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Evaluation of Wound Healing Activity by Mupirocin Loaded Polymer Composite Film

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ABSTRACT

For the evaluation of the wound healing activity polymer composite films were prepared by using Chitosan and in combination with Sodium CMC with and without glutaraldehyde were prepared by solvent casting method. Mupirocin was incorporated into selected polymeric films. All the polymeric composite films were characterized by IR study suggested that there was no chemical reaction has taken place, only ionic complexes were formed. All the films were evaluated for thickness, folding endurance and tensile strength. The thickness of all the films was uniform,The folding endurance suggested good flexibility of the films as propylene glycol was used as a plasticizer, Films shown good tensile strength necessary for better handling . The water vapour penetration suggested that films without cross linker absorbs more moisture compared to films containing cross linking agent. The presence of cross linking agent shown optimum bio-adhesion. All the polymer composite films were evaluated for *in vitro* swelling study. The films showed good swelling in water more than 6 hrs retaining the shape of the films. The addition of cross linking agent decreased the swelling. Selected polymer composite films were evaluated for *in vivo* wound healing activity. All the polymeric films showed more than 80% reduction in wound contraction. The mupirocin loaded polymeric composite containing Sodium CMC, shown more than 95% of reduction in wound area after 12 day. Hence it can be concluded that polymer composite films of chitosan-alginate containing mupirocin along with Sodium CMC showed good wound healing and could be used in effective management of wound.

Keywords: Chitosan; sodium alginate; sodium CMC; pectin; mupirocin; polymer composite films.

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INTRODUCTION

In present scenario of advanced technology, modern wound dressing have been introduced which include hydrocolloid dressing, alginate chitosan dressing and hydrogel dressing not only bandage but in the form of sponges, fibers, films and solutions[1]. The ideal dressing should achieve rapid healing at reasonable cost with minimal inconvience to the patient. Their primary function was to keep the wound dry by allowing evaporation of wound exudates preventing entry of harmful bacteria into the wound[2] .

These modern dressings and are based on the concept of creating an optimum environment to allow epithelial cells to move unimpended for the treatment of wounds[3]. According to the Wound Healing Society, a wound is the result of disruption of normal anatomic structure and function[4]. Based on the nature of repair they are classified as acute and chronic. Acute wounds are tissue injuries that heal completely with minimal scarring, within the expected time frame. Chronic wounds arise from the tissue injuries that heal so slowly and often reoccur and have not healed beyond 12 weeks[5].

Chitosan is currently receiving a great deal of attention for medical and pharmaceutical applications due to its beneficial intrinsic properties.[6] It is one of the natural polymer which has the high potential for helping with wound healing. This polycationic polymer is generally obtained by alkaline deacetylation of chitin which is an extracted component of the crustacean exoskeleton[7].The chitin and chitosan possess many properties that are advantageous for wound dressing namely biocompatibility, biodegradability, haemostatic activity,Wound Healing Accelaration and anti- infection properties[5]. Haemostatis is immediately obtained of the commercial chitin based dressings to traumatic and surgical wounds. Platelets are activated by chitin with redundant effects and superior performances compared with known haemostatic materials. To promote angiogenesis, necessary to support physiologically ordered tissue formation, the production of vascular endothelial growth factor is strongly upregulated in the wound healing when macrophages are activated by chitin or chitosan[8].

Alginate is the another polymer which is a biodegradable and obtained from natural origin having wound healing property and good bio adhesion which is necessary for more retention over the skin[9]. Alginate is used in variety of oral and topical pharmaceutical formulations. Alginate dressing used to treat exuding wounds, often contain significant amount of sodium alginate as this improves the gelling properties. Sponges composed of sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressing[10]. Prajapati et al

worked on polyelectrolyte complex of chitosan alginate for local drug delivery and explain that combination of appropriate drug and chitosan can help to recover topical infections. Polyelectrolyte complex film of chitosan and sodium alginate film can be used for sustained drug delivery of potent antimicrobial and antifungal drugs by transdermal drug delivery[9]. Carboxy methyl cellulose sodium is widely used in oral and topical pharmaceutical formulation primarily for its viscosity increasing properties. Carboxy methyl cellulose sodium is also used in self adhesive ostomy, wound care and dermatological patches as a muco adhesive to absorb wound exudate[10]. Mupirocin is a topical antimicrobial indicated in the treatment of impetigo and secondary skin infection. Mupirocin is an antibiotic produced from pseudomonas fluorescens and structurally unrelated to any other topical or systemic antibiotic. Commercially it is available in the form of creams and ointments for topical application[11].

MATERIALS AND METHODS

Chitosan was obtained as gift sample from India sea foods, Cochin, kerala and mupirocin was obtained as gift sample from Glenmark pharmaceuticals Ltd, Nasik, Pune. Sodium alginate and Sodium CMC was obtained from SD fine chem Ltd. Mumbai.

Preparation of the polymer composite films

The films were prepared by solvent casting method[6] as shown in Table 1. Polymeric films of Chitosan alone and along with Sodium CMC was prepared by dispersing specified amount of chitosan dispersed in 3% v/v lactic acid in water, agitated for 1 h and add sodium CMC into the chitosan dispersion followed by the addition of glutaraldehyde with gentle stirring then add the propylene glycol. The mixed solution was left to stand until air bubbles had disappeared, then poured onto a petri dish and allowed to air-dry at 40°c for 24 h.

Table. 1 Formulation details of blank polymer composite films along with drug incorporated polymer composite films

Ingredients (% w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Chitosan	3	3	2	2	1.5	1.5	1	1	1.5	1.5	1	1
Sodium alginate	--	--	--	--	1.5	1.5	1	1	1.5	1.5	1	1
Sodium CMC	--	--	1	1	--	--	1	1	--	--	1	1
Mupirocin	--	--	--	--	--	--	--	--	2%	2%	2%	2%
Glutaraldehyde	--	0.03%	--	0.03%	--	0.03%	--	0.03%	--	0.03%	--	0.03%
Propylene Glycol	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

To prepare chitosan-alginate composite films, sodium alginate solution was prepared by dissolving the alginate alone and along with sodium CMC in the deionised water followed by chitosan solution which was prepared by dispersion of the chitosan in to 3%v/v lactic acid.

Acetone was added as a solvent moderator to alginate solution. Finally the dispersed solution of the chitosan was added to sodium alginate solution drop wise under rapid agitation,then glutaraldehyde (0.03%v/v) was added followed by propylene glycol. The casting is done similar as explained above.[12] Similarly mupirocin incorporated films were prepare by adding mupirocin (2%) in alginate solution and followed the same procedure as explained above.

CHARACTERIZATION OF POLYMER COMPOSITE FILMS

Foureir-transformation infrared spectroscopy (FTIR):

The drug-polymer and polymer-polymer interaction were studied by FTIR spectrometer, Perkin-Elmer (spectrum-100) japan. Two percent (W/W) of the sample with respect to potassium bromide (KBr ; SD Fine Chem Ltd., Mumbai, India) disc , was mixed with dry KBr. The mixture was ground in to a fine powder using an agate motar and then compressed into a KBr discs in a hydraullic press at a pressure of 10000 psi. Each KBr discs was scanned 16 times at 2 mm/sec at a resolution of 4 cm-1 using adopization. The characterstics peaks were recorded.

EVALUATION OF POLYMER COMPOSITE FILMS

Thickness of film[9]

The thickness of film influence the time required to absorb the polymer into the body. To determine the uniformity in thickness of film and change in thickness film after drug loading, it was measured for each film using screw gauge at three different sites of the film and the mean was calculated.

Folding endurance[13]

It was determined to find the flexibility of film which is needed to handle the film easily and for comfortable, secured application of film on the wound. It was determined by repeatedly folding one film at same place till it breaks or folded up to 300 times manually. The number of times of film could be folded at the same place without breaking give the value of folding endurance.

Swelling index[13]

Weighed pieces (1cm²) of film were immersed in distilled water, then soaked films were removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately. The swelling index was calculated as

$$\% S = \frac{W2 - W1}{W1} x100$$

Where **W1** and **W2** are the weight of the film before and after immersion in the medium, respectively.

Water vapour penetration[13]

To measure the water vapour penetration ,the films were cut and placed on top of open 2.5-cm bottles containing 5g of silica gel and held in place with a screw lid (test area: 4.9 cm^2). The bottles were conditioned in desiccators containing silica gel for 12 h. The bottles were then placed in desiccators containing a saturated solution of sodium chloride at 75%RH.The equilibrium vapour penetration was determined by weighing the bottles at 0, 12, 24, and 48 h respectively.

Tensile strength[15]

The mechanical properties of films were evaluated using a texture analyzer (Instron Univeral Model) equipped with a 500 gm load cell. Film strip in 10mm X 10mm of dimension and free from air bubbles or physical imperfections, was held between two clamps positioned at a distance 1 cm. During measurement the film was pulled by top clamp at a rate of 10mm/minutes. The force and elongation were measured when the films broke. The tensile strength was calculated as,

Tensile strength (kg/mm^2) = Breaking force (kg)/cross sectional area of sample (mm^2)

In vitro bioadhesion study

The bioadhesive property of the film was performed using an in-house pulley system instrument [14]. The proximal portion of a chicken pouch was used to represent the mucous-like texture of a fresh wound. The freshly slaughtered chicken pouch washed with physiological saline at 4°C and attached to a platform (test area : 4.9 cm^2). A prewetted film was placed a top the chicken pouch and held under 100g weight for 2 min, with the other side of the weight connected to a pulley system. The water was added to a container attached to the pulley system until the film was detached. The weight of water needed to detach the film from the chicken pouch was recorded.

Wound healing activity by excision model[14,15,16]

Male wister albino rats (150-250g) in a total 8 groups of each having three animals were used after obtaining approval from institutional animal ethics committee (No.346/CPCSEA) by excision wound model. Animals were housed under standard conditions of laboratory. Excision wound was inflicted under light ether anesthesia by excising a circular piece of (20 mm^2) of full thickness skin from the dorsal intercapular region. Selected films were adhering over the wound and marketed povidone-iodine was used as a standard. Wound contraction was monitored by measuring wound area planimetrically, every alternate day till the wound was completely healed. Wound contraction was calculated as percent reduction in wound.

$$\% \text{ Closure} = 1-(Ad/A0)$$

A0= wound on zero

RESULT AND DISCUSSUION

In the present study natural based polymers composite films were prepared for the effective management of wound. To enhance the therapeutic efficacy of the film antimicrobial agents like mupirocin is incorporated, and Sodium CMC will be incorporated in the film. Chitosan and sodium alginate was used as main polymers alone and along with Sodium CMC is used followed by glutaraldehyde is used as a cross linking agent and propylene glycol used as a plasticizer. All films were prepared by solvent casting method. The characterization of prepared polymer composite films was studied by FTIR (Fourier's transform infrared spectroscopy) and the obtained spectra are represented in figure 1

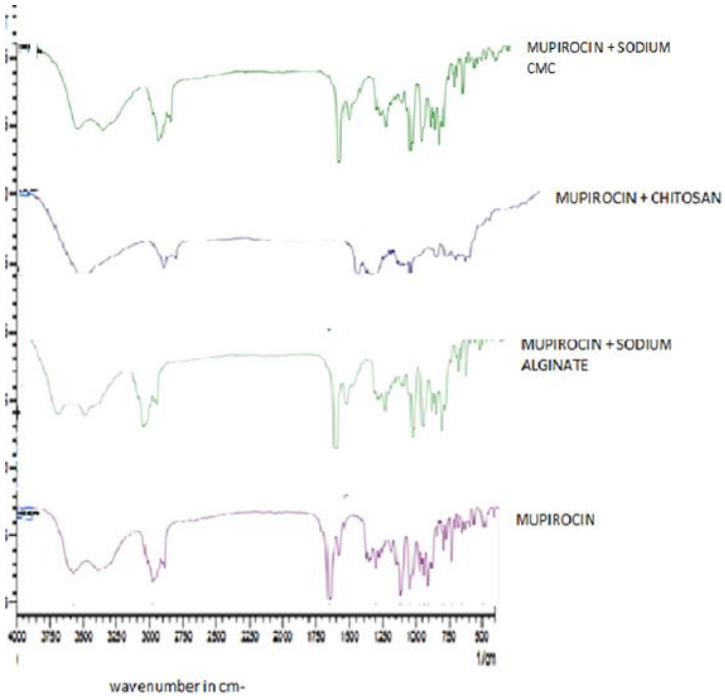

Figure 1: FTIR spectrum

The IR study confirms that mupirocin remains intact in the polymer composite films and also the IR spectrum of chitosan with sodium alginate results in formation of ionic complexes as both the polymers are polyionic. Chitosan contains cationic amino group which interact ionically with anionic carboxylic group of alginate and further glutaraldehyde crosslinked within chitosan to form strong ionic complex.

All the polymer composite films were evaluated for different parameters and results are tabulated in table 2.The thickness was varied from 0.7 to 1.2 mm. The total polymer concentration was kept constant (3% w/w). Chitosan- alginate composite films along with Sodium CMC without glutaraldehyde shows the thickness 0.9 ± 0.152. The thickness of the films was increased when the cross linker was added.

The water vapour penetration of films had showed the % increase in weight in formulations table. 2 from 26.22 ± 0.66 to 76.1 ± 0.77. The water vapour permeability of the films was decrease with the increase in the concentration of the chitosan in the films. Thickness and the water vapour permeability inversely related, with thinnest films showed the highest water permeability of the mupirocin incorporated films showed from 24.32 ± 0.84 to 65.23 ± 0.99%.

Table. 2 Evaluation parameters of polymer composite films

FC	Thickness (mm)	Folding Endurance (no of folds)	Water vapour penetration (%)	Tensile strength Kg/mm^2	Swelling Index (%)	in- vitro bioadhesion gm/cm^2
F1	0.8 ± 0.05	235 ± 5.21	61.61 ± 1.22	0.122 ± 0.01	2542.85 ±12.22	21.28 ±0 .58
F2	1 ± 0.06	258 ± 2.86	26.22 ± 0.66	0.296 ± 0.02	1114.28 ± 8.22	11.59 ± 0.64
F3	0.7 ± 0.1154	194 ± 4.5092	76.1 ± 0.77	0.135 ± 0.0068	2960 ± 13.14	22.20 ± 0.65
F4	1.2 ± 0.1	202 ± 2.6457	30.12 ± 0.35	0.266 ± 0.0085	833.33 ± 7.86	18.47 ± 0.29
F5	0.7 ± 0.0577	194 ± 4.509	77.66 ± 0.42	0.258 ± 0.0065	2900 ± 13.12	26.98 ± 0.39
F6	0.9 ± 0.0577	219 ± 1	57.33 ±0 .88	0.294 ± 0.009	1144.44 ± 8.99	25.95 ± 0.54
F7	0.9 ± 0.1527	201 ± 3.055	64.29 ± 0.74	0.258 ± 0.0035	1542.85 ± 11.14	26.31 ± 0.19
F8	0.9 ± 0.0577	212 ± 2	44.23 ± 0.55	0.287 ± 0.0085	1140.65 ± 9.24	25.61 ± 0.39
F9	0.8 ± 0.0577	195 ± 3.5118	65.23 ± 0.99	0.245 ± 0.007	911.7 ± 7.42	22.12 ± 0.59
F10	1 ± 0.05273	214.3 ± 8.14	30.0 ± 1.0	0.296 ± 0.002	724.42 ± 7.92	21.41 ± 0.12
F11	0.9 ± 0.1527	197.6 ± 8.08	43.23 ± 0.54	0.259 ± 0.0041	1140.5 ± 8.44	22.91 ± 0.21
F12	1.1 ± 0.0577	219 ± 4.582	24.32 ± 0.84	0.291 ± 0.007	949.45 ± 9.12	21.98 ± 0.51

FC= Formulation Code , Note: Values in parenthesis are standard deviation (±SD); n=3.

The tensile strength of polymer composite films expressed in Kg/mm^2 results are depicted in table 2. Tensile strength represents the mechanical property of the films for the safe handling of dressing films. Tensile strength depends upon the polymer, presence of plasticizer and addition of glutaraldehyde in to the films. The tensile strength of polymer composite films F1 to F8 was showed from 0.122 ± 0.01 to 0.296 ± 0.0002 kg/mm^2. The results suggested that films containing glutaraldehyde shows decrease in tensile strength due to more flexibility of films, as compared films did not containing glutaraldehyde. The addition of mupirocin in the chitosan-alginate composite films did not affect the tensile strength.

All the prepared polymer composite films were evaluated for bio-adhesion and results are depicted in table 2. The bio- adhesion is an important property required to adhere to the wound for effective healing of the wound. The bio-adhesion is effect by nature and molecular weight of polymer used, presence of cross linker, contact time and the degree of swelling of polymer. Chitosan-alginates are highly hydrophilic cationic and anionic polymers and hydrated to form slightly adhesive mucilage. The bio-adhesion of polymer composite films was in the range of 11.59 ± 0.64 to 26.98 ± 0.39. The bio-adhesion is decreased by the addition of glutaraldehyde in

to the films. The addition of mupirocin in the chitosan-alginate composite films did not affect the bio-adhesion.

All the prepared composite films were evaluated for swelling index, and average swelling index is depicted in table.2. Also the data up to 9 hrs is represented in table 2, and in figure 2 and 3.

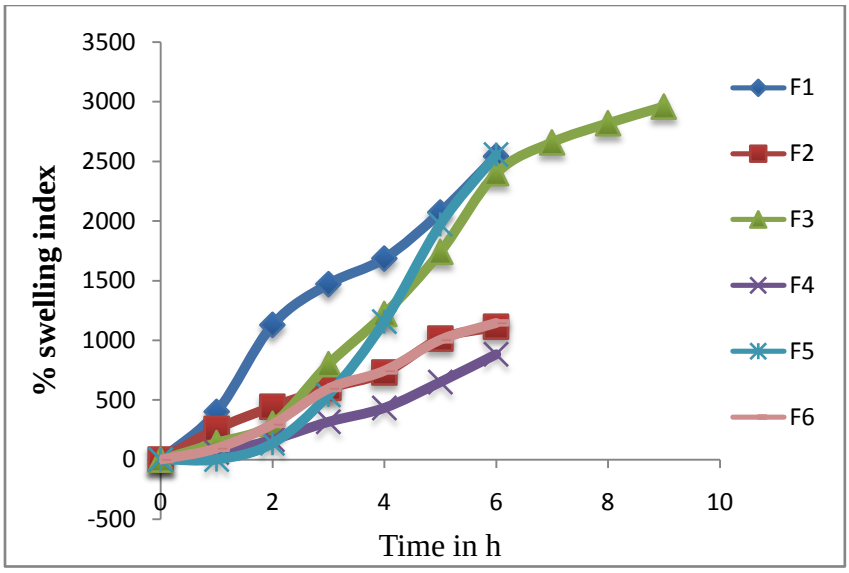

Figure 2: swelling study of chitosan-alginate composite films with and without glutaraldehyde along With Sodium CMC

The swelling behavior is related with the mucoadhesion and depends on the nature and viscosity of polymer, media used and the presence of cross linker and addition of secondary polymers. The degree of swelling increase as the time passes and certain time some of the formulation loose the integrity which did contained glutaraldehyde. In the chitosan composite films, chitosan alone showed rapid swelling up to 6 h and could not hold the shape, whereas addition of Sodium CMC. The percent swelling of polymer composite films was from 911.7 ± 7.42 to 2900 ± 13.12. Mupirocin incorporated films showed the swelling from 724.42 ± 7.92 to 1140.5 ± 8.44 (F9-F12). Addition of glutaraldehyde decreased the swelling due to formation of more rigid network.

Wound healing is a process by which damaged tissue is restored as closely as possible to its normal state. Wound contraction is the process of shrinkage of area of the wound. It mainly depends on the repairing ability of tissue, which may be reduced due to infection. Chitosan-alginate composite films containing Sodium CMC and mupirocin loaded with and without glutaraldehyde, were subjected to in vivo wound healing activity by method of excision model in albino rats. The results were expressed in percent contraction in wound area as depicted in table 3 and 4. Results were also represented in bargraph in figure 4 and 5.

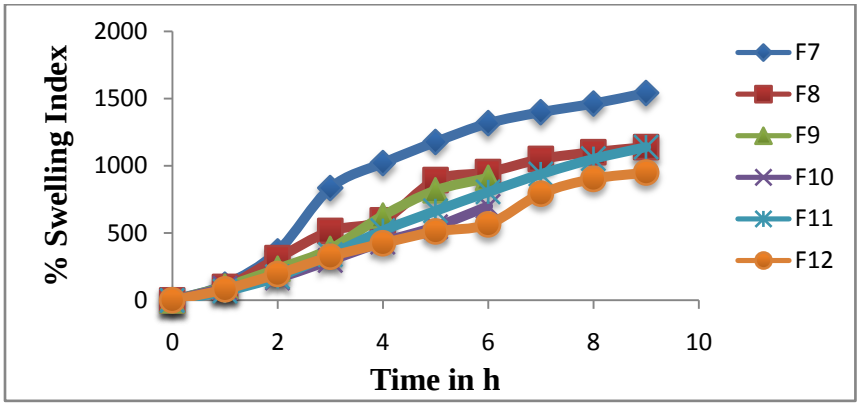

Figure 3: Swelling study of chitosan-alginate composite films with and without glutaraldehyde incorporated mupirocin along with Sodium CMC

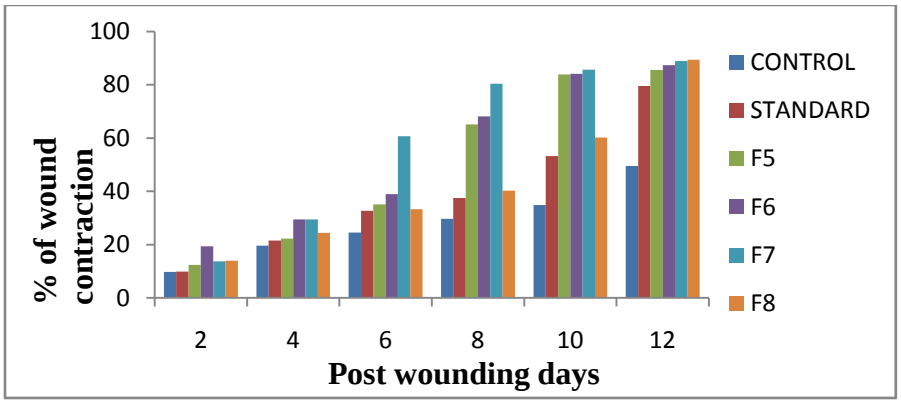

Figure 4: Wound healing area of mupirocin incorporated chitosan-alginate composite films formulated with and without glutaraldehyde along with Sodium CMC

Table. 3 Wound healing data of chitosan-alginate composite films formulated with and without glutaraldehyde along with sodium CMC

Posting wound days	Wound area in (mm)					
	Control	Standard	F5	F6	F7	F8
0	20.03 ± 0.81 (0%)	20.35 ± 0.76 (0%)	20.06 ± 0.42 (0 %)	19.92 ± 0.93 (0%)	19.85 ± 0.91 (0%)	19.95 ± 0.78 (0%)
2	18.06 ± 0.77 (9.7%)	18.02 ± 0.52 (9.9%)	17.52 ± 0.63 (12.4 %)	17.12 ± 0.84 (19.4%)	17.25 ± 0.65 (13.75 %)	17.20 ± 0.39 (14 %)
4	16.09 ± 0.32 (19.6%)	15.69 ± 0.53 (21.55 %)	15.5 ± 0.29 (22.2 %)	18.24 ± 0.25 (24.4 %)	14.21 ± 0.25 (29.4 %)	15.12± 0.48 (24.45%)
6	15.03 ± 0.88 (24.55%)	13.46 ± 1.20 (32.7 %)	12.98 ± 0.95 (35.1 %)	12.22 ± 1.29 (39%)	7.85 ± 1.33 (60.75 %)	13.35 ± 0.71 (33.35 %)
8	14.07 ± 1.04 (29.65%)	12.5 ± 0.5 (37.5 %)	6.98 ± 0.46 (65.1 %)	6.25 ± 0.25 (68.25 %)	3.92 ± 0.66 (80.4 %)	11.95 ± 0.52 (40.25%)
10	13.04 ±0.62 (34.85%)	9.35 ± 0.94 (53.25 %)	3.21 ± 1.25 (83.95 %)	3.12 ± 0.15 (84.14 %)	2.85 ± 0.39 (85.75 %)	7.95 ± 0.35 (60.25%)
12	10.09 ± 0.40 (49.55 %)	4.04 ± 0.38 (79.55 %)	2.9 ± 0.28 (85.54 %)	2.5 ± 0.34 (87.4 %)	2.2 ± 015 (88.9 %)	2.1 ± 0.62 (89.4 %)

Values are mean ± SD of three animals in each group.
Numbers in parenthesis indicates the % wound contraction.

Table. 4 Wound healing data of mupirocin loaded chitosan- alginate composite films formulated with and without glutaraldehyde along with sodium CMC

Posting wound days	Wound area in (mm)					
	Control	Standard	F9	F10	F11	F12
0	20.03 ± 0.81 (0%)	20.35 ± 0.76 (0%)	20.02 ± 0.79 (0%)	19.98 ± 0.32 (0%)	19.84 ± 0.45 (0%)	19.48 ± 0.65 (0%)
2	18.06 ± 0.77 (9.7%)	18.02 ± 0.52 (9.9%)	17.14 ± 0.93 (14.13%)	17.01 ± 0.49 (14.95%)	17.11 ± 0.48 (14.45%)	17.01 ± 0.15 (14.92%)
4	16.09 ± 0.32 (19.6%)	15.69 ± 0.53 (21.55 %)	14.92 ± 1.26 (25.4%)	14.91 ± 0.86 (25.45%)	14.10 ± 0.86 (29.5%)	14.92 ± 0.45 (25.4%)
6	15.03 ± 0.88 (24.55%)	13.46 ± 1.20 (32.7 %)	12.25 ± 0.22 (38.75%)	12.91 ± 0.69 (39.45%)	7.25 ± 0.33 (63.75%)	12.98 ± 0.48 (35.1%)
8	14.07 ± 1.04 (29.65%)	12.5 ± 0.5 (37.5 %)	6.25 ± 0.38 (68.75%)	5.84 ± 0.26 (70.75%)	3.14 ± 0.10 (84.3%)	10.58 ± 1.25 (47.1%)
10	13.04 ±0.62 (34.85%)	9.35 ± 0.94 (53.25 %)	3.14 ± 1.43 (84.3%)	3.1 ± 0.75 (84.48%)	2.12 ± 0.46 (89.4%)	6.98 ± 0.55 (65.1%)
12	10.09 ± 0.40 (49.55 %)	4.04 ± 0.38 (79.55 %)	2.5± 0.21 (87.5%)	2.1 ± 0.15 (89.4%)	1.81 ± 0.34 (91.2%)	0.9 ± 0.35 (95.3 %)

Values are mean ± SD of three animals in each group.
Numbers in parenthesis indicates the % wound contraction

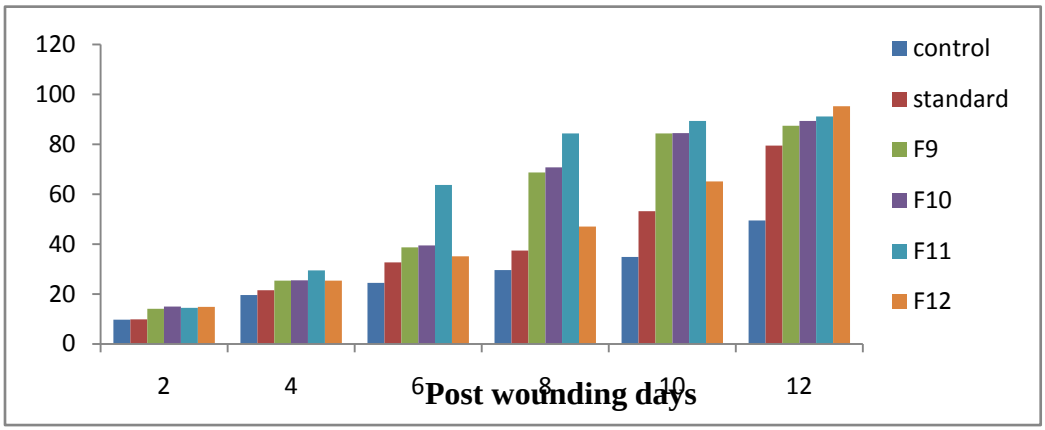

Figure 5: Wound healing area of mupirocin incorporated chitosan-alginate composite films formulated with and with Sodium CMC

All the chitosan composite films without glutaraldehyde showed increase in % wound contraction as compared to control and standard at 12th day control showed (49.55%), standard showed (79.55%), F5 (85.54%), F7 (88.9%). The chitosan-alginate composite films prepared by with glutaraldehyde showed percentage of wound contraction F6 (87.4%), F8 (89.4%). The results of addition of glutaraldehyde in the chitosan – alginate did not showed much deviation as compared to films without glutaraldehyde. Sodium CMC is used in wound care, dermatological patches as muco-adhesive in order to absorb wound exudates. Mupirocin is a broad spectrum topical antibiotic. Mupirocin loaded chitosan-alginate composite films showed % maximum

wound contraction of F9 (87.5%), F10 (89.4%), F11 (91.2%), F12 (95.3%). The results suggested that addition of mupirocin further accelerate the healing by prevention of secondary wound infections and the wound was completely healed within 12 days as shown in figure 6.

Figure 6: Comparatively healed wound after 12th day for mupirocin loaded composite films F11& F12

CONCLUSION

The blank polymer composite films are also conducted for wound healing study because chitosan is having properties like biocompatibility, biodegradability, haemostatic activity, Wound Healing Accelaration. Sodium alginate responsible good bio adhesion, which is necessary for more retention over the skin there by release the drug. The films containing the Sodium CMC absorbs the wound exudates and adhere perfectly over a wound. Sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressing. In conclusion to that the wound healing experiment using rat model have shown that the application of mupirocin loaded polymer composite films of chitosan–alginate on open wound induces significant wound contraction (95.3%) after 12thday, F12 formulation containing mupirocin-chitosan film along with sodium CMC may be promising new dressing for wound occlusion and tissue repairing. Hence mupirocin incorporated chitosan-alginate films along with Sodium CMC containing glutaraldehyde may be promising new dressing for wound management.

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