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The Effect of Molecular Imprinting on the Loading and Release of Poorly Water Soluble Drug in Hydrogel Contact Lenses

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Abstract

Therapeutic contact lenses TCLs is an approach used to enhance corneal residence time and reduce frequent instillation, which is a problem with eye drops. The problem with CLs is loading of hydrophobic drugs. In this research the CLs were prepared with molecular imprinting MI to enhance the loading of itraconazole, which is used as antifungal drug for fungal keratitis. CLs using different concentration of hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA) were prepared with and without MI using polyethylene glycol diacrylate (PEGDA) (25 µL) and 2,2'-Azobis(2-methylpropionitrile) AIBN (37 mg) as crosslinker and initiator respectively. All the CLs contain MAA were clear and have a folding endurance above 250 folds without break which indicates good mechanical properties . MICLs with 10 mg ITZ had significantly higher drug loading with 3.7 folds increase in ITZ loading compared to conventional CLs. F3MI had 8% MAA was chosen as an optimum formula due to maximum drug loading (1077 µg) compared to non-MI (288 µg) and sustained release for more than 24 h. MI was successfully utilized as a tool to enhance the loading of poorly water soluble drug into a hydrogel CL.

Keywords: Contact lenses ,Molecular imprinting, itraconazole, sustained release, ocular drug delivery

تأثير البصمة الجزيئية على تحميل وتحرير دواء ضعيف الذوبان في الماء على العدسات المائية اللاصقة

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الخلاصة

العدسات اللاصقة العلاجية هي طريقة تستخدم لتعزيز وقت مكوث الدواء في القرنية وتقليل التقطير المتكرر، وهو ما يمثل مشكلة مع قطرات العين. مشكلة العدسات اللاصقة هي تحميل الأدوية ضعيفة الذوبان في الماء. في هذا البحث تم تحضير العدسات اللاصقة مع البصمة الجزيئية لتعزيز تحميل ، والذي يستخدم كدواء مضاد للفطريات لالتهاب القرنية الفطري. تم تحضير العدسات اللاصقة باستخدام هيدروكسي إيثيل ميثاكريلات وحمض الميثاكريليك مع وبدون البصمة الجزيئية. كانت جميع العدسات المعدة شفافة ولديها قدرة جيدة على التحمل. كان لدى العدسات مع البصمة الجزيئية تحميل أدوية أعلى بكثير مقارنة بـ العدسات اللاصقة التقليدية. كان تحرير الدواء من العدسات مع الصمة الجزيئية ابطأ من تحرر الدواء من العدسات التقليدية. كانت الصيغة المثلى هي العدسات مع البصمة والتي تحتوي على ٨ ٪ حمض الميثاكريليك حيث تم تحقيق أقصى تحميل للدواء وتحرير مستمر. تم استخدام البصمة الجزيئية بنجاح كأداة لتعزيز تحميل الدواء ضعيف الذوبان في الماء في العدسات اللاصقة المائية.

الكلمات المفتاحية: العدسات اللاصقة ، البصمة الجزئيية ، ايتراكونازول، تحرر الدواء البطئ المستمر ، توصيل الأدوية للعين

Introduction

Fungal keratitis (FK) is a severe eye infection that frequently causes eye damage and blindness if untreated properly. In the last few years, the overall prevalence of FK has increased significantly with a wide range of fungi in various areas, particularly in developing countries[(1)]. Frequent and chronic use of topical corticosteroids, the rapid establishment of antimicrobial drug resistance, previous corneal damage and an increasing number of corneal surgeries are all key pathogenic factors [(2)].

The ultimate goal of treating fungal keratitis is to keep your vision intact. This necessitates early detection of the illness and treatment with the right antifungal medication. Medical or surgical treatment can be used to treat patients with fungal keratitis depending on the severity of the condition[(3)]. Eye drops of antifungal agents are frequently used in the clinic; however, they have several drawbacks. Eye drops are rapidly eliminated from ocular tissues through tears, nasolacrimal drainage and reflex blinking which reduce precorneal residence time PCRT. Several approaches were used and investigated to improve PCRT such as thickening agents, mucoadhasive agents, punctual plug, nanoparticulate systems, in situ formulations, ocular inserts and therapeutic contact lenses TCLs [(4)].

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Itraconazole (ITZ) is a synthetic triazole antifungal drug used to treat fungal keratitis[5]. Itral® eye drops (Jawa Pharmaceuticals, Gurgaon, India) are commercially available and are applied hourly, precipitating in the corneal tissue following topical application. Poor corneal penetration and visual abnormalities are also linked to the formulation, as are lacrimation, tear dilution, nasolacrimal discharge, and tear turnover [6]. TCL can be used to enhance PCRT of ITZ in ocular tissues and as a result reduce the frequency of application and enhance efficacy of the drug.

Due to the low solubility of ITZ [7] , the loading into a hydrophilic CLs could be problematic. Molecular imprinting method (MI) was previously used to increase drug loading[8, 9]. During the imprinting process, monomers are organized and crosslinked around the template molecule (the drug) to provide fixed and defined template sites (cavities). After polymerization the drug is washed creating cavities that are similar to the drug. These cavities will enhance the affinity of the drug for the contact lens which enhance drug loading. The goal of this work was to increase ITZ loading capacity by forming molecular imprint pockets through molecular imprinting (MI) and maintain drug release rate profiles without altering the contact lenses optical transmittance, swelling or folding endurance.

Experimental Work

Materials

Itraconazole was obtained from HyperChem, China. Hydroxyl ethyl methacrylate (HEMA) and 3-(Trimethoxysilyl) propyl methacrylate (TRIS) (Shanghai Ruizheng Chemical Tech Co.,Ltd, China). Polyethylene glycol diacrylate (PEGDA) (Shanghai Macklin Biochemical Technology Co., Ltd.China). Methacrylic acid (MAA) and 2,2'-Azobis(2-methylpropionitrile) (AIBN) (Shanghai Macklin Biochemical Technology Co., Ltd.China). All other chemicals were of analytical grade.

Methods

Contact lenses preparation

Contact lenses (CLs) with different formulations were prepared using crosslinking method. HEMA and MAA were used as monomers in different ratios Table 1. All the monomers were in liquid form so no solvent was used. PEGDA (25 µL) and AIBN (37 mg) were used as crosslinker and initiator respectively. The monomers were added to 10 mL screw capped vial and mixed at room temperature with magnetic agitation (300 rpm) until a clear mixture appeared. For the preparation of molecular imprinted contact lenses (MICLs), ITZ (10 mg/mL) was added into the monomer mixture and thoroughly mixed until a clear solution was observed. After that, the initiator (AIBN) was added, and the mixture was agitated for another 15 minutes. The monomer mixture was then injected into a mold composed of two polypropylene plates (35 mmx80 mm) separated by a silicon sheet (0.45 mm thickness); care was taken during injection of mixture to eliminate air bubbles inside the mold, The mold then placed in the oven at 70°C for 6 hours to polymerize .

After polymerization, each hydrogel formed (non-MI and MI) was submerged in 1000 mL boiling water for 15 minutes to remove unreacted monomers and make cutting into 10 mm discs easier. The MICLs were then soaked into 50% (v/v) methanol to remove suspended ITZ from the polymer matrix formed [10]. Washing with methanol for MICLs was done three times daily for ten days until no signal in the range of 190–800 nm was found (UV-Vis spectrophotometer) which indicates complete removal of ITZ from the CL matrix. The lenses were then immersed in distilled water for 4 hours at 50°C to remove the methanol. When no spectrophotometric signal was obtained, the hydrogels were dried in a 70°C oven for 24 hours and stored in a dark, humidified environment to be used later for evaluation [11, 12].

Table 1. Formulation of conventional and MICLs.

Hydrogel	HEMA (ml)	MAA (ml)	ITZ (mg)	MAA%
F1	**5**	**0**	**0**	**0**
F2	**4.5**	**0.5**	**0**	**10**
F3	**4.6**	**0.4**	**0**	**8**
F4	**4.7**	**0.3**	**0**	**6**
F5	**4.8**	**0.2**	**0**	**4**
F6	**4.9**	**0.1**	**0**	**2**
F1MI	**5**	**0**	**10**	**0**
F2MI	**4.5**	**0.5**	**10**	**10**
F3MI	**4.6**	**0.4**	**10**	**8**
F4MI	**4.7**	**0.3**	**10**	**6**
F5MI	**4.8**	**0.2**	**10**	**4**
F6MI	**4.9**	**0.1**	**10**	**2**

PEGDA (25 µL) and AIBN (37 mg) were used as crosslinker and initiator respectively for each formulation.

Estimation of therapeutic dose

In order to estimate the dose required for (24 h) the usual dosage regime for treatment of fungal eye infections was used; which was (1-2) drops of 1 % (w/v) ITZ eye drops per h. Assuming the use of (1 drop/h), the amount of ITZ delivered per day will be equivalent to (0.6 mg) as calculated below:

- 1% (w/v) is 1 g/100 ml or 1 mg/100 µl
- 1 drop equivalent to 50 µl so the amount instilled will be 50 µl/h or 1200 µl /day
- 1 mg/100 µl = X /1200 µl
  X= 12 mg/day the amount ITZ instilled
- For eye drops only 5-10% of the administered drop reaches ocular tissues so 5% of 12 mg is equivalent to 0.6 mg/day.

As a result the needed dose for each contact lens was calculated to be approximately 600 µg/day (13, 14). If 2 drops were used then 1200 µg/day is needed.

Characterization of the CLs

Optical Transparency and visual inspection

The CLs to be tested were hydrated in DI water at room temperature to allow them to swell until complete hydration was achieved. Complete hydration was considered and achieved when no more increase in weight was observed due to hydration. The CL was attached to the surface of a cubic quartz cell filled with DI water, and the UV-vis spectrum was measured from 400 to 760 nm. At least three specimens were used to calculate the average transmittance for each measurement[15]. Also the CLs were visually inspected after hydration for bubbles and rough surfaces.

Swelling ratio percent (SR %)

The swelling ratio percent (SR %) was calculated for the CL in different solvents and solvent mixtures and compared. For each solvent a dry lens was weighed and recorded as W°. Then the lens was placed in 5 mL solvent and at predetermined time intervals, the lens was carefully removed from the solvent, blotted to remove extra solvent from the surface with filter paper and weighed. The weight in each time was recorded as Wt. SR% was measured in water, phosphate buffer saline with PH 7.4, methanol, ethanol, water: methanol (1:1), water: ethanol (1:1) and acetonitrile to determine which solvent has the higher SR to choose the proper solvent for drug loading. The SR% for each time point was calculated as follows [16]:

$$\boldsymbol{SR}\ \% = \frac{\boldsymbol{Wt - Wo}}{\boldsymbol{Wo}} * \mathbf{100}\%$$

Equilibrium water content (EWC %) and Oxygen permeability

Equilibrium water content (EWC %) was calculated using water. A dry lens was weighed and recorded as W° then placed in 2 mL water. The lens was then periodically removed from water, blotted to remove extra solvent from the surface with filter paper and weighed. The process continuo until a constant weight of the lens was reached and recorded W∞. EWC % was calculated using the following equation:

$$\boldsymbol{EWC}\ \% = \frac{\boldsymbol{W\infty - Wo}}{\boldsymbol{W\infty}} * \mathbf{100}$$

Oxygen permeability of CLs were calculated using EWC values. Oxygen penetrability is defined as Dk, where D is the substance's diffusivity and k is the substance's solubility. DK can be calculated using the below equation[17]:

$$\boldsymbol{Dk} = \mathbf{1.67}\ \boldsymbol{e}^{\mathbf{0.0397EWC}}$$

Where 'e' is the natural logarithm, 'EWC' is the Equilibrium water content of the material. The unit of Dk is known as Barrer.

Folding endurance

The folding endurance test was performed to measure the durability of the CL Each fully hydrated CL was placed between the fingers and thumb from the center (same place) and folded. Opening and folding of the CL was repeated until the CL broke, cracked or pass 250 times without break. For the calculation of folding endurance, the total number of pending operations was used and the results were then recorded[18].

Tensile strength and percentage elongation

A texture analyzer was used to do tensile testing (Tinius Olsen UK). It was tested using the American Society for Testing Materials' standard test method for tensile characteristics of thin plastic sheets (ASTM). The test was performed with a head speed of 10 mm/min and a cell load of 10 kN. Poly (HEMA-MAA) hydrogels were fully equilibrated in DI water and cut into dimensions (10 * 2) cm and free of air bubbles or physical flaws were placed between two clamps, the top one is moveable and the lower one is fixed. To prevent the hydrogel against being cut by the clamp's grooves, cardboard was taped to the clamp's surface. The strips were pulled by the top clamp until the hydrogel ruptured during the measurement. The data was collected using the Exponent software .The elastic modulus was calculated using the initial slope of the stress–strain curves obtained. Tensile strength (TS) is the highest stress applied to a point where the hydrogel specimen breaks (TS). The distance between the tensile grips of the tensile strength testing equipment was measured before and after the hydrogel fracture to determine the % elongation of the hydrogel compositions[19, 20].

Drug loading

The ITZ was loaded into MICLs and conventional CLs by soaking method. To choose the optimum drug soaking solution first the saturated solubility of ITZ was tested in different solvents. An excess of ITZ (50 mg) was placed in a screw-capped containing 10 mL of 7.4 phosphate buffer saline(PBS), PBS + 1% SLS ,methanol and ethanol blended in a magnetic stirrer for 48 hours at 37°C. After equilibration, the liquid phase was filtered

using 0.45 m Millipore filters and the filtrate was measured at the determined λmax 262[21].

Acetonitrile was used to prepare the soaking solution. Each dry lens was placed in 2 mL concentrated solution of ITZ (7mg/ml) in acetonitrile for 24 hours then removed from soaking solution. After removal the CLs were rinsed with distilled water and dried with absorbent paper in order to remove residual drug on the surface and dried to remove acetonitrile from the lens[22].

Quantification of ITZ loading in the contact lenses

Methanol extraction was used to quantify the total amount of medication loaded per CLs. ITZ-loaded CLs were thoroughly blotted with absorbent paper after being taken from the drug soaking solution and placed in glass vials with 3 mL of methanol. CL were withdrawn from vials at pre-determined intervals, rinsed with DD water, blotted, and placed in fresh methanol until no more drug was detectable. Absorbance measurements at = 262 nm were used to determine the quantity of ITZ in the methanol solutions. A calibration curve was previously obtained using carefully prepared ITZ solutions in methanol with concentrations ranging from 0 to 31.5 µg/mL[23, 24].

Drug release

For the release study each loaded CL was placed in a 30-mL screw capped vial with 15 mL of phosphate-buffered saline (PBS) pH 7.4 + 1% SLS at 37°C using magnetic stirrer at (100 rpm)[25]. At regular intervals, the whole release media was removed and replaced with fresh PBS to achieve sink condition. A UV/VIS spectrophotometer set at a wavelength of 262 nm was used to measure the amount of ITZ released into the PBS medium were determined using a calibration curve with known ITZ concentrations ($R^2 > 0.99$). For the construction of the calibration curve, a stock solution of ITZ (35 µg/ml) in (PBS) pH 7.4 + 1% (w/v) SLS was prepared and serial dilutions from the stock solution (7, 10.5, 14, 17.5, 21, 24.5, 28, 31.5 µg/ml) in PBS (pH 7.4) were prepared and scanned to determine the absorbance. The absorbance was plotted against the concentration to construct the calibration curve [26] .

Statistical analysis

Each experiment was done in triplicate and the results were expressed as mean ± SD for each. Analysis of variance (ANOVA) test was used to analyze the difference among many groups. While students' t-test was used to analyze the difference between the two groups by utilizing SPSS20 software window. A probability value ($p < 0.05$) was considered the minimum level of statistical significance.

Results and Discussion

Optical transparency and visual inspection

Several CLs were prepared by crosslinking method using HEMA as main polymer and different concentrations of MAA (F1-F6). One of the main important factors in a CLs is transparency. HEMA CL is known to be clear and already available in the clinic, however the addition of MAA may affect their transparency. When tested, all formulations were transparent up to 10% MAA and above 10% no clear lens was achieved. Similar results were observed for MICL.

Equilibrium water content percent and oxygen permeability

Hydrogels are known for their water absorption properties. Water content has been shown to influence oxygen density, refractive index and oxygen permeability (Dk). Table 2 demonstrated the results of EWC percent studies, as well as the oxygen permeability (Dk) calculated using EWC. Because of the hydrophilic nature of MAA, there was a significant increase ($p < 0.05$) in EWC percent and Dk values for all of the prepared conventional CLs when MAA was increased. Maximum swelling was observed up to 8% MAA (F3), followed by a slight decrease in values. One possible explanation is that the hydrogel has already reached its maximum stretching and swelling with 8 percent MAA, and any further increase will have no effect on EWC percent. Furthermore, a statistical comparison of MICLs and conventional CLs revealed that the addition of MAA had no significant ($p > 0.05$) effect on EWC percent and Dk values.

Table 2. EWC% and oxygen permeability (DK) of the Soft CL

Formula	EWC%	Dk (barrer)
F1	45.41± 0.95	10.131
F2	78.26 ±1.15	37.328
F3	79.42±0.59	39.087
F4	67.29±1.97	24.148
F5	65.39±1.27	22.394
F6	64.30±1.20	21.445
F1MI	50.16±1.48	12.233
F2MI	79.60±0.60	39.367
F3MI	80.28±1.20	40.444
F4MI	70.42±1.55	27.344
F5MI	69.89±0.98	26.774
F6MI	66.32±1.05	23.236

Folding endurance

CLs usually inserted into the eye by the patient who need to fold them to be placed correctly. If the CLs are weak they will be cracked and broken when inserted. All CLs and MICLs prepared were tested regarding folding endurance. The total number of bending recorded for all formulations, except F1 and F1MI, was above 250 folds which indicates good mechanical strength. It was noticed that the folding endurance of F1 and F1MI (HEMA only formulations) was around 100 folds and the addition of hydrophilic MAA monomer possibly enhanced the elasticity of the lenses prepared [22, 27].

Tensile strength and percentage of elongation

The mechanical stiffness of hydrogel lenses is essential because lenses with a low modulus have higher wearing comfort, fitting properties, physical impact, and durability. Corneal epithelial lesions of the eye and eyelids, such as corneal erosions, corneal edema, and papillary conjunctivitis, can be caused by materials with a high modulus. Lenses with a very low modulus, on the other hand, usually have poor handling and durability[28]. As show in the Table 3 the E- modulus value was close to the standard value commercial contact lens such as Biomedics 38 and Biomedics XC (manufactured by Cooper Vision) and Acuvue (manufactured by Johnson and Johnson) have E-modulus value of 0.81 MPa [29].

Table 3. Mechanical properties of soft lenses

Formulation	Tensile strength (MPa)	Elongation at yield %	E- modulus(MPa)
F1	0.2835±0.01	28.40±0.51	1.075±0.19
F2	0.4124±0.12	50.32±0.82	0.921±0.06
F3	0.4358±0.03	55.2±0.34	0.796±0.02
F4	0.4782±0.02	42.52±0.91	0.895±0.07
F5	0.4939±0.09	40.35±0.75	0.891±0.09
F6	0.4143±0.11	52.9±1.09	0.887±0.11

Swelling Ratio percent and drug loading

Drug loading into a CL is usually through soaking method in which a dry lens is soaked in drug solution until complete swelling. It is thought that higher swelling will lead to enhance the loading of the drug. To choose the proper solvent that causes maximum swelling, SR% was studied for different solvents and solvent combinations. The results can be seen in Table 4.

Table 4. Maximum Swelling Ratio % of different formulations using different solvents and solvent combinations .

F code	Water	Buffer	Methanol	Ethanol	M:W	E:W	Acetonitrile
F1	45.41 ±0.95	47.1 0 ±1.11	97.06 ±1.12	83.47 ±0.85	160.02 ±1.27	166.38 ±0.97	58.29 ±1.07
F2	78.26 ±1.15	72.23 ±0.49	120.70 ±2.05	104.01 ±2.50	185.16 ±0.96	201.60 ±1.36	70.16 ±1.16
F3	79.42 ±0.59	73.23 ±1.05	181.55 ±1.03	132.10 ±1.55	218.41 ±1.02	275.61 ±2.16	76.14 ±1.25
F4	67.29 ±1.14	67.20 ±0.95	154.40 ±2.12	123.57 ±1.31	172.65 ±1.16	195.80 ±0.48	74.26 ±0.95
F5	65.39 ±0.91	64.57 ±0.41	115.3 ±0.65	113.41 ±1.40	161.57 ±1.45	190.40 ±0.85	65.26 ±1.71
F6	64.30 ±0.88	62.11 ±0.91	114.85 ±1.05	93.10 ±1.2	153.34 ±0.85	178.25 ±1.23	63.6 ±2.11
F1MI	50.16 ±1.05	52.45 ±1.21	98.36 ±1.06	83.93 ±1.51	160.52 ±1.48	169.10 ±1.21	59.06 ±1.20
F2MI	79.60 ±0.60	72.53 ±1.40	124.20 ±0.80	105.15 ±1.16	185.16 ±0.96	204.06 ±2.15	72.20 ±0.87
F3MI	80.28 ±0.88	76.01 ±0.95	187.26 ±1.06	133.80 ±1.70	218.60 ±1.32	275.17 ±2.01	77.29 ±1.10
F4MI	70.42 ±0.55	69.70 ±0.66	156.08 ±1.65	124.10 ±1.12	172.6 ±0.72	196.05 ±1.78	75.42 ±1.22
F5MI	69.89 ±0.86	67.34 ±1.19	117.30 ±1.10	115.48 ±0.89	161.30 ±1.05	192.06 ±0.85	65.58 ±1.20
F6MI	66.32 ±1.05	65.25 ±2.04	116.13 ±0.90	94.24 ±1.03	153.34 ±0.75	180.40 ±1.49	62.36 ±1.76

The water content of the F1, which is pHEMA, was (45.4 ± 0.95 %). The water content tended to increase as the amount of MAA increased. The highest water content is shown in F3 (79.42±0.59 %) which contains 8% MAA. Both EWC percent and SR (F2-F6) increased significantly ($p>0.05$) as the relative proportion of MAA increased. Furthermore, according to the statistical comparison of MICLs and conventional CLs there

was no significant difference in the percentage of swelling ($p > 0.05$).

As noticed in Table 4 water, buffer and acetonitrile had the lowest SR% compared to methanol, ethanol and their 1:1 combination with water.

The choice of the loading solvent depends not only on SR% but the solubility of the drug in that solvent. ITZ is class II drug that has a very low water solubility and good solubility in organic solvent[30]. However, when methanol:water and ethanol:water were used to prepare soaking solution, the solubility of the drug was not enhanced. The solubility of ITZ in buffer , buffer + 1 % SLS ,ethanol and in methanol was(1.79 ± 0.11),(48.35 ±1.62), (407.56± 1.36) and (772.49 ± 7.56) µg/mL respectively which is low for the purpose of the study[31]. The choice of the loading solvent depends not only on SR% but the solubility of the drug in that solvent. ITZ is class II drug that has a very low water solubility and good solubility in organic solvent (30, 31). Although the SR% was high in methanol, ethanol and their combination with water, the solubility of ITZ was lower than that required for loading(16). Acetonitrile was chosen as loading solvent because of the ITZ is freely high solubility of ITZ and relatively high SR% [32].The loading of both conventional lenses and MICLs can be seen in Table 5. MI significantly ($p<0.05$) enhance the loading of ITZ for all formulations. Formulation F3 with 8% MAA had the highest loading among other MAA percentages. The loading enhanced with increasing MAA% until 8% (F3). Increasing MAA to 10% did not further enhance the loading which could be due to saturation of the lens.

Table 5. The amount of drug loaded in each contact lens.

F code	F1	F2	F3	F4	F5	F6
Amount loaded µg/lens	**93.06 ±1.46**	**249.1 ±1.1**	**288.4 ± 0.7**	**219.8 ±0.63**	**174 ±0.9**	**146 ±0.95**
F code	**F1MI**	**F2MI**	**F3MI**	**F4MI**	**F5MI**	**F6MI**
Amount loaded µg/lens	**276.18 ±5.64**	**620 ±1.2**	**1077 ±0.9**	**662.60 ± 0.93**	**651.4 ±1.14**	**581.14 ±0.66**

Drug release

Treatment of ocular infections (viral, bacterial, and fungal) requires multiple applications of eye drops per day for several days, which reduces treatment efficacy due to poor patient compliance. Reducing instillation time is likely to improve patient compliance and treatment efficacy [33]. The release of ITZ from both conventional CLs and MICLs was studied in order to select the CL with the longest drug release. As shown in Figure 1, having a higher burst release than non MICLs. One possible explanation is that drug loading in MICLs is higher than in conventional CLs.

Although the release of all CLs prepared was prolonged, the amount of drug released in MICLs was greater than in conventional CLs due to higher loading. The amount released from MICLs was higher through the period of the release study (24 h) which will ensure that therapeutic effective concentration of the drug is available through the course of the treatment.

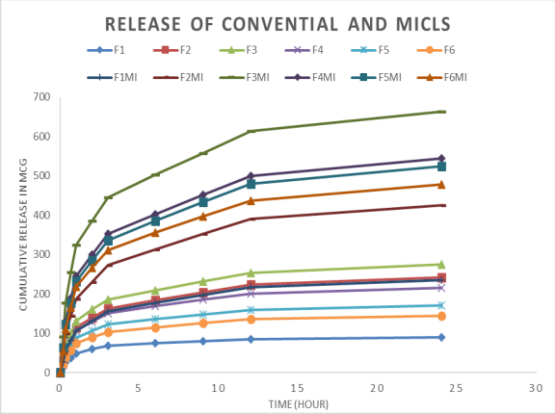

Figure 1. Cumulative release in mcg of ITZ from conventional and MICLs represents the release for 24 h.

Analysis of drug release kinetics

Various mathematical models, such as zero order, first order, and Higuchi, were used to fit in-vitro release data. Furthermore, using the Korsmeyer-Peppas model to experimental data and explaining the release exponent values (n) provides to a better understanding of the mechanism of contact lenses release. Table 5 shows the kinetic data of itraconazole CLs, and all formulations followed the first - order model for release, this means that the release of ITZ from each contact lens is determined by the concentration of the drug remaining in the lens. F1, F1MI, and F3MI, which used Higuchi mode, while F2MI only follow zero order release model.

Table 6. Release Kinetics of Itraconazole Contact Lenses

	Zero order		First order		Higuchi		Koresmyer_peppas		
Formula	R^2	K_0	R^2	K_1	R^2	KH	R2	KKP2	N
F1	0.566	1.904	0.718	0.019	0.773	11.53	0.841	39.536	0.265
F2	0.726	3.339	0.984	0.060	0.912	19.394	0.924	30.938	0.439
F3	0.768	3.303	0.988	0.079	0.939	18.929	0.976	35.620	0.367
F4	0.668	3.031	0.927	0.049	0.872	17.947	0.908	35.416	0.387
F5	0.685	3.290	0.969	0.057	0.884	19.414	0.909	31.002	0.450
F6	0.654	3.040	0.904	0.054	0.864	18.147	0.916	37.739	0.371
F1MI	0.591	2.27	0.701	0.021	0.816	13.85	0.893	29.308	0.38
F2MI	0.544	6.834	0.631	0.016	0.776	12.810	0.862	24.250	0.429
F3MI	0.581	1.750	0.680	0.013	0.797	10.621	0.860	27.694	0.331
F4MI	0.832	3.199	0.992	0.052	0.967	17.863	0.965	31.900	0.373
F5MI	0.808	3.228	0.989	0.049	0.958	18.211	0.975	31.024	0.389
F6MI	0.764	3.145	0.972	0.049	0.937	18.041	0.977	34.538	0.363

The values of n are found to be less than 0.5, which is compatible with processes in the water-containing hydrogel network that are largely governed by Fickian drug diffusion[34].

Conclusion

The aim of our work was to study the impact of MI on loading of poorly soluble drug into a hydrogel CL and the possibility of extended release of the drug. Different formulations with and without MI were prepared and studied regarding SR%, folding endurance, drug loading and release. In general all MICLs had significantly higher loading compared to conventional CLs.

Future work

1- Stability study of ITZ in the MICLs.
2- Study the effect of sterilization on ITZ release and MICLs properties.
3- In-vivo animal studies.

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