SOURCE: Materials and Manufacturing Process, 25: 1477–1481 (2010)

Synthesis of novel hydroxypropyl methyl cellulose acrylate- A novel super-disintegrating agent for pharmaceutical applications

S. Roy[1], K. Pal[2*], G. Thakur[3], and B. Prabhakar[1]

[1] School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai-400056, India

[2] Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela-769008, Orissa, India.

[3] School of Medical Science & Technology, Indian Institute of Technology- Kharagpur, Kharagpur-721302, India.

*** Author for Correspondence:** email: pal.kunal@yahoo.com; phone: +91-661-2462289.

Abstract:

The current study deals with the synthesis of novel hydroxypropyl methyl cellulose acrylate (HPMCAA) by the process of esterification of hydroxypropyl methyl cellulose and acryloyl chloride. The polymers were characterized by FTIR spectrophotometry, DSC, XRD and haemocompatibility studies. The microstructures of the HPMC and HPMCAA powders were studied under a scanning electron microscope. The powders were used as an excipient for the preparation of lactose tablets and their composition was varied from 2% to 8 % (w/w) of the total tablet weight. Disintegration studies for the tablets were carried out. The results indicated formation of a new product, HPMCAA, having properties different from HPMC. HPMCAA was found to be haemocompatible in nature. Disintegration tests indicated that HPMCAA could be tried as a super-disintegrating agent.

Keywords: Hyxypropyl methyl cellulose, Hyxypropyl methyl cellulose acrylate, esterification, disintegrating agent.

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Introduction:

Dissolution is a process by which a solid enters into solution. The dissolution of a bioactive agent incorporated within a tablet may take place by a number of steps. Some amount of the bioactive agent may directly go into the solution without any disintegration of the tablet. But most of the dissolution occurs after the tablet has disintegrated into granules. Occasionally, the granules may further break down so as to form fine particles of the bioactive agents before the same goes into the solution. Substances which have the ability to promote disintegration of tablets into granules are known as disintegrant. If the disintegrant is effective at very low levels (2 to 4 %), then the disintegrant may be regarded as super-disintegrant [1]. The majority of the marketed oral tablets and capsules are designed to disintegrate rapidly. Even though the current trend in the delivery systems focuses on devising controlled delivery vehicles, the development of rapidly disintegrating tablets and capsules have also found importance in the pharmaceutical industry. Various methodologies have been employed to improve the disintegration rate. The methodologies include the use of fast dissolving channeling agents (e.g. sodium chloride) which gives rise to capillary action, gas-releasing agents (e.g. calcium carbonate) and swelling materials (e.g. starch derivatives) [2-6]. Different cellulose derivatives (e.g. croscarmelose, cellulose, carboxymethyl cellulose, alginic acid, β-cyclodextrin and guar gum) have been used as disintegrating agents. The mechanism of imparting disintegration of the tablets by the cellulose derivative has been attributed to the increased rate of wetting [7-9].

Hydroxypropyl methylcellulose (HPMC) is a water soluble polymer and is available as a fibrous or granular free-flowing powder having white to slightly off-white color. It has been used, since long, in various pharmaceutical formulations due to its enteric nature (i.e. polymer retains their integrity at lower pH in the stomach and release the bioactive agent at upper intestine where the pH is on the higher side), matrix binding property, viscosity building agent, gelling agent and film forming agent [10-11]. For the formulation of tablets, HPMC has been used as a binder during the preparation of the granules at concentrations of 2-6 % whereas it has been used to device extended release formulation at concentrations of 15-35%. Though low-substituted hydroxypropyl methylcellulose (LS-HPMC) have been reported to be used in promoting disintegration of tablets when used in conjunction with microcrystalline cellulose Bi *et al.* (1996) [5], no HPMC-based products have not been used alone as a disintegrating agent. The authors reported that when the ratio of the microcrystalline cellulose and LS-HPMC was in the range of 8:2 to 9:1, the disintegration efficiency of the mixture was high. The 9:1 composition was considered to be optimum for fast tablet disintegration [5, 12-13].

In the current study, attempts were made to chemically modify the HPMC by the process of esterification with the acryloyl chloride (ACl). Further attempts were made to characterize the same to study the suitability of the polymer to be used in various pharmaceutical formulations.

Experimental:

Materials

HPMC (low viscous grade) and methyl ethyl ketone (MEK) was obtained from Loba Chemie Pvt. Ltd., Mumbai, India. ACl was procured from Merck Limited, Worli, Mumbai, India and was kept in a moisture-free environment. HPMC was dried at a

temperature of 100 ^{o}C under vacuum before carrying out the reaction. Double distilled water was used throughout the study.

Preparation of Hydroxypropyl Methyl Cellulose Acrylate

HPMCAA was developed by the esterification of HPMC and ACl. The esterified product was prepared by dissolving 2.7 g of HPMC in 100 ml of water with constant stirring so as to avoid lump formation. 30 ml of MEK was added to the aqueous solution of HPMC (Solution-A) and was kept in an ice-bath with constant stirring so as to maintain a temperature of 0-5 ^{o}C. 0.5 ml of ACl was mixed with 30 ml of MEK (Solution-B). Solution-B was added drop wise to the solution-A, kept on stirring in an ice-bath and was stirred for 3 h. The mixture was subsequently transferred to a petri-dish and was kept at 45 ^{0}C temperature for 48 hrs, which resulted in the formation of a film of HPMCAA. The film, so obtained, was repeatedly washed with rectified spirit to wash off the unwanted free acrylic acid, if any. The product was dried at room temperature under vacuum and was subsequently used for further studies.

Characterizations

HPMC was subjected to Fourier Transform Infra-red spectroscopy in the range of 4000-400 cm^{-1} as KBr pellets whereas the developed films were subjected to attenuated total reflectance (ATR) spectroscopy in the range of 4000- 400 cm^{-1}. FTIR spectrophotometer (MAGNA 550, Nicolet Instruments Corporation, USA) was used for the study.

Differential Scanning Calorimeter (Diamond TG/DTA, Perkin Elmer, USA) was used for studying the thermal behavior of the HPMC and the developed film. The temperature and energy scales were calibrated as per the standard protocols supplied by the manufacturer. The melting studies were performed in the temperature range of 0–300°C at the heating rate of 10°C/min in N_2 atmosphere.

HPMC and the esterified product were subjected to X-ray diffraction (XRD-PW 1700, Philips, USA) using CuKα radiation generated at 40KV and 40 mA; the range of diffraction angle 2θ was 10.00-60.00^{o}.

The haemocompatibility test of HPMC and HPMCAA were done as per the reported literatures with necessary modifications [14-16]. This test aims at determining the % haemolysis of the RBCs in the presence of the samples. The % haemolysis may be mathematically defined as:

$$\%\ Haemolysis = \frac{A_{Test} - A_{Negative}}{A_{Positive} - A_{Negative}}\ x\,100 \qquad (1)$$

where, A_{test} *→Absorbance for test samples;* $A_{negative}$ *→ Absorbance for negative control;* $A_{positive}$ *→ Absorbance for positive control*

In short, 5 ml of citrated blood was collected from a pathological laboratory and was subsequently diluted to 20 ml with normal saline. For the preparation of the positive control, 0.5 ml of the diluted blood was transferred to a 15 ml falcon tube with the subsequent addition of the 0.5 ml of 0.01N hydrochloric acid. Thereafter, the volume was made up to 10 ml with normal saline. Hydrochloric acid is a corrosive liquid and leads to the disruption of RBC membrane thereby causing haemolysis. The negative control was prepared in the similar manner where the hydrochloric acid was replaced with normal

saline. For test samples, solutions (10 %, 20 %, 40 % and 80%) of the HPMCAA were prepared in normal saline. 0.5 ml of the solution was diluted to 1 ml with normal saline, which was further diluted to 10 ml with normal saline. The samples (positive control, negative control and test samples), so obtained, were incubated at 37 ^{o}C for 1 hr and were subsequently centrifuged at 3000 rpm for 10 min. The supernatant was analyzed spectrophotometrically at 545 nm. % haemolysis was calculated as per eq. 1. If the % haemolysis ≤5%, the test material is considered as highly hemocompatible, if the % haemolysis in the range of 5-10%, the test material is considered as hemocompatible and if the % haemolysis is ≥20%, the test material is considered as non-hemocompatible.

SEM Analysis

For examining the HPMC and HPMCAA under scanning electron microscope (JEOL JSM-6400), the HPMC powder and the HPMCAA dried films were dissolved in 100 ml of water so as to obtain 1% (w/v) solution and subsequently freeze dried to obtain HPMC and HPMCAA powder.

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Tablet preparation and disintegration test

Preparation of tablets

Directly compressible lactose was mixed with HPMCAA or HPMC powder in a plastic container. Magnesium stearate and talc were passed through sieve no. 60 and subsequently blended with the lactose-HPMCAA or lactose-HPMC mixture in the plastic container followed by compression of the blend. Compression was performed on a 12 station Rimek tablet compression machine (M/s Karnawati Engg. Ltd, Ahemadabad, India) using 8-mm punches. The compositions of the tablets are provided in table 1.

Disintegration test

Disintegrating tests were carried out in the tablet disintegrating apparatus carrying six acrylate baskets and having stainless steel wire gauge at the bottom. 1 tablet was put into each of the baskets. The baskets were allowed to move up and down, at a frequency of 30 ± 1 cycles per minute and through a distance of 5.5 ± 0.2 cm, inside a 1 L beaker containing 900 ml of water. Temperature of the water was maintained by thermostat to 37 ± 2°C. Time required for the complete disintegration of the tablets were noted down measured with the help of a digital stop-watch.

Results and Discussions:

FTIR Characterization

The FTIR spectra of HPMC and the HPMCAA (esterifed product of the HPMC and ACl) are shown in Fig. 2. The spectra of HPMC showed a broad peak in the range of 3050-3200 cm^{-1}indicating the presence of hydroxyl group in the HPMC. The peaks at 1100 cm^{-1} and 1150 cm^{-1} indicated the presence of secondary alcoholic groups. The peak at 3000 cm^{-1} indicated C-H stretching due to the presence of alkane. The peaks at around 980 cm^{-1} indicated the stretching of the C-O-C linkage. With the exception of the presence of the additional peaks at 3150 cm^{-1} and 1680 cm^{-1}, the spectra of HPMCAA similar to the spectra of HPMC. The peak at 3150 cm^{-1} indicated the presence of intermolecular hydrogen bonding amongst the polymeric chains, which might result in the increase in the crystalline nature of HPMCAA whereas the peak at 1690 cm^{-1} indicated the incorporation of ester linkage in the HPMC structure, thereby confirming the esterification reaction.

Thermal characterization

The thermal properties of HPMC and HPMCAA were investigated by DSC technique so as to study the change in the glass-transition (Tg) of the HPMC when compared with HPMCAA, the esterified product (figure 2). Tg may be correlated with the segmental motion of the polymeric chains as a function of temperature [17]. The Tg of the HPMC was found to be at 52 ^{o}C while the Tg of the HPMCAA was found to be at 61 ^{o}C. The increase in the Tg of the HPMC upon esterification may be attributed to the increase in the intermolecular hydrogen bonding, which may be attributed to the incorporation of an ester linkage. The increase in the inter-molecular hydrogen bonding in the HPMCAA was also evident from the FTIR spectra of the HPMCAA.

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XRD Characterization

The XRD profile of HPMC and HPMCAA are shown in figure 3. The XRD profile of HPMC showed two broad peaks at 10^o and 20^o 2θ while the XRD profile of HPMCAA showed to sharp peaks at 7.5^o and 20^o 2 θ in addition to a broad peak at 13^o 2 θ. The change in the XRD profile of HPMC from that of the XRD profile of HPMCAA indicated the formation of a new product whose crystal structure is totally different from that of the parent material. The area under the XRD peak is directly proportional to the % crystallinity of the material. The ratio of A_{HPMCAA} (area under the peak of HPMCAA): A_{HPMC} (area under the peak of HPMC) was determined by the paper weight method. In this method, the weight of the paper under the XRD peaks were determined separately for HPMCAA and HPMC with the subsequent determination of A_{HPMCAA}:A_{HPMC}. The ratio of the A_{HPMCAA}: A_{HPMC} was found to be 1.98 indicating 200 % (approx.) increase in the crystallinity of the HPMC when the same is esterified with ACl. This can be attributed to the increase in inter-molecular hydrogen bonding and the results may be supported by the results obtained from the FTIR and DSC studies.

Haemocompatibility test:

The 10 %, 20 % and 40 % solutions of the HPMCAA were found to be highly haemocompatible whereas the 80 % was found to be haemocompatible (Table 2). It is evident from the results that as the concentration of the HPMCAA was increased in the solution, there was a corresponding increase in the % haemolysis. But the results were well within the haemocompatible range and could be tried as an excipient in the pharmaceutical formulations.

SEM analysis:

Figure 4 shows the scanning electron micrograph of HPMC and HPMCAA powders. The micrograph of HPMC powder showed that though the powder particles were irregular in shape and size, most of the particles may be regarded as cylindrical having a diameter of 30 μm (approx.). The HPMCAA powder particles were found to be irregular in shape and size with no features matching with the HPMC powder particles. This indicates that there has been a complete change in morphology of the HPMC powder particles due to the formation of a new product (HPMCAA).

Tablet disintegration test:

The tablets containing HPMCAA disintegrated within 3 to 5 min whereas those containing HPMC disintegrated after 50 to 60 min indicating the probable use of the HPMCAA as a super-disintegrant. The super-disintegrant property of the HPMCAA may be attributed to the quick dissolution of the HPMCAA in water (Solubility test of HPMCAA showed that the product was freely soluble in water). This may be attributed to the rapid disruption of the intermolecular and intramolecular hydrogen bonding amongst HPMCAA molecules thereby resulting in the rapid swelling and dissolution of the HPMCAA molecules [18]. Depending upon the chemistry of the cellulose derivatives, the swelling property of a cellulosic structure plays an important role in the dissolution of the cellulose derivative [19]. The phenomena of rapid swelling and dissolution of HPMCAA results in the quick formation of porous channels within the

tablet matrix. This results in the easy diffusion of the water into the core of the tablet, which in turn helps in easy wetting and rapid disintegration of the prepared tablets.

Conclusion

The studies performed confirmed that the esterification of HPMC with ACl resulted in the formation of a new derivative, HPMCAA, and was found to be biocompatible. HPMCAA showed promising results to be used as a super-disintegrant.

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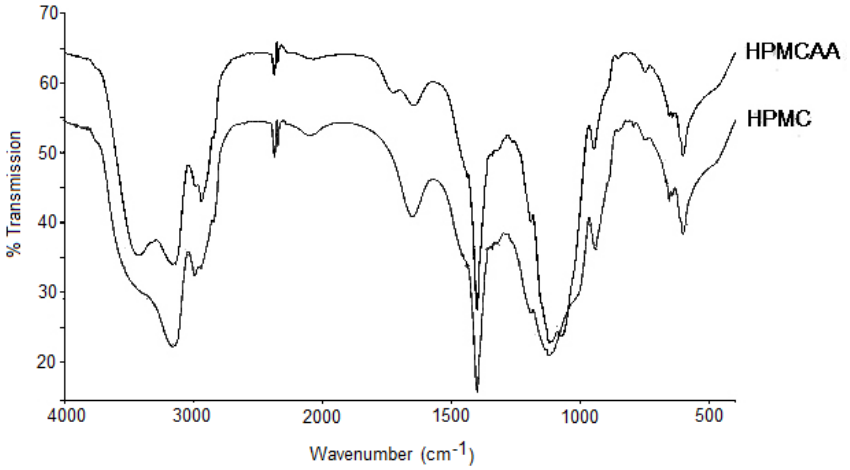

Figure 1. FTIR spectra of HPMC and HPMCAA

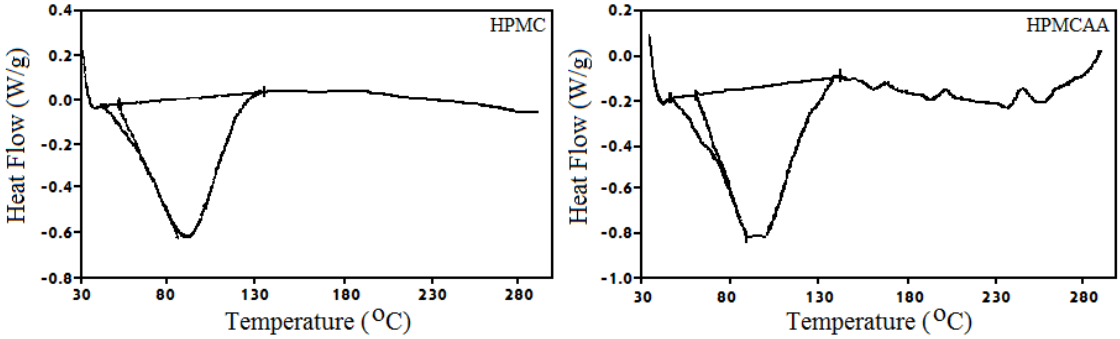

Figure 2. DSC thermogram of HPMC and HPMCAA

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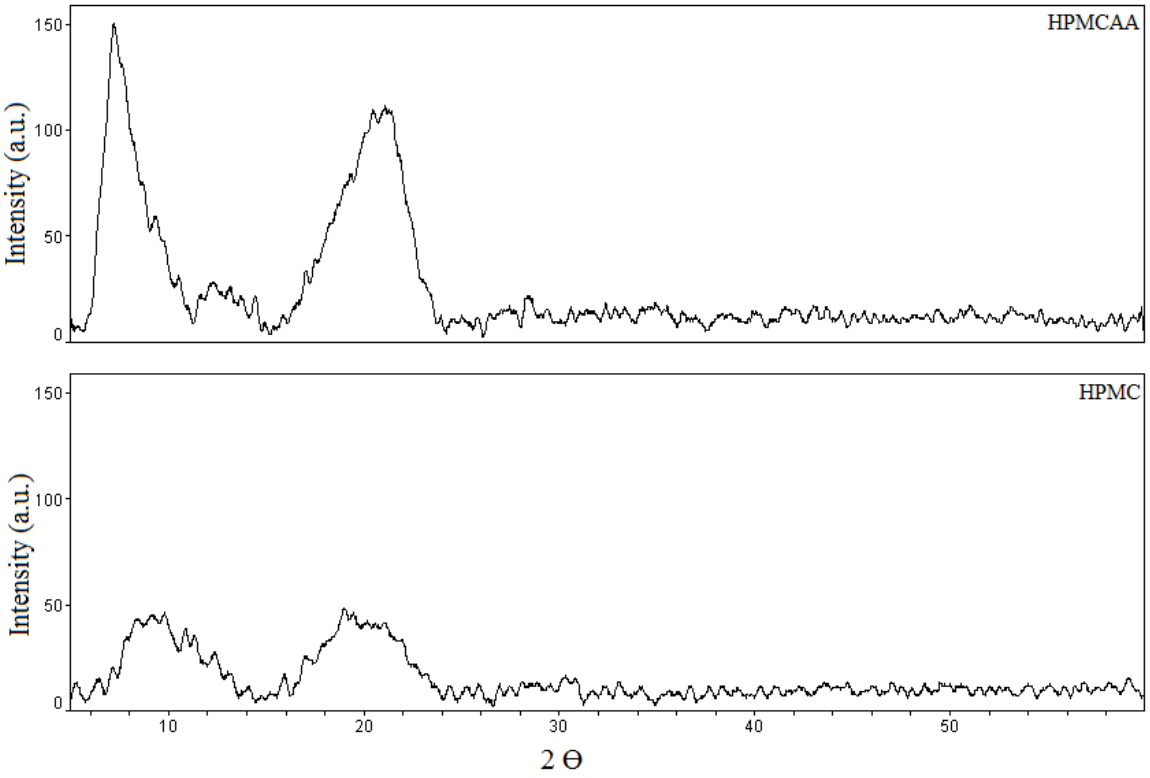
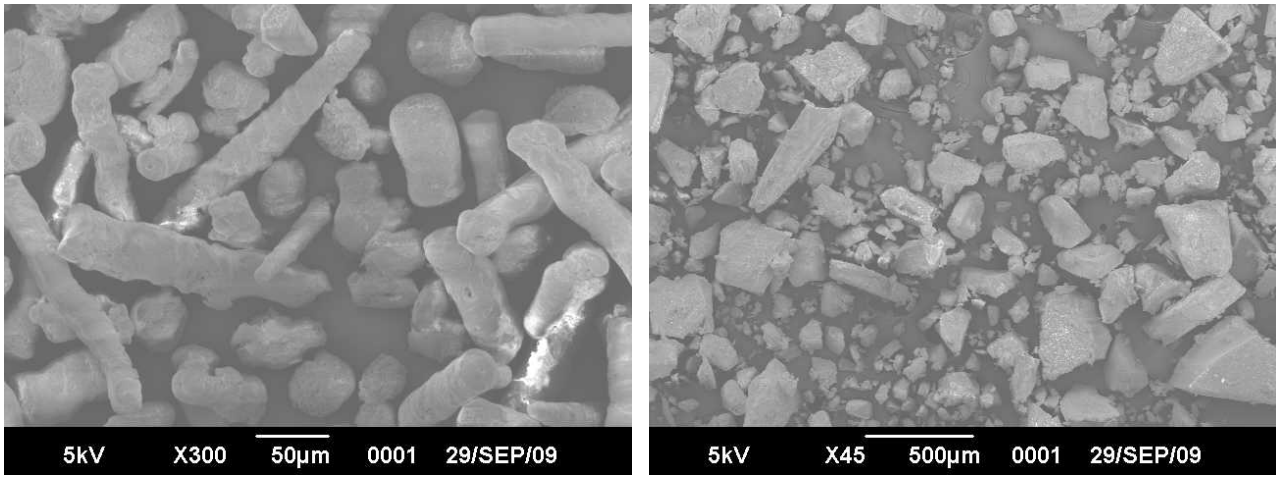


Figure 3. XRD profile of HPMC and HPMCAA



(a) (b)

Figure 4. Scanning electron micrographs of (a) HPMC and (b) HPMCAA

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Table 1: Compositions of the Tablets Formulated

Code	F1	F2	F3	F4	F5	F6
HPMC (%)	0	0	0	2	5	8
HPMCAA (%)	2	5	8	0	0	0
Mg str (%)	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1
Direct compressible Lactose (%)	96	93	90	96	93	90
Total(%)	100	100	100	100	100	100

Table 2: Haemocompatibility

Samples	Absorbance	Haemolysis	Remarks
Control (+)	0.427	-	-
Control (-)	0.073	-	-
10%	0.079	1.69	Highly haemocompatible
20%	0.084	3.10	Highly haemocompatible
40%	0.090	4.80	Highly haemocompatible
80%	0.097	6.78	Haemocompatible