ORIGINAL RESEARCH PAPER

Pharmaceutical

FORMULATION AND EVALUATION OF A POLYHERBAL: *CURCUMIN* AND *BOSWELLIA* LOADED ETHOSOMAL GEL

KEY WORDS: Polyherbal, Ethosomal gel, Diabetic Neuropathy, *Boswellia serrata*, Curcumin

Pranay Wal* Associate Professor & Dean. Institute of Pharmacy. Pranveer Singh Institute of Technology, Bhauti, Kanpur-209305.*Corresponding Author

Ruchi Tiwari Associate Professor . Institute of Pharmacy. Pranveer Singh Institute of Technology, Bhauti, Kanpur-209305.

Priya Singh JRF UPCST Lucknow

ABSTRACT

Diabetic neuropathy is a chronic complication of diabetes mellitus with symptoms of decreased motility and severe pain in peripheral parts. Thus, our objective was to formulate the polyherbal ethosomal gel containing *Boswellia serrata* having anti-inflammatory properties and *Curcuma longa* that possess antioxidant, antibacterial and anti-inflammatory properties and is used in various skin creams. Ethosomes were prepared using cold method and ethosomal gels were prepared in nine different formulations, which were evaluated for its pharmaceutical properties and were assessed using gel parameters. The results showed that the gels were non-irritant and stable. Formulation NE 9 containing lipid (Soya lecithin) surfactant (Propylene Glycol) in ratio 1:2 showed highest drug entrapment efficiency. All the parameters assessed were with good physicochemical properties. Thus, the present study revealed; ethosomal gel as an efficient carrier for herbal extract.

INTRODUCTION

Diabetic Neuropathy is one of the major complications of diabetes since mid-1800s and its indication is the abnormal nerve conduction leading to loss of motility in peripheral parts [Cohen, 2015]. Synthetic drugs used in this have high treatment costs and side effects along with drug resistance which can be overcome by the use of traditional medicine [Lalitha, 2018]. Polyherbalism combines two or more herbs and increase the therapeutic effect by acting on multi-targets [Parasuraman, 2014]. *Curcuma longa* is an anti-inflammatory and has anti-diabetic effects [Kazazis, 2014] and *Boswellia serrata* has antihyperglycaemic and antihyperlipidemic effects. Moreover, a study showed that *Boswellia serrata* has protective effects on diabetic complications in animal model. Thus, its combination can be used for the effective management of pain in Diabetic Neuropathy [Mehrzadi, 2017]. Ethosomal delivery system is the novel mode of drug delivery targeted to the skin which is an easily accessible route for drug delivery [Majeed, 2019]. Ethosomes are defined as the soft malleable vesicles which are composed basically of phospholipids, ethanol in relatively high concentration and water [Verma, 2010]. Ethosomes are mainly composed of water, phospholipids, poly glycol and a high concentration of alcohol (ethanol, isopropyl alcohol), usually about 20%, to 40% ethanol that brings increase in fluidity of lipid hence increase in permeability of skin and improves the drug penetration [Parmar, 2016].

Thus, in the present study, polyherbal ethosomal gel was prepared using *Curcuma longa* and *Boswellia serrata* for the effective management of pain in Diabetic Neuropathy.

MATERIALS AND METHOD

Collection and preparation of plant material

Rhizomes of *Curcuma longa* were procured from local market of Kanpur, Uttar Pradesh and oleo gum resins of *Boswellia serrata* were procured from official website India Mart. They were authenticated from Botany department of Christ Church College (CS/2018-19/ SPEC/135). All the other solvents and reagents were of analytical grade.

Curcuma longa extract: Rhizomes were grounded and fine powder was collected after passing it through sieve no. 60. Soxhlet extraction was done by using pet-ether as solvent and 7-8 cycles were run. Temperature maintained was 35-40°C. After the extraction; solvent was removed by using rotavapour. Resulting oil was packed with aluminium foil in a glass container and kept in refrigerator at 9-10°C till use.

Boswellia serrata: Oleo gum resin was added to hot distilled water on the magnetic heater for 1.5hr, and then the extract was filtered. Solvent was removed using rotavapour. Resulting porous powder was stored in a refrigerator at 4-8°C till use.

Preformulation studies

Identification of extract was carried out by ultraviolet (UV) spectrophotometric methods and Fourier Transform Infrared (FTIR).

Preparation of ethosomes

Polyherbal ethosomes were prepared by using cold method. In this method, phospholipid, lipophillic extract (*Curcuma longa*) and other lipid materials were dissolved in ethanol at room temperature by vigorous stirring with the use of mixer. Propylene glycol was added during stirring. The prepared mixtures were subjected to 30°C ± 1°C in a water bath with constant mixing at 700 rpm with a mechanical stirrer. In other vessel hydrophilic (*Boswellia serrata*) was added into water and heated to 30°C ± 1°C. Aqueous solution was added into non aqueous one drop by drop with stirring for 5 min in a covered vessel. The formulation was kept aside to cool at room temperature for 30 min and then it was sonicated using an ultrasonicator at 4°C for six cycles of 20 seconds each with a 1-minute rest between cycles to get desired size of ethosomes. Finally the complete formulation was stored in refrigerator [Patel, 2007; Grace, 2018].

Preparation of ethosomal gel

The gels were prepared by cold method using carbopol 934. Carbopol 934 was dispersed in distilled water at 300 rpm for 2 hours and kept it to swell for overnight. After one day *Curcuma longa* and *Boswellia serrata* containing ethosome suspension was added drop wise into carbopol with continuous stirring to form a homogenous mixture. After that triethanolamine was added, till a transparent gel was obtained. For the protection from bacteria and fungi, 0.01% benzalkonium chloride was added as a preservative.

Characterization of Ethosomes

In the present study, characterization of ethosomes was done by FTIR studies, Scanning electron microscopy (SEM), Entrapment Efficiency (EE), Drug content and Drug entrapment Efficiency [Gunasekaran, 2008].

FTIR: It was determined by using Perkin Elmer's FTIR spectrophotometer. All formulation was scanned in the wavelength region of 4000-400 cm⁻¹ [Gunasekaran, 2008].

Fig. 1: Calibration curve of *Curcuma longa*

Vesicle shape: Ethosomes can be easily visualized by using scanning electron microscopy (SEM).

Percentage Drug content Study:
For this study, 1 ml of ethosomes in 10 ml volumetric flask was taken and mixed with quantity sufficient ethanol and filtered it with whatman filter paper. Resulting filtrate was used for the determination of drug content. Drug content in prepared preparation were determined by UV-1700 Shimadzu. For *Curcuma longa*, λmax was kept at 423 nm and for *Boswellia serrata*, λmax was kept at 260 nm.

Percentage Drug Entrapment Efficiency:
For the determination of entrapment of drugs, 2 ml of ethosomes was taken in 10 ml volumetric flask and mixed with quantity sufficient phosphate buffer pH 6.8. The mixture was centrifuged at 1500 rpm for 25 minutes and supernatant liquid layer was collected. 1 ml supernatant liquid was mixed with 9 ml methanol and the absorption was measured by UV-1700 Shimadzu. For *Curcuma longa*, λmax was kept at 423 nm and for *Boswellia serrata*, λmax was kept at 260 nm.

The drug entrapment efficiency calculated by given formula:
$\mathbf{D_{EE}(\%) = (W_T - W_F) / W_T * 100}$ where
$D_{EE=}$ Drug entrapment efficiency
W_T= Total amount of ethosomes
W_F= Free amount of ethosomes in Supernatant liquid

In-vitro release of drug loaded ethosomes:
In-vitro release of *Curcuma longa*:
In-vitro release of *Curcuma longa* loaded ethosomal suspension was conducted for eight hour period respectively by using Franz diffusion cell and phosphate buffer saline pH 7.4. The cumulative amount of drug release was calculated for each formulation.

In-vitro release of *Boswellia serrata*:
In-vitro release of *Boswellia serrata* loaded ethosomal suspension was conducted for eight hour period respectively by using Franz diffusion cell and phosphate buffer saline pH7.4. The cumulative amount of drug release was calculated for each formulation.

Characterization of Ethosomal Gel
The polyherbal ethosomes incorporated gels were evaluated for physical characteristics, pH, viscosity and rheological studies, gel strength, extrudability, spreadability, washability based on the methods in literature.

Physical Characteristics
The prepared herbal ethosomal gel formulations were examined visually for their color, appearance, consistency, homogeneity, and phase separation manually [Grace, 2018; Indira, 2015; Shukr, 2013].

Viscosity: Viscosity of ethosomal gel was carried by Brookfield Viscometer (RVDV-II+PRO) by selecting spindle number 5. 50g of prepared preparations were taken into 50 ml beaker. Spindle was dipped into beaker and the viscosity of the prepared formulations was measured at 20, 50 and 100 rpm.

pH: In this method, ethosomal gel weighing accurately 1 gm was dispersed in 100 ml of distilled water and stored for two hours. The pH measurements were done in triplicate and average values were calculated.

Spreadability: Wooden block and glass slide apparatus were used to determine the spreadability. In this method, 2 gm excess gel on the ground slide was placed. Sandwiching of gel was done between this slide and another glass slide having fixed ground slide and provided with the hook. Weight of 1 kg was placed on the top of the two slides for 5 minutes to expel air which helps to provide a uniform film of the gel between the slides. From the edges excess of the gel was scrapped off. With the help of string attached to the hook the top plate was subjected to pull and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. Better spreadability is indicated by the shorter interval. Following formula is used to calculate Spreadibility

S=M×L/T
where, S= Spreadability,
M=Weight in the pan (tied to the upper slide)
L= Length moved by the glass slide
T= Time (Sec) taken to separate the upper slide from the ground slide

FTIR: All Ethosomal gel formulations were scanned in the wavelength region of 4000-400 cm^{-1}.

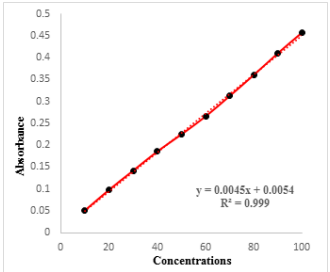
Drug content: Determined using UV spectrophotometer.
Stability studies for ethosomal cream and gel percent entrapment:

Physical Appearance: Optimized gel formulations were kept for 1, 2 and 3 months under 5°C ± 3°C as well as 25°C ± 2 °C temperature conditions to study the effect of storage conditions on their physical appearance.

Content Uniformity of Gel: The uniformity of drug content in ethosomal gel formulation was evaluated in triplicate. For this investigation ethosomal gel (1.0g) was kept in a beaker containing 1000 ml of phosphate buffer pH (7.4) containing sodium lauryl sulphate (SLS) 2.5%w/v for 48 h on magnetic stirrer. Solution was filtered and analyzed by UV spectro photometer at λmax 290nm.

In-vitro drug release: In-Vitro studies for ethosomal gel were performed by Franz-diffusion cell with diffusion area of 0.075 cm^2. In this method, magnetic bead was kept in the receptor compartment. Donor and receptor compartment was separated by the egg membrane. Ethosomal gel was placed in the donor compartment and the receptor compartment received phosphate buffer (pH 6.8). Phosphate buffer was continuously stirred by magnetic bead at 250 rpm. 1 ml of phosphate buffer was withdrawn at the starting of diffusion cell and 1 ml of fresh phosphate buffer was added into diffusion cell. After that, again 1 ml sample was withdrawn from receptor compartment after 30 minutes and again 1 ml. fresh buffer solution was added. Same procedure was repeated 8 times with difference of 1 hour respectively. Absorbance of all samples were measured by UV-1700 Shimadzu in two ranges 423 nm for *Curcuma longa* and 260 nm for *Boswellia serrata*.

RESULT:
Preformulation Studies:
Standard curve of *Curcuma longa* extract and *Boswellia serrata* was prepared using phosphate buffer saline pH 7.4 for each concentration. They were prepared in the range of 10-100 µg/ml and the respective absorbance of *Curcuma longa* extract and *Boswellia serrata* were measured by UV spectrophotometer at 423 nm and 260 nm respectively. Regression coefficient (r^2) was thus found to be 0.9974 and 0.9984 respectively.



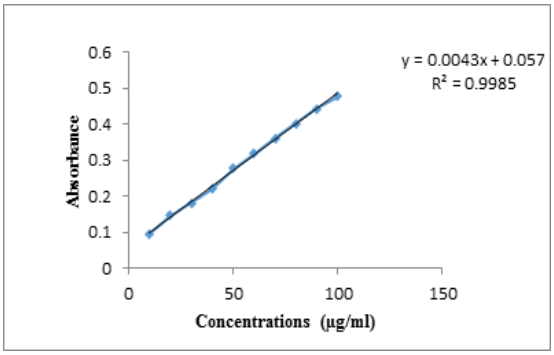


Fig. 2: Calibration curve of Boswellia serrata

Table 1: Formulation design of ethosomes from polyherbal extracts

Formulation Code	*Herbal Extracts (Curcuma longa: Boswellia serrata)*	Soya Lecithin (mg)	Ethanol (ml)
Ne1	2:1	0.9	20
Ne2	2:1	0.9	30
Ne3	2:1	0.9	40
Ne4	2:1	1.2	20
Ne5	2:1	1.2	30
Ne6	2:1	1.2	40
Ne7	2:1	1.5	20
Ne8	2:1	1.5	30
Ne9	2:1	1.5	40

FTIR:

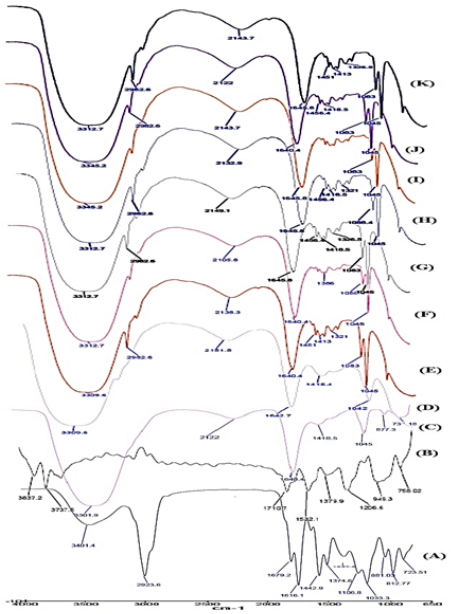


Fig. 3: FTIR of A: *Curcuma longa extract; B: Boswellia serrata*; C: Ne1; D: Ne2; E: Ne3; F: Ne4; G: Ne5; H: Ne6; I: Ne7; J: Ne8; K: Ne9

Vesicle shape:

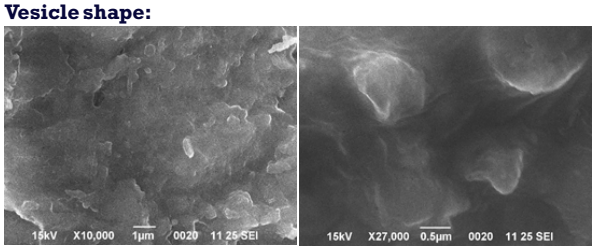


Fig. 4 SEM of Ne 8 and Ne 9

Percentage Drug Content Study: The result obtained showed 13.25% to 14.50% for *Curcuma longa* and 17.99% to 83.11% for *Boswellia serrata* drug content in all the formulations and is tabulated in table 2. The result showed directly indicated that there is no degradation of drug in the process of formulation.

Table 2: Percentage Drug Content Study

S.No.	Formulation Code	Drug Content (%) of *Curcuma longa*	Drug Content (%) of *Boswellia serrata*
1	Ne1	13.25	17.99
2	Ne2	16.71	51.51
3	Ne3	10.13	46.21
4	Ne4	19.84	54.90
5	Ne5	12.37	60.51
6	Ne6	12.97	66.97
7	Ne7	15.26	69.73
8	Ne8	12.74	76.19
9	Ne9	14.50	83.11

Percentage Drug Entrapment Efficiency: The drug entrapment efficiency of prepared formulations was found to be 35% to 90% as indicated in table 3. 88.73% (For *Curcuma longa*), 83.87% (For *Boswellia Serrata*) was maximum entrapment efficiency of ethosome formulation NE9. Formulation NE9 containing lipid (Soya lecithin) surfactant(Propylene Glycol) ratio is 1:2 and formulation NE2, shows lowest drug entrapment efficiency which was found to be 38.89% (for *Curcuma longa*) and 43.78% (for *Boswellia serrata*).

Table 3: Percentage Drug Entrapment Efficiency

S.No	Formulation Code	Percentage Drug Entrapment Efficiency (Curcuma longa)	Percentage Drug Entrapment Efficiency (Boswellia Serrata)
1	Ne1	52.28	57.65
2	Ne2	38.89	43.78
3	Ne3	42.3	55.8
4	Ne4	56.23	66.76
5	Ne5	48.75	45.23
6	Ne6	45.05	48.70
7	Ne7	77.56	75.67
8	Ne8	84.34	79.45
9	Ne9	88.73	83.87

In-vitro release of *Curcuma longa* loaded ethosomes: On the basis of results, it was revealed that highest cumulative of drug released 98.98 possessed by formulation Ne8 and Ne9 because of the optimum surfactant concentration (30%), at this concentration surfactant molecules associated with lipid bi layer resulting in better partitioning of the drug and resulted in higher drug release from the vesicles.

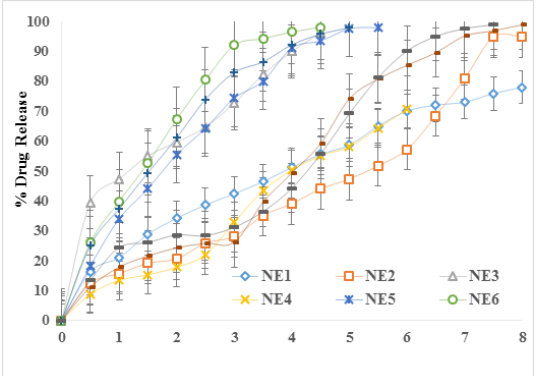


Fig.5: Percentage Drug Release of *Curcuma longa* loaded ethosomes

In-vitro release of *Boswellia serrata:* Results obtained showed that the highest cumulative drug release was possessed by formulation Ne8 (99.82) and Ne9 (99.05). Formulation Ne8 and Ne9 were suitable for further studies because of maximum cumulative release.

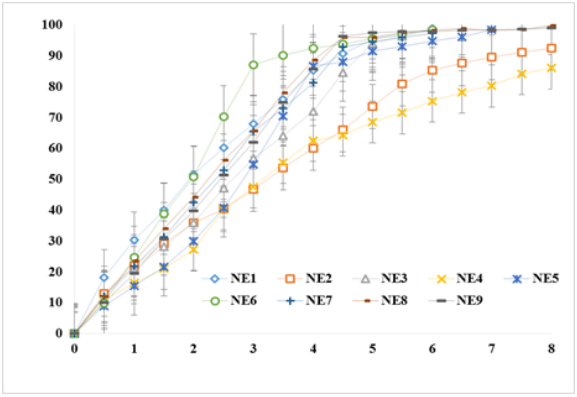


Fig. 6: Percentage drug release of *Boswellia serrata* loaded ethosomes

Characterization of Ethosomal Gel:

Table 4: Viscosity of different ethosomal formulation

S.No.	Formulation	Shear Speed (rpm)	Viscosity (centipoise)
1	NE8	20 50 100	6820 2652 1440
2	NE9	20 50 100	7920 3920 2260
3	Plain Gel	20 50 100	8328 2862 1587

Table 5: pH of different ethosomal formulation

S.No.	Formulation	pH
1	NE8	12.50
2	NE9	13.63
3	Plain Gel	11.53

Table 6: Spreadibility of different ethosomal formulation

S.No.	Formulation	Spreadibility (gm.cm/sec)
1	NE8	12.50
2	NE9	13.63
3	Plain Gel	11.53

DISCUSSION:

In the present work, ethosomal formulation is prepared of the herbals so as to enhance the transdermal permeation of the *Curcuma longa* and *Boswellia serrata*, and was evaluated. Ultraviolet spectrophotometric study was carried in the phosphate buffer pH 7.4 in the scanning range for each i.e. for *Curcuma longa* and *Boswellia serrata* separately. Experimental value of λmax was found to be 423nm for Curcuma longa and 260 nm for *Boswellia serrata* and was compared with the literature value. Value of absorbance of standard concentrations of 10-100 μg/mL was plotted, and linearity was observed with r^2=0.997 and r^2= 0.998 for *Curcuma longa* and *Boswellia serrata* respectively for the phosphate buffer 7.4 when analysed at 423nm and 260nm respectively and thus this wavelength was taken as the working wavelength for UV spectroscopic analysis of *Curcuma longa* and *Boswellia serrata*.

Visualisation by scanning electron microscope (SEM) showed that ethosomes was spherical, as shown in the figure 4. Ethosomes gave an average size of 150 to 200 nm in an ideal condition. An increase in concentration of ethanol from (20-45 percent) generally decreases ethosomal vesicles size. A high concentration of ethanol, however, leads to lipid bilayer interdigestion and vesicle destabilization [Barupal, 2010]. Thus, our image confirmed the formation of ethosomes which were within the 1μm size.

The entrapment efficiency of ethosomes was determined for all formulations. Effect of concentration of ethanol was observed on percentage drug entrapment of ethosomes. The maximum entrapment efficiency of *Curcuma longa* was found to be 88.73±0.19% for formulation NE9 and minimum 38.89±0.31% for formulation NE2, whereas the maximum entrapment efficiency of *Boswellia serrata* was found to be 83.87±0.29% for formulation NE9 and minimum 43.78±0.29% for formulation NE2. Ethanol plays a very important role in the efficiency of trapping of ethosomes; the ethanol concentration is directly proportional to the trapping efficiency. The efficiency of enhancement of penetration is attributed to ethanol effect and ethosomes effect. This relationship was found to be linear, with concentration of ethanol between 20%-40%. Improvement in aqueous solubility of the formulation was achieved with higher concentration of ethanol, which could be due to its co-solvent effect [Somwanshi, 2018].

For the identification of the organic functional groups in the prepared ethosomal suspension formulations, FT-IR study was performed. In the spectrum of extract of *Boswellia serrata*, extract of *Curcuma longa* and all the prepared ethosomal formulations, all the stretching vibrations are tabulated in the table. All vibration found in the spectra of all formulation NE 1-NE 9, and there was no any type of chemical reaction found in the formulation between drug excipients. Similar peaks were found in the spectra of NE 1-NE 9 formulations. FT-IR of all ethosomal formulations were given in figure 3. All the major peaks for the pure drug and the formulation were well supported with the theoretical estimation with respect to the functional groups.

In vitro drug release studies of drug-loaded ethosomal suspensions were conducted for a period of eight hour using Franz diffusion cell, in phosphate buffer of pH 6.8. The release profiles of entire ethosomal suspensions of *Curcuma longa* and *Boswellia serrata* were shown in figure 5 and 6 respectively. From the release profile, it was observed that concentration of phospholipid, and ethanol had an impact on drug release profile. These were main parameters that influenced size and encapsulation efficiencies. Drug release was observed at every 1 hour interval. NE-8 formulation showed maximum in-vitro drug release of *Curcuma longa* which contained 30ml of ethanol and 1.5mg of soya lecithin while the NE-1 formulation showed minimum in-vitro drug release which contained 20ml ethanol and 0.9mg of Soya lecithin, whereas for *Boswellia serrata*, maximum in-vitro drug release was in NE-8 formulation only as in *Curcuma longa* and the minimum was in NE-4 formulation which contained 20ml ethanol and 1.2mg Soya lecithin. This observation indicated that ethanol played important role for penetration compared to lecithin concentration. Ethanol allowed the vesicles to penetrate into deeper layers of the skin by making them soft and flexible. High concentrations (20%-40%) of ethanol caused interpenetration of the ethanol hydrocarbon chain, which leaded to reduction in vesicular membrane thickness and hence reduced vesicular size [Somwanshi, 2018].

In a regular drying rate period, gel contains a lot of moisture that liquid surface exists which will dry in a manner corresponding to an open faced frame of moisture. Diffusion of moisture from inside the droplet keeps saturated surface conditions and so long as these lasts, evaporation takes area at constant rate. When the gel is dried under constant drying conditions, the water content usually drops. The graph is linear at first, then curves and finally flattens. The drying period of the constant rate lasts until free moisture emerges

from the surface, the rate of removal of moisture then decreases. The moisture content at which the drying rate stops being constant is known as critical moisture content (CMC). During a period of constant drying, water vapor from the inside migrates to the surface in various ways and is evaporated. When the moisture level is lowered, the rate of migration to the surface is lowered. CMC of gel formulation (NE8) was 1.93, 1.93 and 1.98 for 2%, 2.5% and 3% w/v concentration of carbopol 934 gel. The maximum constant rate period is found for 2% and 3% w/v gel, which shows all moisture evaporation. The constant rate period ends when the rate of moisture migration from the inside of the surface becomes less than the rate of evaporation from the surface. The period after the critical point is called the "fall rate period". Outside this point, the surface temperature rises, and the drying rate drops rapidly. The falling rate period takes much longer than the constant rate period, although the removal of moisture may be much less. The drying speed is close to zero at some equilibrium moisture content (EMC). The concept of equilibrium moisture content (EMC) is important in the study of formulation drying and storage. This determines the maximum amount of moisture that the formulation can absorb during storage. EMC for 2%, 2.5% and 3% w/v gels were 0.61, 0.91 and 0.91 respectively. Data from CMC and EMC justified 2% w/v gel which is suitable for further evaluation [Jyothi, 2016; Sundari, 2017].

On the basis of the in-vitro drug release of all the formulations, NE8 and NE9 formulations were stabilised and their pH was measured which is tabulated in table no. 5. For analysing the consistency of the gel, a tiny amount of gel was pushed between the thumb and the index finger, whereas homogeneity was also identified of the gels by placing the gel on the rear of the hands skin. All the data are tabulated in table 4 and were found to be normal. Viscosity plays a very significant role in stability & application. According to the results obtained, viscosity of the formulations was observed when the shear rate was increased i.e. pseudoplastic behaviour. Rheological experiments disclosed that viscosity decreased with an increase in shear rate. Thus, it indicated the typical pseudoplastic flow behaviour of the developed optimised formulations. It was clearly attributed to the colloidal network structure that aligned itself with the shear direction, thus reducing the viscosity as the shear rate increases. The polymer chains disarranged to fit in the path of stream with increased shear stress and this orientation decreased the material's internal resistance, which at each consecutive shearing stress enabled a higher shear rate. Thus, the rheological properties matched and met the requirements of the optimal necessity of the topical delivery formulations [Saxena, 2010; Indira, 2015]. As the therapeutic efficacy of the gel depends on its spread, thus the spreadability of optimised gel was considered high by having a low spread of time. The spreading ability of the gel helps in the uniform application of the gel to the skin, and texture was also considered as smooth, so the prepared gels must have a good spreadability and satisfied with ideal quality in topical application [Saxena, 2010]. Extrudability of the gel determines the patient's compliance in using the gel from the collapsible tubes. It was within the standard limits. Furthermore, this was considered an important factor in patient compliance with treatment.

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