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Research Article

Formulation and Evaluation of Ocular Inserts Containing Berberine HCL and Curcumin

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Abstract

Objective: The purpose of this work was to develop an ocular insert for the treatment of allergic conjunctivitis.

Methods: Nine formulations of ocular inserts were prepared by solvent casting method using different ratios of various well-known hydrophilic polymers such as Hydroxy Propyl Methyl Cellulose (HPMC), Poly Vinyl Alcohol (PVA), Pluronic F-68, Glycerine as a plasticizer, benzylkonium chloride as a preservative and distilled water as a solvent. These formulations were evaluated for mechanical properties like tensile strength, folding endurance. The physicochemical properties like surface pH, drug content, thickness, weight variation, percent moisture absorption was also evaluated.

Results: Based on the evaluation, it was found that formulation F9 was highest tensile strength and lowest folding endurance. Formulation F8 posess highest folding endurance as well as good tensile strength.

Conclusion: Based on results, it was selected as the optimized formulation.

Keywords: Curcumin, Berberine Hcl, HPMC, PVA, Pluronic F-68, Glycerine.

INTRODUCTION

Ocular inserts are defined as sterile topical preparations, with a solid or a semi solid consistency. They are composed of a polymeric base containing synthetic and natural compounds, the latter being incorporated as dispersion in the polymeric solution[1]. It also offers accurate dosing to overcome the side effects of pulsed dosing by conventional systems, increases the ocular bio availability of drugs by prolonging the corneal contact time, to avoid the protective barriers like drainage, lacrimation and conjunctival absorption'. Therefore, the possibility of incorporating various novel polymers, technological approaches and are reducing the risk of sensitivity reactions[2]. The basic objective of ocular controlled drug release is to achieve more effective therapies by eliminating the potential for both under and overdosing, maintenance of drug concentration within a desired range, fewer administrations, optimal drug use and increased patient compliance[3]. Curcumin, the principal bioactive compound extracted from the rhizome of Curcuma longa, has been extensively studied for its wide spectrum of therapeutic effects, particularly its anti-inflammatory and anti-allergic properties. As a natural polyphenol, curcumin exerts its biological activities through modulation of various molecular targets involved in immune and inflammatory responses, including cytokines, transcription factors such as NF-κB, and enzymes like cyclooxygenase-2 (COX-2) and lipoxygenase (LOX)[5]. In allergic conditions, curcumin has been shown to inhibit the release of histamine and other pro-inflammatory mediators from mast cells and basophils, thereby reducing hypersensitivity reactions. Additionally, its antioxidant potential contributes to the attenuation of oxidative stress, which plays a critical role in the pathogenesis of allergic inflammation [6]. Despite its potent bioactivity, curcumin's therapeutic application remains challenged by its limited bioavailability.

Berberine hydrochloride, an isoquinoline alkaloid derived from various medicinal plants such as *Berberis* species, has demonstrated notable anti-inflammatory and anti-allergic effects. Its pharmacological activity is primarily attributed to its ability to regulate key signaling pathways, including NF-κB, MAPK, and AMPK, thereby suppressing the production of pro-inflammatory cytokines and mediators. In allergic responses, Berberine HCl has been shown to inhibit mast cell degranulation and the release of histamine, contributing to the attenuation of hypersensitivity reactions[7]. Additionally, its antioxidant properties further support its role in reducing oxidative stress-related inflammation. These characteristics position berberine HCl as a promising natural compound for the management of allergic and inflammatory disorders. The present study was intended to formulate and develop an ocular thin insert formulation loaded with curcumin and berberine for possible therapeutic application in ophthalmic injuries and allergies.

MATERIALS AND METHODS

Berberine Hcl was a gift sample from Himalaya Pharmaceuticals. Curcumin was purchased from Otto Chemie Pvt. Ltd, Mumbai. HPMC, PVA and Pluronic F-68 were obtained from S.D. Fine Chemicals Mumbai. All other reagents and solvent used were of analytical grade.

Organoleptic Properties

Organoleptic properties were observed by visual observation. The organoleptic studies of Berberine HCL such as appearance, colour, odor, state etc. were observed.

Solubility study

The solubility of Curcumin and berberine HCL was determined in various volatile or non-volatile solvents such as water, methanol, ethanol, DMSO, acetone and chloroform. An excess amount of the compound was introduced into 5 mL of each solvent within screw-capped glass test tubes and shaken for a duration of 24 hours at ambient temperature. The mixture was then filtered, diluted, and the solubility was measured using a UV-visible spectrophotometer.

Preliminary screening of selection of polymers

Preliminary study was carried out for screening of various polymers and their concentrations. The selection of Hydroxypropyl Methylcellulose (HPMC), Polyvinyl Alcohol (PVA), and Pluronic F-68 for inserts is based on their complementary physicochemical properties, which contribute to the overall efficacy of ocular drug delivery systems. HPMC is a widely used hydrophilic polymer known for its excellent film-forming ability, swelling capacity, and controlled drug release potential, making it suitable for sustained ocular delivery. PVA is selected for its mechanical strength, flexibility, and mucoadhesive characteristics, which help improve the retention time of the ocusert on the ocular surface. Pluronic F-68, a thermosensitive polymer, offers unique sol-gel transition behavior and enhances drug retention through its viscosity-modulating properties. When combined, these polymers provide a synergistic effect ensuring structural integrity, biocompatibility, and prolonged therapeutic action making them ideal candidates for the formulation of effective and patient-friendly ocular inserts.

Method of Preparation of ocular inserts

The ocular inserts were prepared by solvent casting method. Weighed quantity of PVA was dissolved in 30ml distilled water on hot plate at a temperature 50^0C under continuous stirring and gradually added the remaining polymers at 40^0C as per the quantity mentioned in **Table 1**. Then plasticizer, glycerine and benzylkonium chloride was added under continuous stirring. Each insert containing both Berberine Hcl (0.26mg) and Curcumin (0.26mg) and was then added to the polymeric solution. This polymer solution was sonicated for thirty minutes to remove air bubbles. After proper dispersion, the casting solution was then poured on clean Petri dish and covered with inverted funnel to allow slow and uniform evaporation of solvent at 40'C for 24 hours. The dried ocular inserts thus obtained was punched with sharp edged die into the required pieces. Inserts thus prepared were kept in laminar airflow under UV radiation for at least 60 minutes. The prepared ocular inserts were then packed in sterilized aluminum foil [8].

Table 1: Composition of Ocular inserts of Berberine HCL and Curcumin

Formulation Code	HPMC (mg)	PVA (mg)	Pluronic F-68 (mg)	Glycerine (mg)	BKC (mg)	Distilled Water (q.s. to 30 ml)
F1	300	150	60	600	3	Up to 30 ml
F2	450	150	90	600	3	Up to 30 ml
F3	600	150	120	600	3	Up to 30 ml
F4	300	300	60	600	3	Up to 30 ml
F5	450	300	90	600	3	Up to 30 ml
F6	600	300	120	600	3	Up to 30 ml
F7	300	450	60	600	3	Up to 30 ml
F8	450	450	90	600	3	Up to 30 ml
F9	600	450	120	600	3	Up to 30 ml

Evaluation of ocular insert

Mechanical properties Tensile strength

The tensile strength was measured using a tensile strength instrument. One end of the ocular inserts was attached with an adhesive tape and the other end of the insert was fixed by adhesive tapes with a small pin placed in between the base plate. This fixing assisted in keeping the insert straight while stretching. In the adhesive tape a small hole was made near the pin in which a hook was inserted. The hook was attached with a thread, passed over the pulley where a small pan was attached to hold the weights. A small pointer was attached to the thread, which travelled over the graph paper affixed on the base plate [9]. To determine the tensile strength, weights were gradually added to the pan to increase the pulling force until the patch broke. The distance travelled by the pointer on the graph paper before the breaking of the patch determined the elongation. The weight required to break the patch was noted as break Load. Tensile strength was calculated using the following formula:

Tensile strength= Breaking load / Cross Sectional Area of the sample

Folding endurance

Folding endurance for ocular inserts was calculated by folding the inserts repeatedly in the same position until a crack appeared. Number of folds required to produce the crack were counted. Folding endurance test was repeated using more sets of ocular inserts [10].

Weight of ocular insert

The ocular insert was taken out and weighed using digital balance and the average weight of each insert was determined [10].

Uniformity of thickness

The thickness of the insert was determined using Micrometer gauze (Mitotoyo, Japan) at five random points of each insert. The mean value was calculated [10].

% Moisture absorption

The percentage moisture absorption test was carried out to check the physical stability or integrity of the ocular inserts at humid conditions. The inserts were weighed and placed in decorators containing saturated solutions of sodium chloride and 75+5% RH was maintained. After three days, the inserts were taken out and reweighed. The % moisture absorption was calculated using the following formula [11-12].

% Moisture absorption = [(Final weight - Initial weight) / Initial weight] X 100

Surface pH

Surface pH test was carried out to investigate any possible eye irritation. The inserts were allowed to swell in a closed Petri plate at room temperature for 30 minutes in 0.1 ml of double distilled water. The swollen insert was removed and placed to determine the surface pH by pH paper [13-14].

Sterility testing

Sterility is one of the most vital requirements for an ophthalmic preparation. The tests for sterility are intended for detecting the presence of viable forms of microorganisms in ophthalmic preparations. The principle governing these tests is that if the microorganisms are placed in a medium, which provides nutritive material and water, kept at a favourable temperature, the organisms will grow and their presence can be indicated by turbidity in the originally clear medium. In the present study, two media namely, alternate thioglycolate medium (ATGM) and soyabean-casein digest medium (SBCD) were used to investigate the presence/absence of aerobic, anaerobic bacteria and fungi, in the formulated sterilized ocular inserts.[15-16].

RESULTS AND DISCUSSION

Organoleptic qualities of Berberine and curcumin

Curcumin was checked to have a dark brown colour to it when tested. Curcumin has a slightly aromatic odour and has a solid state powder form, according to research conducted on it. Curcumin exhibited the same appearance, colour, odour and state as the I.P. requirements for these characteristics (Table 2). Berberine Hcl was discovered to have a Dark- Yellow colour to it when tested. Berberine Hcl has a characteristic odor and has a solid state powder form, according to research conducted on it. Berberine Hcl exhibited the same appearance, color, odor and state as the I.P. requirements for these characteristics (Table 2).

Table 2: Organoleptic properties of Curcumin

Drug	Organoleptic properties	Observation
Curcumin	Color	Dark Yellow color
	Odor	Aromatic
	Appearance	Powder
	State	Solid powder
Berberine Hcl	Colour	Dark-Yellow
	Odour	Characteristic
	Appearance	Powder
	State	Solid powder

Solubility studies

Curcumin is freely soluble in Methanol, ethanol and DMSO, Soluble in chloroform and slightly soluble in water. However, the berberine HCL was freely soluble in water and DMSO, slightly soluble in methanol, insoluble in chloroform, acetone and ethanol (Table 3)

Table 3: Solubility profile of Curcumin and berberine

Drug	Solvents	Observation/Inference
Curcumin	Methanol	Freely soluble
	Ethanol	Freely soluble
	DMSO	Freely soluble
	Span 60	Partially soluble
	Span 20	Partially soluble
	Tween 80	Partially soluble
	Water	Sparingly soluble
	Chloroform	Soluble
Berberine Hcl	Water	Freely soluble
	Methanol	Soluble
	Ethanol	Slightly soluble
	Span 60	Partially soluble
	Span 20	Partially soluble
	Tween 80	Partially soluble
	DMSO	Freely soluble
	Acetone	Slightly soluble
	Chloroform	Insoluble

Mechanical properties

Mechanical properties like Tensile strength were investigated to determine the suitability and acceptability of the ocular inserts. The nature of the plasticizer and different ratios of polymers affected the mechanical properties. Inserts made with this selected plasticizer showed good tensile strength. On the other hand, as the concentration of the polymers increases the tensile strength increases. It may happen due to maximum concentration of Poly vinyl alcohol. lt was found that the tensile strength was least for formulation F1 and found to be highest for the formulation F9.

Folding endurance and tensile strength

The folding endurance determined the ability of the inserts to rupture. lt was found that the folding endurance was least for the formulation F9 and found to be highest for the formulation F8 (Table 4). It reveals that the folding endurance increases gradually with increases the concentration of the polymers but when the concentration was too high, its decreases it decreases exponentially. It may happen due to large amount of polymers that also influence the thickness of the inserts. Therefore, inserts prepared with equal ration of HPMC and PVA with moderate amount of pluronic f-68 shows the high tensile strength (Table 2).

Table 4: Tensile Strength and folding endurance of ocular inserts

Formulation	Tensile strength (Kg/cm^2)	Folding Endurance
F1	0.61 ± 0.02	90 ± 4
F2	0.63 ± 0.03	92 ± 5
F3	0.70 ± 0.04	96 ± 6
F4	0.88 ± 0.02	90 ± 5
F5	0.90 ± 0.03	94 ± 4
F6	0.90 ± 0.04	95 ± 6
F7	1.20 ± 0.03	93 ± 4
F8	1.23 ± 0.04	97 ± 5
F9	1.25 ± 0.04	80 ± 6

Weight variation of ocular insert

The weight of the ocular insert was determined using digital balance. The weight variation of ocular insert was found to be in between 1.35+0.09 and 1.72+.0.15 (Table 5).

Uniformity of thickness

The mean thickness of the insert was determined using Micrometer gauze. For all formulations the thickness was found to be between 0.23+0.01 and 0.40+0.02 (Table 5). The low standard deviations indicate the uniformity of the thickness.

Table 5: Physical properties of prepared ocular inserts

Formulation	Weight variation	Thickness (mm)
F1	1.72 ± 0.15	0.23 ± 0.01
F2	1.54 ± 0.12%	0.29 ± 0.02
F3	1.41 ± 0.11%	0.34 ± 0.01
F4	1.63 ± 0.14%	0.26 ± 0.01
F5	1.49 ± 0.13%	0.31 ± 0.02
F6	1.39 ± 0.11%	0.37 ± 0.02
F7	1.57 ± 0.13%	0.28 ± 0.01
F8	1.42 ± 0.10%	0.33 ± 0.01
F9	1.35 ± 0.09%	0.40 ± 0.02

% Moisture absorption

The % moisture absorption was found to be between 4.21 ± 0.12 and 5.45 ± 0.16(Table 4). F1 showed lowest moisture uptake and F9 showed highest moisture uptake. This was attributed to the type of plasticizer and plymers used. (Table 6).

Table 6: Moisture content and moisture uptake by different ocular inserts

Formulation	% Moisture Content (± SD)	% Moisture Uptake (± SD)
F1	4.21 ± 0.12	5.68 ± 0.18
F2	4.35 ± 0.14	6.12 ± 0.21
F3	4.48 ± 0.15	6.55 ± 0.19
F4	4.63 ± 0.11	6.88 ± 0.17
F5	4.78 ± 0.13	7.10 ± 0.16
F6	4.96 ± 0.12	7.45 ± 0.18
F7	5.12 ± 0.15	7.62 ± 0.22
F8	5.30 ± 0.14	7.84 ± 0.19
F9	5.45 ± 0.16	8.10 ± 0.20

Surface pH

Generally, the pH of ophthalmic formulations should be within 7.0 to 7.4. The surface pH for all the nine formulations was within the range.

Sterility testing

The sterility testing of F8 was performed for aerobic, anaerobic bacteria and fungi by using alternate thioglycollate medium and soyabean casein digest medium as per the IP'22 procedure.

Test for aerobic bacteria: Bacillus subtilis was used as a test organism. As shown in Table 7 and Figure 1, there was no evidence of growth found in the 'test' and 'negative control' tubes and there was macroscopic evidence of microbial growth in 'positive control' tube. The results suggest that the F8 tested for aerobic and anaerobic bacteria passed the test for sterility.

Table 7: Sterility test observations in ATGM

S. No.	Samples	Days													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Negative Control	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	Positive control	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	Sterilized (60 min)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(-) Absence of microbial growth, (+) Presence of microbial growth.

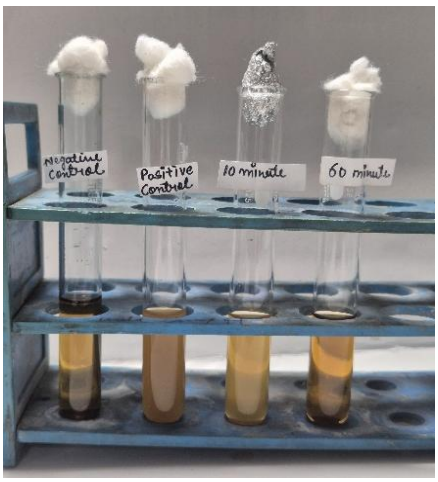

Figure 1: Sterility test observations in ATGM

Test for fungi: *Candida albicans* was used as test organisms. As shown in Table 8 and Figure 2, there was no evidence of growth found in the 'test' and 'negative control' tubes and there was macroscopic evidence of microbial growth in 'positive control' test tube. The results suggest that F8 tested for fungi were passed the test for sterility.The overall results of the sterility test showed that the surface sterilized F8 passed the sterility test and hence they were sterile preparations.

Table 8: Sterility test observations in SBCD medium

S.N.	Samples	Days													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Negative control	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	Positive control	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	Sterilized (120 min)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(-) Absence of microbial growth, (+) Presence of microbial growth.

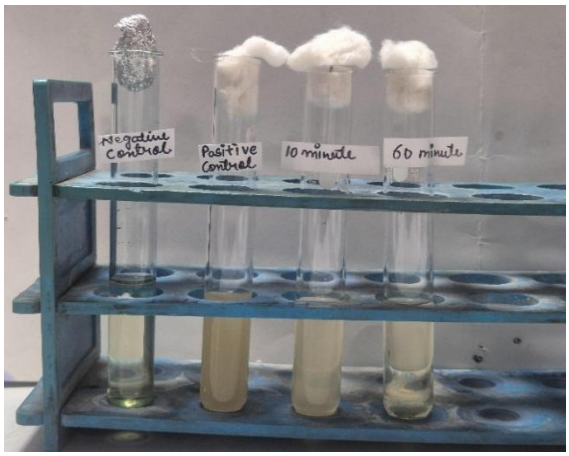

Figure 2: Sterility test observations in SCDM

CONCLUSION

The inserts of Berberine HCL and Curcumin were successfully formulated with different polymers and plasticizers. All the inserts showed reasonably good physical, mechanical properties and drug release suitable for an ophthalmic insert. In the experiment, the different polymers and plasticizers combinations showed varied mechanical properties. Considering all the Physical studies, it can be concluded that an ophthalmic insert of Berberine HCL and Curcumin can be prepared successfully.

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