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Synthesis and characterization of interpenetrating polymeric networks based bio-composite alginate film: A well-designed drug delivery platform

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ABSTRACT

This study aimed to develop and characterize the calcium alginate films loaded with diclofenac sodium and other hydrophilic polymers with different degrees of cross-linking obtained by external gelation process. To the formed films different physicochemical evaluation were performed which showed an initial character of the films. The films produced by this external gelation process were found thicker (0.031–0.038 mm) and stronger (51.9–52.9 MPa) but less elastic (2.3%) than those non-cross-linked films (0.029 mm; 39.7 MPa; 4.4%). The lower water vapor permeability (WVP) values of the films were obtained where maximum level of crosslinking occurs. Composite films can be cross-linked in presence of external crosslinking agent to improve the quality of the produced matrices for various uses. The characterization of the film was performed using Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FT-IR) analysis. The Scanning Electron Microscopy (SEM) study showed the morphology of treated composite films. The kinetic release studies showed a sustained release of the drug from the formulated films as it can be prolonged in composite film. The prepared biodegradable Ca-Alginate bio-composite film may be of clinical importance for its therapeutic benefit.

1. Introduction

Sodium alginate is extensively used in food and pharmaceutical productions such as dispersing, thickening, disintegrating agents [1–3], and as a matrix for the entrapment of drugs, proteins, and cells [4–8]. Now a day's alginate has been used in the biomedical field for controlled drug release, cell encapsulation, scaffolds, tissue engineering and for the preparation of moulds in the dental field [9–12]. It is a water-soluble salt of alginic acid, a naturally occurring non-toxic polysaccharide found in all species of brown algae [13]. Alginate has been shown to have low immunogenicity, biocompatibility, degradability, easily available and low-cost makes alginate suitable for the preparation of natural polymeric films as an alternative to synthetic polymeric films [8,14]. As of a structural information, it contains two uronic acids, β-(1–4)-linked D-mannuronic acid (M) and α-(1–4) linked L-guluronic acid (G), and is composed of homopolymeric blocks M–M or G–G, and blocks with an alternating sequence of M–G blocks [13]. Moreover, sodium alginate has a distinguishing property of cross-linking in the presence of multivalent cations, such as calcium ions in aqueous media [13] through the gelation process [8].

Alginate films have defective moisture barriers due to their hydrophilic nature, but the inclusion of calcium can decrease the water vapor permeability of these films, creating them more hydrophobic in nature. Calcium ions can crosslink with alginate by uniting G; as a result, dissimilar fractions of G produce films showing altered water vapor permeability properties [15,16]. Small drug molecule to biopolymer (proteins) can be released from the alginate gels in an organized fashion, and the drug release dependent on the nature of the cross-linking agent and the procedures used for cross-linking [11].

Over the last few years' many researchers have shown the augmented importance of the use of alginates as a polymer for microspheres preparation and use of calcium chloride as a cross-linking material [17,18] prepared sodium alginate beads comprising with voglibose as a drug candidate using emulsion gelation method. They reported that the oil entrapped calcium alginate gel beads showed

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sustained release of the drug molecule [18]. Researchers have studied the mechanism of external and internal gelation method for the preparation of alginate micropellets and they reported that the external gelation method produces cross-linked micropellets with greater drug encapsulation efficiency (EE) and slower drug release [19,20]. Benavides et al., (2012) formulated alginate films containing oregano essential oil and they evaluated the impact of the degree of crosslinking due to the presence of the cross-linking agent and antibacterial effect, optical, mechanical, microstructural and water vapor barrier properties [20]. Brachkova et al. [21] developed calcium alginate films which contain *Lactobacillus plantarum* ATCC 8040. They concluded that the films help to preserve both viability and antibacterial action of lactobacilli.

However, the scientific literature has not so far reported in details regarding the formulation of alginate composite films with different degrees of crosslinking obtained by external gelation method. Gelation is a more difficult physicochemical method and can be affected by various factors which further influence the final properties of the film. Therefore, considering all of the above facts the alginate films containing diclofenac sodium as a drug candidate was prepared and investigated the application of external gelation method for the film preparation. This investigation demonstrates how the different factors affect the permeability nature of the prepared alginate films. The interaction of the drug with polymers was done by FT-IR and DSC analysis. *In vitro* dissolution studies of the film containing drug was also carried out. Physicochemical characterization of alginate films was further performed to know the different properties of the films in details. The aim of this investigation was to prepare and study the sustained release of the drug from alginate films.

2. Materials and methods

2.1. Materials

Diclofenac sodium was procured from a local supplier as bulk. Sodium alginate, hydroxyl propyl methyl cellulose (HPMC), polyvinylpyrrolidone (PVP), calcium chloride, and hexahydrate were purchased from Merck, India. All other chemicals, solvents used in this research are of analytical grade.

2.2. Preparation of the films

2.2.1. Process 1

In this method, at first sodium alginate is dissolved in water properly. When it is ready, it may give a yellow colour. Then some drops of glycerol were mixed it properly. The solution is ready to dry and when it is dried by vacuum drying oven properly, alginate films are prepared. In 60 ml water, 5% (3 g) sodium alginate is taken. Sodium alginate was dissolved properly into the water. When the solution colour is changed into yellow, then 10 drops of glycerol (25%) for F1 and 12 drops of glycerol for F2 was added. Then it was mixed properly and this solution was taken in four same containers (15 ml*4). Then all of them were dried properly at 60 °C. Two alginate films (F1 and F2) were ready for further use.

2.2.2. Process 2

In this process, at first, HPMC was taken and was dissolved in water properly. When the solution was prepared, sodium alginate was added. It was mixed very well. When this was ready, then add glycerol and the solution was mixed properly. Then the solution was left for drying in the dryer. When the solution was dried properly, alginate/HPMC film was prepared. In 60 ml water, 1.5% (0.9 g) HPMC was taken and was dissolved. Then 3.5% (2.1 g) sodium alginate was added to the solution. Then the solution was mixed properly and 12 drops of glycerol (25%) was mixed. The solution was taken into four same containers and the solution was dried at 60^0C temperatures. When drying is completed, the alginate-HPMC films (F3) were prepared (15 ml* 4).

2.2.3. Process 3

In this process, PVA was dissolved in hot water. Then sodium alginate was added. When it was done, glycerol was added. Then the solution was dried in a vacuum oven. When drying was done, alginate/PVA film was prepared. In 60 ml water, 1.5% (0.9 g) PVA was taken and was mixed properly into hot water. When the solution was ready, then 3.5% (2.1 g) sodium alginate was mixed. Then 12 drops of glycerol (25%) was mixed and was poured into four same containers. After drying at 60 °C temperature properly (15 ml*4), it is dried and alginate-PVA film (F8) is prepared.

2.2.3.1. Treated with $CaCl_2$ for the preparation of the Ca-alginate film

2.2.3.1.1. Treatment 1. When alginate film (F2) was ready, it was treated with $CaCl_2$ (0.2% w/v and 0.3% w/v) solution for 1 h. Then it was dried and treated alginate films were prepared (F4 and F5).

2.2.3.1.2. Treatment 2. When alginate/HPMC film was ready, it was treated with $CaCl_2$ (0.2% w/v and 0.3% w/v) solution for 1 h. Then it was dried and treated alginate/HPMC film was prepared (F6 and F7).

2.2.3.1.3. Treatment 3. When alginate/PVA film was ready, it was treated with $CaCl_2$ (0.2% w/v and 0.3% w/v) solution for 1 h. Then it was dried and treated alginate/PVA film was prepared (F9 and F10).

2.3. Characterization of films

2.3.1. Determination of film weight and thickness

To evaluate the weight of the prepared films, three (3×2 cm^2) square shaped films from each formulation were cut and balanced using a digital balance (Mettler Toledo, USA). The thickness of each film was measured by means of a micrometre. The film thickness at different locations of each film was measured. Finally, the average weight of each film per cm^2 was calculated [22].

2.3.2. Folding endurance

To evaluate the folding endurance of the films, the complete film was used. It was determined by repetitively folding the film at the same place at the rate of 30–35 folds/min till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance of the film [22].

2.3.3. Determination of surface pH and moisture content

To determine the surface pH, two films of (2 cm × 2 cm) each formulation was taken. The film is dissolved in 15 ml of distilled water. Then allow it to rotate for completely dissolve with the help of a magnetic stirrer. For each film, the pH is measured with the help of pH meter [23].

For the determination of moisture content study, two squares (2 cm × 2 cm) shaped film of each formulation was cut by using sharp scissors. The square-shaped film was weight and kept in a vacuum drier for 1 h. Then the film was removed from the drier and weight took until a constant weight was achieved. The percentage moisture content value was determined using the following equation.

$$\text{Moisture content} = (\text{Initial weight of the film} - \text{Final weight of the film})/\text{Initial weight of the film} \times 100$$

2.3.4. Measurement of mechanical properties

The polymeric films which are proposed as a dosage form for drug delivery should possess sufficient mechanical strength to withstand from any damage during manufacture, handling, and use. The tensile strength is defined as the maximum stress (σ) persistent by the material. The tensile strength of the prepared film can be varied according to the compositions of the formulations.

To determine the mechanical properties of the polymeric film, at first the film was cut into a rectangle (30 × 15 mm). Then the

rectangular strip was placed among the upper and the lower grip which was controlled by means of a pneumatic grip controller fixed on a test stand to align the long axis of the sample and the grip through an imagined line linking the points of connection of the grip to the instrument. The two grips were set aside at a space of 100 mm in the identical level. Lower grip was fixed and the upper one was moved linearly away from the previous at a speed of 1 mm/s. The stress-strain curve was documented and tensile strength, percentage elongation at break was determined using the following equation:

$$\%\text{Elongation at breaks} = (\text{increase in length/original length}) \times \mathbf{100}/\text{cross-sectional area } (\text{mm}^{\mathbf{2}}).$$

$$\text{Tensile strength } (\boldsymbol{\sigma}) = \text{force at breaks (gm)/Initial cross-sectional area of the sample.}$$

2.3.5. FT-IR analysis

The Fourier Transform Infrared Spectroscopy of F1, F4, F6, F9, and F10 films were performed by means of an Attenuated Total Reflectance (ATR) Bruker FTIR (Tensor 27 series, Germany) by placing the samples directly employed in sample holder and scanning was accomplished in a range of 4000–400 cm^{-1} wave number with a resolution of 2 cm^{-1}.

2.3.6. Differential scanning calorimetry (DSC)

Differential Scanning Calorimetric (DSC) analysis was performed to characterize the thermal nature of the prepared film. Initially, after removing the moisture by heating those samples, each sample was exactly weighed into a platinum container 40-ml aluminium pan under hermetically closed conditions, where alpha alumina powder was used as a reference. Then each thermogram was recorded from 30° to 400 °C at the heating speed of 10 °C per min under a constant nitrogen gas stream rate of 150 ml/min. Differential scanning analysis was done using a Pyris-Diamond TG/DTA instruments (PerkinElmer, Singapore) [24].

2.3.7. Scanning Electron Microscopy (SEM)

The surface morphology of the selected films was analyzed using Scanning Electron Microscope (SEM, JSM-6700F, JEOL Ltd., Japan) at 17 kV. Prior to the analysis a completely dry film was employed on a metal stub using double-sided adhesive tape and was treated with a skinny layer of platinum for the 60s in reduced pressure of 2.54 Pa; at a voltage of 10 kV, current of 25 mA by means of an ion sputtering device (Auto Fine Coater, JFC-1600, JEOL Ltd., Japan) [25].

2.3.8. Swelling study

Double distilled water was used as a medium for film swelling studies. Each film sample with (2 cm × 2 cm) of the surface area was weighed and placed in the water. At scheduled time intervals, the appearance of the swelled film was observed [26].

2.3.9. Release study

In vitro drug release study was done in phosphate buffer media by means of Franz diffusion cell test apparatus at 50 rpm and 37 °C temperature. The diffusion process was done by selecting a portion of the film in the donor section and 50 ml of phosphate buffer was given to the dissolution bowl. At a regular time interval, 1 ml sample was withdrawn and substituted by the same volume of dissolution media. The amount of drug release was examined with a double beam UV–visible spectrophotometer at a defined wavelength.

2.3.10. Release kinetic study

The drug release kinetics from films are done by using different equations such as Zero-order (cumulative percentage drug release vs. time), First order (log percentage drug remaining to release vs. time), Higuchi (t half vs cumulative percentage drug release), Hixson-Crowell cube root equation (cube root of drug percentage remaining to be released vs time), Korsmeyer-Peppas (log cumulative percentage drug release vs. log time) which can be expressed as $\frac{M_t}{M_\infty} = Kt^n$, where M_t, M_∞ are the quantity of drug release at time t and infinite time correspondingly, K is the constant and n denotes diffusion exponent of drug discharge. If the value of $n = 0.43$ or less, the mechanism of drug release is Fickian and if the value of n lies stuck between 0.43 and 0.85 it is non-Fickian and if the value of $n = 0.85$ it is case II transport and if >0.85, it denotes super case II transport [27].

2.4. Statistical analysis

All the data were expressed as a mean standard deviation (SD). The assessments among groups were done using Student's *t*-test. A p-value < 0.05 was considered as indicative of significance whenever necessary.

3. Results and discussions

Calcium alginate films with altered degrees of cross-linking were produced by external gelation method. Formulation details used for the preparation of films are given in Table 1. The pictures of untreated and treated films are given in and Fig. 1a and b respectively. All the prepared films were found smooth and flexible in nature. The alginate films which were treated are found compact and compressed and they showed slight transparency in nature. In this research work, we developed films comprising with alginate and diclofenac sodium, for its use in an inflammatory condition. Fundamental properties of the film such as thickness, transparency, swelling behaviour and in vitro dissolution studies were carried out to assess the potential use of these films for pain management, inflammation and joint stiffness.

3.1. Film weight, thickness and folding endurance

The variation in weight per cm^2 of the film and the thickness of the film were observed. This difference is seen because of the variation in the nature of the polymer and their different ratios in films. It also depends on crosslinking agents. Results are shown in Table 2. It was observed, an increase of the tensile strength as an amount of glycerol increases in the formulation. Plasticizing property of the glycerol produced improved folding endurance of the films [28]. Treated films showed less flexibility than the untreated films.

3.2. Surface pH and moisture content

Surface pH of the polymeric films (F1–F10) was slightly acidic (pH 4.0–pH 5) in double distilled water, i.e. the skin pH and it will remain unchanged after administration of films. This will ensure the films may act as non-irritant to the skin. The percentage of moisture content of the different films was shown to be in between 6.25 and 10% (w/w). Moisture content prevented films from drying completely.

Table 1
Formulation details used for the preparation of films.

Formulation code	Formulation methods	Treated with $CaCl_2$
F1	–	No
F2	–	No
F3	–	No
F4	Same as F1	Treat with (0.2%)
F5	Same as F2	Treat with (0.3%)
F6	Same as F3	Treat with (0.2%)
F7	Same as F3	Treat with (0.3%)
F8	–	No
F9	Same as F8	Treat with (0.2%)
F10	Same as F8	Treat with (0.3%)

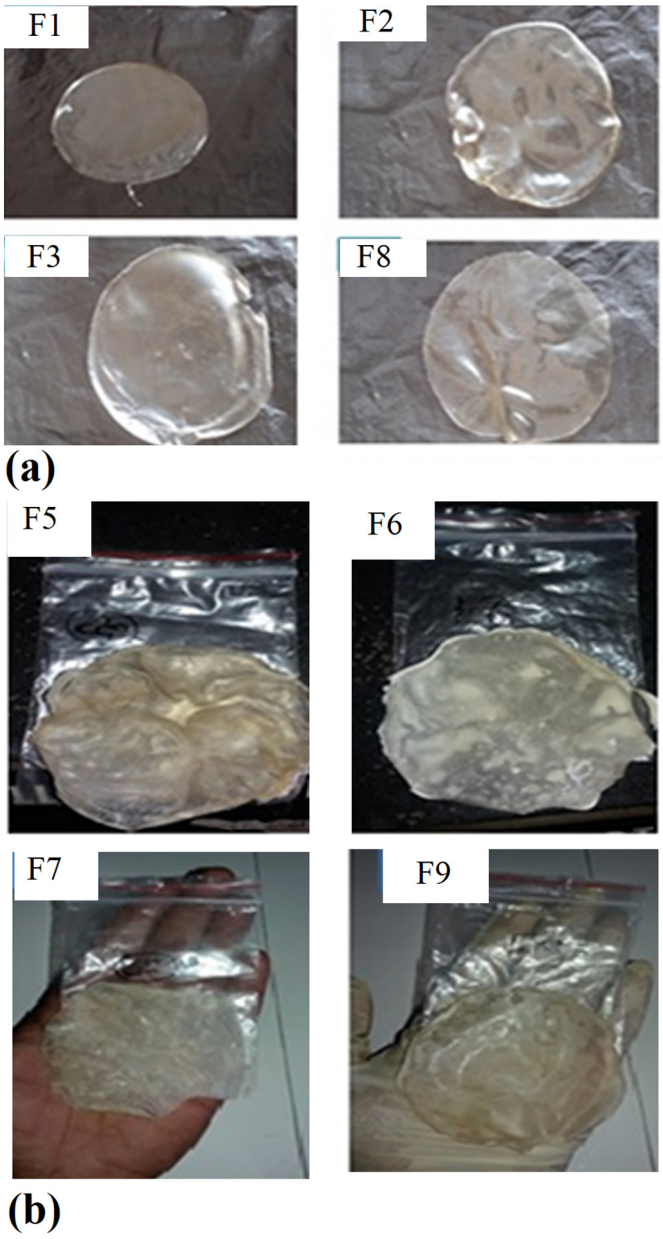

Fig. 1. Untreated films (a), treated films (b).

3.3. Measurement of mechanical property

The mechanical property of alginate films were affect significantly by the level of $CaCl_2$ used in the external gelation process. An increase in the values of tensile strength (TS) was observed with treated films.

These results are explained by the advance of an extra rigid polymer composition with reduced mobility of polymer chains as a consequence of interactions among carboxyl groups of the alginate chain and calcium ions. When some amount of alginate was replaced by HPMC, it produces a smooth and flexible film even after ion treatment.

3.4. FT-IR analysis of alginate films

The FT-IR spectrum of formulation F1 (Fig. 2a), showed the characteristic absorption bands for hydroxyl groups were found at 3430.30 cm^{-1}, stretching vibrations of aliphatic C—H was found at 2931.77 cm^{-1}, carboxylate at 1409.91 cm^{-1} and carbonyl at 1600.04 cm^{-1} which was due to the presence of sodium alginate in the formulation [29,30]. The bands at 1088.20 and 942.34 cm^{-1} were attributed to the C—O stretching vibration of the pyranosyl ring and the C—O stretching with contributions from C–C–H and C–O–H deformation [31]. Whereas in F4 (Fig. 2b) absorption bands for hydroxyl groups was found at 3351.71 cm^{-1}, carboxylate groups at 1415.18 cm^{-1} and carbonyl band were found at 1600.24 cm^{-1} and which was almost similar as formulation F1. The FTIR spectra of F6 (Fig. 2c) showed the characteristic peak at 3371.32 cm^{-1} due to OH vibrational stretching; symmetric stretching mode of methyl and hydroxyl propyl groups was found at 2927.60 cm^{-1} in which all the CH bonds extend and contract in phase; the peak at 1632.97 cm^{-1} indicated the presence of stretching vibration six-membered cyclic rings which were due to the presence of HPMC. In F6, the asymmetric bending vibrations of the methoxy group due to the presence of HPMC in that formulation found at 1416.72 cm^{-1} [30]. In F9, absorption bands found at 2922.40 cm^{-1} for C—H stretching from alkyl groups, 1424.42 cm^{-1} for CH_2 and 1079.61 cm^{-1} for C-O-C stretching (Fig. 2d) and these bands was due to the presence of PVA in the formulation. In F10, absorption bands found at 1419.81 cm^{-1} for CH_2 and 1083.79 cm^{-1} for C-O-C stretching (Fig. 2e) and these bands were due to the presence of PVA in the formulation. FTIR spectra of the pure drug (Fig. 2f) exhibited characteristic peaks at 3218.73 cm^{-1}, 1572.66 cm^{-1} (-C=O stretching of carboxyl ion), 1548 cm^{-1} (⟋⟍C = C⟍⟋ring stretching) and at 747.29 cm^{-1} (C-cl stretching). FTIR spectra of the drug-loaded film (Fig. 2g) containing sodium alginate along with HPMC shows few characteristics peaks of the drug at 1571.09 cm^{-1} (-C=O stretching of carboxyl ion), 1552 cm^{-1} (⟋⟍C = C⟍⟋ring stretching) and at 740.81 cm^{-1} (C-cl stretching) respectively and slightly shifted when compared with the pure drug.

3.5. Thermal characteristics

The DSC curve of formulation F1 (Fig. 3), shows a broad endothermic peak around 90 °C and a sharp exothermic peak at 220 °C and these peaks was due to the presence of sodium alginate in the formulation [32]. In the case of formulation F4, a broad endothermic peak was found at 70 °C and a broad exothermic peak at 250 °C. The DSC curve of formulation F6 shows a broad endothermic peak at around 80 °C and a broad exothermic peak around 250 °C; the endothermic peak

Table 2
Physicochemical properties of films.

Code	Weight (gm)	Thickness (mm)	Wt/cm^2 (gm/cm^2)	Tensile strength (g/mm^2)	Elongation at break (mm^{-2})	Moisture content (%)	pH in water
F1	0.96	0.13	0.0157	7.70	0.646	10	4.5
F2	1.11	0.14	0.0183	8.00	0.779	6.25	5
F3	0.82	0.15	0.0130	5.50	0.805	6.25	5
F4	1.34	0.16	0.0287	Very Strong	Very tough	6.25	5
F5	1.45	0.26	0.0295	Very Strong	Very tough	6.25	5
F6	1.02	0.18	0.0230	Very Strong	Very tough	6.25	4
F7	1.09	0.20	0.0240	Very Strong	Very tough	6.25	5
F8	0.82	0.15	0.0130	Very strong	Very tough	10	4
F9	1.09	0.24	0.0240	Not done	Not done	6.25	4
F10	1.20	0.28	0.0250	Not done	Not done	6.00	4

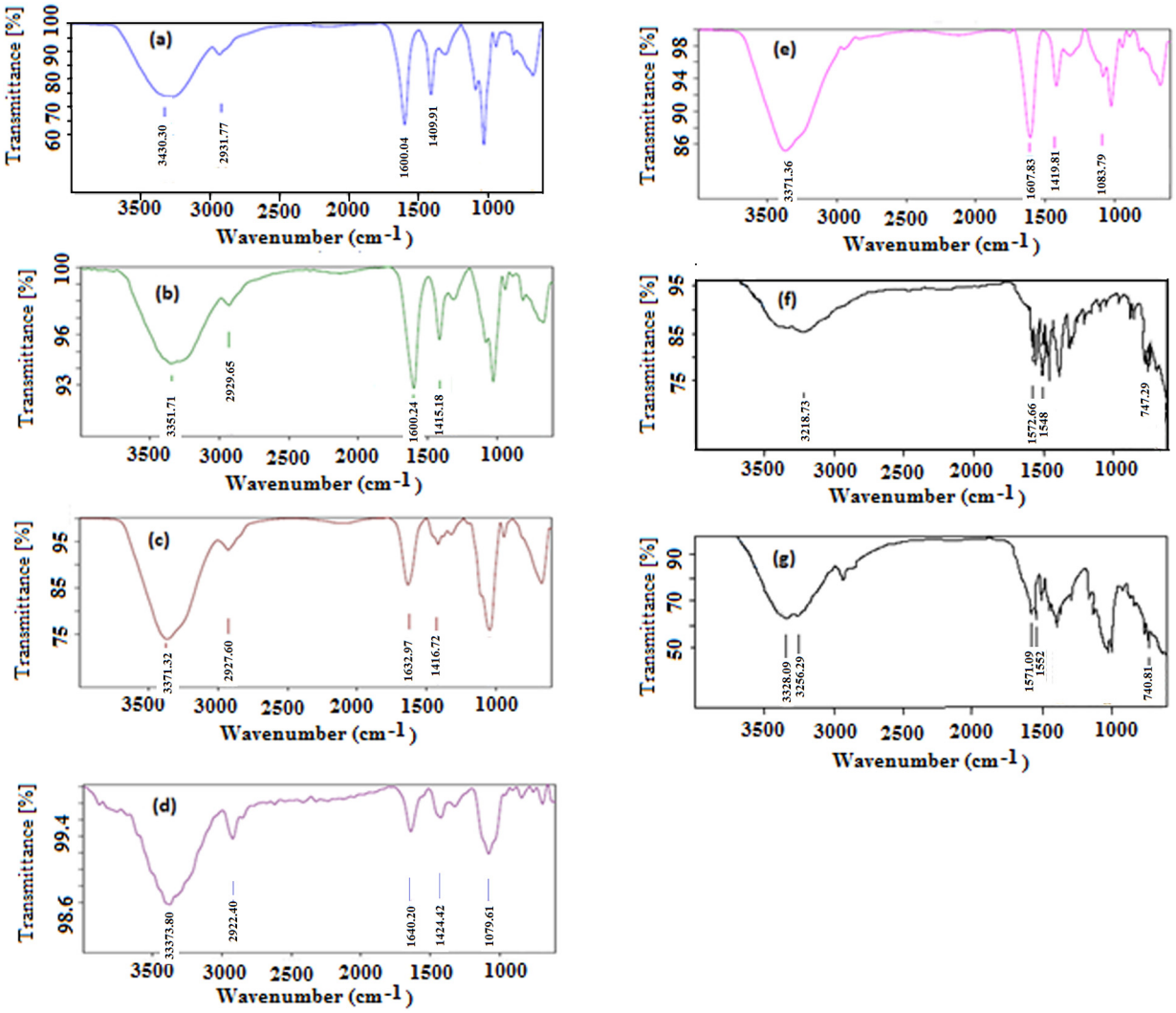

Fig. 2. FTIR spectra of (a) F1, (b) F4, (c) F6, (d) F9, (e) F10, (f) diclofenac sodium, (g) film containing (sodium alginate+ diclofenac sodium + HPMC).

was due to the presence of HPMC and exothermic peak around 250 °C was due to the presence of sodium alginate in the formulation. In case of formulation F9, a broad endothermic peak at 175 °C–199 °C indicating its melting point [33] and a broad exothermic peak at 220 °C. For the formulation F10, a broad endothermic peak was found at 75 °C and a broad exothermic peak at 210 °C. In the DSC graph (Fig. 3b), sharp melting endotherm of diclofenac sodium was observed at 287.89 °C and the data obtained was supported by the earlier researchers [34]. DSC thermogram of the film (Fig. 3c) exhibited a broad endothermic peak at around 95 °C which may be due to the removal of loosely bound water present in sodium alginate. The thermogram also showed a broad exothermic peak at around 254 °C which was owing to the pyrolysis reaction in sodium alginate [35]. In the DSC thermogram showed that the decomposition of the carbonaceous material in sodium alginate was found at a temperature above 320 °C. In this film, the drug peak at 287.89 °C was missing which could be due to the encapsulation of drug in the polymeric material. In this film, there was a peak observed at 142.99 °C which was slightly shifted from reported value and this supports the thermal stability of the film [36].

3.6. SEM images

Ca-alginate films were synthesized in two steps. After preparation of Na-alginate films or composite films, the films were treated with $CaCl_2$ as an external cross-linking agent for the preparation of Ca-alginate film. In some study [37], it had been seen that at the same time with an external cross-linking agent, also an internal cross-linking agent (sucrose) was used and their effects on surface morphology over the films were investigated by SEM. In this research, we have observed exclusively the effect of an external cross-linking agent on the morphology of composite films. After preparation of the Ca-alginate film, the films were not washed with water for the removal of untreated residue present on the film and their presence in the form of small lumps or aggregates was observed in SEM study (Fig. 4). SEM study showed that the films appeared with different physical appearance depending on cross-linking agent concentration and types of polymers. Untreated films such as F1 showed smooth structured films whereas all treated films could be seen folded in different extent. Usage of the cross-linking agent had pronounced on effect on film appearance. The rate of external gelation method both for Na-alginate film and composite film appeared to be rapid which indicated that polymers interpenetrated very well in composite films and gelation method occurred throughout the surface. Presence of other polymers (PVP and HPMC) with Na-alginate didn't hamper cross-linking interaction whereas as the presence of lactose or sucrose did the opposite [38].

3.7. Swelling study

Untreated films dissolved very quickly [39] but treated films keep their structure firm even after 5–6 h study (Fig. 5). Biodegradable and

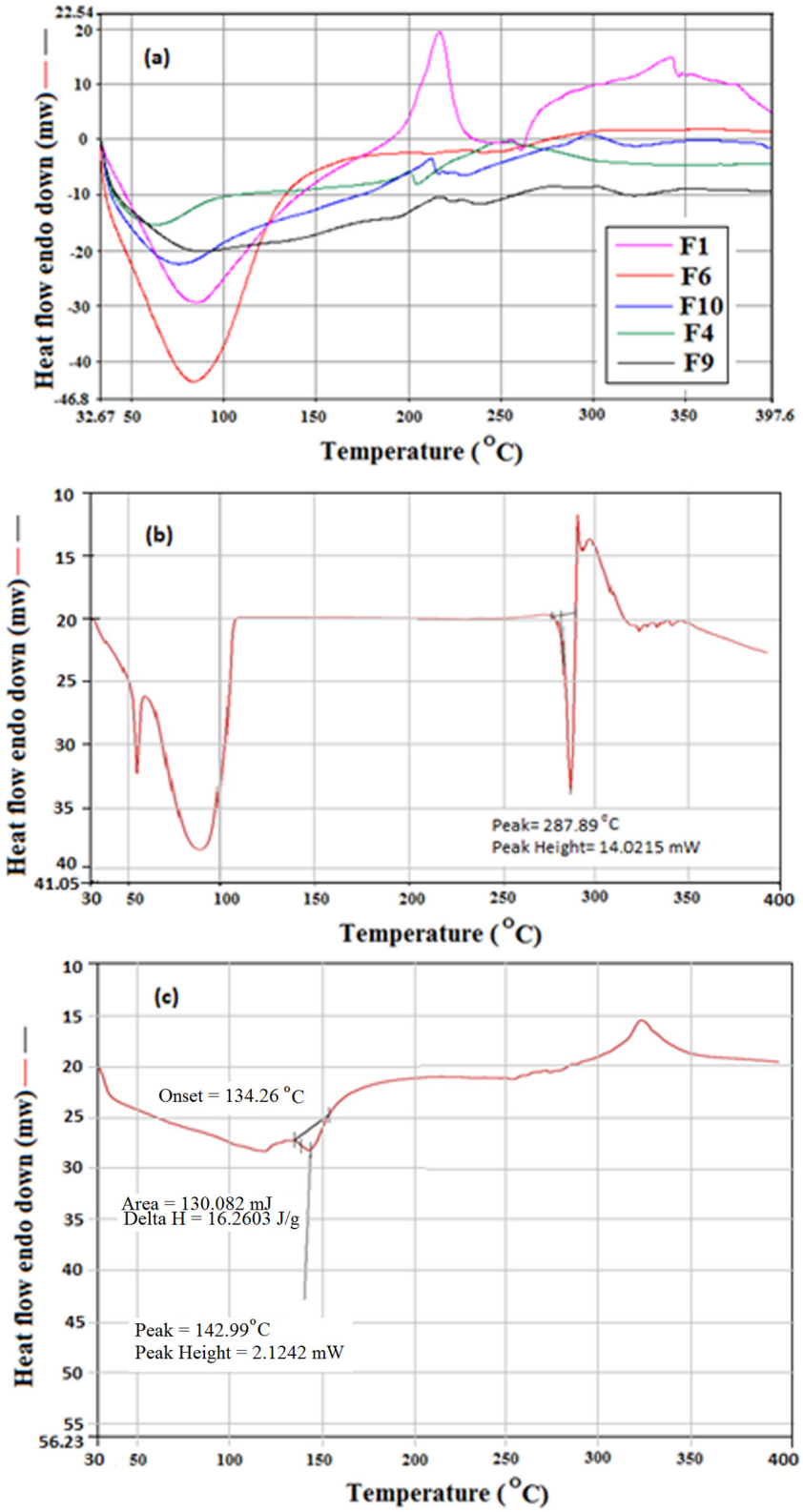

Fig. 3. DSC thermograms of: (a) F1, F4, F6, F9 and F10, (b) diclofenac sodium, (c) film containing (sodium alginate + diclofenac sodium + HPMC).

biocompatible composite films have been synthesized from different polymers (alginate, HPMC and PVP) in different ratios and their polymeric chains have interpenetrated to form interpenetrating polymeric network based composite (IPN) film. All polymers are hydrophilic in nature and these composites films dissolved in presence of water very quickly. The faster rate of swelling and subsequent solubility was seen in Na-alginate film alone along with composite film based on Na-alginate and HPMC based film in comparison to a composite film based on Na-alginate and PVP. Here swelling study proved that without any external gelation methods, the prepared films were not suitable for controlled release formulation. As soon as, the treated film came in contact with the fluid, it started to swell at a very faster rate. But when

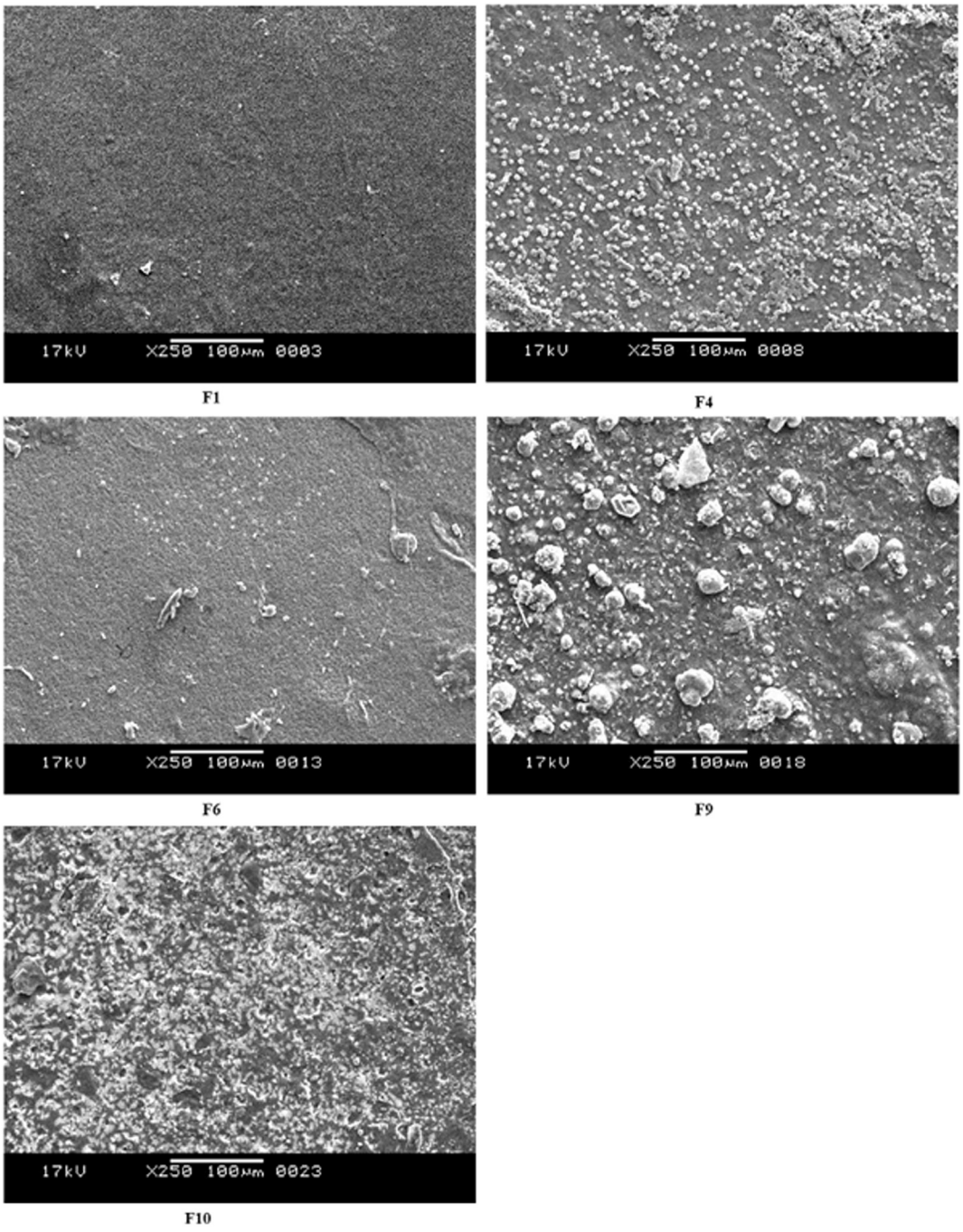

Fig. 4. Micrographs of the surface of F1, F4, F6, F9, and F10 films.

external gelation methods were used to synthesize composite films by using an ionic cross-linking agent, treated films came up with low solubility. The advantages of composite films were that swellability of films can be manipulated in a wider range and these kinds of composites will be useful for drugs that need controlled release which is very requisite for the formulation of the pharmaceutical product. Through changes in swelling property of the composite via external gelation, methods depend on polymer type [40], crosslinking time and concentration. If treated films made of only Na-alginate their swelling property were least and these are more controlled for a prolonged period. But when a certain amount of Na-alginate was replacing by HPMC, swelling improved a bit but still, they are suitable for controlled release of the drug. So these newly synthesized treated composite films may be considered or exploited as a novel formulation for controlled delivery of drugs with a wide range of their features, such as half-life, dose, hydrophobicity, and pH sensitivity.

3.8. Release study

Fig. 6, depicts the cumulative percentage release data of diclofenac from untreated and treated films at different time interval at a temperature of 37 ± 0.5 °C. It was observed that the drug release from different formulations was dependent on the type of polymer used in the formulation. The cumulative percentage release of drug from untreated Na-alginate film (F2) was ~97% after 4 h, whereas the cumulative percentage of drug release from the untreated composite film (Na-alginate and HPMC; F3) was found to be ~99% after 2 h. The presence of HPMC with Na-alginate significantly can enhance the release of the drug. It was

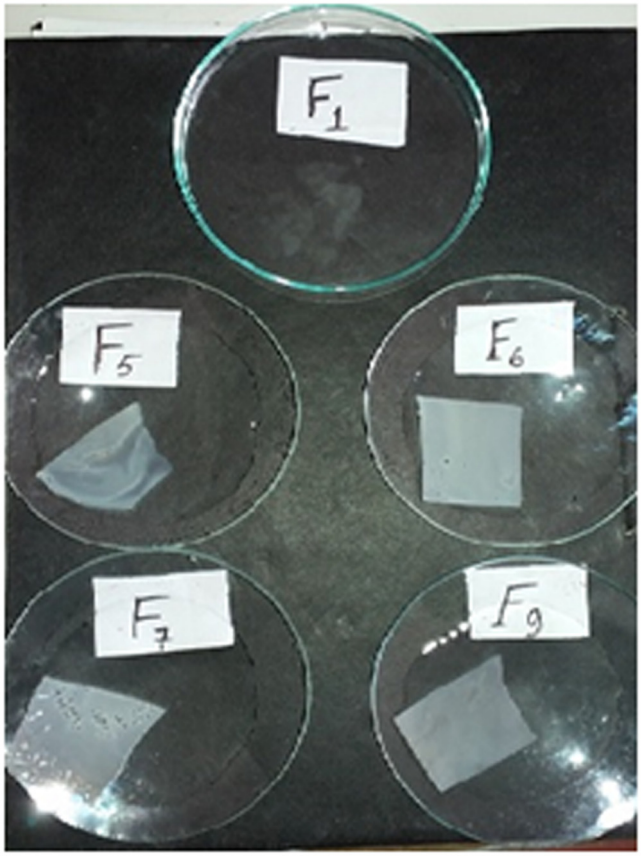

Fig. 5. Swelling study of the films.

mainly controlled by the viscosity of the polymer. Here HPMC of low viscosity was blended with Na-alginate, so retarding efficiency of HPMC toward drug release was comparatively lower than Na-alginate and as a result, the composite film released more amount of drug at specific time intervals. In both of the cases, the release profile mainly followed by the initial burst release of the drug by a continuous release. The release data showed that at the first hour, a maximum of 32% to 35%

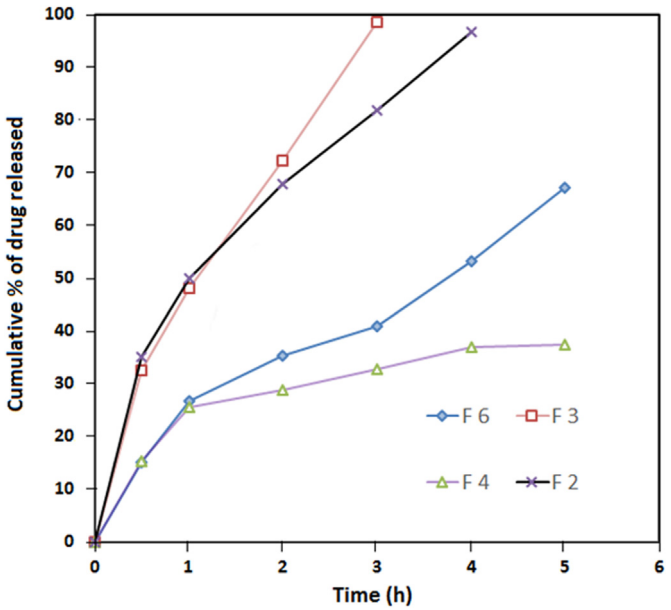

Fig. 6. Cumulative % drug release from films.

of the drug was released from both films. Drug for initial burst release mainly comes from the surface of films where drugs loosely interacted with films. The drug which was trapped inside the matrix only released when the polymer started to swell and drug release started through the loose matrix. Then release study from treated films was performed to study the effect of external gelation method on drug release from formulations. For the release study, F4 and F6 were chosen. Drug release from F4 formulation was found to be 37.34% at 5 h whereas drug release from F6 was found to be 53.25% at 4 h. So in both cases, it has been found that external gelation method has sustained their release film significantly. By this simple procedure, the biocompatible, biodegradable hydrophilic polymer can be manipulated for the requirement of drug release. Differences in drug releases in both F4 and F6 again was the same as stated above, it was mainly due to the type of polymers [41–43].

3.9. Release kinetic study

Amount of drug release or mode of drug release from a formulation is always determined by kinetic models. The release pattern of the drug from dosage form depends on different factors which may be drug's solubility, the particle size of the drug, its crystallinity, amount of the drug and also the type of formulations where the drug is encapsulated. Different kinetic models are used to describe release kinetic patterns such as Zero-order, First order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas. The mathematical expressions for the empirical/semi-empirical models are shown in Table 3.

The drug release from the formulation F6, F3, F4, and F2 were shown in Fig. 6. After fitting the drug release data from above-mentioned films in different kinetics models, it revealed that the release of drug from these formulations was explained by different mechanisms. Based on the observation (Table 4), drug release from F2 was best explained by the Higuchi model.

To determine the best drug release kinetics, the highest correlation coefficient values (r^2) were selected. The drug release kinetics from F6 was best explained by Hixon-Crowell model. According to Korsmeyer-Peppas model, the value of release exponents (n) for F6, F3 and F2 films ranging from 0.47 to 0.59 which indicates non-Fickian transport whereas film F4 ($n = 0.36$) follows Ficikian diffusion [44–49].

3.10. Statistical analysis

All results are calculated as mean values and the values are statistically significant.

4. Conclusions

In the present work, the Ca-alginate films containing diclofenac sodium a potential NSAIDS were formulated using different procedures. Observations showed that the properties of alginate films were affected by the addition of $CaCl_2$. The cross-liked films prepared by external gelation method showed high tensile strength, low elongation with porous microstructure. The selected formulation F4 and F6 showed the drug release was 37.34% after 5 h and 67.11% release after 5 h respectively. The possible mechanism for this sustained release of the drug

Table 3
Mathematical model for the kinetic release.

SL. no.	Model	Equation
1	Zero-order	$Q_t = K_0\, t + C_0$
2	First-order	$Q_t = Q_0 \exp(-K_f)\, t$
3	Higuchi	$Q_t = K_H\sqrt{t} + C_H$
4	Hixon-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s\, t$
5	Korsmeyer-Peppas	$Qt/Q_\infty = Kt^n$

Qt: cumulative percentage of drug released at time t, Q_0 is the initial amount of drug, K_0, K_f, K_H, K_s, K is release rate constants for zero-order, first-order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas respectively.

Table 4
Mathematical models with kinetic fitting results of the Ca-alginate films.

Code	Zero-order		First order		Hixson-Crowell		Higuchi		Korsmeyer-Peppas		
	K_o (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_{HC} ($h^{-1/3}$)	r^2	K_H ($h^{-1/2}$)	r^2	K_{KP} (h^{-n})	r^2	n
F6	9.893	0.9732	−0.0838	0.9288	−0.2637	0.9908	28.4348	0.9707	0.2386	0.9756	0.59
F3	25.275	0.9992	−0.7955	0.8736	−0.4918	0.9982	63.7288	0.9856	0.4836	0.9998	0.57
F4	3.151	0.9579	−0.0201	0.9594	−0.1051	0.9542	16.6952	0.9472	0.2214	0.9302	0.36
F2	15.441	0.9968	−0.3820	0.8916	−0.2987	0.9959	47.6734	0.9990	0.4906	0.9984	0.47

from the films is external gelation method. The functional properties of the films were changed significantly when polymer PVA and HPMC were added. The effect on the release profile was also observed and this is due to the polymer as they alter the alginate films properties. The SEM imaging of the films showed an apparent effect of the polymers on the surface. So from the above findings, it has been found that external gelation method has sustained the drug release from the prepared film significantly.

Conflict of interest

The authors report no conflicts of interest in this research work. The authors alone are responsible for the content and writing of this research paper.

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