Contents lists available at ScienceDirect

Future Journal of Pharmaceutical sciences

journal homepage: www.elsevier.com

Soluble starch-blended Ca^{2+}-Zn^{2+}-alginate composites-based microparticles of aceclofenac: Formulation development and *in vitro* characterization

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ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 16 September 2017
Accepted 10 October 2017
Available online xxx

Keywords:
Polymer composites
Ionotropic gelation
Microparticles
Drug release
Diffusion
Dissolution

ABSTRACT

The present article describes development starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles of aceclofenac for attaining gastric protection and controlled release delivery. Different formulations (F1 to F7) of microparticles were prepared by ionotropic gelation method and subject to characterization studies. *In vitro* drug release studies performed in 0.1 N HCl (pH 1.2) for initial 2 h and additional 5 h in phosphate buffer (pH 7.4). These microparticles were characterized by SEM, FTIR spectroscopy and XRD analyses. The formulation F7 (prepared using sodium alginate of 300 mg, soluble starch 250 mg, 5% $CaCl_2$ and 1% $ZnSO_4$) was selected as the optimized formulation, which exhibited entrapment efficiency of 85.73%, particle size of 1610 μm and viscosity of 802.16 cps. *In vitro* drug release from the formulation F7 revealed maximal 38% drug release within 7 h indicating sustained drug release profile from the prepared formulation. Also, *in vitro* swelling studies raveled maximal swelling within the period of 2 h at pH 7.4 for all these microparticles. The surface morphology studies performed using SEM showed smooth and spherical nature of the microparticles. Evaluation of drug release kinetic indicated fitting as per Korsmeyer-Peppas model and drug release via Fickian diffusion mechanism. Drug-excipient interaction studies using FTIR spectroscopy showed no change in characteristic peaks of the drug, while powder XRD revealed absence of sharp crystalline peaks of the drug. Overall, the present investigation showed successful development of microparticles of aceclofenac as an effective and cost-effective approach for oral delivery of aceclofenac.

1. Introduction

During the past few decades, natural biopolymers have been frequently used as functional excipients in designing drug delivery systems of diverse kinds owing to their excellent biocompatibility, and biodegradability. Among these, alginate, a polyanionic copolymer of mannuronic and guluronic acid residues, has been widely used in various biomedical applications [1]. Alginate undergo ionotropic gelation in the presence of divalent cations like Ca^{2+}, Zn^{2+}, Ba^{2+}, etc., and trivalent cations like Al^{3+}, etc., due to ionic interaction between carboxylic acid groups of alginate and these cations [2,3]. Various drugs have been successfully encapsulated in ionotropically-gelled alginate beads and exhibited different drug release profiles [4,5]. Although, ionotropically-gelled alginate beads can be prepared by simple and mild procedures, this method has a major limitation of drug loss during bead preparation due to leaching of drugs through the pores [6]. Therefore, many modifications of alginate beads based on the use of another polymer as blend with alginate are being investigated for drug delivery applications [1–3,7,8].

Starch is recognized as a widely accepted economical biodegradable polymer with tremendous biocompatibility and non-toxic in nature [9]. Starch is capable of producing quite stable products in the biological milieu. However, native starch is almost completely broken after its oral ingestion, when used alone for oral consumption. Therefore, it is often required to be compounded with other biocompatible polymers for the use as sustained drug release matrices [10–12]. In an investigation, Kim et al. [13] developed multifunctional starch–blended alginate beads containing L-phenyl alanine using additional alginate coating onto dried starch-alginate beads [13]. In the current study, a polymeric-*blend* of soluble starch and sodium alginate was used to develop soluble starch-blended alginate particulate matrices for the use in sustained drug release applications without any coating process. Recent report by Chan et al. [14] reported that the combination of Ca^{2+} and Zn^{2+} ions exhibited more sustained release of encapsulated drug from ionotropically gelled alginate microspheres compared to ions alone [14]. Till date no research is reported on the

Peer review under responsibility of Future University.

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https://doi.org/10.1016/j.fjps.2017.10.001
2314-7245/

preparation of soluble starch-blended alginate particles through ionotropic gelation by a combination of cross-linker ions, namely, Ca^{2+} and Zn^{2+} ions to achieve more sustained release of encapsulated drug. Aceclofenac was used as model drug in the present study to evaluate the sustained drug release potential of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate particles.

Chemically, aceclofenac is 2- [(2,' 6-'dichlorophenyl) amino] phenyl acetoyacetic acid [15]. It is used as a non–steroidal anti-inflammatory drug (NSAID) for the symptomatic treatment of pain and inflammation in arthritis osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [16]. It exhibits short half-life of 4 h and poor stability to acidic condition. Owing to its short half-life, the daily dose of aceclofenac is recommended as 200 mg in divided doses [17,18]. To increase the gastric stability, decrease the dosing frequency and adverse effects due to long-term treatment with aceclofenac, the sustained release drug delivery systems are considered as a right choice to deliver aceclofenac at a slow release rate over an extended period of time [19,20].

In this regard, the proposed research work attempts for the development of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac, which are expected to retard the release of encapsulated aceclofenac in the alkaline pH (7.4) with minimal release in the acidic environment of stomach (pH 1.2).

2. Experimental

2.1. Materials

Aceclofenac (Drakt Pharmaceutical Pvt. Ltd., Kolkata, India), sodium alginate (Central Drug House, New Delhi, India), soluble starch (Central Drug House, New Delhi, India), and calcium chloride ($CaCl_2$; Mark Specialties Pvt. Ltd, Mumbai, India) and zinc sulfate ($ZnSO_4$, Mark Specialties Pvt. Ltd, Mumbai, India) were used. All chemicals and reagents used were of analytical grade.

2.2. Preparation of aceclofenac loaded starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles

The preparation of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate based microparticles loaded with aceclofenac was carried out using a combination of cross-linker ions, containing $CaCl_2$ and $ZnSO_4$ through ionotropic gelation method. Briefly, the required amounts of soluble starch and sodium alginate were dissolved in deionized water (100 mL) using a magnetic stirrer (Remi Instruments, Mumbai, India) at 1500 rpm for 30 min and temperature at 50 ± 0.5 °C. Afterwards, aceclofenac was added to the solutions containing starch-sodium alginate polymer blend for each formulation in drug-polymer ratio of 1:2 and mixed thoroughly using a homogenizer (Remi Instruments, Mumbai, India) with a speed of 1300 rpm for 5 min. The final aceclofenac-polymer dispersions were ultrasonicated for 5 min for debubbling purpose. The bubble-free resulting dispersions were then separately added drop wise into 100 mL of cross-linking solutions containing $CaCl_2$ and $ZnSO_4$ as ionotropic cross-linkers using a 21-gauge needle. Added droplets were retained in the cross-linker solution up to 15 min for complete curing to generate the rigid spherical microparticles. The particles were separated by decantation, washed twice with deionized water and kept overnight in an oven at 40 ± 0.5 °C for drying. The dried soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac were stored in a desiccator. Fig. 1 illustrates the crosslinked chemical structure of Ca^{2+} and Zn^{2+} induced ionotropic gelation of starch with sodium alginate.

2.3. Determination of viscosity

The viscosities of different batches of starch-sodium alginate polymer-blends as 10 mL aqueous solutions were determined by a Brookfield DV III ultra V 6.0 RV Cone and Plate Rheometer (Brookfield Engineering Laboratories, Middleboro, MA) using 1 rpm spindle at 25 °C. The software used for calculation was Rheocalc v2.3 software (Brookfield. Engineering, Middleboro, MA).

2.4. Determination of drug encapsulation efficiency (DEE, %)

Accurately weighed (100 mg) of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac from each formulations were crushed separately using a pestle and mortar and, dissolved in 500 mL of phosphate buffer (pH 7.4), and incubated at 37 ± 0.5 °C with occasional shaking for 24 h. After the specified time period, the resulting solution were stirred using a magnetic stirrer at 500 rpm for 15 min. The polymer debris formed after disintegration of the particles was removed by filtration through Whatman® filter paper (No. 40). The suitably diluted filtrates were assayed spectrophotometrically using a UV-VIS spectrophotometer (Shimadzu/UV-1700, Tokyo, Japan) at the predetermined λ_{ma} of 273 nm % DEE was calculated according to the following equation [1]:

$$\%DEE = \frac{Actual\ \ drug\ \ content}{Theoretical\ \ drug\ \ content} \times 100 \quad (1)$$

2.5. Determination of particles size

Diameters of dried soluble starch-blended Ca^{2+}-Zn^{2+}-alginate particles containing aceclofenac were determined using digital slide calipers (CD-6 CS, Mitutoyo Corporation, Kawasaki, Japan) by placing the particles in between the metallic jaws. The diameters of the particles were noted in micron from the digital screen. The average particle size was calculated after measuring diameter of 20 particles from each batch.

2.6. Surface morphology analysis

The surface morphology of aceclofenac-loaded dried soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing were analyzed by scanning electron microscope (SEM) (ZEOL, JSM-5800, Japan) equipped with secondary electron detector. Sample particles were gold coated to a thickness of about 30 nm by mounting on a brass stub using double-sided adhesive tape under vacuum in an ion sputter with a thin layer of gold (3–5 nm) for 75 s using an accelerating voltage of 20 kV at x1000 and x2000 magnifications.

2.7. Fourier transform-infrared (FTIR) spectroscopy

The FTIR studies were carried out on aceclofenac, sodium alginate, blank microparticles and aceclofenac loaded microparticles, which were subjected to make powder and compressed using KBr to form pellet with the help of pellet press using FTIR spectrometer (Perkin Elmer, Massachusetts, USA). The pellets were placed in the sample holder and spectral scanning was carried out in the wavelength ranging between 3600 and 500 cm^{-1}.

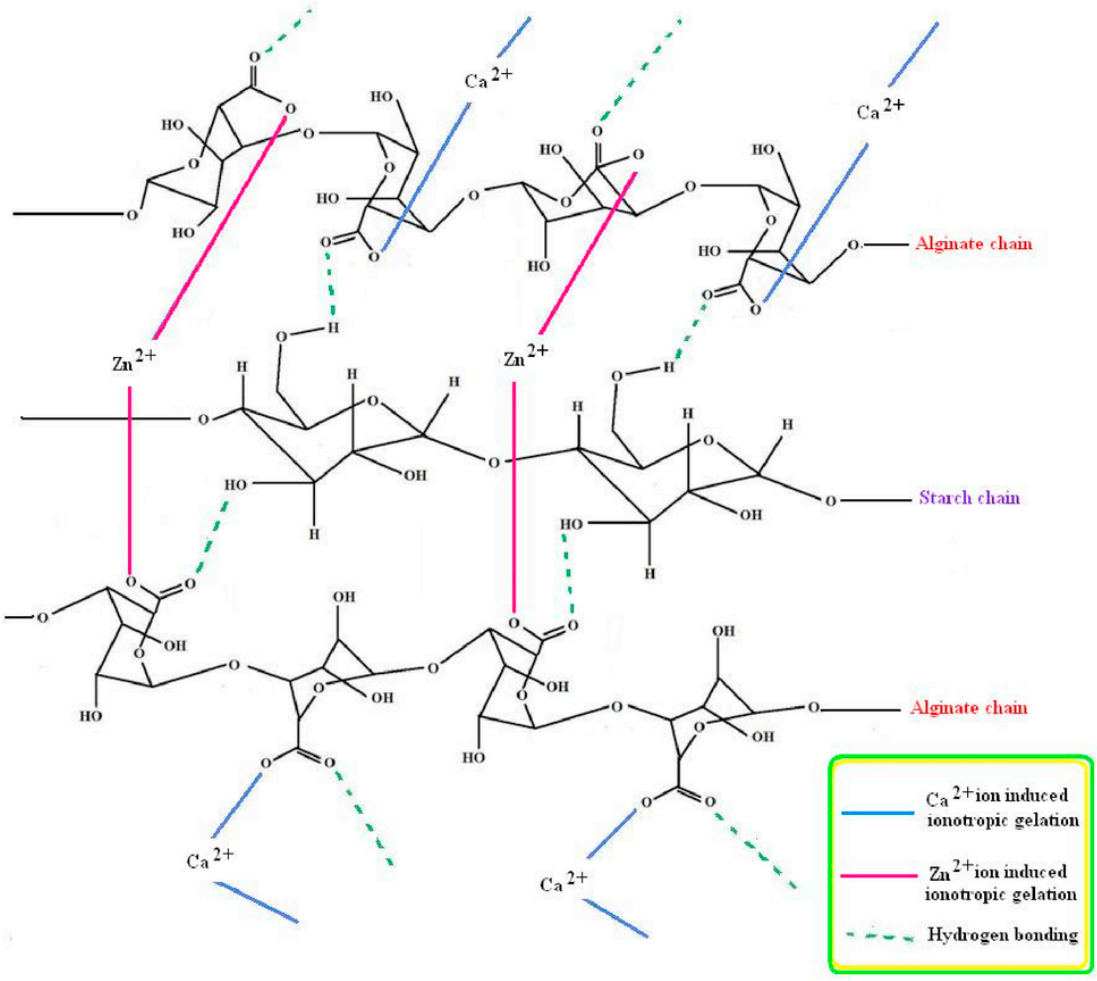

Fig. 1. Schematic structure of starch blended Ca^{2+}-Zn^{2+}-alginate composite.

2.8. Powder X-ray diffraction (P-XRD) analysis

The powder samples were exposed to Cu-Ka radiation at an accelerating voltage of 40 kV and current of 30 mA using a wide-angle X-ray diffractometer (Siemens D5000, Munich, Germany). The samples were then analyzed in the diffraction at an angle of 2θ range from 10 to 40° with scanning angular speed of 5°/min.

2.9. In vitro drug release studies

The *in vitro* release of aceclofenac from various soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles was investigated using a USP Type II dissolution apparatus (Campbell electronics, Mumbai, India). The basket of dissolution apparatus was covered with 100 mesh nylon cloth for averting the escape of the particles tested. Accurately weighed quantities of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing 100 mg of aceclofenac were added to 900 mL of dissolution medium, *i.e.*, 0.1 N HCl (pH 1.2) for initial 2 h, followed by phosphate buffer (pH 7.4) for up to 5 h. The dissolution medium was kept at 37 ± 0.5 °C and paddles speed was maintained at 50 rpm. At regular time intervals, aliquots (5 mL) were collected, and analyzed spectrophotometrically at 273 nm for estimating aceclofenac content by a UV-VIS spectrophotometer (Shimadzu/UV-1700, Japan). At each time of withdrawal, equal volume of fresh dissolution medium was replaced to maintain the sink condition.

2.10. Evaluation of drug release kinetics and release mechanism

The *in vitro* data obtained from drug release study were fitted into various release equations and kinetic models like zero-order ($Q = kt + Q_0$), first-order ($Q = Q_0e^{kt}$), Higuchi ($Q = kt^{1/2}$), and Korsmeyer-Peppas ($Q = kt^n$) model [21]. Q represents the amount of drug released at time t, Q_0 is the initial value of Q and k is the release rate constant [21,22]. The diffusion exponent (n) as mentioned in the Korsmeyer–Peppas model is the indicative of the drug release mechanism. When n is ≤ 0.45, it is Fickian diffusion, when n value between 0.45 and 0.89, it is anomalous transport, while n is ≥ 0.89, it is case-II transport.

2.11. Evaluation of swelling index

Swelling index evaluation of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac were carried out in two different media, i.e., 0.1 N HCl (pH 1.2) for 2 h and phosphate buffer (pH 7.4) for 5 h. Accurately weighed, 100 mg of soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac were placed in USP Type II dissolution apparatus (Campbell electronics,

Mumbai, India) containing 500 mL of respective media. The swelling experiment was carried out at 37± 1 °C under 50 rpm paddle speed. The swelled particles were removed at predetermined time interval and weighed after drying the surface by tissue paper. Swelling index was determined using the following equation [2]:

$$\text{Swelling index (\%)} = \frac{\text{Weight of particles after swelling} - \text{Dry weight of parti}}{\text{Dry weight of particles}} \times 100$$

2.12. Statistical analysis

All the obtained data were statistically analyzed using GraphPad Prism software, version7.0 (GraphPad Inc., Minnesota, USA), and expressed as mean ± standard deviation (S.D.) with triplicate (n = 3) observations.

3. Results and discussion

3.1. Preparation of aceclofenac-loaded starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles

As per the procedure described in experimental section, the soluble starch-blended Ca^{2+}-Zn^{2+}alginate microparticles were prepared. The detail composition regarding different batches of formulations prepared for soluble starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac are enlisted in Table 1. A total of seven formulations were prepared varying the amounts of sodium alginate and starch, at the fixed concentrations of $CaCl_2$ and $ZnSO_4$. All the prepared formulations were subjected to characterization for viscosity, particle size and % DEE.

3.2. Characterization of the starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles

3.2.1. Determination of viscosity

Evaluation of the viscosity of the prepared starch-sodium alginate polymer-blends shows values ranging between 653.4 and 802.1 cps. The values indicated increase in the viscosity of the polymer blends at high levels of both sodium alginate and starch and low viscosity values at low levels of the both the polymers. This can be attributed to the increase in the swelling characteristics of the polymer blends at their high levels upon contact with water. In this context, literature reports suggested that starch upon coming in contact with water undergo increase in the viscosity due to the amylose molecules, which forms a network to hold water molecules to increase the viscosity [23–25]. Sodium alginate also significantly contributed in increasing the viscosity in combination with the starch. As alginate forms gel by aligning its chain structure upon contact with water, it tends to increase the viscosity of polymer blend in combination with the starch [26,27].

3.2.2. Determination of drug encapsulation efficiency (DEE, %)

Evaluation of DEE for all the prepared starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac indicated values ranging between 58.5% and 87.3%. This indicated quite high values of DEE at high levels of both the polymers, which helped in effective encapsulation of the drug in it. Like drug content, the observed results on % DEE also construed suitability of the selection of product and process parameters for the preparation of microparticles [14,28,29]. Similar, results were seen in case of potato starch-blended alginate beads by Malakar et al. [24].

3.2.3. Determination of particles size

The particle size evaluation of microparticles indicated values ranging between 1.45 and 1.69 mm, which confirmed particle size in micron range. Further, observation revealed that comparatively larger particles were produced at higher polymer concentrations and vice-versa. The observed results are in consonance with the reported literature findings [16,30,31].

3.2.4. In vitro drug release studies

The *in vitro* drug release studies of all the prepared starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac were carried out in different media including 0.1 N HCl for initial 2 h and phosphate buffer for additional 5 h time period. Fig. 2 pictographically portrays the *in vitro* drug release profiles from various prepared formulations from F1 to F7. During *in vitro* release study at pH 1.2, a maximum of 20% drug release was observed, thus avoided maximal drug exposure at gastric acidic conditions. All the formulations exhibited sustained drug release characteristics within the studied period of time. Increase in the amount of both sodium alginate and starch revealed increase in the controlled release profile of the drug due to the increase in crosslinking capacity. Maximal drug release control was observed for formulation F7 owing to maximal amount of both the polymers. This can be attributed to the polymer crosslinking behavior helps in retarding the drug release rate from the polymeric matrix by diffusion controlled mechanism [1,9,32,33].

3.2.5. In vitro swelling studies

Fig. 3 illustrates the swelling index of the starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac obtained after 6 h swelling at pH 1.2 and pH 7.4 media. A gradual increase in swelling index profile was observed from formulation F1 to F5, followed by a declining trend for F6 and F7. Maximal swelling was observed from F5 and minimal swelling was seen in F1. The increase in

Table 1
Formulation compositions, drug entrapment efficiency, mean diameter and viscosity of the polymer-blend solutions.

Code	Polymer-blends		Ionic cross-linkers		DEE (%)[a]	Mean diameter (mm)[b]	Viscosity of the polymer-blend solutions (cps)[a]
	Sodium alginate (mg)	Soluble starch (mg)	$CaCl_2$ (%)	$ZnSO_4$ (%)			
F 1	250	150	3	1	58.58 ± 2.17	1.45 ± 0.15	653.46 ± 15.82
F 2	275	150	3	1	62.36 ± 2.54	1.48 ± 0.13	685.87 ± 17.07
F 3	300	150	3	1	67.73 ± 1.86	1.54 ± 0.17	703.08 ± 18.18
F 4	300	200	3	1	72.32 ± 2.04	1.62 ± 0.14	752.36 ± 16.32
F 5	300	250	3	1	78.14 ± 2.57	1.69 ± 0.19	802.16 ± 20.22
F 6	300	250	3	1	81.18 ± 3.17	1.64 ± 0.16	
F 7	300	250	3	1	85.73 ± 2.79	1.61 ± 0.16	

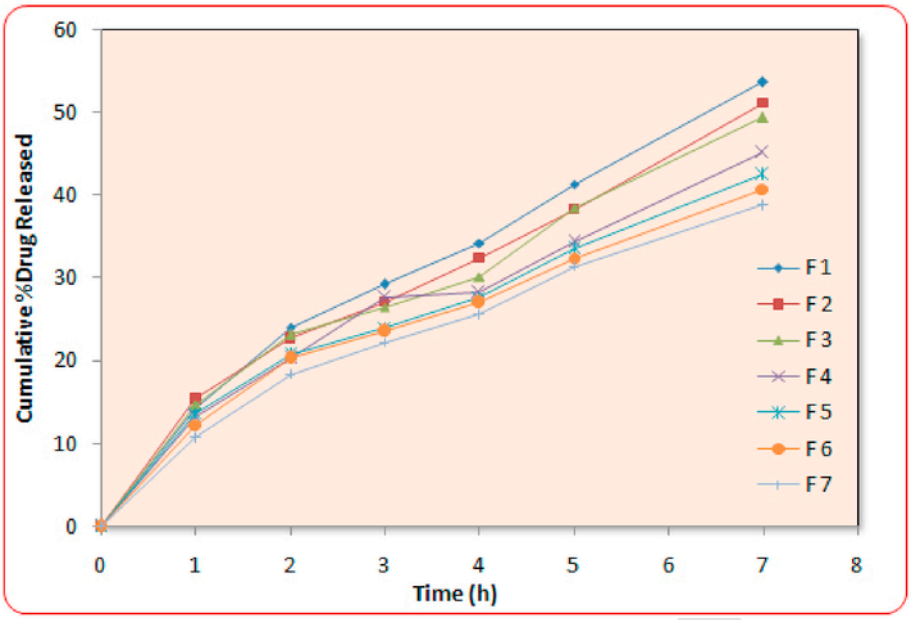

Fig. 2. *In vitro* drug release profile of aceclofenac from different microparticle formulations.

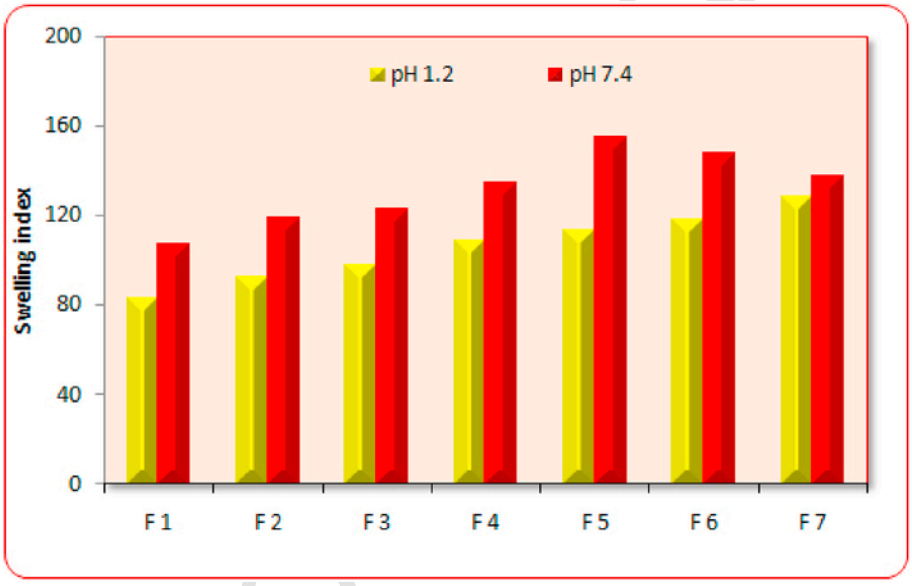

Fig. 3. *In vitro* swelling index of aceclofenac loaded microparticle formulations at pH 1.2 and pH 7.4.

polymer concentration in the microparticle formula might contributed well for higher swelling properties, which could ostensibly owing to the polysaccharide contents contributing towards the drug release behavior dependent on the degree of swelling. After attaining maximum swelling in alkaline pH (7.4), erosion and dissolution of the tested microparticles took place. The swelling profile of these starch-blended Ca^{2+}-Zn^{2+}-alginate microparticles containing aceclofenac in the alkaline pH could be elucidated by ion-exchanging between Na^{+} ions of the phosphate buffer and Ca^{2+} ions of the ionotropically cross-linked alginate microparticles by the influence of Ca^{2+}-sequestrant phosphate ions. This could result in disaggregation in the ionotropically cross-linked alginate matrix structure within these microparticles leading to matrix erosion and dissolution of the swollen beads. The observed results were quite in consonance with literature findings [8,28,34].

3.2.6. Selection of the optimized microparticle formulation

Based on the results of characterization studies, the formulation F7 was selected as the optimized formulation on the basis of higher values for viscosity, particle size and DEE. Further studies were conducted for characterization of the optimized formulation for surface morphology, FTIR, PXRD, drug release evaluation and swelling studies.

3.2.7. Surface morphology analysis

Fig. 4(A) depicts the surface image of starch-sodium alginate blend of composition F7 after crosslinking in presence of Ca^{2+}-Zn^{2+} ions

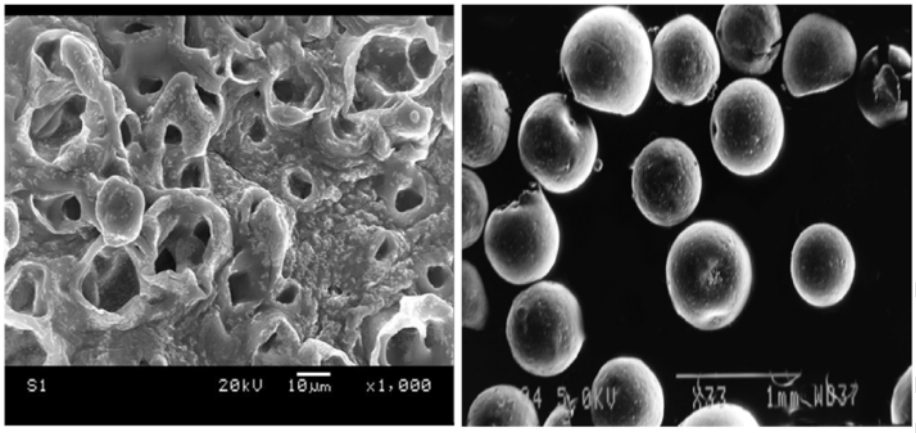

Fig. 4. SEM images (A) F7-microparticles, (B) starch blended Ca^{2+}-Zn^{2+} alginate composite.

(x1000 magnification), while Fig. 4(B) shows the SEM image of the optimized microparticle formulation (x2000 magnification). Rough protruded surface morphology was observed for the starch-alginate blend, while the microparticles were found to be spherical in appearance with quite smooth surface. Moreover, the particles were well visible under 1 mm scale, which indicated their micron sized structure.

3.2.8. Fourier transform-infrared (FTIR) spectroscopy

Fig. 5 portrays the FTIR patterns of the aceclofenac, sodium alginate, starch, blank and optimized aceclofenac loaded starch-blended Ca^{2+}-Zn^{2+} alginate microparticles (formulation F7). In the FTIR spectra of sodium alginate, starch, and formulation F7, the characteristic peaks of the natural polysaccharides were observed within the range, 3600-3200 cm^{-1} as strong and broad absorption band peaks due to —OH stretching along with some complex bands in the region of 1200-1050 cm^{-1} due to —C—O and —C—O—C— stretching vibrations. In addition, the absorption bands in the region 930-820 cm^{-1} and 785-730 cm^{-1} were also observed due to vibrational models of pyranose rings of polysaccharides. In the FTIR spectra of formulation F7, presence of strong asymmetric stretching absorption band between 1620 cm^{-1} and 1650 cm^{-1}, and weaker symmetric stretching band near 1420 cm^{-1} were supported the presence of carboxylate anion of alginate structure. The FTIR spectra of aceclofenac showed that principal peaks at 3027 cm^{-1} and 2936 cm^{-1} due to both aromatic and aliphatic —C—H stretching vibrations, respectively, a band at 1714 cm^{-1} due to C═O stretching, a sharp band at 1772 cm^{-1} due to C═O stretching of carboxylic acid and band at 3320 cm^{-1} due to secondary N—H rocking vibrations. The FTIR studies indicated no change in the characteristic signature peaks of the aceclofenac in the formulation F7 with that of the pure aceclofenac. This confirmed absence of any chemical incompatibility between the drug-excipients employed for the preparation of microparticles.

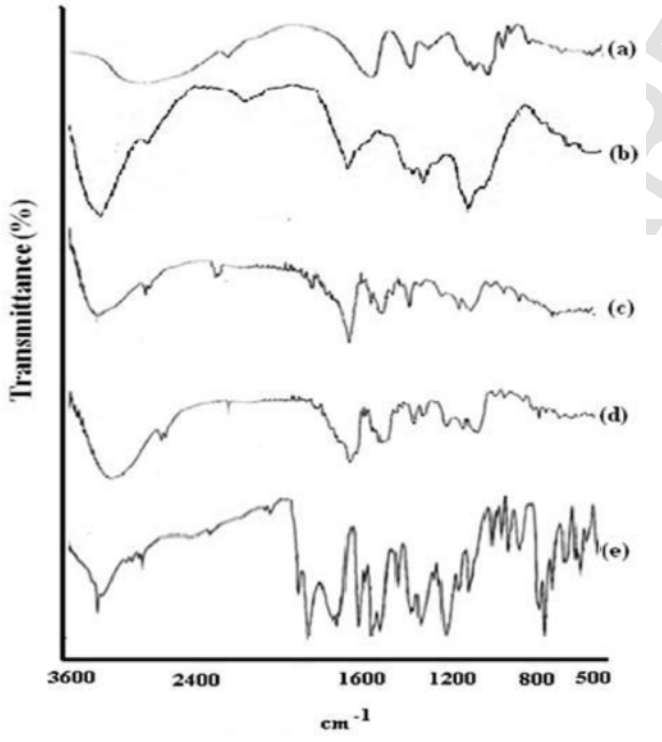

Fig. 5. FTIR spectra of (A) SA-sodium alginate, (B) Starch, (C) Blank microparticles, (D) Aceclofenac loaded microparticles-F7, (E) Plain drug-Aceclofenac.

3.2.9. Powder X-ray diffraction (P-XRD) analysis

Fig. 6 illustrates the P-XRD patterns of the aceclofenac, sodium alginate, starch and optimized aceclofenac loaded starch-blended Ca^{2+}-Zn^{2+} alginate microparticles. The P-XRD evaluation indicated crystalline nature of the aceclofenac. On the contrary, the P-XRD patterns of the sodium alginate and starch showed amorphous nature without any sharp peak. Analogously, the P-XRD pattern of the aceclofenac in the optimized microparticles also showed absence of any sharp peak indicating complete encapsulation of the drug in it.

3.2.10. Evaluation of drug release kinetics and release mechanism

Table 2 summarizes the values of release constants (K) and correlation coefficients (R) obtained after mathematical fitting of *in vitro* drug release *vs*. time data for optimized formulation F7. Higher value of R^2 was observed as per the Korsmeyer-Peppas model indicating drug release analogous to first-order rate kinetics. Moreover, exploration of with other mathematical models (*i.e.,* zero-order, first-order and Higuchi model) also revealed quite high degree of fitting, which can be evident from the values of "R^2".

Evaluation of the drug release mechanism through release exponent (n) of Korsmeyer-Peppas model indicated values for the optimized formulation F7 showed value (n = 0.267) < 0.45 for the spherical

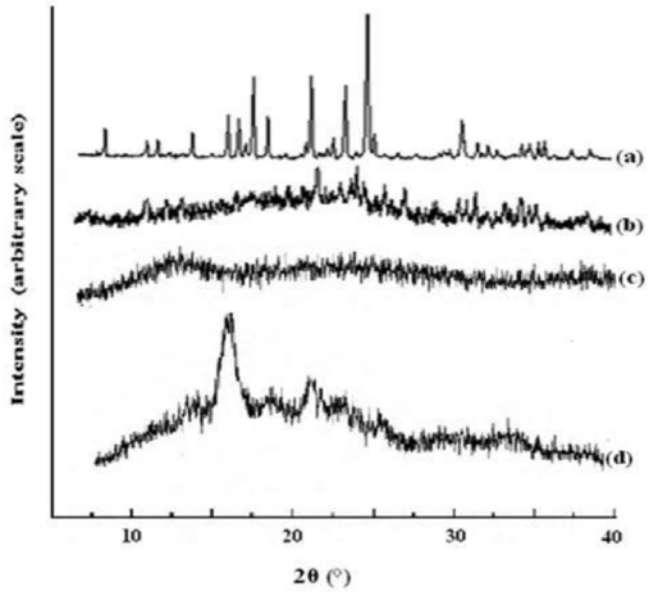

Fig. 6. Powder XRD spectra of (A) Plain drug-Aceclofenac, (B) Aceclofenac loaded microparticles-F7, (A) SA-sodium alginate, (B) Starch.

Table 2
Drug release kinetic modeling for the optimized microparticles (F7).

Models	Model coefficient	R
Zero-order	0.001	0.769
First-order	0.154	0.972
Higuchi	0.616	0.985
Korsmeyer-Peppas	0.001	0.994

shaped system, thus indicated drug release governed by Fickian diffusion mechanism. Such phenomenon is quite usual in case of polymeric drug carrier systems containing polysaccharides. The swellable nature of the carrier causes itself to release drug from the polymeric matrix via diffusion mechanism in a first-order rate. Several literature reports are available on polysaccharide based microparticle systems governing drug release through diffusion controlled mechanisms [6,10,35,36].

4. Conclusion

The present research work pertains to the development of drug loaded microparticles of aceclofenac from the polymer composite containing starch blended Ca^{2+}-Zn^{2+} alginate. The developed formulation revealed high drug entrapment efficiency, particle size in the micron range, along with good swelling properties, controlled drug release behavior and maximal gastric protection of the drug from degradation. Moreover, the developed optimized formulation showed drug release via Fickian diffusion mechanism, which further corroborated the drug diffusion based on the microparticle characteristics. The observed satisfactory results from the work vouch applicability of the developed formulations for other similar type of drugs too.

Conflict of interest

The authors declare no conflict of interest.

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