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FORMULATION DESIGN AND *IN-VITRO* EVALUATION OF NATAMYCIN OCULAR INSERT

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Abstract: There are many eye ailments which affected to eye and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available. These are classified as conventional and non-conventional drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into the cul-de-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner. Major improvements are required in each of the technologies discussed in this review. Some approaches are relatively easy to manufacture, but are limited in their ability to provide sustained drug release.

Keywords: Ocular, Drug Delivery, Ocuserts, Natamycin, Ophthalmic.

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INTRODUCTION

Eye is a unique and very valuable organ. This is considered a window hinge. We can enjoy it and look at the world body. There are many eye diseases that can affect the body and loss of vision as well. Therefore, many eyes in drug delivery systems are available[1]. They are classified as traditional and new drug development system. Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. There are many eye ailments which affected to eye and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available. These are classified as conventional and nonconventional (newer) drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into the culde-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner. Natamycin is a naturally occurring antifungal agent produced during fermentation by the bacterium *Streptomyces natalensis*, commonly found in soil. Natamycin has a very low solubility in water; however, natamycin is effective at very low levels. There is an MIC (minimum inhibitory concentration) of less than 10 ppm for most molds. Natamycin is classified as a macrolide polyene antifungal and, as a drug, is used to treat fungal keratitis, an infection of the eye. It is especially effective against *Aspergillus* and *Fusarium* corneal infections. Other common members of the polyene macrolide antifungal family are amphotericin B, nystatin, and filipin. Natamycin is also used in the food industry as a natural preservative. Natamycin in used to treat fungal infections, in including *Candida, Aspergillus, Cephalosporium*, *Fusarium* and *Penicillium*. It is applied topically as a cream, in eye drops, or (for oral infections) in a lozenge. Natamycin shows negligible absorption into the body when administered in these ways. When taken orally, little or none is absorbed from the gastrointestinal tract, making it inappropriate for systemic infections2.Fig-1:- The structure of Natamycin.

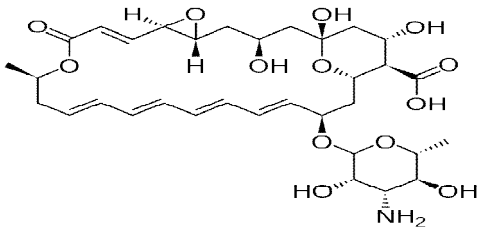

Fig-1:- The structure of Natamycin

MATERIALS AND METHODS

Natamycin was procured from BIMAL Pharma Pvt. Ltd., Mumbai. Methyl cellulose, Gelatin, Sodium alginate and Glycerine were obtained from S.D. Fine Chemicals Mumbai. All other reagents and solvent used were of analytical grade.

Preparation of Simulated Tear Fluid

The ingredients for preparing 100ml of the simulated artificial tear fluid are as follows in table no.1:

Table 1: Ingredients used in simulated tear fluid

Sr. No	Ingredients	Quantity
1	SodiumChloride	0.670 (g)
2	SodiumBi-carbonate	0.200 (g)
3	Calciumchloride	0.008 (g)
4	DistilledWater(Q.S)	100ml

Preparation of Ocusert

The Ocusert was prepared by using Gelatin and sodium alginate as drug carrier and MC as rate controlling membrane [3-10].

Preparation of Drug Reservoir

Natamycin was accurately weighed and dissolved in distilled water. Pre-determined gelatin was weighed and dissolved in distilled water separately in another beaker. Then clear drug solution was poured into polymer solution with constant stirring to get a homogenous solution. Required amount of glycerine was added and mixed well. The resulting solution was casted

over the alimunium foil containing petridish. The method used here was solvent casting method. The dose was calculated and mg of Natamycin was used every time with varying concentration of gelatin. Same procedure was followed for drug resevior containing sodium alginate[4].

Preparation of Rate Controlling Membrane

Methyl cellulose was dissolved in chloroform. Required quantity of glycerine was added and stirred until to get a clear solution. Then, it was poured over a clear glass plate and allowed to dry.

Sealing

The prepared rate controlling membrane and drug reservoir were cut into circular shape by cork borer after sufficient drying. The drug reservoir was sealed on both sides by using methyl cellulose having 8 mm and 10 mm diameter respectively in table no.2.

Table 2: Composition of Different Natamycin Ocuserts

Ocuserts	Methyl Cellulose (Rate Controlling Membrane)	Dibutyl Phthalate (Rate Controlling Membrane)	Sodium Alginate (Drug Reservoir)	Gelatin (Drug Reservoir)	Glycerine (Drug Reservoir)
F1	4%	0.015 ml	-	3%	0.2 ml
F2	5%	0. 015 ml	-	4 %	0.2 ml
F3	6%	0. 015ml	3%	-	0.2 ml
F4	7%	0. 015ml	4%	-	0.2 ml

Evaluation of the Prepared Formulations

Uniformity of thickness

Five films were taken from each batch and their individual thickness was measured using micrometer screw gauge.

Uniformity of weight

Five films were taken from each batch and their individual weights were determined by using electronic balance.

Uniformity of drug content

Three films were taken from each batch and individually dissolved or crushed in 5 ml of simulated tear fluid in a beaker and filter it into the beaker.0.5 ml of the filtered solution was taken in 20ml beaker and diluted to 15 ml with simulated tear fluid. Three reading were taken using UV spectrophotometer at 253 nm.

Swelling index

Three films were weighed and placed separately in beakers containing 4ml of simulated tear fluid. After a period of 5 minutes, the films were removed and the excess water on their surface was removed using a filter paper and then again weighed till there was no increase in the weight and then the swelling index was calculated[6].

Folding endurance

The folding endurance is expressed as the number of folds (number of times the insert is folded at the same place) either to break the specimen or to develop visible cracks. This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The specimen was folded in center, between the fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the insert showed breakage or cracks in centre of insert. The total folding operations were named as folding endurance value.

In Vitro diffusion studies of formulations using the vial method

The *in vitro* diffusion of drug from the different ophthalmic insert was studied using the classical standard cylindrical tube fabricated in the laboratory. A simple modification of open ended glass tube was used. The diffusion cell membrane (pre hydrated cellophane) was tied to end of open cylinder, which acted as a donor compartment[9]. An ophthalmic 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 containing 25 ml of simulated tear fluid in 100ml beaker. The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 370C±0.50C. At specific interval of time, 1ml of the sample solution was withdrawn from the receptor compartment and replaced with fresh simulated tear fluid solution. The aliquot was analyzed for the drug content using

UV-VIS Spectrophotometer at 253 nm after appropriate dilutions against reference using as simulated tear fluid as blank[7].

RESULT

In the present study, an attempt was made to formulate a soluble drug insert of natamycin for its novel drug delivery containing natural hydrophllic polymer Gelatin and sodium alginate while rate controlling membrane was prepared by hydrophobic methyl cellulose using solvent casting method with the aim of increasing the contact time, achieving controlled release, reduction in frequency of administration, improving patient compliance and greater therapeutic efficacy. The formulated ocuserts were then evaluated for their average weight variation, thickness, drug content, *in vitro* drug release[8]. Here Fig-2 shows the calibration curve of natamycin.

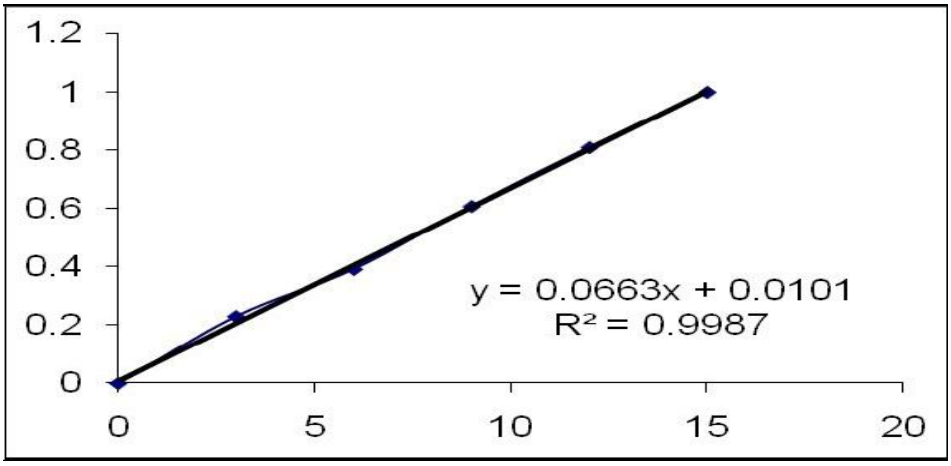

Fig-2:- the calibration curve of Natamycin.

The physicochemical evaluation data presented in table no.3.The prepared films were evaluated for the thickness using micrometer screw gauge. The average of three readings were taken; the mean thickness and standard deviation were calculated. The low standard deviation of the measured thickness of all the 4 formulations may indicate uniform distribution of drug and excipients in prepared inserts. It was found to be in the range of 0.13 ± 0.02 to 0.17 ±0.015. The weight of all the films were found to be in the range of 9.97 **±** 0.0112 to 11.58 ± 0.032. The uniformity of weight of the film indicates good distribution of the drug, polymer and plasticizer. For various formulations, the % drug content was found to vary between 96.18 ± 0.05 % to 99.37 ± 0.056 %. The folding endurance was measured for all formulations manually. It was found in the range of 169.66 ± 2.081 to 188.55 ± 3.605.

Table 3: Physicochemical Properties of the Prepared Ophthalmic Inserts

Formulations	Weight in (mg) ± SD n=3	Thickness in (µm) ± SD n=3	Swelling Index (%) n=3	% Drug content n=3	Folding Endurance n=3
F1	9.97 ± 0.0112	0.13 ± 0.02	1.03 ± 0.0264	97.63 ± 0.052	175.66 ± 1.527
F2	10.59 ± 0.0590	0.17 ±0.015	1.45 ±0.0251	98.18 ± 0.036	169.66 ± 2.081
F3	10.76 ± 0.0850	0.15 ± 0.01	1.36 ± 0.02	96.18 ± 0.05	180.33 ± 2.516
F4	11.58 ± 0.032	0.16 ± 0.015	1.15 ± 0.02	99.37 ± 0.056	188.55 ± 3.605

The release profile of the formulations is shown in the figure 3. The ophthalmic inserts prepared with gelatin sealed with methyl cellulose releases the drug completely in 5 to 6 hrs.

Table 4: Drug Release from the Prepared Ophthalmic Inserts

Time (hrs.)	% Drug Release F1	F2	F3	F4
0	0	0	0	0
1	22.34	16.58	19.33	15.31
2	41.56	35.71	31.88	22.89
3	59.99	49.74	45.74	30.99
4	80.19	65.05	57.39	42.05
5	95.66	81.37	68.87	50.73
6	-	97.63	79.45	69.13
7	-	-	95.85	77.15
8	-	-	-	81.63
9	-	-	-	98.9

The release of the drug from the formulation F1, F2 were found to be 95.66 % and 97.63% at the end of 5 and 6hrs respectively. The formulation with sodium alginate showed complete release in 7 to 9hrs. The release of drug from formulation F3 and F4 was found to be 95.85% and 98.9 % at the end of 7 and 9hrs in table no.4.

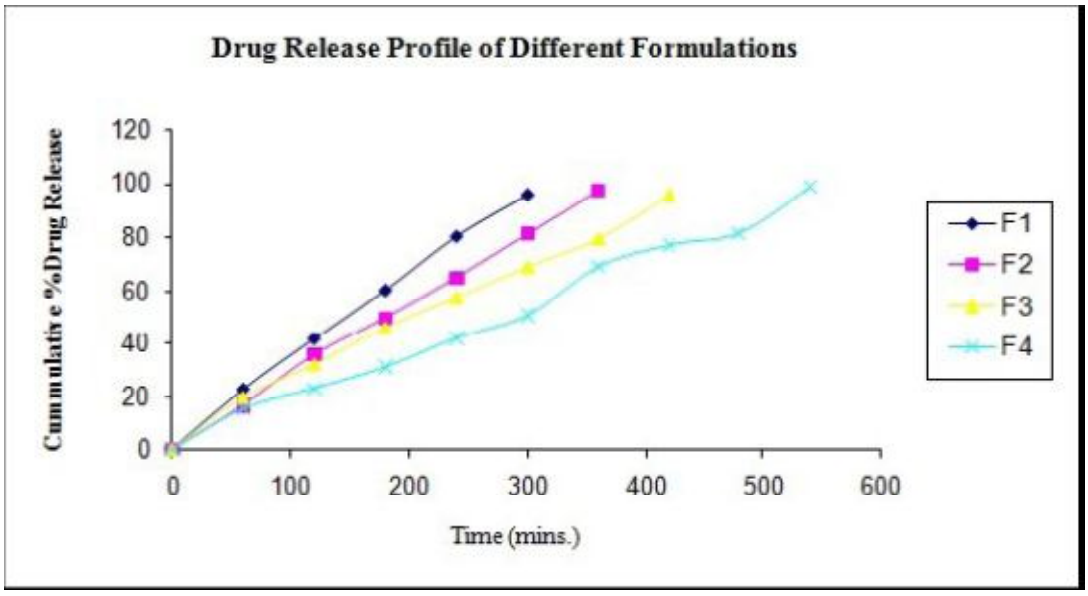

Fig-3:- The release profile of the formulations

CONCLUSION

The purpose to develop a novel drug delivery system like ocular insert of natamycin is to control the release of drug as well as maintain its concentration at the local site. Therefore an attempt to prepare its controlled dosage form has been made in the present work. This present research is aimed to design an ocular insert of natamycin by solvent casting technique to improve patient compliance and over-come the problems of poor patient acceptance which is other-wise faced by the use of conventional dosage forms like ointments. The conventional drug delivery systems are no longer sufficient to fulfill the present day requirements of providing a constant rate delivery and prolonged time. The formulation (F4) containing natamycin and sodium alginate sandwiched between methyl cellulose as polymer satisfied required pharmaceutical characteristics of ocular inserts and was found promising.

REFERENCES

1. Jain, MK; Manqué, SA & Deshpande, SG (2005), "*Controlled and Novel Drug Deliv*ery", CBS publishers, New Delhi, 1st Ed., 82-96.

2. Sikandar *et al*. (2011), "Ocular drug delivery system: an overview", *Int. J. Phar. Sci. Res*, 2(5), 1168-1175.

3. Tripathi, KD (2003), "*Essentials of Medical Pharmacology*", 5th Ed., Jaypee brothers medical publishers (p) Ltd, New Delhi, 767-69.

4. http//en.wikepida.org.wiki/erythromycin. Accessed on 2009

5. Kamath, UR; Singh, UV and Udupa, N (1993), "Evaluation of ciprofloxacin hydrochloride ocular preparations", *Indian J Pharm Sci.*, 148-50.

6. Allen, DJ; Demarco, JD and Kwan, KL (1972), "Free film 1: Apparatus and preliminary evaluation", *J Pharm Sci.*, 61,106.

7. Banker, GS; Gore, AV and Swarbrick, J (1996), "Water vapour transmission properties of free polymer films", *IBID*, 18,458.

8. Knaig, JL and Goodmann, H (1962), *J Pharma Sci.*, 5, 77.

9. Gupta, S and Gilhotra, RM (2011), "Enhancement of antiglaucoma potential by novel ocular drug delivery system", *Int. J. Ph. Pharm. Sci.*, 3, 55-58.

10. Mundada, A and Srikanda, BK (2008), "Formulation and evaluation of Ciprofloxacin hydrochloride soluble ocular insert", *Current Eye Research*, 33, 469-75.