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DEVELOPMENT AND CHARACTERIZATION OF CARBOXYMETHYLCELLULOSE BASED EMULGEL FOR DRY EYE SYNDROME

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ABSTRACT: Dry Eye Syndrome is a common disorder of the normal tear film that results from one of the following: decreased tear production, excessive tear evaporation, an abnormality in the production of mucus or lipids normally found in the tear layer. Carboxymethylcellulose (CMC) is a highly viscous derivative of cellulose that is used as an eye lubricant. CMC moistens the eye to prevent or relieve dry eye and irritation. Emulgels are nothing but emulsions that may be of water-in-oil or oil-in-water type, which, when blended with gelling agents, gets jellified. Emulgels are a slight viscous product that creates the strength of the product to enhance the retention on eye and improve the spreadability of the product. Castor oil and CMC based emulgel were prepared in three different phases like Polymeric Phase (CMC and Carbomer), Oil Phase (Castor oil), and Aqueous Phase (excipient phase). Process variables also identified and design space created by varies the concentration of oil, surfactant, and polymer. Different formulations designed with changes in oil concentration from 0.25% to 1%, polysorbate-80 from 0.5% to 1%, chromophore from 0.25% to 0.5% and Carbomer from 0.025% to 0.05%. Stability studies have been performed with optimized formulation F-11 at different temperature conditions and characterized physicochemical parameters like pH, Osmolality, Viscosity, Zeta potential, Globule size, Assay of CMC, Assay of preservatives and in-vitro release. An *in-vitro* study performed and flux values (ng/cm^2 / min) of released content determined and compared with marketed products in two different lot and found equivalent.

INTRODUCTION: Dry eye is a disorder of the tear film which occurs due to tear deficiency or excessive tear evaporation; it causes damage to the inter palpebral ocular surface and is associated with a variety of symptoms reflecting ocular discomfort [1]. Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles [2].

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Dry eye disease sometimes referred to as dysfunctional tear syndrome, is often a source of frustration for clinicians and patients alike [3]. Based on the study results illustrate the problem of approaching dry eye as a monolithic syndrome. “If you do a high-power study with a lot of patients and enroll them by dry eye criteria, you may not be able to get a treatment effect, because it’s such a mixture of subtypes [4].

Dry eye syndrome, also known as keratoconjunctivitis sicca (KCS), is a common condition reported by patients who seek ophthalmologic care and is characterized by inflammation of the ocular surface and lacrimal glands. Dry eye symptoms may be a manifestation of a systemic disease; therefore, timely detection may lead to recognition of a life-threatening condition.

Additionally, patients with dry eye are prone to potentially blinding infections, such as bacterial keratitis [5] and also at an increased risk of complications following common procedures such as laser refractive surgery. Knowledge of the pathophysiology of dry eye has recently been improved, and the condition is now understood to be a multifactorial disease characterized by inflammation of the ocular surface and reduction in tear production [6].

Etiology: Dry eye syndrome is associated with a long list of causes, which can be divided into primary and secondary. Dry eye may develop secondary to;

- Inflammatory disease (*e.g*., vascular, allergic),
- Environmental conditions (*e.g.,* allergens, cigarette smoke, dry climate),
- Hormonal imbalance (*e.g.,* perimenopausal women and patients under hormone replacement therapy).
- Contact lens wears.
- Systemic disorders, such as diabetes mellitus, thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus, can also lead to dry eye.
- Neurotrophic deficiency, previous eye surgery (such as corneal transplantation, extracapsular cataract procedures, and refractive surgery), or long term use of medications that create hypersensitivity or toxicity in the eye can predispose to dry eye.
- Systemic medications, such as diuretics, antihistamines, antidepressants, psychotropics, cholesterol-lowering agents, beta-blockers, and oral contraceptives, may also be associated with dry eye [7, 19].
- Postmenopausal women may be the largest at-risk group; this is due to a decrease in hormonal levels leading to loss of anti-inflammatory protection and decreased lacrimal secretion [7].

Dry eye is recognized as a consequence of the disruption of the lachrymal functional unit. The lachrymal functional unit consists of lachrymal glands, the ocular surface including cornea, conjunctiva, eyelids, meibomian glands, ocular nerves, and goblet cells [8]. The tear film is composed of three main layers. The innermost mucin or mucus layer is the thinnest, produced by cells of conjunctiva. The mucus helps the overlying watery layer to spread evenly over the eye. The middle or aqueous layer is the largest, thickest layer produced by the glands of upper lids and the accessory tear glands and contains essentially a very dilute saltwater solution [9, 10]. This layer keeps the eye moist and helps in the removal of any dust, debris, or foreign particles. Defects of this layer cause DES in most cases [11, 12].

The main symptom of dry eyes is dry and gritty feeling in the eyes. The additional symptoms include burning or itching in the eyes, foreign body sensation, excess tearing, pain, and redness of the eyes and photophobia in some cases [13, 14]. Sometimes it is also associated with a stringy discharge and blurred, changing vision. Symptoms are found to worsen in dry weather, with low humidity and higher temperatures [15]. Artificial tears are lubricant eye drops used to treat the dryness and irritation associated with deficient tear production in KCS. The lubricant tears are available as OTC products and usually are the first line of treatment. Mild disease conditions require the application of lubricant drops four times a day, while severe cases need greater frequency (10-12 times a day) of administration. These OTC products mainly vary in their ingredients, indications, and availability of preservatives. Ingredients such as cellulose and polyvinyl derivatives, chondroitin sulfate, and sodium hyaluronate determine their viscosity, retention time, and adhesion to ocular surface [17]. The increase in viscosity of teardrops prolongs the duration of action; however, it results in temporary blurred vision [18]. Preservatives are added to multidose containers of artificial tears to reduce the risk of bacterial contamination and to prolong shelf-life. Many ophthalmic products contain preservatives, and the risk of adverse effects increases with the frequency of their administration per day and also the duration of their use [19]. The clinician should take into account the sensitivity of the patient to preservatives, frequency of use, the severity of the disease, contamination risk with the preservative-free product, and cost while recommending artificial tear product.

In addition, many in-office procedures can help with dry eye syndrome. Examples like slow-release lubrication inserts, punctual plugs, meibomian gland expression, and intense pulse light treatments [20].

MATERIALS AND METHODS:

Materials: Castor oil was purchased from A and E Chemicals. Carboxymethylcellulose (CMC) and Carbomer 974P were supplied by Ashland and Lubrizol, respectively. Glycerin was obtained from Dow Chemicals. Kolliphor RH 40 (Polyoxyl 40 hydrogenated castor oil) purchased from BASF. Boric Acid and Polysorbase-80 were procured from Merck. Stabilized Oxychloro Complex (Purite) purchased from Entod. Dexpanthenol purchased from DSM Nutrition.

Methodology of CMC and Carbomer based Ophthalmic Emulgel Preparation: As an emulgel, their manufacturing was done in three different phases.

Polymeric Phase: Hot water (approx 70 ºC) taken in 35% of batch size and add Carbomer 974P and followed by carboxymethyl cellulose. Cool the solution up to room temperature and adjust the pH around 7.5 by using 2.5N sodium hydroxide. Make up the volume about 40% of batch size with ambient water and stir it. Sterilize the polymeric phase through autoclaving for 30 min.

Oil Phase: Required quantity of castor oil was taken in a glass beaker and added the required quantity of polysorbate-80 and Kolliphor RH 40. Mix them well and sonicate for 30 min.

Increase the temperature of oil phase and sterilize it through aseptic filtration. Homogenise the oil phase in continuation at 60 ºC to 70 ºC with around 6000 to 10000 rpm to get the desired globule size. Add and mix the oil phase in the polymeric phase.

Aqueous Phase: Hot water (aprox 70 ºC) taken in 10% of batch size in a separate container. Added and mixed required quantity of dexpenthanol and followed by glycerine. After complete dissolution, add and mix boric acid and stabilized oxychloro complexes in the above mixture. Mix well, the solution further added in a bulk mixture of polymeric and oil phase. Make up the volume to 100% of batch size and mix well.

Optimization of Components for Emulgel Formulations: Oil, polymer, surfactant(s), preservative, and other components were selected respectively to prepare stable emulgel formulation. The selected components were further screened for their emulsifying ability to form an emulsion. The experiments also designed **Table 1** to create the design space wherever any quantitative change in composition will not impact on product stability.

TABLE 1: DESIGN OF EXPERIMENTS

Variables	Range
Castor oil	0.25% to 1%
Polysorbate 80	0.5% to 1%
Cremophore	0.25% to 0.5%
Carbomer	0.025% to 0.05%

Characterization of Emulgel:

Physical and Chemical Stability: Ophthalmic polymeric emulsion was filled in transparent glass bottles. The emulsion was stored for an appropriate period at accelerated (40 ºC ± 2 °C /NMT 25% RH) and long term (25 ºC / 40% RH ± 5% RH) and assayed for physical and chemical stability. The physical appearance, pH, osmolality, globule size and viscosity were used as indicators of physical stability. CMC and oxychloro content were monitored by UV spectroscopy during the stability program.

Measurement of pH, Osmolality, Density and Zeta potential of Emulgel: The pH of emulgel formulations was determined at 25 ºC using the pH 110 digital acidometer (Lovibond, UK) and refractive index were measured with a thermostat Abbe. The osmolality of the product was measured in Osmomate 030 or Advanced Instruments, Inc., model 3250. Approximately 200 µL of the sample was taken with a micropipette and measure the osmolality using a calibrated Osmometer. Check and record the readings (where instrument display osmolality in Osmol/kg, value to be multiplied by 1000 for conversion into mOsmol /Kg) and report the value. A dry relative density bottle was taken and weigh it (W_1). Fill the relative density bottle with purified water. Maintain the temperature of the filled relative density bottle at about 25°C, wipe off any excess liquid from the surface of the relative density bottle and weigh (W_2). Now empty the pycnometer bottle/relative density bottle and dry it. Fill the relative density bottle with sample and weigh it (W_3) while maintaining the

temperature of the filled relative density bottle at about 25 °C.

$$\text{Weight / mL} = (W3-W1) / (W2-W1) \times 0.99602$$

Where, W1 = Weight of empty pycnometer / Relative density bottle, in g, W2 = Weight of pycnometer with water/ Relative density bottle, in g, W3 = Weight of pycnometer with sample/ Relative density bottle, in g, 0.99602 = Weight per mL (g/mL) of water at 25 °C. Zeta potential of CMC based emulgel drug delivery system was carried out by dynamic light scattering through Zetasizer 3000HS, Malvern Instruments Corporation, U.K.

Globule size Analysis: The diameter of the dispersed phase oil droplets in the samples was analyzed using a particle size analyzer (Make: MALVERN, Model: MASTERSIZER 2000).

Viscosity Measurements: The viscosity of emul-gel compositions were measured by Brookfield LV DV-II+ Pro viscometer. Add about 15mL of the sample in the sampling vessel and assemble the small sample adapter. Insert and centrally place the spindle no S-00 in the test material kept in a small sample adapter. Until the fluid level is at proper immersion depth. Attach the spindle to the lower shaft of the viscometer very carefully; lift the shaft slightly, holding it firmly with one hand while screwing the spindle on with others. Verify the proper spindle immersion depth and that the viscometer is level. Adjust the temperature of the sample such that it is maintained at about 25 ± 0.1 ºC throughout the measurement at speed at 60 rpm. No air bubbles trapped around the spindle during analysis. Record the value of viscosity.

Assay of Sodium Carboxymethyl Cellulose (by Colour Development): Dry standard in an oven maintained at 110 ºC for 2 h and kept in the desiccator until it attains room temperature before use. Weight 25 mg of carboxymethyl cellulose sodium working standard into 250 mL volumetric flask and add about 150 ml of hot water (about 85 °C) and stir for 10 min. Cool it to room temperature and then make up the volume with water and mix it to prepare the standard solution. Transfer accurately 1 g of product into a 50 ml volumetric flask. Add 30 ml of hot water and stir for 5 min and allow it to cool to room temperature and make up the volume with water and mix well. Pipette accurately 1 ml of sample solution stock in a dried 10 ml volumetric flask. Add 0.5 ml of 8% phenol and add 3 ml of concentrated Sulphuric acid.

Apply the stopper and mix the contents immediately and incubate the flask immediately into an oil bath maintained at 100 °C for 5 min and then immediately transfer to an ice bath (approx. 4 - 5 °C) for 5 min and then finally to water bath (room temperature) for 5 min and mixed well. Measure the absorbance of the standard and sample solution at a wavelength of 490 nm in suitable UV - Visible spectrophotometer against blank.

Content of Preservative (Stabilized Oxychloro Complex): Accurately weigh about 50 mg of primary standard potassium dichromate (previously dried at 120 °C for 4 h) and dissolve in 100 mL of water in a glass stoppered, 500 mL iodine flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of concentrated hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow standing in the dark for exactly 10 min. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution *vs.* until the solution is yellowish-green in color. Add 3 mL of starch solution (Mix 1 g of soluble starch with 10 mg of red mercuric iodide and sufficient cold water to make a thin paste. Add 200 ml of boiling water and boil for one minute with continuous stirring. Cool and use only the clear solution), and continue the titration until the blue color is discharged.

Stability Study: The optimized formulations were stored at three different stability condition as per ICH for accelerated (40 ºC± 2 °C/NMT 25% RH), intermediate (30 ºC / 65% RH ± 5% RH) and long term (25 ºC / 40% RH ± 5% RH) for a period of six months. Samples were withdrawn after specified intervals and evaluated for drug content, pH, transparency, clarity, non-grittiness, and color change. The centrifuge test was also carried out to assess the physical stability of formulations by centrifuging at 13,000 rpm for 30 min.

***In-vitro* Permeation Study:** To evaluate the *in-vitro* permeation, Glass Franz diffusion cells with

drive console (FDC-6T, Logan Instruments and Somerset, NJ) were used. Phosphate-buffered saline (Gibco® PBS, with calcium and magnesium, Cat. 14040, Thermo Fisher Scientific) at pH 7.4 was used as the receiver buffer. The membrane was dipped in the medium for 24 h before use. The previously dipped cellophane membrane was mounted between the donor and receiver compartment of the Franz diffusion cell, on which the weighed quantity of formulated gel was spread completely to cover most of the area. The receiver fluid was stirred using a small magnetic bead, and the temperature was maintained to 37 ± 2 ºC with the help of a hot plate. At predetermined time intervals, 1 ml sample solution was withdrawn and replaced with fresh STF to maintain sink condition. The collected samples were subjected to quantification of Carboxymethyl cellulose using a UV-visible spectrophotometer at 490 nm. Triplicate experiments were carried out for each release study.

In-vitro release profile of developed formulation was compared with the release profile of marketed refresh active advanced under similar conditions.

RESULTS AND DISCUSSION:

Physical and Chemical Stability: The emulgel formulations consisted of oil, surfactants, and polymers should be a clear, viscous, biphasic liquid. So, different formulations have been prepared with changes in oil concentration and stabilize them by using different concentrations and types of surfactants. Formulations designed with changes in oil concentration from 0.5% to 1%, polysorbate-80 from 0.25% to 1%, cremophore from 0.25% to 0.5% and Carbomer from 0.025% to 0.05%. All the formulations kept at ambient temperature and observed their physical stability. Based on physical screening, **Table 2,** only four formulations (F-6, F-8, F-10, and F-11) found stable. Further, these four formulations have been characterized further.

TABLE 2: COMPOSITIONS OF DIFFERENT FORMULATIONS

Formulations	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Castor oil	0.5%	0.75%	1%	0.5%	0.25%	0.25%	0.5%	0.25%	0.5%	0.5%	0.5%	1%
Polysorbate 80	0.5%	0.5%	0.5%	1%	0.5%	1%	1%	0.5%	1%	0.5%	0.5%	0.5%
Cremophore	--	--	--	--	--	0.05%	--	--	0.3%	0.25%	0.5%	0.5%
Carbomer	0.025%	0.0375%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Observation	Creaming was observed	Emulsion cracked within 12 h	Emulsion cracked within 12 h	Settling was seen in the emulsion within 12 h	Emulsion cracked within an hour	Emulsion is stable, viscosity 6 cps	Emulsion settled within 12 h	Emulsion is stable, viscosity 4 cps	Emulsion was stable at RT, creaming seen after 15 days.	Emulsion stable at RT.	Emulsion stable at RT, Visually stable at 2-8 and 50 °C	Creaming observed after 48 h

Measurement of pH, Osmolality, Density, and Zeta potential of emulgel: The pH, Osmolality, density, and zeta potential were performed on selected formulations at around a temperature of 25 ± 0.1 ºC.

The pH of the product was the target at around 6.7, which is close to neutral pH to avoid eye irritation during installation of the product. Osmolality also targets at around 300, which are iso-osmotic to eye fluids, and density is also around approximately 1.

Zeta potential also measured in developed composition to check the potential difference between the dispersion medium and the stationary layer of fluid attached to the dispersed particle and found stable composition. Results are mentioned in **Table 3** and related graphs in **Fig. 1.**

TABLE 3: PHYSICAL PROPERTIES OF SELECTED FORMULATIONS

Formulations	F-6	F-8	F-10	F-11
pH	6.73	6.63	6.67	6.73
Osmolality (mOsmol/kg)	294	293	293	296
Density (gm/L)	1.001	1.005	1.003	1.006
Zeta Potential	-13.7	-12.4	-14.9	-15.3

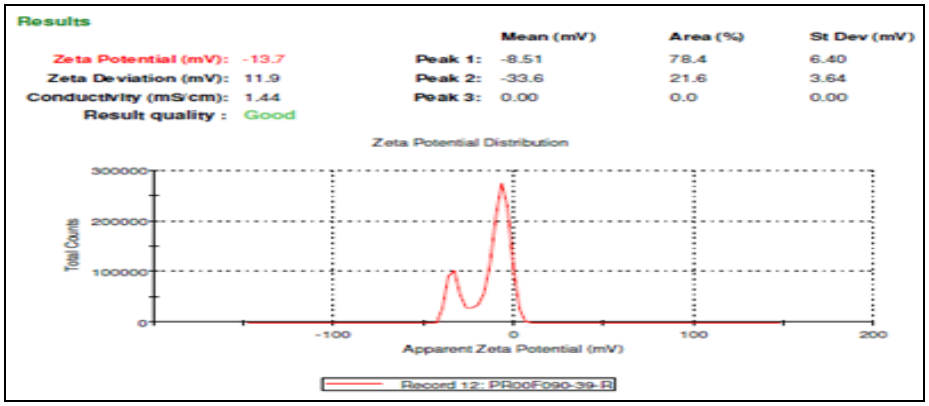

FIG. 1A: ZETA POTENTIAL FOR FORMULATION F-6

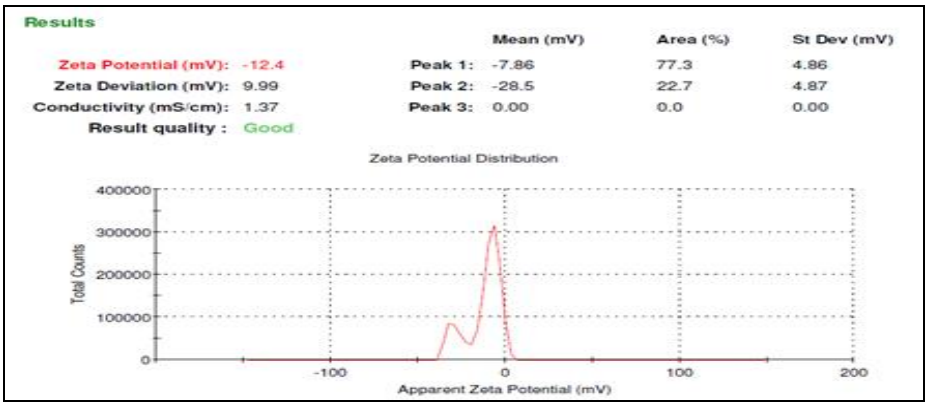

FIG. 1B: ZETA POTENTIAL FOR FORMULATION F-8

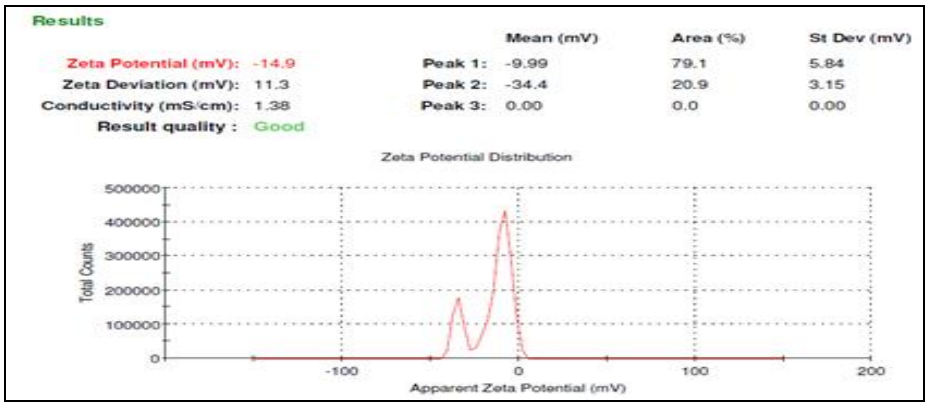

FIG. 1C: ZETA POTENTIAL FOR FORMULATION F-10

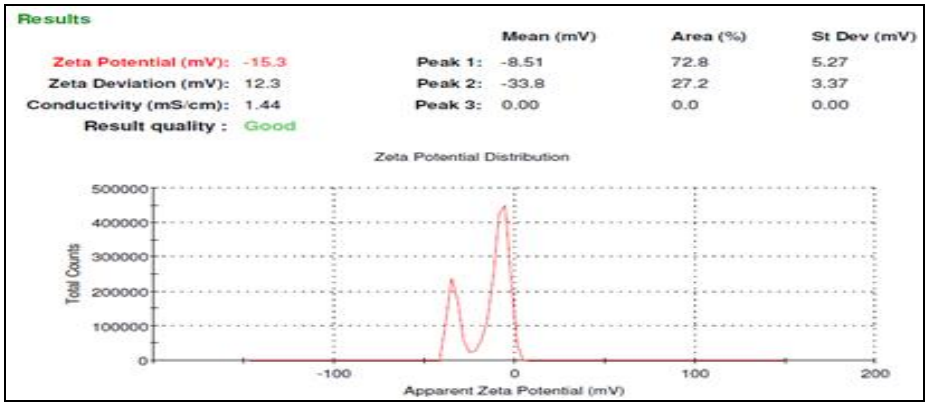

FIG. 1D: ZETA POTENTIAL FOR FORMULATION F-11

FIG. 1: A, B, C AND D (ZETA POTENTIAL FOR SELECTED FORMULATION

Globule Size Determination: Optical part of the instrument aligned properly before use and blank measurement of the particle-free dispersion medium performed. The background signal must be below an appropriate threshold. Shake the sample and transfer to the test tube and pour into the dispersant with a dropper until the obscuration is in the desired range achieved.

Allow the obscuration to be stabilized and perform the analysis. Furthermore, a decrease in the droplet size reflects the formation of a better-packed film of the surfactant at the oil-water interface, thereby stabilizing the oil droplets. Results revealed that formulations F-6, F-8, and F-10 had droplet size larger than 500 nm. While formulation F-11 was followed the criteria of the emulsion by having the droplet size lower than 250 nm, indicating the uniformity of oil globules. Hence, formulations F-11 were selected for further stability.

Viscosity Measurements: Prepared emulgel compositions have been used as such (without dilution) to determine the viscosity and observed that all compositions are having the viscosity 9 ± 2 cps. This viscosity help to retain the product in eye for prolong relief from dry eye disease.

Stability Study: In order to determine the storage stability, the samples were charged on stability as per ICH recommendations for accelerated (40 ºC± 2 °C/NMT 25% RH), intermediate (30 ºC / 65% RH ± 5% RH) and long term (25 ºC / 40% RH ± 5% RH) storage condition and analyzed physico chemical aspect. Formulation F-11 was selected based on their physical stability. Furthermore, F-11 was analyse physically and then chemically (Table-4) to determine the assay of carboxymethyl-cellulose and content of stabilized oxychloro-complex and found F-11 was stable thorough stability design.

TABLE 4: STABILITY STUDIES OF F-11 FORMULATION

		Batch Number – F-11				
Condition	**Initial**	**40 ºC ± 2 °C / NMT 25% RH**		**30 ºC/ 65% RH ± 5% RH**	**25 ºC / 40% RH ± 5% RH**	
Parameter		**3M**	**6M**	**6M**	**6M**	**12M**
Description	White Opalescent viscous solution	White Opalescent viscous solution	White Opalescent viscous solution	White Opalescent viscous solution	White Opalescent viscous solution	White Opalescent viscous solution
pH	6.75	6.70	6.71	6.78	6.77	6.75
Osmolality (mOsmol/kg)	294	297	306	299	294	295
Viscosity (cps)	9.26	9.08	9.70	9.26	9.78	10.5
Assay of CMC (%)	101.4	102.5	101.9	102.3	99.4	101.4
Content of SOC (%)	103.5	102.0	99.1	102.0	101.1	102.0
Globule Size D(0.1)	0.081	0.095	0.090	0.077	0.072	0.083
D(0.5)	0.156	0.152	0.156	0.144	0.141	0.148
D(0.9)	0.208	0.212	0.208	0.224	0.234	0.207

***In-vitro* Permeation Study:** On the day of each study, each cornea was washed thrice with PBS at room temperature before mounting onto the corneal Franz diffusion chambers between the donor and receiver chambers.

PBS pre-warmed to 37 ºC (9 mL) was placed in the receiver chamber, and 200 µL of PBS was placed in the donor chamber (capacity of donor chamber is 0.5 mL) for equilibration 30 min.

After 20 min, the PBS was removed from the donor chamber with a laboratory wipe, and then the appropriate dose was applied. The permeation duration started when each formulation was dosed into the anterior side/donor chamber.

The receiver compartment contained a stirring bar (600 rpm), and the chamber temperature was maintained at 37 °C with a water jacket. The diffusional surface area of the Franz-cell was 0.64 cm^2. Samples were withdrawn from the receiver compartment at pre-defined time points detailed in **Table 2** and were replaced with an equal volume of fresh, warm buffer to maintain sink conditions. The samples were analyzed by UV–Visible spectro-photometer. At the end of the permeation duration, the temperature at the surface of each cornea was measured using an infrared thermometer. The temperature was in the range of 32 ± 2 °C for all studies. The details for each formulation are indicated in **Table 5**.

TABLE 5: *IN-VITRO* STUDIES OF F-10 & F-11 SAMPLES COMPARED WITH MARKETED FORMULATIONS

Formulation	Batch Number
Marketed product-1 (Refresh Optive)	271533F
Marketed product-2 (Refresh Optive)	295950F
Test-1	F-10
Test-2	F-11

Overall Flux Values (ng/cm2/min) of released content **Table 6** also determined and plotted in graph to compare the selected formulation (F-11) with marketed products in two different lot. Also, compare the release criteria of F-11 and F-10, which are equivalent to marketed products.

TABLE 6: OVERALL FLUX VALUES IN F-10 & F-11 COMPARED WITH MARKETED PRODUCTS (ng/cm^2/MIN)

Treatment	Replicate						Mean	SD	%CV
	1	2	3	4	5	6			
Marketed product-1	80.6	81.2	NA[1]	NA[1]	85.9	84.7	83.1	2.63	3.16
Marketed product-2	72.3	NA[1]	31.6	107	76.4	82.8	73.9	27.1	36.7
Test-1	66.1	67.4	NA[1]	77.6	101	86.7	79.7	14.3	18.0
Test-2	80.8	102	104	108	94.3	NA[1]	97.9	10.8	11.1

NA1: This replicate had a non-linear profile. It was excluded from the calculations

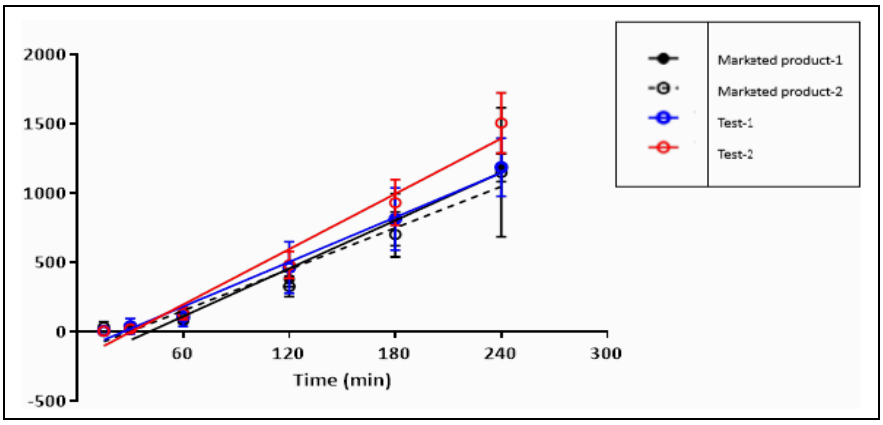

FIG. 2: COMPARISON OF *IN-VITRO* RELEASE

CONCLUSION: The CMC based ophthalmic preparations always the best way for treatment in dry eye disease. Stabilized the Emulgel composition with castor oil, surfactants (polysorbate-80 and Kolliphor RH 40), and Carbomer and compare the release pattern with marketed samples. In conclusion, from the above research work, it has been concluded that developed compositions are equivalent to marketed samples.

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CONFLICTS OF INTEREST: Nil

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