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Research paper

Ketotifen loaded solid lipid nanoparticles laden contact lens to manage allergic conjunctivitis

Tong Zhang [a,*,1], Tianhui Zhu [a,**,1], Fanyin Wang [b], Ling Peng [a], Mingying Lai [a]

[a] Shenzhen Eye Hospital, Shenzhen Eye Hospital Affiliated to Jinan University, Shenzhen Key Laboratory of Ophthalmology, Shenzhen Guangdong Province, 518040, China

[b] Shenzhen Nanshan District Shekou People's Hospital, Shenzhen Guangdong Province, 518067, China

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ABSTRACT

Contact lenses are idea medical device to sustain the release of anti-allergic ocular drugs like ketotifen along with added advantage to act as a physical barrier against airborne antigens. However, the conventional soaking method using ketotifen-packaging solution showed low drug uptake, high burst release and short release duration along with reduction in the optical transmittance and swelling properties of the contact lens. In this paper, ketotifen loaded pegylated solid lipid nanoparticles (p-SNLs) laden contact lenses were fabricated to overcome the issues related to eye drop solution (frequent instillation) and contact lens. The SLNs and p-SLNs soaked contact lenses showed high drug uptake and did not changed the optical, swelling and oxygen permeability of the contact lenses. The *in vitro* release data of the soaked contact lenses (SM-K) showed low drug uptake and short release duration (48 h). The SLNs/p-SLNs soaked contact lenses showed improved drug uptake and sustain ketotifen release up to 72–96 h. The most promising results were shown by direct SLNs/p-SLNs laden contact lenses, which showed sustain release up to 168–192 h (with low burst release). The contact lens was safe in ocular irritation studies and showed high tear ketotifen-concentration (rabbit eye model) in comparison to the eye drop solution. The work demonstrated the promising potential of pegylated solid lipid nanoparticles to deliver ketotifen without compromising the critical contact lens properties to treat and manage various ocular allergic conditions.

1. Introduction

In the last few decades, the incidents of ocular allergic reactions have increased worldwide [1,2]. The most common include seasonal allergic conjunctivitis, which is treated by anti-allergic eye drop solutions [3–5]. The eye drop dosage forms shows low ocular bioavailability due to rapid clearance from the ocular surface (low drug retention) which in turn need frequent dose administration affecting the routine life style of patients [6–9]. The issue can be addressed by using contact lenses as a medical device that can sustain the release of drug (post lens tear film), thereby increasing the drug residence time on the ocular tissue [10–13]. Several studies have demonstrated that the use of contact lenses can improve the ocular bioavailability of drugs [14–17]. The advances in nanotechnology, smart polymeric system and multimodal functionalities have boast the scientist to work on therapeutic contact lenses [18].

Mehta and team coated timolol loaded nanofibers on the contact lens and studied four different penetration enhancers and noted triphasic release profile for 24 h [19]. They also fabricated on-demand novel coated timolol-chitosan contact lens and observed Fickian diffusion for 10 h [20]. Ross and team fabricated contact lenses with dexamethasone-polymer film inside, which showed 200 times more drug-retinal concentration in comparison to the eye drop therapy [21]. Xu and coworker's loaded travoprost laden microemulsion in the contact lenses and observed improvement in the drug retention in the rabbit tear fluid for 48 h [22]. Xue and coworker's loaded olopatadine and observed significant improvement in the drug retention in comparison to the eye drop solution. The developed contact lens showed promising results in Schirmer strip test [23]. Li and coworker's casted diclofenac loaded β-cyclodextrin hyaluronan laden cross linked contact lens and noted improved wettability and sustained release for 72 h [24].

* Corresponding author.
** Corresponding author.
E-mail addresses: zhangtongsz@sina.com (T. Zhang), zth19910106@sina.com (T. Zhu).
[1] These authors contributed equally to this work.

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Torres-Luna loaded ketorolac tromethamine, diclofenac and flurbiprofen sodium in the contact lenses using Vitamin E as barrier to sustain the release of drugs for several days [25]. Ran and coworker's fabricated sparfloxacin and polyvinyl pyrrolidone loaded implant contact lenses to treat conjunctivitis effectively to substitute eye drop therapy [26]. Xu and coworker's loaded bimatoprost microemulsion and noted promising results to manage glaucoma [27].

The studies demonstrated the promising results, however, the key limitations for loading hydrophobic drugs like ketotifen includes changes in the critical contact lens properties like optical transmittance, oxygen permeability and swelling. The other issues related to contact lens includes low ketotifen uptake (soaking method), high burst release and short release duration. To address the above issues, the current paper fabricated ketotifen loaded pegylated solid lipid nanoparticles (p-SNLs) laden contact lenses to continuously deliver ketotifen to treat and manage allergic conjunctivitis. The ketotifen-SLNs and ketotifen-p-SLNs were prepared by solvent diffusion method and loaded in the contact lenses by soaking and direct loading techniques and evaluated for *in vitro* and *in vivo* studies.

2. Materials and methods

2.1. Materials

Ketotifen fumarate was gifted by Beijing Sjar Technology Development Co., Ltd. (Beijing, China). Trimyristin (TM), egg phosphatidylcholine (ePC), disteroyl-phosphatidyl-ethanolamine-N-poly (ethylene glycol)$_{2000}$ (EPG$_{2000}$-DSPE), Pluronic® F68 were purchased from Chemical Reagent Co., Ltd. (Shanghai, China). Other chemicals were of analytical grade. Ultra purified water was obtained from Millipore (MiliQ®, Spain).

2.2. Preparation of ketotifen containing SLNs and pegylated-SLNs

Ketotifen fumarate (pka = 8.43) was converted to ketotifen base by increasing the pH of the aqueous solution using 1 M NaOH and extracted using chloroform. Ketotifen loaded SLNs and pegylated-SLNs was prepared by solvent diffusion method in an aqueous system [28,29]. To prepare p-SLN, ketotifen, TM, ePC (lipid), and PG$_{2000}$-DSPE (phospholipid conjugated with surfactant), were mixed in a glass tube at the ratio of 6:100:30:3 (weight ratio) making total of 139 mg and sonicated (60% pulse frequency) for 1 h at 70 °C. The optimum composition was selected based on the preliminary data and previous studies [30]. One ml of Pluronic® F68 solution (aqueous phase, 0.1% w/v, at 70 °C) was added into the tube and sonicated for 2 h to get milky white homogenous emulsion. The emulsion was further homogenized using high pressure homogenizer (Emulsiflex EF-B3, Avestin Inc.) for 6 cycles (65–70 °C and 100 MPa). The hot emulsion was frozen by dipping into the liquid nitrogen and thawed (10 °C/min) at room temperature using water bath. The SLNs was prepared in a similar way by omitting PG$_{2000}$-DSPE in the lipid mixture.

2.3. Characterization of SLNs and p-SLNs

The hydrodynamic size and zeta potential of SLNs and p-SLNs was determined using Zetasizer (3000HS, Malvern Instruments Ltd., UK) after 100 times dilution in distilled water [31]. The morphological examination of SLNs and p-SLNs were observed by transmission electron microscopy (TEM, JEM-1200EX, JEOL, Japan). The suspension was placed on the copper grids and stained using phosphotungstic acid (2% w/v) [32]. The entrapment efficacy of ketotifen in the SLNs and p-SLNs were estimated by dispersing 10 mg of nanoparticles in deionized water (2 ml), followed by centrifugation in the eppendorf tube using cooling centrifugation (REMI instruments Ltd., India, 10000 rpm, 4 °C) for 30 min [33]. The supernatant was collected and the unentrapped ketotifen was quantified by HPLC using tri-ethylamine phosphate (0.04 M): methanol: tetrahydrofuran (55:43:2, pH 3.4) as the mobile phase and a GraceSmart column (RP-18, 250 × 4.6 mm, 5 μm, USA) equipped with a UV detector at 298 nm [34–36]. The entrapment efficacy (EE) was calculated by following equation.

$$EE\ (\%) = \frac{total\ drug - unentrapped\ drug}{total\ drug} \times 100$$

2.4. Fabrication of the contact lenses and SLNs/p-SLNs loading by soaking method

The monomer mixture composition used to fabricate the contact lenses are shown in supplementary material section 1 [37]. The monomers were mixed at room temperature in a vial using magnetic stirrer (50 rpm), followed by sonication for 5 min. The contact lenses with diameter 14.2 mm and base curve 6.5 mm were fabricated by cast molding technique. The monomer mixture was injected into the molds (polypropylene plastic mold) and exposed to ultraviolet transilluminator (360–370 nm for 20 min) for curing [38]. After curing, the contact lenses were removed from the molds and extracted (to remove unreacted monomers and residual crosslinking agent) individually in the boiling water (50 ml) for 1 h using glass vial (100 ml capacity).

The treated contact lenses were soaked at two levels of ketotifen (50 μg/ml and 100 μg/ml coded as SM-K-50 and SM-K-100 respectively) in simulated tear fluid (STF, which consist of 0.9% w/v NaCl and 0.015% w/v $NaHCO_3$ in water), followed by sterilization (121 °C, 103.4 kPa for 30 min) using autoclave. The soaking period was set for 10 d (according to preliminary trials). The SLNs was loaded by soaking the treated contact lenses in the packaging solution (2 ml) containing 100 μg/ml ketotifen equivalent SLNs (coded as SM-K-SLN-100), followed by sterilization. The soaking period was set for 10 d. Similarly, the p-SLNs was loaded at same strength and coded as SM-K-p-SLN-100. The levels were selected to load >25 μg ketotifen per contact lens.

The eye drop (0.025% w/v) dose of ketotifen is one drop twice a day (2 drops = 100 μL = 25 μg per d) [39,40]. The ocular bioavailability of eye drop solution is <5%, thus actual requirement is 1.25 μg per d for therapeutic effect. The ocular bioavailability with contact lens is >50% [21,41,42], therefore the required dose for contact lens will be 2.5 μg per d. The contact lens was designed for 10 d, thus the target loading is > 25 μg ketotifen per contact lens.

2.5. Fabrication of the direct SLNs/p-SLNs loaded contact lenses

The direct SLNs loaded contact lenses (DL-K-SLN-100) were fabricated by mixing 5 mg of ketotifen equivalent SLNs in 1 ml of monomer mixture to fabricate 100 μg ketotifen per contact lens. The contact lenses were casted, extracted and sterilized as discussed in the above section. Similarly, direct p-SLNs loaded contact lenses (DL-K-p-SLN-100) were fabricated, extracted and sterilized.

2.6. Characterization of the contact lenses

The swelling, optical transmittance and oxygen permeability of the contact lenses should not be altered owing to the presence of ketotifen or SLNs or p-SLNs. The percentage swelling of the contact lenses were monitored as increase in the weight of the dried contact lens (after removal from mold) placed into their respective packaging solution at room temperature (after extraction and sterilization), as follow:

$$Swelling\ (\%) = \frac{W_s - W_o}{W_o} \times 100$$

W_o and W_s represent the weight of the dry contact lens and swell contact lens (after removal from the packaging solution, as hydrogel) respectively. The optical transmittance of the fully hydrated contact lenses (after soaking period in case of soaking method) in their respective packaging solution was measured using UV–vis spectrophotometer

(Shimadzu, Japan) at 480 nm against deionized water [43]. The oxygen permeability of the fully hydrated contact lenses was measured using Createch permeometer (210T Model, Rehder Development Company, CA, USA) fitted with a cell in a 100% RH chamber. The intensity was recorded when the flat cell was stabilized and the dark current was measured and used to calculate the oxygen permeability [44]. The experiments were conducted in triplicate.

2.7. Quantification of ketotifen in the contact lenses

The ketotifen loaded contact lenses were individually shifted to a screw capped glass vials containing 10 ml of methanol (to extract drug) and agitated (100 rpm) for 24 h in an incubator shaker at 37 °C. The ketotifen was quantified by HPLC method at 298 nm after suitable dilution with mobile phase. The experiments were conducted in triplicate.

2.8. In vitro release study

The *in vitro* release of ketotifen from the contact lenses was performed by individual immersion of the contact lenses in a glass vial (30 ml capacity) containing 2 ml of media (STF) at 34 °C (to mimic the ocular surface temperature) under continuous stirring (100 rpm) using incubator shaker [45]. At regular time intervals, the media (2 ml) was replaced with the fresh media to simulate the sink condition. The ketotifen released was quantified by HPLC. The study was performed until no further increase in the ketotifen concentration during two successive reading was observed. The experiments were conducted in triplicate.

2.9. Animal studies

White New Zealand rabbits (1.5–3.5 kg) of either sex were approved (ethic Number: GCP0032-SOP004) by 'Shenzhen Eye Hospital Affiliated to Jinan University' (Shenzhen Guangdong Province, China). The animals were housed under standard laboratory conditions (25 ± 2 °C) with free access to water and food.

2.9.1. Ocular irritation study

The selected DL-K-p-SLN-100 contact lenses were evaluated for the ocular irritation test on the New Zealand white rabbits [46,47]. The contact lenses with cumulative 120 cm^2 surface area were cut and extracted individually in 20 ml of saline solution and 20 ml of sesame oil. The extraction period was 72 h with mild agitation at 37 °C. The individual extract (0.2 ml) were instilled (n = 6 for each extract) in the right eye (lower conjunctival sac) and the left eye was kept control (media without lens extract). The rabbit eyes were examined at regular intervals (1, 24, 48 and 72 h) using an auxiliary light source for ocular reactions and scored according to the USP and ISO system.

2.9.2. In vivo drug release study

The *in vivo* studies were performed to investigate the improvement in the ketotifen retention in the rabbit tear fluid using p-SLNs soaked contact lenses (SM-K-p-SLN-100, loading = 48.5 ± 2.5 μg cumulative release) and p-SLNs direct laden contact lenses (DL-K-p-SLN-100, 70.19 ± 1.7 μg cumulative release) in comparison to 0.025% w/v ketotifen eye drop solution (Ketof®, Ibn-Sina Pharmaceuticals Ltd.) [48–50]. After acclimatization of the rabbits, the contact lenses were placed on the rabbit cornea below the nictitating membrane (n = 6, left eye control). In case of eye drop solution, two drops (≈25 μg) were instilled on the right eye of rabbits (n = 6). At regular time intervals, 5 μL of tear fluid was collected (from the *cul de sac*) using disposable glass capillary and mixed with methanol (up to 1 ml) for protein precipitation, followed by centrifugation (10,000 rpm for 30 min). The supernatant was collected and quantified for ketotifen by LCMS (TSQ Quantum Access, Thermo Scientific, USA).

2.10. Statistical analysis

The statistical analysis was performed using SPSS 21.0 software for Windows. The independent two tailed *t*-test was used to compare the means between two groups.

3. Results and discussion

3.1. Characterization of SLNs and p-SLNs

The ketotifen loaded SLNs/p-SLNs were prepared using trimyristin, egg phosphatidylcholine, disteroyl-phosphatidyl-ethanolamine-N-poly $(ethylene\text{-}glycol)_{2000}$, and Pluronic® F68 by solvent diffusion method. The zetasizer reports (see supplementary material section 2) shows hydrodynamic size of ketotifen loaded SLNs as 221 nm (PDI = 0.195) and ketotifen loaded p-SLNs as 137 nm (PDI = 0.112). The PEGylation (presence of EPG_{2000}-DSPE) of solid lipid nanoparticles showed smaller size and improved polydispersibility index, which is preferred for soaking method for maximum nanocarrier uptake in the matrix of the contact lens. The zeta potential of SLNs and p-SLNs was - 23.11 ± 9.31 mV and - 20.21 ± 6.31 mV respectively (see supplementary material section 3), suggesting the stability of the nanoparticles in the packaging solution during storage. The six months stability data (data not shown here) confirmed the stability of nanoparticles (p-SLNs) in the packaging solution with contact lens (soaking method). The TEM images (see supplementary material section 4) of SLNs and p-SLNs showed spherical morphology with size similar to those observed by Zetasizer. The entrapment efficacy of SLNs and p-SLNs was found to be 81.44% and 79.15% respectively. The PEGylation did not showed significant effect ($p > 0.01$) on the entrapment efficacy.

3.2. Characterization of the contact lenses

The data of swelling, transmittance, and oxygen permeability are shown in Table 1. The percentage swelling of the control contact lenses was 97.9 ± 1.1%, while the conventional ketotifen soaked contact lenses (SM-K-50 = 89.4 ± 1.8% and SM-K-100 = 84.0 ± 1.5%) showed significant ($p < 0.01$) reduction in the swelling property due to hydrophobic nature of ketotifen. The ketotifen loaded SLNs/p-SLNs in the soaked contact lenses (SM-K-SLN-100 = 94.9 ± 1.5% and SM-K-p-SLN-100 = 98.8 ± 1.5%) did not altered the swelling property significantly ($p > 0.01$) in comparison to the control contact lenses, due to encapsulation of hydrophobic drug in the SLNs/p-SLNs. The similar results were noted in the direct SLNs/p-SLNs laden contact lenses (DL-K-SLN-100 = 99.7 ± 0.4 %and DL-K-p-SLN-100 = 101.4 ± 1.5%), which showed insignificant ($p > 0.01$) change in the percentage swelling in comparison to the SM-K-100 batch.

The percentage transmittance of the control contact lenses was 99.2 ± 0.4%, while significant ($p < 0.01$) reduction in the transmittance (SM-K-50 = 93.6 ± 1.3% and SM-K-100 = 89.9 ± 0.4%) was noted with conventional soaked contact lenses due to low solubility of ketotifen in the aqueous channels of the matrix of the contact lens (drug precipitation). The SLNs/p-SLNs soaked contact lenses and direct SLNs/p-SLNs laden contact lenses did not showed significant ($p > 0.01$) reduction in the transmittance value due to nano size of solid lipid nanoparticles. Thus, the encapsulation of ketotifen in the pegylated solid lipid nanoparticles prevents the alteration in the swelling and optical transmittance of the contact lenses.

The oxygen permeability of the control contact lens was 2.34 ± 0.06 × 10^{-14} mol/(m^2 s Pa), which significantly ($p < 0.05$) reduced by ketotifen loading [SM-K-50 = 1.99 ± 0.06 × 10^{-14} mol/(m^2 s Pa) and SM-K-100 = 1.78 ± 0.07 × 10^{-14} mol/(m^2 s Pa)] using ketotifen-packaging solution. However, the presence of ketotifen in SLNs or p-SLNs did not alter the oxygen permeability [2.10–2.27 × 10^{-14} mol/(m^2 s Pa)] statistically ($p > 0.01$). Thus, the SLNs or p-SLNs laden silicone contact lenses can be used for multiple days to treat ocular disease.

Table 1
Data of swelling, optical transmittance and oxygen permeability of the contact lenses. The values are shown as average (n = 3) ± standard deviation.

Batches	Swelling (%)	*p* value	Transmittance (%)	*p* value	Oxygen permeability [mol/(m^2·s·Pa)]	*p* value	Quantification data (μg)	*p* value
Control contact lens	97.9 ± 1.1	–	99.2 ± 0.4	–	2.34 ± 0.06	–	–	–
SM-K-50	89.4 ± 1.8	0.03	93.6 ± 1.3	0.01	1.99 ± 0.06	0.02	13.7 ± 2.1	–
SM-K-100	84.0 ± 1.5	<0.01	89.9 ± 0.4	<0.01	1.78 ± 0.07	0.02	24.3 ± 2.7	–
SM-K-SLN-100	94.9 ± 1.5	0.13	99.2 ± 0.7	0.63	2.14 ± 0.06	0.07	48.3 ± 2.9	<0.01[a]
SM-K-p-SLN-100	98.8 ± 1.5	0.13	99.4 ± 0.2	0.10	2.27 ± 0.05	0.19	53.7 ± 3.1	<0.01[a]
DL-K-SLN-100	99.7 ± 0.4	0.06	96.7 ± 0.6	0.02	2.10 ± 0.06	0.07	98.4 ± 0.9	–
DL-K-p-SLN-100	101.4 ± 1.5	0.01	98.9 ± 0.8	0.93	2.23 ± 0.05	0.07	99.0 ± 0.7	–

SM-K-50 = Soaked in 50 μg/ml ketotifen solution.
SM-K-100 = Soaked in 100 μg/ml ketotifen solution.
SM-K-SLN-100 = Soaked in 100 μg/ml ketotifen equivalent SLNs.
SM-K-p-SLN-100 = Soaked in 100 μg/ml ketotifen equivalent p-SLNs.
DL-K-SLN-100 = Direct SLNs loaded contact lenses (equivalent to 100 μg ketotifen loading).
DL-K-p-SLN-100 = Direct p-SLNs loaded contact lenses (equivalent to 100 μg ketotifen loading).
[a] The comparison is made with SM-K-100.

3.3. Quantification of drug in the contact lenses

The loading of ketotifen in the contact lenses are shown in Table 1. The ketotifen uptake from the drug-packaging solution with concentration 50 μg/ml (SM-K-50) and 100 μg/ml (SM-K-100) was found to be 13.7 ± 2.1 μg and 24.3 ± 2.7 μg respectively. SLNs soaked contact lenses (SM-K-SLN-100 = 48.3 ± 2.9 μg) and p-SLNs soaked contact lenses (SM-K-p-SLN-100 = 53.7 ± 3.1 μg) showed significant ($p < 0.01$) improvement in the uptake of ketotifen in comparison to conventional drug-packaging solution. The p-SLNs batch showed better uptake of nanocarriers in comparison to SLNs, due to smaller size and hydrophilic nature (PEGylation) of p-SLNs. The drug quantification data of DL-K-SLN-100 (98.4 ± 0.9 μg) and DL-K-p-SLN-100 (99.0 ± 0.7 μg) batches were close to the theoretical values of 100 μg, which suggest the compatibility of ketotifen (without degradation) during the fabrication process in the matrix of the contact lens.

3.4. In vitro release study

The cumulative release and release rate of ketotifen from the contact lenses are shown Fig. 1 and Fig. 2 respectively. The conventional soaked contact lenses showed high burst release (56.6–50.9 μg) with cumulative release up to 11.08 μg (24 h) and 23.52 μg (48 h) from SM-K-50 and SM-K-100 batches respectively. The cumulative and release rate profiles improved with increase in the drug-packaging solution (soaking solution) concentration due to higher drug uptake. However, the low swelling and optical transmittance values suggest the limitation of soaking method for ketotifen.

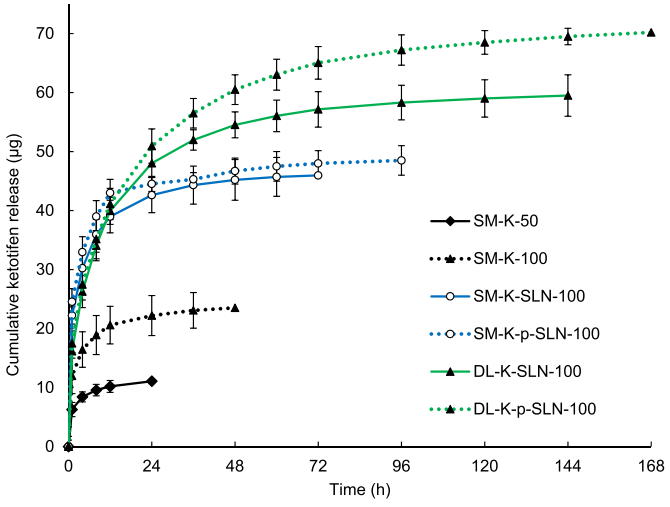

Fig. 1. Cumulative ketotifen release (μg) from the contact lenses (Mean ± standard deviation, n = 3).

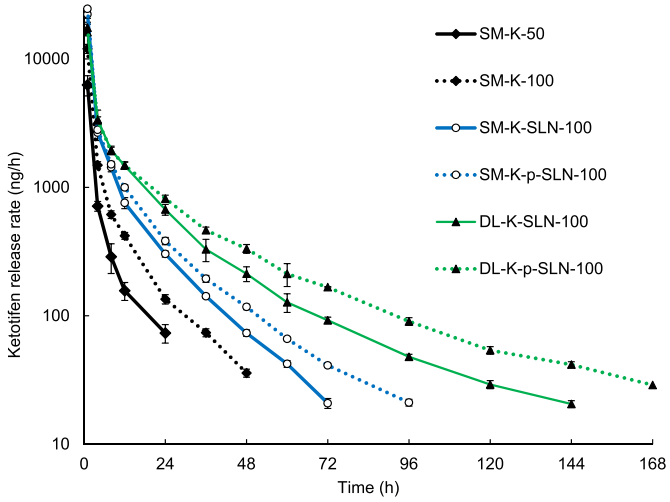

Fig. 2. Ketotifen release rate (ng/h) from the contact lenses (Mean ± standard deviation, n = 3).

The SLNs soaked contact lenses (SM-K-SLN-100) showed high burst release of 48.3% (22.22 μg), followed by sustain release up to 72 h (45.96 μg cumulative release). The p-SLNs soaked contact lenses (SM-K-p-SLN-100) also showed high burst release of 50.6% (24.55 μg) with cumulative release of 48.5 μg (96 h). The high burst release was due to loosely adhered nanoparticles on the surface of the contact lens. The SM-K-p-SLN-100 batch showed relatively higher sustained release in comparison to SM-K-SLN-100 batch due to higher uptake of nanocarriers (small size) because of the presence of PEG (hydrophilic nature). However, statistically it was not significant ($f_2 = 82.45$). The data suggest the potential of SLNs/p-SLNs to improve drug uptake and release rate profiles using soaking method.

In direct SLNs/p-SLNs laden contact lenses, the total amount of ketotifen leached during extraction and sterilization was 20.04 μg and 27.41 μg respectively for DL-K-SLN-100 and DL-K-p-SLN-100 batches. The higher loss of ketotifen with DL-K-p-SLN-100 contact lens was due to hydrophilic nature of p-SLNs. The direct SLNs/p-SLNs laden contact lenses showed low burst release (24.9–27.1%) in comparison to the SLNs/p-SLNs soaked contact lenses, which was due to entrapment of nanoparticles in the matrix of the contact lens creating tortuous pathway to diffuse ketotifen from the contact lens. The DL-K-SLN-100 and DL-K-p-SLN-100 batches showed sustain release up to 144 h (59.5 μg cumulative release) and 192 h (70.2 μg cumulative release) respectively. The higher release rate from the DL-K-p-SLN-100 batch was due to small size

of nanoparticles and its hydrophilic nature (PEG presence). The study demonstrate the potential of pegylated solid lipid nanoparticles to achieve prolong ketotifen release from the contact lenses.

3.5. Ocular irritation study

The ocular irritation studies were conducted on rabbit eyes to investigate the safety of DL-K-p-SLN-100 contact lens. The right eyes were treated with test extract and the left eye was kept control. The gross examination using auxiliary light source indicates no symptoms (see supplementary material section 5) of ocular irritation (conjunctival redness, chemosis, discharge, opacity of cornea, and swelling of iris muscles) in comparison to control eye at various time intervals.

3.6. In vivo drug release study

The *in vivo* study was performed to investigate the ketotifen release in the tear fluid (rabbit eyes) from the SM-K-p-SLN-100 and DL-K-p-SLN-100 contact lenses and compared with the 0.025% w/v ketotifen eye drop solution. The C_{max} of ketotifen from the eye drop solution, SM-K-p-SLN-100 and DL-K-p-SLN-100 contact lens was found to be 57.0 ± 18.3 μg, 581.6 ± 152.7 μg and 445.7 ± 85.3 μg respectively (Fig. 3). The eye drop solution eyes showed low C_{max} and rapid fall in the ketotifen concentration in the rabbit tear fluid, with no drug detected after 1 h due to rapid clearance of drug from the ocular surface. The SM-K-p-SLN-100 and DL-K-p-SLN-100 contact lenses showed prolong drug retention in the rabbit tear fluid, with drug detected up to 48 and 96 h respectively. The direct p-SLNs laden contact lenses (DL-K-p-SLN-100) showed low C_{max} and high drug concentration at all-time points (except 5 and 10 min) in comparison to the p-SLNs soaked contact lenses (SM-K-p-SLN-100) due to entrapment of nanocarriers in the matrix of the contact lens. The analysis of IVIVC (*in vitro – in vivo* correlation) is mandatory to investigate the ability of the *in vitro* flux characteristics to forecast the *in vivo* performance of contact lenses. The contact lenses showed linear relationship [SM-K-p-SLN-100 (R^2 = 949) and DL-K-p-SLN-100 (R^2 = 0.930)] between the *in vitro* drug release and drug retained in the rabbit tear fluid (see supplementary material section 6).

4. Conclusion

The paper demonstrated the potential of ketotifen loaded pegylated solid lipid nanoparticles laden contact lenses to prolong the release of drug without changing the critical lens properties. The SLNs and p-SLNs soaked contact lenses did not reduced the swelling, optical transmittance and oxygen permeability of the contact lenses. The SM-K batch showed low drug uptake and short drug release profile (48 h), while the SLNs/p-SLNs soaked contact lenses showed improved drug uptake and sustained release up to 72–96 h. The direct SLNs/p-SLNs laden contact lenses showed sustain release up to 168–196 h with low burst release. The DL-K-p-SLN-100 batch showed high ketotifen-tear concentration in comparison to the SM-K-p-SLN-100 batch and eye drop solution. The work conclude that the concept of incorporating the ketotifen loaded pegylated solid lipid nanocarriers in the matrix of the contact lens confers its potential to improve the critical lens properties along with sustained drug release to treat and manage various ocular allergic conditions.

Author statement

Tong Zhang: Conceptualization, Validation, Investigation, Writing - Review & Editing **Tianhui Zhu:** Conceptualization, Validation, Investigation, Writing - Review & Editing **Fanyin Wang:** Investigation, Resources, Writing - Original Draft **Ling Peng:** Formal analysis, Writing - Review & Editing **Mingying Lai:** Methodology, Project administration, Data Curation, Visualization, Supervision

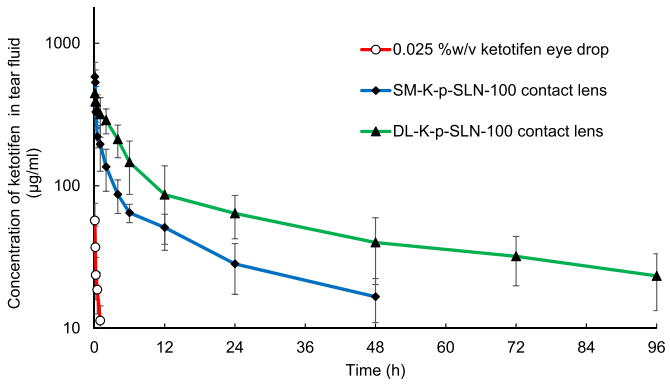

Fig. 3. *In vivo* release of ketotifen in the tear fluid from the contact lenses (Mean ± standard deviation, n = 6).

Declaration of competing interest

The authors declare no known competing financial interest that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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