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Fabrication and characterization of Curcumin Nanoemulgel to Overcome the Challenges in Opthalmic Drug Delivery System

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Abstract: Major challenge in ophthalmic drug delivery system is to locate the drug in precorneal site for some time as the applied dose has been washed out quickly in the lachrymal drainage. As well as it has been always a challenge in the drug delivery to formulate poorly soluble compound as conventional ophthalmic delivery like eye drops. Hence the purpose of the present study is to formulate ophthalmic *in-situ* nanoemulgels which are generally liquids at room temperature but exhibit sol-to-gel phase transition on the ocular surface due to change in specific physicochemical parameter like ionic strength, pH or temperature. The formulation was so designed to prolong the precorneal resident time thereby getting sustained delivery of drug and to improve bioavailability of poorly soluble model drug of curcumin by distributing it in nano globules of dispersed system. Different parameters of fabricated nanoemulgel like gelling capacity, gelation temperature, droplet size analysis, stability study, and refractive index, viscosity, Scanning Electron Microscopy (SEM) and drug release profile are evaluated. The physico-chemical evaluation reveals good rheological properties with instantaneous gelling capacity. Fourier Transform Infrared analysis (FTIR) study showed absence of incompatibility between the drug and polymer. The globular size found in nanometer range (below 200nm) and uniformity in size distribution (ploydispersity index 0.215-0.53) is studied by Malvern Zetasizer. Accelerated stability analysis ascertained the stability of formulation after storing at 40°C ± 2°C/75% RH ± 5% RH for 3 months. The drug release study of the formulations revealed sustained release of drug for the study period of 5 hours ranging from 31.87±2.12 to 61.77%±1.27. The developed thermosensitive nanoemulgel formulation is an effective ophthalmic delivery for getting sustained action of poorly soluble compound like curcumin.
Keywords: Nanoemulgel; Curcumin; In-situ gel; dispersed system.

INTRODUCTION

Conventional ophthalmic drug delivery systems in the form of eye drops result in poor bioavailability and low therapeutic response due to wash out effect of lacrimal secretion. Approximately less than 1% of an applied dose will be absorbed through the cornea due to the barrier effect of corneal epithelium, the blood aqueous barrier and the blood retinal barrier [1]. An instilled aqueous solution will be eliminated from the precorneal area within 90sec. Therefore the designing an ocular drug delivery system has been offering a major challenge in the field of pharmaceutical research [2]. The major challenge of confining the liquid instilled into the eye can be overcome by increasing the contact time of the instilled liquid on the corneal surface. Ophthalmic *in-situ* emulgel by virtue of their instant sol-gel transformation enhances the corneal residence time. The dual advantage of *in-situ* phase conversion of the ophthalmic emulgel are, easy to administer like conventional eye drops, and enhanced contact time of the applied formulation due to instant conversion of sol to gel. The phase conversion effected due to changing in a specific physico-chemical parameter like ionic strength, pH or temperature. The emulsion based liquid formulation is advantageous for effective delivery of hydrophobic therapeutic moiety. When gels and emulsions are used in combined form, the dosage form is referred to as emulgel [3].

Curcumin is a naturally occurring phytochemical, obtained by extraction of the rhizome of Curcuma longa, family Zingiberaceae grown in tropical Southeast Asia. It is well known for its variety of medicinal properties like antioxidant, anti-tumor, anti-inflammatory, anti-viral, anti-HIV and low toxicity makes it much promising candidate for clinical application [4]. Curcumin is also found to be effective for ophthalmic use in various ocular pathologies such as dry eye syndrome and proliferative vitreo-retinopathy

[5]. The anti-inflammatory effects on eye were also confirmed by in-vivo experiments [6]. Curcumin is poorly soluble in water and the maximum solubility is reported to be 11ng/ml in aqueous buffer pH 5.0 [7]. The oral bioavailability is very low. It is found only 1% in rat [8]. The bioavailability of curcumin can be improved by numerous approaches such as Liposomal formulation [9], formation of curcumin phospholipid complex [10], formulation of nanosuspension by high pressure homogenization [11]. Spray dried curcumin nanocrystals may be filled into the capsules to produce solid dosage form.

Nanoemulsions are transparent or translucent systems, which are very fine dispersion of oil in water or water in oil, could be stabilized by the addition of a surfactant, having droplet size range 20–600 nm [12]. Kinetic stability as well as long term physical stability without appearance of flocculation and coalescence makes them unique over other dispersed phase drug delivery system like liposome [13]. *In-situ* ophthalmic Nanoemulgel could be utilized as a potential drug reservoir for sustained release of drugs and to increase drug bioavailability [14]. Nanoemulsions provide higher surface area and free energy that make them suitable as an effective transport system. They do not show the problems associated with micro-emulsions, like creaming, flocculation, coalescence and sedimentation [15].

Opthalmic nanoemulsion **[16]** has been developed into nanoemulgel by fabricating it in thermo-sensitive polymer PF-127, to get *in-situ* sol to gel conversion upon instillation into the eye. Nanoemulgel as an ocular drug delivery system has been developed in our study in virtue of their specific advantages over conventional eye drops. These include easy administration, prolonged contact time, sustained release of the drug, and penetration in the deeper layers of the cornea as well as ease of sterilization. Thus, these systems can produce effective therapeutic action with a smaller dose and little systemic and ocular side effects. It also helps to solubilize the lipophilic drug.

MATERIALS AND METHODS

Materials

Curcumin Ethyl Oleate and Transcutol P were procured from LOBA Chemie (Mumbai); Pluronic F 127 was gifted by Albert David Ltd. (Kolkata); Tween 80, Sodium Chloride, Sodium bicarbonate and Calcium chloride were purchased from MERCK Specialities Pvt. Ltd. (Mumbai) Cellulose Nitrate LA397 cell membrane was procured from Himedia Laboratories Ltd.

Preparation of in-situ ophthalmic nanoemulgel [17]

The preparation of nanoemulsion was done by using ultrasonication method. Curcumin was dissolved in combination of oil (Ethyl oleate), surfactant (Tween-80) and co-surfactant (Transcutol P) using ultrasonic disintegration. Sonication was carried out with intermittent cooling until it becomes a clear solution. Then prepared solution was diluted with the solution of Pluronic F127 (thermosensitive polymer) at the ratio of 1:10 and again sonication was continued to obtain a transparent nanoemulgel formulation. Drug is taken as 1% w/v in the formulation and its quantity remains constant in all the formulation. Three different formulations were prepared (Table-1) using different ratio of oil, surfactant and co-surfactant.

Table-1: Formulation of Nanoemulgel of curcumin:

Formulation Code	Oil:Surfactant:Co-surfactant	Drug (% w/v)
F1	3:2:1	1
F2	2:2:1	1
F3	4:3:2	1

Physical Appearance

The prepared nanoemulgel was inspected visually for their color, odor, homogeneity and clarity.

Determination of pH

The pH of all nanoemulgel formulations was recorded using a calibrated digital pH meter.

Drug content

The determination of drug content was done by accurately taking 0.2 ml of formulations in a test tube and suitably diluted with isotonic buffer solution pH 7.4 to obtain a known concentration of 20µg/ml. UV-Visible spectrophotometer was used to determine the % drug content in the formulation.

Rheological study

Viscosity of instilled formulation is an important factor to be considered to determine the residence time of drug in the eye. The selected Temperature sensitive formulations were allowed to gel in the isotonic buffer solution pH 7.4. Viscosity of the prepared nanoemulgel is determined using Brookfield Viscometer Rotational type. The viscosity of these formulations should be maintained in such a way that, it can be instilled into the eye without any difficulty.

Gelation Temperature

The gelation temperature of three different formulations F1, F2 and F3 was measured by taking the formulation in a test tube and placing it under a water bath gradually increasing the temperature at a constant rate. Into each test tube, 2 mL of each formulation was placed and heated with gentle stirring until the

formulation starts converting into gel. Gel formation was considered to be completed at the particular temperature, where there will be no flow when the test tubes were tilted >90°.

Refractive Index

The refractive index of nanoemulgel was measured by digital Abbes Refractometer.

Gelling capacity

The suitability of the formulation composition is identified by its gelling capacity. The gelling capacity was determined by taking a drop of the system in a vial containing 2 ml of isotonic buffer solution pH 7.4 equilibrated at 37° C and visually assessing the gel formation and noting the time for gelation.

Fourier Transform Infrared analysis (FTIR)

The samples were prepared by the potassium bromide disk method. FTIR was determined by using FTIR 8400S from Shimazdu.

In vitro drug release study

Release of drug from the nanoemulgel formulations was carried out by using Franz Diffusion Cell. The prepared nanoemulgel formulation was placed in donor compartment and the receptor compartment was filled with the isotonic buffer solution pH 7.4. Dialysis membrane was placed in between the donor and receptor compartment. The receptor chamber is stirred by magnetic stirrer at 50 rpm and the temperature of that chamber was maintained by 34 ± 0.5°C. 1 ml of the samples is collected at predetermined time interval, up to 5 hr. the same volume of fresh buffer was replaced in the receptor compartment. Samples were analyzed for drug content by UV-visible spectrophotometer (Model No 1700, Shimadzu) at λmax (421nm) after appropriate dilution. Triplicate experiments were carried out for each release study and the mean value was calculated with standard deviation. The amount of drug released with time is calculated using the equation generated from standard calibration curve and then the % cumulative drug release (%CDR) is plotted against time in minute.

Determination of Droplet size and its distribution

Droplet size and its distribution in the prepared emulgel was determined by Zetasizer Nano ZS90 (Malvern Instruments, Malvern) at 25°C. Samples were diluted with Milli-Q (Millipore Corp.) water and agitated to get homogeneous dispersion before measurement.

Scanning Electron Microscope (SEM)

The morphology of the dispersed globules and their structure has been studied using scanning electron microscopy (SEM). To perform the SEM observations, the formulated nanoemulsion was diluted with water in a ratio of 1:100. A drop of the diluted nanoemulsions was directly deposited on the holey film grid and observed after drying. SEM was determined by using Quanta 200 from FEI.

Accelerated stability study

Formulations are placed in amber color vials and sealed with aluminum foil. For a short term accelerated stability study the formulations are kept at 40±2°C and 75±5% RH was maintained as per International Conference on Harmonization (ICH) Guidelines. Samples are being withdrawn and analyzed every month for Clarity, pH, gelling capacity, drug content, rheological evaluation, and in vitro dissolution.

RESULTS AND DISCUSSION

Physical Appearance

The clarity of the preparation was visualized against black and white background [18]. The prepared nanoemulgel was observed as a yellowish, transparent, homogeneous liquid, free from any foreign particle.

Physico-chemical Evaluation: pH, Viscosity, Drug Content and Gelation temperature and Refractive Index and gelling capacity

The pH of all formulations was tested using a calibrated digital pH meter immediately after preparation. The pH of all the formulations was found in the range of 7.1 to 7.3 (Table-2).

The % drug content of the formulations was determined spectrophotometrically and was observed in the range of 94-97% (Table-2).

Viscosity was measured [19] to determine the rheological properties of formulations. Results are taken into triplicate and average is taken into consideration. The result observed from the ophthalmic in-situ nanoemulgel is in the range of 4.9 to 6.21 Pa-S (Table-2).

It has been found that the gelation temperatures of all the formulations are at about 34°C (Table-2). Hence it is found from the obtained results that the formulations will be converted into a gel upon application into the eye.

Transparency of the formulations was ascertained by studying the refractive index of nanoemulgel. The observed result in the range 1.33 to 1.36 (Table-2), ascertained the transparency of the prepared nanoemulgel [20].

Gelling capacity was studied by placing drop of the prepared nanoemulgel onto the isotonic buffer solution pH 7.4 simulated at 37°C. all the formulations showed instantaneous gelation and remained for extended period of time [19].

Table-2: Physico-chemical Evaluation of Nanoemulgel formulations

Formulation Code	pH	Viscosity (Pa-S)	%Drug content	Gelation Temperature	Refractive Index 30°C
F1	7.2±0.08	6.21±0.10	95.62±0.16	34.2±0.12	1.36+0.17
F2	7.1±0.12	5.9±0.34	94.90±0.27	34.0±0.23	1.34±0.23
F3	7.3±0.05	4.9±0.48	97.85±0.41	34.4±0.09	1.33±0.12

Experiments were carried out in triplicate for each study and the data represented as mean value ± SD

Fourier Transform Infrared analysis (FTIR) [21]

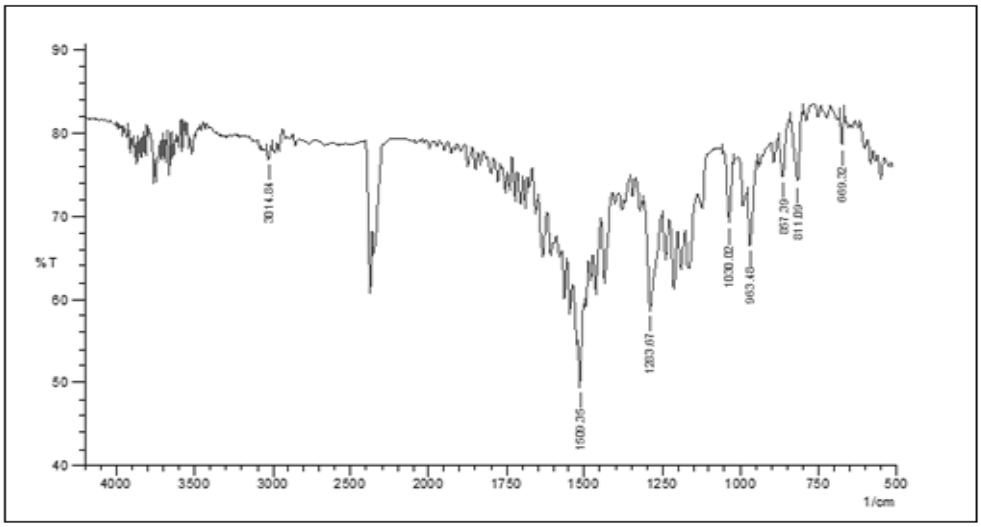

Fig-1: FTIR Spectra of Curcumin

The drug polymer compatibility can be studied by using FTIR Spectra. After running the spectra, significant peaks relating to major functional groups of pure drug (Fig-1), gelling polymer, PF-127 (Fig-2), and their physical mixture (Fig-3) and in formulation (Fig-4) were identified.

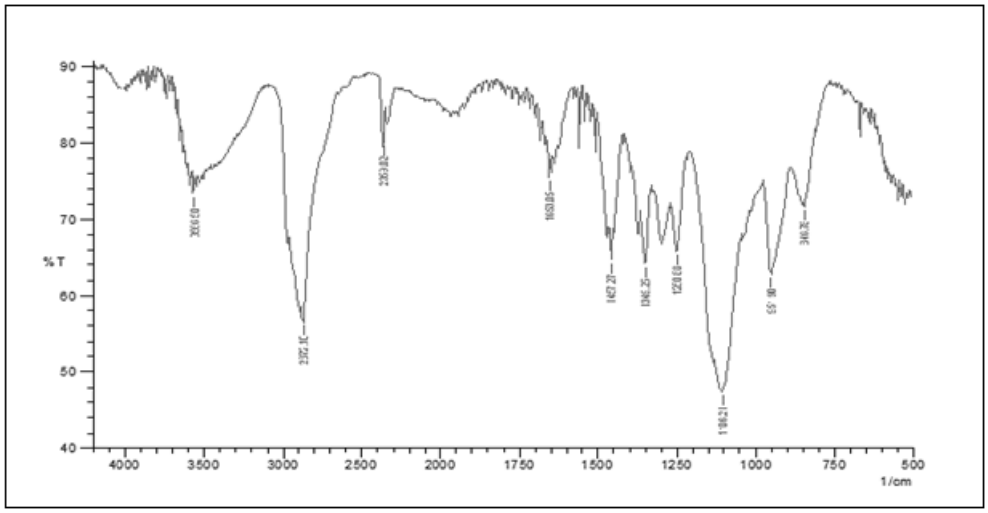

Fig-2: FTIR Spectra of PF-127

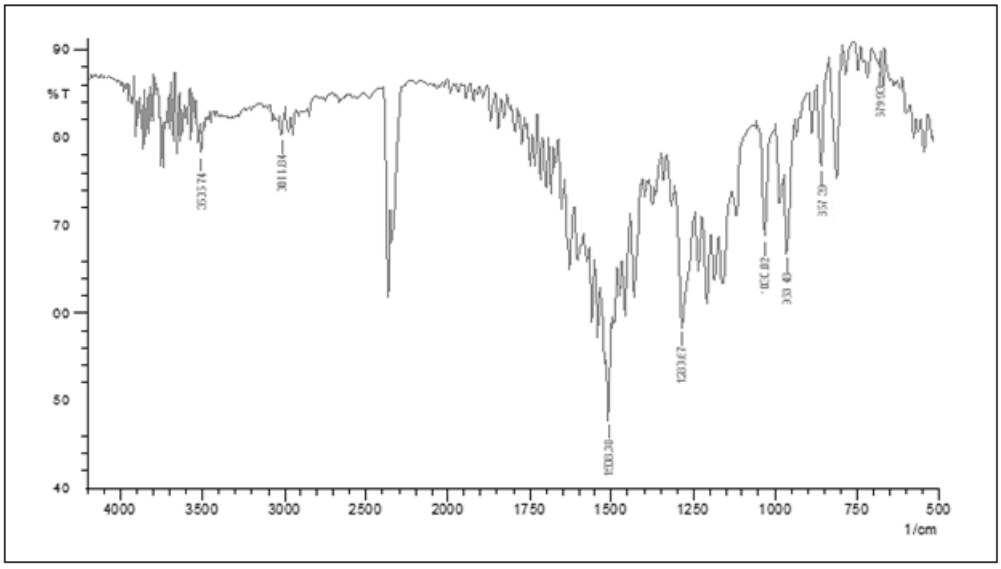

Fig-3: FTIR Spectra of physical mixture of Curcumin and PF-127

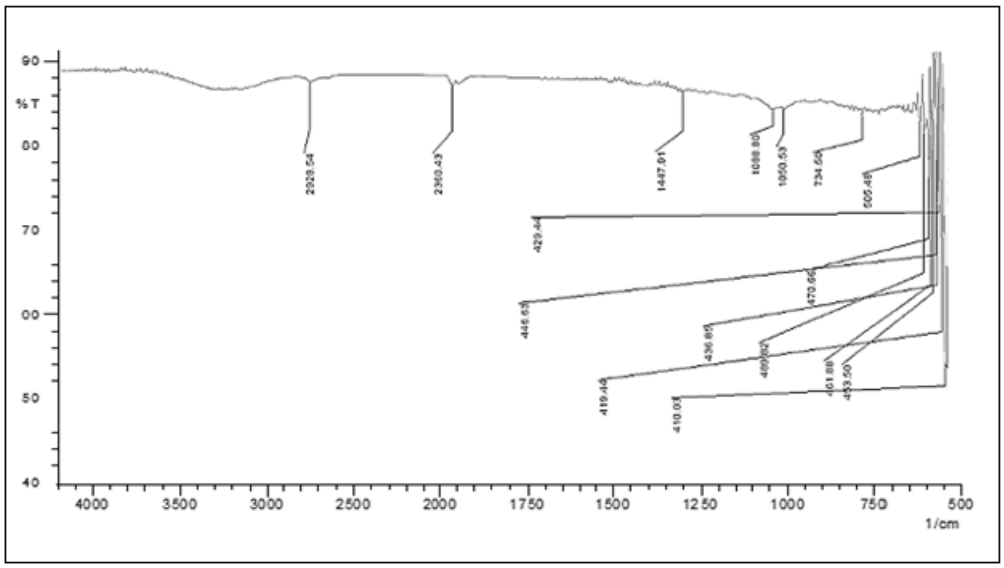

Fig-4: FTIR Spectra of Nanoemulgel Formulation F3

In-vitro drug release studies

In order to mimic physiological dilution process after ocular administration of the prepared nanoemulsions, isotonic buffer solution (pH 7.4) was taken as the drug release study media [22]. Franz diffusion cell [23] was used for the drug release studies. Nanoemulgel (1ml) from the freshly prepared formulation was applied onto the surface of the diffusion dialysis membrane evenly. The diffusion membrane was fixed in between the donor & the receptor chamber. The receptor chamber is filled with isotonic phosphate buffer (pH 7.4). The receptor chamber is stirred by magnetic stirrer at 50 rpm and the temperature of that chamber was maintained by $34 \pm 0.5°C$ to mimic the ocular surface temperature [24]. Franz Diffusion Cell assembly fitted over magnetic stirrer with thermostatically controlled water pumped through the outer jacket of the cell. The samples are collected at suitable interval. Samples were analyzed for drug content by UV-visible spectrophotometer (Model No 1700, Shimadzu) at λmax (421nm) after appropriate dilution. Triplicate experiments were carried out for each release study and the mean value was calculated. Cumulative % drug release was plotted against time in minute (Fig-5).

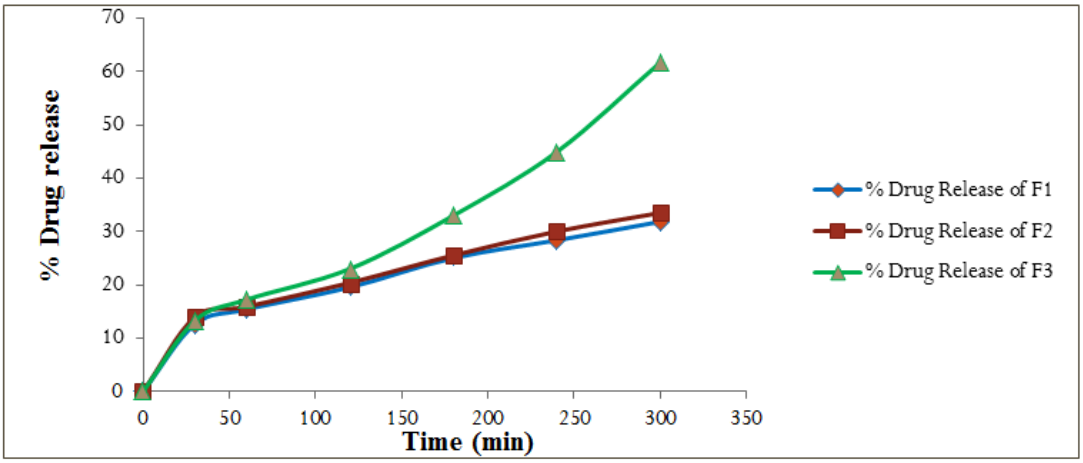

Fig-5: Cumulative % Release vs. Time Plot for In-vitro Release of Curcumin through Cellulose Nitrate Membrane from Different Formulations contains 10% PF 127

Droplet size and its distribution in prepared Nanoemulgel

Droplet size and its distribution in the prepared emulgel was determined by a dynamic light scattering method using Zetasizer Nano ZS90 (Malvern Instruments, Malvern) at 25°C. Samples were diluted with Milli-Q (Millipore Corp.) water and agitated to get homogeneous dispersion before measurement.

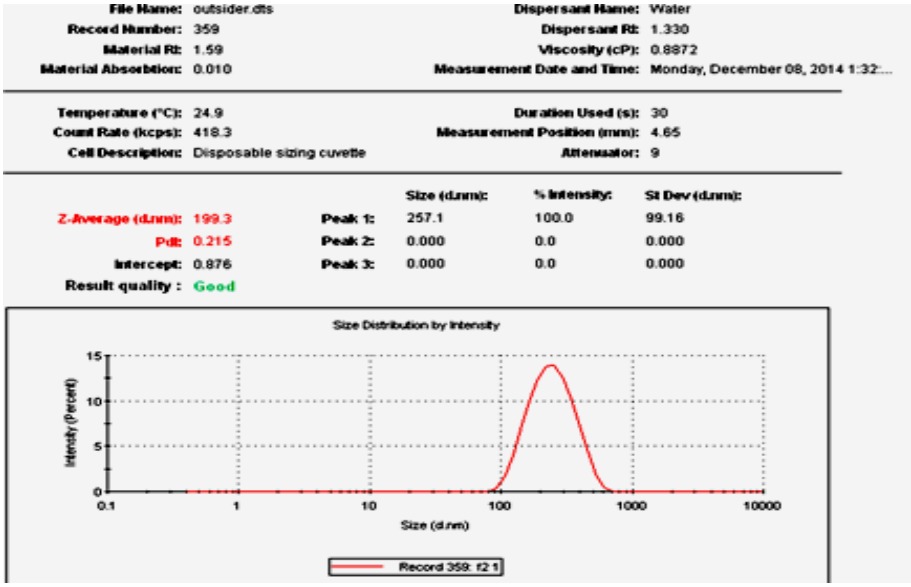

Fig-6: Globule size distribution of Nanoemulsion formulation F2

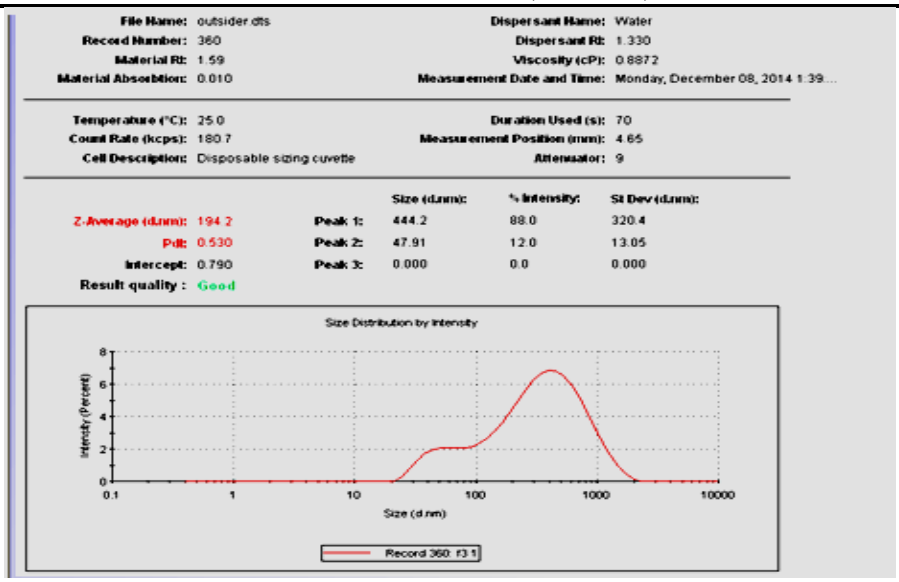

Fig-7: Globule size distribution of Nanoemulsion formulation F3

Scanning Electron Microscope (SEM)

The morphology and structure of the Nanoemulsion has been studied using scanning electron microscopy (SEM). To perform the SEM observations, the nanoemulsion formulation was diluted with water (1/100). A drop of the diluted nanoemulsions was directly deposited on the holey film grid and observed after drying. SEM was determined by using Quanta 200 from FEI.

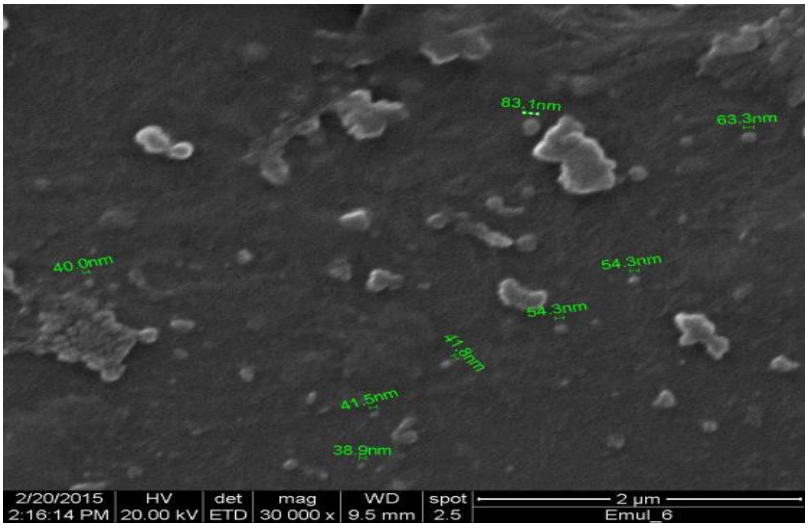

Fig-8: Scanning Electron Micrograph of Nanoemulsion Formulation

Accelerated Stability Study

Nanoemulgel formulations were stored in glass vial kept at accelerated conditions (40°C ± 2°C/75% RH ± 5% RH), we made sampling at one month intervals for the period of three months & tested them for the drug release & particle size.

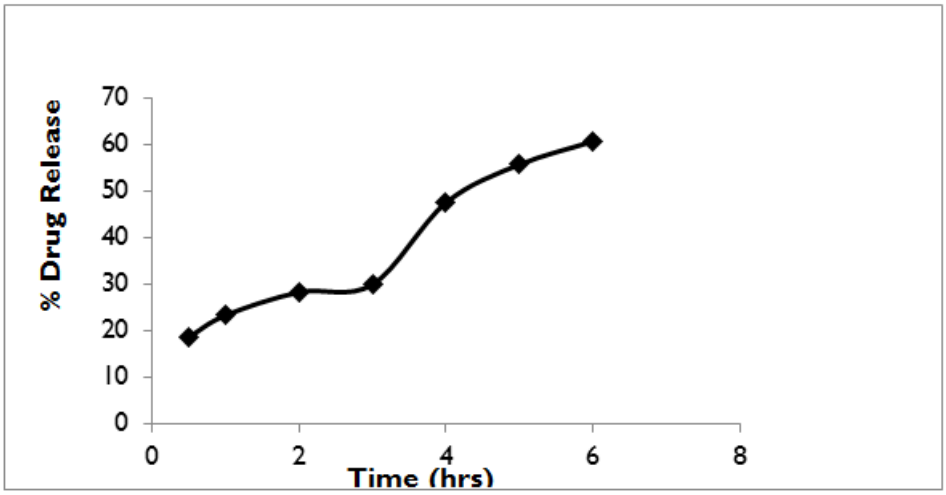

Fig-9: In-vitro Drug release profile of Formulation F3 after storing at 40°C ± 2°C/75 % RH ± 5 % RH for 3 months

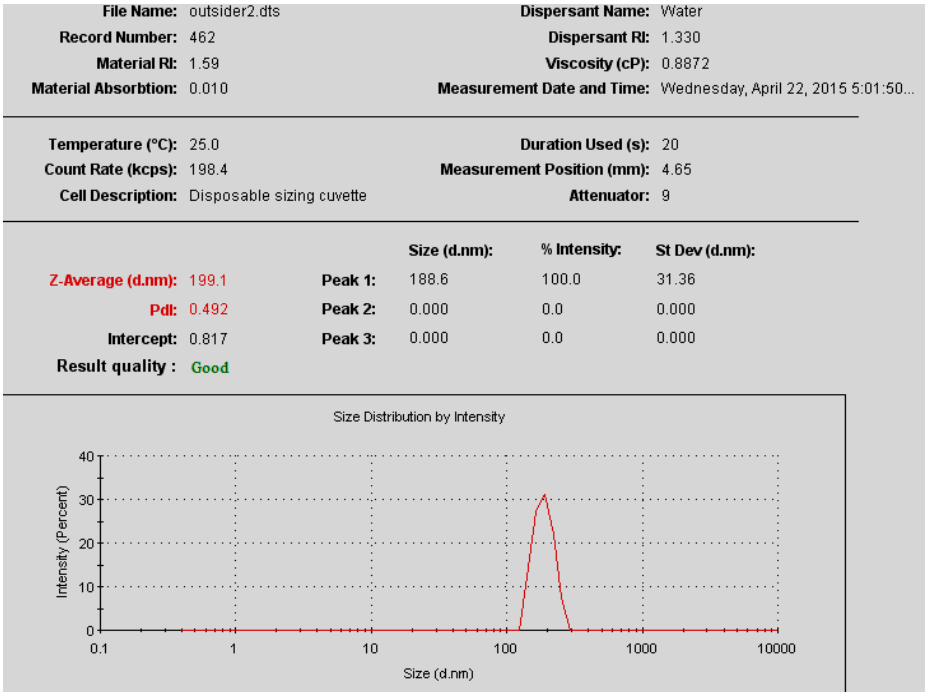

Fig-10: Globule size distribution of Nanoemulsion formulation F3 after storing at 40°C ± 2°C/75 % RH ± 5 % RH for 3 months

Selection of oil, surfactant and co-surfactant were done by literature review. Solubility test for curcumin in different surfactants and oils was conducted using ultrasonication. The ability of Surfactants and oils to solubilize maximum amount of curcumin upon sonication for 30 min was tested individually. Solubility of curcumin was studied in four different oils like paraffin oil, peanut oil, castor oil and ethyl oleate. The solubility in ethyl oleate (0.357±0.032) was found much higher among the four tested oil [25]. The surfactant with maximum curcumin solubility (1%) is Tween 80 than the other tested surfactants like Span-80, Cremophor EL, PEG 400, Campul PG8, Campul PG12, Captex and isppropyl myristate [17]. Transcutol P was used as a co-surfactant, the effects of it on the corneal permeability were studied and potential clinical benefit was found in ocular delivery [26].

The clarity of the prepared nanoemulgel is suitable for ophthalmic application without obscuring the vision. It is recommended that eye drops should have refractive index values not higher than 1.47 [17]. Transparency of the formulations was ascertained from the observed result of refractive index which is found in the range of 1.33 to 1.36. The pH of all formulations was found in the range of 7.1 to 7.3 making it suitable for ophthalmic application [23]. The % drug content of the formulations was observed in the range of 94-97% showing the uniform distribution of drug among the

formulations [19]. Viscosity was measured determine the rheological properties of formulations. The results of viscosity determination were observed in the range of 4.9 to 6.21 Pa-S. The narrow range in variation of viscosity among the formulations was found as because all the formulations contained the same % of gelling polymer (PF-127). All the prepared nanoemulgel formulation of curcumin show that they are in a liquid state when in the freezing temperature and for ease of administration and accurate measurement of dose, when the temperature rose, it is converted to gel with increased residence time at lower limit of the optical temperature range [20]. The main prerequisite of an ophthalmic emulgel is its gelling capacity. The instilled formulation should undergo a rapid sol-to-gel transition before being wash out by lachrymal secretion. Hence gelling capacity was studied and found all the formulations get instantaneous gelation and remained for extended period of time when placed over isotonic buffer solution pH 7.4 simulated at 37°C [19]

From the FTIR spectra of pure curcumin (Fig-1) bands due to carbonyl band (C=O) stretches (1800-1500cm^{-1}) were observed for curcumin at 1509.35 cm^{-1}. Similarly bands of phenolic hydroxyl (-OH) stretching (3200-3550 cm^{-1}) was observed at 3524.34 cm^{-1} and stretching of alkenes (=C-H) in the range 3000-3100 cm^{-1} was observed at 3011.81 cm^{-1}. All the peaks responsible for stretching of major functional groups in pure curcumin were found with no major shifting in the spectrum obtained for physical mixture (Fig-3) of curcumin with the gelling polymer (PF-127) and in the spectra of final formulation ((Fig.4) containing all other ingredients like oil, surfactants and co surfactants.

In-vitro drug release study of in-situ ophthalmic nanoemulgel showed the sustained release properties for all the formulations (Fig-7). Formulation F3 showed higher release (61.77%) during the 5 hours study period than the formulation F2 (release only 33.53%), whereas the formulation F1 released minimum % of drug (31.87%).

From the figures (Fig-6 & 7) we observed that the average globule size of the prepared formulatins is in the nano range (199.3-194.2nm). In formulation F2 the Z-Average size range is 199.3nm with a polydispersity index 0.215 and standard deviation 99.16 (Fig-8) and in the formulation F3 the average size (Z-average) is 194.2 nm with a polydispersity index 0.530 and standard deviation 320.4 (Fig-9). Hence it can be said that the globule size of the nanoemulgel formulations is distributed in the nano range and polydispersity index suggested the more uniform size distribution with little deviation.

From the Figure (Fig-8) we observed that the globules size distribution of the formulation is in the range of 38-100nm. Hence Nano globular size distribution was again established by another method.

It has been found from the drug release studies after 3 months storage at accelerated condition (40°C ± 2°C/75 % RH ± 5 % RH) that the release of drug after 5 hours was 55% which is little less than the release study after freshly preparation 61% of formulation F3. The particle size distribution study after storage was found that the average particle size of formulation F3 was increased to 199nm from 194nm (Fig. , which is not significant increase in size. Hence it can be concluded that the formulation is sufficiently stable even after storing at accelerated conditions.

CONCLUSION

Compatibility study between drug and polymer done by FTIR, shows that there is no incompatibility among the formulation ingredients. The globule size distribution study by Malvern Zetasizer shows uniform globule size distribution in nano range. The physico-chemical evaluation reveals good rheological properties with instantaneous gelling capacity at ocular surface temperature. In-vitro drug release study of in-situ ophthalmic nanoemulgel showed the sustained release properties for all the formulations for the study period of 5hr. Accelerated stability study of the formulations established that the formulations are sufficiently stable for long term storage. Hence formulation of curcumin nanoemulgel can be done for the sustained action of drug in ophthalmologic pathology.

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