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## Formulation and Evaluation of Dental Films for the Treatment of Periodontal Diseases



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### ABSTRACT

A novel film formulation was developed for concomitant delivery of NSAID, Ibuprofen (IBU 1.25% w/v) and antimicrobial, Metronidazole (MTZ 0.75% w/v) for local treatment of periodontal diseases. The plasticized, aqueous dispersions of Ethyl cellulose (EC), sodium carboxy methyl cellulose (Sod CMC), HPMC K4M and Eudragit S100 were cast into thin films. Both the placebo and drug loaded, sterile films were characterized for various structural, physicochemical and mechanical properties. The formulation composed of Sod. CMC (1.20% w/v) with the plasticizer propylene glycol (30% w/w) (DFSMBPG<sub>3</sub>) possessed superior film characteristics such as smooth even surface, thickness (0.263mm), neutral pH (6.54-7.12), consistent average weight (78mg), negligible moisture loss <1.5% w/w, greater tensile strength (2.12 kg), folding endurance (> 290) and prolonged release of both the APIs viz: IBU (92.12%) and MTZ (95.82%) respectively over about 8 hours. The sterile films were devoid of any acute irritancy potential as revealed by intact and dense vasculature around CAM of incubated egg of hen. The selected film composition also demonstrated good antimicrobial efficacy (diameter of the zone of inhibition >20mm) which was also comparable with the bulk of MTZ used as a reference, against pathogenic bacterium *S. mutans* responsible for periodontal diseases. The stability data (30 days) of this film composition indicated only minimal changes in physicochemical, mechanical properties, % contents and release (*in-vitro*) profiles of both the APIs. Hence, the novel periodontal film composition is a promising alternative to conventional local therapy due to the multipronged control of major symptoms of periodontal diseases including gingivitis.

## INTRODUCTION:

Periodontal diseases represent various periodontal tissue infections including gingivitis and periodontitis. These diseases have a direct association with dysbiosis of the bio-flora residing on the periodontal pockets. Unlike, gingivitis, a milder and relatively harmless inflammatory response, periodontal disease causes greater damage to the connective tissue and bone support. Other contributory factors of periodontitis include genetics, prolonged consumption of products containing tobacco and alcohol, malnourishment, immunodeficiency, osteoporosis, diabetes mellitus, emotional stress and antibiotic drug candidates belonging to tetracycline group.

The typical therapy based on oral administration of conventional dosage forms of NSAIDs and antibiotics suffers from poor local concentrations within the affected periodontal pockets as a consequence of flushing action (replacement of gingival crevicular fluid at about 40times/hour within 5mm pocket). Moreover, it suffers from hyperacidity, gastric irritation and hypersensitivity manifestations. More serious disease condition, known as refractory periodontitis requires aggressive treatment with these medications delivered using novel approaches for prolonged residence at the target site.

A few reports have cited the effective use of antibiotics including MTZ for control of infections caused by various aerobic and anaerobic pathogens associated with periodontitis. Manojkumar, Prabhushankar, and Satheshbabu have quoted effective use of MTZ against anaerobes *Porphyromonas gingivalis* and *Prevotella intermedia* while MG Ahmed and co-workers have used Ciprofloxacin in (local treatment) for control of *S. mutans* associated with gingivitis. There is evidence citing effective alteration of progression of certain forms of periodontitis and reduction of gingival inflammation and alveolar bone resorption due to concomitant administration of antibiotic and NSAIDs. Luana Perioli and co-worker have developed buccal film formulation of a drug of choice for anti-inflammatory and analgesic activity in the oral cavity.

Hence, the work was undertaken with the objective of prolonging concomitant delivery of antimicrobial and NSAID using hydrophobic and hydrophilic polymeric periodontal film compositions for the effective control of major symptoms of periodontitis.

## MATERIALS AND METHODS:

### 1. Materials:

The drugs IBU and MTZ were obtained as gift samples from Micro Lab Ltd., Bangalore, and Research Lab Fine Industries, Mumbai respectively. The polymer Eudragit S100 (Eu S100) was a generous donation from Evonik India Pvt. Ltd., Mumbai. All other materials used were of analytical reagent grade. An authentic culture of *S. mutans* was procured from MTCC Chandigarh; India.

### 2. Methods:

#### 2.1 Pre-formulation Studies:

A stock solution (100µg/ ml) was prepared by dissolving accurately weighed the quantity of IBU (20mg) and MTZ (10mg) in an appropriate volume of methanol: distilled water (1:9). The  $\lambda$  max and linearity range values of appropriately diluted (2ml up to 10ml) solution were noted.

#### 2.2 Compatibility studies:

The compatibility of a mixture of APIs with or without polymeric addition was ascertained by exposing to the environmental conditions over the 15 days. The detection of changes in any of the physical or physicochemical characteristics of blends if any was carried out by visual and FT-IR spectrophotometry (BrukerALPHA-T 1.2.4).

#### 2.3 Preparation of periodontal films:

To determine the optimum concentrations of polymer, plasticizer and solvent placebo films were evaluated for structural, physicochemical and mechanical properties. The films, which exhibited all the characteristics, were selected for the inclusion of APIs and taken up for further studies. The polymeric films were prepared by solvent casting technique. Each of the polymers (Ethyl cellulose (EC), Sod. CMC and HPMC K4M) were dissolved in distilled water (DW) where Eu S100 was dissolved in alcohol. The polymeric dispersions were stirred continuously and the required quantity of Propylene glycol (PG) added gradually with careful stirring. (Table 1 reports the typical composition of films selected for loading of IBU (1.50% w/w) and MTZ (0.75% w/w))

in a controlled manner were poured into a clean Petri plates placed on a horizontal plane which was previously lubricated with 2ml Glycerin. The solvent was allowed to evaporate slowly by placing inverted glass funnel with a cotton plug in the stem of the funnel on the Petri plates at room temperature for 24 hrs. The dried films were wrapped into a composite packing of butter paper and aluminum foil.

**Table 1: Formulation of selected periodontal medicated Film**

Sr. No.	Formulation Code	IBU	MTZ	EC	EuS 100	HPMC K4M	Sod. CMC
1.	DFECBPG3	1.5%	0.75%	2.80%	--	--	--
2.	DFEUBPG3	1.5%	0.75%	--	2.80%	--	--
3.	DFHMBPG3	1.5%	0.75%	--	--	1.40%	--
4.	DFSMBPG3	1.5%	0.75%	--	--	--	1.20%
*PG 30% w/w of dry weight of film forming polymer Casting solvent up to 20ml-Alcohol(99.98%v/v) for EuS100 -DW for EC, HPMC K4M, Sod. CMC							

## 2.4 Evaluation of medicated periodontal films:

The periodontal films were assessed visually for appearance, presence of any surface imperfections and entrapment of air. The average weights of film samples of each formulation were noted in triplicate.

### a) Appearance:

The appearance of each film sample was checked visually with or without the aid of magnifying glass (2X) against the dark and white background and surface homogeneity, transparency was noted.

### b) Texture:

The texture characteristics of drug loaded strips ( 7×2 mm) of each film type were noted using scanning electron microscopy (JEOL,Model JFC-1100 E, Japan, room temperature,

magnification 200-20 mm ) before and after 8 hours of dissolution (*in-vitro*, medium simulated gingival fluid, SGF, maintained at temp  $36\pm 2^{\circ}\text{C}$ ). Film samples were coated with gold ( $200\text{ \AA}$ ) under reduced pressure (5 torr) for 2 min using an ion sputtering device before recording the micrographs.

**c) Thickness uniformity:**

Thickness (mm) at different positions (at the margins and center) of strips of each film sample (square sample dimensions 1cm) was noted using digital vernier calipers

**d) Surface pH:**

The pH of aqueous dispersions (50 ml) of dissolved strips of each film formulation was noted in triplicate using the previously calibrated pH meter

**e) Tensile strength**

The tensile strength (gm) of blocks (10\* 70 mm) cut from each film sample was noted at gradually increasing pull until the film sample tears off.

**f) Folding endurance:**

The repeated folding of each type of square sized medicated periodontal film samples (n=3) was carried out at the same point till it broke and the number was noted that which film were broken.

**g) Weight uniformity:**

The strips (square shape  $1\text{cm}^2$  dimensions) cut off from different areas of Casted medicated periodontal films were weighed individually and the uniformity of weight of each film type was calculated.

**h) Moisture contents (%w/w):**

The moisture contents of 3 strips (square shape,  $1\text{cm}^2$ ) of each film sample were calculated Individually on the basis of difference in initial (W1) and final weight (W2) obtained after exposure to anhydrous calcium chloride for 72 hrs.

**i) Sterilization and Sterility:**

The individually packed strips of each film type were irradiated by UV radiation (240nm-280nm) for 120 minutes and tested using Method B of sterility testing with slight modification wherein the strips of dimensions (1 cm<sup>2</sup> square sized) were dissolved in about 50 ml of sterile water for Injection I.P and 20 ml of dispersion of each of the film type was added aseptically, over the surface of each of the three sterile media viz: McConkey Agar (incubation at 30-35°C for 3 days), Chloramphenicol Yeast Glucose Agar (incubation at 30-35°C for 3 days) and Plate Count Agar (incubation at 20-25°C for 5 days). The colony count of each of the film was noted after specified conditions of incubation.

**j) Contents of MTZ and IBU:**

The method described by Naga Priya KR *et al.* was followed, where 2 strips of each type of medicated films (1cm<sup>2</sup>) were individually dissolved (mechanical stirring) using 5 ml of phosphate buffer (pH 6.8) contained in plain glass vials. The resulting solutions were clarified by passing through Whatman filter membrane (#41) and 1 ml of filtrate was withdrawn, diluted suitably and assayed spectrophotometrically for contents of both APIs, using simultaneous estimation method (based on the method reported by Md. El-Ghobashy *et al.*), developed and validated in the laboratory.

**k) Release (*in-vitro*) of MTZ and IBU:**

Simulated Gingival Fluid (SGF, pH 6.6- 6.8, maintained at 37 ± 0.5 °C) contained in the dry test tube was used as dissolution fluid. Each of six strips of known weight and dimensions of selected medicated periodontal films was placed individually in the test tubes for 8 h. At the interval of 1 hr. the supernatant of dissolution medium from each tube was aspirated using a disposable plastic syringe (2ml) and replaced with 1 ml volume of fresh SGF (maintained at conditions described above). The cumulative % release of IBU and MTZ was determined using the experimental method of estimation.

**l) Antibacterial (*in-vitro*) efficacy:**

Antibacterial efficacy of medicated periodontal films described by Manojkumar *et al.* was used where the film samples of selected formulations ( $0.5 \times 0.5$  cm, square shaped) were placed aseptically onto the sterile Petri plates containing sheep blood agar previously seeded with *S. mutans*. Subsequently, the films were incubated at  $37^{\circ}\text{C}$  for 24 hours and their antibacterial efficacy was noted and expressed as (diameter of the zone of inhibition) and compared with the zone created by a solution of combined APIs (equivalent to concentrations used in casting solution) and that created by the placebo film formulation of the same composition.

**m) Mucosal irritancy potential (*in vivo*):**

Mucosal irritation study was carried out by HET-CAM (Hen's Egg Chorioallantoic membrane) test. In this test fertilized three hen's eggs for each formulation weighing between 50 and 60 g were selected and candled in order to discard the defective ones. These eggs were incubated in humidified incubator at a temperature  $40^{\circ}\text{C}$  for 3 days. On day 3, egg albumin (3ml) was taken off from the sharpened end of the egg using sterile techniques. For the development of CAM away from the shell, the eggs were kept in the equatorial position. On the fifth day of incubation, the eggs were candled and non-feasible embryos were removed. On the tenth day, formulations (0.5ml) were installed through the window ( $2 \times 2$  cm) on the equator. A 0.9% Sodium Chloride (NaCl) solution was used as a control as it is reported to be practically non-irritant and the scores were recorded.

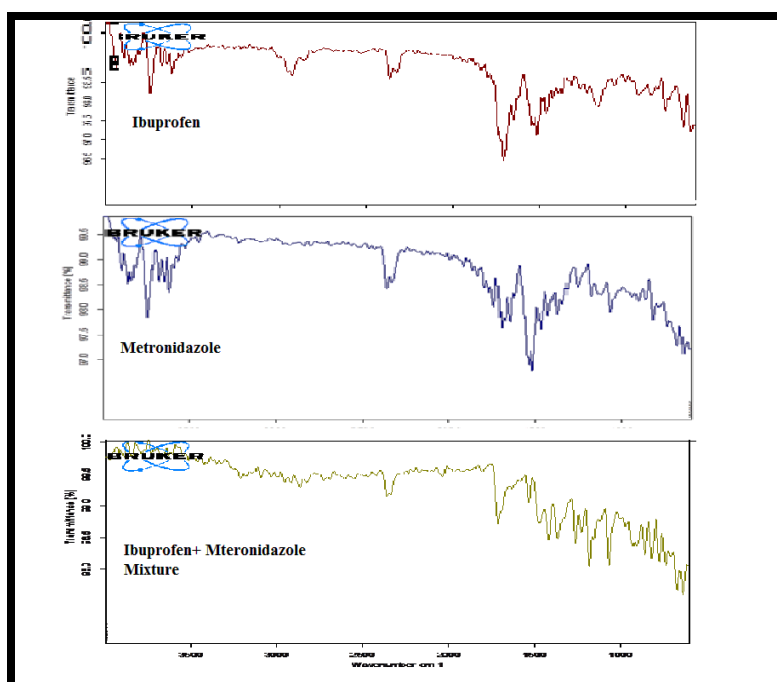
**n) Environmental stability:**

Three sets (5 strips in each set) of medicated periodontal films ( $1\text{cm}^2$ ) were weighed. The films were wrapped individually in butter paper followed by aluminum foil and placed in Petri dishes. The plates were stored at ambient humidity conditions at room temperature ( $25 \pm 2^{\circ}\text{C}$ ) and in a hot oven at  $45 \pm 2^{\circ}\text{C}$  for 30 days. The samples were analyzed for physical changes such as appearance, color, and texture. Drug content was estimated at regular intervals as described earlier.

## RESULTS AND DISCUSSION:

The organoleptic, physicochemical and solubility characteristics confirmed the identity and purity of the drug candidates IBU and MTZ. Moreover, the spectral characteristics (wavelength of maxima and linearity of concentration and absorbance range- 400nm- 200nm) further supported the identity and purity of APIs and formulation excipients.

The IR spectra of physical mixtures of IBU and MTZ and excipients did not indicate gross changes in structure since the position and height of peaks associated with major functional groups in their structures (**Figure 1a, 1b, 1c, 1d, and 1e**).



**Figure 1a: IR spectrum of IBU and MTZ**



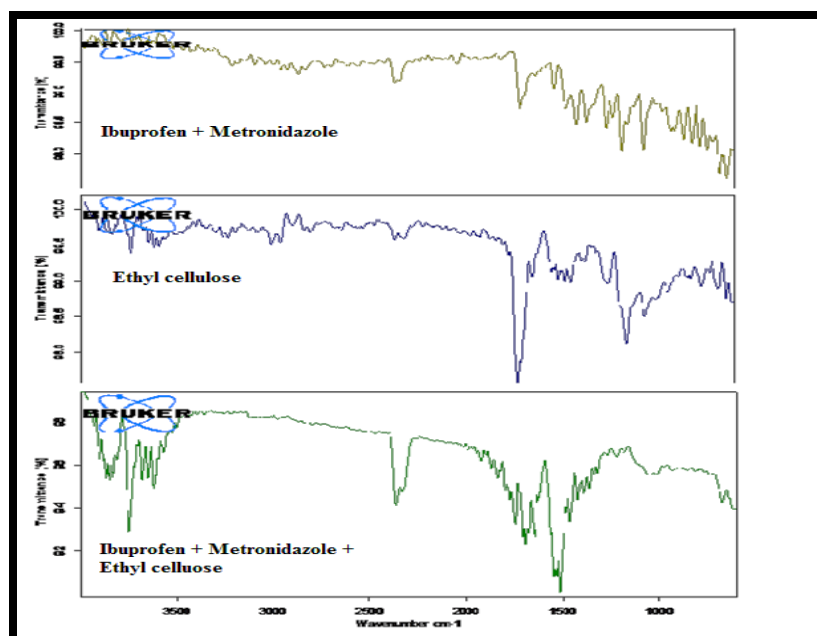


Figure 1b: IR spectrum of IBU, MTZ, and EC

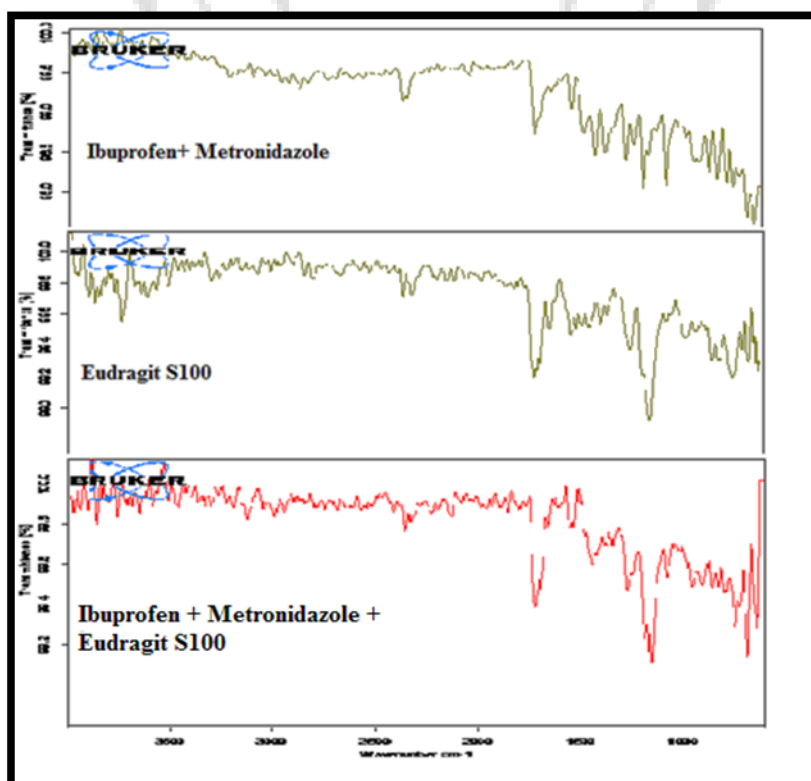


Figure 1c: IR spectrum of IBU, MTZ and Eu S 100

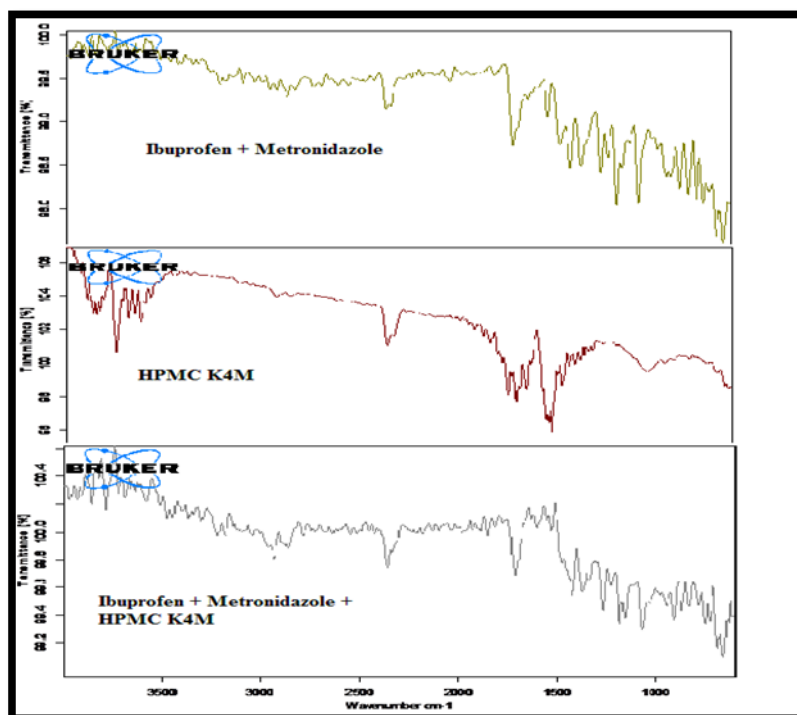


Figure 1d: IR spectrum mixture of IBU, MTZ, and HPMC K4M

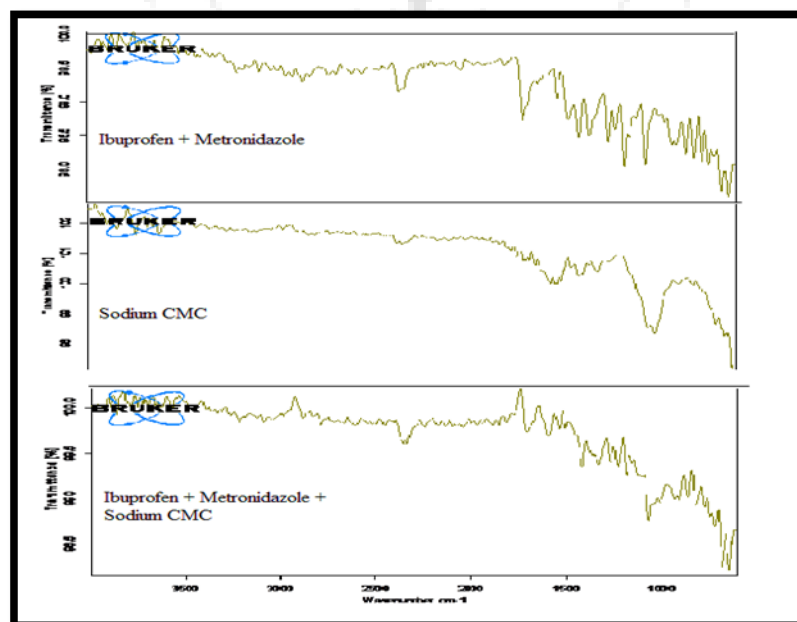


Figure 1e: IR spectrum of IBU, MTZ, and Sod.CMC

Drug loaded periodontal films casted using aqueous dispersions of either Ethyl cellulose or Sodium CMC were opaque and with rough texture while those prepared using either

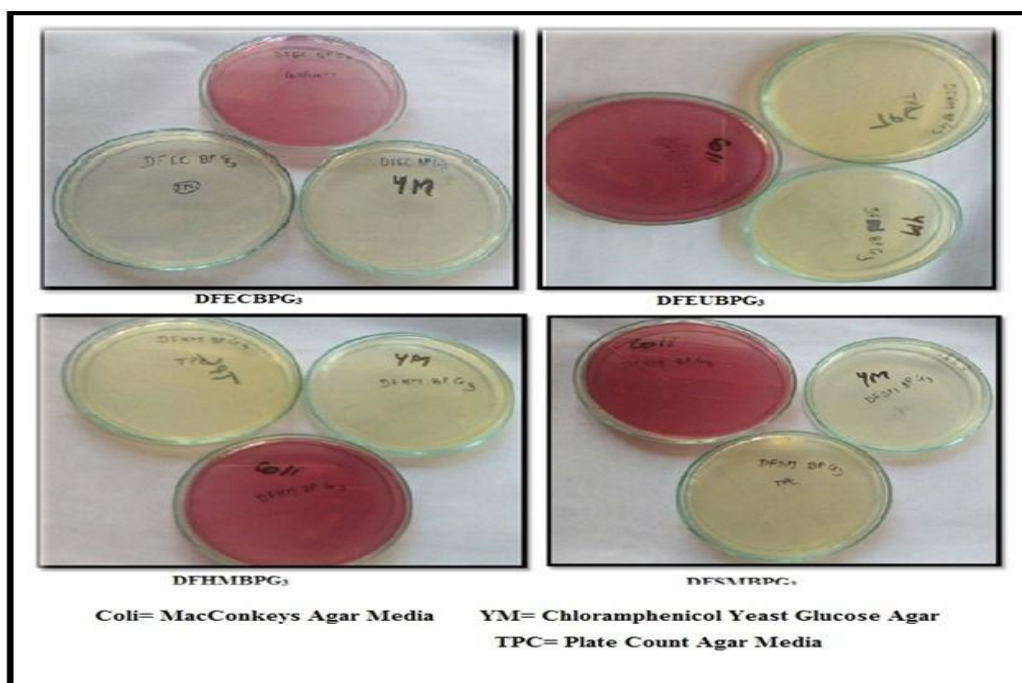
Methacrylate (Eudragit S100) or Methocel (HPMC K4M) polymers were clear, transparent and with a smooth texture. The variation in the thickness of films with different polymeric compositions was in the order Eu S100 <HPMC K4M <EC <Sod. CMC. There was a considerable gain in the average weight of films based on the type and concentration of individual film forming a polymer. Based upon these findings the specific concentration of individual polymer in the aqueous dispersions was selected.

**Table 2: Characteristics of drug loaded periodontal films.**

Sr. No.	Formulation code	TN (mm)	AW (mg)	TS (kg)	FE	pH	MC (%)
1.	<b>DFECBPG<sub>3</sub></b>	0.231	82	0.681	259	6.85	1.5
2.	<b>DFEUBPG<sub>3</sub></b>	0.162	81	1.778	296	6.54	1.0
3.	<b>DFHMBPG<sub>3</sub></b>	0.185	70	0.786	293	7.23	1.6
4.	<b>DFSMBPG<sub>3</sub></b>	0.263	78	2.125	289	7.12	1.5
<b>Standard Deviation (n=3)</b>		<b>0.045</b>	<b>4.86</b>	<b>0.685</b>	<b>14.82</b>	<b>7.12</b>	<b>1.5</b>

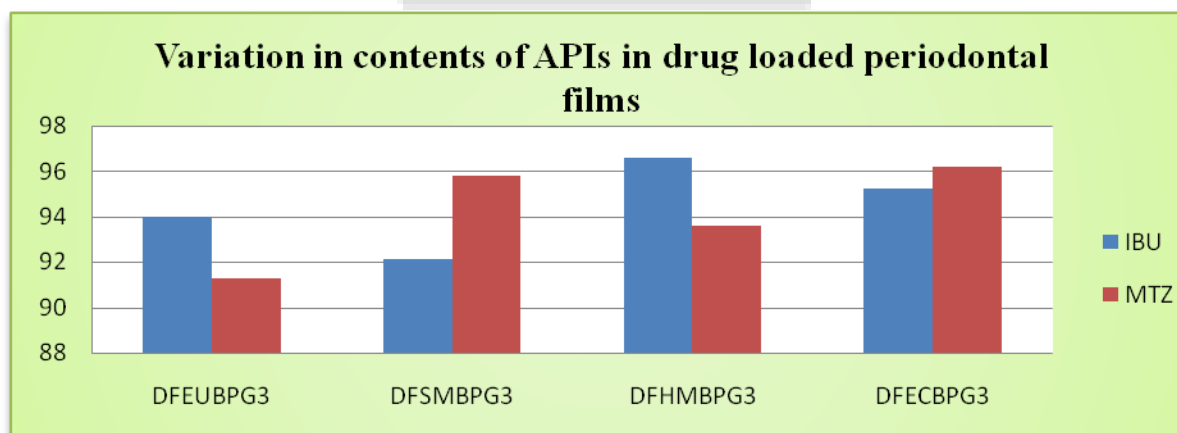
The folding was nearly same at 290 for all films formulations except DFECBPG<sub>3</sub>. All film compositions demonstrated narrow pH range (6.54-7.12) which have almost equaled to a neutral value. The lowest pH was noted for Eu. S 100 because it was weakly acidic in nature. There was desirable minimum moisture content found in the all selected periodontal films which help reduce decomposition.

All the films were found to be sterile and this is an essential feature for the inserts to be placed within the periodontal sulcus (Figure.2).



**Figure 2: Sterility status of selected medicated periodontal films**

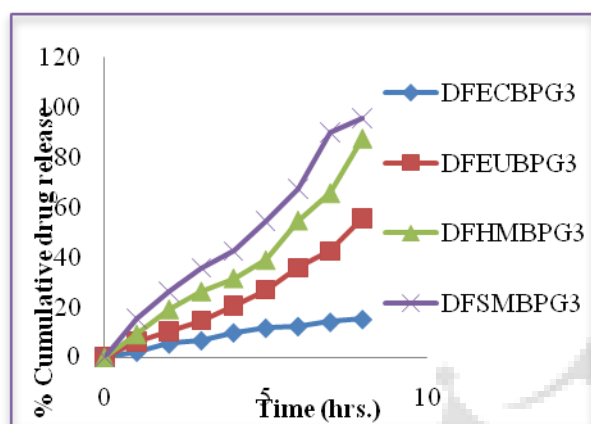
Contents of the loaded APIs were uniform for films with different compositions and it ranged between 91.25% - 96.00% (Figure 3).



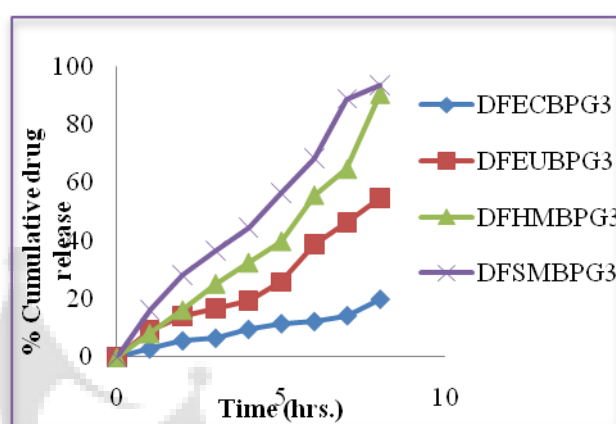
**Figure 3: Variation in contents of APIs in drug loaded periodontal films**

Release characteristics of APIs from the experimental periodontal films indicated variation in the rate as well as the extent of the amount released. Irrespective of the composition of films, the release profiles of IBU and MTZ are almost comparable for all the four types of polymers (Figure 4a and 4b). The lowest release rate of APIs exhibited by films compositions of EC may

be correlated with poor wetting and permeability characteristics of the polymer. The highest release rate of APIs was exhibited by hydrophilic films. This was favored by greater numbers of channels within the swellable matrix formed. The releases of APIs from the methocel polymeric films were slightly lower than the films composed of Sod. CMC and greater than the films compositions of EuS100 and EC.



**Figure 4a: Cumulative (%) drug release (*in-vitro*) of IBU from selected medicated periodontal films**

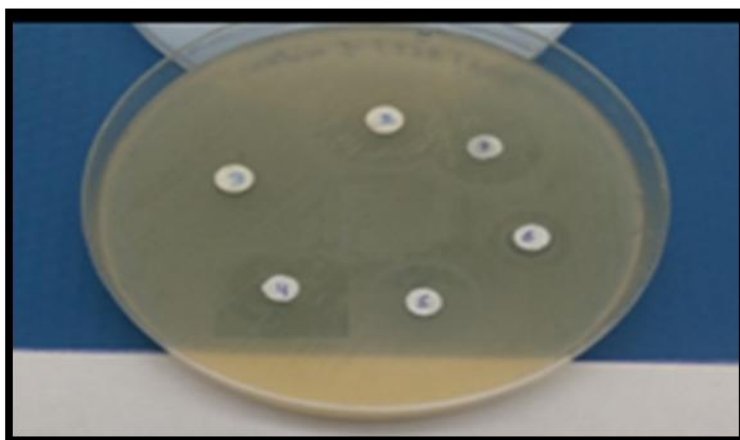


**Figure 4b: Cumulative (%) drug release (*in-vitro*) of MTZ from selected medicated periodontal films**

The drug loaded sterile periodontal films allowed effective diffusion of MTZ in sufficient concentrations which inhibited the growth of *S. mutans* (diameter of the zone of inhibition <15mm) except for EC. Sod. CMC (DFSMBPG<sub>3</sub>) due to the maximum drug was released from the formulation of the film (Table 3).

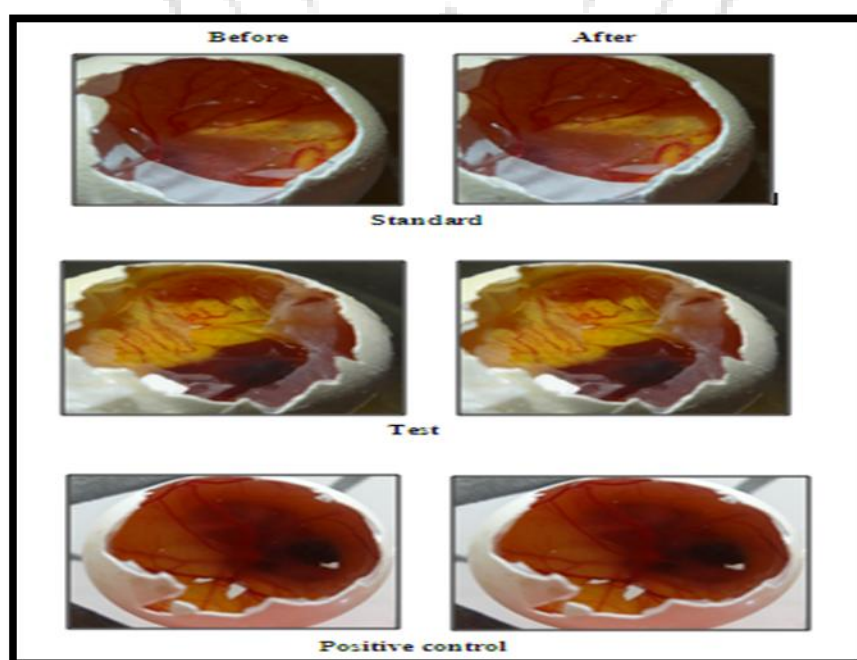
**Table 3: Zone of inhibitions of bulk drug, placebo and selected formulations**

Sr. No.	Formulation code	Zone of inhibition(mm)
1.	MTZ (Bulk)	20
2.	Placebo	NO ZONE
3.	DFECBPG3	NO ZONE
4.	DFEUBPG3	15
5.	DFHMBPG3	18
6.	DFSMBPG3	20



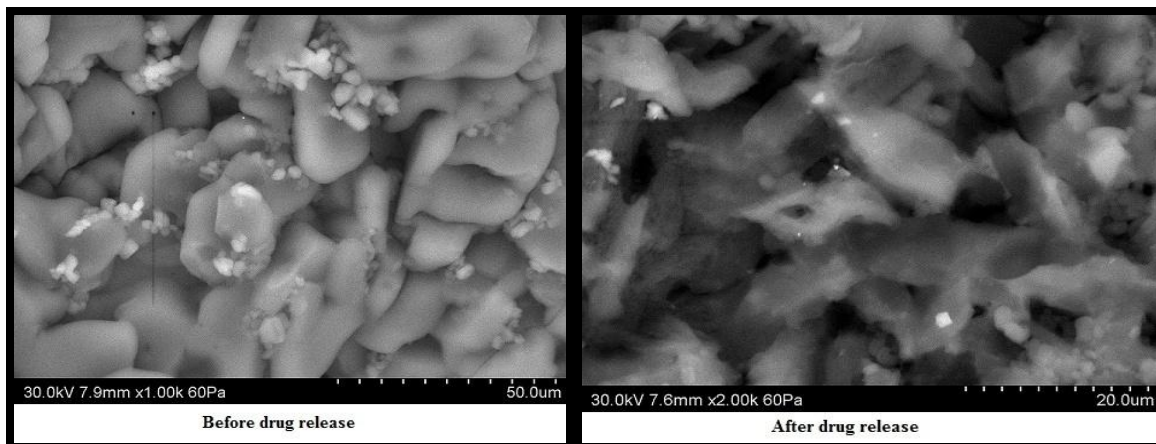
**Figure 5: Comparative antibacterial efficacy of MTZ (bulk) and MTZ loaded periodontal films and control placebo films**

The selected strength of APIs (IBU1.5% w/v and MTZ0.75% w/v) were found to be non-irritant as revealed by intact vascular network around the chorioallantoic membrane (CAM) within the incubated hen's egg (Figure 6).



**Figure 6: Vascularity of eggs exposed to negative control, positive control and experimental formulations on instillation**

The scanning electronic micrographs of the drug loaded periodontal films, composed of Sod. CMC (DFSMBPG<sub>3</sub>) indicated homogeneity of matrix and uniform dispersion of APIs within the film which after leaching out left slightly eroded membrane structures with pores (Figure 7a and 7b).



**Figure 7a: Surface characteristics of drug loaded periodontal film (DFSMBPG<sub>3</sub>)**

**Figure 7b: Surface characteristics of periodontal film after leaching (DFSMBPG<sub>3</sub>)**

The samples of sterile periodontal films exposed to 25 to 45±2°C and ambient humidity over, a period of 30 days retained all the major physicochemical, structural and mechanical properties in addition to more than 91.05% /strip for IBU and 93%/ strip for MTZ contents.

## CONCLUSION:

The experimental findings have indicated the potential of the proposed formulations for concomitant delivery of antimicrobial and NSAID agents over prolonged duration for the control of major symptoms of periodontitis. They are likely to overcome crucial obstacles of maintaining an effective concentration of APIs within the periodontal pockets with different shapes and depths (>5mm). Moreover, the favorable conformation of the mucoadhesive films within otherwise inaccessible pockets will also deter re-colonization of pathogenic bacteria in the periodontal pockets.

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