Esterification of Carboxymethyl Cellulose with Acrylic Acid for Targeted Drug Delivery System

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Esterification of sodium carboxymethyl cellulose (SCMC) was done with acryloyl chloride which contains double bond. The original CMC and the esterified product were characterized by FTIR spectroscopy and XRD. The esterified product showed pH dependent swelling behavior.

Introduction

Oral delivery of drugs to the small intestine is an important area of research in the development of oral dose forms. An overriding theme in drug delivery to the small intestine is how to increase the efficiency of absorption or bioavailability. Enteric coating employs pH sensitive polymers, where the coating does not allow the release of drug in the acidic environment of the stomach but solubilizes or swells in the mildly acidic to neutral environment of the small intestine and thereby releases the drug. Enteric protection is required to prevent gastric irritation caused by drugs like aspirin or to protect the degradation of a drug in gastric fluid eg penicillin or to delay release for local delivery in the intestine.

Enteric polymers currently used to coat pharmaceutical dosage forms include cellulose, vinyl, and acrylic derivatives. These polymers exhibit resistance to gastric fluids yet are readily soluble or permeable in intestinal fluid. Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH. In the low pH of the stomach, the enteric polymers are unionized, and therefore remains insoluble. As the pH increases in the intestinal tract, these functional groups ionize, and the polymer swells or becomes soluble in the intestinal fluid. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine, where the drug is then released for absorption through the intestinal mucosa into the human body where it can exert its pharmacologic effects.

Sodium carboxymethyl cellulose (SCMC) is a semisynthetic water-soluble polymer in which CH₂COOH groups are substituted on the glucose units of the cellulose chain through an ether linkage. It is pale yellow in color, odorless, nontoxic, water soluble powder, stable in pH range 2 - 10 and insoluble in organic liquids. It reacts with heavy-metal salts to form films that are insoluble in water, transparent and unaffected by organic materials. It is mainly used in detergents, soaps, food products (especially dietetic foods and ice cream), where it acts as water binder, thickener, suspending agent, and emulsion stabilizer, textile manufacturing (sizing): coating paper and paper board to lower porosity, drilling muds, emulsion paints, protective colloid, pharmaceuticals, cosmetics.

Esterification of SCMC with acryloyl chloride to give an acrylic acid ester was tried in our laboratory.
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Experimental:

Materials
Sodium carboxymethyl cellulose (SCMC), a commercial product (Loba Chemie Pvt. Ltd., Mumbai, India) of high viscosity grade was dried prior to use at a temperature of 100°C under vacuum. Acryloyl chloride (ACl) was prepared by reacting with benzoyl chloride by following the procedure of Stampel et al. (1988). The organic solvent methyl ethyl ketone (MEK) was obtained from Loba Chemie Pvt. Ltd., Mumbai, India.

Synthesis of Acryloyl Chloride
A mixture of 216g (3 moles) of acrylic acid (AA), 844g (6 moles) of benzoyl chloride, and 0.5g of hydroquinone was distilled at a fairly rapid rate through a distilling column. The distillate was collected in a receiver containing half a gram of hydroquinone, immersed in ice. When the temperature at the top of the column, which remained between 60-70°C for most of the distillation, had reached 85°C the distillation was discontinued. The crude product, weighing between 215-225g, was then redistilled through the same column and the fraction boiling at 72-74°C at 740mm was collected. The yield of the final product was 185-195g or 68-72%.

Esterification of Sodium Carboxymethyl Cellulose and Acrylic Acid
The optimum parameters were found experimentally. In a three-necked flask 500mg of SCMC was dissolved in 10 ml of water with constant stirring. To the above solution 6ml of MEK was added (Solution-A). In a stop-cocked measuring cylinder 0.18ml of ACl was mixed with 6ml of MEK (Solution-B). Solution-A was kept in an ice-bath. To Solution-A, Solution-B was added drop wise and was stirred for 2hrs. and then the mixture was kept at room temperature for 12hrs. A thick gelatinous precipitate of hydrogel, was obtained. This gelatinous precipitate was repeatedly washed with rectified spirit to wash off any unreacted AA from the hydrogel. Then the product was dried at room temperature under vacuum.

Characterization of the esterified product
The confirmation of the esterification reaction and the presence of double bond in sample were confirmed by FTIR Spectroscopy (NEXUS-870, Thermo Nicolet Corporation).

The crystallinity of the esterified product was determined with X-ray diffraction (XRD-PW 1700, Philips, USA) using CuKα radiation generated at 40KV and 40 mA; the range of diffraction angle 2θ was 10.00-70.00°.

Swelling behavior of the esterified product
The esterified product was immersed directly in buffers of pH 1.4 or 5.4 or 7.4 or 9.4 (buffers were prepared as per INDIAN PHARMACOPOEIA-1996) at room temperature for 72 hrs, after that the swollen product was dried at 37°C under vacuum to a constant weight. The equilibrium percentage of swelling (% swelling) of the product was calculated as:

\[ \% \text{Swelling} = \frac{(W_h - W_d)}{W_d} \times 100 \]

where Wh is the weight of the product after hydration for 72hrs while Wd is the weight of the dried product.

Results and Discussions:

FTIR Characterization of the Sodium Carboxymethyl Cellulose-Acrylic Acid Ester
From the above FTIR spectra of the original SCMC and SCMC-AA ester it can be observed that in the spectrum of SCMC-AA as compared to the SCMC, the additional absorption bands appear at 1737 cm⁻¹ and1647 cm⁻¹ which can be ascribed to the bonds >C=O and to >C=C< respectively. In addition, there is also a distinct absorption band within 3700-3140cm⁻¹ corresponding to the hydroxyl group, which testifies to the incomplete esterification of SCMC.

XRD Characterization of the Sodium Carboxymethyl Cellulose-Acrylic Acid Ester
From the XRD pattern of SCMC we can observe that there is only one peak at 19.9° 2θ, while in the XRD pattern of SCMC-AA there are three peaks at 29.45°, 13° and 19.75° 2θ respectively.

Swelling behavior of the esterified product
The swelling studies indicate pH dependent swelling of the esterified product. The degree of swelling increases as the pH is increased.
from 1.4 to 7.4 but further increase in pH to 9.4 decreases the swelling. But even at pH 9.4 the
% swelling is 117 which is quite high compared to that of 43 and 62 at pH 1.4 and 5.4. Since this
polymer swells at high pH and collapses at low pH values, a triggered drug delivery can be
developed upon increase in the pH of the environment. This polymer can be used in oral
delivery, in which the polymer will retard drug release at low pH values in the stomach while
releasing the same at high pH values in the small intestine. Hence this polymer can be used
for the delivery of drugs like aspirin, indomethacin, diclofenac etc in the intestine.

Conclusion

The studies performed confirmed that the esterification of SCMC with ACl resulting in
formation of a new derivative of SCMC. Since the degree of swelling of the esterified product
changes as the pH is varied over a wide range it can be used as a pH responsive polymer for
various biomedical applications. By this method we can incorporate double bonds in cellulosic
structures which can help us to photopolymerize the cellulose for various biomedical application.
Studies on drug release characteristics, cytocompatibility and biodegradability of the
polymer are in progress.

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