13	97.9 ± 0.76
% Moisture loss (n=3)	7.98 ± 1.69	8.21 ± 1.33	11.00 ± 1.12	12.36 ± 1.29
Folding endurance	267 ± 0.35	256 ± 0.48	274 ± 0.18	263 ± 0.23

Note: FX_1= Microparticles strips having 5% glycerol, FX_2= Microparticles strips having 10% glycerol, FY_1= Free drug strips having 5% glycerol, FY_2= Free drug strips having 10% glycerol. All values are mean ± Standard deviation of 3, 20, 3, 3 and 3 respectively

In-vitro Drug Release of Strips

Figure 5 showed the *in-vitro* drug release of the strips. When ornidazole loaded EC containing MPs put into the chitosan matrix, drug has to cross major carrier compared with the chitosan matrix. As the EC has little kind of hydrophobic nature, penetration of the liquid water was hard. So, ornidazole loaded EC containing MPs were not easily dissolved, nearly 40% drug released in first day and magnificently the release rate was extended up to 12 days. The free ornidazole loaded pure chitosan strips have hydrophilic nature and water can easily penetrate into the strip after their contact. So, diffusion of drug from the strips was quick, nearly 80% drug released in first day and almost 100% drug in 5 days. Furthermore, more amount of drug been covered due to higher amount of EC, or more amount of drug in EC containing MPs, so increased in the EC amount been decreased the rate of drug release. As seen in Table 4, the coefficient of correlation 'r^2' value was linear for Korsmeyer-Peppas model. The 'n' values suggest the chitosan carrying ornidazole loaded EC containing MPs strips exhibit anomalous transport.

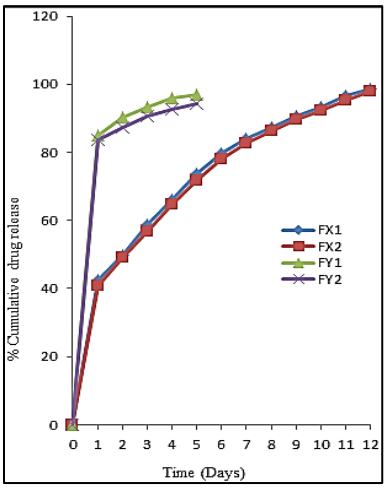

Figure 5: *In-vitro* release profile of chitosan carrying ornidazole loaded EC containing MPs strip. FX1= microparticles strips having 5% glycerol, FX2= microparticles strips having 10% glycerol, FY1= free drug strips having 5% glycerol, FY2= free drug strips having 10% glycerol

Table 4: Kinetic data of different formulations

Formulations code	Zero order kinetic (r2 value)	First order kinetic (r2 value)	Higuchi's model (r2 value)	Peppas's model (r2 value)
FX_1	0.4336	0.9594	0.9581	0.9973
FX_2	0.4686	0.9595	0.9656	0.9977
FY_1	0.1167	0.984	0.7458	1
FY_2	0.1051	0.9641	0.7384	1

Note: FX_1= Microparticles strips having 5% glycerol, FX_2= Microparticles strips having 10% glycerol, FY_1= Free drug strips having 5% glycerol, FY_2= Free drug strips having 10% glycerol

In-vitro Antimicrobial Activity

Figure 6 shows the significance of antimicrobial profile for all fabricated strips. It can be observed that free drug containing chitosan strips (FY_1 and FY_2) have its maximum zone of inhibition after 48 h (around 18 mm) and sustained till 144 h, while chitosan carrying ornidazole loaded EC containing MPs strips have its maximum zone of inhibition after 48 h (around 15 mm) and sustained till 288 h. This may be attributed that being ornidazole in free form the release from chitosan strips was fast and less sustained, while being ornidazole in EC containing MPs form the release from chitosan strips was above the MIC value and sustained.

Ex-vivo Antimicrobial Activity

As seen in Figure 7, the effectiveness of formulations FX_1 and FX_2 against natural microbial flora was remarkable. Depending on the severity of the disease, the antimicrobial activity of fabricated strips was varied. Thus, the maximum antimicrobial activity in term of zone of inhibition was seen in volunteer II. In case of volunteer III, the zone of inhibition was less marked as compared to other two volunteers (Table 5).

Stability Study

The physicochemical properties (appearance, % moisture loss and drug content) of the ornidazole strips remained almost unchanged during stability study (3 months at 25, 4, and 40°C). There was no any sign of discoloration in strips after 3 months (Table 6). In case of % moisture loss, the strips were stable and there was not any drastic change. The % moisture loss showed that the loaded MPs of the strips were stable and % drug content did not reveal any change significantly (Table 6).

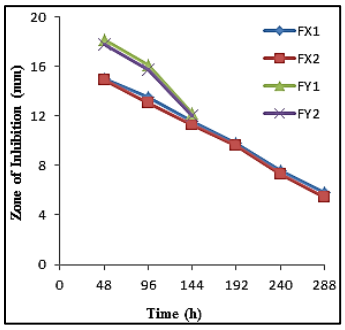

Figure 6: *In-vitro* antibacterial activity of strips. FX1= microparticles strips having 5% glycerol, FX2= microparticles strips having 10% glycerol, FY1= free drug strips having 5% glycerol, FY2= free drug strips having 10% glycerol

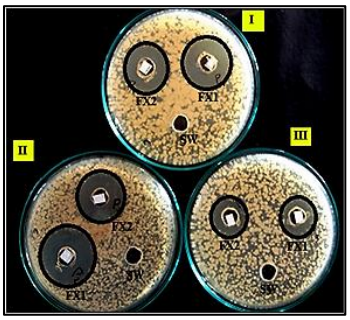

Figure 7: *Ex-vivo* antimicrobial activity of strips. FX1= microparticles strips having 5% glycerol, FX2= microparticles strips having 10% glycerol, SW- sterile water

Table 5: *Ex-vivo* antimicrobial activity of FX1 and FX2 formulations

Formulation code	Volunteer	Zone of inhibition (cm)	Average ± SD (cm)
FX_1	I	1.4	1.2 ± 0.61
	II	1.8	
	III	0.6	
FX_2	I	1.3	1.0 ± 0.36
	II	1.1	
	III	0.6	

Note: FX1= Microparticles strips having 5% glycerol, FX2= Microparticles strips having 10% glycerol

Table 6: Stability testing of ornidazole MPs containing strips

Storage condition	Duration	Formulation	Appearance	% moisture loss	Drug content (%)
Stored at 25°C	1 month	FX_1	Opaque	7.93 ± 0.015	95.03 ± 0.20
		FX_2	Opaque	8.21 ± 0.015	96.73 ± 0.11
	2 month	FX_1	Opaque	7.90 ± 0.010	95.10 ± 0.26
		FX_2	Opaque	8.20 ± 0.010	96.53 ± 0.12
	3 month	FX_1	Opaque	7.87 ± 0.015	94.80 ± 0.10
		FX_2	Opaque	8.19 ± 0.010	96.33 ± 0.25
Stored at 4°C	1 month	FX_1	Opaque	7.95 ± 0.005	95.20 ± 0.10
		FX_2	Opaque	8.20 ± 0.005	96.43 ± 0.15
	2 month	FX_1	Opaque	7.92 ± 0.015	95.06 ± 0.15
		FX_2	Opaque	8.18 ± 0.005	96.02 ± 0.26
	3 month	FX_1	Opaque	7.90 ± 0.010	94.96 ± 0.20
		FX_2	Opaque	8.16 ± 0.005	96.16 ± 0.32
Stored at 40°C and 75% RH	1 month	FX_1	Opaque	7.86 ± 0.010	94.50 ± 0.30
		FX_2	Opaque	8.16 ± 0.010	95.93 ± 0.25
	2 month	FX_1	Opaque	7.78 ± 0.020	94.23 ± 0.45
		FX_2	Opaque	8.14 ± 0.005	95.83 ± 0.11
	3 month	FX_1	Opaque	7.73 ± 0.020	94.13 ± 0.49
		FX_2	Opaque	8.09 ± 0.010	95.46 ± 0.30

Note: FX1= Microparticles strips having 5% glycerol, FX2= Microparticles strips having 10% glycerol

CONCLUSION

In this study, chitosan carrying ornidazole loaded EC containing MPs strips was successfully fabricated, having higher loading capacity of drug. To minimize the clinical symptoms of chronic periodontitis, the fabricated strips were found to be appropriate and more effective. The *in-vitro* experiments and *ex-vivo* clinical results demonstrate that the fabricated strips could be more effective and proficient delivery system for ornidazole.

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