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DESIGN, DEVELOPMENT AND EVALUATION OF ORNIDAZOLE STRIP IN DENTAL INFECTION

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ABSTRACT
Several peoples around the world suffer from dental diseases, number of them will get oral therapy and most of the drug shows irritation in GIT and thus absorbs systemically and imparts toxicity. Hence to reduce gastric irritation and systemic toxicity, authors developed the site specific delivery of ornidazole in treatment of periodontitis, drug has an excellent activity against anaerobic microbes. Formulations were prepared by utilizing polymers PEO and gellan gum, and developed by solvent casting technique with the used of plasticizer (PEG-400). Preformulation studies were performed on drug and excipients. Physical characterization of films was done by thickness, folding endurance, weight variation, drug content, percent moisture loss, tensile strength, percent elongation etc. In vitro diffusion, stability and the antibacterial study was also performed on selected formulations. FT-IR and DSC study revealed no interaction found between drug and polymers utilized hence suitable for films. Formulations showed good uniformity of drug, there is no any kind of effect on moisture loss test. Formulations showed high weight & thickness with gellan gum when compared to PEO also possesses good tensile strength. By increasing the concentration of PEO in the formulation rate of release was retarded when compared with gellan gum. Formulation F5 released 94.56% of the drug at the end of 9 h and was considered as best formulation. A short-term stability study of the optimized formulation F5 was carried out at 40ºC for three months. The formulation was found to be intact when kept at the ambient condition of temperature and humidity.

KEY WORDS: Ornidazole, dental strip, physical characterization, *in vitro* release, stability study, antibacterial study.

INTRODUCTION
Periodontal diseases are renowned as the most important public health problem all over the world. Most of the epidemiological studies find that, dental caries and periodontal disease are the most prevalent oral disorders of humanity. Routine oral hygiene plays an essential role in retaining healthy teeth and gums. Periodontal disease is a common term which includes several pathological conditions affecting the tooth supporting structures. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis. These conditions are characterized by a destruction of the periodontal ligament, a resorption of the alveolar bone and the migration of the junctional epithelium along the tooth surface[1]. It is a localized inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque[2]. Periodontitis is an inflammatory response to the overgrowth of anaerobic organisms in the subgingiva and if unchecked, results in the demolition of the bone and soft tissues supporting the tooth, which results in tooth loss[3]. Periodontal disease can do occur in all age groups, ethnicities, genders and socioeconomic levels. Periodontitis a more severe stage of dental disease results in the resorption of the alveolar bone and detachment of the periodontal ligaments supporting the tooth. Periodontal pathogens grow only where the atmosphere and nutrient composition are strictly suitable to their requirement and once the disease established, causes major changes in the periodontal microenvironment. The gingival crevicular fluid (GCF) flow occurs at extremely low levels in healthy gingival sulci but increases enormously to 3.5 ml/day or more. The most commonly grown anaerobic pathogenic bacteria responsible are *A. actinomycetencomtans, B. gingivalis, B. melaninogenicus* subspecies *intermedius, P. gingivalis* and *P. intermedia.* Clinicians and investigators in periodontology have been suggested that the periodontal diseases may respond to antimicrobial therapy and various antibiotics utilized topically or systemically in the management of dental diseases. The primary cause of these diseases is bacteria and hence the antibacterials are used in the treatment of periodontal diseases.[4]

The objective behind the dental care is to minimize the residents of microorganisms. Slowing or arresting of the oro-dental infections can be achieved by controlling bacterial plaque. Ornidazole is advanced second generation synthetic fluoroquinolone derivative which is a broad-spectrum antibiotic with excellent bacterial coverage. High doses of antibiotics cause side effects such as gastrointestinal disorders, development of resistant bacteria and suprainfection. Systemic therapy has low benefit to high-risk ratio.

Ornidazole is a 5-nitroimidazole derivative and used in the treatment of susceptible protozoal infections and also in anaerobic bacterial infections. It has been used for amebic liver abscesses, duodenal ulcers, giardiasis, intestinal lambliasis and vaginitis[5]. Ornidazole has recently been used with success in patients with active Crohn's disease. It is more effective against amoebiasis than metronidazole, which is the most commonly used nitroimidazole derivative in therapy. Ornidazole has also been suitable for surgical prophylaxis because of its high elimination half-life and excellent penetration into lipidic tissues versus other nitroimidazole derivatives[6, 7].

In the conventional mode of drug administration, many drugs do not reach target areas in the body in sufficient concentration because of premature inactivation and excretion. The systemic drug administration has been useful in treating periodontitis but the disadvantage is that drug is diluted several thousand folds before it reaches the site and exposes the rest of the body to potential side effects. This problem can be overcome by administering the drug directly to the intended site of action with lesser dose[8]. Sustained drug delivery systems are able to provide very precise control over drug release for a prolonged period of time eliminating the need for frequent dosing and minimizing side effects, thereby increasing patient compliance and comfort. A site-specific system aims at delivering the therapeutic agent at sufficient levels inside the pocket and at the same time minimizing the side effects associated with systemic drug administration[9].

Gellan gum is a linear anionic heteropolysaccharide natural hydrophilic, biodegradable and biocompatible polymer, characterized by prolonged release due to the formation of a hydrogen bond with the drug.[10] Polymers confer some adhesive properties to films due to its hydrophilicity. The use of release rate modification agent may either decrease or increase the release of the drug in the range of multiple orders preferably up to a ten fold change. Release rate modification agents which are hydrophilic such as polyethylene glycol may increase the release of the bioactive agents[11]. Clove oil is slightly soluble in water hence their concentration is very low. Clove oil serves for purposes good mouth feel and prevents inflammation.

Polyethylene oxide is a biocompatible polymer, which is marketed as "POLYOX TM". It is a non-ionic, water-soluble resin, possesses good lubricating, binding and film forming properties. PEO delay the release rate of drug/s and therefore widely utilized in pharmaceutical formulations like controlled release dosage forms, hot-melt technology and mucoadhesive dosage forms. PEO plays an essential role in the design of a novel drug delivery system for both highly and poorly soluble drug. It can be used as a matrix system for controlled release.[12]

The study had been undertaken to develop film loaded with Ornidazole which delivers the drug sustainably to the dental cavity. The strip can directly place to the targeted site and thus enhance its activity; it reduces the systemic toxicity of the drug and better patient compliance.

MATERIALS AND METHODS

Materials

Ornidazole was obtained as a gift sample from Zydus Cadila Health Care Ltd, Ahmedabad, India., Polyethylene oxide N-750, Gellan gum was purchased from Sudarshan Scientific Labortories Nashik, Maharashtra (Aldrich Chemicals, Mumbai, India), Polyethylene glycol 400 (Loba Chemie, Mumbai, India) were purchased for carrying out various experiments. All the other chemicals used were of analytical grade.

Methods

Preformulation Study

Preformulation testing is the first step in the rational development of any dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through the determination of physicochemical properties of excipients that could affect drug performance. The overall objective of Preformulation testing is to generate information needed to define the nature of the drug substance and useful to the formulator that provide a framework for the drug combination with pharmaceutical excipients in the dosage form in developing stable and bioavailable dosage forms that can be mass produced.

Confirmation of drug test was carried out by FTIR, Melting point determination by capillary method and DSC.

Drug-Excipients compatibility Studies[13]

The drug-excipients compatibility study was carried out by using FTIR and DSC.

A) Infrared Spectroscopy

FTIR spectra of plane drug and the mixture of polymers were taken to study the interaction between them. A mixture of with Gellan gum and PEO were mixed separately with IR grade KBr in the ratio of 100:1 and compressed using motorized pellet press at 15 tones pressure.

B) Differential Scanning calorimetry (DSC)

The DSC measurements were performed on a differential scanning calorimeter (DSC 822c, Mettler Toledo) with a thermal analyzer. Under nitrogen flow of 20 ml/min, 2 mg of ornidazole, and physical mixture were placed separately in a sealed aluminium pan, and heated at a scanning rate of 50 ºC /min from 20 ºC to 200 ºC. An empty aluminium pan was used as reference.

Film Preparation

The formulations of ornidazole were prepared in the laboratory using the polymer such as polyethylene oxide N-750 and gellan gum with the use of plasticizer (PEG-400) by solvent casting technique. Ornidazole was dissolved in a10 ml distilled water containing polyethylene oxide which is previously dissolved by putting the solution on a magnetic stirrer (rpm 30/min). In another side, the gellan gum was dissolved in a 5 ml distilled water by warming. Then both the solutions were mixed and plasticizer PEG 400 was added, stirred well on a magnetic stirrer (rpm 30/min). To the above solution was allowed to stand for 30 min for deaeration. The solution was cast in a Petri dish (diameter 8.8cm) using mercury as a substrate and dried at room temperature for 24 h. The film was carefully removed from the Petri dish, checked for any imperfections and cut into the required size to deliver the equivalent dose (7×7mm2 per strip) containing 1 mg of the drug. The samples were stored in a desiccator at relative humidity 30-35% until further analysis[14].

Table 1: Composition of formulation.

Formulation Code	F1	F2	F3	F4	F5	F6
Ornidazole	2%	2%	2%	2%	2%	2%
PEO	2	--	3	-	2	1
Gellan Gum	-	2	--	3	1	2
PEG-400	15	15	10	10	10	10
Clove Oil	1%	1%	1%	1%	1%	1%
DW qs	100%	100%	100%	100%	100%	100%

*****PEO indicates polyethylene oxide; PEG, polyethylene glycol

Evaluation of Dental Strip

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

Surface pH

Surface pH of the strip was determined by using digital pH meter. The dental strips were allowed to made contact with double distilled water for 1 hour in glass beaker. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute. The same procedure was repeated for three times[15].

Drug Content

To check the uniform distribution of drug in the strip (7 x 7 mm^2), three strips were taken out from each batch. Each strip was then placed in volumetric flask containing 10ml of distilled water and shaken to extract the drug from strip. One milliliter of above resulting solution was withdrawn, after making suitable dilution with distilled water it was then analyzed by UV-spectrophotometrically at 317 nm using PBS pH 6.8 as a blank. The mean and standard deviation of drug content of three randomly selected strips were calculated. The same procedure was adopted for all the batches and drug content was noted[15].

Strip Thickness

The thickness of strips was measured by using Digimatic Micrometer (Mitutoyo, ABSOLUTE). The thickness of each strip was determined at six different places and the average value was calculated. The standard deviation of thickness was computed from the mean value[16].

Weight Uniformity

Strips (size of 7 x 7 mm^2) were cut from different areas of film. The weight of each strip was taken and the weight variation of six strips was calculated. The standard deviations of weight were computed from the mean value[16].

Folding Endurance

The folding endurance of the strips was determined by repeatedly folding one strip at the same place till it broke or folded up to 300 times, which is considered as satisfactory strip properties. The number of times of strip could be folded at the same place without breaking give the value of the folding endurance. This test was done on all the batches for three times[17].

Flatness

Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of non uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness[18]

$$\text{Constriction (\%)} = \frac{\text{Final length of Patch} - \text{Initial length of Patch}}{\text{Final length of Patch}} \times 100$$

Tensile Strength and Percentage Elongation

Tensile strength and percentage elongation of the Strips was determined with “Texture analyzer” testing machine. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test strip of specific size (4 x 1 cm^2) was fixed between these cell grips and force was gradually increased until the sample breaks apart.

The tensile strength of the strips was taken directly from the dial reading. The percentage elongation of strips was calculated by applying the following equation. Same procedure was repeated for three times[19] and standard deviation was calculated from mean values.

$$\text{Tensile Strength} = \frac{\text{load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

$$\text{Percentage elongation} = \frac{\text{Increase in length}}{\text{original length}} \times 100$$

Percentage moisture absorption

Percentage moisture absorption test was carried out to check physical stability or integrity of the strips maintained at high humidity. Three strips were taken out from each film, weighed and placed in a desiccator maintained with high humidity at about 75% RH. After three days, the films were taken out and reweighed [20]. The percentage moisture absorption was calculated by using following formula

$$\text{Percentage Moisture absorbed} = \frac{\textit{Final weight} - \textit{Initial weight}}{\textit{Initial weight}} \times 100$$

Percentage moisture loss

The percentage moisture loss was determined to check the integrity of the flm at dry condition. Films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed. The percentage moisture loss was calculated using the following formula [20];

$$\text{Percentage Moisture loss} = \frac{\textit{Initial weight} - \textit{Final weight}}{\textit{Initial weight}} \times 100$$

In vitro drug release study

In vitro drug release studies were carried out by using a bi-chambered donor receiver compartment model designed by using commercial semi-permeable membrane (Sigma Dialysis Membrane). The dental strip was placed inside the donor compartment. 10 mL of phosphate buffer pH 6.8 was placed and maintained at the same level throughout the study in the donor compartment. The entire surface of the membrane was in contact with the reservoir compartment which contained phosphate buffer at pH 6.8 which was stirred continuously using a magnetic stirrer at 30 rpm to simulate agitation action of the oral mucosa. Sample were withdrawn from the receptor compartment at periodic intervals and replaced with equal volume of PBS pH 6.8. The drug content was analyzed at 317 nm against reference standard using phosphate buffer pH 6.8 as a blank on a UV visible spectrophotometer (Shimadzu 1700, Japan)[21].

In Vitro antibacterial activity

In vitro antibacterial study was performed on optimized formulations by placing the strip (0.5 x 0.5 cm^2) on agar plates seeded with the oral bacteria '*P. gingivalis* and *'E. coli'*. After 48 h of incubation at 37 ^{0}C, the strips were transferred to freshly seeded agar plates and incubated for an additional 48 h. This procedure was repeated and inhibition of bacterial growth was detected on the agar plate. The zone of inhibition on the agar plate was then measured[22].

Stability Study

Stability studies were carried out on optimized formulation F5, according to ICH guidelines by storing replicates of strips (packaged in aluminium foil) in a humidity chamber, with a RH 75± 5% and a temperature of 40±0.2 °C. At periodic intervals the samples were taken out at 0, 15, 45 and 90 days and the period for their degradation of the strip was checked. Samples were also analyzed for surface pH, thickness, weight, drug content and in vitro diffusion[23].

RESULT AND DESCUSSION

The formulations were prepared by using polymers such as gellan gum and polyethylene oxide (biodegradable) by the utilization of plasticizer (PEG-400) by solvent casting technique. In the present study, the strips were prepared by using different polymeric concentration as well as the concentration of plasticizer 10 and 15%. The prepared strips were evaluated in terms of physico-mechanical properties and their results are given in Table 4.

In FT-IR studies were carried out, it shows the drug was pure. IR spectra showed presence of all the characteristic peaks for ornidazole in the physical mixtures indicated no drug-polymer interaction. In UV-Spectroscopy the drug estimation were carried out, as per given procedure and the λmax was found to be 317 nm, it shows the drug was pure.

Table 2: FTIR experiment values of ornidazole.

Wave number (cm^{-1})	Assingment
3169.15	O-H stretching mode
3091.03	C-H stretching mode
1538.28	NO_2 asymmetric stretching mode
1352.14 & 1271.13	NO_2 symmetric stretching mode
1149.61	C-O stretching mode
829.42	C-N, NO_2 stretching mode

Peaks given by ornidazole drug are present in the FTIR spectra of physical mixture of formulations for both the polymers. Thus, we can conclude that there was no any kind of interaction was found between drug and polymer. Hence it was considered as suitable candidates for the formulations.

Table 3: Drug-Polymer Interaction Studies through IR Spectroscopy.

Drug Peak	Gellan gum Peak	Polyethylene oxide Peak	Drug + Polymer Peaks	Interactions
3169.15, 3091.03, 1538.28, 1352.14, 1271.13, 1149.61, 829.42	2923.22, 1156.36, 1426.41	2890.43, 1474.63, 1341.54, 1058.96, 946.12, 841.96	3117.43, 2937.32, 1518.84, 1424.48, 1351.18, 1272, 1149.61, 1056.45, 830.38	NO

The thermograms of ornidazole exhibited endothermic peak at 78.70^{0}C. The DSC thermograms of physical mixture as well as strips showed identical peaks corresponding to pure drug which indicates the no chemical interaction between drug and polymers. The gellan gum peak was not observed in DSC thermograms, it may be overlap with drug peak because the melting point of ornidazole and gellan gum was near about same. The following DSC thermograms show the peaks given in figure 1, 2 and 3.

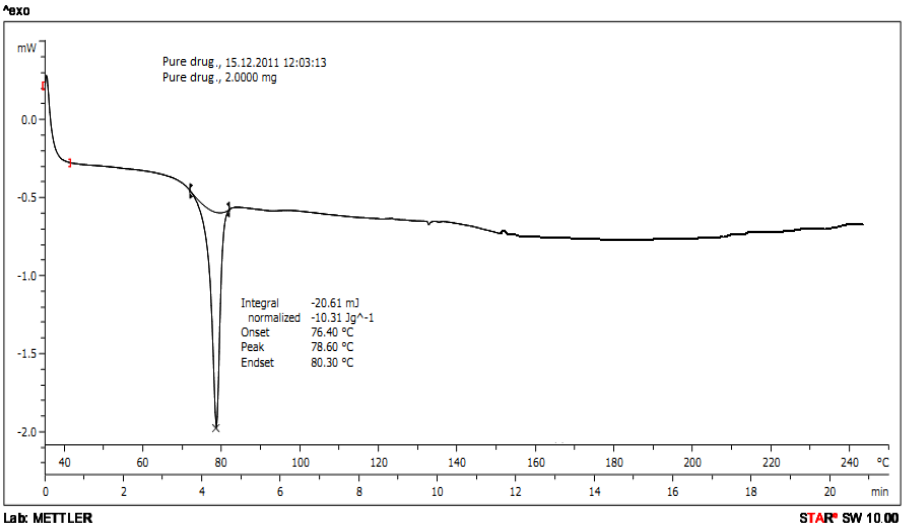

Fig. 1: DSC thermogram of Ornidazole.

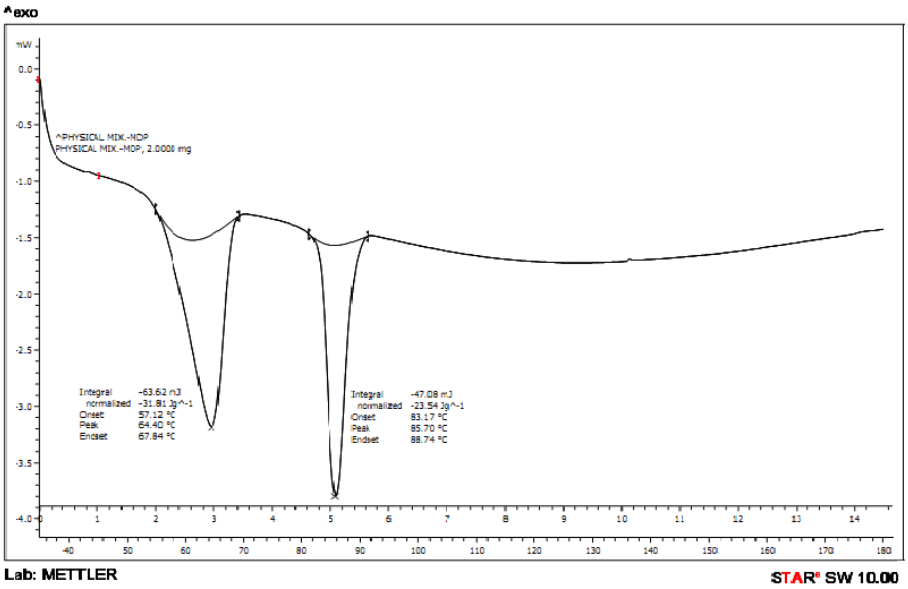

Fig. 2: DSC thermogram of physical mixture of ornidazole and polymer.

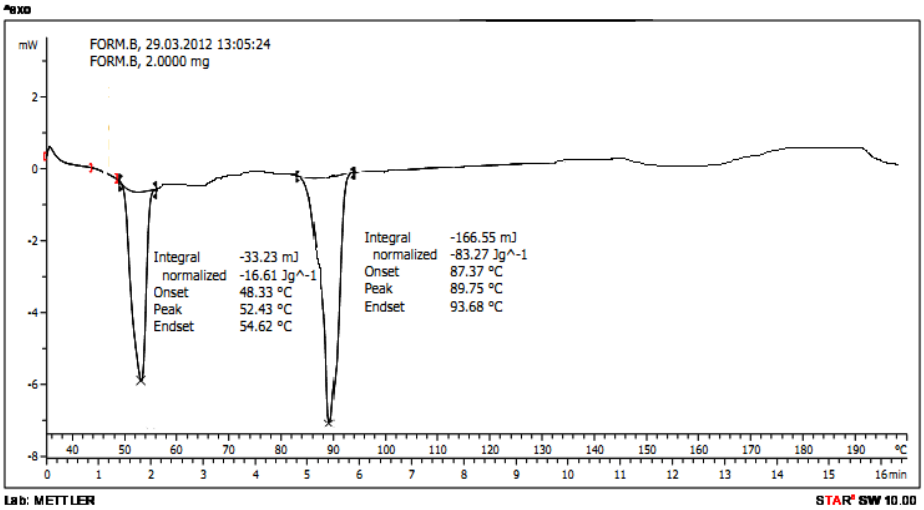

Fig. 3: DSC thermogram of batch F5 (Optimized batch).

Macroscopically features revealed that the drug was dissolved in the polymer matrix rather than dispersing. The formulations prepared with various excipients concentration were observed to be flexible, transperparant, smooth, non-sticky and homogeneous.

The surface pH of the developed formulations was found to be in the range of 6.3-6.8, which is nearly close to the neutral pH, hence it authorized that the films may have less potential to irritate the sublingual mucosa and therefore, additionally acceptable by the patients.

It is ncessary to determine the amount of the drug present in each strip so the content uniformity test is generally employed for unit dosage forms. The drug content from the formulations was analyzed at 317 nm by using suitable blank. It was obsvered that the formulations exhibits more than 96% of the dose of a drug which represents very minute amount of the drug was lost, but it within the acceptable limits. The finding results are mentioned in given table 4. The results indicated that the drug was uniformly dispersed. The thickness of the strips was found to be in between from 0.119(±0.03) to 0.147 (±0.14) mm. The thickness of strips was found to be varies when the concentration of polymer and plasticizer changed.

The average weight of the strips was found to be in the ranges from 11.54(0.1) to 16.22(0.06). The lowest weight was found in case of only with PEO. But when it was combined with gellan gum their weight also increases. It was also found that plasticizer have profound effect on weight. As the concentration of PEG-400 reduced the weight of the respective formulations also decreased. Strips does not show any cracks even after folding for more than 100 times, because the polyethylene oxide gives higher strength to the strips. The results obtained after flatness study no any formulation had the difference in the strip lengths before and after their cuts, thus representing 100% flatness. It also specifies 0% constriction in the strips and thus they could retain a smooth surface when applied to skin leading to intimate contact and therefore which results in better drug permeation. The concentration of polymer and plasticizer shows higher effect on tensile strength of strip. Concentration of polyethylene oxide increases, the tensile strength of strips also increases. The concentration of polymer and Plasticizer shows higher effect on tensile strength of strip especially PEO.

Table 4: Physical Characterization of ornidazole periodontal strips.

Batch Code	Thickness cm*	% Drug Content*	Weight* mg	Folding Endurance*	Tensile Strength* gm	% Elongation*
F1	0.132(0.11)	98.36(0.46)	12.54(0.1)	144	48.44(0.12)	1.13
F2	0.147(0.14)	97.82(0.14)	14.16(0.08)	115	31.27(0.31)	09.57
F3	0.122(0.14)	96.49(0.21)	12.85(0.83)	127	68.87(0.14)	2.4
F4	0.126(1.2)	98.66(0.37)	13.43(0.12)	109	46.92(0.37)	1.8
F5	0.119(0.03)	99.84(0.12)	13.27(0.37)	138	71.93(0.45)	3.22
F6	0.136(0.02)	98.73(0.31)	14.22(0.06)	149	62.13(0.23)	2.02

* n= average of three reading,. S.D. values are given in the parentheses

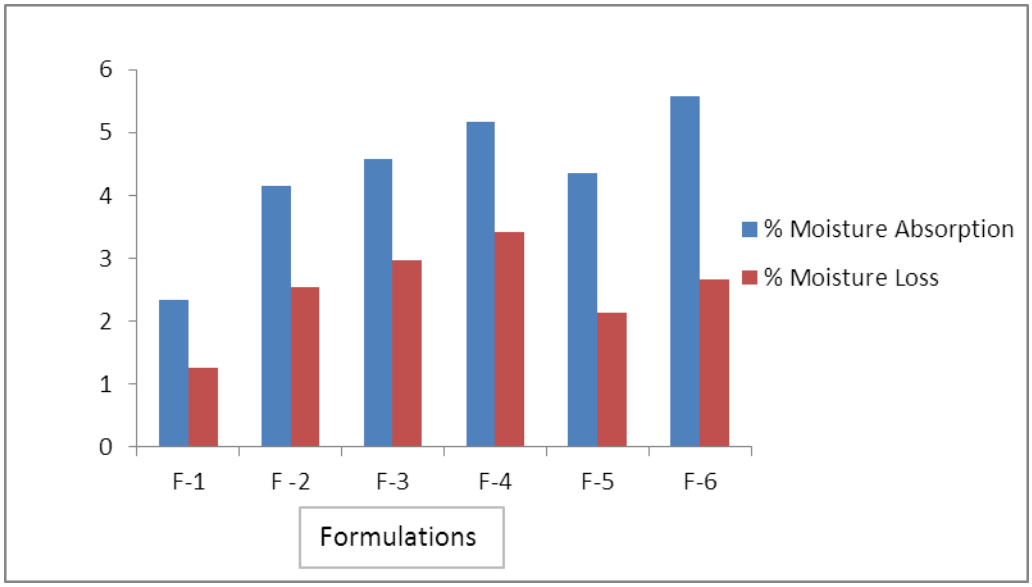

Fig. 4: % Moisture absorption and Loss of the developed formulations.

The percentage moisture absorption was noted for all the formulations in triplicate. According to the results obtained, the moisture absorption was more in the formulations where hydrophilic excipients were present. Formulation F6 had shown the maximum percentage moisture absorption of 5.57 ± 0.46, due to their hydrophilicity. Formulation F1 had shown the minimum moisture absorption of 2.34±0.70 (Fig.4) as it contains polymer of less hydrophilicity. In general, it can be concluded that gellan gum had more tendency to absorb moisture as compared to PEO. At the humid condition, percentage moisture absorption was more. However, there was no change in the integrity of the flm; which was observed by its physical appearance.

The percentage moisture loss was noted for all the formulations in triplicate. It was observed that when the formulations were kept at very dry condition, the maximum moisture loss varied from 1 to 3% (Fig. 4). Te amount of moisture loss might have been due to less hindrance offered by PEO and plasticizer like PEG-400.

In vitro diffusion studies of six formulations are given in the table 5. F5 formulation shows maximum release 94.56% (±0.32) at the end of 9 h. F5 showed sustain release as compared to others. The in-vitro drug release profile is an important tool that predicts in advance how a drug will diffuse and targeted to the site. The cumulative amount of drug released from formulations F1 and F2 showed a faster release profile this might be due to low concentration of polymers and high concentration of PEG-400. Hence we can say that not only polymeric concentrations are resposible for release of drug at different time but also plasticizer also played importment role in release pattern of drug.

Table 5: In-vitro drug release study of prepared Formulations.

Time	F1	F2	F3	F4	F5	F6
0	**0**	**0**	**0**	**0**	**0**	**0**
0.5	7.35±0.23	12.25±1.2	9.46±2.1	11.25±0.23	10.56±0.13	10.68±0.2
1	18.23±0.31	32.16±1.38	20.25±0.23	28.43±0.6	19.52±0.41	28.54±1.3
2	39.41±1.2	51.36±0.24	36.32±0.46	44.36±0.42	31.26±1.23	42.52±0.42
3	56.22±0.42	69.84±0.23	49.86±0.2	63.42±1.23	44.64±0.54	57.68±0.61
4	71.26±0.26	88.94±0.46	64.55±0.47	74.38±0.24	58.26±1.84	66.39±0.12
5	92.41±0.12		72.49±0.7	90.24±1.24	69.86±1.3	78.26±1.1
7			93.76±1.5		83.27±0.26	93.47±0..64
9					94.56±0.32	

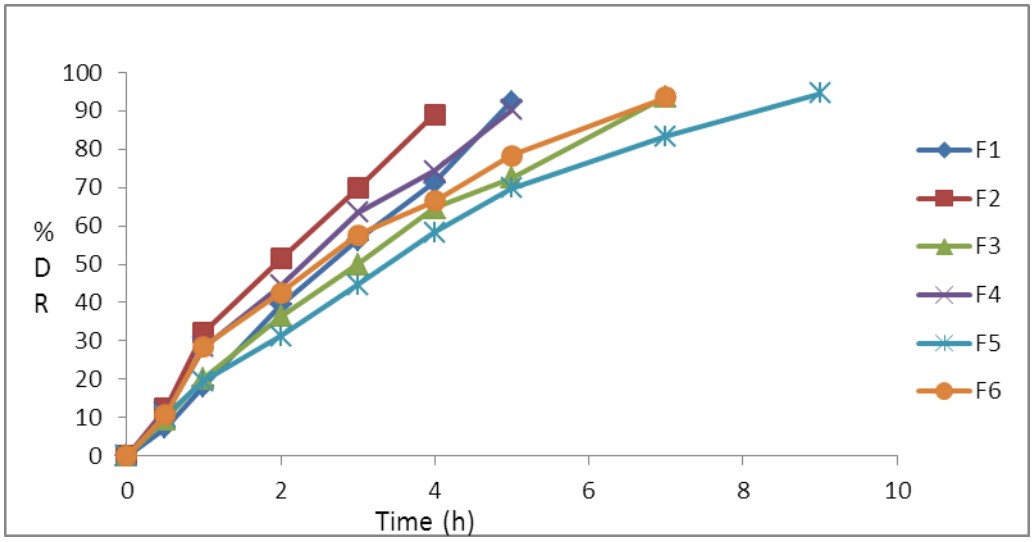

Figure 5: *In vitro* drug release study of prepared formulation.

In vitro antibacterial study

The study indicates that the formulated polymeric strips containing ornidazole retained their antibacterial activity for 48 hours. The zone of inhibition was found to 19 mm for *P. gingivalis* ATCC 33277 and 24 mm for *E. coli* ATCC 25922.The given standard also showed the zone of inhibition which were compared with the given optimized formulations.

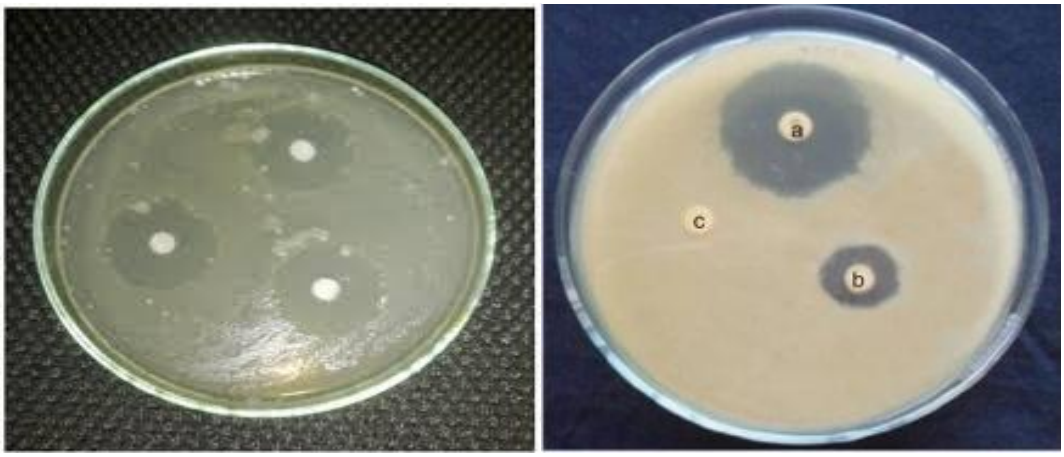

Fig.7: Antibacterial Study of F5 *P. gingivalis* ***E. coli***

Based on the results of initial characterization batch F5 was thought to be the superior formulation and hence further subjected to stability study for 3 months. Results are showed in table 6, no major differences was found between evaluated parameters before and after ageing/storing and all were found to be in acceptable limits. There was no significant decrease in drug release and drug content rate of formulation F5 over the period of 3 months.

Table 6: Stability Study of optimized batch (F5)

Evaluation parameters	Before stabilityStorage	After 15days storage	After 45 days storage	After 90 days Storage
Thickness	0.119	0.116	0.116	0.112
Weight variation	13.27	13.16	13.32	12.75
Drug content (%)	99.84	99.58	99.65	98.45
Drug release (%)	94.56	96.23	97.82	94.68

CONCLUSIONS

In conclusion, we can say that, the formulated periodontal strip as a drug delivery system promising the approach which is utilized for improving the therapeutic efficacy of ornidazole in the treatment of periodontitis. The polymers utilized for the development of strips was proved its efficacy such type of polymers can be used in the preparation of dental strip as both they are biodegradable. PEO form moderately strong films as compared to Gellan gum which forms weak films but the

strength is increased by combining with PEO and gellan gum. All the prepared formulations showed better drug release profile at the end of 9h. But plasticizer has a profound effect on mechanical properties as well as release profile of the drug. Ornidazole showed a good antibacterial activity. The inclusion of ornidazole also improves the therapeutic efficacy of formulation in the management of periodontitis. Hence in future, such type of drug delivery system may utilize for the periodontal treatment.

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