A Novel Polymeric Biomaterial Based on Carboxymethylstarch and its Application in Controlled Drug Release

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ABSTRACT: This study reports investigation of the sustained release behavior of a model drug (acetylsalicylic acid) from carboxymethylstarch (CMS) based matrix. CMS was prepared by incorporation of carboxymethyl groups in the starch moiety; by reacting starch with sodium salt of monochloro acetic acid in presence of sodium hydroxide. The *in vitro* drug release study was performed by United States Pharmacopeia rotating paddle method, at various pH. The rate of drug release from the above matrix was found to increase with increase in pH. Further, the release behavior of the drug from the CMS based matrix was found to be non-Fickian, *n* value being between 0.80 and 0.85, suggesting that the release was controlled by a combination of tablet erosion and diffusion of the drug from the swollen matrix. J Appl Polym Sci 114: 2798–2805, 2009

Key words: biopolymers; control drug release; light scattering; polysaccharides

INTRODUCTION

Modern techniques of drug design are identifying new drug candidates at a much faster pace. However, for safe and practical use as a drug, the efficacy of the molecule against a particular ailment is not enough. Often, many of them are of narrow therapeutic index and have great potential to cause side effects. Evidently, they are of not much benefit to the patient until a suitable controlled drug delivery system is developed side by side, which can maintain the desired level (or therapeutic level) of the drug in intended body tissue (e.g., blood) for a long time.

Among the various possible modes of drug delivery, the oral mode is the most convenient and acceptable option. However, the physiology of the gastrointestinal tract offers a lot of challenge. The gastrointestinal tract is divided into stomach, small intestine and large intestine. The pH varies widely along the gastrointestinal tract. It varies from as low as 1.5–2.0 (fasting condition) in stomach to upto 7.6 in mild colon and left colon. The various enzymes in stomach offer an environment harsh enough for degradation of the peptides and many other drugs.[1–7]

An ideal drug delivery matrix for oral delivery should protect the drug from the low pH harsh environment of the stomach and should preferably release the drug in lower gastrointestinal tract. Consequently, the matrix should not have higher rate of drug release in acidic pH, than in neutral and alkaline pH conditions.

Starch is a low cost abundantly available renewable biopolymer. In its crude form, starch is a mixture of two polymers of anhydroglucose units-amylose and amylopectin.[8] Amylose is present at levels up to 25% depending upon the source and amylopectin is the major fraction with levels up to 95%. Amylose is essentially a linear polymer of 1, 4-linked α-D- glucopyranosyl units,[9] with molecular weight ranging from 10,000 to 60,000 g/mole. On the other hand, amylopectin is a highly branched polymer of α-D- glucopyranosyl residues linked together mainly by 1→ 4 linkages with 1 → 6 bonds at the branch points.[9] It is of high molecular weight, between 10^5 and 10^7g/mole. In authors' laboratory, carboxymethylstarch (CMS) has been developed by inserting carboxymethyl group onto starch backbone. The attachment of carboxymethyl groups to the polymer moiety of starch is expected to result in modified properties like higher

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viscosity in solution, lower biodegradability (hence longer self-life) etc. The starch used here is maize starch which contains 20% as amylose and 80% as amylopectin.

The developed material (CMS) has been characterized by a variety of physicochemical characterization techniques to confirm that carboxymethylation does take place. Further, we have investigated the applicability of CMS as a matrix for controlled drug release (oral mode). A controlled drug release system is formally defined as one that delivers the drug at a predetermined rate, for a time of at least 12–14 h.[10] In the field of drug delivery, polysaccharides (such as starch, chitosan, alginate, cellulose, etc) and modified polysaccharides (e.g., cellulose derivatives) have earned special attention because of their high biocompatibility and hydrophilicity.[11–15]

CMS was processed (direct compression technique) along with a model drug (acetylsalicylic acid) and a suitable binder (polyvinylpyrrolidone), mixed in a definite ratio, into tablets of 250 mg each. *In vitro* drug release from these tablets was determined under standard conditions.[16] The outcome of these studies has been presented as drug release profile (Cumulative Drug Release vs. Time).

Acetylsalicylic acid is a compound with profound physiological effects as an analgesic. It finds use as a therapeutic agent in treatment of mild to moderate pain, migraines, rheumatic fever, rheumatic arthritis and other inflammatory joint conditions. Low doses of aspirin are also recommended for the prevention of stroke in patients with diagnosed coronary artery disease and who have an elevated risk of cardiovascular disease.

As mentioned earlier, the pH along the gastrointestinal tract varies widely (acidic in stomach and neutral/alkaline in the lower gastrointestinal tract). So, in order to avoid release of the drug in the stomach, the rate of drug releases from the matrix should not be high in acidic pH.[17–19] Consequently, to determine the effect of pH, the *in vitro* drug release study was performed at various pH.

In the present investigation, the *in vitro* drug release study of the parent material (starch) was also performed under exactly the same conditions (as that in case of CMS). All procedures i.e, tablet preparation, drug release study etc. were kept identical. The drug release profile of CMS was compared to that of the parent material (starch) to ascertain the matrix with better drug release properties, for oral mode of drug delivery.

To the best of our knowledge, CMS as a matrix for control drug release, in association with polyvinylpyrollidone as binder, for the drug acetyl salicylic acid has never been reported, which has been addressed in this article.

MATERIALS AND METHODS

Materials

Maize starch was supplied by E. Merck (India) Limited, Mumbai, India. Sodium salt of monochloro acetic acid (SMCA), acetone (AR Grade) and sodium hydroxide (AR Grade) were procured from E. Merck (India) Limited, Mumbai, India. Acetylsalicylic Acid (AR Grade) was supplied by E. Merck, Germany. Polyvinylpyrrolidone (AR Grade) was supplied by S. D. Fine Chem, Mumbai, India. Magnesium Stearate (LR Grade) was purchased from Loba Chemie, India. All chemicals were used without further purification.

Synthesis

The carboxymethylation reaction adopted was as follows:

The starch powder (required amount) was slowly dissolved into water in a round bottom flask, maintained at temperature 80°C, with constant stirring. The resulting mixture was cooled down to 50°C and purged with nitrogen for 1 h. Required amount of aqueous solution of sodium hydroxide was added to the slurry and the mixture was stirred for 15 min. Afterwards, the carboxmethylating agent (SMCA) was added under constant stirring. The reaction was continued for 2 h. The reaction mixture was cooled gradually, dispersed in acetone and the excess alkali was neutralized with dil HCl bringing the pH to 7. The product was finally washed with acetone, filtered and then dried under vacuum oven. Various grades were developed by varying the reaction parameters for obtaining carboxymethylstarch with different degree of substitution (DS). The details of the synthesis parameters are summarized in Table I.

Characterization

Intrinsic viscosity measurement

Viscosity measurements of the polymer solutions were carried out with an Ubbelohde viscometer (CS/S: 0.003899) at 25°C. The viscosity was measured in 0.1 mol/L $NaNO_3$ solution. The pH of the solution was neutral. The time of flow of solution was measured at four different concentrations. From the time of flow of polymer solution (t) and that of the solvent (t_0), relative viscosity ($\eta_{rel} = t/t_0$) was obtained. Specific viscosity was calculated from the relation $\eta_{sp} = \eta_{rel} - 1$. Then, the reduced viscosity (η_{sp}/C), and the inherent viscosity ($\ln \eta_{rel}/C$) were calculated, where C is the polymer concentration in g/dL. The intrinsic viscosity was obtained from the point of intersection after extrapolation of two plots, i.e., η_{sp}/C versus C and $\ln \eta_{rel}/C$ versus C to zero

TABLE I
Synthesis Details of Carboxymethylstarch (CMS)

Polymer	Amount of AGU[a] (mole)	Amount of SMCA (mole)	Amount of NaOH (mole)	Degree of substitution (DS)	Intrinsic viscosity (dL/g)	Wt. Avg. Mol. Wt. (g/mole)
CMS 1	0.0062	0.0012	0.0014	0.2	1.4	6.65×10^5
CMS 2	0.0062	0.0018	0.0020	0.3	1.7	7.01×10^5
CMS 3	0.0062	0.0024	0.0027	0.4	1.84	7.86×10^5
CMS 4	0.0062	0.0031	0.0034	0.5	2.06	8.74×10^5
CMS 5	0.0062	0.0037	0.0040	0.6	1.95	8.20×10^5
Starch	–	–	–	–	0.91	5.82×10^5

[a] Calculated based on anhydroglucose unit (AGU). 1 mole of AGU = 162 g.

concentration.[20] The intrinsic viscosity values have been summarized in Table I.

Determination of weight average molecular weight by SLS analysis

The weight average molecular weight (M_w) of starch and different grades of CMS was determined by static light scattering (SLS) analysis using Light Scattering Spectrophotometer, (Model Nano ZS) made by Malvern, UK. The results are summarized in Table I.

Elemental analysis

The elemental analysis was undertaken with an Elemental Analyzer (Model Vario EL III, Elementer, Germany). The estimation of five elements, that is carbon, hydrogen, nitrogen, oxygen and sulfur were performed. The results are described in Table II.

FTIR spectra

The FTIR spectra of starch [Fig. 1(a)] and CMS 4 [Fig. 1(b)] were recorded in solid state using KBr pellets with a FTIR spectrophotometer (Model IR-Prestige 21, Shimadzu, Japan) between 500 and 4000 cm^{-1}.

^{13}C-NMR spectroscopy

^{13}C-NMR spectra of starch [Fig. 2(a)] and CMS 4 [Fig. 2(b)] were recorded at 400 MHz with a Bruker 400P spectrophotometer.

TABLE II
Elemental Analysis Results of Starch and CMS

Polymer	%C	%H	%N	%O	%S
Starch	40.27	10.43	0.00	49.30	0.00
CMS 4	32.11	8.82	0.00	59.1	0.00

Swelling measurements

Equilibrium swelling measurements of both starch and CMS 4 were done in water or in various buffers. A small-preweighted piece (W_1) of the material was immersed in distilled water or in various buffers and left to swell for 24 h. Then, the swollen piece was recovered and the excess water was removed carefully with tissue paper and reweighed (W_2). The swelling index was calculated by the formula given below.[16,21,22]

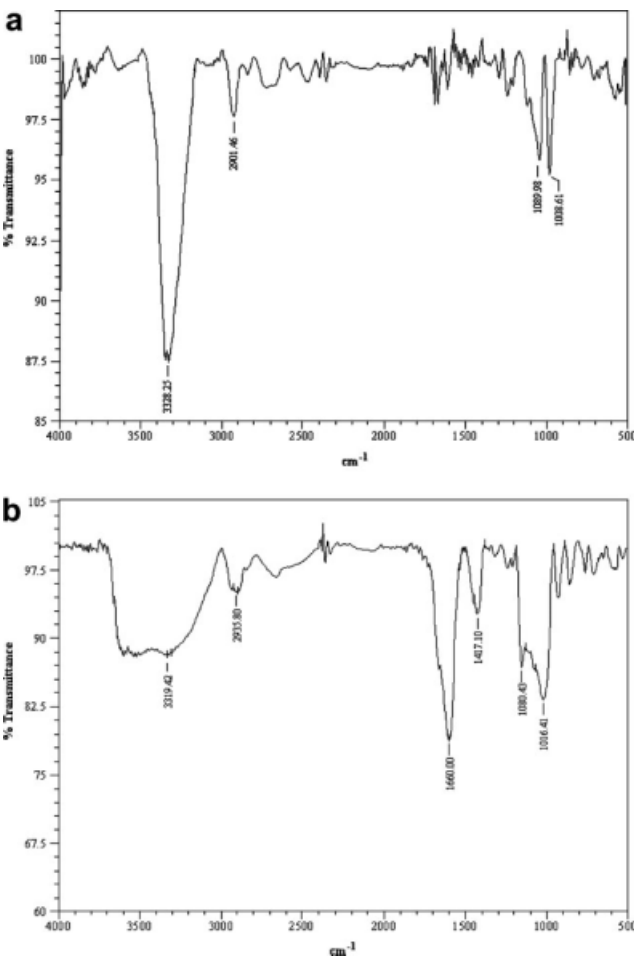


Figure 1 FTIR spectra of (a) Starch and (b) CMS 4.

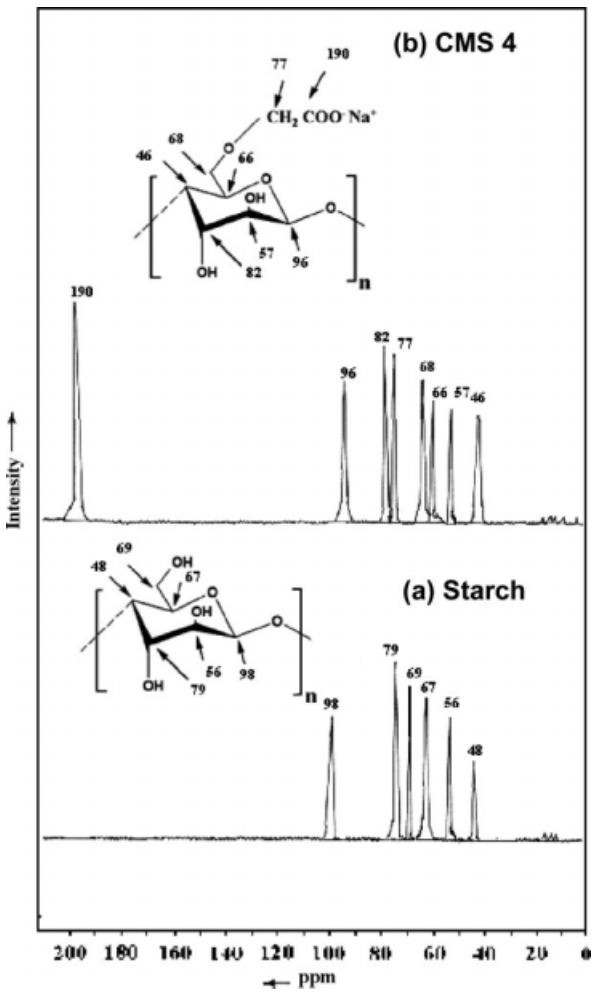


Figure 2 ^{13}C NMR of (a) Starch and (b) CMS 4.

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} \times 100$$

The swelling index of starch and CMS against time, for the first 120 min of immersion in distilled water has been shown in Fig. 3.

In vitro drug release studies

Preparation of tablets

The sample (CMS/starch) under evaluation (as drug delivery matrix) was finely ground in a blender, with the model drug (acetyl salicylic acid) and polyvinylpyrrolidone (binder) in 10 : 1 : 1 ratio. The mixture was wetted with ethanol and mixed further.The paste was dried at 50°C to a constant weight and ground.Then, a mixture of silicon-di-oxide and magnesium stearate (in the ratio 2 : 1) was added as a lubricant, in amount not exceeding 3–5% of the ground powder. After mixing and sieving (20 mesh), tablets of 250 mg each were prepared by compression in a standard carver laboratory press model C at 2–3 t/cm^2.[16] Evidently, the drug load of each tablet was 20.8 mg.

In vitro study of drug release

United States pharmacopeia (USP) rotating paddle method was used for study of controlled drug release from these tablets. The tablet was immersed in 900 mL of buffer solution, maintained at the temparature of 37 ± 0.5°C, under a constant rotation of 60 rpm (using paddle stirrer). Aliquots were drawn after every 30 min and drug (acetylsalicylic acid) concentration was assayed spectrophotometrically. The rate of drug release was graphically represented in form of drug release profile (cumulative drug release vs. time) (Figs. 4 and 5). The drug release study was performed at different pH buffers (4, 7, and 10; Fig. 5).

RESULTS AND DISCUSSIONS

Synthesis and interpretation of intrinsic viscosity

The carboxymethylation reaction employed was designed to provide starch derivatives, in principle, to substitution at hydroxyl groups of the anhydroglucose rings. The synthesis proceeds through

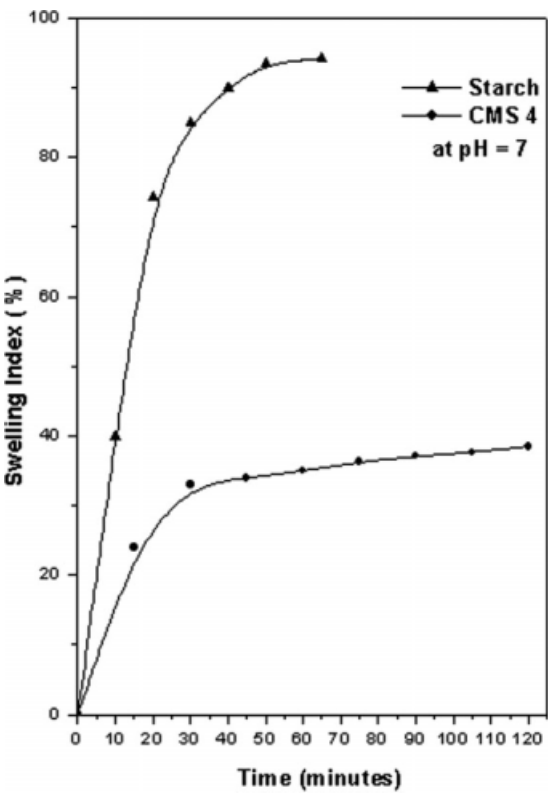


Figure 3 Swelling behavior of Starch and CMS 4 in the first 120 min (i.e., when the rate of swelling is maximum).

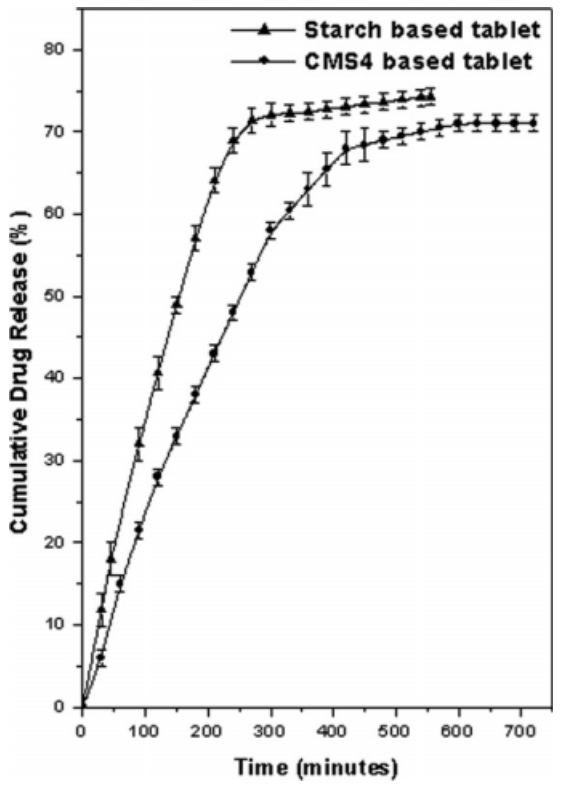


Figure 4 Cumulative drug release profiles of starch and CMS 4 based tablets at pH 7.0, for model drug acetylsalicylic acid (The results are mean ± SD; $n = 3$).

two step reaction which has been represented in Scheme 1.

To diminish the oxidative degradation of polysaccharide backbone, the reaction was carried out in an oxygen free nitrogen atmosphere. The carboxymethylation reaction between starch and SMCA was carried out in presence of a slight excess of sodium hydroxide concentration (preferably 10% in excess), which work both as reactant and catalyst. The sodium hydroxide and the starch interact to form an alkoxide derivative, which reacts with the carboxymethylating agent through a substitution reaction, leading to the carboxymethyl substitution along the polysaccharide backbone. The reaction temperature was maintained at 50°C. Though at relatively high temperature, the reaction is faster, but chance of formation of by-products increases. The carboxymethylation reaction, therefore, being carried out at normal pressure and not at high temperature. By varying the concentration of carboxymethylating agent (SMCA), five grades of CMS with different degrees of substitution (DS) have been developed. The details of the synthesis parameters are summarized in Table I.

From the relative viscosity of various polymer solutions of known strength, inherent viscosity and reduced viscosity were evaluated and plotted against concentration. Intrinsic viscosity was determined from the point of intersection of two extrapolated (to zero concentration) plots[20] i.e, inherent viscosity versus concentration (η_{inh} vs. C) and reduced viscosity versus concentration (η_{red} vs. C).

The reduced viscosity and inherent viscosity were calculated by using the following relations:

$$\eta_{rel} = t/t_0 \quad (1)$$

$$\eta_{sp} = \eta_{rel} - 1 \quad (2)$$

$$\eta_{red} = \eta_{sp}/C \quad (3)$$

$$\eta_{inh} = (\ln\ \eta_{rel})/C \quad (4)$$

The intrinsic viscosity was evaluated for both starch and CMS (Table I).

It is evident that the intrinsic viscosity of various grades of CMS is greater than that of starch (Table I). This can be explained by the higher molecular weight of CMS compared to starch, due to the incorporation of carboxymethyl groups. According to Mark–Houwink-Sakurada relationship, Intrinsic viscosity $\eta = KM^{\alpha}$, where K and α are constants, both related to stiffness of the polymer chains.[23–25] As we move from CMS 1→ CMS 5, it has been observed that with increase in DS, the viscosity values

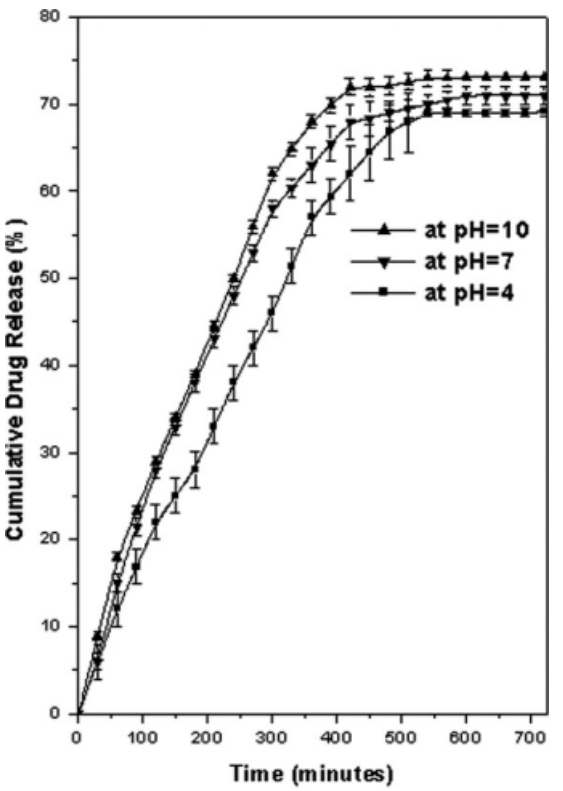
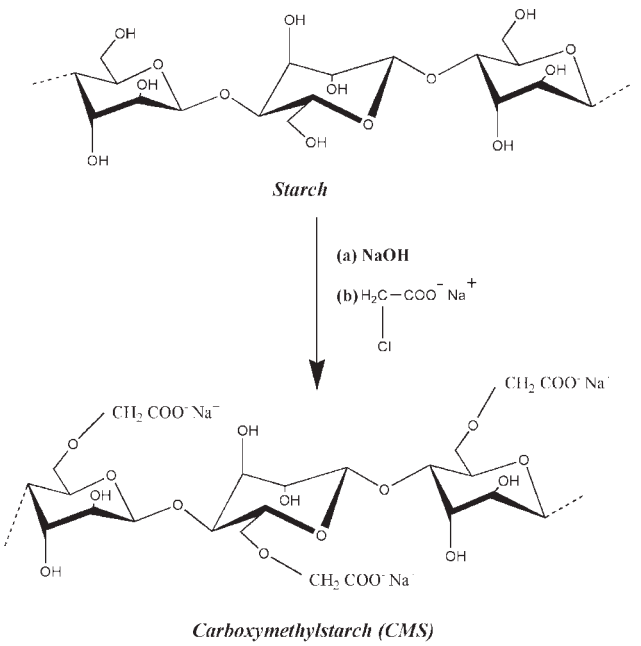


Figure 5 Cumulative drug release profile of CMS 4 based tablets at various pH, for model drug acetylsalicylic acid (The results are mean ± SD; $n = 3$).



Scheme 1 Schematic representation for the synthesis of carboxymethylstarch from starch.

increases up to CMS 4 (which is an optimized grade with respect to intrinsic viscosity and molecular weight – Table I); afterwards it decreases, though the DS is higher. This may be because of the more by-product formation.

Determination of weight average molecular weight by static light scattering technique

The weight average molecular weight of starch and various grades CMS was determined from Debye Plot using SLS analysis. The results are summarized in Table I. From Table I, it is obvious that the weight average molecular weight (M_w) of CMS has increased drastically compared to starch, which can be explained because of the incorporation of carboxymethyl groups onto the backbone of base polysaccharide (starch).

Elemental analysis

The results of elemental analysis for both starch and CMS 4 are given in the Table II. The higher percentage of oxygen in case of carboxymethylstarch compared to starch can be explained by the fact that carboxymethyl group has been inserted onto the backbone of starch.

FTIR spectra

From the FTIR spectrum of starch [Fig. 1(a)], it is being observed that a broad peak at 3328 cm^{-1} is due to the stretching vibrations of O—H, a small peak at 2901 cm^{-1} attributed to the C—H stretching vibrations. The bands at 1089 cm^{-1} and 1008 cm^{-1} are assigned to C—O—C stretching vibrations.

From the FTIR spectrum of CMS 4 [Fig. 1(b)], it is being obvious that apart from the peaks present in starch, there are two additional strong peaks at 1660 cm^{-1} and 1417 cm^{-1}. These are attributed to the COO^- groups, which is a clear indication that carboxymethylation does take place.

^{13}C-NMR spectroscopy

It has been shown that starch [Fig. 2(a)] has six distinct peaks in the ^{13}C-NMR spectrum. The absorption peak at $\delta = 98$ ppm is for anomeric carbon atom and the peak at $\delta = 79$ ppm is for carbon atom connected by —OH group and another peak at $\delta = 69$ ppm is attributed for the carbon atom of $—CH_2OH$ group.

In case of CMS 4 [Fig. 2(b)], apart from the peaks present at starch, there are two additional peaks. The absorption peak at $\delta = 77$ ppm is for the carbon atom of $—O—CH_2—$ of the inserted carboxymethyl group and another peak at $\delta = 190$ ppm is for the carboxyl carbon atom of $—COO^-Na^+$.

Hence, the presence of two additional peaks in case of carboxymethylstarch is a clear evidence of the insertion of carboxymethyl groups onto the starch backbone.

Swelling measurements

Appropriate swelling behavior is essential for uniform and prolonged release of the drug from the matrix. Equilibrium swelling measurements were done for both starch and CMS 4, in various buffer solutions. For starch, the swelling was 212 ± 30 % at buffer solution of pH 7. The corresponding figure for CMS 4 is 73 ± 7.5%. So, it is evident that the swelling of CMS 4 (in aqueous medium) is much lower than that in case of starch. This predicts CMS a better candidate as matrix for controlled drug release than its parent material (starch). From Figure 3 (swelling behavior of starch and CMS for the first 120 min of immersion into distilled water), it is obvious that not only CMS 4 has lower swelling index than starch, but also achieves the equilibrium swelling at a much slower rate; thus further supporting the fact that it would release any drug enclosed in it at a much slower rate.

Again, the equilibrium swelling in case of CMS 4 in acidic buffer solution (of pH 4.0) is only 52 ± 4 %, while this value for alkaline buffer solution (of pH 10.0) is 128 ± 14%. Thus, it is evident that the swelling of CMS 4 is higher in alkaline pH than in acidic and neutral pH. This would result in higher

TABLE III
t_{50} and n Value of Drug Release Profiles for Starch (at pH = 7) and CMS 4 Matrices

Matrix of the tablet	pH of the dissolution medium	t_{50} Value (time taken for release of 50% of the enclosed drug, in minutes)	n value
Starch	7	154	0.88
CMS 4	4	322	0.82
CMS 4	7	252	0.82
CMS 4	10	240	0.83

rate of drug release in alkaline pH environment i.e, in the lower gastrointestinal tract, as desired.

In acidic pH (i.e., pH 4.0) the $-CH_3COO^-Na^+$ groups of CMS gets converted into $-CH_3COOH$, which because of their lower polarity, has lesser tendency to form hydrogen bonding with water. But in alkaline pH, the $-CH_3COO^-Na^+$ remains as such, which are highly polar in nature. Hence they have considerably greater tendency to form hydrogen bonds. This explains the fact that CMS matrix can retain more water molecules in alkaline pH, than in acidic pH. Evidently, the swelling is much higher in alkaline pH, than in acidic pH.

In vitro study of drug release

The *in vitro* study of drug release was performed for both starch and CMS 4 tablets at pH 7. In each case, cumulative drug release (%) was plotted against time. These cumulative drug release profiles of starch and CMS 4 based tablets, at pH 7, have been compared in Figure 4. The corresponding t_{50} value (time taken for release of 50% of the drug) of these drug release profiles have been reported in Table III.

It is evident from the drug release profiles (Fig. 4) that the drug (acetylsalicylic acid) is released rapidly in case of starch-based tablets. On the other hand, sustained drug release for a prolonged period has been noticed for CMS 4 based tablets. This is also as predicted by the swelling studies.

Further, at pH 7, the t_{50} value (Table III) for starch-based tablets (154 min) is much lower than that for the CMS 4 based tablets (252 min). This further confirms the much slower 'sustained' drug release kinetics of CMS 4 based tablets, as opposed to the case of starch-based tablets.

Clearly, CMS 4 unlike its parent material (starch) is a good candidate as a matrix for sustained drug release.

Effect of pH on *in vitro* cumulative drug release

For oral drug delivery systems, the effect of pH on drug release profile is very significant since the pH changes widely along the gastrointestinal tract.[17–19] The *in vitro* cumulative drug release of CMS 4 was studied in acidic pH (pH = 4), neutral pH (pH = 7) and in alkaline pH (pH = 10) buffers. The drug release profile at various pH for CMS 4 based tablets has been shown in Figure 5. The corresponding t_{50} value (time taken for release of 50% of the drug) of these drug release profiles have also been reported in Table III.

It is evident from the drug release profiles as well as from their t_{50} value that the rate of drug release is most rapid in alkaline pH and is slowest in acidic pH. This is in agreement with the outcome of the swellibility studies done above; where higher swelling of CMS 4 had been observed in alkaline pH buffer.

The most undesirable side effects of acetylsalicylic acid are gastrointestinal distress including ulcers and stomach bleeding, especially in higher doses. Therefore, it is desirable to release the drug in lower gastrointestinal tract. Since our matrix releases the drug at a faster rate in alkaline pH (as in lower gastrointestinal tract), so it is an ideal vehicle for delivery of drugs like acetylsalicylic acid which are preferentially to be released in lower gastrointestinal tract.

Drug release kinetics

The drug release kinetics from the different matrices was determined by the exponential equation:

$$\frac{M_t}{M_\infty} = K \cdot t^n$$

Where k is a constant representing the apparent release rate (%/min) that takes into account structural and geometric characteristics of the release device, n is the diffusion exponent. The value of n is useful for the determination of drug release mechanism. This equation must hold only for the first 60% of the fractional drug release from the tablets, for which the one-dimensional diffusion under a perfect sink condition holds true.[16,26]

In case of nonswelling tablets, drug release is generally expressed by Fickian diffusion, for which $n = 0.5$. For most erodible matrices, the drug release follows zero order kinetics, for which $n = 1$. In case of swelling tablets, the drug release is due to a combination of swelling and erosion. They follow non-Fickian release behavior. For them, the value of n lies between 0.5 and 1.0.[27]

The values of n were estimated by linear regression of log (M_t/M_∞) versus log t. The values of n thus calculated for all types of CMS drug release profiles involved in this study have been summarized in Table III.

It is obvious from Table III that in all the cases of CMS 4 matrices, the value of n is between 0.82 and 0.84, indicating that the drug release from the CMS 4 matrix follows non-Fickian release behavior, suggesting that the release was controlled by a combination of tablet erosion and diffusion of the drug from the swollen matrix.

CONCLUSION

Modified polysaccharide synthesized by carboxymethylation of starch is a promising candidate as matrix for controlled drug release (oral mode). This matrix (CMS) releases the enclosed drug at a much faster rate in neutral and alkaline pH than in acidic pH, thus holding the promise of being developed into a vehicle for targeted drug delivery to the lower gastrointestinal tract. Further, the release of the drug acetylsalicylic acid from CMS demonstrated non-Fickian model of drug release; suggesting that the release is controlled by a combination of tablet erosion and diffusion of the drug from the swollen matrix.

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