CARBOXYMETHYL CELLULOSE ESTERS AS STABILIZERS FOR HYDROPHOBIC DRUGS IN AQUEOUS MEDIUM

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In the present study, amphiphilic polymers, carboxymethyl cellulose acetate (CMCA) and carboxymethyl cellulose acetate butyrate (CMCAB), with hydrophobic and hydrophilic moieties, were prepared from cellulose extracted from bagasse. The prepared amphiphilic celluloses were characterized by Fourier transform infrared spectroscopy (FTIR) and transmission electron microscopy (TEM). These esters were investigated as stabilizers of sulfadiazine drug in water dispersion. The results showed that CMCAB had higher drug loading efficiency than CMCA.

Keywords: bagasse, amphiphilic cellulose, carboxymethyl cellulose acetate butyrate, hydrophobic drug, amorphous solid dispersion, sulfadiazine

INTRODUCTION

Amphiphilic polymers (amphiphiles) are composed of two moieties, one hydrophilic and another one hydrophobic, that are covalently connected.[1] In an aqueous medium, amphiphiles can self-assemble into compounds with a hydrophilic surface shell and a hydrophobic core to reduce contact with water.[2] Carboxymethyl cellulose esters, such as carboxymethyl cellulose acetate butyrate (CMCAB) and carboxymethyl cellulose acetate (CMCA), are commonly used in pharmaceutical applications due to their hydrophobic and hydrophilic moieties.[3]

Inadequate solubility of some drugs in an aqueous medium is a problem in the pharmaceutical industry.[4] Amorphous solid dispersion (ASD) is a smart technique to enhance the solubility and bioavailability of poorly soluble drugs. It offers the advantage of drug bioavailability and solubility without changing its structure,[5] in addition to formulating a homogeneous distribution of the drugs in the solid state,[6] as well as protecting the drug from degradation and controlling the drug release rate.[7] CMCAB and CMCA are considered as ASD polymers, which could enhance drug solubility.[8] Cellulose derivatives that contain carboxymethyl groups (CM) are very appropriate for ASD preparation, because they are safe and interact strongly with drugs. The hydrophobicity could be adjusted by virtue of their substituent nature, while their high glass transition temperature values (T_g) impart formulation stability. High T_g keeps the medium in the glassy form, even at high humidity and temperature, regulating the drug molecular motion and hence hindering drug crystallization.[8]

CMCAB and CMCA are hydrophobic polymers due to the high degree of substitution (DS) of their butyrate and acetate groups, which are responsible for the formation of miscible blends with hydrophobic drugs. Their pendant CM groups allow specific interactions with drug functional groups, such as amino groups. At the same time, their CM groups (0.3) have low DS, which is responsible for low water solubility for the polymer, even at a pH above 7. Carboxymethyl cellulose esters swell at neutral and higher pH.[8]

This study investigates the dissolution properties of blends of CMCAB and CMCA with sulfadiazine drug (SD), which is a hydrophobic polymer (Fig. 1).

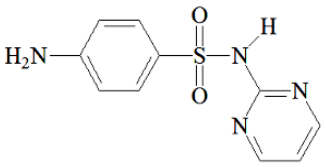


Figure 1: Chemical structure of sulfadiazine drug

EXPERIMENTAL

Materials

Sugarcane bagasse (SCB) was kindly provided by Quena Company for Paper Industry, Egypt. The used chemicals were of analytical grades and used without further purification.

Extraction of cellulose from sugarcane bagasse

SCB was hydrolyzed with 1.5% HCl, based on the raw material, using a liquor to material ratio of 1:10 at 120 °C for 2 h. The prehydrolyzed bagasse was treated with 20% NaOH (based on SCB), using a liquor to material ratio of 1:7 at 170 °C for 2 h. The residual lignin of the pretreated bagasse was removed by bleaching with sodium chlorite. Mercerization of cellulose was carried out with 17.5% NaOH to remove the traces of lignin and other constituents. The α-cellulose, lignin, hemicellulose and ash contents of the pulp were determined according to standard methods[9] and were found to be of 94.2%, 0.3%, 3.4% and 0.4%, respectively.[9]

Synthesis of sodium carboxymethyl cellulose

Carboxymethyl cellulose (CMC) was synthesized from cellulose according to the procedure described by Browning.[10] The degree of substitution of the carboxyl group in CMC was assessed by potentiometric titration according to the standard method.[11]

Synthesis of carboxymethyl cellulose acetate and carboxymethyl cellulose acetate butyrate

The carboxymethyl cellulose acetate (CMCA) and carboxymethyl cellulose acetate butyrate (CMCAB) were prepared from CMC (DS 0.45) in five consecutive steps.[12]

(1) Transformation of CMC-Na to the free acid form. About 100 g CMC (Na salt) was added to 2000 g of 16% aqueous sulfuric acid at 27-30 °C. The slurry was stirred for about 15 min, then the solution was filtered and washed with demineralized water at 80 °C to recover CMC-H.

(2) Activation of CMC (CMC-H). The protonated CMC was transferred to a filtration funnel and the excess water was drained to approximately 20-40% activated solids. CMC-H was dewatered by solvent exchange with three portions of acetic acid, in the case of CMCA. In the case of CMCAB solvent exchange, extra three or four portions of butyric acid (each washing portion of 200-250 g acid to 100 g CMC) were used to give 40% solids of activated butyric acid wet CMC-H. After each washing, the sample was drained to approximately 18% solids.

(3) Esterification. The acetic and butyric acid wet CMC-H was esterified by treatment with 31 g acetic anhydride and 31 g acetic anhydride with 253 g butyric anhydride at 0-10 °C for CMCA and CMCAB, respectively. A catalyst solution consisting of 3.44 g sulfuric acid in 3.44 g acetic acid was added slowly to the reaction mixture, keeping the temperature below 30 °C. At the end of the catalyst addition, the temperature was held at 30-35 °C for 2 h. Then, the temperature of the reaction mixture was raised to 55-60 °C for 4-6 h until the complete dissolution of the solids to give trisubstituted carboxymethyl cellulose, upon precipitation in water.

(4) Hydrolysis and neutralization. As with conventional esters, these esters are usually completely substituted. So, CMCA and CMCAB were hydrolyzed using sulfuric acid to provide a desired partially substituted carboxymethyl cellulose ester. For optimum thermal and hydrolytic stability of the final product, it is important to neutralize the strong acid catalyst.

A solution of 95 g water, 95 g acetic acid and 2 g sulfuric acid was added dropwise to the reaction mixture over 30-45 min at 40-45 °C. The contents were hydrolyzed by heating to 72 °C for 4 h. Then, the excess sulfuric acid was neutralized by addition of 7.53 g magnesium acetate tetrahydrate, dissolved in 25 g water and 25 g acetic acid.

(5) Precipitation and filtration. The reaction mixture was then poured into about 20 times its volume of water, the formed precipitate was filtered, washed well with water, and dried at 60 °C under vacuum to obtain the acid form of CMCA and CMCAB as a white granular powder.

Determination of degree of substitution

The GC analysis was performed using a Thermo Scientific Trace GC Ultra/ISO Single Quadrupole MS system, with TG-5MS fused silica capillary column (30 m, 0.251 mm, 0.1 mm film thickness). For GC/MS detection, an electron ionization system with ionization energy of 70 eV was used. Helium gas was used as carrier gas at a constant flow rate of 1 mL/min. The injector and MS transfer line temperature was set at 280 °C. The acetate and butyrate weight percentage was determined by the hydrolysis GC method, as described by

Shelton *et al.*[13] The reproducibility of CMC, CMCA and CMCAB was checked batch to batch, and the provided results represent the mean values of three experimental results. CMCA had a 0.26 CM DS and 2.27% acetate, while CMCAB had a 0.24 CM DS, 4.75% acetate and 24.04% butyrate.

Self-assembly and encapsulation process

Self-assembling was carried out according to Cheng *et al.*,[14] with slight modifications as described below. Probe sonication of the polymeric amphiphiles (0.1025 g) was carried out in an aqueous solution (10 mL distilled water) for 2 min, on ice, which encouraged the formation of micelles. The hydrophobic drug (sulfadiazine 0.1025 g) was then added into the polymeric self-assemblies and, after sonication for another 2 min on ice, the drug was encapsulated within the hydrophobic core of the self-assemblies. The excess drug was then filtered *via* syringe filtration. The absence of organic solvents in this method eliminates the safety issue concerns associated with the usual methods.[15] The obtained micelle solution was frozen and lyophilized in a freeze-drier system in order to obtain the CMC esters-loaded sulfadiazine nanoparticles (CMC SD NPs).[16]

Micelle stability during storage

Micelle structure is strongly affected by the temperature. The temperature at which micelles are formed is known as critical micellization temperature (CMT). For most copolymers, this value is around 25-40. If micelles were kept in a refrigerator, the temperature would fall lower than CMT, thus micelles would lose their intact structure and drug would precipitate. For this reason, the stability test was performed at 25-40 °C.[17]

Calibration curve of sulfadiazine in the buffer solution

The buffer solution was prepared by adding dropwise 0.1 M NaOH to 0.1 M potassium phosphate monobasic until the solution pH was 7.4.[17] A stock solution of sulfadiazine (SD) was prepared for obtaining the standard curve of the pure drug, by adding 0.01 g of the drug to 10 mL of 7.4 buffer solution and stirred at 37 °C. Dilute solutions were prepared from the stock solution at different drug concentrations (20-100 µg/mL). The absorbance for the resultant dilute solutions was measured at the maximum wavelength of 240 nm and plotted against concentration to obtain the regression equation relating both concentration and absorbance. An average of three scans was taken for each absorbance value.[18]

Fourier transform infrared spectroscopy (FTIR)

Infrared spectra were recorded with a JASCO FT/IR, Nicolet, Model 670, in the region from 4000 to 400 cm^{-1}.

Transmission electron microscopy (TEM)

The morphology and particle size of CMCAB were determined using TEM (JEOL JEM-1230 electron microscope). The sample was prepared by evaporation of one drop of CMCAB suspended in distilled water placed on a carbon coated copper grid.

Drug loading

Drug loading (D.L.) was assessed according to Vedula *et al.*,[18] with slight modification. 10 mg of CMC SD NPs was added to 10 mL of phosphate buffer (concentration 10% w/v, pH 7.4) and kept for 3 days to allow the complete drug extraction from NPs. After 3 days, this solution was diluted and the absorbance was measured at 240 nm. The absorbance obtained was substituted in the regression equation of the standard curve data, and the unknown experimental concentration (C_{drug}) was determined:

$$\text{D.L. (\%, w/ w)} = \frac{\text{Weight of SD in NPs}}{\text{Weight of NPs}} \times 100 \quad (1)$$

Release study

The release of the drug from the CMC SD NPs was determined by using a dialysis membrane (12000-14000, AVWR Company). The membrane was filled with 1.5 mL of phosphate buffer (pH 7.4), maintained at 37 ± 0.5 °C and stirred by a magnetic bar at 80 rpm for 6 h. The membrane was activated in diffusion media by soaking in phosphate buffer. A sample of a particular formulation, equivalent to 1.7 mg of SD, was suspended in 1.5 mL of phosphate buffer (pH 7.4), then placed on the activated membrane and added to 20 mL of dissolution medium. At appropriate time intervals, 1 mL aliquots of the receptor medium were withdrawn and immediately replaced by equal volumes of the fresh receptor solution. These samples were analyzed spectrophotometrically at 240 nm.[19]

$$\text{Drug release \%} = \frac{\text{Released SD drug}}{\text{Total SD drug}} \times 100 \quad (2)$$

RESULTS AND DISCUSSION

Characterization of the lignocellulosic material

The chemical composition of cellulose extracted from bagasse exhibits about 94.2% α-cellulose. This high content shows that bagasse is a competitive source of pure cellulose.

The prepared CMC with DS 0.45 was esterified to produce CMCA (with DS of CM groups of 0.26 and 2.27% acetate) and CMCAB (with DS CM groups of 0.24, acetate 4.75% and 24.04% butyrate). These esters (CMCA and CMCAB) were further suspended in water, after which SD drug was incorporated.

FT-IR spectra

SD and CMC-ester interactions in the prepared ASD could be elucidated by IR studies, whereby the presence of interactions, usually H-bonding is often used to prove miscibility. The CMC SD NPs were examined and compared with pure SD, CMCA and CMCAB. The characteristic peaks of SD (Fig. 3a) were found at 3422.06 and 3353.6 cm^{-1} (N–H_2 vibrations); 1584.24, 1493.6, 1440.56 and 1406.82 cm^{-1} (ring skeletal vibrations); 1322.93 cm^{-1} (SO_2 asymmetric stretching); 1155.15 cm^{-1} (symmetric stretching) and 1322.93, 1155.15, 548.6 cm^{-1} (sulfonamide group, R-SO_2-N).[20] The spectra of the SD mixtures with CMCA and CMCAB NPs (Tables 1-3), designated as CMCA SD NPs and CMCAB SD NPs, respectively, (Fig. 3 b, c) presented the OH vibration band at 3481.85 and 3423.99 cm^{-1}, respectively. However, the IR spectrum of the CMC-esters-SD showed a strong absorption peak at 3233.07 and 3263.93 cm^{-1} for CMCA SD NPs and CMCAB SD NPs, respectively. NH_2 vibrations disappeared due to the reaction between SD and ester groups to form –CONH bonds, appearing at 1426.1, 1640.16 for CMCA SD NPs and at 1586.16, 1640.16 cm^{-1} for CMCAB SD NPs, which confirms the amide bond formed between CMC-ester and SD drug.[21]

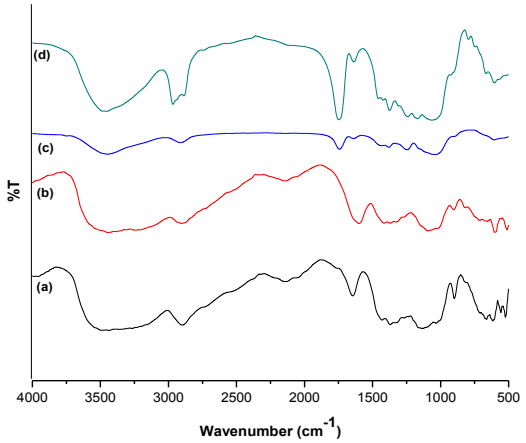


Figure 2: FTIR spectra of (a) cellulose, (b) carboxymethyl cellulose, (c) carboxymethyl cellulose acetate and (d) carboxymethyl cellulose acetate butyrate

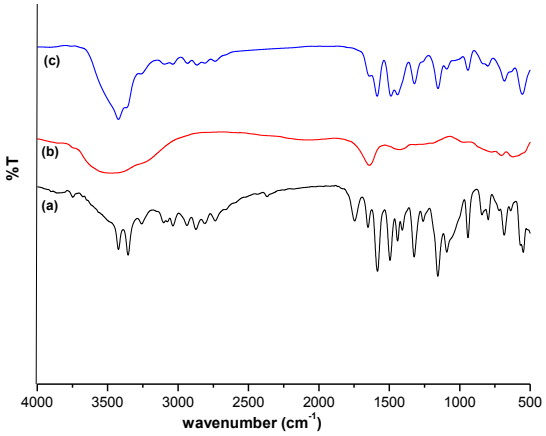


Figure 3: FTIR spectra of (a) sulfadiazine, (b) sulfadiazine loaded carboxymethyl cellulose acetate and (c) sulfadiazine loaded carboxymethyl cellulose acetate butyrate

Table 1
Characteristic IR bands of sulfadiazine drug

Wavenumber (cm^{-1})	Assignment	Relative absorbance
3422.06, 3353.6	N-H symmetric stretching	0.48, 0.58
1584.24, 1493.6, 1440.56, 1406.82	Ring skeletal vibrations	1, 0.82, 0.53, 0.25
1322.93	SO_2 asymmetric stretching	0.75
1155.15	SO_2 asymmetric stretching	0.81
1322.93, 548.6	Sulfonamide group, R-SO_2-N	0.75, 0.66

Table 2
Characteristic IR bands of sulfadiazine loaded carboxymethyl cellulose acetate nanoparticles

Wavenumber (cm^{-1})	Assignment	Relative absorbance
3481.85	OH vibration	1.25
3233.07	NH vibration	0.90
2808.81	Methyl CH_3 of acetate group	0.03
1640.16	C=O group	1
1426.1	NH bending	0.52
1426.1, 1640.16	CO-NH band	0.52, 1
1313.29	SO_2 asymmetric stretching	0.38
1196.61	SO_2 symmetric stretching	0.34
970.983, 943.02	Asymmetric vibrations of C-O-C in ester	0.31, 0.30
1313.29, 1196.61, 622.895	Sulfonamide group, R-SO_2-N	0.38, 0.34, 0.74

Table 3
Characteristic IR bands of carboxymethyl cellulose acetate butyrate loaded sulfadiazine nanoparticles

Wavenumber (cm^{-1})	Assignment	Relative absorbance
3423.99	OH vibration	1.52
3263.93	NH vibration	0.54
2933.2	Methyl –CH_3 of CMCAB	0.58
2865.7	Methylene CH_2 of CMCAB plus SD drug	0.63
1640.16	C=O group	0.59
1586.16	NH bending	1
1586.16, 1640.16	CO-NH band	1, 0.59
1321.96	SO_2 asymmetric stretching	0.74
1154.19	SO_2 symmetric stretching	0.84
1092.48, 942.056	Asymmetric vibrations of C-O-C in ester	0.45, 0.47
1321.96, 1154.19, 682.677	Sulfonamide group, R-SO_2-N	0.74, 0.84, 0.68

However, the bands at 1313.29 and 1321.96 cm^{-1}, assigned to SO_2 asymmetric stretching, and those at 1269.9 and 1154.19 cm^{-1}, assigned to SO_2 symmetric stretching, are remarked in the spectra of CMCA SD NPs and CMCAB SD NPs, respectively. The asymmetric vibration bands of C-O-C, which confirm the existence of the ester, were observed at 1269.9, 1196.6, 970.983 and at 1154.19, 1092.48, 942.056 cm^1 for CMCA SD NPs and CMCAB SD NPs, respectively.

Changes in the OH position can be used to verify intermolecular H-bonding interactions in CMC SD NPs. Lower wavenumber proves stronger intermolecular H-bonding. The OH peaks of CMCA, CMCAB, CMCA SD and CMCAB SD dispersions were listed in Table 4. The position of the OH peak of CMCAB SD NPs was shifted to a lower wavenumber, compared to that of the pure CMCAB polymer – this proves the stronger intermolecular H-bonding between SD and CMCAB. However, in the case of CMCA SD, the position of the OH peak was increased, which means that the intermolecular H-Bonding between SD and CMCA is very low.[22]

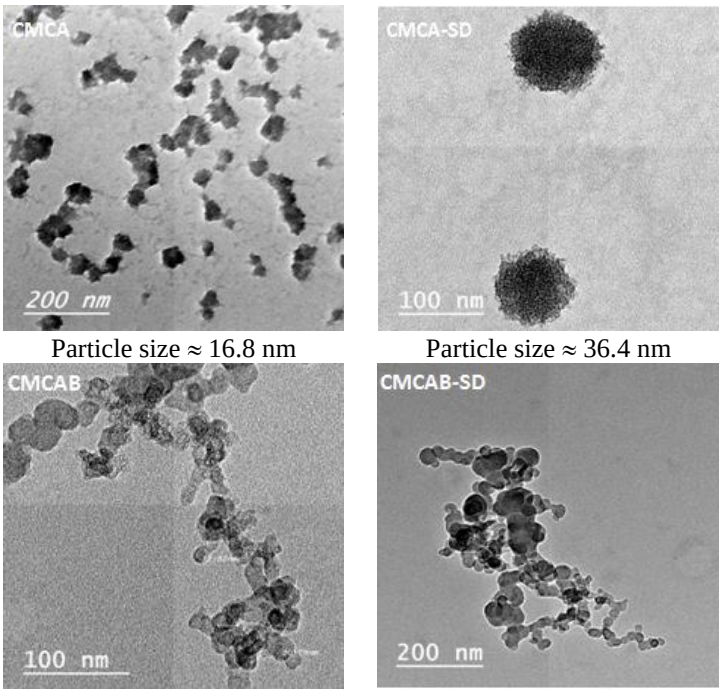
In addition, all of the polymers (CMCA and CMCAB) have C=O groups, which could bond with the NH_2 groups in the SD, resulting from the shift of the C=O stretching frequency to lower wavenumbers (Table 5).[22]

Table 4
OH peak position in IR spectra of carboxymethyl cellulose ester polymer and carboxymethyl cellulose ester sulfadiazine nanoparticles

Sample	OH peak position (cm^{-1})
CMCA	3447.13
CMCA-SD NPs	3481.85
CMCAB	3531.99
CMCAB-SD NPs	3423.99

Table 5
C=O stretching vibration peak positions in IR spectra of carboxymethyl cellulose ester polymer and carboxymethyl cellulose ester sulfadiazine nanoparticles

Sample	C=O peak position in pure polymer (cm^{-1})	C=O peak position with SD drug (cm^{-1})
CMCA	1743.33	1640.16
CMCAB	1748.16	1640.16



Particle size ≈ 16.8 nm | Particle size ≈ 36.4 nm

Particle size ≈ 12.88 nm | Particle size ≈ 95.00 nm

Figure 4: TEM analysis of the prepared samples

Morphological investigation

This study elucidates a method for producing CMCA- and CMCAB- SD NPs (CMC-esters sulfadiazine loaded nanoparticles). The morphology of the samples was portrayed with TEM and the resulted images were analyzed with the help of TEM image analysis software to evaluate the average size.

According to the TEM images, CMCA micelles appeared of irregular shape, while CMCAB micelles were oval or of spherical appearance. CMCAB stabilizes SD in water medium more efficiently than CMCA.

The average particle size of CMCA, CMCA-SD NPs, CMCAB and CMCAB-SD NPs in water was measured by using TEM. The mean particle size was found to be 16.8, 36.4, 12.88 and 95 nm for CMCA, CMCA-SD NPs, CMCAB and CMCAB-SD NPs, respectively (Fig. 4). The higher particle size of loaded CMCA-SD NPs and CMCAB-SD NPs, *i.e.* 36.4 and 95 nm, respectively, may be ascribed to the fact that they encapsulated SD (Fig. 4). The size of CMCAB-SD NPs was higher than

that of CMCA-SD NPs due to the increased drug loading percentage of CMCAB, compared to that of CMCA.

Characterization of the prepared dispersion

D.L.% of the CMC-ester-SD NP micelles was determined by using UV-vis absorption spectroscopy. SD was used as a model drug for D.L.% determination in the hydrophobic core of the amphiphile. After releasing the SD and removing the CMC-ester polymer precipitate, the amount of loaded SD was proportional to its concentration and could be determined from the maximum absorption peak at 242 nm. Figure 6 illustrates the standard calibration curve used for D.L.% calculations. At a constant feed weight ratio (1:1), the maximum D.L.% was 1.78% and 42.88% for the CMCA- and CMCAB-SD NPs, respectively. D.L.% maximized according to the hydrophilicity of the hydrophilic moiety, or to the hydrophobicity of the hydrophobic moiety.[23]

The increasing concentration of hydrophobic groups from that of only acetate (in the case of CMCA) to that of acetate and butyrate (in the case of CMCAB) leads to increasing drug encapsulation and increasing D.L.%. Most of the reported self-assembled polymers often produce a low D.L.%, typically less than 20%.[15]

Amphiphilic CMCAB-SD NPs have higher D.L.%, of up to 42.9%. The increasing DS of amphiphiles contributes to decreasing the release rate, which may be caused by the increment in the thickness of the coating, which slows down the diffusion rate of the drug from the NPs into the dissolution medium. In other words, as concerns the effect of ester types, the decrease in the drug release rate was observed when the content of ester groups in the matrix was increased, as verified. This may be due to the fact that the polymer formulation with higher concentration of ester groups might generate a denser matrix around the drug particles, providing a stronger barrier, which prevents them from escaping and dissolving. However, the hydrophilicity of CMCA was higher than that of CMCAB, corresponding to the order of the release rates (CMCA > CMCAB).

CMCA and CMCAB formulations were able to slow down the release of the SD drug. A modification of 10% (w/v) slows the release rate of the drug, compared to the immediate release of SD in the absence of CMC-esters. CMCA-SD NPs were less effective in slowing down the drug release rate, compared to CMCAB-SD NPs, which exhibited the highest D.L.%. Figure 7 shows the release profiles of the SD from the CMCA and CMCAB micelles. The CMCAB-loaded micelles of the SD exhibited well-developed sustained drug release patterns. The release study of the SD drug showed that the time for nearly complete drug release was 0.5, 0.75 and 6 h for the SD without polymer, CMCA-SD and CMCAB-SD, respectively.

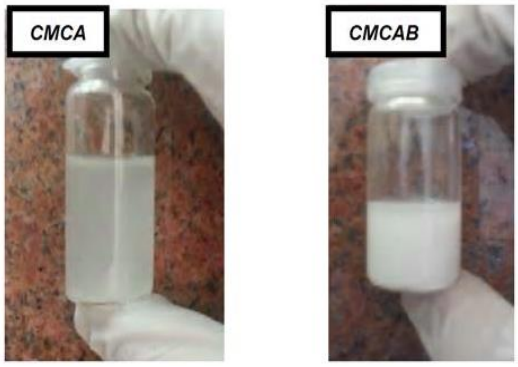


Figure 5: Images of carboxymethyl cellulose acetate and carboxymethyl cellulose acetate butyrate loaded sulfadiazine drug-in-water dispersion

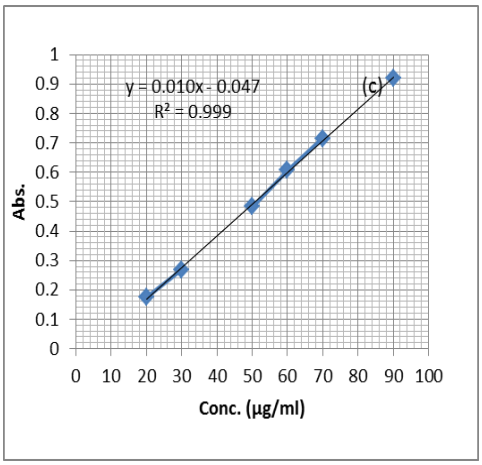


Figure 6: Calibration curve of sulfadiazine dissolved in buffer solution (pH = 7.4) at 240 nm

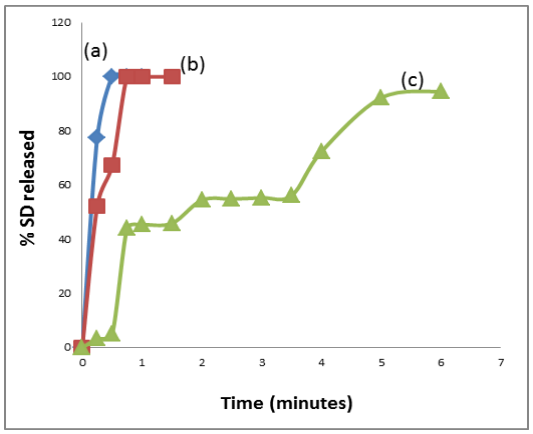


Figure 7: Sulfadiazine drug release (a) in the absence of polymer, (b) from carboxymethyl cellulose acetate and from (c) carboxymethyl cellulose acetate butyrate

Table 6
Stability of prepared dispersions at different temperature

Sample	8 °C ± 1	20 °C ± 2	32 °C ± 1	40 °C ± 1
CMCA ± 2	19	10	8	2
CMCAB ± 2	50	25	22	4

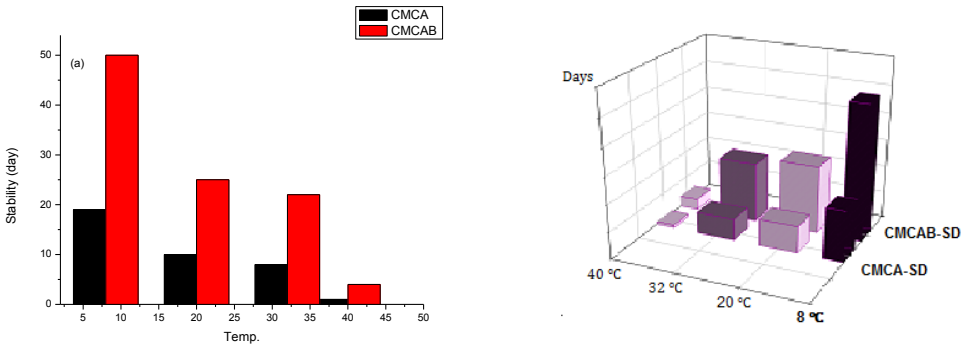


Figure 8: Stability study of prepared dispersions at different temperature

Compared with the released rate in the case of the SD drug without CMC-ester, which was 100% during the first 0.5 h, the release rate of the SD loaded CMCA was 67.33%, while the SD loaded CMCAB had a considerably slower release rate under the same conditions, with approximately 5.14% of the encapsulated SD released in a sustained manner during the same time. At 0.75 h, the release rate of the encapsulated SD from CMCA-SD NPs was 100%, while that from CMCAB-SD NPs was approximately 43.98%. After 6 h, the release rate of CMCAB-SD NPs was 94.56%. These results confirmed that CMCAB was more stable and could be used for sustained drug release, compared to CMCA micelles.

The high stability of CMCAB can be explained by its high T_g and DS, since a higher T_g (138 °C) generally indicates better stability. A single high T_g value is desirable for a particular ASD.[24]

The micellar structure is strongly affected by the temperature and the formulations were more stable at 20 °C. Table 6 and Figure 8 show that the formulations prepared with CMCAB were more stable than those with CMCA. This is due to the increasing hydrophobic content, which participates in encapsulating a large quantity of SD drug.

CONCLUSION

CMCA and CMCAB have attracted great attention in hydrophobic active dispersion. In the present study, the dispersion produced was stable due to the amide bond formation between the CMC-ester and the SD drug. CMCAB has shown higher drug loading efficiency (42.88%) than CMCA (1.78%) due to the high DS of the hydrophobic moieties in CMCAB. It was confirmed by TEM analysis that the particle size of SD loaded CMC-esters is higher than that of empty CMC-esters.

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