

Novel Biocompatible Honey Hydrogel Wound Healing Sponge for Chronic Ulcers

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Abstract

Objective: There is an ever-present need for non-allergenic antibacterial and antifungal wound dressing with a superior healing property for chronic ulcers. Among the entire modern wound healing dressings, hydrogel has a good capacity to donate moisture or absorb exudate and thereby providing a moist environment to facilitate wound healing process and at the same time protect the wound too. In the present study, povidone iodine loaded acrylamide based biocompatible biodegradable hydrogel dressings incorporating alginate, chitosan and gelatin showed good fluid absorbance capacity. The addition of honey showed improved tensile strength and moisture absorbance capacity of the hydrogel sponge. Apart from tensile strength, all the formulations were evaluated and compared for thickness, % elongation, folding endurance, swelling ratio, % of drug loading, thrombus formation, haemolysis assay and dispersion characteristics. Hydrogel containing chitosan and alginate showed better results in terms of tensile strength 4323gm/mm², drug loading (27.17 %), thrombus formation (0.002 gm), drug release (97.99 %) and other parameters compared to gelatin based hydrogel. Wound healing study using well established wistar rat model showed complete healing of wound i.e. 98.28 % within 12 days. Povidone-Iodine and honey loaded acrylamide hydrogel with chitosan and alginate presented a very promising wound healing dressing. This honey hydrogel dressing can be a good alternative for infected chronic wounds and diabetic foot ulcers.

Keywords: Chronic ulcers, wound dressing, Hydrogel, Honey, Iodine-Povidone

Introduction

Wound healing is a complex dynamic process that involves many cascades of events like hemostasis, inflammation, proliferation and remodeling of tissues in order to fill the damage area and re-establish the skin barrier. Wound dressings have a major role to play in the management of wounds. The primary goals of wound care are rapid wound closure and to leave a minimal or aesthetically acceptable scar. In recent years, there have been tremendous advances in the design and composition of bandages. A good wound dressing should maintain a moist environment upon absorption of the wound exudates, protect the wound from secondary infection, provide adequate gaseous exchange, regulate or mediate the release of certain growth factors and cytokines and also be elastic, biocompatible, non-toxic and non-antigenic. [1] Numerous authors have reported on acrylamide based hydrogel technologies providing a suitable biomedical dressing especially in wound management. They are super absorbents and have tough elastic structure which can withhold very high pressure. They are especially useful in exuding wounds. Hydrogels incorporating natural polymers, especially polysaccharides like, chitosan, alginate, gelatine etc. have been used recently as a biomaterial,

because of their unique advantages such as nontoxicity, biocompatibility, biodegradability and abundant availability.

A hydrogel dressing prevents the wound from microbial contamination, inhibits the loss of body fluids, provides free flow of oxygen to the wound, and accelerates the healing process. They possess very good tensile strength and elasticity which is useful as a secondary as well as primary wound care dressing for chronic ulcers. Also, it provides a cushioning effect to the wound. [2] The reports have been made upon the use of honey in hydrogel based dressing. Zohdi et al, prepared honey hydrogel as a burn wound dressing to study potential efficacy of honey hydrogel dressing in accelerating burn wound healing process. They observed that application of honey dressing led to significantly enhanced wound closure, acceleration in the rate of re-epithelization and decrease in inflammatory response as compared to control hydrogel and OpSite film within 7 days.[3]

Honey gives tensile strength and moisture content to the dressing. Both these parameters are very essential for the dressings which are used for a prolonged period. Also, honey has been well proven anti microbial and anti-bacterial since time immemorial.[4] Shukrimi et al used honey and povidone iodine dressing solution for comparative study on wagner type II diabetic foot ulcer.[5]

Povidone iodine (PVI) is a water soluble complex of iodine and polyvinylpyrrolidone. It has a broad spectrum activity against various micro-organisms, hence it use as an antiseptic agent. PVI is safer and easy to classic iodine because it has less systemic toxicity. [6]

The present study is aimed at developing and evaluating a honey hydrogel based wound dressing where natural polymers like, chitosan, alginate and gelatine are incorporated to give haemostatic properties, super absorbent capacity, biocompatibility, adhesiveness and sponge like structure. Chitosan is a polysaccharide comprising copolymers of glucosamine and N acetylglucosamine. It has a derived by partial deacetylation of chitin from crustacean shells, it high molecular weight of 50–2000 kDa.[7] It has been proven that chitosan shows an accelerating effect on the wound healing process by enhancing the epithelisation process.[8] Also, researchers are still in process of developing the chitosan based hemostatic dressing since it has a promising effect on reducing preoperative and post-operative bleeding.[9] P.L.Kang et al prepared and evaluated chitosan dressing treated with sodium hydroxide and sodium tripolyphosphate for haemostatic use and they observed sodium hydroxide-gelled chitosan dressing sponge absorbed blood quickly, accelerating blood clotting, enhancing red cell adhesion and maintaining its original shape after haemostatic testing.[10] In a number of pharmaceutical mucoadhesive formulations it is used as a penetration enhancer. The electrostatic interaction of the positively charged chitosan mediates protracted contact with the epithelium and the negatively charged glycoprotein residues on the cell surface for absorption of drug into the underlying epithelium. With this mechanism, chitosan disrupts the epithelial tight junctions on the skin to enhance the penetration and facilitates the drug permeation. [11]

Alginate product derived from seaweed with differing ratios of D-Mannuronic and L-Guluronic acid of the alginate and the balance of sodium and calcium alginate within the dressing. On contacting blood, the calcium ions in the alginate are exchanged for sodium ions in the blood, increasing the solubility of the dressing.[12] Sikareepaisan et al, studied asiaticoside-loaded alginate films for wound healing. They observed that film has non-adherent properties and asiaticoside -loaded alginate “immersed” films appeared to be non-toxic to the normal human dermal fibroblasts and it helps to wound healing.[13] Kucharska et al prepared chitosan-alginate fibroid for dressing sponge which has sufficient mechanical, very good absorption ability and cytotoxic as well as haemostatic properties which help in wound healing. [14]

Gelatin is also a natural polymer derived from collagen of animal skin and bones. It is a good source of protein. It is translucent, colorless, brittle and tasteless and biodegradable in nature. It has fairly good film forming and wound healing properties by preventing

fluid loss due to exudation.[15] Deng et al prepared chitosan-gelatin sponge to testify the safe reliability, anti-bacterial property and wound healing ability and they observed that wound healing effect of chitosan-gelatin sponge is superior than 0.2 % v/v ethacridine. [16] Also, gelatine is plays an important role in thrombus formation by inducing the clotting factor which plays a role in conversion of prothrombin to thrombin.[17]

Material and method

Material

Povidone iodine as antiseptic and anti-microbial solution and honey were purchased from a local pharma from Mumbai, India. Chitosan was procured as a gift sample from Mehtani Chitosan Pvt Ltd, Veraval, Gujarat, India, and sodium alginate was purchased from Omkar agencies, Mumbai, India. All other reagents were purchased from ultra chemical, Mumbai, India.[18]

Method

The acrylamide hydrogel base was use as per the method described by Mishra et al [17] Briefly, the proportion of monomer, cross linker and other ingredients were 4% of acrylamide, 0.08% of ammonium persulphate (APS) and 0.08% N,N'-methylene bis acrylamide (MBA). The preliminary screening for optimization of concentration of honey for good tensile strength sponge was carried out. Concentrations of honey screened were 5%, 7%, 10% and 15% v/v. From the results of tensile strength and stickiness of the sponge, it was concluded that 10%v/v honey shows best optimized hydrogel sponge characteristics. Different amounts of natural polymer like chitosan / alginate/ gelatin were dispersed separately into 25 ml of double distilled water for 24 hours. Into this soaked polymer the above mentioned acrylamide based was added accordingly. To this mixture 10% vv honey was added at the end and homogenized using a high speed homogenizer. The resultant mixture was transferred into a petridish .The petridish were kept at 60 C for 24 hrs. Various batches were prepared by using polymers at different concentration, alone and in combination, as depicted in Table 1. The resultant dried honey hydrogel sponges were stored until use. We subjected all the batches to evaluation for appearance, thickness, swelling index, folding endurance, tensile strength, dispersibility, water vapour transmission, water uptake capacity, % drug loading, blood compatibility studies and % drug release. The detailed methodology for each of these evaluation parameters are described as follow,



Table 1: Different Wound healing sponge formulations

Sr. no	Ingredient	Batches					
		F1	F2	F3	F4	F5	F6
1.	Chitosan	3 %	-	-	3 %	3 %	-
2.	Alginate	-	3 %	-	3 %	-	3 %
3.	Gelatin	-	-	3 %	-	3 %	3 %
4.	Honey	10 %	10 %	10 %	10 %	10 %	10 %
5.	APS solution	0.08 %	0.08 %	0.08 %	0.08 %	0.08 %	0.08 %
6.	MBA solution	0.08 %	0.08 %	0.08 %	0.08 %	0.08 %	0.08%
7.	AM solution	2%	2%	2%	2%	2%	2%

APS = ammonium persulphate , MBA = N,N'-methylene bis acrylamide, AM = Acrylamide

Determination of loading of drug into hydrogel

The drug loading of PVI was done as per the following method. Swelling method was used for loading PVI into the honey hydrogel. For loading PVI into honey hydrogel, a small piece of honey hydrogel sponge (4c.m²) was put into the beaker containing 50 ml PVI solution of 8 % w/v and allowed swelling for 1 hr into dark place because povidone iodine is a light sensitive drug. The PVI loaded honey hydrogel was taken out after 1 hr and dried at room temperature in a dark place for 48 hrs. Percentage of drug loading was calculated using the following equation [19]

$$\% \text{ loading} = (W_d - W_0) / W_d \times 100$$

Where W_d and W_0 are the weight of unloaded and povidone iodine loaded hydrogels, respectively

Evaluation parameters for Drug loaded honey hydrogel sponge

Appearance of sponge

Appearance of the film was studied visually after the drug loaded hydrogel sponge was completely dried. The surface properties, uniformity of colour, ability to peel from the casting surface, sponge integrity were observed for all the prepared batches.[20]

Thickness

The Thickness of the PVI honey hydrogel sponge influence the time required to absorb the polymer into the body. Thickness of PVI honey hydrogel sponge was measured by using electronic digital vernier callipers (Shiv Scientific, Mumbai, India). Five different sites were selected in ordered to measure the overuse thickness PVI honey hydrogel sponge. The mean value of thickness depicted in table 3 [20]

Swelling index

The swelling capacity is an important characteristic of wound healing dressing especially in exudating wounds. Due to their high fluid holding capacity they can absorb a moderate amount of the

wound exudates by swelling which leads to formation of a dry bed of wound which further aids into healing process. Swelling index was determined by soaking pre-weighed pieces (4cm²) of PVI honey hydrogel in double distilled water. Soaked sponges were removed with blunt forceps and blotted to remove excess liquid from the medium at predetermined time (5, 10,20,30,60,120 min) and their weight was determined by using digital weighing balance and % swelling index was calculated by the following equation.[21]

$$\% S = \frac{W_2 - W_1}{W_1} 100,$$

Where, S is the percentage water adsorption of honey hydrogel sponges at equilibrium.

W_1 is the initial weight of the honey hydrogel sponge.

W_2 is the after immersion weight of the honey hydrogel sponge.

Folding endurance

Folding endurance is to find the flexibility which is needed to handle the PVI honey hydrogel sponge conveniently and comfortably during the application on a chronic wound bed. Folding endurance was determined by repeatedly folding the sponge at the same place till it breaks or folded upto 300 times manually and obtained value of folding endurance are noted in table 3 [22]

Dispersion characteristics

Dispersion characteristics indicate the sponge has the ability to retain its mechanical properties without breaking during the wound healing process. The dispersion characteristic of the PVI honey hydrogels was examined by placing test sample into 50 ml conical flask and it gently swirled for 10 min without causing a vortex and the integrity of the sample was visually check. Results are depicted into table 3 [19]

Tensile strength

Tensile strength measures the ability of the film to withstand rupture, mechanical pressures or the force required to break the film. Tensile strength of the film was determined by using the Brookfield's Texture Analyzer – QTS 25. It was expressed in gm/mm² units and obtained value depicted into table 3 [23]



Scanning electron microscopy (SEM)

Surface morphology of hydrogel sponge can be observed by using SEM. Hydrogel sponge was mounted on aluminium pin stubs using conductive self-adhesive carbon label. The specimens were sputter coated with a layer of gold approximately 50 nm thick in a sputter coater. All samples were examined in a Field emission gun-scanning electron microscope (model- JSM 7600F) [24]

Release of drug

In order to study the release of PVI from drug loaded honey hydrogel sponge, a required size of PVI honey hydrogel was placed in a measured volume (20 ml) of 6.4 pH phosphate buffer at room temperatures and the amount of released PVI was determined at different time intervals (10, 20, 30, 40, 50, 60 min) by taking the absorbance of test sample UV-Vis spectrophotometer (Systronic lab, Mumbai, India). The absorbance of the released PVI was measured at λ max 340 nm. The drug release data are depicted in figure 3.[25]

Blood compatibility

Thrombus formation

For the thrombus formation, PVI honey hydrogel sponges were equilibrated with saline water (0.9% w/v NaCl) at 37 ± 0.5 °C for 24 hrs. Acid citrate dextrose (ACD), 0.5 ml, was added on the surface of the swollen hydrogel sponge followed by the addition of 0.03 ml of CaCl_2 solution (4molL⁻¹) to start the thrombus formation within 3- 4 min. The thrombus formation reaction was stopped by adding 4.0 ml of double distilled water and the thrombus formed was separated by soaking in double water for 10 min at room temperature. The clot was then fixed in 36%v/v formaldehyde solution (2.0 ml) for another 10 min. The fixed clots were placed in double distilled water for 10 min and, after complete drying, the weight of dried hydrogel sponge was recorded. The same procedure was repeated for the glass surface (negative control) and hydrogels of varying compositions and the respective weights of thrombus formed are recorded.

Haemolysis assay

In this experiment, a dry PVI hydrogel sponge was equilibrated in saline water (0.9% NaCl solution) for 24 hrs at 37 ± 0.5 °C. Human ACD blood (0.25ml) was added onto the wet hydrogel sponge. After 20 min, 2.0 ml of saline water was added onto the hydrogel sponge to stop haemolysis and the test sample was incubated for 60 min at 37 ± 0.5 °C. Positive and negative controls were obtained by adding 0.25 ml of human ACD blood and saline solution respectively into 2.0 ml distilled water. Incubated test samples were centrifuged for 45 min, the supernatant was taken and its absorbance at 545 nm was recorded. The % haemolysis was calculated using the following equation:

$$\text{Haemolysis (\%)} = (A \text{ test sample} - A (-) \text{ control}) / (A(+) \text{ control} - A(-) \text{ control}) \times 100$$

Where A is the absorbance. The absorbances of positive and negative controls were found to be 1.20 and 0.008, respectively.

Wound healing activity

For the wound healing study, healthy wistar rats were selected and divided into six groups. The wound healing protocol was sanctioned by the Institutional Animal Ethical Committee. Excision wounds were used for study of rate of contraction of a wound on a wistar rat. These wistar rats were anaesthetized by giving ketamine injection (intra peritoneal) dose of 50 mg / kg. Back side area of each wistar rat was shaved to create an excision. Excision wound sized 2 cm² and 2 mm depth was made by cutting out a layer of skin from the shaved area by using a surgical scissor. The 2 cm² area of PVI hydrogel sponge was cut and fixed it on the excision area with the help of blunt forceps. Wound areas were measured on days 2, 4, 8 and 12 for calculation of wound contraction.[27]

Result and discussion

Preparation and Appearance of honey hydrogel film

The various batches of PVI honey hydrogel Sponge were prepared by using single and combination of polymers to compare the effect of combination of polymer on characteristics of hydrogel based sponges. It was observed that batches containing single polymer (F1, F2, F3) had a good appearance and they formed a thick, yellowish brown layered film. Also, hydrogel sponges containing honey could be easily peeled off from the petriplate. However, the batches containing a combination of polymer (F4, F5) formed a thick yellowish brown film, but they needed little effort to be peeled off from the petriplate. This may be due to higher viscosity and stickiness of combination polymers. The combination sponges showed improved appearance and uniformity of films compared to single polymer film. The batch F6 containing alginate- gelatin polymer formed sticky gelatinous mass and could not be peeled off the glass surface due to very sticky nature of the polymer blend. Thickness of batch F4, F5 was observed as 0.78, 0.77 mm, respectively which was comparatively higher than batch F1, F2, F3 (0.74, 0.73, 0.75 mm, respectively).

Drug loading

Drug loading efficacy of gelatine containing sponge was comparatively little higher than other formulations containing alginate and chitosan, i.e. Batch F3 and F5 (28.57, 25.0%, respectively) and F1 (21.95%), F2 (22.89%), F4 (21.17%). This is probably due to higher capacity of absorption and swelling of gelatine polymer as compared to sponge containing alginate and chitosan. The difference in % of drug loading was not very significant and hence while comparing overall properties of the resultant sponges as gelatine batches did not show good results, they were not considered as a good candidate for honey hydrogel formulations and were not studied further for the rest of the



evaluations parameters. The comparative results of physical properties of all the formulations are depicted in table 2 and 3

Table 2: Evaluation parameters of different batches of hydrogel

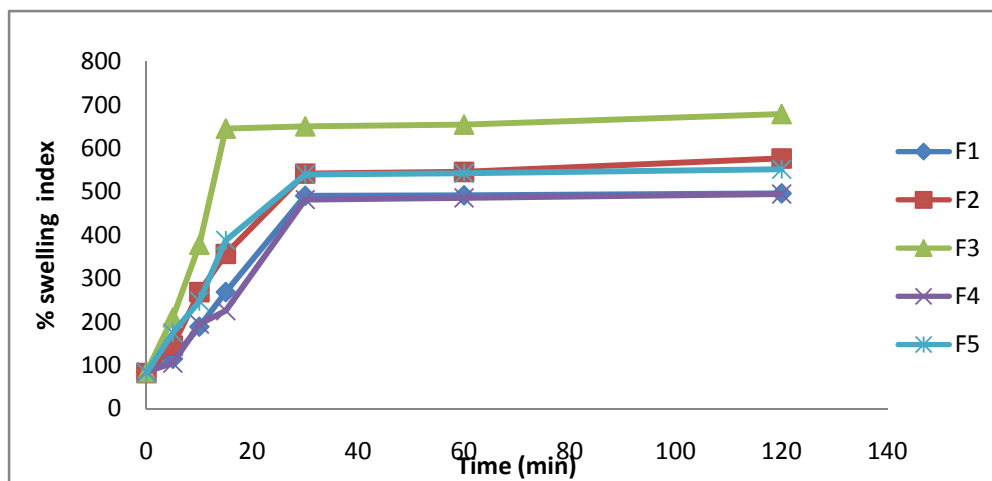
Batch no	F1	F2	F3	F4	F5
Thickness (mm)	0.74	0.73	0.75	0.78	0.77
% Drug loading	21.95	22.89	28.57	21.17	25
% of swelling	496.36%	577 %	679.48%	495%	552.15%
Folding endurance	189	243	287	-	298
Dispersion	Dispersion	Dispersion Immediately	Dispersion	No dispersion	Dispersion

Swelling index

The swelling Index of all hydrogel sponges are approximately the same but the rate of swelling in batches F1 (496.36%), F2 (577.0%), F3 (679.48%) containing single polymer were

comparatively higher, than the sponge containing combination of polymer batches F4 (495%), F5 (552.15%). The difference in swelling Index was not very significant. Batch F6 did not remain intact for the swelling index measurement. Hence, it can be implied that the combination of polymer affects the swelling ability of the hydrogel sponges.

Figure 1. Swelling index of different batches of PVI honey hydrogel sponge



Folding endurance

The value of folding endurance expressed in table 2 shows that batches F1, F2, F3 of hydrogel sponge breaks after 189, 243, 287 time folding respectively. However, batch F5 breaks after 298 foldings and batch F4 did not break by folding it even for more than 300 times at the same place. This proves that batch F4 containing alginate and chitosan combination has the highest mechanical strength and can serve as a good supportive hydrogel dressing for chronic wound management.

Dispersion characteristics

Dispersion study was carried out to study the integrity of swollen hydrogel sponge. Here, batches F1, F2, F3, F5 swelled and dispersed after 10 min into dispersion medium, double distilled water. This is due to higher swelling and lower gelling characteristics of alginate, chitosan and gelatine individually. The dispersion of F5 may be due to gelatine present along with chitosan which reduces the capacity of total gelling and could not maintain the integrity of the sponge in the dispersion media. The batch F4 containing alginate and chitosan (3:3) remained swollen



and maintained its integrity without dispersion even after 24 hrs. The results suggest that the combination of chitosan and alginate maintain the mechanical strength of the sponge which is required for prolonged use in the management of chronic wounds.

By comparing all the batches for their appearance, thickness, drug loading, swelling index, folding endurance and dispersion characteristic, we could come to the conclusion that among all the batches, batch F4 (alginate: chitosan, 3:3) is the best candidate and will undergo further evaluation, in terms of tensile strength, SEM, *in vitro* drug release, biocompatibility and *in vivo* wound healing activity.

Tensile strength

Tensile strength and elongation at break of hydrogel sponge with honey and without honey were investigated to understand the mechanical properties in terms of stress and strain. The tensile strength of with honey and without honey hydrogel sponge was 10.8075 and 10.5950 gm/mm² while the elongation at break of with honey and without honey was 26.53 and 5.53 mm respectively. By comparing obtained value of with honey and without honey

hydrogel sponges , we can assume that honey works as a good plasticizer in honey hydrogel sponge because it gave good elongation strength properties to the honey hydrogel sponge which required for covering and keeping wound bed became moist.

SEM

The SEM of hydrogel sponge is shown in fig 2. All images are observed under the magnification 100 μ m. Surface morphology of hydrogel sponge could depend on the process and material which were used. Image (a) shows that irregular, uneven surface of chitosan-alginate hydrogel sponge which was formed by crosslinking of chitosan-alginate polymer and using hydrogel base acrylamide, APS, MBA. Image (b) shows the PVI loaded honey hydrogel sponge, Here, all the PVI molecule are entrapped into the chitosan-alginate hydrogel sponge which was easily identifiable by observing the grooves which came out from the honey hydrogel sponge and it was equally distribute over the sponge as well as they did not affect or alter the original morphology of the hydrogel sponge.

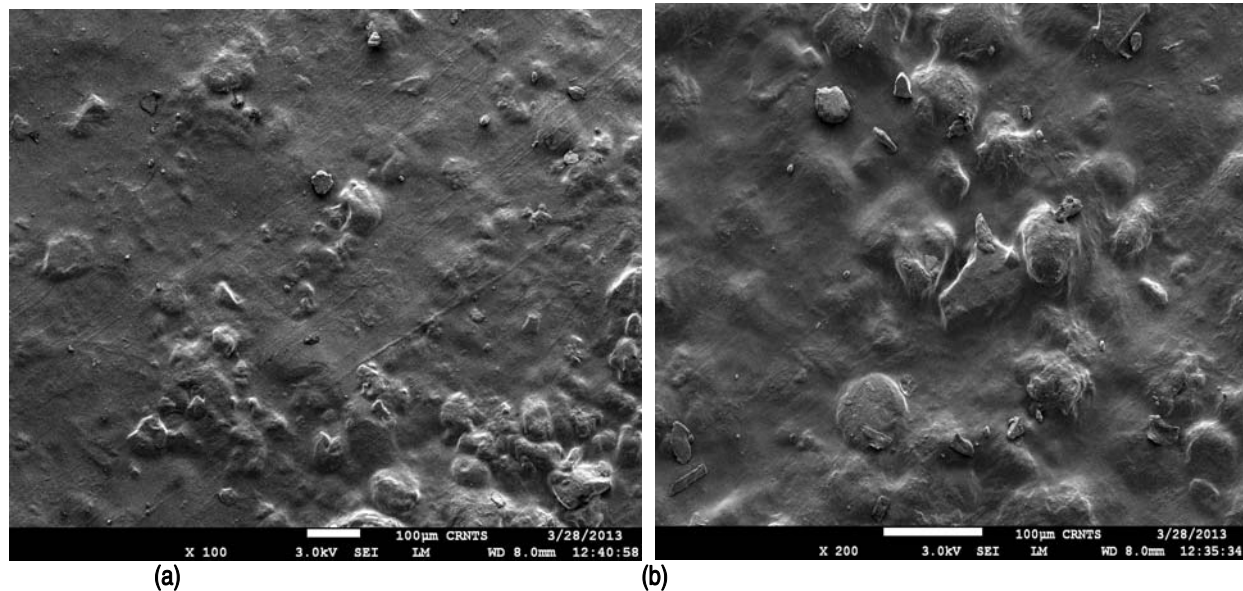


Figure 2: a) SEM image of chitosan-alginate hydrogel sponge. b) SEM image of pvi loaded chitosan-alginate hydrogel sponge.

Release of PVI

The deal primary wound dressing would be one which absorbs the exudates and also, if the dressing is medicated than it should release the drug at a constant rate for a prolonged period of time. Chitosan-alginate honey hydrogel sponge shows better fluid absorbance capacity while maintaining the mechanical strength of the hydrogel dressing. The tight polymeric matrix of chitosan and alginate holds the drug even after swelling due to fluid absorbance.

The drug release study carried out for the optimized batch of hydrogel dressing.

was used for wound dressing apart from absorbing wound exudates during the healing process it should have good mechanical properties to hold the drug into the polymeric network of the sponge to release the drug PVI a controlled rate for prolong period of time or till the wound healing process was completed. The drug release kinetics of batch F4 was analyzed by plotting the cumulative release data verses time which release 97.99% drug after 60 hrs which shown in figure 3.

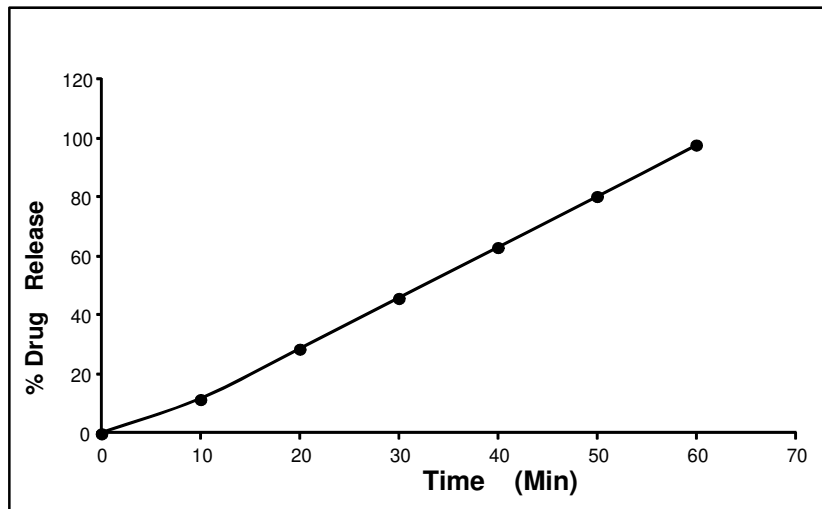


Figure 3: Drug release profile of the PVI honey hydrogel sponge (F4)

Blood compatibility

There are several tests mentioned in the literature to study the blood compatibility of polymeric primary wound dressings as it is very crucial for every sterile wound dressing to show acceptable biocompatibility.

Thrombus formation

An anti-thrombogenic potential of PVI honey hydrogel sponge was carried out by taking the weight of a dry blood clot formed on a PVI honey hydrogel sponge i.e. 0.002 gm as mentioned in the experimental methodology, which is less than clot formed on a glass surface i.e. 0.078 gm. Thus, it shows there is a very low or negligible clot fibre formed on the hydrogel sponge which confirms the considerable biocompatibility and excellent anti-thrombogenic properties. Apart from mechanical strength and fluid absorbance capacity of any hydrogel dressing, blood compatibility is one of the main characteristics of an ideal wound dressing.

Haemolysis assay

Haemolysis assay was carried out to study the haemolytic effect of hydrogel dressing on blood. The basic observation was to find out the release of haemoglobin into plasma due to damage of the

erythrocyte membrane. The prepared PVI honey hydrogels sponges were tested against a glass surface (negative control) to measure the % hemolysis. It was found that hydrogel dressing shows 15.66% haemolysis assay value as per the procedure reported, which can be correlated as an appreciable hemocompatibility compared to a glass surface.

Wound healing

The optimised batch was subjected to the wound healing study on male wistar rats. The rate of wound contraction was taken as a measure of the wound healing process. A fresh batch of F4 was prepared aseptically using sterile equipments and ingredients. The batch F4 was compared with control formulation, povidone-iodine marketed product (Betadine, Wokhardt Pharm, Mumbai, India). The hydrogel formulations showed excellent antimicrobial, anti-inflammatory activity and significant sign of improvement in wound healing i.e. 98.28% within 12 days. The mean healing time of 12 days and % of wound contraction shown in table 3. One interesting observation was made during the entire study of wound healing that, as compared to marketed formulation, hydrogel sponge showed faster and better epithellization and granulation of wound after the 4th day.



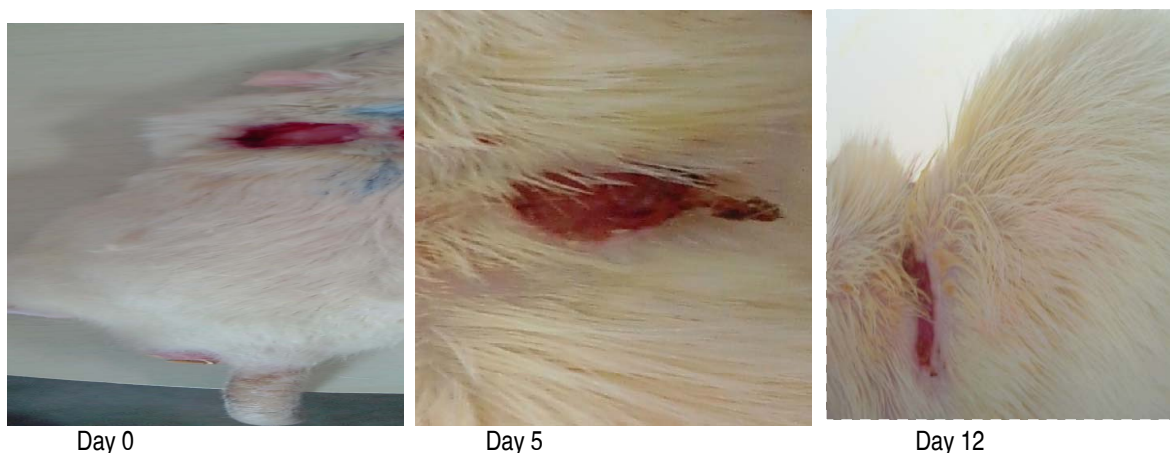


Figure 4: Wound healing activity of PVI honey hydrogel sponge on Wister rat

Table 3: % of wound contraction of PVI honey hydrogel chitosan-alginate sponge (F4)

Sr.no	Days	% of wound contraction (n=6)	
		Control	Test (sponge)
1	0	0	0
2	2	24.28± 1.81	21.07 ± 1.05
3	4	44.51 ±0.64	43.68 ± 0.94
4	6	64.93 ±1.24	62.55 ± 1.45
5	8	85.02 ±1.06	87.14 ± 1.21
6	12	96.57 ±0.99	98.28± 1.81

Conclusion

In the present study efforts were made to design and evaluate a novel acrylamide based biocompatible biodegradable honey hydrogel dressing. Different natural polymers like, gelatin, alginate, chitosan were screened for their suitability to give a good hydrogel based primary wound dressing. Honey was added to improve their tensile strength. It has also been proven as a wound healing agent in literatures. Of all polymers, equal combination of chitosan and alginate (3:3) showed better results in terms of tensile strength, folding endurance, drug loading etc. as compared to gelatin and its combinations. However, gelatin based sponge showed better swelling and hydration capacity but failed in the dispersion study due to its weak gelling capacity comparatively. These results reveal that gelatin alone or in combination with alginate or chitosan do not possess a good mechanical strength to withstand pressure. The optimized formulations of honey hydrogel based Chitosan: alginate (3:3) presented better wound healing activity as compared to marketed formulations. Hence, it can be concluded that the honey hydrogel based wound healing sponge would present a better choice for wound management of chronic wounds.

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