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Investigation of Moisture Sorption, Permeability and Drug Release Behavior of Carrageenan/Poly Vinyl Alcohol Films

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ABSTRACT
This work describes moisture sorption behavior and water vapor permeability of gluteraldehyde –crosslinked Carrageenen/polyvinyl alcohol (Carr/PVA) films. The moisture uptake has been studied under various relative humidity (RH) and the data obtained has been interpreted in the terms of various isotherm models such as GAB, Oswin and Halsey models. The moisture permeability through the films has been characterized in the terms of various parameters like water vapor transmission rate (WVTR), permeance (P) and Water vapor permeability (WVP). It was found that these parameters are greatly affected by the degree of crosslinking of the films. Finally, the model drug Gentamycin Sulphate was loaded in to the films and its release was monitored kinetically in the physiological buffer (PF) at 37^0C. The films exhibited diffusion controlled release mechanism.

Keywords: Films, carrageenan, GAB isotherm, WVTR, drug release

1. INTRODUCTION
Carrageenans, occurring in numerous species of see weeds, are linear sulphated bio-polymers. They are composed of D-galactose and 3,6-anhydro-D-galactose units (1). These polymers are biodegradable, biocompatible and abundant (2).They find a large number of applications which include edible films (3). Wound healing management (4), drug delivery (5) etc. Biopolymers like Carr, which are obtained from low-cost natural resources (from see weeds), have drawn attention of polymer chemist and pharmacist because these polymers offer new market for low value added products. However, in spite of their low cast and biocompatible nature, they have not been used as a single material to fabricate hydrogels that are intended to be used in biomedical applications like wound dressing films. The reason is that they possess poor mechanical properties and hence cannot withstand the stress applied during the application of a wound dressing film (6). Therefore it is required to combine these polymers with some synthetic one which has fair mechanical strength. In recent past, a number of studies have been carried out to reveal significant properties of films composed of natural and synthetic polymers (7).

In our previous work, we had prepared Carr/PVA films and carried out their complete characterization like FTIR, SEM and XRD analysis.These films showed fair mechanical properties due to the presence of poly vinyl alcohol which is reported to have a higher tensile strength and other related parameters (8).However, for a film to be used as wound dressing material, it is essential that it should have good water absorption capacity so that it may be able to absorb the exudates (9). In addition, it must have an appropriate water vapor transmission capacity so that a moist environment exists surrounding the wound area. It is reported that a moist wound shows relatively higher healing rate (10).

In this study we report moisture sorption capacity and water vapor permeation of Car/PVA films cross-linked by gluteraldehyde (GTA). The films have also been investigated for release of model drug Gentamycin Sulphate (GS) under physiological conditions.

2. EXPERIMENTAL

2.1 *Materials*
Carrageenan (Car) and poly (vinyl alcohol) (PVA) were purchased from Hi Media Laboratories, Mumbai, India. The cross-linker Gluteraldehyde (GA; 25-wt percentage aqueous solution), hydrochloric acid (HCl), and other salts used to prepare physiological buffer were purchased from Merck Chemical Industry, Mumbai, India and were analytical grade. In order to create desired relative humidity (RH) environments the various salts i.e. KOH, CH_3COOK, K_2CO_3, Mg $(NO_3)_2$, NaCl, KCl and K_2SO_4 were purchased from SRL. Mumbai, India. The model drug Gentamycin Sulphate (GS) was obtained from SRL, Mumbai, India.(Batch No. AB1583). The double distilled water was used throughout the investigations. Water activities (a_w) of saturated solutions of the above salts at 30^oC were adopted from elsewhere (11), and are listed in Table – I.

2.2 *Preparation of film samples*
The film samples were prepared by the method described in our previous work (8).In brief, pre-calculated quantities of carrageenan and poly vinyl alcohol were dissolved in distilled water at 80^0C under moderate stirring till the polymers dissolved completely. Now, to this solution different quantities of cross-linker GTA were added and the resulting

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solution was transferred into Petri plates and kept in Electric oven (Temp star, India) at 60^0C for a period of 24 h. Finally the films were peeled off and washed with distilled water and then dried in vaccum chamber till they attained constant weight. In all 3 samples were prepared which contained varying amounts of cross linker GTA. The compositions of various samples are given in Table-II.

Table-I: The water activities (a_w) of saturated salt solutions 30°C.

Salt	a_w at 30°C
KOH	0.0738
CH_3COOK	0.2161
K_2CO_3	0.4317
$Mg(NO_3)_2$	0.5140
NaCl	0.7509
KCl	0.8362
K_2SO_4	0.9700

Table-II: Composition of various films synthesized

Sample Code	Carr (g)	PVA (g)	GTA (ml)	H_2O (ml)
F1	0.5	0.5	1.0	11.0
F2	0.5	0.5	1.5	10.5
F3	0.5	0.5	2.0	10.0

2.3 *Surface morphology*

In order to investigate the surface morphology KC/PVA film, SEM images were recorded with a Hitachi S-4700 (New Jersey, USA) operating at an acceleration voltage of 15kV. All samples were dried in vacuum at room temperature and coated with gold before scanning. Surface morphologies were imaged at different magnifications. The surface morphology was also characterized with Atomic Force Microscopy (AFM).

2.4 *Determination of moisture sorption isotherm*

The moisture adsorption isotherms of film samples F1, F2 and F3 were obtained using gravimetric static method described in detail elsewhere (12-13). Before the moisture adsorption isotherm experiments, films were dried in a vacuum oven (Tempstar, India) at 40 ^{0}C for two days. Seven salt solutions were completely saturated and transferred into separate jars. Crystalline salts were presented on the bottom of jars at 30^{0}C. A polypropylene chamber was placed in each jar. Then pre-weighed film samples (about 1 g) were weighed into small crucibles of aluminum foils and placed on polypropylene chamber in the jars, which were then tightly closed. Jars were maintained in a Sanyo MIR 152 incubator at 30^{0}C for the equilibration of samples. The equilibration took about 3 days to attain the equilibrium. . The moisture content of the equilibrated samples was determined using the vacuum oven method (14).The equilibrium moisture contents of samples were expressed as g/g dry solids. All the moisture adsorption experiments were replicated three times. The percentage difference in the equilibrium moisture contents between triplicate samples was, on the average, less than 1% of the mean of the three values. The average values were used in the determination of the moisture adsorption isotherms.

The equilibrium moisture content (EMC) was determined using following formula:

$$\text{EMC} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \text{g/g} \qquad \ldots (1)$$

2.5 *Water vapor permeation studies*

Water vapor permeability (WVP) of the films was determined gravimetrically using a modified ASTM E96-00(2000) procedure (15).The permeation cell (acrylic cups) had an internal diameter (id) of 4.4 cm and an external diameter (ed) of 8.4 cm (exposed area: 15.205 cm^2). They were 3.5 cm deep and contained CaCl2 (0% RH; 0Pa water vapor partial pressure). Film was placed between the cell and its acrylic ring shaped cover (4.4 cm id and 8.4 cm id) which was adjusted to the cup with four screws located describing a cross .A 7 mm air gap was left between the films and the $CaCl_2$ layer. The pre-weighed covered cell was put in a temperature and RH controlled chamber, maintaining desired RH and temperature .Mass measurements of cups were done at regular time intervals using an electronic balance (Denver, Germany) with the accuracy of 0.0001g. All tests were conducted in triplicate and WVP and other related parameter were calculated using following expressions (16).

$$\text{Water Vapor transmission rate (WVTR)} = \frac{\Delta W}{\Delta t\ A} \quad \text{g h}^{-1}\text{ m}^{-2} \qquad \ldots (2)$$

$$\text{Permeance (P)} \quad = \frac{\Delta W}{\Delta t\ A\ \Delta P} \text{ g h}^{-1}\text{ m}^{-2}\text{ Pa}^{-1} \qquad \ldots (3)$$

$$\text{Water Vapor Permeability (WVP)} = \frac{\Delta W\, d.}{\Delta t\, A\, \Delta P}\ g\ h^{-1}\ m^{-1}\ Pa^{-1} \quad \ldots (4)$$

where $\Delta W/\Delta t$ is the amount of water gain per unit time of transfer, d is the film thickness (m), A is the area exposed to the water transfer (m^2) and ΔP is the water vapor difference between both sides of the film. All the experiments were done in triplicate and average values have been reported in the data.

2.6 *Preparation of drug-loaded films*

Model drug GS was loaded into these films by adding a pre-determined quantity into the polymerization mixture. A calculated amount of drug was added into the reaction mixture for all the film samples so that the effect of degree of crosslinking on the release rate could be studied. The per gram drug loading (PGDL) was determined as follows: The drug-loaded film was washed in distilled water for a definite time and the amount of drug leached out of the film was measured spectrophotometrically at 281 nm. The actual drug loading was calculated using the following formula

$$\text{(PGDL) Amount of drug/ g film} = \frac{W1-W2}{W3} \ldots (5)$$

Where, W_1= Amount of drug in the feed mixture
W_2 = Amount of drug leached out in washing
W_3 = Weight of the film

The drug-loaded films were designated as F (x) where the number in parenthesis denotes the quantity of GS loaded per gram of the film.

2.7 *Drug release studies*

The pre-weighed piece of drug-loaded film was placed in 25 mL of release medium (i.e., physiological fluid) at 37^0C. After regular time-intervals, film was transferred into fresh release medium, and the amount of drug released was determined spectrophotometrically at nm. The quantity of drug was calculated using Lambert-Beer's plot obtained for drug solutions of known concentrations. The ratio of volume of release medium to mass of film was maintained at a constant value of 250 (ml/g).

3. RESULTS AND DISCUSSION

3.1 *Preparation of film*

There have been numerous studies, carried out in recent past, which report use of glutaraldehyde as crosslinking agent to prepare cross-linked films, composed of polysaccharides (17), synthetic polymers (18) or combination of both (19). It is also reported that GTA induced crosslinking of polymers like starch, polyvinyl alcohol, chitosan etc. takes place in the catalytic presence of HCl (20). In order to avoid the possible hydrolysis of Carr by HCL we, in our previous work, fabricated Carr/PVA films, catalyzed by GTA in the absence of acid and reported their detailed characterization and water absorption behavior. The films, synthesized in the present study were not much transparent as shown in Fig.1.

Fig-1: <MISSING>

The gentamicin- loaded film is also shown along with the plain film.

3.2 Surface morphology

The SEM images of the surface of the representative film sample F1 are shown in Fig.2 (A) and (B) with 200 and 2000 times magnifications. In Fig. (A), the surface appears to be a little rough with some agglomerations of fine particles throughout the film. In order to further investigate this, the image was magnified 2000 times as shown in Fig. (B). It is very clear that there are less than 10 micrometer sized particles distributed almost throughout the film matrix. This may be attributed to the presence of carrageenan particles which do not have fair solubility in water and they must have precipitated during the drying of the films.

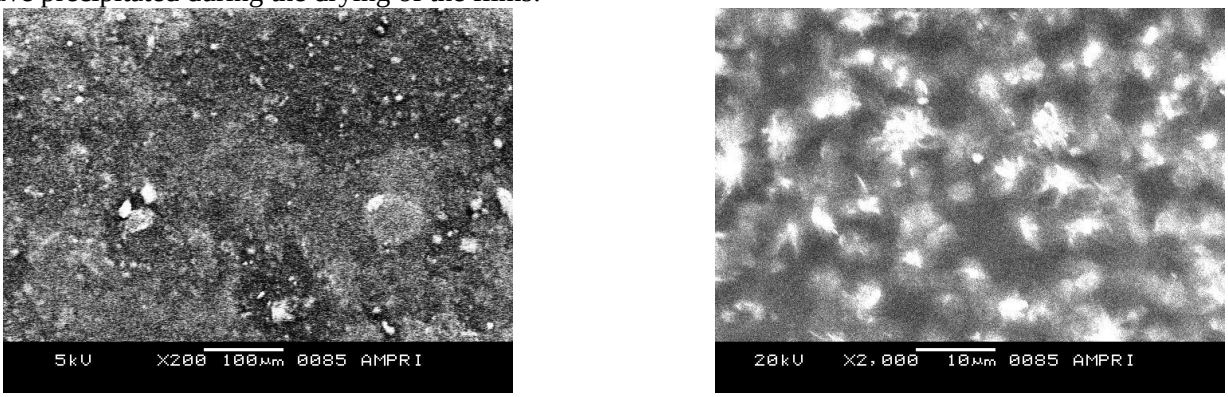

Fig-2: SEM images of the film sample F1

The AFM image of the representative sample F1 is also shown in the Fig.3.It can be observed that the surface of the film is not so smooth but it possesses a little roughness of almost 5 to 6 nm.

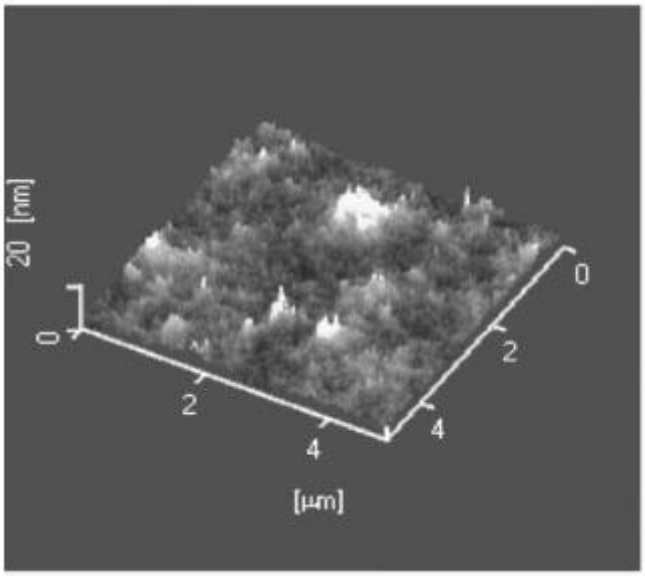

Fig-3: AFM image of the film sample F1

3.3 *Moisture sorption behavior*

Fig-4: shows the experimental moisture uptake data, for the film samples F1, F2 and F3 at 30^0C. It can be seen that all the three curves

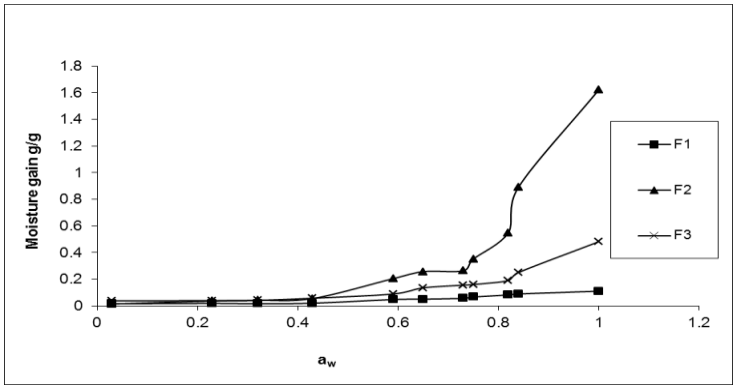

Fig-4: Moisture sorption isotherms for samples F1, F2 and F3.

obtained are sigmoid in shape, exhibiting type-II characteristic isotherms. Such curves are typical for most of the biopolymers like starch (21), chitosan (22) , cellulosic materials (23) etc. Although the film samples are not purely composed of polysaccharide, but it looks that the overall predominance of Carr persists in the moisture absorption behavior. It may also be due to the huge number of polar –OH groups in PVA which contribute equally towards water absorption like those of carrageenan. On the isotherms, obtained, three zones are noted; zone – I (aw : 0.0 to 0.2), zone – II (aw; 0.2 to 0.7) and finally zone – III (aw : 0.7 to 1.0) In the region I (termed as monolayer sorption region), the EMC increases with water activity due to the fact that carrageenan and PVA contain a large number of polar groups along the macromolecular chains. These groups act as strong binding sites for incoming water vapor molecules. This water binds strongly to the polar groups available. In addition, according to Falade and Aworh (24), there is possibility of swelling or unfolding of macromolecular chains thus offering new active sites for binding of water molecules. The zone – II, also termed as multilayer sorption region, includes multilayer moisture which is under transition to natural properties of free water and is available for chemical reactions. In this zone moisture content increases linearly with water activity but relatively at a slower rate. In this zone, sorption takes place at less active site. Finally, in the zone – III (usually termed as capillary condensation zone) there is sharp increase in EMC which may be attributable to diffusion of moisture into voids and capillaries within the film matrix. The water in this zone is in the free State. These isotherms show that substrate adsorbed proportionately more water towards the later part of the curves. It is also noticeable that for a given water activity the moisture uptake decreases with the increase in the degree of crosslinking. In other words, film sample F1, having been cross-linked with minimum amount of cross linker GTA, shows maximum moisture uptake whereas the sample F3 demonstrates minimum moisture absorption. This behavior is quite expected and is attributable to the least cross-linked structure of sample F1 which permits more moisture molecules to enter into the film matrix for sorption.

The moisture sorption behavior of various film samples was analyzed using three models, namely GAB, Oswin (25) and Halsey models (Halsey, G. 1948. Physical adsorption on non-uniform surfaces. Journal of Chemical Physics 16: 931-937). The Table-II describes mathematical expressions for these models

Table-II: Various moisture sorption isotherms studied

Name of model	Equation	Reference
GAB (Guggenheim-Anderson-de Boer)	$M = \frac{M_0 Ck.a_w}{(-ka_w)(-ka_w + cka_w)}$	(Anderson, 1946)
Halsey (Linearized)	$a_w = \exp\left(\frac{-A1}{M^{A2}}\right)$ $\ln M = \ln A_1 + A_2 \ln(-\ln a_w)$	(Halsey, 1948)
Oswin (linearized)	$M = A\left(\frac{a_w}{1-a_w}\right)^B$ $\ln M = \ln A + B \ln \frac{a_w}{1-a_w}$	(Oswin, 1946)

The GAB (Guggenheim-Anderson-de Boer) is a three parameters model which is a theoretically derived isotherm model (26), whereas other models are impirical in nature and do not have sound theoretical basis. The most common form of GAB equation is given as:

$$M = \frac{M_0 Ck.a_w}{(-ka_w)(-ka_w + cka_w)}$$

Where, Mo is the monolayer moisture content, C is a constant related to the first layer heat of sorption and K is a factor related to the heat of sorption of the multilayer.In order to determine the parameters of GAB isotherm model, GAB equation was re-arranged into a second degree polynomial equation.

$$\frac{\mathbf{a_w}}{\mathbf{M}} = \alpha \mathbf{a_w^2} + \beta \mathbf{a_w} + \gamma \qquad \text{... (6)}$$

where

$$\alpha = \frac{k}{M_o}\left[\frac{1}{C-1}\right] \quad \text{... (7)}$$

$$\beta = \frac{1}{M_o}\left[1-\frac{2}{C}\right] \quad \text{... (8)}$$

and

$$\gamma = \frac{1}{M_o Ck} \quad \text{... (9)}$$

A non-linear regression analysis of a_w/M as $a_w$yielded a polynomial of second order as shown in Fig.5.

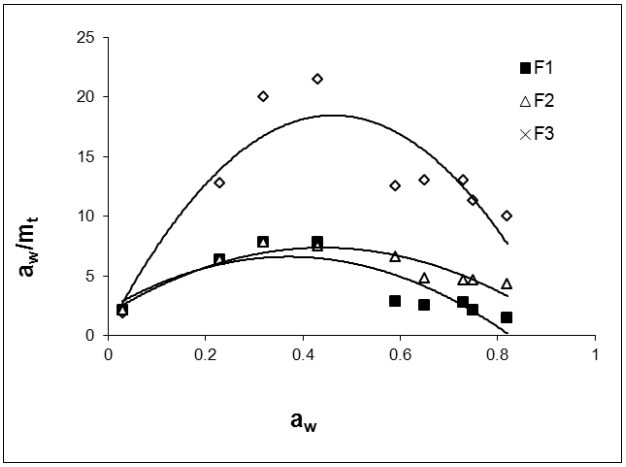

Fig-5: Polynomials of second order

The coefficients α,β and γ were thus obtained from this polynomial equation and substituted one by one to obtain GAB constants. The values of various parameters, obtained, are given in Table-III.

Table-III: GAB parameters for the various film samples

Parameters	Sample F1	Sample F2	Sample F3
K	0.919	0.902	0.959
C	8.415	5.709	5.027
M_0	0.017	0.034	0.042

As stated earlier, GAB model is theoretically sound therefore parameters of GAB isotherm need to be discussed here. The value of the monolayer moisture content (M_0) is of particular interest since it indicates the amount of water that is strongly adsorbed to specific sites at substrate surface and is considered as the optimum value to assure stability of substrate material .Therefore, M_0 is recognized as the moisture content affording the longest time period with minimum quality loss at a given temperature. Below it, rates of deteriorative reactions are minimum. Hence, at a given temperature, the safest water activity level is that corresponding to M_0 or lower. The values of monolayer content M_0, as shown in Table –II, are0.017, 0.034 and 0.042 g/g for F1, F2 and F3 respectively. The M_0 values show an increasing trend with the increase in degree of crosslinking. This may be attributable to the fact that as the amount of cross -linker GTA in the polymerization mixture increases, the number of crosslinks within the film matrix also increases and therefore, more and more compact structure is formed as we move from film sample F1 to F3. The dense network keeps the absorbed moisture strongly bound to the active sites available. Here, it is worth mention that M_0 refers to the quantity of water that is strongly bound to the substrate.

The another GAB constant C describes adsorbent – adsorbate interactions andit is reported that (26) the parameter C should fulfill following relations : for C>2 the GAB model should yield a sigmoidal shape curve with point of inflection (type II of Brunauers (1943) classification): and for 0<C<2 the isotherm is of the type III only (isotherm without point of inflection).In this study the value of C was greater than 2 for all the three film samples studied and the isotherm curves obtained were also sigmoidal ,thus supporting above predictions .Finally ,the value of K provides a measure of the interactions between the molecules in multilayer with the adsorbent ,and tends to fall between the energy values of the molecules in the monolayer and that of liquid water.The prescribed range for K values is $0 < K \leq 1$. As can be seen, the values of K, obtained for the film samples F1, F2 and F3 fall within the prescribed range.

The linear plots obtained for other models, i.e. Oswin and Halsey models are shown in Fig.6 and 7 respectively. The slopes and intercepts of linear plots were used to evaluate different parameters associated with these models and are given in Table-IV.

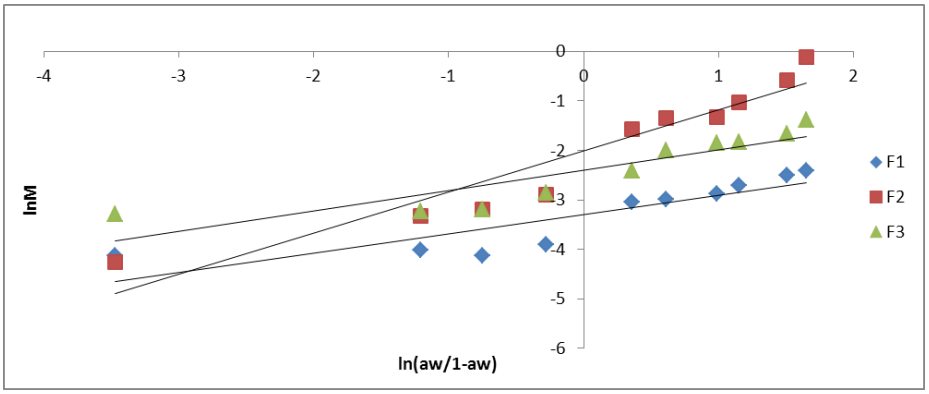

Fig-6: Oswin model for moisture absorption by samples F1, F2 and F3.

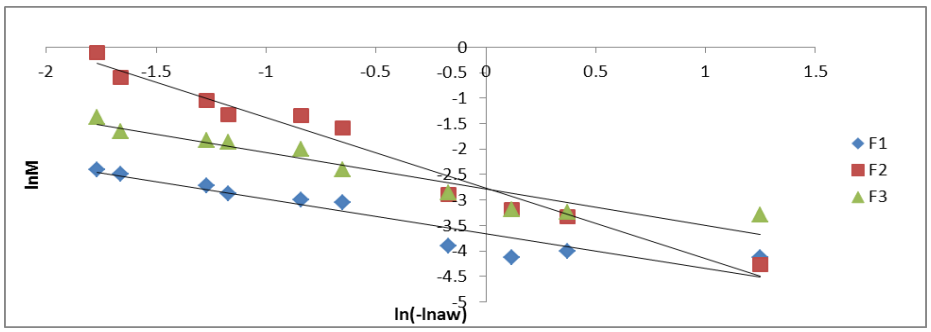

Fig-7: Halsey model for moisture absorption by samples F1, F2 and F3

Table-IV: Parameters for the Oswin and Halsey models

Sample Code	Isotherm models			
	Halsey		Oswin	
	A1	A2	A	B
F1	0.025	-0.679	0.037	0.390
F2	0.062	-1.385	0.133	0.827
F3	0.061	-0.714	0.091	0.412

3.4 *Moisture permeability of films*

The moisture permeation through the wound dressing film is a key factor to control the healing process. If the transmission of moisture through the film is very high then the wound may get dried and this shall retard the healing process. Therefore, it is essential to control the water vapor transmission rate (and other related parameters to keep the wound moist. The dynamic water vapor transmission through the film samples F1, F2 and F3 are shown in Fig.8. It can be seen that the water vapor permeated through the films increases with time and more importantly, it decreases with the increase in the degree of crosslinking. This is due to the fact that for a highly cross-linked film the permeation of water vapor molecules is rather slow due to the presence of compact network within the film matrix. The various permeation parameters, calculated from equations (2), (3) and (4) are given in the Table-V.

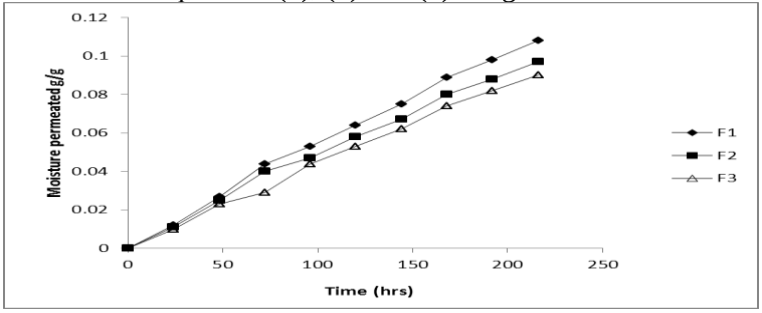

Fig-8: Moisture permeation kinetics for the samples F1, F2 and F3

Table-V: Parameters related with water vapor permeation through films

Parameters	Sample F1	Sample F2	Sample F3
(WVTR) mg $h^{-1}cm^{-2}$	1.26	1.17	1.06
Permeance (P) mg $h^{-1}cm^{-2}$ Pa^{-1}	0.478	0.439	0.401
(WVP) mg h^{-1} cm^{-1} Pa^{-1}	0.014	0.015	0.014

It is clear that the values of WVTR decrease with degree of crosslinking and they fall in the range of 1.402 to 1.195 mg h-1 cm^{-2}. According to a report (27) the WVTR of a normal skin is around 0.85 mg h^{-1} cm^{-2} and the injured skin exhibit a WVTR in the range of 1.16 to 21.41 mg h^{-1} cm^{-2}, depending upon the extent of injury. Thus it appears that the film samples, used in our work, are close to the lower range of the WVTR of an injured skin. Hence, it may be inferred that these films possess lower WVTR and are suitable for wounds which are not very dry. It is also to be noted that film thickness also plays a crucial role in regulating the transmission rates of vapor and thickness may be adjusted suitably to achieve the desired WVTR.

3.5 *Drug release behavior*

While investigating the release of an antibacterial drug from films that are intended to be used as wound dressing, the nature of release medium is very important. The composition of wound fluid depends upon the nature of the wound. For example, Trongrove et al. (28) reported that wound fluid collected from leg ulcers contained 0.6 to 5.9 mM/L glucose and 25-51 g/L protein. Similarly, Bonnema et al (29) analyzed serum fluid formed after auxiliary dissection and reported that on the first operative day the drainage fluid contained blood and high concentration of creatine-phosphokinase while after day 1, it changed to lymph like fluid that contained different cells and more proteins. Therefore, looking to the variation in nature of wound fluid, we carried out in vitro release study in physiological fluid (PF) as suggested by British pharmacopeias. The PF contained 142 mM of NaCl and 2.5 mM of $CaCl_2$.

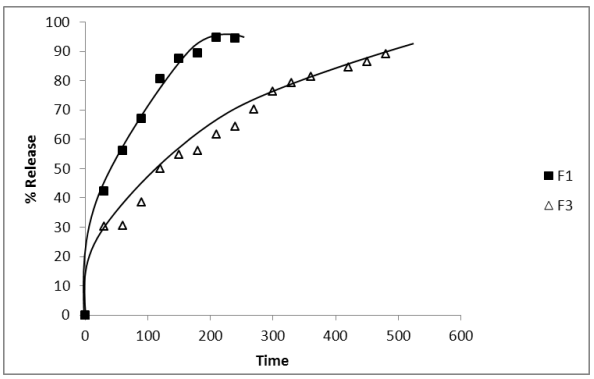

Fig-9: The dynamic release of model drug GS from the film samples F1 and F3 in the PF at 37^0C.

We prepared two film samples namely F1 (23.4) and F3 (23.1) which contained almost same quantity of drugs (denoted in parenthesis as amount in mg present per g of film) and differed in amount of cross-linker used to crosslink films.(see Table-I). The dynamic release of model drug GS from the film samples F1 (23.4) and F3 (23.1) in the physiological fluid has been shown in Fig.9. It can be seen that amount of drug released at any time increases with decrease in the degree of crosslinking of polymeric films. This is attributable to the fact that increased crosslinking produces a denser network within the film matrix and this retards the release of entrapped drug from the hydrogel networks. It may be noticed that the film sample F1released almost 100 % of the entrapped drug over an extended time period of 240 min while the sample F2, having a relatively higher degree of crosslinking, had released only 64 % of the entrapped drug in the same ti9me period. This indicates that sample F2 exhibits a slower release due to higher degree of crosslinking. It was found that it required almost 540 min for the film sample F2 to release 90 % of the entrapped drug. This concludes that degree of crosslinking can be an effective tool to regulate the release of entrapped bioactive material as per demand of the wound.

In order to investigate the quantitative interpretation of the release mechanism, the Ritger-Peppas (30) model was used. This model has been developed for swellable as well as non-swellable drug delivery. According to this model the fractional release may be given as:

$$F = \frac{Mt}{M\infty} = k\, t^n \qquad \ldots (10)$$

Where, M_t and M_∞ are the release at time‘t’ and total release respectively. The above equation may be used in logarithmic form to obtain linear plots, as shown below:

$$\ln F = \ln k + n \ln t \quad \ldots(11)$$

The value of release exponent ‘n’ indicates the nature of the release mechanism followed by the drug delivery device. In case, 0< n< 0.5, the release mechanism is said to be diffusion controlled systems (31). The release data was interpreted as linear plots between ln F and ln t, as shown in Fig.10.

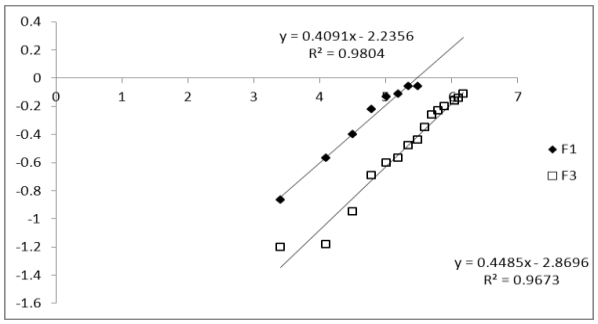

Fig-10: ln t versus t plots for evaluation of release exponent ‘n’

The release exponent ‘n’, as determined from the slopes of the linear plots was 0.40 and 0.44 for the samples F1 and F3 respectively. This indicates that for both of the films release mechanism is diffusion controlled.

The plots obtained were almost linear with quite higher regression values of 0.9804 and 0.9673 for the film samples F1 and F3 respectively. The slopes of the plots yielded values of the release exponents ‘n’, which were 0.40 and 0.44 respectively. These values indicate that both of the film samples demonstrate diffusion controlled release mechanism. In order to further confirm the occurrence of diffusion-controlled mechanism, Higuchi Model was also applied.

The Higuchi model (32), was initially developed for the planar systems and it is based on the following assumptions (1) initial drug concentration in the matrix is much higher than its solubility (2) thickness of drug particles is much smaller than the thickness of the matrix and (3) drug diffusivity is constant and (4) perfect sink conditions are always maintained. The most simplified form of this model is given as:

$$Q = K_H t^{1/2} \quad \ldots (12)$$

Where, Q may be taken as the percent release and K_H is the Higuchi constant. The release data for the film samples F1 and F2 was used to plot between Q and $t^{1/2}$ as shown in Fig.11.

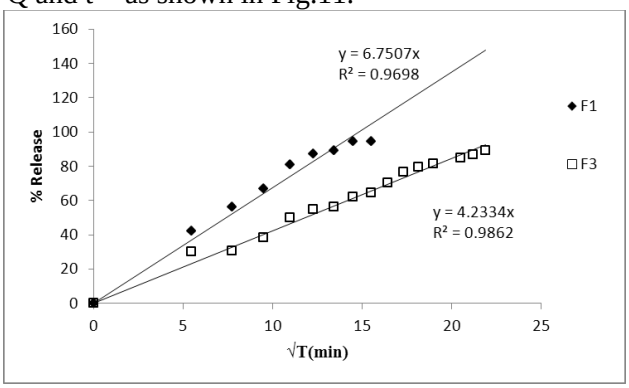

Fig-11: Higuchi plot for the samples F1 and F3

The plots obtained were linear, passing through origin with respective regression values of 0.9698 and 0.9862 respectively. In this way, it appears that this model is fairly applicable on the release data, thus indicating a diffusion-controlled release mechanism.

4. CONCLUSION

This study concludes that Carr/PVA films are suitable for the wounds which are having low exudates. In addition, a ‘diffusion controlled’ release of model drug GS is obtained for the film samples. However, it is still required to investigate complete cytotoxic studies of the films and their in-vivo application on the wounds so that a more realistic conclusion may be drawn regarding its applications. These studies are under investigations.

5. DECLARATION

We, all the authors of this manuscript declare that we do not have any conflict of interest regarding this manuscript.

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