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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Development of Oral Dental Films of Doxycycline Loaded HPMC Films for Efficient Treatment of Periodontitis

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ABSTRACT
The aim of this research work was to develop Doxycycline (DOX) loaded HPMC denatl films for the treatment of periodontitis through intrapocket delivery. The splvent casting technique was adopted to manufacture the films utilising HPMC, PVA, and glycerol as polymer and plasticizer respectively. The physico-chemical characteristics of the developed films were evaluated, including drug release, tensile strength, and bactericidal efficacy against Staphylococcus aureus. The films' physical characteristics were all found acceptable for use in dental cavity. The DOX release was sustained from the films. The optimised formulation was stable under acclerated condition for two month period. This newly developed film has the potential to be an alternate drug delivery technology for treating peridontitis.
Keywords: *Doxyxycline, HPMC, PVA, glycerol, bactericidal*

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INTRODUCTION:

Due to the simplicity of administration, prevention of drug degradation in GIT as well as first-pass metabolism, the oral cavity is a desirable location for drug delivery. A large range of bacteria may colonise the oral cavity due to its diversified habitat [1]. Various organs including tissues, ligaments, and teeth get infected locally as a result of bacterial development in the gingival fissures. This condition is known as periodontitis. Gram negative, anaerobic bacteria that grow in the subgingival area develop more quickly due to the pocket's warm and moist environment [2]. Since periodontal and gingival disease have been affecting people for so long, it is now recognised as a major health issue. A moderate to severe type of periodontitis affects 13% of individuals over 30 and a mild form affects 22% of adults, making up the remaining 35% of adults who have the condition [3]. Controlling the bacterial population is the aim of dental treatment. The development of oral and dental illnesses can be slowed down or prevented with the control of bacterial plaque. Sub-gingival flora can be reduced by systemically delivering antibiotics, although it has been found that discontinuing such treatment might cause bacterial recolonization [4]. In light of these clear limitations, intrapocket administration of active component has attracted interest. For the implantation of a drug delivery device, a periodontal pocket offers an accessible natural reservoir. In addition, gingival crevicular fluid (GCF) serves as a leaching medium for a drug's release from the dosage form and its diffusion throughout the pocket [5]. Local delivery increases the drug's concentration at the targeted site of action while requiring a lower dose, resulting in fewer adverse effects. The dental films may offer a more effective solution to prolong the drug release for local action in order to address the drawbacks associated with the current technologies [5]. The drug release takes place by diffusion or matrix dissolution process from periodontal films in dental cavity. Various dosage forms like gels, sheet, films, delivers an accurate and effective dose of drug in dental cavity [6]. This dosage form is physiologically

MATERIAL AND METHODS

MATERIALS

advantageous for use within the pocket. It is easy to modify the shape and size of the films to fit the size of the pocket to be treated. It may be easily inserted into the base of the pocket with the least amount of

discomfort to the patient. This new approach to therapy has been shown to be more effective than traditional drug delivery systems [7].

HPMC is a hydrophilic matrix material, binder, film former, and thickening agent. There are several viscosity grades of HPMC polymers for the manufacturing of hydrophilic matrix systems, ranging from 4000-100,000 mPa s [8]. Its key characteristics include excellent film-forming ability and hydrophilic swelling capacity, which have significant effects on the integrated drug delivery and storage [9]. Doxycycline (DOX) is a tetracycline antibiotic widely recommended in the treatment of bacterial infection. DOX is significant because, as compared to other drugs, it is 7–20 times more likely to be found in the gingival crevice. Its dual mechanism of action is the second most significant factor. Its greater antibacterial efficacy against *A. Actinomycetes mcomitans* justifies its usage in cases of aggressive periodontitis [10]. Anticollagenase, anti-inflammatory effects, bone resorption inhibition and promotion of reattachment are some of another characteristics [11]. The main objective of the present research work was to manufacture, optimise and evaluate dental films of DOX with controlled release behaviour to treat periodontitis in order to administer drug precisely where it was needed and to reduce periodontal infections. Doxycycline (DOX) was purchased from Cipla Ltd. Mumbai, India, and HPMC K100, Polyvinyl alcohol (PVA), Glycerol, were purchased from Sigma Aldrich, India. Other chemicals, solvents and materials used in this study were of analytical grades.

METHODS:

STATISTICAL DESIGN OF EXPERIMENTS (DOE):

2^3 full factorial design was used in development and optimisation of approach was utilised in the development of DOX-loaded intrapocket films. The concentration of HPMC (A, mg), PVA (B, mg), and Glycerol (C, ml) were considered as independent variables which were varied at two levels (-1 and +1) while tensile strength (Y1) and *in vitro* drug release at 2^{nd} day (DR) (Y2) were considered dependent variables. The details of the variables and three levels are presented in Table 1.

DEVELOPMENT OF DOX-LOADED HPMC FILMS:

Solvent casting was used to manufacture the HPMC (K100) films with DOX loading. In order to increase the tensile strength of the films, PVA was added, and HPMC was employed as a film forming and gelling agent. 20 ml of distilled water was used to completely dissolve a weighed amount of HPMC (K100) polymer. A magnetic stirrer was used to mix the homogenous mixture with the PVA solution, which had previously been dissolved in hot water. Glycerol was added in precisely measured amounts while the polymeric dispersion was continuously stirred to create a homogenous mixture. Weighed DOX was dissolved in a tiny amount of water, added to the polymer solution, and well mixed. To allow the solvent to evaporate from the solution, this mixture was put onto a petri dish and let to stand at room temperature. The developed dental films were taken off the petri plate and stored in desiccators until needed [12]. The details of the batches in coded form are presented in Table 2.

CHARACTERIZATION OF DOX LOADED HPMC FILMS:

THICKNESS:

Thickness of the film (n=3) was measured using screw gauge at different areas of the film and the average was calculated [13].

UNIFORMITY OF WEIGHT OF THE FILMS:

Film (size of 5x5 mm) was taken from different areas of the film. The weight variation of each film was calculated [14].

FOLDING ENDURANCE

The films' folding durability was tested by repeatedly folding it at the same spot until it broke or folded, which is regarded sufficient to demonstrate acceptable film qualities. All of the films were subjected to this test [14].

DRUG CONTENT UNIFORMITY

Uniform films of $5cm^2$ dimensions were randomly cut from the different places of the film. The obtained films were dissolved separately in double distilled water under continuous stirring. The samples were filtered and analysed at 273 λmax using a UV spectroscopy and drug content was calculated [14].

MOISTURE CONTENT:

The films were precisely weighed, placed in desiccators for three days, and then reweighed to determine the percentage moisture loss [14].

$$\textbf{MOISTURE CONTENT (\%)} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} \times 100$$

TENSILE STRENGTH:

A tensile strength tester with a 5 g load cell was used to measure tensile strength. Films that met the specified dimensions and were free of physical flaws like air bubbles were held between two clamps. The

top clamp was pushed during the measurement at a speed of 0.5 mm/s, and the force applied when the film broke was recorded. We only utilised the outcomes from film samples that ruptured between the clamps [14].

IR SPECTROSCOPY:

The drug excipient compatibility was tested using IR spectroscopy. The IR spectra were obtained for DOX, HPMC and optimized film by the KBr pellet method. The IR spectra were compared and possible drug excipient interaction was determined.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES:

A small amount of sample was accurately balanced in an aluminum pan and heated from 40^0C to 400^0C, with the heating rate of 10^0C/min. DSC thermograms of pure drug, optimised formulations were recorded using DSC.

***IN VITRO* DRUG RELEASE STUDY:**

DOX release study was performed in pH 6.8 phosphate buffer (release media) which simulated with gingival fluid. The test was performed under static conditions because after application of film in pockets it will remain immobilize. Six films with 5 cm^2 area were placed separately in test tubes already filled with 1 ml of release media. The entire set up was kept at 37± 0.5 °C. The sampling of 1 ml was done at predetermined time interval and replaced with fresh buffer to maintain sink condition. Using a UV/VIS spectrophotometer, the drug's concentration was found at 273 nm. The operation was carried out for 2 days in a row [15].

ZONE OF INHIBITION STUDY USING CUP PLATE METHOD:

The suspension of the microorganisms (*Staphylococcus aureus* was prepared in the medium at a temperature between 40º C and 50º C. This inoculated medium was poured into previously sterilized Petri plates to give approximately 3 to 4 mm depth with uniform thickness. These plates were stored properly to ensure that no growth or death of the microorganisms occurred till the agar layer gets solidified. The test and standard antibiotic solution were applied in the cavities at the same volume and concentration. The plates were kept for incubation for 18 hours at 35-37^{0}C. At the end of the experiment, the zone of inhibitions was measured and compared [16, 17].

STABILITY STUDY:

The optimized formulations were kept for stability studies after wrapping with aluminium foil and butter paper at 40 ± 2°C, 75% ± 6% relative humidity for 2 months. At the end of stability studies, the samples were analysed and compared with initial results [18].

RESULTS AND DISCUSSION

PHYSICOCHEMICAL PROPERTIES OF THE DENTAL FILMS:

The developed DOX-loaded films were characterized for various physicochemical properties to check whether the formulation satisfies the requirement of the dental pocket. Table 3 describes various parameters of the DOX-loaded film.

THICKNESS:

The thickness of the films was found between 0.278 mm (F6) to 0.321 mm (F1). A wider variation was observed in film thickness that may be due to changes in polymer concentration in each batch. Considering the application site at dental pocket, films with larger size and thickness would not be appropriate. Formulations with lesser thickness that can be ideally placed at the site of application. Considering the thickness of F6 formulation it was found ideal for the application in dental pockets.

WEIGHT UNIFORMITY:

No significant weight variation was observed between the developed films. The weight of the films was ranged between 9.61 ±0.14 mg (F2) to 9.97 ±0.13 mg (F6). The lesser weight variation was due to the uniform mixing of the polymers and other excipients that resulted in to uniform denser mass of the dispersion [19].

FOLDING ENDURANCE:

Folding endurance results of dental film was found to be 254.7 ±0.21 (F2) to 295.5 ±0.14 (F6) indicating that the film would not break and would maintain their integrity with the periodontal pocket. For dental films, a higher folding endurance is highly desirable since it means the film will remain stationary and get integrated with the periodontal pocket [20]. The strength of the films is indirectly correlated with the folding endurance. The higher folding endurance was found due to the sufficient concentration of HPMC, PVA and glycerol in the formulations.

DRUG CONTENT:

For any dosage form, the uniformity of the drug content is highly desired. There was consistency in the drug content (95.21 ±0.25 to 99.11 ±0.23) throughout all batches of films that were developed. These finding suggested that the drug was dispersed uniformly throughout the polymeric matrix.

MOISTURE CONTENT:

For films, moisture content is a highly important factor. When the film is stored at room temperature, a higher moisture level in the film will encourage bacterial development. Lower moisture content films are thought to be the best formulations for preventing bacterial development [21]. It has been noted that the F6 formulation had least moisture content (2.9±0.22 %) with minimum chances of bacterial growth while F1 formulation had maximum chances due to higher moisture content of 5.2±0.26%

IR SPECTROSCOPY:

FTIR spectra of pure drug DOX reveled characteristic peaks at 1500 cm^{-1} corresponding to (CO-NH) group, 1659 cm^{-1} corresponding to (C=O) group, 3000 cm^{-1} corresponding to (C-H) group, 3262 cm^{-1} corresponding to (N-H) group and 3488 cm^{-1} corresponding to (O-H) group. The final optimised formulation F6 also showed all these characteristic peaks of DOX which indicates the absence of any physical as well as chemical incompatibility between DOX and other excipients. The comparative IR spectra of DOX, HPMC and DOX loaded films is presented in Figure 1.

DSC ANALYSIS:

The DSC analysis of the pure DOX showed endothermic peak at 206.09 °C corresponding to its melting point while DOX loaded films showed endothermic peak at 205.73 °C (Figure 2). From the DSC thermograms, it was observed that the DOX did not interact with other excipients present in films indicating good compatibility.

STATISTICAL ANALYSIS OF TENSILE STRENGTH (Y2):

The tensile strength of the films is very important parameters that need to considered during development of film formulations [22]. Glycerol was used as plasticiser in the formulations that contributed in the development of tensile strength. The results of the tensile strength of all the formulations are presented in Table 4 along with the coded levels of the dependent variables.

The tensile strength was varied between 0.625±0.15 (F1) to 0.987±0.15 (F6) Kg/cm^2. The tensile strength was directly related to the HPMC and PVA concentration utilised in the films. The higher polymer concentration might have increased the viscosity of the dispersion leading to the improvement in the tensile strength. In addition, glycerol being excellent plasticiser had also contributed to improve the tensile strength and provided plasticity, flexibility and prevented the breakage of the films [23]. Also, it prevented the brittleness of the film. The effect of independent variables on tensile strength is presented in Figure 3.

The polynomial equation for tensile strength (Y1) can be presented below

$$Y1 = + 47.21+3.37A+17.35B+0.47C \quad \ldots\ldots\ldots\ldots (1)$$

In this polynomial equation Y1 is Y1 is tensile strength, A is HPMC concentration, B is PVA concentration and C is glycerol concentration which are independent variables used in formulation development. All these independent variables showed statistically significant effect on tensile strength with $p< 0.05$. The model was also found to be statistically significant with F value of 0.0033. The 2FI model was suggested for Y1 as shown in Table 5. The correlation coefficient (R^2) was found to be 0.9890 for Y1 indicating a good fit model of 2FI.

The model for Y1 was found to be statistically significant based on the *p*-value of 0.0009. The effect of independent variables was also found to be statistically significant based on the *p*-value shown in Table 6.

STATISTICAL ANALYSIS OF DRUG RELEASE ON THE 2 ND DAY (Y2):

The drug release study was conducted in pH 6.8 phosphate buffer for the period of 2 days. At the end of 2 days, the drug release was found to be in the range of 68.74 (F7) to 97.24 % (F8). The comparative drug release profile of all the formulations is presented in Figure 4.

It has been observed that F6 formulation with higher amount of HPMC and PVA showed excellent drug retarding property in comparison to other formulations [24]. The effect of drug release was found to be concentration dependent. It was observed that, plasticiser in the form of glycerol at lower concentration helped to retard the drug release form the formulation (Figure 5).

The polynomial equation for DR (Y2) can be presented below

$$Y2 = +82.17+2.97A+12.46B+0.87C \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

In the above equation, Y2 is DR at 2 days, A is HPMC concentration, B is PVA concentration and C is glycerol concentration which are independent variables used in formulation development. All these independent variables showed statistically significant effect on DR with $p< 0.05$ (Table 6). The model was also found to be statistically significant with F value of 0.027. The 2FI model was suggested for Y2 as

shown in Table 5. The correlation coefficient (R^2) was found to be 0.9887 for Y1 indicating a good fit model of 2FI.

ZONE OF INHIBITION (ZOI)STUDY:

In the ZOI study, films produced with different concentrations of pure DOX and the effects on *Staphylococcus aureus* were examined. When compared to pure DOX, it was found that HPMC films that had been loaded with DOX had a larger zone of inhibition. Figure 6 shows a comparable graphical presentation of the ZOI. Figure 7 displays the ZOI of films with pure DOX and films loaded with DOX to show the true antibacterial effect.

Table 1: Variables and levels

Variable	(-1) Low level	(+1) High level
Independent		
A= HPMC	10 (mg)	20 (mg)
B= PVA	5 (mg)	10 (mg)
C= Glycerol	2 (ml)	4 (ml)
Dependent, Y1= Tensile strength, Y2 = % DR at 2 nd day		

Table 2: Formulation batches of DOX-loaded HPMC films in coded form

Batch	Factor		
	A	***B***	***C***
F1	+1	+1	+1
F2	+1	-1	+1
F3	+1	-1	-1
F4	-1	+1	+1
F5	-1	+1	-1
F6	+1	+1	-1
F7	-1	-1	+1
F8	-1	-1	-1

Table 3: Physicochemical properties of the DOX-loaded dental films

Batch	Thickness (mm)	Weight Uniformity (mg)	Folding endurance	Drug content (%)	Moisture content (%)
F1	0.321	9.67±0.10	267.1 ±0.11	97.24 ±0.55	5.2±0.26
F2	0.304	9.61 ±0.14	254.7 ±0.21	95.22 ±0.63	4.8±0.72
F3	0.299	9.61 ±0.27	269.4 ±0.31	98.11 ±0.24	4.5±0.11
F4	0.300	9.70 ±0.12	274.3 ±0.25	96.18 ±0.51	4.3±0.21
F5	0.316	9.74 ±0.11	286.4 ±0.55	97.81 ±0.72	4.3±0.26
F6	0.278	9.97 ±0.13	295.5 ±0.14	99.11 ±0.23	2.9±0.22
F7	0.302	9.41 ±0.19	267.2 ±0.24	95.26 ±0.21	4.1 ±0.27
F8	0.309	9.65 ±0.65	277.3 ±0.28	95.21 ±0.25	3.9 ±0.12

Table 4: DOX loaded films with coded form and their responses

Batch	Factor			Response	
	A	B	C	Y1 (kg/cm²)	Y2 (%)
F1	+1	-1	+1	0.625±0.15	89.16
F2	-1	-1	+1	0.721±0.21	94.25
F3	+1	-1	-1	0.711±0.22	90.81
F4	-1	+1	+1	0.645±0.28	89.87
F5	-1	+1	-1	0.767±0.20	92.11
F6	+1	+1	-1	0.987±0.15	68.74
F7	+1	+1	+1	0.745±0.24	75.24
F8	-1	-1	-1	0.667±0.11	97.24

Table 5: Statistical analysis of responses Y1 and Y2

Model	R^2	Adjusted R^2	Predicted R^2	Std. Dev	Press	Remarks
Response Y1						
Linear	0.8082	0.8087	0.6521	5.16	525.21	……
2FI	**0.9992**	**0.9726**	**0.7224**	**4.21**	**511.52**	**Suggested**
Quadratic	0.8921	0.8645	0.6924	0.33	480.51	
Cubic	0.8483	0.8221	0.6326	0.31	294.67	……
Response Y2						
Linear	0.5024	0.4947	0.2715	4.11	100.26	……
2FI	**0.9887**	**0.9227**	**0.5545**	**1.46**	**178.26**	**Suggested**
Quadratic	0.8726	0.8251	0.8116	4.45	121.42	……
Cubic	0.8590	0.8111	0.7926	5.23	116.45	……
Regression equations of the fitted models						
Y1 = **+ 47.21+3.37A+17.35B+0.47C**						
Y2 = **+82.17+2.97A+12.46B+0.87C**						

Table 6: ANOVA of models for Y1 and Y2

Source	DF	Sum of squares	Mean Square	F Value	P value
Model for Y1	3	2020	400.27	16.89	**0.0009**
A	1	70.24	75.26	0.99	0.0169
B	1	1726.45	1945.11	69.25	0.0189
C	1	1.3	1.87	0.012	0.0021
Model for Y2	4	221.56	64.21	12.87	**0.0215**
A	1	17.45	11.34	2.17	0.0126
B	1	201.67	200.24	32.11	0.0078
C	1	12.24	11.87	2.89	0.0216

Table 7: Comparative physicochemical parameters of film stored at 2 M (40 ºC ± 2 ºC/75% ± 5 %)

Sr. No	Parameter	Initial	2 M (40 ºC ± 2 ºC/75% ± 5 %)
1	Thickness (mm)	0.278	0.285
2	Weight Uniformity (mg)	9.97 ±0.13	10.12 ±0.22
3	Folding endurance	295.5 ±0.14	311.2 ±0.25
4	Moisture content (%)	2.9±0.22	3.4±0.26
5	Drug content (%)	99.11 ±0.23	98.45 ±0.11
6	Drug release (%) at 2 days	68.74	72.17

Figure 1 : FTIR spectra of (A): Pure DOX; (B): HPMC; (C): DOX loaded films

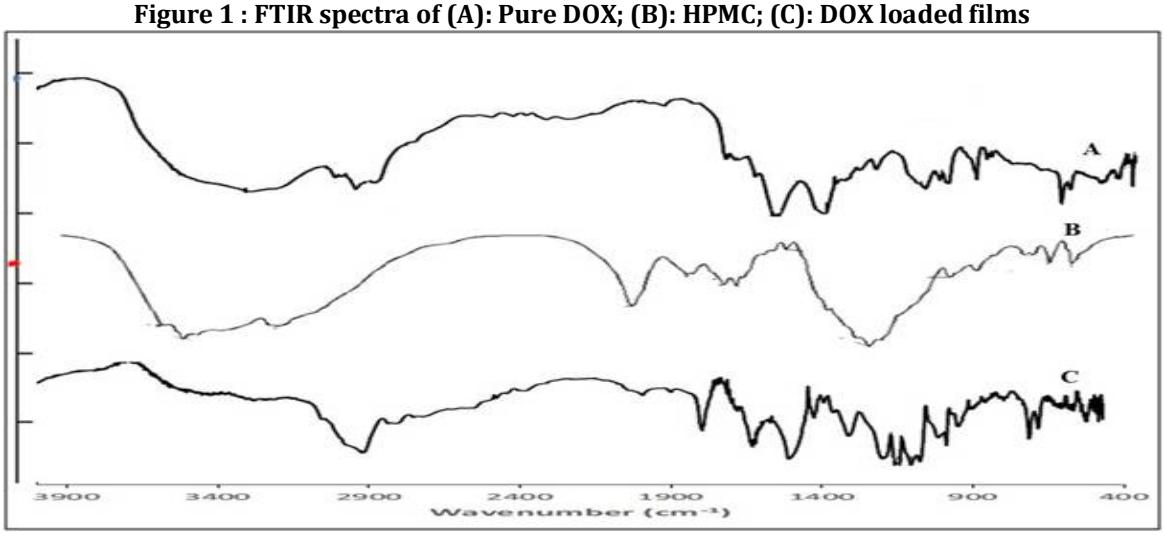


Figure 2: DSC analysis of (A): Pure DOX and (B): Dox loaded films

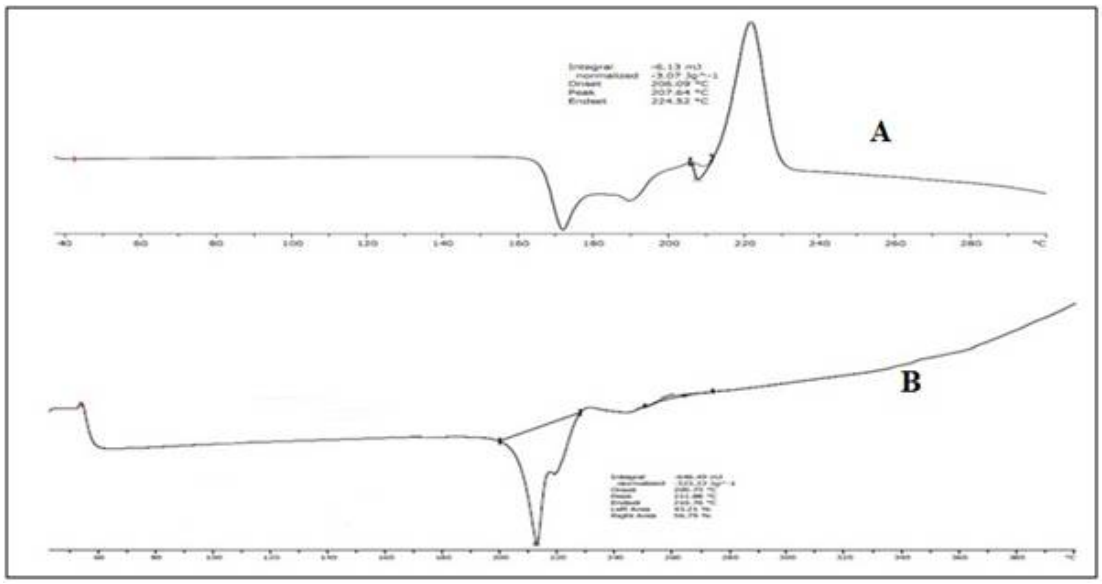


Figure 3 : 3D surface responses of HPMC, PVA and Glycerol on tensile strength

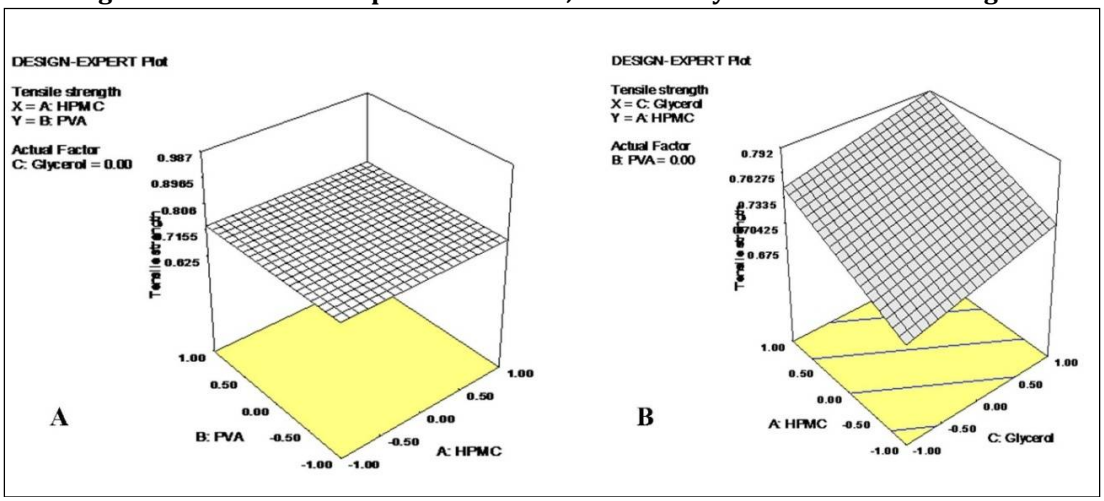


Figure 4 : Comparative % DOX release at 2 days in phosphate buffer pH 6.8

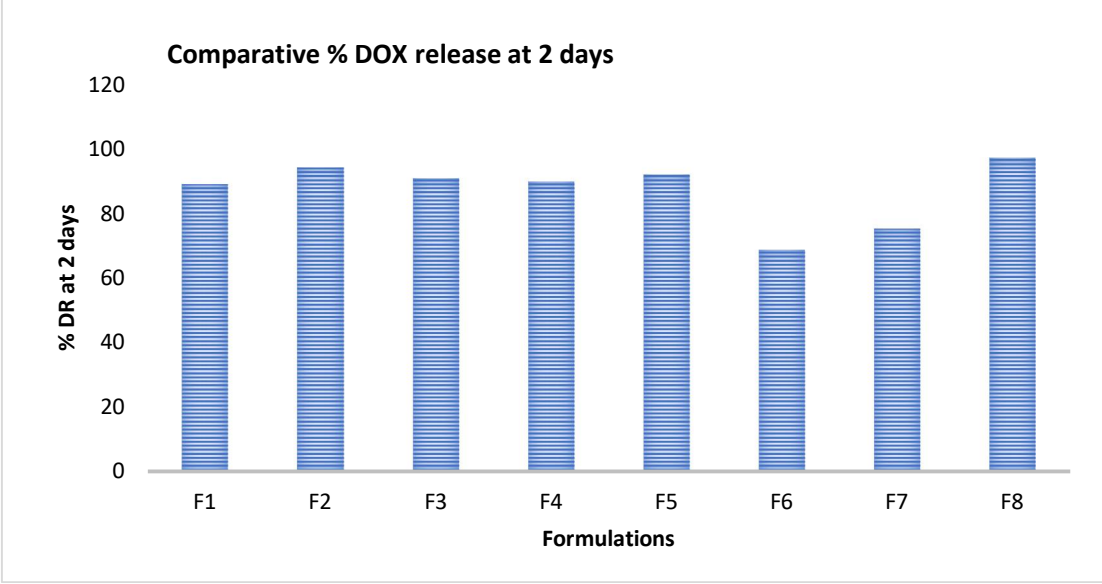


Figure 5 : 3D surface responses of HPMC, PVA and glycerol on % DR

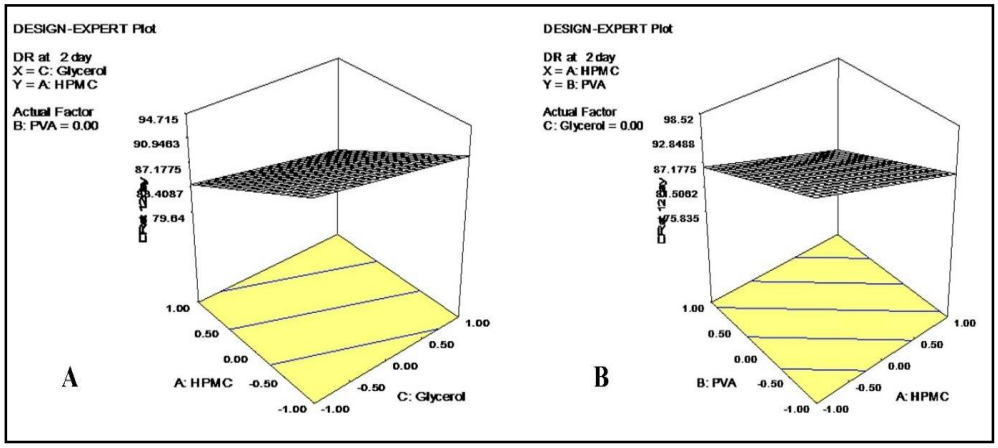


Figure 6 : Comparative ZOI of pure DOX and DOX loaded chitosan films

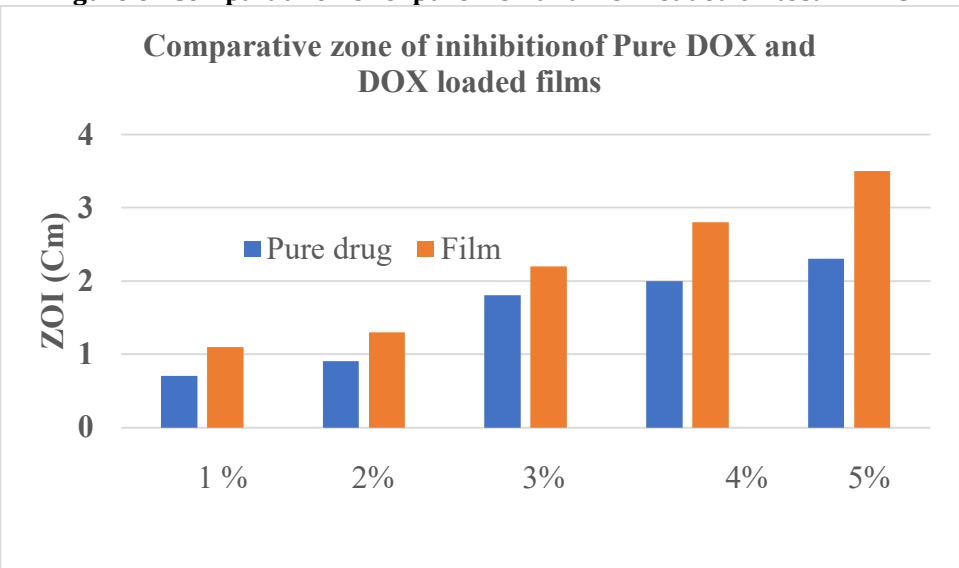
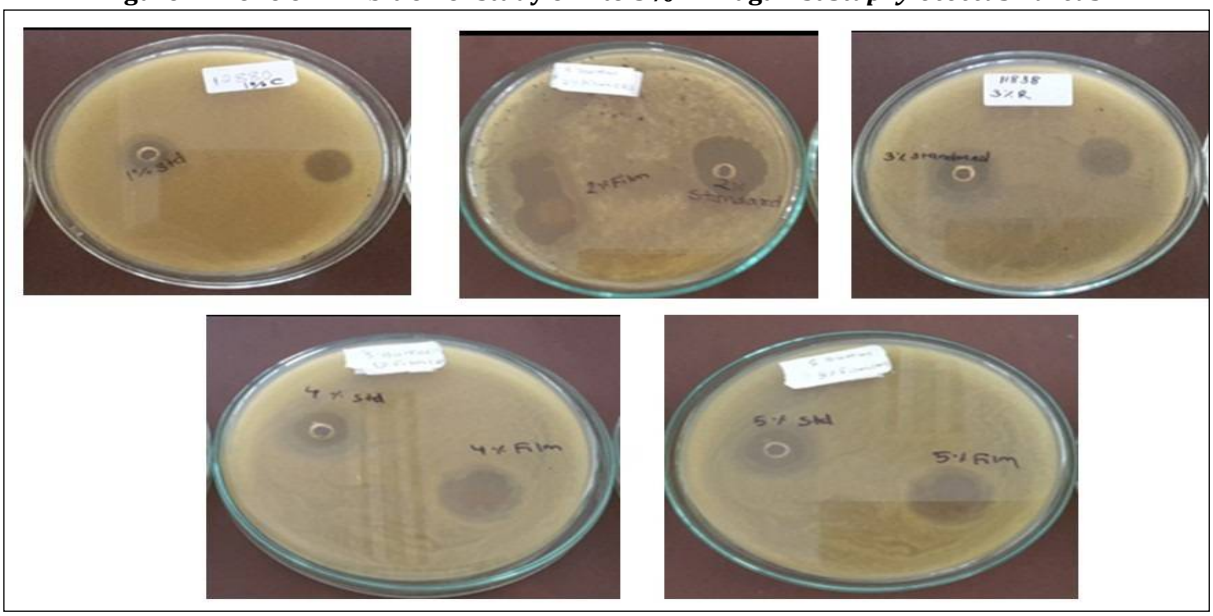


Figure 7 : Zone of inhibition of study of 1 to 5% film against *Staphylococcus Aureus*



STABILITY STUDIES:

For two months, the optimised formulation was stored at 40 ºC ± 2 ºC/75% ± 5 % for stability testing. The physiochemical properties that were assessed after two months of storage did not reveal any

significant change. In Table 7, the comparison parameters are shown. The outcomes showed that the developed films had outstanding stability [25].

CONCLUSION

The study support the use of Doxycycline in films developed using HPMC, PVA, and glycerol as polymer and plasticiser respectively. The physicochemical properties of the films were found to be suitable for application in dental cavity. The DOX release was found to be in sustained manner. *Staphylococcus aureus* were successfully eradicated by the DOX-loaded films. While being kept under acclerated stability conditions, the drug did not chemically interact with the excipients. Future uses for this newly developed film in the treatment of peridontitis may be possible.

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