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DESIGN AND EVALUATION OF BILAYERED MUCOADHESIVE FILM OF CEFPODOXIME PROXETIL

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Keywords:

Hydroxypropyl Methyl cellulose, Ethyl cellulose, bio-adhesion, *In-vitro* studies, *Ex-vivo* studies

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ABSTRACT: The objective of the present work was to formulate and evaluate a sustained release gastroretentive dosage form. A mucoadhesive bilayered film was prepared consisting of an Immediate Release (IR) and a Controlled Release (CR) layer. The film is folded into a Hard Gelatin Capsule which after administration into GIT unfolds and adheres to the GI mucosa. Cefpodoxime Proxetil is an antibiotic of BCS Class IV. Thus by retaining the drug in the gastric region its absorption is enhanced. Hence it is taken as the model drug. Different polymers like HPMC, EC and Carbopol were used for the film preparation and the mucoadhesive property was evaluated which showed that Presence of Carbopol increases the films mucoadhesive property. The in vitro drug release, bio-adhesion and mechanical property of the batches were evaluated to get the best batch. The optimization study of the film was carried out applying 3^2 factorial design. The final batch is subjected to In *vivo* gastroretention test on rabbits which showed a gastric adherence for 12hrs.

INTRODUCTION: The oral route of drug administration, although has many advantages, suffers from the limitation for dugs with short half-life. Due to the fast elimination of the drug from the gastric region there is an increase dosing of the drug. This problem can be answered by formulation of gastroretentive drug delivery. The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several types of gastroretentive drug delivery systems, such as intragastric floating systems, swelling and expandable systems, bioadhesive systems, modified shape systems, high density systems, delayed gastric emptying systems and low density super porous systems.

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The technique applied in this article involves the formation of a bilayered mucoadhesive film for sustained release of the drug [1, 2, 3].

In this, the dose of the drug is so divided that initial loading dose is incorporated in to an immediate releasing layer and the rest of the dose is put in to a sustain release layer.

The bilayered film is folded and incorporated into hard gelatin capsule for administration. When the capsule reaches the gastric region, it dissolves in the acidic environment and the film is free to unfold. On unfolding it goes and adheres to the gastric mucosa. The mucoadhesive polymer is incorporated in the sustain release layer so that the immediate release layer is freely exposed to the gastric fluid and releases the drug quickly [4, 5].

Cefpodoxime Proxetil is used as the model drug. Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic β- lactum

antibiotic of cephalosporin class. Cefpodoxime proxetil is prodrug; its active metabolite is cefpodoxime. After oral administration cefpodoxime proxetil is absorbed from the gastrointestinal tract and de-esterifies to active metabolite cefpodoxime. Over the recommended dosing range (100 to 400 mg), only the 50% of administered cefpodoxime dose was absorbed systemically. Also the drug has only 2 to 3 hours half-life. The mucoadhesive film will be able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil [6].

MATERIAL AND METHOD:

Material: Cefpodoxime Proxetil was provided as a gift sample from CIPLA Pvt. Ltd, Mumbai, India. The Polymers Hydroxypropyl methyl cellulose K 15 M (HPMC K15 M) and Ethyl Cellulose (EC) was obtained as gift sample from Colorcon Pvt. Ltd, Goa. Soluphor was provided as gift sample from BASF chemicals. All other ingredients used were of Pharmaceutical grade. The Animal study Protocol was passed by the College animal ethical committee. The protocol no. is IAEC/PECU-04/2013.

Method of preparation: The mucoadhesive film was prepared by using solvent casting method. The preparation of the film is divided into two steps i.e. preparation of immediate release layer (Solution I) and preparation of sustained release layer (Solution II). Once the two solutions are prepared they are poured in to the glass moulds one after the other and allowed to dry for 1hr at 60^{o}C in the oven.[4]

Solution I: A 12% Polyvinyl Alcohol (PVA) solution in water was prepared and the 0.5ml of Polyethylene Glycol 400 was added to it. In a test tube 2.5ml of soluphore is taken and required amount of drug is dissolved in the same. When the PVA solution becomes clear then the drug solution in soluphore is added to it.

Solution II: The polymeric dispersions of the different polymers were prepared (Table 1) in corresponding solvent phase. To this drug solution in soluphore and isopropyl alcohol with 0.5ml PEG was added. The final solution is sonicated to get a uniform solution.[7]

TABLE 1: FORMULAE OF SUSTAINED RELEASE LAYER

Batches	Polymers	Ratio	Organic solvent
M1	HPMC	5%	IPA : Water (3:1)
M2	HPMC: Carbopol	2.5%:2.5%	HPMC – IPA: Water (3:1) Carbopol – Water Then mix with stirring
M3	HPMC:EC	1%:1%	Ethanol: DCM: IPA (1:1:1)
M4	HPMC: EC: Carbopol	1%:1%:1%	HPMC - Ethanol: DCM: IPA (1:1:1) Carbopol – Water Then mix with stirring

HPMC – Hydroxy Propyl Methyl Cellulose; EC – Ethyl Cellulose; IPA – Isopropyl Alcohol; DCM – Dichloromethane

Solvent casting: The solution II is first added to a glass petri plate and allowed to firmly set for 30mins at 40^{o}C. Then solution I is added above it to form a uniform layer. This plate is then dried in oven for 1hr at 60^{o}C. Once the film is completely dried it is cut into size of 4 x 1 sq. cm, folded and put into a Hard Gelatin Capsule of size 0[4, 5] as shown in **Figure 1**.

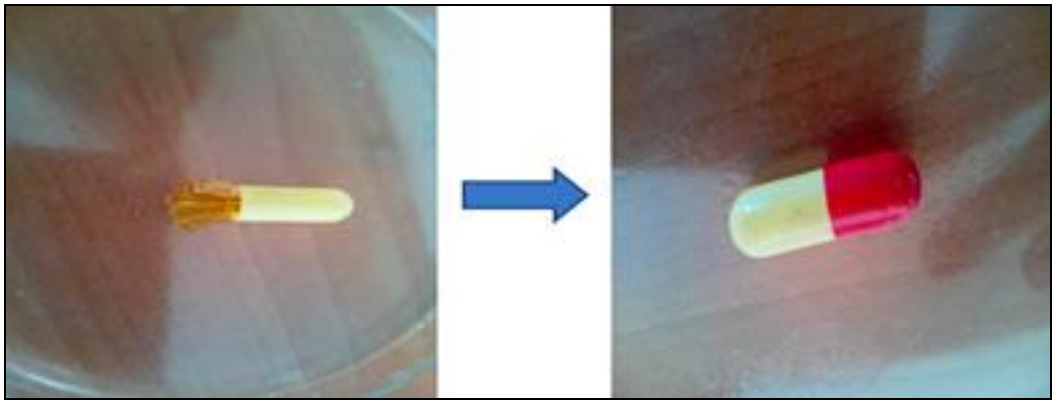


FIGURE 1: FILM FOLDED INTO HARD GELATIN CAPSULE

Optimization Studies: First, a screening approach based on factorial design was used to select the factors displaying the most effects on the Bioadhesion properties of the film. A 3^3 full factorial design was studied on the present formulation. The three obtained factors were: Concentration of HPMC (Factor A), Concentration of EC (Table B) and Concentration of Carbopol (Factor C), which were selected as independent variables (**Table 2**). Then, these factors were investigated according to a response surface, the bioadhesion properties, to optimize preparation (**Table 3**). The experimental results were analysed using Design Expert® software [8, 9, 10, 11].

TABLE 2: 2^3 FULL FACTORIAL DESIGN STUDY LAYOUTS; CODED FORMAT

Batches	Factor A	Factor B	Factor 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: 2^3 FULL FACTORIAL DESIGN STUDY LAYOUT; ACTUAL QUANTITIES:

Batches	Factor A	Factor B	Factor C
F1	100	100	100
F2	100	100	300
F3	100	300	100
F4	100	300	300
F5	300	100	100
F6	300	100	300
F7	300	300	100
F8	300	300	300

Characterization of the Films:

1. **Preformulation studies with FTIR and DSC evaluation [12]:**

   i) **Compatibility Studies**: The drug and excipient compatibility study was conducted by using FTIR and DSC techniques.

   ii) **UV Spectroscopy**: The drug was scanned in UV Spectrophotometer to detect the λmax of the drug and to draw the concentration curve of the drug. The drug was used in the concentration range of 0- 25 ppm.

2. **Drug content:** Accurately cited 2cm diameter of the films taken and dissolved in suitable and constant volume of solvent. The prepared solutions were analyzed by using UV –Visible spectrophotometer [4].

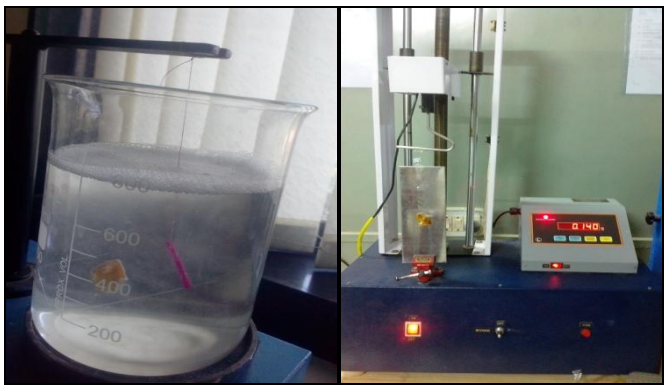
3. **Film Thickness:** The thickness of the prepared films was determined by means of micrometer. The thickness of four films was measured and the average thickness was determined.

4. **Folding endurance:** Three films of each formulation of size (1×4 cm) were cut by using sharp blade. Folding Endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance [4, 13].

5. **Unfolding study:** The unfolding study of the bilayered film was conducted in USP Type-I dissolution apparatus. The capsule is placed in the basket, on immersion into the medium of pH 1.2 the capsules dissolve and then the unfolding of the inner film was observed.

6. **Swelling behaviour:** The swelling behaviour of the sustain release layer was evaluated by allowing it to swell till constant weight is attained in a medium of 1.2 pH buffer [4].

7. **Retention time:** The CR side of a film was applied to freshly prepared rat stomach mucosa fixed to a glass slide with cyanoacrylate glue and suspended from a disintegrating apparatus **DBK Instrument (DBK 502917).** The slide was suspended in a beaker filled with 900mL aqueous hydrochloric acid pH 1.2 and moved vertically in and out of the medium by switching on the motor. The experiment was continued until the film detached or eroded from the mucosa (**Figure 2a**).



a **b**

FIGURE 2: A. RETENTION TIME EVALUATION BY DISINTEGRATION APPARATUS, B. BIOADHESION TEST

8. Bioadhesion tests:

a. ***In-vitro*** **Test:** Bioadhesion of the CR layer of the film to stomach mucosa was evaluated in triplicate using the stomach mucosa of Wistar rats. The bioadhesion was checked using the Peel Adhesion Tester (Lemi Coat Equipment) with the concept of 180^{o} shear stress = (**Figure 2b**). The film and the mucous membrane was kept in contact with each other for 3-5mins and then the machine was switched on to get the weight required to detach the film from the membrane (Bioadhesive Strength) [4]. The force of adhesion was calculated using the formula:

Force of adhesion (N) = (Bioadhesive strength / 1000) x 9.81

b. ***In-vivo*** **bioadhesion test:** In vivo methods are more meaningful than in vitro test as they provide a more realistic picture of expected behaviour. In vivo gastric retention time is determined by X-ray technique in rabbits. For *in vivo* study, barium sulphate containing mucoadhesive films were prepared by the same method as described in the formulation. In this case drug was replaced by barium sulphate. For *in vivo* retention study, the rabbit was overnight fasted and on the next day morning the film in capsule was administered orally followed by giving 25ml water.

X- Ray photographs were taken at different time intervals like 0hrs, 6hrs and 12hrs. The Animal study Protocol was passed by the College animal ethical committee. The protocol no. is IAEC/PECU-04/2013. X-ray photos revealed the nature and position of film upto 12hrs [14, 15].

9. **Mechanical test:** Mechanical properties of films free of physical defects were determined in triplicate using Lemi Coat tester. Rectangular samples of film (30mm_5 mm) were subjected to analysis based on ASTMD-882.

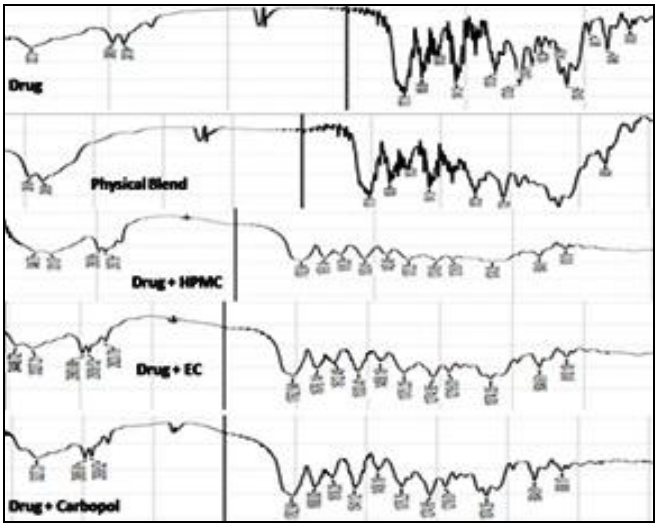
The films were carefully placed between the two vertical grips of the tester and the movable grip then driven upward at5mm/ min until the film ruptured.

From the recorded load-extension profile, the tensile strength, percent elongation at break and Young's modulus were calculated [12].

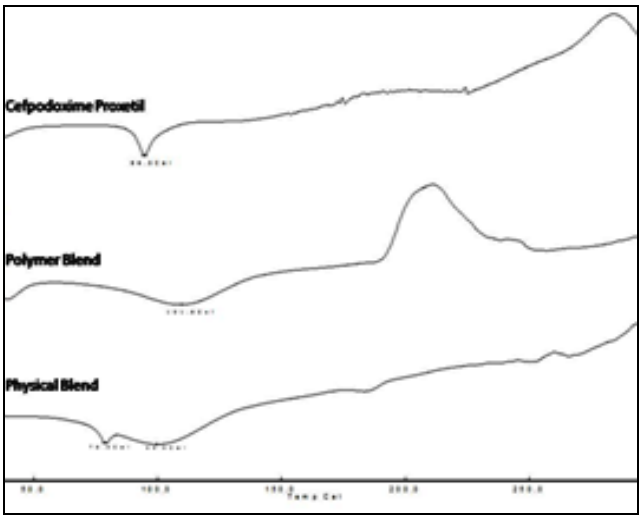
10. ***In-vitro*** **drug release:** Dissolution studies were carried out for all the formulations, employing USP XXIII apparatus (Basket method) at 37 ± 0.5°C rotated at constant speed of 75 rpm using 900 ml of pH1.2 buffer with 0.05% SLS as the dissolution medium. An aliquot of the sample was periodically with drawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analyzed spectrophotometrically [4].

RESULTS AND DISCUSSIONS:

1. **Preformulation studies:** The compatibility of drug and polymers were tested using FTIR (Figure.3.a) and DSC (Figure.3.b) techniques.



A



B

FIGURE 3: A. FTIR OF DRUG AND EXCIPIENTS B. DSC FOR EXCIPIENT COMPATIBILITY

The graphs showed no signs of incompatibility between drug and polymers. Also the calibration curve was constructed using a concentration range of 1-25 ppm at λ_{max} of 263nm. The equation was found to be y = 0.033x - 0.001 and the Regression Coefficient R^2 = 0.999 (**Figure 4**).

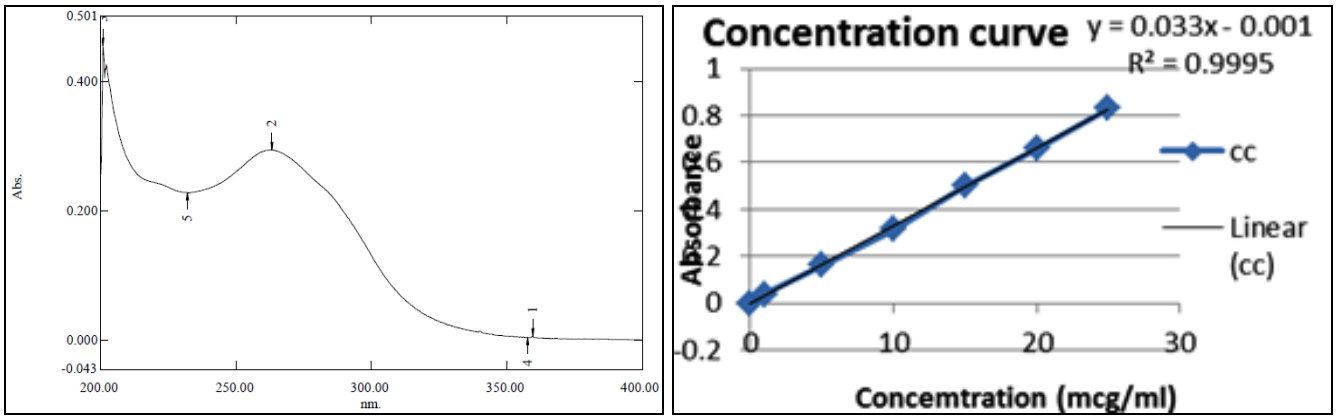


FIGURE 4: SPECTRUM OF CEFPODOXIME PROXETIL AND CONCENTRATION CURVE

2. **Property of the film:** All the basic formulation criteria were evaluated and were found to give acceptable results. Batch M4 gave the least folding endurance but had a very good swelling behaviour. All the batches had an *in vitro* and *in vivo* retention time of more than 10hrs (Table 4).

TABLE 4: PROPERTIES OF THE FILM OF THE BATH M1-M4

Batch	Drug content (% ± SD)	Thickness (mm)	Folding strength	Swelling behaviour (%)	Retention time (hrs)
M1	82.13 ± 0.721	1.4 ± 0.23	290.0 ±3.3	123.5 ±16.12	>10
M2	73.7 ± 0.932	1.54± 0.65	236.8 ± 11.2	145.2±21.1	>10
M3	80.34 ±0.573	1.47 ±0.4	205.3 ±8.5	132.4±22.2	>10
M4	84.6 ±0.765	1.53 ±0.66	167.9 ±6.3	165.7±23.4	>10

3. **Unfolding behaviour:** The films of all the 4 batches were inserted in the capsule. They gave a good unfolding action once the capsule was completely dissolved. Thus the sustained release layer can then goes and attach to the stomach mucosa (**Figure 5**).

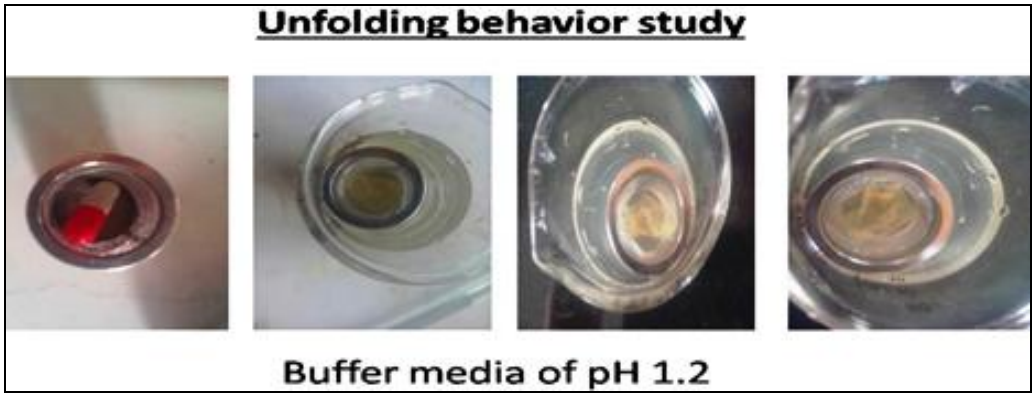


FIGURE 5: UNFOLDING BEHAVIOUR STUDY

4. **Bioadhesion test:** The Batch M2 and M4 which had Carbopol in there formulation gave good bioadhesive strength. Among these batches batch M4 was selected for optimization studies to get the desired bioadhesive strength. The batch M3 which has Ethyl cellulose in the formula gave very poor bioadhesive strength. The optimized batch was tested for *in vivo* bioadhesion is shown in **Figure 6, 7**.

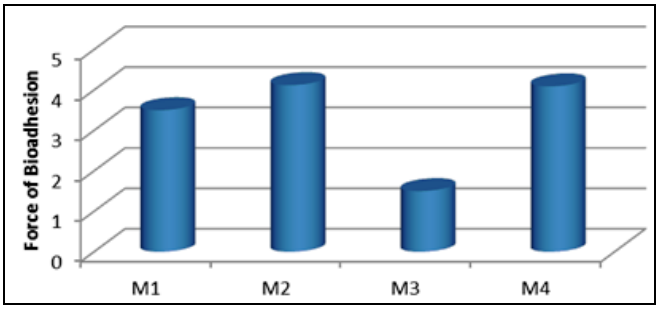


FIGURE 6: BIOADHESIVE STRENGTH OF THE BATCHES

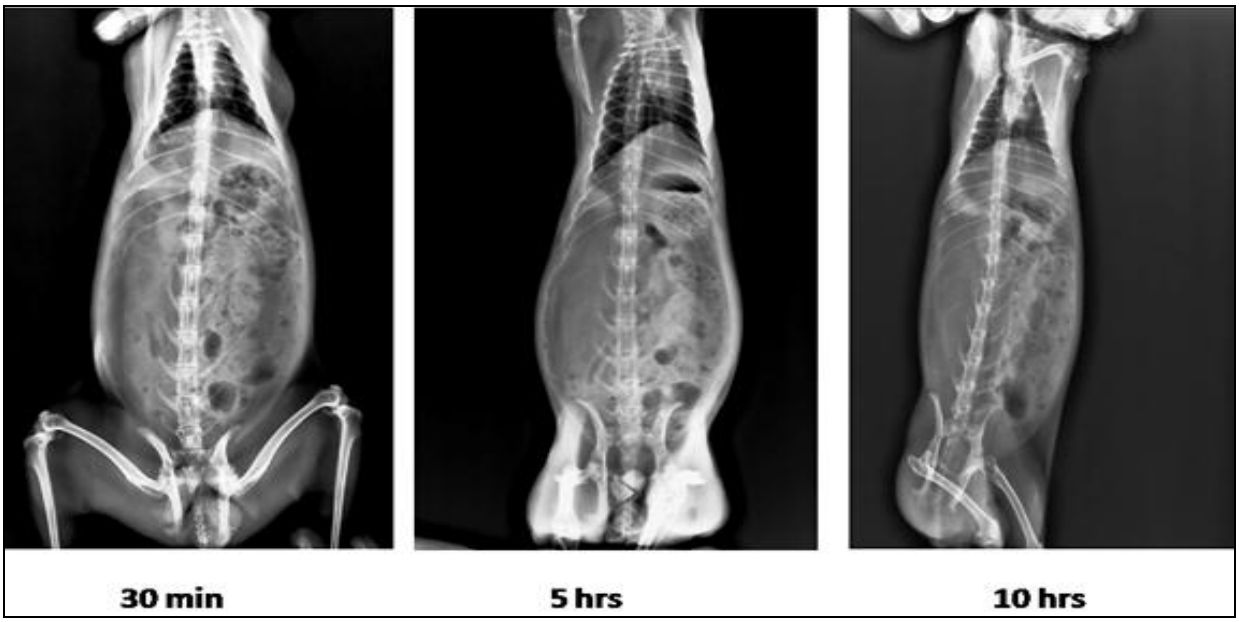
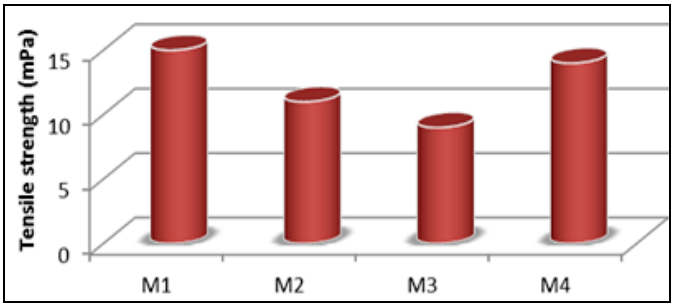


FIGURE 7: *IN VIVO* BIO ADHESION OF THE OPTIMIZED BATCH

5. **Mechanical properties:** The mechanical properties of the film were tested using the parameters like tensile strength, Young's modulus and the deformation at break. The factors are compared using graphical representation (**Figure 8**).



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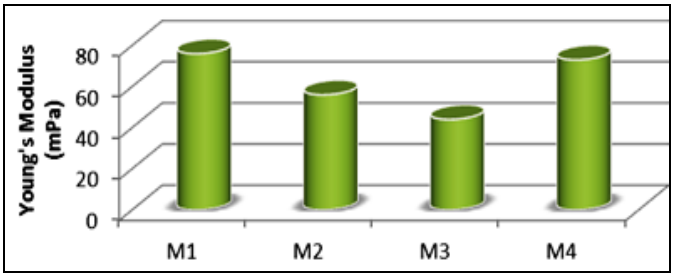

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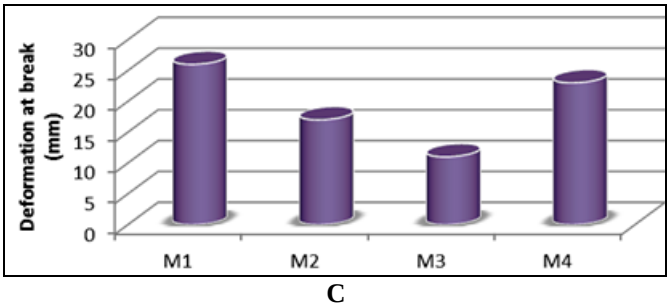


C

FIGURE 8: MECHANICAL PROPERTY OF THE FILM. A: Tensile Strength; B: Young's Modulus; C: Deformation stress

6. **Drug release profile:** After the optimization process of bioadhesion the batches were subjected to *in vitro* drug release evaluation. The batches M1, M2, M3 and M4 were also studied to see the release profile of formulation. Also the release was compared to the conventionally available marketed dosage form. (**Figure 9**).

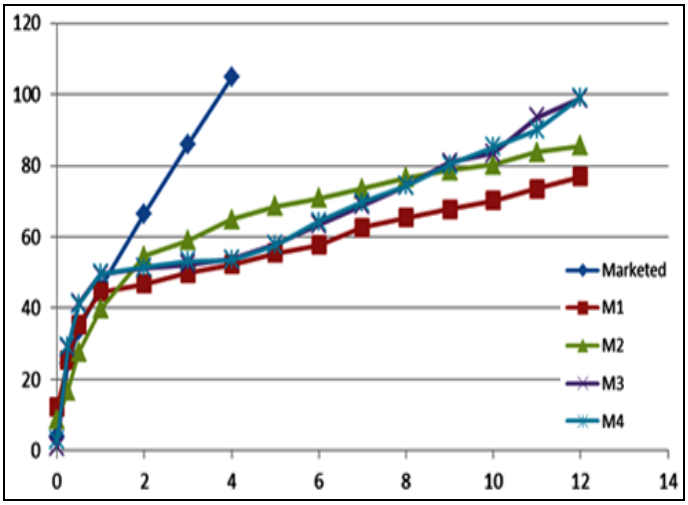


FIGURE 9: DISSOLUTION PROFILE OF THE BATCHES

It can be seen in the above graph that the conventional dosage form releases the entire drug content within the first 3-4 hrs of the study but all the formulations show a sustained drug release.

The first 50 % of the drug is released within one hour and then the rest of the drug in the sustained release layer slowly releases the drug.

The batch M1 gave comparatively slower drug release and at the end of 12 hrs only 80% drug was only released. The Batches M3 and M4 gave a desired drug release of 100% by the end of 12hrs and hence it is considered to be the optimised formulation.

The drug release result of batch M4 was fitted in the different drug release mechanisms to check the release profile of the formulation (**Table 5**).

TABLE 5: KINETIC PROFILE OF THE DRUG

Profile	M1		M2		M3		M4	
	Equation	R^2	Equation	R^2	Equation	R^2	Equation	R^2
Zero order	y = 4.437x + 30.60	0.82	y = 6.307x + 28.28	0.81	y = 5.669x + 30.02	0.79	y = 5.677x + 30.44	0.80
First order	y = 0.033x + 1.550	0.79	y = 0.051x + 1.497	0.67	y = 0.035x + 1.586	0.85	y = 0.035x + 1.588	0.85
Higuchi model	y = 0.133x + 1.443	0.89	y = 0.211x + 1.317	0.82	y = 0.136x + 1.482	0.90	y = 0.137x + 1.482	0.90
Korsemeyer-Peppas	y = 0.24x + 1.593	0.95	y = 0.395x + 1.548	0.95	y = 0.238x + 1.639	0.90	y = 0.239x + 1.641	0.91

From Table.5 we can conclude that the formulation follows Korsemeyer- Peppas dissolution profile. From all the equation we can see that the value of n< 0.5; hence we can conclude that the drug release follows Fickian Diffusion mechanism.

7. **Optimization process:** The optimization study of the formulation was carried out using Design Expert software. Statistical model of interaction and polynomial terms were generated for the response variable. The 3D response curve, 2D contour plot and the Cube design were also generated.

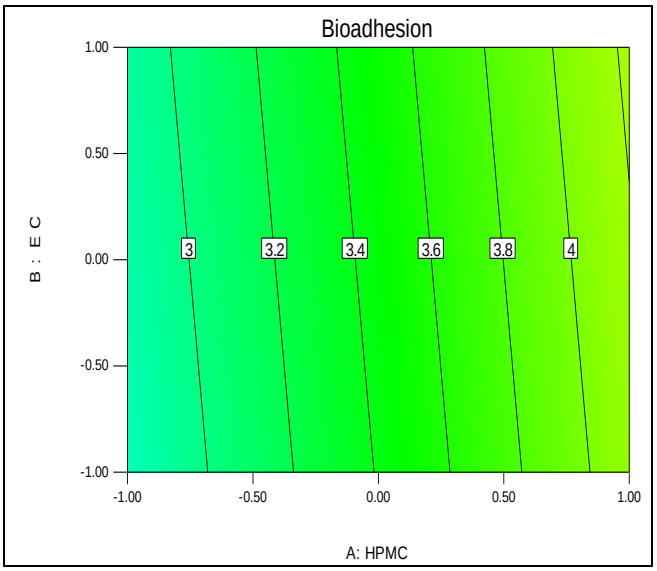
The equation derived for the % Entrapment efficiency of the factorial formulations is:

Bioadhesion = 1.24+ 0.188 A + 0.014 B + 0.355 C

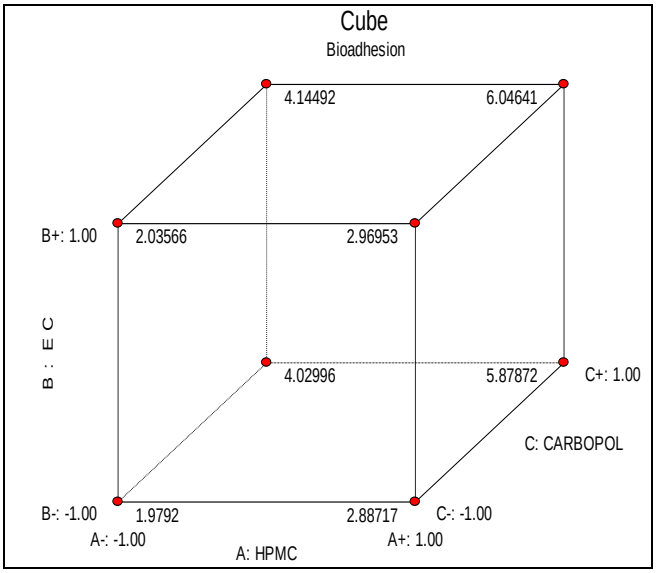
Where; A= Concentration of HPMC; B= Concentration of EC; C = Concentration of Carbopol

From the above equation we can predict that the factor A and C have a significant effect on the bioadhesive strength of the film, as the co-efficient of factor B is comparatively very small. Also as the terms have a positive value thus it is confirmed that they have direct correlation with the bioadhesive strength of the film i.e. the bioadhesive strength will increase with the increase in the concentration of the polymers.

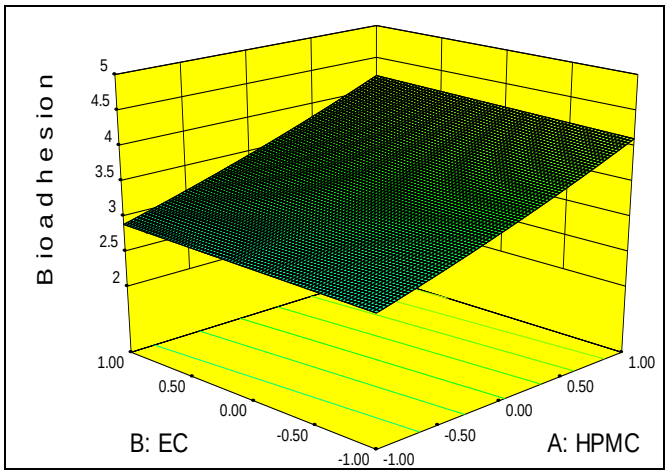
The effect of the independent variable on the dependent response of bioadhesive strength is shown in **Figure 10a, 10b, 10c**.



10a



10b



10c

FIGURE 10: OPTIMIZATION STUDY DETAIL. 10a: 3D- Surface Plot; 10b: Cube design; 10c: Contour Plot

CONCLUSION:

The bilayered mucoadhesive film of Cefpodoxime proxetil was formulated by solvent casting method. It was subjected to various evaluation parameters. The Batch M4 with HPMC, EC and Carbopol showed the best results and was thus selected for optimization studies. The batches were optimized to get the best bioadhesion strength. The film with zig-zag folding undergoes appropriate unfolding and expansion in acidic media which, combined with good bioadhesion, indicates the gastroretentive potential of the dosage form.

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