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Preparation and assessment of ocular inserts containing sulbactum for controlled drug delivery

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ABSTRACT

Ocuserts or Ophthalmic inserts are sterile preparations containing drug as dispersion or as solution in the polymeric support. The sulbactum is highly used as antibacterial agent in combination with other antibacterial agent. This study aims to formulate novel sulbactum ocuserts to enhance patient compliance through providing controlled drugs release from polymeric matrix. Ocuserts were prepared by solvent-casting method using different polymers HPMC, K4M, Polyvinyl alcohol,ethyl cellulose as polymer gelatine and propylene glycol and dibutyl phthalate as plasticizer in different ratios. The prepared ocusters were physic-chemichally evaluated for their weight, thickness, drug content uniformity, surface pH, swelling index (SI) and folding endurance. The viscosity of the polymeric solution used for the formulations was determined using Brookfield viscometer. In-Vitro Drug Release study and Accelerated stability studies were also performed. The prepared ocuserts show uniform weight, thickness and drug content. Their surface pH was in the physiological range and showed acceptable folding endurance. HPMC formulas had higher SI values. Results of *in-vitro* testing for one of the prepared ocuserts shows slow release of drugs up to 24 hours. One of the prepared ocuserts is promising for once-daily effective and safe drug delivery system of sulbactum for glaucoma treatment.

Keyword: Ocuserts, sulbactum, viscosity, Ophthalmic

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INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical researchers[1]. Ocuserts augments contact time, longrunning duration of action, improves bioavailability, diminishes the frequency of administration and therefore achieves good patient compliance. It is also outlook to administer the drug to inflamed eye due to sustained release of the medicament from ocuserts. Furthermore, ocuserts are beneficial in saving time to the healthcare professionals. The efficacy of any ophthalmic preparation depends on the tissues for providing hoped therapeutic response[2]. The advantage of ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulations are numerous. Because of the prolonged retention of the devices and a controlled release, the effective drug concentration in the eye can be ensured over an extended time period. Dosing of the drug is also more accurate and the risk of systemic side-effects is decreased[3]. Viral conjunctivitis and bacterial conjunctivitis may affect one or both eyes. Viral conjunctivitis usually produces a watery or mucous discharge. Bacterial conjunctivitis often produces a thicker, yellow - green discharge and may be associated with a respiratory infection or with a sore throat[4]. Sulbactam, a new 3-lactamase inhibitor, has pharmacokinetic characteristics in humans similar to those of ampicillin and amoxicillin. Sulbactam is a semisynthetic β -lactamase inhibitor which when combined with certain β-lactam antibacterials extends their activity against bacteria that are normally resistant to the antibiotic due to production of β -lactamases. In combination with ampicillin, it extends the antibacterial activity of ampicillin to include β-lactamase-producing strains which are otherwise resistant, including Bacteroides fragilis, and increases the susceptibility of many sensitive strains[5]. Sulbactam is poorly absorbed after oral administration and sulbactam/ampicillin is therefore administered parenterally, although another linked sulbactam-ampicillin compound, sultamicillin, has been developed which is well absorbed after oral administration[6].

The basic pharmacokinetic characteristics of sulbactam after parenteral administration are similar to those of ampicillin. Sulbactam is poorly absorbed orally[7-8].This is an alternate approach to improve the bioavailability is the use of polymeric solutions, which change to a gel as a result of exposure to the physiological temperature, pH or ionic composition of lacrimal fluid.

MATERIALS AND METHODS

Chemicals

Sulbactum, HPMC, K4M, Polivinyl Alcohol and Dibutyl phthalate procured from Nellu medicare, New delhi. Gelatin, Ethyl cellulose and Propylene glycol were obtained from CDH Pvt Limited New Delhi. All solvents and reagents were of analytical grade.

Method of film preparation

The 15 formulations were prepared using various steps. The different formulation of sulbactum ocusert is given in table 1. The ocuserts were prepared by solvent casting. Sulbactum was accurately weighed and dissolved in distilled water. Pre-determined polymer 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 homogeneous solution. Required amount of propylene glycol was added and mixed well. The resulting solution was prepared by casting method. Films are allowed to dry at room temperature for 48hr, after complete drying the films were cut with of cork borer of size 8mm so that each ocuserts will contain 1mg of the drug.

Table 1. Formulation of the sulbactam ocuserts

	Ingredients(mg)						
	Drug reservoir					Plasticizer	Rate controlling
Batch	DRUG	HPMCK4M	PVA	GELATIN	RATIO		
SB1	40	40	-	-	1:1	30% w/w of the dry	4%
SB2	40	40	-	-	1:1	polymer	6%
SB3	40	60	-	-	1:1.5		4%
SB4	40	60	-	-	1:1.5		6%
SB5	40	80	-	-	1:2		4%
SB6	40	80	-	-	1:2		6%
SB7	40	-	40	-	1:1		4%
SB8	40	-	40	-	1:1		6%
SB9	40	-	80	-	1:2		4%
SB10	40	-	80	-	1:2		6%
SB11	40	-	-	40	1:3		4%
SB12	40	-	-	40	1:3		6%
SB13	40	-	-	60	1:1		4%
SB14	40	-	-	60	1:1		6%
SB15	40	-	-	80	1:1.5		4%

Preparation of the rate controlling membrane

Ethyl cellulose was dissolved in chloroform. Required quantitiy of dibutyl phthalate was added and stired 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 using special mould after sufficient drying. The drug –matrix films were kept and fixed in between the rate controlling membrane. The ocuserts containing sulbactum is shown in Figure 1.

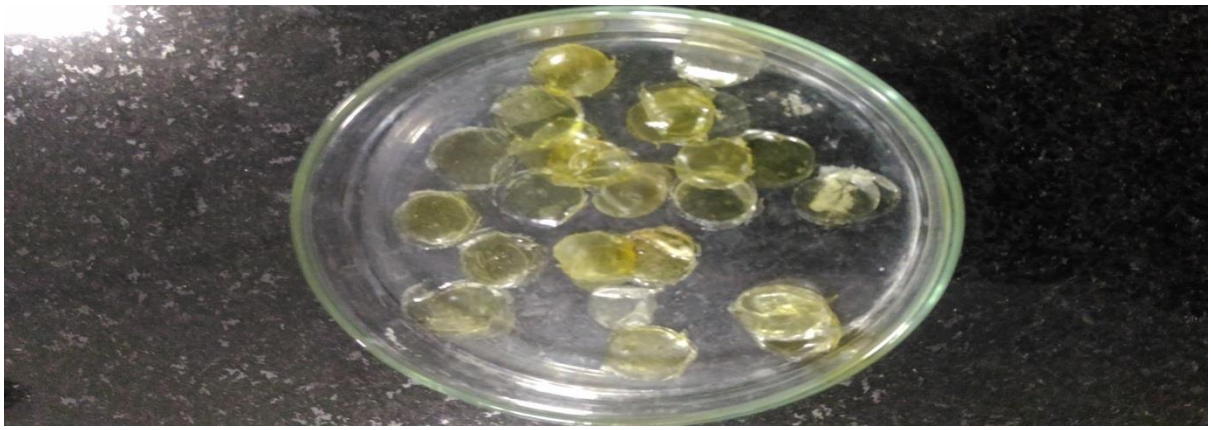

Fig.1 Prepared ocuserts

Evaluation of ocular inserts

The prepared ocular inserts were evaluated for the following parameters as described below.

Physical appearance

All the formulated ocular inserts were evaluated for the physical characters such as size, shape, colour and smoothness.

Uniformity of thickness

Films were evaluated for the thickness using a vernier calliper .The average of three readings was taken at different points of films, and the mean thicknes aws calculated .The standard deviations (SD s) in thickness were computed from the mean value.

Weight Variation

The weight variation test was carried out using electronic balance by weighing 3 patches from each formulation. The mean value was calculated, and the standard deviations of weight variation were computed from the mean value.

Folding Endurance

The folding endurance is expressed as the no of folds (number of times the insert is folded at same place) either to break specimen or to develop visible cracks .This test is important to check the ability of sample to with stand folding .This can also give an indication of brittleness . The specimen was folde in centre, between the fingers and thumbs and then opened.This was termed as 1 folding. This process was repeated till the insert showed breakage and cracks in centre of insert. The total folding operation was named as folding endurance value[9].

Surface pH

Insert film were allowed to swell for 30 minutes in 1 ml of distilled water. These swollen films were then removed and placed under digital p H meter to determine surface pH.

Swelling index

Initially films were weighed and placed separately in beakers containing 4 ml distilled water. At regular intervals of time (every 10 minutes) the films were removed and excess water on their surface was removed using filter paper and in weight . It was then calculated as:

$$\text{Swelling Index} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Estimation of percentage moisture absorbed

The percentage moisture absorbtion test was carried out to check physical stability or integrity of ocular films. Ocular films were weighed and placed in desiccators containing 100 ml of saturated solution of aluminium chloride. After three days the ocular films were taken out and reweighed. The percentage moisture absorption was calculated using the following equation[10].

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content

For drug content uniformity, the ocuserts were placed in 5 ml of p H 7.4 phosphate buffer and were crushed to extract the drug from ocuserts. The solution was filtered through a Whitman's filter paper and filtrate was suitably diluted with buffer solution. The absorbance of the resulting solution was measured at 259 nm.

In vitro diffusion study

The drug release pattern from the ocusert was studied by using a semipermeable membrane that is chorioallantoic membrane from the egg which acts as a corneal epithelium. In vitro diffusion of the drug from different ocular inserts was studied using diffusion cell. In the donor compartment of the cell ocular insert was placed and in receptor compartment phosphate buffer (p H 7.4) is place and in receptor compartment phosphate buffer (PH 7.4) is place .in order to simulate the tear volume, 0.7ml of phosphate buffer (p H 7.4) was placed and maintain at the same level throught the study. Egg membrane (semipermeable membrane) was placed between both the compartments. The surface of the membrane was in contact in media in receptor compartment the media us receptor compartment is stirred continuously using a magnetic stirrer and temperature was maintained 37 + 0.5^{0}C. At definite time intervals, 3ml of aliquots were analyzed spectrophotometrically at λ_{max} 259 nm[12].

Accelerated stability study

Stability of the pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life." The purpose of stability testing is to provide evidence on how the quality of a substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, enabling recommended storage condition, re-test periods and self lives to be established. In the presence study, the formulation was selected for the study, and ocuserts were packed in amber- colored bottles tightly plugged with cotton and capped. They were exposed to various to various temperatures (37^0 C, 50^0 C, 4^0 C) for a period of one month. Films were evaluated for physical appearances, weight variation, thickness, drug content[12].

RESULTS

Physical appearance

The fabricated film was thin, transparent and visually smooth surface. The drug and polymer distribution is uniform.

Table 2. Characterisation of sulbactum

Test	Specification	Observations	Remarks
Description	White powder	White powder	Complies
Solubility	It is freely soluble in water, methanol	It was soluble in water	Complies
Odour	Odourless	Odourless	Complies
Melting point	150-200^{o}C	170	Complies
LOD	NMT 1%	0.52%	Complies

Thickness uniformity

The thickness of drug loaded film was measured at three different points with the help of vernier caliper, result was given in table 3 and the result indicate that prepared ocuserts were uniform in thickness.

Uniformity of weight

Drug loaded films were tested for uniformity in weight and the results was given in table 5.6, indicate that the uniform distribution of drug and polymer.

Folding endurance test

The recorded folding endurance test was found to be in the range of 200-300. This indicates the flexibility of the films; results were given in table 3

Surface pH

Surface pH of all the formulation was measured using digital pH meter values were given in table 3. The surface pH of all the formulation was neutral so no eye irritation was expected.

Table 3. Results of thickness, weight variation, folding endurance and surface pH

Batch	Thickness (mm)	Weight variation (mg)	Folding endurance	Surface pH
SB1	0.25 ± 0.0	24.3 ± 0.1	215±2.9	6.89±0.0
SB2	0.19 ± 0.0	23.5±0.6	195±7.2	7.32±0.1
SB3	0.2 ± 0.1	25.6±0.3	220±5.3	7.65±0.2
SB4	0.21 ± 0.3	25.02±0.3	230±2.7	6.76±0.1
SB5	0.25 ± 0.1	21.68±0.5	215±2.9	6 .89±0.2
SB6	0.26 ± 0.2	24.3±0.1	225±3.9	7.12±0.1
SB7	0.21 ± 0.2	22.09±0.3	275±2.6	7.01±0.2
SB8	0.24±0.1	23.05±0.3	230±5.0	7.28±0.5
SB9	0.26±0.1	26.03±0.2	258±3.5	6.89±0.3
SB10	0.31±0.1	24.1±0.5	267±2.3	6.66±0.01
SB11	0.24±0.1	25.07±0.01	226±4.3	7.3±0.2
SB12	0.25±0.2	27.51±0.4	229±4.1	7.33±0.2
SB13	0.32±0.1	25.08±0.2	222±0.3	7.23±0.1
SB14	0.33±0.1	28.51±0.4	198±.72	6.78±0.3
SB15	0.33±0.2	28.51±0.3	198±.70	6.78±0.32

Swelling index

The swelling of drug loaded films in 4 ml double distilled water was observed till 60 min.The data for increased in weight were given in table no 4.

Table 4. Results of swelling index

Time (min)	Batch							
	SB1	SB2	SB 3	SB4	SB5	SB6	SB7	SB8
0	0	0	0	0	0	0	0	0
10	15.1%	10.2%	20.3%	18.1%	12.8%	15.6%	14.2%	17.6%
20	33.5%	18.6%	27.8%	25.2%	19.4%	21.6%	20.3%	24.5%
30	45.5%	25.2%	36.6%	32.3%	26.5%	29.7%	26.8%	32.8%
40	57.5%	30.5%	45.8%	39.5%	35.8%	36.5	32.6%	41.5%
50	63.5%	45.8%	50.8%	46.7%	32.2%	37.3%	42.5%	47.2%
60	70.2%	47.8%	56.3%	50.3%	52.3%	41.3%	51.3%	55.6%

Time (min)	Batch						
	SB9	SB10	SB 11	SB12	SB13	SB14	SB15
0	0	0	0	0	0	0	0
10	22.1 %	10.2%	15.6%	17.1%	20.1%	21.2%	15.23%
20	28.6%	14.7%	20.1%	22.5%	26.7%	23.8%	23.0%
30	35.2%	20.6%	25.1%	28.6%	33.5%	36.6%	24.2%
40	42.5%	25.7%	32.2%	35.4%	40.5%	44.6%	36.2%
50	49.9%	30.8%	39.4%	42.3%	45.6%	50.6%	47.5%
60	53.2%	37.6%	44.9%	45.1%	50.1%	53.2%	56.5%1

Percentage moisture absorbed

The percentage moisture absorbed was determined and the results were shown in table 5

Percentage moisture loss

The percentage moisture loss was determined and the results were shown in table 5

Drug Content

In order to make sure the uniform dispersion of drug in films, drug content test was carried out. Drug content was analysed by UV spectroscopy at lemda max 259 using blank sample as reference sample. The percentage drug content result was given in table 5

Viscosity

As ration of drug polymer and the percentage of ethyl cellulose vary, there was a slight variation in the viscosity of all the formulation was observed viscosity of all the formulation was in the range of 56.4 to 70.2 cp. It initialized that it had good adhesion with the conjunctiva.

Table 5. Results of moisture absorbed, moisture loss, drug content and viscosity

Batch	%Moisture absorbed	% Moisture loss	%Drug content	Viscosity (Cp)
SB 1	4.8±0.2	4.8±0.3	92.6±0.2	62.1
SB 2	3.7±0.1	3.1±0.2	95.5±0.3	66.2
SB 3	5.6±0.1	5.5±0.1	92.2±0.4	66.3
SB 4	4.4±0.1	5.7±0.1	93.5±0.6	64.7
SB 5	6.7±0.2	7.3±0.1	97.6±0.4	66.2
SB 6	4.2±0.1	4.2±0.1	94.7±0.8	66.5
SB 7	4.8±0.2	5.1±0.1	95.2±0.9	69.8
SB 8	4.3±0.1	5.8±0.2	95.8±0.7	41.4
SB 9	5.2±0.1	6.5±0.5	96.2±0.7	45.3
SB 10	4.7±0.1	5.8±0.0	97.3±0.6	49.4
SB 11	5.3±0.1	5.6±0.1	98.2±0.9	52.2
SB 12	4.5±0.1	4.8±0.2	97.3±0.5	55.6
SB 13	6.3±0.2	5.6±0.2	96.4±0.9	60.3
SB 14	4.6±0.2	6.1±0.1	94.7±0.8	62.3
SB 15	4.2±0.2	6.1±0.6	92.6±0.2	62.1

In-Vitro Drug Release study

The in-vitro drug release study of sulbactam ocuserts was carried out the using egg membrane as semipermeable membrane in phosphate buffer pH 7.4. The apparatus was designed with the objective of mimicking the conditions of ocular activity to certain extent. The release a data were given in table no. 6

Table 6. Results of In-Vitro Drug Release study of sulbactam

Time (hrs)	Cumulative % drug release							
	SB1	SB2	SB3	SB4	SB5	SB6	SB7	SB8
0	0	0	0	0	0	0	0	0
1	2.17±0.90	6.34±0.132	16.8±0.43	15.1±0.12	11.8±0.35	13.8±0.27	10.3±0.33	14.3±0.45
2	6.09±0.45	6.3±0.13	27.60.1	27.30.7	19.5±0.2	20.7±0.4	19.9±0.3	22.3±0.1
3	9.23±0.89	27.5±0.03	30.60.3	31.60.2	24.7±0.4	29.4±0.3	28.4±0.5	27.6±0.2
4	10.6±0.21	28.5±0.7	34.9±0.2	36.2±0.3	28.2±0.4	32.4±0.6	30.4±0.6	31.4±0.6
5	17.1±0.08	29.8±0.5	37.4±0.6	41.8±0.2	32.4±0.5	34.2±0.4	34.1±0.4	35.7±0.2
6	20.1±0.02	31.9±0.6	41.8±0.2	47.7±0.4	34.2±0.6	36.5±0.9	38.9±0.5	37.9±0.6
7	24.5±0.02	39.3±0.3	47.6±0.2	49.9±0.3	36.0±0.6	40.5±0.8	40.6±0.6	44.2±0.3
8	28.6±0.06	42.0±0.4	50.6±0.3	54.2±0.4	39.2±0.3	44.6±0.4	42.9±0.6	50.4±0.3
9	30.4±0.01	46.5±0.2	55.8±0.4	57.0±0.4	43.8±0.6	47.6±0.5	43.4±0.4	53.7±0.3

Time (hrs)	Cumulative % drug release						
	SB9	SB 10	SB11	SB12	SB13	SB14	SB15
0	0	0	0	0	0	0	0
1	11.8±0.09	9.0±0.3	16.6±0.3	22.3±0.9	24.7±0.3	10.5±0.9	22.7±0.3
2	15.2±0.4	15.4±0.4	24.1±0.1	32.5±0.7	32.4±0.6	16 .4±0.4	26.5±0.2
3	26.6±0.3	19.6±0.6	31.3±0.7	37.2±0.4	46.1±0.2	23 .4±0.5	29.6±0.3
4	30.5±0.2	28.4±0.5	35.0±0.1	44.5±0.9	49.8±0.3	26.4±0.6	30.4±0.6
5	34.6±0.5	32.2±0.1	42.5±0.9	51.1±0.2	54.4±0.8	33.9±0.3	35.0±0.3
6	40.4±0.4	35.6±0.6	48.6±0.8	55.4±0.6	57.4±0.3	38.3±0.5	45.1±0.3
7	45.3±0.3	41.3±0.7	52.4±0.6	62.8±0.3	60.9±0.4	40.1±0.6	46.4±0.7
8	47.5±0.6	45.6±0.8	54.9±0.4	68.4±0.6	70.4±0.6	44.8±0.9	49.9±0.4
9	48.5±0.3	51.8±0.5	59.5±0.6	73.4±0.6	74.6±0.6	47.5±0.3	52 .3±0.5

Accelerated stability studies

The optimized formulation was subjected to short term stability testing. Films wrapped in aluminium foil and kept in a humidity chamber maintain at 37^0 C and 50^{0}C and 4^{0}C of period of 1 month at different temperature as per ICH guidelines. Results on stability study were given in table 7. From the above results there are a slight change occurs at a temperature of 50^0 C and there is no significant change was observed at other temperature.

Table 7. Results of accelerated stability studies

Temperature(^{o}C)	Evaluation Parameters			
	Physical appearance	Weight variation(mg)	Thickness(mm)	Drug content(mg)
37	No change	25.2	0.2	1.0
50	No change	25.1	0.2	0.9
4	No change	25.2	0.2	1.0

DISCUSSION

Sulbactum drug is used against many diseases[7]. It is indicated for eye diseases. In the present study an attempt was made to develop various batches of sulbactum ousters using solvent casting method and they were evaluated. Polymers such as HPMC, K4M, PVA, Ethyl cellulose and gelatin were good film forming polymer. The percentage of ethyl cellulose provided a sustained release of the drug from polymeric reservoir. The results of the drug compatibility studies revealed that there was no chemical interaction between the pure drug and the excipients used. In evaluation parameters, the viscosity of all formulation was found to be in between 50 to 72.3 cp. It is indicate that it has good adhesive with the conjunctiva. The thickness of all the films was to be in the range of 0.180 to 0.323mm which shows that it is easily inserted in to the eye and does not produce any irritation in eye, weight of all the films were found to in between 20.01 to 28.02 mg which that there is uniform distribution of the drug and polymer, folding endurance al the formulation were to be in the range of 200-300 and the surface pH of all the formulation was found to be in range 6.60-7.5, compatible with the tear fluid pH that is 7.4. which shows that the preparations are sterile and safe to be used in the eye. All these results showed that ocuserts prepared compatible with the eye and does not produce any inflammation or redness in the eye. In-vitro drug release from SB ocuserts in phosphate buffer p H 7.4. The optimized SB 10 showed 87% drug release.

CONCLUSIONS

From the experimental findings it had been concluded that the said promising batch SB10 would be able to benefits such as increase residence time, prolong drug release, reduction in the frequency of administration and thereby may help to improve the patient compliance with the limitation that the formulation is non-erodible. The drug remained intact and stable in the ocuserts as well as in the storage with no apparent chemical interaction between the drug and excipients in future further work will be progress to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamics studies in humans.

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