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Research Article

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MORPHOLOGY, *IN VITRO* - DEGRADATION AND DRUG RELEASE PROFILE OF POLY (ETHYLENE-CO-VINYL ACETATE) / MICROCRYSTALLINE CELLULOSE ACETATE

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ABSTRACT
Microcrystalline cellulose acetate (MCC) was incorporated in poly (ethylene-co-vinyl acetate) (EVA) at different loading. The morphology, swelling properties and drug release profile were studied with respect to MCC loading to study its potential application as ocular inserts. The XRD patterns showed a good compatibility between the components. However swelling ratio and *in-vitro* degradation of EVA increase with MCC loading. This has been explained in terms of the hygroscopic nature of cellulose acetate. The study shows that EVA/MCC system can be tuned in terms of important parameters such as swelling behavior, in vitro release and degradation by varying blend composition, thus fulfilling specific biomedical requirements.

KEY WORDS: EVA, Cellulose acetate, Controlled drug delivery, Biopolymers.

INTRODUCTION

Controlled drug delivery occurs when a drug system is designed to release the drug in a predetermined manner. The main purpose of these controlled release systems is to achieve a more effective therapy, i.e., a system with a delivery profile that would yield a high blood level of the drug over a long period of time, avoiding the large fluctuations in drug concentration and to reduce the need of several administrations. Many different kinds of controlled drug delivery systems have been proposed for various routes of administration. They require less frequent drug administration, provide more therapeutic effects and reduce the incidence of side effects.

Controlled drug delivery products, using biocompatible or biodegradable polymers, have received considerable attention in the last few years. Polymer blending constitutes a very useful method for the improvement or modification of the physiochemical properties of polymeric materials. Some of the polymer blends exhibit unusual properties, which are different from the constituent polymers. Among them, the blends between biopolymers and synthetic polymers are of particular significance because they can be used as biomedical and biodegradable materials[1-4].

In the present work, EVA\MCC blends containing high strength network of EVA and a soft segment of cellulose acetate were prepared and release profile of different blend ratios were studied using ciprofloxacin as the model drug. Ethylene vinyl acetate (EVA) is the copolymer of ethylene and vinyl acetate. The property of EVA depends on the ratio of monomers. It has been widely used as a membrane or matrix for transdermal drug delivery systems[5, 6]. Application of EVA in ocular applications at commercial level is well known. Pilocarpine releasing Ocusert (Alza, USA) was introduced in the early 1970s in the Western world. This sophisticated system released the drug for a week at constant rate of 40 mg/hour through ethylene vinyl acetate (EVA) membranes. EVA is used in biomedical engineering applications as a drug delivery device to be used within the body. While EVA is not biodegradable within the body, it is quite inert and causes little or no reaction following implantation.

MCC consists of acetate and celluloses, which are polymers of natural origin. It is a natural plastic, which is manufactured from purified natural cellulose. Natural cellulose of the appropriate properties is derived primarily from two sources, cotton linters and wood pulp. In the manufacturing process of cellulose acetate, natural cellulose is reacted with acetic anhydride to produce cellulose acetate. However it can be processed by normal plastics processing techniques in compounded form. For this, cellulose acetate has to be blended with a suitable combination of plasticizers and additives and melt compounded to get cellulose acetate granules.

Though EVA have huge potential as a drug carrier, very few works exists on its blends as drug carriers. Kalachandra *et al*[7] studied stability and release of antiviral drugs from ethylene vinyl acetate (EVA) copolymer. Three different types of drugs were used and the release profiles were found to be varying with the drug characteristics. Zhou *et al*[8] studied release characteristics of three model drugs from chitosan/cellulose acetate. Model drugs with different hydrophilicity were selected to investigate the delivery system - hydrophilic ranitidine hydrochloride (RT), amphoteric acetaminophen (ACP) and hydrophobic 6-mercaptopurine (6-MP). The loading efficiency of 6-MP was more than 30% whereas that of RT and ACP were only 10%. The release profile became slower with the increasing hydrophobicity of drugs. Park *et al*[9] have reviewed in detail targeted delivery of low molecular drugs using chitosan and its derivatives. The main objective of the review was to provide an insight into various target-specific carriers, based on chitosan and its derivatives, towards low molecular weight drug delivery. The subsequent section of the review considers the recent developments of drug delivery carriers for cancer therapy with special focus on various targeting strategies. Nunthanid *et al*[10] studied the use of spray-dried chitosan acetate and ethyl cellulose as compression coating for colonic drug delivery: Swollen CSA gel dissolved at lower pH and became less soluble at higher pH. The mechanism of swelling was Fickian diffusion fitting well into both Higuchi's and Korsmeyer–Peppas models. The lower dip speed and higher pH medium delayed the drug release, while a super disintegrate in the cores enhanced the drug release and no enzyme effect was observed. Kalachandra *et al*[11] studied controlled drug release for oral condition by a noval device based on ethylene vinyl acetate (EVA). Among all drugs studied, minocycline exhibited the least burst effect suggesting that the drug is more homogeneously distributed in the copolymer. It was suggested by them that the drug

loaded EVA thermoplastic copolymer may provide a favorable therapeutic material for the development of a novel local treatment for oral, mucosal and periodontal infections. The same group carried out the stability of drugs in the EVA system by H NMR and solid state CCP/MAS NMR. Drugs tested include chlorohexidine diacetate (CDA), doxycycline hydrochloride (DOH), tetracycline hydrochloride (TTH) and nystatin (NST). For CDA and NST, the chemical and physical structures of the drugs remained unaffected during the film casting process. David Barrow *et al*[12] studied the in vitro drug release of methacrylate polymer blend system: effect of polymer blend composition, drug loading and solubilizing surfactants on drug release. The drug release rates were observed to increase with the addition of surfactants. Yusuf Ali and Kari Lehmussaar [13] reviewed industrial perspective in ocular drug delivery. A review on new techniques for drug delivery to the posterior eye segment was done by Binstock *et al*[14]. Ocular drug delivery has become an increasingly important field of research especially when treating posterior segment diseases of the eye, such as age-related macular degeneration, diabetic retinopathy, posterior uveitis and retinitis. Advances in ocular drug delivery system research are expected to provide new tools for the treatment of the posterior segment diseases, providing improved drug penetration, prolonged action, higher efficacy, improved safety and less invasive administration, resulting in higher patient compliance.

The main objective of the work was to study the effect of incorporation of MCC in EVA on its morphology and drug release profile. EVA\MCC blends were synthesized using various ratios of EVA\CA mixtures. Ciprofloxacin was used as the drug. The XRD analysis of samples was carried out to know the nature of blending and dispersion of drug in the cellulose acetate and EVA blend.

MATERIALS AND METHODS

EVA with 18% Ethylene acetate was obtained from polyolefin. MCC is from SD Fine Chemical Limited. All other chemicals like dichloromethane, etc, were of reagent grade.

Preparation of samples

EVA was dissolved in dichloromethane. To the solution the requisite amount of cellulose acetate was added and stirred. Then it is allowed to evaporate to get the dry samples. A different formulation of EVA and MCC has been given in Table 1.

Characterization

The swelling behaviors of the samples were monitored as a function of composition and were determined by immersing the completely dried samples in double distilled water at 37°C. Swollen samples were weighed by an electronic balance at predetermined time points after wiping a surface liquid using a tissue paper. The swelling ratio (SR) was calculated from the following equation

$$SR=\frac{Mt-M0}{M0}$$

Where M_t is the mass of the swollen sample at time's' and M_o is the mass of dry sample at time '0.

Equilibrium water content (EWC) of the samples was determined in PBS of pH 4 at 37 °C. Samples were allowed to swell and equilibrate for 48 hours. Excess surface liquid was wiped and swollen samples were weighed. EWC was determined by using equation.

$$EWC = \frac{Me-Mo}{Me}\times 100$$

where M_e is the weight of the sample after attainment of equilibrium at time't'

The releases of drug from the blends were studies at a pH as 4 at room temperature for 24 hours. The release rates were studied using UV-Visible spectrophotometer at 278 nm.

XRD patterns were measured using BRUKER (Germany D8 Advance) X- ray diffractometer. The target was Ni filter with Iynx Eye detector (silicon strip detector technology).

RESULTS AND DISCUSSION

The swelling ratios of different formulations are shown in Table 2. The incorporation of MCC was found to increase the water imbibing. EVA being hydrophobic in nature generally swells very less or shows negligible swelling in water. On incorporation of MCC, which is hygroscopic in nature, the swelling properties of EVA increases. The incorporation of the drug was observed to have not much effect on the polymer system with respect to its swelling. The swelling ratios of the polymers with and without drug were found to be almost similar. Generally the presence of water soluble drugs should increase the swelling ratio of the polymer. The water soluble drugs gets dissolved in water and allows more free passage of the solvent molecules in the polymer network thereby increasing the swelling ratio. However in the present case, the drug might have leached out from polymer matrix almost compensating the increased weight due to swelling.

The *in-vitro* degradation of the blend systems are given in Table 3. *In vitro* degradation increased with increase of MCC content in EVA. As the degradation studies were conducted in a media with water as a major constituent, the degradation behavior also shows the same trend as that of swelling ratio. The degradation mostly happens due to the hydrolysis of the polymers. The results obtained can be explained in terms of constituent polymers. EVA being hydrophobic in nature with highly dense crosslinking and semi-crystalline nature shows good resistance against hydrolysis and degradation. MCC being more prone to hydrolysis gets degraded faster and much more than EVA. Consequently it becomes easier for the solvents to enter the polymer network and hence the degradation process gets accelerated. However there is not much difference between the samples loaded with drug and without drug.

In-vitro releases of the blend systems are given in Figure 1. The blends displayed different release profiles depending on their composition. The blend having more amount of MCC showed maximum release when compared to other blends. From this we understood that the release rate can be regulated by controlling the amount of MCC. Release of drug from blend is governed by several factors such as nature and molecular weight of the drug, degree of cross linking density, pore size of the matrix, solvent type, etc. The release of the drug molecules into the solution may be occurring in two ways – the polymer networks get loosened on exposure to the solution and the drug molecules gets larger path way to move and come out of the polymer system and enter the solution. Secondly the solution molecules diffusing through the polymer networks reaches the drug molecules and dissolve the drug and makes the release faster. In either of the case – diffusion of the solution molecules into the polymer matrix or the drug molecules diffusing in to the solution through the polymer networks- the rate depends totally on how the polymer interacts with the solution. Since the solution used here is made up of water, the hydrophobic and semi crystalline EVA having a highly cross linked structure shows very less loosening of the net work. This results in lowering of the molecules through the polymer network. This factor is also supported by the above observations in the case of swelling properties and *in vitro* degradation. This indicates that the release profile of EVA/MCC can be tuned to requirement by varying the MCC composition.

Figure 2, 3 and 4 represents the XRD pattern of ciprofloxacin, pure EVA and MCC. Pure MCC and ciprofloxacin shows peaks indicating highly crystalline nature of these materials. Figure 5 represents the XRD pattern of EVA/MCC system which shows a

good compatibility between the components. Figure 6 represents the XRD pattern of EVA/MCC system with drug. Figure 5 does not show any crystalline peak of ciprofloxacin. Therefore it is presumed that the drug molecule was dispersed at molecular level and crystallinity of drug was not shown by X-ray diffraction studies. This result implies that ciprofloxacin is present as an amorphous form in the EVA/MCC blend which leads to increased drug release.

CONCLUSION

MCC was incorporated into EVA at different loading to study the drug release profile and morphology. The drug release was found to increase with MCC percentage in the blend. Swelling behavior and in-vitro degradation were found to be increased with decrease in EVA percentage. The drug incorporation has been observed to have no effect on these properties.

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Table 1: Formulation of the blends

Sample Code	Sample ratio
A	Pure EVA
B	EVA(1g)/CA(0.07g)
C	EVA(1g)/CA(0.135g)
D	EVA(1g)/CA(O.07g)/ ciproflaxcin (0.007g)
E	EVA(1g)/CA(0.14g)/ciproflaxcin(0.007g)

Table 2: Swelling ratio of EVA/CA System

Blend ratio	Swelling ratio at one hour
A	1.04
B	1.12
C	1.25
D	1.10
E	1.20

Table 3: Degradation of EVA/CA System

Blend ratio	%mass remaining
A	0.0150
B	0.0138
C	0.0106
D	0.0130
E	0.0110

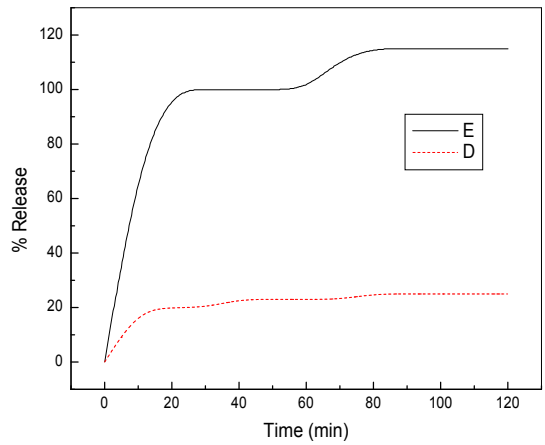

Figure 1: Drug release profile of D and E

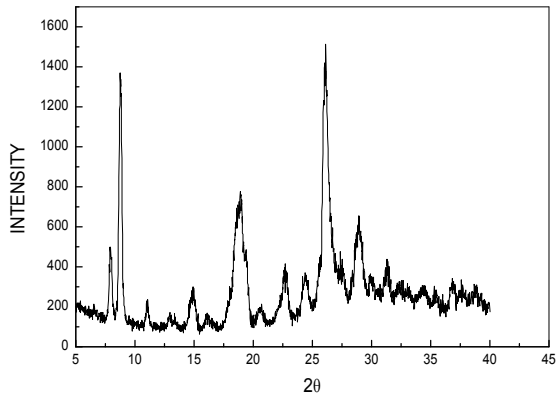

Figure 2: XRD pattern of ciprofloxin

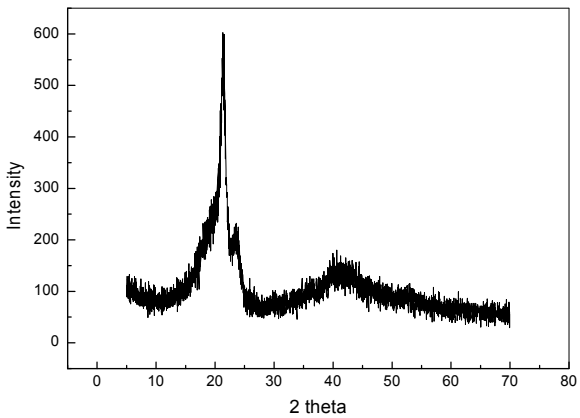

Figure 3: XRD pattern of pure EVA

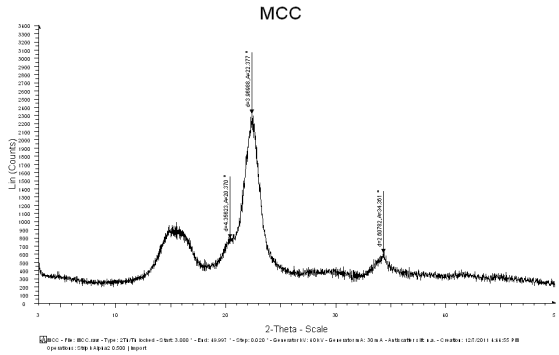

Figure 4: XRD pattern of MCC

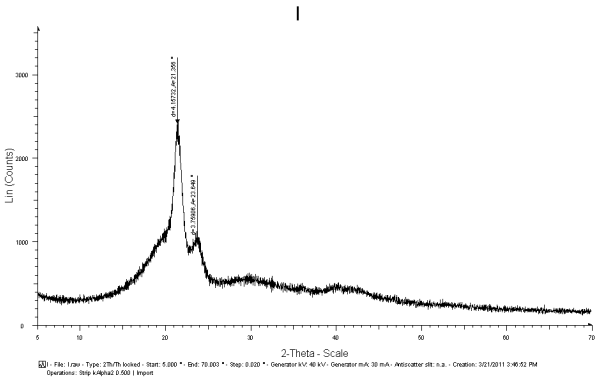

Figure 5: XRD pattern of EVA/MCC

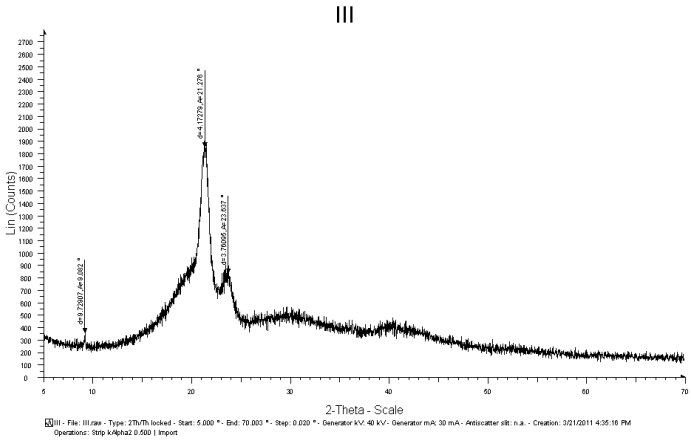

Figure 6: XRD pattern of EVA/MCC/ciprofloxacin