Hydrogel Contact Lense for Extended Delivery of an Anti-Biotic in Combination with Anti-Inflammatory Drug for Ophthalmic Application

Chethana SR and Mohammed Gulzar Ahmed*
Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara, India.

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ABSTRACT :
The main objective of present study is to formulate and evaluate hydrogel contact lenses of sparfloxacin and diclofenac sodium by using HEMA (hydroxyl ethyl methacrylate) and 4- Vinyl pyridine (monomers) for the treatment of ocular infections. Sparfloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. The incorporation of ionic/hydrophobic monomer would increase the interaction between hydrogel and drugs so that drugs will take long time to diffuse from the hydrogel. The developed formulations were evaluated for water content, center thickness, in–vitro drug release and stability studies. Compatibility study performed by FT-IR method showed no interaction between drug and other excipients. Water content of formulations S1, S2 and S3 were found be 4.2, 3.2 and 4.1% respectively. Centre thickness of the formulations S1, S2 and S3 was found to be 6.6, 6.5 and 6.4µm respectively. Drugs are delivered by soaking the contact lenses in drug solution to load the drugs. In-vitro release study revealed that release rate of drug from hydrogel contact lenses dependent on concentration of 4-polyvinyl pyridine. The antimicrobial studies against p.aureginus were performed for the formulation S2 which showed more drug release compared other formulations. All the results were found that pure drug has more bacterial inhibition activity initially compared to formulation S2. Thus, it can be concluded that formulation S2 containing 0.5% w/v of 4-poly vinyl pyridine as monomer was considered as an optimized formulation, as it provided sustained release of the drug for the treatment of ocular infections.

Keywords: Hydrogel contact lens, Sparfloxacin, diclofenac sodium, HEMA, 4-Vinyl pyridine.

INTRODUCTION:

Amongst the various routes of drug delivery, the field of ocular drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist for past 10-20 years. Eye is an isolated organ, and it is very difficult to study from a drug delivery point of view. From last few years, in response to the advent of potent and versatile therapeutic agents, the diversity of conventional ophthalmic formulations has gradually evolved, extending well beyond simple solutions, ointments, and suspensions, now includes a variety of types of drug administration [1].

On the ground of anatomy and physiology eye is a complex and incomparable structure and guarded by a number of defensive attitude machineries. The physiology of the eye set down this organ tremendously impervious to strange entities. Eye is guarded by noxious entities and agents such as lacrimation, reflex blinking, rapid tear turnover drainage, and pre-corneal loss concludes in remarkably inadequate absorption of topically executed ophthalmic drugs [2].

Hydrogels are water-swollen polymeric materials and it can absorb a large amount of water. As poly-hydroxy ethyl methacrylate (pHEMA) hydrogels were first prepared as soft contact lenses in the 1960s, the hydrogel contact lenses have been used to deliver ophthalmic drugs. However, the conventional contact lenses have some limitations in the application of long therapy due to fast release rate of drugs and low loaded drug amount. In order to increase the potential capacity of hydrogel to load drugs and prolong the sus-

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*Corresponding author:
Dr. Mohammed Gulzar Ahmed,
Professor and Head, Department of Pharmaceutics, S.A.C. College of Pharmacy, B.G. Nagar, Karnataka, India.
Tel: +91-8234-287870. 9448401238 (m).
E.mail : mohammedgulzar1@gmail.com

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tained release time of drugs, hydrophobic monomer such as 4-vinylpyridine (VP) or ionic monomer such as N-(3-aminopropyl) methacrylamide (APMA) was incorporated to pHEMA hydrogels. The incorporation of ionic/hydrophobic monomer would enhance the interaction between hydrogel and drugs had more difficulties diffusing from the hydrogel [3].

Most conventional hydrogel contact lenses were used to deliver the ophthalmic drugs by soaking the contact lenses in solution of drug to load the drugs, applying eye drops on contact lenses after being inserted into eyes, or incorporating the drugs into the monomer of hydrogel contact lenses. Recently, supercritical fluid (SCF) assisted method was used to increase the drug loading amount in hydrogel contact lenses and to control their release. The sustained release time of drugs using the above mentioned methods is no longer than 24h, which is not suitable for extended drug delivery. In recent years, many strategies are operated to modify the conventional contact lenses for extended drug delivery with the emergence and development of novel hydrogel contact lenses.

Antibiotic agents are always exhibit either bactericidal or bacteriostatic in nature. When bacteriostatic drugs are used to treat ocular infection, the host defence mechanisms are ultimately responsible for clearing and eradicating the infective organism. In bacterial keratitis, the infection develops in the vascular cornea, and in and endophthalmitis it develops in the fluid-filled aqueous or vitreous cavity. In either case, the immune system may be unable to control the organism fast enough to prevent sight-threatening sequelae. With the first 24 hours pathogens may multiply and release toxins and degradative enzymes that destroy the function and integrity of ocular tissue. Thus, bactercidal drugs are preferred for the treatment of severe ocular infection. The penicillins, cephalosporins, aminoglycosides, and fluoroquinolones are bactericidal agents and are generally used to treat ocular infection. Tetracycline, erythromycin, chloramphenicol, and sulphonamide are bacteriostatic and are often reserved for less severe infections or where there is a specific benefit such as tetracycline in the treatment of ocular rosacea [4].

Sparfloxacin is a newer- generation hydrophobic fluroquinolone used in the bacterial conjuctivitis. The poorly water soluble drugs are difficult to develop as a conventional ocular drug delivery system. Sparfloxacin is reported to be more active *in vitro* than ciprofloxacin against mycobacteria and gram-positive bacteria, including streptococcus pneumonia and other streptococci and staphylococci [5].

Ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used by clinical to manage ocular inflammation and pain. Diclofenac sodium is a non-steroidal anti-inflammatory drug which acts specifically on inflammatory sites and there by decreases the inflammation. It is also used as 0.05% and 0.1% eye drops for the inhibition of intraoperative miosis (but it does not possess intrinsic mydriatic activity) and to prevent post-operative inflammation in cataract surgery [6].

Hence an attempt has been made in the present work to design a novel contact lenses based hydrogels for extended ophthalmic drug delivery containing the combination of an anti-biotic with an anti-inflammatory agents.

MATERIALS AND METHODS

Materials

Sparfloxacin and diclofenac sodium were purchased from yarrow drugs and chemicals pvt .Ltd. All other polymers and reagents used were of analytical grade.

Methods

Solubility

Solubility is an important consideration in ophthalmic formulations as clarity of the solution is an essential requirement. The solubility of sparfloxacin and diclofenac sodium was tested in various solvents such as distilled water, ethyl alcohol, propanol and acetone. The drug was added in maximum amount in the respective solvent selected till the saturation is seen. Filtered the saturated solution and made dilutions as required. The solubility was determined by measuring the absorbance at 291 nm for sparfloxacin and at 276 nm for diclofenac sodium by using UV-Visible spectrometer[7,8].

Compatibility studies

The compatibility studies of the drug with polymers are studied using FT-IR spectroscopy. The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug [7,8].

Preparation of Hydrogel Contact Lens

2HEMA with a fixed weight percentage of ethylene glycol methacrylate (EGDMA) as a cross linker was polymerized with Benzoin isobutyl ether as a UV sensitive initiator. Varying amounts of 4-polyvinyl pyridine was added as co-monomer and deionized water was added finally. The mixture was gently stirred for approximately 20 minutes. The formulation was then cast into flat moulds that were clamped shut using a stainless steel clam assembly designed to hold 10 flat moulds at a time. Then it will keep in water bath for longer period at 72^0C polymerization. After polymerization was complete, the hydrogel disc was carefully removed from the moulds and formulation design showed in table no1[9].

Drug loading

Prepared lens were placed into 4ml of 0.3% (3000 µg/ml) sparfloxacin and 0.1% (1000 µg/ml) solution prepared in acetate buffer (pH 4.0). Then the lenses

were autoclaved, and allowed to take up drugs from the solution for one week, the amount of drugs loaded into the lenses was determined using fluorescence spectrometry in comparison with previously generated standard curves. (excitation wavelength 291nm (sparfloxacin) and 276nm (diclofenac sodium)[10].

Characterization of hydrogel contact lens Water content

The water content was determined by taking the weight of wet and dry lenses using the gravimetric method. Where the change in weight as the lens was heated to 105^0c over the course of 7 minutes was correlated to the water content of the lens[10].

Center thickness

The advancing contact angle, a measure of the surface wettability was determined using the sessile drop method employing the optical contact analyzer. A fully hydrated lens was removed from the PBS soaking solution, and the surface dried on lens paper for 20 seconds before being placed on a custom-designed lens holder. Then, 5ml of high performance liquid chromatography (HPLC) water was dispensed from a syringe, captured using a speed camera. The contact angle between the settled drop and the lens surface was analyzed using custom software [10].

***In vitro* drug release**

After loading the drugs the lenses were removed from the acetate buffer and the surface dried before being placed into 2ml of phosphate buffer solution (PBS). Then PBS was removed at set intervals over the course of 24 hours, and concentration of sparfloxacin and diclofenac sodium determined by spectrophotometer and released curves are obtained[10].

Drug release kinetics

Investigation for the drug release from the hydrogel contact lens was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsemeyer Peppas model [10].

Antimicrobial efficacy studies

Test lenses were removed from the loading solution and briefly dipped in PBS before being added to 2ml of nutrient agar seeded with 0.2ml of *p.aeruginosa*. Then, 0.1 ml was sampled hourly into neutralizing broth, and serial dilutions plated on nutrient agar plates. The plates were incubated at 34^0 C 18 hours before counting for colony forming units (CFU). The lenses were removed from solution after 24 and 48 hours, briefly dipped in PBS, and placed into fresh bacterial solutions, and the procedure repeated[10].

Stability studies

Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. The samples were stored at different storage conditions of elevated temperature at RH of 75%. The samples were withdrawn at 7 days interval for 2months and were evaluated for Water content, Center thickness Drug content and *In vitro* drug release[10].

RESULTS

Compatibility studies

Infrared spectra of pure drug Sparfloxacin and combination of drug with polymers (HEMA and 4-vinyl pyridine) were obtained and the profile is shown in figure 1. All the characteristic peaks of sparfloxacin were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of drug. All the characteristic peaks of diclofenac sodium and combination of drug with polymers were obtained and shown in figure 1. Diclofenac sodium was present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers.

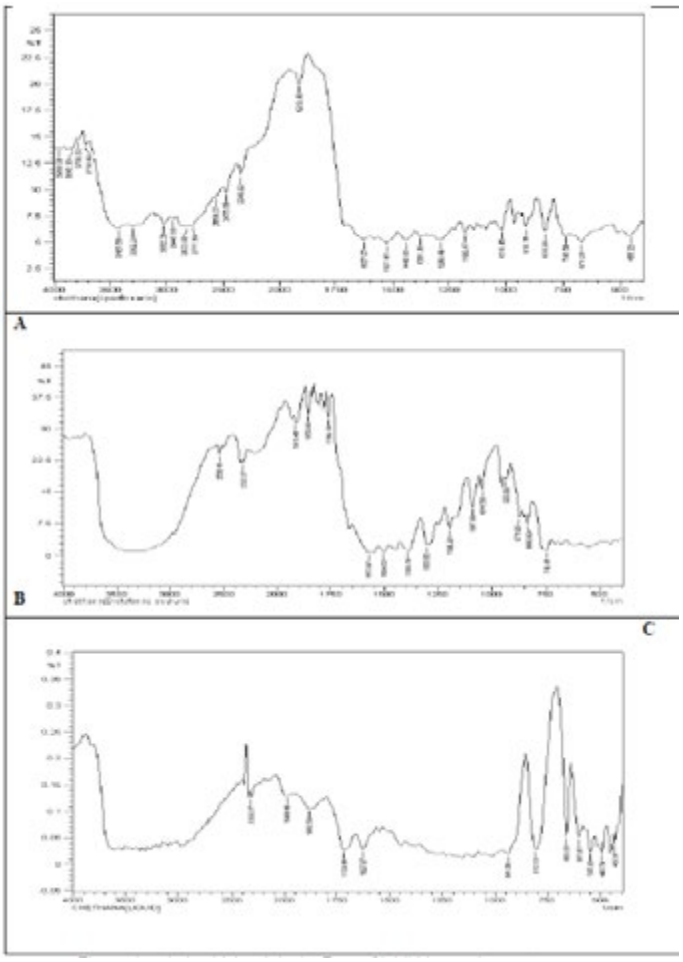

Figure :1 antimicrobial activity by Zone of inhibition against *p. Aeruginosa* **A) sparfloxacin (pure drug) B) Formulation S2**

Evaluation of contact lenses

The water content and centre thickness of all the formulations S1, S2, & S3 were done and the results were shown in table 2.

Drug content of hydrogel contact lenses

The drug content estimation was done and the absor-

bance was measured by UV spectrophotometer (Shimadzu UV"1800), drug content was calculated. Drug content of all formulations S1, S2, & S3was found 93.36, 96.16, & 95.54% respectively and it is represented graphically shown in figure 2.

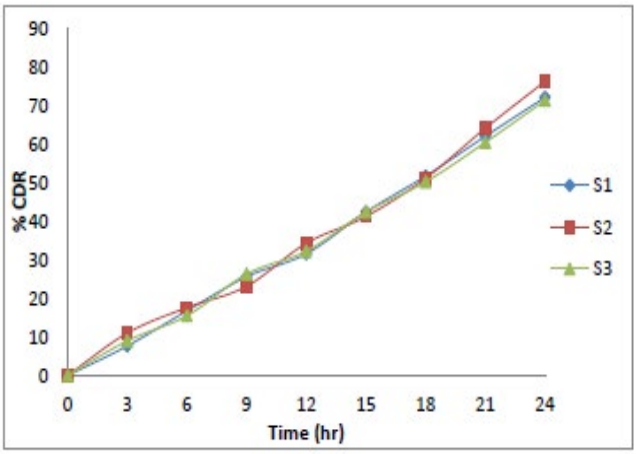

Figure 2: *In vitro* **release studies**

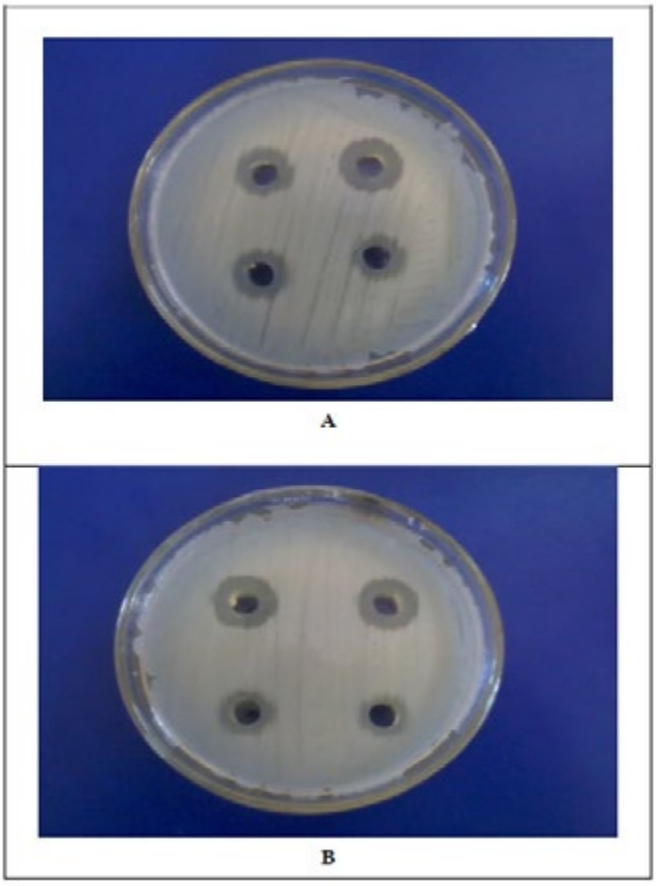

Figure 3 antimicrobial activity by Zone of inhibition against *p. Aeruginosa* **A) sparfloxacin (pure drug) B) Formulation S2**

Release kinetics:

The examination of the correlation coefficient 'r' indicated that the drug release followed diffusion controlled mechanism from the hydrogel contact lens, as the values of 'r' for first order (ranged from 0.910 to 0.95) found to be less in comparison to zero order (ranged from 0.997 to 0.983) and Higuchi's square root of time (ranged from 0.89 to 0.96). It was understood to be predominant zero order release pattern. Further, to understand the drug release mechanism, the data were fitted into Peppas exponential model $M^t/M^\infty=Kt^n$, where M^t/M^∞ is the fraction of drug released after time 't' and 'K' is kinetic constant and 'n' is release exponent which characterizes the drug transport mechanism. The values 'n' were in the range of 0.81 to 1.3 and the results were shown in table 3.

Microbiological studies of sparfloxacin

The microbiological studies of sparfloxacin imprinted lenses compared with pure drug has done and results were showed in table 4

Stability studies

The stability studies were carried out for prepared hydrogel contact lenses. All the formulations were analysed for visual appearance, water content, wet and dry weight, center thickness, drug content and *in vitro* release studies. 8 weeks of stability studies revealed that there was no change in visual appearance center thickness, and water content. All the studies pertaining to drug content and *in vitro* drug release revealed that there was no definite change observed to justify for drug degradation.

Ingredients	Quantity in 1ml (w/v)%		
	S1	S2	S3
Sparfloxacin	0.3	0.3	0.3
Diclofenac sodium	0.1	0.1	0.1
2hydroxy ethyl methylate % W/V	0.89	0.89	0.89
4-polyvinyl pyridine %W/V	0.3	0.5	0.7
Ethylene glycol dimethacrylate	0.5	0.5	0.5
Benzoin isobutyl ether	0.5	0.5	0.5
De-ionized water	q.s	q.s	q.s

Table 1: Formulation design of hydrogel contact lenses

Formulation code	Water content (%)	Centre thickness (μm)
S1	40.2(4.2)	6.6(16)
S2	35.2(3.2)	6.4(15)
S3	44.3(4.1)	6.5(15)

Table 2: Water content and centre thickness

Formulation Code	KINETIC MODELS				
	Zero order	First order	Higuchi	Korsmeyer *et al.*	
	R^2	R^2	R^2	N	R^2
S1	0.987	0.939	0.887	1.09	0.987
S2	0.978	0.901	0.926	0.81	0.965
S3	0.987	0.940	0.955	0.95	0.983

Table3: Release exponent values and rate constant values for different formulations.

Name of the Microorganisms 50 (µg/ml)		Zone of inhibition (Diameter(mm)			
		100 (µg/ml)	150 (µg/ml)	200 (µg/ml)	
P. aeruginosa	Pure drug	14	18	24	28
	S2	9	14	21	24

Table 4: Anti bacterial activity of Sparfloxacin on *p.aeruginosa* microorganisms

DISCUSSION

FT-IR spectrum

The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug. It was found that all the polymers were compatible with pure drug of sparfloxacin and diclofenac sodium.

EVALUATION OF HYDRO GEL CONTACT LENSES

Water content

The water content and wet and dry weight of lenses were determined and it was found that the formulation S3 was showing more water content compared to S1&S2 and S2 was showing very less water content compared to another formulations.

Center Thickness

Center thickness of all formulations S1, S2 & S3 were determined and it was found that the formulation S3 was showing more thickness compared to S1&S2 and S2 was showing very less thickness compared to other formulations.

Drug content:

Drug content of all formulations was found between 95.1 to 97.23 % w/w. And the formulation S2 was showing more percentage of drug content compared to other formulations.

In vitro release studies

The *in vitro* diffusion profile of Sparfloxacin and diclofenac sodium from the hydrogel contact lens containing different concentration of HEMA and 4-vinyl pyridine is shown in fig 15. Formulation S1 (HEMA 0.89% & 4-vinyl pyridine 0.3%) have shown least drug release (72.1%) in 24 hrs compared to formulation S3 (HEMA 0.89% & 4-vinyl pyridine 0.7%) that is (71.3) and formulation S2 (HEMA 0.89% & 4-v 0.5%) have shown maximum drug release (77.3 %).

Release kinetics:

The correlation coefficient 'r' indicated that the drug release followed diffusion controlled mechanism from the hydrogel contact lens as the values of 'r' for first order (ranged from 0.910 to 0.95) found to be less in comparison to zero order (ranged from 0.997 to 0.983) and Higuchi's square root of time (ranged from 0.89 to 0.96). It was understood to be predominant zero order release pattern.

Antimicrobial activity studies:

The as tested MIC of the *P. aeruginosa* strain 6294 was 0.4 µg/ ml. All lenses loaded with 0.3% sparfloxacin were able to inhibit the growth of bacteria completely for the first two days, suggesting that inhibitory amounts of the antibiotic were being released from the lenses. The ability of the lenses to inhibit the growth of *P. aeruginosa* strain 6294 in nutrient agar media on the third day there was an initial decrease in concentration of bacteria as the final reserves of sparfloxacin were released from the lenses. The rate at which the number of viable bacteria was decreasing is indicative of concentration of antibiotic in solution, suggesting that the pure drug is initially reaches a higher concentration than the imprinted lenses (S2). And it is shown in fig no: 2 A (sparfloxacin pure drug) B (formulation S2).

Stability studies:

8 weeks of stability studies revealed that there was no change in visual appearance, centre thickness, and water content. All Study of drug content and *in vitro* drug release revealed that there were no definite changes observed to justify for drug degradation.

CONCLUSION:

The present work is an attempt to develop sustained ocular delivery of sparfloxacin from hydrogel contact lenses. The study has demonstrated various aspects and from the results obtained, it was concluded that sparfloxacin shows broad antibacterial activity against Gram-positive bacteria. Diclofenac sodium shows anti-inflammatory activity against inflammation in hydrogel contact lens formulation of Sparfloxacin and diclofenac sodium is useful to prolonging pre-corneal residence time in eye. The developed formulation can release the drug at controlled rate for prolonged duration.

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