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Swelling and drug release kinetics of composite wound dressing

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The aim of this study is to analyze the swelling and drug release kinetics of composite wound dressing material in different *p*H buffer solutions, simulating the *p*H range of wounds. Composite dressing material is prepared by grafting polyacrylic acid-co-acrylamide hydrogel on the cotton fabric using polyethylene glycol as crosslinking agent. Results show maximum equilibrium swelling at pH 7.0. Swelling kinetics at *p*H 5.5 and *p*H 7.0 solutions follow first order kinetics model, while that at *p*H 8.5 solution follow second order kinetics model. The drug release kinetics of composite dressing is investigated at different *p*H using model drug Bovine serum albumin. Drug release kinetics follows Peppas model and drug is released by Fickian diffusion mechanism. The surface morphology of the composite dressing is analyzed by scanning electron microscopy. The pores of different size are observed at different *p*H. The drug release from composite dressing is directly influenced by swelling and pore size. These composite wound dressing materials have a great potential to be used as a medicated dressing in wound healing process for non chronic wounds.

Keywords: Composite dressing, Cotton fabric, Drug release, Polyethylene glycol, Release exponent, Swelling degree, Wound dressing

1 Introduction

Over the past few decades, a number of research groups have been working on strategies to promote the wound healing process and the development of newer wound dressing materials. An ideal wound dressing should meet following criteria such as debridement, retention of moist wound environment, low adherence, prevention of infection and absorption of blood & exudates, etc. Different types of materials such as hydrogel, hydrocolloid, alginate and silicone gel have been used to produce the modern dressings[1, 2].

Hydrogels possess most of the desirable characteristics of an ideal dressing such as moist healing, non-adherence and absorption of excess exudate. They also facilitate the autolysis of necrotic tissue and do not support bacterial growth[3]. Highly porous structure and aqueous swelling of hydrogel permit the loading of drug into the gel matrix and subsequent release at the desired site. All *p*H sensitive polymers contain pendant acidic or basic groups that either accept or donate protons in response to the environmental *p*H. The water content of hydrogels at equilibrium swelling condition is one of the basic properties that make them useful in drug delivery at wound site. The network porosity of these hydrogels changes with electrostatic repulsion. Swelling of a hydrogel increases as the external *p*H increases in the case of weakly acidic (anionic) groups, but decreases if the polymer contains weakly basic (cationic) groups. Hydrogels based on poly(AAm) and poly(AAc) have the capacity to absorb a substantial amount of water, so these hydrogels may be considered a potential candidate for drug delivery systems at wound site[4-6]. Many formulations have been developed for various drug release using MEPBA[4], Ascorbic acid[5], Gentamicin sulphate[6], Theophylline[7,8], BSA[9,10] as therapeutic agents.

Solute diffusion, polymeric matrix swelling, and material degradation are the main driving forces for solute transport from drug containing polymeric matrices. When a drug is incorporated into a swellable polymer, diffusivity of encapsulated molecules of drug is strongly affected by the degree of swelling and cross-linking density of the gel[11]. Many mathematical models such as Peppas model, Higuchi model, first order kinetics and second order kinetics model have been developed to interpret the swelling and drug release profile of a polymer network. The quantitative interpretation of the results obtained in swelling or drug release assays is easier using these mathematical models which describe the swelling or release profile as a function of kinetic parameters[12].

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The most widely used kinetic model for swelling and drug release profile is Korsermeyer–Peppas model [4-9]. This model is generally used to analyse the release of drug, when the release mechanism is not well known or when more than one type of release phenomena could be involved[13]. Korsermeyer–Peppas model uses semi-empirical equation to analyze the kinetic data of the drug released at the initial stages (approximately 60% release)[14]. To use this equation, it is also considered that release occurs in one-dimensional way and that the system width–thickness or length–thickness relation should be at least 10. To obtain a better model for release beyond 60%, models other than Peppas model should be considered. Zero order kinetics model shows that the hydrogels do not disaggregate and release drug slowly[13]. Hydrogels, which contain water soluble drug in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in the dressing material, it is shown by first order kinetics. If the drug particles dispersed in a uniform matrix behave as a dispersing media, it can be best described by Higuchi model[13].

Swelling can also be described by second order kinetic model[15,16]. This equation indicates that the swelling rate is a function of the treatment time. So, mathematical modelling, whose development requires the comprehension of all the phenomena affecting drug release kinetics, has a great importance in the process optimization of controlled release formulation[11-13].

Hydrogels can be used as medicated dressing to incorporate drug or antibiotics which have therapeutic value. But their application as medicated dressing is hindered by its low mechanical strength which can be improved by using hydrogels as composites, hybrids or copolymers[4,5,8]. Radical precipitation copolymerization[17], RAFT controlled synthesis[18] and composite dressings (where hydrogel is coated on the fabric material)[10,19] have also been used to improve its low mechanical strength. A composite wound dressing has been synthesized by our research group by grafting hydrogel layer on the cotton fabric for drug release application. Composite dressing showed good tensile strength in wet conditions and drug release at different *p*H[10].

Protein nanocarriers such as gelatine, collagen, albumin and zein are used as drug delivery devices due to their exceptional characteristics, such as biodegradability, nonantigenicity, high nutritional value, abundant renewable sources and extraordinary binding capacity for various drugs. Over the past few decades, albumin has emerged as a versatile macromolecular carrier for therapeutic and diagnostic agents. Albumin has been shown to be non-toxic, non-immunogenic, biocompatible, biodegradable and metabolizable into non-toxic degradation end products. So we have used Bovine serum albumin (BSA) as a model drug for our experiment[20,21].

Kinetics of swelling and drug release have been studied for different hydrogels. In case of composite dressing, no study has been reported on kinetics of swelling and drug release. In view of above, present study has been aimed at evaluating the swelling and drug release kinetics, so as to ascertain the mechanism involved in drug release from composite wound dressing. The wound dressing is prepared by grafting poly(acrylic acid-co-acrylamide) hydrogel onto cotton fabric using PEG as crosslinker and BSA as a model drug.

2 Materials and Methods

2.1 Materials

Analytical grade acrylamide (AAm; Sisco Research Laboratories, Mumbai, India), acrylic acid (AA; Central Drug House, Delhi, India), ammonium per sulphate (APS; Central Drug House, Delhi, India), polyethylene glycol (PEG 6000; Loba Chemi, Mumbai, India), bovine serum albumin (BSA or fraction–v; Himedia Laboratories Pvt. Ltd., India), and cotton fabric (139 g/m^2) were used as supplied. Phosphate buffer salines (PBS) of different *p*H (5.5, 7.0 and 8.5) were prepared in the laboratory. All the experiments were conducted in distilled water.

2.2 Methods

2.2.1 Synthesis of Composite Wound Dressing

The composite dressing is synthesized by grafting hydrogel on the cotton fabric using free radical polymerization of acrylic acid (AA) and acrylamide (AAm), and then crosslinking of the formed polyacrylic acid (PAA) and polyacrylamide (PAAm) in aqueous media using the same method as reported earlier[13]. In brief, woven cotton fabric (thickness 0.22 mm) was first washed with distilled water and dried. Then samples were cut into pieces (1cm x 5 cm) and immersed in solution of APS (5% w/v) for 24 h, after that samples were squeezed between filter papers to remove excess solution. APS treated fabric is grafted first with acrylamide and acrylic acid monomers (monomer ratio 1:2 wt/wt, 5% and 10% w/v) for 30-45 min at temperature 50-55°C. Then PEG (0.1% by wt of the monomer) was added for cross-linking and

the reaction was allowed to continue for 15-30 min. Samples were washed with water to extract homopolymer and unreacted monomers and then dried at room temperature. The final thickness of wound dressing after drying was 0.61± 0.1 mm.

2.2.2 Swelling Analysis of Composite Dressing

The *p*H environment of chronic wounds has been recorded within the range of 7.15–8.9. As the wound progresses towards healing, the *p*H moves to neutral and then becomes acidic[22,23]. For this reason, we have selected the range of *p*H 5.5- 8.5 for our experiment. Swelling tests was conducted by incubating dry samples in 25 mL buffer solutions (PBS) at three different *p*H (5.5, 7.0 and 8.5), separately at 25°C. To determine the change in weight, samples were retrieved, paper-blotted and weighed at predetermined time intervals until equilibrium is reached. For each *p*H value, three swelling measurements were performed and the mean value was used for analysis.

The amount of water retained in the dressing can be expressed mathematically in different ways as a swelling degree. Swelling degree may be classified as isothermal swelling degree, equilibrium swelling degree and normalized swelling degree[24]. The isothermal swelling degree (SD) can be defined as the difference between the weight of the wound dressing sample (m_t) at time t and the weight of dried sample (m_o) divided by the weight of dried sample (m_o). It may be expressed as a function of time at constant temperature:

$$\mathrm{SD}\% = \left({}^{(m_t - m_0)}/_{m_0}\right) \times 100 \quad \ldots (1)$$

The equilibrium swelling degree (SD_{eq}) is the swelling degree of the wound dressing at equilibrium. The normalized swelling degree (α) is defined as the ratio of the swelling degree at time t (SD) and the equilibrium swelling degree (SD_{eq}) for certain temperature and *p*H values [24]:

$$\alpha = {}^{\mathrm{SD}}/_{\mathrm{SD}_{eq}} \quad \ldots (2)$$

2.2.3 Swelling kinetics

In order to characterize the structure of the networks of composite dressing, the study of swelling kinetics has been accomplished at constant temperature. Swelling kinetics can be determined by analyzing the results of swelling experiment using different mathematical models and then calculating the kinetic constants for swelling. The model, that shows the highest coefficient of correlation (R^2) amongst all, best explains the swelling kinetics[13]. Most widely used mathematical models are[4-9,24]:

(i) Peppas model— the mathematical formulation of this model may be expressed as

$$\alpha = kt^n \quad \ldots(3)$$

where α is the normalized swelling degree; n, the swelling exponent which describes the mode of the transport mechanism of the penetrant; k, the constant of the hydrogel; and t, the swelling time[18].

(ii) First order kinetics—it may be expressed as

$$\alpha = \left(1 - Ae^{-kt}\right) \quad \ldots(4)$$

where A is the pre-exponential factor[13].

(iii) Second order kinetics— the formulation of this model may be expressed as

$${}^{t}/_{M_t} = {}^{1}/_{kM_\infty^2} + \left({}^{1}/_{M_\infty}\right)t \quad \ldots (5)$$

where M_∞ is the weight of wound dressing at equilibrium; and M_t, the weight of wound dressing at time t[15,16].

2.2.4 Drug Release Experiments

To conduct the drug release experiment, BSA was used as a model drug and phosphate buffer saline (at 37°C and *p*H 5.5, 7.0 and 8.5) were used as release media. Dried composite wound dressing was loaded with drug by immersing it in an aqueous solution of BSA (1%) for 48 h at 37°C and then dried at room temperature. The BSA loading in hydrogels is determined from the difference in the solution concentration before and after drug loading[9], as shown below:

$$\%\ \mathrm{Loading} = \left({}^{\text{total drug loaded}}/_{\text{initial amount of drug}}\right) \times 100 \quad \ldots (6)$$

Aliquots of 1 mL of the release medium were withdrawn at predetermined time intervals and analysed by using Cary 300 UV-Visible spectrophotometer (Agilents Technologies) at 278 nm after suitable dilution. The removed release medium was replaced with the same volume of fresh buffer solution at the same temperature[9]. Cumulative drug release amount is determined with the help of standard calibration curve. All the experiments were conducted in triplicate and mean value was used for analysis. Results obtained from drug release were used to calculate the release constants by using various kinetic models. Prevalent kinetic model is Korsermeyer–

Peppas model[4-9,24] which uses semi-empirical equation to analyze the kinetic data of the drug released at the initial stages (approximately 60% release)[14]. Mathematically this model may be expressed as:

$$M_t/M_\infty=K_p t^n \quad \ldots (7)$$

where M_t and M_∞ are the cumulative amounts of the drug released at time t and at infinite time respectively; K_p, the constant incorporating structural and geometric characteristics of composite wound dressing; and n, the release exponent, indicative of the mechanism of drug release.

Other most commonly used kinetic models are:

Zero order kinetics model [13]$\rightarrow M_t=M_\infty+k_0 t$ … (8)

First order kinetics model[13] $\rightarrow [M_t/M_\infty]$ *or* $\alpha' = 1-Ae^{-k_1 t}$ … (9)

Higuchi model[25]$\rightarrow M_t=M_\infty+k_H t^{1/2}$ … (10)

Results obtained by drug release experiment were analyzed using these mathematical models and the model which shows highest correlation coefficient (R^2) amongst all, was considered as the best for the drug release mechanism.

2.3 Characterization

2.3.1 SEM Study

The surface morphology of composite dressing was examined by using Hitachi S-3700N scanning electron microscope (Germany). Prior to examination, samples were kept in liquid nitrogen for 10 min and then freeze dried. After that samples were gold-sputter coated to render them electrically conductive and then scanned at an accelerating voltage of 15 kV.

3 Results and Discussion

3.1 Swelling Behaviour

A unique feature of acrylic polymers is the dependence of their properties on the *p*H of the medium. Environmental *p*H value has a large effect on the swelling behaviour of the acrylic hydrogels[4-9,24]. It is observed that the swelling degree changes with the change of *p*H of the swelling medium[9]. As the *p*H of the wound lies between 5.5 and 8.5, therefore in this study we have chosen three different *p*H (5.5, 7.0 and 8.5).

The influence of change in *p*H values of the buffer solution on the equilibrium swelling behaviour of composite wound dressing at room temperature (25°±2°C) is shown in Fig. 1. The maximum equilibrium swelling is observed at *p*H 7.0, while minimum equilibrium swelling takes place at *p*H 5.5 and that of *p*H 8.5 lies in middle. It shows initially fast swelling rate at *p*H 8.5 but later on swelling rate at *p*H 8.5 decreases rapidly and that of *p*H 7.0 increases very fast.

It can be described by the fact that pKa value of carboxylic group is around 4.6, and below this *p*H value, carboxylic groups remain in unionised position. Above *p*H 4.6, carboxylic group starts to ionize and resulting negative charged COO^- repels each other. As the *p*H of solution increases to 7.0, all the carboxylic groups get ionised and pore size of gel network increases[11,24]. The decrease in equilibrium swelling above *p*H 7.0 is due to the starting of dissociation of –COOH groups. It leads to the weakening of structure so the pore size starts decreasing. As the pore size at *p*H 8.5 is less than that at *p*H 7.0 due to the weakening of physical forces, equilibrium swelling at *p*H 8.5 is less.

In fact, at high and low *p*H, the presence of high concentration of the ions results in high ionic strength. As the ionic strength of the solution increases, the difference in osmotic pressure between the hydrogel and the medium decreases, thus the swelling capacity of the hydrogel also decreases[3].

3.2 Swelling Kinetics

To determine the swelling kinetics, swelling data get fitted into different kinetic models such as Peppas model, first order model and second order model. Figures 2(a)—(c) show the swelling data analyzed by using Peppas model, first order and second order kinetic models respectively. The plot that shows maximum linearity will be considered as best kinetic model. Kinetic constants obtained for swelling at

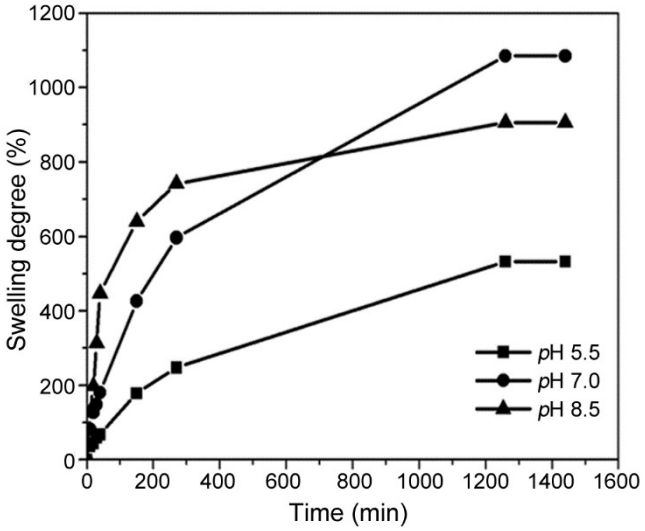

Fig. 1 — Plots of swelling degree *vs.* time at different *p*H

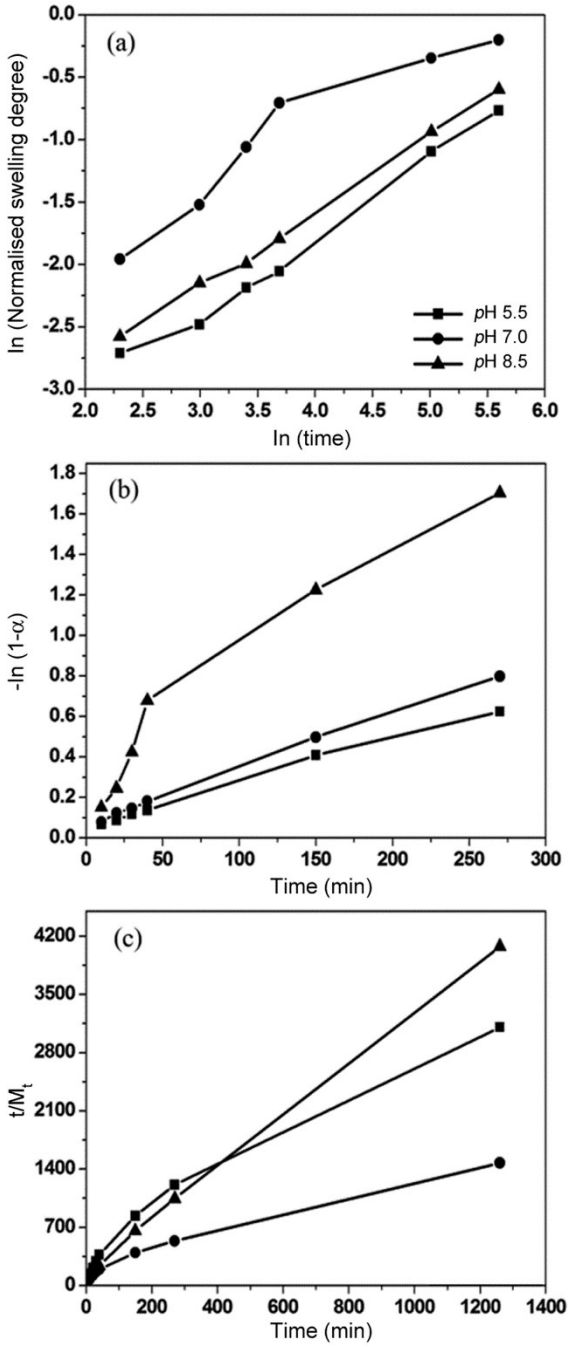

Fig. 2 — (a) Plots of ln (normalised swelling degree) *vs.* ln (time) at different *p*H (Peppas model), (b) –ln (1-α) *vs.* time at different *p*H (First order kinetics model) and (c) t/M_t *vs.* time at different *p*H (Second order kinetics model)

different *p*H buffer solutions using different kinetic models have been summarised in Table 1. Values of correlation coefficient (R^2) show that the swelling at *p*H 5.5 and 7.0 follows the first order kinetics while swelling at *p*H 8.5 follows the second order kinetics.

The swelling kinetics of polymer hydrogels is classified as diffusion-controlled (Fickian) and relaxation-controlled (non-Fickian)[5]. The phenomenon of water sorption by hydrogel depends on the diffusion of water molecules into the gel matrix and subsequent relaxation of macromolecular chains of the hydrogel. It is found that the swelling kinetics of poly(acrylic acid) hydrogel follows first order kinetics model in all the investigated buffer solutions[24] while the swelling of polyacrylamide-co-itaconic acid/chitosan hydrogels follows second order kinetics[5].

In this study, swelling kinetics follows diffusion as well as relaxation controlled mechanism as it is governed by first order kinetics model at *p*H 5.5 and *p*H 7.0, while second order kinetics model is followed at *p*H 8.5. It shows that at *p*H 8.5 rate of swelling is directly proportional to the square of water content that wound dressing has to be attained before equilibrium. So, as the time passes, the rate of swelling decreases rapidly. This is due to the fact that the swelling is dependent on osmotic pressure difference. The increase of external ionic strength decreases the osmotic pressure difference between gel network and external solution[3,5,24].

3.3 SEM Analysis

SEM analysis is used to determine the change in surface morphology of grafted hydrogel before and after swelling. Figure 3 shows the SEM images of composite dressing before and after swelling at different *p*H buffer solutions. After swelling, maximum pore size of 3.0 ±0.5 µm is shown at *p*H 7.0 and minimum pore size of 1.5 ±0.3 µm is shown at *p*H 5.5, while pore size at *p*H 8.5 is around 2.5 ± 0.5 µm which lies in middle. This is due to the fact that at *p*H 7.0 all the carboxylic groups remain present in ionised form so maximum repulsion occurs as explained earlier[24]. It favours maximum swelling and drug release at *p*H 7.0.

Table 1 — Kinetic constants for swelling at different *p*H

*p*H	Peppas model			First order kinetics		Second order kinetics	
	k	n	R^2	k	R^2	k	R^2
5.5	0.015	0.595	0.992	0.002	0.995	0.045	0.952
7.0	0.022	0.551	0.990	0.005	0.998	0.023	0.953
8.5	0.079	0.397	0.861	0.002	0.946	0.210	0.995

k— Constant of hydrogels, n—Swelling exponent and R^2—Correlation coefficient.

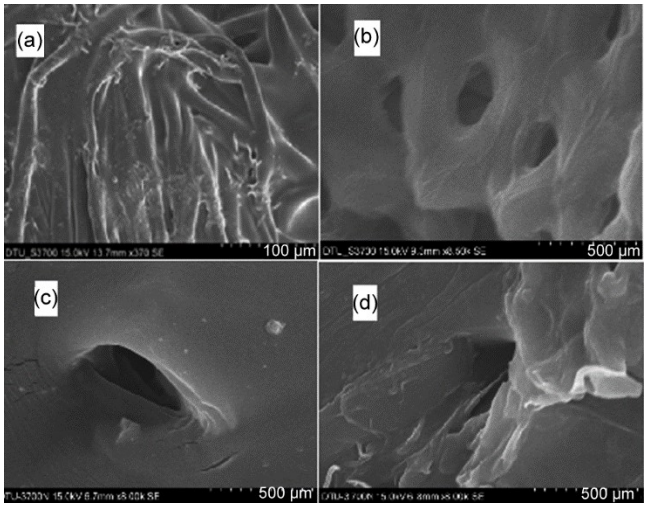

Fig. 3 — SEM images of composite wound dressing (a) before swelling and (b), (c) and (d) after swelling at *p*H 5.5, 7.0 and 8.5 respectively

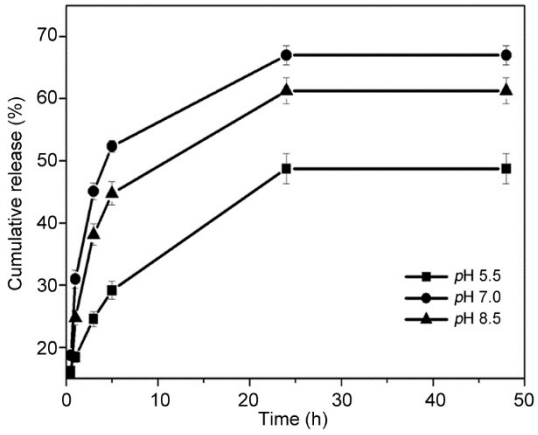

Fig. 4 — Plots of cumulative release *vs.* time at different *p*H

3.4 Drug Loading

The amount of drug remaining in the BSA solution after drug loading is determined by using UV-VIS spectrophotometer and the difference is considered as the amount of drug loaded in the wound dressing, which is found to be 87.21%. It shows a good amount of drug is loaded in the dressing. This value (0.8721 g) is used as the maximum amount of drug to be released from the dressing (M_∞) for further calculations.

3.5 Drug Release Kinetics

Figure 4 shows the amount of drug released as a function of time at different *p*H and it is clear from the plots that a considerable amount of drug is released at all *p*H. Maximum drug release takes place at *p*H 7.0 and at high and low *p*H, the amount of total drug released is less. Upto 70% of the drug is released in first 24 h.

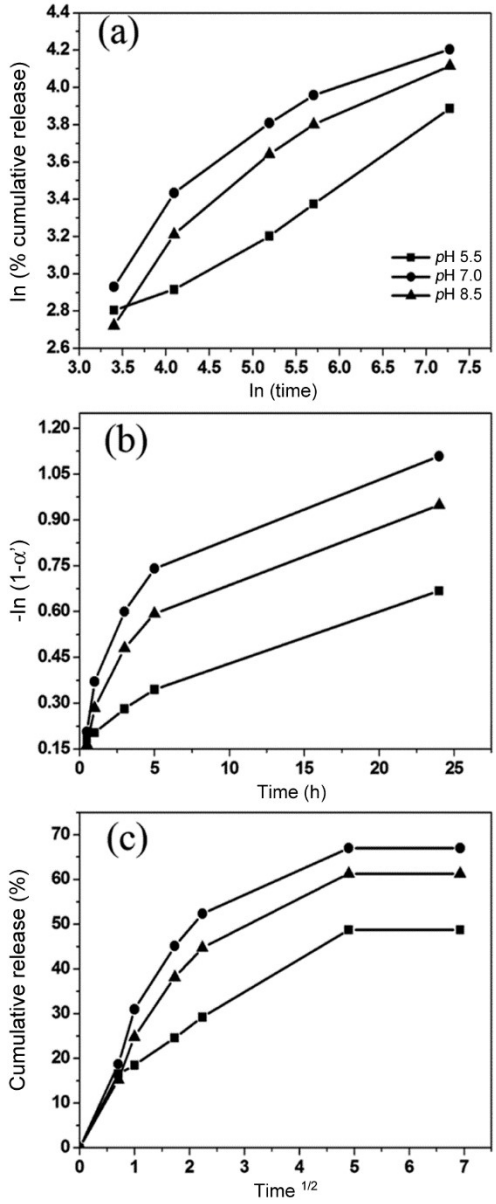

Fig. 5 — (a) Plots of ln (% cumulative release) *vs.* ln (time) at different *p*H (Peppas model), (b) –ln(1-α') *vs.* time at different *p*H (First order kinetics model), and (c) Cumulative release (%) *vs.* time$^{1/2}$ at different *p*H (Higuchi model)

In order to determine the drug release kinetics, the results obtained by drug release experiment are analyzed using different kinetic models, namely Peppas model, first order kinetics model and Higuchi model[13]. Figures 5(a)—(c) show the plots of Peppas model, first order kinetics and Higuchi model respectively. The plot that shows maximum linearity will be considered as best kinetic model. Table 2

Table 2 — Kinetic constants for drug release at different pH

*p*H	Peppas model			First order kinetics model		Higuchi model	
	k	n	R^2	k	R^2	k	R^2
5.5	18.95	0.283	0.987	0.019	0.975	8.769	0.700
7.0	28.16	0.316	0.907	0.031	0.806	12.66	0.469
8.5	23.00	0.349	0.934	0.028	0.845	11.37	0.599

k—Constant of hydrogels, n—Release exponent and R^2—Correlation coefficient.

summarizes the kinetic constants for drug release at different *p*H using different kinetic models and it shows that the value of correlation coefficient is highest for Peppas model at all *p*H. So, drug release kinetics is best described by Peppas model at all *p*H.

For a drug delivery system having slab geometry, the values of release exponent(n) corresponding, to a Fickian diffusion, anomalous transport and case II transport (zero order release), are ≤ 0.5, $0.5 < n < 1.0$ and equal to 1.0 respectively[26]. It is observed that the release of Theophylline from poly(acrylic acid-co-acrylamide) hydrogels follows an anomalous kinetics[7], while that of Gentamicin sulfate from poly (acrylamide-co-acrylic acid) shows anomalous diffusion at low acrylic acid concentration and fickian diffusion at high acrylic acid concentration in hydrogels[6].

In the present study, the release exponent is less than 0.5 which shows fickian diffusion at all *p*H. So, the rate of drug diffusion is less than the rate of relaxation of polymer network. It also shows that the value of constant K_p increases as *p*H increases upto 7.0 and then decreases. As the value of K_p depends on the geometry of the hydrogel[13], it can be concluded that hydrogel has maximum pore size at *p*H 7.0. These results are in agreement with the certain findings[11,24] and verified by the SEM images also. As *p*H increases from 5.5 to 7.0, the drug release increases, while further increase in *p*H results in the decrease in drug release. This behaviour can be explained by the fact that at *p*H 7.0, pore size is maximum due to the presence of anionically charged carboxylate groups. The decrease in drug release at *p*H 8.5 is due to the presence of the lesser pore size resulting from the dissociation of the physical forces between polyacryl acid and poly acrylamide[3,24].

4 Conclusion

Cotton fabric is grafted with polyacrylic acid-co-acrylamide hydrogel, crosslinked with polyethylene glycol to prepare the composite dressing material. Composite dressing is loaded with drug BSA. The swelling and drug release tests are conducted on these materials. Based on the experimental results, the following conclusions are made:

4.1 Results show maximum equilibrium swelling at *p*H 7.0 which causes maximum drug release. At *p*H 5.5 and 8.5, the swelling is less, leading to slow drug release in these *p*H solutions.

4.2 It is also shown that swelling kinetics at *p*H 5.5 and 7.0 solutions follows first order kinetics model while that at *p*H 8.5 follows second order kinetics model. So, the swelling process, for long time period, is not governed by the diffusion but by the relaxation of the polymeric chains. These all factors contribute in the controlled drug release, as it is directly influenced by swelling and pore size.

4.3 Drug release kinetics follows Peppas model and value of release exponent is less than 0.5 at all *p*H, so drug release follows diffusion controlled mechanism.

This system is modulated release system which shows *p*H dependent swelling behaviour and it is also a matrix system which shows diffusion controlled drug release. So these new wound dressing materials have a great potential as delivery hosts for wound healing process in the pharmaceutical field.

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