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Research Article

Formulation and Evaluation of Moxifloxacin Ocusert

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ABSTRACT

Moxifloxacin,an antibacterial is effective against bacterial conjunctivitis and is new fourth generation of fluoroquinolone antibacterial drug. Ocuserts prepare by using different combination of polymer for better ocular drug delivery and increased retention time. In which ocusters have shown advantages to overcome disadvantages of conventional dosage form. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity. The ocuserts were prepared by solvent casting technique. ocusert were characterized using different analytical techniques UV spectroscopy, FTIR, DSC. The drug content of the ocusert was found to be varied between 96.00 - 97.90 %. Ocusert provide better in vitro controlled release i.e. 77.13%was found to be better than the other formulations over an extended period of 8 hours and showed excellent microbiological activity for 3 days and remained stable and intact at ambient conditions.

Keywords: Ocusert, Moxifloxacin, In vitro release pattern, controlled release.

INTRODUCTION

Moxifloxacin is rapid passage across the cornea and extensive penetration into ocular tissue as compared to conventional ocular dosage form Moxifloxacin is an 8-methoxy fluoroquinolone (4th generation) having half life nearly 12 hours. It has a broad-spectrum antibiotic activity, with efficacy against various gram-positive and gram-negative microorganisms through inhibition of DNA gyrase and topoisomerase IV and is indicated for treating bacterial conjunctivitis. The conventional dosage form having less therapeutic efficacy due to their bioavailability they giving sustained release pattern. the ocusert is one of best option, they giving control release pattern without any irritation to patient. In this study ocusert were developed as alternative delivery systems to treat the conjunctivitis. The ocuserts are mostely placed in lower fornix but less frequently, in upper fornix. These Ocuserts are based on the rate limiting stesp for controlled release. As compared to conventional ocular dosage form, ocusert having more advantages like increased residence time of drug in the eye, decreased frequency of drug administration, low dose is required for treatment, minimize local or systemic side effects, improved patient compliance[1].

MATERIAL AND METHODS

Moxifloxacin was purchased by Cipla Pharmaceuticals Pvt.Ltd, Patalganga. The polymers HPMC(E-50) from colorcon Asia pvt.ltd.goa., EC, PVP, Poly ethylene glycol-400, ehanol, glycerine were purchased from SD fine chemical, mombai.all ingredients were of analytical grade.

Method for preparation of ocuserts

The preparation ocusert involved three steps

Preparation of the drug containing reservoir film of hydrophilic polymers

For preparation of the drug containing reservoir film, polymeric solution were prepared by dissolving hydrophilic polymer (HPMC/ PVP), along with moxifloxacin and poly ethylene glycol 400, in doubly distilled water. The solution were poured into a glass ring placed in a Teflon coated petri dish. The solvent was allowed to evaporate by placing it inside an oven.

Preparation of rate controlling films

To prepare the rate controlling films, hydrophobic polymer along with plasticizer were dissolved in ethanol / acetone mixture. The solution were poured into a glass ring placed in a Teflon coated petri plate.

Placing rate controlling films around the drug reservoir and sealing them to obtain ocular inserts

Circular shaped ocular inserts were cut out of medicated reservoir film with the help of a cork borer. These ocular inserts were placed on a rate controlling membrane and another rate controlling membrane was kept over it. The two rate controlling membranes containing the reservoir film between them were placed over a beaker saturated with ethanol / acetone vapours for 1-2 minutes.the ocusert were stored in an airtight container under ambient conditions[5].

Evaluation

P^H

The ocuserts were allowed to swell in closed Petri dish at room temperature for 30 minutes in 0.1 mL of distilled

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water. The swollen device was removed and placed under digital pH meter (shimadzu) to determine the surface pH.

Uniformity of thickness

The thickness of the insert was determined using a Vernier caliper at five separate points of each insert. For each formulation, five randomly selected inserts were tested for their thickness[6].

Uniformity of weight

From each batch, five inserts were taken out and weighed individually using digital balance (Shimazdu). The mean weight of the insert was noted[7].

% Moisture absorption

It was carried out to check the physical stability or integrity at wet condition. The prepared ocusert was accurately weighed and placed in a dessicator containing aluminium chloride with 79.5% moisture and it was kept for 3 days. The ocusert was taken out and reweighed after 3 days. The amount of moisture absorbed by the ocusert was calculated by using the following formula[5]

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 10$$

% Moisture Loss

The prepared ocusert was initially weighed and kept in a dessicator containing fused anhydrous calcium chloride and it was kept for 3 days. The ocusert was taken out and reweighed after 3 days. The % of moisture loss was calculated by using the following formula[5]

$$\% \text{ moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content

Five films were taken from each batch and dissolved or crushed in 10 ml of simulated tear fluid in a beaker and were filtered into 25 ml volumetric flask and the volume was made up to the mark with STF. 1 ml of the above sample was withdrawn and the absorbance was measured by UV spectrophotometer 296 nm after suitable dilutions[2].

In Vitro Drug Release Studies

The in vitro drug release from the different ocular insert was studied using the classical standard cylindrical tube fabricated in the laboratory (bi-chambered donor receptor compartment model). A simple modification of glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane (prehydrated cellophane) was tied to one end of open cylinder, which acted as a donor compartment. An ocular insert was placed inside this compartment. The diffusion cell membrane acted as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment comprising of 12 ml of simulated tear fluid ph (7.4) in a 50 ml beaker The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 37±0.5°C. At specific intervals of time, 1 ml aliquot of solution was withdrawn from the receptor compartment and replaced with fresh buffer solution. The aliquot was analyzed for the drug content using UV spectrophotometer at 296 nm after appropriate dilutions against reference using simulated tear fluid pH 7.4 as blank[2].

Sterility Test

All ophthalmic preparations should be sterile therefore the test for sterility is very important evaluation parameter. The sterility test was performed according to Indian Pharmacopoeia. Direct inoculation method was used. 2 ml of prepared moxifloxacin ocusert solution was removed with a sterile pipette or with a sterile syringe or a needle. The test liquid was aseptically transferred to fluid thioglycolate medium and soyabean-casein digest medium separately. The liquid was mixed with the media. The inoculated media were incubated for not less than 14 days at 30°C to 35°C in the case of fluid thioglycolate medium and 20°C to 25°C in the case of soyabean-casein digest medium[10,11].

Microbiological Studies

The selected ocusert, control and placebo were evaluated for microbiological study. The microbiological studies were carried out to ascertain the biological activity of the selected formulation against test microorganism. Nutrient agar seeded with the test organism (*S. aureus*) was allowed to solidify in the petri dish. An ousters were removed from the pack and carefully placed over the agar layer at a suitable distance. The plates were then incubated at 37±0.5°C for 24 h. After incubation the zone of inhibition was measured around the ocusert[6].

Stability Studies

Stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of its manufacture. Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. Stability studies were carried out on ocular inserts MHF4, according to ICH guidelines. The stability studies were carried out at 40ºC/75% RHfor 30 days. The samples were tested for drug content after 0, 7, 15, 21 and 30 days respectively were evaluated for following parameters.

Drug content

Invitrodrug release[9]

RESULT AND DISCUSSIONS

from the above experimental data following result obtained

The pH of the formulations was found to be satisfactory and was in the range of 6-7.4.

The thickness of ocuserts (MHF1 to MHF4) was found to be in range of 0.131± 0.01 mm to 0.138± 0. The Uniformity of weight ocular inserts were found to be in the range of 5.34± 0.21 to 5.69 ±0.16mg. The uniformity of the weights of the films indicates good distribution of the drug, polymer and plasticizer. The fig.1 showed the FTIR spectra of ocusert. The pure drug, placebo formulations and selected ocular inserts were subjected to the FTIR analysis. The FTIR spectra shows one peak at 3352 nm indicating the –NHStretching and two peaks at 1713 nm and 1351 nm for the –C=O stretching of –COO and –F group respectively. All the above peaks were also found in drug loaded ocusert that confirms the presence of drug in the polymers without any

Table 1: Preparation table of Moxifloxacin ocuserts.

Ingredients	MHF1	MHF2	MHF3	MHF4
Moxifloxacin	100mg	100mg	100mg	100mg
Hydroxyproylmethylcellulose(E50)	600mg	400mg	600mg	400mg
Polyvinylpyrolidone(K30)	400mg	600mg	-	-
Ethyl cellulose	-	-	400mg	600mg
Poly ethylene glycol-400	0.5ml	0.5ml	0.5ml	0.5ml
Glycerine	20mg	20mg	20mg	20mg
Ethanol	q.s.	q.s.	q.s.	q.s.
Distilled water	q.s.	q.s.	q.s.	q.s.

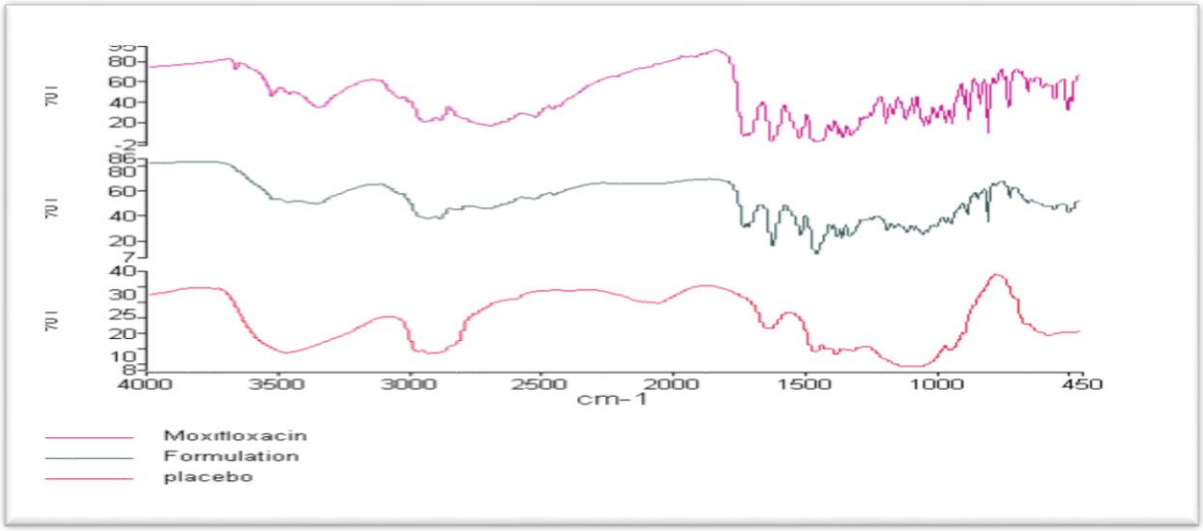

Figure 1: FTIR spectra of moxifloxacin+formulation+placebo.

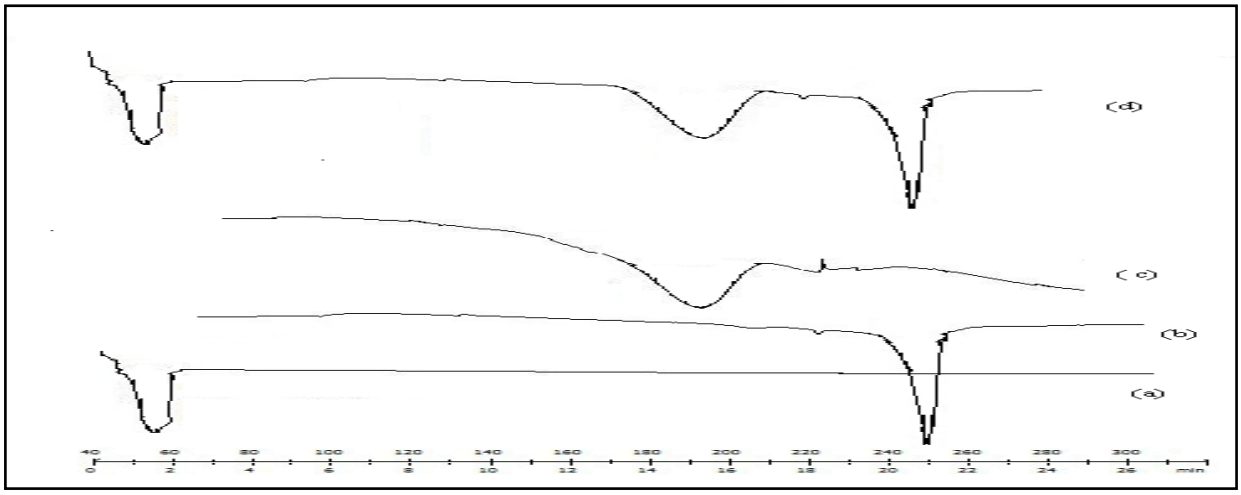

Figure 2: Combination of (a)HPMC (b) Moxifloxacin (c) Ethyl cellulose (d) Optimised formulation MHF4.

interaction.

The results of DSC study are showing in fig. DSC thermograms showed endothermic peak of moxifloxacin (pure drug at 242.42°C, which corresponded to its melting point. The results of the thermograms obtained from DSC revealed no interaction between the polymers and the drug in the ocuserts

Drug content was found to vary between 0.960 ± 0.04mg to 0.979 ± 0.03 mg. The % moisture absorption was found to be 31.54 ± 0.14 as it contains polymers of less hydrophilicity or lipophilic nature. In general, it can be concluded that the hydroxyl propyl methyl cellulose have more tendency to absorbs moisture as compared to polyvinyl pyrrolidone and ethyl cellulose. The % Moisture loss of prepared ocusert was found to 30.23±0.12. In the present study, in vitro drug release was carried out at different time intervals, the sample was withdrawn and

Table 2: In Vitro Drug Release Profile of Moxifloxacin from Ocusert of MHF 4. (EC 600 mg +HPMC 400 mg).

Time (hrs)	Abs	Slope	µg/1ml	µg /5ml	µg/50ml	mg /50ml	% Drug release
0	0	0.0422	0	0	0	0	0
1	0.118	0.0422	2.79620	13.9810	139.810	0.139	13.981
2	0.217	0.0422	5.14218	25.7109	257.109	0.257	25.710
3	0.297	0.0422	7.03791	35.1895	351.89	0.351	35.189
4	0.339	0.0422	8.03317	40.1658	401.658	0.401	40.165
5	0.426	0.0422	10.0947	50.4739	504.739	0.504	50.473
6	0.523	0.0422	12.3933	61.9668	619.668	0.619	61.966
7	0.598	0.0422	14.1706	70.8530	708.530	0.708	70.853
8	0.651	0.0422	15.4265	77.1327	771.327	0.771	77.132

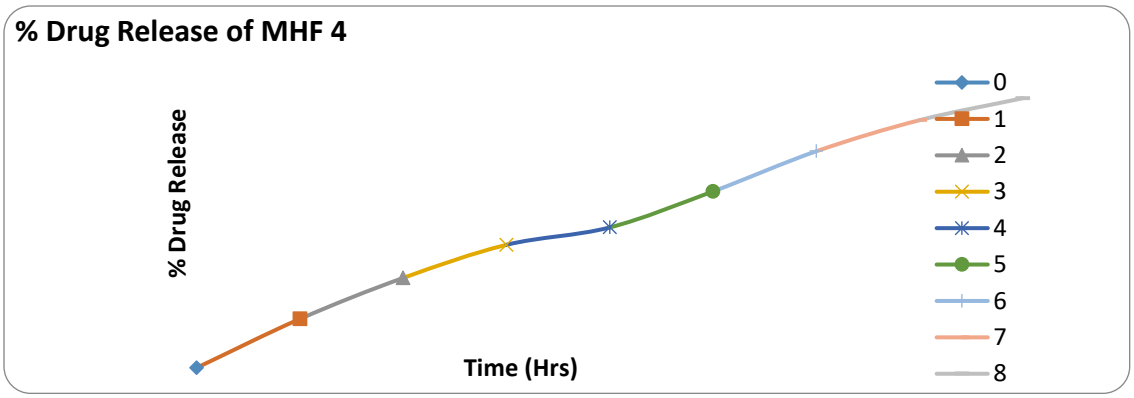

Figure 3: In Vitro Release Profile of Moxifloxacin from Ocusert of MHF 4.

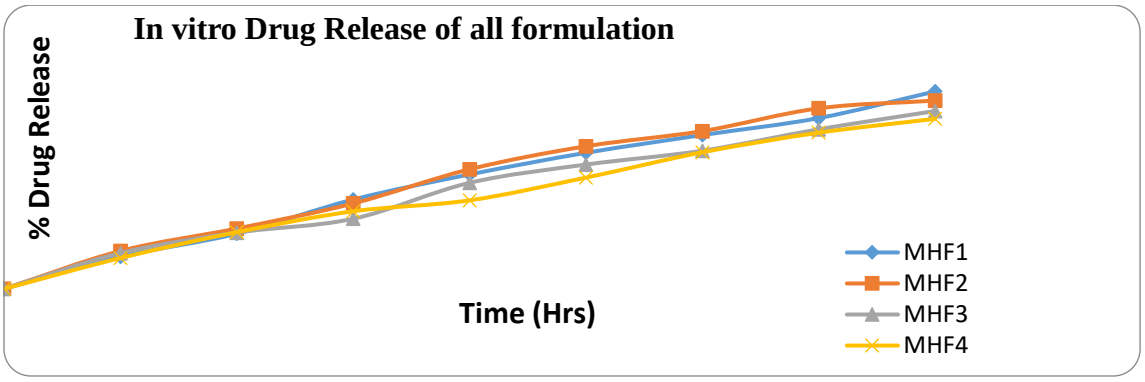

Figure 4: In VitroRelease Profile of Moxifloxacin of all formulation.

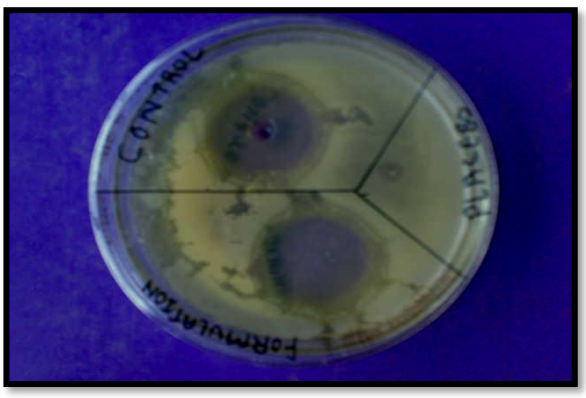

Figure 5: Zone of inhibition of moxifloxacin ocusert against control and placebo.

percentage drug release was calculated on the basis of mean amount of drug present in the respective ocusert. In vitro drug release study for formulations MHF1 toMHF4 revealed that these formulations were capable of extending the drug release upto 8hrs.FormulationMHF1 containing PVP (600mg) and HPMC (400mg) has shown maximum drug release of about89.57% at the end of 8 hrs, which indicate that the polymer combination of same quantities can be used the formulation of ocusert for therapeutic drug management in the systemic circulation. Whereas Formulation MHF 4containing EC (600 mg) and HPMC (400mg) has shown77.13%drug release at the end of 8hrs.The percentage of drug release of all four formulations is presented in Fig. The formulations (MHF3 and MHF4) gave good controlled release pattern.

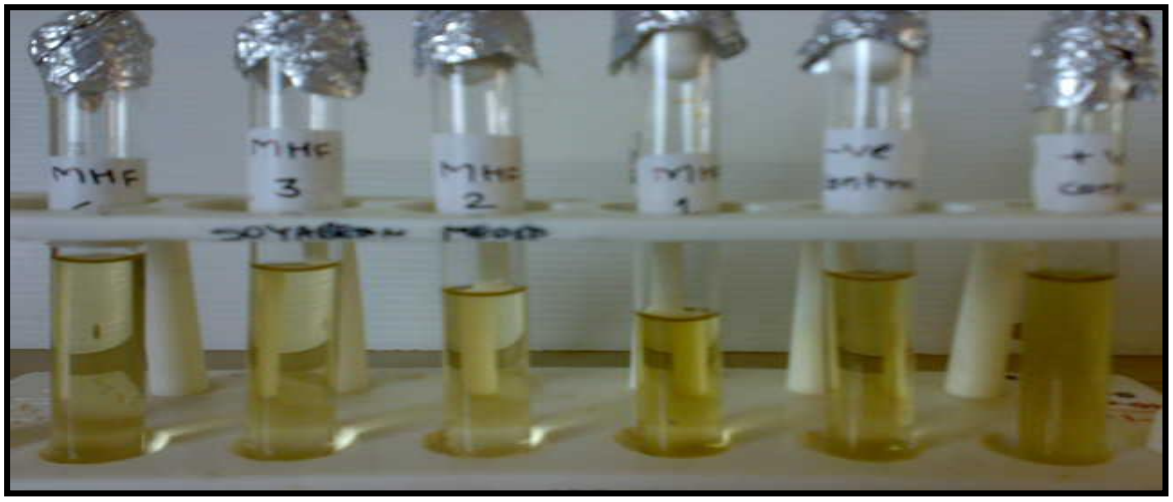

Figure 6: Sterility test for Moxifloxacin ocusert in soybean casein mediu.

Figure 7: Sterility test for Moxifloxacinocusert in Fluid thioglycolate medium.

Table 3: Dissolution profile of moxifloxacin formulation.

Time (hrs)	MHF4
0	0
1	13.98
2	25.71
3	35.18
4	40.16
5	50.47
6	61.96
7	70.85
8	77.13

So, the formulation(MHF4) was selected for sterility test and microbiological studies.

The result indicates formulation MHF 4 has better drug release through an artificial membrane over an extended period of 8 hours. This shows in vitrorelease of drug from the ocusert formulation follows diffusion mechanism.

Microbiological Studies

The selected ocusert (MHF4) showed good antimicrobial activity against control when tested microbiologically on solidified agar. Clear zones of inhibition were obtained in said formulations against test organisms namely*S.aureus*. Microbiological efficacy was evaluated on the around the ocusert. As per the observation (Fig.5) in the first 3days ocusert showed excellent microbiological activity with proper zone of inhibition.

Sterility Test

There was no appearance of turbidity and hence no evidence of microbial growth when the formulation were incubated for not less than 14 day at 30^0 C to 35^0Cin case of fluid thoiglycolate medium and at 20^oC to 25^0C in case of soyabean casein digest medium the formulation being examined there for passed the test for sterility.

Stability study

Stability studies of the formulation MHF4 of Moxifloxacin ocuserts were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at40ºC/75%RH for 30days. There was no significant change in the physical property and drug content during the study period. The overall degradation is less than5% tentative shelf-life of 2 years may be assigned to formulation as per ICH guidelines.

Table 4: Antibiotic sensitivity for prepared ocusert against control.

No. of Days	Zone Of Inhibition		
	Control	Optimized Formulation (MHF 4)	Placebo formulation
1	++	++	_
2	_	+++	_
3	_	+++	_
4	_	++	_
5	_	+	_
6	_	+	_
7	_	+	_

1)─:No Release 2)+ : Moderate Release
3)++: Good Release 4) +++: Excellent Release

Table 5: % Drug Content in Optimized formulation MHF4.

Sampling interval	%Drug content 40^0C/ 75%RH
0 th Days	97.90
7 th Days	97.34
15 th Days	96.78
21 th Days	96.14
30th Days	95.67

CONCLUSION

From the above results it can be concluded that Moxifloxacin is compatible with all the polymers used. The pH of all formulations was found to be satisfactory in the range of 6 - 7.4.The drug content of the prepared formulation was within the acceptable range, and ensures dose uniformity. The formulation MHF 4 showed maximum drug content. Formulation MHF4 showed most controlled drug release. Results of sterility test confirmed that all the ousters were sterile. From the stability studies it was confirmed that ocusert formulations of Moxifloxacin remained more stable at ambient temperature(25°C) and humidity. The maximum in stability of ocusert formulations was observed at 40□1□C.The ocusert would be able to offer benefits such as i.e., increasing residence time, prolonging drug release, reducing frequency of administration, and thereby may help to improve patient compliance.

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