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Formulation development and compatibility study of ofloxacin ophthalmic solution in various packaging containers

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ABSTRACT

The ophthalmic solution with minimum concentration of preservative preparation in an appropriate packaging material appears to be most attractive approach for the process development and scale-up point of view. A simple high performance liquid chromatographic (HPLC) method for the simultaneous determination of ofolaxin in eye drops formulation was presented. Benzalkonium chloride in concentrations from 0.1% to 0.0001% induced dose-dependent growth arrest and conjunctival epithelial cell death, either delayed or immediately after administration The HPLC separation was undertaken on a inertsil C18 column using a mobile phase of water for injection. Compatibility study was assessed through measurement of factors affecting column peak symmetry, calculated using peak area and peak height of chromatogram. Assay decreased from 104 % to 102.89 % in three pieces to 101.27% in BFS, and 102.24 in glass container. Chromatographic analytical data indicated the stability of parenteral preparations in containers good enough till three months.

Introduction

Second-generation fluoroquinolones derivative ofloxacin is an important group of synthetic antibiotics with antibacterial action shown in fig.1 [1]. Ofloxacin are widely used to prevent diseases both to treat human and veterinary complications [2]. Ofloxacin is also available for topical use inform of ocular and intraocular drug delivery [3]. Ofloxacin was developed as a broader-spectrum analog of norfloxacin which inhibits DNA gyrase, a type II topoisomerase, and topoisomerase IV [4].

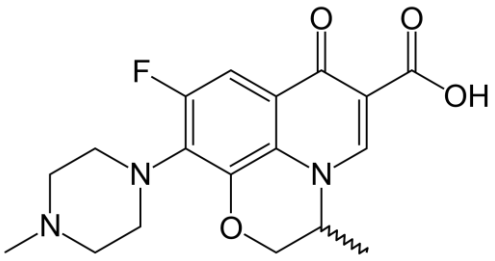

Figure 1. Chemical structure for ofloxacin.

The ofloxacin MICs were inoculum dependent and ranged from 0.03 to 0.125 microgram/ml against L pneumophila and 0.2 to 0.8 µg/ml against *B. anthracis* [5]. fluoroquinolones suffer degradation processes by UV irradiation that Depending chemical and environmental conditions, such as the instrumental irradiation parameters and irradiation time and byproduct production [6]. Drugs are administered to the eye for local effects such as bacterial infection, miosis, mydriasis, or to reduce intraocular pressure [7]. Every ophthalmic product must be sterile in its final container to prevent the microbial contamination of the eye [8]. Ofloxacin shows good activity against Chlamydia and Mycoplasma.Other susceptible organisms include – Enterobacter, E.coli, H.influenzae, K.pneumonae, N.gonorrhoea, Proteus, Pseudomonas aeruginosa, Staph.aureus, Step. pneumonae, Step. pyogens, anaerobes such as Bacteroides spp. Clostridium spp, Gardnerella vaginelis, Peptostreptococcus spp. [9]. There is an optimum pH level at which the solution of individual drugs should be buffered in order to obtain the maximum efficiency and stability [10]. Containers commonly used for ophthalmic products include glass containers, and polyethylene containers. Glass containers and polyethylene containers are said to be superior in maintaining stability of ophthalmic preparations [11].

The purity of a medicinal preparation may also change during storage due to leaching of chemical or chemicals into the drug preparation from the container materials, from the labels on the containers, or from the environment where the packaged ophthalmic product is stored. Thus, containers used for packaging medicinal preparations can significantly affect the stability and purity of the preparations. Ophthalmic preparations are similar to parenteral dosage form in their requirements for sterility as well as consideration for osmotic pressure (tonicity), preservation, and tissue compatibility, avoidance of pyrogens and particulate matter and suitable packaging.

Materials and Methods

Rawmaterial

Ofloxacin USP provide by Shanghai pharma (Pukang, China). Benzalkonium chloride USP, Disodium EDTA USP, Sodium chloride USP, Sodium hydroxide USP and Hydrochloric acid USP were obtained from Merck Ltd. (Mumbai). Growth Media and Neutralizer media were obtained as gift sample from High Media (Mumbai). Three piece containers and BFS containers were provided by Rexam (Bangalore). Glass containers was obtained from Kaisha

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Manufacturers Pvt.Ltd.(Mumbai). Water for Injection USP was used in all of experiments.

Spectrophotometric Analysis

The spectrophotometric analysis of all Ofloxacin samples in 0.1 M hydrochloric acid was performed at 440 nm is not greater than 0.25. (1700, Pharmaspec, Shimadzu,Japan).

Preparation of ofloxacin ophthalmic solution

The proposed formula was optimized by varying the concentration of benzalkonium chloride (BAK). The quantities of ofloxacin and other excipients were kept constant. Briefly the optimized concentration of BAK was formulated for ofloxacin (0.3%) ophthalmic solution. Batches were planned by taking different concentrations viz.0.0 % v/v, 0.01 %, 0.012%, 0.016%, and 0.02% ,0.024 % v/v of BAK, ofloxacin 0.3%, disodium EDTA, sodium chloride, sodium hydroxide and hydrochloric acid to adjust pH between 6.3 and 6.5 and volume was made up by water for injection as shown in Table 1.

Preservative Efficacy Test for Ofloxacin 0.3% Ophthalmic Solution

The concentration of an added antimicrobial preservative can be kept at minimum if active ingredients of the formulation possess an intrinsic antimicrobial activity. Sample from all six batches were subjected to preservative efficacy test of benzalkonium chloride in Ofloxacin 0.3% ophthalmic solution. The most stringent criteria of British pharmacopoeia was followed for experiment.

Results and discussion

In stability/container compatibility study drug product was evaluated for assay of Ofloxacin at initially, stress condition and at accelerated condition shown in Fig.2. Analysis was done by using HPLC. The chromatograms for ofloxacin reported from Fig.2 to Fig.4. Assay of ofloxacin was evaluated at initial, at stress condition and at accelerated condition. Initially assay of ofloxacin was found to be 102.7 %. At stress condition of temperature (60^0C) up to two week assay decreased to 101.97% in three piece container to 100.33% in BFS container; to 98.70 in amber colored glass container. At accelerated condition of temperature and relative humidity (40°C± 2°C/ NMT 25 % R H for plastic and 40°C± 2°C/ NMT 75 % RH for glass container) assay was estimated up to three months. Assay decreased to 101.14 in Three piece container, to 99.31 in BFS container and to 97.81 in Glass container up to the three month. Significant loss in assay was found in glass and BFS (3020 D) container as compared to three piece container (PE 1840 H). Loss of ofloxacin may be due to chemical interaction of cross linking present in the MOC of container with the components of drug product. Possibility is that the attachment of carbon atoms from ofloxacin to long polymeric chain of carbon present in MOC. Another possible reason is that entrapment of Ofloxacin molecule in to the complex entanglement of polymer chain. In case of glass containers, interaction of rubber closure with product may responsible for the loss of drug by adsorption and/or chemical reaction.

Initial

Initial (a), stress condition (b)

Assay of ofloxacin was evaluated at initial, at stress condition and at accelerated condition. In fig.3 at stress condition of temperature (60^0C) up to two week assay decreased from 104 % to 102.89 % in three piece to 101.27% in BFS, and 102.24 in amber colored glass container. At accelerated condition of temperature and relative humidity (40°C± 2°C/ NMT 25 % R H for plastic and 40°C± 2°C/ 75 ± 5% RH for glass container) assay was estimated up to three months as per Table.2. Significant loss in assay was found in glass and BFS container (100.05) as compared to three piece container. Benzalkonium chloride has the tendency for adsorption on to the surface of plastic. From the results it has been found that up to third month in accelerated condition drop size of BFS containers (40.72 µL) was comparatively more increased than Three piece container (35.03 µL). Increase in drop size may be caused due to widening of the nozzle aperture or thinning of the solution. In case of BFS container whole structure is intact made of same composition of polymer. Nozzle aperture causes increase in the drop size of BFS container.

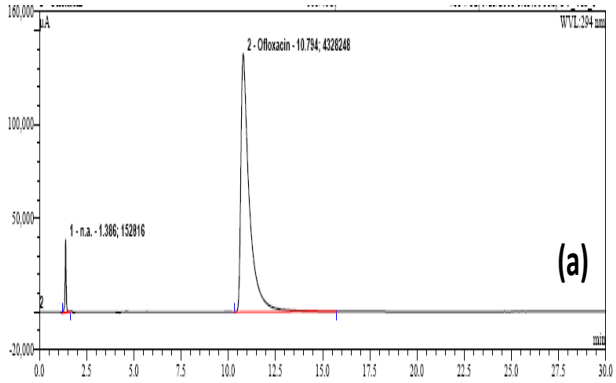

Fig 2: Chromatograms for ofloxacin assay at Three piece container

Water Loss Study- Three Piece Containers

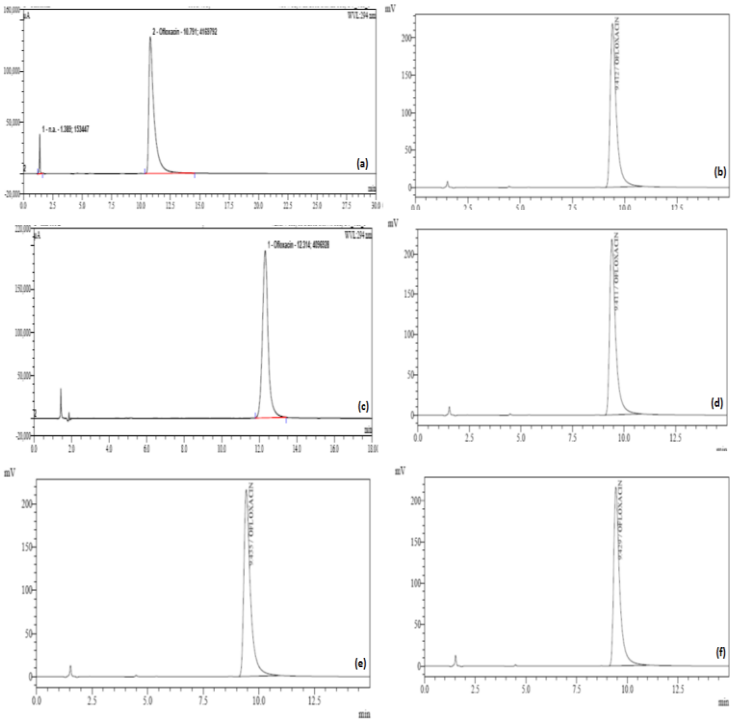

Fig 3: Chromatograms for Ofloxacin assay at Stress condition in three piece containers 1 week (a), 2 week (b), in BFS containers 1 week (c), 2 week (d) and condition in Glass containers 1 week (e), 2 week (f)

Acceerated Condition

Though the both type of containers passed the criteria of water loss i.e. not more than 5.0%. BFS containers are showing the more water loss up to 2.1043% and three piece containers are showing water loss just up to 0.8119%. Environmental stress cracking resistance (ESCR) number of three piece container (PE 1840 H) is higher than ESCR number of BFS (PE 3020 D) container. Hence there may be more cracking and increased permeability in case of BFS container as compared to the three piece container.

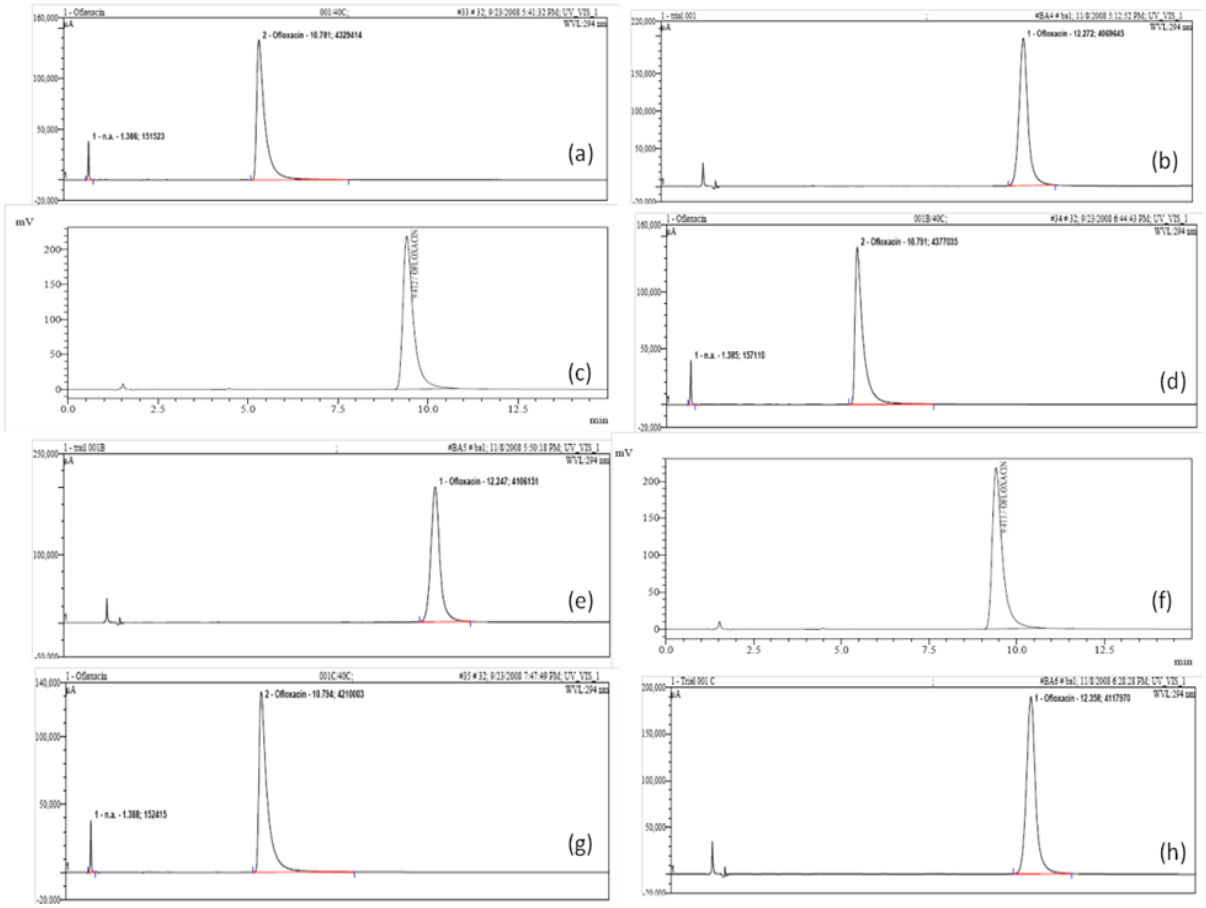

Fig 4: Chromatograms for Ofloxacin assay at accelerated condition in three piece containers. For 1 month (a), for 2months (b), for three months (c), in BFS containers For 1 month (d), for 2months (e), for three months (f) and in Amber Colored Glass containers For 1 month (g), for 2months (h)

Table 1. Formulation batches

Name of ingredients	Formulation Batches					
	OPT/OFL/ T-001	**OPT/OFL/ T-002**	**OPT/OFL/ T-003**	**OPT/OFL/ T-004**	**OPT/OFL/ T-005**	**OPT/OFL/ T-006**
Ofloxacin	3 mg/mL	3 mg/mL	3 mg/mL	3 mg/mL	3 mg/mL	3 mg/mL
Benzalkonium chloride*	0.0%v/v	0.01%,v/v	0.012% v/v	0.016% v/v	0.02% v/v	0.024% v/v
Disodium EDTA	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL
Sodium chloride	9 mg/mL	9 mg/mL	9 mg/mL	9 mg/mL	9 mg/mL	9 mg/mL
Hydrochloric acid	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH
Sodium hydroxide	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH	QS to adjust pH
Water for injection	QS	QS	QS	QS	QS	QS

Table 2. Stress condition

Sr. No.	Containers	Specification	Initial	Stress condition	
				1Week	2Week
1	Three piece	6.0 - 6.8	6.62	6.53	6.48
2	BFS	6.0 - 6.8	6.62	6.41	6.21
3	Glass	6.0 - 6.8	6.62	6.46	6.16

Hence it can be concluded that the MOC of BFS container is more semi permeable as compared to the three piece container's MOC. Water loss from the semi- permeable containers may hamper the drug content and preservative content. The chromatograms for assay of ofloxacin at each time point of the stability are as shown in Fig.4.

Conclusion

The present research work was also planned to provide the data about the selection of suitable primary packaging material for ofloxacin (0.3%) ophthalmic solution to achieve the better stability during the shelf life of the product. Evaluation of product was to optimize the concentration of BAK in formulation for ofloxacin (0.3%) ophthalmic solution. Batches were planned by taking different concentrations viz.0.0 % v/v, 0.01%, 0.012%, 0.016%, and 0.02%, 0.024 % v/v of BAK. Optimized batch was filled into three types of container and were subjected to accelerated conditions. Accelerated condition for semi-permeable containers (40ºC ± 2ºC/ NMT 25%) and for glass containers (40ºC ± 2ºC/ 75% ± 5% RH) were analyzed that the stability maintained both of container were good.

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