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ORIGINAL ARTICLE

Chitosan/cyclodextrin nanoparticles as drug delivery system

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Abstract One of the most attractive areas of research in drug delivery is the design of nanomedicines consisting of nanosystems that are able to deliver drugs to the right place, at appropriate time. Natural polysaccharides, due to their outstanding merits, have received more and more attention in the field of drug delivery systems. In particular, polysaccharides seem to be the most promising materials in the preparation of nanometric carriers. The main goal of the present study was to investigate the potential of a recent generation of hybrid polysaccharide nanocarriers, composed of chitosan (CS) and an anionic cyclodextrin, carboxymethyl-β-cyclodextrin (CM-β-CD), for the encapsulation of a model drug, sulindac. CS and CM-β-CD were processed to nanoparticles (NPs) via the ionotropic gelation technique. The stoichiometric ratio between these two polymers was found to influence particle size and zeta potential. Decreasing CS:CM-β-CD ratio led to an increase in particle size and decrease in zeta potential. DSC and FTIR analyses confirmed formation of NPs and encapsulation of sulindac inside them. Release profiles indicate a continuous release of the drug throughout 24 h. However, the rate of release was more rapid during the first hours; about 55–90% of the drug being released after 3 h.

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Introduction

Over the past few decades, there has been considerable interest in developing biodegradable NPs as effective drug delivery devices [1–3].

NPs can be made from inorganic and polymer materials. Polymeric NPs are more desirable because they can be chemically designed to be biodegradable and biocompatible. NPs can also be made from synthetic polymers or modified natural polymers for the delivery of small molecular drugs, proteins/peptides and genes chemotherapy. They are made by forming drug–polymer complexes in which the drug is uniformly dispersed or by creating nanoscale vesicles (such as liposomes and micelles) to entrap drug molecules [4].

Polymeric materials used for preparing NPs for drug delivery must be biocompatible at least and biodegradable best [5]. Different types of polymers used for the preparation of polymeric biodegradable NPs include poly(methylmethacrylate), polyacrylamide, polyalkylcyanoacrylate, polylactic acid, poly(glycolic acid), polycaprolactone, polysaccharides (particularly chitosan), proteins or polypeptides (such as gelatin), etc.; among them, polysaccharides are the most popular polymeric materials to prepare NPs for drug delivery [5–8].

Chitosan is a cationic polymer [9]. It is a natural linear biopolyaminosaccharide obtained by alkaline deacetylation of chitin, which is the second abundant polysaccharide next to cellulose [10, 11]. Chitosan has one primary amino and two free hydroxyl groups for each C6 building unit. Due to the easy availability of free amino groups in chitosan, it

carries a positive charge and thus, in turn, reacts with many negatively charged surfaces/polymers.

The cationic nature of chitosan has been conveniently exploited for the development of particulate drug delivery systems [12]. There are different methods used for the preparation of chitosan NPs. However, selection of any of these methods depends upon the nature of the active molecule as well as the type of the delivery device [13]. These methods comprise ionotropic gelation, microemulsion, emulsification solvent diffusion and polyelectrolyte complex [14].

Cyclodextrins are cyclic oligosaccharides derived from starch containing six (α-CD), seven (β-CD), eight (γ-CD), nine (δ-CD), ten (ε-CD) or more (α-1,4)-linked α-D-glucopyranose units [15]. They are cylinder-shaped and possess a cage-like supramolecular structure [16]. Their outer surface is hydrophilic and therefore, they are usually soluble in water but the cavity has a less hydrophilic character [17]. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution [18]. As a result of this cavity, cyclodextrins are able to form inclusion complexes with a wide variety of hydrophobic guest molecules.

The anionic CD, carboxymethyl-β-cyclodextrin (CM-β-CD) was chosen in the present study because it was expected to favourably interact with the cationic molecules of CS. CS-CM-β-CD NPs were therefore prepared via the ionotropic gelation method using varying amounts of CM-β-CD [19].

Sulindac is an indene acetic analogue of the NSAID, indomethacin [20]. It has also antipyretic and analgesic properties [21]. It is a pro-drug which, in vitro and in cellular systems, is readily and reversibly converted to the active sulphide metabolite. The sulphide metabolite is some 500 times more active as an inhibitor of prostaglandin synthesis than the parent drug.

Sulindac is indicated for rheumatoid arthritis, osteoarthritis, acute gout, ankylosing spondylitis and periarticular disorders. It has been observed also that sulindac and its derivatives may effectively prevent colorectal cancer. The anticancer effect of the novel sulindac derivatives has been demonstrated in over 50 different tumor cell lines, as well as in animal models of a variety of human cancers such as mammary, prostate, lung and pancreatic carcinomas [21].

Materials and methods

Materials

Sulindac was kindly provided by Sigma Pharmaceutical Indust., Egypt. High molecular weight chitosan, was purchased from Fluka, BioChemika, Japan. Carboxymethyl-β-cyclodextrin sodium salt (DS = 3) was supplied from Fluka, BioChemika, Hungary. Phosphotungstic acid was acquired from Fluka, Japan. Mucin from porcine stomach, type II, was obtained from Sigma, USA. Dialysis tubing cellulose membrane (molecular weight cut-off 12000 g/mol) was acquired from Sigma–Aldrich Chemical Company, St. Louis, USA.

Methods

Phase-solubility studies

Solubility measurements were carried out according to the method of Higuchi and Connors [22]. An excess of sulindac was added to distilled water containing different concentrations of carboxymethyl-β-cyclodextrin (CM-β-CD). The suspensions were shaken using shaking incubator (GFL 3032, Germany) at 25 ± 0.5 °C for 72 h and then filtered through a Millipore filter (0.45 μ). Aliquot portions of the filtrates were analyzed for their drug contents by measuring their absorbance-values using Shimadzu UV spectrophotometer (model 2410/PC, Japan) against blank solutions containing the same concentrations of cyclodextrins (CDs). Each experiment was carried out in triplicate.

Preparation of carboxymethyl-β-cyclodextrin crosslinked chitosan NPs

(a) *Investigation of the conditions for nanoparticle formation* NPs were spontaneously obtained using the ionotropic gelation method which involves the interaction between the positively charged amino groups of CS and the negatively charged CM-β-CD. Preliminary experiments were done in order to determine the formation zones of NPs. One mL of aqueous solutions of CM-β-CD (4, 8, 12, 16, 20, 28, 32, 36, 40, 44 and 48 mg/mL) was added to 3 mL of aqueous acetic acid solutions containing 0.067, 0.133, 0.2, 0.267, 0.333, 0.4, 0.467 and 0.533% (w/v) of CS under magnetic stirring (Stuart, CB162, UK) at room temperature, thus achieving a final concentration of CS ranging from 0.05 to 0.4% (w/v) and a final CM-β-CD concentration ranging from 1 to 12 mg/mL. Samples were then visually analyzed and three different systems were identified: clear solution, opalescent suspension and aggregates. A figure was then constructed representing the different systems obtained at different CS and CM-β-CD concentrations. A CS concentration of 0.267% (w/v) was found to produce the widest region of NPs.

(b) *Preparation of sulindac-loaded carboxymethyl-β-cyclodextrin crosslinked chitosan NPs* An excess of sulindac was added to aqueous solutions of different concentrations of CM-β-CD (16, 20, 24, 28, 32, 36 and 40 mg/mL) and stirred, with a magnetic stirrer, for 1 h at room temperature. The obtained suspensions were then filtered

and analyzed for their drug contents spectrophotometrically. NPs were formed by adding 1 mL of the filtrate dropwise to 3 mL of CS solution (0.267%, w/v) under magnetic stirring at room temperature. The resulting NPs were then isolated by centrifugation using refrigerated large capacity centrifuge (Union 32R, Korea) at 9000 rpm for 100 min under cooling. Supernatants were collected for determination of the amount of unbound drug.

Determination of drug encapsulation efficiency and loading capacity for NPs

Encapsulation efficiency (E.E.) refers to the percentage of drug that is entrapped with respect to the total amount of drug added in the NP preparation process. This was determined indirectly from calculating the non-encapsulated drug which remained dissolved in the NP suspension medium according to the following equation:

$$\text{E.E.} = \frac{\text{Total amount of drug} - \text{amount of unbound drug}}{\text{Total amount of drug}} \times 100$$

On the other hand, the loading capacity (L.C.) refers to the percentage amount of drug entrapped in NPs according to the following equation:

$$\text{L.C.} = \frac{\text{Total amount of drug} - \text{amount of unbound drug}}{\text{Nanoparticles weight}} \times 100$$

Determination of yield of NPs

This was calculated by weighing dried samples of the isolated NPs and referring them to the initial amounts of NP components according to the following equation:

$$\text{Yield} = \frac{\text{Nanoparticles weight}}{\text{Total initial solids weight}} \times 100$$

Characterization of chitosan NPs

(a) *Morphological characterization of NPs*

(i) *Transmission electron microscopy* NP samples were stained with 2% (w/v) phosphotungstic acid and placed on copper grids with Formvar films for viewing by a transmission electron microscope (JEOL, JEM-120 transmission electron microscope, Japan) operated at 120 kV.

(ii) *Scanning electron microscopy* For scanning electron microscopy (SEM),JEOL-JXA840A electron probe microanalyzer, Japan, was used. NPs were first spray dried using a laboratory-scale spray dryer (Mini spray dryer, Büchi®, B-290, Switzerland) with a two fluids external mixing 0.7 mm nozzle. The feed rate was 2.5 mL/min, inlet and outlet temperatures were 120 and 80 ± 2 °C, respectively, while the air flow rate and the aspirator were constants at 400 NL/h and 80%, respectively [23]. Spray dried NPs were fixed on a brass stub using double-sided adhesive tape and then made electrically conductive by coating, in a vacuum, with a thin layer of gold for 30 s.

(b) *Measurement of NPs size* This was assessed by a dynamic laser light scattering apparatus (Malvern mastersizer, Malvern Instr., UK) at 25 °C.

(c) *Zeta potential measurements* 0.01 g of the NP sample was placed in 50 mL double distilled water with definite electrolyte concentration at ionic strength of 2×10^{-2} M NaCl. The suspension was then shaken for 1 h and allowed to settle for 3 min. About 10 mL of the supernatant were transferred into a standard cuvette for zeta potential measurements (Laser zetameter "Malvern Instruments" model "Zeta Sizer 2000", UK). Solution temperature was maintained constant at 25 °C.

(d) *Differential scanning calorimetry* Twenty mg samples of pure drug, components, physical mixture and lyophilized loaded NPs were crimped in a standard aluminium pan and heated from 20 to 800 °C at a constant heating rate of 10 °C/min under constant purging of argon at 20 mL/min (Labsys^{TM} TG-DSC16, Setaram instrumentation, France).

(e) *Fourier transformation infrared spectroscopy* The pure drug, components, physical mixture and loaded NPs were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding discs were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The discs were scanned over a wave number range 4000–400 cm^{-1}, using Shimadzu IR/FTIR Spectrophotometer, Japan.

In vitro drug release studies

These studies were performed using horizontal water bath shaker (SV1422, Memert, Germany) [24]. The release medium was 20 mL of phosphate buffer (pH 6.8) and the temperature was set at 37 ± 0.5 °C. A 50 mg-sample of the drug-loaded CS NPs was instilled in a dialysis bag secured with two clamps at each end. At definite time intervals, 2 mL samples were withdrawn and assayed for sulindac spectrophotometrically. Withdrawn samples were replaced by equal volumes of fresh buffer. Triplicate experiments were carried out for each release study and the mean values were calculated. Release efficiency (R.E.), defined as percentage of the area of the rectangle corresponding to 100% release for the same total time, was calculated according to the following equation:

$$\text{R.E.} = \frac{\int_0^t \text{y} \times \text{dt}}{\text{y100} \times \text{t}} \times 100$$

where y is the percentage drug released at time t.

Assessment of the mucoadhesive properties of chitosan NPs

This was based on evaluating the influence of mucin on the zeta potential of CS NPs which was measured after their incubation in aqueous solution of mucin (0.4 mg/mL), at 37 °C, under moderate stirring [25].

Results and discussion

Phase-solubility studies

Figure 1 shows the effect of CM-β-CD on the solubility of sulindac in distilled water at 25 °C. It is evident that solubility of the drug increases with increasing CD concentration. This increase is linear as indicated by the R^2-value (0.999).

Carboxymethyl-β-cyclodextrin crosslinked chitosan NPs

NPs of CS and CM-β-CD were pre-pared via the ionotropic gelation method. This method utilizes the ionic interaction between the positively charged CS and the negatively charged CM-β-CD, and the ability of CS to form a gel by forming inter- and intramolecular linkages [26]. The ionic gelation process is extremely mild and involves the mixing of two aqueous phases at room temperature. CS/CM-β-CD NPs combine the excellent capacity of CS nanocarriers to load hydrophilic drugs with a higher efficiency when encapsulating hydrophobic molecules [26, 27]. The anionic CM-β-CD was utilized for its dual action as a solubilizing agent for the drug and for crosslinking with CS to form NPs.

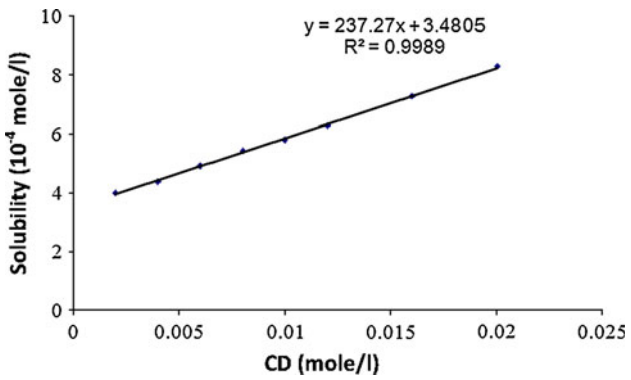

Fig. 1 Effect of CM-β-CD on the solubility of sulindac in distilled water

Formation of chitosan/carboxymethyl-β-cyclodextrin NPs

Preliminary studies were performed to identify the range of concentrations of each of CS and CM-β-CD capable of NP formation. CS was used in concentrations of 0.05–0.4% (w/v), while CM-β-CD was used in concentrations of 1–12 mg/mL, i.e., 96 systems were prepared, with each repeated thrice for triple checking the results. Figure 2 indicates that NPs were formed at all studied CS concentrations, at a CM-β-CD concentration range of 4–10 mg/mL. However, the NP formation region became more wider on increasing CS concentration from 0.05 to 0.2% (w/v) and narrower on further increasing its concentration to 0.4% (w/v). The narrow regions of NP formation at low CS concentrations might be attributed to the relatively low positively charged amino groups of CS molecules available for crosslinking. On the other hand, the low NP formation at CS concentrations higher than 0.2% (w/v) might be related to increased viscosity at these concentrations.

On the basis of the above study, a CS concentration of 0.2% (w/v) was selected for subsequent studies. Confirmation of NP formation in the opalescent zone produced with 0.2% CS was performed via microscopic examination and particle size measurements. NPs of the opalescent zones were found to have diameters ranging from 137 ± 11 to 727 ± 63 nm. NP formulations were, thus, prepared using 0.2% (w/v) of CS and 4–10 mg/mL of CM-β-CD (Table 1). Polydispersity index was found to have values less than one indicating size uniformity of the NPs.

Sulindac-loaded carboxymethyl-β-cyclodextrin crosslinked chitosan NPs

CS/CM-β-CD NPs were loaded with sulindac using the incorporation method, where sulindac–CM-β-CD solutions were added dropwise, under magnetic stirring, to the CS solutions.

(a) *Drug encapsulation efficiency, drug loading capacity and yield of NPs* Table 2 shows drug E.E., drug L.C. and yield-values for the sulindac-loaded NPs. It is evident that E.E. increased significantly on decreasing CS:CM-β-CD w/w ratio from 1:2 (F1) to lower values reaching 1:5 (F7).

(b) *Characterization of chitosan/carboxymethyl-β-cyclodextrin NPs*

(i) *Transmission electron microscopy* TE micrographs show that CS/CM-β-CD NPs are spherical (Fig. 3).

(ii) *Scanning electron microscopy* By SEM, NPs appear as spheres with smooth surfaces (Fig. 4).

(iii) *Particle size* Table 3 shows diameters and polydispersity index-values for CS/CM-β-CD NPs. It is obvious that particle diameters increased significantly by decreasing CS:CM-β-CD w/w ratio from 1:2 (F1) to lower values

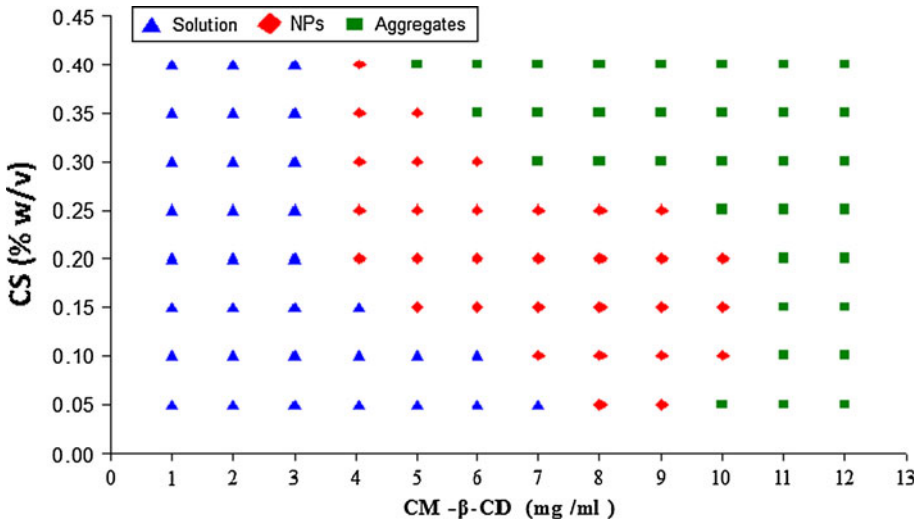

Fig. 2 Identification of CS/CM-β-CD NPs domain formation

Table 1 Composition, particle diameter and polydispersity index-values for NP formulations prepared with CM-β-CD

Formula	CM-β-CD Conc. (mg/mL)	CCS/CM-β-CD ratio (w/w)	Particle diameter (nm)	Polydispersity index
F1	4	1: 2.0	137 ± 11	0.084
F2	5	1: 2.5	317 ± 15	0.048
F3	6	1: 3.0	403 ± 25	0.062
F4	7	1: 3.5	447 ± 41	0.093
F5	8	1: 4.0	483 ± 5	0.012
F6	9	1: 4.5	613 ± 11	0.019
F7	10	1: 5.0	727 ± 63	0.087

Table 2 E.E., L.C. and yield-values for CS/CM-β-CD NP formulations

Formula	E.E. (%)	L.C. (%)	Yield (%)
F1	47.88 ± 3.83	1.39 ± 0.16	11.01 ± 0.50
F2	60.93 ± 4.30	6.07 ± 0.74	41.82 ± 1.73
F3	81.20 ± 5.05	7.80 ± 0.78	50.57 ± 4.10
F4	84.62 ± 4.62	9.74 ± 0.52	51.65 ± 2.56
F5	85.87 ± 2.47	9.11 ± 0.47	44.36 ± 2.86
F6	87.06 ± 3.01	8.80 ± 1.22	40.75 ± 3.80
F7	85.12 ± 6.00	8.84 ± 0.99	36.49 ± 1.96

(F2–F7); the most pronounced increase was found at CS/CM-β-CD w/w ratio values of 1:4.5 and 1:5 (F6 and F7).

With respect to the parameter of polydispersity index, there was no consistent relation between values of this parameter and the CS:CM-β-CD ratio (Table 3). All studied formulations had polydispersity index-values lower than one indicating uniformity of particle size.

(iv) *Zeta potential* Table 3 shows zeta potential-values for sulindac-loaded CS/CM-β-CD NPs. It is observed that all formulations showed positive zeta potential and that values of zeta potential decreased gradually on decreasing CS:CM-β-CD w/w ratio in the range 1:2–1:5 (F1–F7). The low zeta potential-values at high CM-β-CD concentrations might be related to increased masking of the free positively charged amino groups of CS due to their interaction with CM-β-CD [19, 28].

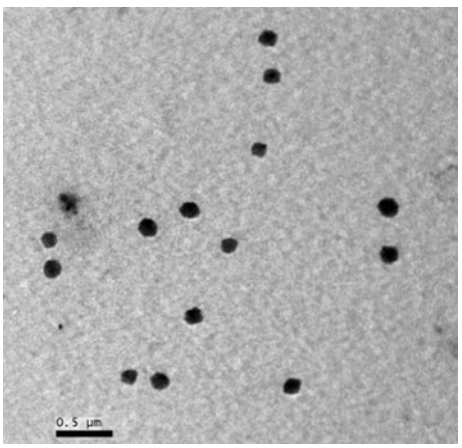

Fig. 3 TE micrograph for NP formulation containing 0.2% (w/v) CS and 7 mg/mL CM-β-CD

Maintenance of the polycation on the external surfaces of the NPs is very important since it is critical for their interaction with mucosal surfaces [29].

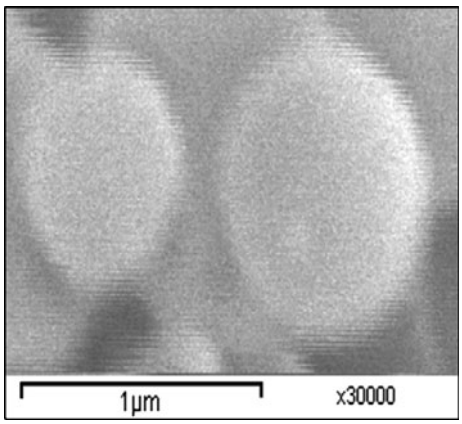

Fig. 4 SE micrograph for NP formulation containing 0.2% (w/v) CS and 7 mg/mL CM-β-CD

Table 3 Diameters, polydispersity index and zeta potential-values of sulindac-loaded CS/CM-β-CD NPs

Formula	Particle diameter (nm)	Polydispersity index	Zeta potential (mV)
F1	183 ± 11	0.063	+38.7
F2	393 ± 6	0.015	+34.5
F3	470± 10	0.021	+33.7
F4	577 ± 15	0.026	+32.8
F5	603 ± 55	0.091	+28.1
F6	700 ± 30	0.043	+25.9
F7	790 ± 85	0.108	+24.0

(v) *Differential scanning calorimetry* Differential scanning calorimetry (DSC) was performed for sulindac-loaded CS NP formulation F4, as an example of NP formulations in addition to the pure components and the physical mixture in order to assess the physical structure of NPs in the solid state (Fig. 5).

DSC thermogram of sulindac indicated its crystalline state, exhibiting a sharp characteristic endothermic peak at 187.59 °C.

DSC scan of the CS polymer exhibited an endothermic peak at 89.06 °C which may be attributed to evaporation of absorbed water. An exothermic baseline deviation, beginning around 285.05 °C and gaining its maximum at 300.53 °C indicating CS degradation, was also observed.

DSC thermogram of CM-β-CD showed an initial endothermic peak at 104.24 °C correlated to loss of absorbed water associated to the hydrophilic groups of the polymer. Exothermic peaks related to degradation of the CD were found at 294.4 and 308.58 °C.

DSC scan of the physical mixture was characterized by broad endothermic and exothermic peaks at 98.78 and 300.01 °C, respectively representing coalescence of the individual peaks of the components. The endothermic peak of sulindac at 187.59 °C did not appear in the thermogram; this might be due to its low content in the polymer matrix [30].

DSC thermogram of sulindac-loaded CS/CM-β-CD NPs was characterized by a broader exothermic peak, at 310.86 °C, compared to those of the separate components which may indicate an interaction between these components. The thermogram was also characterized by the absence of the characteristic endothermic peak of sulindac, indicating its entrapment in the NP matrix [30].

(vi) *Fourier transformation infrared spectroscopy* The nature of interactions between components was established with FTIR spectroscopy (FTIR), since any kind of physicochemical interaction that may take place will automatically lead to frequency shifts or splitting in absorption peaks.

FTIR spectroscopy was performed for sulindac-loaded CS NP formulation F4 and for the pure components and physical mixture (Fig. 6).

Several characteristic peaks could be identified in the FTIR spectrum of CS. At 3438 cm^{-1}, the characteristic peak of the hydroxyl group was recorded, overlapped with N–H stretch. The characteristic peak of CS appeared at 1637 cm^{-1} with high intensity that corresponded to the vibration of primary amine band. At 1158 cm^{-1}, the C–N stretch was recorded, while at 1037 cm^{-1}, the peak of C–O stretch group appeared in the spectrum.

The FTIR spectrum of CM-β-CD showed absorption bands at: 3390 cm^{-1} of O–H stretching vibration; 2922 cm^{-1} of alkane C–H stretching; 1330 cm^{-1} of OH deformation and 1159 and 1029 cm^{-1} of C–O–C stretching.

In case of sulindac, aromatic bending vibration was observed at 842 cm^{-1}. At 1080 cm^{-1} was recorded the C–F bonding and at 1595 cm^{-1} the aliphatic C=C bond. The aromatic C=C was recorded at 1464 cm^{-1}.

The FTIR spectrum of the physical mixture showed peaks of all components.

In the spectrum of CS/CM-β-CD NPs, the absorption band at 1637 cm^{-1} assigned to the amino groups of CS was shifted to 1606 cm^{-1} indicating ionic interaction with CM-β-CD. This interaction reduces CS solubility and is responsible for CS separation from the solution in the form of NPs. Hydroxyl groups had a broad absorption with maximum at 3410 cm^{-1}, which remained almost at the same position in the formed NPs. In contrast to the spectrum of the physical mixture, the specific peaks of sulindac at 842, 1080, 1595 and 1464 cm^{-1} could not be detected which indicates a strong interaction between the drug and CM-β-CD.

(c) *In vitro drug release studies* Figure 7 shows release of sulindac from CS/CM-β-CD NP formulations. It is evident that all formulae studied showed similar release profiles. These profiles indicate a continuous release of the drug throughout 24 h. However, the rate of release was

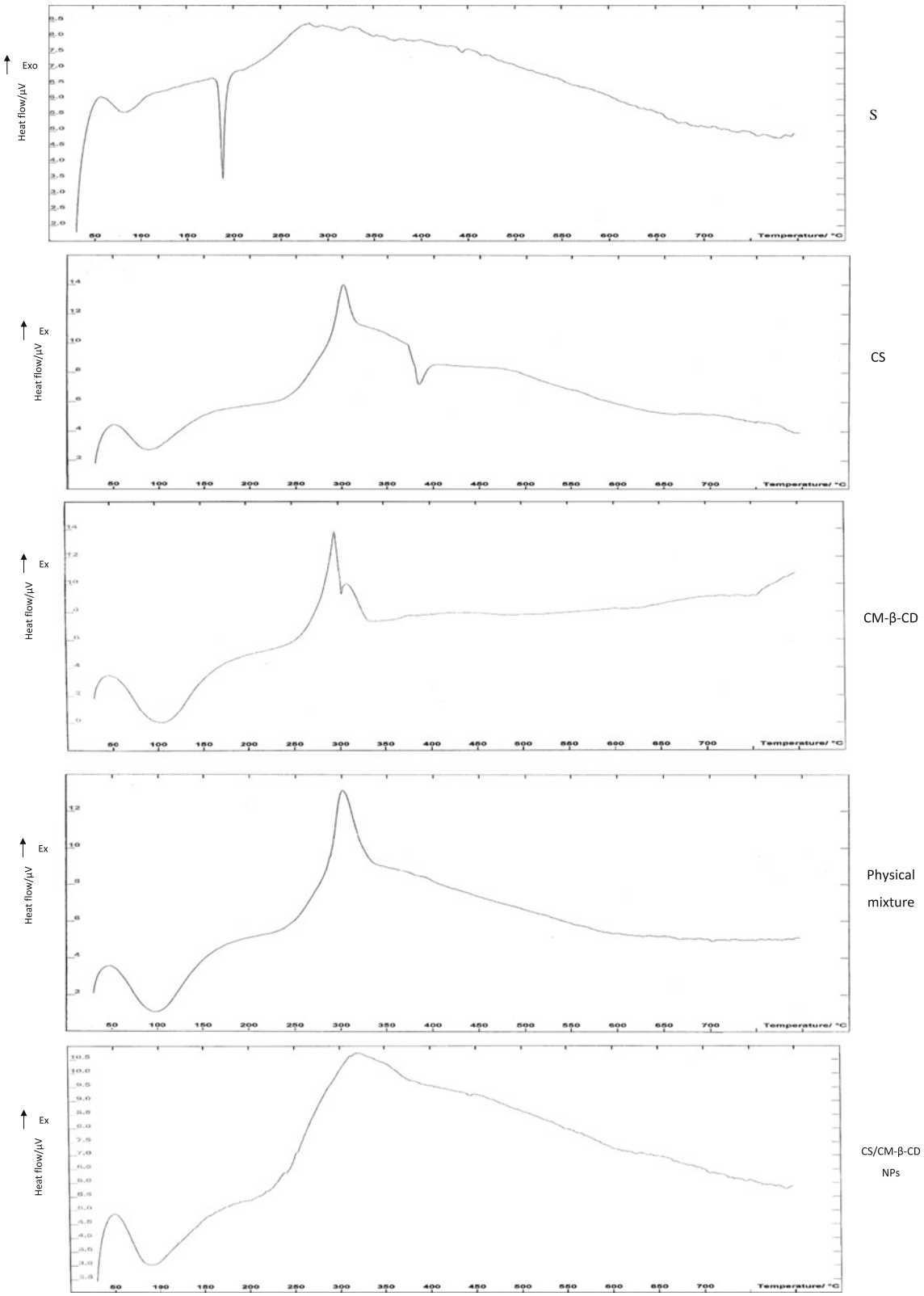

Fig. 5 Thermograms of sulindac, CS, CM-β-CD, physical mixture and CS/CM-β-CD NPs

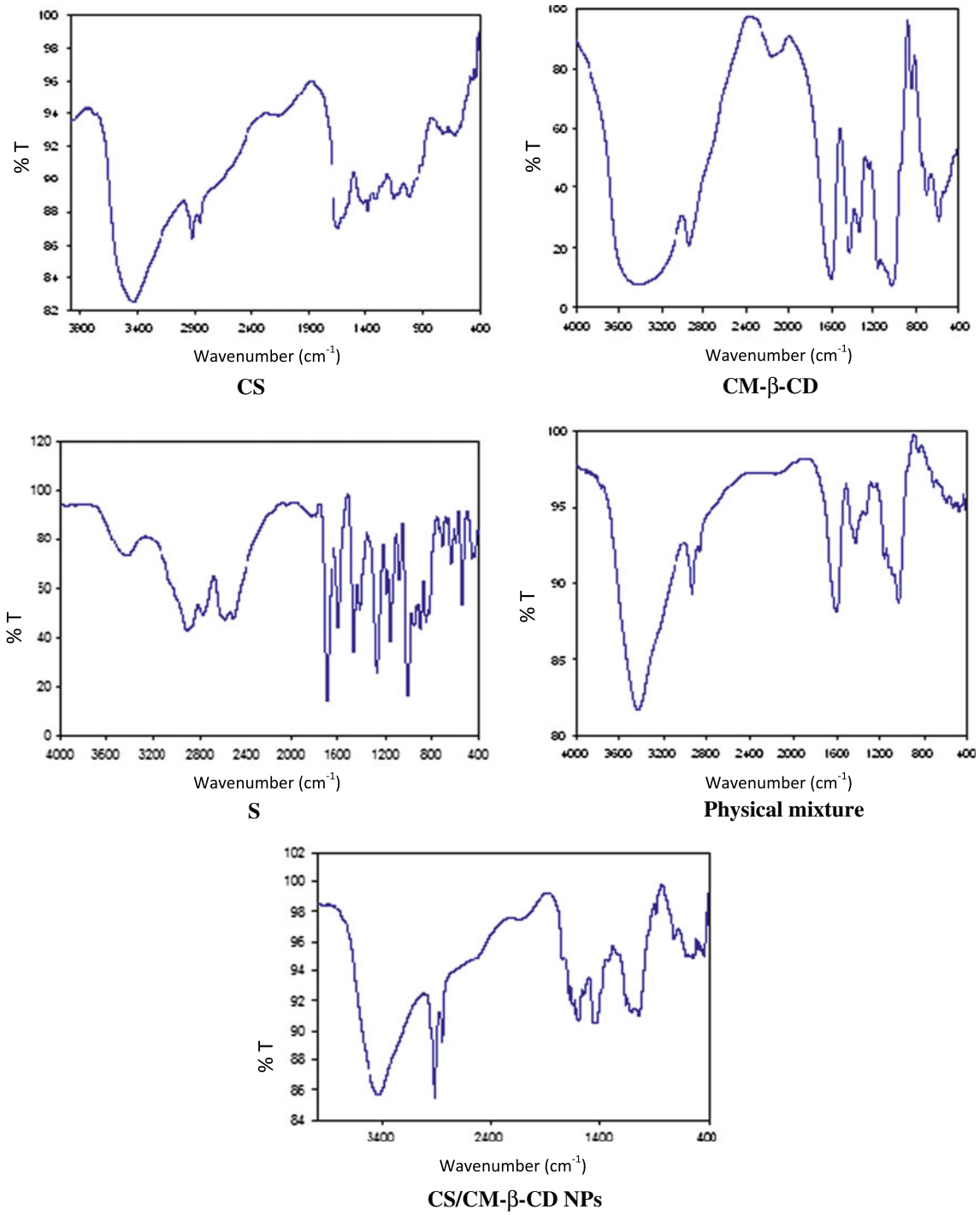

Fig. 6 FTIR spectra of CS, CM-β-CD, sulindac, physical mixture and CS/CM-β-CD NPs

more rapid during the first hours so that about 55–90% of the drug was released after 3 h (Fig. 7).

There was no consistent relation between the release efficiency-values and the CS/CM-β-CD weight ratios. However, all formulas had R.E.-values exceeding 70%.

From the above studies on sulindac-loaded CS/CM-β-CD NP formulations, it is evident that the formulation containing 0.2% (w/v) CS and 7 mg/mL CM-β-CD (F4) was characterized by having high values for E.E., L.C. and yield and exhibit suitable particle diameters.

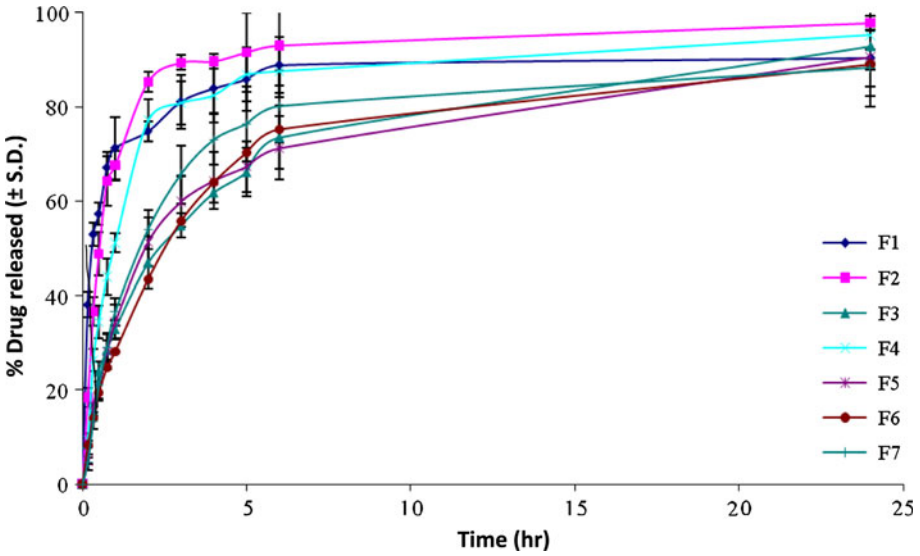

Fig. 7 Release of sulindac from CM-β-CD crosslinked CS NPs

(d) *Assessment of the mucoadhesive properties of chitosan nanoparticles* CS NPs are known to exhibit good mucoadhesive properties. These properties increase the residence time of these NPs at sites of drug action or absorption leading to an increase of drug bioavailability and duration of its action [31]. The mucoadhesive properties of CS are due to molecular attractive forces formed by electrostatic interaction between the positively charged chitosan and the negatively charged mucosal surfaces. These properties may be attributed to the strong hydrogen bonding groups like –OH, strong charges, high molecular weight, sufficient chain flexibility and surface energy properties favoring spreading into mucous [32].

The mucoadhesive properties of the selected CS NP formulation (F4) were evaluated via measuring the influence of mucin (zeta potential $= -13.3$ mV) on zeta potential of the NPs.

Zeta potential of NPs formulation (F4) changed from $+32.8$ to $+1.6$ after incubation with mucin. It is evident that the selected NP formulation had good mucoadhesive properties as indicated by the obvious decrease in its zeta potential-value.

Conclusion

We have used a new nanoparticulate delivery carrier for encapsulation of sulindac, which consists of the mucoadhesive polymer CS and a negatively charged CD, via the very mild ionotropic gelation technique. The resulting NPs exhibited a small size, a positive zeta potential, a great capacity for association with sulindac and good mucoadhesive property. The results suggest that sulindac loaded CS/CM-β-CD NPs could be taken into consideration for controlled delivery of sulindac.

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