Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Ramaiah, Sidda , Kumar, T. M. Pramod and Ravi, Valluru(2007) 'Studies on Biopolymers for Ophthalmic Drug Delivery', Journal of Macromolecular Science, Part A, 44: 2, 229 — 234
To link to this Article: DOI: 10.1080/10601320601031416
URL: http://dx.doi.org/10.1080/10601320601031416

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2007) **44**, 229–234

ISSN: 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320601031416

Studies on Biopolymers for Ophthalmic Drug Delivery

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Received May, 2006, Accepted August, 2006

A series of polyvinyl alcohol (PVA)-hydroxy propyl methyl cellulose (HPMC) based films and gelrite (gellan gum) based *in situ* gels were formulated with ciprofloxacin hydrochloride as the drug. Drug diffusion studies were carried out for both the film and *in situ* gel formulations. The prepared PVA/HPMC blends have been characterized for tensile strength behavior and percent elongation at break. Fourier transfer infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) studies were carried out to study the compatibility of the drug and polymers used. Drug diffusion results indicate that the film and gel formulations containing ciprofloxacin were compatible and showed a prolonged drug release pattern. The gelrite formulation was non-irritant and had a good gelling property compared to PVA/HPMC blends.

Keywords: Ophthalmic delivery; ciprofloxacin; polyvinyl alcohol; hydroxy propyl methyl cellulose; gellan gum; gelrite

1 Introduction

The ophthalmic drug delivery system can be defined as drug delivery to the eyes in the form of solution, suspension, gel, film etc. The field of ocular delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. As an isolated organ, the eye is very difficult organ to study in terms of the administration of drugs (1).

Improvements have been made with the objective of maintaining the drug in the biophase for an extended period. It is a challenge to the formulator to circumvent the protective barriers of the eyes so that the drug reaches the biophase in sufficient concentration. Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints responsible for the poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption. Drug solution drain away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently, ocular bioavailability of topical dosage of drainage, especially takes 5 to 10 min. Topical application of ophthalmic drugs is further made insufficient by tear turnover, which is about 1.6% in humans (2).

A considerable amount of effort has been made in ophthalmic drug delivery since 1970's. The two main approaches attempted are improvement in bioavailability and controlled release drug delivery. Topical bioavailability can be improved by use of viscosity modifiers (3), gel formers (4), penetration enhancers (5), prodrugs (6), cyclodextrins as carriers (7) and the use of bioadhesive polymers (8). Improvement in controlled drug delivery is made by *in situ* forming gels (9). Here gelling can be triggered by pH of the solution, temperature and ionic strength. Some new ophthalmic delivery systems are; liposomes (10–11), nanoparticles (12), microparticulates (13), inserts/ocuserts (14), minidisk (15), implants (16), soft contact lenses (17), niosomes (18) etc.

Ophthalmic inserts/ocuserts/films are polymeric systems in which the drug is incorporated as a solution or dispersion. Ophthalmic inserts have been achieved by using polymers such as alginate salts, poly vinyl pyrrolidone (PVP), collagen, hydroxy propyl cellulose (HPC) etc (1). Due to difficulty with self insertion and foreign body sensation, only few insert products are developed for commercialization. Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers, so the dosing frequency can be decreased to once in a day (4). The progress has been made in gel technology in the development of droppable gel. They are liquids upon installation and undergo phase transition in the ocular cul-de-sac to form

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viscoelastic gel and this provides a response to environmental changes (19). Three methods viz., change in pH, change in temperature and ionic activation have been developed for effective cause phase transition in the eye surface (20).

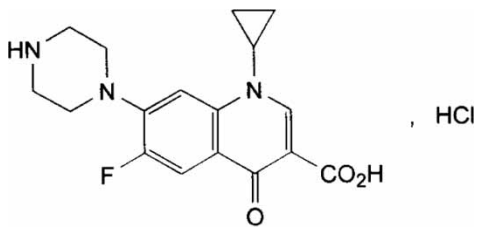
The medications usually given for ocular delivery are in the form of eye drops, ointments, etc. All these forms of conventional drug delivery systems when instilled into the cul-de-sac rapidly drain away from the ocular cavity due to tear flow and lacrimal nasal drainage (21). Only a small amount of drug will be available for its therapeutic effect resulting in frequent dosing. They also cause other problems such as irritation of the eye, blurring of the vision etc.

Ciprofloxacin is an efficient antibiotic usually given for prevention of infection after cataract surgery. In the present study, the effect of polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose (HPMC) blend films (inserts/ocuserts) on drug delivery to the eye has been studied. A known amount of drug, ciprofloxacin is incorporated in to the PVA/HPMC films and the prepared films are characterized by several methods. In the present article, the authors also reported the drug delivery system formulated by *in situ* forming gel prepared using gelrite (gellan gum). Gellan gum is an anionic polysaccharide secreted by the microorganism *Pseudomonas elodea.* Before application, this will be in the form of solution and gels after it is exposed to the lacrimal fluid of the eye.

2 Experimental

2.1 Materials

Ciprofloxacin HCl (Scheme 1) was obtained from M/s Triveni Pharmaceuticals, Vijayawada, India as a gift sample. It is a pale yellow, crystalline powder freely soluble in water and slightly soluble in alcohol. Its molecular weight is 367.8 and melting point is 255°C. Polyvinyl alcohol (PVA) was procured from M/s Otto Kemi, Mumbai. It has a molecular weight of about 1,25000 and T_m is greater than 200°C. HPMC was obtained from M/s B.P.R.L Pharmaceuticals, Bangalore, India as a gift sample, having T_m of about 225-230°C and gelrite is the brand name of gellan gum which was procured from M/s Sigma Labs, USA. All the chemicals were used as procured.



Sch. 1. Chemical structure of ciprofloxacin HCl.

2.2 Preparation of PVA/HPMC-drug Films

The PVA/HPMC-drug films for ophthalmic delivery were prepared by the solvent casting method. Different compositions of PVA/HPMC viz., 0/100, 20/80, 40/60, 50/50, 80/20 and 100/0 were prepared by dissolving the required quantities (2% w/v) of polymers in ethyl alcohol using ethylene glycol (15% w/w of polymer weight) as plasticizer. 75 mg of ciprofloxacin was added to the above prepared solutions. Films were prepared by pouring the solution on previously sterilized glass molds which were kept at room temperature for 24–30 h for drying the solvent. The casted polymer films were then peeled off from the glass molds, covered with aluminium foil, and stored in a desiccator till further study.

2.3 Preparation of Gellan-Drug In Situ Gel Solution

Gelrite (0.8% w/v) was taken in a beaker containing water and was kept at 85°C for about 15–20 min. To this solution, drug (0.1% w/v) was added. The solution was filtered and kept in a hot air oven for 15–20 min at 120°C. This solution forms a gel when it comes in contact with lacrimal fluid (sodium bicarbonate 0.2, calcium chloride dehydrate 0.008, and NaCl 0.067% w/v in water).

The likely gelling mechanism of the deacetyled gellan is based on the formation of double-helical junction zones followed by aggregation of the double helical segments, which leads to a three dimensional network, which is induced by cation. The reason for formation of gels with divalent cations at a much reduced concentration than required with monovalent cations is due to the presence of uronic acid groups at junctional zones resulting from the parallel alignment of the helical polymers in the dispersed gelrite molecules. It is believed that each divalent cation gives rise to a much stronger double helical interaction with these groups by displacing two monovalent cations such as K^+. The coordination of divalent cations between the double-helices is so strong that aggregation can occur readily even in the presence of very low ionic concentrations.

2.4 Techniques

2.4.1 FTIR Spectrophotometry

In order to evaluate the integrity and compatibility of the drug with the carrier polymers in the polymer-drug matrix formulations, IR spectra of the pure drug and its formulations were recorded by FTIR spectrophotometer (Perkin-Elmer-1000, Japan) using the potassium bromide pellet method.

2.4.2 Mechanical Properties

The mechanical properties of PVA and its blends were measured as per ASTM D 685 using Universal Testing Machine (UTM) (Model 4309, Instron). A minimum of six samples were tested for each composition and the average value was recorded. The prepared films were evaluated for

optical properties such as percent transmittance of light and haze. Haze and loss of clarity indicates discontinuations within, or at the surface of, the material and these could be due to impurities, minute bubbles, surface roughness, etc. The prepared gellan gels were tested for specific gravity by using a specific gravity bottle and refractive index using Abbe's refractometer.

2.4.3 Content Uniformity

The wavelength of maximum absorbance (λ_{max}) of ciprofloxacin HCl drug was determined by scanning a known concentration of drug solution in the wavelength region 200–400 nm by using a Shimadzu 1601 UV/Visible spectrophotometer. The λ_{max} was found to be 276 nm and this wavelength was used for evaluating the concentration of drug.

In order to ascertain the drug distribution in the polymer membranes, the content uniformity test has been performed using a UV/Visible spectrophotometer. A specimen sample of 1 cm^2 was dissolved in 100 ml of pH 6.8 buffer by slightly warming. After cooling, the extracted drug concentration from the polymer membrane was determined by measuring the absorbance at 276 nm. In the case of *in situ* gels, 2 ml of solution was dissolved in 100 ml of 6.8 buffer and the absorbance was recorded.

2.5 Drug Diffusion Studies

Drug diffusion studies were carried out in an open glass diffusion tube. One end of the glass tube was covered with cellophane membrane in order to simulate the eye tissue. A specimen dimension of 2 cm^2 (for drug incorporated blends) and/or 4 ml (for gel) was kept at one end of the open glass tube and placed in the donor compartment containing the buffer solution (pH 6.8 buffer). The assembly was placed on a magnetic stirrer and continuously stirred at 100 rpm. The temperature of the system was maintained at $37 \pm 1^{\circ}C$. A known amount of receptor medium (buffer) was withdrawn at regular intervals of time for 4 h and sink condition was maintained by replacing an equal volume of buffer (22). The drug concentration was determined by measuring the absorbance of solution at 276 nm by UV spectroscopy.

2.6 Peppas Model Fitting (23)

The Koresmeyer-Peppas model is one of the mathematical expressions to evaluate the mechanism of drug delivery. The mathematical expression of Koresmeyer-Peppas equation is as follows:

$$M_t/M_\infty = 1 - A(\exp^{-kt}) \quad (1)$$

$$\log(1 - M_t/M_\infty) = \log A - kt/2.303 \quad (2)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hours. In this study, the release constant, k and constant, A were calculated from the slopes and intercepts of the plot of 1n $(1 - M_t/M_\infty)$ vs. time t.

2.7 Stability of the Drug Formulation

The stability of the drug incorporated polymer matrix films and gels is a very important parameter for storage and drug administration. The specimen sizes of 4 cm^2 (films) and 5 ml vials (gels) were exposed to a temperature of $37^{\circ} \pm 1^{\circ}C$ and at a relative humidity (RH) of 75% for 6 weeks. The exposed samples were evaluated initially for its content uniformity and at regular time intervals for six weeks.

2.8 Differential Scanning Calorimetry (DSC)

DSC studies have been carried out in the temperature range, from ambient to 300°C at a heating rate of 10°C/min under nitrogen gas flow of 20 ml/min, by using DuPont DSC. About 6–8 mg of accurately weighed sample was placed in sealed aluminum pan and an empty aluminum pan was used as reference.

3 Results and Discussion

3.1 FTIR Spectrophotometry

The IR spectral data of ciprofloxacin HCl and its formulations viz., films and gel were found to be identical. The characteristic IR absorption peaks of ciprofloxacin at 3450–3550 (OH stretching), 2962–2853 (C-H stretching), 1700 (carbonyl stretching), 1630 (C-N stretching), 1470–1430 (C-H bending), 1000–1400 (C-F stretching) and 800 cm^{-1} (C-Cl stretching) were obtained. The FTIR spectra of the pure drug, as well as drug incorporated formulations, indicated that no chemical interaction occurred between the ciprofloxacin and the polymers used. But, a slight shift in absorption peaks position was noticed. This may be due to some kind of physical interaction such as dipole–dipole, Van der Waal's force of attraction or hydrogen bonds may have occurred between drug and the polymer.

3.2 Mechanical Properties

The measured mechanical properties such as tensile strength and percentage elongation at break for PVA/HPMC blends are given in Table 1. The tensile strength of PVA and HPMC films are 12 and 23 MPa, respectively. From the Table, it was also noticed that the tensile strength values of PVA/HPMC blends lie in the 21–14 MPa range. These values fall in between the corresponding pure systems. The reduction in tensile strength was observed with an increase in PVA content in the blend. This is due to an increase in low tensile strength PVA in the PVA/HPMC blend.

The PVA and HPMC possess an average percentage elongation at break of 92 and 28, respectively. The percentage

Table 1. Mechanical properties of PVA, HPMC and their blends

Composition (wt/wt%) PVA/HPMC	Tensile strength (MPa)	Percentage elongation at break
0/100	23 ± 1.26	92 ± 6.64
20/80	21 ± 1.08	64.6 ± 6.46
40/60	19 ± 2.04	56.8 ± 7.27
50/50	18 ± 2.64	45.6 ± 6.6
60/40	15 ± 1.28	44.0 ± 7.16
80/20	14 ± 1.94	34 ± 6.49
100/0	12 ± 2.08	28 ± 7.23

elongation of the PVA/HPMC blends lies in the 34–64.6 range. Theoretically, the tensile strength and percentage elongation at break of the PVA/HPMC blends have been calculated using the volume additive method. The variation in experimental and theoretical tensile strength and percentage elongation at break are shown in Figures 1(a) and (b), respectively. The figures clearly indicate that, there is a slight variation between theoretical and practical values.

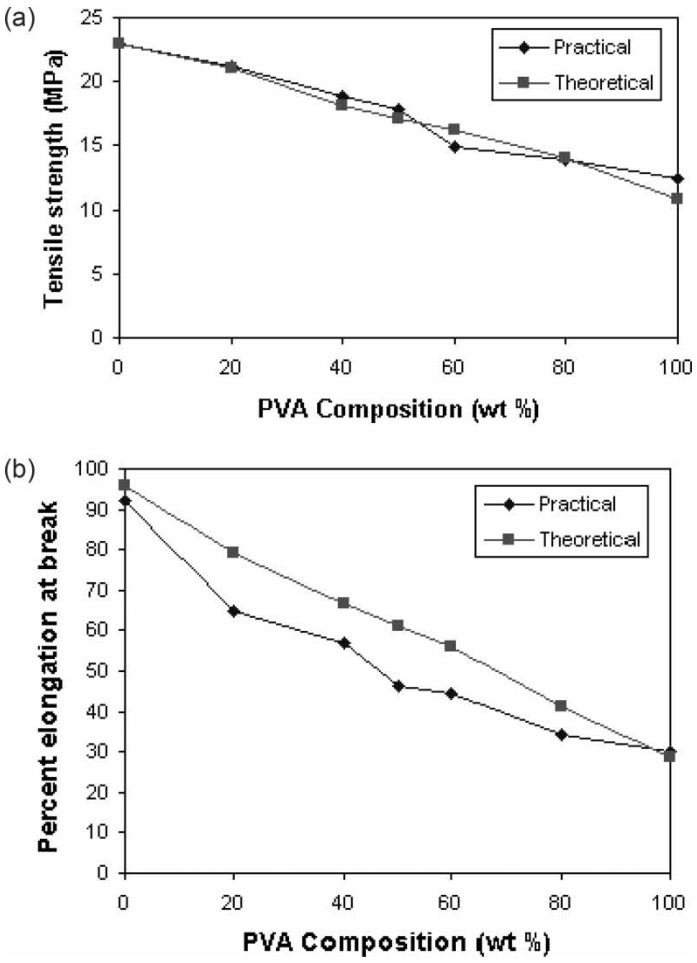


Fig. 1. Variation of practical and theoretical values of tensile behavior of PVA/HPMC films as a function of PVA composition for; (a) tensile strength and (b) percentage elongation at break.

3.3 Optical Properties

Optical properties such as percent transmittance and haze values of PVA/HPMC films, with and without drug, have been measured using a Suga test haze meter and the obtained values are given in Table 2. Percent transmittance of the blends measured at wavelength of 430 nm, lies in the range 88.4–93.8 and corresponding values for drug incorporated films are 87.0–91.3.

The percentage transmittance values for PVA and HPMC films are 88.7 and 91.3, respectively. After the incorporation of drug, they maintained optical clarity. From the Table, it was noticed that all the blends are transparent in nature. A drastic increase in haze values was noticed after incorporation of the drug. This can be attributed to the scattering of light by the drug particles. The percent transmittance result clearly indicates that there is no chemical interaction between polymer blends and drug. The drug maintained its chemical identity in the matrix. This result is in support of the IR data.

Refractive index values of drug, gelrite, with and without drug, are 1.308, 1.309, and 1.306, respectively. Specific gravity of gelrite gels, with and without drug, was found to be 1.003 and 1.002, respectively. From these results, it was noticed that the refractive index value has been retained which indicates that there is no interaction between drug and gelrite.

3.4 Content Uniformity

The drug distribution data in PVA/HPMC films and gellan gel is given in Table 3. From the Table, it was noticed that the content uniformity value lies in the range 0.5–0.87 mg/cm^2. The result of content uniformity studies clearly indicates that the drug was uniformly distributed throughout the

Table 2. Optical properties of PVA/HPMC blends with and without drug

Composition (wt/wt%) PVA/HPMC	Percent transmittance		Haze	
	Without drug	With drug	Without drug	With drug
0/100	88.7	87.5	7.2	89.2
20/80	88.4	87.0	50.2	88.9
40/60	93.3	92.8	76.7	85.4
50/50	92.2	88.2	77.7	87.4
60/40	93.8	91.3	79.9	90.7
80/20	88.5	87.3	53.6	89.5
100/0	91.3	89.7	31.5	85.7

Table 3. Content uniformity data of PVA/HPMC films obtained from UV/visible spectra at 276 nm

Formulation PVA/HPMC	Content uniformity (mg/cm^2)
0/100	0.60 ± 0.026
20/80	0.71 ± 0.046
40/60	0.66 ± 0.021
50/50	0.74 ± 0.035
60/40	0.87 ± 0.028
80/20	0.50 ± 0.031
100/0	0.69 ± 0.026

films (9). These values are in expected line as per Indian Pharmacopoeia (IP) standards (0.2–0.8 mg/cm^2).

The content uniformity of ciprofloxacin drug in the gel solution was found to be 0.76 mg/ml. This shows that the drug is uniformly distributed in the solution. This value lies in the pharmaceutically accepted range 0.2–0.8 mg/ml.

3.5 Diffusion Studies

Diffusion of drug through the polymer films and gel was carried out in an open glass tube diffusion cell (Table 4). Diffusion studies for all the formulations with drug (ciprofloxacin) were carried out for 4 h in 6.8 pH buffer solution. The data given in Table 4 indicates that the diffusion of drug from HPMC film occurred at a faster rate than PVA film. In the polymer/drug system, the volume of the polymer matrix increases in the buffer media due to swelling, followed by drug release to the surrounding media. The swelling behavior of HPMC is more compared to PVA, so it releases drug at a faster rate in the medium used. Sanker et al. and Thilek Kumar et al. made similar observations for HPMC semi-permeable membrane (2, 9). From Table 4, it can be noticed that, the amount of drug release increases with an increase in time. The rate of drug release from the gelrite system is slow compared to PVA/HPMC systems. At the end of 240 min, gelrite releases about 68.6% of the incorporated drug, whereas in the PVA/HPMC system it ranges from 50 to 99%. From the table it was also noticed that there is no systematic variation in rate of drug release from the polymer blends. The drug release from the polymer membrane depends upon the nature of the polymer, solubility parameter, rate of swelling of membrane, morphology, chemical structure and microvoids. Different blends have different morphology, rate of swelling and microvoid contents. Hence, the rate of drug release is different for different blends.

From the data obtained from the Peppas model fitting (Table 5), it is observed that the value of A lies between 0.5 and 1 for all the formulations indicating that the drug release from the formulations is by non-fickian mechanism, i.e., release due to the relaxation of polymer chain.

3.6 Differential Scanning Calorimetry (DSC)

DSC is a fast and reliable method to screen drug compatibility and on the basis of melt curve it is possible to predict the

Table 4. Diffusion studies data of drug (Ciprofloxacin) from PVA/HPMC blends

	% Drug release from formulations						
	PVA/HPMC films						
Time in min	0/100	20/80	40/60	50/50	80/20	100/0	*In situ* gel
30	56.6 ± 1.26	26.0 ± 1.47	39.3 ± 2.04	44.3 ± 1.86	26.0 ± 2.42	48.3 ± 3.08	16.6 ± 2.58
60	64.0 ± 2.24	35.1 ± 1.62	43.3 ± 1.28	53.5 ± 2.16	32.6 ± 2.94	56.0 ± 2.62	27.7 ± 3.02
90	78.0 ± 1.48	39.6 ± 2.08	50.4 ± 1.94	60.4 ± 2.30	36.6 ± 2.60	67.5 ± 1.34	32.3 ± 2.64
120	87.5 ± 1.62	43.7 ± 2.34	57.0 ± 2.40	66.9 ± 2.58	40.7 ± 2.05	73.2 ± 1.98	44.5 ± 2.38
180	92.7 ± 1.94	47.7 ± 1.52	69.8 ± 1.68	77.5 ± 2.08	45.9 ± 1.94	83.3 ± 2.24	53.5 ± 2.82
240	99.5 ± 2.34	59.0 ± 2.42	74.4 ± 2.18	88.2 ± 1.18	51.3 ± 1.82	91.8 ± 2.60	68.6 ± 2.60

Table 5. Data obtained from Peppas model fitting for the polymer coated optimized formulations

	PVA/HPMC films						
Parameters	0/100	20/80	40/60	50/50	80/20	100/0	*In situ* gel
Release constant (k) × 10^2	1.74	2.8	4.9	6.6	2.1	8.5	5.0
Constant (A)	0.6414	0.7758	0.7184	0.673	0.766	0.663	0.9750
Regression coefficient (R^2)	0.9861	0.9827	0.9940	0.9990	0.9952	0.9950	0.9910

Table 6. Data obtained from DSC curves for drug, PVA/HPMC blends and gelrite gel

Composition	Melting range (°C)	T_m(°C)	Area under DSC curve, ΔH(cal/g)
Drug	126–185	175	11.8
PVA/HPMC (50/50)/Drug	127–190	176	12.4
Gellan gel/Drug	124–189	177	11.4

interaction between the drug and the polymers used in the formulation and stability. DSC thermograms were taken for the pure drug, its film formulations and gel after stability studies to find out whether the drug has undergone any degradation during the study period. From the DSC data (Table 6), it was evident that the melting range and melting point of ciprofloxacin HCl is unchanged after exposing the specimens to stability measurement. Hence, it may be inferred that the drug retained its chemical identity throughout the process.

3.7 Animal Studies

Drug incorporated gelrite gel is administered to a rabbit eye in order to evaluate the influence of gelrite on eye. In this case, studies were carried out on albino rabbit eyes to mimic the conditions of the human eye. From the studies, it was noticed that gelrite did not cause any irritation to the rabbit eye (9, 21). It was observed that the gel is eroded after 24 h.

4 Conclusions

PVA/HPMC membranes and smart gels (gelrite) for ophthalmic drug delivery were prepared. The following conclusions have been drawn on the above said results.

From the mechanical properties data, it was observed that pure HPMC film showed higher tensile strength values, compared to PVA. The tensile strength of blends lies in between the corresponding homopolymers. From content uniformity data, the drug was found to be uniformly distributed throughout the PVA/HPMC films and gelrite solution. This lies in the range of pharmaceutical standards.

The drug diffusion studies revealed that the amount of drug release from pure PVA and HPMC membranes was more than the PVA/HPMC blend systems. The drug diffusion studies of gelrite also revealed that the drug was diffused at a uniform rate. Peppas model fitting indicates that the drug release from the polymers is by a non-Fickian mechanism i.e., release of drug due to the relaxation of polymer chain.

Among the films and the gel, it can be concluded that gel is better than the films for drug release. This is because the insertion of gelrite solution is easier than the PVA and HPMC films. Therefore, it can be concluded that *in situ* gel formulation of ciprofloxacin is an ideal approach for better bioavailability and patient compliance compared to conventional solutions.

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