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Pectin–gelatin and alginate–gelatin complex coacervation for controlled drug delivery: Influence of anionic polysaccharides and drugs being encapsulated on physicochemical properties of microcapsules

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ABSTRACT

Microencapsulations using pectin and alginate by complex coacervation with gelatin were studied using metronidazole hydrochloride (MH), diclofenac sodium (DS) and indomethacin (IM) as core material. MH was poorly encapsulated (4–7% w/w) than DS (49–53% w/w) and IM (62–66% w/w). Pectin produced coacervation with gelatin with all acidifiers but alginate produced coacervation only with acetic acid. Addition of sodium carboxymethyl cellulose reduced aggregation between the microparticles. FT-IR confirmed the complexation between pectin or alginate with gelatin and intact nature of encapsulated drug. Microencapsulation of MH produced microspheres and DS/IM resulted in irregular particles. Alginate–gelatin produced smaller microparticles than pectin–gelatin. DSC of microcapsules revealed change in physical nature of DS whereas IM produced no changes. The microcapsules showed low drug release in gastric fluid and sustained release in intestinal fluid. Alginate was better than pectin for coacervation with gelatin in terms of less aggregation, smaller particle size and easy dispersion.

1. Introduction

Complex coacervation is the one of the oldest and simplest method (Deasy, 1984) of encapsulating drugs for sustained drug delivery. Because of simple preparation conditions such as use of non-toxic solvent and low agitation, they are also employed in the encapsulation of protein (Polk, Amsden, Yao, Peng, & Goosen, 1994) and human cells (Wen, Alexander, Inchikel, & Stevenson, 1995). Complex coacervation involves reaction between two oppositely charged polymers to yield a polymer rich and polymer poor region. The polymer rich region used to coat the core (drug) particles. Various negatively charged polysaccharides (Kruif, Weinbreck, & Vries, 2004) such as acacia, pectin, alginate and carboxy methyl cellulose were used with positively charged protein molecules such as gelatin and chitosan. Acacia–gelatin complex coacervation (Palmieri, Lauri, Martelli, & Wehrle, 1999) is the most widely used system than others.

The concentration of polymer employed and pH of coacervation are most important characters in the microencapsulation by coacervation. Apart from this, nature of carbohydrate polymer and core material used also influence the end product. Cohesion and adhersion are the limitations in microencapsulation by complex coacervation. There are few research articles available about pectin–gelatin (Joseph & Venkatram, 1995; McMullen, Newton, & Becker, 1982; Saravanan, Kishore, Ramachandran, Rao, & Sridhar, 2002) and alginate–gelatin coacervation (Joseph & Venkatram, 1995; Shinde & Nagarsenker, 2009) systems. Only little information available in the literature about the influence of polymers and core material in the physicochemical properties (such as polymorphism, crystalline or amorphous form, microcapsules or microspheres etc.) of the end product obtained by the microencapsulation by these systems. In addition, very little work done to compare and select suitable negatively charged carbohydrate polymer to use against gelatin.

In the present work we have compared the efficiency of pectin–gelatin and alginate–gelatin coacervation systems to encapsulate core material (drugs) with different water solubility. The pectin–gelatin and alginate–gelatin coacervation systems were compared in terms of loading/encapsulation efficiency, size distribution, shape, agglomeration of end product and *in vitro* drug release. Three drugs namely metronidazole hydrochloride, diclofenac sodium and indomethacin with different water solubility were selected for this purpose. Metronidazole hydrochloride is a water soluble drug and well soluble in acidic pH. Diclofenac sodium is soluble in alkaline pH and insoluble in acidic pH. Indomethacin is

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insoluble in water irrespective of the pH. The complex coacervation of pectin–gelatin and alginate–gelatin are pH dependent and will take place at pH around 3.5–4. The solubility of selected core material will differ in the pH at which coacervation takes place and thus affect the physicochemical nature of microcapsules or end products. Influence of acid used to adjust the pH to induce coacervation and effect of addition of anti-adhering agent on the end product were also studied.

Microcapsules produced by the pectin–gelatin and alginate–gelatin complex coacervation were evaluated by drug loading, encapsulation efficiency, optical microscopy, scanning electron microscopy (SEM), size distribution, Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and *in vitro* release studies.

2. Experimental

2.1. Materials

Sodium alginate and pectin was purchased from Fluka AG, Switzerland. Gelatin obtained from Oxoid Ltd, England. Sodium carboxymethyl cellulose was purchased from Loba Chemie, India. Glutaraldehyde was purchased from S.D. fine chemicals, India. Diclofenac sodium IP, metronidazole hydrochloride IP and indomethacin IP were gift samples obtained from MARAL, Chennai, India. All other reagents and chemicals used were of analytical grade.

2.2. Microencapsulation using pectin–gelatin complex coacervation

Fifty milliliters of 2% w/v of pectin and gelatin solutions were prepared separately by heating at 45 °C. The pH of each solution was adjusted to 7.5 using 1 N sodium hydroxide before making up the volume to 50 ml. One gram of drug as mentioned in Table 1 was dissolved (metronidazole hydrochloride and diclofenac sodium) or suspended (indomethacin) in gelatin solution by magnetic stirring for 15 min to get clear solution or lump free suspension. Then 50 ml of pectin solution was added to gelatin solution and stirred well using magnetic pellet (Approx 500 rpm). The temperature of the mixture was maintained at 45 °C and pH was reduced from 7.5 to 5 by fast addition of 0.5 N HCl. Then the 0.5 N HCl was added drop wise to bring down the pH to 3.8 to induce coacervation.

The temperature of the whole system was lowered to 5 °C by keeping the mixture in an ice bath and stirring was continued with magnetic pellet. Ten ml of 1% w/v of sodium carboxy methyl cellulose was added to the above mixture and stirred continuously at 5 °C for 1 h. Then one ml of 25% w/w aqueous glutaraldehyde was added and stirred for 3 h at room temperature and the cross-linking was quenched by the addition of 4 ml of 1 M glycine solution. The whole system was kept in undisturbed condition for complete settling of the microspheres. The upper clear liquid was decanted and the lower sedimented mass was washed with water to remove unencapsulated drug. The product thus obtained was washed with 50 ml of 50%, 75%, 99% v/v of isopropyl alcohol and dried at room temperature.

2.3. Microencapsulation using alginate–gelatin complex coacervation

Fifty milliliters of 2% w/v of sodium alginate and gelatin solutions were prepared separately by heating at 45 °C. The drugs were encapsulated by alginate–gelatin complex coacervation similarly as described in microencapsulation by for pectin–gelatin complex coacervation except 10% v/v of acetic acid was used instead of HCl.

2.4. Determination of drug content

2.4.1. Estimation of metronidazole hydrochloride

One-hundred milligrams of the microencapsulated product was digested in 10 ml of 5 N HCl at room temperature. Then it was diluted to 100 ml with water, filtered to remove debris and analyzed for metronidazole hydrochloride content at 277 nm using a UV visible spectrophotometer (Shimadzu 2100S).

2.4.2. Estimation of diclofenac sodium/indomethacin

One-hundred milligrams of microcapsules containing diclofenac sodium or indomethacin was added to 50 ml of boric acid buffer (pH 9.0) and stirred at 50 °C for 5 h. Allowed to cool, filtered and analyzed for drug content using spectrophotometer at 277 nm for diclofenac sodium or 320 nm for indomethacin.

2.5. Determination of percentage of drug loading

The percentage of drug loading can be estimated by using the following formula:

$$L = \frac{Q_m}{W_m} \times 100$$

where, L is the percentage loading of microcapsules, Q_m is the quantity of drug in g present in W_m of microcapsules and W_m is the weight of microcapsules in g.

2.6. Determination of encapsulation efficiency

The amount of metronidazole hydrochloride or diclofenac sodium or indomethacin encapsulated in the microcapsules was determined by using the following formula:

$$E = \frac{Q_p}{Q_t} \times 100$$

where, E is the% of encapsulation of microcapsules, Q_p is the quantity of drug encapsulated in microcapsules (g), Q_t is the quantity of drug added for encapsulation (g), Q_p is the product of drug content per gm of microcapsules and yield of microcapsules (g).

Table 1
Formula and physicochemical parameters of pectin–gelatin and alginate–gelatin microcapsules prepared by complex coacervation.

S. No	Pectin (g)	Sodium alginate (g)	Gelatin (g)	Drugs[a] used (g)	Drug–polymer ratio	Yield in g ($n = 3 \pm SD$)	Percentage of loading ($n = 3 \pm SD$)	Percentage of encapsulation	Average particle size (μm)	Specific surface area (m^2/g)
1	1	0	1	MH 1 g	2:1	0.55 ± 0.14	5.32 ± 0.31	2.92	45.14	0.2301
2	1	0	1	DS 2 g	1:1	2.64 ± 0.46	57.61 ± 0.47	76.03	94.46	0.1422
3	1	0	1	IM 2 g	1:1	2.94 ± 0.51	62.42 ± 0.71	91.76	120.94	0.097
4	0	1	1	MH 1 g	2:1	0.96 ± 0.37	6.51 ± 0.43	6.25	41.34	0.2827
5	0	1	1	DS 2 g	1:1	2.86 ± 0.32	59.91 ± 0.66	85.66	82.93	0.1608
6	0	1	1	IM 2 g	1:1	3.07 ± 0.21	62.73 ± 0.42	96.3	110.64	0.1034

[a] MH, DS, IM represents metronidazole hydrochloride, diclofenac sodium and indomethacin, respectively.

2.7. Optical microscopy

Optical micrographs were taken with a Reichert, Polyvan 2 MET, Austria optical microscope using 35 mm 125 ASA/ISO black and white film.

2.8. Scanning electron microscopy

The sample for the scanning electron microscopy (SEM) analysis was prepared by sprinkling the microspheres one side of double adhesive stub. The stub was then coated with gold using Jeol JFC 1100 sputter coater. The SEM analysis of the microspheres was carried out by using Jeol JSM 5300, Japan. The microspheres were viewed at an accelerating voltage of 15 kV.

2.9. Particle size analysis

Microcapsules were dispersed in 25% v/v isopropyl alcohol containing 0.05% w/v of Tween 80 and vortexed for 3 min. Then the particle size analysis was carried out using Malvern sizer with a focal length of 300 mm and plotted for size distribution using the software supplied by the manufacturer.

2.10. Fourier-transform infrared spectroscopy

Infrared spectrum of pectin, sodium alginate, gelatin, diclofenac sodium, indomethacin and drug loaded microcapsules were taken using KBr pellet technique and were recorded on a Nicolet 20 DXB FT-IR spectrophotometer.

2.11. Differential scanning calorimetry

Differential scanning calorimetry (DSC) of diclofenac sodium, indomethacin and microcapsules were performed using Perkin–Elmer DSC-7 model. The instrument was calibrated with indium. All the samples (≈5 mg) were heated in aluminum pans using dry nitrogen as the effluent gas. The analysis was performed with a heating range of 50–350 °C and at a rate of 20 °C min^{-1}.

2.12. In vitro release studies

The *in vitro* release studies of drug loaded microcapsules were carried out at 37 °C using simulated gastric fluid and intestinal fluid (without enzymes). Microcapsules equivalent to 50 mg of drug were individually added to 100 ml of simulated gastric fluid in a 250 ml Erlenmeyer flask. The flasks were shaken (100 rpm) in an incubator at 37 °C. After two hours microcapsules were filtered and transferred to Erlenmeyer flask containing 100 ml of simulated intestinal fluid and the study was continued for 15 h. One milliliter of samples was withdrawn at regular time intervals and same volume of medium was replaced. Diclofenac sodium and indomethacin released were estimated at 277 and 320 nm, respectively.

3. Results and discussion

Complex coacervation is a simple method of microencapsulation to encapsulate drugs, living cells and enzymes. It has wider application in the delivery of drugs, biological and flavoring agents. Complex coacervation involves interaction between an anionic and a cationic substance. Though the method is simple, it is very difficult to optimize conditions such as pH of coacervation, concentration of polymers and ratio of anionic polymer to cationic polymer. Apart from this, microcapsules produced my complexation will tend to adhere them self as well as to the container in which they are prepared. The physicochemical property of microcapsules depend on various parameters like (McMullen, Newton, & Becker, 1984; Saravanan et al., 2002) core: coat ratio, anionic vs. cationic polymer ratio, degree of cross-linking, addition of anti-adhesive agent, nature and source of polymer used.

In the present work we have compared two carbohydrate polymers namely pectin and alginate for their efficiency in producing microcapsules with gelatin by complex coacervation. Pectin is methoxy ester of pectic acid. Pectic acid is an aldobionic acid (Wallis, 1985) and these acidic groups provide negative charge to pectin. Alginate consists of alginic acid, a polyuronic acid (Wallis, 1985) that provides negative charges to alginate. Gelatin is amphoteric in nature (Deasy, 1984) due to presence of carboxylic and amino guanidine groups. At acidic pH gelatin will have net positive charge and hence can able to form complex with negatively charged polysaccharide molecules such as pectin and alginate. The model drugs chosen are metronidazole hydrochloride, diclofenac sodium and indomethacin. These drugs were chosen based on different water solubility.

3.1. Effect of acid employed to produce complex coacervation

Various acidifiers like hydrochloric acid, citric acid, sulphuric acid, nitric acid and acetic acid were used to adjust the pH of the system to induce complex coacervation between pectin/alginate with gelatin. The pectin–gelatin coacervation was induced with all tested acidifiers. The alginate–gelatin coacervation was induced only with acetic acid. We have observed the stages of alginate–gelatin coacervation with help of microscope after the each addition of acid near coacervation pH (3–4.5). The coacervation was induced with acetic acid, other acids produced precipitate and weak acid (citric acid) produced no coacervation. Even though hydrochloric acid was used to induce complex coacervation by Joseph and Venkatram (1995) and Shinde and Nagarsenker (2009) between alginate and gelatin, however in the present study under given preparation conditions alginate–gelatin coacervation produced only with acetic acid. This could be due to precipitation of free alginic acid from sodium alginate solution during the addition of strong acid such as HCl. The precipitated alginic acid is insoluble in water, hence unable to form complexation with gelatin. Addition of acetic acid in alginate–gelatin system produced coacervation which was confirmed by formation of spherical droplets observed under microscope near coacervation pH 3.5–4. Acetic acid may be weaker than the alginic acid to induce precipitation from its sodium salt; at the same time it is good enough to induce coacervation. However we are unclear why only acetic acid produced coacervation in alginate–gelatin system and no information available in the literature about this effect. Apart from acid, source of the material employed (gelatin, alginate) is also an important factor for coacervation. Change in type of gelatin and alginate may also influence formation of coacervate.

3.2. Sodium carboxymethyl cellulose as an anti-adhesive agent

Aggregations of coacervated particles are common problem in microencapsulation by complex coacervation. During the preparation the particles were adhered with each other as well as to the glass vessels where they are being prepared. This may be due to strong attractive forces held between two oppositely charged particles. The problem continued till the filtration stage as the particles adhered on the surface of the filter paper. To reduce aggregation we have tried different agents (Deasy, 1984) such as colloidal silica, calcium chloride, glycerin and sodium carboxymethyl cellulose (SCMC) in the coacervation system. We found SCMC as an effective agent than others in terms of easy recovery of particles, easy dispersion in water and less aggregation. SCMC

has negative charges due to free carboxyl group and presence of SCMC around the coacervated particle might have repelled each other due to same electric charges and thereby acted as anti-adhesive agent.

3.3. Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency of pectin–gelatin and alginate–gelatin microcapsules obtained by complex coacervation was shown in Table 1. Metronidazole hydrochloride was poorly encapsulated by both pectin–gelatin and alginate–gelatin coacervation system. This may be due to escape of drug molecules from the coacervation phase due to its higher solubility in water. Diclofenac sodium though soluble in alkaline pH, but crystallized during the adjustment of pH (around 5.5) to induce coacervation, has shown good loading and encapsulation efficiency. A water insoluble drug indomethacin was better encapsulated than metronidazole hydrochloride and diclofenac sodium. No comparative data available in the literature about the encapsulation of various drugs with different water solubility by pectin/alginate–gelatin complex coacervation. However, Joseph and Venkatram (1995) reported 75–99% encapsulation of indomethacin by pectin–gelatin and alginate–gelatin microcapsules. As shown in Table 1, alginate–gelatin showed greater loading and encapsulation efficiency than the pectin–gelatin. This may be due to higher yield obtained in alginate–gelatin complex coacervation.

To understand the physicochemical nature of the microcapsules obtained from complex coacervation, the particles were further characterized by size distribution, optical microscopy and SEM. FT-IR analyses were done to confirm the complexation between the pectin–gelatin and alginate–pectin as well as intact nature of encapsulated drug. DSC was done to find out the physical nature

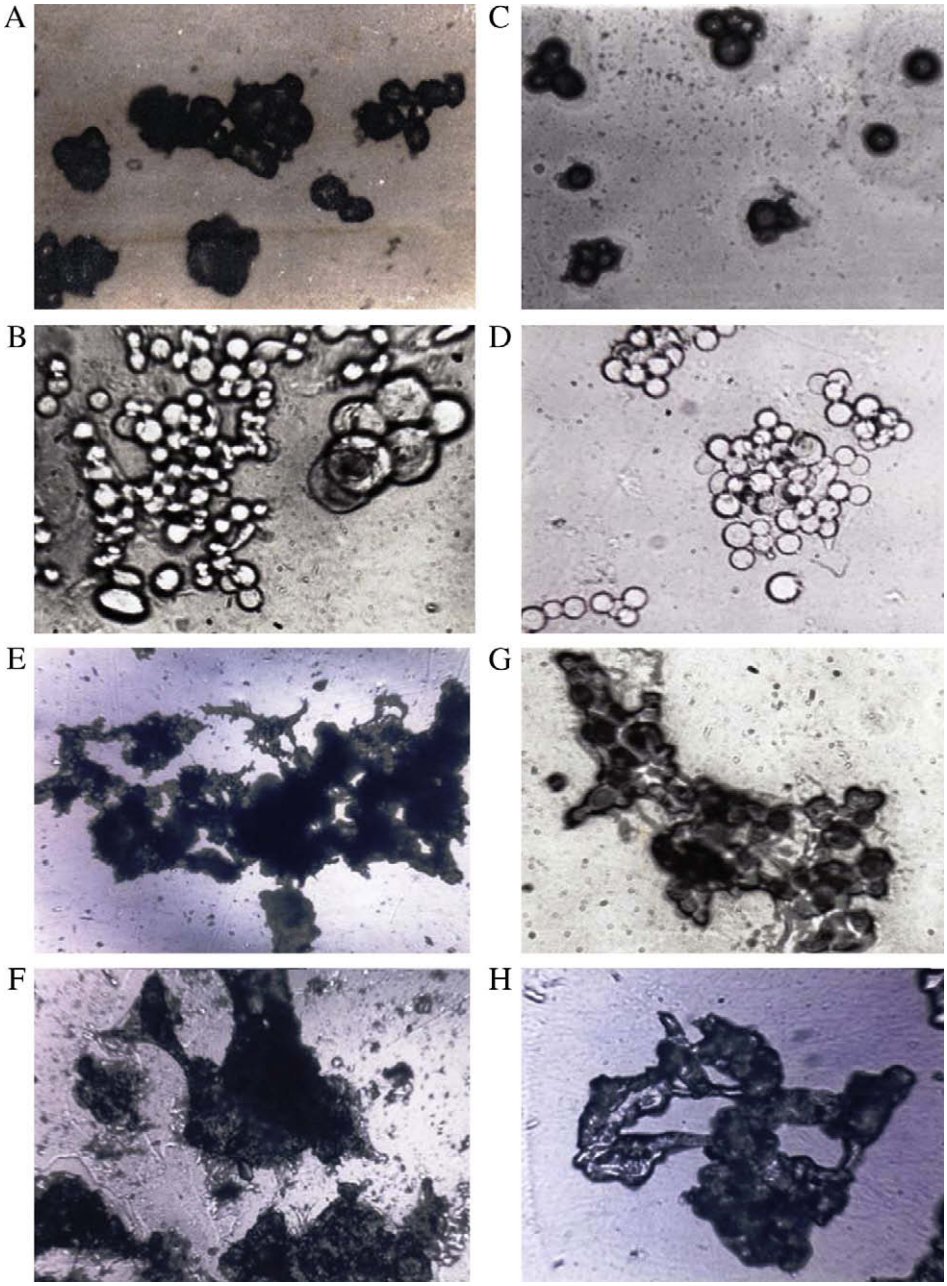

Fig. 1. Photomicrographs of pectin–gelatin microspheres loaded with metronidazole hydrochloride in dry (A) and wet (B) conditions, alginate–gelatin microspheres loaded with metronidazole hydrochloride in dry (C) and wet (D) conditions. It also shows pectin–gelatin microcapsules loaded with diclofenac sodium (E) and indomethacin (F), alginate–gelatin microcapsules loaded with diclofenac sodium (G) and indomethacin (H). (400× magnification).

of entrapped drug in the microcapsules. Because of poor loading and encapsulation efficiency metronidazole hydrochloride loaded microparticles were not further characterized by FT-IR DSC and *in vitro* release.

3.4. Optical microscopy

Photomicrographs of product obtained by pectin–gelatin and alginate–gelatin complex coacervation are shown in Fig. 1. Encapsulation of water soluble drug produced spherical particles as the coacervate phase is not coalesced and remains as individual coacervate globules. The metronidazole loaded microspheres were spherical and aggregated as evidenced by the photograph (Fig. 1A–D). alginate–gelatin produced lesser aggregation and few individual spheres were also seen (Fig. 1C). The coacervate globules swell and separate when dispersed in water as seen in photograph Fig. 1B and D. The alginate–gelatin system showed more distinct microspheres (Fig. 1D) than pectin–gelatin which was slightly oval and larger in shape (Fig. 1B). The encapsulation of diclofenac sodium (Fig. 1E and G) and indomethacin (Fig. 1F and H) produced irregular particles as seen in photomicrograph. Fig. 1G shows diclofenac crystals surrounded by the alginate–gelatin coacervate globules to form wall of the microcapsule.

3.5. SEM

SEM Photomicrographs of product obtained by pectin–gelatin and alginate–gelatin complex coacervation are shown in Fig. 2. SEM confirms the spherical nature of pectin–gelatin (Fig. 2A) and alginate–gelatin microglobules (Fig. 2B) loaded with metronidazole hydrochloride. The alginate–gelatin produced comparatively uniform and smaller microspheres with lesser aggregation (Fig. 2B) than pectin–gelatin system (Fig. 2A). The microspheres of alginate–gelatin coacervation were found to be less than 10 micrometer where as pectin–gelatin microspheres were 30 μm. Encapsulation of diclofenac and indomethacin produced irregular clusters (Fig. 2C–F). SEM also revealed the coalescence of coacervate globules around the drug particles (Fig. 2F) to form wall of the microcapsules. This picture indicates the presence of alginate–pectin coacervate globules around the indomethacin crystal.

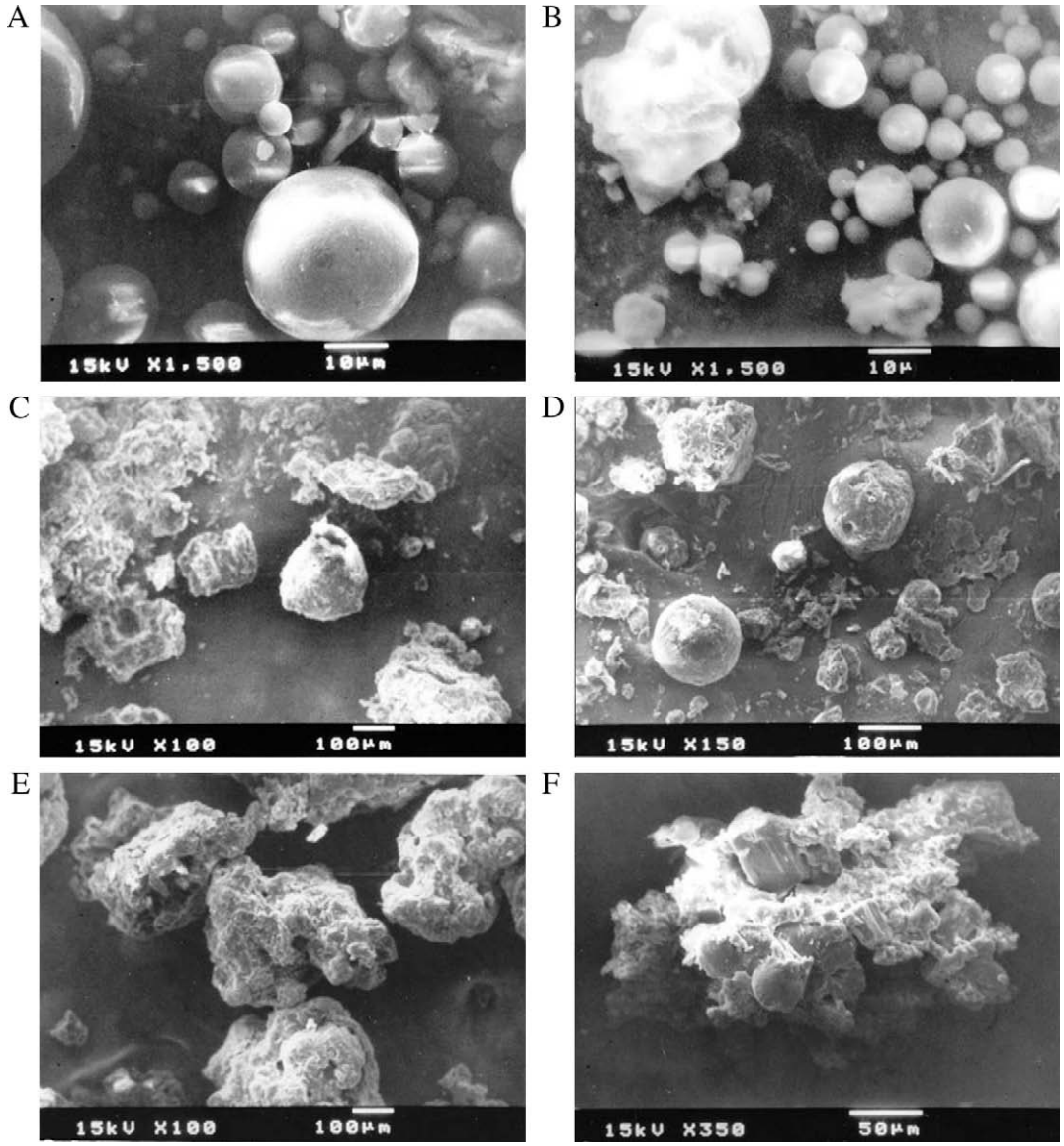

Fig. 2. SEM photographs of metronidazole hydrochloride loaded pectin–gelatin (A) and alginate–gelatin microspheres (B), diclofenac loaded pectin–gelatin (C) and alginate–gelatin (D) microcapsules, indomethacin loaded pectin–gelatin (E) and alginate–gelatin microcapsules (F).

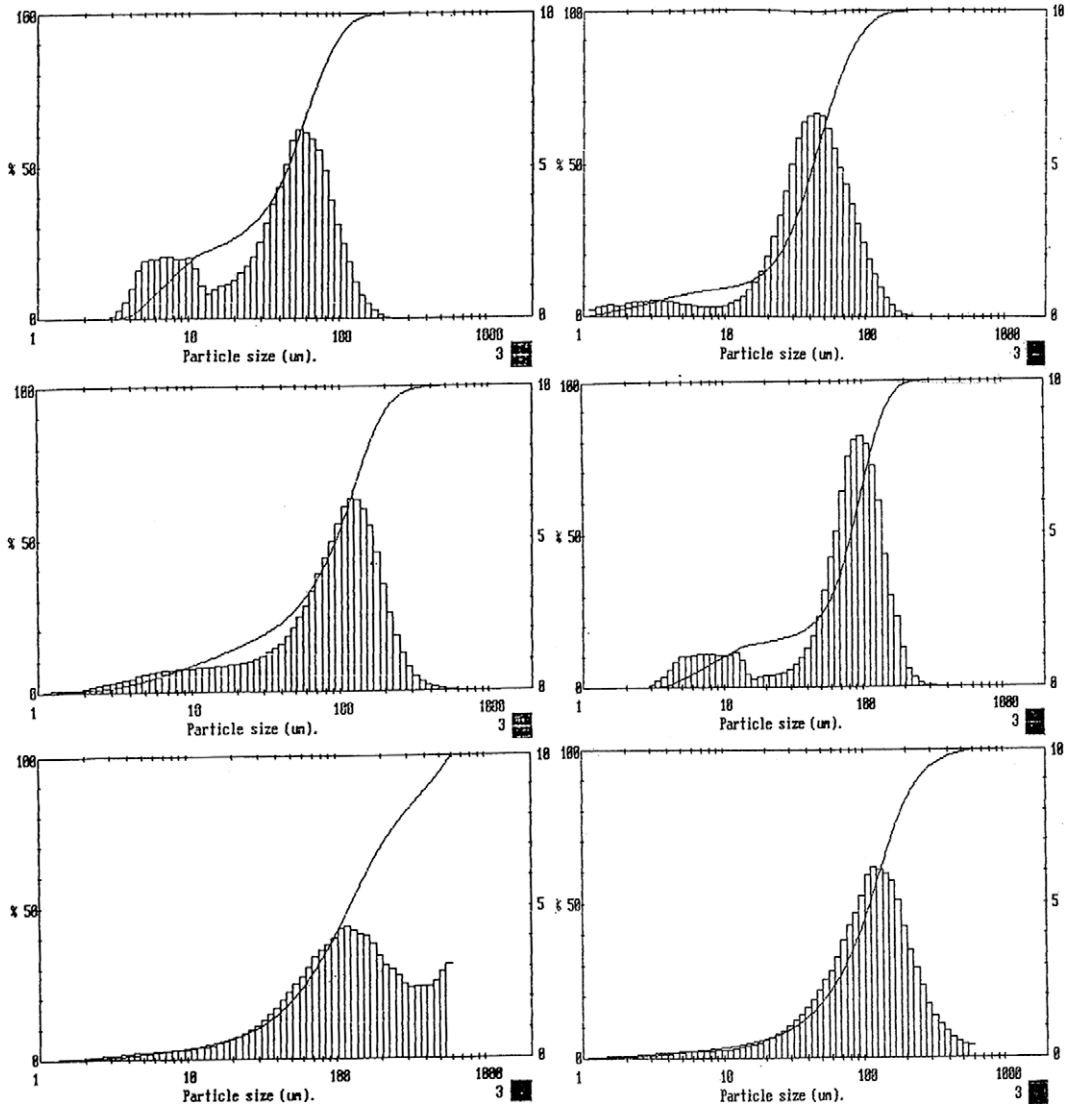

Fig. 3. Particle size distribution of microcapsules loaded with metronidazole hydrochloride (top), diclofenac sodium (middle) and indomethacin (bottom). Gelatin–pectin and gelatin–alginate system are shown on left and right side, respectively.

3.6. Particle size analysis

Size distribution of pectin–gelatin and alginate–gelatin microcapsules loaded with metronidazole hydrochloride, diclofenac sodium and indomethacin were shown in Fig. 3. Alginate–gelatin complex coacervation produced small size microcapsules with relatively narrow distribution than pectin–gelatin system. Metronidazole hydrochloride loaded microcapsules were smallest one among others and has an average particle size of 45 and 41 μm for pectin–gelatin and alginate–gelatin, respectively. The average sizes of diclofenac sodium loaded pectin–gelatin and alginate–gelatin microcapsules were 94.6 and 82.3 μm, respectively. The average sizes of indomethacin loaded pectin–gelatin and alginate–gelatin microcapsules were 120.94 and 110.64 μm, respectively. During the preparation as diclofenac is precipitated it might have produced smaller size particles and hence the resulted microcapsules were smaller than the indomethacin loaded one.

3.7. FT-IR analysis

Polysaccharides such as pectin and alginate has free carboxyl group that imparts negative charge to these molecules. Protein molecule such as gelatin has positive charge at acidic pH due to presence of amino groups. During complex coacervation carboxyl groups in polysaccharides interact with amino groups in protein to form a complex that contains amide. FT-IR analysis was carried out to confirm formation of amide due to interaction of free carboxyl and amino group present in polysaccharides and proteins, respectively. FT-IR spectrum of gelatin (Fig. 4a) revealed the presence of characteristic functional group at 3415; 3476; 3551 cm^{-1} for amino group. FT-IR spectrum of pectin (Fig. 4b) showed stretching frequency for carboxylic acid group at 2927 cm^{-1}. The peaks of free amino groups that present in gelatin was disappeared in pectin–alginate complex coacervate (Fig. 4c). A characteristic peak for amide in the region of 1500–1650 cm^{-1} was appeared in the complex coacervate (Fig. 4c) and confirms formation of complex due to reaction between amino group of gelatin and carboxylic group of pectin.

FT-IR spectrum of drug loaded microcapsules (Fig. 5) showed characteristic peaks of the corresponding drug and revealed intact nature of the drug in the microcapsules. FT-IR spectrum of indomethacin showed (figure not shown) characteristic peaks at 1028, 1700 and 1601 cm^{-1} for –C–Cl, C═O, five member ring, respectively. These peaks were intact in the FT-IR spectrum of

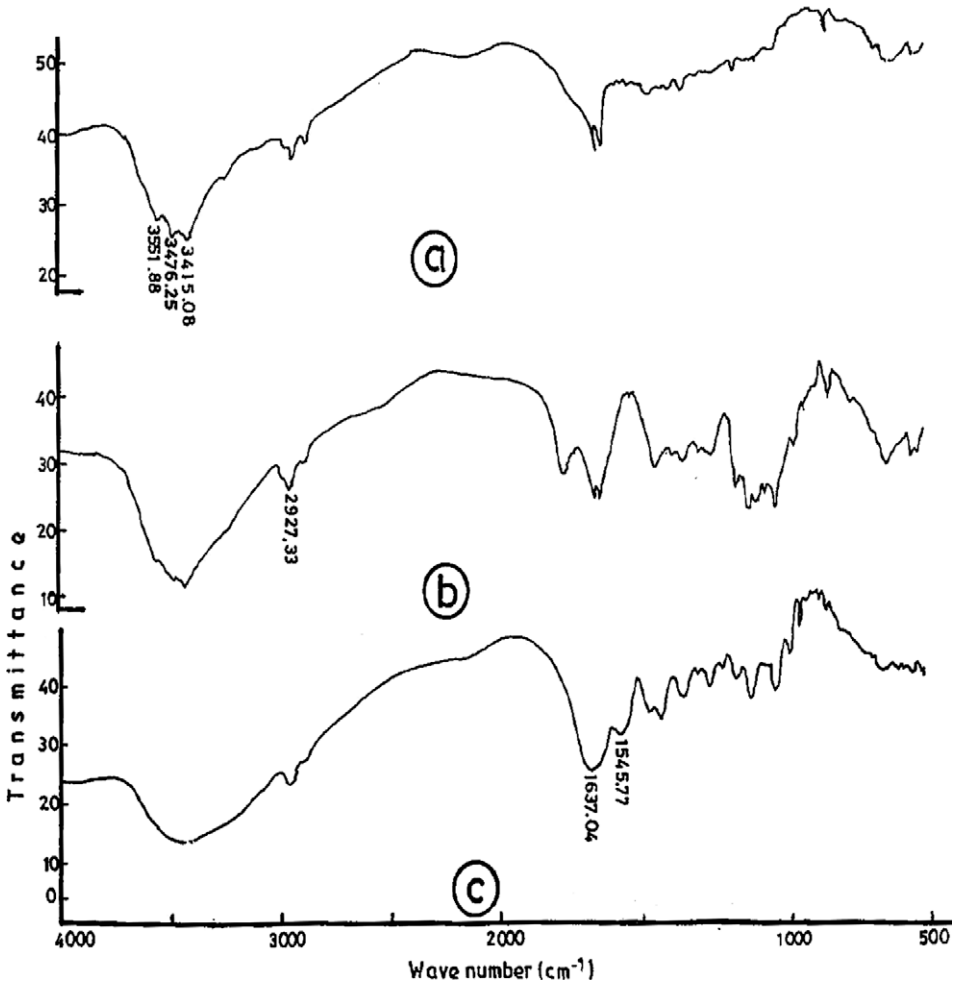

Fig. 4. FT-IR spectra of gelatin (a), pectin (b) and gelatin–pectin complex coacervate (c).

indomethacin loaded pectin–gelatin microcapsules (Fig. 5A). The FT-IR spectrum of diclofenac sodium showed (figure not shown) peaks at 1028, 3300, 1700 cm^{-1} for functional groups –C–Cl, –NH– and C═O, respectively. These peaks were also present in the FT-IR spectrum of pectin–gelatin microcapsules loaded with diclofenac sodium (Fig. 5B). Similar characters were also observed in the products obtained by alginate–gelatin complex coacervation (IR spectrum not shown). These observations reveal intact nature of diclofenac sodium and indomethacin in pectin–gelatin and alginate–gelatin microcapsules. Because of poor loading, metronidazole hydrochloride loaded microparticles were not further characterized by FT-IR, DSC and *in vitro* release.

3.8. DSC

DSC thermogram of pectin–gelatin complex coacervate, diclofenac loaded pectin–gelatin microcapsules, diclofenac, diclofenac sodium, indomethacin loaded pectin–gelatin microcapsules and indomethacin was shown in Fig. 6A–F, respectively. DSC of pectin–gelatin complex coacervate showed (Fig. 6A) no peak and indicates amorphous nature these molecules. Diclofenac sodium loaded pectin–gelatin microcapsules showed (Fig. 6B) an exothermic peak at 177 °C. DSC of diclofenac free acid (Fig. 6C) and diclofenac sodium (Fig 6D) showed an exothermic peak at its melting point 177 and 297 °C, respectively. These observations clearly indicated that the diclofenac sodium was encapsulated as free acid in the microcapsules. This conversion happed during the preparation of the microcapsules. DSC of indomethacin loaded pectin–gelatin microcapsules showed an exothermic peak (Fig. 6E) at 160 °C and same peak was also present in the thermogram of indomethacin (Fig. 6F). This confirms crystalline and intact nature of indomethacin in the formulated microcapsules. Tamilvanan and Sa (2000) were observed similar effects in indomethacin loaded polystyrene microspheres.

3.9. In vitro release studies

In vitro release of diclofenac sodium and indomethacin from pectin–gelatin and alginate–gelatin microcapsules were shown in Fig. 7. Diclofenac sodium is soluble in water but the free acid diclofenac and indomethacin are insoluble in water. Though diclofenac sodium is employed in the microencapsulation process, due to addition of acetic acid it was encapsulated as diclofenac. The release of diclofenac and indomethacin from formulated microcapsules was very less in gastric fluid and it could be due to poor solubility of drugs in acidic pH or due to enteric nature polymers (pectin and alginate) employed. Once the microcapsules were shifted to simulated intestinal fluid, a burst release (Fig. 7) was found and then the release was sustained over 16 h. The burst release may be due to poorly encapsulated drug or surface drug that present in the microcapsules. In addition, the burst release is due to higher solubility of the drug (diclofenac and indomethacin) and the polymer employed in alkaline pH. At alkaline pH acidic drugs will form corresponding salt and thus enables their dissolu-

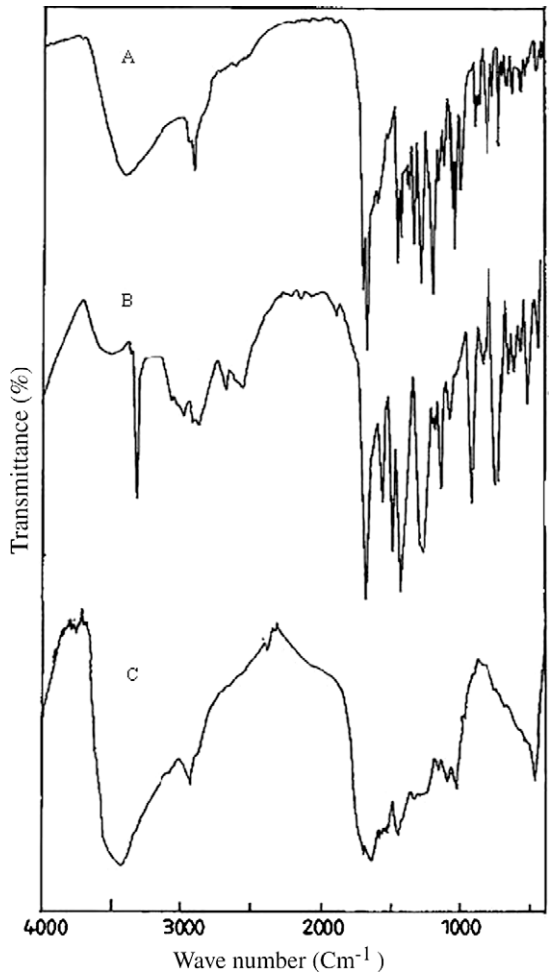

Fig. 5. FT-IR spectrums of gelatin–pectin coacervate (C), gelatin pectin microcapsules loaded diclofenac sodium (B) and indomethacin (A).

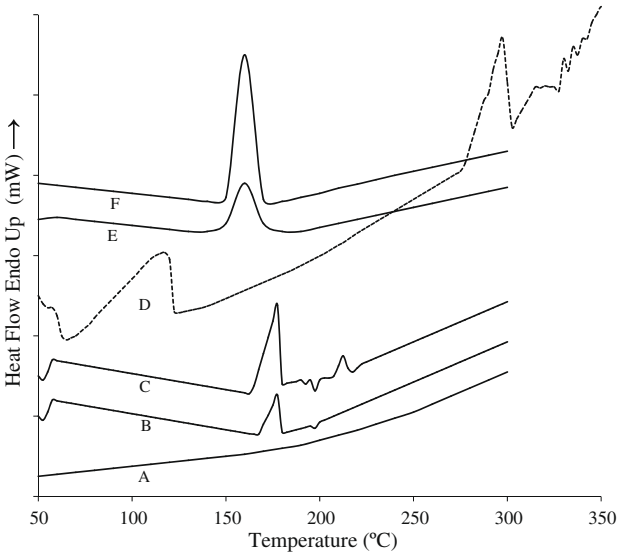

Fig. 6. DSC thermogram pectin–gelatin coacervate (A), diclofenac loaded pectin–gelatin microcapsules (B), diclofenac free acid (C), diclofenac sodium (D), indomethacin loaded pectin–gelatin microcapsules (E) and indomethacin (F).

tion. About 70–80% of drug released within 6 h. Similar effect was also reported by Joseph and Venkatram (1995). As time progress

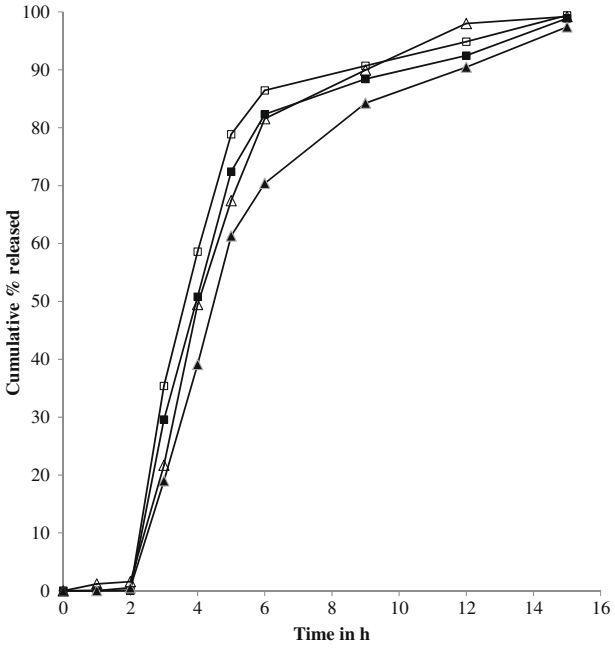

Fig. 7. *In vitro* release of diclofenac sodium (■, □) and indomethacin (▲, Δ) from microcapsules prepared by complex coacervation. Closed and open symbol indicate pectin–gelatin (■, ▲) and alginate–gelatin (□, Δ) microcapsules, respectively. Each data represents average of three determinations.

the release was slow and about 20–30% was released in next 10 h. This may be due to deep seated drug particles in the microcapsules. These drug particles may be encapsulated by the several layers of coacervate droplets and slowly released.

Drug releases from pectin–gelatin microcapsules were slower than the alginate–gelatin microcapsules. This could be due to smaller size and less aggregation of alginate–gelatin microcapsules. Indomethacin (Fig. 7) release from microcapsules was slower than the diclofenac sodium. This is due to larger surface area in diclofenac microcapsules because of their smaller particle size (Table 1). The overall release during 16 h is high in alginate–gelatin than in pectin–gelatin. This may be due to solubilizing effect of alginate on indomethacin (Shiraishi, Imai, & Otagiri, 1991) and similar results are also reported by Joseph and Venkatram (1995).

4. Conclusion

In the present study two polysaccharides pectin and alginate were compared to find the most suitable anion for complex coacervation with gelatin. Water soluble model drug metronidazole hydrochloride yielded microspheres with poor encapsulation efficiency. Water insoluble core produced microcapsules with irregular shape. Drug with pH dependant solubility such as diclofenac sodium showed change in physical nature in the microcapsule due to crystallization as free acid during coacervation process. This may affect the stability of the final product as salt forms are more stable than the free acid. Water insoluble drug such as indomethacin seems to be an ideal core for encapsulation by complex coacervation in terms of stability and prolonged release. Sodium carboxymethyl cellulose acted as anti-adhesive agent and minimized aggregation among the microcapsules. Alginate was found to be more suitable than pectin in terms of less aggregation, small/uniform particle size, easy dispersion in water and free flowing. The drug release from pectin–gelatin and alginate–gelatin microcapsules was poor in acidic medium. The drug release started only in intestinal pH and extended to 16 h, hence it could be used

in developing colon targeted drug release, however further study required to confirm their ability as enteric polymer.

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