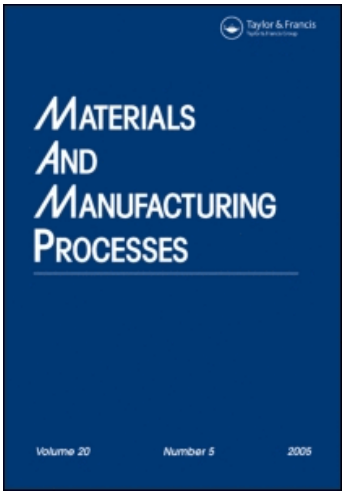

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Synthesis of Novel Hydroxypropyl Methyl Cellulose Acrylate— A Novel Superdisintegrating Agent for Pharmaceutical Applications

S. Roy[a]; K. Pal[b]; G. Thakur[c]; B. Prabhakar[a]
[a] School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai, India [b] Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela, Orissa, India [c] School of Medical Science & Technology, Indian Institute of Technology, Kharagpur, Kharagpur, India

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Synthesis of Novel Hydroxypropyl Methyl Cellulose Acrylate—A Novel Superdisintegrating 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, India*
[2]*Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela, Orissa, India*
[3]*School of Medical Science & Technology, Indian Institute of Technology, Kharagpur, Kharagpur, India*

The current study deals with the synthesis of novel hydroxypropyl methyl cellulose acrylate (HPMCAA) by the process of esterification of hydroxypropyl methyl cellulose (HPMC) and acryloyl chloride. The polymers were characterized by Fourier transform infrared (FTIR) spectrophotometry, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and hemocompatibility 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 hemocompatible in nature. Disintegration tests indicated that HPMCAA could be tried as a superdisintegrating agent.

Keywords Disintegrating agent; Esterification; Hydroxypropyl methyl cellulose; Hydroxypropyl methyl cellulose acrylate.

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 to form fine particles of the bioactive agents before the same goes into the solution. Substances that have the ability to promote disintegration of tablets into granules are known as *disintegrants*. If the disintegrant is effective at very low levels (2–4%), then the disintegrant may be regarded as a *superdisintegrant* [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 has 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 give 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., croscarmellose, 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 in various pharmaceutical formulations due to its enteric nature (i.e., polymer retains its integrity at lower pH in the stomach and releases the bioactive agent in the 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 devise extended-release formulations at concentrations of 15–35%. Though low-substituted hydroxypropyl methylcellulose (LS-HPMC) has been reported to be used in promoting disintegration of tablets when used in conjunction with microcrystalline cellulose [5], no HPMC-based products have been used alone as a disintegrating agent. Bi et al. [5] 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 optimal for fast tablet disintegration [5, 12, 13].

In the current study, attempts were made to chemically modify HPMC by the process of esterification with 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) were obtained from Loba Chemie Pvt. Ltd.,

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Address correspondence to K. Pal, Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela 769008, Orissa, India; E-mail: pal.kunal@yahoo.com

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°C under vacuum before carrying out the reaction. Double-distilled water was used throughout the study.

Preparation of Hydroxypropyl Methyl Cellulose Acrylate

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 to avoid lump formation. Thirty milliliters of MEK was added to the aqueous solution of HPMC (Solution A) and kept in an ice bath with constant stirring to maintain a temperature of 0–5°C. Then 0.5 mL of ACl was mixed with 30 mL of MEK (Solution B). Solution B was added drop-wise to solution A with 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°C for 48 h, 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 infrared spectroscopy (FTIR) in the range of 4,000–400 cm^{-1} as KBr pellets, whereas the developed films were subjected to attenuated total reflectance (ATR) spectroscopy in the range of 4,000–400 cm^{-1}. An FTIR spectrophotometer (MAGNA 550, Nicolet Instruments Corporation) was used for the study.

A differential scanning calorimeter (Diamond TG/DTA, Perkin Elmer) 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 a 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) using CuKα radiation generated at 40 KV and 40 mA; the range of diffraction angle 2θ was 10.00–60.00°.

The hemocompatibility test of HPMC and HPMCAA was done as per the reported literature with necessary modifications [14–16]. This test aims at determining the percentage hemolysis of the RBCs in the presence of the samples. The percentage hemolysis may be mathematically defined as:

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

where A_{Test} is absorbance for test samples; A_{Negative} is absorbance for negative control; and A_{Positive} is 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 0.5 mL of 0.01 N 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 the red blood count (RBC) membrane, thereby causing hemolysis. The negative control was prepared in a 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. Then 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°C for 1 h and were subsequently centrifuged at 3,000 rpm for 10 min. The supernatant was analyzed spectrophotometrically at 545 nm. Percentage hemolysis was calculated as per Eq. (1). If the percentage hemolysis $\leq$5%, the test material was considered highly hemocompatible, if the percentage hemolysis was in the range of 5–10%, the test material was considered hemocompatible, and if the percentage hemolysis $\geq$20%, the test material was considered as nonhemocompatible.

SEM ANALYSIS

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

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. One tablet was put into each of the baskets. The baskets were allowed to move up and down, at a frequency of

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

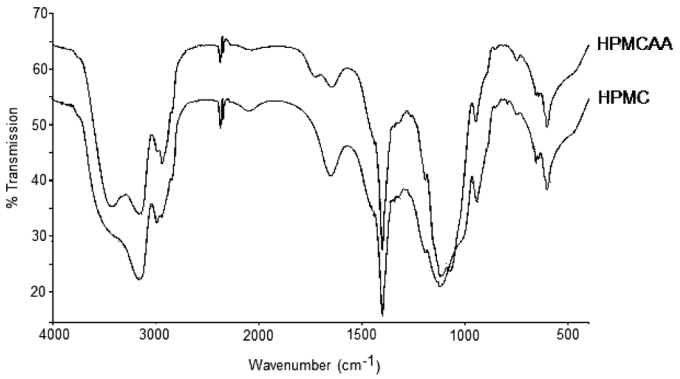


FIGURE 1.—FTIR spectra of HPMC and HPMCAA.

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. The temperature of the water was maintained by thermostat to 37 ± 2°C. Time required for the complete disintegration of the tablets was noted, measured with the help of a digital stopwatch.

RESULTS AND DISCUSSION

FTIR Characterization

The FTIR spectra of HPMC and the HPMCAA (esterifed product of the HPMC and ACl) are shown in Fig. 1. The spectra of HPMC showed a broad peak in the range of 3,050–3200 cm^{-1}, indicating the presence of a hydroxyl group in the HPMC. The peaks at 1,100 and 1,150 cm^{-1} indicated the presence of secondary alcoholic groups. The peak at 3,000 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 3,150 and 1,680 cm^{-1}, the spectra of HPMCAA were similar to the spectra of HPMC. The peak at 3,150 cm^{-1} indicated the presence of intermolecular hydrogen bonding among the polymeric chains, which might result in the increase in the crystalline nature of HPMCAA, whereas the peak at 1,690 cm^{-1} indicated the incorporation of an ester linkage in the HPMC structure, thereby confirming the esterification reaction.

Thermal Characterization

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

XRD Characterization

The XRD profiles of HPMC and HPMCAA are shown in Fig. 3. The XRD profile of HPMC showed two broad peaks at 10° and 20°2θ, whereas the XRD profile of HPMCAA showed to sharp peaks at 7.5° and 20°2θ in addition to a broad peak at 13°2θ. 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 percentage 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 was 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 a 200% (approx.) increase in the crystallinity of the HPMC when the same is esterified with ACl. This can be attributed to the increase in intermolecular hydrogen bonding and the results may be supported by the results obtained from the FTIR and DSC studies.

Hemocompatibility Test

The 10, 20, and 40% solutions of the HPMCAA were found to be highly hemocompatible, whereas the 80% solution was found to be hemocompatible (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 percentage hemolysis.

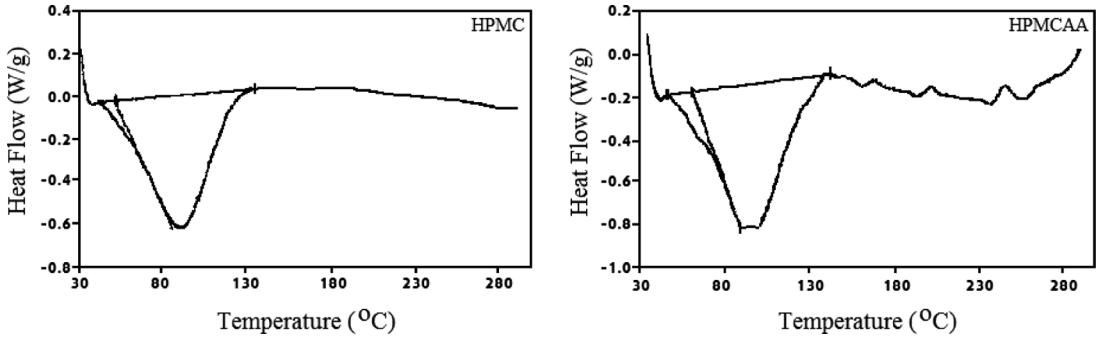


FIGURE 2.—DSC thermogram of HPMC and HPMCAA.

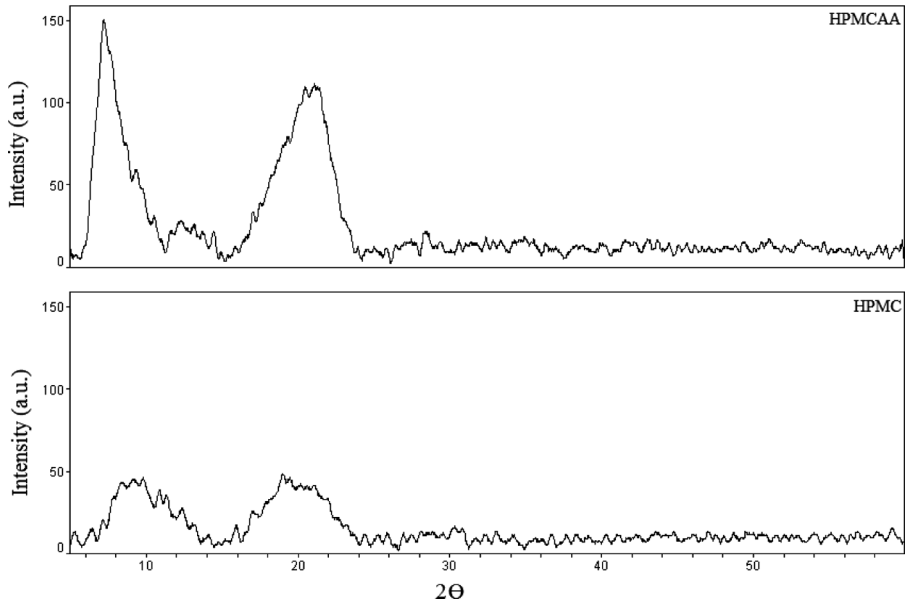


FIGURE 3.—XRD profile of HPMC and HPMCAA.

TABLE 2.—Hemocompatibility.

Samples	Absorbance	Hemolysis	Remarks
Control (+)	0.427	–	–
Control (-)	0.073	–	–
10%	0.079	1.69	Highly hemocompatible
20%	0.084	3.10	Highly hemocompatible
40%	0.090	4.80	Highly hemocompatible
80%	0.097	6.78	Hemocompatible

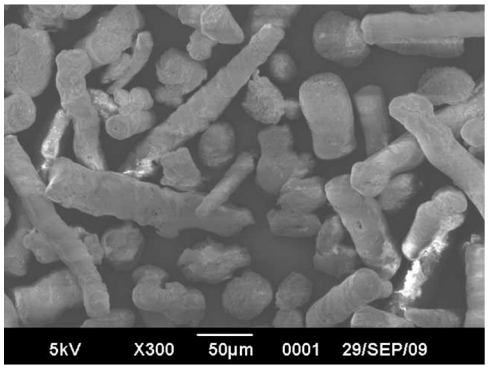
But the results were well within the hemocompatible range and could be tried as an excipient in pharmaceutical formulations.

SEM Analysis

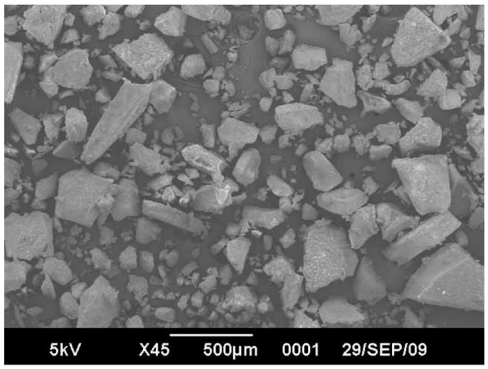
Figure 4 shows the scanning electron micrograph of HPMC and HPMCAA powders. The micrograph of HPMC powder showed that though the powder particles were irregular in shape and size, most of the particles may be regarded as cylindrical, having a diameter of 30 μm (approx.). The HPMCAA powder particles were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



(a)



(b)

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

the intermolecular and intramolecular hydrogen bonding among 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 result in the quick formation of porous channels within the tablet matrix. This results in the easy diffusion of 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 for use as a superdisintegrant.

References

1. Fernandes, N.C.; Jagdale, S.C.; Chabukswar, A.R.; Kuchekar, B.S. Superdisintegrants effect on three model drugs from different BCS classes. Research Journal of Pharmacy and Technology **2009**, *2* (2), 335–337.
2. Zhao, N.; Augsburger, L.L. Functionality comparison of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. Pharmaceutical Development & Technology **2005**, *11* (1), 47–53.
3. Bi, Y.X.; Bi, Y.X.; Sunada, H.; Yonezawa, Y.; Danjo, K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Development and Industrial Pharmacy **1999**, *25* (5), 571–581.
4. Sallam, E.; Ibrahim, H.; Abu-Dahab, R.; Shubair, M.; Khalil, E. Evaluation of fast disintegrants in terfenadine tablets containing a gas-evolving disintegrant. Drug Development and Industrial Pharmacy **1998**, *24* (6), 501–507.
5. Bi, Y.; Sunada, H.; Yonezawa, Y.; Danjo, K.; Otsuka, A.; Iida, K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chemical & Pharmaceutical Bulletin **1996**, *44* (11), 2121–2127.
6. González-Rodríguez, M.L.; Gonzalez-Rodriguez, M.L.; Perez-Martinez, J.I.S.; Fini, A.; Rabasco, A.M. Channeling agent and drug release from a central core matrix tablet. Drug Development and Industrial Pharmacy **2001**, *27* (5), 439–446.
7. Rawas-Qalaji, M.M.; Simons, F.E.R.; Simons, K.J. Fast-disintegrating sublingual tablets: Effect of epinephrine load on tablet characteristics. AAPS PharmSciTech **2006**, *7* (2), E72–E78.
8. Zeitoun, P.; Brisard, P. US Patent: Title: Compressed tablets for disintegration in the colon comprising an active ingredient containing nucleus coated with a first layer containing microcrystalline cellulose which is coated with an enteric organic polymer coating. US4432966 (1984)
9. Rao, V.; Haslam, J.; Stella, V. Controlled and complete release of a model poorly water-soluble drug, prednisolone, from hydroxypropyl methylcellulose matrix tablets using (SBE) 7m-cyclodextrin as a solubilizing agent. Journal of Pharmaceutical Sciences **2001**, *90* (7), 807–816.
10. Jones, D. Pharmaceutical applications of polymers for drug delivery. Smithers Rapra Technology **2004**, *15*, 13–14.
11. Daicel Chemical Industries. Hydroxypropyl methyl cellulose. Available at: http://chemicalland21.com/specialtychem/finechem/HYDROXY%20PROPYL%20METHYL%20CELLULOSE.htm (accessed June 15, 2010).
12. Watanabe, Y.; Koizumi, K.; Zama, Y.; Kiriyama, M.; Matsumoto, Y.; Matsumoto, M. New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biological and Pharmaceutical Bulletin **1995**, *18* (9), 1308.
13. Shiraishi, T.; Matsumoto, N.; Watanabe, Y. Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules by direct compression method. Chemical and Pharmaceutical Bulletin **2001**, *49* (2), 134–139.
14. Pal, K.; Banthia, A.K.; Majumdar, D.K. Biomedical evaluation of the prepared polyvinyl alcohol-gelatin esterified hydrogel. Journal of Materials Science: Materials in Medicine **2007**, *18*, 1889–1894.
15. Mishra, R.K.; Datt, M.; Pal, K.; Banthia, A.K. Preparation and characterization of amidated pectin based hydrogels for drug delivery system. Journal of Materials Science: Materials in Medicine **2008**, *19*, 2275–2280.
16. Pal, K.; Bag, S.; Pal, S. Development of porous ultra high molecular weight polyethylene scaffolds for the fabrication of orbital implant. Journal of Porous Materials **2008**, *15*, 53–59.
17. Swamy, M.; Ramaraj, T.M.; Siddaramaiah, B. Thermal and morphological properties of SA/HPMC blends. Journal of Applied Polymer Science **2009**, *112*, 2235–2240.
18. Pesonen, T.; Paronen, P.; Ketolainen, J. Disintegrant properties of an agglomerated cellulose powder. International Journal of Pharmaceutics **1989**, *57* (2), 139–147.
19. Uhumwangho, M.; Okor, R. Effect of humidity on the disintegrant property of cellulose, Part II: A technical note. AAPS PharmSciTech **2005**, *6* (1), 31–34.